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Review article

Can ketamine and other glutamate receptor modulators be considered entactogens?

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ABSTRACT

Subanesthetic-dose ketamine has recently been reported to improve hedonic pleasures associated with social interactions and altruism in individuals with treatment-resistant depression. However, whether ketamine—among other glutamate receptor modulators—also improves empathy and/or prosocial behavior in humans remains unknown. Under a framework grounded in neurobiology that proposes that prosocial behavior is preceded by empathy, this systematic review sought to: (1) explore the entactogenic effects of glutamate receptor modulators observed in clinical trials (as either primary or secondary outcomes), and (2) synthesize the findings regarding which glutamate receptor modulators produce entactogenic effects. Thirty studies that included self-reported ratings, neuroimaging, and/or behavioral task outcomes met inclusion criteria suggesting potential entactogenic effects associated with ketamine and, to less convincing extent, D-cycloserine (DCS). The findings suggest that ketamine and DCS may modulate self- and other-perception, involving changes in activity in brain regions involved in empathetic concerns and mentalizing, the ability to understand one's own and others' thoughts and feelings. These findings may guide potential therapeutic interventions for neuropsychiatric conditions associated with impaired empathy and prosocial behavior, including mood disorders, neurodevelopmental disorders, psychotic disorders, and personality disorders.

1. Introduction

"Entactogens" and "empathogens" are compounds that enhance prosocial behaviors and empathy by affecting self-perception, social interaction, and fear memories without necessarily possessing hallucinogenic properties (De Gregorio et al., 2021; Heifets and Olson, 2024). While the terms prosocial behavior and empathy are often used interchangeably, the former typically refers to other-benefiting and social affiliative behaviors seen in mammals, including humans, primates, and rodents (Wu and Hong, 2022), and the latter is believed to be a much more complex phenomenological ability specific to humans (Neumann et al., 2015). Empathic individuals tend to engage in affiliative behaviors that seek to benefit others, necessitating the following components: (1) perceiving others' feelings and perspectives (other-perception); (2) integrating emotional information (self-perception); (3) regulating one's own emotional response; and (4) taking action (prosocial behavior) and experiencing satisfaction as a result of alleviating others' distress (reinforcement) (Wu and Hong, 2022). In humans, empathy drives prosocial behavior and learning (Lockwood et al., 2016). Empathogenic effects are characterized by an induced feeling of connection with others (items 1 and 4 from the list above), while entactogenic effects denote feeling more connected to oneself, hence the connotation of 'touching within' (items 2 and 3 from the list above) (Stocker and Liechti, 2024).

The conceptual basis of our mechanistic framework for empathy, prosocial behavior, and their neurobehavioral markers has been explained elsewhere (Decety and Cowell, 2015; Wu and Hong, 2022). Briefly, the framework states that perceiving others' emotional states triggers empathetic responses; when witnessing others' suffering (other-perception), the perceiver adjusts their attentional processes to salient cues and activates aversive behaviors that seek to alleviate the

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observer's distress. This emotional resonance (self-perception) motivates prosocial decision-making, often referred to as the "prosocial drive". Execution of prosocial actions, followed by improvement in others' conditions, reinforces empathetic behaviors through the experience of reward or pleasure, further enhancing prosocial tendencies.

In some neuropsychiatric conditions, disrupting any of the aforementioned steps can impair empathy and prosocial behaviors and produce distressing symptoms, such as social withdrawal, isolation, and antagonistic behavior. For example, individuals with autism spectrum disorder (ASD) or schizophrenia may have difficulty both perceiving others' emotions and integrating their own emotional information. This observation led to prior investigations of intranasal oxytocin for these two disorders in an attempt to "rescue" empathic and prosocial behaviors, but most clinical trials yielded negative results (Kiani et al., 2023; Sabe et al., 2021). Social relationships and empathy can also be disrupted in mood disorders such as major depressive disorder (MDD). Interestingly, subanesthetic-dose ketamine was recently found to improve social anhedonia in a sample of individuals with MDD, with similar effects reverse-translated into an animal model (Hess et al., 2024). Such findings suggest that ketamine may exert entactogenic effects by altering the internal hedonic experience associated with social interactions. This invites further review of other potential studies suggesting that ketamine may have entactogenic effects and, if so, through which pharmacodynamic mechanism(s) these might occur.

Methylenedioxymethamphetamine (MDMA) is an amphetamine-like compound with known empathogenic and entactogenic effects (Hysek et al., 2014), attributed largely to its action on the serotonergic (Rein et al., 2024) and oxytocinergic systems (Atila et al., 2023), which may underlie its promising results as an adjunctive treatment to psychotherapy for post-traumatic stress disorder (PTSD) (Feduccia et al., 2019; Shahrour et al., 2024). Unlike MDMA, ketamine is a dissociative anesthetic that, at subanesthetic doses, has rapid-acting antidepressant and hallucinogenic properties, the latter broadly defined as producing transient alterations in perception (Zarate et al., 2006). Although ketamine is primarily known as an N-methyl-d-aspartate receptor (NMDAR) antagonist, its (*R,S*) enantiomers and metabolites, such as hydroxynorketamine (HNK), are more accurately defined as broad glutamate receptor modulators due to their multiple pharmacologic actions in the glutamate pathway (Henter et al., 2021). d-cycloserine (DCS), another compound with known NMDAR modulator effects through the glycine

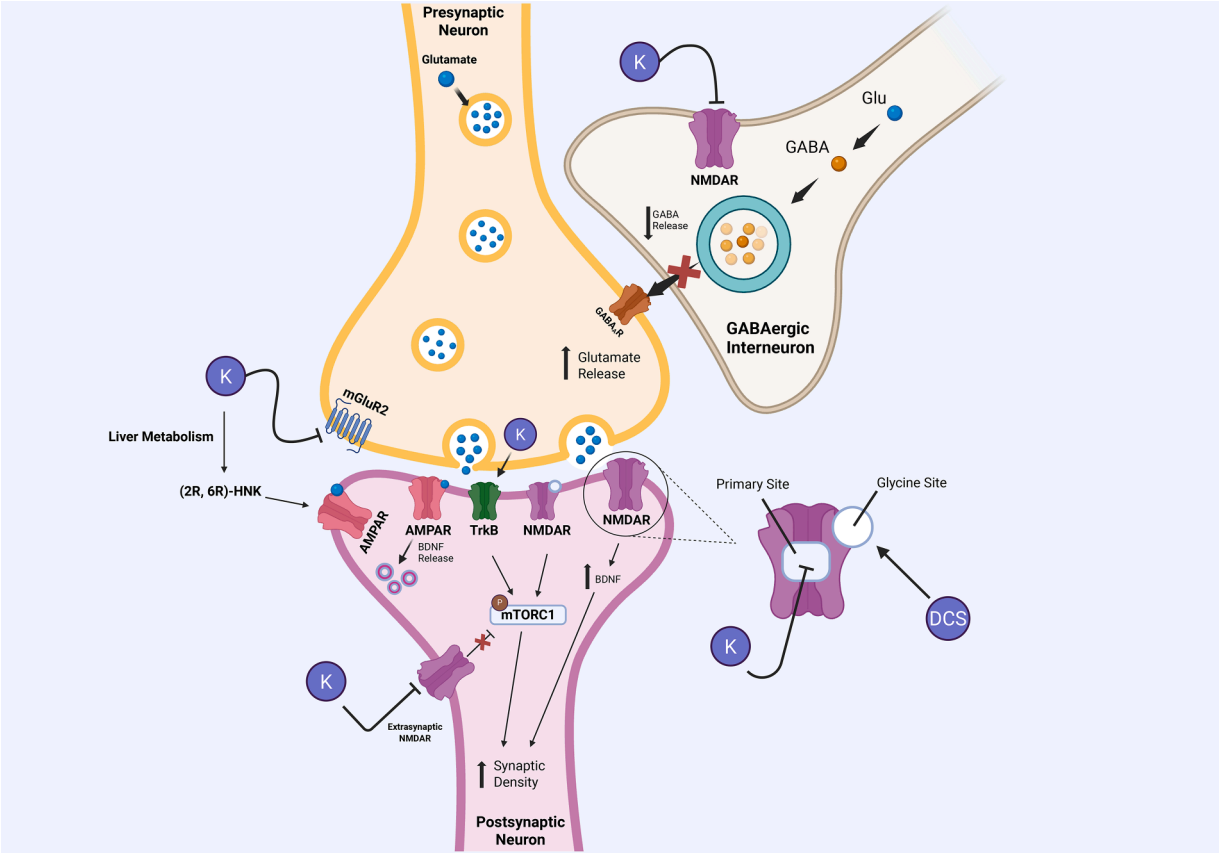

Fig. 1. Proposed Neurobiological Mechanisms of Action for Ketamine and D-Cycloserine (DCS) as Glutamate Receptor Modulators. **D-cycloserine's (DCS) mechanism of action:** DCS is a broad-spectrum antibiotic that also acts as a functional N-methyl-D-aspartate receptor (NMDAR) modulator and partial agonist at the glycine site. Increased NMDAR functioning is thought to enhance neuroplasticity and influence learning and memory. **Ketamine's mechanism of action:** Racemic (*R,S*)-ketamine and esketamine (collectively denoted as "K" for ketamine), affect various glutamatergic receptors shown in the figure. Ketamine binds at the primary site on NMDARs. Two main theories have been proposed to explain ketamine's mechanism of action. The first theory suggests that ketamine exerts its effects via disinhibition, in which ketamine preferentially antagonizes NMDARs expressed on gamma-aminobutyric (GABA)-ergic inhibitory interneurons. Inhibiting the activity of these inhibitory interneurons leads to disinhibition of excitatory pyramidal neurons. The second theory posits that ketamine directly inhibits NMDARs; by suppressing tonic NMDAR activation by circulating glutamate, ketamine is thought to decrease suppression of eukaryotic elongation factor 2 (EEF2; not shown in the figure) and promote protein synthesis, including translation of brain-derived neurotrophic factor (BDNF). Both theories agree that circulating glutamate is a downstream activator of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). Ketamine also antagonizes metabotropic glutamate receptor subtype 2 (mGluR2) on presynaptic neurons and enhances synaptic glutamate levels, which boost AMPAR transmission. AMPARs are also activated by (2*R*,6*R*)-hydroxynorketamine (HNK), one of ketamine's metabolites, which exerts antidepressant actions independent of the NMDAR inhibition mechanisms outlined above. In addition to AMPAR activation, ketamine directly binds to tropomyosin receptor kinase B (TrkB) receptors, which de-suppresses mammalian target of rapamycin complex 1 (mTORC1) function. This, in turn, promotes protein synthesis and BDNF expression, which increase neuronal synaptic density.

site (Fig. 1), is used off-label to treat post-traumatic stress disorder (PTSD) and has also been investigated in relation to empathy (Nowacki et al., 2020). In this context, it is worth exploring whether glutamate receptor modulators, as a drug class, have entactogenic effects. The findings may shed light on additional pharmacological mechanisms beyond the serotonergic and oxytocinergic systems elucidated by studies on MDMA.

Under the framework that prosocial behavior is preceded by empathy, this systematic review sought to: (1) explore the entactogenic effects of glutamate receptor modulators observed in clinical trials (as either primary or secondary outcomes), and (2) synthesize the findings regarding which glutamate receptor modulators have been found to produce entactogenic effects.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) reporting guidelines (Page et al., 2021). The protocol was pre-registered on PROSPERO (registration code: CRD42024595078), where the full details of the review process are available (see Supplement for the PRISMA checklist and additional methodology).

2.1. Inclusion criteria

Studies were included if they: (1) were conducted in humans; (2) had participants between the ages of 7 to 75; (3) investigated pre-specified glutamate receptor modulators, including broad glutamate receptor modulators, NMDAR antagonists, their (*R*)- or (*S*)-enantiomers and metabolites, and metabotropic glutamatergic modulators; (4) measured empathy/prosocial behavior; (5) were randomized controlled trials (RCTs), non-randomized controlled or uncontrolled studies, or observational/naturalistic studies; and (6) and were published in English. The Supplement contains detailed inclusion criteria, including compound names for all glutamate receptor modulators and a list of the empathy-related self-report, behavioral, and neuroimaging outcomes that were searched and included.

