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Predicting Cognitive Change During Treatment for Inpatient Depression: Secondary Analysis From a Randomized Controlled Trial

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ABSTRACT

Introduction: Individuals hospitalized with depression are particularly impacted by cognitive impairment. Identifying variables that predict improvements in cognition across treatment may inform more targeted and effective treatment approaches. We conducted secondary analyses to investigate baseline predictors of objective cognitive change in a severely depressed inpatient sample.

Methods: A randomized controlled trial (RCT) comparing 2 weeks of Activation Therapy (AT; Cognitive Activation combined with Behavioural Activation) with treatment-as-usual (TAU) was conducted in inpatients with major depression. Research assessments were conducted at baseline (on admission) and at 14 weeks (12 weeks after treatment-end).

A series of analyses of covariance models were conducted to examine associations between change in executive functioning/attention, verbal learning and memory, visuospatial learning and memory, and psychomotor speed, in global cognition, and a range of putative baseline predictor variables (e.g., demographic, mood, cognition, general functioning, childhood trauma) across the whole RCT sample. Treatment arm was included as a fixed factor in all models. Sensitivity analyses were run in the AT group only to examine predictors of cognitive change in those receiving this targeted cognitive treatment.

Results: Sixty-eight individuals completed baseline and follow-up cognitive testing assessments in the RCT (AT, $n = 32$, TAU, $n = 36$). Significantly poorer domain-specific baseline cognitive functioning was associated with greater cognitive improvement in all four domains. Older age was associated with less cognitive change in verbal learning and memory, visuospatial learning and memory, psychomotor speed, and global cognition. Sensitivity analyses (AT group only) identified these same factors as significant predictors.

Conclusion: Age and domain-specific baseline cognitive performance were consistently associated with cognitive change in this RCT. Findings suggest that cognition seems to recover better in younger inpatients with poorer baseline cognitive functioning.

Clinical Registration: Australian New Zealand Clinical Trials Registry [ANZCTR], ACTRN12617000024347p.

Summary

- Significant outcomes
  - Age and baseline objective cognitive functioning were identified as significant predictors of cognitive change in inpatients being treated for depression.
  - Younger inpatients with poorer baseline cognitive functioning showed improved verbal learning and memory with the targeted cognitive treatment (Activation Therapy [AT]).
  - The finding of baseline cognitive functioning as a significant predictor was consistent with the existing literature, while the significant finding of age is a novel finding.
- Limitations
  - The study may have been underpowered to identify predictors with small effects.
  - The sample predominantly comprised individuals with very severe depression, limiting variability across potential clinical predictors.

1 | Introduction

Depression is pervasive worldwide and highly disabling [1, 2]. Impairment in cognitive functioning is acknowledged as a key feature of major depressive episodes (MDE), as part of major depressive disorder (MDD) or bipolar disorder (BD) presentations [3, 4]. Cognitive domains affected in depression can include executive functioning, sustained attention, learning and memory, and psychomotor speed [5]. The extent of cognitive impairment within each domain may range from no impairment to severe impairment [6] and may differ depending on whether it is assessed objectively (neuropsychological testing) or subjectively (self-report questionnaires). However, when impairment is present, it negatively impacts an individual's functioning in workplace and academic performance, as well as psychosocial functioning and interpersonal relationships [7, 8].

Those hospitalized for depression represent a subgroup particularly impacted by high levels of ongoing morbidity and impaired cognitive functioning [9, 10]. There is minimal research examining treatment for cognitive impairment in the depressed inpatient population. However, there is a clear need for such studies given the prevalence and severity of cognitive impairment in this group, and the limitations of current treatment, which tends to focus on safety and crisis stabilization, primarily with the use of medication [11]. Identifying variables that predict cognitive change has been suggested as a potential way to improve outcomes for patients, through the identification of those who may benefit most and the targeting of treatment. We recently conducted a systematic review examining predictors of cognitive change during the treatment of MDE in 24 identified studies [12]. Preliminary evidence for both baseline depression severity and baseline severity of cognitive impairment in predicting cognitive change was found, and limited evidence for other clinical and biological factors [12]. Few studies in this review utilized an inpatient sample ($k = 3$ of 24), or a sample with very severe depression, meaning little is known about potential predictors of cognitive change in this group [12].

