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Research paper

Association between discrepancy in objective and subjective cognitive abilities and treatment response in patients with major depressive disorder: A CAN-BIND-1 study report

Katerina Rnic [a,*], Young-Eun Jung [b], Ivan Torres [c], Trisha Chakrabarty [c], Joelle LeMoult [a], Anthony L. Vaccarino [d], Emma Morton [c], Venkat Bhat [e], Peter Giacobbe [e], Shane McInerney [f], Benicio N. Frey [g], Roumen V. Milev [h], Daniel Müller [e], Arun V. Ravindran [e], Susan Rotzinger [e], Sidney H. Kennedy [e], Raymond W. Lam [c], On behalf of the CAN-BIND Investigator Team

[a] Department of Psychology, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada,
[b] Department of Psychiatry, College of Medicine, Jeju National University, Jeju 63241, Korea
[c] Department of Psychiatry, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada
[d] Indoc Research, Toronto, Ontario M5H 3W4, Canada
[e] Department of Psychiatry, University of Toronto, Toronto, Ontario M5T 1R8, Canada
[f] Department of Psychiatry, National University of Ireland, Galway H91 Tk33, Ireland
[g] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario L8N 3K7, Canada
[h] Departments of Psychiatry and Psychology, Queen's University, Kingston, Ontario K7L 3N6, Canada

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ABSTRACT

Background: Major Depressive Disorder (MDD) is characterized by objective and subjective cognitive deficits. Discrepancies between objective and subjective cognitive performance can reflect under- to over-estimations of cognitive abilities, and these discrepancies are referred to as cognitive self-appraisals. Despite evidence that low self-appraisals are associated with depression, the modifiability of self-appraisals and their association with treatment outcome remains unclear. The current study examined whether self-appraisals change following antidepressant treatment. Furthermore, we investigated the association of self-appraisals with treatment outcome.
Methods: As part of the CAN-BIND-1 clinical trial, 154 patients with MDD completed measures of objective and subjective cognitive abilities, depressive symptoms, and functional outcomes (work productivity, psychosocial functioning, and quality of life) at baseline and post-escitalopram treatment. Self-appraisals were calculated based on discrepancies between objective and subjective cognitive abilities, with higher scores indicating overestimation of cognitive abilities.
Results: Baseline self-appraisals were not predictive of treatment outcomes. However, self-appraisals increased from pre- to post-treatment. Moreover, pre-post treatment increases in self-appraisals were associated with positive treatment response and remission, decreases in depressive symptoms, and improvements in work productivity, psychosocial functioning, and quality of life.
Limitations: The pre-post intervention design precluded examining the temporal precedence of change in self-appraisals versus depressive symptoms and functional outcomes.
Conclusions: Findings are the first to demonstrate that self-appraisals are treatment-sensitive and are associated with treatment outcomes and recovery from MDD. Cognitive self-appraisals may represent a key marker of treatment response and a valuable target for assessment and intervention, as well as a potential mechanism underlying risk and recovery.

* Corresponding author.
E-mail address: krnic@psych.ubc.ca (K. Rnic).

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1. Introduction

Mechanisms underlying treatment response and functional recovery in Major Depressive Disorder (MDD) are not fully understood. One promising line of inquiry for better understanding and treating depression is cognitive abilities. Studies using standardized and objective neuropsychological assessments have found that depression is associated with cognitive deficits in attention, concentration, memory, processing speed, and executive functions (e.g., Austin et al., 1992; Porter et al., 2003; Snyder, 2013). These deficits reduce occupational productivity (Clark et al., 2016), impair interpersonal and psychosocial functioning (McInerney et al., 2020), increase disability (Jaeger et al., 2006), and are associated with reduced quality of life (Cotrena et al., 2016). Cognitive abilities can also be assessed using self-report measures, which assess individuals' subjective impressions of their cognitive performance. Similar to objective cognitive deficits, subjective cognitive deficits are common among individuals with depression (Sumiyoshi et al., 2019) and negatively influence patients' social and occupational functioning (Alonso-Prieto et al., 2019; Haro et al., 2019) and quality of life (McIntyre et al., 2015).

