REVIEW

Neurocognitive Effects of Ketamine and Esketamine for Treatment-Resistant Major Depressive Disorder: A Systematic Review

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Learning objective: After participating in this activity, learners should be better able to:
• Analyze the effects of ketamine and esketamine on individuals with treatment-resistant depression

Introduction: Cognitive impairment is commonly present in individuals with treatment-resistant depression, especially in attention, memory, and executive functions. These deficits are related to symptom severity, remission rates, and functional impairments during and after the acute phase of the disorder. Ketamine, an N-methyl-D-aspartate antagonist previously used as an anesthetic, brings promising antidepressant results. This study systematically reviews the neurocognitive effects of ketamine and esketamine in patients with treatment-resistant major depressive disorder.

Methods: Systematic searches were conducted at Embase, PubMed, and PsycINFO using the terms depression, ketamine, and cognition. Title, abstract, and full-text reading were conducted independently by two of the authors (BSM and CSL). Risk of bias, study design, neuropsychological outcomes, and neuroimaging data were recorded.

Results: From a total of 997 hits, 14 articles were included. One study reported cognitive impairment after ketamine treatment for processing speed and verbal memory. Five studies reported improvements in processing speed, verbal memory, visual memory, working memory, or cognitive flexibility. The esketamine study suggested no changes to performance. Lower attention, slower processing speed, and higher working memory are reported as predictors of antidepressant response. Brain areas for emotional and reward processing, including the amygdala, insula, and orbitofrontal cortex, show a normalizing tendency after ketamine.

Conclusions: Ketamine and esketamine do not seem to exert significant deleterious neurocognitive effects in the short or long term in individuals with treatment-resistant depression. Results suggest neuropsychological functions and brain areas commonly impaired in treatment-resistant depression may especially benefit from subanesthetic ketamine infusions. Key questions that remain unanswered are discussed.

Keywords: cognition, ketamine, major depressive disorder, neuropsychological tests, treatment-resistant depression

INTRODUCTION

Major depressive disorder (MDD) is a highly common and disabling illness that affects more than 265 million people worldwide.[1] Among the diagnostic criteria for MDD are cognitive symptoms experienced as difficulty thinking and concentrating.[2] Accordingly, research on cognitive functions

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in individuals with MDD has consistently reported deficits in attention, memory, and executive functions during the depressive episode.[3–5] Recent findings suggest that these cognitive dysfunctions may occur not only in the acute phase of the disorder; cognitive deficits identifiable during a person's first MDD episode[6] can persist independently of mood symptoms,[4,7,8] supporting a diathesis hypothesis for cognitive deficits in MDD. Cognitive deficits in individuals with MDD may be causally linked to a large portion of the commonly reported functional difficulties after remission.[9–12]

Currently available pharmacological treatments for MDD face important challenges, such as treatment-resistant depression (TRD), where response rates to first-line monoaminergic antidepressants remain around 50%.[13] There are still no pharmacological treatments especially effective for cognitive symptoms in TRD. Despite some evidence suggesting pro-cognitive effects following current antidepressant therapy,[14–16] the effects are modest at best and seem dependent on mood-symptom improvements.[17] Thus, identifying drugs that could directly ameliorate cognitive deficits in depression may substantially lessen its impacts at individual and societal levels.

The search for new agents implicated in the pathophysiology of TRD has brought forward some promising alternative therapeutic targets, one of which is the abundant neurotransmitter glutamate, which binds to N-methyl-D-aspartate receptors (NMDARs).[18,19] The NMDAR antagonist (R-S)-ketamine has been extensively studied over the past two decades.[20] Ketamine was developed as an anesthetic, but its antidepressant effects are more frequently studied at subanesthetic doses of its racemate composite (R-S)-ketamine, an equal-parts mixture of the isomers S(+)-ketamine and R(−)-ketamine.[21] Multiple research efforts have replicated evidence that (R-S)- and S(+)-ketamine exerts rapid-acting antidepressant effects, from 24 hours up to 7 days posttreatment in TRD individuals.[22,23] These results eventually led to the approval of an S(+)-ketamine nasal spray as pharmacotherapy for TRD in 2019 by the U.S. Food and Drug Administration.[24] In addition to its antidepressant effects, ketamine has been associated with key mechanisms of action that may be of particular interest in studying cognition in TRD.

