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Environmental determinants of ketamine's prohedonic and antianhedonic efficacy: Persistence of enhanced reward responsiveness is modulated by chronic stress

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ABSTRACT

Ketamine, a dissociative anesthetic with well documented abuse liability, can also provide rapid-onset and persistent antidepressant effects and is currently used for the management of treatment-resistant depression. Although the precise neurobiological mechanisms underlying its antidepressant actions are not fully determined, a critical feature of ketamine's clinical efficacy may be its antianhedonic action. Anhedonia is an endophenotype of depression defined by decreased responsivity to previously rewarding stimuli and is generally not ameliorated by conventional antidepressants, emphasizing the need to examine underlying behavioral mechanisms of action. In this study, the probabilistic reward task, a reverse-translated assay originally designed to objectively quantify anhedonic phenotypes in human subjects, was used in rats to examine ketamine's effects on reward responsiveness under conditions without programmed stressors (3.2–32.0 mg/kg) or during ongoing chronic exposure to ecologically relevant stress (10.0 mg/kg). Results showed that under conditions without programmed stress, ketamine produced significant prohedonic effects in the probabilistic reward task, defined by increases in reward responsiveness that dissipated within 24 hours. In rats exposed to ongoing chronic stress, ketamine produced significant antianhedonic effects, defined by the rescue of blunted reward responsiveness, that persisted for nearly 1 week. Taken together, the prolonged antianhedonic effects of ketamine in rats experiencing chronic stress, compared with the shorter-lived prohedonic effects in subjects without exposure to programmed stressors, are striking and highlight the role of environmental determinants in the effects of ketamine on behavioral processes. Moreover, the translational nature of this experimental design may offer the opportunity to accelerate development of novel antianhedonic therapeutics.

Significance Statement: Although ketamine is used for the management of treatment-resistant depression, its precise behavioral mechanisms of action are not fully delineated. Emerging evidence suggests the attenuation of anhedonia plays a key role in its rapid-acting therapeutic efficacy. To evaluate this possibility, the effects of ketamine were studied using a reverse-translated assay of reward responsiveness in rats and documented to be short-lived (prohedonic) under nonstressful conditions and persistent (antianhedonic) under stressful conditions, informing ketamine effects in healthy versus depressed individuals.

1. Introduction

Clinical use of the dissociative anesthetic ketamine for the management of treatment-resistant depression (TRD) represents an unprecedented circumstance within the context of medications development for neuropsychiatric illness. The availability of

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ketamine's *S*-(+) enantiomer, esketamine, following approval by the Food and Drug Administration (FDA; Kim et al, 2019) was a significant therapeutic advance in view of the limited efficacy and delay in onset of frontline antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), which leave many patients with unmet treatment needs. For example, only approximately one-third of those diagnosed with major depression are estimated to report full clinical and functional recovery following standard SSRI treatment regimens (Al-Harbi, 2012; Sussman et al, 2019). Moreover, anhedonia, the loss of pleasure in previously rewarding activities, often remains unabated even when SSRIs reduce other depressive symptoms (Calabrese et al, 2014; Admon and Pizzagalli, 2015). Determining the precise behavioral and neurobiological mechanisms responsible for ketamine's rapid-acting antidepressant efficacy is an active research domain (Johnston et al, 2024; Krystal et al, 2024). Clinically, emerging evidence points to ketamine's ability to attenuate anhedonic symptoms (Almeida et al, 2024; Kwaśny et al, 2024; Patarroyo-Rodriguez et al, 2024), and, possibly, this recovery of hedonic tone contributes critically to its therapeutic efficacy.

Although ketamine was FDA-approved for use as an anesthetic in 1970 and, as described, more recently its *S*-(+)enantiomer, esketamine, in the management of TRD, it also has long been a recreational drug with well-documented reinforcing effects and abuse liability (Liu et al, 2016; Le et al, 2022). Ketamine is not the first FDA-approved medication with addiction potential (eg, prescription opioids); however, its use is notable considering the comorbid relationship between major depression and substance use disorders (Davis et al, 2008; Hunt et al, 2020). As in the treatment of TRD, it is likely that the reinforcing properties of ketamine also involve its ability to alter hedonic tone—here, reflected in its reported pleasurable effects in healthy individuals (Kalsi et al, 2011). In view of ketamine's use in both recreational and medicinal situations, it may be useful to distinguish between a drug's effects on hedonic mechanisms in those contexts. Thus, *prohedonic efficacy* can be defined by a drug treatment that increases responsiveness to reward in subjects not experiencing anhedonia, for example, in a purely recreational context. Conversely, *antianhedonic efficacy* can be defined by a drug treatment that attenuates a deficit in reward responsiveness that develops in response to environmental variables such as chronic stress (Kessler, 1997; Schmidt et al, 2008; Davis et al, 2017). From this perspective, ketamine may be said to produce prohedonic effects in healthy users and antianhedonic effects in patients with TRD.