While both objective and subjective cognitive abilities are independently associated with psychosocial impairment, past studies of depressed cohorts have found little to no correlation between them (Baeza-velasco et al., 2020; Lahr et al., 2007; Miskowiak et al., 2016; Petersen et al., 2019; Srisurapanont et al., 2017). This indicates that objective and subjective cognitive abilities represent distinct constructs with different underlying processes. Whereas objective cognitive abilities are assessed using neuropsychological tests that quantify objective abilities across cognitive domains, subjective cognitive abilities reflect *perceptions* of abilities. Therefore, they may be shaped not only by objective cognitive deficits experienced in daily life (Lam, 2016), but also by negative self-relevant or mood-congruent biases, which are commonly observed in depression (LeMoult and Gotlib, 2019).

Discrepancies of subjective cognitive abilities with objective performance can reflect an overestimation of cognitive abilities - wherein subjective cognitive scores are *higher* than objective scores – or an underestimation of cognitive abilities – in which subjective cognitive scores are *lower* than objective scores (Miskowiak et al., 2016; Serra--Blasco et al., 2019; Srisurapanont et al., 2017; Torres et al., 2016; Van Camp et al., 2019). Objective-subjective cognitive ability concordance scores, referred to here as 'self-appraisals' of cognitive abilities, are associated with depressive symptoms and episodes. Acutely depressed patients *underestimate* their cognitive abilities, possibly as a result of negative self-relevant or mood-congruent biases, whereas remitted patients and healthy controls *overestimate* their abilities (Baeza-Velasco et al., 2020; Lahr et al., 2007; Serra-Blasco et al., 2019; Van Camp et al., 2019). Moreover, greater severity of depression is correlated with lower self-appraisal scores (i.e., greater underestimation) and lesser severity of depression is associated with higher self-appraisals (i.e., overestimation; Baeza-velasco et al., 2020; Petersen et al., 2019; Srisurapanont et al., 2017). Importantly, low self-appraisals are also cross-sectionally associated with greater socio-occupational disability and lower quality of life (Petersen et al., 2019).

Despite evidence that cognitive self-appraisals are associated with depression and functional impairment, researchers have not examined whether self-appraisals are associated with treatment outcomes or are modifiable with treatment. This is particularly critical given that self-appraisals may represent a risk factor underlying MDD and MDD-related impairment. Importantly, experimental work has documented that selective serotonin reuptake inhibitors (SSRIs) can reduce biases for negative information and can increase positive biases by influencing underlying neurocircuits (Harmer et al., 2017). Consistent with this idea, research has also found that negative self-perceptions decrease, and positive perceptions increase, over the course of SSRI treatment (Quilty et al., 2014). Together, these findings suggest that self-appraisals of cognitive abilities may similarly increase over the course of antidepressant treatment with an SSRI, and may represent an important marker of treatment response for clinicians to assess and monitor.

Our objectives were to investigate 1) whether cognitive self-appraisals change following escitalopram treatment for MDD, and 2) whether baseline and pre-post treatment changes in self-appraisals are associated with clinical and functional outcomes. We hypothesized that self-appraisals would increase from pre- to post-treatment and would be associated with positive treatment outcomes.

