Journal of Affective Disorders 308 (2022) 289–297

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Neurocognitive effects of repeated ketamine infusions in comorbid posttraumatic stress disorder and major depressive disorder

C. Sophia Albott [a,b,*], Kelvin O. Lim [a,c], Christopher Erbes [a,b,1], Paul Thuras [a,b], Joseph Wels [d], Susanna J. Tye [e], Paulo R. Shiroma [a,b]

[a] Department of Psychiatry & Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, United States of America
[b] Mental Health Service Line, Minneapolis VA Health Care System, Minneapolis, MN, United States of America
[c] Geriatric Research Education and Clinical Center, Minneapolis VA Health Care System, Minneapolis, MN, United States of America
[d] Department of Anesthesiology, Minneapolis VA Health Care System, Minneapolis, MN, United States of America
[e] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States of America

ARTICLE INFO

Keywords:
Ketamine
Posttraumatic stress disorder
PTSD
Major depressive disorder
Cognition
Comorbidity

ABSTRACT

Background: The glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine rapidly ameliorates posttraumatic stress disorder (PTSD) and depression symptoms in individuals with comorbid PTSD and major depressive disorder (MDD). However, concerns over ketamine's potential neurocognitive side effects have yet to be assessed in this population. The current study investigated 1) changes in neurocognitive performance after a repeated ketamine dosing regimen and 2) baseline neurocognitive performance as a predictor of ketamine treatment effect.

Method: Veterans with comorbid PTSD and MDD ($N = 15$) received six infusions of 0.5 mg/kg ketamine over a 12-day period. Neurocognitive and clinical outcomes assessments occurred at baseline and within 7 days of infusion-series completion using the CogState battery.

Results: Repeated ketamine infusions did not significantly worsen any measures of cognition. Rather, significant improvement was observed in working memory following completion of the infusion series. In addition, greater improvements in PTSD and MDD symptoms were associated with lower working memory, slower processing speed and faster set shifting at baseline. Lower verbal learning was also predictive of improvement in depression.

Limitations: This study applied an open-label design without a placebo control. As such, it is not known to what extent the correlations or improvement in neurocognitive performance may have occurred under placebo conditions.

Conclusion: This is the first study to examine the neurocognitive effects of repeated ketamine in participants with comorbid PTSD and MDD. Our findings suggest potential baseline neurocognitive predictors of ketamine response for comorbid PTSD and MDD symptoms.

1. Introduction

Ketamine, a phencyclidine hydrochloride derivative and a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor, has demonstrated rapid antidepressant effects in previously medication-refractory individuals with major depressive disorder (Murrough et al., 2013; Zarate et al., 2006). Esketamine, an enantiomer of racemic ketamine, received recent FDA approval for depression that has not responded to medications or therapy (Popova et al., 2019). Research has begun to explore ketamine's efficacy for other diagnoses known to co-occur with depression, such as posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and bipolar depression, all with promising results (Albott et al., 2018; Diazgranados et al., 2010; Rodriguez et al., 2013).

Despite increasing clinical use, little is known about the long-term neurocognitive effects of ketamine. Risks associated with adverse effects of ketamine, including neurocognitive risks, have led some groups to emphasize the public health significance associated with wide-spread

* Corresponding author at: Department of Psychiatry, University of Minnesota Medical School, F282/2A West, 2450 Riverside Avenue, Minneapolis, MN 55454-1495, United States of America.
E-mail address: albot002@umn.edu (C.S. Albott).
[1] Died on May 30, 2021.

https://doi.org/10.1016/j.jad.2022.04.066
Received 17 March 2021; Received in revised form 27 January 2022; Accepted 10 April 2022
Available online 14 April 2022
0165-0327/Published by Elsevier B.V.

use (Singh et al., 2017). In 2013, following the recommendations of the Advisory Council on the Misuse of Drugs, the United Kingdom government raised ketamine from a Class C drug to a Class B drug due to concerns about bladder damage in ketamine drug users. Regarding long-term neurocognitive side effects, this body noted that more research is needed (Great Britain. Advisory Advisory Council on the Misuse of Drugs, 2013).

Cognitive side effects and dissociation have been associated with acute ketamine administration in healthy volunteers. Dissociative side effects peak immediately following ketamine administration and typically resolve within 1 to 2 h following cessation of the drug. Corresponding to dissociative effects, cognitive function has been shown to be affected after a single infusion. A single subanesthetic dose of ketamine was shown to interrupt short-term learning without impairment of previously learned information (Krystal et al., 2005; Morgan et al., 2004a; Rowland et al., 2005). Additional studies of the acute effects of ketamine in healthy volunteers have shown selective impairments in aspects of executive functioning including vigilance and verbal fluency (Krystal et al., 1994; Morgan et al., 2009), acute deficits in episodic, recognition, and working memory as well as slowed semantic processing and procedural learning. (Morgan et al., 2004a; Parwani et al., 2005).

Data on the long-term effects of ketamine exposure derive primarily from observational studies of recreational ketamine users. Findings from these studies are mixed and cognitive deficits appear to be dose related (that is, worse in frequent heavy users). Cognitive deficits in frequent recreational users align with the deficits observed in controlled studies of acute ketamine administration in healthy volunteers (Morgan et al., 2009). Chronic frequent ketamine use has also been associated with disruption of spatial working memory and pattern recognition memory tasks (Morgan et al., 2010). For individuals with less frequent recreational use, improvements in semantic memory were observed when ketamine use is reduced or stopped. However, for frequent recreational users, it appears that episodic memory impairments and attention deficits do not improve following ketamine use reduction (Morgan et al., 2004b).

Studies assessing neurocognition in repeated dosing strategies of ketamine in psychiatric populations are inconsistent with the data in frequent recreational ketamine users. A randomized controlled trial of six ketamine infusions compared to one ketamine infusion for treatment-resistant depressed veterans found repeated ketamine infusions to result in greater improvements in speed of processing, set shifting, and spatial working memory compared to a single ketamine infusion (Shiroma et al., 2020a). In an open label study, Shiroma and colleagues demonstrated that repeated infusions of ketamine are associated with improvements in working memory and visual memory without any decrement in baseline cognitive measures (Shiroma et al., 2014a). Zheng and colleagues found that six ketamine infusions were associated with improvement in speed of processing and verbal learning in bipolar and unipolar depressed patients treated with repeated infusions (Zheng et al., 2019). Likewise, an open-label study of 28 patients receiving three or six ketamine infusions found no change in autobiographical memory with some improvement in immediate and delayed recall following either ketamine regimen (Diamond et al., 2014).

