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Illness Phase as a Key Assessment and Intervention Window for Psychosis

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ABSTRACT
The phenotype of schizophrenia (SZ), regardless of etiology, represents the most studied psychotic disorder with respect to neurobiology and distinct phases of illness. The early phase of illness represents a unique opportunity to provide effective and individualized interventions that can alter illness trajectories. Developmental age and illness stage, including temporal variation in neurobiology, can be targeted to develop phase specific clinical assessment, biomarkers and interventions. We review an earlier model whereby an initial glutamate signaling deficit progresses through different phases of allostatic adaptation, moving from potentially reversible functional abnormalities associated with early psychosis and working memory dysfunction, and ending with difficult-to-reverse structural changes after chronic illness. We integrate this model with evidence of dopaminergic abnormalities, including cortical D1 dysfunction, which develop during adolescence. We discuss how this model and a focus on a potential “critical window” of intervention in the early stages of schizophrenia impact the approach to research design and clinical care. This impact includes stage-specific considerations for symptom assessment as well as genetic, cognitive and neurophysiological biomarkers. We examine how phase-specific biomarkers of illness phase and brain development can be incorporated into current strategies for large-scale research and clinical programs implementing coordinated specialty care. We highlight working memory and D1 dysfunction as early treatment targets that can substantially affect functional outcome.
**Background/Introduction**

**Neurodevelopment of psychotic disorders**

In the late 20th Century, phenomenological descriptions of young persons characterized alterations in behavior, motoric and cognition as antecedents of later development of psychosis (1-3). While non-specific, findings offered indirect evidence of altered neurodevelopment in those at-risk for psychosis, in line with a neurodevelopmental model of schizophrenia (SZ) (4-6). Psychosis, as a syndrome, is characterized by symptoms including hallucinations, delusions, and changes in behavior and communication; these can be present in different disorders, however the SZ phenotype, as a disorder, is viewed as the representative psychotic disorder. We acknowledge that the diagnosis of SZ is based on expression of a common phenotypic pathway arising from various possible genetic and environmental interactions. The recent NIMH Research Domain Criteria emphasis on dimensional biological and cognitive processes that lead to mental health and illness does not result in diagnostic classifications, which in the past have posed limitations in elucidating neurobiology associated with psychiatric symptoms. Indeed, there have been ongoing considerations regarding alternatives to the SZ construct that may lead to new nomenclature and novel phenotypic classifications (7). To accommodate the evolving shift away from viewing SZ as a distinct disorder with unitary causality we will refer to the phenotype of SZ in this article. This phenotype of SZ has provided the opportunity to study genetics and environment, biomarkers and phases of illness in an enriched sample. Family studies led to discovery of heritable markers of brain processing associated with the SZ phenotype, for example, smooth pursuit eye movement dysfunction (8, 9), sensory gating deficits (10) and certain cognitive deficits, such as working memory (WM) (11, 12) associated with familial vulnerability for psychosis. Potential risk genes, such as SNPs, CNVs and de novo mutations, were associated with later development of psychosis (13). A recently updated large genome wide association study (14) in the SZ phenotype and controls identified 270 risk loci. The role of environmental factors in psychosis risk is also critical, including numerous nonspecific influences during prenatal, perinatal, early childhood and adolescent development (15). In the diathesis stress model, genetic risk interacts with environmental influences to result in altered brain development. According to this concept, transition to psychosis and subsequent chronic illness relates to neurodevelopment mediated by common and/or rare gene alterations in interaction with various adverse environmental influences at any time during brain development, starting in utero up to close to onset of illness (16). Thus, early environmental influences (e.g., infections, nutritional deficiency, and neglect during intrauterine to early childhood period) may exert influences that can alter neurodevelopment directly, or indirectly through gene expression. Later events (e.g., drugs, brain injury) more proximal to onset of psychosis may disrupt dopaminergic homeostasis. This model is not unitary or discrete and a person may undergo exposure to multiple risk factors. This developmental perspective promotes understanding of how distinct phases in the pathophysiology of the phenotype of SZ deviate from neurotypical brain development spanning the prenatal period through adulthood.

