OXFORD

International Journal of Neuropsychopharmacology (2022) 25(12): 992–1002

https://doi.org/10.1093/ijnp/pyac045
Advance Access Publication: August 5, 2022
Regular Research Article

REGULAR RESEARCH ARTICLE

Assessment of Objective and Subjective Cognitive Function in Patients With Treatment-Resistant Depression Undergoing Repeated Ketamine Infusions

Jennifer L. Phillips, PhD, Amanda Van Geel, MSc, Patricia Burhunduli, MSc, Dominique Vasudev, BSc, Lisa A. Batten, PhD, Sandhaya Norris, MD, Jeanne Talbot, MD, PhD, Abigail Ortiz, MD, Olabisi Owoeye, MD, Pierre Blier, MD, PhD

University of Ottawa Institute of Mental Health Research at The Royal, Ottawa, Ontario, Canada (Dr Phillips, Ms Van Geel, Ms Burhunduli, Ms Vasudev, Dr Batten, Dr Norris, Dr Talbot, Dr Ortiz, Dr Owoeye, and Dr Blier); Department of Psychiatry, University of Ottawa, Ottawa, Ontario, Canada (Drs Phillips, Norris, Talbot, Ortiz, Owoeye, and Blier); Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada (Drs Phillips, Norris, Talbot, Ortiz, Owoeye, and Blier); Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada (Dr Phillips, Ms Van Geel, and Ms Vasudev); Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ontario, Canada (Dr Phillips); Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada (Ms Burhunduli and Dr Blier); Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Dr Ortiz); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Dr Ortiz).

Correspondence: Jennifer L. Phillips, PhD, University of Ottawa Institute of Mental Health Research at The Royal, 1145 Carling Avenue, Ottawa, Ontario, K1Z7K4, Canada (Jennifer.Phillips@theroyal.ca).

Abstract

Background: Subanesthetic ketamine infusions can elicit rapid and sustained antidepressant effects, yet the potential cognitive impact of ketamine has not been thoroughly examined. This study measured changes in objective and subjective cognitive function following repeated ketamine treatment.

Methods: Thirty-eight patients with treatment-resistant depression were administered cognitive assessments before and after undergoing 7 i.v. ketamine infusions (0.5 mg/kg over 40 minutes) within a clinical trial examining the efficacy of single and repeated administrations. Depression severity and perceived concentration were evaluated with the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptoms Self-Report.

Results: Twenty-three participants (60.5%) responded after repeated infusions (≥50% decrease in MADRS total scores). We measured significant improvements in several cognitive domains, including attention, working memory, verbal, and visuospatial memory (effect sizes ranging from Cohen $d = 0.37–0.79$). Cognitive changes were attributed to reduction in depressive symptoms except for improvement in verbal memory, which remained significant after adjustment for change in MADRS total score ($P = .029$, $\eta_p^2 = 0.13$). Only responders reported improvement in subjective cognitive function with repeated

Received: February 10, 2022; **Revised:** June 20, 2022; **Accepted:** September 16 2022

ketamine administration (MADRS item 6, $P < .001$, $d = 2.00$; Quick Inventory of Depressive Symptoms Self-Report item 10, $P < .001$, $d = 1.36$).

Conclusion: A short course of repeated ketamine infusions did not impair neurocognitive function in patients with treatment-resistant depression. Further research is required to understand the potential mediating role of response and remission on improved cognitive function accompanying ketamine treatment as well as to examine longer-term safety outcomes. ClinicalTrials.gov identifier NCT01945047

Keywords: Treatment-resistant depression, major depressive disorder, intravenous ketamine, neurocognitive function

Significance Statement

Recent evidence has shown that subanesthetic dose ketamine has rapid antidepressant effects in patients with treatment-resistant depression. In this study, we tested objective and subjective cognitive function in a sample of patients before and after they were administered a short course of repeated ketamine infusions within a clinical trial. The cognitive domains examined included processing speed, attention, executive function, and memory (working, verbal, visuospatial, and autobiographical). Our results showed lack of negative cognitive side effects following repeated ketamine treatment adding to the growing body of evidence supporting the safety of this treatment strategy in terms of short-term cognitive outcomes. Measured improvements in objective cognitive scores following ketamine were largely associated with changes in depressive symptoms. Only patients who responded with treatment perceived an improvement in their concentration and decision-making. Further research is needed to explore longer-term outcomes with prolonged ketamine treatment.

Introduction

Major depressive disorder (MDD) is one of the leading causes of disability, with over 264 million people affected worldwide (World Health Organization, 2020). Cognitive impairment is considered a core symptom of MDD (Rock et al., 2014), with approximately 40% of patients having deficits in at least 1 cognitive domain (Bortolato et al., 2014). Moreover, cognitive symptoms have been suggested to mediate functional impairment in depression and further increase disease burden (McIntyre et al., 2013). Despite the prevalence and persistence of cognitive deficits in MDD, current treatments largely target affective symptoms, thus leaving cognitive symptoms unaddressed (Zuckerman et al., 2018). Approximately 30% of patients with MDD do not adequately respond to existing monoaminergic-modulating medications (Rush et al., 2006; Trivedi et al., 2006). While electroconvulsive therapy (ECT) remains one of the most effective treatments for resistant major depressive episodes (Milev et al., 2016), side effects, including the potential for neurocognitive deficits, limit its use. For patients with treatment-resistant depression (TRD), often defined as failure to respond to at least 2 mechanistically distinct medications for depression administered at adequate dose and duration (Gaynes et al., 2020), there is a clear and continued need for alternative treatment strategies (Rosenblat et al., 2015).

Ketamine, a primarily glutamatergic N-methyl-D-aspartate receptor antagonist, is an emerging treatment strategy for TRD (Walsh et al., 2022). Ketamine elicits more rapid antidepressant effects compared with traditional pharmacological strategies for depression, with higher response and remission rates (Kryst et al., 2020). The antidepressant effects of single subanesthetic doses of i.v. racemic ketamine are transient, however, appearing within 40–60 minutes of administration, peaking at 24 hours post administration, and dissipating after approximately 1 week (Kishimoto et al., 2016). Repeated ketamine administrations have been found to not only sustain the antidepressant effects of ketamine (Murrough et al., 2013a) but also to increase response rates in patients with TRD (Shiroma et al., 2014; Phillips et al., 2019).

Despite the increased use of serial ketamine infusions as a treatment strategy for depression, there remain concerns about its safety with repeated dosing (Sanacora et al., 2017; Short et al., 2018). Safety concerns around repeated ketamine administration largely stem from reports of adverse health effects in recreational ketamine users who commonly take much higher doses than those used to treat depression (Sassano-Higgins et al., 2016). Such findings include an association between frequent recreational ketamine use and cognitive impairment (Morgan et al., 2010; Morgan and Curran, 2012). Moreover, evidence from preclinical studies suggests dose-dependent impairment of learning and memory function with ketamine according to its differential regulation of brain-derived neurotrophic factor levels at anesthetic vs subanesthetic doses (Wu et al., 2020). Although ketamine is administered at low, subanesthetic doses to treat depression with less risk of neurotoxic effects associated with higher doses, it is essential to examine any potential for cognitive impairment with repeated and/or prolonged exposure.