Despite extensive research in healthy volunteers, and an emerging literature on the neurocognitive effects of ketamine in depressed patients, no study has examined neurocognitive outcomes following repeated ketamine treatment in individuals with PTSD. Neurocognitive functioning is well known to be affected in individuals with PTSD (Aupperle et al., 2012b; Jak et al., 2018). Recent evidence suggests working memory deficits may serve as a premorbid vulnerability factor that promotes the development of PTSD and depression (Millan et al., 2012). It is well established that a large majority of individuals with a diagnosis of PTSD also meet criteria for major depressive disorder (Kehle et al., 2011; Rytwinski et al., 2013). Individuals with comorbid PTSD and MDD have also been shown to demonstrate greater neurocognitive impairment than individuals with either disorder alone (Johnsen et al., 2008; Nijdam et al., 2013; Sachinvala et al., 2000). The commonality of comorbid PTSD and MDD following trauma exposure as well as heighted frequency of cognitive dysfunction suggest a shared underlying deficit (Albott et al., 2021). It has been suggested that dysfunction in glutamatergic signaling in concert with trauma-related activation of the hypothalamic-pituitary-adrenal axis account for the cognitive deficits observed in comorbid PTSD and MDD. Importantly, ketamine is hypothesized to modulate glutamatergic signaling with significant implications for both psychiatric symptoms and cognitive functioning.

Ascertaining the effect of ketamine over neurocognition is imperative to both prevent exacerbation of clinical symptoms and cognitive dysfunction and to identify novel treatment approaches for post-traumatic psychiatric disorders. Thus, the aims of this study were to (1) examine the neurocognitive performance changes after completing six ketamine infusions among participants with comorbid PTSD and MDD and (2) to examine baseline neurocognitive performance predictors of change in PTSD and depression symptoms after six ketamine infusions.

2. Methods

2.1. Participants

The study was approved by the Minneapolis VA Health Care System (MVAHCS) Institutional Review Board and registered at http://ClinicalTrials.gov (identifier: NCT02577250). Written informed consent was obtained from all participants before participation. Study participants included male and female veterans, aged 18–75 years, with diagnoses of chronic PTSD and moderate to severe treatment-resistant MDD. It is well established that the large majority of individuals diagnosed with PTSD also meet criteria for another psychiatric diagnosis (Kehle et al., 2011). Because major depressive disorder is the most common comorbid diagnosis to co-occur with PTSD, a cohort of veterans with comorbid PTSD and major depressive disorder was selected to ascertain the effects of repeated ketamine infusions on neurocognition in trauma-exposed individuals. A trained study clinician determined PTSD diagnosis using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Blake et al., 1995; Weathers et al., 2013) and MDD diagnosis using the Structured Clinical Interview for DSM-IV (First et al., 2007). Treatment resistance was operationalized as a failure to achieve recovery from a minimum of 2 antidepressant medications according to the Antidepressant Treatment History Form (Sackeim, 2001). Participants continued on stable doses of their current psychotropic medication(s) for the study duration. Exclusion criteria included any unstable medical or non-psychiatric central nervous system condition, moderate to severe traumatic brain injury, active substance use disorder in the previous 6 months, lifetime history of psychosis or bipolar disorder, or active suicidal ideation judged to present imminent risk. Women of childbearing potential were required to have a negative urine pregnancy test and to remain on a medically accepted contraceptive for the study duration.

2.2. Procedures

Baseline assessments occurred within 1 week before infusion commencement. All infusions occurred on the Flexible Acuity Ward at the MVAHCS. Standard telemetry monitoring occurred throughout the infusion and recovery period. Participants completed six IV infusions (0.5 mg/kg ketamine hydrochloride given over 40 min) on a Monday-Wednesday-Friday schedule over a 12-day period. Side effects were recorded before each infusion, following infusion completion (40 min), and at 100 and 160 min post-infusion. All participants were monitored for a minimum of 2 h post-infusion to ascertain the absence of clinically significant side effects. Side effects associated with ketamine infusions are described in the original report of this study (Albott et al., 2018).

2.3. Measures

The primary outcomes were change in PTSD symptom score, assessed with the PTSD Checklist for DSM-5 (PCL-5) (Weathers et al., 2013; Wortmann et al., 2016), and change in depression score, assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Secondary outcomes included change in CAPS-5 score, proportion of individuals in remission[2] from PTSD (defined as PCL-5 total score < 33)(Bovin et al., 2016) following completion of the infusion series, proportion of individuals meeting depression response criteria ($\geq$50% improvement in baseline MADRS score) and depression remission criteria (MADRS score ≤ 9) (Hawley et al., 2002) at the conclusion of the infusion series, change in PTSD symptom domains (intrusion, avoidance, negative alterations in cognition and mood, and marked alterations in arousal and reactivity), and proportion of individuals relapsing for either PTSD or depression during the follow-up period. The PCL-5 and MADRS were administered 1 h before and 24-h after each infusion. The CAPS-5 and MADRS were collected within 1 week of infusion series commencement and within 1 week of series completion. Primary and secondary outcome measures were obtained weekly throughout an 8-week period following the sixth infusion. After completion of the infusion series and post-infusion outcome assessments, participants exited the study when they no longer demonstrated clinically significant response in either PTSD or depression symptoms.

2.4. Neurocognitive assessment

All participants completed a 2-h battery of cognitive tests at baseline and within one week following infusion series completion. See Fig. 1 for study design. The neurocognitive testing was selected from the CogState battery (www.cogstate.com; (Maruff et al., 2009). Tasks were designed to test attention, memory (working, visual, and verbal), speed of processing, and set shifting. The tests were selected for their brevity, utility for within-subjects experimental designs, parametric outcome measures, and their use in psychopharmacology trials (Snyder et al., 2005; Falleti et al., 2006). The CogState battery was also selected for test–retest reliability in the absence of significant practice effects (Collie et al., 2003; Falleti et al., 2006). Neurocognitive tasks were administered in a fixed sequence presented on laptop computers in a quiet room to minimize distractions. Responses were indicated by pressing keys on the laptop or using a computer mouse if preferred. Participants were allowed to take breaks between tasks to ameliorate any fatigue associated with the testing procedures. Brief descriptions of the tasks are provided in Table 1 with further details to be found elsewhere (Fredrickson et al., 2010; Maruff et al., 2009).

