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Ketamine Improves Anhedonic Phenotypes Across Species: Translational Evidence From the Probabilistic Reward Task

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ABSTRACT

BACKGROUND: Ketamine is increasingly used as a therapeutic option for treatment-resistant depression (TRD) due to its rapid antidepressant properties; however, the mechanisms underlying these effects remain elusive. Preclinical evidence suggests ketamine acts on neural pathways implicated in reward processing, but translational efforts have proven challenging due to a lack of paradigms allowing for analogous assessment of depressive phenotypes across species.

METHODS: We investigated the effects of a single, subanesthetic dose of ketamine on reward responsiveness in individuals with TRD (0.5 mg/kg) and rats exposed to chronic stress (10 mg/kg) using functionally identical tasks. Humans completed the Probabilistic Reward Task (PRT) twice within 48 hours, either without intervention (healthy control [HC] participants, n = 36, 26 women) or 24 hours before and after ketamine administration (individuals with TRD, n = 24, 16 women). Rats (all male) completed a reverse-translated version of the PRT on 3 consecutive days (HC group, n = 10) or before and after chronic stress exposure as well as 2 hours and 24 hours after ketamine administration (experimental group, n = 10).

RESULTS: Ketamine significantly increased response bias toward the more frequently rewarded stimulus in both species, resulting in levels comparable with HCs 24 hours postadministration. Exploratory analyses in humans suggested that this effect was strongest among individuals with more pronounced baseline anhedonia. Furthermore, in both species, ketamine had no effect on measures of discriminability, suggesting that ketamine selectively improved reward learning rather than overall task performance.

CONCLUSIONS: Results highlight a shared behavioral mechanism through which ketamine alleviates anhedonic behaviors and offers important implications for the treatment of people with anhedonia in TRD and related psychopathologies.

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Despite continued research on the neurobiology and treatment of major depressive disorder (MDD), approximately 30% of individuals with depression do not benefit from multiple treatment options within a given depressive episode and thus are considered to have treatment-resistant depression (TRD) (1,2). TRD is associated with increased rates of hospitalization and suicidality as well as an overall reduced quality of life, emphasizing the need to identify effective interventions (3). Following reports of rapid antidepressant effects of ketamine, a noncompetitive NMDA receptor antagonist (4), recent work has evaluated the therapeutic use of ketamine in TRD (5–9). However, whereas the acute clinical effects of ketamine are well-characterized, its effects on cognitive, behavioral, or affective mechanisms that may modulate its antidepressive response remain poorly understood.

Ketamine has been proposed to be particularly effective for alleviating anhedonia, defined as the lack of interest in or pleasure from previously enjoyable activities and one of the cardinal symptoms of MDD (5,10–16). Anhedonia is associated with altered reward processing, including reduced responsiveness to anticipated or received rewards and impaired learning from rewarding outcomes (17,18). Critically, symptoms of anhedonia are generally not improved by common frontline pharmacological treatments, such as selective serotonin reuptake inhibitors (19,20). In contrast, ketamine, administered either intravenously as racemic (*R,S*)-ketamine or intranasally as esketamine (the [*S*]-enantiomer of ketamine), has been shown to reduce self-reported and clinician-assessed anhedonia within hours (6,14,21,22). Moreover, preclinical work and neuroimaging studies have highlighted

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rapid and widespread effects of ketamine on brain structures associated with reward processing, including the anterior cingulate cortex (ACC), ventromedial prefrontal cortex, orbitofrontal cortex, nucleus accumbens, and (lateral) habenula, as well as changes in activity, connectivity, and synchronicity of large-scale brain networks (6,23–32). These changes are thought to be mediated by molecular mechanisms that ultimately result in increased dopaminergic tone in mesocorticolimbic pathways critical for reward learning and incentive motivation (8,33–35).

The current understanding of the mechanisms underlying antidepressant effects of ketamine stems primarily from preclinical models, and it is unclear whether these findings apply to humans. A major challenge in translational efforts is the lack of behavioral end points that are functionally analogous across species (36,37). For example, human studies often use changes in self-reported symptom severity to highlight treatment success (5,6,21). Conversely, common experimental paradigms probing anhedonic-like phenotypes in animals (e.g., intracranial self-stimulation) cannot easily be used with humans (38).

To address this issue, we recently reverse-translated the Probabilistic Reward Task (PRT), an established paradigm to investigate reward learning in humans (39) and a recommended task within the Positive Valence Systems in the Research Domain Criteria framework (40), for rodents and nonhuman primates (41–43). In the PRT, subjects make relatively difficult visual discriminations between 2 stimuli. Importantly, unbeknownst to subjects, correct responses to one stimulus are rewarded 3 times more frequently (rich stimulus) than correct responses to the other stimulus (lean stimulus). Among healthy humans and laboratory animals, this asymmetrical reinforcement schedule reliably induces a response bias toward the rich stimulus (44). Conversely, humans with anhedonia and animals exposed to early-life adversity or chronic stress display blunted response bias (45–50).

Leveraging the PRT, in this study we aimed to investigate whether a single, subanesthetic dose of ketamine would enhance reward responsiveness in individuals with TRD and rats with anhedonic phenotypes. Therefore, before receiving a single dose of ketamine, rats were exposed to a validated chronic stress paradigm known to induce anhedonic-like behavior in the PRT (45). Their PRT performance before and after stress exposure as well as after ketamine administration was compared with that of unstressed control rats. Similarly, we tested response bias in treatment-seeking individuals with TRD 24 hours before and 24 hours after their first administration of ketamine and compared their performance to healthy control (HC) participants.

Based on prior findings (15,16,21,51), we hypothesized that ketamine would lead to a rapid prohedonic effect (i.e., significantly increased response bias) in both species. In rats, we expected that ketamine would rescue the experimentally induced reduction in response bias in the chronic stress group, with a return to levels observed at the prestress baseline and comparable with those in nonstressed control animals. For participants with TRD, we expected a decrease in self-reported depressive symptom severity following ketamine treatment. Furthermore, we expected a lower response bias in participants with TRD during their first session (i.e., pretreatment) compared with HC participants and an increase in response bias in their second session (i.e., posttreatment) to levels comparable with those of HC participants. Finally, we explored whether treatment-related changes in response bias were correlated with individual differences in self-reported depressive symptoms, especially anhedonia, both at baseline and across sessions.

METHODS AND MATERIALS

Animals

Twenty adult male Long-Evans rats weighing approximately 200 g were obtained from Charles River Laboratories. The study protocol (also see the Supplement) was approved by the Institutional Animal Care and Use Committee at McLean Hospital in accordance with established guidelines (52).

Human Participants

As part of a larger study (clinical trial: NCT04239963), we recruited 24 individuals with TRD (16 female, 8 male, mean ± SD age = 44.35 ± 15.86 years, range = 21–69 years) through McLean Hospital's ketamine service and 36 psychologically healthy control participants (26 female, 10 male, mean ± SD age = 33.18 ± 14.49 years, range = 19–68 years) from the Greater Boston area. All participants were ketamine-naive and screened for depressive symptoms prior to the beginning of the study using the Mini International Neuropsychiatric Interview (53) and the Hamilton Depressive Rating Scale (HAMD) (54). Participants also completed the Beck Depression Inventory (BDI-II) (55), Quick Inventory of Depressive Symptomatology (QIDS) (56), and Snaith-Hamilton Pleasure Scale (SHAPS) (57). To ensure PRT data quality, well-established quality checks were applied (58,59), resulting in the exclusion of 8 HC participants and 6 participants with TRD for a final sample size of $N = 46$ (28 HC, 18 TRD). Demographic and clinical characteristics are summarized in Table 1 (also see Supplement).

