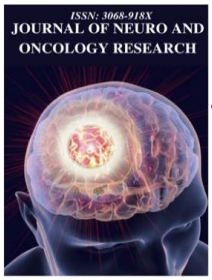

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Review Article

Psychosis as a Neurodevelopmental Spectrum: Beyond the Degeneration Paradigm

Yanan Dai[1,2*], Yunhao Xie[3], Jing Ding[4], Leilei Cheng[1,2]

[1]Department of Echocardiography, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai Institute of Medical Imaging, Shanghai, China

[2]Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, NHC Key Laboratory of Ischemic Heart Diseases, Key Laboratory of Viral Heart Diseases, Chinese Academy of Medical Sciences, National Clinical Research Center for Interventional Medicine, Shanghai, China

[3]Zhongshan Hospital, Fudan University, Shanghai, China

[4]Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China

***Correspondence author:** Yanan Dai, Department of Echocardiography, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai Institute of Medical Imaging, Shanghai, China and Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, NHC Key Laboratory of Ischemic Heart Diseases, Key Laboratory of Viral Heart Diseases, Chinese Academy of Medical Sciences, National Clinical Research Center for Interventional Medicine, Shanghai, China; Email: daiyanan855@gmail.com

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Abstract

For decades, prevailing models of psychosis-including schizophrenia and various neurodegenerative disorders have largely interpreted hallucinations and delusions through the lens of neurodegeneration and neurotransmitter imbalance. In this view, psychotic symptoms emerge as the consequence of progressive and largely irreversible neural decline. Yet, an alternative picture has begun to emerge from accumulating evidence. Rather than reflecting only loss, psychosis in a subset of cases may represent a fundamentally different developmental trajectory one that resembles a re-emergence of early, highly plastic brain states. We refer to this hypothesis as "pathological neoteny," in which the brain appears, in certain respects, to revert toward immature modes of cognition characterized by heightened plasticity and reduced constraints on internal representations. Intriguingly, many phenomenological features of psychosis-such as vivid internal imagery, weakened boundaries between perception and imagination and intensified associative thinking echo aspects of normative childhood cognition. However, while these similarities are striking, the underlying mechanisms remain poorly understood and the boundary between developmental plasticity and clinical pathology remains unclear. In this Perspective, we bring together emerging neuroimaging and molecular evidence that points toward atypical developmental timing, including delayed maturation and sustained plasticity in specific psychotic subgroups. We situate these findings against established frameworks in developmental neuroscience, particularly synaptic pruning, critical period closure and the adaptive advantages of childhood neural flexibility. Importantly, we emphasize that psychosis is heterogeneous: not all cases can be explained within a single framework. We therefore highlight the need to carefully distinguish normative childhood imagination from pathological states, while also acknowledging the conceptual, methodological and ethical challenges inherent in this distinction. Looking forward, we propose a research agenda centered on longitudinal, multi-modal developmental comparisons, biologically grounded subgroup stratification and mechanistic mapping of how plasticity itself might become dysregulated. Such work also raises translational questions both promising and cautionary-regarding whether and how brain plasticity could be therapeutically modulated. Taken together, this re-evaluation challenges the long-standing assumption that psychosis is solely a story of decline, instead suggesting a more nuanced narrative in which altered developmental timing and plasticity may play a central role in shaping mental experience and its disorders.

