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Mapping cognitive trajectories across the course of illness in psychosis

Kathryn E. Lewandowski *

[a] Schizophrenia and Bipolar Disorder Program, McLean Hospital, Belmont, MA, United States of America
[b] Department of Psychiatry, Harvard Medical School, Boston, MA, United States of America

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Cognitive impairment has long been recognized as a core feature of schizophrenia and more recently of bipolar disorder as well, and is strongly predictive of disability and poor community functioning (Barch, 2009). However, considerable cognitive heterogeneity exists both between and within diagnostic categories, limiting our understanding of the pathophysiology and hindering development of effective interventions to target these symptoms. Historically, cognitive impairment in schizophrenia has been thought to be a function of early disruption and aberrant neurodevelopment, whereas cognitive impairment in bipolar disorder has been thought to follow a neuroprogressive course beginning around the time of illness onset after typical premorbid functioning. However, recent studies of cognitive heterogeneity across the psychoses suggest that neurocognitive deficits and the processes underpinning them may be highly variable, and may not conform to diagnostic boundaries (Lewandowski et al., 2014; Clementz et al., 2016). Understanding neuroprogressive trajectories across the course of illness and between diagnostic groups is essential in clarifying the pathophysiology and etiology of cognitive deficits in these illnesses, with implications for effective intervention.

To address some of the questions noted above concerning neurocognitive progression in psychosis, Menkes et al. (in press) evaluated cognitive impairment by diagnosis, illness stage, and by cognitive subgroups in a large cross-sectional cohort of patients with schizophrenia or bipolar disorder. Cognitive impairment was more severe in patients with schizophrenia compared to patients with bipolar disorder early in the illness, consistent with greater neurodevelopmental involvement in schizophrenia. However, the authors did not find significant illness stage by diagnosis interactions, suggesting similar neuroprogressive trajectories across diagnostic groups after illness onset. The authors used a pre-defined grouping strategy to classify patients' cognition as "normal," "deteriorated," or "compromised," and found that all three neurocognitive subgroups were represented in both diagnostic categories, although not equally, with the compromised subgroup overrepresented in patients with schizophrenia and the normal subgroup overrepresented in patients with bipolar disorder.

These findings are consistent with reports that, at the group level, patients with schizophrenia exhibit greater neurocognitive impairment than patients with bipolar disorder, and that chronic patients are more impaired than early phase patients across disorders. Indeed, while the proportion of deteriorated patients did not change from early to chronic phases, the proportion of both bipolar disorder and schizophrenia patients classified as "normal" was smaller in chronicity, dropping from 60.8% to 34.4% in bipolar disorder patients and from 34.6% to 21.1% in schizophrenia patients, although these differences were not statistically significant. These findings also highlight the lack of diagnostic specificity of cognitive course; subgroup analyses were consistent with cross-sectional cluster analyses showing considerable heterogeneity in cognitive subtypes across diagnoses (e.g. (Lewandowski et al., 2014; Van Rheenen et al., 2017)). Together with studies showing differing patterns of brain structure and connectivity abnormalities across cognitive subgroups (Lewandowski et al., 2018; Woodward and Heckers, 2015), the study by Menkes et al. (in press) suggests that psychotic disorders are not only heterogeneous cross-sectionally, but that subgroups of patients may follow different neurodevelopmental/neuroprogressive trajectories across diagnoses.

Of course, this study and others rely on cross-sectional data, and can only provide indirect evidence of neurodevelopmental and neuroprogressive cognitive changes over time. Cross sectional study design introduces the possibility of cohort effects which may be particularly problematic in studies comparing early and late phases of illness. Additionally, the inclusion of only two "time-points" forces an assumption of linearity which may not characterize the actual trajectories of neuroprogressive change. Longitudinal studies are needed to carefully characterize cognitive trajectories and identify key inflection points of cognitive change and stabilization over the time period of interest, involving relatively dense assessments (e.g. less than 1 year apart) and more than two assessment points to allow for the possibility of non-linear trends (Bartholomeusz et al., 2017; Zalesky et al., 2015). Additionally, while numerous studies have attempted to characterize one or more aspect of cognitive change during various phases of illness (premorbid/high risk; first episode; chronicity), the literature is considerably sparser throughout the "bridging" years from onset/early course

* 115 Mill Street, AB South 349, Belmont, MA 02478, United States of America.
E-mail address: klewandowski@mclean.harvard.edu.

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to established illness – years that are central in determining long-term patient outcomes and developing targeted interventions.

Longitudinal study of patients across illness stages is undeniably challenging, and barriers to such work include attrition and feasibility in terms of duration of study. Novel approaches such as the use of accelerated longitudinal designs may aid in the characterization of illness trajectories over a timeframe that would not be feasible in the context of a single cohort longitudinal design. Together with mixed modelling techniques, such studies may offer key insights into neuroprogressive course along constructs of interest, and permit characterization of heterogeneity of cognitive trajectories within and between diagnostic groups. Findings from these studies are critical to refinement of clinical staging models, for instance, which suggest that symptom progression occurs in predictable, dynamic stages (e.g. (McGorry et al., 2018; Nelson et al., 2017)). Staging models attempt to define boundaries between illness stages, and map how and when patients transition across these boundaries. Cognitive progression is likely a key dimension in defining clinical staging in psychosis, with implications for prognosis, and when and how to intervene. Characterization of heterogeneity across diagnoses and over time provides an empirical basis for refinement of staging models.

The study by Menkes et al. (in press) offers insights into both the course and heterogeneity of cognitive impairment in psychosis, and highlights that cognitive course may be less strongly linked to diagnosis than previously believed. These findings have implications for understanding the course of these illnesses and their pathophysiology and etiology, characterizing heterogeneity both cross-sectionally and longitudinally, and the development of effective interventions targeting cognitive deficits across illness stages.

Conflict of interest

The author has no conflict of interest to report in association with this work.

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Kathryn E. Lewandowski: Conceptualization, Writing - original draft.

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