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Title:

Towards personalizing cognitive remediation therapy: Examining moderators of response for euthymic people with bipolar disorder.

Running title: Cognitive remediation response moderators in BD

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Abstract:

Background. Recent evidence suggests that cognitive remediation (CR) may reduce cognitive and functional difficulties in people with bipolar disorder (BD). However, there is a limited understanding of whether, and which, pre-treatment factors influence who will benefit from CR and this information could help to develop optimal therapy delivery. We aim to identify and examine baseline factors moderating post-treatment improvement.

Methods. This is a secondary analysis of data from a randomized controlled trial comparing CR (n=40) to treatment-as-usual (TAU; n=40) in euthymic people with BD. Elastic net regression was used to identify patient characteristics and baseline measures associated with post-treatment improvement in cognition, psychosocial functioning, and goal attainment. We then tested the moderating effect of retained variables on each outcome using multivariable linear regression.

Results. Despite lower baseline cognitive performance being associated with greater post-treatment changes in cognition and psychosocial functioning, there was no evidence of treatment response moderation. CR effect on goal attainment was larger for participants with better baseline cognitive performance, but this moderating effect did not reach significance (p = 0.09). Those with more severe baseline subjective cognitive complaints (p = 0.03) and more previously completed psychological therapies (p = 0.02) had also larger gains in goal attainment.

Conclusions. Treatment benefits in cognition and psychosocial functioning might not be affected by pre-treatment factors and patient characteristics. However, baseline cognition and perceived deficits may influence the effect of CR on achieving recovery goals. Therapy adaptations may be required to exert greater benefits for less responsive patients.

Keywords: Bipolar disorder; cognitive remediation; cognition; functioning; moderator; personalized treatment.

Introduction

A substantial proportion of people with bipolar disorder (BD) experience impairments in cognitive processes such as attention, memory and executive functioning (Burdick et al., 2014; Cullen et al., 2016). These deficits are associated with real-world difficulties such as work performance, psychosocial functioning, and quality of life (Brissos, Dias, & Kapczinski, 2008; Tse, Chan, Ng, & Yatham, 2014; Wingo, Harvey, & Baldessarini, 2009). The relevance of cognitive impairment for functional difficulties highlights the need for evidence-based therapies targeting cognition not only to improve cognitive abilities, but also to enhance functional outcomes and promote long-term functional recovery.

Cognitive remediation (CR) is a psychological therapy with well-documented and durable effects on cognitive and functional outcomes in people with schizophrenia (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Similarities in the cognitive profiles between people with schizophrenia and mood disorders prompted the application of CR treatment paradigms to mood disorders, with preliminary evidence indicating effects on cognition broadly comparable to those detected in psychotic disorders (Anaya et al., 2012). For people with BD, recent reviews suggest promising effects on cognition and functioning, although these studies had methodological limitations (Bellani et al., 2019; Tsapekos et al., 2020). Two recent randomized controlled trials (RCTs) examined CR in larger groups reporting medium-to-large cognitive benefits across multiple domains which were maintained at follow-up (Lewandowski et al., 2017; Strawbridge et al., 2021), while another RCT reported a medium-to-large effect of CR on executive functioning which disappeared at follow-up (Ott et al., 2020).

Despite increasing evidence on the CR benefits for people with BD, some participants show no improvement and there is a limited understanding about the patient characteristics associated with outcome variability. An uncontrolled study found reduced cognitive improvement for patients with a history of comorbid anxiety disorders (Deckersbach et al., 2010), while a secondary analysis of a functional remediation two trials showed greater verbal memory improvements for participants with poorer cognition at baseline (Bonnin et al., 2016) and larger cognitive gains for those with higher premorbid IQ (Lewandowski et al., 2017). The examination of factors moderating CR outcomes has therefore not only been limited but is also contradictory.

Putative moderators of response have been examined more extensively in people with a diagnosis of schizophrenia. However, systematic reviews suggest that the literature is still missing high-quality and well-replicated evidence on factors influencing CR outcomes for people with schizophrenia (Biagianti, Castellaro, & Brambilla, 2021; Reser, Slikboer, & Rossell, 2019; Seccomandi, Tsapekos, Newbery, Wykes, & Cella, 2019). Likewise, a recent large-scale meta-analysis of CR trials revealed a moderating effect only for education, premorbid IQ, and baseline symptom severity, with more compromised participants receiving greater benefits in cognition and functioning (Vita et al., 2021). A better understanding of moderating factors is crucial to tailor and adapt CR treatment paradigms according to patient characteristics and needs (Cella, Reeder, & Wykes, 2015; Wykes & Spaulding, 2011). Personalization of CR through such adaptations may improve therapy delivery and maximize treatment benefits (Medalia, Saperstein, Hansen, & Lee, 2018). Likewise, identifying whether certain patient subgroups are more or less likely to benefit from CR may help clinical services use their limited resources (e.g., time, personnel) more efficiently.