We conducted a randomized controlled trial (RCT), comparing 2 weeks of Activation Therapy (AT), a combination of Behavioural Activation and Cognitive Activation, with treatment-as-usual (TAU), in an inpatient setting [13]. Cognitive Activation is an intervention aimed at improving cognitive functioning through repeated practice of exercises that target specific cognitive skills and is often supported by coaching of problem-solving strategies [14, 15]. Cognitive Activation is typically a component of broader Cognitive Remediation (CR) interventions. CR has good evidence to demonstrate efficacy in schizophrenia, with more recent research supporting its use in other psychiatric disorders, such as depression [16, 17]. As described in the primary outcomes paper [13], for intention-to-treat analysis, the AT treatment arm improved significantly more than the TAU arm on objectively measured verbal learning and memory between baseline and 14-week follow-up ($F_{(1,93)} = 4.30$, $p = 0.04$, $d = 0.42$). There was no significant difference between treatment arms for the remaining cognitive domains. This secondary analysis explores potential predictors of objective cognitive change in a severely depressed inpatient sample. Based on our systematic review [12], we hypothesized that poorer baseline objective cognitive performance would predict greater cognitive improvement. Other variables (e.g., age, premorbid IQ, gender, illness duration, depression severity, childhood trauma) were included based on theoretical and empirical relevance to cognitive functioning in mood disorders, with the a priori hypotheses that they may also influence cognitive change.

2 | Methods

2.1 | Study Details

Full study details are available in the study protocol paper [18] and primary outcomes paper [13]. The study was an RCT, comparing an intensive, 2-week course of AT with TAU. Ninety-seven inpatients with a primary diagnosis of MDE (unipolar or bipolar) were randomized. Inpatients completed measures of cognitive functioning, general functioning, and mood at baseline and at 14-week follow-up (12 weeks after treatment-end, described below).

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 2013. All procedures involving patients were approved by the New Zealand Health and Disability Ethics Committees (Northern B; reference [18]/NTB/75) and all participants provided written informed consent.

2.2 | Participants

Inpatients were approached by ward staff within 2 days of admission. Recruitment occurred at four adult inpatient mental health services across the South Island of Aotearoa New

Zealand. Eligibility criteria included: a primary DSM-5 diagnosis of MDE (unipolar or bipolar), aged between 18 and 65 years; computer literate; able to complete questionnaires and therapy in English; and able and willing to provide informed consent. Exclusion criteria were: a primary diagnosis of schizophrenia; current severe substance or alcohol misuse; a serious comorbid endocrinological, neurological, or chronic medical condition known to impact cognitive functioning; previous severe head injury (loss of consciousness for more than 1 h); pregnancy; or completion of a course of CR in the prior 24 months.

2.3 | Measures

A demographic questionnaire was administered to inpatients at baseline. The National Adult Reading Test (NART; [19]) was administered at baseline to obtain estimated premorbid verbal IQ.

2.3.1 | Cognitive Functioning

Cognitive measures were administered by a trained Research Nurse (independent to study therapist and blinded to randomization). With consideration of recommendations by the International Society for Bipolar Disorders (ISBD) Targeting Cognition Task Force [20], objective cognitive functioning outcomes from baseline to follow-up were measured as changes in "Global Cognition" a composite score comprised of all tests completed by participants. The cognitive tests were additionally grouped into cognitive domains as detailed below. Supporting Information Data S1 contains details of the variables extracted from the cognitive tests for calculation of domain and global scores.

2.3.2 | Executive Functioning and Attention

- Trail Making Test Part B (TMT-B; [21])
- Category Fluency and Switching [22]
- Digit Span Forward and Backwards [23]
- Stroop Colour-word Test (Trials 3 and 4; [24])

2.3.3 | Verbal Learning and Memory

- The Rey Auditory Verbal Learning Test (RAVLT; [25])

2.3.4 | Visuospatial Learning and Memory

- Brief Visuospatial Memory Test Revised (BVMT-R; [26])

2.3.5 | Psychomotor Speed

- Trail Making Test Part A (TMT-A; [21])
- Digit Symbol Substitution Test (DSST; [23])
- Stroop Colour-word Test (Trials 1 and 2 [24];)

The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA; [27]) was included as a self-report measure of subjective cognitive functioning in mood disorders.