Each cognitive task yielded multiple outcome measures. For each task, a single metric was selected for the greatest ability to detect change (i.e. a small probability of floor or ceiling effects and no restriction in the range of possible performance values). Each outcome measure was normally distributed or corrected to normality through the use of mathematical transformation (e.g. logarithmic base 10, or square root arcsine proportion correct).

2.5. Data analysis

Descriptive statistics were calculated to summarize the characteristics of the study sample. Changes in neurocognitive domain scores from baseline (pre-test) to within 1 week after the sixth infusion (post-test) were examined using paired samples *t*-tests to test for significant mean within-subjects change. After normality assessment, bivariate parametric (Pearson) correlations were performed with baseline neurocognitive performance indices and CAPS-5 and MADRS change at the 1 week post-infusion time-point. Significance was determined at an alpha level of 0.05.

To assess the potential influence of confounding factors baseline neurocognitive performance scores were compared using ANOVAs with gender, education, and concurrently prescribed medication classes as grouping variables. Hierarchical (or sequential) linear regressions were used to further explore any significant effects of covariates on the association between baseline neurocognitive scores and changes in PTSD and depression symptoms. The factors that were identified as having a significant effect during univariate analyses were used as covariates to assess the extent that the second predictor added to the model. The first model was a standard linear regression with a simple regression using one predictor (baseline neurocognitive score) of change in PTSD or depression symptoms. The second model assessed the influence of confounding factors by forcing an additional predictor into the model in a separate block.

3. Results

3.1. Demographic and clinical characteristics

24 individuals provided signed consent and underwent screening procedures. Eligibility criteria were met by 19 participants; 2 participants withdrew consent prior to treatment and 1 individual withdrew from the study after the first infusion due to personal circumstances. Table 2 presents sociodemographic and baseline characteristics of participants who received all 6 infusions ($N = 16$). A PTSD outcome measure was changed (from the CAPS-IV to the CAPS-5) after the first participant completed the infusion series. The data for the first participant were therefore not included in the analyses ($n = 15$).

3.2. Neurocognitive effects after six ketamine infusions

There were significant changes in repeated neurocognitive performance over time after completion of six ketamine infusions. Significant improvement was found in scores of working memory (mean improvement in total errors during Groton Maze Learning task = 14.4 (95% CI: 2.329–26.471; $t(14) = 2.559$, $p = .023$) after the last ketamine infusion compared to baseline. This improvement was associated with a medium effect size. All other cognitive tasks showed non-significant changes with small effect sizes after repeated ketamine infusions. No significant worsening of neurocognitive functioning was observed for any domain. Table 3 presents mean changes in cognitive performance across all cognitive tasks with associated effect sizes.

3.3. Association of baseline neurocognitive performance and change of MADRS and CAPS-5 over six ketamine infusions

We used Pearson correlations to assess the relationship between both PTSD and depression symptom change over time (baseline to 1-week post infusion series) with baseline neurocognitive task performance. Greater improvement in PTSD symptoms (as measured using the CAPS-5) was significantly associated with worse performance in working memory (assessed by the one-back test (ONB); $r = -0.545$, $p = .036$; and Groton maze learning test (GML); $r = 0.609$, $p = .016$), slower processing speed (assessed by the detection task (DET); $r = 0.586$, $p = .028$), and better performance in set shifting (assessed by the set shifting task (SETS); $r = -0.545$, $p = .036$). Greater improvement in depression symptoms (as measured using the MADRS) was associated with worse performance on tasks of working memory (assessed by the one-back task (ONB): $r = -0.564$, $p = .029$; two-back test (TWOB): $r = -0.566$, $p = .028$), verbal memory (assess by the international shopping list task (ISL): $r = -0.528$, $p = .043$)), slower processing speed (assessed by the Groton-maze chase task ((GMCT): $r = -0.591$, $p = .020$) and better

[2] Although depression symptom response is a well-defined metric in depression research, there is no equivalent metric for PTSD. Thus, only remission from PTSD was assessed as an outcome.

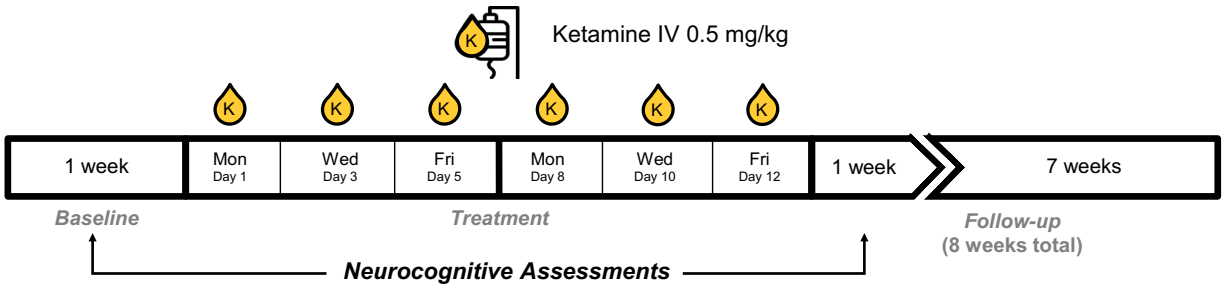

Fig. 1. Schematic depicting study design including timing of neurocognitive and clinical assessments in relation to 2 week infusion series.
Briefly, participants underwent neurocognitive testing and clinical interviews within 1 week prior to commencement of the infusion series and within 1 week following completion of the infusion series. Ketamine hydrochloride 0.5 mg/kg infusions were administered on a Monday, Wednesday, Friday schedule over two weeks.

Table 1
Demographic and clinical characteristics of the study population.