Keywords: Neurodevelopmental Spectrum; Neurodegeneration; Neurotransmitter Imbalance; Psychosis

Introduction

Psychotic symptoms delusions, hallucinations and reality distortions remain defining features of severe neuropsychiatric illness, most notably schizophrenia, bipolar disorder with psychosis and various neurodegenerative dementias [1,3,4]. Over decades, neurobiological research has attributed these phenomena to a combination of neurotransmitter dysregulation particularly dopaminergic dysfunction but also involving glutamatergic, serotonergic and cholinergic systems and progressive structural abnormalities, including prefrontal-striatal circuit impairment, hippocampal and basal ganglia atrophy and abnormal connectivity networks, as demonstrated through neuroimaging and histopathological studies [1,3,8]. These models prioritize irreversible degeneration, casting psychosis as a disorder of functional and anatomical loss. Yet, striking phenomenological parallels exist between core aspects of psychosis and features of normal early childhood cognition where vivid, convictional fantasy and a porous boundary between imagination and perception are normative rather than pathological. As established in foundational developmental neuroscience, children routinely animate imaginary worlds, identify with fictional characters and interact with AI agents as if sentient, all reflecting adaptive explorations enabled by elevated brain plasticity and open association networks [1,8]. Such cognitive modes correspond with periods of intense synaptic growth and delayed pruning, underlying the brain's capacity for flexible learning and creative inference [5]. Incorporating these perspectives poses a provocative question: Could certain manifestations of adult psychosis reflect not neural decay, but rather the pathological persistence or re-emergence of developmental neural architectures typically associated with earlier life stages? Instead of restricting interpretation to degenerative trajectories, this alternative framework situates psychosis within a broader neurodevelopmental context. In particular, it integrates multiple converging lines of evidence, including theories of critical period plasticity, longitudinal studies of lifespan neural trajectories and observations of delayed or incomplete cortical maturation reported in specific psychosis subgroups [3,4,6]. Within this view, psychotic phenotypes may, in part, arise from atypical stabilization or reactivation of neural states that are normally transient during development. Fig. 1 illustrates these competing conceptual models, contrasting degeneration-based explanations with developmentally anchored accounts. Ultimately, reconciling the heterogeneity of psychosis through a neurodevelopmental lens may provide new opportunities to refine mechanistic understanding and inform more targeted clinical interventions.

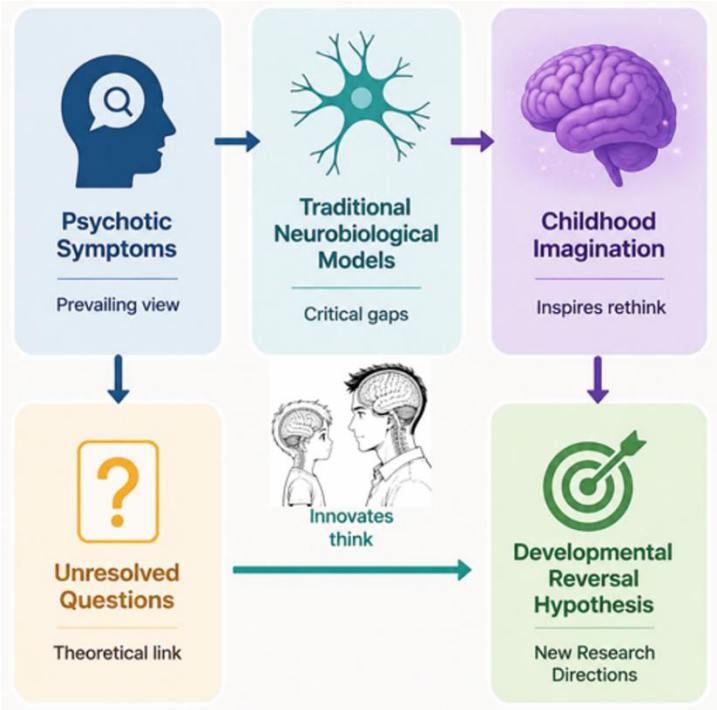

Figure 1: Overview of the perspective: Traditional degeneration-focused models of psychosis leave key questions unresolved. Bridging insights from childhood imagination, the developmental reversal hypothesis reframes delusions as potential reactivation of youth-like neural features, opening novel research and clinical directions.