This study in rats was conducted to further illuminate the relationship between ketamine and reward responsiveness by comparing ketamine-induced changes in reward responsiveness in both nonstressful and stressful environments. Drug testing protocols in nonstressful environments were based on previous studies in subjects without exposure to programmed stressors (Wooldridge et al, 2021; Adam et al, 2024). Drug testing protocols in stressful environments arranged conditions of chronic inescapable ice water stress based on recent work confirming the ability of this ecologically relevant stressor in the rat to reliably produce anhedonic phenotypes (Gonzalez et al, 2024). Both approaches used the probabilistic reward task (PRT). The PRT, based on signal detection theory (Luc et al, 2021), was developed to objectively quantify reward responsiveness in clinical populations with anhedonia (Pizzagalli et al, 2005) and is used to supplement traditional self-report questionnaires designed to diagnose anhedonia. In the latest revision of the Research Domain Criteria (Insel et al, 2010; https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/behavioral-assessment-methods-for-rdoc-constructs.shtml), the PRT is a recommended means for probing the positive valence systems. In this computerized task, subjects make visual discriminations under asymmetric probabilistic contingencies such that correct responses to one stimulus are more likely to result in reward (rich) than are correct responses to the other (lean). As documented across numerous studies, healthy subjects readily develop the adaptive response bias toward the more richly rewarded stimulus. In contrast, subjects with anhedonia reliably exhibit a blunted response bias indicative of deficits in responsiveness to reward, which correlates with current and predicts future anhedonia (Vrieze et al, 2013; Fletcher et al, 2015). More recently, the PRT also has been reverse-translated using touchscreen technology for preclinical drug development studies in rodents and nonhuman primates (Luc et al, 2021). It previously has proven sensitive to the effects of drugs, including ketamine in the marmoset (Wooldridge et al, 2021), and chronic stress in the mouse (Hisey et al, 2023) and rat (Gonzalez et al, 2024).

2. Materials and methods

2.1. Subjects

Twenty-four adult male Long-Evans rats obtained from Charles River Laboratories were used in this study. Previous characterizations of PRT performance in female and male rats did not reveal sex differences (Kangas et al, 2020). Upon arrival, rats were approximately 10 weeks of age and weighed between 175 and 200 g. They were group-housed in 3s to a home cage within a climate-controlled vivarium with a 12-hour light/dark cycle (lights on at 7 AM). Water was available ad libitum in the home cage. To establish sweetened condensed milk as a reinforcer, rats were restricted to approximately 10–15 g of rodent chow (Laboratory Rodent Diet 5001; LabDiet), given daily after the experimental session. The study protocol was approved by the Institutional Animal Care and Use Committee at McLean Hospital in accordance with established guidelines (National Research Council, 2011).

2.2. Touchscreen chamber

Schematics of the touch-sensitive experimental chamber have been reported previously (Kangas and Bergman, 2017). Briefly, the right-hand wall of a 25.0- × 30.0- × 35.0-cm Plexiglas chamber was equipped with a 17-inch touchscreen (1739L; ELO TouchSystems), above which a speaker bar (NQ576AT; Hewlett-Packard) was mounted. The chamber was housed in a 40.0 × 60.0- × 45.0-cm sound-attenuating and light-attenuating enclosure (ENV-022MD; Med Associates). An infusion pump (PHM-100-5; Med Associates) located outside the enclosure delivered 0.1 mL of a 30% sweetened condensed milk solution (Casa Solana; Sysco Corporation) into the reservoir of a custom-designed aluminum receptacle (4.0 × 5.0 × 1 cm) on the center of the left-hand wall. Reward delivery was paired with an 880-millisecond yellow screen flash and 440 Hz tone. All task events and data collection were programmed in E-Prime Professional 2.0.

2.3. PRT

2.3.1. Initial training

The PRT is a computerized assay originally designed for humans (Pizzagalli et al, 2005) and subsequently reverse-translated using touchscreen technology for rats (Kangas et al, 2020) to examine responsiveness to reward as it relates to anhedonic behavioral phenotypes. Rats were first trained to respond on the touchscreen and, using previously published protocols, subsequently trained to discriminate stimuli that varied in line length (Kangas et al, 2020). Trials began with presentation of a white line on a black background, with its lower edge 3.0 cm above 5.0 × 5.0 cm left and right blue

response boxes (Fig. 1). The length of the line was either 600 × 60 px (31.5 × 3.25 cm: long line) or 200 × 60 px (10.5 × 3.25 cm: short line). Long line and short line length trial types varied in a quasi-random manner across 100-trial sessions such that there were exactly 50 trials of each type. Rats were differentially reinforced to respond to the left or right response box depending on the length of the white line (long line: respond left, short line: respond right, or vice versa, counterbalanced across rats). Each correct response was reinforced as described earlier and followed by a 5-second blackout period, whereas each incorrect response immediately resulted in a 10-second blackout period. Discrimination training sessions continued until accuracies for both line length trial types were ≥80% correct for 2 consecutive sessions, concordant with the performance criteria in previous human PRT studies (Pizzagalli et al, 2005, 2008, 2020). After this criterion was met, rats were assigned to either conditions without programmed stress or conditions of chronic stress.

