Defining Heterogeneous Cognitive Trajectories in Bipolar Disorder: A Perspective

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Abstract: Bipolar disorder (BD) is a highly disabling mental illness that affects approximately 1% of the global population. Cognitive capacity is a strong predictor of "everyday" functional outcome in BD and should thus be considered a key treatment target. Interventions to improve cognition have been largely unsuccessful, likely due to the substantial heterogeneity inherent to the illness. It is known that 40%–60% of people with BD have cognitive impairment, yet impairment is not "one size fits all"; in fact, the literature supports discrete cognitive subtypes in BD (e.g., intact, globally impaired, and selectively impaired). Gaining a better understanding of these cognitive subtypes, their longitudinal trajectories, and their biological underpinnings will be essential for improving patient outcomes. The prevailing hypothesis for the development of cognitive impairment in BD postulates a stepwise cumulative effect of repeated mood episodes causing wear-and-tear on the brain. However, a paucity of data supports this idea at the group level. We propose that studying *heterogeneity* longitudinally will allow for clearer delineation of the natural history of cognitive trajectories in BD. In sum, parsing heterogeneity in BD will allow us to identify causal mechanisms and optimize treatment at the level of the individual.

Keywords: cognition, heterogeneity, immune, mood disorder, staging

Bipolar disorder (BD) is one of the most heterogeneous and disabling mental health conditions in the world.[1] BD is an episodic illness marked by fluctuations in mood and energy, which manifest as mania or hypomania (high energy), depression (low energy), or mixed affective states.[2] Not surprisingly, people with BD often experience substantial functional impairment in work, family, and social aspects of life.[3,4] The functional difficulties and protracted course of BD directly contribute to the high disability associated with this illness.[1,5] Despite the existence of front-line pharmacotherapy options (e.g., lithium, antipsychotics, anticonvulsants)[6] and psychotherapy, full remission of BD is exceedingly rare.[2] In fact, it has been estimated that only 40% of the burden associated with BD could be averted using existing gold-standard interventions.[7] Moreover, although BD is traditionally characterized by inter-episode recovery, neither complete symptomatic nor functional recovery is the norm.[8–10] Among the most persistent symptoms are cognitive deficits,[11] which have a profound impact on clinical and functional outcome.[12,13] In fact, cognition is one of the best predictors we have of "everyday" functional capacity in BD, as measured by subjective ratings, performance-based tasks, and functional milestones.[14] Specifically, trait-like impairment is seen in attention, verbal learning, and executive function.[15–18] Deficits in cognitive control may underpin the regulatory failure that leads to mood instability in BD, acting to drive recurrence.[14] Thus, targeting cognitive impairment may not only improve everyday functioning but also help to stabilize mood in BD.

Ample evidence suggests that some, but not all, BD patients show substantial cognitive impairment even during affective remission; however, our understanding of why some patients appear to be resilient to cognitive decline and others are vulnerable to it is not complete. Several clinical factors are thought to contribute to poor cognitive outcomes in BD.[19] Early data indicated that cognitive dysfunction may be more severe in BD-I relative to BD-II, purportedly due to the enhanced severity of BD-I, including more psychotic symptoms and full-blown manic episodes.[20,21] Our own data suggest that the pronounced cognitive heterogeneity seen within BD is not driven by our recognized clinical subtypes (e.g., BD I/II or psychotic/non-psychotic),[22] and a recent meta-analysis indicated that differences in cognitive dysfunction among these clinical subtypes were subtle.[21] It is likely that other illness-related features contribute to the cognitive differences previously ascribed to clinical subtypes, such as illness recurrence rates, sleep quality, psychiatric and medical comorbidities, and history of childhood trauma. Importantly, many of these risk factors for poor cognitive outcomes are *modifiable*. Interventions focused on ameliorating existing cognitive dysfunction alongside efforts to prevent decline from occurring in the first place will be key to improving the quality of life of those suffering from BD.

