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Commentary on 'Methodological Recommendations for Cognition Trials in Bipolar Disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force'.

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The ISBD Taskforce report by Miskowiak et al presents clear direction for researchers seeking to undertake trials to enhance cognition in BD. Taskforce recommendations are important, however, two points that warrant elaboration relate to prerequisite cognitive screening and secondary outcome measures. Within this cognitive heterogeneity should be considered, especially when selecting from psychological cognitive remediation treatment approaches for BD.

Prerequisite cognitive screening

Since a proportion of individuals with BD appear to have intact cognitive functioning (1, 2), the need for prerequisite screening for meaningful cognitive deficits at trial admission is a critical issue raised by the Taskforce. Our review of the sparse BD cognitive enhancement trial literature suggests that in the absence of a control group, which is typical of BD trials to date, failure to screen for cognitive impairment at the outset confounds results (3). A tool for screening for objective cognitive deficits is therefore crucial, but requires brevity for practical reasons. The taskforce recommends two alternatives: i) use of two individual neuropsychological tests tapping into different cognitive domains, or ii) use of the Screen for Cognitive Impairment in Psychiatry (SCIP), a brief neuropsychological measure tapping five core domains of cognition.

The former option raises the question about which two measures would be most effective for appropriate screening. Given that the largest BD-related impairments are typically for verbal learning and executive functioning, one could argue that tests tapping these domains are necessary. This of course, introduces the potential for exclusion of participants with cognitive impairments that are missed on the basis of these domains – a possibility given evidence of cognitive variability in BD. Emerging research indicating the presence of a selectively impaired BD cognitive subgroup absent of measured executive deficits (2), or of globally impaired BD subgroups differentiated by severity (1), suggests that a better approach (and one raised in the report) may be to exclude subjects based on performance deficits <0.5 SDs below the control mean on a global cognitive score reflecting a '*g*' factor. Theoretically, the use of single screening tests shouldn't matter given that shared variance between tests contributes to '*g*'. But research, including our work, has shown that in BD some domains contribute to '*g*' more strongly than others. Indeed, we showed that a single underlying factor represented most strongly by working memory and processing speed, explained the data structure of n=402 BD subjects and clearly differentiated subgroups considered to have intact (<0.5 SD performance vs controls) vs. impaired performance (1). In this context the SCIP seems the optimal choice for screening especially because it samples the spectrum of cognitive ability broadly (including processing speed and working memory measures), and a global composite score can be derived from its subtests.

Social cognitive outcome measures

The Taskforce recommends inclusion of a *global* measure of cognitive function to assess primary outcomes in the absence of specific cognitive targets. The inclusion of secondary social cognitive outcomes is also recommended. Again there is research indicating that neurocognitive impairment in BD predicts performance on measures of facial emotion recognition and theory of mind, where a social cognitive performance decline of between 0.3 - 0.5 standard deviations is evident for every one point decrease in performance on a global neurocognitive score (4); and analyses that show only BD patients with global neurocognitive impairments have deficits on facial emotion recognition measures, relative to their cognitively unimpaired BD counterparts and controls (5). These findings and others (e.g. 1, 2) suggest that social cognitive deficits may scale with the severity of global cognitive deficits in BD - raising the possibility that treatment of cognitive deficits may indirectly, and at least partially, remediate social cognitive deficits. Inclusion of social cognitive secondary outcome measures in cognitive trials should therefore be strongly encouraged. Particularly given that prerequisite screening for social cognitive impairments would be unnecessary beyond screening using a general cognitive score, and as such measures are widely available and demonstrate good reliability and tolerability.

Psychological cognitive interventions.

Although not raised within the Taskforce report, a comment on the *content* of psychological cognitive remediation treatment is appropriate given the potential impact that different approaches may have on treatment efficacy and participant retention. Preliminary evidence indicates differences in the severity of general cognitive deficits between BD cognitive subgroups (e.g. 1, 2). Thus, careful consideration regarding which type of overarching cognitive enhancement approach may be most effective and practical for different individuals with the disorder is needed. Such approaches may utilize either a i) sequential (bottom up) strategy following a progressive course from which training of elementary cognitive skills evolves to training of higher order executive and metacognitive skills, or a ii) parallel (top down) strategy focusing on complex executive skills that simultaneously train lower-order abilities and have a clearer relevance to daily functioning.

Although preliminary, research has shown that more severely globally cognitively impaired BD subjects have greater dispersion of performance across cognitive domains compared to less severely globally impaired subjects (1). It is therefore possible that broad, concurrent training of higher-order cognition in severely globally impaired individuals may not generalize enough across domains to be recognized as effective through a global cognitive primary outcome score. Further, an initial focus on training higher-order cognitive abilities in this subgroup may be too arduous given profound concentration difficulties. A bottom-up approach involving simple, individual drill and practice exercises progressively training lower-to-higher order cognitive abilities may therefore be of greater benefit here, and may be more appropriately captured by a global outcome measure at the trial conclusion. On the other hand, in individuals for whom cognitive performance impairment is more subtle or selective, a top-down approach may have the advantage of maintaining attention and interest. Although not comprehensive, it is hoped that this suggestion will encourage further thought around accounting for cognitive heterogeneity in the formulation of psychologically based cognitive treatments.

Conclusions

The Taskforce guidelines provide an excellent resource for researchers conducting cognition enhancing clinical trials in BD. The adoption of these guidelines will no doubt benefit the literature by eliminating confounds that have impeded measurement efficacy of cognitive treatments in BD so far, and by aiding the comparability of results across samples.

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