2. Methods

2.1. Study overview

The Canadian Biomarker Integration Network in Depression trial 1 (CAN-BIND-1) is the first study in a series of intervention trials for patients with MDD, and is registered under the identifier NCT01655706 at the U.S. National Library of Medicine. A detailed description of the CAN-BIND-1 sample and study design is available elsewhere (Kennedy et al., 2019; Lam et al., 2016). Participants were recruited at six clinical centers in Canada between August 2013 and December 2016. Phase 1 involved 8 weeks of open-label treatment with escitalopram (10-20 mg/day), with responders continuing this treatment phase for a further 8 weeks, and non-responders receiving adjunctive treatment with aripiprazole (2-10 mg/day; Phase 2). At the baseline visit (Week 0), extensive clinical assessments were conducted. All patients started treatment with escitalopram and received standardized clinical management. Clinical assessments were conducted again at Weeks 2, 8, and 16. For the purpose of the current study, only assessments collected at baseline and Week 8 (before and after Phase 1 treatment with escitalopram; referred to here as pre- and post-treatment) were of interest. CAN-BIND-1 conforms to the Declaration of Helsinki, and ethical approval was obtained by institutional review boards at each participating centre. All participants provided written informed consent to participate.

2.2. Participants

Participants were eligible if they were between 18 and 60 years of age, scored 24 or more on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979; Williams and Kobak, 2008) and had a diagnosis of MDD with a current major depressive episode confirmed using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) Individuals were excluded if they had bipolar I or II disorder, a significant personality disorder, acute suicidal risk, clinically significant substance abuse or dependence in the past six months, were pregnant or breastfeeding, had initiated psychological treatment within the past three months with the intent to continue, a history of failing four or more adequate pharmacological interventions, past use of electroconvulsive therapy or other neurostimulation treatment, and treatment failure with, or intolerance to, escitalopram. Patients were required to stop taking psychotropic medications for five half-lives before the baseline assessment. Objective cognitive ability score was not used as a criterion for inclusion in the study.

2.3. Measures

2.3.1. Objective and subjective cognitive abilities

Objective cognitive abilities were assessed with Central Nervous System Vital Signs (CNS-VS), a computerized neuropsychological battery that has been validated for individuals with mood disorders (Gualtieri and Johnson, 2006; Iverson et al., 2009). This battery assesses five main cognitive domains: Composite Memory, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility. Executive Functioning is subsumed under the Complex Attention and Cognitive Flexibility domains. A measure of global cognitive ability, the

Neurocognition Index (NCI), is calculated as an average of the domain scores. Raw scores are transformed into standard scores with a mean of 100 and a standard deviation (*SD*) of 15 based on an age- and gender-matched normative sample. The CNS-VS has good test-retest reliability, ranging from $r = 0.66$ to 0.88 over $M = 62$ days (Gualtieri and Johnson, 2006).

Patients' subjective cognitive abilities were assessed using the Depression Inventory Development (DID) cognition items (Vaccarino et al., 2016, 2020). The DID is a self-report measurement tool for use in clinical trials of MDD. Clinicians administer the DID and record patient's responses. The DID reflects current conceptualizations of depression and diagnostic criteria, and the DID cognition scale consists of four items: cognitive slowing, difficulties with concentration and paying attention, difficulties with recent memory, and difficulties with executive functions. Patients rate each item on a five-point scale (0-4) using a grid that operationalizes both the intensity and frequency of symptoms, with higher scores indicating greater cognitive deficits.

2.3.2. Depressive symptoms

Depressive symptom severity was assessed using the clinician-rated MADRS (Montgomery and Asberg, 1979; Williams and Kobak, 2008). The MADRS is comprised of 10 items that are scored on a scale from 0 to 6. Treatment response was defined as a ≥50% reduction in MADRS score from baseline to post-treatment at Week 8, and remission was defined as a total score ≤10 at Week 8.

2.3.3. Functional outcomes

Occupational productivity was assessed using the productivity subscale of the Lam Employment Absence and Productivity Scale (LEAPS; Lam et al., 2009) This 3-item self-report scale assesses work productivity over the past two weeks in patients with MDD. Individuals rate each item on a Likert scale from 0 to 4, with higher scores indicating greater problems with productivity. The LEAPS has demonstrated sensitivity to change within a clinical trial (Lam et al., 2009, 2013)

The Sheehan Disability Scale (SDS; Leon et al., 1997) was used to assess psychosocial impairment. This self-report questionnaire consists of 3 items that assess the degree to which symptoms have disrupted an individual's work/school, social life, and family life. Items are rated on a 0-10 scale, with higher scores indicating greater disability. The SDS has good validity and reliability and is sensitive to change (Leon et al., 1997).