Previous work seeking to identify factors moderating CR outcomes in people with schizophrenia has been limited by methodological issues, such as not considering all potential contributing factors, investigating factors independently of other relevant variables, or problems with multiple comparisons due to inadequate sample size (Seccomandi et al., 2019). This may lead to a lack of

evidence convergence and an increased risk of false positive findings. Using traditional analytic methods (e.g., correlation, linear regression) to select response moderators might be contributing to these limitations. Considering multiple factors with these approaches can result in overfitted models which accurately explain the variation of an outcome in a particular sample but have limited predictive value (Yarkoni & Westfall, 2017). Adopting more advanced analytic approaches may facilitate the identification of factors moderating CR response. Elastic net regularized regression is such an approach allowing the examination of multiple variables while reducing the model variance and minimizing the risk of overfitting or false positives (Zou & Hastie, 2005).

Here, we will explore baseline factors potentially moderating response to CR using data from a cohort of euthymic patients with BD taking part in a randomized trial (Strawbridge et al., 2021). Cognitive and functional outcomes were assessed before and after the intervention and putative moderators, such as sociodemographic variables, illness characteristics and clinical symptoms, premorbid IQ, subjective complaints and objective cognition measures, were collected at baseline. Our findings will generate hypotheses to be tested in future studies and provide initial indications about patient subgroups that are less likely to respond to CR and may require adaptations on the way therapy is delivered.

Materials and methods

Study design

This is a secondary analysis of longitudinal data from the Cognitive Remediation in Bipolar (CRiB) study, an RCT comparing CR to treatment-as-usual (TAU) in euthymic patients with BD (Strawbridge et al., 2021). Compared to the main CRiB, this study includes a sample extended by 20 participants, randomized to CR (n=11) or TAU (n=9). These participants, recruited under the same criteria following a recruitment extension, were not included in the primary CRiB analysis conducted according to the published protocol (N=60) (Strawbridge et al., 2016), before all 80 participants had completed trial participation. The additional 20 participants are included in this study to increase the power of moderation analyses. Written informed consent was obtained from all participants. All baseline assessment procedures were conducted prior to random group allocation. The trial was approved by the City Road & Hampstead NHS Research Ethics Committee (reference 15/LO/1557).

Participants

Participants were recruited from primary and secondary services, community mental health teams, online advertising and mental health charities. All included participants had a DSM-5 diagnosis of BD, were fluent in English, and aged between 18 and 65 years. The Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was used to confirm diagnosis and BD subtype. Participants were on stable psychiatric medication and had been free of acute mood symptoms for ≥1 month prior to inclusion, with euthymia defined as a score of ≤7 on the *Hamilton Depression Rating Scale 17-item* (HAMD) (Hamilton, 1960) and *Young Mania Rating Scale* (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) over the 1-month period. Participants with a neurological disorder, personality disorder diagnosis, abuse or dependence on alcohol or illicit substances over the past six months were excluded.

2.3 Intervention

2.3.1 Cognitive remediation

Participants in the intervention arm received 12 weeks of therapist-led CR focusing on strategy use, metacognition and transfer of cognitive skills to daily life activities and individual goals. The online

software 'Computerised Interactive Remediation of Cognition – Interactive Training for Schizophrenia' (CIRCuiTS; https://www.circuitstherapyinfo.com) was adopted for CR delivery. CIRCuiTS is a manualized CR approach validated for patients with a diagnosis of schizophrenia (Reeder et al., 2017; Reeder et al., 2016).

Therapy was delivered by trained postgraduate psychologists with supervision from an experienced clinical psychologist. Therapy comprised one-on-one sessions, either in person or remotely (e.g., video call), and supplementary independent homework sessions, adjusted to participant needs. The target for therapy engagement was 2-3 hourly sessions per week, aiming for a total of 30-40 sessions. A threshold of 20 hours of CIRCuiTS training was predefined as the minimum for treatment completion. Further details in Supplementary Methods.

2.3.2 Treatment-as-usual

Participants in both the active and the control group continued any treatments they were previously receiving, including medications and psychosocial interventions not explicitly targeting cognitive functioning, throughout the trial without any interference from the study team.

2.4 Measures

Baseline measures and treatment outcomes were assessed blind to treatment allocation.

2.4.1 Baseline assessments

Information on sociodemographic characteristics (age, gender, education) and clinical variables (BD subtype, age of onset, illness duration, current medications) was collected using a structured interview. Residual depressive and (hypo)manic symptoms were assessed using the HAMD and the YMRS. The *Hamilton Rating Scale for Anxiety* (HAMA) (Hamilton, 1959) was used to evaluate anxiety symptoms. Premorbid IQ was estimated using the *Test of Premorbid Function* (TOPF) (Wechsler, 2011), and subjective cognitive complaints were examined with the self-report *Perceived Deficits Questionnaire* (PDQ) (Sullivan, Edgley, & Dehoux, 1990).