Domain	Cognitive task name	Outcome
Attention	Identification Task (IDN)	Transformed reaction times for correct responses. (Lower score = better performance)
Working memory	One Back (ONB)	Transformed proportion of correct responses. (Higher score = better performance)
	Two Back (TWOB)	Transformed proportion of correct responses. (Higher score = better performance)
	Groton Maze Learning (GML)	Total number of errors on five consecutive trials. (Lower score = better performance)
Visual learning	Continuous Paired Associative Learning (CPAL)	Total number of errors across five rounds. (Lower score = better performance)
	One Card Learning (OCL)	Transformed proportion of correct responses. (Higher score = better performance)
	Groton Maze Learning – Delayed Recall (GMLD)	Total number of errors after a delay. (Lower score = better performance)
Verbal learning	International Shopping List (ISL)	Total number of correct responses on three consecutive trials. (Higher score = better performance)
	International Shopping List – Delayed Recall (ISLD)	Total number of correct responses after a delay. (Higher score = better performance)
Processing speed	Groton Maze Chase (GMCT)	The total number of correct moves made per second. (Higher score = better performance)
	Detection Task (DET)	Mean of transformed reaction times for correct responses. (Lower score = better performance)
Set shifting	Set-Shifting Task (SETS)	Total number of errors across five rounds. (Lower score = better performance)

performance in set shifting ((SETS): $r = -0.565$, $p = .028$)). Fig. 2 presents correlations between changes in PTSD symptoms, depression symptoms and baseline cognitive task performance by task domain.

Table 2
List of test measures and corresponding cognitive domains.

Variable	Total sample
Sociodemographics	
Age at Enrollment, mean ± SD, y	52.1 ± 14.4
Female gender, n (%)	5 (33.3)
Ethnic minority, n (%)	1 (6.7%)
Education mean ± SD, y	14.8 ± 2.3
Married, n (%)	11 (73.3)
Depression characteristics	
Baseline depression (MADRS score), mean ± SD	35.6 ± 4.8
Age at onset of MDD, mean ± SD, y	24.5 ± 11.0
Duration of current MDE, mean ± SD, y	24.3 ± 17.7
No. of failed antidepressant trials (current MDE), mean ± SD	3.1 ± 1.0
Lifetime history of ECT, n (%)	1 (6.7)
Lifetime history of suicide attempt, n (%)	3 (20.0)
PTSD characteristics	
Baseline PTSD (CAPS-5 score), mean ± SD	39.7 ± 9.3
Age at onset of PTSD, mean ± SD, y	26.0 ± 12.3
Duration PTSD symptoms, mean ± SD, y	26.1 ± 18.4
Primary trauma:	
Combat exposure, n (%)	8 (53.3)
Sexual assault, n (%)	5 (33.3)
Accident or Fire, n (%)	1 (6.7)
Physical assault or abuse, n (%)	1 (6.7)
Additional comorbid psychiatric conditions (current or lifetime)	
Obsessive-compulsive disorder, n (%)	1 (6.7)
Panic disorder, n (%)	1 (6.7)
Attention-deficit hyperactivity disorder, n (%)	1 (6.7)
Borderline personality disorder, n (%)	1 (6.7)
Past substance use disorder, n (%)	4 (26.7)
No. of psychoactive medications per participant at enrollment, mean ± SD	2.9 ± 1.9
No. of antidepressant medications per participant at enrollment,[a] mean ± SD	1.3 ± 0.9
Concomitant psychotropic medications by class per participant at enrollment:	
SRI, n (%)	2 (13.3%)
SNRI, n (%)	5 (33.3%)
Tricyclic/Heterocyclic antidepressant, n (%)	2 (13.3)
Other antidepressant,[b] n (%)	7 (46.7)
Mood stabilizer,[c] n (%)	5 (33.3)
Antipsychotic, n (%)	2 (13.3)
Benzodiazepine,[d] n (%)	2 (13.3)
Z-drug sedative hypnotic, n (%)	5 (33.3)
Stimulant, n (%)	3 (20)
Opiate, n (%)	3 (20)
Prazosin, n (%)	4 (26.7)

3.4. Confounding variables

No significant effect of gender, marital status, or education was found for clinical or cognitive outcomes (Table S1). Antidepressant use was associated with better performance on a task of attention and faster processing speed (Table S2). Benzodiazepine use was also significantly

Table 3
Neurocognitive performance changes after completing six ketamine infusions.

Cognitive domain	Measure	Mean change (post-treatment vs baseline) (95% CI)		P	Cohen's *d*
Attention	Identification task (IDN)	−0.005	(−0.079–0.089)	0.900	0.05
Working memory	One Back (ONB)	−0.008	(−0.215–0.231)	0.940	0.03
	Two Back (TWOB)	−0.086	(−0.109–0.281)	0.359	0.30
	Groton Maze Learning (GML)	−14.400	(2.329–26.471)	0.023*	0.72
Visual learning	Continuous Paired Associative Learning (CPAL)	−9.000	(−22.304–40.304)	0.545	0.14
	One Card Learning (OCL)	−0.054	(−0.049–0.156)	0.279	0.31
	Groton Maze Learning Delayed (GMLD)	−1.857	(−1.501–5.215)	0.254	0.33
Verbal learning	International Shopping List (ISL)	0.667	(−2.975–1.642)	0.546	0.13
	International Shopping List Delayed (ISLD)	0.571	(−2.336–1.193)	0.497	0.24
Processing speed	Groton Maze Chase (GMC)	0.107	(−0.492–0.278)	0.559	0.24
	Detection Task (DET)	0.067	(−0.211–0.078)	0.337	0.34
Set shifting	Set-Shifting Task (SETS)	0.027	(−0.097–0.043)	0.418	0.24

Note. Table shows mean changes in neurocognitive performance after completing 6 ketamine infusions. Cognitive assessments occurred within 7 days of infusion series commencement and infusion series completion. Significant improvement was observed in the Groton maze learning task which assessed working memory. No significant worsening of neurocognitive functioning was observed.
* $p < .05$.

