

## Guest Editorial

# Early detection and intervention through the lens of the neurodevelopmental framework: the salience of developmental years and related services

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## Summary

Broadening prediction efforts from imminent psychotic symptoms to neurodevelopmental vulnerabilities can enhance the accuracy of diagnosing severe mental disorders. Early interventions, especially during adolescence, are vital as these disorders often follow a long prodromal phase of neurodevelopmental disturbances. Child and adolescent mental health services should lead a developmentally-sensitive model for timely, effective detection and intervention.

## Keywords

Prediction; prevention; risk; child and adolescent mental health; developmental

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How good is our current ability to predict the risk of onset of severe mental illness? A balanced evaluation of current evidence can help refocus early risk detection efforts, leveraging information gathered from childhood premorbid stages to adolescent prodromal stages. Indeed, early prodromal psycho-behavioural manifestations, which are linked to a higher lifetime risk of severe mental illness, typically emerge during childhood and adolescence. Furthermore, there is growing recognition that psychopathological symptoms, traits and disorders observed in adolescence and early adulthood often stem from altered neurodevelopment that is already evident in childhood through neurocognitive and behavioural abnormalities.<sup>1</sup>

Therefore, child and adolescent mental health services (CAMHS) are a strategic hotspot, crucially situated at the crossroads where neurodevelopmental trajectories and putative early indicators of risk for later severe mental illness intersect. This increases the likelihood of detecting these signs early, enabling secondary prevention strategies to mitigate the risk of progression to full-blown disorders.<sup>2,3</sup>

Our current ability to predict the risk of onset of severe mental illness does not simply depend on the observational spot (i.e. the segment of the mental health service nexus where we place the detection emphasis) but also on the target states and tools we focus on.

## Mitigating currently overhyped expectations of crude genetic prediction

Consider schizophrenia: allegedly a prime example of a heritable, complex syndrome where thousands of common genetic variants each have a small impact on individual risk, while collectively increasing susceptibility to other neuropsychiatric conditions. Decades of research on the genetic architecture of this syndrome have led to substantial advance in the field. However, genetic prediction appears still rather overhyped.

Indeed, despite identifying rare variants associated with increased risk in a few individuals, the clinical implications of genetic findings in schizophrenia are still scarce. Moreover, assortative mating, which enhances the contribution of additive genetic variance for any trait on which it acts, is rarely considered in discussing these genetic findings. The same goes for random fluctuations in the numbers of gene variants in a population, i.e. genetic drift. As a consequence, technically elegant

models of prediction based on polygenic risk scores yield poor accuracy, with an area under the curve (AUC) below 0.70, plausibly because they invariably overlook factors involved in genetic variance beyond polymorphisms<sup>4</sup> and that the transgenerational transmission of the risk for schizophrenia goes well beyond the mere genetic contribution.<sup>5</sup>

## En attendant biomarkers: shifting the phenotypic focus

Whereas specific biomarkers regularly populate the diagnostic landscape in other branches of medicine, not a single diagnostic biomarker has been translated to the clinic for schizophrenia or other severe mental disorders. Indeed, even predictive proxies extrapolated from underlying neurobiological mechanisms are currently unable to precisely and specifically predict the prospective individual risk of schizophrenia or severe affective disorders. While we are waiting for biomarkers and refining relatively coarse-grained socio-biographical risk factors (e.g. urbanicity, migration status, childhood adverse experiences), what can be leveraged to predict the individual risk of developing severe mental disorders?