All participants provided written informed consent prior to participation and received monetary compensation of $75 for the screening visit and either $75 or $125/day for the experimental sessions (remuneration increased partway through the study to aid recruitment). Study procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Massachusetts General Brigham Healthcare Institutional Review Board.

Drug

For the rat protocol, ketamine hydrochloride was obtained from Sigma-Aldrich, dissolved in 0.9% saline solution, and administered through subcutaneous injection in volumes of 0.5 mL or less 2 hours before the experimental session. The dose (10 mg/kg) was based on 1) previous studies indicating its approximation in rats with the clinically efficacious outcomes in humans (60–62) and 2) its production of peak prohedonic effects in previous rat PRT studies (51).

Human participants received a subanesthetic ketamine dose of 0.5 mg/kg, delivered intravenously over 40 minutes. This procedure is consistent with earlier human ketamine

Table 1. Demographic and Clinical Characteristics (Human Samples)

	HC, *n* = 28	TRD, *n* = 18	t/χ^2	*p*
Screening Session				
Female	22 (78.6%)	12 (66.7%)	$\chi^2_1 = 0.31$	.580
Age, years	33.49 ± 14.36	45.42 ± 16.62	$t_{32.52} = -2.50$	.018*
Education, years	16.29 ± 4.23	16.78 ± 3.56	$t_{40.77} = -0.42$	.673
Asian	10 (35.7%)	–	–	–
White	18 (64.3%)	18 (100%)	$\chi^2_1 = 6.90$	.009**
HAMD	0.21 ± 0.49	16.89 ± 4.86	$t_{17.22} = -14.09$	<.001***
QIDS	0.11 ± 0.31	15.56 ± 3.29	$t_{17.19} = -19.43$	<.001***
BDI-II	0.86 ± 1.43	35.78 ± 6.66	$t_{18.02} = -21.91$	<.001***
SHAPS	19.89 ± 6.29	38.88 ± 5.29	$t_{38.21} = -10.63$	<.001***
First Experimental Session (24 h Preketamine for TRD Group)				
HAMD	0.33 ± 0.78	14.83 ± 4.27	$t_{17.77} = -14.24$	<.001***,[a]
QIDS	0.15 ± 0.46	13.24 ± 3.73	$t_{16.30} = -14.38$	<.001***,[a]
BDI-II	0.70 ± 1.14	33.47 ± 8.79	$t_{16.34} = -15.29$	<.001***,[a]
SHAPS	18.86 ± 5.45	37.33 ± 6.22	$t_{32.90} = -10.31$	<.001***,[a]
Second Experimental Session (24 h Postketamine for TRD Group)				
HAMD	0.18 ± 0.61	10.24 ± 5.12	$t_{16.28} = -8.07$	<.001***,[a]
QIDS	0.21 ± 0.63	8.59 ± 4.35	$t_{16.41} = -7.90$	<.001***,[a]
BDI-II	0.62 ± 1.13	27.50 ± 9.85	$t_{17.31} = -11.53$	<.001***,[a]
SHAPS	19.57 ± 5.95	35.06 ± 6.50	$t_{34.03} = -8.14$	<.001***,[a]

Values are presented as mean ± SD or *n* (%). Statistical differences refer to comparisons between HC and TRD groups.

**p* < .05, ***p* < .01, ****p* < .001.

ANOVA, analysis of variance; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; HC, healthy control; QIDS, Quick Inventory of Depressive Symptomatology; SHAPS, Snaith-Hamilton Pleasure Scale; TRD, treatment-resistant depression.

[a] Bonferroni-corrected *p* values for post hoc *t* tests following a 2-way ANOVA (group × session).

treatment studies (7,63) and followed current recommendations (64), highlighting this dose as being effective, safe, well-tolerated, and leading to no/minimal general anesthetic effects, respiratory problems, or cognitive impairments 24 hours postadministration (65,66). Injections were administered at McLean Hospital's ketamine service as part of patients' treatment plan.

Probabilistic Reward Task

Procedures for the human PRT have been described elsewhere (39,49) (Figure 1). Briefly, participants completed 3 blocks of 100 trials each in which they were presented with schematic face stimuli featuring a long (13.0 mm) or short (11.5 mm) mouth. Participants were asked to indicate the length of the mouth stimulus by button press as fast as possible. Importantly, the reward schedule in the PRT was asymmetrical, so that correct responses to one stimulus (rich stimulus, 60%) were rewarded 3 times more often compared with the other (lean stimulus, 20%). Conditions (i.e., whether long or short stimuli were assigned to rich or lean) and keys assigned to rich and lean stimuli were counterbalanced across participants and sessions.

For the rat version, subjects completed the PRT in a touch-sensitive experimental chamber (Figure 1) (41,43,47,67). In each session, rats were presented with 100 stimuli that varied in line length (long line: 600 × 60 px/31.5 × 3.25 cm; short line: 200 × 60 px/10.5 × 3.25 cm). As in the human version, reward contingencies were asymmetrical with a 3:1 ratio (rich stimuli: 60% vs. lean stimuli: 20%).

For both PRT versions, the primary measure of interest was response bias, which was computed following classic signal detection theory (44,68,69) (equation 1):

$$\log b = 0.5 * \log\left(\frac{(Rich_{Correct} + 0.5) * (Lean_{Incorrect} + 0.5)}{(Rich_{Incorrect} + 0.5) * (Lean_{Correct} + 0.5)}\right) \tag{1}$$

Discriminability, which assesses task difficulty, served as control variable and was computed as (equation 2):

$$\log d = 0.5 * \log\left(\frac{(Rich_{Correct} + 0.5) * (Lean_{Correct} + 0.5)}{(Rich_{Incorrect} + 0.5) * (Lean_{Incorrect} + 0.5)}\right) \tag{2}$$

A constant of 0.5 was used to allow log-transformation and avoid division by zero in cases where there are no responses to a given category (70).

Procedure

Rats were trained in the PRT using previously published protocols (41) (see Supplement for full procedure) until discrimination accuracy reached ≥80% for 2 consecutive sessions. Then, animals were assigned to either testing conditions without programmed stress (*n* = 10, HC group) or conditions of ongoing chronic stress (*n* = 10, anhedonic phenotype group). For the former, PRT testing consisted of 3 daily 100-trial sessions. For the latter, prestress baseline PRT performance was examined during one session before animals were exposed to chronic inescapable ice water stress (45) daily until a blunted response bias (i.e., at least half of the subject's prestress baseline value) was observed in the PRT. The following day, during continued chronic stress exposure, rats received ketamine 30 minutes after stress exposure and 2 hours before behavioral testing. The stress procedure continued the next day, followed by another PRT test session, to examine the effects of ketamine treatment on PRT metrics 24 hours postadministration.

Human participants completed 2 testing sessions (2.5 hours each) separated by 48 hours. For participants with TRD, sessions were scheduled 24 hours before and 24 hours after administration of their first dose of ketamine. Healthy participants did not receive any intervention between the 2 sessions.

