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Review Article

Neurocognitive impact of ketamine treatment in major depressive disorder: A review on human and animal studies

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ABSTRACT

Background: Most recent evidence support a rapid and sustained antidepressant effect of subanesthetic dose of intravenous ketamine in patients with major depressive disorder (MDD). However, clinical and animal studies investigating the effects of intravenous ketamine on specific functional domains disrupted by depression reported conflicting results. Therefore, the aim of this review is to provide an overview of the recent findings exploring the cognitive effects of ketamine in depression.

Methods: After a bibliographic search on PubMed, Medline and PsycInfo, we retrieved 11 original studies meeting our research criteria, 7 in humans with MDD or Treatment Resistant Disorder and 4 using rats models for depression.

Results: Overall the results showed that a) ketamine reduced activation and normalized connectivity measures of several brain regions related to depressive behaviors and reversed deficits in cognitive flexibility and coping response strategy in rats with depressive features, and b) ketamine leads to a no significant impairment on neurocognitive functions in most of the studies, with only three studies observing improvements in speed of processing, verbal learning, sustained attention and response control, verbal and working memory.

Limitations: The methodological heterogeneity, in terms of neuropsychological tests used and cognitive domain explored, of the studies included.

Conclusions: Most of the studies included showed no significant cognitive impairments in MDD patients after ketamine treatment. Furthermore, the results of the fMRI studies considered suggest that ketamine may have a normalizing effect on brain functions during attentional and emotional processing in MDD patients. However, further studies are needed to confirm these preliminary evidences.

1. Background

Major depressive disorder (MDD) is a common psychiatric disease, representing a relevant cause of disability worldwide and determining an high burden for health systems (World Health Organization, 2017). Besides the typical clinical symptomatology characterizing MDD patients, such as severe depressed mood, anhedonia, suicidal ideation, fatigue or loss of energy (Malhi and Mann, 2018), a disruption of cognitive functions frequently affects depressed patients. Indeed, cognitive impairment is a core feature of mood disorders (Trivedi and Greer, 2014), which has been also included as a diagnostic criteria for MDD in the DSM-5 classification. Although some patients with MDD experience mild to moderate cognitive deficits, for the majority of them the cognitive disfunctions are so significant to constitute one of the symptoms most frequently reported by patients and their relatives (Roca et al., 2015). Specifically, MDD patients often show deficits in selective cognitive domains, including attention, executive functions, memory and processing speed (Roca et al., 2015), which seem to persist even after remission, resulting in poor functional outcome, especially when executive and attentive functions are altered. More specifically, residual cognitive deficits account for occupational and relational difficulties, regardless the improvement of the others depressive symptoms (Bortolato et al., 2015).

Notably, traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRI) and serotonin–norepinephrine reuptake inhibitors (SNRI), demonstrated just a little effect on cognitive symptoms in various placebo-controlled clinical trials (Bortolato et al., 2015; Knight and Baune, 2018; Lam et al., 2014). In this context, an exception is represented by vortioxetine, which, by inhibiting the serotonin transporter (SERT) and by modulating the effects of several serotonin

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Table 1
Summary of studies investigating the cognitive effects of intravenous ketamine administration in both patients with MDD or TRD and rodent models of depression.

Authors	Study design	Population (Female/ Male; age [years] ± SD	Exclusion criteria	Medication and dose	Diagnostic and clinical scale	Neuropsychological tests	Neuroimaging/ Electrophysiology	Main results
Chen et al., 2018b	Randomized clinical trial placebo controlled and standard therapy controlled	24 TRD 0,5 mg/kg ketamine infusion group (21 F, 3 M; age 48.46 ± 11.08)	Any major medical or neurological illness	Single iv ketamine infusion 0,2 mg/ kg or 0,5 mg/kg over 40 min	HAM-D	Working memory task	NA	No cognitive function impairment after single low dose of ketamine infusion in TRD.
		23 TRD 0,2 mg/kg ketamine infusion group (17 F, 6 M; age 44.96 ± 12.31) 24 TRD placebo group (15 F, 9 M; 48.63 ± 8.12)	History of alcohol or substance abuse			Go/No-go task		Specific cognitive ↑ in the Go/No- go task in TRD 0,5 mg/kg responders group. Higher correct and lower omission in the Go/No-go task was negatively associated with depressive symptoms in the 0,5 mg/kg ketamine infusion group.
Gass et al., 2019	Veterinary prelinical trial	24 negative cognitive state strain genetic rat model of depression,based on electrical footshocks 25 Non-depressed positive cognitive state .	NA	Sc Ketamine 10 mg/kg	NA	NA	fMRI	Ketamine's acute strain-independent effect: ↓network strength of amygdala, anterodorsal hippocampus and ventral pallidum. ↑ network strength in prefrontal cortex. Ketamine's acute strain-specific effect: change in network strength with opposite direction in depressed and non-depressed rats in the parietal association cortex network. Strain-specific long-term effect: In depressed rats, ketamine normalizes connectivity measures for habenula and midline thalamus
Jett et al., 2015	Veterinary prelinical trial	186 male Sprague-Dawley healthy rats	NA	Ip Ketamine 10 mg/kg	NA	Set-shifting Test	High Frequency direct brain stimulation (vHipp)	Acute ketamine treatment 24 h prior to testing CUS restores the performance of the CUS-rats in the set-shifting test
		Depression model CUS				SPDB		No effects of ketamine on ED Set Shifting task performance in unstressed rats.
						Forced swim test		Ketamine treatment restored burying behavior in CUS rats.

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Table 1 (*continued*)