2.3.6 | Daily Functioning

The clinician-administered Functioning Assessment Short Test (FAST) and self-report Quality of Life in Bipolar Disorder (QoL.BD) were administered as measures of general functioning and quality of life.

2.3.7 | Clinical Measures

The Structured Clinical Interview for the DSM-5 Research Version (SCID-5-RV) was administered by a trained Research Nurse to confirm mood disorder diagnosis and to screen for other DSM-5 mental disorders. To assess depression severity, the clinician-administered Montgomery Åsberg Depression Rating Scale (MADRS) and self-report Beck Depression Inventory, Second Version (BDI-II) were administered. To measure activation levels, patients completed the self-report Behavioural Activation for Depression Scale Short Form (BADS-SF; [28]). An "activation composite" score was calculated based on items from the MADRS and BDI-II, as suggested by Uher et al. [29]. The Childhood Trauma Questionnaire (CTQ) was administered as a self-report measure of childhood trauma.

2.4 | Predictor Variables

Predictor selection was informed by a combination of prior empirical findings and theoretical relevance to cognitive functioning in mood disorders. Baseline cognitive performance was included based on evidence that poorer functioning predicts greater improvement [30, 31]. Other variables, including age, estimated premorbid IQ, gender, and clinical illness characteristics (e.g., duration), were selected based on their established associations with cognitive functioning in mood disorders [6, 7], and on an a priori hypothesis regarding their potential to influence cognitive change over time, even if prior research has shown mixed evidence for their role as predictors of change [12].

Table 1 outlines the full list of variables included in the analyses, including a description of the variable composition. The putative predictors included: age, sex, estimated premorbid verbal IQ (NART score), clinician-rated depression severity (MADRS), self-rated depression severity (BDI-II), activation symptoms (BADS and activation composite), quality of life (QoL.BD), subjective general functioning (FAST), subjective cognitive complaints (COBRA), and self-reported childhood trauma, including physical and sexual abuse specifically (CTQ total, and subscales). Physical and sexual abuse were selected as these are most consistently associated with worse cognitive performance in mood disorders [32].

The following variables were analyzed as categorical measures:

TABLE 1 | Variables included in analysis of covariance analyses of baseline predictors of cognitive change.

Variable	Variable type	Description
Demographic		
Age	Continuous	Age in years
Sex	Categorical	Male or female
Education	Categorical	Binary variable created—"yes" or "no" to any tertiary education
Estimated verbal IQ	Continuous	NART score
Clinical factors		
Mood disorder diagnosis	Categorical	Unipolar or bipolar depression
Depression severity—clinician rated	Continuous	MADRS total score
Depression severity—self-rated	Continuous	BDI-II total score
Number of episodes	Categorical	Ternary variable created—"1 episode," "2–9 episodes," "10+ episodes"
Illness duration	Categorical	Binary variable created—illness duration "≤10 years" or "≥11 years"
Psychotic features	Categorical	Binary variable created—"yes" or "no" to any of the delusion or hallucination questions on the SCID-5-RV
Comorbid anxiety disorder	Categorical	Binary variable created—"yes" or "no" to any comorbid anxiety disorder identified on the SCID-5-RV
Activation symptoms	Continuous	BADS total score
Subjective functioning		
COBRA	Continuous	COBRA score
FAST	Continuous	FAST total score
Quality of life	Continuous	QOL.BD total score
Social functioning	Continuous	FAST interpersonal subtest score
Childhood trauma		
Childhood trauma	Continuous	CTQ total score
Childhood trauma—physical abuse	Continuous	CTQ physical abuse score
Childhood trauma—sexual abuse	Continuous	CTQ sexual abuse score

Abbreviations: BADS, behavioural activation for depression scale; BDI-II, beck depression inventory 2nd version; COBRA, cognitive complaints in bipolar disorder rating assessment; CTQ, childhood trauma questionnaire; FAST, functioning assessment short test; MADRS, montgomery-åsberg depression rating scale; NART, national adult reading test; QOL.BD, quality of life in bipolar disorder; SCID-5-RV, structured clinical interview for the diagnostic statistical manual of mental disorders 5 research version.