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COGNITIVE TRAJECTORIES IN BIPOLAR DISORDER

BD is a dynamic illness, not only marked by frequent changes in mood state but also characterized by a burden of illness recurrence that accumulates over time. The hypothesis of *neuroprogression* postulates that the longitudinal course in BD is marked by a decline in cognition and function, and by an increase in treatment resistance,[23] where later phases of illness are marked by persistent cognitive deficits, in contrast to earlier phases where cognitive and functional resilience is evident.[23] Further, it is theorized that cognitive decline in BD has a stepwise course, which is influenced by clinical features such as the number of prior mood episodes[24] and a history of psychosis,[25] which are thought to cause "wear-and-tear" on the brain. Exacerbation of a mood state is often coupled with temporary worsening of cognition, with state-dependent cognitive deficits that attenuate to some degree upon affective remission; however, it is the persistent cognitive impairment that presents during euthymia that contributes most to functional disability in BD. Likewise, structural and functional brain abnormalities are thought to show a similar pattern of progressive decline in BD, particularly cortical and limbic brain regions.[26] Imaging studies have consistently shown hippocampal atrophy and ventricular enlargement,[26] white matter microstructural changes,[27] and diffuse cortical thinning in BD[28]—abnormalities that are more prominent after multiple acute episodes[29,30] and that correlate with the degree of cognitive impairment.[31]

Although these hypothetical models of neuroprogression suggest that BD has a declining cognitive course, there is a paucity of longitudinal data to support this suggestion. The assumptions of cognitive decline are largely based on cross-sectional data, and the limited results from longitudinal studies are convincingly mixed. The bulk of the existing data on cognitive development across the lifespan suggests that, unlike schizophrenia, where neurodevelopmental abnormalities are clear, the premorbid cognitive trajectory in BD is marked by normal or even supernormal cognitive capacity[32] and that it is only after disease onset that cognitive deficits emerge. Yet, studies that have focused on premorbid intellectual functioning in individuals who later develop BD have been inconsistent, with some showing no effect of premorbid IQ,[33] whereas others show that higher IQ is associated with an increased risk of a subsequent BD diagnosis.[34] Indeed, one study reports that *both* high IQ and low IQ increase the risk for developing BD in the same cohort of patients,[35] leading some to hypothesize that cognitive impairment as a premorbid risk marker for BD may follow a U-shaped curve, unlike the linear trend seen in schizophrenia.[36] Several studies have noted the presence of cognitive impairment immediately following the onset of the illness, with similar effect sizes as those reported in later phases[3,6,16,37]—pointing toward a relatively stable cognitive profile over the course of the illness, as opposed to a declining course. Likewise, the few meta-analyses of existing longitudinal data do not support cognitive decline after onset of BD over either a one- or five-year period at the group-level;[25] however, other recent data identify a *subgroup* (up to 48%) that do show some decline in specific domains over short-term follow-up.[38] Several smaller-scale individual studies report cognitive decline in processing speed, white matter microstructure,[39] and resting-state connectivity in BD.[40] One longer-term study (over nine years) found a decline in executive function in BD,[41] and recent data converge to suggest that BD patients are at elevated risk for dementia,[42] with still other studies suggesting that the long-term rate of decline is similar to that seen in normal aging.[43,44] We believe that these discrepancies are driven by the substantial heterogeneity seen in BD and that by directly addressing this heterogeneity using empirical data–driven approaches, we can better understand the natural course of cognition in BD.

