# Entactogen Effects of Ketamine: A Reverse-Translational Study

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**Objective:** The authors sought to assess the prosocial, entactogen effects of ketamine.

**Methods:** Pleasure from social situations was assessed in a sample of participants with treatment-resistant depression from randomized, double-blind, placebo-controlled studies, using four items of the Snaith-Hamilton Pleasure Scale (SHAPS) at five time points over 1 week following treatment with ketamine (0.5 mg/kg intravenously) or placebo. The primary endpoint was postinfusion self-reported pleasure on the four SHAPS items pertaining to social situations, including the item on helping others, between the ketamine and placebo groups. In a rodent experiment, the impact of ketamine on helping behavior in rats was assessed using the harm aversion task. The primary endpoint was a reduction in lever response rate relative to baseline, which indicated the willingness of rats to forgo obtaining sucrose to help protect their cage mate from electric shock.

**Results:** Relative to placebo, ketamine increased ratings of feeling pleasure from being with family or close friends, seeing other people's smiling faces, helping others, and receiving praise, for 1 week following treatment. In the rodent experiment, during the harm aversion task, ketamine-treated rats maintained lower response rates relative to baseline to a greater extent than what was observed in vehicle-treated rats for 6 days posttreatment and delivered fewer shocks overall.

**Conclusions:** In patients with treatment-resistant depression, ketamine treatment was associated with increased pleasure from social situations, such as feeling pleasure from helping others. Ketamine-treated rats were more likely to protect their cage mate from harm, at the cost of obtaining sucrose. These findings suggest that ketamine has entactogen effects.

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Empathy is a behavioral trait among mammalian species that facilitates social cohesion and consequently improves the biological fitness of groups over individuals. Empathy is defined by three core facets: cognitive, emotional, and compassionate empathy or the ability to understand, share, and act upon the emotions of others, respectively (1–3). Disordered empathy, in any one or all its core facets, is transdiagnostic and has been associated with numerous psychiatric disorders, including major depression, autism spectrum disorder, substance abuse, and antisocial personality disorder (4–7). Disordered empathy in patients with major depression most commonly involves an imbalance in cognitive and emotional empathy, which can lead to feelings of loneliness and despair due to an inability to connect socially (8–10). Despite the tremendous benefit of alleviating disease burden associated with disordered empathy, there is currently no pharmacotherapy approved by the U.S. Food and Drug Administration that is recognized to facilitate expression of empathy. However, this could change with the emergence of psychedelic compounds such as 3,4-methylenedioxymethamphetamine (MDMA). MDMA belongs to the entactogen or empathogen class of drugs, which are characterized by their ability to facilitate emotional and social cohesion (11–13). Other psychedelic compounds, such as lysergic acid diethylamide (LSD) (14) and psilocybin (15), also appear to have prosocial, empathy-facilitating effects. While research into these compounds is ongoing, financial and time constraints as well as regulatory hurdles may be a challenge for clinical use.

To bridge the gap between unmet medical needs and availability of therapeutics in a timely manner, one strategy could involve assessing whether currently approved medications have entactogen properties. Of particular interest to this study is (*R*,*S*)-ketamine (henceforth referred to as ketamine), which was first characterized as a dissociative anesthetic but which more recently has been established to have efficacy as a rapid-acting antidepressant for patients with treatment-resistant depression (TRD) (16). A single administration of ketamine to individuals with TRD can result in alleviation of depressive symptoms, including not only mood symptoms but also anhedonia (17, 18) and suicidal ideation (19–21), suggesting the possibility that it might be used in the treatment of other psychiatric conditions that share these symptoms, and that other symptom dimensions

of TRD distinct from mood may similarly be positively affected. Despite its current indications, the full therapeutic potential of ketamine may not yet be fully realized, and research into its clinical benefits should therefore continue. Indeed, there is growing support for investigating ketamine to treat social anxiety (22), autism spectrum disorders such as activity-dependent neuroprotective protein syndrome (23), and Rett syndrome (e.g., ClinicalTrials.gov identifier NCT03633058). Considering the social deficits observed in these disorders and their considerable impact on patient functioning and health outcomes, the objective of this study was to assess the prosocial, entactogen effects of ketamine in patients with TRD and reverse translate these findings into a rodent model of empathy, the harm aversion task (24, 25).

## METHODS

Additional methods are described in the online supplement.

### Participants

All participants were studied at the National Institute of Mental Health (NIMH) Mood Disorders Research Unit in Bethesda, Md. Eligible participants (N=68) were combined from three previous studies with similar design (26–28), which included men (N=29) and women (N=39) ages 18–65 years (average age, 42.82 years) diagnosed with recurrent major depressive disorder (N=27) or bipolar I or II disorder (N=41), with a current major depressive episode without psychotic features, using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders–Patient Version (29). Participants had not responded to at least one antidepressant during their current episode (4-week minimum duration), as assessed by the Antidepressant Treatment History Form (30). Participants with bipolar disorder had to have failed to respond during a prospective open trial of a mood stabilizer (lithium or valproate for 4 weeks) while at NIMH. Each participant was required to have a score ≥20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) before each infusion. All participants provided written informed consent prior to participation in the study.

### Treatment Procedures

In a double-blind, placebo-controlled, crossover design, a ketamine infusion (0.5 mg/kg intravenously over 40 minutes) and a placebo (saline) infusion were administered 2 weeks apart, with infusion order randomized. Participants did not receive structured psychotherapy.