Authors	Study design	Population (Female/ Male; age [years] ± SD	Exclusion criteria	Medication and dose	Diagnostic and clinical scale	Neuropsychological tests	Neuroimaging/ Electrophysiology	Main results
								HFS of the vHipp reduced immobility on the forced swim test. HFS in the vHipp recapitulated ketamine's therapeutic effects on the ED task.
Murrough et al., 2014	Open label longitudinal clinical trial	25 TRD (10 F, 15 M; mean age of responders 53.82; mean age of non responders 40.44).	Current psychotic symptoms	Single iv ketamine infusion 0,5 mg/kg	MADRS	Estimated premorbid IQ (WRAT-3 Reading)	NA	Slower baseline processing speed was associated with greater antidepressant response.
			Lifetime history of Bipolar Disorder, Schizophrenia or Schizoaffective disorder Current anorexia or bulimia nervosa Alcohol or drug abuse within the past 6 months Unstable medical illness		BPRS	Current IQ (WAIS-III, Vocabulary and Matrix Reasoning) Tests from MCCB (Trails A, WMS, Spatial Span, BAC-S, Digit Symbol, Letter-Number Sequencing, HVLT Category Fluency, and CPT I/P)		↓ of memory recall. Negative cognitive effects immediately after ketamine, predict lower response rate at 24 h.
Murrough et al., 2015	Randomized controlled trial placebo-controlled	Ketamine infusion group 43 TRD (24 F, 19 M; 47.1 ± 12.6)	Lifetime history of a psychotic illness or bipolar disorder	Single iv ketamine infusion 0,5 mg/kg	IDS-CR	Subset of the MCCB (Trails A, WMS, Spatial Span, BAC-S, Digit Symbol, Letter-Number Sequencing, HVLT BVMT)	NA	No adverse neurocognitive effects at 7 days post ketamine.
		Midazolam infusion group 19 TRD (10 F, 9 M; 43.8 ± 11.0)	Alcohol or substance abuse in the previous 2 years Unstable medical illness Serious and imminent suicidal or homicidal risk Score <27 on the Mini Mental State Examination	Single iv midazolam infusion 0.045 mg/kg	MADRS	NAB: Mazes, and Category Fluency		Slower baseline processing speed was associated with greater antidepressant response after ketamine.
Papp et al., 2017	Veterinarypreclinical trial	Population not specified. Male Wistar rats depression model CMS	NA	Ip ketamine 5,10,15 or 30 mg/kg	NA	Novel object recognition test	NA	Ketamine 10 mg/kg reversed deficits in NORT in both the subacute (3–5 days) and chronic (5 weeks) cohorts of rats
Patton et al., 2017	Veterinary preclinical trial	179 male Sprague-Dowley Rats depression model CIC	NA	Ip ketamine 10 mg/kg	NA	Attentional set shifting task	NA	Ketamine corrected CIC-induced deficits in reversal learning task and did not affect reversal learning in non-stressed controls
Reed et al., 2018	Double-blind, placebo-controlled, crossover study	33 MDD (12 M, 21 F; 36.06 ± 9.74) 26 HCs (10 M, 16 F; 33.88 ± 10.42)	History of drug or alcohol dependency within the past three months Prior Axis I diagnosis or any psychiatric disorder in a first-	Single iv ketamine infusion 0,5 mg/kg	MADRS	NA	fMRI dot probe task with emotional face stimuli	↑ activation post ketamine compared to post placebo in the left middle occipital gyrus across groups. ↓ activation post-ketamine compared to post placebo in

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Table 1 (*continued*)

Authors	Study design	Population (Female/ Male; age [years] ± SD	Exclusion criteria	Medication and dose	Diagnostic and clinical scale	Neuropsychological tests	Neuroimaging/ Electrophysiology	Main results
			degree relative, except MDD for the MDD group.					the left temporal and inferior frontal cortices. HCs: ↑activation of the right frontal cortex, dACC and left inferior occipital gyrus post ketamine vs. post placebo. MDD: ↓ activation post ketamine vs post placebo in right prefrontal cortex, dACC, and left inferior occipital gyrus. In HCs an activation of large medial prefrontal and ACC during angry trials and deactivation during happy trials during placebo which reverse after ketamine was found; An opposite pattern was observed in MDD patients.
Salvadore et al., 2010	Open label longitudinal clinical trial	15 MDD (50.5 ± 13.1)	DSM-IV diagnoses of drug or alcohol dependence or abuse within the past 3 months	Single iv ketamine infusion 0,5 mg/ kg over 40 min	MADRS	N-back task	Magnetoencephalography	Correlation between PgACC and clinical improvement after ketamine in MDD.
			Unstable medical illness		HAM-D			Subjects who showed the least engagement of the pgACC with increased working memory load showed the greatest symptomatic improvement within 4 hour of ketamine administration.
			Uncorrected hypo or hyperthyroidism					
Shiroma et al., 2014	Open label trial	15 MDD (0 F, 15 M; 52.0 ± 14.8)	Inability to speak English	Six iv ketamine infusion 0,5 mg/ kg over 40 min	MADRS	CogState battery	NA	↑ of visual memory, simple working memory and complex working memory after six ketamine infusions.
			Inability or unwillingness to provide written informed consent		BPRS			
			Moderate to severe cognitive impairment current or lifetime diagnoses of PTSD, acute stress disorder, psychosis-related disorder, bipolar disorder I or II, substance-induced disorder, any mood disorder. Diagnoses of Parkinson's desease, dementia of any type, multiple sclerosis, seizures or other central		CADSS			

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Table 1 (*continued*)

Authors	Study design	Population (Female/ Male; age [years] ± SD	Exclusion criteria	Medication and dose	Diagnostic and clinical scale	Neuropsychological tests	Neuroimaging/ Electrophysiology	Main results
			nervous system history of moderate/severe brain injury comorbid substance abuse or dependence, clinical unstable medical illness, pregnancy inability or unwillingness to use a medically accepted contraceptive method active suicidal ideation judged to cause imminent danger.					
Zheng et al., 2019	Open label longitudinal clinical trial	64 TRD (39 F, 25 M; 33.3)	Lifetime history of psychotic or bipolar disorder Positive urine toxicology screening Past or current alcohol or substance abuse Imminent suicidal and/or homicidal risk in the current episode Lactating, pregnancy or planning pregnancy during the study period	Six iv Ketamine infusion 0,5 mg/ kg over 40 min.	MADRS	MCCB	NA	No short-term neurocognitive impairments in MDD after six ketamine consecutive infusions. ↑ of speed of processing with moderate effect size and verbal learning with small effect size. No relationship between baseline neurocognitive function and improvement of depressive symptoms following six ketamine infusions.

ACC: Anterior Cingulate Cortex; BPRS: Brief Psychiatric Rating Scale; BVMT: Brief Visual Memory Test; CADSS: Clinician Administered Dissociative State Scale; CIC: Chronic Intermittent Cold; CMS: Chronic Mild Stress; CUS: Chronic Unpredictable Stress; CPT: Continuous Performance Test; dACC: dorsal Anterior Cingulate Cortex; ED: Extra Dimensional; F: Female; fMRI: functional Magnetic Resonance Imaging; HAM-D: Hamilton Rating Scale for Depression; HFS: High Frequency Stimulation; HVLT: Hopkins Verbal Learning Test; IDS-CR: Inventory of Depressive Symptomatology- Clinical Rated; Ip: intraperitoneal; Iv: intravenous; M: Male; MADRS: Montgomery-Asberg Depression Rating Scale; MCCB: MATRICS Consensus Cognitive Battery; MDD: Major Depression Disorder; NA: Not applicable; NAB: Neuropsychological Assessment Battery; pgACC: pre genual Anterior Cingulate Cortex; QIDS-SR: Quick Inventory of Depressive Symptomatology- Self Report; *Sc*: Subcutaneous; SPDB: Shock-probe defensive burying test; TRD: Treatment Resistant Depression; vHIPP: ventral Hippocampal Cortex; WAIS: Wechlser Adult Intelligence Scale.