Following an early report of selective impairment in verbal memory recall immediately following single ketamine infusions in patients with TRD (Murrough et al., 2013b), recent reviews report no short-term neurocognitive impairments following ketamine infusions for depression (Crisanti et al., 2020; Gill et al., 2021; Souza-Marques et al., 2021; Vaccarino et al., 2022). Indeed, the results of several recent studies suggest potential pro-cognitive effects associated with single (Murrough et al., 2015; Chen et al., 2018; Keilp et al., 2021) and repeated ketamine infusions (Shiroma et al., 2014, 2020; Zhou et al., 2018; Liu et al., 2019; Zheng et al., 2019; Basso et al., 2020). Despite these findings there remain inconsistencies in currently available data regarding ketamine's effects on specific cognitive domains, and further research on the impact of ketamine on cognition in the context of repeated infusions is warranted (Vaccarino et al., 2022). Finally, recent evidence suggests that subjective cognitive impairment (perceived diminished ability to think, concentrate, or make decisions) is more closely related with symptom severity, remission status, and social and occupational functioning than objective cognitive measures (Potvin et al, 2016; Sawada et al., 2019). Accordingly, it is not known whether (1) patient perception of changes (i.e., subjective improvement) in cognitive function associated with ketamine treatment is also

related to changes in objective measures and (2) subjective measures of cognition vary in accordance with antidepressant response status.

In this study, neurocognitive function in the domains of processing speed, attention, executive function, and memory (working, verbal, visuospatial, and autobiographical) were assessed in participants undergoing a clinical trial of repeated subanesthetic ketamine infusions alongside measurement of depressive symptoms. The aims of this study were to (1) assess changes in objective neurocognitive performance following repeated ketamine infusions; (2) assess changes in clinical ratings and subjective neurocognitive function in accordance with antidepressant response status; and (3) examine the relationship between changes in objective and subjective measures of cognitive function with repeated ketamine treatment. We hypothesized that there would be no short-term adverse effects on cognition with repeated ketamine treatment and that improvements in objective and subjective measures of cognition would accompany reductions in symptom severity.

METHODS

Study Design

Neurocognitive function was assessed as part of a 3-phase single-center clinical trial examining the effects of single, repeated, and maintenance i.v. ketamine infusions for TRD. The trial was conducted at the University of Ottawa Institute of Mental Health Research at the Royal Ottawa Mental Health Centre in Ottawa, Canada (ClinicalTrials.gov identifier NCT01945047). Primary clinical outcomes of the trial were previously reported (Phillips et al., 2019). Cognitive assessments were conducted twice: Time 1: prior to treatment initiation in the trial, before Phase 1, a randomized, double-blind, crossover comparison of single infusions of ketamine and midazolam, and Time 2: within 1 week of completing a course of 6 thrice-weekly open label repeated ketamine infusions (post Phase 2) (see **Figure 1**). Phase 1 infusions occurred at least 7 days apart, and participants were required to have a relapse of depressive symptoms (return to 80% of their baseline Montgomery Åsberg Depression Rating Scale [MADRS] scores) to receive the second infusion. The same criteria (i.e., return to 80% of the baseline MADRS score) were used to determine participant progression to Phase 2. These trial requirements resulted in variation in the number of days between cognitive assessments, yet all participants underwent the second cognitive assessment within 1 week of completing the short course of open-label repeated infusions and after receiving a total of 7 ketamine infusions. The primary outcome measure for the clinical trial was change in depressive symptom severity assessed with the clinician-administered MADRS (Montgomery and Åsberg, 1979) using the structured interview guide (SIGMA) to increase test-retest reliability (Williams et al., 2008). Antidepressant response to repeated infusions was defined as ≥50% decrease in MADRS total scores from Time 1 (pretreatment) to Time 2 (postrepeated infusions). Self-reported depressive symptoms were assessed using the 16-item Quick Inventory of Depressive Symptoms Self Report (QIDS-SR_{16}; Rush et al., 2003).

Drug Administration

Detailed drug administration methodology, safety, and tolerability data appear in Phillips et al., 2019. Briefly, ketamine hydrochloride (Ketalar, ERFA Canada Inc., Montreal, QC, Canada; 0.5 mg/kg, diluted in 0.9% saline) was administered throughout Phases 1 and 2, and midazolam (30 μg/kg diluted in 0.9% saline) was administered once during Phase 1 as an active control for ketamine (Murrough et al., 2013a). Medications were administered by i.v. pump over 40 minutes by a study physician and research nurse in an outpatient setting. Ketamine was administered as an adjunctive treatment; participants remained on stable doses of concomitant psychotropic medication with no changes to treatment regimen for at least 6 weeks prior to trial initiation and throughout the clinical trial.

Participants

Male and female outpatients with TRD (age range, 18–65 years) were recruited into the ketamine trial from physician referrals and advertisements between January 2013 and December 2017. Participants were required to meet DSM-IV-TR criteria for MDD (American Psychiatric Association, 2000) confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). TRD was defined as the failure to respond to at least 2 antidepressant medications of different pharmacological classes plus 2 augmentation strategies at adequate dosages for at least 6 weeks during the current major depressive episode using the Antidepressant Treatment History Form (Sackeim, 2001). Inclusion criteria required a baseline total score ≥25 on the MADRS at screening and randomization. Exclusion criteria included history of drug abuse or dependence as defined by DSM-IV-TR criteria or by positive urine toxicology screen; body mass index ≥35; history of mania, hypomania, or psychosis; and

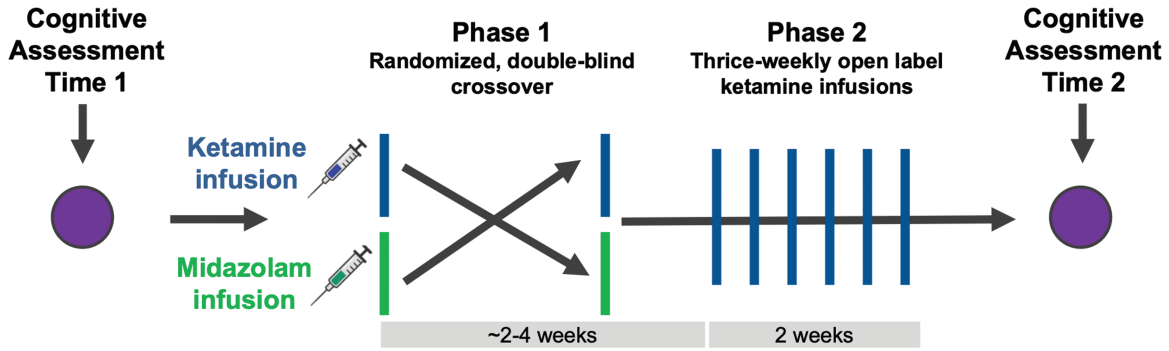

Figure 1. Study design. The first cognitive assessment occurred prior to Phase 1, the randomized, double-blind, crossover comparison of single infusions of ketamine and midazolam. The second cognitive assessment was administered within 1 week of completing a course of 6 thrice-weekly administered open label ketamine infusions in Phase 2.

unstable medical conditions. The study protocol was approved by the Research Ethics Board at the Royal Ottawa Mental Health Centre. All participants provided written informed consent.