*Early phase of illness*
Alterations in behavior across various dimensions, lasting from weeks to years, have been described prior to emergence of psychosis. Nonspecific at-risk symptoms in childhood and adolescence may include anxiety, depression, reduced emotional experience, cognitive difficulties, and social withdrawal(17). Specific syndromes identifying psychosis prodrome are embodied in clinical high risk (CHR)(18) and ultra-high risk (UHR)(19, 20) constructs. CHR/UHR classifications are primarily based on acute or increasing subthreshold positive symptoms, including unusual thought content, perceptual anomalies, and disordered thinking/speech, with relatively intact reality testing. In individuals identified as experiencing attenuated psychosis syndrome (APS), transition to threshold psychosis occurs in an estimated 20-35% within 2-3 years(21). Young persons who do not transition may experience persistent symptoms, in some cases consistent with schizotypy or another non-psychotic disorder, or may experience symptom resolution. Innovative transdiagnostic clinical staging models developed in recent years aim to provide conceptual frameworks for characterizing risk, development, and progression of a broad array of youth mental health outcomes (22-26). Risk calculator(27-32) and machine learning approaches(33, 34), which incorporate an array of risk factors, have been developed to predict progression to first-episode psychosis (FEP). Thus, the FEP outcome is inherently probabilistic rather than determined (24), as delineated in a growing literature supporting the construct of transdiagnostic pluripotential risk (35).

Emergence of FEP is often associated with changes in mood, anxiety, cognition, and substance use problems resulting in uncertain/inconsistent endorsement of target symptoms, phenomenological heterogeneity and diagnostic uncertainty. Yet as clinical course evolves over time, eventual clinical diagnosis in FEP becomes evident and remains relatively stable for SZ(36). In the US, about 100,000 young people experience FEP annually, with a lifetime prevalence of 3%. About one-third of those with FEP develop the phenotype of SZ; the remainder are diagnosed with a range of nonaffective, affective, and substance-induced psychoses. Traditionally, SZ has been viewed as an illness with limited recovery rates, high disability adjusted life years and a 20% reduction in average life expectancy, which underscores the need for more effective interventions.

**Importance of early intervention**

Intervention programs in young persons at CHR have been implemented in numerous countries and aim to attenuate or possibly prevent progression to psychosis, mostly through nonspecific treatments and education(37). In FEP, early intervention can preserve or improve functional abilities(38-40) and potentially alter neurobiological progression of untreated illness. Educational and social developments proceed rapidly during adolescence and young adulthood and even brief disruption can produce enduring consequences for attaining important maturational milestones. These in turn lead to challenges for young persons and their supports, most commonly their family. Consequently, individuals may experience emotional distress, social alienation and stigma(41). It has been postulated, although with inconsistent empirical support, that duration of untreated psychosis (DUP) appears to exert adverse or “toxic” effects on brain functioning(42). DUP has been associated with poorer outcome(43), even years later(44) leading the World Health Organization to recommend constraining DUP to <3 months. Long mean DUP of several years in the representative North American FEP trial (45) illustrates
how far the field is from attaining the goal of early intervention, particularly in community settings in the United States. This critical delay is due to multiple contributors, including limited mental health literacy in the general public, absence of universal screening and mobile detection strategies, limited access to dedicated care, and societal stigma. In addition, lack of significant improvement within a few months to years after onset is associated with limited long-term recovery(46, 47). These harsh findings highlight the pressing need to invest in effective prevention and early intervention approaches to reduce rates of outcome and disability that have not changed significantly in many years despite novel antipsychotics and other treatment modalities.

Typical FEP treatment in general psychiatric settings makes little differentiation between illness phases, and young persons with FEP may receive similar treatment as individuals with chronic illness. Consequently, individuals with FEP are particularly sensitive to both therapeutic and side effects of medications(48). They can easily experience excessive exposure to antipsychotics and a failure to implement recovery-oriented interventions. For young patients, traditional intervention approaches in settings serving more chronically ill persons can contribute to resistance to illness acceptance and proposed treatment, demoralization and enforced stigma of serious mental illness leading to poor outcome.