Quality of life was examined using the Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF; Endicott et al., 1993). This 14-item self-report questionnaire measures satisfaction across life domains of physical health, mood, sexual drive and interest, ability to function in everyday life, ability to get around physically, living/housing situation, economic status, social relationships, work performance, leisure activities, and household duties, as well as an overall sense of well-being. Items are rated on a 5-point Likert scale, with higher scores indicative of greater quality of life. This questionnaire was developed and validated for depressed outpatients, has good reliability and validity, and is sensitive to change (Endicott et al., 1993).

2.4. Data pre-processing

NCI standard scores and raw DID cognition scale scores at Weeks 0 and 8 were *z*-transformed by referencing baseline (Week 0) scores, which ensures that Week 0 and 8 scores can be directly compared with each other. We adopted our previous method to derive self-appraisal scores from Serra-Blasco et al. (2019). Total DID *z*-transformed scores were reversed, such that higher scores reflect better perceived cognitive abilities. Self-appraisal scores at both Week 0 and Week 8 were obtained by subtracting corresponding NCI *z*-scores from the reversed composite DID cognition *z*-scores. Thus, a score of zero corresponds to maximal concordance between objective and subjective cognitive abilities (i.e., accurate appraisals). Positive scores indicate that individuals rated their cognitive abilities as higher than did objective tests (i.e., overestimation), whereas negative scores indicate that individuals rated themselves below objective measures (i.e., underestimation).

2.5. Statistical analysis

Multilevel linear growth analyses were conducted to assess pre-post treatment change in self-appraisal scores, as well as associations of both baseline self-appraisal scores and pre-post treatment changes in self-appraisals with changes in depressive symptoms and functional outcomes. Analyses controlled for baseline depressive symptoms. Measurement occasions (pre- and post-treatment) were nested within patients. Models were estimated in HLM 8.0 using restricted maximum likelihood (REML) and robust standard errors, and all tests were two-tailed. Measurement occasions were dummy-coded and all predictors were grand-mean centered. In models examining pre-post treatment changes in self-appraisals as predictors of changes in depressive symptoms and functional outcomes, changes in self-appraisals were assessed using residualized change scores. Residualized change scores reduce the measurement error introduced into the model as compared to simple change or difference scores (Cronbach and Furby, 1970).

Binary logistic regression analyses were conducted to investigate whether baseline self-appraisals predicted membership in post-treatment responder/nonresponder and remitter/nonremitter groups. To examine whether pre-post treatment changes in self-appraisals predicted response and remitter classification, residualized self-appraisal change scores were computed and entered as predictors of response and remitter classification in a series of two binary logistic regression models. Regression analyses controlled for baseline MADRS scores and were conducted in SPSS version 27.

3. Results

Of 211 participants who were screened and eligible for the study, 154 enrolled and completed both baseline and post-treatment assessments.[1] Table 1 shows the demographic and clinical characteristics of the sample. Patients had a mean baseline MADRS score in the moderate range of severity. Baseline self-appraisals were not associated with age, sex, ethnicity, marital status, years of education, number of past episodes of MDD, or whether participants were in a first episode of depression (all *ps* > .086). Baseline self-appraisals were significantly associated with baseline MADRS scores, $r(152) = -.21$, $p = .009$.

3.1. Change in Self-appraisals following Treatment

A multilevel linear growth model indicated that there was a significant increase in self-appraisal scores from baseline to post-treatment, $\beta = 0.64$, $SE = .11$, $t(153) = 6.10$, $p < .001$. Follow-up linear growth models indicated that there was significant improvement in both DID and NCI scores from pre- to post-treatment (*ps* < .001).