2.3.2. PRT testing under conditions without programmed stress

Following discrimination training, drug testing was conducted in accord with the following protocol: saline or a dose of ketamine (3.2, 10, and 32 mg/kg; $n = 8$) was studied each week, using 5-session testing protocols as previously described (Kangas et al, 2020; Wooldridge et al, 2021; Adam et al, 2024). Specifically, each weekly testing protocol comprised nonprobabilistic (100%) reward following correct responses during both trial types (long and short lines) on Monday and Tuesday. This was followed by asymmetric 60%–20% (rich-lean) probabilistic reward contingencies on Wednesday, Thursday, and Friday. In these sessions, a correct response to one of the line lengths (long or short) was reinforced 60% of the time (rich stimulus), whereas a correct response to the other line length was reinforced 20% of the time (lean stimulus). Incorrect responses were never reinforced. Saline or a dose of ketamine was administered on Thursday 2 hours before the PRT session across weeks in a mixed order among rats using a Latin square design. PRT performance was therefore evaluated across 4 consecutive 5-session testing protocols at baseline (Wednesday), following acute saline or ketamine treatment (Thursday), and 24 hours after administration (Friday).

2.3.3. PRT testing under conditions of chronic stress

Following discrimination training and characterization of baseline PRT performance, rats were exposed to chronic inescapable ice

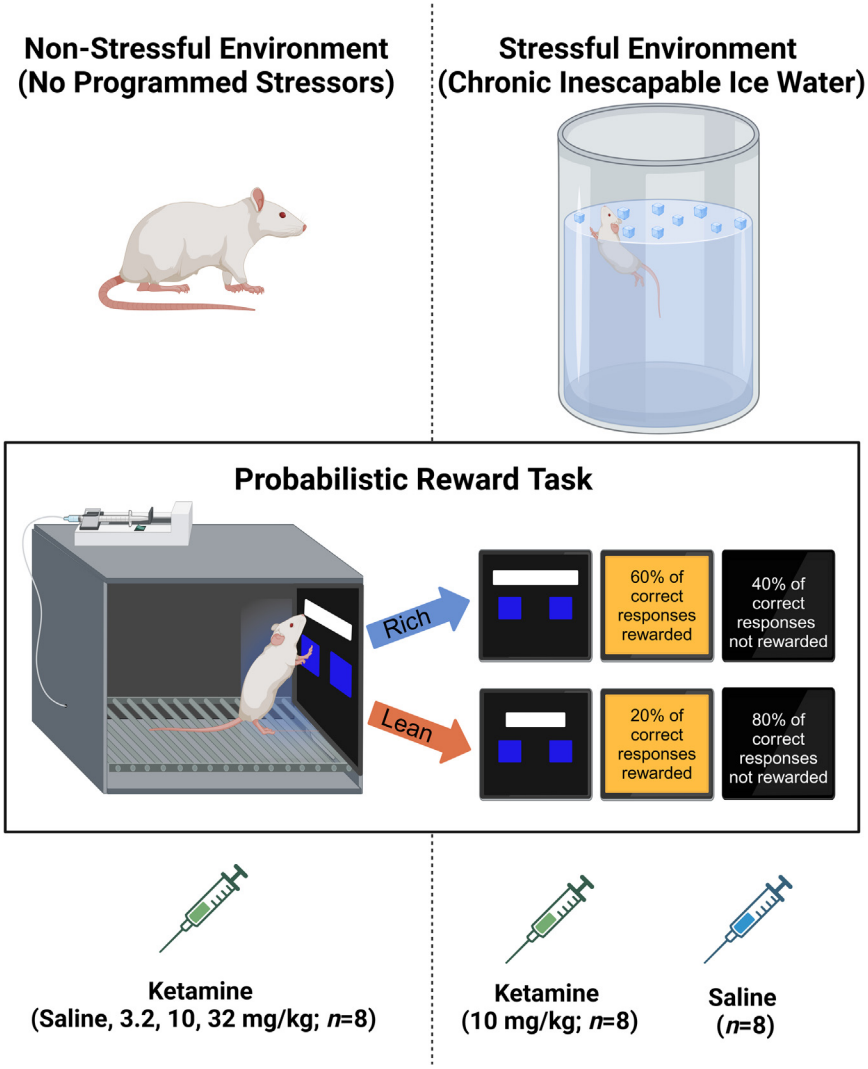

Fig. 1. Schematics of the chronic ecologically relevant stressor and touchscreen cognition task used in the present studies. Groups of subjects ($n = 8$/group; $n = 24$/total) were tested under conditions without programmed stress with saline and doses of ketamine ($n = 8$). Additional groups were tested under conditions of chronic stress with 10 mg/kg ketamine ($n = 8$) or saline ($n = 8$).