The exact mechanisms by which (R-S)-ketamine exerts its antidepressant effects are still unclear. A "cascade" framework posits a series of fast, downstream intracellular events that move beyond ketamine's NMDAR blockade of GABAergic interneurons and subsequent glutamatergic neurotransmission in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs).[25] Ketamine rapidly increases the AMPAR-related mechanistic target of rapamycin (mTOR)-signaling pathways in the prefrontal cortex[26] and hippocampus.[27] Higher syntheses of brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TrkB) have also been shown to follow subanesthetic ketamine doses.[28–30] Further strengthening this pathway, ketamine has been found to selectively reverse lost dendritic spines in the prefrontal cortex,[31] which points toward a neuroplasticity hypothesis[32] that associates ketamine's acute antidepressant effects and rapid increases in neuroplasticity.[33,34]

In essence, ketamine's antidepressant efficacy is a promising alternative for TRD patients, but there are safety concerns over possible neurotoxic consequences. Ketamine is a highly sought-after recreational drug that is associated with memory impairments in chronic users.[35,36] Evidence from studies of subanesthetic doses in healthy subjects has established that acute neurotoxic effects follow a single dose of (R-S)-ketamine and either of its enantiomers[37,38] for up to 60 minutes. Ketamine acutely and selectively impairs memory encoding and recall in healthy volunteers,[39,40] which brings up some concerns about its continued use, even in subanesthetic doses.

We systematically review studies of neurocognitive effects in TRD individuals following antidepressant treatment using ketamine.

METHODS

A thorough search for already published or ongoing systematic reviews related to this topic was performed via the Cochrane Database of Systematic Reviews and the International Prospective Register of Systematic Reviews (PROSPERO). A review protocol was then registered (CRD42020178335). This systematic review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[41]

Systematic searches were conducted on PubMed, Embase, and PsycINFO, identifying studies that focused on ketamine use for TRD and that included neuropsychological outcomes. The following basic search terms were used: depression AND ketamine AND cognition, tailored for the specific terms in each thesaurus (full search strategy in Supplemental Text Box 1, http://links.lww.com/HRP/A172). Searching took place from 1 June to 30 November 2020, and included studies from 1999 onward, in accordance with the following inclusion criteria:

1. Randomized clinical trials, open-label studies, and case series
2. Written as articles or letters to the editors
3. Included TRD individuals and reported their data separately from individuals with other disorders
4. Used ketamine either as monotherapy or adjuvant therapy, in one or more doses, in any chemical presentation, frequency, and administration route
5. Assessed at least one neuropsychological function, using validated measures or experimental tasks

Studies were excluded if they met any of the following exclusion criteria:

1. Included patients with a history of convulsions without clear etiology, alcohol use disorder, or any other substance use disorder
2. Presented neuropsychological results of TRD patients mixed with other individuals with different diagnoses such as bipolar depression, schizophrenia, or any other psychotic disorder

3. Included patients undergoing any concomitant intervention with potential neurological effects such as electroconvulsive therapy, vagal nerve stimulation, or transcranial magnetic stimulation

Study quality was assessed for possible risks of bias using the Cochrane risk-of-bias tool (RoB 2).[42] Pilot searches in the selected databases showed both randomized clinical trials and open-label pilot studies among published articles regarding ketamine and cognition in TRD patients. Aiming for a more conservative approach, risk-of-bias assessment within included studies was measured using randomized clinical trial standards, which punish open-label trials more severely. If an included study reported secondary findings from an already published clinical trial, we referred to its parent articles for a more precise assessment of methods and risks of bias. Title, abstract, full-text screening, and bias estimation were independently conducted by the first two authors (BSM and CSL), with discrepancies being resolved by consensus.