(5-HT) receptors, demonstrated to enhance cognitive performance in various animal models and human clinical trials (Frampton, 2016). Moreover, an increasing amount of studies are revealing the potential antidepressant effect of N-methyl-D-aspartate (NMDA) receptors antagonist, such as ketamine, with consistent evidence of efficacy and a short latency of antidepressant activity onset (Amidfar et al., 2019). In humans, ketamine has traditionally been used as an anesthetic agent (Eldufani et al., 2018) and only in the last two decades research focused on the potential antidepressant properties of low-dose ketamine administered in treatment refractory mood disorders (Mathew et al., 2012; Murrough, 2012). Specifically, ketamine is a high-affinity, non-competitive NMDA glutamate receptor antagonist that was found to exert an antidepressant effect, which occurs as early as 40 min from the administration and usually lasts 7 days, in treatment resistant major depression (TRD) patients, therefore representing a new therapeutic option for depressed patients (aan het Rot et al., 2010; Mathew et al., 2010; Zarate et al., 2006). During the years, several clinical studies evaluated the efficacy of intravenous administration of low-dose ketamine in TRD with positive results in terms of reduction of depressive symptoms (Berman et al., 2000; Murrough, 2016; Zarate et al., 2006).

Interestingly, the antidepressant effect of ketamine has been also confirmed in animal models of depression, with several preclinical studies reporting an antidepressant-like behavior after ketamine administration in rats. Specifically, the most relevant results have been observed in tasks evaluating anhedonia and escape paradigm, such as learned helplessness paradigm and sucrose intake (Brachman et al., 2016; Koike et al., 2011; Papp et al., 2017).

Therefore, the evidence supporting the efficacy of ketamine in treating depression led to the recent FDA approval of nasal esketamine, the S-enantiomer of ketamine, as augmentation therapy in patients with TRD (Daly et al., 2019; Kim et al., 2019).

However, although studies that evaluated neurocognitive and neuroradiological outcomes in both intra-operatory and intensive care unit patients reported that ketamine exert a neuroprotective activity, just a limited and heterogenous number of studies explored the effects of ketamine on cognitive symptoms in MDD patients.

Therefore, this review aims to summarize the results from studies investigating the cognitive effects of intravenous ketamine administration in both patients with MDD and rodent models of depression.

2. Methods

A bibliographic search was conducted by two investigators in PubMed, Medline and PsycInfo using the following search terms: ("Ketamine) AND ("Depression" OR "Major Depressive Disorder") AND ("Cognition" OR "Cognitive functions"). We included open label clinical studies and randomized controlled clinical trials (RCTs), evaluating cognitive functions in patients with MDD treated with single or repeated doses of intravenous ketamine. We selected studies that evaluated cognitive outcome by means of validated neuropsychological tests and/or functional neuroimaging techniques, possibly including a complementary morphological neuroimaging and electrophysiologic study. We excluded a) investigations performed on patients with a diagnosis different from MDD, b) studies not investigating the efficacy of ketamine on cognitive functions, and c) case reports and case series. We also included 4 studies that employed different animal models of depression for evaluating cognitive outcome after treatment with intravenous ketamine in rats (Gass et al., 2019; Jett et al., 2015; Papp et al., 2017; Patton et al., 2017). Specifically, Gass et al. (2019) carried out their study on two groups of rats: a) rats with a genetical model of depression (negative cognitive state strain), produced with electrical footshocks administration and b) rats with a non-depressed phenotype as control group. Jett et al. (2015) employed the Sprague-Dawley healthy rats depression model, induced by chronic unpredictable stress (CUS) whereas Papp et al. (2017) used a male Wistar rats depression model induced by chronic mild stress (CMS) and, lastly, Patton et al. (2017) employed adult male Sprague Dawley rats Depression model induced by chronic intermittent cold (CIC). The inclusion criteria were met by 11 studies, whose methods and results are summarized in Table 1.

3. Results

3.1. Preclinical studies in rats

Results of the 4 studies that explored the effect of ketamine in rats demonstrated an antidepressant effect of this substance. Specifically, Gass et al. (2019) carried out a functional Magnetic Resonance (fMRI) study exploring the ketamine's effects on depressed and healthy rats on brain activity. The authors demonstrated that ketamine had two distinct actions over time: a short-term effect and a long-term effect. The former was represented by a reduced activation of several brain regions related to depressive behavior, including amygdala, anterodorsal hippocampus and ventral pallidum. This effect has been observed both in depressed and healthy control rats. The long-term effect was characterized by a normalization of connectivity measures observed after ketamine administration in habenula and midline thalamus of rats with depressive features. Similarly, Jett et al. (2015) found that a single subanesthetic dose of ketamine was able to reverse chronical unpredictable stress (CUS)-induced cognitive deficits on the extradimensional (ED) set-shifting task, occurring 24 h after administration in chronically stressed rats. Further, the authors found that ketamine reduced immobility and increased burying behaviours in chronically stressed rats on the shock-probe defensive burying (SPDB) test, ultimately suggesting a restoration of active coping strategy. Similarly, Papp et al. (2017) found that the dyscognitive effects of CMS in the Novel Object Recognition Test were fully reversed by both subacute (3–5 days) and chronic (5 weeks) intraperitoneal ketamine 10 mg/kg treatment. Finally, the results obtained by Patton et al. (2017) showed that a single intraperitoneal injection of ketamine, administered at the dosage of 10 mg/kg 24 h prior to testing, reversed the CIC induced reversal learning deficit.