FEP-specific interventions in dedicated settings were developed in Australia and Europe in the past three decades and have been more widely implemented in the US since 2015 through support of the Substance Abuse and Mental Health Services Administration. FEP-specific interventions are provided by a dedicated team of coordinated specialty care (CSC), including case management, psychotherapy, medication management, supported employment and education, and family support and education. A recent meta-analysis(49) of ten RCTs in FEP provides empirical support for improved outcomes in individuals engaged in 6-24 months of early intervention services, compared to treatment as usual. However, ten-year outcome data from the OPUS trial did not support sustained clinical and functional improvements in individuals with CSC compared to usual care, highlighting the need for additional longer term outcome studies(50). CSC programs in the US, remain scarce in many regions (51), thus inaccessible to many individuals experiencing FEP.

**Neurodevelopmental Mechanisms**

**Prior phase-specific model of schizophrenia pathophysiology**

Individuals with FEP are more sensitive to standard D2R-blocking antipsychotics compared to those with chronic illness(52, 53). Similar early-stage sensitivity was recently noted with respect to novel glutamatergic interventions(54). Thus, treatment response appears greater in early stages, suggesting that pathophysiology of illness differs according to illness stage. Krystal and Anticevic(55) previously outlined a model of stage-specific pathophysiology and its dynamic evolution over time. In this model, the earliest illness stage ("predrome") is marked by minimally-symptomatic glutamatergic hypofunction. Allostatic adaptations to this initial excitatory deficit, particularly reduced GABA signaling, lead to cortical disinhibition/over-excitation during the prodromal phase. This in turn causes abnormalities in neural tuning, oscillations, and functional hyperconnectivity, which produce frank psychotic symptoms, and cognitive impairment including WM dysfunction. Further adaptations to hyperexcitation and hyperconnectivity, such as
accelerated synaptic pruning, cause atrophy and worsening neural circuit dysfunction over time, producing worsening psychosis and potentially irreversible structural changes. One limitation of this exciting model is that it addressed dopaminergic systems only in passing. Here we expand this model (Figure 1) to incorporate literature on developmental and phase-specific changes in dopaminergic function, with a particular focus on dopamine D1 receptors in the prefrontal cortex (PFC).

Normal and abnormal development, focusing on PFC dopamine D1 system
The Krystal & Anticevic model coheres with earlier suggestions that SZ pathophysiology reflects abnormal early neurodevelopmental vulnerability, with frank illness only manifesting in the context of further adolescent brain development(56, 57). Adolescence is marked by profound normative changes in dopaminergic innervation, receptor levels and signaling, and behavioral responses to dopaminergic agents (e.g., stimulants) peak during adolescence(56-59). This contributes to broader maturation of the PFC, which involves synaptic pruning and myelination continuing well into the third decade in humans(60, 61). Indeed, adolescence has been proposed as a neurodevelopmental "critical window" of heightened plasticity for PFC and its functions, including WM(58).

Dopaminergic midbrain neurons continue to arborize into the nucleus accumbens as well as PFC across adolescence. While these changes affect the entire PFC, dopaminergic innervation is particularly increased during adolescence in cortical layer 3 of dorsolateral PFC, which is strongly implicated both in WM and SZ phenotype pathophysiology(59, 62, 63). Human postmortem data indicate that D1 receptor (D1R) levels increase from infancy through adulthood, while D2 receptor (D2R) levels decrease(64). Response to dopamine receptor stimulation in PFC also changes dramatically during adolescence. Dopamine effects on PFC neurons are complex, with a mix of excitatory and inhibitory impacts varying across cell types, subcellular components, and developmental stages. D1R signaling at low levels directly increases PFC pyramidal neuronal firing by enhancing NMDA response, while at higher dopamine levels D1R has a net inhibitory effect on pyramidal cells via modulation of dendritic potassium channels(63, 65) as well as through excitation of interneurons, particularly parvalbumin-positive fast-spiking interneurons (FSN)(63, 66, 67). D1R responsivity in PFC neurons generally increases across adolescence(68-70). D1R and D2R signaling have a complex interaction in PFC, with some similar and some opposing effects(69, 71). This interaction varies according to basal dopamine levels which can shift direction of D1R effects, contributing to inhibitory tuning(63). The interaction also varies dramatically across adolescence, as D2R effects change direction from inhibitory to excitatory on FSNs during this period (thereby increasing cortical inhibition)(56). FSN, implicated in WM and in SZ pathophysiology, show progressive increases in synaptogenesis throughout primate development including adolescence, and are also particularly sensitive to dopamine modulation compared to other interneurons(62, 65). Dopamine also directly accelerates the development of
FSNs and their synapses(72). Dopaminergic maturation in PFC thus interacts with the maturing GABAergic system, contributing to increased inhibition and reduced excitatory:inhibitory balance (E:I) across adolescence(62, 69). Developmental dopamine dysregulation can be impacted by abnormalities of perineuronal nets, extracellular matrix structures that increase across adolescence and protect parvalbumin interneurons from damage while also reducing their plasticity and more broadly contributing to closure of developmental critical windows (73, 74).