water stress as previously described (Gonzalez et al, 2024). This chronic ecologically relevant stressor involved placing the rats in an opaque polycarbonate cylinder (52.0 cm high, 40.0 cm diameter) filled with water to a depth of 38.0 cm, which was deep enough to prevent the rats from resting on its tail but not too full to prevent the rat from climbing out of the arena (Fig. 1). Prior to stress exposure, water was iced to 10 °C, which is an ecologically relevant water temperature in many rodent environments during winter (DuBose et al, 2007) and associated with reliable swim durations of approximately 4–8 minutes prior to subsequent submersion. Rats were placed into the iced water, observed continuously during their swim duration, and rescued by the observer after submerging for >7 seconds without an apparent ability to resurface. After rescue from the ice water arena, rats were placed singly in a clean home cage, without the aid of towel drying or heat lamp, for a 2.5-hour period and then transferred to a touchscreen chamber for behavioral testing. This 2.5-hour recovery interval was designed to accommodate the administration of ketamine 30 minutes following ice water rescue and a 2-hour interval between ketamine treatment and testing. Although rats were, by design, in a moderately hypothermic state (defined by Gagarinskiy et al, 2022, as 30–32 °C) upon rescue, full recovery in baseline rectal temperature (~37 °C) was reliably observed at the 2.5-hour time point. This process was repeated daily for chronic inescapable ice water stress. PRT testing also continued daily, and when a reduced response bias was observed, defined as at least half of the related signal detection value (log *b*, see *Data analysis* section) observed during prestress baseline conditions, either saline ($n = 8$) or 10.0 mg/kg ketamine ($n = 8$) was administered to the rat on the following day while chronic stress conditions continued. The dose of ketamine chosen for study under conditions of chronic stress was based on (1) previous studies indicating its approximation in rats with the clinically efficacious outcomes in humans (Garcia et al, 2008, 2009; Wang et al, 2011) and (2) its production of peak increases in response bias in this study under conditions without programmed stress (10.0 mg/kg). Chronic inescapable ice water stress continued daily for 7 days, with PRT test sessions also occurring 1, 3, and 7 days after dosing, to examine the enduring effects, if any, of drug treatment on response bias during chronic stress conditions.

2.4. Data analysis

2.4.1. PRT

The implementation of probabilistic contingencies yields 2 primary dependent measures: response bias and task discriminability, which can be quantified using equations derived from signal detection theory (McCarthy and Davison, 1979; McCarthy, 1983; Luc et al, 2021) by examining the number of correct and incorrect responses in rich and lean trial types.

Specifically, response bias is calculated using the following log *b* equation:

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

Task discriminability is calculated using the following log *d* equation:

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

High response bias (log *b*) values are produced by high numbers of correct responses in the presence of the rich stimulus and incorrect responses in the presence of the lean stimulus, both of which are expected and adaptive psychophysical responses under these asymmetric probabilistic contingencies (McCarthy, 1983). High task discriminability (log *d*) values are produced by high numbers of correct responses for both rich and lean trials, similar to standard percent correct accuracy measures but on traditional signal detection logarithmic coordinates. A value of 0.5 is added to all parameters in both equations to address instances where no errors are made on a given trial type, thus making log transforms impossible (Hautus and Lee, 1998). The utility of these signal detection metrics has been repeatedly confirmed in human (Pizzagalli et al, 2005, 2008, 2020) and rat (Der-Avakian et al, 2013, 2017; Kangas et al, 2020, 2022) PRT studies. Reaction time metrics of PRT performance were also calculated by averaging across trials the time (seconds) from line length presentation to the response (visual discrimination). They were examined by trial type (ie, rich vs lean) because previous studies in humans (Pizzagalli et al, 2005) and animals (Luc and Kangas, 2024) have commonly observed slightly longer reaction times during lean trials than during rich trials, presumably due to conflict during the behavioral process of misclassifying the lean stimulus as rich (due to the programmed asymmetric probabilistic contingencies).

2.4.2. Statistics

PRT outcomes following treatment with saline or doses of ketamine in rats without exposure to programmed stress were subject to one-way repeated-measures ANOVA and a Greenhouse-Geisser correction. The 7-day time course of ketamine or saline under conditions of chronic stress was examined via a two-way repeated-measures ANOVA with a Greenhouse-Geisser correction. Drug treatment (ketamine vs saline) and time course session (across the 7 days) served as factors. When appropriate, ANOVAs were followed by Dunnett's multiple comparisons post hoc tests to examine the statistical significance of PRT performance relative to saline control. The criterion for significance was set at $P < .05$. Statistical analyses were performed using Graph Pad Prism 10.

2.4.3. Drug

Ketamine hydrochloride was obtained from Sigma-Aldrich. It was dissolved in 0.9% saline solution and administered via subcutaneous injection in volumes of 0.5 mL or less 2 hours prior to the experimental session. Dose range (3.2–32.0 mg/kg ketamine) and pretreatment interval were based on previous depression-related studies of ketamine in rats (Garcia et al, 2008, 2009; Wang et al, 2011).