3.2. Clinical studies in humans

With regard to human clinical trials, the study carried out by Zheng et al. (2019) in a population of sixty-four patients with MDD reported that 6 ketamine consecutive infusions were not associated with short-term neurocognitive impairments. However, significant improvements were found in speed of processing and verbal learning, with moderate effect sizes after completing six ketamine consecutive infusions. The authors underlined that these effects could be just partially explained by the improvement of depressive symptoms. Similarly, the RCT carried out by Chen et al. (2018b) in a cohort of 71 patients with TRD, found that a single low dosage ketamine infusion did not impair cognitive functions. However, a specific cognitive improvement, evaluated using the Go/No-go task, was observed only among the responders to the intravenous 0.5-mg/kg ketamine dosage. In addition, the improvement of sustained attention and response control functions, which was considered if the subject had higher correct responses and lower omissions in the Go/No-go task, was associated with a reduction in depressive symptoms in the 0.5-mg/kg ketamine infusion group. Specifically, higher responders in the 0.5 mg/kg infusion groups showed a higher improvement in terms of depressive symptoms and cognitive functions.

Moreover, among the studies supporting a pro-cognitive effect of ketamine, Shiroma et al. (2014) observed an improvement of visual memory, simple working memory and complex working memory after six repeated ketamine infusions in a cohort of 15 patients with TRD. In contrast, mixed results were found in an open label clinical trial and in a RCT, performed by the same research group, assessing cognitive effects of a single intravenous ketamine infusion in MDD patients

(Murrough et al., 2014; 2015). Specifically, this RCT, performed in a cohort of 62 MDD patients, revealed, that, compared with midazolam, a single, sub-anesthetic dose of ketamine did not impair neurocognitive performance 7 days after treatment. However, the authors observed that performances in processing speed, verbal learning, and visual learning improved from baseline to study end, regardless of treatment condition or changes in depression severity, likely reflecting a non-specific learning effect. Moreover, by evaluating the impact of baseline cognitive performance on the Montgomery-Asberg Depression Rating Scale scores change at 24 h from ketamine administration, they found that a slower baseline processing speed was associated with a greater antidepressant response. Interestingly, this result replicated their previous finding of a minimal acute neurocognitive effect, confined to the delayed recall, after the administration of low-dose ketamine found in a sample of 25 MDD patients (Murrough et al., 2014).

Finally, two studies (Reed et al., 2018; Salvadore et al., 2010) assessed neurocognitive effects of a single intravenous ketamine infusion, by employing fMRI and Magnetoencephalography (MEG) techniques. Specifically, Salvadore et al. (2010) performed a MEG study during a working memory task (N-back) in 15 drug-free patients with MDD. MEG recordings were taken 1 to 3 days before the administration of a single intravenous ketamine infusion, to assess the activity of the pregenual anterior cingulate cortex (pgACC). The results showed that in MDD patients, the pre-treatment pgACC activity during the N-back task performance was positively correlated with the clinical improvement after treatment with ketamine. Specifically, subjects who showed the least engagement of the pgACC, with an increased working memory load, showed the greatest symptomatic improvement within 4 h from ketamine administration. Similarly, Reed et al. (2018) performed an fMRI study with a dot probe attentional bias task used for the assessment of cognitive outcome with emotional face stimuli in 33 patients affected by MDD and 26 healthy controls (HCs). The authors found a significantly greater activation in the left middle occipital gyrus in the ketamine treatment group compared to placebo group and a significantly reduced activation in the left temporal and inferior frontal cortices in the post-ketamine group when compared to post placebo group. Moreover, HCs showed an increased activation of the right frontal cortex, dACC and left inferior occipital gyrus in the post ketamine vs. post placebo group. In contrast, post ketamine MDD patients had a decreased activation in right prefrontal cortex, dACC, and left inferior occipital gyrus compared to the post placebo group. Finally, HCs treated with placebo reported the activation of large medial prefrontal and anterior cingulate cortices during angry trials and the deactivation during happy trials, which reversed after ketamine treatment. Interestingly, an opposite activation/deactivation fMRI pattern was observed in MDD patients group.

4. Discussion

In the last decades, psychopharmacological research broadly focused on molecules able to modulate the glutamatergic system (Hashimoto, 2019; Lener, Kadriu, and Zarate, 2017). In this regard, a growing amount of studies explored the role of glutamatergic NMDA receptors in MDD, with a particular interest for their possible role in the pathogenesis of cognitive alterations affecting depressed patients. Indeed, glutamatergic NMDA receptors are involved in both working and long-term memory in humans (Volianskis et al., 2015) and preclinical studies have shown that NMDA-receptor antagonists, such as ketamine, caused a disruption of hippocampal long-term potentiation (LTP), the putative mechanism underlying neuronal learning (Guo et al., 2017; Huang et al., 2014).

Furthermore, research studies exploring antidepressant mechanism of ketamine revealed different properties potentially explaining its pro-cognitive functions, including its neuroprotective (Brunson et al., 2001) and neuroplasticity (Clarke et al., 2017) effects as well as its role in the synthesis of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) (Allen et al., 2015; Zanos and Gould, 2018).

Overall, the studies exploring the cognitive outcome of intravenous ketamine therapy in depressed patients included in this review provided mixed and heterogenous results, probably due to the employment of different assessment tools and the investigation of different cognitive domains.

Nonetheless, some studies reported a positive effect of ketamine on selective cognitive domains. Specifically, Zheng et al. (2019) reported a significant improvement in speed of processing and, to a lesser extent, on verbal learning, in MDD patients who received treatment with intravenous ketamine. These results are not surprising especially because, as observed in many studies, both speed of processing and verbal learning are two cognitive domains severely compromised in patients with MDD (Baune et al., 2010; Lee et al., 2012; Milak et al., 2019; Tsourtos et al., 2002). Similarly, Chen et al. (2018b) observed an improvement in the Go/No-go task performance, which was directly proportional to the amelioration of the depressive symptomatology, in a group of MDD patients treated with ketamine. This result is in line with previous evidence showing selective impairments in cognitive inhibition, as measured with the Go/No-go task, in depressed patients compared to HCs (Richard-Devantoy et al., 2015; Tozzi et al., 2020)

Finally, two studies observed a significant improvement of memory functions after ketamine administration in MDD patients (Murrough et al., 2014; Shiroma et al., 2014). Although a frequent and severe impairment of working memory in MDD has been consistently reported (Chen et al., 2018a), the biological mechanisms underpinning this cognitive symptom remain unclear. However, studies observing that NMDA receptors play a major role in working memory activity could support a role of the glutamatergic system in the pathogenesis of memory function deficits described in MDD (Skoblenick and Everling, 2012; Wang et al., 2013). Moreover, recent studies demonstrated that patients with mood disorders not only showed a dysfunction of the glutamatergic neurotransmission during a working memory task (Jelen et al., 2019) but also that the preservation of NMDA receptor functions is critical for an optimal cognitive performance, at least in the context of working memory (Anticevic et al., 2012).