Core Perspective

Traditional conceptions of psychosis emphasize neurodegenerative pathology-marked by neurotransmitter imbalance and progressive atrophy in regions such as the hippocampus and prefrontal cortex-as foundational to clinical manifestations [3,5,8]. However, recent literature, including neuroimaging studies, has identified overlapping features between the immature brain of childhood and aspects of some adult psychoses, particularly heightened synaptic plasticity, incomplete pruning and globally integrative neural networks [3,8]. For example, magnetic resonance imaging and PET studies have reported patterns of increased cortical thickness in ultra-high-risk youths and persistence of 'immature' connectivity in some patients with schizophrenia, suggesting a delay or arrest of normative maturation [3]. Importantly, while children's vivid imagination, role-play and credulity toward AI or fictional agents are adaptive and contextually appropriate, adult psychosis is defined by distress, lack of insight and significant impairment of social and occupational functioning [4,8]. Core to diagnosis is the inability to distinguish fantasy from reality in a manner that creates harm or dysfunction-a sharp contrast with healthy childhood fantasy, which is flexible, playful and integrated with social learning. Thus, phenomenological overlap does not negate critical differences: psychosis involves maladaptive reactivation or persistence of such cognitive states beyond developmental appropriateness, compounded by contextual, neurobiological and psychological factors [8]. The hypothesis of 'pathological neoteny' posits that in specific psychosis subtypes-possibly early-onset schizophrenia, adolescent psychotic disorders and some cases of psychosis in neurodevelopmental syndromes-there may be measurable neurobiological evidence of arrested or reversed maturation. Such a framework could involve atypically elevated synaptic density, as indexed by SV2A PET ligands, persistence of critical period-related gene programs (including altered BDNF or NRG1 signaling) or the maintenance of an excitatory-inhibitory balance more characteristic of early neurodevelopment [1]. However, the current evidence base remains preliminary, with most observations being correlational and subject to important confounds, including antipsychotic exposure, illness chronicity and comorbid medical conditions. Moreover, the marked heterogeneity of psychotic disorders necessitates careful phenotypic stratification. At one end of the spectrum, neurodegenerative psychoses, such as those associated with Alzheimer's disease are primarily characterized by progressive neuronal loss [2]. In contrast, neurodevelopmental or mixed forms of psychosis may exhibit overlapping signatures of degeneration alongside features suggestive of arrested or atypical maturation. Recognizing psychosis as a spectrum thus motivates the search for intermediate biomarkers-such as alterations in cortical gyrification, delayed myelination trajectories and region-specific synaptic marker expression-that may help disentangle subtypes and clarify whether pathological neoteny represents a primary mechanism, a secondary adaptation or a coincident developmental phenomenon alongside degeneration.

Discussion

Translating the 'pathological neoteny' hypothesis into actionable research requires a staged, multi-modal roadmap. First, explicit hypotheses should be tested: (1) Do adults with clinical psychosis exhibit structural (e.g., cortical thickness, gyrification), functional (e.g., resting-state connectivity) or molecular (e.g., SV2A PET, BDNF levels) markers characteristic of the immature brain, compared to healthy adults and children? (2) Are these features specific to certain psychosis subtypes (e.g., adolescent-onset or schizophrenia-spectrum) and independent of illness chronicity or antipsychotic exposure? (3) Can intermediate biomarkers (e.g., critical period gene expression, synaptic density) reliably distinguish neurodevelopmental from neurodegenerative psychosis? Experimental design should prioritize cross-sectional and longitudinal MRI and PET studies enrolling children (ages 5-10), healthy adults, adults with early and late-onset psychosis (with careful assessment of subtype) and adults with neurodegenerative psychosis [1,2,8]. Behavioral paradigms quantifying imagination, fantasy-reality discrimination and social inference (potentially leveraging interactive AI agents or virtual reality) will allow phenotypic linking to neural measures [10-12]. Statistical modeling should control for confounders including medication status, comorbid medical and psychiatric conditions, illness duration and age at onset. Multi-variate group comparisons and machine learning classifiers could be employed to identify distinguishing feature sets. Longitudinal cohort studies in at-risk populations (e.g., children or adolescents with neurodevelopmental syndromes or strong familial risk [5]) can assess if persistence of immature neural features prospectively predicts psychosis onset, severity or response to interventions. Importantly, supplementary Fig. 2 illustrates this roadmap, mapping imaging, molecular and behavioral endpoints across development and disease. Translational applications require careful definition. If pathological neoteny is confirmed in relevant psychosis subgroups, interventions could target the promotion of cortical maturation e.g., via neurotrophic agonists, plasticity modulators or environmental enrichment protocols rather than mere antipsychotic-induced dampening of positive symptoms [5,13,14]. However, ethical and practical concerns must be weighed: artificially enhancing plasticity may exacerbate symptoms, destabilize cognition or produce off-target effects [4,15,16]. Rigorous preclinical validation and adaptive clinical trial design are prerequisites to deployment. Further, we urge