2.4.2 Cognitive and functional outcomes of CR

Four cognitive tests showing significant improvement between groups in the original study were used for this analysis, assessing different cognitive domains:

- *Processing speed*, with the *Digit-symbol coding* from the Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2014)
- *Attention and working memory*, using the *Digit span* (forward, backward and sequencing) from the Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2014)
- *Verbal memory*, using the *Verbal paired associates II* (VPA2; delayed free recall) from the Wechsler Memory Scale 4th edition (Wechsler, 2009)
- *Executive functioning*, using the *Hotel test* (Manly, Hawkins, Evans, Woldt, & Robertson, 2002).

Raw scores from each test were transformed to age- and education-corrected standardized scores (*z* scores; *Mean* = 0, *SD* = 1) using the test manuals. Higher scores reflected better performance for all tests. A global cognition composite score was calculated by averaging the *z* scores of individual tests.

Psychosocial functioning was assessed using the *Functional Assessment Short Test* (FAST) (Rosa et al., 2007), a validated scale designed to measure functional difficulties regularly reported by people with BD. FAST evaluated six different domains of daily life functioning (i.e., autonomy, occupation,

cognition, financial issues, interpersonal relationships, leisure time) with score reduction from baseline representing greater levels of functional improvement.

Attainment of personal recovery goals was examined using the Goal Attainment Scale (GAS) (Turner-Stokes, 2009). GAS provided a systematic format for quantifying the extent to which participants achieved the expected levels of performance in their goals (defined at baseline according to the needs and personal objectives of each participant) during the intervention period. Attainment was scored in a standardized way across participants with higher scores indicating greater goal achievement.

2.5 Statistical analysis

Analyses were conducted using the R software (version 3.6, www.r-project.org) and SPSS (version 26; IBM, New York). All continuous variables, including potential moderators and outcomes, were checked for normality of distributions using the Shapiro-Wilk test and log transformation was applied to conform non-normally distributed variables.

2.5.1 Estimating treatment outcomes

Given that here we examine an extended sample compared to the original trial, we estimated the effect of CR versus TAU for post-treatment cognitive and functional outcomes using repeated measures ANOVA models (estimating main effects of treatment group and time, and a group x time interaction effect), which accounted for baseline scores in the outcomes of interest. For each outcome, we computed Cohen's *d* (i.e., mean post-treatment difference between groups divided by pooled baseline SD) as an estimate of CR effect size.

2.5.2 Identifying and examining response moderators

Our analysis sought to identify and examine potential moderators of the CR effect compared to TAU (Kraemer, Wilson, Fairburn, & Agras, 2002). We considered factors previously examined in research for people with schizophrenia and BD, as well as variables showing a significant association with baseline cognitive and functional measures in our cohort (16 variables, Supplementary Table 1). The list included sociodemographic and illness-history characteristics, medication use at study entry, measures of symptom severity, perceived cognitive deficits and normative cognition at baseline (i.e., performance compared to general population norms). None of these putative moderators had missing data.

To identify potential response moderators for each outcome we first ran Pearson's correlations to evaluate whether baseline variables were individually associated with post-treatment outcome changes in the CR group. We then performed model selection with elastic net regularized regression (Zou & Hastie, 2005), using the GLMNET package in R (Friedman, Hastie, & Tibshirani, 2010). Regularized regression is an extension of linear modelling penalizing coefficient estimates to avoid overfitting. Elastic net selects predictor variables with a combination of the LASSO (Tibshirani, 1996) and the Ridge regression (Hoerl & Kennard, 2000) penalties which enables variable selection and coefficient shrinking. It was applied with repeated 10-fold cross-validation to identify the optimal tuning parameters (*alpha* and *lambda*) corresponding to the model with the minimum cross-validated prediction error (*MSE*). Cross-validation was repeated 10 times to take the average MSE of the optimal tuning parameters and to minimize results variation. The final model retained only predictors with non-zero coefficients.

Finally, we tested retained variables as moderators of the CR effect relative to TAU, to examine whether the effect of baseline variables predicting improvement was specific to the CR group (Kraemer, 2016). Moderation models were fitted for each outcome including the treatment group

(CR/TAU), the putative moderator, and their two-way interaction term as predictors, while also controlling for the baseline score of the respective outcome, age and education (Kraemer et al., 2002). Moderation analysis was conducted with the PROCESS macro for SPSS which uses percentile bootstrapping (5000 repetitions) to estimate coefficients and confidence intervals for interaction effects (version 3.5) (Hayes, 2017). This analysis was conducted separately for each outcome and was restricted to participants with complete post-treatment outcome data. Missing data were assumed to be missing at random (MAR) and observed baseline variables (including outcomes) were examined as factors driving missingness (Jakobsen, Gluud, Wetterslev, & Winkel, 2017). Any predictors of missingness were included in the analysis as covariates.