- Tertiary education was recorded as a binary variable, according to whether the patient had completed any tertiary education.
- Unipolar versus bipolar depression was recoded as a binary variable.
- Number of depressive episodes was recoded as a three-category variable, coded as either one episode, two to nine episodes, or 10 or more episodes.
- The presence of psychotic features as a binary variable
- Illness duration data was not normally distributed and was coded as a binary variable; "up to and including 10 years" (42.3% of the sample) and "11 years or longer."

Medication at baseline was initially considered for inclusion as a predictor variable, as evidence suggests that psychotropic medication can impact cognitive functioning in mood disorders [14]. However, in assessing this data, sample numbers were too small for analyses (e.g., only four participants in the AT group and seven in the TAU group were not prescribed an antidepressant). Furthermore, medications were strongly associated with diagnosis. For example, lithium would only be prescribed for inpatients with a BD diagnosis.

2.5 | Statistical Analysis

As the present paper examined predictors of change in cognitive functioning, only participants who completed both

baseline and follow-up cognitive testing were included in the analyses. Statistical analyses were conducted using IBM SPSS, version 27.0 for Windows. Change *Z* scores were calculated for each cognitive measure between baseline and 14-week follow-up (raw score difference from the mean of the full sample divided by the standard deviation of the full sample). Scores for each cognitive domain were calculated by averaging the relevant item variable *z* scores. The Global Cognition *z*-score was calculated by averaging the four cognitive domain z scores. A series of analysis of covariance (ANCOVA) models were run to assess the associations between change in each of the four cognitive domains and each of the putative predictor variables. For each ANCOVA, baseline cognitive functioning for the specific domain was included as a covariate and treatment arm (AT vs. TAU) was included as a fixed factor. All variables with a significance of $p < 0.15$ from the ANCOVA models were then entered into multivariate stepwise models for each cognitive domain. These models were repeated as forwards and backwards stepwise regressions including in the final model only factors that were significant at $p < 0.05$. To explore predictors that were more specifically related to the procognitive effects of AT, sensitivity analyses were conducted using the same process as above, but in the AT treatment group only.

3 | Results

Ninety-seven participants were recruited and randomized to AT ($n = 47$) or TAU ($n = 50$), with 68 participants completing both baseline and follow-up cognitive assessments (AT, $n = 32$; TAU, $n = 36$); see Supporting Information Table S1 for baseline, follow-up, and change *z* scores. Baseline demographic and clinical characteristics are presented in Table 2. The majority of the sample had a primary diagnosis of MDD (85%, 15% BD) and scores on the depression rating scales (MADRS and BDI-II) reflected "severe" depression (Table 2).

Table 3 presents the full list of variables included in the univariate ANCOVA analyses, including *F*-test and significance results. The subsequent stepwise models are described below by domain. The number of participants included in analyses ranged from 43 for CTQ data to 64 for basic demographic variables and MADRS data (see Table 3).

3.1 | Global Cognition

For global cognition, age was the only variable significantly associated with change in cognitive functioning. Older age was associated with less improvement in global cognition over time $F_{(1,56)} = 4.60$, partial $\eta^2 = 0.08$, $p = 0.04$. There was no significant effect of baseline global cognition. The interaction between group and baseline performance was nonsignificant ($p = 0.63$) indicating that the relationship between baseline functioning and cognitive change did not differ by treatment group.

In the sensitivity analysis models (AT treatment arm alone), older age was no longer significantly associated with less improvement in global cognition over time $F_{(1,27)} = 2.20$, partial $\eta^2 = 0.08$, $p = 0.15$.

3.2 | Executive Functioning and Attention

For this model, there was a significant effect of baseline executive functioning and attention: $F_{(1,59)} = 6.69$, partial $\eta^2 = 0.10$, $p = 0.01$, where poorer performance at baseline was associated with greater cognitive improvement. No other variables were significantly associated with change in executive functioning and attention. The interaction between group and baseline performance was nonsignificant ($p = 0.25$) indicating that the relationship between baseline functioning and cognitive change did not differ by treatment group.

In sensitivity analysis models with just the AT arm, poorer performance at baseline was again the only variable associated with greater cognitive improvement $F_{(1,29)}$ 16.10, partial $\eta^2 = 0.36$, $p < 0.001$.