### Clinical Measures

The MADRS and the Snaith-Hamilton Pleasure Scale (SHAPS) (31) were administered 60 minutes before infusion and at multiple time points after infusion (at 230 minutes and at 1, 2, 3, and 7 days). Four of the 14 SHAPS items were of particular interest for this study, as they assess pleasure from social situations or interactions: items 2, 7, 13, and 14, which respectively read "I would enjoy being with my family or close friends," "I would enjoy seeing other people's smiling faces," "I would get pleasure from helping others," and "I would feel pleasure when I receive praise from other people." The remaining SHAPS items correspond to other aspects of anhedonia and were not relevant to the aims of this study. There are four response options for each item in the SHAPS (strongly agree, agree, disagree, and strongly disagree), which were used to assess the degree of pleasure or enjoyment the patient feels from each item.

### Harm Aversion Task (HAT)

Experimental procedures (Figure 1A) were conducted as previously described (24) and adapted from reference 25. Rats were pair housed, and one rat in each pair was designated as the observer and the other as the demonstrator. Observers were placed in a two-sided operant chamber and trained to press a lever to receive a sucrose pellet (Figure 1B,C). Upon successful completion of training, observers were then placed into the opposite side of the chamber (the demonstrators' side) and exposed to foot shocks. On the following day, observers were placed back into their side of the chamber, and lever responding for sucrose was assessed to establish a baseline response rate. After the baseline test, the demonstrators were placed in their side of the chamber and the first HAT session was initiated. During HAT sessions, which consisted of 10 trials, observer lever responses delivered a sucrose pellet but also delivered a foot shock to the demonstrator. After the first HAT session, the observer and demonstrator were placed back into their home cage for 15 minutes. The observer received a subcutaneous injection of either 0.9% saline or (*R,S*)-ketamine hydrochloride dissolved in saline (10 mg/kg/mL, Sigma-Aldrich) and was placed back into the chamber for 30 minutes to maintain experimenter blinding. Seven HAT sessions were conducted across 7 days.

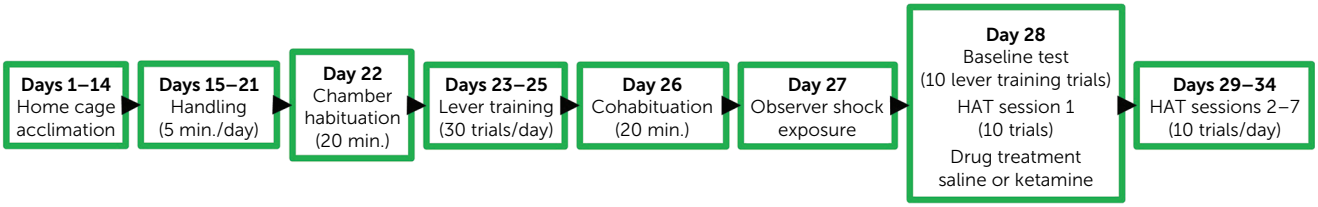
### Statistical Analysis

Human data were analyzed using R (www.r-project.org). For each SHAPS item, we used a multilevel ordinal regression model (32) to test the effect of ketamine (vs. placebo) on SHAPS item responses. All models included a random intercept to account for multiple observations per treatment per person, and the following covariates: age, sex, infusion, study, period-specific baseline item value, and the average value per person, as per Jones and Kenward (33), to avoid cross-level bias. Initial models for each item included a drug-by-time interaction to determine whether the drug effect varied by time. All interaction p values were greater than 0.05, and interaction terms were dropped in the final models. The proportional odds assumption for drug was checked by comparing (using the likelihood ratio test) a model that assumed proportional odds with a corresponding model that allowed the effect of drug to vary by cutoff or threshold.

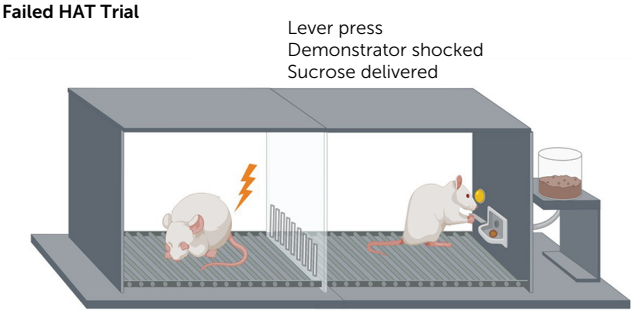
Rodent data were analyzed and illustrated using GraphPad Prism, version 9.0.2. All data are presented as mean and standard error, with statistical significance defined as a

**FIGURE 1. Harm aversion task (HAT) workflow**[a]

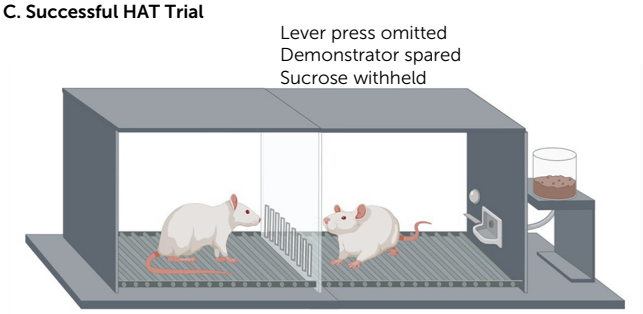
**A. Paradigm Workflow**




**B. Failed HAT Trial**




**C. Successful HAT Trial**




[a] Panel A illustrates the experimental workflow for the HAT. Panels B and C illustrate the operant chamber design and outcomes associated with a failed and successful HAT trial, respectively (created with Biorender.com). The central clear acrylic divider has small perforations at the bottom to allow the rats to smell and hear each other. The observer rat's chamber, on the right side, is equipped with a retractable lever with a cue light and a centrally located sucrose delivery tray. In panel B, a failed HAT trial resulted from the observer pressing the lever, which immediately delivered a shock to the demonstrator, followed by a sucrose pellet being delivered to the tray. A successful HAT trial resulted from the observer omitting a lever response, thus ensuring the safety of the demonstrator at the cost of the sucrose pellet, which was withheld.