RESULTS

A total of 997 articles were retrieved: 236 at PubMed, 675 at Embase, and 86 at PsycINFO (see Supplemental Figure 1, http://links.lww.com/HRP/A173). After removing duplicates, 879 titles and abstracts were independently reviewed, and 37 were selected for full-text analysis. Following a full-text reading, 13 studies were selected, and an additional one was included by handsearching (see Supplemental Table 1, http://links.lww.com/HRP/A174).[43–56] Three of the included studies are secondary reanalyses of the same sample;[49,51,54] none of these studies corrected for multiple testing in secondary analyses. Two pairs of studies are reanalyses of the same sample in different study settings.[43–45,47] Results are described below in the following topics: study design and sample characteristics; neuropsychological assessment strategies; results of neuropsychological functions indicating impairment, maintenance, and improvement; neurocognitive aspects associated with antidepressant treatment outcomes; and functional imaging results and associated experimental tasks.

Study Design and Sample Characteristics

In summary (and not considering reanalyses of the same samples), neuropsychological outcomes are available for 1019 patients. Of those, 715 were from a single study and 304 from the other 13 studies (see Supplemental Table 1, http://links.lww.com/HRP/A174). For the single-dose (R-S)-ketamine studies, the times between patient drug use and assessment in studies that used validated measures of neuropsychological performance were as follows: 1 study at 40 minutes (n = 15 patients);[43] 1 study at 24 hours (n = 25);[55] 1 study at 3 days (n = 47);[48] 1 study at 7 days (n = 47);[45] and 1 study at 14 days (n = 47).[48] For the six-infusion (R-S)-ketamine studies, the times between patient drug use and assessment were as follows: 4 studies at 24 hours (n = 86);[49,51,54,55] 2 studies at 7 days (n = 31);[44,50] and 3 studies at 13 days (n = 68).[49,51,54] For the large intranasal S(+)-ketamine study, the assessments were made at 28 days (n = 623), 20 weeks (n = 426), 32 weeks (n = 270), and 44 weeks (n = 185).[56]

Of the 14 studies, 8 (57%) were open observational studies, and 6 used some form of control strategy or randomization. Among those 6 studies, 1 included healthy controls at baseline; 3 randomized MDD individuals between ketamine and placebo or midazolam; and 2 used crossover designs between ketamine and placebo. A total of 13 studies used (R-S)-ketamine, and only 1 study used S(+)-ketamine. Treatment regimens varied between 7 studies with single infusions, 5 with six total infusions thrice weekly, 1 with six total infusions twice weekly, and an esketamine study with intranasal doses once weekly for 44 weeks. A total of 4 studies reported a washout period, with 2 using a two-week period, and 2 using a one-week period.

Regarding sampling strategies, a total of 10 studies reported minimum treatment-resistant criteria: 9 included only patients with at least two failed therapies, and 1 included patients with at least one failed treatment of adequate time and dosage. Among selected studies, 10 used minimum depression severity cutoff criteria: 4 used the Inventory of Depressive Symptomatology–Clinician Rated (ICS-C30 scores $\geq$32); 2 used Hamilton Depression Rating Scale scores $\geq$17, and 1 used a score $\geq$14 on this same scale; 1 used Montgomery-Åsberg Depression Rating Scale scores $\geq$25, and 2 others used scores $\geq$22 and $\geq$20, respectively, on this same scale.

Risk of Bias

The risk-of-bias assessment indicates that most included studies present cause for concerns (see Supplemental Table 2, http://links.lww.com/HRP/A175), especially with regard to the lack of randomization or blinding.

Neuropsychological Assessment Strategies

Regarding the neuropsychological assessment (see Table 1), 5 (35%) of the selected studies used the MATRICS Consensus Cognitive Battery, 3 (21%) used CogState, 1 (7%) used the Wechsler Memory Scale, and 1 (7%) used a computerized test of attention.[39] A total of 3 studies used modified facial emotion-recognition tasks, and 1 study used both a modified task for emotional judgment of images and a modified reward task. Working memory and verbal memory, assessed in 9 (64%) studies were the most frequently observed neuropsychological functions; visual memory and processing speed were assessed in 8 studies (57%); attention and cognitive flexibility were each assessed in 3 studies (21%); and inhibitory control was assessed in 1 study (7%).