3.2. Association between Baseline Self-Appraisals and Treatment Outcome

At Week 8, 77 patients (50.0%) achieved treatment response and 50 (32.5%) had remitted. A binary logistic regression model was conducted to assess whether, controlling for baseline depressive symptoms, baseline self-appraisals predicted treatment response status. The model was nonsignificant, $\chi^2(2, N = 154) = 1.40$, p = .498, and baseline self-appraisal scores were not associated with likelihood of responding to treatment, $B = .09$, Wald $\chi^2(1) = .44$, $p = .509$, $OR = 1.10$, 95% CI [0.83,

[1] Patients who remained in the study versus those who dropped out or did not complete the Week 8 assessment did not differ in age, sex, ethnicity, marital status, years of education, or depressive symptoms, all *ps* > .086

Table 1
Demographic and clinical characteristics.

Characteristics	Descriptive Statistics (*n*=154)
Sex: Female *n* (%)	96 (62.3)
Age *M* (*SD*)	34.93 (12.43)
Years of Education *M* (*SD*)	14.17 (1.94)
<12 years *n* (%)	6 (3.9)
12 years *n* (%)	25 (16.2)
13-14 years *n* (%)	70 (45.5)
15-16 years *n* (%)	39 (25.3)
17-18 years *n* (%)	14 (9.1)
Ethnicity *n* (%)[†]	
Arab	1 (0.6)
Black	8 (5.2)
Chinese	9 (5.8)
East Asian	1 (0.6)
Filipino	3 (1.9)
Indigenous	1 (0.6)
Jewish	2 (1.3)
Korean	1 (0.6)
Latinx/Hispanic	11 (7.1)
South Asian	7 (4.5)
Southeast Asian	5 (3.2)
West Asian	1 (0.6)
White	146 (76.4)
Marital Status *n* (%)	
Never Married	88 (57.1)
Separated/Divorced/Widowed	21 (13.6)
Married/Domestic Partnership	45 (29.2)
Depression History *n* (%)	
First Episode	33 (21.4)
Recurrence	112 (72.7)
Unknown	9 (5.8)
Week 0 MADRS *M* (*SD*)	30.10 (5.71)
Week 8 MADRS *M* (*SD*)	15.45 (9.79)
Week 0 LEAPS Productivity Scale *M* (*SD*)	5.40 (3.04)
Week 8 LEAPS Productivity Scale *M* (*SD*)	2.98 (2.90)
Week 0 SDS *M* (*SD*)	18.96 (6.75)
Week 8 SDS *M* (*SD*)	12.61 (7.88)
Week 0 Q-LES-Q-SF *M* (*SD*)	33.38 (7.03)
Week 8 Q-LES-Q-SF *M* (*SD*)	43.16 (10.15)

Note. MADRS = Montgomery Asberg Depression Rating Scale; LEAPS = Lam Employment Absence and Productivity Scale; SDS = Sheehan Disability Scale; QLESQ-SF = Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form.

[†] Participants could report more than one ethnicity.

1.44]. Furthermore, the model assessing baseline self-appraisals as a predictor of remission status was significant, $\chi^2(2, N = 154) = 8.46$, p = .015. However, baseline self-appraisals did not predict remission, B = .12, Wald $\chi^2(1) = .64$, $p = .424$, $OR = 1.13$, 95% CI [0.84, 1.52]. See Table 2 for descriptive statistics, and see Fig. 1 for self-appraisal scores stratified by responder and remitter groups.

A linear growth model indicated that baseline self-appraisals did not predict pre-post treatment change in MADRS scores, β = -0.14, $SE = .67$, $t(152) = -.21$, $p = .831$. Controlling for baseline MADRS symptoms, baseline self-appraisals also were not associated with pre-post treatment changes in occupational productivity, β =0.17, $SE = .35$, $t(111) = .50$, $p = .617$, psychosocial functioning, β = .16, $SE = .50$, $t(151) = .31$, $p = .754$, or quality of life, β = -0.99, $SE = .59$, $t(151) = -1.67$, $p = .097$.

