Title: Babies, bathwater and bipolar disorder: Is it time to call curtains on staging?

Running title: Staging bipolar disorder: A reply

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Conflicts of Interest
The authors do not have any conflicts of interest to report.
With great interest we read our colleagues’ recent debate 1. We emphatically agree with the recommended cautious approach to progressing staging research in bipolar disorder (BD). This commentary expands on the important issues raised with a focus on clinical utility, the central unrealised promise of staging. Additionally, we offer concrete directions to navigate the rocky terrain of staging BD. We similarly advocate for a cautious approach, built upon consensus definitions and improved conceptualization and measurement of staging-related constructs. Further, we acknowledge the necessity of examining our assumptions carefully and propose that in so doing, we make space for replacing those no longer serving the scientific pursuit of advancing staging research in BD.

Multifactorial conceptualization

Several of the issues raised by our colleagues are not unique to BD or disorder-specific staging models, they apply across the spectrum of mental ill health and extend to transdiagnostic staging models. For example, Malhi and colleagues 1 addressed the challenge of relying on clinical features to identify a predictable progressive trajectory, arguing that multiple processes interact in a complex manner and create a range of presentations. We concur that a unidirectional trajectory driven by neuroprogression specific to BD appears highly improbable. However, we propose that it is unnecessary to identify a singular, unique and linear process for BD to be deemed stageable or for staging investigations to offer clinical utility. Our models need to better account for the complexity of mental ill health, rather than seeking to characterize it reductionistically. The heterogeneous nature of the evolution of mental disorder must be accounted for and extend beyond illness progression (based on clinical phenomenology) to integrate additional dimensions of illness extension, such as the emergence of mental or physical comorbidities. Further, those in the earliest
stages (in any model) are unlikely to present with a distinguishable pattern of symptoms and may only be identifiable retrospectively. This pluripotentiality reflects the reality of the clinical picture, not necessarily evidence BD is not staged or stageable.

We assert that examining constellations of features and processes will have more utility than agreement on a singular underlying process or trajectory, despite the complexity this approach attracts. Data-driven approaches offer potential for understanding such interrelationships and their predictive utility. Additional information (e.g. functioning, cognition, and comorbidities) can contribute to more precise staging models in the vein of precision psychiatry, for example as ‘stage specifiers’, offering additional nuance to decision-making. Using big data and machine learning (ML) to develop models of the complex relationships between stage related phenomena and/or risk factors, such as episodes, functioning, cognition, brain changes, comorbidities, illness duration, and biomarkers, may enable the identification of prognostic subgroups and targeted therapies.

For example, ML of structural neuroimaging has distinguished between individuals with BD and healthy controls, and between those classified into the later (but not earlier) stages and controls. While ML for mental health is in its infancy, these techniques offer the potential to overcome issues obstructing the staging literature, such as how to meaningfully integrate multivariate information in operationalising stage, and to move beyond theory-driven or reductionistic conceptualisations towards data-derived models.

**Consistent definitions**

The International Taskforce for Staging in Bipolar Disorder has provided consensus nomenclature for staging in BD (under review). This essential and significant step provides a common language and framework for staging investigations and applications, and should become a reference point for any future discourse in staging in BD.

**Better measurement**

Variation in the conceptualisation and measurement of staging and related phenomena has contributed to the lack of parity and ultimately slowed progress within the BD staging literature. For example, a recent examination of the role of staging (via proxies) in psychosocial interventions for BD identified considerable inconsistency in the definitions and measurement of both functioning and number of episodes, obstructing meaningful synthesis of these data. As these constructs reflect the most common proxies used to operationalize
staging models in BD, these inconsistencies present a significant roadblock to advancing our understanding of stage of illness. To address this, we recently published a critical review aiming to improve the previously inconsistent conceptualization and measurement of number of episodes in BD.

**Conclusion**

We broadly concur with the points made by our colleagues and add to their well-informed cautions for guiding BD future staging research. Regardless of whether staging hypotheses are ultimately deemed valid, what we learn in staging investigations will improve the treatment of BD. While BD is heterogenous, multi-dimensional and difficult to predict, this reality motivates us to explore innovative, precise and personalised solutions. We contend that staging remains among these potentially promising innovations and as such, that calling curtains on staging in BD is premature.

**References**

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