In addition to indirect effects via GABAergic interneurons, dopamine’s direct effects on glutamatergic neurons also change across adolescence. In particular, the excitatory component of D1R signaling on PFC pyramidal neurons increases across adolescence, partly through alterations in NMDA receptor function(56, 69, 75, 76).

While we focus on PFC here, PFC dopaminergic systems also interact with striatal dopamine systems and related limbic circuitry(57, 77). Activity of the striatal dopamine system peaks during adolescence(78, 79), and striatal hyperdopaminergia is strongly associated with psychosis(80). In contrast, PFC dopamine is abnormally low in SZ(77, 81). Dopamine systems in PFC and accumbens can have reciprocal or antagonistic effects(82, 83), and this interaction changes dynamically across adolescence(84-86). Striatal dopamine is already elevated in the prodromal phase, increasing further with progression to frank psychosis(87). Beyond direct cortico-striatal interactions, hippocampus and amygdala also participate in circuits linking PFC as well as ventral striatum, and are likely to be important in neurodevelopmental risks for psychosis. Early-developmental injury to the hippocampus recapitulates features of schizophrenia in animal models in part through dysregulation of PFC, and disruption of PFC may in turn cause dysregulated hippocampal and amygdala function, particularly in the context of elevated stress(57). Disturbance of PFC maturation may thus contribute to progression of the striatal dopamine and limbic dysfunction component of pathophysiology, and vice versa. Adolescent neurodevelopmental vulnerabilities can be exacerbated by adverse environments that produce anxiety and stress. In animal models, non-dopaminergic agents including GABAergic modulators used clinically as anti-anxiety medications, as well as metabotropic glutamate modulators, demonstrate the ability to prevent development of hyperdopaminergic states(57, 88). Such mechanisms may have important interactions with environmental risk and resilience factors - environmental enrichment also blocks development of hyperdopaminergia(89), and adverse environmental effects on psychosis risk are likely mediated at least in part by the increase in anxiety and stress they cause(90-92).

**Updated model incorporating dopamine systems**

While many details remain unknown, the above literature points to the need to incorporate dopaminergic systems into the prior model of allostatic phase-specific pathophysiology. Dopaminergic maturation in adolescence and early adulthood represents a key illness phase vulnerability point in SZ pathophysiology, and PFC dopamine abnormalities contribute to a disinhibited and hyperconnected PFC associated with WM impairment(57, 93). In models of SZ, the PFC dopamine system appears to be shifted towards greater D1R-sensitivity and reduced D2R-sensitivity. Reduced D2R-sensitivity directly impacts interneuron activity leading to pyramidal disinhibition. This disinhibition likely drives the PFC hyperglutamatergia and
hyperconnectivity found using MRI in early-stage but not later-stage illness perhaps due to progressive synaptic loss(94-96); D1R-agonism reduces PFC pyramidal cell hyperconnectivity in primates(97). The impact of increased D1R-sensitivity may depend on basal dopamine levels, as D1R is more excitatory for pyramidal cells when dopamine levels are low, but more inhibitory when dopamine levels are high; the weight of the evidence indicates DA levels are low in PFC in SZ. These dopamine effects are likely to be greatest during adolescence and young adulthood, although dopamine abnormalities may also impact earlier stages of pathophysiology.