3.3. Association between changes in self-appraisals and treatment outcome

A binary logistic regression model assessing residualized change in self-appraisals as a predictor of treatment response status and controlling for baseline depression was significant, $\chi^2(2, N = 154) = 22.36$, p < .001, such that increases in self-appraisals predicted positive treatment response, $B = .76$, Wald $\chi^2(1) = 17.44$, $p < .001$, $OR = 2.14$, 95% CI [1.50, 3.06]. The logistic regression model assessing residualized self-appraisal change scores as a predictor of remission status was also significant, $\chi^2(2, N = 154) = 24.14$, p < .001. Increases in self-appraisals were associated with classification in the remitter group, $B = .73$, Wald $\chi^2(1) = 13.78$, $p < .001$, $OR = 2.08$, 95% CI [1.41, 3.05]. Furthermore, a linear growth model indicated that as self-appraisal scores increased from baseline to post-treatment, MADRS scores decreased, β = -4.02, $SE = 0.67$, $t(152) = -6.02$, $p < .001$.

Linear growth models were conducted to examine the association of baseline-Week 8 change in self-appraisal scores with changes in functional outcomes, controlling for baseline MADRS scores. As self-appraisals increased, problems with productivity decreased, β = -1.31, $SE = 0.25$, $t(111) = -5.15$, $p < .001$. Similarly, post-treatment increases in self-appraisal scores were associated with decreases in problems with psychosocial functioning, β = -2.24, $SE = 0.71$, $t(151) = -3.14$, $p = .002$, and with increases in quality of life, β = 3.23, $SE = 0.71$, $t(151) = 4.52$, $p < .001$.[2]

4. Discussion

So far as we are aware, the current study was the first to investigate whether objective and subjective concordance in cognitive abilities ('self-appraisals') change following pharmacological treatment for MDD. This study was also the first to assess whether cognitive self-appraisals predict treatment outcomes. Findings indicated that self-appraisals increased from pre- to post-treatment. Furthermore, whereas baseline self-appraisals did not predict treatment outcomes, pre- to post-treatment increases in self-appraisals were associated with treatment response and remission status as well as with improvements in depressive symptoms, work productivity, psychosocial impairment, and quality of life.

Consistent with hypotheses, cognitive self-appraisals increased from pre- to post antidepressant treatment, indicating that escitalopram may reduce the negative biases that underlie low self-appraisals. Together with past research documenting that high self-appraisals are associated with lower depressive symptoms, this finding suggests that high self-appraisals are adaptive. This is consistent with the 'depressive realism' hypothesis, which posits that non-depressed individuals tend to make positively-biased inferences (Alloy et al., 1990), whereas individuals who are depressed tend to make more realistic inferences (Moore and Fresco, 2012). High self-appraisals, which represent a positive bias, may therefore be more consistent with a euthymic mood state. Consistent with this idea, past research has found that healthy individuals tend to overestimate their cognitive abilities (Kruger and Dunning, 1999).

Findings for the association of baseline and pre-post treatment changes in self-appraisals with treatment outcomes were mixed. Baseline self-appraisals did not prospectively predict treatment response or remission status, nor were they associated with reductions in depressive symptoms at post-treatment. Furthermore, controlling for baseline depressive symptoms, baseline self-appraisals were not predictive of changes in the functional outcomes of work productivity, psychosocial impairment, and quality of life at post-treatment. However, we did find that depressive symptoms ameliorated as self-appraisals increased. Similarly, increases in self-appraisals were associated with positive treatment response and remission status, and with improvements in work productivity, psychosocial impairment, and quality of life, even while controlling for depressive symptoms. These associations are not attributable to improvements in objective cognitive abilities, given that in this sample, changes in objective cognitive abilities were not associated with improvements in functional outcomes (McInerney et al., 2020). It is therefore possible that, regardless of self-appraisals to begin with, *changes* in self-appraisals may foster changes in symptoms and functioning. Together, these findings suggest that baseline

[2] All analyses were also conducted after excluding $n = 3$ individuals with NCI scores in the *Very Low* (percentile scores < 2) range. The same pattern and significance of results was obtained. Thus, findings including the entire sample are presented.

