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A randomised controlled trial of psychotherapy and cognitive remediation to target cognition in mood disorders

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Abstract

Objective: To examine the impact of a treatment package combining Interpersonal and Social Rhythm Therapy (IPSRT) and cognitive remediation (CR), vs IPSRT alone, on cognition, functioning, and mood disturbance outcomes in mood disorders.

Methods: A pragmatic randomised controlled trial in adults with bipolar disorder (BD) or major depressive disorder (MDD), recently discharged from mental health services in Christchurch, New Zealand, with subjective cognitive difficulties. Individuals were randomised to a 12-month course of IPSRT with CR (IPSRT-CR), or without CR (IPSRT). In IPSRT-CR, CR was incorporated into therapy sessions from approximately session 5 and continued for 12 sessions. The primary outcome was change in Global Cognition (baseline to 12 months).

Results: Sixty-eight individuals (BD $n = 26$, MDD $n = 42$; full/partial remission $n = 39$) were randomised to receive IPSRT-CR or IPSRT (both $n = 34$). Across treatment arms, individuals received an average of 23 IPSRT sessions. Change in Global Cognition did not differ between arms from baseline to treatment-end (12 months). Psychosocial functioning and longitudinal depression symptoms improved significantly more in the IPSRT compared with IPSRT-CR arm over 12 months, and all measures of functioning and mood symptoms showed moderate effect size differences favouring IPSRT (0.41–0.60). At 18 months, small to moderate, non-significant benefits (0.26–0.47) of IPSRT vs IPSRT-CR were found on functioning and mood outcomes.

Conclusions: Combining two psychological therapies to target symptomatic and cognitive/functional recovery may reduce the effect of IPSRT, which has implications for treatment planning in clinical practice and for CR trials in mood disorders.

KEYWORDS
bipolar disorder, clinical trial, cognitive remediation, major depressive disorder, psychotherapy

1 | INTRODUCTION

Cognitive impairment in mood disorders (major depressive disorder, MDD, and bipolar disorder, BD) is evident in a substantial portion of patients,[1,2] across a range of domains (memory, executive function, attention, processing speed).[3,4] Significant heterogeneity in cognitive profiles exists across the mood disorder spectrum, with some patients affected across all cognitive domains, some affected on specific cognitive domains, and some showing no cognitive impairment.[1,2,5] In general, however, the degree and proportion of patients affected is greater in BD.[3] Cognitive impairment often persists into recovery,[6] and relates to problems in occupational and psychosocial functioning.[6,7] Aspects of cognitive impairment have also been associated with increased risk of relapse.[8] Cognition has thus been identified as an important treatment target in mood disorders in attempting to improve overall recovery.[9]

Systematic reviews examining the effectiveness of cognitive remediation (CR) interventions in BD have reported preliminary pro-cognitive effects[10] or inconclusive results.[11,12] Two recent randomised controlled trials (RCTs) in euthymic BD reported improved aspects of cognitive function, particularly executive function, following CR interventions (10–12 weeks in duration). Strawbridge et al.[13] reported additional improvement in psychosocial functioning at treatment-end and 3-month follow-up, while Ott et al.[14] showed improvement in subjective cognitive function at treatment-end only. In MDD, recent meta-analysis reported short-term, moderate pro-cognitive effects, and small effects on daily functioning and mood symptoms, but none of these effects were durable.[15] In comparison with CR trials in BD, MDD trials have generally been smaller, shorter in CR duration, more variable in whether CR commences in the acute or remitted phase, and often focus on short-term symptom reduction rather than longer-term functional outcomes. Clearly, larger RCTs of CR interventions in mood disorders, examining durability of multiple outcomes, are required.

There is limited evidence of structured psychological therapy for mood disorders having a beneficial impact on cognitive function,[16] although Metacognitive Therapy (MCT), which involves a simple cognitive training component (Attention Training Technique), has been reported to improve measures of visuospatial working memory (large effect) and sustained attention (moderate effect) compared with Cognitive Behavioural Therapy (CBT).[17] This finding suggests that cognitive training within an existing therapeutic relationship can produce pro-cognitive effects.

No trials combining a standard, structured psychological therapy with CR have been conducted in mood disorders, even though in schizophrenia, it is well-established that combining CR with rehabilitative therapies benefits wider functioning.[18] Preliminary evidence suggests that CR interventions that integrate principles of psychological therapy (eg, role-play, goal setting) alongside a therapeutic relationship produce better retention rates, and improved subjective cognitive and functional competence compared with traditional CR approaches.[19] Interpersonal and Social Rhythm Therapy (IPSRT) is a psychological therapy developed for BD which focuses on stabilising circadian and social rhythms (eg, sleep), as well as improving interpersonal functioning. Data suggests a link between disrupted sleep and cognitive[20] and functional impairment[21] in BD; thus, improving sleep patterns alongside a CR intervention has a solid theoretical basis. Furthermore, IPSRT has been shown to be effective in reducing depression symptoms and reducing risk of relapse in BD,[22,23] and similar preliminary effects have been reported in MDD.[24] A treatment package including IPSRT and CR has potential to improve several key aspects of recovery from mood disorders.

An issue for psychosocial treatments has been translatability into clinical practice.[25] Conducting trials in patients with rigorously defined characteristics has advantages for establishing effectiveness of treatments and

Significant Outcomes

- No clear effect of cognitive remediation (CR) was observed on cognition.
- Merging an individual CR intervention into Interpersonal and Social Rhythm Therapy (IPSRT) sessions appeared to dilute the beneficial effects of IPSRT on functional and mood outcomes.
- Future studies should consider commencing CR at a point of greater stability of the illness.

Limitations

- Feedback from therapists regarding difficulties providing CR when patients were often still acutely unwell led to the RCT being stopped early. The study is thus underpowered.
- Due to the pragmatic nature of this RCT, screening for cognitive impairment used a subjective rather than objective approach.
- The dose of CR received in the IPSRT-CR arm was lower than in many previous CR trials, which may have limited potential to show pro-cognitive effects.

understanding their mechanisms but has disadvantages in translation since in clinical practice it is necessary and more feasible to provide treatments to broader groups of patients. We therefore used a pragmatic design in which all patients with mood disorders, at a particular point in their contact with services, could be included. This point was on discharge from specialist mental health services. We used a simple screening procedure for subjective cognitive impairment which could realistically be implemented in community mental health settings. Outcome measures were in line with ISBD task force recommendations for CR trials in BD,[9] and strengthened by the use of a longitudinal, rather than cross-sectional, measure of mood disturbance (Longitudinal Interview Follow-up Evaluation).

1.1 | Aims of the study

In this pragmatic randomised controlled trial, the primary aim was to investigate the impact of long-term IPSRT, with or without cognitive remediation, on cognitive function in individuals with mood disorders. The secondary aims were to examine the impact of these treatments on general functioning and mood outcomes. Secondary aims were also to examine durability of effects on cognitive, functioning, and mood outcomes, 6 months after treatment-end.