2.2. Exclusion criteria

Studies were excluded if they: (1) were animal, laboratory, and/or *in-vitro* studies; (2) enrolled participants below the age of 7 or over the age of 75; (3) did not include any glutamate receptor modulators; (4) did not include outcomes pertaining to empathy and prosocial behavior as outlined in the Supplement; (5) were systematic reviews, meta-analyses, commentaries, or letters to the editor; (6) did not include individuals with psychiatric disorders as well as healthy volunteers (HVs) as study subjects (i.e., studies focused solely on patients with a medical illness); (7) enrolled patients who were using ketamine for different indications, such as anesthesia or recreationally; and (8) were not written in English.

2.3. Search strategy

The search sought to identify articles on studies that investigated glutamate receptor modulators and outcomes (self-reported, behavioral, and neuroimaging) pertaining to empathy. The articles were found and incorporated using PubMed (MEDLINE), PsychInfo, and Embase. The search was conducted on October 7, 2024 and was not restricted by date, although it was restricted to the English language (see Supplement for the finalized string search terms).

2.4. Data collection and synthesis

All titles and abstracts were uploaded into Rayyan review management software (Ouzzani et al., 2016) and screened for eligibility by at least two independent reviewers (HH, AT, MF). The two reviewers reached a consensus on eligible studies; conflicts were resolved by discussing the papers with an additional reviewer (YL). Full texts of potentially eligible articles were again assessed using a similar approach between at least two independent reviewers (HH, YL, AT, MF, MY), and any conflicts were resolved through discussion between three reviewers. Following the screening process (Fig. 2), data were extracted by HH and AT from included publications. These data included: 1) study methodology (design, types of outcomes, diagnosis, intervention, dose, frequency, route of administration, duration of treatment); 2) study results (patient demographics, primary and/or secondary outcomes that met inclusion criteria); and 3) interpretation of whether the glutamatergic modulator had any entactogenic effect(s). A narrative synthesis of the results was collected, guided by Synthesis Without Meta-Analysis (SwiM) reporting guidelines (Campbell et al., 2020) to ensure the comprehensive, appropriate, and representative reporting of the results.

2.5. Risk of bias (quality) assessment

Due to the variability in study designs and patient populations, several risk of bias tools were used throughout the systematic review process. To minimize bias during the screening phase, both abstract and full-text reviews were conducted using a double-blind approach within the Rayyan platform, and any discrepancies were resolved in consultation with a senior researcher. Once the initial double-blind screening was completed, the reviewers were unblinded and discussed the articles with an independent reviewer to address and resolve any remaining conflicts. The following tools were applied: the JBI Critical Appraisal Checklist for Case Reports (Moola et al., 2020), the ROBINS-I V2 for Non-Randomized Studies of Interventions (NRSIs) (Sterne et al., 2016), and the RoB 2 for RCTs (Sterne et al., 2019). Each study subsequently received an overall risk of bias rating based on the specific guidelines of the tool used.

3. Results

A total of 3449 articles were detected in the initial database search. After uploading the Microsoft Excel file into the Rayyan system, 1,114 duplicate entries were removed, leaving 2,335 unique articles. After the initial title and abstract screening, 213 articles were left for full-text screening. Twenty-nine papers met the predefined inclusion criteria, and one additional paper was identified via a reference list. Thirty papers were included in the final analysis, derived from 26 unique trials[1] comprising 16 RCTs (two single-blind parallel group design, five double-blind parallel group design, and nine double-blind crossover design), 12 non-randomized studies (11 single-arm open-label design and one naturalistic design), and one case report. Of these, 16 studies investigated the effects of racemic (*R,S*)-ketamine, six studies investigated intravenous esketamine (ketamine'*S*-enantiomer, which is more potent than racemic ketamine), two studies investigated intranasal esketamine, and six studies investigated DCS (Table 1). No studies investigating any other pre-specified glutamatergic modulators met inclusion criteria (see Supplement).

The outcome types were heterogeneous. Five studies included behavioral tasks without neuroimaging, four studies included ratings without neuroimaging, three studies focused on neuroimaging alone, 15 studies examined neuroimaging-focused behavioral tasks, three studies had multimodal outcomes that combined behavioral tasks, neuroimaging, or ratings, and one study included qualitative data from patient experiences via a semi-structured interview. The study designs and key findings of the 30 included papers are summarized in Table 1.

[1] Three of these unique trials resulted in two publications each (Scheidegger et al., 2016a, 2016b; Norwacki et al., 2020, 2021; Urbano et al., 2014, 2015).

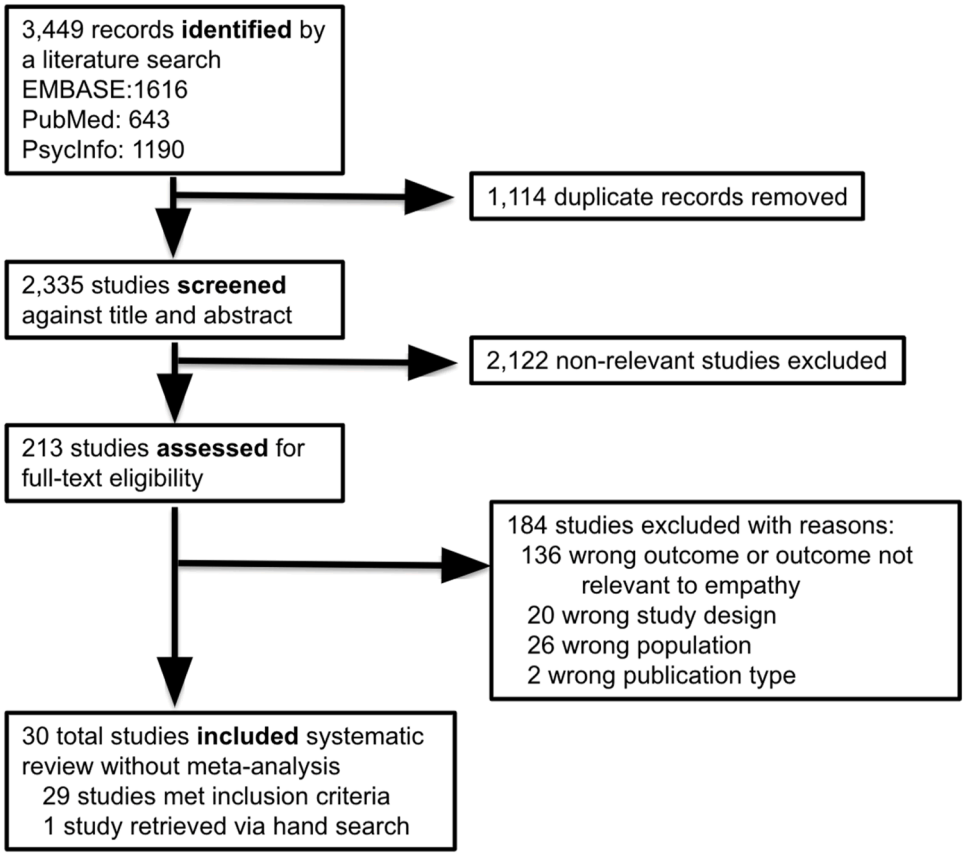

Fig. 2. Consort diagram of the systematic review.

3.1. Risk bias assessment

Most included RCT trials were deemed low risk except for four studies, which were assessed as presenting some concerns pertaining to missing outcome data or outcome measures (see Supplemental Table S2) (Lundin et al., 2021; Norbury et al., 2021; Urbano et al., 2015; 2014). Six NRSIs were assessed as presenting moderate risk of bias (Loureiro et al., 2020; Murrough et al., 2015; Starr et al., 2020; Thai et al., 2020; Weigand et al., 2022; Wu et al., 2023). Risk of bias in one case report included in this review was assessed as low (Olivola et al., 2022).

3.2. Healthy volunteers

Studying the effects of glutamatergic modulators on HVs may shed light on the entactogenic effects of the compounds isolated from any psychopathological effects or social deficits associated with neuropsychiatric conditions. Of the 22 studies that included HVs, 14 studied HVs as the main population of interest rather than as a comparator group. Many of these studies investigated changes in emotion recognition and self-other perception, as measured by self-report ratings, behavioral tasks, or neuroimaging or some combination of these outcome types. Thirteen of the 14 studies investigated the effects of intravenous ketamine, and only one studied DCS.

Several well-designed, double-blind, placebo-controlled RCTs measured behavioral tasks related to self- and other-perception during neuroimaging in HVs. One recent novel study used functional magnetic resonance imaging (fMRI) to investigate changes in self-report ratings measuring social touch seeking (Social Touch Questionnaire) and interoception (Multidimensional Assessment of Interoceptive Awareness) as well as a behavioral task called the Self-Other Touch Paradigm. The study found that, compared to placebo, ketamine increased social touch seeking by self-report and reduced the neural distinction between self- and other-produced affective touch (Kaldewaij et al., 2024).

Broadly, neuroimaging studies that used behavioral tasks pertaining to emotion recognition (other-perception) found that ketamine modulated neural activity involved in emotion processing, including facial recognition tasks and tasks testing emotional memory formation. For instance, one study found that fearful faces no longer activated the amygdala and other limbic regions in HVs receiving ketamine versus placebo (Abel et al., 2003). An fMRI study found that intravenous esketamine resulted in negative blood oxygenation level dependent responses to negative and aversive stimuli in the pregenual anterior cingulate cortex (pgACC) during an emotional picture-viewing task, suggesting that esketamine may attenuate increased self-focus during negative experiences (Lehmann et al., 2016). Schmidt and colleagues used electroencephalography (EEG) to compare the effect of intravenous esketamine versus oral psilocybin on emotional face perception tasks and found that both agents reduced encoding of fearful faces as expressed by reduction in N170 over parieto-occipital brain regions, but that esketamine also impaired the encoding of happy facial expressions (Schmidt et al., 2013). Another study found that, during emotion memory formation, ketamine had both valence-specific effects (decreasing connectivity between the amygdala and orbitofrontal cortex in response to negative cues, thereby enhancing executive control and memory processing relevant to social cognition) as well as valence-unspecific effects (increasing connectivity between the left medial prefrontal cortex (mPFC) and right hippocampus, thereby reducing attentional orientation to negative cues) (Becker et al., 2017). While the behavioral tasks employed across these studies as outcomes of neural correlates were heterogeneous, the results collectively suggest that ketamine appears to modulate neural response to negatively valenced stimuli.

Non-randomized open label studies in HVs similarly found that ketamine altered performance on cognitive tasks related to emotion

Table 1
The Entactogenic Effects of Glutamate Receptor Modulators.

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
Abel et al. (2003)	RCT, double-blind, crossover	Behavioral task assessed during fMRI	HV	IV ketamine (bolus dose of 0.23 mg/kg over 0-5 minutes, followed by 0.5mg/kg from 5-45 minutes) or normal saline placebo.	N=8 males	28.75y; 23–42y	FERT during fMRI	In response to fearful vs. neutral faces, individuals showed increased neural activity in the cerebellum during the placebo condition but reduced activity in the precuneus and caudate nucleus post-ketamine infusion.
Becker et al. (2017)	RCT, double-blind crossover	fMRI	HV	IV ketamine (2 mg/ml with a constant target plasma level of 100 ng/ml) or normal saline placebo.	N=21 males	25.1y (3.5)	Event-related ESM paradigm 5 minutes post-infusion	Ketamine increased connectivity between the left mPFC and the right hippocampus, regardless of valence. Ketamine also decreased connectivity between the amygdala and OFC in response to negative cues.
Chen et al. (2021)	RCT, double-blind	Behavioral tasks	HV	Single dose of 250 mg DCS or placebo	N=40 19 males 21 females	18-40y	FERT, ECAT, FDOT, EREC, EMEM	DCS increased positive bias in emotional word categorization in the ECAT and free recall in the EREC. No significant differences in the FERT, FDOT, or EMEM.
Danyeli et al. (2024)	RCT, double-blind, crossover	Self-reported rating scale scores and structural MRI	HV	IV esketamine (bolus 0.11 mg/kg followed by a maintenance dose (0.22 mg/kg) or placebo (0.9% saline) over 40 minutes	N=35 males	25.1y (4.2)	-5D-ASC (disembodiment and experience of unity) -Cortical thickness of DMN regions (PCC, pgACC)	Negative correlation between PCC cortical thickness and disembodiment scores.
Ebert et al., (2012)	Open-label	Behavioral tasks	HV	IV ketamine (0.5 mg/kg)	N=18 males	25.5y (4.6)	Ekman 60 Faces Test	Ketamine significantly reduced the ability to detect sad expressions after 24 hours. There was a trend in diminished recognition of other emotions but it was not statistically significant.
Gilbert et al. (2021)	RCT, double-blind, crossover	Behavioral task assessed during MEG	TRD vs. HV	IV ketamine (0.5 mg/kg) over 40 minutes or normal saline placebo	N=19 TRD (11 females, 8 males) N=15 HV (11 females, 4 males)	-TRD 36.7y (10.9) -HV 34.7y (11.8)	FDOT	Based on dynamic causal modeling from MEG activity, ketamine administration led to slower NMDA signal transmission in the amygdala.
Hess et al., (2024)	RCT, double-blind, crossover design	Rating scale scores	MDD, BD I and II	IV ketamine (0.5 mg/kg) over 40 minutes or normal saline placebo	N=68 29 males 39 females	42.82y 18-65y	SHAPS (not composite score, but 4 questions pertaining to social pleasures)	Ketamine treatment was associated with greater likelihood of reporting feeling enjoyment from being with close friends or family overall, enjoyment individuals felt when seeing other people's smiling faces, pleasure felt from helping others, and pleasure when receiving praise from other people.