2.5.3 Power considerations

Power analyses were carried out using G*Power (version 3.1). Given the sample size after accounting for attrition (n=72) and the number of repeated measurements (i.e., two time-points), our study was 80% powered at an *alpha* level of 0.05 to detect post-treatment outcome differences equivalent to small or higher effect sizes ($d \geq 0.26$) between the CR and the TAU group. For moderation models, given the sample size (n=72) and the number of included predictors (n=6), our analysis was powered at 80% to detect small-to-medium or higher effect sizes ($f^2 \geq 0.08$) for the interaction coefficient between the treatment and the moderator, at an *alpha* level of 0.05.

3. Results

A total of 80 participants were randomized to CR (n=40) or TAU (n=40). Baseline characteristics for the whole sample and the two treatment groups are presented in Table 1. There were no missing data for participant characteristics and baseline measures. All baseline variables were comparable between the two groups. From the outcome measures, only the GAS was missing for two participants at baseline (one per group). Post-treatment data were obtained for 93% and 88% of participants in the CR and TAU groups, respectively. No baseline predictors of missingness were identified.

-- Table 1 around here --

3.1 Intervention outcomes

Findings for the extended sample were in line with the primary CRiB analysis, showing that CR significantly benefited treatment outcomes compared to TAU (Table 2). Adjusted mean differences between groups corresponded to a medium effect size for global cognition and small-to-medium effect sizes for individual cognitive domains. Between-group effect sizes indicated medium improvement in psychosocial functioning and large improvement in goal attainment for the CR group.

-- Table 2 around here --

3.2 Selection of moderators

After adjusting the significance level for multiple comparisons (corrected *alpha* = 0.003) no participant characteristics or baseline measures were significantly correlated with any outcome changes (Supplementary Table 2). Elastic net regression retained only poorer normative cognitive performance as a potential moderator of improvement in global cognition following CR. Lower baseline performance was also predictive of post-treatment improvement for verbal memory (Supplementary Table 3). No variables were retained for other individual cognitive domains.

Improvement in psychosocial functioning was associated with poorer baseline global cognition, fewer education years, and higher residual depressive symptoms at baseline. These were the factors considered in the moderation analysis. For goal attainment, the variables associated with improvement and considered as moderators were younger age, female gender, more previous psychological therapies, more subjective cognitive complaints and better cognitive performance at baseline (Supplementary Table 3).

3.3 Moderation of CR effects

No baseline factors predicting post-treatment improvement in cognition and psychosocial functioning for therapy recipients moderated the effect of CR compared to TAU (all $p > 0.02$; Supplementary Tables 4-5). The effect of baseline factors was not specific to the treatment group and benefits for CR recipients compared to TAU were of a similar size across the range of each putative moderator. For baseline cognitive performance, this is illustrated in Figure 1.

-- Figure 1 around here --

For goal attainment, baseline perceived deficits and previous psychological therapies significantly moderated treatment response with small-to-medium effect sizes (Figure 2): the effect of CR over TAU was greater for participants who reported more subjective cognitive complaints at baseline (interaction β = 0.28, 95% CI: 0.12 to 0.53, $p = 0.03$, $f^2 = 0.09$) and those who had completed more psychological therapies in the past (interaction β = 0.29, 95% CI: 0.02 to 0.57, $p = 0.02$, $f^2 = 0.08$).

-- Figure 2 around here --

Unlike cognition and functioning, CR benefits in goal attainment were more pronounced for participants with higher baseline cognitive performance (Figure 1). However, this moderating effect was not significant (interaction β = 0.48, 95% CI: -0.03 to 0.98, $p = 0.09$, $f^2 = 0.04$). Details for all GAS models in Supplementary Table 6.

4. Discussion

This is one of the first studies to examine multiple pre-treatment factors as response moderators following CR in euthymic people with BD. Baseline cognitive performance was associated with post-treatment changes across outcomes for participants receiving CR. However, there was no response moderation for cognition and psychosocial functioning, while this interaction only trended towards significance for goal attainment. A moderating effect was detected for baseline subjective cognitive complaints, with those who reported more severe deficits showing larger improvements on personal recovery goals. Pre-treatment level of cognitive performance and severity of cognitive complaints may be useful patient characteristics to inform the personalization of CR for people with BD.