Data Analysis

Analyses were performed in R (version 4.2.2) using RStudio (version 2022.12.0) and the tidyr (version 1.1.3) (71), rstatix (version 0.7.2) (72), lme4 (version 1.1-37) (73), and lmerTest (version 3.1-3-2) packages (74). Questionnaire and interview scores for human participants were analyzed using mixed-model analyses of variance with group (TRD vs. HC) as between-subjects factor and session (first vs. second) as within-subjects factor. Linear mixed effects regression models were used to analyze changes in response bias and discriminability in the PRT across groups and between sessions. Rat

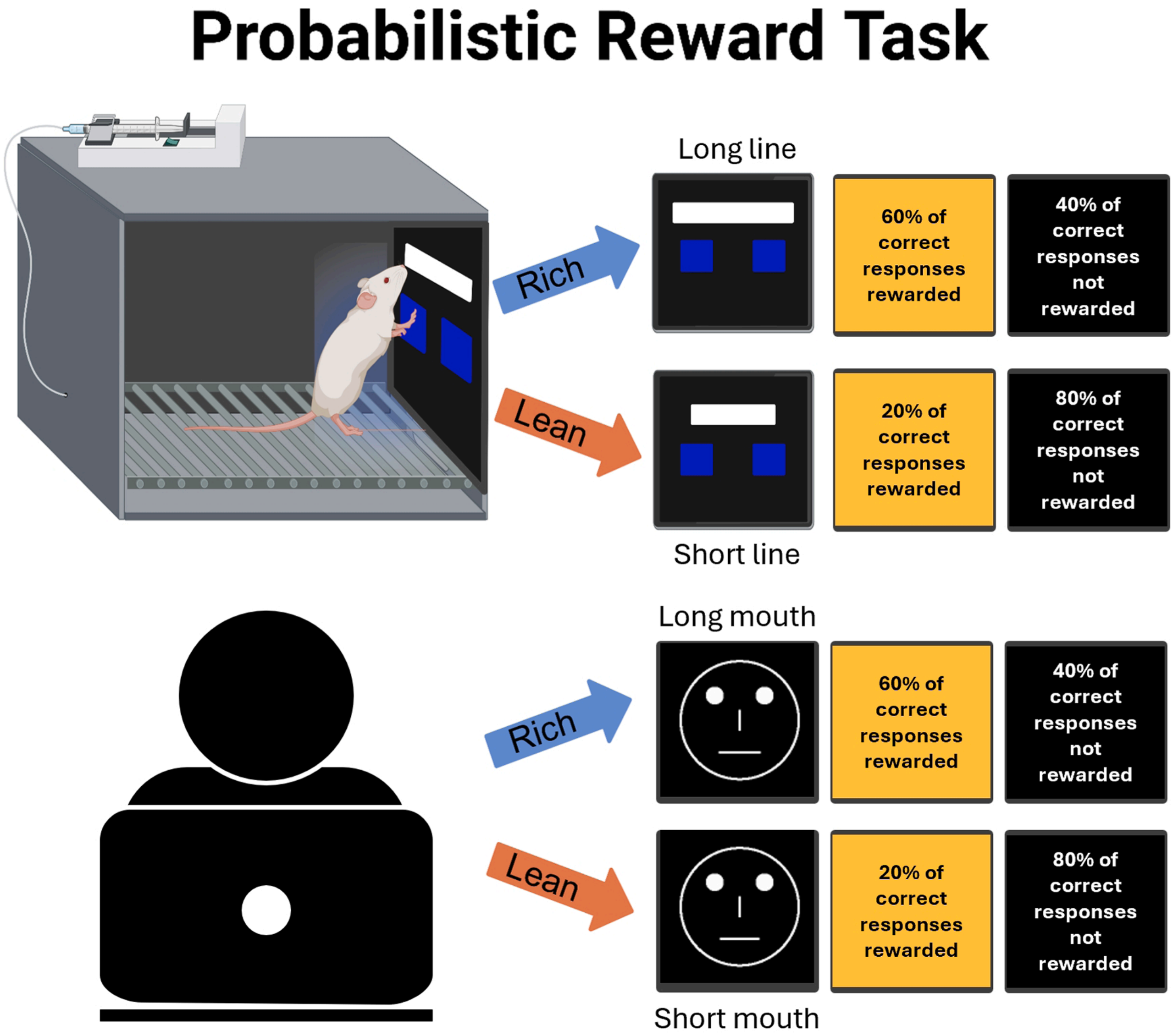

Figure 1. The human and rat version of the Probabilistic Reward Task. Rats responded to short or long line stimuli presented on a touchscreen. Humans judged the length of the mouth stimulus of a schematic face presented on a computer screen. Across species, identical asymmetrical reward schedules (3:1) were used to induce a response bias toward the more frequently rewarded stimulus.

and human data were analyzed separately. To align the analysis approach across species, we chose a similar dummy-coding scheme for both data sets. Specifically, we defined the clinical phenotype (i.e., chronically stressed rats and participants with TRD) as the baseline category for the group predictor and the first testing session (i.e., prestress in rats/pretreatment in humans) as the baseline category for the session predictor. In this operationalization, effects of group and session in both rats and humans can be similarly interpreted as changes in response bias or discriminability from the respective baseline category, i.e., the clinical group at their first testing session (75–77). Note that the number of testing sessions was asymmetrical in the rat sample (stressed group: 4 sessions, control group: 3 sessions). Thus, although our models allow assessments of changes in outcomes across all time points in the stressed group, there was no comparison between groups for one of them (here, we chose this time point to be the 2-hour postinjection session in the stress group). For humans, we also included a linear block term in the model (coded as −0.5, 0, 0.5 for blocks 1, 2, and 3, respectively). Regression models included all main and interaction terms as fixed effects as well as a random intercept. Additional regression models controlling for age indicated no significant effect of age on any outcome measure and did not change the significance level of any of the other predictors in the models (Table S3). Finally, we conducted exploratory analyses probing potential moderating effects of self-reported depressive symptoms on the relationship between ketamine and response bias. To this end, we added baseline questionnaire scores and the change in scores between sessions in the regression analyses described above.

RESULTS

Rats

Regression analyses suggested that, at baseline, rats in the stress group displayed a slightly larger response bias than the control group ($p = .049$; full results in Table 2, Figure 2A). As expected, response bias in all rats in the stress group was significantly reduced following 3.9 (±0.4) days of chronic stress exposure (session_stress: $p < .001$), an effect not seen in unstressed rats (group × session_stress: $p < .001$). Critically, after ketamine injection, stressed rats' response bias returned to levels comparable with their baseline (session_2_hours and session_24_hours: $p = .092$ and $p = .421$, respectively). Both groups showed similar degrees of change from their first to their last session (group × session_24_hours: $p = .505$). A targeted post hoc comparison using a 2-sample Welch's t test indicated that response bias in stressed rats was not significantly different from response bias during the third PRT session of the unstressed rats at 24 hours postinjection ($t_{11.36} = 2.16$, $p = .053$).

Discriminability did not differ between groups at baseline (group: $p = .659$) and was unaffected by chronic stress exposure (session_stress: $p = .167$), indicating that stress led to a specific reduction in reward responsiveness in stressed rats but not in their general ability to perform the task (Figure 2B). Ketamine injection enhanced discriminability acutely at 2 hours postinjection (session_2_hours: $p = .001$), but levels largely returned to baseline at the 24-hour mark (session_24_hours: $p = .087$). No group effects emerged for discriminability in later sessions (all $ps > .386$), suggesting that discriminability remained similarly stable in both groups over time (note that the increased discriminability in stressed rats 2 hours postinjection has no direct comparison in healthy subjects per our modeling choices). We also analyzed the effects of ketamine on subjects' response times (RTs) in the PRT (for results, see Table S1, Figure S1).