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Table 1 (*continued*)

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
Kaldewaij et al. (2024)	RCT, double-blind, crossover	Self-reported rating scale scores, behavioral task assessed during fMRI	HV as ketamine-induced model of altered states of self-perception	IV ketamine (0.5 mg/kg over 40 minutes) or normal saline placebo	N=30 15 females 15 males	24.8y 19–30y	STQ, MAIA self-other touch paradigm during fMRI started 20 minutes after start of infusion	Ketamine lowered STQ scores, indicating a relative increase in social touch seeking (or decrease in social touch avoidance) during infusion. Ketamine reduced the neural distinction between the self- and other-produced affective touch, as evidenced by enhanced connectivity between the right TPC, somatosensory cortex, and insula during the other-produced touch condition.
Lehmann et al. (2016)	RCT, double-blind, crossover	Behavioral task assessed during fMRI	HV	IV esketamine (0.25 mg/kg) or normal saline placebo over 45 minutes	N=17 (sex not reported)	40.5y (7.5)	-Emotional picture-viewing task during fMRI -ROIs: pACC and dPCC	Ketamine resulted in NBRs to negative and aversive stimuli in pACC emotional processing of HVs.
Loureiro et al. (2020)	Non-randomized naturalistic design	Behavioral task assessed during fMRI	TRD vs. HV	TRD participants received ECT or repeated IV ketamine (0.5 mg/kg)	N=32 HV N=44 TRD -ECT: 17 -Ketamine: 27 (sex not reported)	-ECT: 36.8y (11.0) -Ketamine: 37.3y (10.8)	Emotional face discrimination task during fMRI	Ketamine decreased activation in amygdala seen on fMRI during emotional face discrimination task.
Lundin et al. (2021)	RCT, double-blind, crossover	Behavioral task assessed during MEG	TRD vs HV	IV ketamine 0.5mg/kg over 40 minutes	Baseline N=55 (31 TRD, 24 HV), post-ketamine recordings N=45 (25 TRD, 20 HV), post-placebo N=40 (22 TRD, 18 HV) HV: 14 females, 10 males TRD: 19 females, 12 males	TRD: 35.77y (9.61) HV: 32.96y (10.21)	-Baseline MEG, ketamine infusion MEG, and placebo infusion MEG -Emotional Evaluation Tasks during each MEG: 1) happy-neutral facial expressions; 2) sad-angry facial expressions.	TRD participants had slower reaction times post-ketamine than post-placebo, and HVs had the opposite reaction time pattern. TRD participants more accurately identified negatively valenced faces than HVs. In the left fusiform region, participants overall had larger M170 amplitudes post-ketamine than post-placebo. TRD participants who had a greater antidepressant response to ketamine had lower M170 amplitudes in the left fusiform in response to sad-angry faces and higher amplitudes in response to happy-neutral faces post-ketamine. In the right fusiform, M170 amplitudes in TRD post-ketamine became more similar to those of HVs post-placebo.
Murrough et al. (2015)	Open-label	Behavioral task assessed during fMRI	TRD vs. HV	IV ketamine 0.5mg/kg over 40 minutes	N=18 TRD 8 females, 10 males N=20 HV 9 females, 11 males	-TRD: 38.1y (13.8) - HV: 35.0y (8.9)	-fMRI pre- and post-ketamine -Two emotion perception tasks: 1) happy and neutral facial expressions;	Compared with HVs at baseline, TRD participants showed reduced neural responses to positive faces within the right

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Table 1 (*continued*)

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
							2) sad and neutral facial expressions.	caudate. Ketamine regulated neural responses to positive emotion within the right caudate in TRD individuals. Increased caudate connectivity during positive emotion perception was positively correlated with antidepressant effects following ketamine (as measured by MADRS).
Norbury et al. (2021)	RCT, double-blind, crossover	Behavioral task assessed during fMRI	PTSD	IV ketamine 0.5 mg/kg or IV midazolam 0.045 mg/kg, administered 3x/week for 2 weeks.	N=21 18 females 3 males	-Ketamine 42.3y (12.4) -Midazolam 42.5y (14.1)	-Emotional face-processing task and face Stroop task during fMRI -Resting state fMRI -ROIs: dorsal and rostral ACC, vmPFC, anterior hippocampus, anterior insula, and amygdala	Improvements in PTSD severity were associated with increased functional connectivity between the vmPFC and amygdala during emotional face-viewing. Improvement post-ketamine infusion was predicted by decreased dorsal anterior cingulate activity during emotional conflict regulation and increased task-free connectivity between the vmPFC and anterior insula.
Nowacki et al., (2020)	RCT, double-blind	Behavioral tasks	MDD (N=116), HV (N=116)	Randomized to four conditions: 1) Only MR stimulation (fludrocortisone 0.4 mg) + placebo, 2) Only NMDAR stimulation (DCS 250 mg) + placebo, 3) MR + NMDAR stimulation (both drugs), 4) No stimulation (placebo only)	N=232 50 males 182 females	34y 18-65y	Multifaceted Empathy Test	NMDAR stimulation decreased cognitive empathy in MDD participants. Independent of receptor stimulation, MDD participants showed decreased emotional empathy for positive emotions compared with HVs. Emotional empathy was not affected by NMDAR stimulation in MDD participants or HVs.
Nowacki et al., (2021)							FDOT, FERT	MDD participants and HVs did not differ in performance on the emotional dot probe task and FERT independent of receptor stimulation. NMDAR stimulation had no effect on selective attention on the emotional dot probe task and there was increased recognition accuracy for angry, but not sad, faces on FERT.
Olivola et al., (2022)	Case report	Behavioral tasks	ASD, comorbid TRD	Intranasal esketamine (84 mg twice weekly for 4 weeks, then once weekly for 4 weeks).	N=1 female	24y	RMET	Slight increase in social cognition assessed by the RMET, potentially

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Table 1 (*continued*)

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
				Maintenance dose of twice monthly				attributed to learning effect.
Reed et al. (2018)	RCT, double-blind, crossover	Behavioral task assessed during fMRI	TRD vs. HV	IV ketamine (0.5 mg/kg over 40 minutes) or normal saline placebo	TRD: N=33 12 male, 21 female HV: N=26 10 male, 16 female	-TRD: 36.1y (9.7) - HV: 33.9y (10.4)	Attentional bias dot probe task with emotional face stimuli during fMRI with whole-brain analysis	Ketamine downregulated inferior occipital gyrus, cingulate gyrus, and precentral gyrus activity during the emotional dot probe task
Scheidegger et al. (2016a)	Open-label	Behavioral task assessed during fMRI	HV	IV esketamine (bolus of 0.12mg/kg ~ 25 min prior to the fMRI task, followed by a continuous infusion of 0.25mg/kg/h during the entire scanning and task period)	N=23 12 males 11 females	25.5y (5)	Working memory task involving Berlin Affective Word List under fMRI	Ketamine abolished enhancement of deactivation normally observed during cognitive effort in emotion-related cortical midline regions. In the right dlPFC and the left insula, activation due to emotional content was blunted exclusively for negative stimuli.
Scheidegger et al. (2016b)							-Emotion-picture viewing task using International Affective Picture System under fMRI -ROIs: pgACC, amygdala, hippocampus	Ketamine reduced neural reactivity in the bilateral amygdalo-hippocampal complex during emotional stimulation, which correlated with resting-state connectivity to the pgACC.
Schmidt et al. (2013)	RCT, double-blind	Behavioral task during EEG	HV	Participants were randomized to ketamine vs. placebo group or psilocybin vs. placebo group: - IV esketamine (bolus 10 mg over 5 minutes, followed by maintenance 0.006 mg/kg/min) or normal saline placebo over 80 minutes. -Oral psilocybin (115 μg/kg) or lactulose placebo administered in gelatin capsules	Esketamine group N=10 male Psilocybin group N=13 male	Esketamine group: 26y (5.39) Psilocybin group: 23y (2.22)	- 64-channel EEG. - Conscious and non-conscious, two emotional face perception tasks: 1) happy and neutral facial expressions; 2) fearful and neutral facial expressions	Both esketamine and psilocybin impaired the encoding of fearful faces as expressed by a reduced N170 over parieto-occipital brain regions. Only esketamine impaired the encoding of happy facial expressions.
Shiroma et al. (2015)	Open label	Behavioral task	TRD	Six repeated infusions of IV ketamine 0.5 mg/kg administered over 40 minutes on a M-W-F schedule over a 12-day period	N=15 male	52y	FERT	No significant changes in repeated measures of emotion recognition after completion of infusions; authors suggest correction of emotional bias may not be a necessary prerequisite for ketamine's antidepressant effects, and/or that TRD participants represent a different subset of neural correlates from MDD participants.
Sprenger et al. (2006)	Single-blind, non-randomized	fMRI	HV	Four infusions, each with fMRI session: normal saline placebo, then IV esketamine at	N=12 male	27y (4.6); 23-36y	-Pain ratings -Painful stimuli under fMRI -ROIs: rostral ACC,	Esketamine decreased pain perception, a finding associated with dose-dependent

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Table 1 (*continued*)

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
	placebo-controlled			increasing doses of 0.05, 0.1, and 0.15 mg/kg/hr (participants were unaware of order of placebo and different doses of esketamine)			mid-cingulate ACC, thalamus, S1, S2, PFC, inferior parietal cortex, insula, amygdala	decreased activation of the ACC, insula, and S2.
Starr et al. (2020)	Open-label	Self-reported qualitative data	TRD	Esketamine as adjunct to oral antidepressant treatment	N=23 9 male 14 female	46y 28-64y	Semi-structured interviews	TRD participants reported changes in activities with friends and relatives (n=6) and being around others/more likely to socialize/more connected (n=4).
Sterpenich et al. (2019)	Open-label	Behavioral task assessed during fMRI	TRD	IV ketamine (0.5 mg/kg as bolus over 1 minute)	N=10 4 male 6 female	51y 38-58y	-Game-like reward task and emotional judgement task (i.e. rating potentially emotionally charged images as positive, negative, neutral) during fMRI -Whole-brain analysis and ROIs involved in reward and emotion processing: amygdala, insula, ACC, OFC, ventral striatum	In the reward task, ketamine increased activity in the OFC, ventral striatum, and VTA that persisted for 1 week. In the emotional judgement task, ketamine rapidly modified activity in the amygdala and insula that decreased in response to negative pictures. Ketamine also modified local brain activity in response to emotionally negative, positive, or neutral stimuli in the amygdala, insula, ACC, and VTA.
Takiguchi et al. (2017)	RCT, double-blind, crossover	Structural MRI	Schizo-phrenia	Adjunctive DCS 50 mg daily or placebo pill for six weeks in crossover design with three-week washout period in between; participants remained on antipsychotics at stable dose	N=36 22 male 14 female	48.4y (16.1)	-PANSS (negative symptoms) -EQS -White matter integrity	DCS did not improve negative, positive, or cognitive symptoms of schizophrenia. White matter integrity and treatment effects of DCS were context-specific. No association observed between DCS and negative symptoms of PANSS, indicating that NMDA and social eagerness are not directly related.
Thai et al. (2020)	Open-label	Behavioral task assessed during fMRI	TRD	Six repeated infusions of IV ketamine 0.5 mg/kg over 40 minutes over a 12-day period	N=11 teenagers 8 male 3 female	17.02y (1.18); 14-18.3y	-Word face Stroop task -fMRI task (emotional valence recognition) ROIs: bilateral hippocampus, amygdala, subcallosal cortex, ACC (corticolimbic network), bilateral accumbens (corticostriatal network), precuneus, PCC (DMN)	Ketamine decreased activation in regions involved in corticolimbic and corticostriatal circuits and the DMN across conditions of word-face pairings. Ketamine did not reduce negativity bias, but improved performance on positive stimuli was associated with improved depressive symptoms. This suggests that clinical improvement may require attenuation of the negativity bias via

