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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 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%)	χ^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%)	χ^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):

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

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

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

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

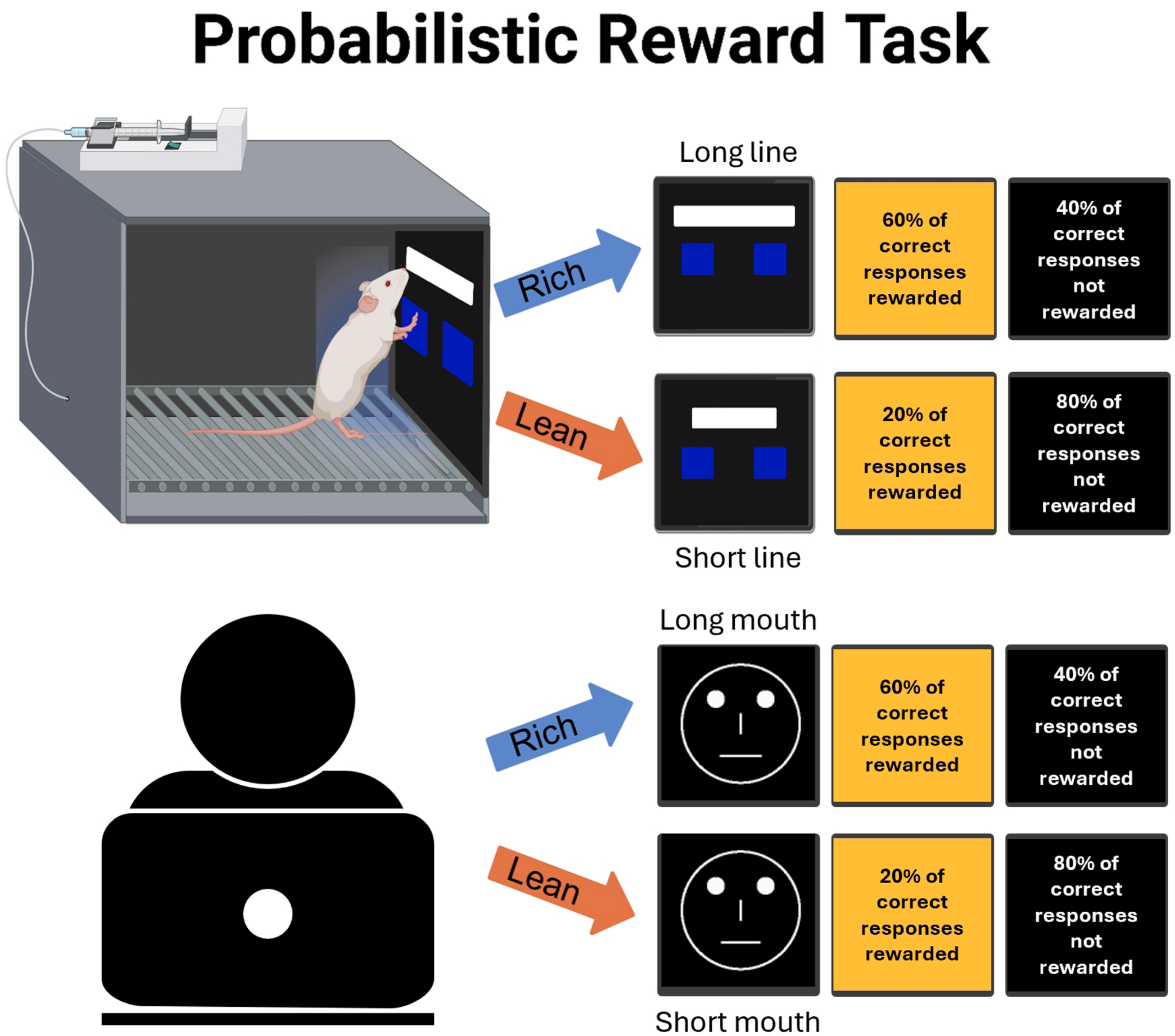

Figure 1. The human and rat version of the Probabilistic Reward Task. Rats responded to short or long line stimuli presented on a touchscreen. Humans judged the length of the mouth stimulus of a schematic face presented on a computer screen. Across species, identical asymmetrical reward schedules (3:1) 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, $p < .001$, η^2 = 0.81; QIDS: $F_{1,41}$ = 306.35, $p < .001$, η^2 = 0.81; BDI-II: $F_{1,40}$ = 362.19, $p < .001$, η^2 = 0.86; SHAPS: $F_{1,44}$ = 99.16, $p < .001$, η^2 = 0.69). Across all participants, we saw reductions in scores for HAMD ($F_{1,42}$ = 18.46, $p < .001$, η^2 = 0.13), QIDS ($F_{1,41}$ = 18.81, $p < .001$, η^2 = 0.17), and BDI-II ($F_{1,40}$ = 7.31, p = .010, η^2 = 0.06), but not SHAPS scores ($F_{1,44}$ = 1.77, p = .191, η^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, $p < .001$, η^2 = 0.11; QIDS: $F_{1,41}$ = 20.05, $p < .001$, η^2 = 0.17; BDI-II: $F_{1,40}$ = 7.11, p = .011, η^2 = 0.05; SHAPS: $F_{1,44}$ = 6.47, p = .015, η^2 = 0.02). Bonferroni-corrected post hoc comparisons revealed that these interactions represented selective decreases in HAMD (HC: corrected t_{26} = 1.44, $p_{adjusted\ (adj)}$ = .161, TRD: corrected t_{16} = 3.30, p_{adj} = .005), QIDS (HC: corrected t_{26} = −1.00, p_{adj} = .327, TRD: corrected t_{15} = 3.38, p_{adj} = .004), and BDI-II (HC: corrected t_{24} = 0.44, p_{adj} = .664, TRD: corrected t_{16} = 2.20, p_{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_{adj} = .210, TRD: corrected t_{17} = 1.91, p_{adj} = .073).

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

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

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

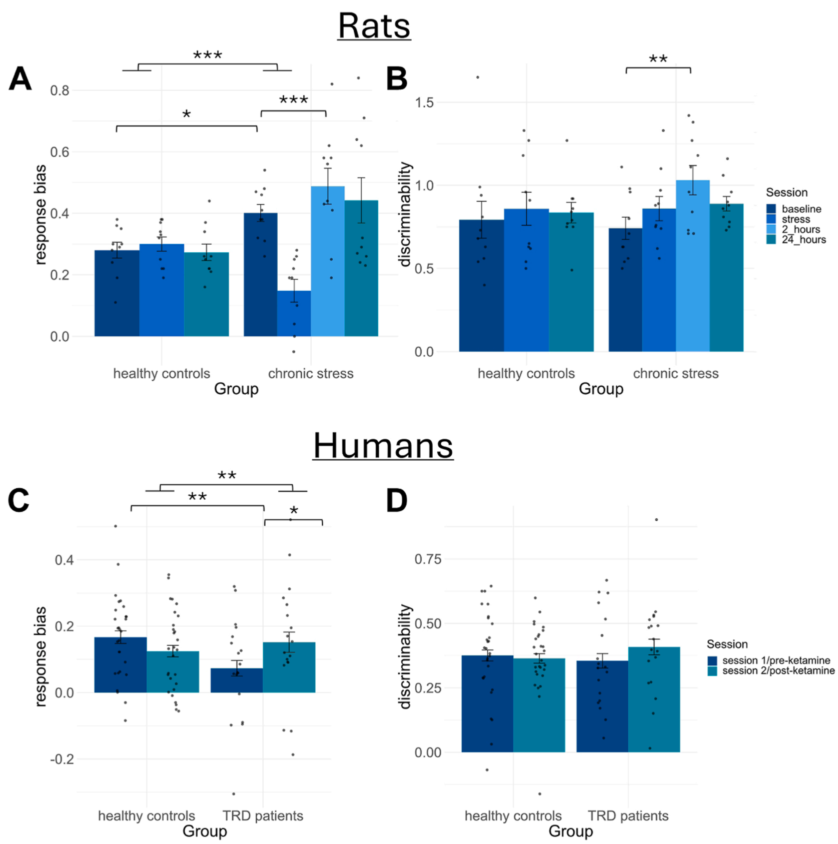

Figure 2. Effects of ketamine administration on response bias and discriminability. In rats, ketamine rescued the stress-induced response bias deficit in the anhedonic phenotype group and returned levels to baseline. The control group displayed stable response bias across 3 sessions **(A)**. The stress 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 $ps > .624$).

Discriminability did not differ by group status, session, or block (all $ps > .078$). 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