p value $<0.05$. Dependent variables were assessed using three-way repeated-measures analyses of variance (ANOVAs) with treatment, sex, and session as independent variables; when sex differences were not significant, models were simplified to a two-way repeated-measures ANOVA (treatment, session). A mixed-effects model was utilized when data were missing by random chance (for example, rats that did not hit the lever during a HAT session cannot have a response or tray entry latency). Multiplicity-adjusted p values are reported for post hoc tests. Adjustments were not made to account for multiple analyses completed to address distinct experimental outcomes. Unpaired two-tailed t tests were used to ascertain mean differences between saline and ketamine treatment groups. A two-sided Fisher's exact test with Koopman's asymptotic score was used to calculate p values and relative risk of an omission or response/tray entry occurring during HAT sessions with a 95% confidence interval. Simple linear regression was used to infer correlations between the total number of shocks delivered during post-treatment HAT sessions and tray activity. The p values indicate whether the slope significantly deviated from zero.

## RESULTS

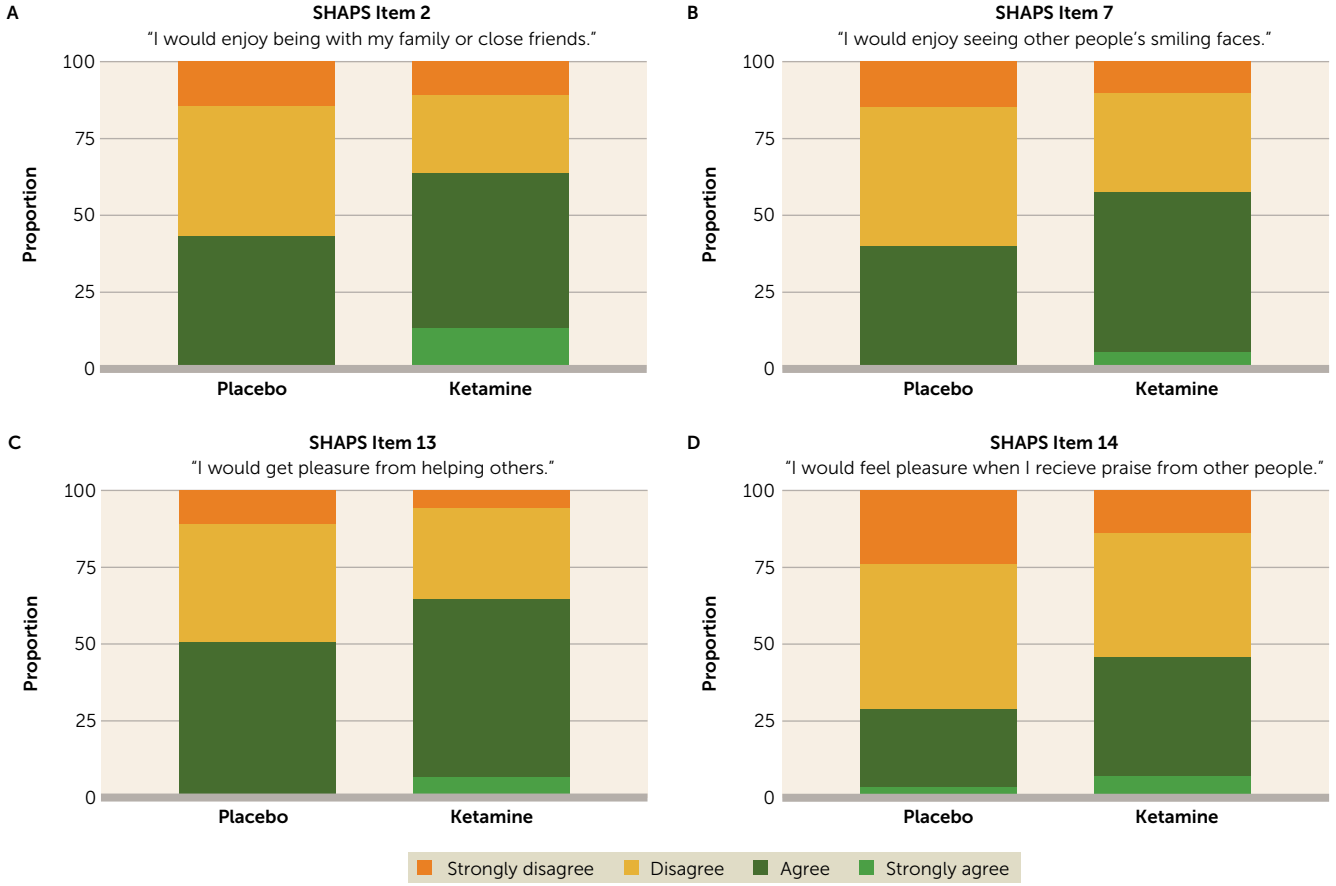
### Human Results

In a crossover design, each patient was given placebo and ketamine, administered 2 weeks apart, and pleasure from social situations was self-reported at five time points after treatment (see Figure S1A–D in the online supplement) using the Snaith-Hamilton Pleasure Scale (SHAPS). As shown in Figure 2, relative to placebo, ketamine treatment was associated with a greater likelihood of reporting feeling enjoyment from being with family or close friends overall (SHAPS item 2). This was likewise the case for items 7, 13, and 14, which assessed enjoyment the patient felt when seeing other people's smiling faces, pleasure felt from helping others, and pleasure when receiving praise from other people, respectively. Violations of the proportional odds assumption for the drug effect were evident for SHAPS items 2, 7, and 13, although the general pattern of results from models that allowed the drug effect to vary by threshold were consistent with ketamine being associated with greater reported pleasure from social interactions. Specifically, for all thresholds, the drug effect odds ratio was positive (higher scores [less pleasure] being more likely in placebo), although for the first threshold for item 7 (score $\leq 1$), the odds ratio was zero because none of the participants endorsed the lowest score (most enjoyment) in the placebo condition (data not shown). When we controlled for ketamine's overall antidepressant effects by including the MADRS total score at each postinfusion time point in the model, the effect of ketamine on each SHAPS item was no longer significant (data not shown). As assessed in previous studies, SHAPS scores improved overall after ketamine treatment and correlated with improvements in MADRS scores (26–28).

### Rodent Results

Given the positive outcomes of ketamine on SHAPS items related to social interaction, we sought to assess effects of ketamine in a rat model of social behavior. Of particular interest was SHAPS item 13, "I would get pleasure from helping others," as this item pertains the most to empathetic behavior. We hypothesized that ketamine would facilitate

**FIGURE 2. Increased probability of reporting feeling pleasure from social interaction after single-dose ketamine treatment among patients with treatment-resistant depression[a]**