Neurocognitive Assessment

All clinical trial participants underwent cognitive assessment. The Mini Mental State Exam (MMSE; Folstein et al., 1975; Tombaugh and McIntyre, 1992) was used to provide a baseline estimate of global cognitive function. Administered neurocognitive tests included Trail Making Test Parts A and B (TMT-A and TMT-B; Morris et al., 1989; Bowie and Harvey 2006), Digit Span (Wechsler, 1945; Wechsler, 2008), California Verbal Learning Test short form, second edition (CVLT-II; Delis et al., 2000), Rey Complex Figure Test (Meyers and Meyers, 1995), a computerized version of the Stroop Colour and Word Test (Stroop, 1935), and the Columbia Autobiographical Memory Interview-Short Form (AMI-SF; McElhiney et al., 2001) (**Table 1**). Each cognitive assessment required approximately 1 hour to complete, with individual tests administered in a fixed sequence in a quiet room by 1 of 2 individuals (study authors J.L.P. and L.A.B.). For the CVLT-II, which includes the presentation of specific words, an alternate word list/test version was used at the second cognitive assessment to minimize practice effects. Each cognitive test yielded multiple outcome measures, and raw scores from each test are reported herein. Change scores (change in raw data in percentage) were computed for each test and averaged to create composite objective cognitive scores for each cognitive domain assessed (Table 1). The composite attention/processing speed score combined change scores for TMT-A and Stroop congruent condition. The composite executive function score combined change scores for TMT-B, Stroop incongruent condition, and Digit Span backwards. For tests where higher values or faster speeds represent better cognitive performance, the signs of the percent change scores were reversed so that positive numbers represent improvement across all scales.

For the AMI-SF, at Time 1 participants were asked to describe specific details for 6 different personal past events. At Time 2, the percentage of correctly recalled information about the events originally described at Time 1 was used to obtain a percent consistency score. Improvement over baseline is not possible, and a decline in scores over time is expected (Semkovska and McLoughlin, 2013).

Alongside the validated neurocognitive tests, subjective measures of cognition were estimated from clinician ratings and participants' self-reported concentration difficulties using MADRS item 6 (concentration difficulties, with ratings ranging from 0 to 6, representing "difficulties in collecting one's thoughts mounting to incapacitating lack of concentration") and QIDS-SR_{16} item 10 (concentration and decision-making, which ranges from 0 to 3, representing "usual capacity to concentrate and make decisions" progressing to inability to "concentrate well enough to read" or "make even minor decisions"). Percent change in MADRS item 6 and QIDS-SR_{16} item 10 scores was calculated and averaged to create a composite subjective cognitive score.

Table 1. List of Objective Cognitive Tests and Corresponding Cognitive Domains

Cognitive domain	Cognitive tests/subtests
Attention and processing speed	Trail making Test-Part A
	Stroop congruent condition
Executive function	Trail making Test-Part B
	Stroop incongruent condition
	Digit span backwards
Working memory	Digit span forward
Verbal memory	California Verbal Learning Test- Short form
Visuospatial memory	Rey Complex Figure Test
Autobiographical memory	Autobiographical Memory Interview-Short form

Statistical Analysis

Changes in MADRS total scores and raw neurocognitive assessment scores from Time 1 to Time 2 were compared using paired *t* tests. To account for change in depressive symptom severity with treatment, change in neurocognitive assessment scores from Time 1 to Time 2 were also compared using repeated-measures ANCOVA models with change in MADRS total scores from Time 1 to Time 2 as a covariate. AMI-SF percent consistency scores were explored using descriptive statistics. Exploratory correlation analyses were conducted to test for relationships between elapsed time between cognitive assessments and change in individual cognitive test scores, and between baseline neurocognitive test scores and change in MADRS total scores. The relationship between clinician-rated (MADRS item 6) and participant self-report concentration scores (QIDS-SR_{16} item 10) at Time 1 was tested using a Pearson correlation. Changes in MADRS item 6 and QIDS-SR_{16} item 10 scores from Time 1 to Time 2 were tested using repeated-measures ANCOVAs with antidepressant response status as a between-participant factor. Relationships between percent improvement in composite objective cognitive domain scores and composite subjective concentration scores were tested using Pearson's correlations. Effect sizes were estimated using Cohen *d* for paired *t* tests and partial eta squared (η_p^2) for ANCOVAs. Results were considered significant at $P<.05$. Data were analyzed using SPSS software (IBM SPSS Statistics; v27).

RESULTS

Demographic and Clinical Characteristics

Forty-three participants were randomized and received at least 1 infusion in the clinical trial (Phillips et al., 2019). Neurocognitive data were incomplete or missing for 5 participants due to study withdrawal (n = 4) or inability to complete cognitive battery due to severe depressive symptoms (n = 1). Therefore, 38 participants completed repeated ketamine treatment and both cognitive assessments and were included in this analysis. Participant baseline demographic and clinical characteristics are summarized in **Table 2**.

Mean (±SD) MADRS total score at Time 1 was 34.7 (±3.9), corresponding to moderate-severe depression (Snaith et al., 1986) (range, 27–41). At Time 2 (following repeated open label ketamine infusions), the mean (±SD) MADRS total score was 18.3 (±11.1), corresponding to mild depression (Snaith et al., 1986) (range, 0–44). The 16.4-point decrease in mean MADRS total score with repeated ketamine infusions was statistically significant ($t_{37}=6.05$, $P<.001$, $d=4.51$), and 23 participants (60.5) were responders at Time 2 (**Figure 2A**).

Objective Cognitive Function

Prior to treatment initiation, no participants displayed global cognitive impairment according to MMSE scores. Participants

Table 2. Demographic and Clinical Characteristics of the Study Sample at Baseline

	Total sample (n = 38)
Age, y (mean± SD)	41.4 (12.5)
Sex, males/females, % (n)	45 (17)/ 55 (21)
BMI, kg/m^2 (mean± SD)	26.4 (4.4)
MDEs, single/recurrent, % (n)	53 (20)/ 47 (18)
Duration of current MDE, y (mean± SD)	5.8 (5.9)
Failed antidepressant trials (mean ± SD)[a]	3.3 (1.7)
Failed augmentation strategies (mean ± SD)[a]	2.9 (1.3)
MADRS total score (mean ± SD)	34.7 (3.9)
QIDS-SR$_{16}$ total score (mean ± SD)	17.8 (4.3)
Current comorbid diagnoses[b]	
Generalized anxiety disorder, % (n)	26 (10)
Agoraphobia, % (n)	24 (9)
Social phobia, % (n)	24 (9)
Panic disorder, % (n)	8 (3)
Obsessive compulsive disorder, % (n)	3 (1)
Alcohol dependence, % (n)	3 (1)
Bulimia nervosa, % (n)	3 (1)

Abbreviations: BMI, body mass index; MADRS, Montgomery Åsberg Depressive Rating Scale; MDE, major depressive episode; QIDS-SR$_{16}$, 16 item Quick Inventory of Depressive Symptomatology Self-Report.

[a]Data represent the number of failed antidepressant trials and augmentations during the current major depressive episode according to the Antidepressant Treatment History Form.

[b]Assessed with the Mini-International Neuropsychiatric Interview.

had a mean (±SD) MMSE score at Time 1 of 29.0 (±1.1), with individual scores ranging from 26 to 30, all above the accepted cutoff of 24, suggesting general cognitive impairment (Lezak et al., 2004). The average time between cognitive assessments was 58.9 ± 12.5 days (range, 39–94 days).