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Table 1 (*continued*)

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
								DMN and limbic regions and that re-tuning these three critical neural networks may allow more efficient recruitment of the reward network to enhance social pleasure.
Urbano et al. (2014)	RCT, double-blind	Rating scale scores	ASD	8 weeks of DCS at either weekly or daily dosing and a two-week follow-up visit. Two dosing strategies: 50 mg weekly (placebo taken for the remaining 6 days of the week) or 50 mg daily	N=20 14 male 6 female	17.9y (2.5) 14-25y	ABC Subscale 2 (social/lethargy)	The secondary outcome measures of the ABC subscales showed no clinical or statistical differences between the dosage groups on subscale 2 (social/lethargy) and subscale 3 (stereotypies).
Urbano et al. (2015).		Rating scale scores					ABC, SRS	There was a statistically significant improvement in the SRS, as well as the Social Perception Affecting Naming subtest after both DCS dosing approaches. There was no improvement in the Social-Perception-Prosody-Face Matching task.
		Behavioral task					Social Perception Affecting Naming subtest. Social Perception Prosody Face Matching task	There was a statistically significant improvement in the Social Perception Affecting Naming subtest after both DCS dosing approaches. There was no improvement in the Social Perception Prosody Face Matching task.
Weigand et al. (2022)	Open-label	Behavioral task assessed during fMRI and MRS	MDD	IV esketamine 0.25 mg/kg or IV racemic ketamine (1:1) 0.5 mg/kg, depending on the center where the participant was treated	N=24 10 male 14 female	44.4y (11.8); 25-64y	-Emotion-picture viewing task using International Affective Picture System during fMRI and MRS -ROIs: NBRs in the pgACC	Activity in the pgACC during an emotional stimulation task predicted the antidepressant efficacy of ketamine and was associated with glutamate increase 24 hours after infusion and better clinical outcomes. DMN includes the pgACC, and its aberrant activation may be associated with decreased NBRs during emotional stimulation task in depression.
Wu Z, et al. (2023)	Open-label	Rating scale scores	MDD, BD	6 intravenous infusions (0.5 mg/kg) of ketamine over 2 weeks	N=103 52 male 51 female	34.3y (11.6)	GAF (includes domains on social ability and ability to maintain normal social life), SDS-2	Direct and indirect effects of ketamine on psychological and social functioning on SDS and GAF were

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Table 1 (*continued*)

Reference	Study Design	Study Outcomes	Diagnosis	Glutamate Receptor Modulator, Dosing, Frequency, Duration of Treatment	Number of Participants Treated and Sex	Mean Age (SD); Range (Years)	Entactogenic Outcome Measured	Results Suggesting Entactogenic Effect
							(social domain), SF-MPQ	statistically significant, regardless of the presence of pain. Improvement in social functioning was partially mediated by improved depressive symptoms, but a stronger mediation effect was observed for reductions in affective pain measured by SF-MPQ.

Abbreviations: 5D-ASC: Dimensional Altered States of Consciousness questionnaire; ABC: Aberrant Behavior Checklist; ACC: anterior cingulate cortex; ASD: autism spectrum disorder; BD I & II: bipolar disorder I & II; DCS: D-cycloserine; dlPFC: dorsolateral prefrontal cortex; DMN: default mode network; dPCC: dorsal posterior cingulate cortex; ECAT: Emotional Categorization Task; ECT: electroconvulsive therapy; EEG: electroencephalography; EMEM: Emotional Recognition Memory Task; EQS: Emotional Intelligence Scale; EREC: Emotional Recall Task; ESM: Experience Sampling Method; FDOT: Facial Dot-Probe Task; FERT: Facial Emotion Recognition Task; fMRI: functional magnetic resonance imaging; GAF: Global Assessment of Functioning scale; HV: healthy volunteer; IV: intravenous; MADRS: Montgomery-Asberg Depression Rating Scale; MAIA: Multidimensional Assessment of Interoceptive Awareness; MDD: major depressive disorder; MEG: magnetoencephalography; mPFC: medial prefrontal cortex; MR: mineralocorticoid receptor; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NBRs: Negative BOLD responses; NMDA: N-methyl-D-aspartate; NMDAR: NMDA receptor; OFC: orbitofrontal cortex; pACC: pregenual anterior cingulate cortex; PANSS: Positive and Negative Syndrome Scale; PCC: posterior cingulate cortex; PFC: prefrontal cortex; pgACC: pregenual anterior cingulate cortex; PTSD: post-traumatic stress disorder; RCT: randomized, controlled trial; RMET: Reading the Mind in the Eyes Test; ROI: region of interest; SDS: Sheehan Disability Scale; SF-MPQ: Simple McGill Pain Questionnaire; SHAPS: Snaith-Hamilton Pleasure Scale; SRS: Social Responsiveness Scale; STQ: Social Touch Questionnaire; TPC: temporoparietal cortex; TRD: treatment-resistant depression; vmPFC: ventromedial prefrontal cortex; VTA: ventral tegmental area.

recognition and processing, such as reducing the ability to detect sad expressions on the Ekman 60 Faces Test (Ebert et al., 2012); attenuating cognitive efforts in emotion-related cortical midline activity (particularly the right dorsolateral prefrontal cortex (dlPFC) and left insula) during a working memory task using affective words (Scheidegger et al., 2016b); and reducing neural reactivity in the bilateral amygdala-hippocampal complex during emotion-picture viewing task, which in turn correlated with resting-state connectivity to the pgACC, a region previously implicated in the psychedelic-induced psychomimetic state (Scheidegger et al., 2012).

Other double-blind, placebo-controlled RCTs included a neuroimaging component that examined correlates of ketamine's neural effects on change in self-perception. For example, posterior cingulate cortex (PCC) cortical thickness measured via structural MRI was negatively correlated with self-reported disembodiment scores, suggesting that ketamine may attenuate PCC-mediated self-referential thought processes within the default mode network (DMN) (Danyeli et al., 2024). The PCC has previously been associated with psychedelic-induced alterations in sense of self (Doss et al., 2021; Palhano-Fontes et al., 2015) and with ketamine's mechanism of action (Li et al., 2020).

The only study to examine the effects of DCS on emotion perception in HVs reported mixed results. Chen and colleagues found that DCS increased positive bias in emotional word categorization in the Emotional Categorization Task (ECAT) and free recall in the Emotional Recall Task (EREC), though no significant differences were found in other tasks including the Facial Expression Recognition Task (FERT), Facial Dot-Probe Task (FDOT), or Emotional Recognition Memory Task (EMEM) (Chen et al., 2021). In contrast to the studies suggesting that ketamine has possible emotional blunting effects (particularly to negatively valenced stimuli), this study suggested that DCS may facilitate bias towards positively valenced stimuli (i.e., participants were more attentive towards positive emotions).

3.3. Schizophrenia

Only one study in individuals with schizophrenia met inclusion criteria (Takiguchi et al., 2017). This double-blind, placebo-controlled, crossover RCT evaluated the effects of DCS (50 mg daily) on positive, negative, and cognitive symptoms in individuals with schizophrenia. DCS did not improve negative symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) nor cognitive symptoms pertaining to interpersonal, intrapersonal, and situational domains as measured by the emotional intelligence scale (EQS); however, response to DCS was influenced by heterogeneity in neurobiological predictors, including age of onset and white matter integrity measured by structural MRI. The lack of response to DCS for negative and cognitive symptoms is consistent with findings from prior studies investigating DCS as an adjunctive treatment for schizophrenia (Buchanan et al., 2007; Goff et al., 2005; 1999; Heresco-Levy et al., 2002).

3.4. ASD

Three papers examining the effects of glutamate receptor modulators on empathy in individuals with ASD (without medical comorbidities or other comorbid neurodevelopmental disorders) met inclusion criteria. One case report found that an adult female with ASD and comorbid treatment-resistant depression (TRD) who received intranasal esketamine for several weeks had a slightly improved performance on the Reading the Mind in the Eyes Test (RMET), a measure of one's ability to recognize and understand another's mental state (other-perception) (Olivola et al., 2022).

Two papers examined the effects of DCS. One double-blind, placebo-controlled RCT found that individuals with ASD treated with DCS for eight weeks had statistically significant improvement in ASD-related social deficits as measured by the Social Responsiveness Scale (SRS), a self-reported measure (Urbano et al., 2014). In the same trial, DCS demonstrated statistically significant improvements in the Social Perception Affecting Naming subtest, though performance on the Social-Perception-Prosody Face Matching Task did not improve (Urbano et al., 2015).

3.5. PTSD

Social isolation (Vlachos et al., 2020) and heightened empathic ability (Wendt et al., 2022) are both thought to predispose individuals to develop PTSD. One double-blind, parallel group RCT found that ketamine, compared to midazolam, was associated with increased functional connectivity between the ventromedial PFC (vmPFC) and the amygdala during an emotional face-processing task, regardless of the presence of comorbid depressive symptoms. Improvement in PTSD symptoms also predicted decreased dorsal ACC activity during emotional conflict regulation (in the face Stroop paradigm) and increased task-free connectivity between the vmPFC and the anterior insula. The authors suggested that ketamine might exert entactogenic effects in individuals with PTSD by modulating neural response to social threat signals (Norbury et al., 2021). These findings suggest that ketamine-induced improvements may be driven by suppression of dorsal ACC hyperactivity during emotional conflicts and increased empathetic processes via the enhanced connectivity between the vmPFC and anterior insula, enabling individuals to more effectively manage conflicting social cues and process empathetic signals, thereby supporting improved prosocial learning.

3.6. Mood disorders

Mood disorders are frequently associated with impaired social functioning and communication (Kupferberg and Hasler, 2024). Dysregulated emotional processing such as attentional bias towards negative emotional stimuli has also been reported, and correcting such biases has been postulated as an antidepressant mechanism (Dalgleish and Watts, 1990; Ma, 2015). Our systematic review identified 13 studies of individuals with mood disorders that measured a pre-specified empathy-related outcome. Ten studies used intravenous ketamine, one used intranasal esketamine, and two used DCS (Table 1).

Several double-blind, placebo-controlled crossover pharmaco-imaging RCTs found that ketamine attenuated attentional bias to negative emotional stimuli. One magnetoencephalography (MEG) study found that, in individuals with TRD versus HVs, ketamine slowed NMDA signal transmission in the amygdala when performing the dot probe task with emotional face stimuli (Gilbert et al., 2018). When using fMRI to assess the same task, whole-brain analysis revealed an interaction between the drug group (ketamine vs. placebo) and emotional valence (angry vs. happy) in the mPFC. Interestingly, ketamine appeared to correct attentional bias towards angry and happy faces in TRD participants to the pattern seen in HVs; this change correlated with improved depressive symptoms, suggesting that ketamine may reduce brain response to negative stimuli and increase response to positive stimuli in emotional processing regions (Gilbert et al., 2018). In a similar study using an emotion evaluation task under MEG, MDD participants exhibited higher accuracy for sad-angry than happy-neutral faces, and HVs exhibited the opposite pattern, though the performance became similar between the two groups post-ketamine (Lundin et al., 2021). It is worth noting that ketamine's deactivation of neural response to negative stimuli in these studies of TRD participants mirror the results obtained in the aforementioned similarly designed RCTs that examined HVs (Lehmann et al., 2016; Scheidegger et al., 2016b).