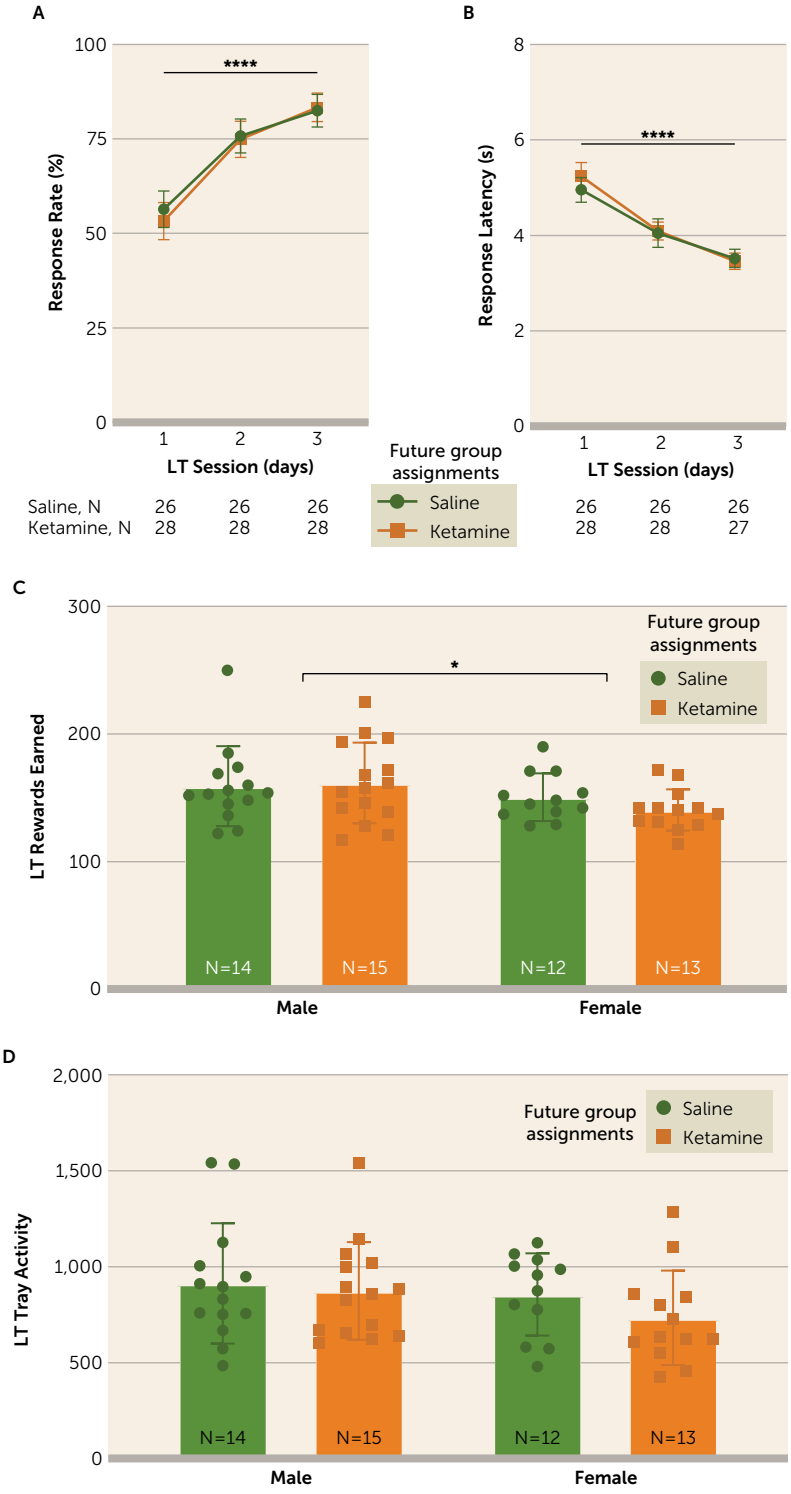



[a] The plots illustrate the distribution of responses made by patients with treatment-resistant depression, proportional to the total number of responses for each treatment group, on four items of the Snaith-Hamilton Pleasure Scale (SHAPS). Each plot is the cumulative distribution of responses across five posttreatment time points (230 minutes, 1 day, 2 days, 3 days, 7 days). Each item has four possible responses (strongly agree, agree, disagree, and strongly disagree), which indicate the degree of pleasure or enjoyment the patient would feel in each of the social scenarios. This study utilized a crossover design, with each patient receiving both ketamine (0.5 mg/kg intravenously over 40 minutes) and placebo (saline). In panel A, patients were more likely to report enjoying being with their family or close friends after ketamine treatment relative to placebo (log odds ratio=1.4, 95% CI=0.97–1.7; $p<0.001$). In panel B, patients were more likely to report enjoying seeing other people's smiling faces after ketamine treatment relative to placebo (log odds ratio=1.2, 95% CI=0.79–1.6; $p<0.001$). In panel C, patients were more likely to report feeling pleasure from helping others after ketamine treatment relative to placebo (log odds ratio=1.2, 95% CI=0.79–1.6; $p<0.001$). In panel D, patients were more likely to report feeling pleasure from receiving praise from other people after ketamine treatment relative to placebo (log odds ratio=1.5, 95% CI=1.1–2.0; $p<0.001$).

the expression of helping (or empathetic) behavior in rats. To test our hypothesis, we utilized the HAT, which measures the willingness of rats (designated as observers) to forgo pressing a lever to obtain sucrose to protect their cage mate (the demonstrator) from receiving an electric shock (24, 25). Using a two-sided operant chamber, we trained male and female observers to press a lever to obtain a sucrose pellet (Figure 1). Across the first three lever training sessions, we observed male and female observers rapidly increase lever response rate (Figure 3A) and press the lever more quickly (response latency) (Figure 3B), independently of sex and their eventual treatment pairing. Furthermore, overall performance during lever training was consistent across subsequent treatment groups, with no difference in total number of rewards earned (Figure 3C) or in total activity within the reward tray (Figure 3D). We observed a modest sex difference in total rewards earned, with females obtaining fewer rewards (Figure 3C). These data demonstrate that prior to assessment of empathy and administration of treatments, observer rats' lever responding was consistent, which would otherwise have confounded our interpretation of performance during HAT sessions.