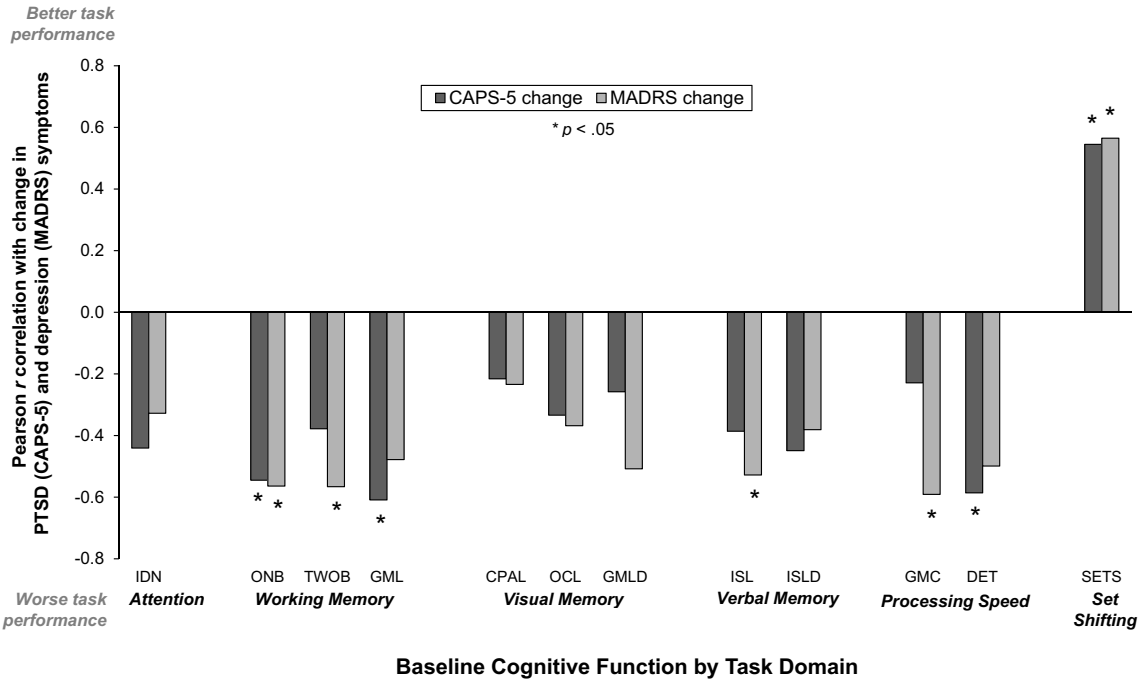

Fig. 2. Correlations between baseline cognitive task performance and change in mean PTSD symptoms and depression symptoms after repeated ketamine infusions. PTSD symptoms were assessed using the Clinician Administered PTSD symptom Scale for DSM-5 (CAPS-5). Depression symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS).

associated with worse performance on a working memory task (Table S2). There was a significant association between processing speed (detection task) and change in PTSD symptoms which remained significant after adjusting for antidepressant use (Table 4). There was also a significant relationship between baseline working memory performance (2-back task) and changes in depression symptoms, however, this relationship was no longer significant after adjustment for benzodiazepine use (Table 4).

4. Discussion

We report a *post-hoc* analysis of the neurocognitive effects of an open label study of six ketamine infusions for the treatment of comorbid PTSD and depression. To our knowledge, this is the first study to examine neurocognitive effects of ketamine in a trauma-exposed cohort of veterans. The main finding is that six ketamine infusions were not associated with short-term neurocognitive impairments in veterans with comorbid PTSD and MDD. There were no significant changes in tests of attention, visual memory, verbal memory, speed of processing, or set shifting. Rather, repeated ketamine infusions were associated with significant improvement in spatial working memory and this improvement was associated with a medium effect size.

Despite ketamine's promise as a novel and urgently needed treatment for PTSD and depression, concerns have been expressed regarding its potential adverse neurocognitive effects. These concerns have the potential to be magnified by the most likely clinical dosing strategies which involve multiple administrations of ketamine. Indeed, the strategy of repeated ketamine infusions suggests that more than a single infusion achieves better outcomes with greater durability (Albott et al., 2018; Murrough et al., 2013; Rasmussen et al., 2013; Shiroma et al., 2020b, 2014b). Consistent with other studies of both single and repeated infusions of ketamine for depression, we found no significant worsening of cognitive function following repeated infusions (Basso et al., 2020; Diamond et al., 2014; Murrough et al., 2015; Permoda-Osip et al., 2014;

Table 4
Hierarchical linear regression analysis of baseline cognitive function domains and change in PTSD and MDD symptoms following 6 ketamine infusions.

Antidepressant use	Change in PTSD symptoms (CAPS-5 total score change)			
	Unadjusted		Adjusting for medication class	
Baseline cognitive performance score	Beta[a]	p	Beta[a]	p
Attention (identification task)	0.441	0.1	0.206	0.08
Processing speed (detection task)	0.586	0.028*	0.401	0.047*

	Change in depression symptoms (MADRS total score change)			
	Unadjusted		Adjusting for medication class	
Baseline cognitive performance score	Beta[a]	p	Beta[a]	p
Attention (identification task)	0.325	0.238	0.138	0.261
Processing speed (detection task)	0.499	0.069	0.375	0.156

Benzodiazepine use	Change in PTSD symptoms (CAPS-5 total score change)			
	Unadjusted		Adjusting for medication class	
Baseline cognitive performance score	Beta[a]	p	Beta[a]	p
Working memory (2-back)	−0.378	0.165	−0.405	0.392

	Change in depression symptoms (assessed with MADRS)			
	Unadjusted		Adjusting for medication class	
Baseline cognitive performance score	Beta[a]	p	Beta[a]	p
Working memory (2-back)	−0.585	0.022*	−0.458	0.059

Note. Hierarchical linear regression analyses explored the effect of confounding factors on the association between baseline neurocognitive scores and changes in PTSD and depression symptoms. Factors identified in univariate analyses as having a significant effect on baseline cognitive function were used as covariates for hierarchical linear regressions.
*$p < .05$; [a]Standardized Beta; CAPS-5 = Clinician Administered PTSD Scale for DSM-5; MADRS = Montgomery-Asberg Depression Rating Scale.

Shiroma et al., 2020a, 2014a; Zheng et al., 2019) in any of the domains tested. Likewise, changes in cognitive task domain pre to post-infusion series were associated with small clinical effects sizes for all task domains with the exception of improvement in working memory. Working memory was found to be associated with a significant change and medium effect size.

The finding of improvement in working memory is consistent with other studies assessing cognitive functioning in individuals receiving repeated ketamine infusions. Improvement in speed of processing was reported in three studies of depressed patients using a repeated dosing strategy (Liu et al., 2019; Zheng et al., 2019; Zhou et al., 2018). Similarly, Basso and colleagues reported improvements in domains of attention, visual memory, and executive functions in hospitalized patients with major depressive disorder treated with 6 infusions over a 2 week period (Basso et al., 2020). In a randomized controlled trial of six ketamine infusions compared to a single infusion, our group reported improvements in working memory, speed of processing, and set shifting in patients receiving 6 ketamine infusions (Shiroma et al., 2020a). This finding aligned with our previous report of improvements in working memory in an open-label study of 15 patients with TRD who completed a six-infusion ketamine regimen (Shiroma et al., 2014a). Moreover, it has been suggested that ketamine differentially improves cognitive symptoms and may have a pro-cognitive effect (Stippl et al., 2021).