Non-randomized studies in individuals with MDD or TRD post-ketamine, though at higher risk of bias, obtained similar results. These findings included decreased activation in the amygdala during an emotional face discrimination task assessed via fMRI (Loureiro et al., 2020); increased caudate connectivity during positive emotion perception in two separate emotion perception tasks that correlated with antidepressant effects (Murrough et al., 2015); modification of activity in the amygdala, insula, and anterior cingulate cortex (ACC) in response to negative pictures during an emotional judgement task assessed via fMRI (Sterpenich et al., 2019); and negative blood oxygenation level dependent response in the pgACC during an emotional stimulation task using fMRI, which also predicted the antidepressant efficacy of ketamine and glutamate increases observed using magnetic resonance spectroscopy (MRS) (Weigand et al., 2022). However, although most pharmaco-imaging studies highlighted changes in regions associated with empathy seen via neuroimaging, Shiroma and colleagues observed no differences, which challenges the theory that correcting negative emotional bias is a prerequisite for ketamine's antidepressant effects (Shiroma et al., 2015).

Subjective improvement in hedonic pleasure associated with engaging in prosocial behaviors has also been reported with varying evidence levels. For example, one double-blind, placebo-controlled, crossover RCT found that ketamine improved social hedonic pleasure, as assessed via the Snaith-Hamilton Pleasure Scale (SHAPS) (Hess et al., 2024). Another open-label trial of repeat-dose IV ketamine in teenagers with TRD found that clinical improvement in depression was associated with improved ability to identify positive stimuli on an emotional valence identification task, even though ketamine did not reduce negativity bias, as reported in other studies of adults with depression (Thai et al., 2020). Another study that collected qualitative data via semi-structured interviews found that, after administration of adjunctive esketamine, TRD participants reported changes in activities with friends and relatives and being around others/more likely to socialize (Starr et al., 2020). Finally, an open-label trial of social functioning in relation to mood and affective pain found that ketamine improved social functioning in individuals with MDD and bipolar depression (BD), an improvement partially mediated by improved depressive symptoms but more strongly by reduced affective pain (Wu et al., 2023).

Only one trial studied DCS in MDD. In a double-blind, placebo-controlled RCT, DCS decreased cognitive empathy measured with the Multifaceted Empathy Test (MET) in MDD participants but not in HVs. In both groups, DCS had no effect on emotional empathy measured by the MET (Nowacki et al., 2020) or on the FERT (Nowacki et al., 2021). Another study in the same sample showed that, independent of receptor stimulation, MDD participants showed decreased emotional empathy for positive emotions compared with HVs, and DCS increased recognition accuracy for angry faces on the FERT (Nowacki et al., 2021). These results suggest that DCS (which stimulates NMDARs) may increase attentional bias to negative emotional stimuli and decrease cognitive empathy in MDD participants, contrary to ketamine, which mainly antagonizes NMDARs.

4. Discussion

This systematic review explored the potential entactogenic effects of glutamate receptor modulators. Although both older and newer glutamate receptor modulators were included in the search terms (see Supplement), only 30 publications using ketamine (either racemic ketamine or esketamine) and DCS met inclusion criteria—no studies investigating any other pre-specified glutamatergic modulator met inclusion criteria. Ketamine is an NMDAR antagonist and broad glutamatergic modulator (Henter et al., 2021). DCS is a partial NMDAR agonist at the glycine binding site and has been thought to promote synaptic plasticity for learning and memory processes (Vestring et al., 2024). In this context, the entactogenic effects observed with these compounds may be related to their modulating effects primarily on NMDARs (Fig. 1).

4.1. Self- and other-perception

The findings reviewed above suggest that ketamine (both racemic ketamine and esketamine) and DCS may modulate self- and other-perception. Such effects may involve activity in the ACC, prefrontal cortex (PFC), orbitofrontal cortex (OFC), insula, amygdala, ventral tegmental area (VTA), cuneus, precuneus, or PCC, brain regions involved in mentalizing (the ability to understand one's own and others' thoughts and feelings) and empathetic concerns (Lamm et al., 2019; Stevens and Taber, 2021). Across randomized and non-randomized

studies of both HVs and individuals with mood disorders or PTSD, ketamine reduced cognitive processing of negative social cues on behavioral tasks (Ebert et al., 2012), possibly by suppressing activity in the pgACC, dlPFC, amygdala, PCC, or parieto-occipital brain regions (Abel et al., 2003; Becker et al., 2017; Gilbert et al., 2018; Lehmann et al., 2016; Loureiro et al., 2020; Norbury et al., 2021; Reed et al., 2019; Scheidegger et al., 2016a; 2016b; Schmidt et al., 2013). These findings are consistent with previous research showing that negative bias correlated with pgACC activity (Ito et al., 2017), reduced dlPFC connectivity (Amemori et al., 2024; Clarke et al., 2020), and increased amygdala activity (Dannlowski et al., 2007). Other studies found ketamine-induced enhanced response to positive social cues in brain regions such as the dorsal ACC, amygdala, and insula (Sterpenich et al., 2019). Collectively, this suggests that ketamine may reduce amygdala-driven negative biases, offering a potential therapeutic pathway in depression and PTSD.

The evidence reviewed above also underscores that ketamine's pharmacologic effects are associated with cognitive perception and high-order executive functioning at neural and behavioral levels, with valence-specific effects. Valence-specific neural response to emotional stimuli precedes empathic decision-making processes before prosocial behaviors or social affiliative behaviors are enacted. Interestingly, the few studies examining DCS in MDD or schizophrenia found no clinically meaningful changes in outcomes related to self- and other-perception (Nowacki et al., 2020; Takiguchi et al., 2017), perhaps as a result of the site-specific effects that each drug has within the NMDAR complex (i.e., ketamine at the PCP site, and DCS at the glycine site).

Ketamine's transient psychomimetic effects also appeared to affect the distinction between self and others. For instance, one well-designed study found that ketamine reduced the distinction between touch initiated by oneself versus by others, potentially blurring the boundaries between self and others in cutaneous sensation (Kaldewaij et al., 2024). This reduction in sensitivity to self- and other-driven touch has been positively associated with decreased neural activity in the temporal-parietal cortex (van Buuren et al., 2022). Blurring of the self-other interoceptive and proprioceptive boundaries during a ketamine-induced psychomimetic state may represent a mechanistic subcomponent of empathy, such that the act of "putting oneself in another's shoes" may require neural modulation of the self-other distinction (Lamm et al., 2016, 2019). Indeed, the self-other distinction appears to be diminished in neural responses to distress in extraordinarily altruistic individuals (Brethel-Haurwitz et al., 2018; Bukowski et al., 2021).

4.2. Prosocial drive, reward-seeking, and reinforcement of prosocial behavior

Prosocial behavior follows empathic resonance coupled with motivational decision-making. No studies included in this systematic review used self-report ratings (e.g. Prosociality Scale) (Luengo Kanacri et al., 2021) or behavioral paradigms (Marsh et al., 2007; McDonald and Kanske, 2023) that measure prosocial behaviors and motivation. Future studies of glutamate receptor modulators beyond ketamine/esketamine and DCS should incorporate such outcomes.

Hedonic pleasure associated with social affiliative behavior can drive and reinforce prosocial behaviors. Preliminary findings suggest that entactogens may promote prosocial behaviors, particularly in mood disorders where the hedonic pleasure associated with social interaction is compromised. For example, individuals with depression reported enhanced social pleasure and improved cognitive and social functioning following intravenous ketamine or intranasal esketamine administration, respectively (Hess et al., 2024; Starr et al., 2020). Interestingly, many ketamine/esketamine studies assessed for inclusion in this systematic review used the SHAPS as an outcome measure, though many of these were excluded from our final analysis because they reported the SHAPS composite score only. If data are available, a focused sub-analysis of the SHAPS questions pertaining to social anhedonia from ketamine/esketamine trials may be enlightening. Similarly, investigating whether improvements in social anhedonia correlate with improvements in depressive symptoms may elucidate the relationship between ketamine's antidepressant and entactogenic effects.

Despite these promising findings, more research is needed to validate the role of ketamine in fostering prosocial behaviors. Although Hess and colleagues found that ketamine had entactogenic effects in a rodent model of prosocial behavior (Hess et al., 2024), prosocial behaviors measured via behavioral paradigms have yet to be tested in humans. It remains unclear whether entactogens directly trigger prosocial behaviors or enhance the learning of such behaviors and what brain correlates may underpin these effects.

4.3. Implications for the pharmacological mechanisms of entactogens and potential transdiagnostic clinical applications

Deficits can occur across the spectrum of our framework that cognitive and affective empathy drive prosocial behavior, which in turn brings hedonic pleasure and reinforces prosocial learning. Although antisocial personality disorder may be a prototypical model of empathic deficits that lead to deficits in prosocial behaviors and learning, deficits in social cognition and behavior are widely observed to varying severity in a range of neuropsychiatric conditions, including schizophrenia, ASD, personality disorders and, to a more subtle extent, mood disorders and PTSD.

The findings presented in this systematic review convincingly demonstrate that ketamine/esketamine may have entactogenic effects, in part by reducing neural response to negative stimuli, which offers possible clinical applications for depression and PTSD. A handful of preliminary results also support the notion that ketamine/esketamine's ability to alleviate anhedonia symptoms improves pleasure associated with social interactions. In this sense, real-world clinical applications that leverage the entactogenic effects of ketamine or esketamine may be quite impactful. Esketamine nasal spray, in particular, is comparatively more accessible than other compounds studied in relation to empathy and prosocial behavior, such as intranasal oxytocin or MDMA, which are not commercially available; furthermore, the wide use of esketamine in Europe has generated clinical data demonstrating its effect on dimensions connected to empathy and prosocial behavior, such as anhedonia and affective blunting (Pettorruso et al., 2023).

The underlying mechanisms of the entactogenic effects observed with ketamine/esketamine are likely to overlap with the known mechanisms of MDMA, an established entactogen whose presumed mechanism of action is modulation of the serotonergic and oxytocinergic systems. While ketamine's primary mechanism of action is NMDAR antagonism, its broad modulatory effects on glutamate receptors may have downstream effects on these systems (Fig. 1); in fact, rodent models have demonstrated that ketamine activates both the serotonergic (Ago et al., 2019; Fukumoto et al., 2016) and oxytocinergic systems (Edem et al., 2023). Ketamine and phencyclidine (PCP) both occupy the same binding site at the NMDAR, but PCP is not known to produce any entactogenic effects. Therefore, the pharmacological mechanism underlying ketamine's entactogenic effects likely involves a mechanism beyond simple NMDAR antagonism.

Furthermore, the phenomenology of ketamine administration (notably dissociative and some hallucinogenic effects) is reported to be quite distinct from those of classic serotonergic psychedelics such as psilocybin and other known entactogens, such as substituted amphetamines (e.g., MDMA, methylenedioxyamphetamine), phenethylamines (e.g., metaescaline), and cathinones (e.g., mephedrone). It is unclear whether ketamine's entactogenic effects are a product of downstream serotonergic effects or specific to one or more of its broad glutamate receptor modulating effects. Future research should seek to elucidate the glutamate-related mechanisms that explain ketamine/esketamine's entactogenic effects in humans and both compare them with and

distinguish them from the mechanisms of other known entactogens that modulate the monoaminergic system (Table 2). Therapeutically, however, glutamate receptor modulators may be of more urgent interest with regard to their clinical use in potentiating prosocial behaviors in humans, given that they are more accessible, have fewer side effects, and have less abuse potential than other known entactogens, which are mostly substituted amphetamines and MDMA-related compounds.