2 | METHODS

2.1 | Study design

This was a prospectively registered (Australian New Zealand Clinical Trial Registry, ANZCTR: ACTRN12616001328460), single-blinded, randomised controlled trial (RCT) comparing IPSRT and cognitive remediation (IPSRT-CR) with IPSRT alone for individuals with mood disorders. The trial was conducted in the Department of Psychological Medicine, University of Otago, Christchurch, in collaboration with the Canterbury District Health Board. Study recruitment occurred between 17 October 2016 to 5 August 2019 (last follow-up assessment was 5 February 2021). Ethical approval was from the Northern A Health and Disability Ethics Committee, New Zealand (ref: 16/NTA/64). The study design and assessment timeline is presented in Figure 1. Assessment conducted 12 months after baseline is referred to as 'treatment-end' and 18 months after baseline as 'follow-up' from this point. Reporting of this RCT follows Consolidated Standards of Reporting Trials (CONSORT) guidelines.[26]

2.2 | Participants

Participants were recruited from adult specialist mental health services (Canterbury District Health Board) in

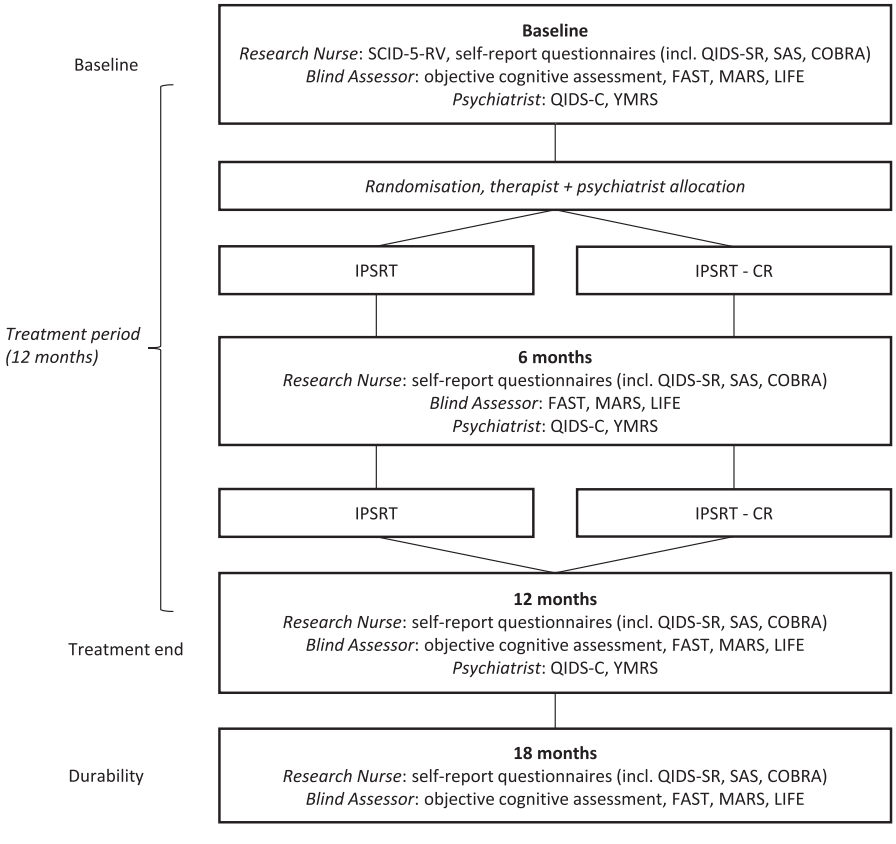

FIGURE 1 Study design. COBRA, Cognitive Complaints in Bipolar Disorder Rating Assessment; FAST, Functioning Assessment Short Test; IPSRT, Interpersonal and Social Rhythm Therapy; IPSRT-CR, Interpersonal and Social Rhythm Therapy and Cognitive Remediation; LIFE, Longitudinal Interview Follow-up Evaluation; MARS, Medication Adherence Rating Scale; QIDS-C, Quick Inventory for Depressive Symptomatology – Clinician-administered; QIDS-SR, Quick Inventory for Depressive Symptomatology – Self Report; SAS, Social Adjustment Scale; SCID-5-RV, Structured Clinical Interview for DSM-5 Disorders – Research Version; YMRS, Young Mania Rating Scale

Christchurch, New Zealand. Treating clinicians at these services referred patients to the trial at the point of discharge (patients would typically have been referred back to primary care at this point). Participants were eligible if they had a diagnosis of BD (I, II, or Other Specified) or MDD, were within 3 months of discharge from adult specialist mental health services, were aged over 18 years, and had subjective cognitive difficulties judged by self or by referring clinician. Subjective cognitive difficulties were assessed with a single yes/no question ('are you having any difficulties with concentration, memory or decision-making?'). Rationale for this choice of cognitive screening approach is outlined in Appendix S1.

Exclusion criteria were: current severe substance use disorder, schizophrenia, schizoaffective disorder or neurodegenerative disease, history of severe brain injury (loss of consciousness for more than 1 h), having had a course of IPSRT in the last 18 months or a CR intervention or electroconvulsive therapy in the past 6 months, actively engaged in another psychotherapy concurrently, and not being able to communicate in English. Written informed consent was obtained from all individuals before participating.

2.3 | Randomisation

Participants were assigned to receive CR in addition to IPSRT, or IPSRT alone, following completion of baseline assessment. Computerised permuted block randomisation was undertaken by the team's biostatistician (CF) prior to the commencement of the study. Randomisation was stratified according to mood disorder type (BD or MDD). Sequentially numbered envelopes were stored in a locked cabinet by an independent research coordinator and given to therapists after the pre-treatment assessment was completed. Delay between randomisation and commencing treatment was no more than 1 week.

2.4 | Interventions

2.4.1 | Interpersonal and Social Rhythm Therapy

Interpersonal and Social Rhythm Therapy combines interpersonal psychotherapy with a focus on social rhythms or routines in a person's life. IPSRT was delivered in an individual format by clinicians (two clinical psychologists, three mental health nurses, one social worker) trained in the provision of IPSRT, according to a manualised protocol. This was adapted from the original IPSRT manual[27] by experienced IPSRT therapists (MI, MC) for patients with MDD as well as BD.[24]

IPSRT was conducted over a period of 12 months (weekly for the first 10–12 weeks, fortnightly for 4 months, and then monthly). Therapy frequency could, however, be increased according to the patient's mental state. A total of 24 sessions was considered a full therapy dose, and 18 sessions deemed as an adequate dose.