We also found that baseline neurocognitive performance was associated with improvements in PTSD and depression symptoms. Specifically, we found that improvements in both PTSD and depression symptoms were significantly correlated with worse performance on tasks of working memory, slower processing speed, and better performance in set shifting. Improvements in depression were also significantly correlated with poor performance on a verbal learning task. The literature on baseline neurocognitive domains predicting response to ketamine are mixed. Murrough and colleagues found that slower processing speed was associated with greater improvement in depression in a RCT of a single ketamine infusion compared to midazolam (Murrough et al., 2015). Shiroma and colleagues found that greater antidepressant response was associated with better performance on tasks assessing working memory (Shiroma et al., 2020a). Similarly, open label studies of repeated ketamine infusions have demonstrated depression response to be associated with attention (Shiroma et al., 2014a) and working memory (Liu et al., 2019). The association between decreased working memory, decreased processing speed but intact set shifting suggests a potential baseline neurocognitive profile that may predict response to repeated ketamine infusions in individuals with comorbid PTSD and TRD.

Assessment of confounding factors impacting baseline cognitive function was largely negative (Tables S1 and S2). Antidepressant comedication was found to contribute to the association between processing speed and change in PTSD symptoms while benzodiazepine comedication contributed to the association between baseline working memory performance and change in depression symptoms. Exploration of the association of baseline processing speed predicting improvement in PTSD symptoms via hierarchical linear regression analysis demonstrated that this relationship remained significant even after accounting for antidepressant use. Exploratory hierarchical linear regression analysis showed the association between baseline working memory performance predicting improvement in depression lost significance after adjusting for benzodiazepine use. The impact of benzodiazepine use on depression response to ketamine infusions aligns with other reports in the literature attesting to impairment of ketamine response by benzodiazepines (Albott et al., 2017; Frye et al., 2015).

4.1. *Impact of ketamine on neurocognition in a trauma-exposed cohort*

This is the first study to report neurocognitive outcomes associated with repeated ketamine infusions in a cohort of individuals with PTSD. There is a robust literature attesting to the relationship between PTSD and neurocognition with some authors suggesting neurocognitive function is a premorbid risk and resilience factor relevant to the development and course of PTSD. For example, Aupperle and colleagues suggest that persistent re-experiencing and hyperarousal symptoms following trauma exposure may be related to deficits in inhibition and attentional control that make it more difficult for individuals to disengage from both internal (e.g. emotions, memories) and external stimuli (e.g., triggers) related to trauma exposure (Aupperle et al., 2012a). Similarly, cognition may also influence the course of PTSD via its impact on coping mechanisms and treatment response. In this line, adaptive coping strategies (e.g., cognitive reappraisal, problem solving) and interventions targeting adaptive coping (e.g., cognitive behavioral interventions) rely in part on intact cognitive functioning. Specifically, adaptive coping strategies presuppose an individual is able to reliably recall a trauma memory and flexibly manipulate this information in working memory to problem solve and/or inhibit automatic responses to trauma triggers. This is supported by the treatment literature showing that better pretreatment performance on neuropsychological measures of memory (e.g. word lists and stories) is associated with better treatment response following group and individual cognitive behavioral therapies (Haaland et al., 2016; Scott et al., 2017).

The current study adds to this literature by demonstrating that individuals with both dysfunctional and functional neurocognitive processes were most likely to benefit from repeated ketamine infusions. It is proposed that greater deficits in domains of working memory and processing speed reflect downregulated functioning of the prefrontal cortex catalyzed by over-activation of the amygdala. Cognitive resources in individuals with PTSD may be over-allocated to networks involved with emotion processing (i.e. amygdala and medial prefrontal cortex) and under-allocated to cognitive control networks (i.e. dorsolateral prefrontal cortex). This imbalance may lead to diminished neurocognitive integrity, specifically in information processing speed and working memory (Aupperle et al., 2012a). From a cognitive perspective, the burden of PTSD symptoms may chronically tax neurocognitive resources that might otherwise be allocated to flexible manipulation of attentional and memory processes.

Ketamine infusions may promote recovery from PTSD symptoms by enabling appropriate allocation of cognitive resources to non-threat related tasks. The mechanism of this effect may occur in two ways. First, ketamine may enable improved cognitive function by decreasing symptoms associated with PTSD such as hyperarousal, intrusive thoughts and emotions related to trauma. Reduction in symptoms would allow more cognitive resources to be dedicated to the prefrontal cortex thereby enabling it to function appropriately when faced with a cognitively challenging task. Alternatively, ketamine infusions may act as a pro-cognitive agent which enables individuals to better allocate cognitive resources (or compensate for dysfunctional cognitive processes) to enable adaptive coping with PTSD symptoms. The latter mechanism has been suggested by studies identifying differential improvement to ketamine in cognitive domain symptoms in individuals with MDD (Stippl et al., 2021). Future studies powered to examine mediator and moderator effects between PTSD symptomatology and neurocognition are warranted.

4.2. Limitations

This *post-hoc* analysis had several limitations. The open-label design without a placebo control limits the interpretation of the observed associations. As such, it is not known to what extent the correlations or improvement in neurocognitive performance may have occurred under placebo conditions. These preliminary findings warrant further examination in a larger placebo-controlled clinical trial. The impact of antidepressant and benzodiazepine medications on PTSD and depression symptoms aligns with other reports in the literature. These findings should be explored in larger cohorts of patients, ideally in the context of a placebo-controlled clinical trial.

5. Conclusion

In conclusion, the current study found that serial ketamine infusions were devoid of adverse neurocognitive effects assessed within 7 days of infusion-series completion. Greater improvement in depression symptoms was associated with worse baseline working and verbal memory performance, slower baseline processing speed, and better baseline set shifting. Similarly, greater improvement in PTSD symptoms was associated with decreased baseline working memory performance and better baseline set shifting.

Funding/support

This research was supported by the Mental Health Service Line at the Minneapolis VA Health Care System. Dr. Albott is supported by a Career Development Award (K23MH117219) from the National Institute of Mental Health. Dr. Shiroma receives support from the Veterans Health Administration Office of Research and Development, Clinical Science Research and Development Merit Review Award for Clinical Trials.