Humans

Effects of Ketamine on Self-Reported Depressive Symptoms and PRT Behavior. First, we examined whether ketamine affected self-reported depressive symptom severity scores. Reduction in symptoms were observed for all measures 24 hours after the first dose (for mean scores, see Table 1). Participants with TRD scored higher on all measures compared with HC participants (group, HAMD: $F_{1,42} = 260.99$, $p < .001$, $\eta^2 = 0.81$; QIDS: $F_{1,41} = 306.35$, $p < .001$, $\eta^2 = 0.81$; BDI-II: $F_{1,40} = 362.19$, $p < .001$, $\eta^2 = 0.86$; SHAPS: $F_{1,44} = 99.16$, $p < .001$, $\eta^2 = 0.69$). Across all participants, we saw reductions in scores for HAMD ($F_{1,42} = 18.46$, $p < .001$, $\eta^2 = 0.13$), QIDS ($F_{1,41} = 18.81$, $p < .001$, $\eta^2 = 0.17$), and BDI-II ($F_{1,40} = 7.31$, $p = .010$, $\eta^2 = 0.06$), but not SHAPS scores ($F_{1,44} = 1.77$, $p = .191$, $\eta^2 = 0.01$), indicated by main effects of session. Critically, we found significant group × session interaction effects for all measures (HAMD: $F_{1,42} = 16.14$, $p < .001$, $\eta^2 = 0.11$; QIDS: $F_{1,41} = 20.05$, $p < .001$, $\eta^2 = 0.17$; BDI-II: $F_{1,40} = 7.11$, $p = .011$, $\eta^2 = 0.05$; SHAPS: $F_{1,44} = 6.47$, $p = .015$, $\eta^2 = 0.02$). Bonferroni-corrected post hoc comparisons revealed that these interactions represented selective decreases in HAMD (HC: corrected $t_{26} = 1.44$, $p_{\mathit{adjusted}\ (\mathrm{adj})} = .161$, TRD: corrected $t_{16} = 3.30$, $p_{\mathrm{adj}} = .005$), QIDS (HC: corrected $t_{26} = -1.00$, $p_{\mathrm{adj}} = .327$, TRD: corrected $t_{15} = 3.38$, $p_{\mathrm{adj}} = .004$), and BDI-II (HC: corrected $t_{24} = 0.44$, $p_{\mathrm{adj}} = .664$, TRD: corrected $t_{16} = 2.20$, $p_{\mathrm{adj}} = .043$) scores for the TRD participants in session 2 (i.e., after receiving ketamine) but not for HC participants. The same pattern was also observed for SHAPS scores, but the direct comparison did not quite reach the threshold for statistical significance (HC: corrected $t_{27} = -1.28$, $p_{\mathrm{adj}} = .210$, TRD: corrected $t_{17} = 1.91$, $p_{\mathrm{adj}} = .073$).

Table 2. Results From Dummy-Coded Linear Mixed Model Regressions on Response Bias and Discriminability in Rats and Humans

Predictor	*b* (SE)	*t*	*p*
Rats			
Response Bias			
Intercept	0.401 (0.043)	$t_{52.569} = 9.424$	<.001***
Group	−0.121 (0.060)	$t_{52.569} = -2.011$	.049*
Session_stress	−0.253 (0.050)	$t_{46.506} = -5.010$	<.001***
Session_2_hours	0.087 (0.050)	$t_{46.506} = 1.723$	.092
Session_24_hours	0.041 (0.050)	$t_{46.506} = 0.812$	.421
Group × session_stress	0.273 (0.071)	$t_{46.506} = 3.823$	<.001***
Group × session_24_hours	−0.048 (0.071)	$t_{46.506} = -0.672$	.505
Discriminability			
Intercept	0.742 (0.081)	$t_{40.440} = 9.149$	<.001***
Group	0.051 (0.115)	$t_{40.440} = 0.445$	.659
Session_stress	0.118 (0.084)	$t_{44.686} = 1.404$	.167
Session_2_hours	0.289 (0.084)	$t_{44.686} = 3.439$	.001**
Session_24_hours	0.147 (0.084)	$t_{44.686} = 1.749$	.087
Group × session_stress	−0.052 (0.119)	$t_{44.686} = -0.438$	.664
Group × session_24_hours	−0.104 (0.119)	$t_{44.686} = -0.875$	.386
Humans			
Response Bias			
Intercept	0.073 (0.025)	$t_{145.556} = 2.947$	.004**
Group	0.094 (0.032)	$t_{145.556} = 2.952$	.004**
Session_post	0.079 (0.035)	$t_{223.996} = 2.246$	.026*
Block	0.003 (0.030)	$t_{223.996} = 0.123$	.902
Group × session_post	−0.121 (0.045)	$t_{223.996} = -2.697$	.008**
Group × block	0.019 (0.039)	$t_{223.996} = 0.491$	.624
Session_post × block	−0.004 (0.043)	$t_{223.996} = -0.103$	.918
Group × session_post × block	0.012 (0.055)	$t_{223.996} = 0.216$	.829
Discriminability			
Intercept	0.355 (0.035)	$t_{65.330} = 10.004$	<.001***
Group	0.021 (0.045)	$t_{65.330} = 0.456$	.650
Session_post	0.054 (0.030)	$t_{224.000} = 1.770$	.078
Block	−0.002 (0.026)	$t_{224.000} = -0.062$	.951
Group × session_post	−0.065 (0.039)	$t_{224.000} = -1.675$	.095
Group × block	0.008 (0.034)	$t_{224.000} = 0.238$	.812
Session_post × block	−0.013 (0.037)	$t_{224.000} = -0.357$	.722
Group × session_post × block	0.024 (0.047)	$t_{224.000} = 0.495$	.621

*$p < .05$, **$p < .01$, ***$p < .001$.

Furthermore, we explored whether ketamine administration might have reduced questionnaire scores more strongly in

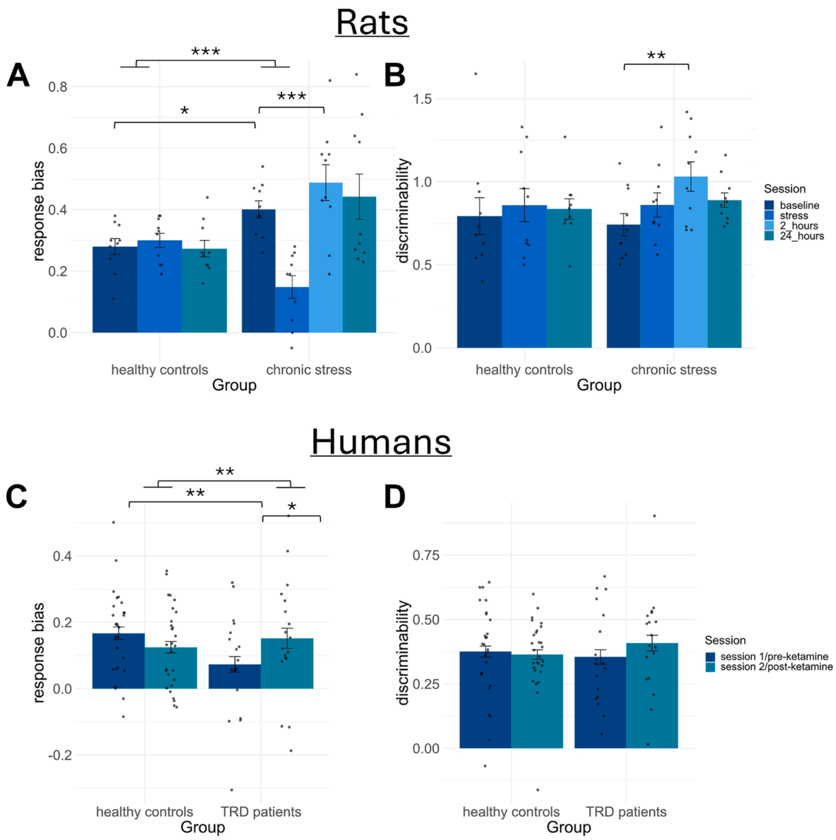

Figure 2. Effects of ketamine administration on response bias and discriminability. In rats, ketamine rescued the stress-induced response bias deficit in the anhedonic phenotype group and returned levels to baseline. The control group displayed stable response bias across 3 sessions **(A)**. The stress manipulation did not affect discriminability, but it was increased in stressed rats 2 hours after ketamine administration before returning to baseline **(B)**. In humans, ketamine increased response bias in patients with treatment-resistant depression (TRD). Response bias in healthy control (HC) participants did not change significantly between sessions **(C)**. Discriminability remained stable across sessions in both groups **(D)**. $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$.

