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Do we really need a “new” cognitive therapy for bipolar disorder? Paradigm refinements and treatment mechanisms for cognitive remediation.

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Although more pronounced during mood episodes, widespread cognitive deficits also persist after symptom remission for a significant proportion of individuals with bipolar disorder (BD). These cognitive difficulties limit recovery and are strongly associated with a wide range of functional goals such as employment and interpersonal relationships. This mounting evidence of the importance of cognitive functions now requires action if we are to improve recovery outcomes for the long-term. Cognitive Remediation (CR), originally developed to treat people with a diagnosis of schizophrenia, has recently emerged as a potential treatment option to promote functional recovery by targeting cognitive difficulties in people with BD. Numerous controlled trials have established the efficacy of CR paradigms for people with schizophrenia and these provide a basis for CR programs to be tested in other mental health conditions also characterized by cognitive difficulties.

Cognitive difficulties heterogeneity in people with BD

Adopting CR paradigms from schizophrenia appears reasonable for BD research when considering the similarities in the cognitive profiles across schizophrenia and BD. However, there are also differences between these two populations and appropriately adjusting treatment manuals could improve treatment outcomes. For example, whereas most patients with schizophrenia experience severe cognitive impairment across many cognitive domains, there are subgroups of BD patients presenting with discrete cognitive problems while others remain cognitively intact.

Profile differences might result from differing developmental trajectories and illness progression among patient subgroups. Unlike in schizophrenia, where cognitive impairment is predominantly associated with neurodevelopmental factors, the longitudinal course of cognitive dysfunction for some people with BD seems to involve neurodevelopmental (e.g., early-life premorbid deficits) and for others neuroprogressive (e.g., effect of manic episodes) factors [1].

Thus, it is unclear whether we can just provide the same therapy paradigms developed for schizophrenia to people with BD or whether adaptations of CR paradigms are needed to account for the distinct characteristics of different BD subgroups.

Paradigm adaptations: beyond terminology

In a recent debate article published in *Australian & New Zealand Journal of Psychiatry*, Douglas et al. [2] argue that CR is more suited to its origins in schizophrenia and traumatic brain injury, and suggest that the term “Cognitive Enhancement Therapy for Mood Disorders” (CET-MD) is more appropriate for this population. Their rationale relates to cognitive improvements not necessarily related to reversing a deficit but targeting both impaired and preserved areas of cognition with the overall aim of long-term functional recovery. In the context of mood disorders, where not all patients experience objectively defined cognitive impairment, CET-MD might appear as a more inclusive name.

For Douglas et al. [3], the key components of CET-MD are psychoeducation on the importance of cognition, cognitive training with the use of strategies and transfer of the acquired skills and strategies into daily-life activities. These are exactly the components that define compensatory CR in other populations and particularly in people with schizophrenia. In fact, our recent systematic review of psychological interventions targeting cognitive and functional difficulties for people with BD identified comparable treatment paradigms in the majority of the existing studies [3]. These compensatory approaches include therapy components very similar to those suggested for the CET-MD paradigm

and fall either under the umbrella-term CR or under a name indicating their specific therapeutic aim (e.g., cognitive training, functional remediation).

Although we understand the rationale for proposing a new term to describe therapies targeting cognition in mood disorders, we believe that advancing research in the field requires decisive adjustments beyond terminology changes. An important step would be acknowledging the heterogeneity of cognitive difficulties among BD patients and addressing this issue in CR clinical trials to optimize cognitive interventions [3]. Here we attempt to expand this discussion by considering how CR might be refined, including an examination of transfer mechanisms to advance functional outcomes.

Refining treatment paradigms to target diverse needs

The research corpus of CR interventions for people with BD is small with studies including small samples and most testing therapy feasibility or proof-of-concept. Despite encouraging findings of benefits on both cognitive and functional outcomes, results are often inconsistent and not replicated across studies. These inconsistencies are probably attributable to cognitive heterogeneity in the samples [3].

BD subgroups may have distinct cognitive trajectories that result in cognitive impairments of diverse nature and severity, and potentially differing relationships between cognitive outcomes and functional recovery. These subgroups may require different treatment approaches and therapy to be more specifically tailored to their needs. For example, people with severe deficits across multiple domains may require a treatment paradigm emphasising strategy use to compensate for the magnitude of their cognitive deficits. Alternatively, a subgroup with moderate difficulties in a specific domain and high cognitive reserve may achieve a clinically meaningful improvement through targeted cognitive practice in tasks relevant to daily-life activities. The subgroup of patients not experiencing significant cognitive difficulties might still benefit from a paradigm focusing on attainment of personal goals. Incorporating these paradigm refinements into clinical trials would require pre-specified eligibility criteria and rigorous assessment of cognitive performance.

Mechanisms to maximize transfer of gains to daily life

Establishing the efficacy of different treatment paradigms for cognitive outcomes is imperative but would be insufficient for a clinically meaningful impact if research designs do not evaluate whether and how cognitive benefits translate to improvements in real-life functional outcomes. The mechanisms by which cognitive gains transfer to functional benefits are unknown for BD and it is essential for future trials to consider this mechanism. Findings from schizophrenia research suggest that metacognitive training may be a key mechanism to support the transfer of therapy gains to everyday life.

Metacognitive skills refer to a person's awareness of their own cognitive strengths and shortcomings, as well as the ability to 'manipulate' their cognitive processes during an activity. Improving these skills might drive functional improvement following therapy in people with schizophrenia [4]. People with BD also experience metacognitive difficulties and so a similar mechanism may apply. We have recently conducted a CR trial in people with BD where therapists reported 'regaining cognitive control' as a theme commonly brought up by participants to describe their treatment experience and how the treatment affected their daily-life activities. It is likely that other mechanisms or "active therapy

ingredients" may be also be instrumental. Reports suggested that some of these may be related to therapist contact and suggest that CR also capitalizes on basic psychological therapy skills and should be considered a form of psychological therapy [5].

In summary, we agree with Douglas et al. [2] about the key treatment paradigm components, particularly the use of strategies in cognitive training and the transfer of newly acquired skills. However, these are not new and have all been well articulated for schizophrenia. Renaming an established umbrella-term will cause confusion among clinicians, researchers, and potentially even patients. Instead, we advocate that priority should be given to finding evidence-based methods for treatment adaptation for different BD subgroups. In addition, more research is needed to understand how functional outcomes benefit from cognitive improvements. While this necessitates robust clinical trials, standardising CR paradigms between research groups would enable aggregating data to test moderating and mediating effects. This would facilitate a more efficient therapy process to really benefit recovery goals.

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Conflict of interest

AHY reports paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZeneca (AZ), Eli Lilly, Lundbeck, Sunovion, Servier, LivaNova, and Janssen. No shareholdings in pharmaceutical companies. Lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study. Investigator initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth, Janssen. RS reports a paid lecture from Lundbeck. DT, MC and TW report no conflict of interest for this work.

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