**Application of the developmental model to illness phase and potential interventions**

This updated model integrates glutamatergic and dopaminergic abnormalities into a dynamic model of pathophysiology that can guide biomarker development and therapeutic development specific to illness phase and brain development. An implication is that dopamine modulators other than D2R-blocking antipsychotics should be considered in early illness and for symptoms outside the positive symptom domain. The combination of abnormally low dopamine, increased D1R-sensitivity, and reduced D2R-sensitivity points to potential benefits of a D1R-agonist which in the low dopamine regime would be expected to bring pyramidal neuronal firing into a more optimal range, improving inhibitory tuning and reducing hyperconnectivity. Given the inverted-U effects of D1R on PFC physiology and WM(63, 98), a partial D1R agonist would be expected to have a similar effect but with reduced risk of overshooting the optimal range, compared to a full D1R agonist. Challenges of effective PFC D1R stimulation and selection of a novel partial D1R agonist as a candidate to improve WM have been described(98).

Another critical implication is that biomarker and treatment studies should stratify according to illness phase, and further work is needed to identify appropriate definitions of illness and brain development phases. Initially, specific age or DUP cutoffs may be selected, but eventually, biomarker-based staging may specify an individual's neurodevelopmental phase and illness phase, providing more accurate stratification. The critical window hypothesis suggests that adolescence and early adulthood represent a period where treatments work differentially and that aberrant plasticity developed may get “cemented” once this window closes. This highlights the urgency of implementing treatments specifically effective during this critical window to prevent illness progression or even reverse it. A more speculative implication of the critical window concept is that treatments which re-open this window of neuroplasticity (for example histone deacetylases), could potentially reinstate sensitivity even during the chronic phase of illness(92). Interventions to prolong neuroplasticity could be combined with other treatments to normalize circuit functioning.

Advances in phase-specific treatment will depend critically on biomarker development. These could include measures that more precisely capture an individual's developmental stage and illness phase and/or different components of the pathophysiological model and its behavioral sequelae, including prefrontal dopamine levels, D1R-sensitivity, prefrontal tuning, and WM. These considerations have driven the design of the TRANSCENDS study including D1R intervention and WM biomarker(98).

**Unique Challenges and Opportunities in Early Psychosis Assessment and Treatment**
Stage specific screening, assessment and treatment
Warning signs of early psychosis (EP) may arise in non-clinical settings (e.g., school or work) or clinical settings without proper recognition and the condition often goes unaddressed contributing to DUP. Interventions for CHR/UHR persons include different, mostly nonpharmacological, modalities and may protect against transition to psychosis, which occurs in a minority of persons. Reasons for non-transition remain to be better elucidated(99) and may include protective behavioral, environmental and genetic factors. Young persons with FEP commonly endorse changes in mood, anxiety, and cognition, and may use substances, contributing to phenomenological heterogeneity and delayed identification of psychosis. The clinician needs to be comfortable with diagnostic uncertainty in FEP(100, 101). Initial diagnoses of affective psychosis (i.e., major depressive or bipolar disorder), may change to non-affective psychotic disorders and (less commonly) vice versa. Over time, considering clinical course, resolution of symptoms, relapse or chronic illness, the clinical diagnosis becomes evident and remains relatively stable for SZ(36). Conveying diagnostic fluidity to the person with EP and their family members protects them from confusion and potential stigma associated with premature diagnosis and allows treatment to remain symptom focused.

Over the past 20 years the psychiatric field has moved towards implementation of CSC in persons with EP. Here, a small interactive team of providers offers multiple treatment components in settings dedicated to young persons. Longitudinal assessment of psychosis and non-psychosis symptom domains represent an important component of CSC and allows for more accurate eventual diagnosis. Stage-specific assessments of core psychosis symptoms include brief screeners(102-104) and structured assessments(18, 105) for CHR and FEP(106, 107). Other important EP assessments include mood, anxiety, cognition, substance use, and developmental disorders (e.g., ADHD, autism spectrum). Assessment of functional (role/social) capacity informs an individualized treatment plan across CSC components minimizing disruption of the expected developmental trajectory in this vital developmental period. For FEP, the Early psychosis Intervention Network (EPINET) Core Assessment Battery(108) was specifically developed, incorporating validated and widely used instruments.