Role of the sponsors

The funding source had no role in the study design, analysis, interpretation, writing of the report, or in the decision to submit this study for publication.

Previous presentation

Poster including preliminary results was presented at the 71st Annual Meeting of the Society for Biological Psychiatry, San Diego, CA, May 9, 2017.

CrediT authorship contribution statement

Drs. Albott, Lim, Erbes, Thuras, Wels, Tye and Shiroma designed the study. Drs. Albott, Lim, Erbes, Wels and Shiroma wrote the protocol, and oversaw data collection. Drs. Albott and Shiroma managed the literature searches. Drs. Albott and Thuras undertook the statistical analyses. Dr. Albott wrote the first draft of the manuscript as well as the revised manuscript. All authors contributed to and have approved the original manuscript. Dr. Christopher Erbes died on May 30, 2021, prior to the submission of the revised manuscript. All authors, except Dr. Erbes, approved the revised version. Dr. Albott and all co-authors agreed that Dr. Erbes continued to meet the definition of authorship despite his inability to approve the revised version.

Conflict of interest

Drs. Albott, Lim, Erbes, Tye, Thuras, Wels and Shiroma report no financial or other relationship relevant to the subject of this article.

Acknowledgements

We wish to thank the nursing staff at the MVAHCS Flexible Acuity Ward for their assistance with study procedures and care of study participants. Foremost, we wish to thank the patients and their families for their participation in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.04.066.

References

Albott, C.S., Shiroma, P.R., Cullen, K.R., Johns, B., Thuras, P., Wels, J., Lim, K.O., 2017. The antidepressant effect of repeat dose intravenous ketamine is delayed by concurrent benzodiazepine use. J. Clin. Psychiatry 78, e308–e309.

Albott, C.S., Lim, K.O., Forbes, M.K., Erbes, C., Tye, S.J., Grabowski, J.G., Thuras, P., Batres-Y-Carr, T.M., Wels, J., Shiroma, P.R., 2018. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. J. Clin. Psychiatry 79. https://doi.org/10.4088/JCP.17m11634.

Albott, C.S., Lee, S., Cullen, K.R., Thuras, P., Lissek, S., Wels, J., Friedrich, K.J., Krueger, A.M., Lim, K.O., 2021. Characterization of comorbid posttraumatic stress disorder and major depressive disorder using ketamine as an experimental medicine probe. J. Psychiatr. Brain Sci. 6 https://doi.org/10.20900/jpbs.20210012.

Aupperle, R.L., Allard, C.B., Grimes, E.M., Simmons, A.N., Flagan, T., Behrooznia, M., Cissell, S.H., Twamley, E.W., Thorp, S.R., Norman, S.B., Paulus, M.P., Stein, M.B., 2012a. Dorsolateral prefrontal cortex activation during emotional anticipation and neuropsychological performance in posttraumatic stress disorder. Arch. Gen. Psychiatry 69, 360–371.

Aupperle, R.L., Melrose, A.J., Stein, M.B., Paulus, M.P., 2012b. Executive function and PTSD: disengaging from trauma. Neuropharmacology 62, 686–694.

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. Psychiatr. Res. 123, 1–8.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., Keane, T.M., 1995. The development of a clinician-administered PTSD scale. J. Trauma. Stress. 8, 75–90.

Bovin, M.J., Marx, B.P., Weathers, F.W., Gallagher, M.W., Rodriguez, P., Schnurr, P.P., Keane, T.M., 2016. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. Psychol. Assess. 28, 1379–1391.

Collie, A., Maruff, P., Darby, D.G., McStephen, M., 2003. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. J. Int. Neuropsychol. Soc. 9, 419–428.

Diamond, P.R., Farmery, A.D., Atkinson, S., Haldar, J., Williams, N., Cowen, P.J., Geddes, J.R., 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.

Diazgranados, N., Ibrahim, L., Brutsche, N.E., Newberg, A., Kronstein, P., Khalife, S., Kammerer, W.A., Quezado, Z., Luckenbaugh, D.A., Salvadore, G., Machado-Vieira, R., Manji, H.K., Zarate Jr., C.A., 2010. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch. Gen. Psychiatry 67, 793–802.

Falleti, M.G., Maruff, P., Collie, A., Darby, D.G., 2006. Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. J. Clin. Exp. Neuropsychol. 28, 1095–1112.

First, M.B., Williams, J.B.W., Spitzer, R.L., Gibbon, M., 2007. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT). Biometrics Research, New York State Psychiatric Institute, New York.

Fredrickson, J., Maruff, P., Woodward, M., Moore, L., Fredrickson, A., Sach, J., Darby, D., 2010. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. Neuroepidemiology 34, 65–75.

Frye, M.A., Blier, P., Tye, S.J., 2015. Concomitant benzodiazepine use attenuates ketamine response: implications for large scale study design and clinical development. J. Clin. Psychopharmacol. 35, 334–336.

Great Britain. Advisory Advisory Council on the Misuse of Drugs, 2013. Ketamine: A Review of Use And Harm.

Haaland, K.Y., Sadek, J.R., Keller, J.E., Castillo, D.T., 2016. Neurocognitive correlates of successful treatment of PTSD in female veterans. J. Int. Neuropsychol. Soc. 22, 643–651.

Hawley, C.J., Gale, T.M., Sivakumaran, T., Hertfordshire Neuroscience Research group, 2002. Defining remission by cut off score on the MADRS: selecting the optimal value. J. Affect. Disord. 72, 177–184.

Jak, A.J., Crocker, L.D., Aupperle, R.L., Clausen, A., Bomyea, J., 2018. Neurocognition in PTSD: treatment insights and implications. In: Vermetten, E., Baker, D.G., Risbrough, V.B. (Eds.), Behavioral Neurobiology of PTSD. Springer International Publishing, Cham, pp. 93–116.

Johnsen, G.E., Kanagaratnam, P., Asbjørnsen, A.E., 2008. Memory impairments in posttraumatic stress disorder are related to depression. J. Anxiety Disord. 22, 464–474.

Kehle, S.M., Reddy, M.K., Ferrier-Auerbach, A.G., Erbes, C.R., Arbisi, P.A., Polusny, M.A., 2011. Psychiatric diagnoses, comorbidity, and functioning in National Guard troops deployed to Iraq. J. Psychiatr. Res. 45, 126–132.

Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R., Bremner, J.D., Heninger, G.R., Bowers Jr., M.B., Charney, D.S., 1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatry 51, 199–214.