Raw mean (±SD) neurocognitive test scores at Time 1 and Time 2 appear in **Table 3**. For several cognitive tests, scores improved from Time 1 to Time 2, with significant differences generally characterized by small to medium effect sizes (d = 0.37–0.79). Significant improvements were detected in Digit Span forward (P = .001), CVLT-II short (P = .026) and long delay (P = .031) free recall tests, Stroop congruent condition (P = .001), Rey Complex Figure Test intermediate (P < .001) and delay (P < .001) recall trials, and recognition (P = .026). For all but 1 cognitive test showing posttreatment improvement, changes in cognitive scores following treatment were no longer statistically significant when controlled for change in MADRS total scores over the same time period (**Table 3**). The exception was for CVLT-II long-delay free recall, where on average, participants recalled more words at Time 2 than Time 1, even when adjusted for change in depressive symptoms ($F_{1,36}$ = 5.18, P = .029, η_p^2 = 0.13). Tests that showed no significant change over time included TMT-A and TMT-B, Digit Span backward and sequencing, CVLT-II immediate, cued recall, and recognition trials, Stroop incongruent condition, Stroop errors, and Rey Complex Figure Test copy trial.

Exploratory analyses examining the potential impact of assessment interval on change in cognitive test performance revealed a significant negative Pearson correlation between time interval and only 1 administered cognitive test; greater improvement in TMT-B scores was associated with less elapsed time between assessments (r = –0.35, P = .033). Importantly however, the change in TMT-B scores from Time 1 to Time 2 was nonsignificant. Correlation analyses revealed no significant associations between baseline neurocognitive test scores and change in MADRS total scores (all P > .05).

Retrograde autobiographical memory consistency was measured using the AMI-SF. The 37 participants with complete AMI-SF data had a mean (±SD) AMI-SF percent consistency score of 86.0% (±11.3%) from Time 1 to Time 2 (median, 89.7%; range, 50%–100%).

Subjective Cognitive Function

At Time 1 prior to treatment initiation, participants had a mean (±SD) MADRS item 6 score of 3.8 (±0.7), approaching the anchor point score of 4, "difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation." The Time 1 mean (±SD) QIDS-SR$_{16}$ item 10 score was 2.0 (±0.7), corresponding to "most of the time, I struggle to focus my attention or to make decisions." There was a significant positive correlation between MADRS and QIDS-SR$_{16}$ concentration items at Time 1 (r = 0.58, P < .001).

Overall, a repeated-measures ANCOVA revealed that MADRS item 6 scores significantly decreased from Time 1 to Time 2 (main effect of time, $F_{(1,36)}$ = 45.57, P < .001, η_p^2 = 0.56). There was a significant main effect of response status ($F_{(1,36)}$ = 14.35, P = .001, η_p^2 = 0.29) with lower mean MADRS item 6 scores in responders across time and a significant time by response status interaction ($F_{(1,36)}$ = 30.23, P < .001, η_p^2 = 0.46). Posthoc tests revealed a significant decrease in MADRS item 6 scores among ketamine responders only (t_{22} = 9.61, P < .001, d = 2.01) (**Figure 2B**). Similarly, participant scores on the QIDS-SR$_{16}$ item 10 significantly decreased from Time 1 to Time 2 ($F_{(1,34)}$ = 12.42, P = .001, η_p^2 = 0.27), with a significant main effect of response status ($F_{(1,34)}$ = 9.49, P = .004, η_p^2 = 0.22) and a significant time by response status interaction ($F_{(1,34)}$ = 23.77, P < .001, η_p^2 = 0.41). On the QIDS-SR$_{16}$ item 10, self-reported concentration and decision-making significantly improved in ketamine responders only (t_{22} = 6.50, P < .001, d = 1.36) (**Figure 2C**).

Relationship Between Objective and Subjective Measures of Cognition

Composite objective cognitive scores (percent improvement in objective cognitive performance in specific cognitive domains from Time 1 to Time 2) were not significantly correlated with composite subjective concentration scores. Nonsignificant correlations were found for composite attention/processing speed scores (r = 0.20, P = .239), composite executive function scores (r = 0.11, P = .513), and for working, verbal, and visuospatial memory domains (all P > .05).

Discussion

This clinical trial demonstrated the rapid and sustained antidepressant effects of ketamine in a sample of patients with TRD (Phillips et al., 2019). In accordance with previous studies, our findings reveal that a short course of repeated open label ketamine infusions did not negatively impact objective neurocognitive function. Indeed, our findings suggest that ketamine may have pro-cognitive effects on verbal memory that are not accounted for by improvement in depressive symptoms. This study is among the first to examine changes in objective and subjective cognitive function in association with ketamine response. Findings of improved subjective cognitive function among ketamine responders only suggest the potential of ketamine treatment to improve perceived cognitive outcomes alongside other depressive symptoms.

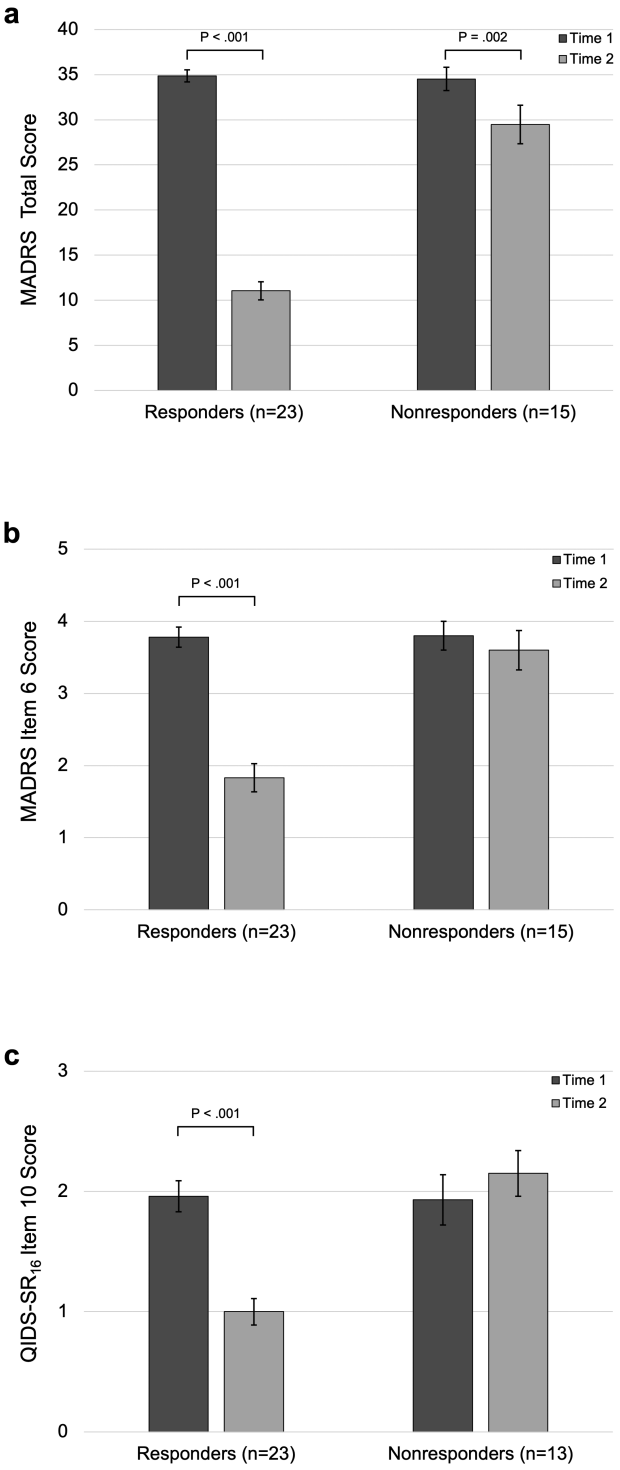

Figure 2. Mean (±standard error) change in rating scale scores before and after repeated ketamine infusions. (A) Montgomery Åsberg Depression Rating Scale (MADRS) total scores, (B) MADRS item 6 concentration scores, and (C) Quick Inventory of Depressive Symptoms Self-Report (QIDS-SR_{16}) item 10 concentration and decision making scores (QIDS-SR_{16} item 10 scores missing for 2 participants).

