CNS Spectrums

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The mediational role of cognitive function on occupational outcomes in persons with major depressive and bipolar disorder

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Original Research

Cite this article: Tamura JK, Harangi D, Rodrigues NB, Mansur RB, Subramaniapillai M, Johnson DE, Rosenblat JD, Lee Y, Di Vincenzo JD, Ho R, Sukhdeo R, Cao B, Lui L, Ceban F, and McIntyre RS (2025). The mediational role of cognitive function on occupational outcomes in persons with major depressive and bipolar disorder. *CNS Spectrums* https://doi.org/10.1017/S1092852924002293

Received: 23 May 2024
Accepted: 03 November 2024

Keywords:
Cognition; workplace function; depression; ketamine; vortioxetine; infliximab

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Abstract

Background. Improving functioning in adults with major depressive disorder (MDD) and bipolar disorder (BD) is a priority therapeutic objective.

Methods. This retrospective post hoc secondary analysis evaluated 108 patients with MDD or BD receiving the antidepressants vortioxetine, ketamine, or infliximab. The analysis aimed to determine if changes in objective or subjective cognitive function mediated the relationship between depression symptom severity and workplace outcomes. Cognitive function was measured by the Perceived Deficits Questionnaire (PDQ-5), the Digit Symbol Substitution Test (DSST), and the Trail Making Test Part B (TMT-B). Depression symptom severity was measured by the Montgomery–Åsberg Depression Rating Scale (MADRS). Workplace function was measured by the Sheehan Disability Scale (SDS) work–school item.

Results. When co-varying for BMI, age, and sex, the association between MADRS and SDS work scores was partially mediated by PDQ-5 total scores and DSST total scores, but not DSST error scores and TMT-B time.

Limitations. This study was insufficiently powered to perform sub-group analyses to identify distinctions between MDD and BD populations as well as between antidepressant agents.

Conclusions. These findings suggest that cognitive impairment in adults with MDD and BD is a critical mediator of workplace function and reinforces its importance as a therapeutic target.

1. Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are recurrent and chronic mood disorders associated with multi-domain functional impairment.[1,2] At the population level, MDD and BD are the leading causes of disability globally.[3] Moreover, cost-of-illness studies report that indirect costs (eg, presenteeism and absenteeism) make up a large proportion of the yearly US $200 billion costs of MDD and BD, reflecting the substantial impairments in workplace function associated with these disorders.[4–7] The foregoing observatin is even more salient in light of rising presenteeism in the digital workplace during the COVID-19 pandemic.[8] Functional recovery has thus become well-recognized by both clinicians and workplaces alike as a key therapeutic target in mood disorder populations.[9–12]

Replicated evidence has established a strong association between functional impairment in the workplace and several features of MDD and BD, including depressive symptoms and cognitive impairment.[13,14] Depressive symptom severity has been associated with loss of productive employment, increased disability payments, and poor time management.[15–18] Additional evidence suggests that cognitive impairment is a robust predictor of workplace outcomes and role functioning in MDD and BD populations. Cognitive impairment remains a strong predictor even after controlling for the relationship between cognitive impairment and mood symptoms.[19–22]

Both depressive symptoms and cognitive function have been identified as modifiable targets to improve workplace performance in BD and MDD populations.[23] There are few treatments

with demonstrated efficacy for cognitive impairment in populations with mood disorders.[24–26] However, some antidepressants have been shown to improve workplace outcomes through reductions in depressive symptoms and, in some cases, through pro-cognitive effects.[27–29] For example, vortioxetine, a multimodal antidepressant with effects on norepinephrine, serotonin, histamine, and cholinergic neurotransmitter systems, has well-established pro-cognitive effects in mood disorder populations.[30–32] Emerging evidence also suggests that ketamine, an *N*-methyl-*D*-aspartate receptor antagonist with rapid efficacy in treatment-resistant depression (TRD), and infliximab, a tumor necrosis factor antagonist with efficacy in BD and TRD, may also demonstrate pro-cognitive effects.[33–38]

Extant literature suggests that cognitive impairment mediates the relationships between depressive symptoms and both psychosocial and functional outcomes.[39–41] More specifically, recent studies suggest that cognitive impairment mediates the relationship between depressive symptoms and workplace outcomes.[23,42,43] Notwithstanding, there have been relatively fewer studies that have evaluated the specific cognitive domains involved in this relationship and still fewer that have focused on BD populations.[44–46] Herein, we further substantiate the relationship between depressive symptoms, cognitive function, and workplace outcomes in populations with MDD or BD. Specifically, we assess how overall cognitive function, executive function, and subjective cognitive function mediate the relationship between depressive symptoms and workplace function in BD and MDD populations receiving vortioxetine, ketamine, or infliximab therapy.

2. Methods

2.1. Dataset study design

The data used in the analysis herein were combined from three separate datasets: an open-label vortioxetine trial with individuals with MDD[47] (ClinicalTrials.gov Identifier: NCT03053362), an observational study of outpatients with TRD receiving intravenous (IV) ketamine at the Canadian Rapid Treatment Center of Excellence (CRTCE)[48] (ClinicalTrials.gov Identifier: NCT04209296), and a double-blind placebo-controlled infliximab trial with individuals with bipolar I/II depression[37] (ClinicalTrials.gov Identifier: NCT02363738). The three studies will hereafter be referred to by the intervention evaluated in the study (ie, the vortioxetine trial, the ketamine trial, and the infliximab trial). The methodologies used in the foregoing studies are described extensively in their original reports. An outline of key study features is provided in Table 1.

