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The prodromal phase: time to broaden the scope beyond transition to psychosis?

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Over the past two decades, the focus of research on the prodromal phase of schizophrenia (SCZ) and other psychotic disorders has been primarily on the risk of developing psychosis, on the transition to full blown psychosis, and on its prediction (Studerus et al., 2017). Several large-scale, multi-site research studies have been conducted and hundreds of articles have been published worldwide. From this impressive body of work, a number of putative biomarkers predicting transition to psychosis, including a calculator assessing the clinical risk of developing a psychotic disorder (Cannon et al., 2016), have emerged(Riecher-Rossler and Studerus, 2017). Along with these promising findings, this body of research indicates that prodromal individuals, also described as individuals at clinical high risk (CHR) for psychosis, have a relatively low conversion rate to SCZ and related disorders. Specifically, based on their clinical course, CHR can be categorized as: a) remitting (35–45%); b) persisting and/or progressing (30–40%); or c) converting to full-blown psychosis (20–30%) (Addington et al., 2015). That is, almost half of the CHR show full remission of symptoms, whereas less than a third of them ends up transitioning to psychosis. Furthermore, the role of antipsychotic medications in affecting the transition to psychosis remains unclear, as shown by a recent meta-analysis of intervention studies in CHR youth, which failed to show an obvious prognostic advantage in those individuals following medication exposure(Devoe et al., 2019). On the other hand, the genetic, neurobiological, and treatment response differences between CHR individuals who fully recover from their prodromal symptoms (remitters), relative to those who show persistent/progressive prodromal symptoms (non-remitters), have been hardly explored. Altogether, these findings lead to a debate within the prodromal research field regarding which findings, if any, constitute major insights or scientific advances, as well as what the focus of future work in the field should be. Here, we decided to take up this challenge by: 1) discussing how future work in CHR remitters vs. CHR non-remitters may provide novel insights into the development, manifestation, and

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Conflict of Interest

All authors declare that there are no potential conflicts of interest.

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longitudinal course of emerging psychosis; and by 2) debating how this approach could lead to novel, early treatment interventions for SCZ and related psychotic disorders.

Future studies comparing CHR remitters and CHR non-remitters (above and beyond the focus on conversion to a clinically diagnosable psychotic disorder) may offer several advantages. First, CHR remitters likely have biological factors conferring “resilience” to psychosis, which may be observable in the early phases of the psychosis prodrome. So far, prodromal research has primarily searched for biomarkers to predict conversion to psychosis (Cannon et al., 2015). However, neurophysiological and/or neuroimaging measures that can reliably differentiate CHR remitters from non-remitters could be used as prognostic biomarkers of better clinical outcomes. Consistent with this prediction, it was recently demonstrated that a component of the auditory P300 oddball, the target P3b amplitude, predicted clinical remission in a large cohort of CHR individuals (Hamilton et al., 2019). The P300 oddball novel amplitude(Tang et al., 2019), as well as baseline mismatch negative (MMN) amplitude, assessed with magneto-encephalogram(Kim et al., 2018), were also found to predict remission in CHR subjects. Second, CHR remitters, by definition, show transient prodromal psychotic symptoms, which is a relatively common experience in the general population (8%), thus providing potential insights into mechanisms underlying reversible “state-like” psychosis(van Os et al., 2009). In other words, the pattern of brain activity observed in CHR remitters, assessed with neuroimaging and/or neurophysiological measures, could be used to predict early on the reversibility of psychosis in previously healthy individuals. Third, CHR remitters and non-remitters could undergo longitudinal assessments of psychosis and other clinical symptoms to investigate the development of major psychiatric disorders, beside and beyond SCZ. It is well established that prodromal individuals, in addition to sub-syndromal psychotic symptoms, often present with a variety of mental health issues (Fusar-Poli et al., 2014). However, for those CHR individuals who do not transition to full psychosis, it is unknown how the persistence of prodromal psychotic symptoms affects their overall clinical prognosis. For example, CHR non-remitters could be vulnerable to other significant comorbid psychiatric conditions, from anxiety to depression, that may require more aggressive, intensive interventions. While those comorbidities may not affect the conversion to psychosis, as recently shown (Addington et al., 2017), they could nonetheless be associated with worse clinical outcomes. Fourth, the presence and the extent of cognitive and social deficits, regardless of the persistence and/or transition to full-blown psychosis, may significantly differ between CHR non-remitters and remitters. Cognitive impairments are among the most persistent, treatment-resistant features observed in patients with SCZ, markedly interfering with their overall social and occupational functioning(Guo et al., 2019). It would therefore be important to see whether the persistence of sub-syndromal symptoms *per se* leads to worse functional outcomes, or whether milder baseline cognitive and social impairments are predictive of clinical remission.

Broadening the scope of prodromal research beyond transition to psychosis will also have several implications for treatment planning. First, CHR remitters are not good candidates for antipsychotic or other pharmacological compounds, due to the placebo effect (e.g., they are likely to remit regardless of treatment). Consistent with this prediction, a recent article from the second North American Prodrome Longitudinal Study (NAPLS-2) cohort reported that about 30% of CHR individuals during an observational study had a reduction in positive

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symptoms severity to below-prodromal intensity during follow-up assessments (Addington et al., 2019). In contrast, CHR non-remitters may be candidates for more aggressive treatments, including antipsychotic medication. Indeed, given that this subgroup of prodromal individuals is unlikely to experience a "spontaneous" remission of their prodromal symptoms, treatment studies including only CHR-non remitters will minimize the chances of "false positive" results and large placebo effects, thus allowing more rigorous assessment of the effectiveness of pharmacological interventions. Second, characterizing both neurobiological similarities and differences between CHR remitters and non-remitters will help identify more precise and specific target engagement biomarkers, which in turn may lead to the development of more effective pharmacological, as well as non-pharmacological, interventions in CHR youth. Third, CHR individuals who have been recruited into observational research studies and clinical trials are usually in distress and help-seeking. Typical intervention for such help-seeking individuals tend to be crisis-oriented and non-specific, with a primary focus on preventing worsening of prodromal psychotic symptoms, while impairments in cognitive functioning and/or social/interpersonal skills may not be addressed. Future randomized clinical trials involving CHR individuals should therefore consider using remission from the CHR syndrome as a primary outcome, although other outcomes such as cognitive or social function should also be pursued in those trials, since effective treatments here could improve functioning while not substantially affecting prodromal symptoms *per se*.

Prodromal research has contributed to advancing our understanding of the neurobiological mechanisms underlying the risk for, and the development of, psychosis. It has also brought attention to the importance of early detection, intervention, and possibly even prevention of SCZ and related psychotic disorders. Given the tremendously negative impact of these disorders on patients, their families, and the entire society, conversion to full-blown psychosis will remain a key outcome measure in future studies. However, future work should broaden the scope beyond transition to psychosis, by focusing on remission (or lack thereof) as a novel area of scientific inquiry as well as a primary endpoint of intervention studies. Findings from this more comprehensive approach would hopefully hold greater potential to be translated into clinical practice, doing more to improve the clinical and functional outcomes of psychosis-prone youth.

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