2.4.2 | Cognitive remediation

The CR intervention was delivered according to a manual developed specifically for this study (KD), in collaboration with Professor Christopher Bowie (Queen's University, Canada). Feasibility and content have been described in detail.[28] Key components were: (1) psychoeducation about cognitive impairment in mood disorders, (2) repeated practice of computerised cognitive exercises and strategy coaching, and (3) discussions of transferring skills to functioning in daily life.[29] CR was provided in an individualised, face-to-face format, giving therapists flexibility to tailor intervention to each patient's cognitive strengths and weaknesses. Computerised exercises were provided by Scientific Brain Training Pro (SBT Pro; https://www.scientificbraintrainingpro.com/), with patients able to access up to 12 exercises, all of which primarily targeted executive functions, working memory, and/or verbal and visuospatial learning and memory. More detail on the rationale behind selection of SBT Pro tasks in the current trial, as well as how therapists selected SBT Pro tasks to practice in session, is provided in Appendix S1.

For the combined IPSRT-CR intervention, CR was integrated into IPSRT sessions from approximately session 5, and continued for 12 sessions. The IPSRT-CR intervention did not involve extra therapy time; the intention was for CR to take approximately 20–30 min of a 60-min therapy session, however, this could be adapted according to patient need. Between therapy sessions, patients were asked to complete at least three online practice sessions, for 30 min each, per week on SBT Pro. The SBT Pro platform provided data including number of practice sessions, time spent on practice sessions, types of tasks practised, and levels achieved.

The same six clinicians who administered IPSRT also delivered the CR intervention. All were trained by KD. With regards to fidelity of both IPSRT and CR interventions, therapy sessions were audio-taped and 10% were randomly selected and rated to ensure adherence to IPSRT and CR therapy protocols using checklists for key components of each therapy. Therapists all participated in fortnightly group supervision, led by therapists with extensive experience in training and delivery of IPSRT (MI) and CR (KD).

2.4.3 | Medication management

Six consultant psychiatrists provided medication management. Patients were accepted into the trial on any medication regimen, with treating psychiatrists using clinical judgement and the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders[30] to inform medication management decisions. The psychiatrist saw each patient at study entry, and 6 and 12 months, as well as when requested by the patient's therapist or the patient.

2.5 | Procedure

Patients entered the study within 3 months of discharge from specialist community mental health services in Christchurch, New Zealand. Baseline assessment (see Figure 1) involved Structured Clinical Interview for DSM-5 Disorders, Research Version[31] (SCID-5-RV) administered by a Research Nurse, self-report questionnaires on subjective cognitive function (Cognitive Complaints in Bipolar Disorder Rating Assessment,[32] COBRA), social functioning (Social Adjustment Scale,[33] SAS), and depression symptoms (Quick Inventory for Depressive Symptomatology – Self Report,[34] QIDS-SR). A blind assessor conducted objective cognitive assessment (described below) and verbal IQ (National Adult Reading Test[35]; NART) in person and measures of longitudinal mood disturbance (Longitudinal Interview Follow-up Evaluation,[36] LIFE), general functioning (Functioning Assessment Short Test,[37] FAST), and medication adherence (Medication Adherence Rating Scale,[38] MARS) via telephone, within 1 week of baseline assessment. At the end of baseline assessment, the Research Nurse opened randomisation envelopes and therapy arm was allocated. Prior to commencing therapy, the psychiatrist completed the clinician-administered versions of the Quick Inventory of Depressive Symptomatology[34] (QIDS-C) and Young Mania Rating Scale[39] (YMRS). Therapy commenced within 1 week of baseline assessment and continued for 12 months for both treatment arms. With the exception of the SCID-5-RV, measures completed at baseline were repeated at treatment-end (12 months) and follow-up (18 months).

2.6 | Outcomes

2.6.1 | Primary outcome

As recommended by the ISBD Targeting Cognition Task Force,[9] the primary outcome was change from baseline to treatment-end in 'Global Cognition', which was a composite score from all tests completed during cognitive assessment. Cognitive tests were: Rey Auditory Verbal Learning Test[40] (RAVLT), Groton Maze Learning Test (GMLT; CogState, www.cogstate.com), Timed Chase Test (CogState, www.cogstate.com), Controlled Oral Word Association Test[41] (COWAT), Delis-Kaplan Executive Function System (D-KEFS) Category Fluency,[42] D-KEFS Category Switching,[42] Digit Span Test.[43] See Appendix S1 for details of variables extracted from cognitive tests for calculation of Global Cognition scores.

2.6.2 | Secondary outcomes

Secondary outcomes measures, including rationale, description and time-points of administration, are described in detail in Appendix S1. Measures included individual cognitive test variables (12 variables), subjective cognitive functioning (COBRA), general functioning (FAST), psychosocial functioning (SAS), longitudinal mood disturbance (LIFE), treatment satisfaction, and adverse events.

2.7 | Change to protocol

The proposed original sample size was 160 patients (ANZCTR: ACTRN12616001328460). However, due to concerns raised by therapists regarding the dilution of IPSRT with CR at a time when many patients were still 'in episode', a decision was made to terminate at a sample size of 68 patients (see Discussion).

2.8 | Statistical analysis

Power was based on cognitive outcomes in our study of MCT (involving a cognitive training exercise called Attention Training Technique[44]) vs CBT (no cognitive training component) for depression.[17] Positive effect size differences were shown for MCT compared with CBT of 0.5–0.7 on working memory and attention measures. For a similar effect size of 0.5 for cognitive outcomes in the current study, 64 patients per group would be necessary for 80% power. We aimed to recruit 160 participants to allow up to 20% attrition, to ensure a final group size in each arm of 64 (however, see Change to Protocol, above). All statistical tests utilised a 2-tailed p-value of <0.05 to indicate statistical significance.

Statistical analyses were conducted using IBM SPSS, version 27-x for Windows. Group comparisons for demographic and clinical characteristics at baseline were performed using independent samples t-tests or chi-squared tests. To assess the effect of IPSRT-CR vs IPSRT,