2.1.1. Vortioxetine trial

The vortioxetine trial is an open-label trial of vortioxetine in adults with MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) and healthy controls (HC). Participants were included in the study if they were experiencing a current major depressive episode (MDE), and at least one other MDE in the past.[37] Exclusion criteria included current alcohol and/or substance use disorder, concurrent diagnosis with a psychiatric disorder other than MDD, and medication intended for, or presumed to, affect cognitive function.

A total of 158 participants were included in the study ($n_{MDD} = 100$; $n_{HC} = 58$). Patients received 10–20 mg/day of open-label vortioxetine for 8 weeks. The primary outcome was a change in cognition from baseline to study endpoint, as measured by the THINC-integrated tool (THINC-it), a screening tool for cognition and cognitive impairment. Assessments were completed at weeks 0, 2, 4, and 8 of the study.

2.1.2. Ketamine trial

Data were also obtained from the CRTCE, a clinical and research facility located in Mississauga, Canada.[49] The CRTCE provides intravenous (IV) ketamine infusion treatment to eligible adults with TRD of least Stage 2 in severity and a primary diagnosis of DSM-5-defined MDD or BD. Ketamine infusions are administered adjunctively to current medications for most patients; however, those taking an irreversible monoamine oxidase inhibitor (MAOI), naltrexone, or benzodiazepines discontinued use prior to ketamine therapy. Psychiatric comorbidities and suicidal ideation were not considered exclusion criteria for treatment.

The data from the CRTCE analyzed herein were collected from July 2018 to July 2020 and comprised a total sample of 238 patients. Patients received a total of four IV ketamine infusions over a period of 1.5–2 weeks for acute treatment. Patients received the first two ketamine infusions at 0.5 mg/kg diluted in 0.9% saline solution over a period of 40–45 minutes. If a suboptimal decrease in depressive symptom severity was observed, the dosing was optimized to 0.75 mg/kg for the following two infusions. The primary outcome was a change in depressive symptoms as measured by the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16). Measures were completed at the first infusion, fourth infusion, and post-initiation treatment visit.

2.1.3. Infliximab trial

The infliximab trial is a double-blind, placebo-controlled randomized trial of the antidepressant efficacy of adjunctive infliximab in outpatient adults with BD I/II experiencing a current MDE. Participants were eligible if they received a minimum of two treatments

Table 1. Dataset Characteristics of the Vortioxetine Trial, Ketamine Trial, and Infliximab Trial

Study	ClinicalTrials.gov Identifier	Study type	Participants	Intervention	Study length	*n*
Vortioxetine trial	NCT03053362	Open-label trial	MDD with depressive symptoms and healthy controls	10–20 mg/day vortioxetine	8 w	158
Ketamine trial	NCT04209296	Outpatient data	TRD as part of BD or MDD	0.5–0.75 mg/kg IV ketamine	1.5–2 w	238
Infliximab trial	NCT02363738	Double-blind, placebo-controlled randomized trial	Bipolar I/II with a major depressive episode	5 mg/kg infliximab infusions	12 w	60

https://doi.org/10.1017/S1092852924002293 Published online by Cambridge University Press

for BD at least 4 weeks before participation in the trial. Participants were not excluded based on current medications.

Sixty participants were randomized to receive a placebo (n = 31) or 5 mg/kg IV infliximab infusions (n = 29). Infusions were administered over 120 minutes at weeks 0, 2, and 6. The primary outcome was a change in depressive symptoms between baseline and endpoint, as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS). Clinical assessments were completed at weeks 0, 1, 2, 3, 4, 6, 8, 10, and 12. Cognitive assessments were completed as secondary outcomes at weeks 0, 2, and 12.

2.2. Variable operationalization

2.2.1. Depressive symptoms

In the vortioxetine and infliximab trials, depressive symptoms were measured using MADRS.[50] In the ketamine trial, depressive symptoms were measured using the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16) assessments.[51] For the purposes of the analysis herein, QIDS-SR16 scores were converted into MADRS scores using a standardized table.[52]

2.2.2. Workplace function

The Sheehan Disability Scale (SDS) is a self-rated scale that assesses functional impairment in the domains of work–school, social life, and family life/home responsibilities.[53] It is a validated measure of functional outcomes in depression and is sensitive to treatment effects.[54] The patient rates 3 items on an analog scale of 0 to 10 to indicate the degree to which their symptoms have interfered with each of the 3 functional domains. A rating of 0 corresponds to "not at all" disruptive and a rating of 10 corresponds to "extremely" disruptive. A score over 5 is associated with significant functional impairment. The three items may be summed to obtain a global measure of functional impairment, ranging from 0 to 30. The analysis herein used the work–school item of the SDS as a measure of function in the workplace and/or educational setting.

