Rethinking the First Episode of Schizophrenia: Identifying Convergent Mechanisms During Development and Moving Toward Prediction

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The neurodevelopmental hypothesis of schizophrenia has long suggested that the cardinal psychotic symptoms that have traditionally defined the disorder, and which most commonly appear in late adolescence or early adulthood, are a late-stage manifestation of early disruptions in brain developmental processes (1–3). Over the past two decades, findings from two major bodies of research have lent increasing support to this hypothesis and begun to define more specific pathogenic processes underlying schizophrenia, as well as early markers of future psychosis. In particular, large-scale genetic studies have increasingly implicated genes involved in synaptic signaling and plasticity in the pathogenesis of schizophrenia, and studies of individuals at high risk for psychosis have shown that those who later develop schizophrenia have alterations in cognitive, social, motor, and neurobiological processes long before the emergence of full-blown psychotic symptoms (reviewed in 4, 5). On average, impairments in cognitive and broader psychosocial functioning increase in magnitude across development among individuals who later develop psychosis, and generally persist despite successful treatment of positive symptoms, contributing to the chronic disability associated with the illness (6, 7). This body of research has also highlighted the heterogeneity and undifferentiated nature of clinical symptoms that are present among individuals in the years leading up to a first psychotic episode. Together, these findings are paving the way for a focus on earlier interventions that can reduce the likelihood of full-blown psychosis among high-risk individuals. However, with growing recognition that the specific genetic and environmental factors that contribute to psychosis risk often vary from one person to the next and overlap with risk for other disorders, a key goal of future research is to clarify what interventions will work best for whom and how to optimize illness prediction models.

Here, we first briefly review the normal brain developmental processes that provide the background context on which schizophrenia-associated signs and symptoms emerge and genetic and environmental risk factors act. We then review recent advances in large-scale genetic studies of schizophrenia and how this research has informed our understanding of the biology of schizophrenia. We discuss findings from clinical and genetic high-risk-for-psychosis paradigms, which follow high-risk individuals longitudinally to define precursor signs and symptoms or biomarkers that are predictive of psychosis, as well as complementary population-representative studies. We also consider how environmental factors in key developmental periods may interact with genetically mediated vulnerability to schizophrenia to influence risk and prognosis. Finally, we discuss current directions in the development of interventions for individuals at high risk or with recent-onset psychosis, including new directions based on patient stratification.

NORMAL BRAIN DEVELOPMENT AND PLASTICITY

Human brain development is protracted and unfolds across three decades of life to produce a mature brain that is efficient and finely tuned for our environments. Prenatal development progresses through a series of intricate processes in which billions of cells proliferate, migrate, and differentiate into specific cell types and form an overproliferation of immature synapses with one another. The subsequent primary task of postnatal development is to use environmental inputs to refine these connections into the efficient neural circuits that characterize an adult brain. This refinement involves the mass elimination of approximately half of these initial synapses (8, 9) and the concurrent strengthening of remaining synapses, corresponding to the activity-dependent elimination or enlargement of dendritic spines where the majority of excitatory synapses are located. In the case of synapse strengthening, dendritic spine enlargement and functional expression of long-term potentiation (LTP) largely reflect the insertion of new glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors into the membrane, as well as the recruitment of scaffold and actin cytoskeleton-associated proteins to the synapse to structurally enlarge the spine and stabilize newly
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interneurons mature, their cell bodies and dendrites become ensheathed by PNNs, which are extracellular matrix structures that help stabilize and limit receptor mobility at synapses, protect cells and synapses from potential neurotoxic stimuli, and establish microenvironments around cells and synapses that regulate where new synapses can form (28). The expression of PNNs is crucial for closing critical periods of heightened developmental plasticity and instead supporting stability for existing synapses and circuits (24, 28).

CLINICAL, COGNITIVE, AND NEUROBIOLOGICAL MARKERS

The heterochronic nature of normative brain maturation described above has long been assumed to underlie the emergence of increasingly complex sensory, motor, and cognitive functions across normal development, and provides an important context for understanding the broad signs and symptoms associated with schizophrenia. At the onset of the first psychotic episode, subtle abnormalities in motor, sensory, cognitive, and social functioning are present for many patients (29–34). Meta-analyses of first-episode patients indicate deficits that are 0.5–1.5 standard deviations below functioning levels in control subjects, depending on domain of functioning and assessment measure used (35–37). Deficits in verbal memory, processing speed, and executive functioning are among the most prominent, whereas deficits in motor skills are more subtle. Overall IQ estimates are approximately one standard deviation below those of control subjects (35).