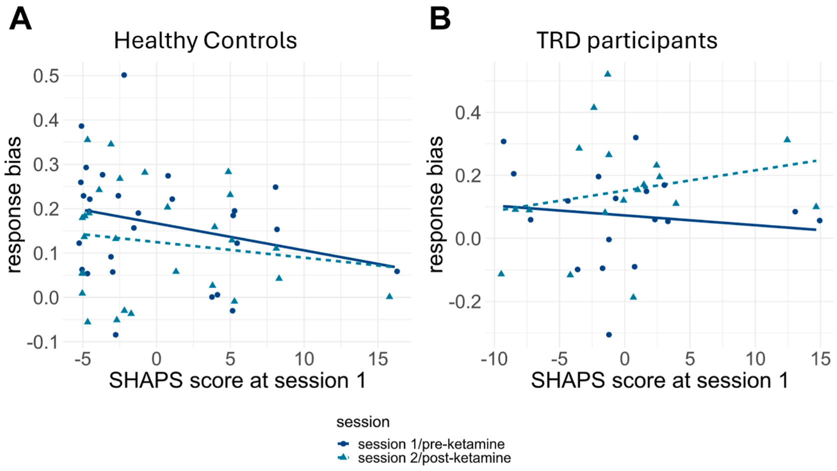

Figure 3. Effects of Snaith-Hamilton Pleasure Scale (SHAPS) scores at session 1 on response bias across sessions. For healthy control (HC) participants, higher baseline SHAPS scores were marginally associated with lower response bias in both sessions **(A)**. In participants with treatment-resistant 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 post-injection 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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SUPPLEMENTARY INFORMATION

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

Bogdanov *et al.*

Supplemental Methods

Group-level and individual exclusion criteria for human participants

For screening purposes, exclusion criteria for both groups consisted of: current substance use or lifetime history of seizures, psychosis, bipolar disorder, or unstable medical illness. Healthy controls were excluded if they reported scores of ≥ 7 (i.e., a cut-off for minimal depression) in the Hamilton Depressive Rating Scale (HAMD *(1)*), a history of psychiatric illness, or currently use of psychotropic medication. TRD participants were required to meet DSM criteria for a current major depressive episode and to have not experienced a 50% reduction in depressive symptoms following at least two full trials of any antidepressant in the current episode, as assessed by the MGH Antidepressant Treatment Response Questionnaire (ATRQ *(2)*).

For analysis purposes, participants were excluded if, in any of the two experimental sessions, they had less than 80% valid trials in a given block of the PRT, received reward feedback in less than 20 rich or 6 lean trials per block, or if their reward ratio of rich vs. lean trials fell below 2:1 in any block.

Sample size was determined based on the requirements of the parent study and is comparable to previous experimental work on ketamine in TRD (3–6) and is sufficient to detect differences in PRT performance between clinical and healthy individuals (7,8).

Detailed List of Inclusion and Exclusion Criteria

Healthy control (HC):

1. All genders, races, and ethnic origins.
2. Aged between 18 and 70 years.
3. Absence of medical, neurological, and psychiatric illness (including alcohol and substance abuse), as assessed by subject history and the Mini International Neuropsychiatric Inventory (MINI) interview.
4. A baseline Quick Inventory of Depression Scale (QIDS) score less than or equal to 5.
5. A baseline Hamilton Depression Rating Scale (HAMD) score less than or equal to 7.
6. Capable of providing written informed consent and fluent in English.
7. No first-degree relative with mood or psychotic disorder.

Participants with treatment resistant depression (TRD):

1. All genders, races, and ethnic origins.
2. Aged between 18 and 70 years.
3. Currently meet DSM-5 diagnostic criteria for Major Depressive Disorder (MDD) as assessed via the MINI.

4. A baseline HAMD (17-item version) score greater than 16, or a QIDS score greater than 12 and a Beck Depression Inventory - II score greater than 14.
5. Capable of providing written informed consent, and fluent in English.
6. Treatment Resistant as assessed via the Massachusetts General Hospital Antidepressant Response Questionnaire.
7. Have already decided to receive ketamine treatment as part of their standard clinical care.

Global exclusion criteria:

1. Any serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic or hematologic disease.
2. History of seizure disorder.
3. History or current diagnosis of any of the following DSM-5 psychiatric illnesses: schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified.
4. Current diagnosis of substance use disorder.
5. Clinical or laboratory evidence of hypothyroidism, hyperthyroidism, or other thyroid disorder that is not controlled by medication.
6. Substance use assessed by physician as dangerous for ketamine treatment.
7. Untreated glaucoma.
8. Complex PTSD with dissociation.
9. Patients treated with electroconvulsive therapy (ECT) in the past 2 weeks.
10. Participants with a lifetime history of previous ketamine use.

Table S1. Medication use in participants with TRD

Drug Class	**Number of participants (N = 24)**
Anticonvulsant (including GABA analogues)	5
Anxiolytic/Sedative	5
Atypical Antipsychotic	11
Benzodiazepine	9
Central Nervous System Stimulant	6
Miscellaneous Antidepressant	6
Monoamine Oxidase Inhibitor (MAOi)	1
Serotonin Antagonist and Reuptake Inhibitor (SARI)	3

Serotonin-Noradrenaline reuptake inhibitor (SNRI)	5
Selective Serotonin Reuptake Inhibitor (SSRI)	12
Tri/Tetracyclic Antidepressant	2

Note: Participants commonly used several medications and are thus counted in multiple categories.