Subanesthetic doses of i.v. ketamine show promising results as a rapid antidepressant strategy for TRD, yet clinical consensus recommends assessment of cognitive function with prolonged administration (Sanacora et al., 2017). Thus far, several papers have reported an overall lack of negative cognitive side effects associated with single or short-term repeated ketamine administration for depression (reviewed in Crisanti et al., 2020; Gill et al., 2021; Souza-Marques et al., 2021; Vaccarino et al., 2022); nevertheless, studies examining cognitive function with repeated ketamine administration warrant further replication. In our study, following a total of 7 ketamine infusions, participants demonstrated no negative neurocognitive effects. We report small to medium effect sizes for improvement in several neurocognitive domains, including attention (Stroop congruent condition), working memory (Digit Span forward), verbal memory (CVLT-II short and long delay recall), and visuospatial memory (Rey Complex Figure Test immediate and delay recall, and recognition). To date, previous studies have reported cognitive improvement following repeated ketamine infusions in the domains of attention and executive function (Basso et al., 2020), processing speed (Zhou et al., 2018; Liu et al., 2019; Zheng et al., 2019; Shiroma et al., 2020), working memory (Shiroma et al., 2014, 2020), visual memory (Shiroma et al., 2014, 2020; Basso et al., 2020), and verbal memory (Zhou et al., 2018; Zheng et al., 2019). Despite these replicated findings of post-ketamine improvements in specific cognitive domains, there remain inconsistencies in the literature that may be due to the use of different test batteries, analysis strategies, and varied patient populations (MDD, TRD, bipolar depression). Regardless, our data add to the evidence suggesting no overall worsening of cognitive test performance and potential pro-cognitive effects of ketamine with repeated treatment, albeit the possibility of practice effects cannot be discounted.

The mechanisms underlying the potential pro-cognitive effects of ketamine are hypothesized to result from its effects on neuroplasticity (Price and Duman, 2020). Subanesthetic ketamine doses have been shown to rapidly activate the mammalian target of rapamycin signaling pathway and increase synthesis of medial prefrontal cortex and hippocampal brain-derived neurotrophic factor and tropomyosin-related kinase B (Li et al., 2010; Autry et al., 2011; Duman et al., 2016). Importantly, cortical and hippocampal synaptic plasticity and synaptogenesis, thought to contribute to the antidepressant effects of ketamine (Li et al., 2010; Moda-Sava et al., 2019; Deyama and Duman, 2020), play a critical role in learning and memory (Lu et al., 2014). Further research is necessary to understand measured improvements in cognitive performance observed with ketamine treatment and its potential underlying mechanisms, while consideration must be paid to the role of improved depressive symptoms and practice effects on changes in cognitive scores especially in open label studies.

In our study, for all but 1 cognitive test that demonstrated significant improvement in scores from Time 1 to Time 2, when models were adjusted for change in depressive symptom severity, pre- and posttreatment scores no longer significantly differed. This suggests that our findings of improved cognitive performance in attention, working memory, and visuospatial memory following repeated ketamine treatment may be attributed at least in part to reduction in depressive symptoms, as has been previously reported for various cognitive domains (Shiroma et al., 2014; Zhou et al., 2018). In contrast, improvement in verbal memory performance (CVLT-II delayed recall scores) following repeated ketamine treatment remained significant when adjusted for change in depressive symptoms. This finding is consistent with several previous reports of improved verbal learning/memory performance following single and repeated ketamine infusions independent of depressive symptom improvement (Murrough et al., 2015; Zhou et al., 2018; Liu et al., 2019; Zheng et al., 2019). However, there have also been

Table 3. Change in Objective Cognitive Test Scores With Repeated Ketamine Infusions

Cognitive test	Time 1 score (mean ± SD)	Time 2 score (mean ± SD)	Paired *t* test	ANOVA controlling for change in depressive symptoms
TMT-A	23.1 (9.7)	21.6 (11.7)	$t_{37} = 1.65$, $P = .107$, $d = 0.27$	$F_{1,36=}$ 0.002, $P = .965$, $\eta_p^2 =$ 0.00
TMT-B	61.0 (52.3)	56.1 (49.0)	$t_{37} = 0.59$, $P = .559$, $d = 0.10$	$F_{1,36=}$ 1.11, $P = .299$, $\eta_p^2 =$ 0.03
DS forward	10.1 (2.2)	10.9 (2.3)	$t_{37} = 3.75$, $P = .001$, $d = 0.61$	$F_{1,36=}$ 0.95, $P = .336$, $\eta_p^2 =$ 0.03
DS backward	9.3 (2.5)	9.4 (2.2)	$t_{37} = 0.39$, $P = .697$, $d = 0.06$	$F_{1,36=}$ 0.72, $P = .401$, $\eta_p^2 =$ 0.02
DS sequencing	10.0 (2.0)	10.4 (2.2)	$t_{37} = 1.82$, $P = .077$, $d = 0.30$	$F_{1,36=}$ 2.68, $P = .111$, $\eta_p^2 =$ 0.07
CVLT-II immediate	30.0 (4.0)	30.9 (4.2)	$t_{37} = 1.78$, $P = .084$, $d = 0.29$	$F_{1,36=}$ 1.52, $P = .226$, $\eta_p^2 =$ 0.04
CVLT-II short delay	8.1 (1.1)	8.4 (0.86)	$t_{37} = 2.32$, $P = .026$, $d = 0.38$	$F_{1,36=}$ 3.87, $P = .057$, $\eta_p^2 =$ 0.10
CVLT-II long delay	7.9 (1.3)	8.2 (1.2)	$t_{37} = 2.25$, $P = .031$, $d = 0.37$	$F_{1,36=}$ 5.18, $P = .029$, $\eta_p^2 =$ 0.13
CVLT-II cued recall	8.0 (1.1)	8.1 (1.1)	$t_{37} = 0.78$, $P = .440$, $d = 0.13$	$F_{1,36=}$ 1.14, $P = .293$, $\eta_p^2 =$ 0.03
CVLT-II recognition	8.9 (0.4)	8.8 (0.4)	$t_{37} = 1.00$, $P = .324$, $d = 0.16$	$F_{1,36=}$ 1.27, $P = .267$, $\eta_p^2 =$ 0.03
Stroop congruent[a]	1.0 (0.5)	0.8 (0.26)	$t_{36} = 3.46$, $P = .001$, $d = 0.57$	$F_{1,35=}$ 1.78, $P = .190$, $\eta_p^2 =$ 0.05
Stroop incongruent[a]	1.2 (0.5)	1.0 (0.6)	$t_{36} = 1.79$, $P = .083$, $d = 0.29$	$F_{1,35=}$ 0.17, $P = .684$, $\eta_p^2 =$ 0.01
Stroop errors[a]	2.5 (6.5)	2.0 (5.1)	$t_{36} = 0.34$, $P = .737$, $d = 0.06$	$F_{1,35=}$ 1.23, $P = .275$, $\eta_p^2 =$ 0.03
RCFT copy	33.5 (2.2)	33.4 (2.7)	$t_{37} = 0.16$, $P = .876$, $d = 0.03$	$F_{1,36=}$ 0.71, $P = .405$, $\eta_p^2 =$ 0.02
RCFT intermediate	19.1 (6.9)	23.3 (7.0)	$t_{37} = 4.90$, $P < .001$, $d = 0.79$	$F_{1,36} = 1.52$, $P = .226$, $\eta_p^2 = 0.04$
RCFT Delay	19.1 (6.6)	22.9 (7.2)	$t_{37} = 4.80$, $P < .001$, $d = 0.78$	$F_{1,36=}$ 0.91, $P = .346$, $\eta_p^2 =$ 0.03
RCFT Recognition	20.7 (1.8)	21.3 (2.0)	$t_{37} = 2.33$, $P = .026$, $d = 0.38$	$F_{1,36=}$ 0.85, $P = .362$, $\eta_p^2 =$ 0.02