Deficits across domains of functioning are consistent with MRI-based findings of reduced gray matter volume and cortical thinning across many brain regions in schizophrenia, apparent by first episode, as well as alterations in neural activation and connectivity between distributed brain regions (38–40). Notably, these changes in brain volume and connectivity have been widely suggested to at least partially reflect changes in underlying synaptic density, given that volume reductions are particularly prominent in prefrontal and temporal cortical regions in chronic schizophrenia (41, 42), and these are the same regions most affected by reductions in dendritic spine density in schizophrenia (43–46). Postmortem studies indicate that spine density loss occurs in the absence of changes in neuron number or gliosis, the scarring associated with CNS damage (47–52). Furthermore, multiple studies have found no relationship between degree of spine loss and duration of illness, age at onset of psychosis, or antipsychotic use in schizophrenia, indicating that spine changes are unlikely to reflect factors related to illness chronicity (53–55). Together with recent findings that individuals who later develop schizophrenia show accelerated cortical thinning, particularly in prefrontal and temporal regions (56–61), these brain abnormalities appear to be best explained within a neurodevelopmental framework, a theory further supported by findings of subtle signs of anomalous or
delayed development in infancy and childhood in individuals who later develop schizophrenia.

Specifically, children and youths who later develop schizophrenia show overall IQ estimates that are approximately 0.5 standard deviations below estimates for control subjects (62, 63), and this gap appears to increase with proximity to illness onset (64). Individuals who later develop schizophrenia also show delayed motor milestones in infancy and impairments in verbal, social, and learning and memory function during childhood (65–70). Furthermore, a prospective, longitudinal study that assessed 1,037 individuals in Dunedin, New Zealand, multiple times between ages 7 and 13 found that deficits in verbal and visual knowledge acquisition were evident in childhood and remained stable through early adolescence for those who later developed schizophrenia, whereas performance on processing speed, working memory, and attention tests showed a developmental lag (71, 72). This seminal study highlighted that, parallel to the heterochronic maturation of brain regions and circuits involved in more basic versus complex functions, antecedents of schizophrenia may also emerge hetero-chronically, with deficits in higher cognitive functions emerging more clearly later in development, as activity-dependent synaptic refinement progresses to association cortices and circuits supporting these functions. Such patterns also align with the broad, undifferentiated nature of the early prodromal symptoms of schizophrenia, such as anxiety, depression, and sleep disturbance, which progressively evolve into discernible psychotic symptoms (73, 74). This body of literature has underscored the need for explanatory models that can account for the diverse clinical, cognitive, and neuroanatomic markers associated with schizophrenia, including their relative magnitude and timing of emergence across development.