participants who endorsed more severe symptoms at baseline. To this end, we ran additional exploratory analyses in the TRD group only, correlating questionnaire scores in session 1 with the change in scores between sessions (calculated as session 1 minus session 2, so that positive values reflect stronger reduction in scores across sessions). For the QIDS, we found that participants with higher scores in session 1 reported stronger ketamine-related reductions in self-reported symptom severity ($r = 0.593$, $p = .015$). This was also true for BDI-II ($r = 0.482$, $p = .050$) and HAMD scores ($r = 0.481$, $p = .051$) at a trend level but not for SHAPS scores ($r = 0.349$, $p = .156$), indicating that changes in the latter were more evenly spread across the range of initial scores.

As in the rodent sample, our main analysis concerned the effects of ketamine on participants' response bias, our behavioral index of anhedonic responding, and discriminability (Figure 2C, D). As expected, the TRD group displayed a significantly lower response bias compared with HC participants in their first session (group: $p = .004$; Table 2). However, 24 hours after their first ketamine dose, response bias was substantially increased in patients with TRD (session_post: $p = .026$). Crucially, this increase was specific to the TRD group (group × session_post: $p = .008$), whereas response bias in HC participants remained stable between sessions (a targeted post hoc *t* test in HC participants revealed that the numerical decrease in response bias between sessions was not significant: [$t_{45.14} = -0.35$, $p = .725$]). We did not find any significant effects involving block (all *p*s > .624).

Discriminability did not differ by group status, session, or block (all *p*s > .078). Overall, these findings mirror the rodent results. Additional results from a regression on RTs are presented in the Supplement (Table S2, Figure S2). In brief, participants with TRD responded significantly faster in session 2 ($p = .007$). No other main or interaction effect was significant.

Exploratory Analyses. Given the general improvements in patients' depressive symptom severity between sessions on all questionnaires, we explored whether the observed behavioral increase in response bias was modulated by those clinical measures. More specifically, we probed whether increases in response bias were larger for participants who 1) endorsed more severe symptoms before ketamine treatment and 2) displayed greater degrees of change in these symptoms between sessions (see Supplement for additional details).

As can be seen in Table 3, we found the general pattern of results as in our initial analysis. Interestingly, findings also indicated that the association between preketamine anhedonia symptoms and response bias in the PRT differed significantly between sessions in the TRD group (session_post × SHAPS baseline score: $p = .001$). More specifically, although higher SHAPS scores in session 1 were associated with lower response bias in participants with TRD as expected, the same individuals showed larger response

Table 3. Results From an Exploratory Dummy-Coded Linear Mixed Model Regression Examining the Effects of Preketamine SHAPS Scores and Change in SHAPS Scores Across Sessions on Response Bias in Humans

Predictor	*b* (SE)	$t_{264.000}$	*p*
Intercept	0.073 (0.024)	3.064	.002**
Group	0.094 (0.031)	3.069	.002**
Session_Post	0.079 (0.034)	2.326	.021*
SHAPS Score Session 1	0.004 (0.030)	0.125	.901
SHAPS Difference Score	−0.007 (0.004)	−1.603	.110
Group × Session_Post	−0.121 (0.043)	−2.792	.006**
Group × SHAPS Score Session 1	−0.001 (0.006)	−0.026	.980
Group × SHAPS Difference Score	0.003 (0.008)	0.376	.707
Session_Post × SHAPS Score Session 1	0.017 (0.006)	2.830	.005**
Session_Post × SHAPS Difference Score	−0.026 (0.007)	−3.511	<.001***
Group × Session_Post × SHAPS Score Session 1	−0.014 (0.008)	−1.772	.078
Group × Session_Post × SHAPS Difference Score	0.018 (0.012)	1.481	.140

Difference score is calculated as session 1 minus session 2.

*$p < .05$, **$p < .01$, ***$p < .001$.

SHAPS, Snaith-Hamilton Pleasure Scale.

bias in session 2, suggesting that increases in response bias following ketamine were larger in patients who reported more severe anhedonia symptoms before starting ketamine treatment (see Figure 3A, B). Furthermore, we found an unexpected effect of change in SHAPS scores on response bias across sessions (session_post × SHAPS change score: $p <$ .001), indicating that participants with TRD with the largest improvement in SHAPS scores showed overall lower improvements in response bias after ketamine administration. This may hint at a possible dissociation between the effects of ketamine on self-reported versus behavioral indices of anhedonia. Notably, separate analyses on each of the other clinical measures (BDI-II, QIDS, HAMD) did not show comparable effects of baseline symptom scores on response bias (see Tables S4–S6), potentially indicating that acutely, ketamine was particularly effective in increasing reward responsiveness in participants with more severe pretreatment anhedonia.

DISCUSSION

Although ketamine has been shown to exert rapid antidepressant and prohedonic effects in humans and animals (4,5,16,21,60,62), the underlying neurocognitive mechanisms are not well-understood, partially due to challenges in translating preclinical findings across species (36–38). Here, we investigated whether a single, subanesthetic dose of ketamine would enhance reward responsiveness in people with TRD and chronically stressed rats that displayed anhedonic-like behavior, using functionally identical versions of an established reward learning paradigm, the PRT (39,41). Consistent with our hypotheses, both species showed a significant increase in response bias toward the rich (i.e., more frequently rewarded) stimulus after ketamine infusion. In rats, this increase was apparent as soon as 2 hours postadministration and remained stable after 24 hours, returning response bias magnitude to levels observed prior to chronic stress exposure and comparable with those observed in the control (unstressed) group. Similarly, response bias in participants with TRD 24 hours after their first dose of ketamine was comparable with that of HC participants, equalizing the difference in response bias observed prior to ketamine treatment. Together, our results provide cross-species evidence for a ketamine-induced increase in reward responsiveness, highlighting an evolutionary-conserved mechanism through which ketamine alleviates depressive phenotypes.

Consistent with previous work, we observed meaningful reductions in depressive and anhedonic symptoms across all clinical measures following ketamine administration in participants with TRD (5,10,12–16,21). However, these measures rely heavily on self-report. In humans, comparatively few studies have investigated the effects of ketamine on more objective markers, such as changes in cognition or behavior that may mediate symptomatic improvements, and of those, most have