detailed policy guidance for communicating these findings to patients/families to avoid misunderstanding or stigmatization [7,9].

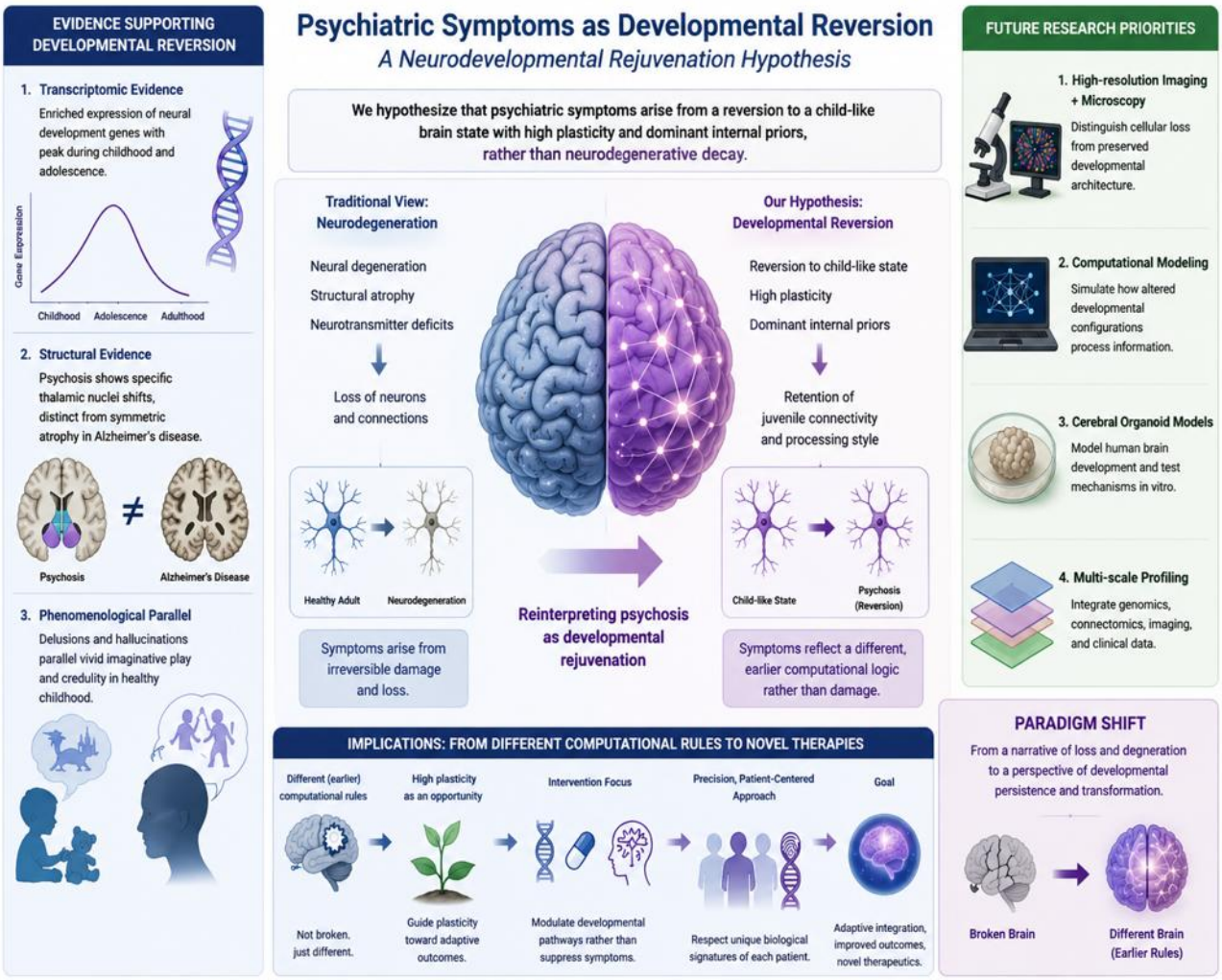

Figure 2: This infographic presents the "Developmental Reversion Hypothesis" regarding psychiatric symptoms, offering an innovative theory on how psychosis may arise. On the left side, it outlines evidence supporting the hypothesis, including transcriptomic, structural and phenomenological parallels, which suggest that psychotic symptoms might stem from a reversion to a childlike brain state, rather than neurodegenerative decay. The hypothesis posits that, in some cases, psychotic states could reflect the reactivation of immature, highly plastic neural circuits, drawing on developmental features commonly observed in childhood. On the right side, the infographic illustrates the proposed future research directions, such as high-resolution imaging, computational modeling, cerebral organoid models and multi-scale profiling. These approaches are designed to test and validate the hypothesis further. It also emphasizes a shift from traditional degenerative models to new therapeutic strategies based on the high plasticity of the brain, offering a paradigm change from the idea of brain degeneration to a perspective of ongoing developmental transformation. By challenging the conventional neurodegenerative disease model, this infographic provides a fresh framework for understanding psychosis and highlights potential implications for both theoretical research and clinical interventions.