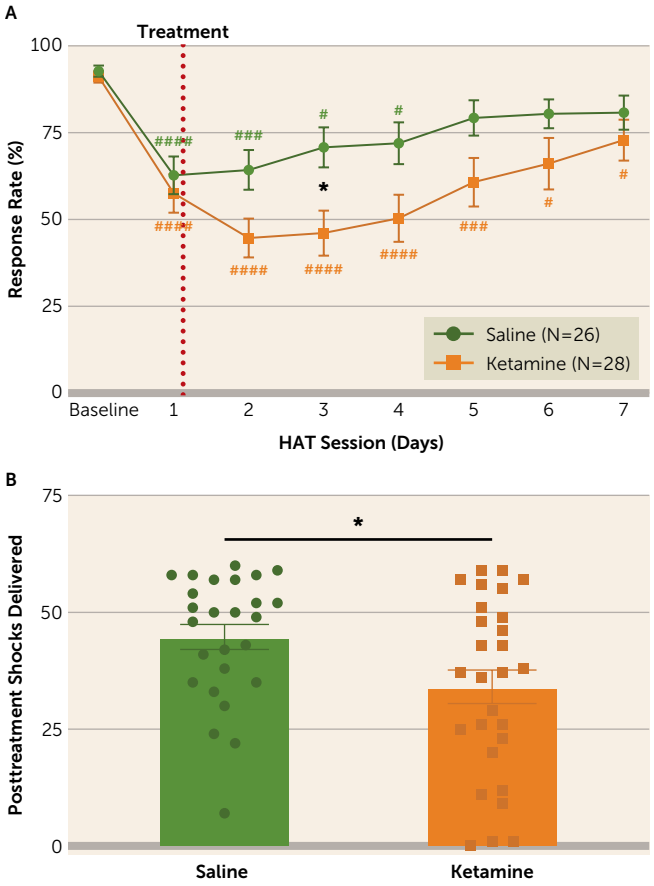
After lever training and exposing the observer rats to foot shocks on the demonstrators' side of the chamber, observers were given a baseline test. This baseline test was used to confirm that lever responding for sucrose was intact after exposure to shocks in the absence of the demonstrator. Immediately after completion of the baseline test, the demonstrator was placed into its side of the chamber and the first HAT session was initiated. During HAT sessions, lever responses by the observer still delivered a sucrose pellet but also delivered a shock to the demonstrator (failed trial, Figure 1B).

**FIGURE 3. Lever response training among observer rats prior to treatment**[a]




[a] In panel A, lever response rate during observer rats' lever training (LT) to obtain sucrose pellets consistently increased across sessions, independently of sex or eventual treatment pairing (sex, p=0.29; treatment, p=0.82; session, p<0.0001; session-by-treatment interaction, F=0.297, df=2, 100, p=0.74). In panel B, latency to press the lever (response latency) during rats' lever training consistently decreased across sessions independently of sex or eventual treatment pairing (sex, p=0.89; treatment, p=0.77; session, p<0.0001; session-by-treatment interaction, F=0.602, df=2, 99, p=0.55). In panel C, the total number of rewards earned during lever training was not significantly different among eventual treatment pairing groups, but male rats earned more rewards relative to females overall (sex, p=0.041, mean difference=14.89; treatment, p=0.27; sex-by-treatment interaction, F=0.773, df=1, 50, p=0.38). In panel D, the total amount of tray activity during lever training did not differ significantly across eventual treatment groups or sex (sex, p=0.17; treatment, p=0.26; sex-by-treatment interaction, F=0.336, df=1, 50, p=0.57). These data demonstrate that rats rapidly associate lever presses with reward delivery. Three-way analysis of variance with Dunnett's post hoc test for panel A and a mixed-effects analysis with Dunnett's post hoc test for panel B, ****p<0.0001 effect of session relative to session 1. Two-way analysis of variance for panels C and D, *p<0.05 effect of sex.