Krystal, J.H., Perry Jr., E.B., Gueorguieva, R., Belger, A., Madonick, S.H., Abi-Dargham, A., Cooper, T.B., Macdougall, L., Abi-Saab, W., D'Souza, D.C., 2005. Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch. Gen. Psychiatry 62, 985–994.

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.

Maruff, P., Thomas, E., Cysique, L., Brew, B., Collie, A., Snyder, P., Pietrzak, R.H., 2009. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch. Clin. Neuropsychol. 24, 165–178.

Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141–168.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Morgan, C.J.A., Mofeez, A., Brandner, B., Bromley, L., Curran, H.V., 2004a. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29, 208–218.

Morgan, C.J.A., Monaghan, L., Curran, H.V., 2004b. Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. Addiction 99, 1450–1461.

Morgan, C.J.A., Muetzelfeldt, L., Curran, H.V., 2009. Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. Addiction 104, 77–87.

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

Murrough, J.W., Perez, A.M., Pillemer, S., Stern, J., Parides, M.K., aan het Rot, M., Collins, K.A., Mathew, S.J., Charney, D.S., Iosifescu, D.V., 2013. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol. Psychiatry 74, 250–256.

Murrough, J.W., Burdick, K.E., Levitch, C.F., Perez, A.M., Brallier, J.W., Chang, L.C., Foulkes, A., Charney, D.S., Mathew, S.J., Iosifescu, D.V., 2015. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. Neuropsychopharmacology 40, 1084–1090.

Nijdam, M.J., Gersons, B.P.R., Olff, M., 2013. The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder. Eur. J. Psychotraumatol. 4 https://doi.org/10.3402/ejpt.v4i0.19979.

Parwani, A., Weiler, M.A., Blaxton, T.A., Warfel, D., Hardin, M., Frey, K., Lahti, A.C., 2005. The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology 183, 265–274.

Permoda-Osip, A., Kisielewski, J., Bartkowska-Sniatkowska, A., Rybakowski, J., 2014. Single ketamine infusion and neurocognitive performance in bipolar depression. Pharmacopsychiatry. https://doi.org/10.1055/s-0034-1394399.

Popova, V., Daly, E.J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M.E., Shelton, R.C., et al., 2019. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am. J. Psychiatry 176, 428–438.

Rasmussen, K.G., Lineberry, T.W., Galardy, C.W., Kung, S., Lapid, M.I., Palmer, B.A., Ritter, M.J., Schak, K.M., Sola, C.L., Hanson, A.J., Frye, M.A., 2013. Serial infusions of low-dose ketamine for major depression. J. Psychopharmacol. 27, 444–450.

Rodriguez, C.I., Kegeles, L.S., Levinson, A., Feng, T., Marcus, S.M., Vermes, D., Flood, P., Simpson, H.B., 2013. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology 38, 2475–2483.

Rowland, L.M., Bustillo, J.R., Mullins, P.G., Jung, R.E., Lenroot, R., Landgraf, E., Barrow, R., Yeo, R., Lauriello, J., Brooks, W.M., 2005. Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. Am. J. Psychiatr. https://doi.org/10.1176/appi.ajp.162.2.394.

Rytwinski, N.K., Scur, M.D., Feeny, N.C., Youngstrom, E.A., 2013. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. J. Trauma. Stress. 26, 299–309.

Sachinvala, N., von Scotti, H., McGuire, M., Fairbanks, L., Bakst, K., McGuire, M., Fairbanks, L., Bakst, K., McGuire, M., Brown, N., 2000. Memory, attention, function, and mood among patients with chronic posttraumatic stress disorder. J. Nerv. Ment. Dis. 188, 818–823.

Sackeim, H.A., 2001. The definition and meaning of treatment-resistant depression. J. Clin. Psychiatry 62 (Suppl. 16), 10–17.

Scott, J.C., Harb, G., Brownlow, J.A., Greene, J., Gur, R.C., Ross, R.J., 2017. Verbal memory functioning moderates psychotherapy treatment response for PTSD-related nightmares. Behav. Res. Ther. 91, 24–32.

Shiroma, P.R., Albott, C.S., Johns, B., Thuras, P., Wels, J., Lim, K.O., 2014a. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. Int. J. Neuropsychopharmacol. 17, 1805–1813.

Shiroma, P.R., Johns, B., Kuskowski, M., Wels, J., Thuras, P., Albott, C.S., Lim, K.O., 2014b. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J. Affect. Disord. 155, 123–129.

Shiroma, P.R., Thuras, P., Wels, J., Albott, C.S., Erbes, C., Tye, S., Lim, K.O., 2020a. Neurocognitive performance of repeated versus single intravenous subanesthetic ketamine in treatment resistant depression. J. Affect. Disord. 277, 470–477.

Shiroma, P.R., Thuras, P., Wels, J., Albott, C.S., Erbes, C., Tye, S., Lim, K.O., 2020b. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. Transl. Psychiatry 10, 206.

Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., McShane, R., 2017. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. Lancet Psychiatry 4, 419–426.

Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M., Grimm, S., 2021. Ketamine specifically reduces cognitive symptoms in depressed patients: an investigation of associated neural activation patterns. J. Psychiatr. Res. 136, 402–408.

Snyder, P.J., Werth, J., Giordani, B., Caveney, A.F., Feltner, D., Maruff, P., 2005. A method for determining the magnitude of change across different cognitive functions in clinical trials: the effects of acute administration of two different doses alprazolam. Hum. Psychopharmacol. 20, 263–273.

Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., Keane, T.M., 2013. The clinician-administered PTSD scale for DSM-5 (CAPS-5). Interview available from the National Center for PTSD at www.ptsd.va.gov.

Wortmann, J.H., Jordan, A.H., Weathers, F.W., Resick, P.A., Dondanville, K.A., Hall-Clark, B., Foa, E.B., Young-McCaughan, S., Yarvis, J.S., Hembree, E.A., Mintz, J., Peterson, A.L., Litz, B.T., 2016. Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members. Psychol. Assess. https://doi.org/10.1037/pas0000260.

Zarate Jr., C.A., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate

antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry 63, 856–864.
Zheng, W., Zhou, Y.-L., Liu, W.-J., Wang, C.-Y., Zhan, Y.-N., Li, H.-Q., Chen, L.-J., Li, M.-D., Ning, Y.-P., 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 (10), 1118–1126.