3. Results

The effects of saline and doses of ketamine are presented in Fig. 2 following acute treatment (top row) and 24 hours later (bottom row) on PRT outcomes under conditions without programmed stress. As the dose–response functions in the top row show, acute treatment with ketamine produced significant dose-related increases in response bias ($F[2.6,18] = 3.7$; $P = .04$), relative to performance following saline administration, with 10.0 mg/kg producing the peak increase in log *b* ($P < .05$) among the doses tested. Critically, such increases in response bias were not accompanied by dose-related alterations in task discriminability ($F[2.1,15] = 1.4$; $P = .27$), suggesting that response bias findings were not confounded by changes in task difficulty. Likewise, although reaction times during lean trials were, as expected, slightly longer than during rich trials, there were no significant changes in this metric following ketamine treatment ($F[1.55,21.69] = 2.32$; $P = .13$). As shown in the bottom row of panels in Fig. 2, the increases in log *b* following acute ketamine treatment were no longer evident in the PRT 24 hours later. Response bias ($F[2.2,15] = 1.4$; $P = .28$), task discriminability ($F[2.6,18] = 0.51$; $P = .66$), and reaction time

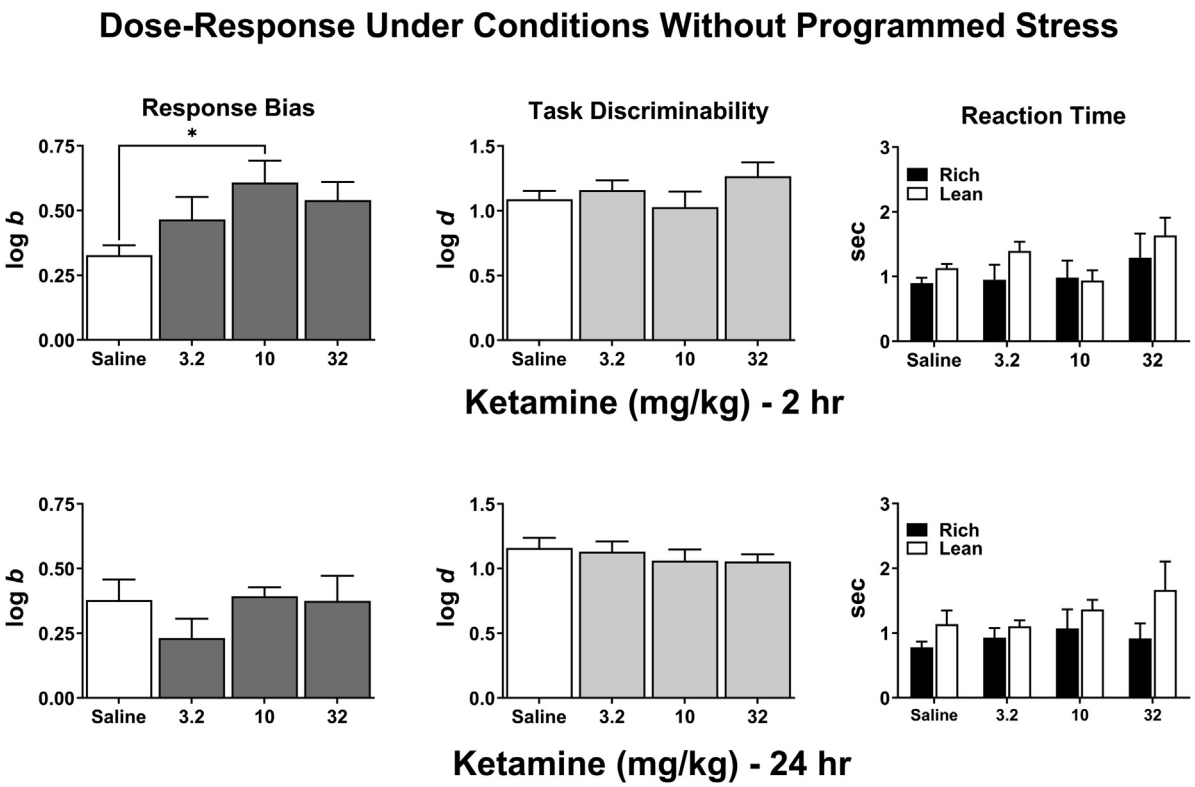

Fig. 2. Dose–response functions under conditions without programmed stress following 2 h (top row) and 24 h (bottom row) of ketamine treatment on mean (±SEM) PRT outcomes of response bias (log *b*, left column of panels), task discriminability (log *d*, middle column of panels), and reaction time (sec, right column of panels) during rich (black bars) and lean (white bars) trial types. $n = 8$, $^*P < .05$.

(F[2.26,33.66] = 0.97; $P = .40$) were highly similar to outcomes following saline treatment at the 24-hour time point.