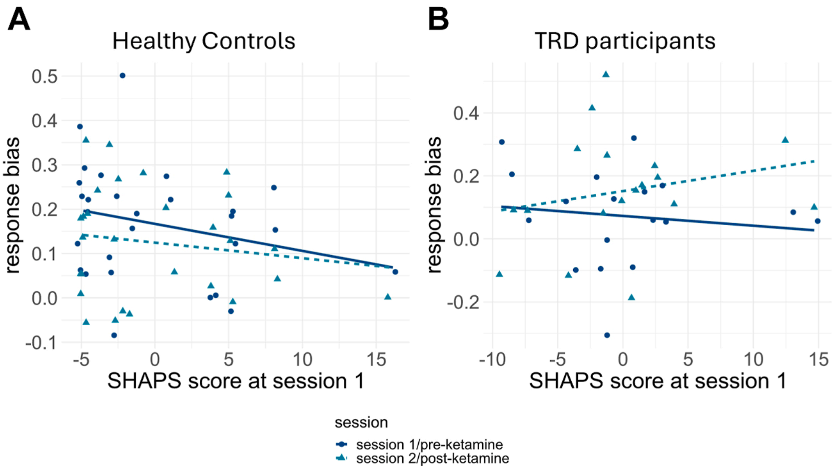

Figure 3. Effects of Snaith-Hamilton Pleasure Scale (SHAPS) scores at session 1 on response bias across sessions. For healthy control (HC) participants, higher baseline SHAPS scores were marginally associated with lower response bias in both sessions **(A)**. In participants with treatment-resistant depression (TRD), the relationship between baseline SHAPS scores and response bias changed direction following ketamine administration, suggesting highest increases occurred in patients with more severe self-reported anhedonia symptoms at baseline **(B)**.

focused on attentional processes or general cognitive capacity rather than reward processing (78–81). In animal models relevant to depression, acute and chronic ketamine administration have been associated with increases in sucrose preference and intake in animals following exposure to chronic stress, implying that ketamine may act by modifying responsiveness to anticipated or received reward (15,32,61,82–87). Our results provide evidence that ketamine may act through similar mechanisms in humans given the nearly identical patterns of changes in response bias in rats and humans tested with functionally identical versions of the PRT.

Interestingly, ketamine acted specifically on subjects' reward responsiveness rather than general task difficulty given that it did not affect discriminability in either species, except for a transient increase in chronically stressed rats at 2 hours postadministration. Moreover, exploratory analyses revealed that, among participants with TRD, ketamine-related changes in response bias were moderated by preketamine SHAPS scores but not by BDI-II, QIDS, or HAMD scores, indicating that ketamine improved reward responsiveness primarily in individuals with more anhedonia. This is consistent with previous work reporting the prohedonic effects of ketamine to be unrelated to its effects on other symptoms of depression (5,25). Interestingly, higher baseline SHAPS scores were not associated with larger improvements in self-reported anhedonia symptoms postketamine. Instead, larger decreases in SHAPS scores were associated with lower increases in response bias, which may suggest a dissociation of ketamine administration on subjective versus more objective markers of anhedonia. However, we would like to emphasize that these analyses were exploratory, and future studies are needed to replicate these effects and confirm their specificity.

On a neural level, response bias in the PRT has been linked to activation in the dorsal ACC and ventral striatum in both humans and rats (37,88). Interestingly, prior work using positron emission tomography in participants with MDD and healthy individuals identified ketamine-related modulations of glucose metabolism in various nodes of the reward system, including the dorsal ACC and ventral striatum (6,30,31), highlighting a possible role of these regions in mediating the observed effects of ketamine on response bias. However, we do not propose that the prohedonic properties of ketamine result from specific modulations of isolated brain areas. Instead, they likely reflect widespread neuroplastic changes within reward networks. Specifically, in rodents, ketamine has been observed to trigger a rapid and transient surge of extracellular glutamate levels and a reversal in stress-related synaptic deficits in the medial prefrontal cortex; moreover, ketamine has been found to decrease burst firing in the lateral habenula, which may drive anhedonic behavior by inhibiting dopaminergic and serotonergic midbrain areas, including the ventral tegmental area and dorsal raphe nuclei (25,32,82,89). Given the evolutionary preserved nature of frontostriatal pathways, it is possible that the observed increases in response bias in both humans and rats resulted from ketamine's effect on these key reward network nodes that orchestrate activity in downstream areas across the brain. Functional neuroimaging studies will be required to test this conjecture.

We would like to acknowledge that this study presents some limitations, most notably the modest size of our human sample, the lack of vehicle (saline) control groups in both sets of experiments, and the difficulty choosing the proper animal stress model for translational research in psychopathology. For a detailed discussion, please refer to the Supplement.

Conclusions

We found translational evidence that ketamine administration rapidly affects reward responsiveness in individuals with TRD and rats exposed to chronic stress. These effects may be specific to ketamine-induced changes in hedonic processes, as we did not see effects on discriminability 24 hours postinjection and also given that the ketamine-related improvements were largest for individuals with more severe self-reported anhedonic symptoms before treatment. Although more work is necessary to fully characterize the neurobiological, psychological, and computational mechanisms at play, as well as the longevity of these effects, our findings may have important implications for the treatment of individuals with anhedonia beyond the context of TRD given that motivational deficits related to anhedonia are commonly observed after stress and across diagnostic domains (90–93). As there is not yet an approved treatment for these symptoms, our findings may contribute to an objective quantification in the evaluation of novel treatments designed to improve quality of life for people experiencing anhedonia.

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DAP and BDK designed the human and rodent study, respectively. JNS, SME, ML, SEW, and ARJ acquired the data. MB, BDK, and DAP analyzed and interpreted the data. MB, BDK, and DAP wrote the initial draft of the manuscript. All authors contributed to the revision and editing of the manuscript and gave final approval before submission.

The data used in the current work are available upon reasonable request to the corresponding author.