3.3 | Verbal Learning and Memory

In the ANCOVA analyses, two variables were associated with change in verbal learning and memory: age, $F_{(1,60)} = 5.37$, partial $\eta^2 = 0.08$, $p = 0.02$; sex, $F_{(1,61)} = 3.36$, partial $\eta^2 = 0.07$, $p = 0.08$, and comorbid anxiety disorder, $F_{(1,59)} = 4.38$, partial $\eta^2 = 0.07$, $p = 0.04$. The multivariate model indicated that sex and anxiety were no longer significantly associated ($p = 0.23$ and 0.14, respectively), and age alone was independently associated with change in verbal learning and memory, where older age was associated with less improvement. Additionally, in this model, there was a significant effect of baseline verbal learning and memory: $F_{(1,60)} = 16.82$, partial $\eta^2 = 0.22$, $p < 0.001$, where poorer baseline performance was associated with greater improvement. The interactions between group and baseline performance and group and age were nonsignificant ($p = 0.67$ and 0.98, respectively), indicating that these relationships did not differ by treatment group.

Similarly, in the sensitivity analysis models with just the AT arm, there was a significant effect of baseline visuospatial learning and memory: $F_{(1,28)} = 11.57$, partial $\eta^2 = 0.29$, $p = 0.002$, where poorer baseline performance was associated with greater improvement. Older age was not significantly associated with change in visuospatial learning and memory over time, $F_{(1,28)} = 2.72$, partial $\eta^2 = 0.09$, $p = 0.11$.

3.4 | Visuospatial Learning and Memory

Age was significantly associated with change in visuospatial learning and memory, $F_{(1,60)} = 4.72$, partial $\eta^2 = 0.07$, $p = 0.03$, where older age was associated with less improvement. There was additionally a significant main effect of baseline visuospatial learning and memory: $F_{(1,60)} = 5.12$, partial $\eta^2 = 0.08$, $p = 0.03$, where poorer baseline performance was associated with greater improvement.

The interaction between group and baseline performance was significant: $F_{(1,60)} = 6.24$, partial $\eta^2 = 0.09$, $p = 0.02$. Follow-up regression analysis showed that in the TAU group, lower baseline visuospatial learning and memory predicted greater improvement ($\beta = -0.474$, $p = 0.004$), whereas in the AT group, no significant relationship was observed ($\beta = 0.102$, $p = 0.58$). The interaction between group and age was nonsignificant ($p = 0.56$).

TABLE 2 | Demographic and clinical characteristics at baseline.

Variable	Labels	All ($n=68$)	AT ($n=32$)	TAU ($n=36$)
Age (years)	Mean (SD)	37.44 (14.06)	38.06 (14.06)	36.89 (14.23)
Gender	Female, *n* (%)	27 (40)	14 (56)	13 (36)
	Male *n* (%)	41 (60)	18 (44)	23 (64)
Estimated verbal IQ (NART)	Mean (SD)	108.53 (6.97)	110.10 (7.23)	107.23 (6.57)
Education (years)	Secondary, mean (SD)	4.25 (1.46)	4.25 (1.85)	4.25 (1.03)
	Tertiary, mean (SD)	1.94 (1.94)	2.27 (1.86)	1.67 (2.00)
Employment	Employed *n* (%)	32 (48)	16 (52)	16 (44)
	Unemployed *n* (%)	35 (52)	15 (48)	20 (56)
Ethnicity	NZ European *n* (%)	44 (65)	20 (63)	24 (67)
	Māori *n* (%)	13 (19)	5 (16)	8 (22)
	Other *n* (%)	11 (16)	7 (21)	4 (11)
Primary diagnosis	MDD *n* (%)	58 (85)	28 (88)	30 (84)
	BD *n* (%)	10 (15)	4 (12)	6 (16)
	BD I *n* (%)	5 (7)	2 (6)	3 (8)
	BD II *n* (%)	5 (7)	2 (6)	3 (8)
Depression symptom, MADRS	Median (IQR)	40.00 (12)	40.00 (9.5)	38 (12.75)
Depression symptoms, BDI-II	Median (IQR)	42.00 (17.25)	44.00 (16.75)	40.50 (17.75)
Illness duration (years)	Median (IQR)	14.00 (19.0)	15.50 (14.75)	12.00 (22)
Mood disorder onset (age in years)	Median (IQR)	16.00 (10.5)	16.50 (11.5)	16.00 (8)
Single or recurrent depression	Single *n* (%)	9 (15)	2 (7)	7 (23)
	Recurrent *n* (%)	49 (85)	25 (93)	24 (77)
Number of previous MDEs	Median (IQR)	3 (3)	3 (3)	3 (4)
	"Too many to count" *n*	27	12	15
Psychotic symptoms	Yes *n* (%)	23 (34)	14 (45)	9 (25)
	No *n* (%)	44 (66)	17 (55)	27 (75)
Medication type	Anticonvulsants *n* (%)	9 (13)	4 (13)	5 (14)
	Antidepressants *n* (%)	60 (90)	30 (94)	30 (86)
	Antipsychotics *n* (%)	39 (58)	19 (59)	20 (57)
	Anxiolytics *n* (%)	57 (85)	28 (88)	29 (83)
	Lithium *n* (%)	4 (6)	2 (6)	2 (6)