The effects of 10.0 mg/kg ketamine (top row) and saline (bottom row) on PRT outcomes under conditions of chronic stress are presented in Fig. 3. Acute treatment with 10.0 mg/kg ketamine, but not saline, was able to significantly rescue blunted log *b* values produced by chronic inescapable ice water stress. These effects restored log *b* values to prestress baseline values and were confirmed statistically by main effects of drug treatment (F[1,14] = 11.82; $P = .004$) and time course session (F[3.63,50.83] = 4.06; $P = .008$). These differences in response bias were not accompanied by differences in task discriminability by drug (F[1,14] = 1.31; $P = .27$) or time course session (F[3.39,47.48] = 0.91; $P = .45$) or by differences in reaction time by drug (F[1,14] = 0.61; $P = .45$) or time course session (F[4.11,57.58] = 0.72; $P = .58$). Specifically, as the top row of panels show, a significant blunting of log *b* values was observed following 4.9 ± 0.61 days of exposure to chronic inescapable ice water stress (0.17 ± 0.02), relative to characterization of prestress baseline response bias (0.38 ± 0.04; $P < .05$). Acute treatment with 10 mg/kg ketamine fully rescued blunted values evident by an elevation of log *b* that closely approximated values observed during prestress baseline (0.42 ± 0.05; $P < .01$). Moreover, these effects persisted during the test session conducted 24 hours later (0.42 ± 0.06; $P < .01$) and, to a lesser extent, 3 days (0.33 ± 0.08; $P > .05$) and 7 days (0.27 ± 0.08; $P > .05$) following ketamine treatment but still under ongoing conditions of chronic stress. This persistence over time of ketamine's effects on response bias was not accompanied by changes in task discriminability (F[3.0,21] = 1.70; $P = .21$), which remained fairly steady throughout the 7-day testing protocol ranging from 0.75 ± 0.10 to 1.12 ± 0.05 or reaction time (F[3.33,46.64] = 1.12; $P = .35$), which ranged from 0.60 ± 0.07 to 1.21± 0.14 seconds depending on time point and trial type. Conversely, as the bottom panels show, in other subjects with significantly blunted response biases following 4.6 ± 0.65 days of exposure to chronic stress (0.16 ± 0.03) relative to prestress baseline values (0.41 ± 0.03; $P < .001$), saline administration did not significantly increase log *b* values during the 7 days under conditions of ongoing chronic stress ($P > .05$ at each time point), which ranged from 0.14 ± 0.05 to 0.24 ± 0.03. Administration of saline under conditions of chronic stress also did not alter task discriminability, which ranged from 0.82 ± 0.08 to 0.96 ± 0.11 or reaction time, which ranged from 0.62 ± 0.03 to 1.19 ± 0.03 depending on time point and trial type.

4. Discussion

Many lines of investigation within behavioral pharmacology over the past 70 years have shown that the qualitative, as well as quantitative, effects of drugs on behavior can be greatly influenced by the conditions under which they are studied (Dews, 1955; Schuster et al, 1966; Spealman, 1979; Barrett and Katz, 1981). This body of research has reflected a strong appreciation of the multiple determinants of the effects of psychoactive drugs, including the roles of subject-based (genomic or trait) features and environmental conditions as well as their pharmacologic actions. It also has helped foster the current emphasis on using translationally relevant conditions in preclinical drug discovery and development—especially in work focused on depressive or other affective disorders. In this regard, Research Domain Criteria-based taxonomies and methodologies (Insel et al, 2010; https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/behavioral-assessment-methods-for-rdoc-constructs.shtml) have emerged for studying contributing factors to depressive disorders, including deficits in hedonic tone (ie, anhedonia). For example, the PRT provides a well-validated assay of response bias as a measure