4.1 Who benefits from CR?

Our results mirror those in schizophrenia suggesting that therapy recipients with lower cognitive performance at baseline are more likely to improve in response to CR (DeTore, Mueser, Byrd, & McGurk, 2019; Rodewald et al., 2014; Tan et al., 2019; Twamley, Burton, & Vella, 2011). This relationship has been observed particularly for CR approaches similar to the one we used in this study. In contrast, CR approaches relying heavily on intensive, drill-and-practice training have found better treatment response for those with higher cognitive performance at baseline (Fiszdon, Cardenas, Bryson, & Bell, 2005; Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009; Lindenmayer et al., 2017). Baseline cognitive performance did not moderate CR effects relative to TAU, despite affecting

cognitive and psychosocial functioning improvement for the treatment group (Figure 1). Thus, we cannot exclude that this improvement reflects a natural regression to the mean for lower baseline scores. More pronounced gains observed in patients with poorer cognition may be because these people benefit from greater *"room for improvement"*, while those with milder or no deficits might be more susceptible to ceiling effects (Miskowiak et al., 2017).

The absence of a moderation effect suggests that most euthymic patients with BD may substantially benefit from CR compared to only receiving the routinely available treatment (e.g., pharmacotherapy), independently of their pre-treatment cognitive level. This contradicts findings from functional remediation where a significant treatment effect on verbal memory was observed only for cognitively impaired participants at baseline (Bonnin et al., 2016). The difference might be explained by the characteristics of our therapy paradigm. CIRCuiTS combines rigorous cognitive training with an emphasis on strategy use and metacognitive skills to facilitate new learning, which might explain why the intervention was able to benefit not only most severely impaired individuals but also participants across the range of baseline cognitive performance.

Achievement of personal goals was significantly moderated by the level of subjective cognitive complaints at baseline, with greater response for those with more pronounced complaints (Figure 2). This is consistent with previous evidence suggesting larger improvements after CR for patients with higher self-reported cognitive difficulties (Twamley et al., 2011). A possible explanation is that these participants perceived a therapy targeting cognition as more useful and were more likely to value the input of CR than people with fewer subjective deficits. This may have led to greater motivation to engage with the therapy. Likewise, participants with greater previous experience with psychological therapies were likely more familiar with the way these therapies work and so were prepared to engage with the therapeutic process.

The association between baseline cognitive performance and CR effects on goal attainment was not significant. The direction of this effect differed from those of cognition and psychosocial functioning though, with higher cognitively performing CR participants being more likely to benefit (Figure 1). The GAS is a personalized measure which represents a treatment outcome different than traditional cognitive and functional measures (Wykes et al., 2018). This might explain the inconsistency between outcomes in relation to the role of baseline cognition. If assessed in an appropriately powered sample, it is possible that this effect would have reached statistical significance. Our *post-hoc* power analysis, given the estimated effect size, suggested that a sample size of 139 participants would be required for this effect to reach significance. We speculate that cognitively intact or high-performing patients might be more competent in persistently pursuing selected recovery goals during the therapy, but this is yet to be evidenced.

4.2 Research and clinical implications

Our study provides a framework for future, hypothesis-driven studies to investigate the moderating effect of baseline variables using larger samples or aggregated datasets from multiple trials. As previously suggested, in the process of identifying CR moderators it is important to consider for which outcomes patient characteristics are relevant, since these potentially require therapy adaptations to improve treatment benefits (Seccomandi et al., 2019). Based on our findings, improvements in cognition and psychosocial functioning do not appear to be affected by sociodemographic, illness-history, clinical or cognitive characteristics at baseline. For these outcomes, most people with BD can benefit without adaptations.

Attainment of personal recovery goals might be a more suitable outcome to consider for personalizing CR. For example, patients with less pronounced subjective complaints could benefit from therapy adaptations, as they may underestimate their cognitive difficulties which is common in people with BD (Torres, Mackala, Kozicky, & Yatham, 2016; Van Camp, Sabbe, & Oldenburg, 2019). One possible explanation is that the mismatch between subjective complaints and objective cognitive difficulties might reflect a poor level of metacognitive knowledge, one's awareness about their own cognitive problems (Cella, Reeder, & Wykes, 2015). Although metacognitive training is embedded in our CR paradigm, patients with poor awareness of their difficulties may further benefit from additional strategy use and therapist input to prompt metacognitive skills. Associating these therapy components with selected recovery goals might be useful for achieving greater benefits. In addition, devoting more therapy time on transfer activities bridging cognitive training with selected goals might be another adjustment to facilitate goal attainment for these patients.

4.3 Strengths and limitations

Moderation analyses in this study were based on data from a high-quality randomized trial showing CR-related improvements in cognitive and functional outcomes for people with BD. Our cohort was in full clinical remission and treatment groups were balanced both in terms of numbers and baseline characteristics. We used robust analytical approaches to select putative moderators and to estimate interaction effects.

Our study had a number of limitations. We only included normative performance in global cognition as a predictor of improvement. Future research will need to parse out the relative contributions of different cognitive abilities at baseline for cognitive improvement after CR (Ramsay et al., 2018). In addition, we only examined baseline factors predicting changes in the CR group to identify response moderators. Thus, we might have missed moderation effects driven by differential changes in the control group. However, such effects cannot be interpreted based on the impact of CR or inform therapy adaptations to improve outcomes.