Training procedure in the rat sample

Subjects were housed in a climate-controlled vivarium on a 12-h light/dark cycle (lights on at 7AM) three to a home cage. Besides social housing, no other sources of environmental enrichment were provided. To establish sweetened condensed milk as a reinforcer, rats were maintained at approximately 85% of their free feeing weights by restricted feeding to approximately 10-15 grams of rodent chow given daily after the experimental session. Water was available ad libitum in the home cage.

Using previously published protocols (9), rats were first trained to respond on the touchscreen and, subsequently, to discriminate line stimuli. Trial types varied in a quasi-random manner across 100 trial sessions, with 50 trials of each type. Subjects were differentially reinforced to respond to the left or right response box depending on the length of the white line. Correct responses yielded small amounts of a palatable food reward (0.1 mL of a 30% sweetened condensed milk solution) that was paired with an 880 ms yellow screen flash and 440 Hz tone and followed by a 5-sec blackout period, whereas each incorrect response immediately resulted in a 10-sec blackout period. Training continued until discrimination accuracy was ≥80% for 2 consecutive sessions (9,10).

Detailed experimental procedure:

Rats

Rats were trained in the PRT using previously published protocols (9) until discrimination accuracy reached ≥80% for two consecutive sessions. Previous rat PRT studies have indicated that a sample size of n=8 is sufficiently powered based on predicted effect sizes (9,10,21); however, 10 rats per experimental group were used here. Animals were then assigned to either testing conditions without programmed stress (n=10, “healthy control” group) or conditions of ongoing chronic stress (n=10, “anhedonic phenotype” group). For the former, PRT testing consisted of three daily 100-trial sessions. For the latter, pre-stress baseline PRT performance was examined during one session before animals were exposed to chronic inescapable ice water stress (11).

The **chronic inescapable ice water stress protocol** can be traced back to early chronic stress paradigms in rats for medications development for depression (13) in which rats were subjected to 5 min periods of inescapable exposure to 4°C water which, in concert with other stressors such as unpredictable electric shock, produced depressive-like phenotypes that could be reversed by imipramine (12). Researchers have subsequently used versions of this chronic inescapable ice water stress paradigm in rats to investigate a wide range of biomedical targets, including immune (14,15), developmental (16), neurobiological (17,18), and endocrine (19,20) endpoints. More recently, chronic inescapable ice water stress has been shown to readily produce behavioral deficits, including anhedonic-like phenotypes in the PRT, as well as in other cognitive domains relevant to MDD, such as attention (11). Subsequently, this chronic stressor has been used in tandem with the PRT to probe the anti-anhedonic efficacy of ketamine (21) and the neuroplastogen (+)-JRT (22). Importantly, the stress-induced deficits are evident in the absence of any other untoward effects on rodent health.

The present study employed methods similar to those previously used in the above referenced studies: rats were placed in an opaque polycarbonate cylinder (52 cm high, 40 cm diameter) filled with water maintained at 10°C which, although warmer than in most of the studies referenced above, is nevertheless associated with reliable swim durations of approximately 4-8 min prior to submersion. Rats were observed continuously during their swim duration and rescued after submersion for >7s. After rescue, animals were placed singly in a clean home cage, without the aid of towel drying or heat lamp, for a 2.5-hour period.

This process was repeated daily until a blunted response bias (i.e., at least half of the subject's pre-stress baseline value) was observed in the PRT. The following day, during continued chronic stress exposure, rats received ketamine 30min after stress exposure and 2h 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 24h post-administration.

<u>Humans</u>

Human participants completed two testing sessions (2.5h each) separated by 48 hours. For TRD participants, 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 two sessions. If the first testing session took place more than one month after screening, participants were re-assessed to confirm continued eligibility. On both days, participants were fitted with a 96-channel electrode cap before they completed 8min of resting state EEG recording, followed by an unrelated flanker task and the PRT. EEG findings will be presented elsewhere. Further, we collected HAMD, QIDS, BDI-II, and SHAPS scores at each testing session.

Supplemental Results

In addition to response bias and discriminability, we also performed regression analyses on response time (RT) in the PRT. For this purpose, we added trial type (rich vs. lean, effect-coded as 0.5 and -0.5, respectively) as a predictor to our regression models, which were otherwise identical to the ones used for response bias and discriminability.