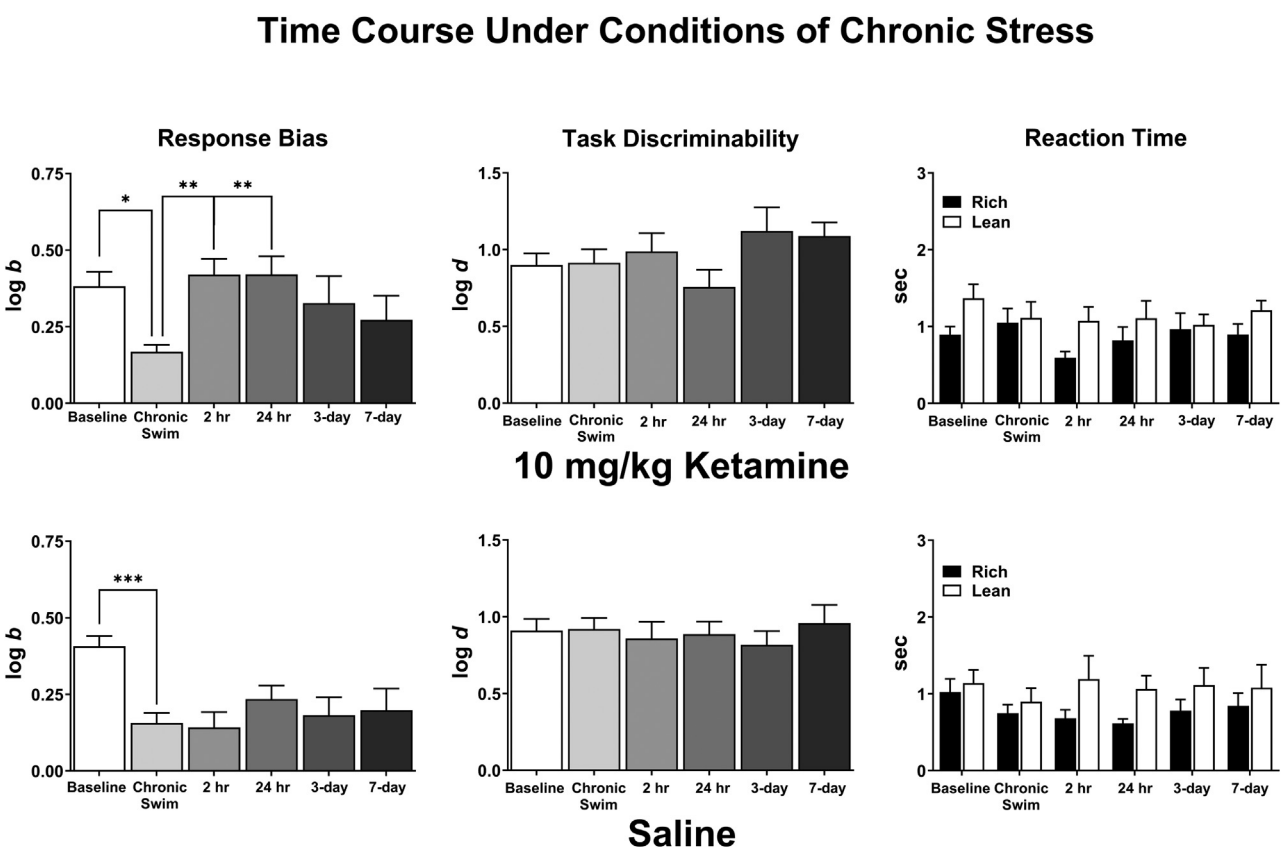

Fig. 3. Time course of ketamine (top row) and saline (bottom row) under conditions of chronic stress on mean (±SEM). PRT outcomes of response bias (log *b*, left column of panels), task discriminability (log *d*, middle column of panels), and reaction time (sec, right column of panels) during rich (black bars) and lean (white bars) trial types during the last session of their prestress training protocol (baseline) and throughout a 7-day time course with continued daily inescapable ice water: $n = 8$/group, ** $P < .01$, ** $P < .001$.

of reward responsiveness in human subjects. Since its development, this assay has been instrumental in both probing the role of anhedonia and evaluating the antianhedonic effects of established and candidate antidepressant drugs, especially for the treatment of TRD (Pizzagalli et al, 2005, 2008, 2020). As demonstrated in this and previous studies, the PRT also recently has been reverse-translated in nonhuman species for preclinical studies of drugs that may alter reward responsiveness (Luc et al, 2021), providing uniquely valuable cross-species information in this research area.

In keeping with a focus on the behavioral and environmental determinants of drug action (the theme of this Special Issue), this study in rats were conducted to compare the effects of ketamine on PRT performance under stressful and nonstressful conditions. As the results show, dissimilar log *b* values were observed in the 2 groups of subjects, reflecting differing levels of response bias under the dissimilar environmental conditions. However, notwithstanding the difference in the log *b* values during which ketamine was studied, the behavioral effects of ketamine treatment were qualitatively similar under the 2 conditions. In the nonstressful environment, ketamine produced dose-related and short-lived (<24-hour) increases in response bias. This systematically replicates previous ketamine findings using the PRT in unstressed marmoset monkeys (Wooldridge et al, 2021).

Ketamine was also able to increase log *b* values in a stressful environment, that is, under ongoing conditions of exposure to inescapable ice water that markedly reduced response bias. Although this outcome is similar in direction to ketamine's prohedonic actions in a nonstressed environment, the rescue of such blunted reward responsiveness may more accurately be termed an antianhedonic effect. It is noteworthy that such antianhedonic actions also have been reported to mediate the antidepressant effects of ketamine in human subjects as first documented by Lally et al (2014, 2015) and summarized in recent reviews and meta-analyses of the clinical literature (Almeida et al, 2024; Kwaśny et al, 2024; Patarroyo-Rodriguez et al, 2024). Importantly, the time course of ketamine's effects under the ongoing stressful conditions used in this study were evident over a protracted period (nearly 7 days) of elevated mean log *b* values relative to those observed during chronic stress prior to drug administration, contrasting sharply with its short-lived (<24 hours) effects on response bias in nonstressful conditions. Although this extended duration of action is not necessarily a defining feature of antianhedonic action per se, it is highly consistent with ketamine's therapeutic effects in patients with TRD, which persist approximately 1 week following their first acute infusion (Kishimoto et al, 2016).