Moderation analysis was not powered to detect small moderating effects (i.e., potential type II errors) due to the modest sample size. However, effects of larger strength are more informative for potential therapy adaptations. Our sample consisted primarily of middle-aged participants (mean age: 42 years old), with an average illness duration of approximately 10 years. Our findings might be representative of patients with an established BD diagnosis, but may not generalize to early-stage BD patients. Finally, this was a complete case analysis, however we had only a small percentage of missing data (>10%; only in dependent variables) and did not identify any predictors of missingness.

5. Conclusions

The effect of CR on cognition and psychosocial functioning does not seem to be influenced by pre-treatment patient characteristics, indicating that most people with BD will be able to benefit without therapy adaptations. For recovery goals though, individuals seem to respond to CR differently depending on baseline characteristics. Goal attainment might be a key outcome for progressing therapy personalization and improving treatment benefits through adaptations. Future, hypothesis-driven studies are warranted to consolidate our knowledge on CR moderators and evaluate whether tailoring CR according to baseline characteristics would increase therapy benefits for attainment of recovery goals and other relevant outcomes.

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Contributors

DT, TW and AHY conceived the study idea and planned this study. DT and RS were involved in data collection. DT carried out the analysis and prepared the first manuscript with support from RS. MC, TW and AHY supervised the project. All authors provided feedback, contributed to the final draft of the paper and approved the manuscript.

Ethics statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the City Road & Hampstead NHS Research Ethics Committee (reference 15/LO/1557).

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Tables

Table 1. Demographic and clinical characteristics of the treatment groups at baseline.

	CR group (*n*=40)	**TAU group (*n*=40)**	**Test statistic**	***p* value**
Age (years), mean (s.d.)	41.8 (13.9)	42.6 (11.8)	*F*=0.08	0.78
Gender, *n* (%)				
Women	30 (75.0)	27 (67.5)	χ^2=0.55	0.46
Men	10 (25.0)	13 (32.5)		
Education (years), mean (s.d.)	15.8 (2.7)	15.9 (2.1)	*F*=0.03	0.87
Premorbid IQ (TOPF), mean (s.d.)	108.9 (7.3)	109.4 (7.3)	*F*=0.10	0.75
BD type, *n* (%)				
Type I	26 (65.0)	27 (67.5)	χ^2=0.06	0.81
Type II	14 (35.0)	13 (32.5)		
History of psychosis, *n* (%)	23 (57.5)	26 (65.0)	χ^2=0.47	0.49
Age of onset (years), mean (s.d.)	30.4 (12.5)	31.5 (10.9)	*F*=0.18	0. 68
Diagnosis duration (years), mean (s.d.)	11.1 (10.2)	10.6 (7.4)	*F*=0.05	0.83
Number of hospitalizations, mean (s.d.)	2.5 (2.9)	2.4 (2.9)	*F*=0.07	0.79
Number of current medications, mean (s.d.)	2.3 (1.5)	2.6 (1.5)	*F*=0.79	0.38
Use of antipsychotic medication, *n* (%)	29 (72.5)	30 (75.0)	χ^2=0.07	0.80
Previous psychological therapies, mean (s.d.)	1.8 (1.1)	2.1 (1.9)	*F*=0.64	0.43
HAMD, mean (s.d.)	4.1 (2.6)	3.6 (2.5)	*F*=0.75	0.39
YMRS, mean (s.d.)	2.4 (2.3)	2.2 (2.4)	*F*=0.11	0.75
HAMA, mean (s.d.)	5.6 (4.8)	5.9 (4.1)	*F*=0.09	0.76
PDQ, mean (s.d.)	35.7 (14.9)	35.9 (12.9)	*F*=0.01	0.94
Global cognition, mean (s.d.)	-0.18 (0.63)	-0.27 (0.64)	*F*=0.42	0.52

Notes: BD: Bipolar Disorder; CR: Cognitive remediation; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale 17 items; PDQ: Perceived Cognitive Deficits; TAU: Treatment-as-usual; TOPF: Test of Premorbid Functioning; YMRS: Young Mania Rating Scale.
F-statistic: Statistic for One-way Analysis of Variance; χ^2-statistic: Statistic for Chi-squared test.

Table 2. Summary statistics and adjusted between-group mean differences (CR minus TAU) for cognitive and functional outcomes at post-treatment.