Increasingly, psychiatry has moved away from placing undue emphasis on a single intervention in FEP (i.e., antipsychotic monotherapy), instead embracing combination treatments of mostly pharmacological interventions with different behavioral modalities. CSC effectiveness and its longer-term effects beyond CSC(109) may result from synchronized delivery of multiple treatment components by a small team, albeit early benefits may not be sustained(50). In the US, FEP services are modeled after the Recovery After an Initial Schizophrenia Episode (RAISE) trial (45) and longstanding EP services in other countries. Many young persons with EP make their own treatment decisions but remain dependent on logistical, financial and emotional support from their families. Including families in formulating an individualized treatment plan can increase implementation of services and potentially improve outcomes. While we do not want to overstate the benefits of CSC, the dedicated setting and treatment team are best positioned to adopt new approaches.

Potential role of biomarkers in EP assessment
For many years the field has explored potential biomarkers associated with psychosis. Biomarkers can improve our understanding of neuropathological mechanisms involved in development of psychosis and assist in illness staging by contrasting the clinical phenotype against static or illness-phase dynamic biological markers resulting in improved diagnosis and prediction of clinical course. Biomarkers could potentially be targeted for individualized treatment or serve as endpoints in treatment studies. Candidates for biomarkers are derived from findings in genetics, electrophysiology, neuroimaging, neurocognition, inflammation and neuroendocrinology.(110) For example, in 40 individuals with CHR(111), conversion to psychosis was predicted with high accuracy by combining demographic and clinical data with blood biomarkers and qEEG. Similarly, a baseline panel of 15 serum analytes modulating immune system function, hypothalamic-pituitary function, and oxidative stress differentiated CHR persons who developed psychosis from unaffected individuals with high predictive validity.(112) While promising, larger scale and adequately powered studies are necessary to explore the role of biomarkers in psychosis detection and how they can inform treatment course.

Cognition represents a strong predictor of functional outcome and quality of life in SZ(113). The illness is associated with dysfunction in multiple domains, including attention, WM, semantic memory, executive functioning and social cognition. Cognitive difficulties may present in the “predromal” phase, can worsen during prodomal and FEP phases, and respond poorly to existing interventions. Even in EP patients whose positive psychotic symptoms are effectively treated, cognitive difficulties(114), particularly in WM, significantly affect independent daily functioning, scholastic and occupational advancement. PFC-dependent WM impairment (98, 115, 116) presents an endophenotypic marker of psychosis given its occurrence irrespective of clinical acuity(117-119) and in unaffected first-degree family members(120, 121). In fact, WM may differentiate between those who do versus do not transition to psychosis (122). Thus, WM represents a highly suitable candidate as a biomarker and target of novel interventions in EP. The recently established Accelerating Medicines Partnership-Schizophrenia (AMP-SZ) represents a ground-breaking new phase in EP research(123). AMP-SZ is a global partnership among the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), and multiple public and private organizations. AMP-SZ focuses specifically on CHR to identify promising biological targets and biomarkers and build an infrastructure for testing CHR-specific treatments in over two-thousand youth. Over two years, participants will undergo clinical and biomarker assessments, including psychopathology, cognition, genetics, behavior, language analysis, and brain structure and function, to evaluate whether biomarkers can predict individual clinical trajectories. EPINET(124), through 8 regional hubs including over 100 FEP clinics in 17 states, represents a similar but more intervention-oriented initiative to develop improved CSC models.