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REFERENCES

1. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, *et al.* (2020): Defining treatment-resistant depression. Depress Anxiety 37:134–145.
2. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, *et al.* (2023): Treatment-resistant depression: Definition, prevalence, detection, management, and investigational interventions. World Psychiatry 22:394–412.
3. De Carlo V, Calati R, Serretti A (2016): Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. Psychiatry Res 240:421–430.
4. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000): Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354.
5. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA (2014): Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. Transl Psychiatry 4:e469., 469.
6. Lally N, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA (2015): Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. J Psychopharmacol 29:596–607.
7. Serafini G, Howland RH, Rovedi F, Girardi P, Amore M (2014): The role of ketamine in treatment-resistant depression: A systematic review. Curr Neuropharmacol 12:444–461.
8. Zanos P, Gould TD (2018): Mechanisms of ketamine action as an antidepressant. Mol Psychiatry 23:801–811.
9. Medeiros GC, Demo I, Goes FS, Zarate CA, Gould TD (2024): Personalized use of ketamine and esketamine for treatment-resistant depression. Transl Psychiatry 14:481.
10. Naughton M, Clarke G, O'Leary OF, Cryan JF, Dinan TG (2014): A review of ketamine in affective disorders: Current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J Affect Disord 156:24–35.
11. McIntyre RS, Rodrigues NB, Lee Y, Lipsitz O, Subramaniapillai M, Gill H, *et al.* (2020): The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: Results from the Canadian Rapid Treatment Center of Excellence. J Affect Disord 274:903–910.
12. Zhuo C, Ji F, Tian H, Wang L, Jia F, Jiang D, *et al.* (2020): Transient effects of multi-infusion ketamine augmentation on treatment-resistant depressive symptoms in patients with treatment-resistant bipolar depression—An open-label three-week pilot study. Brain Behav 10:e01674.
13. Bahji A, Vazquez GH, Zarate CA (2021): Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. J Affect Disord 278:542–555.
14. Delfino RS, Del-Porto JA, Surjan J, Magalhães E, Sant LCD, Lucchese AC, *et al.* (2021): Comparative effectiveness of esketamine in the treatment of anhedonia in bipolar and unipolar depression. J Affect Disord 278:515–518.
15. Nogo D, Jasrai AK, Kim H, Nasri F, Ceban F, Lui LMW, *et al.* (2022): The effect of ketamine on anhedonia: Improvements in dimensions of anticipatory, consummatory, and motivation-related reward deficits. Psychopharmacology 239:2011–2039.
16. Patarroyo-Rodriguez L, Cavalcanti S, Vande Voort JL, Singh B (2024): The use of ketamine for the treatment of anhedonia in depression. CNS Drugs 38:583–596.
17. Halahakoon DC, Kieslich K, O'Driscoll C, Nair A, Lewis G, Roiser JP (2020): Reward-processing behavior in depressed participants relative to healthy volunteers: A systematic review and meta-analysis. JAMA Psychiatry 77:1286–1295.
18. Guineau MG, Ikani N, Rinck M, Collard RM, Van Eijndhoven P, Tendolkar I, *et al.* (2023): Anhedonia as a transdiagnostic symptom across psychological disorders: A network approach. Psychol Med 53:3908–3919.
19. Ang Y-S, Kaiser R, Deckersbach T, Almeida J, Phillips ML, Chase HW, *et al.* (2020): Pretreatment reward sensitivity and frontostriatal resting-state functional connectivity are associated with response to bupropion after sertraline nonresponse. Biol Psychiatry 88:657–667.
20. Cao B, Zhu J, Zuckerman H, Rosenblat JD, Brietzke E, Pan Z, *et al.* (2019): Pharmacological interventions targeting anhedonia in patients with major depressive disorder: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry 92:109–117.
21. Rodrigues NB, McIntyre RS, Lipsitz O, Cha DS, Lee Y, Gill H, *et al.* (2020): Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment Center of Excellence. J Affect Disord 276:570–575.
22. Vasavada MM, Loureiro J, Kubicki A, Sahib A, Wade B, Hellemann G, *et al.* (2021): Effects of serial ketamine infusions on corticolimbic functional connectivity in major depression. Biol Psychiatry Cogn Neurosci Neuroimaging 6:735–744.
23. Abdallah CG, Ahn K-H, Averill LA, Nemati S, Averill CL, Fouda S, *et al.* (2021): A robust and reproducible connectome fingerprint of ketamine is highly associated with the connectomic signature of antidepressants. Neuropsychopharmacology 46:478–485.
24. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, *et al.* (2017): Ketamine treatment and global brain connectivity in major depression. Neuropsychopharmacology 42:1210–1219.
25. Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T, *et al.* (2017): Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. J Affect Disord 218:195–200.
26. Evans JW, Szczepanik J, Brutsché N, Park LT, Nugent AC, Zarate CA Jr (2018): Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. Biol Psychiatry 84:582–590.
27. Lucantonio F, Roeglin J, Li S, Lu J, Shi A, Czerpaniak K, *et al.* (2025): Ketamine rescues anhedonia by cell-type- and input-specific adaptations in the nucleus accumbens. Neuron 113:1398–1412.e4.
28. Mkrtchian A, Evans JW, Kraus C, Yuan P, Kadriu B, Nugent AC, *et al.* (2021): Ketamine modulates fronto-striatal circuitry in depressed and healthy individuals. Mol Psychiatry 26:3292–3301.
29. Moujaes F, Ji JL, Rahmati M, Burt JB, Schleifer C, Adkinson BD, *et al.* (2024): Ketamine induces multiple individually distinct whole-brain functional connectivity signatures. eLife 13:e84173.
30. Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkun SA, *et al.* (1998): Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and 11C-raclopride in normal human subjects. Neuropsychopharmacology 18:18–25.
31. Vollenweider FX, Vontobel P, Øye I, Hell D, Leenders KL (2000): Effects of (S)-ketamine on striatal dopamine: A [11C]raclopride PET study of a model psychosis in humans. J Psychiatr Res 34:35–43.
32. Yang Y, Cui Y, Sang K, Dong Y, Ni Z, Ma S, Hu H (2018): Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature 554:317–322.
33. Duncan WC Jr, Slonena E, Hejazi NS, Brutsche N, Yu KC, Park L, *et al.* (2017): Motor-activity markers of circadian timekeeping are related to ketamine's rapid antidepressant properties. Biol Psychiatry 82:361–369.
34. Can A, Zanos P, Moaddel R, Kang HJ, Dossou KSS, Wainer IW, *et al.* (2016): Effects of ketamine and ketamine metabolites on evoked