**GENETIC ARCHITECTURE AND NEUROBIOLOGICAL MECHANISMS IN SCHIZOPHRENIA**

Crucially, over the past decade, large-scale genetic studies have increasingly suggested that disruptions in synaptic signaling and plasticity are a fundamental mechanism through which genetic variants associated with schizophrenia increase risk. Thus, it is now clear that the genetic architecture of schizophrenia is complex and highly polygenic, likely involving hundreds to thousands of genes, and that risk variants span a range of variant classes and allele frequencies in the population (i.e., common to rare). Early insights came from a seminal genome-wide association study (GWAS) of common single-nucleotide polymorphisms (SNPs) in 36,989 schizophrenia patients and 113,075 control subjects by the Psychiatric Genomics Consortium (PGC), in which 108 distinct loci across the genome were associated with schizophrenia (75). Many of these loci spanned genes that are critical for glutamatergic signaling and plasticity, including genes encoding subunits of the AMPA (i.e., GRIA1) and NMDA receptors (i.e., GRIN2A) as well as multiple calcium channels (e.g., CACNA1C, CACNB2, and CACNA1I1), which modulate neurotransmitter release, neuronal excitability, and dendritic development (76). Furthermore, the strongest association signal was located within a region of the major histocompatibility complex that was subsequently determined to map onto structural variation at the complement component 4 (C4) genes (77). This structural variation alters the expression of C4 proteins that are involved in the complement cascade that tags synapses for elimination. Follow-up studies in animal models and schizophrenia patient-derived induced pluripotent stem cell models found that C4 risk alleles cause increased complement deposition on synapses and excessive synaptic pruning by microglia during development (77–79), providing a potential direct link to long-standing hypotheses that schizophrenia may arise in part as a result of excessive synaptic pruning (80, 81). The most recent GWAS, involving 76,758 schizophrenia patients and 243,649 control subjects from the Schizophrenia PGC, confirmed and expanded on these findings, implicating additional genes involved in synaptic signaling and plasticity, including genes encoding other neurotransmitter receptors and ion channels (e.g., GABBR2, GRM1, CLCN3), and additional components or modulators of synapse organization and signaling (e.g., DLGAP2, MAPK3, GPM6A). Exome sequencing studies have similarly found that rare and de novo damaging variants in schizophrenia are enriched at the pathway level for genes involved in synaptic signaling and plasticity (82–85). Furthermore, the largest exome sequencing study to date, involving 24,248 cases and 97,322 control subjects, identified the NMDA receptor subunit gene GRIN2A, the AMPA receptor subunit gene GRIA3, and a calcium channel ion gene, CACNA1G, to be among 10 genes that were individually associated with schizophrenia (85), highlighting convergence between common and rare variants at both the individual gene and pathway levels. Studies of rare copy number variants in schizophrenia, in which large stretches of DNA (>50 bp) are deleted or duplicated, have shown similar enrichment for excitatory and inhibitory signaling pathways (86–88). Some genes involved in earlier aspects of neuronal development and broader transcriptional regulation have also been implicated in schizophrenia and overlap genes implicated in earlier-onset neurodevelopmental disorders such as autism spectrum disorder and intellectual disability (e.g., 85, 89, 90). However, enrichment of synapse-associated genes remains the clearest point of biological convergence across genetic variants associated with schizophrenia, and on average, genes associated with early-onset neurodevelopmental disorders have been found to show a strong bias for prenatal expression, whereas genes associated with schizophrenia do not (85, 91, 92).

As normal synaptic signaling inherently shapes the hierarchical maturation of brain circuits during postnatal life, we and others have hypothesized that genetically mediated aberrations in synaptic signaling and plasticity may result in the emergence of motor, sensory, cognitive,
and neurobiological signs and symptoms associated with schizophrenia across development, finally culminating in psychotic symptoms as dysregulation in late-maturing dopaminergic signaling imbibes innocuous stimuli with aberrant salience (e.g., 3, 11, 93). Indeed, while dopamine signaling has figured prominently in models of psychotic symptoms for decades, largely because dopamine D2 receptor blockade is the primary therapeutic mechanism underlying most antipsychotic medications (7), genetic risk variants for schizophrenia clearly converge on much broader aspects of synaptic signaling and plasticity. However, projections from dopamine neurons in the striatum onto prefrontal cortex mature during adolescence (94) and are shaped, in turn, by prefrontal cortex projections to the midbrain dopamine nuclei—the ventral tegmental area (VTA) and substantia nigra (SN) (95). Animal models have shown that genetically determined deficits in activity-dependent spine remodeling can yield a progressive emergence of behavioral abnormalities during development, dendritic spine loss in adulthood, and downstream dysregulation of dopamine signaling via altered input from pyramidal neurons in frontal cortex onto dopamine neurons in the VTA and SN (96–98). As the early presence of genetically mediated disruptions in spine remodeling appears sufficient to produce diverse behavioral symptoms during development and dysregulated dopamine signaling in adulthood, this suggests a compelling primary mechanism through which altered synaptic plasticity during development could give rise to the broad signs and symptoms associated with schizophrenia by first psychotic episode.

**PREDICTION IN AT-RISK POPULATIONS**

Findings from genetic studies that alterations in synaptic signaling and plasticity during development are likely a key pathogenic pathway to schizophrenia have emerged in tandem with findings from longitudinal studies focused on identifying markers that can predict future psychosis onset among individuals at clinical high risk for psychosis (CHR-P). Thus, the “first episode” of schizophrenia is typically preceded by a prodromal period involving subthreshold psychotic-like symptoms and functional decline (99–101). Efforts to prospectively identify those who will ultimately develop the disorder, prior to overt psychotic symptom onset, led to operationalization of these clinical features via structured clinical interviews to facilitate reliable identification of a CHR-P syndrome across research groups (102). However, as only 10%–25% of individuals who meet CHR-P criteria develop full-blown psychosis within 2 years (103), there has been particular focus on developing models and identifying specific prognostic biomarkers that can improve outcome prediction and shed light on biological mechanisms associated with overt illness onset, to facilitate more mechanistically informed treatment development. (For an umbrella review on this topic, see reference 104.)