**FIGURE 4. Reduction in response rate during the harm aversion task (HAT) after a single dose of ketamine[a]**



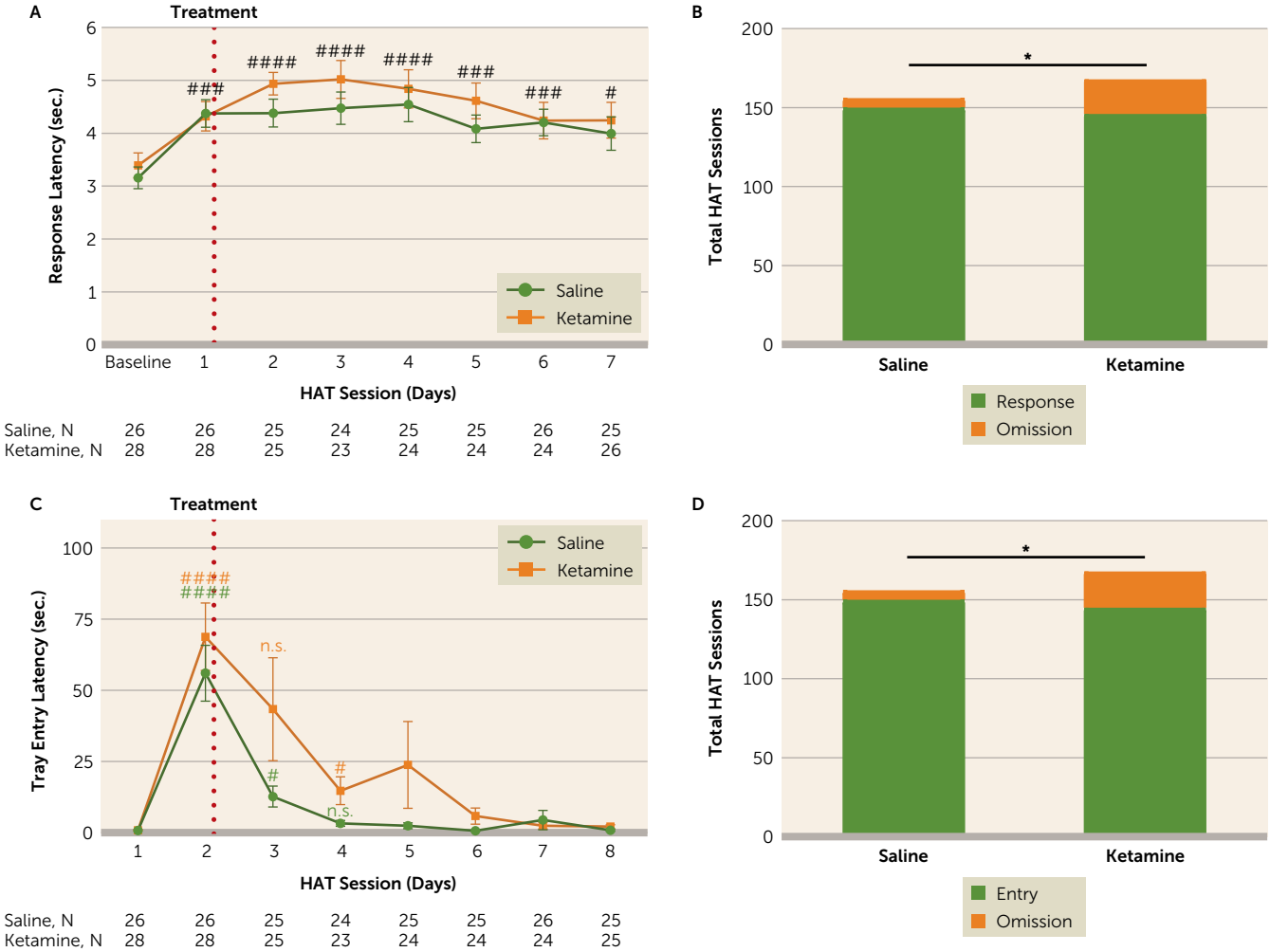

[a] Panel A illustrates lever response rate of the observer rats during a baseline session, in which lever presses delivered a sucrose pellet, and during the HAT, in which lever presses delivered a shock to the demonstrator rat in addition to delivering a sucrose pellet to the observer rat. Independently of sex, rats treated with saline after HAT session 1 maintained response rates significantly lower than baseline during HAT sessions 2–4, whereas rats treated with ketamine (10 mg/kg/mL, subcutaneous injection) after HAT session 1 maintained response rates significantly lower than baseline during HAT sessions 2–7. Within HAT session 3 specifically, ketamine-treated rats had significantly lower response rates relative to saline-treated rats (sex, $p=0.064$; treatment, $p=0.029$; session, $p<0.0001$; treatment-by-session interaction, $F=2.711$, $df=7, 350$, $p=0.0095$; treatment-by-sex interaction, $F=2.519\times10^{-5}$, $df=1, 50$, $p=0.996$; sex-by-session interaction, $F=1.334$, $df=7, 350$, $p=0.23$). In panel B, the total number of shocks delivered during HAT sessions 2–7 (posttreatment sessions) was significantly lower for rats treated with ketamine relative to rats treated with saline. Three-way analysis of variance with Dunnett's post hoc test for panel A, $^{\#}p<0.05$, $^{\#\#\#}p<0.001$, $^{\#\#\#\#}p<0.0001$ effect of session within treatment compared to baseline; $^{*}p<0.05$ effect of treatment within session. Two-tailed, unpaired t-test for panel B, $^{*}p<0.05$.