Furthermore, although Murrough et al. (2015) found no correlation between ketamine administration and the improvement in processing speed, verbal learning and visual learning in TRD patients, the authors observed that ketamine had no adverse effects in terms of neurocognitive performance in these patients. Interestingly, this finding is in contrast with previous studies carried out on HCs, which found selective impairments in working, episodic and procedural memory as well as perceptual disturbances, after ketamine administration (Morgan et al., 2004). These differential effect among HCs and MDD patients could be explained by the normalization of an unbalance in neurotransmitters in the group of affected subjects, as already proved in different pathways (Pigoni et al., 2019). This unbalance would not be present in HCs, which, in contrast, might present a perturbation of cognitive functions due to ketamine. Moreover, most of the studies conducted on HCs assessed immediate cognitive effects (i.e. 20 min after the start of the infusion), while the studies carried out on MDD patients focused on the short-term delayed cognitive effect of the drug (i.e. 2–3 days after the infusion). For this reason, a direct comparison between these studies is difficult and standardized studies in terms of assessment and duration would be important in order to evaluate real differences between affected and healthy groups.

However, the absence of adverse effects of ketamine on neurocognitive performance in depressed patients was confirmed by other studies reported in this review (Chen et al., 2018b; Zheng et al., 2019), ultimately suggesting the need of a risk-benefit analysis to further validate the use of ketamine as therapy for TRD. At this purpose large RCTs, comparing the effectiveness of ketamine respect to the current therapeutic golden standard of TRD, represented by the electroconvulsive therapy (ECT), are mandatory (Semkovska and McLoughlin, 2010).

It should be noted that two of the human clinical trials discussed in this review (Shiroma et al., 2014; Zheng et al., 2019) explored the effect of six repeated ketamine infusions, instead of a single dose, on cognition. This strategy is based on the hypothesis that repeated ketamine infusions could achieve better antidepressant outcomes than a single one (Murrough et al., 2013). Interestingly, these studies reported an improvement in speed of processing and verbal learning (Zheng et al., 2019), as well as visual memory, simple and complex working memory (Shiroma et al., 2014) after six ketamine repeated infusions. These results suggest that repeated infusions of ketamine are feasible and effective both in terms of the reduction of depressive symptoms and in the improvement of cognitive impairments. However, these results need to be further confirmed, since both the studies were not placebo controlled, nor tested against the single dose of ketamine. Indeed, in the light of results obtained by Ionescu et al. (2019), which showed that six repeated ketamine infusions did not outperform placebo in terms of depressive symptoms in a sample of TRD subjects with chronic suicidal ideation, further placebo controlled RCTs and studies comparing different protocols of administration are necessary to better define the effects of repeated ketamine infusion on cognitive domains.

Furthermore, with regards to preclinical studies, it has been observed that ketamine had pro-cognitive effects in CMS (Papp et al., 2017), CIC (Patton et al., 2017) and CUS (Jett et al., 2015) animal models. Specifically, overall these studies found that the antidepressant and pro-cognitive effects of ketamine appeared to be the result of improved cognitive dimensions associated with mPFC, OFC and ventral hippocampus functions, such as cognitive flexibility and active coping responses.

Finally, the fMRI studies included in our review showed that in both rats (Gass et al., 2019) and humans (Reed et al., 2018), ketamine acts by restoring connectivity in brain areas impaired in subjects affected by MDD, such as ACC (and pgACC), amygdala, anterodorsal hippocampus, ventral pallidum, habenula and midline thalamus. Interestingly, habenula and midline thalamus are two brain structures that mediate cognitive flexibility, a function profoundly impaired in MDD and PTSD patients (Pehrson et al., 2015). Moreover, by reducing strength of amygdala, anterodorsal hippocampus and ventral pallidum, ketamine exerts anxiolytic, pro-cognitive and reinforcing effects. Similarly, two meta-analyses reported that also the ACC is implicated in attentional and emotional abnormalities in depression (Groenewold et al., 2013; Hamilton et al., 2012) and several studies observed functional and morphological alterations of this brain area in terms of decreased connectivity, altered glucose metabolism, and reduced volume, in depressed patients (Barthas et al., 2015; Pizzagalli, 2011). In particular, the pgACC has shown to be involved in the processing of the negatively valanced stimuli and to contribute to cognitive functions, such as social cognition, including theory of mind tasks, and conflict-monitoring (Palomero-Gallagher et al., 2019; Salvadore et al., 2010). Therefore, overall the fMRI studies revealed that brain activity in MDD patients post ketamine infusions resembles brain activity in HCs post placebo, ultimately suggesting that ketamine may have a normalizing effect of brain function during attentional and emotional processing. Furthermore, normalization of the disrupted connectivity within the habenula-midthalamic-hippocampal circuitry and within ACC in depressed patients may presumably reflect ketamine's pro-cognitive effects. Therefore, in light of these evidence, ketamine seems to improve synaptic plasticity and functional connectivity in brain areas involved in executive functions and cognitive emotional processing, such as ACC, mPFC and OFC, ultimately suggesting that its antidepressant effect could be due, at least in part, to the restoration of these altered neural circuits (Lee et al., 2016). Interestingly, ketamine's pro-cognitive effect might impact also on behavioural aspects of MDD, such as suicidal ideation, as suggested by a recent study (Lee et al., 2016).

Importantly, these results, should be considered in light of few limitations. First, the studies considered present methodological heterogeneity, especially regarding neuropsychological tests used and, consequently, the cognitive domain explored, limiting the comparison of study results. Further, only three studies evaluated the neurocognitive activity of ketamine in MDD employing neuroimaging techniques, and only two of them were conducted in humans. Therefore, more studies are needed to establish the real neurofunctional outcome of ketamine in MDD patients.

In conclusion, overall these findings suggest that ketamine administration on MDD patients did not result in significant impairments of cognitive functions, differently from previous findings observed on HCs (Morgan et al., 2004). However, it is important to point out that ketamine administration seemed to determine an improvement in selective cognitive domains, such as speed of processing, verbal learning (Zheng et al., 2019), cognitive inhibition (Chen et al., 2018b) and memory (Shiroma et al., 2014). However, further studies are needed in order to define a possible role of ketamine in the treatment for MDD and related cognitive symptoms, which often do not respond to treatment with conventional antidepressant therapy.

Finally, the neuroimaging studies seem to suggest a possible role of ketamine in normalizing brain connectivity in altered brain regions observed in depressed patients. Therefore, these findings should guide future studies with the aim to better define ketamine's mechanism of action in the brain and its effects on cognitive symptoms, which are among the most frequent and disabling symptoms in MDD.