Neuropsychological Outcomes

The single S(+)-ketamine study included in this systematic review followed at least 185 patients for 44 weeks.[56] This study used a descriptive, non–hypothesis-testing approach, showing that mean neuropsychological performance remained stable from baseline to week 44. A different trend was reported on measures of processing speed and attention in patients aged 65 years or older, who showed slower mean

Table 1

Neuropsychological assessment and study outcomes

Study	Neuropsychological outcomes assessed	Results
Murrough et al. (2014)[43]	MATRICS Consensus Cognitive Battery: Trails A, WMS Spatial Span, BACS Digit Symbol, Letter-Number Sequencing, HVLT, Brief Visual Memory Test, Category Fluency, and Continuous Performance Test	Impairments in HVLT delayed recall at 40m post-infusion No other significant changes to neuropsychological performance Slower processing speed at baseline predicted better ketamine response
Shiroma et al. (2014)[44]	CogState battery: Identification Task, One Back & Two Back Task, Groton Maze Learning Test, Continuous Paired Associate Learning Task, One Card Learning Task, International Shopping List Task, Detection Task, Set-Shifting Task	Improvements in One Card Learning Task (visual memory) and Two Back Task (complex working memory) after six infusions No other significant changes to neuropsychological performance Accounting for change in depressive symptoms removes significance of neuropsychological improvements
Murrough et al. (2015)[45]	MATRICS Consensus Cognitive Battery: Trails A, WMS Spatial Span, BACS Digit Symbol, Letter-Number Sequencing, HVLT, Brief Visual Memory Test, Neuropsychological Assessment Battery Mazes, and Category Fluency	Improvements in processing speed, verbal learning, and visual learning 7d after single infusion, across experimental and placebo groups, while accounting for change in depressive symptoms No other significant changes at 24h or 7d posttreatment Worse processing speed at baseline predicts MADRS score changes
Murrough et al. (2015)[46]	fMRI and facial emotion-perception task	Hypoactivation of the left insula and right caudate at baseline for TRD group in comparison to healthy controls At 24h posttreatment of single infusion, higher neural responses for TRD group at the right caudate in positive emotions condition; no changes to negative emotion
Shiroma et al. (2015)[47]	Facial emotion-recognition task	No significant changes in facial recognition of sadness, fear, or happiness emotions after six ketamine infusions Behavioral results were not related to treatment outcomes of response or remission
Chen et al. (2018)[48]	Working memory task and go/no-go task	No significant changes to neuropsychological performance between 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, or placebo groups after six infusions
Zhou et al. (2018)[49]	MATRICS Consensus Cognitive Battery: processing speed, working memory, visual learning, and verbal memory	Improved processing speed at 24h and 13d after six infusions; improved verbal learning at 24h No other significant changes to neuropsychological performance Accounting for change in depressive symptoms removes significance of processing speed but not of verbal learning at 24h posttreatment
Kheirabadi et al. (2019)[50]	WMS	No significant changes to performance in the WMS after six infusions at 1 week and 1 month posttreatment.
Liu et al. (2019)[51]	MATRICS Consensus Cognitive Battery: processing speed, working memory, visual learning, and verbal memory	Improved processing speed at 24h and 13d after six ketamine infusions for patients with anxious depression; improved verbal memory at 24h posttreatment Patients with nonanxious depression had no significant changes No significant changes to the other neuropsychological functions
Reed et al. (2019)[52]	fMRI, emotion recognition task	At baseline, frontal gyri, anterior cingulate cortex, insula, and posterior cingulate areas more activated in TRD patients versus healthy controls 1d–3d after treatment this pattern is reversed

Table 1

Continued

Study	Neuropsychological outcomes assessed	Results
Sterpenich et al. (2019)[53]	fMRI, reward task and emotion-judgment task	Faster reaction times to positively cued trials 24h and 7d posttreatment, accompanied by higher activation of the insula and orbitofrontal cortex in anticipatory trials of the reward task Improved reaction times at 24h and 7d posttreatment at the emotion-judgment task, with reduced activation of the amygdala and insula in response to negative versus positive pictures
Zheng et al. (2019)[54]	MATRICS Consensus Cognitive Battery: processing speed, working memory, visual learning, and verbal learning	Improved verbal learning and speed of processing 24h after the last of six infusions; improved speed of processing 13d posttreatment Accounting for change in depressive symptoms does not change the significant neuropsychological outcomes No other significant changes
Shiroma et al. (2020)[55]	CogState battery: attention, working memory, visual memory, verbal memory, processing speed and set shifting	Improved processing speed, set shifting, complex working memory, and visual memory, but decreased verbal memory performance for the six ketamine infusions group Decreased processing speed for the single ketamine infusion group 24h after infusion No other significant changes to performance in both groups Patients in the six ketamine infusions group showed greater processing speed, set shifting, and spatial working memory in comparison to single ketamine infusion patients
Wajs et al. (2020)[56]	CogState battery: simple and choice reaction time, visual memory, visual learning, verbal memory, verbal learning, working memory, and executive function; HLTV-R	Stabilization or improvement of mean performance for all tests in the total sample through week 44 Simple and choice reaction time slowed from week 20 onward in ≥65-year-old patients