Omitting lever responses prevented shock delivery at the cost of sucrose being withheld (successful trial, Figure 1C). The primary outcome measure was response rate across seven HAT sessions (Figure 4A). If response rate during a HAT session was significantly lower than baseline, this indicates that the observers are harm averse. Drug treatments were administered after HAT session 1, with 26 observers receiving saline (N=14 males, N=12 females; 1 mL/kg, subcutaneous injection) and 28 observers receiving ketamine (N=15 males, N=13 females; 10 mg/kg/mL, subcutaneous injection). Consistent with our prediction, ketamine-treated observers had lower response rates overall during subsequent HAT sessions relative to saline-treated observers, which peaked during session 3 (48 hours posttreatment). Indeed, ketamine-treated observers delivered fewer shocks overall during the posttreatment sessions relative to saline-treated observers (Figure 4B). Furthermore, while we observed induction of harm aversion during session 1 in both groups, the ketamine-treated group remained harm averse through session 7, whereas the saline-treated group returned to baseline levels by session 5. Notably, although it fell short of significance ($p=0.064$; see Figure S2 in the online supplement), female observers showed higher overall response rates relative to males, which is consistent with a previous finding (24). Thus, these data lend support to a single dose of ketamine facilitating empathetic behaviors in rats for up to 6 days posttreatment.

Secondary outcome measures during the HAT include the latency to lever press and to enter the reward tray after shock delivery (Figure 5A–D). Regarding response latency, we observed significant increases in both treatment groups, which persisted through session 7 with no significant difference in increase between groups (Figure 5A). However, this analysis includes data only from observers that responded during a given session. Thus, we plotted the total number of sessions in which observers responded or omitted a lever press (Figure 5B). This revealed that ketamine-treated observers had an increased likelihood of omitting lever responding during a session. Regarding tray entry latency, we observed significant increases in both treatment groups during session 1 relative to baseline. However, saline-treated observers returned to baseline levels by session 3, whereas ketamine-treated observers returned to baseline, and were stable, by session 4. Furthermore, ketamine-treated observers had an increased likelihood of not entering the reward tray (Figure 5D). Together, these data illustrate an increased hesitancy to press the lever and enter the reward tray after ketamine treatment relative to saline treatment.

Given previous reports in rodents suggesting that ketamine increases preference for sucrose, which is considered an anti-anhedonia, antidepressant-like effect (34), we assessed whether ketamine influenced sucrose-seeking behavior, as measured by tray activity. During HAT sessions, we observed greater tray activity overall in females relative to males (see Figure S3A in the online supplement). Additionally, ketamine-treated observers had significantly lower total tray activity during session 3 relative to saline-treated rats. Despite this, when we plotted total tray activity during the posttreatment sessions against total shocks delivered, we found no difference in the positive correlation between shocks delivered and sucrose seeking between saline-treated and ketamine-treated observers (see Figure S3B in the online supplement). In other words, total sucrose seeking is a function of the number of failed trials (where a shock was delivered) and thus a function of the amount of time each

**FIGURE 5. Likelihood of rats omitting responding and entering the reward tray during the harm aversion task (HAT)[a]**




[a] In panel A, latency to press the lever (response latency) during HAT sessions 1–7 was significantly increased, independently of sex and treatment, relative to baseline (sex, $p=0.69$; treatment, $p=0.28$; session, $p<0.0001$; treatment-by-session interaction, $F=0.489$, $df=7, 322$, $p=0.84$; treatment-by-sex interaction, $F=0.665$, $df=1, 50$, $p=0.42$; sex-by-session interaction, $F=0.595$, $df=7, 322$, $p=0.79$). As shown in panel B, rats treated with ketamine were more likely to omit pressing the lever during a HAT session relative to saline-treated rats (relative risk=1.106; $p=0.003$; 95% CI=1.037–1.193). In panel C, latency to enter the reward tray (tray entry latency) was significantly increased relative to baseline in HAT session 1 in both saline- and ketamine-treated rats. Saline-treated rats maintained heightened tray entry latency relative to baseline during HAT session 2, whereas ketamine-treated rats maintained heightened tray entry latency relative to baseline during HAT session 3 (sex, $p=0.44$; treatment, $p=0.034$; session, $p<0.0001$; treatment-by-session interaction, $F=1.548$, $df=7, 321$, $p=0.15$; treatment-by-sex interaction, $F=0.058$, $df=1, 50$, $p=0.81$; sex-by-session interaction, $F=0.668$, $df=7, 321$, $p=0.70$). Panel D illustrates how rats treated with ketamine were more likely to omit entering the tray during a HAT session relative to saline-treated rats (relative risk=1.114; $p=0.0029$; 95% CI=1.044–1.203). Three-way analysis of variance with Dunnett's post hoc test for panels A and C, $^{\#}p<0.05$, $^{\#\#\#}p<0.001$, $^{\#\#\#\#}p<0.0001$ effect of session compared to baseline (session within treatment for panel C). Two-sided Fisher's exact test for panels B and D, $^{*}p<0.05$.

observer was in the chamber, independent of treatment. This phenomenon was consistent when tray activity was stratified into distinct phases of the session. Indeed, tray activity during the 5-minute failure intertrial interval followed a pattern similar to total overall tray activity (see Figure S3C,D in the online supplement). Likewise, tray activity during the success intertrial interval (after response omission) was negatively correlated with shocks delivered (see Figure S3E,F in the online supplement). Lastly, sex and treatment differences were observed in tray activity during the 10-second interval immediately following shock and reward delivery. However, the treatment difference is a function of failed trials, not a direct effect of ketamine (see Figure S3G,H in the online supplement). Given these data, we conclude that ketamine did not significantly affect sucrose seeking but rather affected the observers' decision making on choosing sucrose over protecting their cage mate.