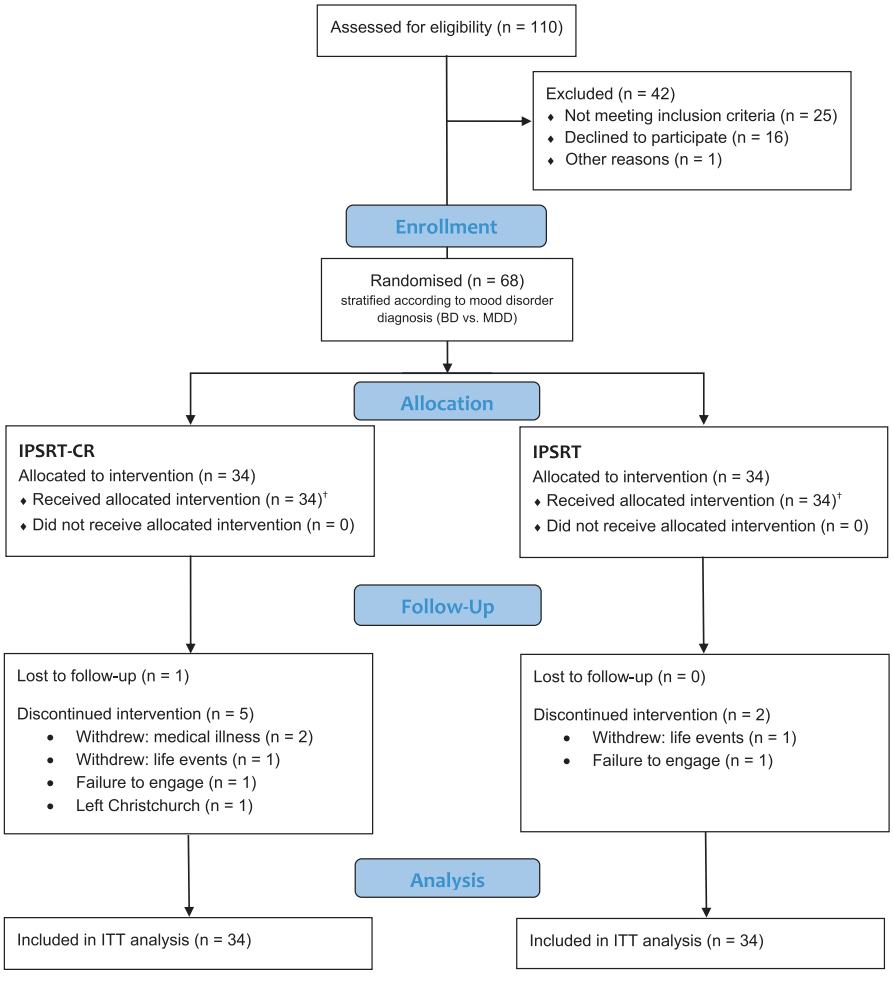

FIGURE 2 CONSORT diagram. †All participants who were allocated to an intervention received at least some of the intervention (at least 5 therapy sessions)

all primary and secondary outcomes were analysed using general linear models. These models used treatment arm and stratum (MDD vs BD) as fixed factors. The α-level of 0.05 was set for study outcomes. All analyses of primary and secondary outcomes adopted an intention-to-treat (ITT) approach. Effect size differences (Cohen's *d*) between treatment arms at both treatment-end (12 months) and follow-up (18 months) were calculated for change scores on all primary and secondary outcomes. The following convention was used to interpret effect size: small 0.2–0.49, moderate 0.5–0.79, large ≥0.8.

Further analysis was conducted on the primary outcome for those individuals who completed the 12-month IPSRT treatment course. Individuals who completed at least 18 individual therapy sessions (regardless of proportion of time spent on IPSRT or CR) were classified as treatment completers.

2.8.1 | Calculation of global cognition

All objective cognitive variables were normally distributed. *Z* scores for change in each cognitive variable were calculated (baseline to 12 months, and baseline to 18 months) as change between baseline and follow-up divided by the standard deviation of the whole participant sample at baseline. In each case, these scores were computed so that a positive score indicated an improvement from baseline, regardless of whether the cognitive variable produced outcomes of accuracy, errors, or reaction time. The Global Cognition change score was computed based on the mean of all variables for each patient.

3 | RESULTS

3.1 | Participant flow and missing data

Sixty-eight participants were recruited and randomised (IPSRT-CR $n = 34$, IPSRT $n = 34$) and included in analysis. The flow of participants throughout the trial is displayed in the CONSORT diagram (Figure 2). No significant difference between groups in discontinuation rate was found (IPSRT-CR $n = 6$; IPSRT $n = 2$; $p = 0.22$). All patients were included in ITT analyses (IPSRT-CR $n = 34$, IPSRT $n = 34$). Appendix S2 describes missing data and statistical approach in accounting for this in more detail.

3.2 | Group characteristics

Mean (SD) age of the sample was 35.6 (12.1) years, and 42 (62%) were female. Forty-two (62%) individuals had a diagnosis of BD (26 [38%] with MDD), and 39 (57%) were in full or partial remission (29 [43%] in episode). Table 1 displays baseline demographic and clinical characteristics of the sample, with no statistically significant differences between treatment groups observed.

3.3 | Treatment adherence and satisfaction

Treatment arms did not differ in number of therapy sessions delivered (IPSRT-CR 23.3 [SD 7.3] sessions; IPSRT 23.5 [SD 5.6] sessions, $p = 0.9$), total time spent in therapy (IPSRT-CR 20.9 [SD 6.8] h; IPSRT 19.5 [SD 5.3] h, $p = 0.3$), or total time spent focusing specifically on IPSRT over the treatment period (IPSRT-CR 19.8 [SD 6.2] h; IPSRT 19.1 [SD 6.2] h; $p = 0.6$). When re-running these analyses for treatment completers only ($n = 60$), the IPSRT-CR group received significantly more total therapy hours compared with the IPSRT group (23.4 [SD 4.2] h vs 20.3 [SD 4.2] h, respectively; $t_{1.58} = 2.9$, $p = 0.006$), but still no significant difference in number of hours spent focussed on IPSRT within these sessions ($p = 0.1$).

Details of the dose and duration of the CR intervention are presented in Table 2. The median CR treatment period (first to last CR session) was 12.3 (IQR 6.8, 17.3) weeks. Within the IPSRT-CR arm, median total time spent on CR in therapy sessions (face-to-face) was 1.0 (IQR 0.7, 2.4) hour and outside of therapy sessions (computerised practice) was 2.2 (IQR 1.4, 7.9) hours. Over the period in which CR was undertaken, the median number of computerised practice sessions was 11.0 (IQR 4.0, 22.3). In IPSRT-CR treatment completers only ($n = 28$), median total time spent on CR in therapy sessions was 1.1 (IQR 0.8, 2.6) hours and outside of therapy sessions was 4.0 (IQR 1.6, 9.6) hours.

With regards to patients' satisfaction with the treatment package as a whole, across both treatment arms, 87% were satisfied with the therapeutic relationship (rated as 'valuable' or 'very valuable') and 83% were satisfied with the content of sessions (rated as 'valuable' or 'very valuable'). In recommending the treatment package to others, 85% reported that they would be 'confident' or 'very confident' in doing so. In rating the CR intervention, 54% of patients in the IPSRT-CR arm reported being 'satisfied' or 'very satisfied' with the CR intervention, with a further 25% holding a neutral stance.

