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Can biomarkers aid stratification of individuals with mood disorders for cognitive remediation interventions?

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Targeting cognition in mood disorder treatment has been established as a priority due to the negative impact that persisting cognitive impairment has on general functioning and associated societal costs, and on the course of illness. In both bipolar disorder (BD) and major depressive disorder (MDD), evidence for efficacy and effectiveness of cognitive remediation (CR) interventions is preliminary, with relatively few randomised controlled trials (RCT) in small samples. While there are some promising pro-cognitive effects seen in these trials, outcomes are often inconsistent and non-replicated. Variability across trials is likely related, at least in part, to heterogeneity in cognitive profiles of those affected by mood disorders. Across both disorders, studies using data-driven approaches have identified distinct neurocognitive subgroups, with some individuals presenting with normal cognitive function and others showing moderate to severe impairments.

Emerging evidence indicates that each individual's profile of cognitive functioning impacts on whether and how they respond to a CR intervention. A number of studies have found that baseline cognitive function relates to CR treatment response, typically (but not always) with greater impairment being associated with better CR response. As well as examining cognitive predictors, increasing research is investigating a wide range of other potential predictors of CR response, including blood-based, neuroimaging, and diagnostic measures.

This paper provides insights from our recent RCTs of CR for people with mood disorders and discusses the challenges of synthesising CR studies that examine multimodal predictors. Challenges and recommendations are outlined particularly in relation to being able to progress these findings into practical clinical utility (i.e., being able to identify individuals who will respond to particular CR interventions in clinical practice).

Predictors of Response to Cognitive Remediation

We conducted three independent RCTs of CR interventions in Denmark (group-based CR for BD),[1] United Kingdom (individual CR for BD),[2] and New Zealand (individual CR merged into psychotherapy sessions for mood disorders),[3] (see Table 1 for study characteristics) involving baseline assessments

spanning biological (e.g., blood analysis), neuroimaging, clinical, cognitive and psychological measures. These measures pave the way for conducting analyses investigating multimodal predictors of CR response.

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Predictor analyses have produced the following published and soon-to-be published findings: (I) Neuroimaging biomarkers: Reduced thickness and working memory-related hypoactivity in the dorsolateral prefrontal cortex (dPFC) were associated with greater treatment-related improvement in executive function in the RCT by Ott et al. (2020)[1,4] of group Action-Based Cognitive Remediation (ABCR) in BD individuals pre-screened for objective cognitive impairment. It was concluded that these structural and functional differences in dPFC may represent neurocircuitry biomarkers for CR efficacy on executive function; (II) Blood-based biomarkers: In relation to the RCT by Strawbridge et al. (2021)[2] investigating individual CR for people with BD (not screened for cognitive impairment), as-yet unpublished findings indicate specific neurotrophic factors and a regulatory cytokine as candidate outcome predictors, moderators and/or mediators. In these cases, higher pre-CR levels predicted better subsequent outcomes, interacting with CR compared with usual care, and were increased further by CR compared with usual care; (III) Non-biological (cognitive/clinical/demographic): In relation to cognitive predictors, data from the Strawbridge et al. trial found cognition at baseline was the only predictor of CR-related cognitive change (i.e., poor cognition at baseline was associated with better CR response) out of a total of 16 candidate predictors (cognitive, functional, demographic, clinical).[5] In contrast, data from the RCTs by Ott et al. and Douglas et al. showed no associations between baseline objective (executive function[1] and global cognition[3]) and subjective cognition and CR-associated improvement in cognition. Douglas et al., in as-yet unpublished analyses, have reported predictive effects of demographic and clinical

variables on CR-related cognitive effects. Specifically, female gender and a diagnosis of BD (versus MDD) predicted better cognitive response to CR.

Methodological considerations and recommendations

Between these three RCTs, significant heterogeneity exists in main outcomes, as well as in the methodology and examined predictors. Clearly, larger studies and/or data aggregation across several (comparable) CR studies is required to more comprehensively examine baseline variables associated with CR efficacy. Further considerations are important in planning CR trials to aid subsequent data aggregation across studies for prediction analyses.

First, similar samples in terms of diagnoses and inclusion criteria across studies are needed to be able to pool data for larger-scale prediction analyses. Regarding the impact of diagnosis on CR response, while Strawbridge et al.[2] did not observe a difference in CR response between BD type I and II, Douglas et al[3] reported that their BD sample showed larger pro-cognitive effects than MDD. Thus, pooling data in MDD and BD samples separately may identify predictors specific to each group. At this stage, an understanding of CR predictors specific to MDD are extremely preliminary, with only one other small study undertaken to our knowledge. This is thus, a particular area of research need. Further, the RCTs in BD populations presented in this article differed markedly in approaches for screening prior to study entry, from rigorous objective cognitive screening (Ott), to simple subjective cognitive screening with a single Yes / No question (Douglas), to no formal cognitive screening (Strawbridge). This likely impacts on findings of predictor analyses, with highly enriched samples having less baseline variation in cognitive function, leading to less statistical power for the association analyses.