m/h/d, minute/hour/day; BACS, Brief Assessment of Cognition in Schizophrenia; fMRI, functional magnetic resonance imaging; HLTV, Hopkins Verbal Learning Test; MADRS, Montgomery-Asberg Depression Rating Scale; TRD, treatment-resistant depression; WMS, Wechsler Memory Scale.

performance from week 20 onward. The same trend was not found in measures of visual learning, working memory, and executive functioning, which remained stable throughout the study.

Of the 14 total studies, 2 presented results suggestive of worse neuropsychological performance after treatment but from different study designs (see Table 1). One study, in an open-label design with 25 patients, found acute verbal memory impairments 40 minutes after a single ketamine infusion.[43] Another study reported worse performance from two different study arms.[55] On one arm, 25 patients were randomized to five midazolam and one ketamine infusions, following a two-week, thrice-weekly regime, and presented slower processing speed 24 hours after the single ketamine infusion. The other arm, with 18 patients randomized for six ketamine infusions using the same regime, demonstrated worse verbal memory 24 hours after the last infusion.

A total of 5 (36%) studies reported results of neuropsychological improvement in validated instruments following ketamine infusions. All used six ketamine infusions in a thrice-weekly, two-week regime. An open-label trial assessed 15 patients and found improved visual and working memory 24 hours after the last infusion, but no changes were observed in the other functions.[44] These results did not remain significant, however, after controlling for changes in MADRS scores. A latter study conducted by this group—which has been mentioned above—also found neuropsychological improvements that differ between groups with single versus six ketamine infusions.[55] In the group with six ketamine infusions, authors observed better processing speed, visual memory, verbal working memory, and cognitive flexibility, but no significant improvements were found in the single-infusion group. When comparing between groups, the one with six ketamine infusions had better processing speed, spatial working memory, and cognitive flexibility after treatment.

Three other studies included in this review reported results of improved performance, but they were reanalyses of the same sample. The first study assessed 84 patients from a larger clinical trial in China, 68 of whom were diagnosed with TRD and 16 with bipolar depression.[49] Authors observed better verbal memory and processing speed 24 hours after

the last infusion, with processing-speed improvements remaining significant 7 days after and with no other significant changes to performance. Of these results, only the verbal memory improvement at 24 hours posttreatment remained significant after controlling for changes in depressive symptoms, as measured by the Hamilton Depression Rating Scale. It is worth mentioning that no group effect for cognitive performance was found in the analysis of unipolar and bipolar individuals.

A different study from the same larger sample of Chinese patients assessed 50 TRD patients in an open-label design, dividing the sample between anxious (n = 30) and non-anxious (n = 20) individuals.[51] Anxious TRD patients had better processing speed and verbal memory 24 hours posttreatment; improvements in processing speed remained significant 7 days after the last infusion. These changes were not observed in the non-anxious TRD group, and no other significant changes to performance were found.

The last study to report neuropsychological improvements using validated instruments also included patients from the same larger clinical trial of ketamine in Chinese individuals.[54] Following an open-label design, they assessed 64 TRD patients in the same regime of six infusions, finding better verbal memory and processing speed 24 hours after the last infusion. Processing-speed improvements remained significant 13 days after the last infusion, and no other significant changes to performance were found. Their results indicate that changes in processing speed and verbal memory remained significant after controlling for changes in depressive symptoms, as measured by MADRS scores. It is important to note that no method to control for multiple testing was employed by these separate studies of the same sample.