The EEG-based mismatch negativity (MMN) is one candidate biomarker that has been extensively studied. MMN is a negative voltage event-related potential component elicited automatically 100–250 milliseconds following the presentation of infrequent deviant sounds (i.e., pitch, duration, and intensity) randomly embedded within a series of frequent standard sounds (105). MMN amplitude reduction is one of the most widely replicated abnormalities in schizophrenia (106, 107) and is related to NMDA receptor hypofunction (108), a pathophysiological mechanism implicated in both psychotic symptoms and cognitive dysfunction, as a result of its critical role in mediating experience-dependent plasticity (109, 110). Theoretical models of MMN posit that repetition of standard sounds builds a memory trace that predicts recurrence of the standard sound. Detecting a violation in this prediction is therefore assumed to depend on short-term plasticity processes because it requires intact representation of what was “standard” in the recent processing stream (111–113). Notably, reduced MMN has been found to predict conversion to overt psychosis in CHR-P individuals (114–116), as well as time to conversion, over and above positive symptom severity (117). There is also some evidence that it may predict remission from CHR-P symptoms and functional recovery (117–119). These findings suggest that MMN may be a useful target for novel therapies, possibly involving strategies to modulate NMDA receptor glutamate transmission (110, 120).

Accelerated cortical thinning in CHR-P youths is another promising biomarker. As briefly described above, recent studies have observed a steeper rate of cortical thinning in CHR-P youths who convert to psychosis compared with those who do not (56–61), most consistently in frontal and temporal regions critical for higher-order cognition and language. Indeed, recent evidence from the North American Prodromal Longitudinal Study-3 (NAPLS-3) indicates that accelerated cortical thinning is present prior to onset of overt psychosis and is detectable in subsequent converters within a short (<3-month) follow-up period (121). This decrease was not attributable to antipsychotic medication usage and predicted conversion at an individual level, with an area under the curve (AUC) of 0.74. The AUC provides a summary of model performance indicating the proportion of correct predictions, ranging from 0 to 1.0, with 0.5 indicating chance performance. Disrupted synaptic plasticity and/or inappropriate complement system activation leading to excessive synaptic pruning have been proposed as possible mechanisms (81, 121, 122). While synaptic pruning presents a challenging therapeutic target, this collection of novel well-replicated findings suggests that accelerated cortical thinning may be a valuable biomarker of target engagement.

Adding biological markers into clinically based prediction algorithms may improve prediction of individual outcomes. Indeed, the utility of a clinical risk calculator from NAPLS-2 for predicting conversion to psychosis within 2 years among CHR-P youths (123), which includes variables for verbal learning and processing speed performance, age at assessment, family history of psychosis, symptom severity for a subset of positive symptoms, and decline in social
functioning, has been replicated in multiple independent samples (e.g., 124–126). However, predictive performance of these models appears to vary depending on ascertainment characteristics of the CHR-P sample and possibly cultural context (125, 126). Notably, initial evidence suggests that incorporating baseline levels of the stress hormone cortisol into the model can improve prediction of later psychotic illness (127). Similarly, adding cortical thinning improved model performance in NAPLS-3, particularly for individuals who had experienced subthreshold psychotic symptoms for a shorter duration (128). Interestingly, psychosis prediction among CHR-P individuals based on polygenic risk score (PRS) for schizophrenia alone, which reflects the weighted sum of common risk alleles based on independent GWASs, yielded AUC values of 0.65 in European-ancestry individuals and 0.59 in non-European-ancestry individuals in NAPLS-2. Adding schizophrenia PRS to the clinical calculator modestly improved prediction for European-ancestry individuals (i.e., C-index increase from 0.70 to 0.71), but not for non-European-ancestry individuals (i.e., C-index with or without PRS of 0.67) (129). Although the small samples of converters split by ancestry was a limitation of this study, these findings are notable given that genetic testing is already regularly incorporated in some clinical contexts for diagnostic purposes (e.g., for known monogenic diseases [130]), and there is considerable interest in developing procedures to incorporate PRSs for complex diseases in clinical settings as well (131). However, substantial ethical issues remain, including the potential to amplify existing health disparities, given reduced accuracy of PRSs for individuals with increasing distance in genetic ancestry relative to the discovery GWAS cohort (132), which for schizophrenia has involved a substantial overrepresentation of European-ancestry individuals thus far (133). Interestingly, the amount of variance in risk prediction accounted for by schizophrenia PRS in the combined clinical and PRS NAPLS-2 model was estimated at 15% and 7% for European-ancestry and non-European-ancestry individuals, respectively (129). These proportions were lower than the variance accounted for by the strongest predictor in this model, subthreshold psychosis symptom severity, which explained 68% and 25% of variance for European-ancestry and non-European-ancestry individuals, respectively, but greater than or similar to the other variables in the model, whose variance explained ranged from 0% to 8% for European-ancestry individuals and 0% to 9% for non-European-ancestry individuals. The poorer explanatory power of these models overall in non-European-ancestry CHR-P youths highlights the importance of considering sociodemographic factors and patient stratification to develop the most robust prediction models. Additionally, findings are consistent with evidence that while schizophrenia PRS is robustly associated with psychotic diagnoses in independent samples (75, 134), its discriminatory power is modest in general health care settings (e.g., maximum odds ratio of 4.6 for individuals in the highest vs. lowest deciles of schizophrenia PRS, in a large U.S. study of four health care systems [135]). Nevertheless, schizophrenia PRS has been found to be associated with neuromotor impairment in infancy (136), poorer social, verbal, and overall cognitive functioning in childhood (137), and anxiety and negative symptoms in adolescence (138) in general population studies, underscoring the fact that biological and clinical/neurocognitive antecedents of schizophrenia are often linked. Together, this suggests that the most powerful predictive models will likely require multiple clinical and biological markers (139), possibly incorporating genetic risk scores that reflect multiple classes of genetic variants, rather than PRSs alone, which only capture risk due to common variants.