2.2.3. Cognitive function

Cognitive function was measured using the 5-item version of the Perceived Deficits Questionnaire (PDQ-5), the Digit Symbol Substitution Test (DSST), and/or the Trail Making Test Part B (TMT-B). The PDQ-5 is a patient-reported measure of cognitive function originally developed for patients with multiple sclerosis.[55] More recently, the PDQ-5 has been used to assess subjective cognitive function in other populations, including MDD and BD.[56] The DSST and TMT-B are 2 objective assessments of cognitive function. The DSST is a pencil-and-paper cognitive test that involves the use of a key to match a series of symbols to numbers.[57,58] The DSST is a polyfactorial cognitive test; the time taken to complete the task and the number of matching errors made are indicators of cognitive function in domains including attention, visuospatial processing, working memory, and psychomotor speed.[59] The TMT-B is also a polyfactorial cognitive test. This test requires the individual to draw lines to connect alternating numbers and letters.[60] The time taken to correctly complete the task reflects psychomotor speed, visuospatial processing, and attention.[61]

2.3. Inclusion and exclusion criteria

A summary of the inclusion criteria for the original studies is outlined in Section 2.1. In the analysis herein, further inclusion–exclusion criteria were applied. Participants were excluded if they did not receive an antidepressant intervention (ie, participants receiving a placebo in the infliximab trial and healthy controls in the vortioxetine trial). Participants were also excluded if data were not available for MADRS, SDS work, and at least one test of cognitive function at baseline and endpoint measures.

2.4. Data extraction

Two reviewers (JKT and DH) compiled data from the three datasets. Data were collected for primary measures of interest (ie, MADRS total score, SDS work score, TMT-B time, PDQ-5 total score, DSST errors, DSST time) and demographic variables (ie, age, sex, race, marital status, primary diagnosis, BMI), where available. The ketamine trial did not report race or marital status. The infliximab trial did not assess cognition using the TMT-B. The infliximab trial also employed the full PDQ assessment instead of PDQ-5, and thus these scores were not included in the analysis herein.

2.5. Statistical analysis

The statistical analysis was conducted using SPSS Statistics Software, Version 25. Descriptive statistics were generated to characterize sociodemographic characteristics (ie, age, sex, race, marital status, BMI, primary diagnosis, education, and employment status). Chi-squared and Kruskall–Wallis tests were conducted to compare demographic measures between the three datasets.

The mediation model was generated using PROCESS Macro for SPSS, Version 3.5 (Hayes, 2013). Model 4 was used to determine if the relationship between MADRS and SDS work scores was mediated by changes in PDQ-5 total scores, TMT-B time, DSST error scores, and DSST symbols scores from baseline to endpoint. Each model was controlled by covariates (age, BMI, sex). A bias-corrected 95% confidence interval (CI) was calculated using bootstrapping of 5000 samples. The significance of associations was defined as a two-tailed P-value of $< .05$. Sub-analyses were originally planned to be conducted for the primary diagnosis (ie, MDD and BD) and treatment type (ie, vortioxetine, ketamine, or infliximab) subgroups. However, these sub-analyses were not sufficiently powered to complete and thus were not included in the current study.

3. Results

3.1. Baseline demographic and clinical characteristics

The combination of the 3 datasets yielded a total sample of 456 individuals. There were 31 participants excluded as they received a placebo in the infliximab trial. There were an additional 58 participants excluded as healthy controls of the vortioxetine trial. Of the remaining participants, there was insufficient data for 21 of the vortioxetine trial participants, 229 of the ketamine trial participants, and 9 of the infliximab trial participants. This resulted in a final sample of 108 individuals.

A summary of the sample sociodemographic characteristics is located in Table 2. Overall, the sample was mostly female (67%), white (69%), and single (49%), with an average BMI of 29.4 (SD = 7.7) and an age of 40 (SD = 12.5). The mean baseline MADRS score was 32.8 (SD = 7.5), corresponding to moderate to severe

https://doi.org/10.1017/S1092852924002293 Published online by Cambridge University Press

Table 2. Clinical and Demographic Characteristics at Baseline

	Total				
Category	Total (n = 108)	Vortioxetine (n = 79)	Ketamine (n = 9)	Infliximab (n = 20)	Chi-squared
Sex					
Male	36	28	3	5	X(2) = 0.783
Female	72	51	6	15	P = .676
Unreported	0	0	0	0	
Race					
White	75	58	0	17	X(4) = 3.389
Black	2	2	0	0	P = .495
Asian	15	14	0	1	
Latin American	0	0	0	0	
Arabic	1	1	0	0	
Indigenous	0	0	0	0	
Other	6	4	0	2	
Unreported	9	0	9	0	
Primary diagnosis					
MDD	85	79	6	0	X(2) = 96.07
BD	23	0	3	20	P = .000
Unreported	0	0	0	0	
Education					
High school	16	11	0	5	X(3) = 3.266
College	65	54	0	11	P = .352
Graduate school	14	10	0	4	
Other	4	4	0	0	
Unreported	9	0	9	0	
Marital status					
Single	53	47	0	6	X(4) = 18.424
Married	32	23	0	9	P = .001
Common law	7	7	0	0	
Separated	2	0	0	2	
Divorced	5	2	0	3	
Widowed	0	0	0	0	
Unreported	9	0	9	0	
	Total (n = 108)	Vortioxetine (n = 79)	Ketamine (n = 9)	Infliximab (n = 20)	
Category	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Kruskal–Wallis
Age	40.18	39.24	40.00	43.95	H(2) = 2.59
	(12.45)	(12.66)	(12.67)	(11.36)	P = .27
BMI baseline	29.43	28.66	29.96	33.28	H(2) = 3.23
	(7.72)	(6.46)	(6.47)	(11.10)	P = .20
MADRS baseline	32.76	32.38	39.22	31.35	H(2) = 9.56
	(7.51)	(7.48)	(3.53)	(7.74)	P = .01
SDS work baseline	7.52	7.03	8.89	8.85	H(2) = 12.10
	(2.80)	(2.83)	(3.33)	(1.66)	P = .00
PDQ–5 baseline	12.0	11.96	13.50	N/A	H(1) = 0.285
	(4.30)	(4.34)	(0.71)		P = .59

https://doi.org/10.1017/S1092852924002293 Published online by Cambridge University Press