Behavioral Tasks and Functional Imaging

Three studies presented functional magnetic resonance imaging (fMRI) data for either emotional or reward tasks, and a fourth study used an emotion-recognition task. An open-label study assessed 18 TRD individuals in a facial emotion-perception task with fMRI data before and after a single ketamine infusion, with 20 healthy volunteers also being assessed at baseline.[46] The authors found hypoactivation at the left insula and right caudate for the TRD group, at baseline, when compared to the healthy group. At 24 hours posttreatment, the TRD group had higher neural responses at the right caudate for positive emotions but no significant changes in response to negative emotions.

Another fMRI study presented both behavioral and functional-imaging results in two experimental tasks, from a sample of 10 patients, in an open-label trial of a single ketamine infusion.[53] In the reward task, patients had faster reaction times to positively cued trials at 24 hours and 7 days posttreatment, in comparison to baseline performance. These changes were accompanied by higher activation of the insula and orbitofrontal cortex at the anticipatory phase of positively cued trials both at 24 hours and 7 days posttreatment. In the emotion-judgment task, improved reaction times at 24 hours and 7 days posttreatment were also observed. These changes were accompanied by reduced activation of the amygdala and insula regions in response to negative versus positive pictures, both at 24 hours and 7 days posttreatment.

The last study to use fMRI follows a double-blind, placebo-controlled, crossover design of 33 TRD individuals and 24 healthy controls.[52] Both groups were randomized to a single ketamine or placebo infusion and then crossed over to the other intervention the following week. An fMRI scan was conducted 1 to 3 days after each infusion, during an emotion-recognition task. Results showed no group or session effect on reaction times, but significant changes in neuroimaging were reported. A drug-effect comparison between the TRD and healthy controls, after placebo, showed that brain areas of the frontal gyri, anterior cingulate cortex, insula, and posterior cingulate were less active in the TRD group. This pattern was reversed after a ketamine infusion, with decreased activity activation in the TRD group and greater activity in the healthy controls.

Finally, one study used only an experimental task and followed a six-infusion regime on an open-label design,[47] using a facial emotion-recognition task at baseline and 24 hours after the last ketamine infusion. Results show no significant changes in facial recognition of sadness, fear, or happiness emotions after six ketamine infusions. The behavioral results were not related to treatment outcomes of response or remission.

Neuropsychological Profiles Predictive of Treatment Response

Some studies assessed the predictive power of neuropsychological functioning profiles on treatment response. An open-label trial found that worse attention at baseline increased the likelihood of treatment response through six ketamine infusions.[44] Another study, also an open-label trial, found that ketamine responders at 40 minutes had worse processing speed than non-responders.[43] This finding was replicated in a subsequent randomized, controlled trial by the same group, which reported that slower processing speed at baseline predicted greater symptom improvement 24 hours post-infusion.[45] Finally, a randomized trial found that, after five ketamine infusions, better working memory at baseline was a significant predictor of MDD symptom improvements when compared to the group with five midazolam infusions.[55]

DISCUSSION

The relationship between neuropsychological deficits and mental disorders has been at the forefront of psychiatric research in the last decade. For individuals with TRD, these changes in neuropsychological performance seem to persist even after symptom remission and can also explain a substantial portion of the functional impairments of this group.[11,12] Understanding the impact of antidepressant agents on cognition is crucial for developing new treatments and for mitigating psychosocial problems related to TRD. Although the antidepressant efficacy of sub-anesthetic ketamine in TRD

has been established, a systematic appraisal of the available literature regarding the neurocognitive effects of sub-anesthetic ketamine is warranted. This systematic review assessed the extant literature on neurocognitive effects of ketamine in TRD patients and includes a longitudinal assessment of esketamine's effects.

Acute Effects in TRD Patients

Previous evidence supports a disruptive effect in delayed recall directly after ketamine administration in healthy individuals.[37,57] One study in this systematic review, an open-label single-infusion trial, is the only one to focus on ketamine's acute effects in individuals with TRD.[43] The researchers found a disruption in delayed recall 40 minutes after treatment. No acute impairments were observed in immediate recall and verbal fluency, which suggests that their findings of memory deficits were probably related to a disruption in the early consolidation stages of episodic memory encoding.