CRediT authorship contribution statement

Camilla Crisanti: Conceptualization, Writing - original draft. **Paolo Enrico:** Conceptualization, Writing - original draft. **Alessio Fiorentini:** Writing - review & editing. **Giuseppe Delvecchio:** Writing - review & editing. **Paolo Brambilla:** Writing - review & editing, Supervision.

Conflict of Interest

None

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References

aan het Rot, M., Collins, K.A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S., Mathew, S.J., 2010. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol. Psychiatry 67 (2), 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038. https://doi.org/.

Allen, A.P., Naughton, M., Dowling, J., Walsh, A., Ismail, M.F., Shorten, G., Scott, L., McLoughlin, D.M., Cryan, J.F., Dinan, T.G., Clarke, G., 2015. Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: a comparison of ketamine and ECT. J Affect Disord 186, 306–311. https://doi.org/10.1016/j.jad.2015.06.033. https://doi.org/.

Amidfar, M., Woelfer, M., Réus, G.Z., Quevedo, J., Walter, M., Kim, Y.-K., 2019. The role of NMDA receptor in neurobiology and treatment of major depressive disorder: evidence from translational research. Prog. Neuropsychopharmacol. Biol. Psychiatry 94, 109668. https://doi.org/10.1016/j.pnpbp.2019.109668. https://doi.org/.

Anticevic, A., Gancsos, M., Murray, J.D., Repovs, G., Driesen, N.R., Ennis, D.J., Niciu, M.J., Morgan, P.T., Surti, T.S., Bloch, M.H., Ramani, R., Smith, M.A., Wang, X.-J., Krystal, J.H., Corlett, P.R., 2012. NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. Proc. Natl. Acad. Sci. U.S.A. 109 (41), 16720–16725. https://doi.org/10.1073/pnas.1208494109. https://doi.org/.

Barthas, F., Sellmeijer, J., Hugel, S., Waltisperger, E., Barrot, M., Yalcin, I., 2015. The anterior cingulate cortex is a critical hub for pain-induced depression. Biol. Psychiatry 77 (3), 236–245. https://doi.org/10.1016/j.biopsych.2014.08.004. https://doi.org/.

Baune, B.T., Miller, R., McAfoose, J., Johnson, M., Quirk, F., Mitchell, D., 2010. The role of cognitive impairment in general functioning in major depression. Psychiatry Res