<u>Rats</u>

For the rat sample (Table S2), we used median RT as the dependent variable (see also Figure S1). Results suggest that, at baseline, rats in the stress group responded faster to rich compared to lean stimuli (main effect Trial Type: $p = .014$), which can be seen as a further manifestation of a preference in favor of the more frequently rewarded stimulus. This RT advantage for rich trials was observed across both groups and sessions as indicated by the absence of significant interaction effects involving trial type (i.e., indicating that the difference in RTs seen in the baseline category did not change by group or session, all $p > .206$). We also found a significant Group × Session_24hours interaction ($p = .019$), indicating an increase in RTs for both rich and lean stimuli in unstressed rats compared to a decrease in stressed rats, in relation to their respective baseline session. We did not observe any changes in RTs in stressed rats following ketamine administration (main effects Session_2_hours and Session_24_hours: p > .214)

Table S2. Results from a linear mixed-effects regression predicting median RT by Group, Session, and Trial Type in the rat sample.

Predictor	*b (SE)*	*df*	*t*	*p*	
Intercept	1.409 (0.252)	37.398	5.597	< .001	***
Group	0.377 (0.356)	37.398	1.059	.296	
Session_Stress	-0.161 (0.238)	108.092	-0.675	.501	
Session_2_hours	-0.298 (0.238)	108.092	-1.250	.214	
Session_24_hours	-0.251 (0.238)	108.092	-1.055	.294	
Trial Type	-0.838 (0.337)	108.092	-2.490	.014	*
Group × Session_Stress	0.222 (0.337)	108.092	0.660	.511	
Group × Session_24hours	0.801 (0.337)	108.092	2.380	.019	*
Group × Trial Type	0.478 (0.476)	108.092	1.004	.317	
Session_Stress × Trial Type	0.605 (0.476)	108.092	1.271	.206	
Session_2_hours × Trial Type	0.403 (0.476)	108.092	0.847	.399	
Session_24_hours × Trial Type	0.596 (0.476)	108.092	1.252	.213	
Group × Session_Stress × Trial Type	-0.278 (0.673)	108.092	-0.413	.680	
Group × Session_24hours × Trial Type	-0.278 (0.673)	108.092	-0.413	.680	

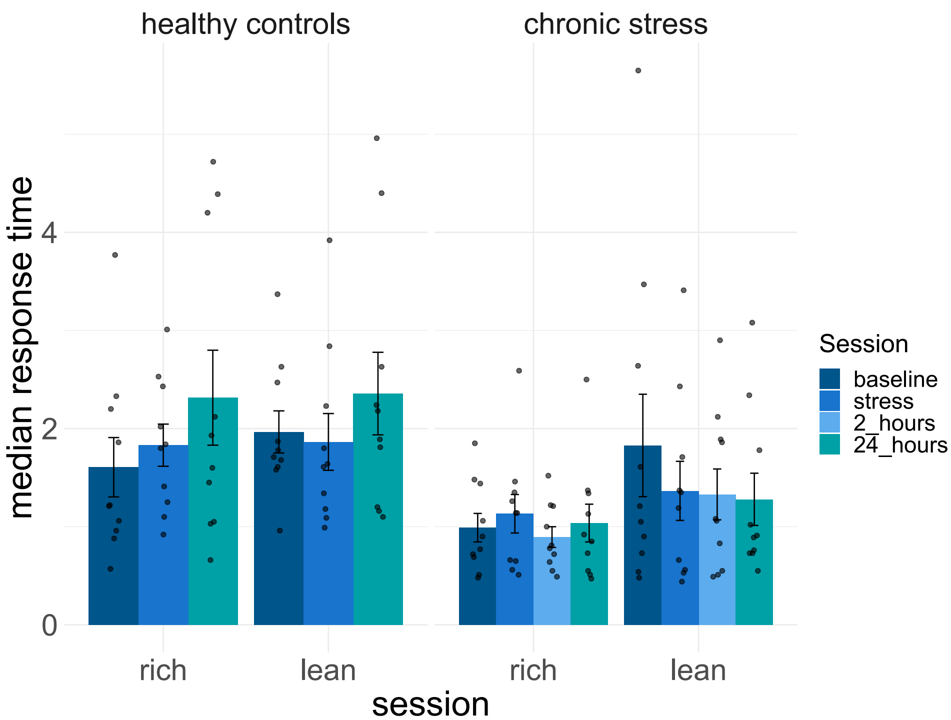

Figure S1. Median response times for each group of rats and session split by trial type. Note that in controls, there was no equivalent to the 2h post-ketamine session in the stressed rats.

Humans

In humans (Table S3), we used natural-log-transformed RTs as the dependent variable (see also Figure S2). To reduce model complexity, and because we did not find effects of block in the initial analysis, we excluded block from the model. Results suggested TRD participants responded overall faster in their second session (i.e., after ketamine administration), independent of trial type (main effect Session_post: p = .007). No other effects were significant (all ps > .248).