Abbreviations: BD, bipolar disorder; BDI-II, beck depression inventory, 2nd version; IQR, interquartile range; MADRS, montgomery-åsberg depression rating scale; MDD, major depressive disorder; MDE, major depressive episode, NART, national adult reading test; SD, standard deviation.

In the sensitivity analysis models with just the AT arm, age and baseline visuospatial learning and memory were no longer significant ($p=0.25$ and 0.87, respectively).

3.5 | Psychomotor Speed

Change in psychomotor speed was significantly associated with age, $F_{(1,58)}=7.68$, partial $\eta^2=0.12$, $p=0.008$, and tertiary education, $F_{(1,58)}=2.99$, partial $\eta^2=0.05$, $p=0.09$, where having tertiary education was associated with less improvement. The multivariate model indicated that tertiary education did not reach significance ($p=0.07$), and age alone was independently associated with change in psychomotor speed, where older age was associated with less improvement. Additionally, in this model, there was a significant main effect of baseline psychomotor speed: $F_{(1,58)}=22.66$, partial $\eta^2=0.28$, $p<0.001$, where poorer performance was associated with greater improvement.

Similarly, in the sensitivity analysis models with just the AT arm, a change in psychomotor speed was significantly associated with

TABLE 3 | Analysis of Covariance *F*-test and significance outcomes for first round models of predictors of cognitive change for the patient sample ($N = 68$).

		Global		EFA		VLM		VSLM		PS	
Predictor variable	***n***	F^a	p^a	F^a	p^a	F^a	p^a	F^a	p^a	F^a	p^a
Demographic											
Age	64	**4.60**	**0.04**	1.64	0.21	**5.37**	**0.02**	**4.72**	**0.03**	**7.68**	**0.008**
Sex	64	1.19	0.28	0.80	0.11	**3.36**	**0.07**	1.53	0.22	0.59	0.45
Tertiary education	64	0.85	0.36	0.58	0.45	0.99	0.32	0.09	0.77	**2.99**	**0.09**
Estimated verbal IQ	60	0.86	0.36	1.15	0.29	1.48	0.23	1.98	0.17	0.60	0.44
Clinical factors											
Depression severity—clinician rated	64	0.22	0.64	0.00	0.97	0.30	0.59	1.39	0.24	0.06	0.81
Depression severity—self-rated	62	0.45	0.51	1.52	0.22	0.76	0.39	0.02	0.89	0.47	0.50
Number of episodes	63	0.57	0.57	1.16	0.29	0.46	0.63	0.13	0.72	1.35	0.27
Illness duration	62	0.16	0.69	0.01	0.93	0.57	0.42	1.95	0.17	0.30	0.59
Psychotic features	64	0.53	0.47	0.07	0.80	0.22	0.64	0.10	0.75	1.84	0.18
Comorbid anxiety disorder	63	1.82	0.18	0.99	0.33	**4.38**	**0.04**	1.64	0.21	0.56	0.46
Activation symptoms	62	0.02	0.89	0.51	0.48	0.05	0.83	0.00	0.96	0.01	0.92
Activation composite	63	0.01	0.93	0.25	0.62	1.11	0.30	0.56	0.46	0.00	0.97
Mood disorder diagnosis	64	0.01	0.93	0.75	0.39	0.01	0.95	0.41	0.52	0.28	0.60
Subjective functioning											
COBRA	62	0.33	0.57	0.73	0.40	0.34	0.56	0.02	0.90	0.04	0.85
FAST	64	0.07	0.79	1.07	0.30	0.29	0.59	0.19	0.66	0.00	0.99
Quality of life	62	0.07	0.80	0.10	0.75	0.00	0.99	0.66	0.42	0.03	0.86
Other											
Childhood trauma	43	0.39	0.54	0.55	0.46	0.06	0.81	0.66	0.42	0.05	0.83
CT Physical abuse	44	0.87	0.36	0.55	0.46	0.44	0.51	0.63	0.43	0.04	0.84
CT Sexual abuse	43	0.14	0.71	0.03	0.87	0.21	0.65	0.43	0.51	0.05	0.83