Several important limitations should be acknowledged. First, the proposed neurodevelopmental framework for psychosis remains largely theoretical and is primarily based on the integration of indirect and heterogeneous evidence. Direct causal validation of key hypotheses-such as the pathological persistence of developmental neural states remains limited. Second, much of the current empirical literature is correlational in nature, making it difficult to disentangle whether observed neurodevelopmental features represent primary mechanisms, compensatory adaptations or epiphenomena of disease progression and treatment exposure. Confounding factors such as antipsychotic medication use, illness chronicity, lifestyle

variables and comorbid neurological or systemic conditions further complicate interpretation. Third, psychosis is highly heterogeneous across diagnostic categories, disease stages and individual trajectories. This variability limits the generalizability of any single explanatory framework and highlights the risk of over-unifying distinct pathophysiological processes under a single conceptual model. Fourth, available biomarkers such as imaging-based measures of synaptic density, cortical maturation or functional connectivity-remain indirect proxies of underlying cellular and molecular processes and their specificity for distinguishing developmental versus degenerative mechanisms is still uncertain. Finally, longitudinal multimodal datasets spanning early neurodevelopment through disease onset and progression remain scarce. Without such data, it is challenging to establish temporal causality or to determine whether observed "development-like" signatures in adult psychosis reflect arrested maturation, reactivation of latent programs or convergent downstream effects of neurodegeneration. Together, these limitations underscore the need for rigorous longitudinal, multimodal and mechanistically grounded studies to critically evaluate the proposed framework. Table 1 is the overall structured comparation of the degeneration-centric model and our proposed perspective.