Table S3. Results from a linear mixed-effects regression predicting lnRT by Group, Session, and Trial Type in the human sample.

Predictor	*b (SE)*	*df*	*t*	*p*	
Intercept	6.324 (0.047)	47.780	134.181	< .001	***
Group	0.012 (0.060)	47.780	0.194	.847	
Session_post	-0.053 (0.019)	132.000	-2.765	.007	**
Trial type	-0.031 (0.027)	132.000	-1.160	.248	
Group × Session_post	0.018 (0.024)	132.000	0.733	.465	
Group × Trial type	0.005 (0.034)	132.000	0.143	.887	
Session_post × Trial type	0.010 (0.038)	132.000	0.256	.798	
Group × Session_post × Trial type	-0.005 (0.049)	132.000	-0.103	.918	

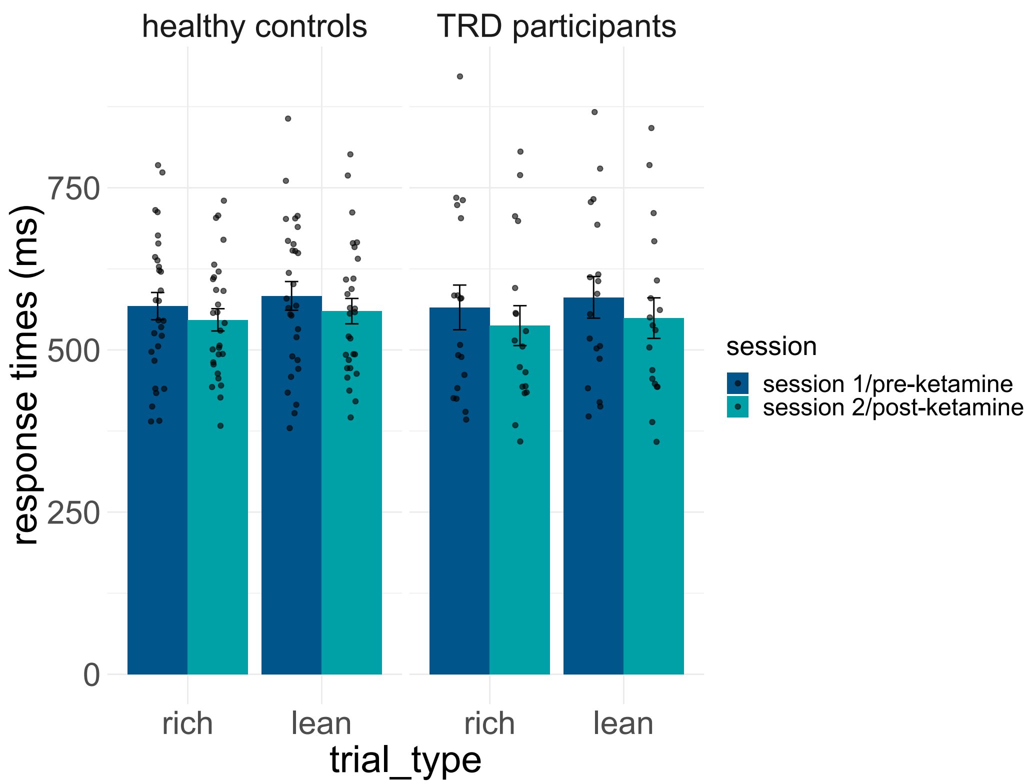

Figure S2. Response times for each group of human participants and session split by trial type.

Age effects

Given the significant difference in age between groups, we performed control analyses that additionally included age at assessment (mean-centered across all participants) as a main effect and in interaction with group and session to investigate whether it changes our results. We did not find any significant effects of age in these analyses (Table S4).

Table S4. Results from linear mixed-effects regression models controlling for age effects on response bias and discriminability.