Table 2
Objective and subjective cognitive abilities and self-appraisal scores by treatment response and remission status.

Cognitive Measure	Responders (*n*=77) *M* (*SD*)	Non-responders (*n*=77) *M* (*SD*)	Remitters (*n*=50) *M* (*SD*)	Non-remitters (*n*=104) *M* (*SD*)	Total (*n*=154) *M*(*SD*)
NCI standard score					
Baseline	99.50 (13.04)	99.53 (12.10)	100.35 (12.47)	99.12 (12.61)	99.52 (12.54)
Post-treatment	104.64 (11.49)	104.40 (10.19)	105.35 (10.53)	104.13 (10.99)	104.52 (10.82)
DID cognition score					
Baseline	7.96 (4.09)	8.57 (3.53)	7.30 (4.33)	8.73 (3.47)	8.27 (3.82)
Post-treatment	2.60 (2.66)	5.99 (3.67)	1.82 (2.32)	5.48 (3.53)	4.29 (3.62)
Self-appraisal score					
Baseline	0.08 (1.23)	-0.08 (1.15)	0.19 (1.20)	-0.09 (1.18)	0.00 (1.19)
Post-treatment	0.95 (1.07)	0.09 (1.14)	1.10 (0.95)	0.24 (1.19)	0.64 (1.21)
Pre-post treatment change	1.00 (1.32)	0.29 (1.21)	1.04 (1.27)	0.45 (1.29)	0.64 (1.31)

Note. DID = Depression Inventory Development; NCI = Neurocognition Index.

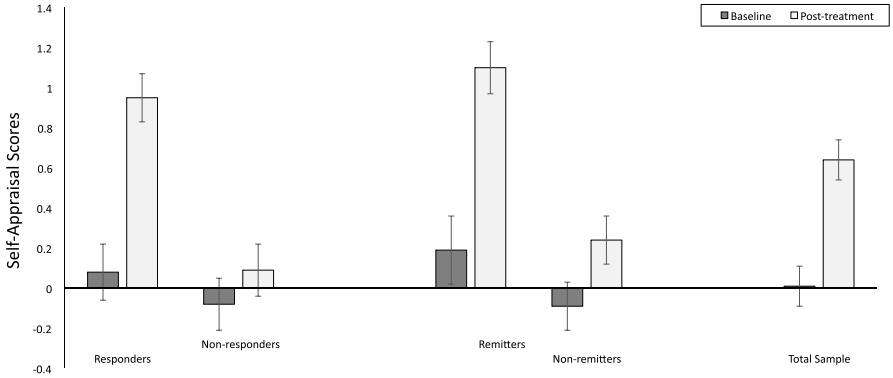

Fig. 1. Self-appraisal Scores Stratified by Treatment Responder and Remitter Groups.
Note. Total $n = 154$. There were 77 responders, 77 non-responders, 50 remitters, and 104 non-remitters. Scores above 0 represent over-estimations of cognitive abilities, and scores below 0 represent under-estimations. Error bars represent standard errors.

self-appraisals do not prospectively predict depressive symptom reduction or treatment response. However, *increases* in self-appraisals are associated with a positive treatment response and outcome.