Although some studies found that DCS facilitated clinical improvement in ASD, results for DCS were mixed. Given its ability to promote neuroplasticity (Forsyth et al., 2015) and reduce attention bias to negative stimuli (Britton et al., 2007), DCS has been investigated as an adjunctive treatment in social anxiety disorder (Hofmann et al., 2006), phobic disorders (Aupperle et al., 2009), obsessive compulsive disorder (Andersson et al., 2015), and PTSD (de Kleine et al., 2012), but some well-designed trials found negative results (Hofmann et al., 2019). It should be noted that fear extinction results from both change in other-perception and learning; given the confounding factor of learning, our review did not focus on fear extinction as an entactogenic outcome. Nevertheless, the existing literature suggesting that DCS facilitates fear extinction had study designs that used a cognitive or behavioral learning component (i.e., psychotherapy). DCS has no dissociative or psychomimetic effects and binds to the glycine-site receptor—a different area of the NMDAR than ketamine. In this context, it may have overlapping downstream effects with ketamine and other glycine site modulators to produce potential entactogenic effects (Fig. 1), given that it appears to also modulate self- and other-perception. Thus, comparing the entactogenic effects of ketamine/esketamine versus DCS may shed light on possible mechanistic overlaps (such as neuroplastic properties) as well as differences (entactogenic effects deriving from other glutamate receptor modulating effects and/or changes in the serotonergic and/or oxytocinergic systems).

4.4. Limitations

Our systematic review results are limited by several factors. First, very few studies were designed to assess the effects of glutamate receptor modulators on empathy and prosocial behaviors as the primary outcome. Most of our included studies examined ketamine, and the few studies investigating DCS limited our ability to fully compare entactogenic effects between these two compounds. It should also be noted that our systematic review protocol included studies investigating glutamate receptor modulators with known or suspected psychoactive effects but did not include other compounds that interact with the NMDAR or other glutamate receptors, such as memantine and magnesium. Studies that focused on ketamine misuse or addiction were excluded due to the many external variables that would be difficult to control for outside of the study design.

Second, there are notable limitations to the sample size and study design of the included studies that may have affected our ability to compare results across studies. Study designs varied between open-label, double-blind, crossover, and parallel randomized control trials. The participant populations also varied from HVs to individuals with mood disorders, neurodevelopmental disorders, and psychotic disorders. Sample sizes were relatively small, and these also varied between the included studies, ranging from one female participant in a case study to 232 participants (116 with MDD, 116 HVs). Some of the studies included in our review did not incorporate a proper control group.

Third, our risk of bias assessment identified four RCTs and six NRSIs with moderate risk of bias. Several studies were found to have reliability and bias concerns in the context of missing outcome data. The missing data were not characterized with regard to whether this was random or intentional, which may have affected the overall results. Future studies should prioritize consistent reporting of all outcome data and transparent assessment of missing data, both of which are both crucial for minimizing bias and improving the validity of conclusions.

Finally, due to the nature of the systematic review, it is possible that some studies relevant to our topic were not identified and reviewed. More broadly, the findings of this systematic review must be interpreted with caution given the complexity of empathy and prosocial behaviors in humans, the varying degrees of judgement assigned to the included studies, and the variability in the outcomes and experimental designs of the included studies.

4.5. Conclusions and future directions

This systematic review identified potential entactogenic effects associated with ketamine and, to less convincing extent, DCS. NMDAR modulators are generally safe and—given their broad pharmacologic profile that also facilitates neuroplasticity and promotes learning—have the potential to offer a safe and effective clinical solution for improving empathy and prosocial behaviors. Therapeutic interventions that seek to improve empathy and social functioning may also consider combining potential entactogens with modalities known to positively affect social cognition and behavior, such as intranasal oxytocin, cognitive behavioral therapy, interpersonal psychotherapy, mindfulness-based cognitive therapy, psychedelic-assisted psychotherapy, or neuromodulation (Kupferberg and Hasler, 2024). Future studies may also wish to explore whether newer glutamate receptor modulators such as HNK, Nuedexta, AVP-786, GLYX-13, or basimglurant have similar entactogenic effects to ketamine and DCS that can be measured via self-report, behavioral tasks, and/or neuroimaging outcomes; Table 2 lists considerations for future experimental designs.

Because empathy is a construct that has yet to be operationalized by definitive biological correlates, there is considerable variability in the outcomes of our reviewed studies (Table 1), as well as potential future experimental designs (Table 2). Behavioral neuroimaging paradigms that assess specific components of an entactogen's mechanism of action are of particular interest for bridging psychological constructs like empathy with neurobiological correlates and for further evaluating the entactogenic effects of psychotropics; these include social pain (Ferguson et al., 2024), self-other distinction by touch (Kaldewaij et al., 2024), and egocentricity bias in self- versus other-related affective states (Silani et al., 2013). Results from rigorously conducted trials using paradigms to assess self- and other-perception, affective regulation in interpersonal domains, social reward processing, and empathy would significantly advance the social processing domains within the NIMH Research Domain Criteria, which have historically been underexplored.

Author statement

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CRediT authorship contribution statement

Hiroe Hu: Writing – original draft, Project administration, Investigation, Data curation, Conceptualization. **Alaina N. Tillman:** Writing – original draft, Investigation, Data curation. **Miyu Fujita:** Writing – review & editing, Investigation. **Mayu Yoshikawa:** Writing – review & editing, Visualization, Investigation. **Elizabeth D. Ballard:** Writing – review & editing, Supervision. **Yoojin Lee:** Writing – original draft, Supervision, Investigation, Conceptualization. **Carlos A. Zarate:** Writing – review & editing, Supervision, Funding acquisition.

Table 2
Considerations for Research Questions and Experimental Designs for Future Trials Investigating the Entactogenic Effects of Glutamate Receptor Modulators.

Research Questions	Glutamate Receptor Modulators to Investigate as Candidate Entactogens	Self-Reported Questionnaires to Consider Pre- and Post-Drug	Behavioral Tasks and Paradigms to Consider Pre- and Post-Drug	Other Research Modalities and Methodology to Consider Pre- and Post-Drug
Do glutamate receptor modulator(s) modify self- and other-perception in a prosocial way?	IV ketamine ((*R/S*) or *S*-ketamine) and derivatives - esketamine nasal spray - HNK Glycine Site Modulators - DCS, NRX-101 (DCS + Lurasidone) - Rapastinel (GLYX-13) - 4-Chlorokynurenine (AV-101) Dextromethorphan and derivatives - Deudextromethorphan (AVP-786), Nuedexta, AXS-05 (Axsome) mGluR modulators - Basimglurant - AZD2066 - TS-161 Non-competitive NMDA receptor antagonists - Dextromethadone (REL-1017)	Questionnaires to assess change in self-perception - Self-Perception Profiles - Physical Self-Perception Profile Questionnaires to assess change in other-perception - Other-Perception Assessment Tool Specific questions within a questionnaire that assess self-perception pre- and post-drug - CADSS Questions 3, 4, 5, 6, 7, 8, 18, 20, 21, and 22	Tasks to assess other-perception and theory of mind - The Picture Stories Task - Reading the Mind in the Eyes - Multifaceted Empathy Test - Movie for the Assessment of Social Cognition - Emotional Stroop Task Behavioral tasks under neuroimaging - Self Other Touch Paradigm under fMRI - A novel visuo-tactile paradigm developed by Silani et al. (2013) to assess egocentricity bias in the emotional domain under fMRI	Qualitative data collection Behavioral tasks under MEG instead of fMRI Comparison (via parallel design or cross-over) of glutamate receptor modulator with other known entactogens such as MDMA Peripheral measurement (via plasma or saliva) of oxytocin
Do glutamate receptor modulator(s) modify emotional regulation with regard to social cues?	- Nitrous Oxide	Interpersonal Emotion Regulation Questionnaire Emotion Regulation of Others and Self Questionnaire	Social Reappraisal Task Conflict Resolution Task Behavioral tasks under neuroimaging - Hariri Hammer task under fMRI - Picture Viewing Paradigm under fMRI	Qualitative data collection Behavioral tasks under MEG instead of fMRI Comparison (via parallel design or cross-over) of glutamate receptor modulator with other known entactogens such as MDMA Peripheral measurement (via plasma or saliva) of oxytocin
Do glutamate receptor modulator(s) modify performance in empathy-proxy paradigms, such as through pain?		Social Pain Questionnaire Hurt Feelings Scale	EEG-coupled social pain vs. physical pain (Ferguson et al., 2024)	Qualitative data collection Conducting social pain task under MEG instead of EEG
Do glutamate receptor modulator(s) modify social reward processing or prosocial drive?	IV ketamine ((*R/S*) or *S*-ketamine) and derivatives - Single infusion of racemic ketamine has been shown to increase hedonic pleasure associated with social interaction and prosocial acts (Hess et al., 2024), but has yet to be investigated in repeated administration of intravenous ketamine/esketamine and intranasal esketamine - HNK Glycine site modulators - DCS, NRX-101 (DCS + Lurasidone) - Rapastinel (GLYX-13) - 4-Chlorokynurenine (AV-101) Dextromethorphan and derivatives - Deudextromethorphan (AVP-786), Nuedexta, AXS-05 (Axsome) mGluR modulators - Basimglurant - AZD2066 - TS-161 Non-competitive NMDA receptor antagonists - Dextromethadone (REL-1017) - Nitrous Oxide	Questionnaires to assess empathy - Balanced Emotional Empathy Scale - Multidimensional Emotional Empathy Scale - Empathy Quotient - Feeling and Thinking Scale - Griffith Empathy Measure - Toronto Empathy Questionnaire - Questionnaire of Cognitive and Affective Empathy - Hogan Empathy Scale - Emotional Empathic Tendency Scale -Interpersonal Reactivity Index - Empathic Experience Scale - Basic Empathy Scale Questionnaires assessing empathy within a specific context - Jefferson Scale of Physician Empathy - Nursing Empathy Scale - Consultation and Relational Empathy Measure - Autism Quotient - Scale of Ethnocultural Empathy Specific questions within a questionnaire that assess social anhedonia - SHAPS Questions 2, 7, 13, 14	Empathy Selection Task Social Value Orientation Test Prosocial Learning Task	Qualitative data collection Conducting behavioral tasks under fMRI or MEG Comparison (via parallel design or cross-over) of glutamate receptor modulators with other known entactogens such as MDMA Peripheral measurement (via plasma or saliva) of oxytocin

Abbreviations: CADSS: Clinician-Administered Dissociative States Scale; DCS: D-cycloserine; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; HNK: hydroxynorketamine; IV: intravenous; MDMA: 3,4-Methylenedioxymethamphetamine; MEG: magnetoencephalography; mGluRs: metabotropic glutamate receptors; NMDA: N-methyl-D-aspartate; SHAPS: Snaith Hamilton Pleasure Scale.

Declaration of competing interest

Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R*,*S*)-ketamine in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorder. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

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Supplementary materials

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References

Abel, K.M., Allin, M.P., Kucharska-Pietura, K., Andrew, C., Williams, S., David, A.S., Phillips, M.L., 2003. Ketamine and fMRI BOLD signal: distinguishing between effects mediated by change in blood flow versus change in cognitive state. Hum. Brain Mapp. 18 (2), 135–145.

Ago, Y., Tanabe, W., Higuchi, M., Tsukada, S., Tanaka, T., Yamaguchi, T., Igarashi, H., Yokoyama, R., Seiriki, K., Kasai, A., Nakazawa, T., Nakagawa, S., Hashimoto, K., Hashimoto, H., 2019. (R)-Ketamine induces a greater increase in prefrontal 5-HT release than (S)-Ketamine and Ketamine metabolites via an AMPA receptor-independent mechanism. Int. J. Neuropsychopharmacol. 22 (10), 665–674.

Amemori, S., Graybiel, A.M., Amemori, K.I., 2024. Cingulate microstimulation induces negative decision-making via reduced top-down influence on primate fronto-cingulo-striatal network. Nat. Commun. 15 (1), 4201.

Andersson, E., Hedman, E., Enander, J., Radu Djurfeldt, D., Ljótsson, B., Cervenka, S., Isung, J., Svanborg, C., Mataix-Cols, D., Kaldo, V., Andersson, G., Lindefors, N., Rück, C., 2015. D-Cycloserine vs Placebo as adjunct to cognitive behavioral therapy for Obsessive-compulsive disorder and interaction with antidepressants: a randomized clinical trial. JAMa Psychiatry 72 (7), 659–667.