A second key consideration is that consistency in measuring pro-cognitive effects is needed to advance compatibility of findings on predictors of CR response. Specifically, it would be helpful if studies apply similar cognitive test batteries to examine pro-cognitive effects, and group their respective tests into cognitive domains in a uniform way, for the purposes of data aggregation. The

International Society of Bipolar Disorders (ISBD) Targeting Cognition Task Force has offered useful recommendations for choice of cognitive measures and outcomes in CR trials for BD, which we believe could reasonably be used in MDD as well. Specifically, these advise selecting a broad cognitive composite score (e.g., global cognition) spanning sustained attention, verbal memory, and executive functions as the primary outcome, based on cognitive tests comparable to those included in the ISBD – Battery for Assessment of Neurocognition (ISBD-BANC). Related to consistency of cognitive measures, is also the need to have a consistent approach to examining predictors of CR-related change. Studies which show improvement in certain cognitive domains with CR would, naturally, examine predictors of improvements in these specific cognitive outcomes (e.g., executive function as in the trial by Ott et al). In contrast, other trials that show broader CR-related cognitive change across multiple domains (e.g., in global cognition) would focus on predictors of more broad cognitive response to these CR interventions.

Third, standardisation of statistical methodology applied for investigation of predictors of treatment response is warranted. Predictive modelling techniques require much consideration to ensure statistical assumptions are met. Use of regression analysis (rather than simple correlations) with inclusion of clinical and demographic covariates is helpful in getting insight into baseline variables that are *directly* related to treatment efficacy. Simple regression analyses also have the benefit of not requiring extensive sample sizes, but are limited in the type and extent of relationships that can be modelled. Moderation analyses could be argued as more clinically relevant, indicating characteristics predicting a better response to one condition (or intervention) over another. Machine learning artificial intelligence models have the potential to incorporate complex relationships between many different predictor variables, but require very large sample sizes and can be liable to overfit data from a training model. As we recommend comprehensive baseline assessment in CR trials in order to be able to assess multimodal predictors of CR response (e.g., neuroimaging, biological, psychological, cognitive, clinical, demographic), statistical approaches need to accommodate these. Elastic net regression, which incorporates variable selection, is one example

of an approach which is suitable for multimodal prediction modelling, with reduced likelihood of overfitting and an ability to cater for different types of relationships between included variables.

Finally, the clinical utility of predictors is key. Keeping in mind that the long-term goal of examining predictors of CR response is to be able to directly target individuals in clinical practice who will benefit most from CR, the practical clinical utility of potential measures/predictors in mental health services needs consideration. A caveat in this regard of neuroimaging assessments is its high cost, which likely limits its clinical utility. Other less costly measures, such as baseline assessment of objective cognitive status with a brief cognitive screener like the SCIP (Screen for Cognitive Impairment in Psychiatry) or clinical interview, perhaps combined with a blood test, would be more readily implemented in clinical settings. Notably, prediction of *individual* treatment response would require sophisticated machine learning methods. However, machine learning prediction models generally perform poorly at the individual level and therefore currently have limited clinical use.

Conclusions

In summary, as large-scale research into the development of CR interventions for mood disorders increases, the need to determine who benefits most from CR is crucial in establishing clinical utility. Predictive modelling analyses across our three RCTs have shown several potential predictors of CR response, including structural and functional differences in the dPFC from neuroimaging measures, neurotrophic factors and a regulatory cytokine from blood-based measures, and a variety of non-biological measures including objective cognition, mood disorder subtype and gender. We have provided considerations and recommendations for CR studies that aim to examine multimodal predictors and to aggregate data, including the importance of consistent inclusion criteria (particularly regarding cognitive screening) and cognitive assessment across studies, suitable predictive modelling techniques that fit the data, and importantly, always keeping in mind clinical utility of CR predictors.

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Table 1. Overview of Three Randomised Controlled Trials of Cognitive Remediation for Mood Disorders

Authors	Country	Sample characteristics	Eligibility (cognition)	CR intervention	Sample size	Key cognitive outcomes
Ott et al., 2020	Denmark	BD, full or partial remission	Objective cognitive impairment	10 weeks of group Action-based Cognitive Remediation (ABCR), using Happy Neuron (20 group sessions) versus control treatment (10 group sessions).	n = 64	No effect of ABCR on primary outcome (global cognition), but large effect of ABCR on secondary outcomes (objective executive function and subjective cognition) compared with control at treatment-end.
Strawbridge et al., 2021	United Kingdom	BD, euthymic phase	No screening for cognitive impairment	12 weeks of individual, partly computerised (CIRCuiTS) CR (at least 1 therapist-guided session per week) versus treatment as usual.	n = 60	Significant improvement in working memory and executive function in CR vs TAU, but not on global cognition.
Douglas et al., 2022	New Zealand	BD or MDD (in episode or in remission)	Subjective cognitive impairment	12 sessions of partly-computerised CR using Happy Neuron (mean duration – 12 weeks) merged into IPSRT sessions versus IPSRT alone.	n = 68	No effect of CR on primary outcome (global cognition), but significant improvement in one secondary cognitive outcome in CR versus non-CR groups (verbal working memory).

BD = bipolar disorder; **CIRCuiTS** = Computerised Interactive Remediation of Cognition and Thinking Skills; **CR** = cognitive remediation; **IPSRT** = Interpersonal and Social Rhythm Therapy; **MDD** = major depressive disorder; **TAU** = treatment-as-usual