striatal dopamine release, dopamine receptors, and monoamine transporters. J Pharmacol Exp Ther 359:159–170.
35. Xu S, Yao X, Li B, Cui R, Zhu C, Wang Y, Yang W (2022): Uncovering the underlying mechanisms of ketamine as a novel antidepressant. Front Pharmacol 12:740996.
36. Pizzagalli DA (2022): Toward a better understanding of the mechanisms and pathophysiology of anhedonia: Are we ready for translation? Am J Psychiatry 179:458–469.
37. Iturra-Mena AM, Kangas BD, Luc OT, Potter D, Pizzagalli DA (2023): Electrophysiological signatures of reward learning in the rodent touchscreen-based Probabilistic Reward Task. Neuropsychopharmacology 48:700–709.
38. Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH (2016): Assessing anhedonia in depression: Potentials and pitfalls. Neurosci Biobehav Rev 65:21–35.
39. Pizzagalli DA, Jahn AL, O'Shea JP (2005): Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. Biol Psychiatry 57:319–327.
40. Insel TR (2014): The NIMH research domain criteria (RDoC) project: Precision medicine for psychiatry. Am J Psychiatry 171:395–397.
41. Kangas BD, Wooldridge LM, Luc OT, Bergman J, Pizzagalli DA (2020): Empirical validation of a touchscreen probabilistic reward task in rats. Transl Psychiatry 10:285.
42. Wooldridge LM, Bergman J, Pizzagalli DA, Kangas BD (2021): Translational assessments of reward responsiveness in the marmoset. Int J Neuropsychopharmacol 24:409–418.
43. Luc OT, Kangas BD (2024): Validation of a touchscreen probabilistic reward task for mice: A reverse-translated assay with cross-species continuity. Cogn Affect Behav Neurosci 24:281–288.
44. Luc OT, Pizzagalli DA, Kangas BD (2021): Toward a quantification of anhedonia: Unified matching law and signal detection for clinical assessment and drug development. Perspect Behav Sci 44:517–540.
45. Gonzalez PM, Jenkins AR, LaMalfa KS, Kangas BD (2024): Chronic ecologically relevant stress effects on reverse-translated touchscreen assays of reward responsivity and attentional processes in male rats: Implications for depression. J Neurochem 168:2190–2200.
46. Hisey EE, Fritsch EL, Newman EL, Ressler KJ, Kangas BD, Carlezon WA (2023): Early life stress in male mice blunts responsiveness in a translationally-relevant reward task. Neuropsychopharmacology 48:1752–1759.
47. Kangas BD, Short AK, Luc OT, Stern HS, Baram TZ, Pizzagalli DA (2022): A cross-species assay demonstrates that reward responsiveness is enduringly impacted by adverse, unpredictable early-life experiences. Neuropsychopharmacology 47:767–775.
48. Lamontagne SJ, Wash SIJ, Irwin SH, Zucconi KE, Olmstead MC (2022): Effects of dopamine modulation on chronic stress-induced deficits in reward learning. Cogn Affect Behav Neurosci 22:736–753.
49. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M (2008): Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. J Psychiatr Res 43:76–87.
50. Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, *et al.* (2013): Reduced reward learning predicts outcome in major depressive disorder. Biol Psychiatry 73:639–645.
51. Jenkins AR, Radl DB, Kornecook TJ, Pizzagalli DA, Bergman J, Buhl DL, *et al.* (2025): Environmental determinants of ketamine's prohedonic and antianhedonic efficacy: Persistence of enhanced reward responsiveness is modulated by chronic stress. J Pharmacol Exp Ther 392:103572.
52. National Research Council, Division on Earth, Life Studies, Institute for Laboratory Animal Research (2011): Guidance for the Description of Animal Research in Scientific Publications. Washington, DC: National Academies Press, US.
53. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(suppl 20):22–33.. quiz 34.
54. Hamilton M (1960): A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.
55. Beck AT, Steer RA, Brown GK (1996): Beck Depression Inventory–II (BDI-II): Manual. San Antonio, TX: Psychological Corporation.
56. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, *et al.* (2003): The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. Biol Psychiatry 54:573–583.
57. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P (1995): A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. Br J Psychiatry 167:99–103.
58. Pizzagalli DA, Smoski M, Ang Y-S, Whitton AE, Sanacora G, Mathew SJ, *et al.* (2020): Selective kappa-opioid antagonism ameliorates anhedonic behavior: Evidence from the Fast-fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS). Neuropsychopharmacology 45:1656–1663.
59. Dillon DG, Lazarov A, Dolan S, Bar-Haim Y, Pizzagalli DA, Schneier FR (2022): Fast evidence accumulation in social anxiety disorder enhances decision making in a probabilistic reward task. Emotion 22:1–18.
60. Garcia LSB, Comim CM, Valvassori SS, Réus GZ, Barbosa LM, Andreazza AC, *et al.* (2008): Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry 32:140–144.
61. Garcia LSB, Comim CM, Valvassori SS, Réus GZ, Stertz L, Kapczinski F, *et al.* (2009): Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. Prog Neuropsychopharmacol Biol Psychiatry 33:450–455.
62. Wang J, Goffer Y, Xu D, Tukey DS, Shamir DB, Eberle SE, *et al.* (2011): A single subanesthetic dose of ketamine relieves depression-like behaviors induced by neuropathic pain in rats. Anesthesiology 115:812–821.
63. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, *et al.* (2020): Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry 25:1592–1603.
64. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, *et al.* (2017): A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry 74:399–405.
65. Su T-P, Chen M-H, Li C-T, Lin W-C, Hong C-J, Gueorguieva R, *et al.* (2017): Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. Neuropsychopharmacology 42:2482–2492.
66. Wilkinson ST, Farmer C, Ballard ED, Mathew SJ, Grunebaum MF, Murrough JW, *et al.* (2019): Impact of midazolam vs. saline on effect size estimates in controlled trials of ketamine as a rapid-acting antidepressant. Neuropsychopharmacology 44:1233–1238.
67. Kangas BD, Bergman J (2017): Touchscreen technology in the study of cognition-related behavior. Behav Pharmacol 28:623–629.
68. McCarthy D, Davison M (1979): Signal probability, reinforcement and signal detection. J Exp Anal Behav 32:373–386.
69. McCarthy D (1983): Measures of response bias at minimum-detectable luminance levels in the pigeon. J Exp Anal Behav 39:87–106.
70. Hautus MJ (1995): Corrections for extreme proportions and their biasing effects on estimated values ofd'. Behav Res Methods Instrum Comput 27:46–51.
71. Wickham H, Vaughan D, Girlich M (2020): tidyr: Tidy Messy Data. R package version 1.1. 3. CRAN R-project org/package= *tidyr*. Available at: https://cran-e.com/package/tidyr. Accessed April 1, 2025.
72. Kassambara A (2023): rstatix: Pipe-friendly framework for basic statistical tests. CRAN: Contributed Packages, R package version 0.7.2. Available at: https://kassambara.r-universe.dev/rstatix. Accessed April 1, 2025.
73. Bates D, Maechler M (2009): Fitting linear mixed-effects models using lme4. Journal of Statistical Software 67:1–48.
74. Kuznetsova A, Brockhoff PB, Christensen RHB (2017): lmerTest package: Tests in linear mixed effects models. J Stat Soft 82:1–26.
75. Gelman A, Hill J (2006): Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge: Cambridge university press.

76. Sharp ME, Foerde K, Daw ND, Shohamy D (2015): Dopamine selectively remediates 'model-based' reward learning: A computational approach. Brain 139:355–364.
77. Bogdanov M, LoParco S, Otto AR, Sharp M (2022): Dopaminergic medication increases motivation to exert cognitive control by reducing subjective effort costs in Parkinson's patients. Neurobiol Learn Mem 193:107652.
78. Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO (2014): Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. Int J Neuropsychopharmacol 17:1805–1813.
79. Chen M-H, Li C-T, Lin W-C, Hong C-J, Tu P-C, Bai Y-M, *et al.* (2018): Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. J Affect Disord 241:1–7.
80. Gill H, Gill B, Rodrigues NB, Lipsitz O, Rosenblat JD, El-Halabi S, *et al.* (2021): The effects of ketamine on cognition in treatment-resistant depression: A systematic review and priority avenues for future research. Neurosci Biobehav Rev 120:78–85.
81. Singh B, Parikh SV, Voort JLV, Pazdernik VK, Achtyes ED, Goes FS, *et al.* (2024): Change in neurocognitive functioning in patients with treatment-resistant depression with serial intravenous ketamine infusions: The Bio-K multicenter trial. Psychiatry Res 335:115829.
82. Li N, Liu R-J, Dwyer JM, Banasr M, Lee B, Son H, *et al.* (2011): Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry 69:754–761.
83. Sarkar A, Kabbaj M (2016): Sex differences in effects of ketamine on behavior, spine density, and synaptic proteins in socially isolated rats. Biol Psychiatry 80:448–456.
84. Papp M, Gruca P, Lason-Tyburkiewicz M, Willner P (2017): Antidepressant, anxiolytic and procognitive effects of subacute and chronic ketamine in the chronic mild stress model of depression. Behav Pharmacol 28:1–8.
85. Tornese P, Sala N, Bonini D, Bonifacino T, La Via L, Milanese M, *et al.* (2019): Chronic mild stress induces anhedonic behavior and changes in glutamate release, BDNF trafficking and dendrite morphology only in stress vulnerable rats. The rapid restorative action of ketamine. Neurobiol Stress 10:100160.
86. Aricioğlu F, Yalcinkaya C, Ozkartal CS, Tuzun E, Sirvanci S, Kucukali CI, Utkan T (2020): NLRP1-mediated antidepressant effect of ketamine in chronic unpredictable mild stress model in rats. Psychiatry Investig 17:283–291.
87. Vecchia DD, Kanazawa LKS, Wendler E, Hocayen PAS, Vital MABF, Takahashi RN, *et al.* (2021): Ketamine reversed short-term memory impairment and depressive-like behavior in animal model of Parkinson's disease. Brain Res Bull 168:63–73.
88. Santesso DL, Evins AE, Frank MJ, Schetter EC, Bogdan R, Pizzagalli DA (2009): Single dose of a dopamine agonist impairs reinforcement learning in humans: Evidence from event-related potentials and computational modeling of striatal-cortical function. Hum Brain Mapp 30:1963–1976.
89. Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, *et al.* (2010): mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.
90. Shafiei N, Gray M, Viau V, Floresco SB (2012): Acute stress induces selective alterations in cost/benefit decision-making. Neuropsychopharmacology 37:2194–2209.
91. Husain M, Roiser JP (2018): Neuroscience of apathy and anhedonia: A transdiagnostic approach. Nat Rev Neurosci 19:470–484.
92. Bogdanov M, Nitschke JP, LoParco S, Bartz JA, Otto AR (2021): Acute psychosocial stress increases cognitive-effort avoidance. Psychol Sci 32:1463–1475.
93. Kuhn M, Palermo EH, Pagnier G, Blank JM, Steinberger DC, Long Y, *et al.* (2025): Computational phenotyping of effort-based decision making in unmedicated adults with remitted depression. Biol Psychiatry Cogn Neurosci Neuroimaging 10:607–615.