Table 2. *Continued*

Category	Total (n = 108) Mean (SD)	Vortioxetine (n = 79) Mean (SD)	Ketamine (n = 9) Mean (SD)	Infliximab (n = 20) Mean (SD)	Kruskal–Wallis
TMT-B baseline	73.75	72.78	82.27	N/A	H(1) = 1.08
	(31.70)	(31.6)	(33.3)		P = .30
DSST error baseline	0.17	0.14	0.11	0.33	H(2) = 0.00
	(0.61)	(0.416)	(0.33)	(1.19)	P = 1.00
DSST symbols baseline	54.64	52.27	56.00	47.26	H(2) = 5.39
	(15.4)	(15.00)	(18.72)	(14.04)	P = .07

depressive symptoms. The mean baseline SDS work score was 7.5 out of 10 (SD = 2.80).

3.2. Mediation analysis

The mediation analysis was conducted to compare how changes in PDQ-5 total score, DSST symbols score, DSST error score, and TMT-B time mediated the association between changes in MADRS scores and changes in SDS work scores.

Changes in PDQ-5 total scores from baseline to endpoint partially mediated the association between changes in MADRS scores and changes in SDS work scores (Figure 1). Increases in MADRS scores were significantly associated with increases in PDQ-5 total scores (a = 0.32, P < .05, SE = 0.03) and PDQ-5 total scores correlated with SDS work scores (b = 0.15, P < .05, SE = 0.05). Both indirect ($a \times b$ = 0.05, 95% CI [0.01, 0.08]) and direct (c' = 0.12, $t(156)$ = 4.82, P < .05, 95% CI [0.07, 0.17]) effects of changes in MADRS on changes in SDS work scores were significant. Overall, the change in PDQ-5 total score was a significant partial mediator of the relationship between changes in MADRS and changes in SDS Work scores.

Changes in TMT-B time from baseline to endpoint did not significantly mediate the association between changes in MADRS scores and changes in SDS work scores (Figure 1B). Increases in MADRS scores were significantly associated with increases in TMT-B times (a = 0.98, P < .05, SE = 0.22), but the effect of changes in TMT-B time on SDS work scores was insignificant (b = 0.00, P > .05, SE = 0.06). Indirect ($a \times b$ = 0.00, 95% CI [−0.01, 0.01]) effects of changes in MADRS on changes in SDS work scores were insignificant. However, the direct effects of changes in MADRS on SDS work scores were significant (c' = 0.17, $t(170)$ = 9.25, P < .05, 95% CI [0.13, 0.20]). Overall, change in TMT-B time was not a significant mediator of the relationship between changes in MADRS and changes in SDS work scores.

Changes in DSST symbols scores from baseline to endpoint partially mediated the association between changes in MADRS scores and changes in SDS work scores (Figure 1C). Increases in MADRS scores were associated with decreases in DSST symbols scores (a = −0.40, P < .05, SE = 0.08) and increases in DSST symbols scores were associated with decreases in SDS work scores (b = −0.04, P < .05, SE = 0.15). Both indirect ($a \times b$ = 0.02, 95% CI [0.00, 0.03]) and direct effects of changes in MADRS on changes in SDS work scores were significant (c' = 0.17, $t(209)$ = 10.90, P < .05, 95% CI [0.14, 020]). Overall, change in PDQ-5 total scores was a significant partial mediator of the relationship between changes in MADRS and changes in SDS work scores.

Finally, changes in DSST error score from baseline to endpoint did not significantly mediate the association between changes in MADRS scores and changes in SDS work scores (Figure 1D).

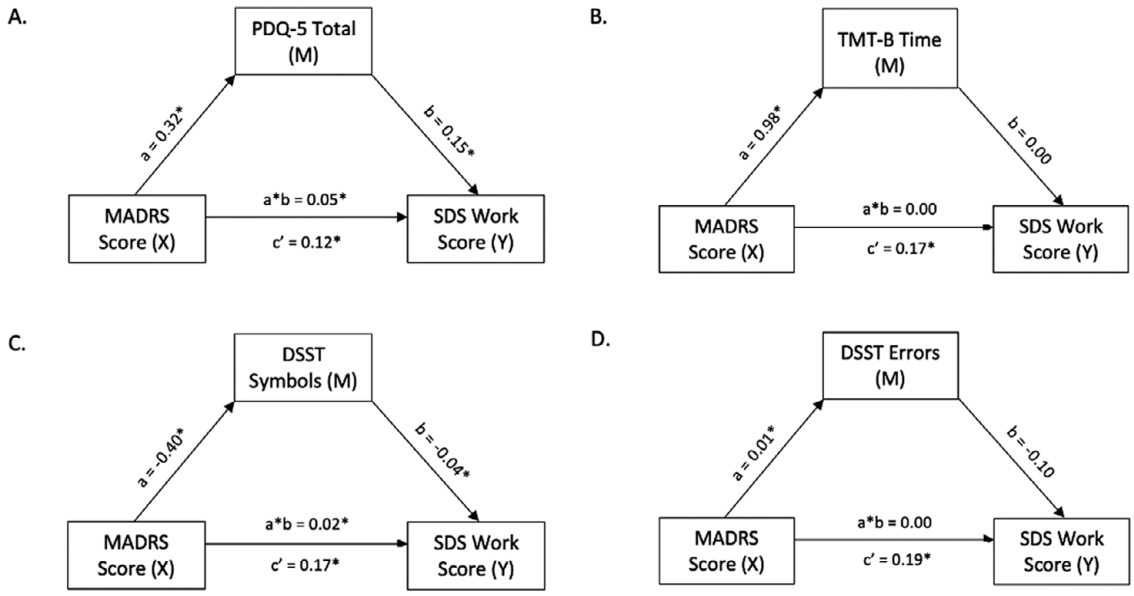

Figure 1. Direct and indirect effects (via subjective/objective cognitive measures) of depression on workplace function.