Abbreviations: CVLT-II, California Verbal Learning Test, short form; DS, Digit Span; RCFT, Rey Complex Figure Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B.
[a]Stroop data missing for 1 participant.

contradictory findings with reports of impaired verbal memory delayed recall after single (Murrough et al., 2013b) and repeated infusions (Basso et al., 2020) independent of change in clinical symptom findings. More definitive assessment of the observed changes in cognition with i.v. ketamine and the potential mediating or moderating roles of co-occurring improvements in depressive symptoms requires randomized controlled trials with cognition as the primary outcome measure, large sample sizes, and the use of standardized neurocognitive batteries (Vaccarino et al., 2022).

Autobiographical memory deficit is commonly assessed in ECT trials as it has been identified as a critical adverse side effect of ECT (Fraser et al., 2008). To our knowledge, only 1 previous study has examined the potential impact of repeated ketamine infusions on autobiographical memory (Diamond et al., 2014). Although the AMI-SF is difficult to interpret in the absence of a comparison group, the median consistency score of 89.7% obtained in the present study compares favorably with median scores reported by Diamond et al. (2014) following 3 or 6 ketamine infusions (92 and 94%, respectively). Further, mean post-ECT AMI-SF percentage consistency scores reported in the literature have generally been lower than those obtained in the present study (approximately 72%; Kessler et al., 2014; Napierala et al., 2019). Further research is necessary to confirm lack of autobiographical memory deficit following short-term repeated ketamine infusions. Ongoing randomized clinical trials that directly compare the effects of ketamine and ECT across multiple cognitive domains will better inform whether ketamine has a more favorable cognitive profile relative to ECT (Mathew et al., 2019; Phillips et al., 2020).

Although several studies have examined objective neurocognitive function in patients undergoing ketamine treatment for depression, to date, few have specifically reported on changes in subjective or perceived cognitive function (Chen et al., 2021; McIntyre et al., 2021). Subjective cognitive impairment has been suggested to be more closely associated with functional disability than objective impairments (Potvin et al 2016), underscoring the importance of exploring perceived cognitive changes with treatment. In the present study, following repeated ketamine infusions there was an improvement in mean concentration scores using both clinician-administered (MADRS) and self-report (QIDS-SR_{16}) scale items. Only participants who responded to ketamine reported significant improvements in concentration. These findings reveal a link between improved perceived concentration and improvement in other depressive symptoms following repeated ketamine infusions consistent with previous studies (McIntyre et al., 2021). Of course, reporting bias is possible as participants were unblinded to treatment and their own symptom recovery in the trial.

There was no correlation between changes in composite objective cognitive domain scores and subjective cognitive scores. This is consistent with previous reports of discrepancies between measures of objective and subjective cognition in depression (Srisurapanont et al., 2017; Petersen et al., 2019; Serra-Blasco et al., 2019) and in clinical trials assessing the cognitive effects of medications for depression (Mahableshwarkar et al., 2015). Srisurapanont et al. (2017) reported that age and education predict objective cognition function, whereas depression severity and treatment better predict subjective cognitive deficits. Persistence of cognitive impairment following remission of other symptoms (Bortolato et al., 2014) further supports the disconnect between objectively measured vs subjective cognitive function. Consequently, although objective measurement of cognition may be less biased (Schwert et al., 2018), the strong association between subjective cognitive deficit and functional recovery highlights the importance of assessing both outcomes while patients undergo novel treatment strategies for depression.

This study examined longitudinal changes in objective and subjective cognitive function as patients with TRD underwent a short course of repeated ketamine infusions within a rigorously conducted clinical trial. Strengths of the study include the homogenous and clinically well-defined patient sample, the low dropout rate, the use of validated neurocognitive tests assessing multiple domains of cognition, and the reporting of subjective cognitive ratings considered in relation to treatment

response. Despite these strengths, this study has certain limitations that merit discussion. First, the sample was relatively small. Larger samples would allow for meaningful examination of the potential effects of sex, gender, and age on cognitive measures. There was no control group, and we lacked data on participant education level precluding comparison of longitudinal changes in participant cognitive function to normative data or to account for potential practice effects. Ketamine was administered as an adjunctive treatment, and participants maintained their concomitant medications (although no medication changes were permitted from 6 weeks preceding randomization and throughout the trial). Repeated ketamine infusions were administered open label without a control condition. The clinical trial was designed to evaluate the efficacy of the antidepressant effects of single and repeated ketamine infusions. Cognitive function was a secondary outcome, and thus the timing of cognitive assessments was not standardized. For example, study design–related limitations include the administration of a single midazolam infusion in the double-blind crossover phase and the requirement for depressive symptom relapse following the first single ketamine infusion prior to receiving repeated infusions; this later condition resulted in between-participant variation in the time between cognitive assessments. Despite these limitations, the methodology remained consistent for all participants, with cognitive assessments administered prior to receipt of any treatment in the randomized phase and within 1 week of completing the course of open label repeated infusions. Further, exploratory analyses revealed little to no evidence of an effect of differences in elapsed time between assessments on cognitive test performance. Another limitation was estimation of subjective cognitive function using single items from clinical scales (MADRS item 6 and QIDS-SR$_{16}$ item 10). Future studies would benefit from the use of a full scale designed and validated for the assessment of subjective cognitive function such as the Perceived Deficits Questionnaire for Depression (Lam et al., 2018). Approximately one-quarter of the sample had comorbid anxiety disorder diagnoses, yet we did not control for anxiety symptoms in our analyses. While few studies have examined the independent impact of anxiety symptoms on cognitive function, previous studies have reported no differences in cognitive performance in MDD patients with and without comorbid anxiety (Lyche et al., 2010; Jin et al., 2020). Finally, longer treatment and follow-up periods would better identify any potential longer-term cognitive side effects or benefits associated with subanesthetic ketamine infusions for depression.

In summary, a short course of repeated subanesthetic dose ketamine infusions did not impair objective neurocognitive outcomes in patients with TRD. Together with findings of perceived improvement in concentration among ketamine responders, our findings support the continued investigation into possible cognitive benefits of ketamine for TRD. Further research is required to understand the potential mediating role of improved depressive symptoms on measured changes in cognitive function accompanying ketamine treatment as well as to examine longer-term safety outcomes.