## DISCUSSION

In this study, patients with TRD receiving a single dose of ketamine had an increased likelihood of reporting pleasure from social interactions, as measured by the SHAPS, relative to when they received placebo, up to 1 week posttreatment.

This included feeling pleasure from receiving praise and from helping others as well as enjoying seeing other people's smiling faces and being with family or close friends. Notably, this observation was not independent of changes in MADRS scores and therefore is not distinguishable from the general antidepressant, anti-anhedonia effect of ketamine. We next assessed whether the prosocial effects of ketamine were consistent across species, and perhaps separable from its broader antidepressant-like effects, by utilizing the HAT, which measures the willingness of observer rats to forgo sucrose reward to protect their cage mate (the demonstrator) from harm, a preclinical model of helping behavior and empathy. We observed that a single dose of ketamine reduced the total number of shocks observers delivered to the demonstrator during the HAT relative to those receiving saline. Ketamine-treated observers also maintained a significantly lower response rate relative to baseline through session 7, whereas saline-treated observers returned to baseline rates by session 5, which indicates that ketamine maintained harm aversion (i.e., increased helping behavior or empathy) to a greater extent across time. Importantly, the pro-empathy effects of ketamine are independent of any change in sucrose seeking, given that tray activity per trial was consistent across treatment groups. Taken together, these findings lend support to ketamine positively influencing social interactions and behaviors in both humans and rats. It is possible that this outcome contributes to the alleviation of symptoms associated with TRD, and potentially other disorders, after ketamine treatment.

This study has limitations. The SHAPS does not specifically ask whether the patients' behavior has changed after treatment. Future studies should assess whether the change in mood regarding social situations induced by ketamine corresponds to patients' being more likely than control subjects to help other people. Alternatively, further studies utilizing clinical questionnaires that more comprehensively assess empathy could be used to confirm the findings we observed with ketamine using the SHAPS. This could include utilization of the Toronto Empathy Questionnaire, which assesses emotional contagion, emotional comprehension, physiological arousal, and conspecific altruism (35). Additionally, it will be important to assess how structured psychotherapy in addition to ketamine may provide additional clinical benefits. Regarding our rat study, our assertion that the HAT is an accurate model of empathy is contingent upon being able to demonstrate that the observers were perceiving, internalizing, and acting upon the condition of the demonstrator. Increases in response and tray entry latency provide evidence that the observer rats were perceiving a change in their environment (i.e., the demonstrator being shocked) given their hesitation to lever press and retrieve sucrose. Internalization of the condition of the demonstrator was not assessed in observers. In future experiments, measurements such as heart rate in real time would provide evidence that the observer is physiologically responding to shocks being delivered to the demonstrator. Despite this, our primary endpoint, response rate during HAT sessions, assesses changes in behavior in response to the perception of social cues. These provide confidence, but not certainty, in our interpretation of the HAT modeling empathy in rats.

The emergence of ketamine as a rapid-acting, efficacious, and long-lasting therapy for TRD was a revolutionary advancement in psychiatric medicine (16). Since then, much has been learned about the mechanisms underlying how ketamine positively impacts patients with major depression, yet a consensus has not been reached (36). Prevailing theories assert the importance of ketamine's inhibitory actions at the *N*-methyl-D-aspartate (NMDA) glutamate receptor expressed by GABAergic interneurons, which lead to a disinhibition of excitatory output, and thus a net effect of increased excitatory output, in key brain regions involved in cognition and mood, such as the anterior cingulate cortex (ACC) (37). Intriguingly, deactivation of the ACC in rats was found to prevent the expression of empathy during the HAT (25), which suggests that activity in the ACC may be a locus for both the antidepressant and entactogen effects of ketamine. Despite this potential link, an emerging viewpoint is that the actions of ketamine at NMDA receptors do not fully explain its therapeutic effects, as antidepressant-like effects in mice are still observed with ketamine metabolites, namely, (*2R,6R*)-hydroxynorketamine, which do not target NMDA receptors (38). It is unknown whether the ketamine metabolites improve depression symptoms in humans, and there is also a need to assess their entactogen effects.

Therapeutic strategies aimed at increasing pleasure from social situations and improving social cohesion through empathy have the potential to positively impact many neuropsychiatric disorders. This study provides evidence for ketamine improving social dysfunction in patients with TRD and empathy in otherwise healthy rats, which suggests that ketamine may be an entactogen. Given this, it is possible that ketamine may be efficacious in other disorders with marked social dysfunction, such as social anxiety disorder, posttraumatic stress disorder, and autism. Indeed, there is growing evidence (22, 39, 40) and ongoing clinical trials (e.g., ClinicalTrials.gov identifier NCT02611921) in support of this strategy, which warrants further study.

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Drs. Zarate and Gould are listed as inventors on patents and patent applications related to the pharmacology and use of ketamine metabolites in the treatment of depression, anxiety, anhedonia, neuropathic pain, suicidal ideation, and/or posttraumatic stress disorders. Dr. Zarate has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. Dr. Gould has assigned his patent rights to the University of Maryland, Baltimore, but will share a percentage of any royalties that may be received by the university. The other authors report no financial relationships with commercial interests.

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