https://doi.org/10.1017/S1092852924002293 Published online by Cambridge University Press

Increases in MADRS scores were significantly associated with an increased DSST error ($a = 0.01$, $P < .05$, SE = 0.00), but the effect of changes in DSST error scores on changes in SDS work scores was insignificant ($b = -0.09$ $P > .05$, SE = 0.26). Indirect ($a \times b = -0.00$, 95% CI [−0.00, 0.00]) effects of changes in MADRS on changes in SDS work scores were insignificant. However, the direct effects of MADRS on SDS work scores were significant ($c' = 0.19$, $t(208) = 12.02$, $P < .00001$, 95% CI [0.15, 0.22]). Overall, the change in DSST error score was not a significant mediator of the relationship between changes in MADRS and changes in SDS work scores.

4. Discussion

Our analysis further substantiates the mediational role of cognitive impairment on workplace function in persons with MDD and BD. Data were obtained from 3 studies: an open-label vortioxetine trial with patients with MDD, a double-blind placebo-controlled infliximab trial with patients with bipolar I/II depression, and a trial with outpatients with TRD receiving IV ketamine. The results of our analysis suggest that both objective cognitive function and subjective cognitive function partially mediate the relationship between depressive symptoms and workplace outcomes.

One measure of objective cognitive function, the DSST symbols score, was a partial mediator of workplace function in our analyses herein. The DSST is a polyfactorial measure of objective cognitive function that encapsulates psychomotor speed, attention, learning/memory, and executive function.[60,62] The foregoing findings cohere with the literature on the role of objective cognitive function in functional outcomes.[63–66] Notably, a study of 182 participants with remitted MDD and healthy controls found that, of the 6 cognitive domains assessed, executive functioning was the only cognitive domain that significantly predicted workplace function.[65] Taken together, this finding reiterates the role of objectively evaluated cognitive function and, specifically, executive function, as mediators of workplace function in mood disorder populations.

The PDQ-5 was employed as a measure of subjective cognitive function in the analysis herein and was found to be a significant mediator of workplace function in our model. The mediational role of subjective cognitive function must be differentiated from objective cognitive function as the two measures are not always in alignment. For example, an individual may perceive their cognition as impaired while objectively being cognitively intact, and vice versa.[67,68] Subjective cognitive impairment was also reported to mediate workplace function in a non-clinical sample of 477 Japanese adult workers using the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) measure of subjective cognitive function .[23] Furthermore, a post hoc analysis of 260 patients with MDD noted that subjective cognitive function is a significant predictor of occupational outcomes.[22] Overall, this study substantiates the importance of recognizing the contributions of subjective cognitive function to workplace outcomes.

Two measures of objective cognitive function, the TMT-B time and DSST error scores, were not significant mediators in the current model. The TMT-B and DSST overlap in the cognitive domains they reflect (ie, executive function, psychomotor agility, and visuospatial processing). As such, it is unclear why the DSST symbols score was a significant mediator in the current model, and not the TMT-B or DSST errors score. The DSST involves a greater memory/learning component compared to the TMT-B, which may suggest a role for memory in workplace function[57]. However, it is challenging to draw conclusions regarding differences between cognitive tests due to their lack of specificity to cognitive domains[57]. Other possible explanations for the lack of significant mediational relationships relate to limitations to the data. For example, the DSST scores data had a small range; most participants had a score of 0 (ie, made no errors in the test), and those who did make errors did so infrequently. Regardless, further research to evaluate the specific cognitive domains implicated in the relationship between depressive symptoms and workplace outcomes is warranted.

The findings of the analysis herein must be understood within the context of several limitations. One such limitation was that SDS work scores and cognitive assessments were measured as secondary or tertiary outcomes in the ketamine and infliximab trials. Furthermore, as vortioxetine and ketamine were delivered to patients open-label, awareness of the medication may have influenced outcomes. It should also be noted that there was significant heterogeneity in the patient sample and between subgroups, which included a variety of diagnoses and degrees of disease severity. Finally, subgroup analyses of BD and MDD populations, as well as separate analyses of the contributions of individual antidepressant agents could not be completed given the lack of power. Future studies would be warranted to elucidate the differential impacts of these specific mediations and differences between MDD and BD populations. Attention may also be paid to patient populations with TRD, which demonstrate a higher incidence and severity of cognitive impairments compared to non-treatment-resistant populations.[69] Finally, the analysis herein included mechanistically different agents (ie, vortioxetine, ketamine, infliximab), which serve as both a strength and limitation. It is a strength as the results suggest a common effect across diagnoses and antidepressant agents, but also a weakness as the results may not be ascribed to any specific agent.