Predictor	*b (SE)*	*df*	*t*	*p*	
Response Bias					
Intercept	0.073 (0.025)	134.172	2.926	.004	**
Group	0.094 (0.032)	134.172	2.931	.004	**
Session	0.079 (0.035)	218.000	2.263	.025	*
Block	0.004 (0.030)	218.000	0.124	.902	
Age	0.000 (0.002)	134.172	0.007	.995	
Group × session	-0.121 (0.044)	218.000	-2.716	.007	**
Group × block	0.019 (0.039)	218.000	0.495	.621	
Session × block	-0.004 (0.042)	218.000	-0.103	.918	
Group × age	-0.003 (0.002)	134.172	-1.258	.211	
Session × age	0.001 (0.002)	218.000	0.458	.647	
Block × age	0.002 (0.002)	218.000	1.310	.192	
Group × session × block	0.012 (0.054)	218.000	0.218	.828	
Group × session × age	0.004 (0.003)	218.000	1.469	.143	
Group × block × age	-0.002 (0.003)	218.000	-0.723	.471	
Session × block × age	-0.003 (0.003)	218.000	-1.055	.292	
Group × session × block × age	0.002 (0.004)	218.000	0.698	.486	
Discriminability					
Intercept	0.355 (0.036)	62.267	9.981	< .001	***
Group	0.021 (0.046)	62.267	0.455	.651	
Session	0.054 (0.030)	218.000	1.770	.078	
Block	-0.002 (0.026)	218.000	-0.062	.951	
Age	-0.002 (0.002)	62.267	-0.905	.369	
Group × session	-0.065 (0.039)	218.000	-1.674	.096	
Group × block	0.008 (0.034)	218.000	0.238	.812	
Session × block	-0.013 (0.037)	218.000	-0.357	.722	
Group × age	0.003 (0.003)	62.267	1.022	.311	
Session × age	-0.001 (0.002)	218.000	-0.546	.586	
Block × age	-0.001 (0.002)	218.000	-0.269	.789	
Group × session × block	0.024 (0.048)	218.000	0.495	.621	
Group × session × age	-0.003 (0.003)	218.000	-1.037	.301	
Group × block × age	0.001 (0.002)	218.000	0.274	.785	
Session × block × age	0.002 (0.002)	218.000	0.841	.401	
Group × session × block × age	-0.003 (0.003)	218.000	-0.844	.400	

Additional clinical measures

Full description of the exploratory analysis

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.

In a set of exploratory analyses, we thus added participants' session 1 questionnaire scores and the difference scores (calculated as session 1 – session 2, so that positive values reflect symptom improvements) to our regression model. Both scores were mean-centered across sessions but within groups, given the (intended) large difference in symptom severity between TRD patients and HCs. This allowed proper comparisons of how symptom severity affects response bias in each group (23). To reduce model complexity and given the lack of significant effects in the initial analyses, we removed *block* from these exploratory regressions, but including it did not change any of the results. We were specifically interested in SHAPS scores, given the established link between anhedonia and reduced response bias on the PRT.

As can be seen in Table 3 (main manuscript), we retained the general pattern of results found in our initial analysis. Interestingly, findings also indicated that the association between pre-ketamine 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, while higher SHAPS scores in session 1 were associated with lower response bias in TRD participants as expected, the same individuals showed larger response 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 and 3B in the main manuscript). Further, we found an unexpected effect of change in SHAPS scores on response bias across sessions (*Session_post* × SHAPS change score: p<.001), indicating that TRD participants with the largest improvement in SHAPS scores showed overall lower improvements in response bias after ketamine administration. This might 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 (Tables S4-S6), potentially indicating that acutely, ketamine was particularly effective in increasing reward responsiveness in participants with more severe pre-treatment anhedonia.

As with Snaith-Hamilton Pleasure Scale (SHAPS; (24), we included the remaining clinical measures (Hamilton Depressive Rating Scale (HAMD; (1)), Beck Depression Inventory (BDI; (25)), Quick-Inventory of Depression (QIDS; (26)) in the regression models to evaluate whether changes in response bias were associated with depressive symptoms at session 1 (i.e., pre-ketamine administration for TRD participants) or the change in these symptoms (calculated as session 1 – session 2). However, we did not find any modulations related to those measures, with the exception of a significant Group × BDI difference score interaction (p = .008) (see Tables S5 – S7).

Table S5. Response bias by BDI

Predictor	*b (SE)*	*df*	*t*	*p*	
Intercept	0.065 (0.026)	121.123	2.526	.013	*
Group	0.098 (0.034)	121.123	2.932	.004	**
Session_post	0.090 (0.036)	204.000	2.464	.015	*
BDI score session 1	0.001 (0.003)	121.123	0.175	.861	
BDI difference score	0.004 (0.003)	121.123	1.308	.193	
Group × Session_post	-0.132 (0.047)	204.000	-2.799	.006	**
Group × BDI score session 1	-0.003 (0.020)	121.123	-0.169	.866	
Group × BDI difference score	0.029 (0.049)	121.123	0.585	.559	
Session_post × BDI score session 1	0.008 (0.005)	204.000	1.568	.119	
Session_post × BDI difference score	-0.011 (0.004)	204.000	-2.691	.008	**
Group × Session_post × BDI score session 1	-0.001 (0.028)	204.000	-0.050	.960	
Group × Session_post × BDI difference score	-0.094 (0.069)	204.000	-1.363	.175	

Note. BDI = Beck Depression Inventory II.