Last, in relation to psychiatrist input, groups did not differ in number of psychiatrist appointments attended over the treatment period (IPSRT-CR 6.1 [SD 4.0] appointments; IPSRT 5.7 [SD 2.9] appointments; $p = 0.7$), or in total time spent seeing their psychiatrist (IPSRT-CR 179.4 [SD 112] minutes; IPSRT 162.1 [SD 83.9] minutes; $p = 0.5$).

3.4 | Primary outcome

Table 3 presents results from ANCOVA for primary and secondary outcome measures. Change in Global Cognition between baseline and treatment-end was not significantly different between IPSRT-CR and IPSRT groups (change Z scores: IPSRT-CR 0.03 [SD 0.1]; IPSRT −0.03 [SD 0.1], $F_{1,65} = 0.25$, $p = 0.6$).

Subsequent analysis investigated the effect of IPSRT-CR compared with IPSRT on the primary outcome (Global Cognition) in individuals considered treatment completers (at least 18 therapy sessions for both treatment arms). No significant between-group difference was found ($F_{1,57} = 0.1$, $p = 0.7$).

3.5 | Secondary outcomes

Objective cognitive performance: Between baseline and treatment-end, the IPSRT-CR group improved significantly more on RAVLT distractor list recall compared with the IPSRT group ($F_{1,65} = 4.4$, $p = 0.04$, $d = 0.52$). Between baseline and 18 months, GMLT total learning (trials 1–4) improved more so in the IPSRT-CR compared with IPSRT group ($F_{1,65} = 6.5$, $p = 0.01$, $d = 0.67$). Change on Digit Span Forwards in IPSRT-CR vs IPSRT reached trend level at this time-point ($F_{1,65} = 3.4$, $p = 0.07$, $d = 0.41$). No other cognitive variables changed significantly differently between treatment groups over time at treatment-end or follow-up (see Table 3).

Subjective cognitive function: No difference in change scores between treatment groups on the COBRA was found at treatment-end or follow-up.

Mood disturbance: LIFE depression score improved significantly in the IPSRT vs IPSRT-CR group from baseline to treatment-end ($F_{1,65} = 4.3$, $p = 0.04$, $d = 0.60$). A trend in the same direction was found for the LIFE affective disturbance score over the same period ($F_{1,65} = 3.0$, $p = 0.08$, $d = 0.42$). No differences on LIFE depression or LIFE affective disturbance scores were found between baseline and follow-up (18 months) when comparing IPSRT and IPSRT-CR groups.

Functioning: From baseline to treatment-end, the IPSRT group improved significantly more than the IPSRT-CR group on the SAS ($F_{1,65} = 5.0$, $p = 0.03$, $d = 0.43$). A trend on the FAST was found from baseline

TABLE 1 Demographic and clinical characteristics at baseline

Variable	Labels	IPSRT-CR ($n = 34$)	IPSRT ($n = 34$)	All ($n = 68$)	t/χ^2	p
Age (years)	Mean (SD)	35.7 (11.1)	35.6 (13.0)	35.6 (12.1)	0.04	0.97
Gender[a]	Female *n* (%)	23 (68)	19 (56)	52 (62)	0.81	0.37
	Male *n* (%)	11 (32)	15 (44)	26 (38)	—	—
Estimated verbal IQ (NART)	Mean (SD)	106.3 (6.1)	105.1 (7.4)	105.7 (6.8)	0.73	0.47
Education (years)	Secondary education, mean (SD)	4.9 (1.9)	4.7 (0.9)	4.8 (1.5)	0.56	0.58
	Tertiary education, mean (SD)	2.7 (2.2)	3.4 (2.7)	3.0 (2.4)	1.30	0.20
Employment	Employed *n* (%)	19 (55.9)	16 (47.1)	35 (51.5)	0.53	0.47
	Unemployed *n* (%)	15 (44.1)	18 (52.9)	33 (48.5)	—	—
Ethnicity	NZ European *n* (%)	26 (77)	26 (77)	52 (77)	0.29	0.86
	Māori *n* (%)	3 (9)	2 (6)	5 (7)	—	—
	Other *n* (%)	5 (15)	6 (18)	11 (16)	—	—
Mood disorder diagnosis[b]	BD I *n* (%)	12 (35)	8 (24)	20 (30)	0.25	0.62
	BD II *n* (%)	10 (29)	11 (32)	21 (31)	—	—
	BD other *n* (%)	0 (0)	1 (3)	1 (2)	—	—
	MDD *n* (%)	12 (35)	14 (41)	26 (38)	—	—
Remission	Full remission *n* (%)	5 (15)	6 (18)	11 (16)	0.54	0.76
	Partial remission *n* (%)	13 (38)	15 (44)	28 (41)	—	—
	In episode *n* (%)	16 (47)	13 (38)	29 (43)	—	—
Illness duration (years)	Median (IQR)	14.0 (10.8, 27.0)	11.0 (5.5, 23.3)	14.0 (6.3, 24.0)	0.70	0.49
Mood disorder onset (age in years)	Median (IQR)	17.0 (13.0, 20.25)	16.5 (13.0, 20.0)	17.0 (13.0, 20.0)	0.77	0.44
Depression severity (QIDS-C)	Median (IQR)	6.0 (2.8, 10.0)	8.0 (4.0, 11.0)	7.0 (4.0, 10.8)	0.96	0.34
Mania severity (YMRS)	Median (IQR)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.29	0.77
Longitudinal depression symptoms (LIFE[c])	Median (IQR)	1.9 (0.5, 2.9)	2.4 (1.1, 3.3)	2.0 (0.9, 3.0)	0.93	0.36
Longitudinal mania symptoms (LIFE[c])	Median (IQR)	0.0 (0.0, 0.3)	0.0 (0.0, 0.2)	0.0 (0.0, 0.2)	0.09	0.93
Affective disturbance (LIFE[c])	Median (IQR)	2.1 (0.9, 3.0)	2.5 (1.4, 3.4)	2.2 (1.0, 3.2)	0.99	0.33
Medication adherence (MARS)	Median (IQR)	8.0 (7.0, 9.0)	7.5 (6.8, 9.0)	8.0 (7.0, 9.0)	0.62	0.53
Medication type	Total number, median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.50	0.62
	Lithium *n* (%)	9 (27)	11 (32)	20 (29)	0.28	0.60
	Anticonvulsants *n* (%)	9 (27)	9 (27)	18 (27)	0.00	1.00
	Antidepressants *n* (%)	21 (62)	21 (62)	42 (62)	0.00	1.00
	Antipsychotics *n* (%)	12 (35)	11 (32)	23 (68)	0.07	0.80
	Other *n* (%)	1 (3)	4 (12)	5 (7)	1.94	0.16
	No medication *n* (%)	3 (9)	2 (6)	5 (7)	0.22	0.6

Abbreviations: BD, bipolar disorder; IPSRT, Interpersonal and Social Rhythm Therapy; IPSRT-CR, Interpersonal and Social Rhythm Therapy with Cognitive Remediation; IQR, interquartile range; LIFE, Longitudinal Interview Follow-up Evaluation; MARS, Medication Adherence Rating Scale; MDD, major depressive disorder; NART, National Adult Reading Test; QIDS-C, Quick Inventory for Depressive Symptomatology – Clinician Rated; YMRS, Young Mania Rating Scale.