Reports of Worse Neurocognitive Performance After Treatment

Only 1 of the 14 studies reported worse neurocognitive performance after treatment.[55] Authors reported worse verbal memory 24 hours after six ketamine infusions and worse processing speed 24 hours after a single ketamine infusion, but no impairments at seven days posttreatment were observed. This result is not further discussed by the authors, as they suggest that future, more powered studies should test the replicability of their findings. The other investigations in this systematic review do not replicate these results, finding that neuropsychological functions either improved or remained at the same level.

Reports of Neurocognitive Improvement After Treatment

Processing speed Processing speed was the neuropsychological function most frequently reported as having improved posttreatment, with 4 studies reporting better processing speed after six ketamine infusions. It is noteworthy that three of these studies were reanalyses of the same sample.[49,51,54] Two studies assessed if processing speed improvements remained significant after accounting for changes in mood symptoms; it did in one study[49] but not in the other.[54]

These are important results, given that processing speed is among the most commonly impaired cognitive functions in TRD patients[5,58,59] and seems to be impaired even in euthymic individuals.[60] Adequate processing speed performance seems dependent on the integrity of cerebral white matter of parietal, frontal, and temporal lobes,[61] and impairments in these areas are associated with worse processing speed performance.[62–64] Previous results have shown processing speed improvement following current monoaminergic antidepressant pharmacotherapy, without asserting whether these changes were independent from changes in mood symptoms.[16,17,65]

In chronic users, ketamine seems to induce dose-dependent abnormalities in brain white matter, suggesting disrupted or damaged connectivity.[66] Opposite findings of enhanced white matter integrity have been reported in depressed patients after sub-anesthetic ketamine treatment,[67] in line with ketamine's "neuroplasticity" hypothesis.[32] Results from the extant literature assessed in this systematic review are inconclusive as to whether (R-S)-ketamine can induce processing speed deficits at 24 hours or whether it can actually improve processing speed in the mid-term following serial infusions. The only study of continuous S(+)-ketamine use suggests that processing speed performance is not altered in adults for up to a year but that it may be altered in older patients, which should be addressed if ketamine is to be used by this older group.

Working memory Two studies in our review reported better working memory after ketamine treatment. Working memory, one of the core executive functions,[68] is among the frequently impaired neuropsychological functions in TRD patients, during and after the depressive episode.[3,7] Both studies by Shiroma and colleagues[44,55] found better working memory performance after six infusions in open-label trials; this improvement was nonsignificant, however, when controlling for changes in depressive symptoms. In the latter study, working memory improvements were found only in the group with six ketamine infusions and not in the single-infusion group.

Studies in animal models show the critical importance of NMDARs for working memory, as damage to these receptors impairs the adequate functioning of brain areas associated with working memory.[69–71] Considering that ketamine improves neuroplasticity in the medial prefrontal cortex[31,72] and increases glutamate neurotransmission,[73] improvements in working memory following six ketamine infusions suggest a possible pro-cognitive effect for this neuropsychological function in TRD patients. Results suggestive of such improvements are scarce in this systematic review. Current evidence does not support such changes in the short term for (R-S)-ketamine treatments and in the long term for S(+)-ketamine regimes.

Cognitive flexibility Improvements following ketamine infusions were reported for another core executive function, cognitive flexibility, which is classically defined as a complex ability of alternating between mental sets and thoughts that also subsides behavior changes according to external feedback. Impairments in cognitive flexibility are associated with persistent behavioral patterns and negative thought schemas commonly experienced by MDD patients.[74] Lower cognitive flexibility performance can also predict worse remission rates and greater chances of relapse.[75,76]

In animal models, damages to glutamatergic neurotransmission that impair cognitive flexibility[77] can be prevented by ketamine infusions.[78,79] In the previously mentioned study by Shiroma and colleagues,[55] patients in the group with six ketamine infusions showed better cognitive flexibility 24 hours posttreatment. Although isolated, the finding by Shiroma and colleagues should be further investigated, given the importance of cognitive flexibility for TRD patients' remission rates and chances of relapse.

Neuropsychological Predictors of Antidepressant Response

Some studies assessed whether specific neuropsychological profiles could predict antidepressant response. Results vary, with lower attention,[44] slower processing speed,[43,45] and higher working memory[55] being significant predictors of response status. The finding that patients with lower attention and slower processing speed may especially benefit from ketamine infusions could be an interesting insight into ketamine's mechanism of action. Given that ketamine can selectively improve synaptogenesis in prefrontal brain areas responsible for cognitive functions commonly impaired in depression,[26,31] one hypothesis is that patients with reduced neuroplasticity in these areas may have better results after ketamine treatment.