Atila, C., Holze, F., Murugesu, R., Rommers, N., Hutter, N., Varghese, N., Sailer, C.O., Eckert, A., Heinrichs, M., Liechti, M.E., Christ-Crain, M., 2023. Oxytocin in response to MDMA provocation test in patients with arginine vasopressin deficiency (central diabetes insipidus): a single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial. Lancet Diabetes Endocrinol. 11 (7), 454–464.

Aupperle, R.L., Hale, L.R., Chambers, R.J., Cain, S.E., Barth, F.X., Sharp, S.C., Denney, D. R., Savage, C.R., 2009. An fMRI study examining effects of acute D-cycloserine during symptom provocation in spider phobia. CNS Spectr. 14 (10), 556–571.

Becker, B., Steffens, M., Zhao, Z., Kendrick, K.M., Neumann, C., Weber, B., Schultz, J., Mehta, M.A., Ettinger, U., Hurlemann, R., 2017. General and emotion-specific neural effects of ketamine during emotional memory formation. Neuroimage 150, 308–317.

Brethel-Haurwitz, K.M., Cardinale, E.M., Vekaria, K.M., Robertson, E.L., Walitt, B., VanMeter, J.W., Marsh, A.A., 2018. Extraordinary altruists exhibit enhanced self-other overlap in neural responses to distress. Psychol. Sci. 29 (10), 1631–1641.

Britton, J.C., Gold, A.L., Feczko, E.J., Rauch, S.L., Williams, D., Wright, C.I., 2007. D-cycloserine inhibits amygdala responses during repeated presentations of faces. CNS Spectr. 12 (8), 600–605.

Buchanan, R.W., Javitt, D.C., Marder, S.R., Schooler, N.R., Gold, J.M., McMahon, R.P., Heresco-Levy, U., Carpenter, W.T., 2007. The cognitive and negative symptoms in schizophrenia trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. Am. J. Psychiatry 164 (10), 1593–1602.

Bukowski, H., Ahmad Kamal, N.F., Bennett, D., Rizzo, G., O'Tuathaigh, C., 2021. Association between dispositional empathy and self-other distinction in Irish and Belgian medical students: a cross-sectional analysis. BMJ Open 11 (9), e048597.

Campbell, M., McKenzie, J.E., Sowden, A., Katikireddi, S.V., Brennan, S.E., Ellis, S., Hartmann-Boyce, J., Ryan, R., Shepperd, S., Thomas, J., Welch, V., Thomson, H., 2020. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ 368, l6890.

Chen, R., Capitão, L.P., Cowen, P.J., Harmer, C.J., 2021. Effect of the NMDA receptor partial agonist, D-cycloserine, on emotional processing and autobiographical memory. Psychol. Med. 51 (15), 2657–2665.

Clarke, P.J.F., Van Bockstaele, B., Marinovic, W., Howell, J.A., Boyes, M.E., Notebaert, L., 2020. The effects of left DLPFC tDCS on emotion regulation, biased attention, and emotional reactivity to negative content. Cogn. Affect. Behav. Neurosci. 20 (6), 1323–1335.

Dalgleish, T., Watts, F.N., 1990. Biases of attention and memory in disorders of anxiety and depression. Clin. Psychol. Rev. 10 (5), 589–604.

Dannlowski, U., Ohrmann, P., Bauer, J., Kugel, H., Arolt, V., Heindel, W., Suslow, T., 2007. Amygdala reactivity predicts automatic negative evaluations for facial emotions. Psychiatry Res. 154 (1), 13–20.

Danyeli, L.V., Sen, Z.D., Colic, L., Opel, N., Refisch, A., Blekic, N., Macharadze, T., Kretzschmar, M., Munk, M.J., Gaser, C., Speck, O., Walter, M., Li, M., 2024. Cortical thickness of the posterior cingulate cortex is associated with the ketamine-induced altered sense of self: an ultra-high field MRI study. J. Psychiatr. Res. 172, 136–143.

De Gregorio, D., Aguilar-Valles, A., Preller, K.H., Heifets, B.D., Hibicke, M., Mitchell, J., Gobbi, G., 2021. Hallucinogens in mental health: preclinical and clinical studies on LSD, psilocybin, MDMA, and ketamine. J. Neurosci. 41 (5), 891–900.

de Kleine, R.A., Hendriks, G.J., Kusters, W.J., Broekman, T.G., van Minnen, A., 2012. A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. Biol. Psychiatry 71 (11), 962–968.

Decety, J., Cowell, J.M., 2015. Empathy, justice, and moral behavior. AJOB Neurosci. 6 (3), 3–14.

Doss, M.K., Považan, M., Rosenberg, M.D., Sepeda, N.D., Davis, A.K., Finan, P.H., Smith, G.S., Pekar, J.J., Barker, P.B., Griffiths, R.R., Barrett, F.S., 2021. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. Transl. Psychiatry 11 (1), 574.

Ebert, A., Haussleiter, I.S., Juckel, G., Brune, M., Roser, P., 2012. Impaired facial emotion recognition in a ketamine model of psychosis. Psychiatry Res. 200 (2–3), 724–727.

Edem, E.E., Oguntala, O.A., Ikuelogbon, D.A., Nebo, K.E., Fafure, A.A., Akinluyi, E.T., Isaac, G.T., Kunlere, O.E., 2023. Prolonged ketamine therapy differentially rescues psychobehavioural deficits via modulation of nitro-oxidative stress and oxytocin receptors in the gut-brain-axis of chronically-stressed mice. Psychoneuroendocrinology 158, 106370.

Feduccia, A.A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Mithoefer, M.C., Doblin, R., 2019. Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and Sertraline. Front. Psychiatry 10, 650.

Ferguson, H.J., De Lillo, M., Woodrow-Hill, C., Foley, R., Bradford, E.E.F., 2024. Neural empathy mechanisms are shared for physical and social pain, and increase from adolescence to older adulthood. Soc. Cogn. Affect. Neurosci. 19 (1).

Forsyth, J.K., Bachman, P., Mathalon, D.H., Roach, B.J., Asarnow, R.F., 2015. Augmenting NMDA receptor signaling boosts experience-dependent neuroplasticity in the adult human brain. Proc. Natl. Acad. Sci. U. S. A. 112 (50), 15331–15336.

Fukumoto, K., Iijima, M., Chaki, S., 2016. The antidepressant effects of an mGlu2/3 receptor antagonist and ketamine require AMPA receptor stimulation in the mPFC and subsequent activation of the 5-HT neurons in the DRN. Neuropsychopharmacology 41 (4), 1046–1056.

Gilbert, J.R., Yarrington, J.S., Wills, K.E., Nugent, A.C., Zarate, C.A., 2018. Glutamatergic signaling drives ketamine-mediated response in depression: evidence from dynamic causal modeling. Int. J. Neuropsychopharmacol. 21 (8), 740–747.

Goff, D.C., Herz, L., Posever, T., Shih, V., Tsai, G., Henderson, D.C., Freudenreich, O., Evins, A.E., Yovel, I., Zhang, H., Schoenfeld, D., 2005. A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. Psychopharmacology 179 (1), 144–150. . (Berl).

Goff, D.C., Tsai, G., Levitt, J., Amico, E., Manoach, D., Schoenfeld, D.A., Hayden, D.L., McCarley, R., Coyle, J.T., 1999. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch. Gen. Psychiatry 56 (1), 21–27.

Heifets, B.D., Olson, D.E., 2024. Therapeutic mechanisms of psychedelics and entactogens. Neuropsychopharmacology 49 (1), 104–118.

Henter, I.D., Park, L.T., Zarate, C.A., 2021. Novel glutamatergic modulators for the treatment of mood disorders: current status. CNS Drugs 35 (5), 527–543.

Heresco-Levy, U., Ermilov, M., Shimoni, J., Shapira, B., Silipo, G., Javitt, D.C., 2002. Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia. Am. J. Psychiatry 159 (3), 480–482.

Hess, E.M., Greenstein, D.K., Hutchinson, O.L., Zarate, C.A., Gould, T.D., 2024. Entactogen effects of ketamine: a reverse-translational study. Am. J. Psychiatry 181 (9), 815–823.

Hofmann, S.G., Meuret, A.E., Smits, J.A., Simon, N.M., Pollack, M.H., Eisenmenger, K., Shiekh, M., Otto, M.W., 2006. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. Arch. Gen. Psychiatry 63 (3), 298–304.

Hofmann, S.G., Papini, S., Carpenter, J.K., Otto, M.W., Rosenfield, D., Dutcher, C.D., Dowd, S., Lewis, M., Witcraft, S., Pollack, M.H., Smits, J.A.J., 2019. Effect of D-cycloserine on fear extinction training in adults with social anxiety disorder. PLoS One 14 (10), e0223729.

Hysek, C.M., Schmid, Y., Simmler, L.D., Domes, G., Heinrichs, M., Eisenegger, C., Preller, K.H., Quednow, B.B., Liechti, M.E., 2014. MDMA enhances emotional empathy and prosocial behavior. Soc. Cogn. Affect. Neurosci. 9 (11), 1645–1652.

Ito, T., Yokokawa, K., Yahata, N., Isato, A., Suhara, T., Yamada, M., 2017. Neural basis of negativity bias in the perception of ambiguous facial expression. Sci. Rep. 7 (1), 420.

Kaldewaij, R., Salamone, P.C., Enmalm, A., Östman, L., Pietrzak, M., Karlsson, H., Löfberg, A., Gauffin, E., Samuelsson, M., Gustavson, S., Capusan, A.J., Olausson, H., Heilig, M., Boehme, R., 2024. Ketamine reduces the neural distinction between self- and other-produced affective touch: a randomized double-blind placebo-controlled study. Neuropsychopharmacology 49 (11), 1767–1774.

Kiani, Z., Farkhondeh, T., Aramjoo, H., Aschner, M., Beydokhti, H., Esmaeili, A., Arab-Zozani, M., Samarghandian, S., 2023. Oxytocin effect in adult patients with Autism: an updated systematic review and meta-analysis of randomized controlled trials. CNS. Neurol. Disord. Drug Targets 22 (6), 906–915.