[a]Gender was determined by asking patients their gender as an open-ended question; all responded as male/female.

[b]Chi-squared test for proportion of mood disorder diagnoses between treatment arms used two categories, MDD vs BD.

[c]The LIFE assessed mood symptoms in the 6-month period prior to study intake.

TABLE 2 Cognitive remediation intervention dose and duration

CR variable	Group[a]	Mean (SD)	Median (IQR)[b]	Range
Length of CR treatment period (days) (from first to last CR session)	ITT Treatment completers	82.5 (50.4) 93.43 (47.7)	86.0 (47.3, 121.0) 110.0 (55.3, 130.0)	0–184 0–184
Length of CR treatment period (weeks) (from first to last CR session)	ITT Treatment completers	11.8 (7.2) 13.3 (6.8)	12.3 (6.8, 17.3) 15.7 (7.8, 18.6)	0–26.3 0–26.3
Total minutes spent on face-to-face CR	ITT Treatment completers	85.9 (74.2) 95.3 (76.2)	60.0 (42.5, 146.0) 67.5 (45.5, 156.8)	0–325 0–325
Number of therapy sessions over CR treatment period	ITT Treatment completers	7.2 (3.9) 8.1 (3.6)	8.0 (5.0, 11.0) 8.0 (6.0, 11.8)	0–12 0–12
Minutes per session spent on CR over treatment period	ITT Treatment completers	9.6 (6.3) 10.4 (6.3)	8.6 (5.5, 13.6) 9.8 (5.8, 14.9)	0–27 0–27
Number of sessions with focus on CR over treatment period[c]	ITT Treatment completers	6.5 (3.9) 7.3 (3.8)	6.0 (3.8, 10.3) 7.5 (5.0, 11.0)	0–12 0–12
Minutes per session spent on CR (in focussed CR sessions)[c]	ITT Treatment completers	10.5 (6.2) 11.4 (6.0)	10.0 (6.8, 15.2) 11.0 (7.8, 16.0)	0–27 0–27
Total minutes spent practising computerised exercises for homework	ITT Treatment completers	323.2 (383.1) 375.9 (401.3)	131.5 (81.0, 476.0) 238.5 (93.5, 576.5)	0–1531 0–1531

Abbreviations: CR, cognitive remediation; IQR, interquartile range; ITT, intention-to-treat analysis; SD, standard deviation.

[a]ITT, $n = 34$; treatment completers (18 or more therapy sessions), $n = 28$.

[b]Mean (SD) provided for ease of comparison with other CR studies, median (IQR) provided as data was not normally distributed.

[c]"Focused CR sessions' refers to sessions during the CR treatment period which were logged by therapists as spending at least some time during the session on CR (>1 min).

to follow-up (18 months) in the IPSRT vs IPSRT-CR group ($F_{1,65} = 3.7$, $p = 0.06$, $d = 0.47$).

3.6 | Impact of diagnosis

A trend was found for the interaction between treatment arm and mood diagnosis (MDD vs BD) for Global Cognition between baseline and 12 months ($F_{1,64} = 4.1$, $p = 0.05$). Post-hoc analysis in BD and MDD groups separately showed a trend effect for Global Cognition improving in patients with BD randomised to IPSRT-CR vs IPSRT ($F_{1,40} = 3.9$, $p = 0.06$), and no significant change in Global Cognition for patients with MDD randomised to IPSRT-CR vs IPSRT ($F_{1,24} = 1.0$, $p = 0.3$).

Of all secondary outcome variables at treatment-end and follow-up time-points, only one produced a significant treatment by diagnosis interaction; change in GMLT delayed recall from baseline to treatment-end ($F_{1,64} = 4.3$, $p = 0.04$). Within the BD group, those randomised to IPSRT-CR improved in GMLT delayed recall while those randomised to IPSRT worsened on this task; again, this was a trend effect ($F_{1,40} = 3.7$, $p = 0.06$). GMLT delayed recall did not change differentially for patients with MDD in IPSRT-CR vs IPSRT arms ($F_{1,24} = 1.3$, $p = 0.3$).

3.7 | Dose of cognitive remediation

No significant correlations were found when examining associations between the primary outcome (Global Cognition) and time spent on CR in therapy sessions or outside of therapy sessions.

3.8 | Adverse events

No serious adverse events were deemed to be related to study interventions. Two participants required psychiatric hospitalisation over the intervention period (one from each treatment arm) and one participant underwent cardiac surgery. There were no deaths over the intervention period.

4 | DISCUSSION

In this pragmatic RCT, IPSRT-CR did not significantly improve the primary outcome, Global Cognition, more than IPSRT alone. In fact, significantly greater improvement in psychosocial functioning (SAS) and longitudinal depression symptoms (LIFE) was evident in the IPSRT group compared with the IPSRT-CR group at treatment-end (12 months). This difference between treatment groups in

TABLE 3 Mean change scores[a] and effects of therapy on primary and secondary outcomes at 12 and 18 months