**Implementing biomarkers into CSC for EP and potential novel compounds**

Large scale networks focused on phenotyping EP provide a promising platform to investigate specific and individualized treatments, based on both conceptual models of neurodevelopmental staging and empirical findings provided by biomarkers. During this stage of neurodevelopment and early illness, a time-limited window of opportunity exists to change the curve from poor outcome and prognosis commonly associated with more chronic illness. This assertion is
supported by neuroplasticity during brain development in adolescence and early adulthood which diminishes with aging and illness chronicity. Higher rates of treatment response and remission in early psychosis(52) support temporary potential reversibility of neurochemical brain changes associated with psychosis.

Recent biomarker studies in EP, including neuroanatomical(125, 126), neurochemical(127, 128), EEG(129), peripheral inflammatory markers(129-131), and oxidative stress(132) were found to relate to conversion to psychosis(126), antipsychotic response(127, 130), and functional outcome(125, 131-133). Current advances of in-depth phenotyping in EP combining demographic, clinical and stage-specific biomarker findings offer the exciting potential for earlier detection and more targeted treatment options improving clinical and functional outcome. Potential biomarkers in EP settings include digital phenotyping, serum analytes, genetic markers, cognitive functioning, EEG and MRI. Digital phenotyping in behavioral science(134) is rapidly expanding and has been implemented in persons with psychosis(135), in particular actigraphy (136) and ecological momentary assessment(137) to monitor mood and activity. Serum analytes can include markers of stress, inflammation and oxidative stress(138). Molecular genetic studies(13, 139) have identified variations in neurotrophic, serotonin, cell adhesion, and sodium channel systems and their association with neurocognition and social cognition in SZ. Lastly, commercial pharmacogenetic testing is rapidly expanding and provides information about medication metabolism to tailor medication choices to individuals(140). Cognitive testing, EEG, and MRI can monitor possible biomarkers, but are more labor intensive and costly, requiring access to suitable equipment. Cognitive batteries exist in paper and computerized format that can be administered online. The MATRICS Consensus Cognitive Battery(141) has been widely implemented in SZ. The PhenX Toolkit, a web-based catalogue of high-priority assessment measures(142) for close to 1000 conditions also includes neurocognition(143). Promising biomarker paradigms in EEG include mismatch negativity(144), steady state responses(145) and resting EEG(146). Structural brain MRI can reveal minor developmental abnormalities or, rarely, clinically significant abnormalities; multivariate patterns of subtle structural changes can help predict psychosis transition risk and functional outcomes in CHR(33). Potential utilization of biomarkers, either alone or in combination, in identify illness, monitor progression and govern treatment choices remains a promising concept.

An area of particular promise is the incorporation of biomarkers into interventional studies. Past studies have shown that antipsychotics do not prevent psychosis(147), but modulation of the dopaminergic system remains a focus of psychosis intervention. For example, as outlined above, selective enhancement of prefrontal D1R signaling may enhance prefrontal cortical activity and downregulate mesolimbic hyperactivity associated with psychosis symptoms. Over the past 20 years, multiple efforts have attempted to augment cortical glutamate functioning based on the NMDA hypothesis in SZ(148). While exploration of NMDA receptor hypofunctioning has informed our understanding of SZ pathophysiology, modulation of NMDA activity has produced variable success using glycine, d-serine and cycloserine(149) or allosteric mGlu R agonists(150). Other potential agents exist for addressing cortical E:I imbalance proposed by the model put forth by Krystal & Anticevic(55), and warrant further investigation. These include GABA agonists, N-acetylcysteine, alpha-7 nicotinic receptor agonists and D-
amino acid oxidase inhibitors. Potential candidate interventions via non-dopaminergic mechanisms include fatty acids, modulation of serotonergic or cannabinoid systems, and immunomodulators (e.g., nonsteroidal anti-inflammatory medications, anti-oxidants, nutrients, vitamins, and anti-inflammatory herbal products). Beyond pharmacological approaches, cognitive and neuromodulatory interventions, either alone or in combination, also hold promise and may benefit from incorporation of phase-specific biomarkers.