Kupferberg, A., Hasler, G., 2024. From antidepressants and psychotherapy to oxytocin, vagus nerve stimulation, ketamine and psychedelics: how established and novel treatments can improve social functioning in major depression. Front. Psychiatry 15, 1372650.
Lamm, C., Bukowski, H., Silani, G., 2016. From shared to distinct self-other representations in empathy: evidence from neurotypical function and socio-cognitive disorders. Philos. Trans. R. Soc. Lond. B Biol. Sci. 371 (1686), 20150083.
Lamm, C., Rütgen, M., Wagner, I.C., 2019. Imaging empathy and prosocial emotions. Neurosci. Lett. 693, 49–53.
Lehmann, M., Seifritz, E., Henning, A., Walter, M., Böker, H., Scheidegger, M., Grimm, S., 2016. Differential effects of rumination and distraction on ketamine induced modulation of resting state functional connectivity and reactivity of regions within the default-mode network. Soc. Cogn. Affect. Neurosci. 11 (8), 1227–1235.
Li, M., Woelfer, M., Colic, L., Safron, A., Chang, C., Heinze, H.J., Speck, O., Mayberg, H. S., Biswal, B.B., Salvadore, G., Fejtova, A., Walter, M., 2020. Default mode network connectivity change corresponds to ketamine's delayed glutamatergic effects. Eur. Arch. Psychiatry Clin. Neurosci. 270 (2), 207–216.
Lockwood, P.L., Apps, M.A., Valton, V., Viding, E., Roiser, J.P., 2016. Neurocomputational mechanisms of prosocial learning and links to empathy. Proc. Natl. Acad. Sci. U. S. A. 113 (35), 9763–9768.
Loureiro, J.R.A., Leaver, A., Vasavada, M., Sahib, A.K., Kubicki, A., Joshi, S., Woods, R. P., Wade, B., Congdon, E., Espinoza, R., Narr, K.L., 2020. Modulation of amygdala reactivity following rapidly acting interventions for major depression. Hum. Brain Mapp. 41 (7), 1699–1710.
Luengo Kanacri, B.P., Eisenberg, N., Tramontano, C., Zuffiano, A., Caprara, M.G., Regner, E., Zhu, L., Pastorelli, C., Caprara, G.V., 2021. Measuring prosocial behaviors: psychometric properties and cross-national validation of the prosociality scale in five countries. Front. Psychol. 12, 693174.
, Jr. Lundin, N.B., Sepe-Forrest, L., Gilbert, J.R., Carver, F.W., Furey, M.L., Zarate, C.A., Nugent, A.C., 2021. Ketamine alters electrophysiological responses to emotional faces in major depressive disorder J. Affect. Disord. 279, 239–249.
Ma, Y., 2015. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. Mol. Psychiatry 20 (3), 311–319.
Marsh, A.A., Kozak, M.N., Ambady, N., 2007. Accurate identification of fear facial expressions predicts prosocial behavior. Emotion 7 (2), 239–251.
McDonald, B., Kanske, P., 2023. Gender differences in empathy, compassion, and prosocial donations, but not theory of mind in a naturalistic social task. Sci. Rep. 13 (1), 20748.
Moola, S., Munn, Z., Tufanaru, C., Aromataris, E., Sears, K., Sfetcu, R., Currie, M., Lisy, K., Qureshi, R., Mattis, P., Mu, P., 2020. In: Aromataris, E., LC., P.K., Pilla, B., Jordan, Z. (Eds.), Systematic reviews of etiology and risk. BI Manual for Evidence Synthesis. JBI.
Murrough, J.W., Collins, K.A., Fields, J., DeWilde, K.E., Phillips, M.L., Mathew, S.J., Wong, E., Tang, C.Y., Charney, D.S., Iosifescu, D.V., 2015. Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. Transl. Psychiatry 5 (2), e509.
Neumann, D.L., Chan, R.C.K., Boyle, G.J., Wang, Y., Rae Westbury, H., 2015. Measures of Empathy. Measures of Personality and Social Psychological Constructs, pp. 257–289.
Norbury, A., Rutter, S.B., Collins, A.B., Costi, S., Jha, M.K., Horn, S.R., Kautz, M., Corniquel, M., Collins, K.A., Glasgow, A.M., Brallier, J., Shin, L.M., Charney, D.S., Murrough, J.W., Feder, A., 2021. Neuroimaging correlates and predictors of response to repeated-dose intravenous ketamine in PTSD: preliminary evidence. Neuropsychopharmacology 46 (13), 2266–2277.
Nowacki, J., Wingenfeld, K., Kaczmarczyk, M., Chae, W.R., Abu-Tir, I., Deuter, C.E., Piber, D., Hellmann-Regen, J., Otte, C., 2020. Cognitive and emotional empathy after stimulation of brain mineralocorticoid and NMDA receptors in patients with major depression and healthy controls. Neuropsychopharmacology 45 (13), 2155–2161.
Nowacki, J., Wingenfeld, K., Kaczmarczyk, M., Chae, W.R., Salchow, P., Deuter, C.E., Piber, D., Otte, C., 2021. Selective attention to emotional stimuli and emotion recognition in patients with major depression: the role of mineralocorticoid and glutamatergic NMDA receptors. J. Psychopharmacol. 35 (8), 1017–1023.
Olivola, M., Arienti, V., Bassetti, N., Civardi, S., Brondino, N., 2022. Use of intranasal esketamine in a girl with treatment-resistant depression and autism spectrum disorders: a case report. EXCLI J. 21, 540–543.
Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5 (1), 210.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71.
Palhano-Fontes, F., Andrade, K.C., Tofoli, L.F., Santos, A.C., Crippa, J.A., Hallak, J.E., Ribeiro, S., de Araujo, D.B., 2015. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. PLoS One 10 (2), e0118143.
Pettorruso, M., Guidotti, R., d'Andrea, G., De Risio, L., D'Andrea, A., Chiappini, S., Carullo, R., Barlati, S., Zanardi, R., Rosso, G., De Filippis, S., Di Nicola, M., Andriola, I., Marcatili, M., Nicolò, G., Martiadis, V., Bassetti, R., Nucifora, D., De Fazio, P., Rosenblat, J.D., Clerici, M., Maria Dell'Osso, B., Vita, A., Marzetti, L., Sensi, S.L., Di Lorenzo, G., McIntyre, R.S., Martinotti, G., 2023. Predicting outcome with Intranasal Esketamine treatment: a machine-learning, three-month study in Treatment-Resistant Depression (ESK-LEARNING). Psychiatry Res. 327, 115378.
Reed, J.L., Nugent, A.C., Furey, M.L., Szczepanik, J.E., Evans, J.W., Zarate, C.A., 2019. Effects of ketamine on brain activity during emotional processing: differential findings in depressed versus healthy control participants. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4 (7), 610–618.
Rein, B., Raymond, K., Boustani, C., Tuy, S., Zhang, J., St Laurent, R., Pomrenze, M.B., Boroon, P., Heifets, B., Smith, M., Malenka, R.C., 2024. MDMA enhances empathy-like behaviors in mice via 5-HT release in the nucleus accumbens. Sci. Adv. 10 (17), eadl6554.
Sabe, M., Zhao, N., Crippa, A., Strauss, G.P., Kaiser, S., 2021. Intranasal oxytocin for negative symptoms of schizophrenia: systematic review, meta-analysis, and dose-response meta-analysis of randomized controlled trials. Int. J. Neuropsychopharmacol. 24 (8), 601–614.
Scheidegger, M., Henning, A., Walter, M., Boeker, H., Weigand, A., Seifritz, E., Grimm, S., 2016a. Effects of ketamine on cognition-emotion interaction in the brain. Neuroimage 124 (Pt A), 8–15.
Scheidegger, M., Henning, A., Walter, M., Lehmann, M., Kraehenmann, R., Boeker, H., Seifritz, E., Grimm, S., 2016b. Ketamine administration reduces amygdalo-hippocampal reactivity to emotional stimulation. Hum. Brain Mapp. 37 (5), 1941–1952.
Scheidegger, M., Walter, M., Lehmann, M., Metzger, C., Grimm, S., Boeker, H., Boesiger, P., Henning, A., Seifritz, E., 2012. Ketamine decreases resting state functional network connectivity in healthy subjects: implications for antidepressant drug action. PLoS One 7 (9), e44799.
Schmidt, A., Kometer, M., Bachmann, R., Seifritz, E., Vollenweider, F., 2013. The NMDA antagonist ketamine and the 5-HT agonist psilocybin produce dissociable effects on structural encoding of emotional face expressions. Psychopharmacology 225 (1), 227–239. . (Berl).
Shahrour, G., Sohail, K., Elrais, S., Khan, M.H., Javeid, J., Samdani, K., Mansoor, H., Hussain, S.I., Sharma, D., Ehsan, M., Nashwan, A.J., 2024. MDMA-assisted psychotherapy for the treatment of PTSD: a systematic review and meta-analysis of randomized controlled trials (RCTs). Neuropsychopharmacol. Rep. 44 (4), 672–681.
Shiroma, P.R., Albott, C.S., Johns, B., Thuras, P., Wels, J., Lim, K.O., 2015. The effect of repeated ketamine infusion over facial emotion recognition in treatment-resistant depression: a preliminary report. J. Neuropsychiatry Clin. Neurosci. 27 (4), 362–364.
Silani, G., Lamm, C., Ruff, C.C., Singer, T., 2013. Right supramarginal gyrus is crucial to overcome emotional egocentricity bias in social judgments. J. Neurosci. 33 (39), 15466–15476.
Starr, H.L., Abell, J., Larish, A., Lewis, S., DeMuro, C., Gogate, J., Jamieson, C., Daly, E., Zaki, N., Kramer, M., 2020. Self-reported review of the value of esketamine in patients with treatment-resistant depression: understanding the patient experience in the STRIVE Study. Psychiatry Res. 293, 113376.
Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.-W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F., Higgins, J.P., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919.
Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C. J., Cheng, H.Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernán, M.A., Hopewell, S., Hróbjartsson, A., Junqueira, D.R., Jüni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898.
Sterpenich, V., Vidal, S., Hofmeister, J., Michalopoulos, G., Bancila, V., Warrot, D., Dayer, A., Desseilles, M., Aubry, J.M., Kosel, M., Schwartz, S., Vutskits, L., 2019. Increased reactivity of the mesolimbic reward system after ketamine injection in patients with treatment-resistant major depressive disorder. Anesthesiology 130 (6), 923–935.
Stevens, F., Taber, K., 2021. The neuroscience of empathy and compassion in pro-social behavior. Neuropsychologia 159, 107925.
Stocker, K., Liechti, M.E., 2024. Methylenedioxymethamphetamine is a connectogen with empathogenic, entactogenic, and still further connective properties: it is time to reconcile "the great entactogen-empathogen debate". J. Psychopharmacol. 38 (8), 685–689.
Takiguchi, K., Uezato, A., Itasaka, M., Atsuta, H., Narushima, K., Yamamoto, N., Kurumaji, A., Tomita, M., Oshima, K., Shoda, K., Tamaru, M., Nakataki, M., Okazaki, M., Ishiwata, S., Ishiwata, Y., Yasuhara, M., Arima, K., Ohmori, T., Nishikawa, T., 2017. Association of schizophrenia onset age and white matter integrity with treatment effect of D-cycloserine: a randomized placebo-controlled double-blind crossover study. BMC Psychiatry 17 (1), 249.
Thai, M., Basgoze, Z., Klimes-Dougan, B., Mueller, B.A., Fiecas, M., Lim, K.O., Albott, C. S., Cullen, K.R., 2020. Neural and behavioral correlates of clinical improvement to ketamine in adolescents with treatment resistant depression. Front. Psychiatry 11, 820.
Urbano, M., Okwara, L., Manser, P., Hartmann, K., Deutsch, S.I., 2015. A trial of D-cycloserine to treat the social deficit in older adolescents and young adults with autism spectrum disorders. J. Neuropsychiatry Clin. Neurosci. 27 (2), 133–138.
Urbano, M., Okwara, L., Manser, P., Hartmann, K., Herndon, A., Deutsch, S.I., 2014. A trial of D-cycloserine to treat stereotypies in older adolescents and young adults with autism spectrum disorder. Clin. Neuropharmacol. 37 (3), 69–72.
van Buuren, M., Sijtsma, H., Lute, N., van Rijn, R., Hollarek, M., Walsh, R.J., Lee, N.C., Krabbendam, L., 2022. Development of the neural correlates of self- and other-referential processing across adolescence. Neuroimage 252, 119032.
Vestring, S., Dorner, A., Scholliers, J., Ehrenberger, K., Kiss, A., Arenz, L., Theiss, A., Rossner, P., Frase, S., Du Vinage, C., Wendler, E., Serchov, T., Domschke, K.,

Bischofberger, J., Normann, C., 2024. D-cycloserine enhances the bidirectional range of NMDAR-dependent hippocampal synaptic plasticity. Transl. Psychiatry 14 (1), 18.
Vlachos, I.I., Papageorgiou, C., Margariti, M., 2020. Neurobiological trajectories involving social isolation in PTSD: a systematic review. Brain Sci. 10 (3).
Weigand, A., Gartner, M., Scheidegger, M., Wyss, P.O., Henning, A., Seifritz, E., Stippl, A., Herrera-Melendez, A., Bajbouj, M., Aust, S., Grimm, S., 2022. Predicting antidepressant effects of ketamine: the role of the pregenual anterior cingulate cortex as a multimodal neuroimaging biomarker. Int. J. Neuropsychopharmacol. 25 (12), 1003–1013.
Wendt, F.R., Warrier, V., Pathak, G.A., Koenen, K.C., Stein, M.B., Krystal, J.H., Pietrzak, R.H., Gelernter, J., Goldfarb, E.V., Baron-Cohen, S., Polimanti, R., 2022. Polygenic scores for empathy associate with posttraumatic stress severity in response to certain traumatic events. Neurobiol. Stress. 17, 100439.
Wu, Y.E., Hong, W., 2022. Neural basis of prosocial behavior. Trends Neurosci. 45 (10), 749–762.
Wu, Z., Gan, Y., Li, N., Lan, X., Wang, C., Zhang, F., Liu, H., Li, W., Ye, Y., Hu, Z., Ning, Y., Zhou, Y., 2023. Pain mediates the improvement of social functions of repeated intravenous ketamine in patients with unipolar and bipolar depression. J. Affect. Disord. 334, 152–158.
, Jr. 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.