A rational option seems to capitalise on clinical observation to capture more individually informative (endo)phenotypic features. Kraepelin was well aware that dementia praecox/schizophrenia does not usually debut with paranoid delusions and/or auditory hallucinations but rather with earlier, subtle developmental endophenotypic deviations, expressed in the motor, social and cognitive domains. Therefore, shifting the focus from the onset of psychotic symptoms in schizophrenia (i.e. a syndromic configuration of relatively late onset) to what precedes it presupposes going back from the prodromal to the premorbid stages and re-conceptualising the related vulnerability phenotypes.<sup>6</sup>

## Rethinking prodromal and premorbid stages of severe mental illness

## The clinical high-risk paradigm: clinical utility and blind spots

In recent decades, the construct of clinical high risk for psychosis (CHR-P) and its derivative, the DSM-5 diagnostic category

‘attenuated psychosis syndrome’, emerged as central tools for the early identification of first-episode psychosis as well as paradigmatic examples of the possibility to detect early the risk for severe mental illness. Indeed, when applied prospectively, CHR-P criteria successfully identify individuals at risk of psychosis. However, only a fraction of those at CHR-P progress to schizophrenia and not all people with schizophrenia experience a documented prodromal phase as defined by CHR-P criteria. This is partly related to the basic assumption of the CHR-P paradigm, i.e. that quantitative variations in positive symptoms are the primary predictor of psychosis. However, it has been well-known since Kraepelin that negative and cognitive symptoms are more prevalent in schizophrenia and almost invariably emerge earlier than positive symptoms.<sup>7</sup>

Consequently, despite its clinical usefulness in intercepting a broad risk for mental illness, the CHR-P concept overlooks critical aspects of first-episode schizophrenia that fall outside of the domain of attenuated positive psychotic symptoms and the time frame of their imminent progression towards first-episode psychosis. According to classic descriptions from Kraepelin, Bleuler and Meehl, as well as to the neurodevelopmental model, schizophrenia is better conceptualised as a syndromic diagnostic end-state, in which the eventual onset of psychosis in adolescence is an advanced stage along the disorder trajectory. Privileging the earlier inception of a broad childhood endophenotype of vulnerability for manifestations of the schizophrenia spectrum over the later narrower and less specific ‘attenuated’ positive psychosis might prove a rational step forwards for prevention and research.

The CHR paradigm has been applied also to the risk of bipolar disorder, with putative prodromal manifestations mainly derived from the study of offspring with the disorder. Similarly to the emphasis of the CHR-P paradigm on early attenuated positive psychotic symptoms for the prediction of psychosis, the bipolar at-risk (BAR) criteria mostly estimate the risk for bipolar disorder based on early affective symptoms (subthreshold mania or depression with cyclothymic features or depression associated with genetic risk). Although prodromes are described as more frequent in bipolar disorder than in psychosis, transition rates from BAR states to bipolar disorders are analogous to those from the CHR-P state to first-episode psychosis (almost one out of three at-risk individuals).<sup>8</sup>

Overall, accumulating evidence based on at-risk paradigms suggests de-emphasising the primacy of homotypic clinical manifestations and transitions (from attenuated psychotic or affective symptoms to psychotic or bipolar episodes), and instead zooming in on other clinical manifestations and further moving the target from prodromal to premorbid expressions of risk for severe mental illness.

### Looking at the premorbid period of mental illness through a neurodevelopmental prism

Considering schizophrenia as the prototypical example of severe mental illness, its neurodevelopmental model implies that the emergence of the first attenuated psychotic symptoms during adolescence or young adulthood is merely the visible tip of an iceberg. What lies beneath the surface, although less visible, is more voluminous, including the subtle, gradual accumulation of delays/difficulties in cognitive, motor and social-interpersonal domains, their interaction and their cumulative effect, starting from childhood and spanning the developmental years. This may be exacerbated in puberty, because of the increased complexity of social dynamics and contextual neuronal/somatic changes. Therefore, a developmentally oriented focus on endophenotypic correlates of putative neurophysiological processes associated with schizophrenia proneness is of strategic importance.<sup>6</sup>

In this perspective, early specific alterations in neurophysiological processes, such as corollary discharges, may be implicated in the developmental ontogenesis of schizotaxic vulnerability, representing the substrate on which subjective experiences and symptomatic manifestations may emerge along development and clinical stages.