5. Conclusion

This study presents further evidence in support of the partial mediational role of both objective and subjective cognitive function in the relationship between depressive symptoms and workplace outcomes. Our results further instantiate the promise of improved psychosocial functioning and workplace performance in persons receiving treatments that improve cognitive functions. Further research is required to demonstrate improvement in cognitive function by functional neuroimaging based on other cognitive paradigms (eg, verbal fluency test).[70,71]

Author contribution. The authors confirm their contribution to the paper as follows: Conceptualization and methodology: JT, DH, NR, and RSM; Data curation: JT, DH, NR, RBM, MS, and YL; Formal analysis: JT, DH, NR, and RS; Writing - original draft: JT and DH; Writing – review & editing: All authors. All authors reviewed the results and approved the final version of the manuscript.

Disclosures. DEJ receives salary support from the Canadian Institutes of Health Research (CIHR), the Canada Graduate Scholarship - Master's (CGS-M), and the University of Toronto. JDR has received research grant support from the Canadian Cancer Society, Canadian Psychiatric Association, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund, and Timeposters Fellowship and industry funding for speaker/consultation/research fees from Allergan, Lundbeck, and COMPASS. He is the medical director of a private clinic providing off-label ketamine infusions for depression. LMWL has received personal fees from Braxia Scientific Corp. RSM has received research grant support from CIHR/

https://doi.org/10.1017/S1092852924002293 Published online by Cambridge University Press

GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, Atai Life Sciences. YL received salary support from the Global Alliance for Chronic Diseases/Canadian Institutes of Health Research (CIHR)/National Natural Science Foundation of China's Mental Health Team Grant and the CIHR Frederick Banting and Charles Best Canada Graduate Scholarship; personal fees from Braxia Scientific Corp. BC, DEJ, DH, FC, JDV, JKT, JV, MS, NR, RBM, RH, and RS declare no competing interests.

References

1. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. *CNS Drugs*. 2010. doi:10.2165/11530230-000000000-00000
2. McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. *Lancet*. 2020; **396**: 1841–1856.
3. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018; **392**: 1789–1858.
4. Ho RCM, Mak K-K, Chua ANC, Ho CSH, Mak A. The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. *Expert Rev Pharmacoecon Outcomes Res*. 2013; **13**: 549–559.
5. Levinson D, Lakoma MD, Petukhova M, Schoenbaum M, Zaslavsky AM, Angermeyer M, et al. Associations of serious mental illness with earnings: Results from the WHO World Mental Health surveys. *Br J Psychiatry*. 2010. doi:10.1192/bjp.bp.109.073635
6. Rodrigues AP, Sousa-Uva M, Fonseca R, Marques S, Pina N, Matias-Dias C. Depression and unemployment incidence rate evolution in Portugal, 1995–2013: General Practitioner Sentinel Network data. *Rev Saúde Pública*. 2017; **51**. doi:10.11606/S1518-8787.2017051006675
7. Zuelke AE, Luck T, Schroeter ML, Witte AV, Hinz A, Engel C, et al. The association between unemployment and depression–Results from the population-based LIFE-adult-study. *J Affect Disord*. 2018; **235**: 399–406.
8. Ferreira AI, Mach M, Martinez LF, Miraglia M. Sickness presenteeism in the aftermath of COVID-19: Is presenteeism remote-work behavior the new (ab)normal? *Front Psychol*. 2021; **12**: 748053.
9. Cao B, Xu L, Chen Y, Wang D, Lee Y, Rosenblat JD, et al. Comparative efficacy of pharmacological treatments on measures of self-rated functional outcomes using the Sheehan Disability Scale in patients with major depressive disorder: A systematic review and network meta-analysis. *CNS Spectr*. 2021; 1–9.
10. Joyce S, Modini M, Christensen H, Mykletun A, Bryant R, Mitchell PB, et al. Workplace interventions for common mental disorders: A systematic meta-review. *Psychol Med*. 2016; **46**: 683–697.
11. McIntyre RS, Suppes T, Tandon R, Ostacher M. Florida best practice psychotherapeutic medication guidelines for adults with major depressive disorder. *J Clin Psychiatry*. 2017. doi:10.4088/jcp.16cs10885
12. Sheehan DV, Harnett-Sheehan K, Spann ME, Thompson HF, Prakash A. Assessing remission in major depressive disorder and generalized anxiety disorder clinical trials with the discan metric of the Sheehan disability scale. *Int Clin Psychopharmacol*. 2011; **26**(2): 75–83. doi: 10.1097/YIC.0b013e328341bb5f.
13. Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry*. 2020; **19**: 269–293.
14. McIntyre RS, Alda M, Baldessarini RJ, Bauer M, Berk M, Correll CU, et al. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. *World Psychiatry*. 2022; **21**: 364–387.
15. Bender A, Farvolden P. Depression and the workplace: A progress report. *Curr Psychiatry Rep*. 2008; **10**: 73–79.
16. Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE. Employer burden of mild, moderate, and severe major depressive disorder: Mental health services utilization and costs, and work performance. *Depress Anxiety*. 2010; **27**: 78–89.
17. Burton WN, Pransky G, Conti DJ, Chen C-Y, Edington DW. The association of medical conditions and presenteeism. *J Occu. Environ Med*. 2004; **46**: S38–S45.
18. Woo J-M, Kim W, Hwang T-Y, Frick KD, Choi BH, Seo Y-J, et al. Impact of depression on work productivity and its improvement after outpatient treatment with antidepressants. *Value Health*. 2011; **14**: 475–482.
19. Cha DS, Carmona NE, Subramaniapillai M, Mansur RB, Lee Y, Lee JH, et al. Cognitive impairment as measured by the THINC-integrated tool (THINC-it): Association with psychosocial function in major depressive disorder. *J Affect Disord*. 2017; **26**(2):75–83; https://doi.org/10.1016/j.jad.2017.06.036
20. Evans VC, Iverson GL, Yatham LN, Lam RW. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: A systematic review. *J Clin Psychiatry*. 2014; **75**: 1359–1370.
21. Kim JM, Chalem Y, di Nicola S, Hong JP, Won SH, Milea D. A cross-sectional study of functional disabilities and perceived cognitive dysfunction in patients with major depressive disorder in South Korea: The PERFORM-K study. *Psychiatry Res*. 2016; **239**: 353–361.
22. McIntyre RS, Soczynska JZ, Woldeyohannes HO, Alsuwaidan MT, Cha DS, Carvalho AF, et al. The impact of cognitive impairment on perceived workforce performance: Results from the International Mood Disorders Collaborative Project. *Compr Psychiatry*. 2015; **56**: 279–282.doi: 10.1016/j.comppsych.2014.08.051.
23. Toyoshima K, Inoue T, Shimura A, Masuya J, Ichiki M, Fujimura Y, et al. Associations between the depressive symptoms, subjective cognitive function, and presenteeism of Japanese adult workers: A cross-sectional survey study. *Biopsychosoc Med*. 2020; **14**: 10.
24. Bortolato B, Miskowiak KW, Köhler CA, Maes M, Fernandes, BS, Berk M, et al. Cognitive remission: A novel objective for the treatment of major depression? *BMC Med*. 2016; **14**: 19.
25. Tamura JK, Carvalho IP, Leanna LMW, Feng JN, Rosenblat JD, Mansur R, et al. Management of cognitive impairment in bipolar disorder: A systematic review of randomized controlled trials. . *CNS Spectr*. 2021;**28**:1–22. doi: 10.1017/S1092852921000092.
26. Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, et al. Recognition and treatment of cognitive dysfunction in major depressive disorder. *Front Psychiatry*. 2018; **9**: 655.
27. Finkelstein SN, Berndt ER, Greenberg PE, Parsley RA, Russell JM, Keller MB. Improvement in subjective work performance after treatment of chronic depression: Some preliminary results. Chronic Depression Study Group.. *Psychopharmacol Bull*. 1996; **32**: 33–40.
28. Lee Y, Rosenblat JD, Lee J, Carmona NE, Subramaniapillai M, Shekotikhina M, et al. Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: A systematic review. *J Affect Disord*. 2018; **227**: 406–415.
29. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014; **17**: 1557–1567.
30. Cao B, Park C., Subramaniapillai M, Lee Y, Iacobucci M, Mansur RB, et al. The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. *Front Psychiatry*. 2019; **10**: 17.
31. McIntyre RS, Florea I, Tonnoir B, Loft H, Lam RW, Christensen MC. Efficacy of vortioxetine on cognitive functioning in working patients with major depressive disorder. *J Clin Psychiatry*. 2017; **78**: 115–121.
32. Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: A systematic review and meta-analysis of randomized clinical trials. *Int J Neuropsychopharmacol*. 2015; **19**. doi: 10.1093/ijnp/pyv082
33. Dadsetan S, Balzano T, Forteza J, Cabrera-Pastor A, Taoro-Gonzalez L, Hernandez-Rabaza V, et al. Reducing peripheral inflammation with infliximab reduces neuroinflammation and improves cognition in rats with hepatic encephalopathy. *Front Mol Neurosci*. 2016; **9**: 106.
34. Gill H, Gill B, Rodrigues NB, Lipsitz O, Rosenblat JD, El-Halabi S, et al. The effects of ketamine on cognition in treatment-resistant depression: A