Indeed, among the most highly penetrant individual genetic risk variants for schizophrenia are deletions at the 22q11.2 locus (estimated odds ratio for schizophrenia, 67.7) (85), in which one copy of a ~2.5-megabase segment of chromosome 22, spanning 46 protein coding genes, is most typically deleted (140). This rare deletion occurs in approximately 1 in 3,000–4,000 live births but is estimated to account for 0.3–1% of schizophrenia cases (87, 141). Up to 25% of individuals with 22q11.2 deletion syndrome (22q11DS) develop schizophrenia or a related psychotic disorder, and 22q11DS is also strongly associated with other neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and attention deficit hyperactivity disorder (142, 143). Neuroimaging studies of individuals with 22q11DS, regardless of psychotic illness status, indicate large overall reductions in total brain volume (Hedges’ g = −0.96) (144), which are driven by widespread reductions in surface area (145). Conversely, cortical thickness is increased overall in 22q11DS, in contrast to the pattern in idiopathic schizophrenia. However, it is notable that 22q11DS patients with psychosis show cortical thinning in fronto-temporal regions relative to 22q11DS patients without psychosis, indicating overlap with brain regions most affected in idiopathic schizophrenia (145). Furthermore, prospective longitudinal studies have revealed altered trajectories of fronto-temporal cortical thinning in adolescence in 22q11DS patients who develop psychosis (146, 147), in line with findings in idiopathic CHR-P youths (57, 121). Higher PRS for schizophrenia was also associated with increased risk for psychosis in the context of this highly penetrant risk variant, and was associated with cognitive decline from pre- to post–psychotic illness onset (148, 149), although schizophrenia PRS was lower in 22q11DS cases with psychosis compared with schizophrenia cases with unknown genetic cause (149). These findings indicate that notable convergence exists between clinical, neuroanatomic, and genetic risk markers for psychosis in the context of 22q11.2 deletions compared with idiopathic schizophrenia. However, as these markers occur against a clinical and neuroanatomic backdrop that differs from idiopathic schizophrenia (e.g., global surface area reductions and overall cortical thinning, high rates of early neurodevelopmental disorders and intellectual disability), this also highlights the importance of complementary approaches for
patient stratification that may include genetic or other neurobiological moderators of disease risk, in order to maximize psychosis prediction under different contexts.