Acknowledgments

The authors thank Wendy Fusee, RN, Holly English, BSN, Sara de la Salle, PhD, Taylor Hatchard, PhD, Meagan Birmingham, MA, MBA, Maria da Silva, Hassan Khan, BA, Elizabeth Kamler, BSN, MPH, Mostafa El Mansari, PhD, and Jean Blier, MD, for their contributions. This study was presented in part at the Society of Biological Psychiatry 73rd Annual Scientific Convention and Program, New York City, NY, USA, May 10–12, 2018.
This study was supported by the Canadian Institutes of Health Research (grant no. 274324 to Dr. Blier) and a Tier 1 Canada Research Chair (to Dr. Blier).

Interest Statement

Dr. Blier received grant funding and/or honoraria for lectures and/or participation in advisory boards for Abbvie, Bristol-Myers Squibb, Eisai, Elvium Life Sciences, Janssen, Lundbeck, Otsuka, Pierre Fabre Médicaments, Pfizer, Shire, and Takeda. All other authors declare no conflicts of interest.

References

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th ed, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng P, Kavalali ET, Monteggia LM (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475:91–95.

Basso L, Bönke L, Aust S, Gärtner M, Heuser-Collier I, Otte C, Wingenfeld K, Bajbouj M, Grimm S (2020) Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. J Psychiatry Res 123:1–8.

Bortolato B, Carvalho AF, McIntyre RS (2014) Cognitive dysfunction in major depressive disorder: a state-of-the-art clinical review. CNS Neurol Disord Drug Targets 13:1804–1818.

Bowie CR, Harvey PD (2006) Administration and interpretation of the Trail Making Test. Nat Protoc. 1:2277–2281.

Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, Cheng CM, Su TP (2018) Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. J Affect Disord 241:1–7.

Chen MH, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, Tu PC, Bai YM, Mao WC, Su TP (2021) Low-dose ketamine infusion for treating subjective cognitive, somatic, and affective depression symptoms of treatment-resistant depression. Asian J Psychiatry 66:102869.

Crisanti C, Enrico P, Fiorentini A, Delvecchio G, Brambilla P (2020) Neurocognitive impact of ketamine treatment in major depressive disorder: a review on human and animal studies. J Affect Disord 276:1109–1118.

Delis DC, Kramer JH, Kaplan E, Ober BA (2000) California verbal learning test manual. 2nd ed. pp. 287. London: Pearson.

Deyama S, Duman RS (2020) Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine. Pharmacol Biochem Behav 188:172837.

Diamond PR, Farmery AD, Atkinson S, Halder Jm Williams N, Cowen PJ, Geddes JR, McShane R (2014) Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice-weekly in an ECT clinic. J Psychopharmacol 28:536–544.

Duman RS, Aghajanian GK, Sanacora G, Krystal JH (2016) Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 22:238–249.

Folstein MF, Folstein SE, McHugh PR (1975) A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Fraser LM, O'Carroll RE, Ebmeier KP (2008) The effect of electroconvulsive therapy on autobiographical memory: a systematic review. J ECT 24:10–17.

Gaynes GN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, Boland E, Weber RP, Randolph C, Bann C, Coker-Schwimmer E, Viswanathan M, Lohr KN (2020) Defining treatment-resistant depression. Depress Anxiety 37:134–145.

Gill H, Gill B, Rodrigues NB, Lipsitz O, Rosenblat JD, El-Halabi S, Nasri F, Mansur RB, Lee Y, McIntyre RS (2021) The effects of ketamine on cognition in treatment-resistant depression: a systematic review and priority avenues for future research. Neurosci Biobehav Rev 120:78–85.

Jin L, Qiangli D, Xiaowen L, Jinrong S, Liang Z, Wang M, Bangshan L, Yumeng J, Ping W, Hua G, Futao Z, Xiangyang Z, Yan Z, Lingjiang L (2020) Influence of comorbid anxiety symptoms on cognitive deficits in patients with major depressive disorder. J Affect Dis 260:91–96.

Keilp JG, Madden SP, Marver JE, Frawley A, Gluck M, Mann JJ, Grunebaum MF (2021) Effects of ketamine versus midazolam on neurocognition at 24 hours in depressed patients with suicidal ideation. J Clin Psychiatry 82:21–m13921.

Kessler U, Schoeyen HK, Andreassen OA, Eide GE, Malt UF, Oedegaard KJ, Morken G, Sundet K, Vaaler AE (2014) The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. J Clin Psychiatry 75:e1306–e1313.

Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, Correll CU (2016) Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. Psychol Med 46:1459–1472.

Kryst J, Kawalec P, Mikrut Mitoraj A, Pilc A, Lasoń W, Brzostek T (2020) Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. Pharmacol Rep 72:543–562.

Lam RW, Lamy FX, Danchenko N, Yarlas A, White MK, Rive B, Sragoussi D (2018) Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. Neuropsychiatry Dis Treat 14:2861–2877.

Lezak MD, Howieson DB, Loring DL (2004) Neuropsychological assessment. 4th ed. New York: Oxford University Press.

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li ZY, Aghajanian G, Duman RS (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.

Liu W, Zhou Y, Zheng W, Wang C, Zhan Y, Lan X, Zhang B, Li H, Chen L, Ning Y (2019) Repeated intravenous infusions of ketamine: neurocognition in patients with anxious and nonanxious treatment-resistant depression. J Affect Disord 259:1–6.

Lu B, Nagappan G, Lu Y (2014) BDNF and synaptic plasticity, cognitive function, and dysfunction. Handb Exp Pharmacol 220:223–250.

Lyche P, Jonassen R, Stiles TC, Ulleberg P, Landrø NI (2010) Cognitive control functions in unipolar major depression with and without co-morbid anxiety disorder. Front Psychiatry 1:149.

Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RSE (2015) A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. Neuropsychopharmacology 40:2025–2037.

Mathew SJ, Wilkinson ST, Altinay M, Asghar-Ali A, Chang LC, Collins KA, Dale RM, Hu B, Krishnan K, Kellner CH, Malone DA, Murrough JW, Ostroff RB, Sanacora G, Shao M, Anand A (2019) ELEctroconvulsive therapy (ECT) vs. ketamine in patients with treatment-resistant depression: the ELEKT-D study protocol. Contemp Clin Trials 77:19–26.

McElhiney M, Moody B, Sackeim H (2001) The autobiographical memory interview - short form, version 3. New York: New York State Psychiatric Institute.

McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, Alsuwaidan M, Baskaran A (2013) Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety 30:515–527.

McIntyre RS, Rosenblat JD, Rodrigues NB, Lipsitz O, Chen-Li D, Lee JG, Nasri F, Subramaniapillai M, Kratiuk K, Wang A, Gill H, Mansur RB, Ho R, Lin K, Lee Y (2021) 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 302:113993.

Meyers JE, Meyers KR (1995) Rey complex figure test and recognition trial professional manual, pp. 119. Lutz, FL: PAR.

Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, Modirrousta M, Patry S, Vila-Rodriguez F, Lam RW, MacQueen GM, Parikh SV, Ravindran AV, CANMAT Depression Work Group (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatry 61:651–675.

Moda-Sava RN, Murdock MH, Parekh PK, Fetcho RN, Huang BS, Huynh TN, Witztum J, Shaver DC, Rosenthal DL, Always EJ, Lopez K, Meng Y, Nellissen L, Grosenick L, Milner TA, Deisseroth K, Bito H, Kasai H, Liston C (2019) Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science 364:eaat8078.

Montgomery SA, Åsberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.

Morgan CJA, Curran HV (2012) Ketamine use: a review. Addiction 107:27–38.