ADDRESSING COGNITIVE HETEROGENEITY IN BIPOLAR DISORDER

In 2014, we applied empirical classification approaches to parse cognitive heterogeneity in a cross-sectional study of affectively stable BD patients.[22] We identified three cognitive subgroups—(1) intact, (2) selectively impaired, and (3) globally impaired—by using hierarchical cluster analysis of the seven domains from the MATRICS Consensus Cognitive Battery. Importantly, the intact subgroup did not differ from healthy controls on six of the seven domains and were superior on social cognition. In stark contrast, the globally impaired subgroup did not differ cognitively from demographically matched patients with schizophrenia. The selectively impaired group had moderate deficits of a few cognitive domains and had a normal premorbid IQ. Premorbid IQ estimates also differed by subgroup, with only the globally impaired subgroup showing lower-than-average premorbid IQ, consistent with some neurodevelopmental anomalies. In a subsequent study, which included BD patients and their unaffected siblings, we found that the selectively impaired and globally impaired BD patients were equally impaired on verbal learning measures but that only the unaffected siblings of the globally impaired BD patients evidenced deficits relative to unrelated healthy controls; by contrast, the siblings of the selectively impaired BD patients showed no such deficits.[45] Taken together, these studies provide evidence that in a subgroup of BD patients, a neurodevelopmental basis of cognitive impairment is likely (e.g., our globally impaired subgroup) and that in another subgroup of BD patients, cognitive impairment might develop after the onset of the illness (e.g., our selectively impaired subgroup). Notably, however, since the clustering analyses have all been cross-sectional thus far, the true cognitive trajectories of purported clusters remain to be determined.

At least eight studies, including ours, have applied a similar methodology for cognitive classification in affectively stable BD, with remarkably consistent results. Cognitive subgroups have been identified in each study, indicating either a three-group or four-group pattern.[45–51] Relevant clinical differences have also been identified between cognitive subgroups; the *intact* subgroup has higher premorbid IQ, level of education, and rate of