Note: If $p \leq 0.15$, proceed to next model.
Abbreviations: CT, childhood trauma; EFA, executive functioning and attention; PS, psychomotor speed; VLM, verbal learning and memory; VSLM, visuospatial learning and memory.
[a]Univariate ANCOVAs, fixed factor randomisation, covaried for baseline performance on respective cognitive domain.

age, $F_{(1,28)} = 4.89$, partial $\eta^2 = 0.15$, $p = 0.04$, where older age was associated with less improvement, while poorer baseline psychomotor speed predicted greater improvement: $F_{(1,28)} = 14.60$, partial $\eta^2 = 0.34$, $p < 0.001$.

4 | Discussion

4.1 | Summary of Findings

Age and domain-specific baseline cognitive performance were consistently associated with cognitive change across most domains from baseline to 14-week follow-up in this study of patients admitted to hospital for depression. For global cognition, verbal and visuospatial learning and memory, and psychomotor speed, older age was significantly associated with less cognitive improvement following treatment. Except for global cognition, poorer baseline cognitive performance on the respective cognitive domain was associated with greater improvement within the cognitive domain. Effect sizes for significant predictors ranged from medium to large (partial $\eta^2 = 0.08$–0.29), indicating clinically meaningful associations between baseline characteristics and cognitive change.

To maximize power, main analyses were conducted across the whole study group (AT and TAU combined), identifying baseline predictors of cognitive change with treatment for acute, inpatient depression. When considering predictors of cognitive change more specifically within the AT group, sensitivity

analyses showed that domain-specific baseline cognitive performance remained a significant predictor in several domains, while the effect of age was less consistent. These differences may reflect reduced statistical power in subgroup analyses. Overall, baseline cognitive functioning appears to be a more robust and reliable predictor of response to targeted cognitive training therapies than age.

4.2 | Baseline Objective Cognitive Functioning as a Predictor of Cognitive Change

Building on these overall findings, we examined individual predictors, beginning with baseline objective cognitive functioning. This variable has been consistently associated with cognitive change in studies in mood disorders in both CR and medication trials, with greater cognitive impairment associated with greater improvement evident for patients both in-episode and in euthymia (e.g., [30, 31, 33]). In the present study, baseline cognitive functioning for each domain was therefore included in all the predictor models. The results provided further supporting evidence for this association, as baseline cognitive functioning was significant for all domains in the main analysis and remained significant in several domains in sensitivity analyses.

The association between baseline objective cognitive functioning and cognitive change may be, in part, due to the inclusion of patients in the trial who were not cognitively impaired. Participants in the present study were not screened for cognitive impairment, and studies show that even in those with severe depression, a proportion are not cognitively impaired [6]. If inpatients were not impaired at baseline, there may be a "ceiling effect" whereby they have little room for improvement compared with inpatients who were cognitively impaired. An alternative explanation is regression to the mean in the context of random variation, where those inpatients with more extreme test scores at baseline have scores closer to average at follow-up.

Notably, a group by baseline interaction emerged for visuospatial learning and memory, where baseline performance predicted change in the TAU group but not the AT group. This finding suggests that, for this domain, the relationship between baseline performance and change may reflect group-specific mechanisms beyond general regression to the mean. For all other domains, the nonsignificant interaction terms indicate that baseline performance was similarly predictive across both groups, supporting a more general relationship between initial impairment and subsequent improvement.

4.3 | Age as a Predictor of Cognitive Change

Participant age also emerged as a consistent predictor of cognitive change across domains. This finding of older age being significantly associated with less improvement in cognitive functioning across domains in this study was somewhat surprising, given the lack of evidence for an association in the literature; our recent systematic review identified 11 studies examining age as a predictor of cognitive change during treatment of a current MDE, but only two studies found significant results [12]. The literature in schizophrenia does tend to show that older age is associated with less improvement following CR interventions [34–36].