176 (2–3), 183–189. https://doi.org/10.1016/j.psychres.2008.12.001. https://doi.org/.
Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H., 2000. Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry 47 (4), 351–354. https://doi.org/10.1016/S0006-3223(99)00230-9. https://doi.org/.
Bortolato, B., Carvalho, A., McIntyre, R., 2015. Cognitive Dysfunction in Major Depressive Disorder: a State-of-the-Art Clinical Review. CNS & Neurological Disorders - Drug Targets 13 (10), 1804–1818. https://doi.org/10.2174/1871527313666141130203823. https://doi.org/.
Brachman, R.A., Mcgowan, J.C., Perusini, J.N., Lim, S.C., Pham, T.H., Faye, C., Gardier, A.M., Mendez-David, I., David, D.J., Hen, R., Denny, C.A., 2016. n.d.. Ketamine as a prophylactic against stress-induced depressive-like behavior. https://doi.org/10.1016/j.biopsych.2015.04.022. https://doi.org/.
Brunson, K.L., Khanna, A., Cromwell, H.C., Cohen, R.W., 2001. Effect of the non-competitive NMDA antagonists MK-801 and ketamine on the spastic Han-Wistar mutant: a rat model of excitotoxicity. Dev. Neurosci. 23 (1), 31–40. https://doi.org/10.1159/000048694. https://doi.org/.
Chen, C., Jiang, W., Wang, W., Ma, X., Li, Y., Wu, J., Hashimoto, K., Gao, C., 2018a. Impaired visual, working, and verbal memory in first-episode, drug-naive patients with major depressive disorder in a Chinese population. https://doi.org/10.1371/journal.pone.0196023. https://doi.org/.
Chen, M.H., Li, C.T., Lin, W.C., Hong, C.J., Tu, P.C., Bai, Y.M., Cheng, C.M., Su, T.P., 2018b. Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. J Affect Disord 241, 1–7. https://doi.org/10.1016/j.jad.2018.07.033. https://doi.org/.
Daly, E.J., Trivedi, M.H., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A.R., Hough, D., Thase, M.E., Zajecka, J., Winokur, A., Divacka, I., Fagiolini, A., Cubala, W.J., Bitter, I., Blier, P., Shelton, R.C., …, Singh, J.B., 2019. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: a Randomized Clinical Trial. JAMA Psychiatry 76 (9), 893–903. https://doi.org/10.1001/jamapsychiatry.2019.1189. https://doi.org/.
Eldufani, J., Nekoui, A., Blaise, G., 2018. Nonanesthetic Effects of Ketamine: a Review Article. Am. J. Med. 131 (12), 1418–1424. https://doi.org/10.1016/j.amjmed.2018.04.029. https://doi.org/.
Frampton, J.E., 2016. Vortioxetine: A Review in Cognitive Dysfunction in Depression. https://doi.org/10.1007/s40265-016-0655-3. https://doi.org/.
Gass, N., Becker, R., Reinwald, J., Cosa-Linan, A., Sack, M., Weber-Fahr, W., Vollmayr, B., Sartorius, A., 2019. Differences between ketamine's short-term and long-term effects on brain circuitry in depression. Transl Psychiatry 9 (1). https://doi.org/10.1038/s41398-019-0506-6. https://doi.org/.
Groenewold, N.A., Opmeer, E.M., de Jonge, P., Aleman, A., Costafreda, S.G., 2013. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci Biobehav Rev 37 (2), 152–163. https://doi.org/10.1016/j.neubiorev.2012.11.015. https://doi.org/.
Guo, D., Gan, J., Tan, T., Tian, X., Wang, G., Kevin, •., Ng, T.-.P., 2017. Neonatal exposure of ketamine inhibited the induction of hippocampal long-term potentiation without impairing the spatial memory of adult rats. Cogn Neurodyn 12https://doi.org/10.1007/s11571-018-9474-4. https://doi.org/.
Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., Gotlib, I.H., 2012. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. Am J Psychiatry 169 (7), 693–703. https://doi.org/10.1176/appi.ajp.2012.11071105. https://doi.org/.
Hashimoto, K., 2019. Rapid-acting antidepressant ketamine, its metabolites and other candidates: a historical overview and future perspective. Psychiatry and Clinical Neurosciences 73. Blackwell Publishing, pp. 613–627. https://doi.org/10.1111/pcn.12902. https://doi.org/.
Huang, S., Dai, Y., Zhang, Z., Hao, W., Chen, H., 2014. Docosahexaenoic acid intake ameliorates ketamine-induced impairment of spatial cognition and learning ability in ICR mice. Neurosci. Lett. 580, 125–129. https://doi.org/10.1016/j.neulet.2014.08.011. https://doi.org/.
Ionescu, D.F., Bentley, K.H., Eikermann, M., Taylor, N., Johnson-Akeju, O., Swee, M.B., Pavone, K.J., Petrie, S.R., Dording, C., Mischoulon, D., Alpert, J.E., Brown, E.N., Baer, L., Nock, M.K., Fava, M., Cusin, C., 2019. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. J Affect Disord 243, 516–524. https://doi.org/10.1016/j.jad.2018.09.037. https://doi.org/.
Jelen, L.A., King, S., Horne, C.M., Lythgoe, D.J., Young, A.H., Stone, J.M., 2019. Functional magnetic resonance spectroscopy in patients with schizophrenia and bipolar affective disorder: glutamate dynamics in the anterior cingulate cortex during a working memory task. European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology 29 (2), 222–234. https://doi.org/10.1016/j.euroneuro.2018.12.005. https://doi.org/.
Jett, J.D., Boley, A.M., Girotti, M., Shah, A., Lodge, D.J., Morilak, D.A., 2015. Antidepressant-like cognitive and behavioral effects of acute ketamine administration associated with plasticity in the ventral hippocampus to medial prefrontal cortex pathway. Psychopharmacology (Berl.) 232 (17), 3123–3133. https://doi.org/10.1007/s00213-015-3957-3. https://doi.org/.
Kim, J., Farchione, T., Potter, A., Chen, Q., Temple, R., 2019. Esketamine for Treatment-Resistant Depression - First FDA-Approved Antidepressant in a New Class. The New England Journal of Medicine 381 (1), 1–4. https://doi.org/10.1056/NEJMp1903305. https://doi.org/.
Knight, M.J., Baune, B.T., 2018. Cognitive dysfunction in major depressive disorder. Curr Opin Psychiatry 31 (1), 26–31. https://doi.org/10.1097/YCO.0000000000000378. https://doi.org/.
Koike, H., Iijima, M., Chaki, S., 2011. Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. Behav. Brain Res. 224 (1), 107–111. https://doi.org/10.1016/j.bbr.2011.05.035. https://doi.org/.
Lam, R.W., Kennedy, S.H., McIntyre, R.S., Khullar, A., 2014. Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. Canadian Journal of Psychiatry 59. Canadian Psychiatric Association, pp. 649–654. https://doi.org/10.1177/070674371405901206. https://doi.org/.
Lee, R.S.C., Hermens, D.F., Porter, M.A., Redoblado-Hodge, M.A., 2012. A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. J Affect Disord 140 (2), 113–124. https://doi.org/10.1016/j.jad.2011.10.023. https://doi.org/.
Lee, Y., Syeda, K., Maruschak, N.A., Cha, D.S., Mansur, R.B., Wium-Andersen, I.K., Woldeyohannes, H.O., Rosenblat, J.D., McIntyre, R.S., 2016. A New Perspective on the Anti-Suicide Effects With Ketamine Treatment: a Procognitive Effect. J Clin Psychopharmacol 36 (1), 50–56. https://doi.org/10.1097/JCP.0000000000000441. https://doi.org/.
Lener, M.S., Kadriu, B., Zarate, C.A., 2017. Ketamine and Beyond: investigations into the Potential of Glutamatergic Agents to Treat Depression. Drugs 77. Springer International Publishing, pp. 381–401. https://doi.org/10.1007/s40265-017-0702-8. https://doi.org/.
Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392 (10161), 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2. https://doi.org/.
Mathew, S.J., Murrough, J.W., AanHet Rot, M., Collins, K.A., Reich, D.L., Charney, D.S., 2010. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. International Journal of Neuropsychopharmacology 13 (1), 71–82. https://doi.org/10.1017/S1461145709000169. https://doi.org/.
Mathew, S.J., Shah, A., Lapidus, K., Clark, C., Jarun, N., Ostermeyer, B., Murrough, J.W., 2012. Ketamine for treatment-resistant unipolar depression: current evidence. CNS Drugs 26 (3), 189–204. https://doi.org/10.2165/11599770-000000000-00000. https://doi.org/.
Milak, M.S., Potter, W.A., Pantazatos, S.P., Keilp, J.G., Zanderigo, F., Schain, M., Sublette, M.E., Oquendo, M.A., Malone, K.M., Brandenburg, H., Parsey, R.v., Mann, J.J., 2019. Resting regional brain activity correlates of verbal learning deficit in major depressive disorder. Psychiatry Research - Neuroimaging 283, 96–103. https://doi.org/10.1016/j.pscychresns.2018.12.006. https://doi.org/.
Morgan, C.J.A., Mofeez, A., Brandner, B., Bromley, L., Curran, H.V., 2004. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology 29 (1), 208–218. https://doi.org/10.1038/sj.npp.1300342. https://doi.org/.
Murrough, J.W., 2012. Ketamine as a novel antidepressant: from synapse to behavior. Clin. Pharmacol. Ther. 91 (2), 303–309. https://doi.org/10.1038/clpt.2011.244. https://doi.org/.
Murrough, JamesW., 2016. Ketamine for Depression: an Update. Biol. Psychiatry 80 (6), 416–418. https://doi.org/10.1016/j.biopsych.2016.07.005. https://doi.org/.
Murrough, JamesW., 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. https://doi.org/10.1038/npp.2014.298. https://doi.org/.
Murrough, JamesW., 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 (4), 250–256. https://doi.org/10.1016/j.biopsych.2012.06.022. https://doi.org/.
Murrough, JamesW., Wan, L.ben, Iacoviello, B., Collins, K.A., Solon, C., Glicksberg, B., Perez, A.M., Mathew, S.J., Charney, D.S., Iosifescu, D.v., Burdick, K.E., 2014. Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. Psychopharmacology (Berl.) 231 (3), 481–488. https://doi.org/10.1007/s00213-013-3255-x. https://doi.org/.
Palomero-Gallagher, N., Hoffstaedter, F., Mohlberg, H., Eickhoff, S.B., Amunts, K., Zilles, K., 2019. Human Pregenual Anterior Cingulate Cortex: structural, Functional, and Connectional Heterogeneity. Cerebral Cortex (New York, N.Y. : 1991) 29 (6), 2552–2574. https://doi.org/10.1093/cercor/bhy124. https://doi.org/.
Papp, M., Gruca, P., Lason-Tyburkiewicz, M., Willner, P., 2017. Antidepressant, anxiolytic and procognitive effects of subacute and chronic ketamine in the chronic mild stress model of depression. Behav Pharmacol 28 (1), 1–8. https://doi.org/10.1097/FBP.0000000000000259. https://doi.org/.
Patton, M.S., Lodge, D.J., Morilak, D.A., Girotti, M., 2017. Ketamine Corrects Stress-Induced Cognitive Dysfunction through JAK2/STAT3 Signaling in the Orbitofrontal Cortex. Neuropsychopharmacology 42 (6), 1220–1230. https://doi.org/10.1038/npp.2016.236. https://doi.org/.
Pehrson, A.L., Leiser, S.C., Gulinello, M., Dale, E., Li, Y., Waller, J.A., Sanchez, C., 2015. Treatment of cognitive dysfunction in major depressive disorder–a review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetine. Eur. J. Pharmacol. 753, 19–31. https://doi.org/10.1016/j.ejphar.2014.07.044. https://doi.org/.
Pigoni, A., Lazzaretti, M., Mandolini, G.M., 2019. The impact of COMT polymorphisms on cognition in Bipolar Disorder: a review: special Section on "Translational and Neuroscience Studies in Affective Disorders" Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience

with particular regards to specific innovative topics in mood and anxiety disorders. J Affect Disord 243, 545–551. https://doi.org/10.1016/j.jad.2018.08.009.
Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology 36 (1), 183–206. https://doi.org/10.1038/npp.2010.166. https://doi.org/.
Reed, J.L., Nugent, A.C., Furey, M.L., Szczepanik, J.E., Evans, J.W., Zarate, C.A., 2018. Ketamine normalizes brain activity during emotionally valenced attentional processing in depression. Neuroimage Clin 20, 92–101. https://doi.org/10.1016/j.nicl.2018.07.006. https://doi.org/.
Richard-Devantoy, S., Ding, Y., Lepage, M., Turecki, G., Jollant, F., 2015. Cognitive inhibition in depression and suicidal behavior: A neuroimaging study. https://doi.org/10.1017/S0033291715002421. https://doi.org/.
Roca, M., Vives, M., López-Navarro, E., García-Campayo, J., Gili, M., 2015. Cognitive impairments and depression: a critical review. Actas Esp Psiquiatr 43 (5), 187–193. http://www.ncbi.nlm.nih.gov/pubmed/26320897.
Salvadore, G., Cornwell, B.R., Sambataro, F., Latov, D., Colon-Rosario, V., Carver, F., Holroyd, T., Diazgranados, N., MacHado-Vieira, R., Grillon, C., Drevets, W.C., Zarate, C.A., 2010. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology 35 (7), 1415–1422. https://doi.org/10.1038/npp.2010.24. https://doi.org/.
Semkovska, M., McLoughlin, D.M., 2010. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol. Psychiatry 68 (6), 568–577. https://doi.org/10.1016/j.biopsych.2010.06.009. https://doi.org/.
Shiroma, P.R., Albott, C.S., Johns, B., Thuras, P., Wels, J., Lim, K.O., 2014. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. The International Journal of Neuropsychopharmacology 17 (11), 1805–1813. https://doi.org/10.1017/S1461145714001011. https://doi.org/.
Skoblenick, K., Everling, S., 2012. NMDA antagonist ketamine reduces task selectivity in macaque dorsolateral prefrontal neurons and impairs performance of randomly interleaved prosaccades and antisaccades. Journal of Neuroscience 32 (35), 12018–12027. https://doi.org/10.1523/JNEUROSCI.1510-12.2012. https://doi.org/.
Tozzi, L., Goldstein-Piekarski, A.N., Korgaonkar, M.S., Williams, L.M., 2020. Connectivity of the Cognitive Control Network During Response Inhibition as a Predictive and Response Biomarker in Major Depression: evidence From a Randomized Clinical Trial. Biol. Psychiatry 87 (5), 462–472. https://doi.org/10.1016/j.biopsych.2019.08.005. https://doi.org/.
Trivedi, M.H., Greer, T.L., 2014. Cognitive dysfunction in unipolar depression: implications for treatment. J Affect Disord 152–154 (1), 19–27. https://doi.org/10.1016/j.jad.2013.09.012. https://doi.org/.
Tsourtos, G., Thompson, J.C., Stough, C., 2002. Evidence of an early information processing speed deficit in unipolar major depression. Psychol Med 32 (2), 259–265. https://doi.org/10.1017/S0033291701005001. https://doi.org/.
Volianskis, A., France, G., Jensen, M.S., Bortolotto, Z.A., Jane, D.E., Collingridge, G.L., 2015. Long-term potentiation and the role of N-methyl-D-aspartate receptors. Brain Res. 1621, 5–16. https://doi.org/10.1016/j.brainres.2015.01.016. https://doi.org/.
Wang, M., Yang, Y., Wang, C.J., Gamo, N.J., Jin, L.E., Mazer, J.A., Morrison, J.H., Wang, X.J., Arnsten, A.F.T., 2013. NMDA Receptors Subserve Persistent Neuronal Firing during Working Memory in Dorsolateral Prefrontal Cortex. Neuron 77 (4), 736–749. https://doi.org/10.1016/j.neuron.2012.12.032. https://doi.org/.
World Health Organization, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. Licence: CC BY-NC-SA 3.0 IGO. WHO Document Production Services, Geneva, Switzerland.
Zanos, P., Gould, T.D., 2018. Mechanisms of ketamine action as an antidepressant. Mol. Psychiatry 23 (4), 801–811. https://doi.org/10.1038/mp.2017.255. https://doi.org/.
Zarate, 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 (8), 856–864. https://doi.org/10.1001/archpsyc.63.8.856. https://doi.org/.
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. https://doi.org/10.1016/j.jad.2018.12.005. https://doi.org/.
Clarke, M., Razmjou, S., Prowse, N., Dwyer, Z., Litteljohn, D., Pentz, R., Anisman, H., & Hayley, S., 2017. Ketamine modulates hippocampal neurogenesis and pro-inflammatory cytokines but not stressor induced neurochemical changes. Neuropharmacology, 112(Pt A), 210–220 https://doi.org/10.1016/j.neuropharm.2016.04.021.