As previously discussed, these neuropsychological functions are at the core of cognitive symptoms in TRD and could indicate which patients would benefit the most from ketamine infusions. Due to the potentially major importance of these results for the daily practice of clinicians and for TRD patients, future studies should try to replicate these findings.

Functional Brain Imaging and Experimental Tasks

The results from studies of functional brain imaging suggest a normalizing effect after ketamine treatment in TRD patients, in accordance with a neuroplasticity framework for the antidepressant mechanisms of ketamine.[73,80] Before treatment, key brain areas for emotion processing, such as the amygdala, right caudate, and insula, were found to be less active in positive conditions and more active in negative conditions. This pattern was corrected following a single ketamine infusion.[46,53] Another study in TRD patients that further strengthens these findings reported that after a single ketamine infusion, hyperactive brain areas in TRD patients return to levels similar to what was observed in healthy controls at baseline.[52] As more efficient emotion processing may enable these patients to sustain antidepressant responses to psychotherapeutic treatment for longer periods,[81] future efforts should seek to replicate these findings of normalization and add to the understanding of ketamine's antidepressant effects.

One study reported that brain areas related to reward processing—more specifically, the orbitofrontal cortex and insula—were more active in TRD patients responding to positively cued trials, 24 hours after a single ketamine infusion.[53] Higher activation in brain areas such as the prefrontal cortex and insula in TRD patients after ketamine suggests that an improvement in anticipatory responses to reward could be part of ketamine's antidepressant mechanisms. This finding further strengthens a neuroplasticity hypothesis, supporting previous evidence that has shown enhanced functional connectivity in the dorsolateral and orbitofrontal cortex after ketamine.[82] Abnormal response to negative feedback and hyposensitivity to rewards are associated with failures in motivation and performance monitoring,[83] symptoms commonly present in MDD patients. If the results of higher mesolimbic engagement are replicated, ketamine could offer an augmentation to psychotherapeutic processes that influence brain areas related to reward processing, such as behavioral activation.[84]

Results from two of these experimental studies, which assessed changes to the emotional rating of images after a single ketamine infusion, show no significant changes.[47,53] A possible hypothesis is that ketamine may exert antidepressant effects without correcting pathological emotional bias at a conscious level.[47] When reaction times were measured, results differed between experimental studies. One study found no improvements in reaction times during an emotion-processing task,[52] whereas another study found improved reaction times to positively cued trials, 24 hours and 7 days after a ketamine infusion.[53] These results should be further investigated for their value in understanding both ketamine's mechanism of action and the cognitive profile of remitted TRD patients.

LIMITATIONS

This systematic review has some important limitations, mainly attributed to the novelty of the subject. The literature on neuropsychological functioning of TRD patients during ketamine treatment is still small, and the possible effects are still understudied. The included studies also assess different neuropsychological functions with distinct tests. The general lack of effect-size reporting further hinders a more precise, meta-analytical analysis, while also calling for a cautionary appraisal of any significant findings.

CONCLUSIONS

Current evidence suggests that ketamine and esketamine do not appear to exert significant deleterious neurocognitive effects in TRD patients. Improvements in processing speed, working memory, and cognitive flexibility were found between 7 and 13 days after repeated (R-S)-ketamine infusions; these functions may especially benefit from a ketamine pro-cognitive effect. Some of the studies in this review have found that these improvements may happen independently of mood symptoms changes, but data from a longitudinal S (+)-ketamine study do not support such improvements.

Results suggest possible neuropsychological profiles predictive of antidepressant response to ketamine, such as lower attention, slower processing speed, or higher working memory, that should be further assessed in future studies, as these results could provide time-saving evidence to clinicians and mental health practitioners. Finally, a rapid normalizing effect in key brain areas for emotion and reward processing, which are commonly impaired in patients with TRD, is a promising hypothesis for ketamine's antidepressant mechanisms. If further replicated by future studies, findings of restored connectivity can help establish a neuroplasticity framework for depression,[32,73,80] for which ketamine—and its resultant synaptogenesis—may prove particularly helpful.

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