systematic review and priority avenues for future research.: *Neurosci Biobehav Rev*. 2021; **120**: 78–85.
35. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021; **178**: 383–399.
36. McIntyre RS, Rosenblat JD, Rodrigues NB, Lipsitz O, Chen-Li D, Lee JG, et al. The effect of intravenous ketamine on cognitive functions in adults with treatment-resistant major depressive or bipolar disorders: Results from the Canadian rapid treatment center of excellence (CRTCE). *Psychiatry Res*. 2021; https://doi.org/10.1016/j.psychres.2021.113993
37. McIntyre RS, Subramaniapillai M, Lee Y, Pan Z, Carmona NE, Shekotikhina M, et al. Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: A randomized clinical trial. *JAMA Psychiatry*. 2019;**76**(8):783–790. doi:10.1001/jamapsychiatry.2019.0779
38. Pan Z. *A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Evaluating the Effect of Infliximab on General Cognition in a Population of Depressed Individuals With Bipolar Disorder Type I/II*. University of Toronto (Canada), Ann Arbor, United States; 2018.
39. Kiosses DN, Alexopoulos GS. IADL functions, cognitive deficits, and severity of depression: A preliminary study. *Am J Geriatr Psychiatry*. 2005; **13**: 244–249.
40. Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS. Executive dysfunction and disability in elderly patients with major depression. *Am J Geriatr Psychiatry*. 2001; **9**: 269–274.
41. Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. *J Affect Disord*. 2005; **89**: 125–135.
42. Liu W, Zhou Y, Zheng W, Wang C, Zhan Y, Li H, et al. Mediating effect of neurocognition between severity of symptoms and social-occupational function in anxious depression. *J Affect Disord*. 2019; **246**: 667–673.
43. Woo YS, Rosenblat JD, Kakar R, Bahk W-M, McIntyre RS. Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clin Psychopharmacol Neurosci*. 2016;**274**: 903–910. doi:10.9758/cpn.2016.14.1.1
44. Bonnín Cdel M, González-Pinto A, Solé B, Reinares M, González-Ortega I, Alberich S, et al. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. *J Affect Disord*. 2014; **160**: 50–54.
45. Knight MJ, Baune BT. The direct and indirect relationship between social cognition and psychosocial dysfunction in major depressive disorder. *Front Psychiatry*. 2019; **10**: 347.
46. Knight MJ, Baune BT. Executive function and spatial cognition mediate psychosocial dysfunction in major depressive disorder. *Front Psychiatry*. 2018; **9**: 539.
47. McIntyre RS, Subramaniapillai M, Park C, Zuckerman H, Cao B, Lee Y, et al. The THINC-it tool for cognitive assessment and measurement in major depressive disorder: Sensitivity to change. *Front Psychiatry*. 2020d; **11**: 546.
48. McIntyre RS, Carvalho IP, Lui LMW, Majee, A, Masand PS, Gill H, et al. The effect of intravenous, intranasal, and oral ketamine in mood disorders: A meta-analysis. *J Affect Disord*. 2020. doi:10.1016/j.jad.2020.06.050
49. McIntyre RS, Rodrigues NB, Lee Y, Lipsitz O, Subramaniapillai M, Gill H et al. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: Results from the Canadian Rapid Treatment Center of Excellence. *J Affect Disord*. 2020; **274**: 903–910. doi: 10.1016/j.jad.2020.05.088.
50. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; **134**: 382–389.
51. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation; Psychometrics of the QIDS in public sector patients; MH Trivedi and others. *Psychol Med*. 2004; **34**: 73.
52. Carmody TJ, Rush AJ, Bernstein IH, Brannan S, Husain MM, Trivedi MH. Making clinicians lives easier: Guidance on use of the QIDS self-report in place of the MADRS. J. *Affect Disord*. 2006; **95**: 115–118.
53. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996; **11**(3): 89–95.
54. Sheehan KH and Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. *Int Clin Psychopharmacol*. 2008; **23**: 70–83.
55. Sullivan MJ, Edgley K, Dehoux E. A survey of multiple sclerosis: I. Perceived cognitive problems and compensatory strategy use. *Can J Rehabil*. 1990; **4**: 99–105.
56. Lawrence C, Roy A, Harikrishnan V, Yu S, Dabbous O. Association between severity of depression and self-perceived cognitive difficulties among full-time employees. *Prim Care Companion CNS Disord*. 2013; **15**.
57. Jaeger J. Digit Symbol Substitution Test: The case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol*. 2018a; **38**: 513–519.
58. McLeod DR, Griffiths RR, Bigelow GE, Yingling J. An automated version of the digit symbol substitution test (DSST). *Behav Res Methods Instrument*. 1982; **14**: 463–466.
59. Amaresha AC, Danivas V, Shivakumar V, Agarwal SM, Kalmady SV, Narayanaswamy JC, et al. Clinical correlates of parametric digit-symbol substitution test in schizophrenia. *Asian J Psychiatr*. 2014; **10**: 45–50.
60. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004; **19**: 203–214.
61. Kortte KB, Horner MD, Windham WK. The trail making test, part B: Cognitive flexibility or ability to maintain set? *Appl Neuropsychol*. 2002; **9**: 106–109.
62. Jaeger J. Digit symbol substitution test. *J Clin Psychopharmacol*. 2018b. doi: 10.1097/jcp.0000000000000941
63. Bonnín CM, Martínez-Arán A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, et al. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: A long-term, follow-up study. *J Affect Disord*. 2010; **121**: 156–160.
64. Buist-Bouwman MA, Ormel J, De Graaf R, De Jonge P, Van Sonderen E, Alonso J, et al. Mediators of the association between depression and role functioning. *Acta Psychiatr Scand*. 2008;**118**: 451–458.
65. Knight MJ, Air T, Baune BT. The role of cognitive impairment in psychosocial functioning in remitted depression. *J Affect Disord*. 2018; **235**: 129–134.
66. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013; **30**: 515–527.
67. Fava M, Mahableshwarkar AR, Jacobson W, Zhong W, Keefe RS, Olsen CK, et al. What is the overlap between subjective and objective cognitive impairments in MDD? *Ann Clin Psychiatry*. 2018; **30**: 176–184.
68. Maor Y, Olmer L, Mozes B. The relation between objective and subjective impairment in cognitive function among multiple sclerosis patients--The role of depression. *Mult Scler*. 2001; **7**: 131–135.
69. Gregory E, Torres IJ, Ge R, Blumberger DM, Downar JH, Daskalakis ZJ,et al. Predictors of cognitive impairment in treatment-resistant depression. *J Affect Disord*. 2020; **274**: 593–601. doi: 10.1016/j.jad.2020.05.101.
70. Husain SF, Tang T-B, Tam WW, Tran BX, Ho CS, Ho RC. Cortical haemodynamic response during the verbal fluency task in patients with bipolar disorder and borderline personality disorder: A preliminary functional near-infrared spectroscopy study. *BMC Psychiatry*. 2021. doi: 10.1186/s12888-021-03195-1
71. Husain SF, Yu R, Tang T-B, Tam WW, Tran B, Quek TT, et al. Validating a functional near-infrared spectroscopy diagnostic paradigm for Major Depressive Disorder. *Sci Rep*. 2020; **10**: 9740.