Corollary discharges are copies of motor commands involved in the prediction of sensations from self-generated actions and they play a crucial role in early sensorimotor integration, motor coordination and distinguishing between self-generated and externally generated actions. In children with schizotaxic vulnerability, corollary discharges are presumed to be altered early, as suggested by studies of offspring of parents with schizophrenia showing early abnormalities in intermodal integration and motor coordination that are predictive of subsequent psychotic manifestations. Notably, altered corollary discharges, through their putative role in the ontogenesis of the feeling of agency (the implicit experience of volitionally controlling one’s own acts), may be implicated in the ontogenesis of highly specific anomalies of subjective experience (i.e. self-disorders) that antedate in late childhood or adolescence the emergence of attenuated clinical symptoms, identified by CHR-P criteria, and possible later diagnostic symptoms of schizophrenia.<sup>9</sup>

Although schizophrenia is a mental disorder whose premorbid neurodevelopmental antecedents have been more investigated and robustly identified, there may also be a higher prevalence of childhood antecedents in those who develop bipolar disorder, or even major depression or obsessive-compulsive disorder, than in the general population, supporting the hypothesis of a neurodevelopmental milieu of vulnerability on which clinical manifestations can subsequently emerge,<sup>1</sup> based on life events and on the individual balance between protective and risk factors.

Overall, this suggests that utilising clinical data from the premorbid period is crucial for acknowledging that the altered neurodevelopment leading to mental illness in young adulthood may recognisably emerge during childhood and adolescence. These manifestations are often documented during first contact with CAMHS and may align with various categorical diagnoses.

The path from CHR-P to schizophrenia constitutes just a portion of potential neurodevelopmental trajectories that can lead to schizophrenia; other heterotypic variations exist across developmental and preclinical stages, and schizophrenia is also among the potential diverse outcomes of a CHR-P state. A similar scenario applies to the onset of bipolar disorders from a BAR state as well as the heterotypic onset of bipolar disorders from childhood developmental disorders.

### The strategic role of CAMHS in detection

In light of the discussed evidence, CAMHS are in a crucial position to implement secondary prevention<sup>2,3</sup> aimed at reducing the risk that attending children and adolescents develop severe mental illness. Indeed, not only do prodromal symptoms typically emerge during adolescence, but there is also growing recognition that the emerging adolescent vulnerability to mental illness often stems from an altered neurodevelopment,<sup>1</sup> which can manifest in childhood through early broad unspecific neurocognitive and behavioural deviations.<sup>6</sup> These deviations, often falling under categorical diagnoses in neurodevelopmental disorders (as outlined in DSM-5) prompt families to seek CAMHS support for therapeutic interventions. The early detection of risk for severe mental illness in children and adolescents attending CAMHS requires that greater attention be paid to heterotypic trajectories leading to psychopathological outcomes (i.e. from the same starting childhood phenotype to distinct psychopathological outcomes


in adolescence/young adulthood, or from distinct childhood phenotypes to the same psychopathological outcome in adolescence/young adulthood), rather than focusing on homotypic continuity, which captures only a fraction of possible developmental and clinical trajectories.

## Conclusions

Expanding the scope of prediction from the imminent emergence of psychotic or affective symptoms to a broader spectrum of premorbid neurodevelopmental vulnerabilities may enhance the reliability of predicting severe mental disorders and improve prognostic accuracy.

Key points in implementing this approach are:

- interventions for severe disorders must occur before the ‘end-state’ diagnosis, as complications and biopsychosocial consequences often begin long before diagnosis
- the majority of these disorders have onset during adolescence and early adulthood, yet need of care and help-seeking often occur in developmental years
- these disorders are often preceded by a prodromal phase, which itself follows a long period of neurodevelopmental disturbances
- neurodevelopmental deviations may involve a limited range of alterations, but these manifest differently across disorders, depending on specific genetic and epigenetic interactions
- only a fraction of prodromal clusters result in a homotypically consistent diagnosis; many outcomes are heterotypic, and prodromes themselves can be heterotypic (e.g. attention-deficit hyperactivity disorder can precede schizophrenia or bipolar disorder)
- this entire psychopathological landscape becomes evident through contact with CAMHS, which should be at the centre of a renewed, developmentally sensitive model of early detection aimed at timely intervention.

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## Author contributions

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## Declaration of interest

None.

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