One reason for age being associated with less cognitive change with treatment may be reduced neuroplasticity in older aged adults, and therefore less capacity for adaptation [37]. While evidence suggests changes in cognitive functioning in this group are still possible [37], in older participants, hippocampal atrophy or other neurobiological changes may limit improvement [38]. It is also possible that the association reflects illness chronicity rather than age itself. While duration and number of episodes were not significant in the current analysis, this may be due to limited power and the challenges of quantifying these variables.

4.4 | Childhood Trauma as a Predictor of Cognitive Change

Childhood trauma has been investigated as a potential predictor of cognitive change in just one study. Kinney-Huang et al. [39] found that childhood trauma was associated with poorer baseline cognitive performance, but not with cognitive change following treatment, as was also the case in the present study. The authors suggested that, given that childhood trauma is associated with poorer cognitive performance generally, there may be overlap between these variables, so those with greater severity of childhood trauma are already captured by including the effects of baseline cognitive functioning. There was additionally a loss of power for these analyses, as the CTQ was added as a measure partway during the study.

4.5 | Clinical Factors as Predictors of Cognitive Change

We also examined clinical characteristics, including depression severity, psychotic features, and diagnosis, as potential predictors of cognitive change. The finding that depression severity was not significantly associated with cognitive change is generally in line with the extant literature. Results are mixed across age groups, but for studies in adult samples (18–65 years), findings tended to be nonsignificant [31, 33, 40], and greater severity of depression is not necessarily associated with impaired cognitive functioning [6]. However, the present study has a narrow range of severity because only people with very severe depression are admitted to hospital, statistically limiting the likelihood that this will be predictive.

4.6 | Limitations

Taken together, these findings must be interpreted in light of several limitations. The study was underpowered to detect small effects, particularly for variables with few positive cases. Variables with fewer than 10 participants were excluded; for example, only seven patients reported no comorbid anxiety, so its effects were not analyzed. The final sample size was smaller than anticipated due to COVID-19 disruptions. The sample also primarily included patients with very severe depression, limiting variability across clinical predictors. Data on medication classes, dosages, and polypharmacy were not systematically

analyzed, despite their potential impact on cognition. Future research with detailed medication records is needed. Additionally, while the number of depressive episodes was included, other indicators of illness chronicity, such as psychiatric hospitalizations and manic episodes, in the small number of patients with BD, were not available, limiting the scope of chronicity-related analyses.

4.7 | Implications

These findings highlight the value of baseline cognitive assessment in inpatient settings to identify those most likely to benefit from cognitive interventions. Poorer baseline cognitive functioning consistently predicted improvement, supporting a personalized approach to cognitive training. The influence of age, though less consistent, suggests younger patients may experience greater benefit, with older adults potentially requiring adapted strategies. Differences by treatment group, particularly for visuospatial memory, indicate that predictors may vary by intervention type and warrant further study.

5 | Conclusions

This study identified younger age and poorer baseline objective cognitive functioning as significant predictors of cognitive improvement during inpatient treatment for an MDE. These findings generally align with previous literature regarding baseline cognitive functioning, while the finding of age as a significant predictor across several domains was more surprising based on previous study findings. Most hypothesized clinical predictors were not significantly associated with change, possibly due to power or that the sample was relatively homogeneous in terms of depression severity, thereby limiting the variability of clinical predictors.

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Ethics Statement

This study was approved by the New Zealand Health and Disability Ethics Committees (Northern B; reference [18]/NTB/75) on 01/06/2018. All procedures were conducted in accordance with the Declaration of Helsinki and institutional ethical standards.

Consent

All participants provided written informed consent prior to participation in the study.

Conflicts of Interest

K.D. and R.P. use software provided free-of-charge by Scientific Brain Training Pro for Cognitive Remediation trials. R.P. has received support for travel to educational meetings from Servier and Lundbeck.

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 can be found online in the Supporting Information section. **Data S1:** Variables extracted from the cognitive tests for calculation of domain and global scores. **Table S1:** Mean (SD) of Baseline, Follow-Up, and Change[a] *Z*-Scores for Cognitive Outcomes in Activation Therapy (AT; $N = 32$) and Treatment as Usual ($N = 36$) Groups.