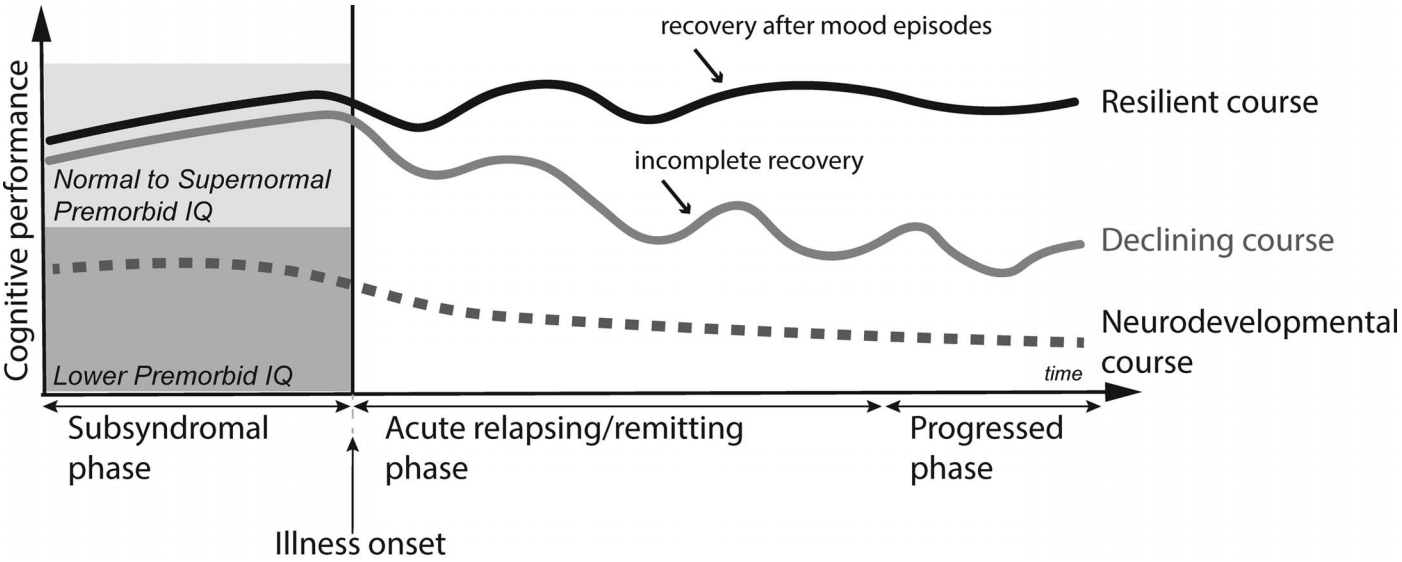

Figure 1. Theoretical model of differential cognitive trajectories in bipolar disorder. We devised a theoretical, illustrative model of cognitive trajectories, based on existing evidence in literature. We propose three theoretical cognitive trajectories, based on cross-sectional data indicating discrete cognitive subtypes in bipolar disorder: (1) the "resilient" trajectory, which has a normal to supernormal premorbid IQ (light gray shading) and stable cognition in adulthood, is cognitively comparable to healthy individuals; (2) the "declining" trajectory is marked by vulnerability to decline post-illness onset due to "wear-and-tear" on the brain and body from repeated mood episodes and comorbid health factors (i.e., cognitive impairment experienced during mood episodes does not rebound fully); (3) the "neurodevelopmental" trajectory is marked by lower premorbid IQ (dark gray shading) and severe, global cognitive impairments in adulthood, which may also evidence some decline after illness onset. Clinical variables that are known to affect cognition are largely unknown within cross-sectional cognitive clusters, including socioeconomic status, medical and psychiatric comorbidities, exercise and diet regimens, and sleep quality. These factors should be explored in greater detail longitudinally within the cluster framework to further delineate this theoretical model.

employment.[49] The intact subgroup also has lower stress levels,[48] better occupational functioning,[22,48] and better social adjustment,[48] and in at least one study, this subgroup took fewer antipsychotic medications than their cognitively impaired counterparts.[46] Perhaps unsurprisingly, the intact subgroup had an overall higher quality of life[48] and experienced fewer depressive episodes[22] than the selectively impaired subgroup. By contrast, the globally impaired subgroup had higher levels of childhood trauma,[49] fewer years of education,[46,49] lower social and global functioning,[50,51] and lower premorbid IQ[22,45,51] than the other two subgroups. Of note, traditionally defined clinical subtypes (BD-I/BD-II; psychotic/non-psychotic) were equally distributed across these cognitively defined subgroups, suggesting that this approach does not simply recapitulate existing diagnostic/clinical subtypes but rather represents a novel, neurobiologically informed classification.[22]

Despite these intriguing findings, all of these studies were done using cross-sectional data; the neurocognitive trajectories of these cognitive subgroups have yet to be delineated. Additional longitudinal studies are needed to examine cognitive change over time within these subgroups. Based on what is currently known, we propose that some BD patients have a declining cognitive course, whereas others have a more stable, resilient cognitive course, and still others have a "neurodevelopmental" trajectory (similar to that seen in populations with schizophrenia) (Figure 1). Identifying clinical and biological markers of risk versus resilience to cognitive dysfunction and decline will be critical in efforts to prevent it from occurring—a goal that can be aided by parsing heterogeneity.

SUMMARY AND NEXT STEPS

Neurocognitive deficits are common in BD; they contribute to incomplete recovery; and they warrant attention as a target for intervention. If cognitive deficits develop after the onset of disease (as in some patients with BD), then there is an opportunity to slow or even prevent cognitive decline and thereby functional disability. Heterogeneity has impeded progress in identifying causes of cognitive dysfunction in BD, and as such, modifiable targets for intervention are unknown. Classification approaches that parse heterogeneity can define the extent of illness progression for every individual at the time of evaluation, with the goal of refining diagnosis, adjusting prognosis, and choosing the best treatment for that patient. It will be important to identify (1) which BD patients are likely to follow an unstable cognitive course, (2) the biological mechanisms underlying cognitive decline in BD, and (3) modifiable targets for cognitive intervention. In doing so, we can identify subgroups that will benefit most from specific interventions. For example, anti-inflammatory agents may be most beneficial in patients with objective evidence of elevated inflammation; formal cognitive remediation may be suited to targeting specific deficits; and other compensatory approaches, such as "cognitive adaptation training," may be more relevant to grossly impaired individuals. Identification of modifiable behavioral targets (e.g., sleep, substance use) that predict decline

will help to focus treatment on the things we can actively change in an effort to slow or even prevent the development of cognitive deficits in BD.

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