Conclusions
Development and dissemination of standardized CSC in EP has been a fairly recent development. CSC care, providing an individualized multi-modal approach, represents our best option to retain patients in treatment and can be further enhanced through implementation of biomarkers. Early years of illness represent a critical and narrow window for potential recovery or significant clinical improvement. CSC programs also offer ideal settings to explore novel interventions in EP. In concert with biomarkers, employing pharmacological or behavioral interventions in EP before progression to more chronic or relapsing illness offers the opportunity to stabilize or reverse the proposed dynamically developing cortical dysfunction. WM functions mediated by prefrontal physiology holds particular promise as an early biomarker with a strong relationship to outcome(98, 115, 116). Based on our conceptual model, WM provides a promising target of specific interventions in early illness, before PFC maturation is completed and this impairment becomes more difficult to modulate. Rapidly developing knowledge regarding potential mechanistic biomarkers, linked with new large-scale efforts towards standardized assessment in CHR/UHR and early psychosis, positions the field to discover developmentally-informed phase-specific interventions that are both standardized and personalized. These efforts should ultimately encompass a broad array of options for prevention and treatment, including medications, neuromodulation, psychotherapy, and cognitive remediation to improve long-term outcomes.
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PsychoGenics. He is a co-sponsor of a patent for the intranasal administration of ketamine for the treatment of depression and for the treatment of suicide risk that was licensed by Janssen Pharmaceuticals; has a patent related to the use of riluzole to treat anxiety disorders that was licensed by Biohaven Pharmaceuticals; has stock or stock options in Biohaven Pharmaceuticals, Blackthorn Therapeutics, Luc Therapeutics, Cadent Pharmaceuticals, Terran Biosciences, Spring Healthcare, and Sage Pharmaceuticals. He serves on the Board of Directors of Inheris Pharmaceuticals. He receives compensation for serving as editor of the journal Biological Psychiatry.

JDM: Technology Advisory Board Member for RBNC Therapeutics; Co-founder of Manifest Sciences

ZT: Consult for RBNC Therapeutics

DLG: Employee and shareholder of Cerevel Therapeutics (which owns rights to CVL-562 and has other D1R agonists in development)

JAL: Dr. Lieberman neither accepts nor receives any personal financial remuneration for consulting, speaking or research activities from any pharmaceutical, biotechnology or medical device companies. He receives support administered through Columbia University and the Research Foundation for Mental Hygiene in the form of funding and medication supplies for investigator initiated research from Denovo, Taisho, Sunovion, and Genentech, and for company sponsored phase II, III and IV studies from Alkermes, Allergan and Boehringer Ingelheim. However, none of this research support contributes to his institutional compensation. He is a consultant to or member of the advisory board of Intracellular Therapies, Pear Therapeutics and Gilgamesh Therapeutics for which he receives no remuneration. He is a paid consultant for Signant, a clinical research services organization, and holds a patent from Repligen that neither has nor currently yields any royalties.

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Illness Phase and Psychosis Intervention 22


Figure 1 Legend:

Developmental schema for neurobiological progression of schizophrenia, adapted from Krystal & Anticevic (55) by incorporating dopaminergic components.
Allostatic Phase-Specific Pathophysiology

Prefrontal Function & Dopamine (DA) Interactions

**Predrome**
- **Deficit:** Glutamate synaptic dysfunction
- **DA Component:** D2R genetic risk variant of unknown function
- **Consequence:** Glutamate signaling deficit
- **Allostatic Adaption:** GABA deficit and programmed synaptic proliferation

**Prodrome**
- **Normative adolescent:** increase in DA in striatum and PFC; increased PFC sensitivity to D1; D2 response in PFC interneurons shifts from inhibitory to excitatory
  - **Abnormal in psychosis:** excessive striatal DA, low prefrontal DA, low prefrontal D2 sensitivity, high prefrontal D1 sensitivity
- **Consequence:** E/I Imbalance (Disinhibition); tuning deficit, oscillation abnormalities; hyperconnectivity

**Syndrome**
- **Allostatic Adaption:** Synaptic downscaling and programmed synaptic elimination
- **DA Component:** Persistent DA abnormalities, reduced sensitivity to D2 antagonism
- **Consequence:** Atrophy compounds synaptic deficit
  - Tuning deficits persist
  - Network functions decline
  - Resistance to multiple treatments increased