It is unclear whether increases in self-appraisals preceded or followed improvements in depressive symptoms, and this has important implications for determining whether self-appraisals are a mechanism of action in symptom recovery. Future research using intensive longitudinal sampling methods is needed to determine the temporal precedence of increases in self-appraisals versus reductions in depressive symptoms and improvements in functional outcomes during treatment. For example, cognitive self-appraisals may represent a by-product of the disorder that is driven by biased self-evaluations that are active only during depressive mood states (e.g., Petersen et al., 2019). In this case, improvements in depressive symptoms would be expected to precede changes in self-appraisals. Alternatively, negative self-appraisals may represent a vulnerability factor for the onset and maintenance of depressive episodes (eg., Van Camp et al., 2019), whereby low self-appraisals may cause individuals to disengage from reinforcing activities due to thoughts that they don't have the capacity to successfully engage, leading to depressed mood. If so, increases in self-appraisals over the course of treatment could lead individuals to feel more capable and to reintegrate themselves in various activities. In this scenario, increases in self-appraisals would be expected to precede reductions in depressive symptoms and improvements in functioning and quality of life. This, in turn, would determine whether cognitive self-appraisals represent a potentially worthwhile target for better optimizing treatments.

Findings from the current study should be interpreted in the context of its strengths and limitations. Given that this study was a clinical trial of escitalopram treatment for MDD, protocols ensured that all participants had diagnosed MDD of at least moderate severity. Moreover, whereas the majority of past studies examining cognitive self-appraisals reported on cross-sectional data, we used a longitudinal design. Cognitive assessments were conducted before and after treatment, allowing us to assess longitudinal, treatment-related changes in self-appraisals and their prospective associations with key outcomes. We also used sophisticated analytic techniques to assess changes in self-appraisals and outcomes rather than relying on methods that are biased by measurement error, such as change scores. In terms of limitations, assessments of objective and subjective cognitive abilities were limited to pre-post measures, which precluded examination of the temporal dynamics of self-appraisals, depression, and functional outcomes and their rate and timing of change over the course of treatment. Moreover, without a control group, it is unclear whether changes in self-appraisals are attributed to treatment, and future randomized controlled trials are needed to explore this further. There was also a potential for practice effects resulting from multiple administrations of our objective cognitive ability measure. However, practice effects would have made it *more* difficult to detect the current finding that self-appraisals increase from pre- to post-treatment, as practice effects would have resulted in inflated increases in objective cognitive abilities relative to changes in subjective cognitive abilities. Moreover, concerns about practice effects are mitigated by all participants in the sample having completed the measure at both pre- and post-treatment. It is also important to note that, while we made the a priori decision to use our earlier method for computing self-appraisal scores as described in Serra-Blasco et al., (2019), alternative methods are available (e.g., Miskowiak et al., 2016). Future research should examine the implications of using different methods for deriving self-appraisal scores. It would also be valuable to assess the implications of using other self self-report scales of subjective cognitive abilities, such as the Perceived Deficits Questionnaire (PDQ; Sullivan et al., 1990) or the British Columbia Cognitive Complaints Inventory (BC-CCI; Iverson

and Lam, 2013).

The present study represents the most comprehensive investigation into cognitive self-appraisals in MDD to date. Self-appraisals increased from pre- to post-treatment, and greater increases in self-appraisals were associated with favorable treatment outcomes. Self-appraisals are an important correlate of MDD-related impairment and recovery that may serve as a useful marker of treatment response for clinicians. Self-appraisals may also represent an underlying risk factor for depression that propels changes in symptoms and functioning, and a valuable target for assessment and intervention.

Contributors

RWL, ALV, VB, PG, SM, BF, RVM, DM, AVR, SR, and SHK were responsible for study design, obtaining funding, and data acquisition. RWL, KR, YJ, IT, TC, and JL developed the research questions and hypotheses. KR and YJ prepared the data for analysis. YJ conducted preliminary analyses and drafted sections of the methods under the supervision of RWL, IT, and TC. KR formulated the analysis plan, performed the data analysis and interpretation, and drafted the 'manuscript under the supervision of RWL, IT, TC, and JL. All authors provided critical revisions, and all authors approved the final version of the paper for submission.

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Data availability

The CAN-BIND-1 data will be available from Brain-CODE, based at the Ontario Brain Institute (https://braininstitute.ca/research-data-sharing/brain-code).

Declaration of Competing Interest

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