ENVIRONMENTAL INFLUENCES ON PSYCHOSIS RISK AND POTENTIAL NEUROBIOLOGICAL MECHANISMS

While dramatic advances have been made in our understanding of the genetic architecture of schizophrenia over the past decade, long-standing evidence also implicates environmental factors such as adverse childhood experiences (ACEs) and cannabis use in schizophrenia, and growing evidence suggests that environmental factors may converge with genetic risk via disrupted synaptic signaling and dendritic spine refinement during development. Thus, twin studies have long pointed to an important role for the environment in schizophrenia, as monozygotic twins have only a 50% concordance rate for schizophrenia, despite sharing nearly 100% of their DNA sequence (150, 151). Environmental factors, including poverty, immigration status, low social support/social fragmentation, and ACEs such as physical or sexual abuse or neglect, are strongly associated with psychosis-related outcomes (152–154). For example, a recent meta-analysis estimated the population attributable risk of ACEs on schizophrenia risk at 33% (odds ratio = 2.8) (155). Moreover, a Swedish population-based study of 2.1 million individuals found increasing psychosis risk with increasing numbers of adverse social factors present in fetal development and early childhood, suggesting a dose-response relationship (156). In individuals with first-episode schizophrenia, stressful life events are associated with both increased symptom severity (157) and relapse risk (158), with recent findings of dose-dependent effects of stressful life events on risk of relapse strongly suggesting a causal role for stress (159). Recently, the impact of systemic factors—namely, structural racism—on psychosis risk in the United States has been more closely examined. As these factors perpetuate inequity in community-wide access to resources and wealth, individuals in minoritized communities are disproportionately affected by the adverse environmental risk factors noted above (160). This could contribute to observations that schizophrenia diagnoses are elevated in Black Americans compared with White Americans in the United States (161, 162), with similar patterns reported in the United Kingdom (163), although bias in diagnosis by providers is another possible explanation (164).

The specific mechanisms through which stress contributes to psychosis risk and course of illness are difficult to isolate, given the limitations of studying molecular mechanisms in humans. However, it is notable that the primary glucocorticoid stress hormones, cortisol in humans and corticosterone in rats and mice, are critical modulators of synaptic transmission and dendritic spine dynamics during normal brain maturation and learning, as well as in response to stress (165–169). Thus, in addition to being released during stress, cortisol (or corticosterone in rodents) is released from the adrenal gland via the hypothalamic-pituitary-adrenal (HPA) axis in a diurnal rhythm; in humans, cortisol typically peaks within the first hour of wakefulness and is relatively suppressed during the night (170). Glucocorticoids readily cross the blood-brain barrier, where they bind to mineralocorticoid (MR) and glucocorticoid (GR) receptors in many regions of the brain, including the hippocampus, amygdala, and cortex. As reviewed by Hall et al. (171), the diurnal rhythm of tonic glucocorticoid release appears to be crucial for maintaining a relative homeostasis of dendritic spine density during development. Glucocorticoid peaks facilitate new spine formation following learning, while the troughs facilitate stabilization of a subset of these spines and the concurrent pruning of a subset of preexisting spines during development (172, 173). Excessive glucocorticoid release following chronic stress, on the other hand, has been found to blunt the glucocorticoid trough, disrupting this rhythm, and results in reduced survival of newly formed dendritic spines and excessive pruning of existing spines (172, 174–176).

The detailed molecular mechanisms underlying these effects is an active area of research; however, it is important to note that unlike neurotransmitter receptors, which largely reside on cell membranes to facilitate communication between cells, MRs and GRs are best known as ligand-activated transcription factors. Thus, MRs and GRs are expressed at both the cell membrane and in the cytosol. Following glucocorticoid binding, cytosolic MRs and GRs translocate to the nucleus, where they bind to regulatory DNA sequence for hundreds of genes to modulate their expression (177, 178). Genes bound by MRs and GRs under conditions of stress and circadian arousal were recently shown to be strongly enriched for canonical plasticity-related pathways such as dendritic branching, synaptic transmission, and long-term potentiation and depression, and included key plasticity- and spine morphology–associated genes, such as the NMDA and AMPA glutamate receptor genes Grin2a, Gria1a, and Gria2, and the postsynaptic density scaffold protein Dlgap1 (177). Furthermore, changes in the expression of genes involved in synaptic transmission and axonal guidance following overexpression of GRs in the cortex were found when GR overexpression was introduced during early life, but not adulthood (168), highlighting a hypersensitivity of the developing brain to altered glucocorticoid function. This is consistent with the increased plasticity of immature synapses and circuits prior to critical-period closure via the mechanisms described above, and with a wealth of evidence indicating that HPA responsivity, dendritic spine integrity, and corticolimbic circuitry are particularly sensitive to the effects of early-life stress (166, 167, 171, 179).