Outcomes	CR group		TAU group		Adjusted mean difference (95% CI)	*F*-statistic	*p*	*d*
	Mean (SD)	*n*	Mean (SD)	*n*				
Cognition composite								
Baseline	-0.18 (0.63)	40	-0.28 (0.64)	40				
Week13	0.35 (0.56)	37	-0.12 (0.56)	35	0.45 (0.30, 0.61)	34.562	<0.001	0.71
Hotel test								
Baseline	-0.50 (1.07)	40	-0.40 (1.16)	40				
Week13	0.59 (0.78)	37	0.00 (0.90)	35	0.64 (0.30, 0.98)	14.341	<0.001	0.58
VPA2								
Baseline	-0.19 (1.12)	40	-0.52 (1.08)	40				
Week13	0.28 (1.00)	37	-0.38 (0.96)	35	0.41 (0.12, 0.69)	8.138	0.006	0.37
Coding								
Baseline	-0.21 (0.70)	40	-0.29 (0.75)	40				
Week13	0.16 (0.85)	37	-0.20 (0.71)	35	0.33 (0.10, 0.57)	8.191	0.007	0.46
Digit span								
Baseline	0.07 (0.66)	40	0.12 (0.78)	40				
Week13	0.36 (0.72)	37	0.09 (0.64)	35	0.36 (0.13, 0.59)	9.995	0.002	0.50
FAST total score								
Baseline	23.5 (10.1)	40	20.2 (9.5)	40				
Week13	19.1 (9.5)	37	20.5 (9.8)	35	-4.7 (-2.6, -6.9)	18.921	<0.001	0.48
GAS total score								
Baseline	33.9 (4.1)	39	33.9 (4.4)	39				
Week13	52.0 (9.9)	36	38.8 (7.7)	34	13.2 (9.3, 17.2)	44.926	<0.001	3.14

Notes: CR: Cognitive remediation; FAST: Functional Assessment Short Test; GAS: Goal Attainment Scale; TAU: Treatment-as-usual; VPA2: Verbal Paired Associates – delayed free recall; *d* = Cohen's *d* effect size (mean difference between groups divided by pooled baseline standard deviation).

Figure legend

Figure 1. The effect of global cognitive performance at baseline on post-treatment global cognition, psychosocial functioning and goal-attainment per treatment group.

CR: Cognitive remediation; FAST: Functional assessment short test; GAS: Goal attainment scale; TAU: Treatment-as-usual.

Figure 2. Moderating effect of previous psychological therapies (Panel A) and subjective cognitive complaints at baseline (Panel B) on goal attainment per treatment group.

CR: Cognitive remediation; PDQ: Perceived cognitive deficits; TAU: Treatment-as-usual.