Morgan CJA, Muetzelfeldt L, Curran HV (2010) Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction 105:121–133.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellitis ED, Clark C (1989) The consortium to establish a registry for Alzheimer's disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 39:1159–1165.

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV (2013a) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 74:250–256.

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ (2013b) Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 170:1134–1142.

Murrough JW, Burdick KE, Levitch CF, Perez AM, Brallier JW, Chang LC, Foulkes CF, Charney DS, Mathew SJ, Iosifescu DV (2015) Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. Neuropsychopharmacology 40:1084–1090.

Napierala M, Bodnar A, Chlopocka-Wozniak M, Permoda-Osip A, Rybakowski J (2019) Electroconvulsive therapy and autobiographical memory in patients with treatment-resistant depression. Psychiatry Pol 53:589–597.

Petersen JZ, Porter RJ, Miskowiak KW (2019) Clinical characteristics associated with the discrepancy between subjective and objective cognitive impairment in depression. J Affect Disord 246:763–774.

Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, Owoeye O, Batten LA, Blier P (2019) Single, repeated, and maintenance ketamine infusions for treatment resistant depression: a randomized controlled trial. Am J Psychiatry 176:401–409.

Phillips JL, Jaworska N, Kamler E, Bhat V, Blier J, Foster JA, Hassel S, Ho K, McMurray L, Milev R, Moazamigoudarzi Z, Placenza FM, Richard-Devantoy S, Rotzinger S, Turecki G, Vazquez GH, Kennedy SH, Blier P; On Behalf of the CAN-BIND Investigator Team (2020) A randomized, crossover comparison of ketamine and electroconvulsive therapy for treatment of major depressive episodes: a Canadian Biomarker Integration Network in Depression (CAN-BIND) study protocol. BMC Psychiatry, 20:268.

Potvin S, Charbonneau G, Juster RP, Purdon S, Tourjman SV (2016) Self-evaluation and objective assessment of cognition in major depression and attention deficit disorder: implications for clinical practice. Compr Psychiatry 70:53–64.

Price RB, Duman R (2020) Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry 25:530–543.

Rock PL, Roiser JP, Riedel WJ, Blackwel AD (2014) Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 44:2029–2040.

Rosenblat C, McIntyre RS, Alves GS, Fountoulakis KN, Carvalho AF (2015) Beyond monoamines-novel targets for treatment-resistant depression: a comprehensive review. Curr Neuropharmacol 13:636–655.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB (2003) The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 54:573–583.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 163:1905–1917.

Sackeim HA (2001) The definition and meaning of treatment-resistant depression. J Clin Psychiatry 62:10–17.

Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, Summergrad P, Nemeroff CB, American Psychiatric Association A Council of Research Task Force on novel Biomarkers Treatments (2017) A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry 74:399–405.

Sassano-Higgins S, Baron D, Juarez G, Esmaili N, Gold MA (2016) Review of ketamine abuse and diversion. Depress Anxiety 33:718–727.

Sawada K, Yoshida K, Ozawa C, Mizuno Y, Rubinstein EB, Suzuki T, Mimura M, Uchida H (2019) Impact of subjective vs. objective remission status on subjective impairments in depression. J Affect Disord 246:99–104.

Schwert C, Stohrer M, Aschenbrenner S, Weisbrod M, Schröder A (2018) Biased neurocognitive self-perception in depressive and in healthy persons. J Affect Disord 232:96–102.

Semkovska M, McLoughlin DM (2013) Measuring retrograde autobiographical amnesia following electroconvusive therapy: historical perspective and current issues. J ECT 29:127–133.

Serra-Blasco M, Torres IJ, Vincent-Gil M, Goldberg X, Navarra-Ventura G, Aguilar E, Via E, Portella MJ, Figuereo I, Palao D, Lam RW, Cardoner N (2019) Discrepancy between objective and subjective cognition in major depressive disorder. Eur Neuropsychopharmacol 29:46–56.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59:22–33, quiz 34.

Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO (2014) Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. Int J Neuropsychopharmacol 17:1805–1813.

Shiroma PR, Thuras P, Wels J, Albott CS, Erbes C, Tye S, Lim KO (2020) Neurocognitive performance of repeated versus single intravenous subanesthetic ketamine in treatment resistant depression. J Affect Disord 277:470–477.

Short B, Fong J, Galvez V, Shelker W, Loo CK (2018) Side-effects associated with ketamine use in depression: a systematic review. Lancet Psychiatry 5:65–78.

Snaith RP, Harrop FM, Newby DA, Teale C (1986) Grade scores of the Montgomery-Åsberg depression and the clinical anxiety scales. Br J Psychiatry 148:599–601.

Souza-Marques B, Santos-Lima C, Araújo-de-Freitas L, Vieira F, Jesus-Nunes AP, Quarantini LC, Sampaio AS (2021) Neurocognitive effects of ketamine and esketamine for treatment-resistant major depressive disorder: a systematic review. Harv Rev Psychiatry 29:340–350.

Srisurapanont M, Suttajit S, Eurviriyanukul K, Varnado P (2017) Discrepancy between objective and subjective cognition in adults with major depressive disorder. Sci Rep 7:3901.

Stroop JR (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18:643–662.

Tombaugh TN, McIntyre NJ (1992) The Mini-Mental State Examination: a comprehensive review. J Am Geriatr Soc 40:922–935.

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 163:28–40.

Vaccarino SR, Adamsahib F, Milev RV, Parikh SV, Lam RW, Blier P, Kennedy SH, Ladha KS, Bhat V (2022) The effects of ketamine on cognition in unipolar and bipolar depression: a systematic review. J Clin Psychiatry 83:21–r13870.

Walsh Z, Mollaahmetoglu OM, Rootman J, Golsof S, Keeler J, Marsh B, Nutt DJ, Morgan CJA (2022) Ketamine for the treatment of mental health and substance use disorders: comprehensive systematic review. BJPsych Open 8e:1–12.

Wechsler D (1945) Wechsler memory scale. San Antonio, TX: Psychological Corporation.

Wechsler D (2008) WAIS-IV administration and scoring manual, pp. 257. London: Pearson.

Williams JB, Kobak KA (2008) Development and reliability of a structured interview guide for the Montgomery Åsberg Depression Rating Scale (SIGMA). Br J Psychiatry 192:52–58.

World Health Organization (2020) Depression. https://www.who.int/news-room/fact-sheets/detail/depression. Accessed July 21, 2020.

Wu C, Wang Y, He Y, Wu S, Xie Z, Zhang J, Shen J, Wang Z, He L (2020) Sub-anesthetic and anesthetic ketamine produce different long-lasting behavioral phenotypes (24 h post-treatment) via inducing different brain-derived neurotrophic factor (BDNF) expression level in the hippocampus. Neurobiol Learn Mem 2019:107136.

Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, Chen LJ, Li MD, Ning YP (2019) Neurocognitive performance and repeated dose intravenous ketamine in major depressive disorder. J Affect Disord 246:241–247.

Zhou Y, Zheng W, Liu W, Wang C, Zhan Y, Li H, Chen L, Li M, Ning Y (2018) Neurocognitive effects of six ketamine infusions and the association with antidepressant response in patients with unipolar and bipolar depression. J Psychopharmacol 32:1118–1126.

Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, Iacobucci M, Yim SJ, Lui LMW, Rong C, McIntyre RS (2018) Recognition and treatment of cognitive dysfunction in major depressive disorder. Front Psychiatry 9:655.