Epidemiological and animal studies similarly suggest that cannabis use during development is an important risk factor for schizophrenia. In particular, adolescent cannabis use is strongly associated with psychosis risk (180–182), with a population-based study finding a significant increase in incidence of schizophreniform disorder among those who

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initiated cannabis use before age 15, but not before age 18 (183). Moreover, a large prospective longitudinal study recently found that initiation of cannabis use during adolescence (ages 14–19) was associated with accelerated cortical thinning in prefrontal regions between ages 14 and 22, overlapping key regions identified for CHR-P youths who later develop schizophrenia, whereas adult cannabis initiation was associated with thinning in parietal, midline, and temporal cortex (184, 185). In animal models, chronic exposure to Δ-9-tetrahydrocannabinol (THC) during adolescence has been found to disrupt cortical development, dendritic spine pruning, and subcortical dopamine firing (186–190), whereas many of these changes were not found following exposure in adulthood. It is not yet known whether such changes occur in humans, and debate exists on whether associations between cannabis use and psychosis may be partly, or fully, accounted for by an increased propensity to use cannabis among individuals at elevated genetic risk for schizophrenia (e.g., 191). However, recent meta-analytic and epidemiological studies identifying dose-dependent relationships between frequency and potency of cannabis use and later incidence of psychotic disorders, across both individuals and geographic locations, have provided strong evidence that cannabis is likely to be a causal factor in at least some cases of schizophrenia (192–194).

Notably, THC, the primary psychoactive cannabinoid in cannabis, produces its effects via activation of the cannabinoid type 1 (CB1) receptor, which is critically involved in retrograde modulation of synaptic transmission in the brain (195, 196). Thus, endogenous endocannabinoids are typically synthesized in postsynaptic neurons in response to specific events, such as strong postsynaptic depolarization and/or changes in postsynaptic calcium influx. From there, they are transported back across the synapse to target CB1 receptors on the presynaptic terminals of inhibitory and excitatory neurons, where they act to inhibit GABA or glutamate release (197, 198). CB1 receptors are expressed widely in the brain, including in the cortex, hippocampus, and basal ganglia, and their activation shapes both short- and long-term forms of plasticity, depending on cell type and brain region (186, 199, 200). Interestingly, a large body of research also indicates that the endocannabinoid and glucocorticoid systems themselves interact to modulate synaptic signaling. In particular, in addition to the gene regulatory effects exerted by cytosolic MRs and GRs that translocate to the nucleus following glucocorticoid binding, membrane-associated MRs and GRs appear to generate rapid effects on neurotransmission in part by initiating signaling cascades that induce the synthesis of endocannabinoid ligands, which then suppress neurotransmitter release presynaptically (201, 202).

Taken together, this body of literature suggests that chronic stress and cannabis use can exert potent modulatory effects on synaptic transmission and dendritic spine dynamics during development and thereby intersect with genetically mediated alterations in synaptic plasticity to accelerate spine loss and/or disrupt circuit maturation in schizophrenia. Indeed, a recent study of 1,699 patients with schizophrenia and 1,542 control subjects found that the relative risk for schizophrenia associated with adverse experiences such as childhood bullying, emotional abuse, sexual abuse, and emotional neglect, as well as regular cannabis use, was increased over and above that expected by an additive model with PRS for schizophrenia. This suggests that beyond potential additive effects of genetic and environmental factors on schizophrenia risk, genetic risk for schizophrenia may confer greater vulnerability of the brain to the effects of some adverse experiences and cannabis use (203). More work remains to be done to definitively demonstrate this. Nevertheless, growing clarity that genetic and environmental risk factors for schizophrenia could converge on related molecular and neurodevelopmental processes is consistent with the long-standing diathesis-stress model of schizophrenia (204) and with evidence from genetic studies that the specific combinations of alleles that underlie risk can vary substantially from one patient to the next.

**IMPLICATIONS FOR TREATMENT**

The literature to date, which we have summarized above, suggests that schizophrenia results from disrupted synaptic signaling and experience-dependent plasticity processes during a sensitive period of brain development that may ultimately manifest as escalating alterations in neural microcircuits, dysfunctional cortical representational systems (11, 205, 206), and downstream alterations in dopamine signaling (93). Regardless of the specific origins of this disrupted coordinated neuronal activity, this implies that a multimodal treatment approach in which corrective learning experiences are provided alongside pharmacological interventions may have the most beneficial effect on circuit maturation, symptom reduction, and possibly even psychosis prevention. Supporting this notion is that most psychosocial interventions (e.g., cognitive-behavioral therapy, family interventions, social skills training, and supported employment) improve functional outcomes, quality of life, and core illness symptoms among adults with schizophrenia compared with treatment as usual, and several reduce relapse frequency (207). Furthermore, in the seminal Recovery After an Initial Schizophrenia Episode (RAISE) study, a comprehensive program for first-episode psychosis involving medication management, family psychoeducation, resilience-focused individual therapy, and supported employment and education, yielded greater improvements in symptoms, quality of life, and work and school outcomes compared with usual care, with duration of untreated illness noted as a key moderator of treatment outcome (208).