Figure 1

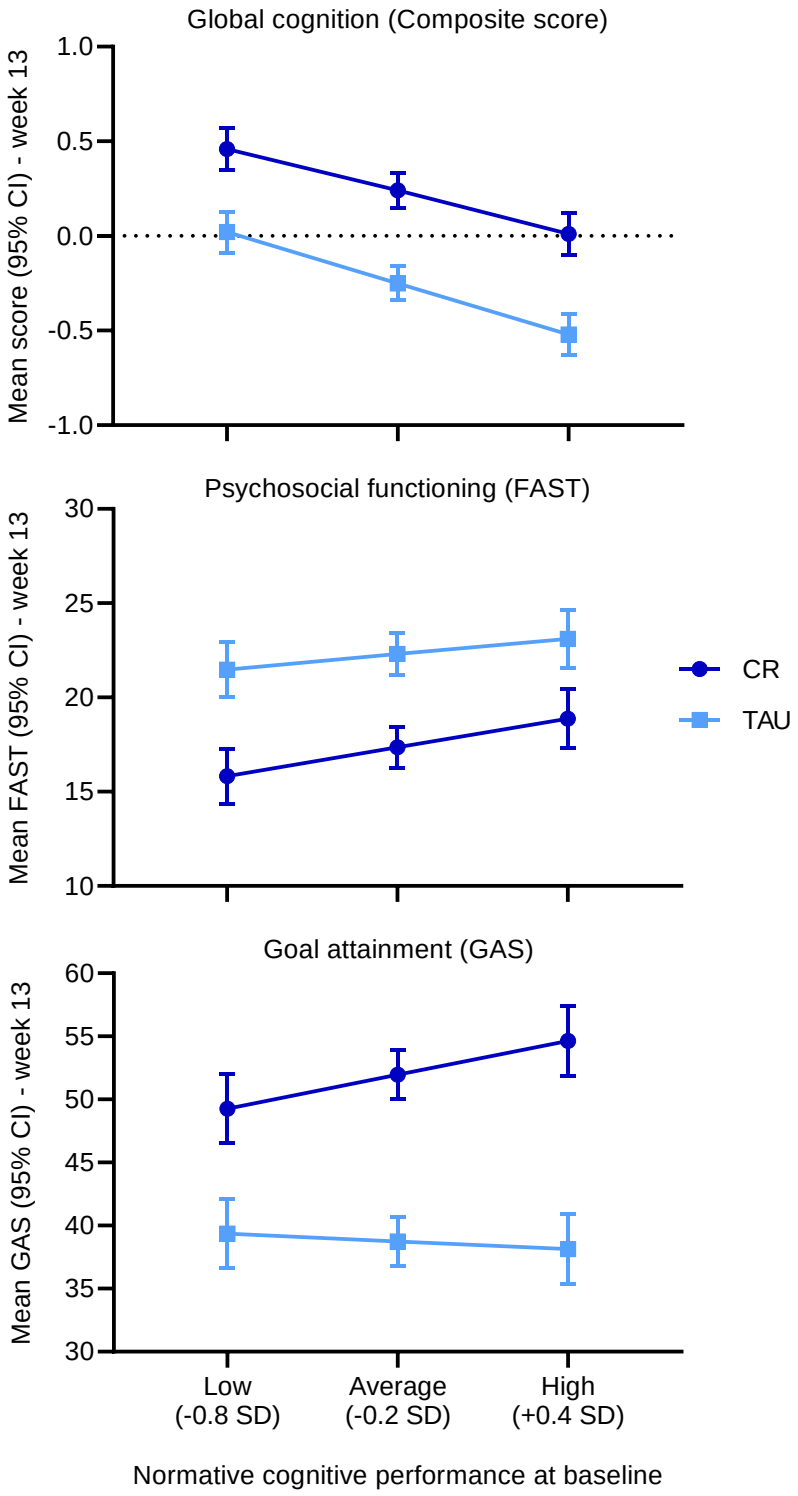
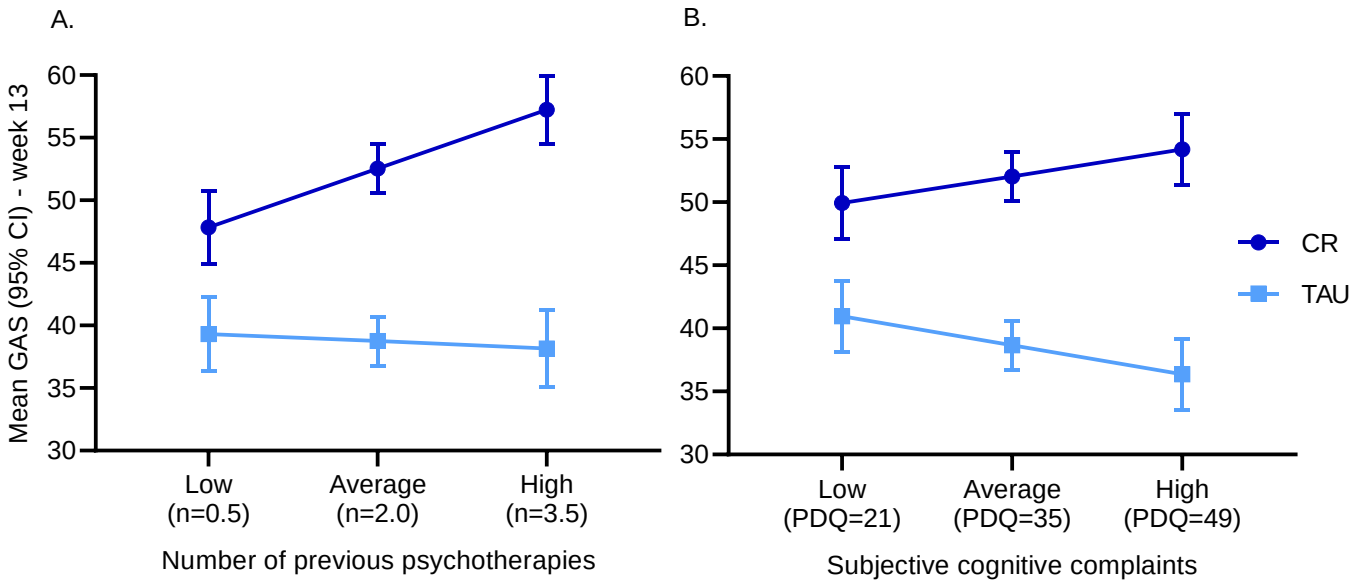

Global cognition (Composite score)
Mean score (95% CI) - week 13
1.0
0.5
0.0
-0.5
-1.0
Psychosocial functioning (FAST)
Mean FAST (95% CI) - week 13
30
25
20
15
10
CR
TAU
Goal attainment (GAS)
Mean GAS (95% CI) - week 13
60
55
50
45
40
35
30
Low
(-0.8 SD)
Average
(-0.2 SD)
High
(+0.4 SD)
Normative cognitive performance at baseline

Figure 2


A.
B.
Mean GAS (95% CI) - week 13
60
55
50
45
40
35
30
Low
(n=0.5)
Average
(n=2.0)
High
(n=3.5)
Number of previous psychotherapies
Low
(PDQ=21)
Average
(PDQ=35)
High
(PDQ=49)
Subjective cognitive complaints
CR
TAU