	Baseline to 12 months					Baseline to 18 months				
	IPSRT-CR	IPSRT				IPSRT-CR	IPSRT			
	Mean (SEM)	Mean (SEM)	*F*	*p*	*d*[b]	Mean (SEM)	Mean (SEM)	*F*	*p*	*d*[b]
Objective cognitive function[c]										
Global cognition	0.03 (0.1)	−0.03 (0.1)	0.3	0.6	0.12	0.03 (0.1)	−0.03 (0.1)	0.5	0.5	0.10
RAVLT total learning (List A 1–5)	−1.14 (1.1)	−4.71 (1.5)	2.5	0.1	0.47	0.76 (1.3)	0.18 (1.1)	0.2	0.6	0.08
RAVLT List B	0.47 (0.4)	−0.74 (0.4)	**4.4**	**0.04**	**0.52**	0.18 (0.2)	−0.21 (0.3)	1.1	0.3	0.26
RAVLT immediate recall (List A 6)	−0.83 (0.4)	−1.03 (0.4)	0.1	0.8	0.08	−0.38 (0.3)	−0.06 (0.5)	0.2	0.6	0.13
RAVLT delay recall (List A 7)	−0.91 (0.4)	−1.10 (0.5)	0.0	0.9	0.07	−0.32 (0.4)	0.06 (0.4)	0.5	0.5	0.16
GMLT total learning (trial 1–4)	3.90 (2.6)	0.17 (2.5)	0.6	0.4	0.25	6.21 (1.8)	−0.79 (1.8)	**6.5**	**0.01**	**0.67**
GMLT delay recall (trial 5)	−0.07 (0.7)	−0.26 (0.7)	0.0	0.9	0.05	−0.07 (0.5)	0.08 (0.5)	0.0	0.8	0.05
COWAT (total words)	−0.23 (1.4)	0.29 (1.9)	0.1	0.7	0.05	4.23 (1.3)	3.55 (1.9)	0.0	0.9	0.07
Category Fluency (total words)	0.53 (1.9)	−3.10 (1.5)	1.5	0.2	0.36	1.14 (1.1)	−0.74 (1.5)	1.7	0.2	0.25
Category Switching (total switches)	2.26 (0.6)	2.14 (0.7)	0.0	0.9	0.03	0.38 (0.8)	0.59 (0.5)	0.0	0.9	0.05
Digit Span (forwards)	0.18 (0.3)	0.11 (0.2)	0.1	0.7	0.05	0.59 (0.3)	−0.12 (0.3)	3.4	0.07	0.41
Digit Span (backwards)	0.32 (0.4)	0.17 (0.3)	0.0	0.9	0.32	0.21 (0.2)	0.50 (0.2)	0.7	0.4	0.25
Timed chase test (total correct moves)	−2.80 (1.2)	−1.00 (0.9)	0.8	0.4	0.29	−0.26 (1.1)	−0.88 (1.2)	0.7	0.4	0.09
Subjective cognitive function										
COBRA	3.25 (1.2)	3.64 (1.2)	0.1	0.8	0.06	4.02 (1.3)	4.44 (1.2)	0.1	0.8	0.06
General functioning										
FAST	−0.59 (2.2)	4.57 (2.1)	2.8	0.1	0.41	−1.57 (2.3)	4.59 (2.2)	3.7	0.06	0.47
SAS	0.09 (0.1)	0.34 (0.1)	**5.0**	**0.03**	**0.43**	0.20 (0.1)	0.35 (0.1)	1.7	0.2	0.26
Mood disturbance										
LIFE depression score (previous 6 months)	0.53 (0.2)	1.23 (0.2)	**4.3**	**0.04**	**0.60**	0.83 (0.2)	1.14 (0.2)	0.9	0.4	0.27
LIFE affective disturbance (previous 6 months)	0.57 (0.3)	1.20 (0.2)	3.0	0.08	0.42	0.77 (0.2)	1.15 (0.2)	1.2	0.3	0.33

Abbreviations: COBRA, Cognitive Complaints in Bipolar Disorder Rating Assessment; COWAT, Controlled Oral Word Association Test; FAST, Functional Assessment Short Test; GMLT, Groton Maze Learning Test; IPSRT, Interpersonal and Social Rhythm Therapy; IPSRT-CR, Interpersonal and Social Rhythm Therapy with Cognitive Remediation; LIFE, Longitudinal Interview Follow-up Evaluation; RAVLT, Rey Auditory-Verbal Learning Test. Bolded values indicate those comparisons between IPSRT-CR and IPSRT groups with p -values < 0.05

[a]Change scores were calculated so that a positive change score reflects improvement from baseline.

[b]Cohen's d effect size.

[c]Except for Global Cognition (change z score), change scores on individual cognitive variables use raw values from tests.

psychosocial and longitudinal depression symptoms was no longer significant at follow-up (18 months).

4.1 | Dilution of the effect of Interpersonal and Social Rhythm Therapy

This finding is important since it may otherwise be assumed that adding an extra complementary component to a psychotherapy would improve, or at least not impair, the effects of that psychotherapy. Indeed, we predicted that IPSRT and CR would be complimentary based on research suggesting an association between sleep disruption and cognitive impairment in BD,[20,21] and evidence for the relationship between cognition and functioning and relapse.[7,8] However, there was a significant reduction of positive effects of IPSRT on longitudinal depression symptoms and psychosocial functioning when IPSRT was combined with CR. This is notable since it is uncommon to report differences in head-to-head comparisons of psychological therapies.[45]

There are several possible explanations of this finding. First, the combined IPSRT-CR treatment arm may have reduced therapy focus by requiring individuals to follow two therapy frameworks. Second, merging CR into IPSRT sessions may have reduced the amount of time available to focus on IPSRT strategies. However, our data show no difference in total time spent focussed on IPSRT between treatment arms and therefore does not support this explanation. Third, the focus on cognitive functioning at a time when patients were relatively unwell may be counterproductive. Despite recent discharge from specialist mental health services, 43% of patients were still 'in episode' when entering this trial according to the SCID-5 interview. It is of note that IPSRT may be more effective when delivered in a more acute phase[22] and introducing a second component of therapy at this point may have reduced this efficacy at a crucial stage. Therapists noted that it was difficult to incorporate CR when patients were still unwell and indeed we made the decision to terminate the study for this reason, prior to achieving the stated recruitment target. The severity of mood symptoms in this sample at baseline relates to an issue of early discharge from mental health services. In New Zealand, secondary mental health services are under significant pressure and discharge patients back to primary care at an early stage following acute stabilisation or sometimes even following an early but incomplete improvement. Early discharge in this case, however, may also relate to referring clinicians from secondary mental health services being aware of the fact that patients would receive ongoing specialist treatment as part of this trial.

4.2 | Limited pro-cognitive effects

There was no significant benefit of IPSRT-CR compared with IPSRT on the primary outcome (Global Cognition). A small number of individual cognitive test variables either improved significantly in the IPSRT-CR vs IPSRT group at treatment-end (RAVLT distractor list recall) or follow-up (GMLT total learning), or showed an advantage for IPSRT-CR over IPSRT with a moderate effect size but not statistically significant difference at treatment-end (Category Fluency, Digit Span Backwards) or follow-up (Digit Span Forwards). While we are cautious in interpreting these individual findings due to the possibility of Type I error, it is of note that all of the above cognitive measures assess aspects of working memory or executive function, which are domains that have shown sensitivity to CR interventions in BD[13,14] and MDD.[15,46] We have not applied a correction for multiple comparisons since the examination of individual cognitive variables was exploratory. We note that had such a correction been applied these results would no longer have been significant, although the small sample size also limits our ability to detect true effects.

There are several possible reasons for limited pro-cognitive effects of the IPSRT-CR intervention.