This framework also implies potential benefit of treatments targeting plasticity. Evidence to date for the efficacy of such treatments, whether pharmacological (e.g., NMDA receptor co-agonists) or psychosocial (e.g., neuroplasticity-informed interventions such as exercise and cognitive training), suggests that this may be a promising avenue for
some subgroups (209), particularly early in the course of illness given that adolescence represents a critical plasticity period for social and cognitive development (reviewed in detail in reference 205). Notably, a range of treatments have been shown to reduce risk of conversion to overt psychosis in CHR-P individuals by up to half, for up to 48 months following treatment (210, 211). However, to date these beneficial effects do not seem to extend to other symptom areas, such as depression or broader psychosocial functioning (201, 202). Furthermore, there is substantial heterogeneity in clinical presentation, risk architecture, and outcomes among CHR-P youths, highlighting the continued need for better prediction models and valid biomarkers that may define more etiologically distinct subgroups to better guide personalized approaches to treatment.

FUTURE DIRECTIONS AND CONCLUSIONS

The “first episode” of schizophrenia is defined by the onset, whether acute or gradual, of fully psychotic positive symptoms (i.e., delusions, hallucinations) and is commonly operationalized by the first treatment contact for such symptoms (212). Yet, as reviewed here, the first positive symptoms typically develop long after the emergence of cognitive, negative, and other signs and symptoms (6, 7). Given the wealth of evidence for subtle indicators of cognitive and socioemotional disruption long before the onset of overt psychotic symptoms, the first episode may be better conceptualized as the culmination of a cascade of neurodevelopmental events that finally “tips” into this clinical presentation.

We have made substantial progress in understanding the genetic architecture and biology of schizophrenia, but this has not yet yielded the transformative changes we are hoping for, for patients and families affected by the illness. The extended time frame within which adverse genetic and environmental factors converge, along with the presence of a distinct prodromal phase, highlights a potential window for therapeutic intervention prior to onset of full-blown positive symptoms (213). In other areas of medicine, quantitative biological measures (e.g., lipid profiles for cardiovascular disease) are an essential component of treatment selection, concomitant with clinical presentation. Thus, well-validated, sensitive biomarkers and/or multivariate predictive models are urgently needed to improve treatment development for patients in the earliest stages of illness, stratify patients by disease mechanism, measure disease progression, and quantify treatment response (214). To that end, the Schizophrenia Spectrum Biomarkers Consortium (https://ssbcio.org/) was established, which aims to create a repository of putative fluid biomarkers (CSF and blood), linked with genetic data and rigorous clinical, neurocognitive, and neuroimaging phenotypic data from patients and control subjects. These efforts dovetail with those of the Accelerating Medicines Partnership-Schizophrenia (https://www.ampscz.org/), a major international research effort aimed at generating tools to fast-track the development of effective early-stage treatments for CHR-P youths. Given that undifferentiated mood and anxiety symptoms are common among CHR-P youths, identifying biomarkers that can improve differential prediction between outcomes of psychotic and nonpsychotic disorders, as well as remission of CHR-P symptoms, is also a priority of this effort.

From a clinical standpoint, the artificial separation between “child” and “adult” psychiatry impacts continuity of care during this key developmental period. Greater exposure to working with youths and families, and additional training regarding neurodevelopmental context, will be necessary for providers serving young adults to improve patient care and address this gap. Similarly, child-focused providers will need training to recognize subthreshold disturbances in thought content, mood, anxiety, and broader functioning as potential antecedents to psychotic disorders that may mark a key window for early intervention. Translating the wealth of recent findings regarding the behavioral and neurobiological antecedents of schizophrenia, its genetic risk architecture, and the potential convergent mechanisms of environmental risk factors into predictive models and treatments that substantively change the lives of patients with schizophrenia and psychotic spectrum conditions is the next major challenge.

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