Dimension	Degeneration-Centric Model	Neurodevelopmental / Plasticity-Based Model	Integrated Spectrum Model
Core Explanation	Neurotransmitter imbalance and progressive structural/functional brain degeneration	Persistence or reactivation of immature, highly plastic neural circuits	Combined degenerative and neurodevelopmental mechanisms
Primary Mechanisms	Dopaminergic/glutamatergic dysregulation; cortical/subcortical atrophy; connectivity disruption	Delayed maturation; excessive/atypical plasticity; persistence of developmental programs	Interaction between degeneration, developmental delay and maladaptive plasticity
Representative Conditions	Late-stage schizophrenia; dementia-related psychosis	Subtypes of schizophrenia; neurodevelopmental psychosis	Spectrum of psychotic disorders across etiologies
Neural Substrate	Cortical thinning; hippocampal/basal ganglia atrophy	Reduced synaptic pruning; prolonged critical periods; altered excitatory-inhibitory balance	Heterogeneous regional combination of atrophy and immature-like circuitry
Key Evidence	Neuroimaging atrophy; dopamine hypothesis; clinical progression	Childhood cognition parallels; developmental trajectory studies; SV2A-related findings	Longitudinal multimodal imaging and molecular convergence evidence
Clinical Interpretation	Primarily functional and structural loss	Atypical developmental state expression	Mixed mechanisms depending on subtype and stage
Relation to Childhood Cognition	Indirect or absent	Strong phenomenological overlap (fantasy, blurred reality boundaries)	Partial overlap; not equivalent but mechanistically informative
Pathological Nature	Unidirectional neurodegeneration	Developmental arrest or reactivation	Continuum model across developmental trajectories
Therapeutic Implications	Neurotransmitter modulation; anti-degenerative strategies	Plasticity modulation; developmental window targeting	Stratified treatment (stage- and subtype-specific)
Limitations	Cannot explain developmental-like features	Limited causal evidence	Requires longitudinal validation and biomarker stratification

Table 1: Overall structured comparation and illustration.

Conclusion

This Perspective critically re-examines prevailing degeneration-centric views of psychosis in light of emerging developmental neuroscience and comparative neuroimaging evidence [17-19]. While classical models anchored in neurotransmitter abnormalities and progressive atrophy remain valid for many cases-particularly late-onset and neurodegenerative psychoses-a subset of psychotic states may instead reflect persistence or reactivation of immature, highly plastic neural circuits [2,3,5]. Key

distinctions between adaptive childhood fantasy and adult psychotic pathology lie in the context and consequences of these mental states-most crucially, the presence of distress, lack of insight and functional impairment in the latter [8,20,21]. Taken together, existing neurobiological accounts have provided a robust foundation for understanding psychosis as a disorder rooted in neurotransmitter imbalance, circuit-level dysfunction and progressive structural and functional brain alterations. These degeneration-centered models have been instrumental in elucidating key clinical and imaging findings; however, they do not fully capture the phenomenological richness and developmental parallels observed in psychotic states. By revisiting psychosis through a neurodevelopmental lens, this Perspective highlights an alternative and not mutually exclusive interpretation in which certain psychotic features may reflect the aberrant persistence, reactivation or dysregulation of neural systems characteristic of earlier developmental stages. The striking overlap between psychotic experiences and features of childhood cognition further supports the possibility that altered developmental timing, alongside degenerative processes, may jointly shape clinical phenotypes. Importantly, this reframing does not replace established degeneration-based theories but rather extends them into a more integrative framework that accommodates heterogeneity across psychotic disorders. Within this spectrum, psychosis may emerge from multiple interacting mechanisms, ranging from progressive neurodegeneration to atypical maturation trajectories and maladaptive stabilization of high-plasticity brain states. Future work integrating longitudinal neurodevelopmental imaging, molecular profiling and biomarker-informed stratification will be essential to disentangle these pathways. Such efforts may ultimately refine diagnostic boundaries, improve mechanistic precision and enable interventions tailored not only to disease stage but also to underlying developmental architecture.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

All authors contributed equally to this paper.

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