1. *Dose of CR*: individuals randomised to IPSRT-CR received a lower dose of CR than in previous positive studies (mean total of 7 h of face-to-face and homework practice in the current study vs a minimum of 20 h in Strawbridge et al.[13] and an average of 21 h in Ott et al.[14]). The dose of CR was larger (8 h total) in our analysis of treatment completers. There are no published comparative 'dosing' studies of cognitive interventions in MDD,[29] nor has duration of training been considered in analyses. However, effective programmes for participants with MDD have entailed a wide range of sessions, from 6 to 64.[46] It is also of note that in schizophrenia, meta-analysis has shown that low dose (an average of 7 sessions of CR) appears to have similar pro-cognitive effects to high dose (an average of 33 sessions of CR).[47] With regards to duration of CR interventions, there is a general recommendation in BD for cognitive psychological interventions to be administered for 10–21 weeks, which is line with the mean duration of treatment in the current study (11–12 weeks).
2. *Screening for cognitive impairment*: The ISBD Targeting Cognition Task Force[9] recommends screening for objective cognitive impairment in CR trials based on the knowledge that individuals with the most severe cognitive impairment are likely to benefit most from CR.[48,49] However, we chose not to enrich our sample for objective cognitive impairment for a number of reasons. First, this

was a pragmatic RCT, with the intention of translating interventions into clinical practice if findings were positive. It would not be feasible for community mental health services in New Zealand to complete objective cognitive assessments for screening. Second, recent research suggests that improved cognitive and functional outcomes from CR interventions can occur even for those without objective cognitive scores below particular norm values.[13] Last, screening for subjective cognitive impairment, as we did in the current trial, may result in a sample of individuals who are more motivated to participate in a cognitive intervention. We note, however, that there is a generally poor relationship between subjective and objective cognitive function in mood disorders,[50,51] meaning that patients with greater subjective cognitive difficulties may not display the most severe objective impairment. Thus, while patients in this trial were experiencing subjective cognitive difficulties, a proportion may not have displayed objective cognitive impairment at baseline, leading to difficulties demonstrating improvement in cognition.

3. *Active control intervention*: the current trial involved a very active control intervention (IPSRT), which has been shown to positively impact on mood disturbance and functioning,[23,24] and more preliminarily so, to aspects of cognitive function.[49] Utilising a non-active control intervention that does not produce behaviour change associated with a cognitively-enriched environment (eg, treatment-as-usual) may have resulted in stronger pro-cognitive effects.
4. *Mixed diagnostic sample*: we chose to recruit individuals with MDD or BD into the trial to be able to produce a more generalisable sample of relevance to community mental health services in New Zealand. We note, however, that most CR trials in mood disorders to date have recruited either BD or MDD samples. It is possible that having a mixed diagnostic sample may have diluted any findings specific to BD or MDD. Indeed, we found a trend-level interaction between diagnosis type (MDD, BD) and treatment arm (IPSRT-CR, IPSRT), which was driven by the BD group showing greater improvement in Global Cognition when randomised to IPSRT-CR vs IPSRT, while treatment arm did not impact on Global Cognition in the MDD group.
5. *Timing of 'treatment-end' assessment*: the treatment-end assessment point often occurred 5–6 months after completion of the CR aspect of the intervention in the IPSRT-CR group, which essentially reflects a durability effect.

4.3 | Strengths and limitations

This trial is the first RCT to examine CR in combination with a structured psychological therapy in individuals with mood disorders. We note that our study design is consistent with a number of recent ISBD taskforce recommendations for CR trials[9] including: (1) selection of Global Cognition as the primary outcome, (2) inclusion of a functional measure as a secondary outcome, (3) exclusion of patients with current substance or alcohol use disorders, neurological disease or unstable medical illness. Patients were recruited at a specific point in their recovery (on discharge from specialist mental health services), which is consistent with the Research Domain Criteria Initiative. The use of the LIFE as our measure of longitudinal mood disturbance, rather than assessing mood symptoms cross-sectionally at each assessment point, was also a strength of this trial. Other notable strengths include high retention rate of participants and blinding of assessment researchers.

Over and above the specific issues outlined above in explaining lack of pro-cognitive effects of CR (lower CR dose, active control intervention, and timing of follow-up assessment), the most notable limitation is the fact that this trial was discontinued early, and was thus underpowered. The trial was stopped because of clinical concerns regarding the loss of focus on IPSRT as a result of introducing CR at a point at which many patients were still in episode and requiring acute stabilisation of mood. Second, with regards to cognitive screening, the ISBD taskforce on cognition recommends screening for both objective and subjective cognitive impairment in clinical trials of cognitive interventions.[9] However, various approaches could be used to categorise an individual as 'objectively cognitively impaired',[1,52] and consensus regarding a specific definition has not been reached. We opted to use a brief subjective assessment of cognitive impairment as the screening method in this trial due to our focus on being able to translate interventions to clinical practice and to allow those with subjective cognitive impairment the opportunity to benefit from CR. We acknowledge, however, that subjective cognitive impairment may be more influenced by clinical characteristics such as depression severity and chronicity than objective cognitive impairment.[53] Third, although recruiting individuals across the mood disorder spectrum can be seen as a strength of the study from a translatability perspective, having a sample with varied mood disorder diagnoses, and at different stages of remission, could obscure more specific effects that CR has on particular presentations (eg, individuals with BD in the euthymic phase). Fourth, while not statistically significant, a higher drop-out rate was observed in the IPSRT-CR ($n = 6$) vs IPSRT ($n = 2$) groups, which may have affected outcomes. Reasons for drop-out appeared to be unrelated to therapy.

5 | CONCLUSIONS

While the addition of CR to standard IPSRT did not improve Global Cognition, it appears that it reduced the effectiveness of IPSRT in addressing mood and functioning outcomes, although by 18 months there was no difference between groups. The results highlight an important issue – that combining two interventions targeting different outcomes may impair the therapeutic effects of one of the interventions. Adding targeted cognitive intervention to an evidence-based psychological therapy to improve long-term recovery may still have value for individuals with mood disorders, particularly when patients have achieved remission and when CR is delivered separately from individual therapy sessions. This is the focus of a current RCT underway (ANZCTR: ACTRN12619001080112) examining group-based CR in addition to IPSRT.

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AUTHOR CONTRIBUTIONS

KD is the principal investigator and has been involved in all aspects of study conception and design. RP, MC, MI, JJ, and CL are co-investigators and have contributed to study design. CL provides Māori health advice and supervision. KD, MC, MI, JJ, RP and CB provided expertise in the design of IPSRT and CR interventions. KD, MC, MI, JJ, DC, and HW delivered therapy and BB, CL, RM, SL, KE and RP were treating psychiatrists. CF and RP provided statistical expertise and KD and SG completed data analysis. KD and RP have drafted this paper, but all authors have edited and critically reviewed the paper for intellectual content and approved the final version.

CONFLICT OF INTEREST

KD, CB, and RP use software provided free-of-charge by Scientific Brain Training Pro for Cognitive Remediation trials. RP has received support for travel to educational meetings from Servier and Lundbeck. CB has grant support from Lundbeck, Takeda, and Pfizer and has recevied consulting fees from Boehringer Ingelheim, Pfizer, Lundbeck.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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