Table S6. Response bias by QIDS

Predictor	*b (SE)*	*df*	*t*	*p*	
Intercept	0.064 (0.026)	246.000	2.413	.017	*
Group	0.099 (0.033)	246.000	2.968	.003	**
Session_post	0.074 (0.037)	246.000	1.981	.049	*
QIDS score session 1	-0.016 (0.009)	246.000	-1.771	.078	
QIDS difference score	0.002 (0.006)	246.000	0.418	.676	
Group × Session_post	-0.105 (0.047)	246.000	-2.228	.027	*
Group × QIDS score session 1	-0.054 (0.047)	246.000	-1.154	.250	
Group × QIDS difference score	-0.073 (0.055)	246.000	-1.349	.179	
Session_post × QIDS score session 1	0.008 (0.013)	246.000	0.630	.529	
Session_post × QIDS difference score	-0.004 (0.009)	246.000	-0.538	.591	
Group × Session_post × QIDS score session 1	0.073 (0.066)	246.000	1.103	.271	
Group × Session_post × QIDS difference score	0.038 (0.077)	246.000	0.495	.621	

Note. QIDS = Quick-Inventory of Depression.

Table **S7.** Response bias by HAMD

Predictor	*b (SE)*	*df*	*t*	*p*	
Intercept	0.067 (0.026)	118.524	2.532	.013	*
Group	0.096 (0.034)	118.524	2.839	.005	**
Session_post	0.082 (0.036)	214.000	2.278	.024	*
HAMD score session 1	-0.004 (0.007)	118.524	-0.530	.597	
HAMD difference score	-0.005 (0.006)	118.524	-0.921	.359	
Group × Session_post	-0.113 (0.046)	214.000	-2.456	.015	*
Group × HAMD score session 1	-0.019 (0.035)	214.000	-0.552	.582	
Group × HAMD difference score	0.005 (0.051)	118.524	0.094	.925	
Session_post × HAMD score session 1	0.004 (0.010)	214.000	0.424	.672	
Session_post × HAMD difference score	0.011 (0.008)	214.000	1.468	.143	
Group × Session_post × HAMD score session 1	0.032 (0.048)	214.000	0.660	.510	
Group × Session_post × HAMD difference score	-0.023 (0.070)	214.000	-0.334	.739	

Note. HAMD = Hamilton Depression Rating Scale.

Supplemental Discussion

Detailed discussion of study limitations

Although the use of functionally identical tasks across species is a strength of the current study, we would like to acknowledge some important limitations. First, as we relied on referrals of treatment-eligible individuals with TRD instead of active recruitment, the size of our human sample was relatively modest. Second, healthy controls did not receive an intervention comparable to the TRD participants (e.g., saline injection), leaving open the possibility that the observed effects occurred due to procedural differences or placebo effects. Future studies should thus assess larger human samples and implement double-blinded, randomized control designs, ideally including longitudinal measures to test the longevity of acute ketamine administration, given that they have been shown to be short-lived (27,28). Similarly, rats in the control group did not receive vehicle (saline) injections. However, earlier pharmacological work investigating behavior in the PRT in rats injected with saline reported similar magnitudes and across-session stability in response bias as we found here, suggesting against the possibility that saline injections would have drastically changed our results in healthy control subjects (9,10). Third, in the rodent sample, non-stressed rats did not receive ketamine, making it difficult to assess whether the response bias increase observed in stressed rats post-ketamine administration selectively ameliorated stress-induced anhedonia-like behavior or whether ketamine would have induced a more global increase in response bias in both groups. Prior work demonstrated that the dose of ketamine used here (10 mg/kg) may engender a response bias increase even in non-stressed rats at 2h, but not 24h post-injection, suggesting partially selective and more persistent improvements in chronically stressed rats (21). Fourth, we recognize that our choice of chronic stressor in the rat is one of several available rodent models (e.g., chronic mild stress (29). We expressly chose this paradigm based on its widespread use across biomedical science, as detailed above, and its ability to readily produce anhedonic-like behavioral phenotypes within the context of the PRT (11) that can be reversed following administration of putative anti-anhedonic drugs (21,22). However, it must be emphasized that no single rodent model of stress can recapitulate the numerous and diverse controlling variables involved in human depression. Thus, future studies examining ketamine during other chronic stress models within the context of PRT testing are needed to further illuminate this phenomenon. Finally, to further increase translational utility, future rodent studies on anhedonic-like behavior should include female subjects, given emerging evidence that female rats may be more sensitive to ketamine (30) and the fact that women are disproportionally affected by affective disorders (31,32). Such limitations notwithstanding, our findings in humans and rats provide converging evidence for similar anti-anhedonic effects of acute ketamine administration in both species.

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