The differentiation of prohedonic and antianhedonic effects of ketamine under stressful and nonstressful conditions is based on the comparison of response bias in the 2 contexts. This analysis derives from signal detection methodology, which allows for the evaluation of sensitivity and, independently, response bias in decision-making processes (Green and Swets, 1966). Signal detection methodology is infrequently used to evaluate the influence of stressful conditions or psychoactive drugs in laboratory animals (but see the study by Dykstra and Appel, 1974). However, the relationship between the actual magnitude of log *b* prior to treatment—which differed under the 2 conditions—and ketamine's effects remains ambiguous. It might be that ketamine's effects and their persistence under stressful conditions are evident across a

range of log *b* values or, alternatively, that the effects of ketamine under stressful conditions are associated more directly with low log *b* values, whether they are produced under stressful or nonstressful conditions. While this study's data do not address the latter possibility, it can be directly evaluated in future studies in which the asymmetry of probabilistic contingencies of the task is decreased to reduce log *b* values in the absence of a stressful environment as previously described (Luc and Kangas, 2024). In addition, recent PRT studies in rats using a limited bedding and nesting protocol (Kangas et al, 2022) and in mice using juvenile chronic social defeat (Hisey et al, 2023) have shown that programmed exposure to early life stress can produce decreases in response bias that persist into adulthood. The further development of such diversity in stress-related procedures will provide the opportunity to evaluate the generality of ketamine's antianhedonic actions.

The secondary signal detection metric within the context of the PRT, log *d*, which quantifies the ability of the subject to discriminate the stimuli under the task conditions arranged, did not differ between stressful and nonstressful conditions or between saline-treated and ketamine-treated rats under the 2 conditions. Thus, ketamine's ability to enhance response bias under stressful conditions reflects changes in log *b* that are independent of discriminative sensitivity to the visual stimuli in the PRT. Interestingly, measures of discriminability using signal detection methodology also have been used previously in human subjects to analyze ketamine's effects on a continuous performance task as a measure of vigilance and executive function. This analysis revealed ketamine-induced alterations in perceptual sensitivity (ie, distractibility) that the authors associated with schizophrenia-like negative symptoms (Krystal et al, 2000). Those effects, however, were consequent to a dosage of ketamine considerably higher than is used clinically to produce antidepressant effects and, thus, their relevance to this study data is uncertain.

The neurobiological mechanisms that may mediate ketamine-induced increases in log *b* were not addressed experimentally in this study. However, it is unlikely that the same mechanisms are responsible for both ketamine's short-lived increases in response bias and longer-lived rescue of blunted response bias. The duration of ketamine's prohedonic effects are consistent with the relatively short duration of its other behavioral effects resulting from NMDA receptor antagonism, for example, its dissociative anesthetic or reinforcing effects (Liu et al, 2016). However, it is questionable whether ketamine's prohedonic effects reflect only NMDA-antagonist actions, as *d*-amphetamine, which increases synaptic levels of dopamine in reward-related brain regions (eg, ventral striatum) (Drevets et al, 2001) also has been shown to produce dose-related increases in log *b* under nonstressful conditions (Der-Avakian et al, 2013; Lamontagne et al, 2018; Kangas et al, 2020). Possibly, ketamine's prohedonic effects also are the product of changes in dopamine activity, that is, the result of downstream actions on reward processing in dopamine-rich brain regions that are secondary to its NMDA receptor-mediated modulation of glutamatergic actions (Rincón-Cortés and Grace, 2020; Kotoula et al, 2021; Marcus and Bruchas, 2021). While the role of such actions in ketamine's prohedonic effects deserve serious consideration, they alone do not easily explain ketamine's long-acting effects on response bias under stressful conditions. Indeed, *d*-amphetamine and other dopaminergic drugs are generally not associated with antidepressant efficacy (however, see McIntyre et al, 2017), supporting the idea that the therapeutic effects of ketamine involve mechanisms other than or in addition to simple increases in dopamine activity. Along these lines, accumulating evidence indicates that, in addition to increasing dopamine activity, the glutamatergic actions of subanesthetic doses of ketamine robustly stimulate synaptic plasticity and via multiple processes (eg, increases in expression of brain-derived neurotrophic and other growth factors, canonical long-term potentiation, and recovery of neuronal spine densities) can strengthen functional connectivity in reward circuitry and, hence, restore hedonic tone (Duman and Duman, 2015; Monteggia and Zarate, 2015; Kotoula et al, 2021). Currently, although the precise cascade of molecular events is not yet fully defined, the role of synaptic plasticity in the rapid and long-lasting antidepressant actions of ketamine has gained widespread acceptance and is supported by preclinical studies showing that other means of stimulating synaptic plasticity also may lead to long-acting antidepressant-like effects (Zanos et al, 2023). Thus, ketamine's stimulation of synaptic plasticity also may promote its long-acting reparative effects on response bias that has been blunted by exposure to stressful conditions.

Several limitations of this study warrant discussion. First, only male rats were tested. Although previous work has indicated no significant sex differences in PRT performance (Kangas et al, 2020), it is not known whether sex differences might emerge in response to the programmed stressor or to ketamine under nonstressful or chronic stress conditions. This will be important to examine in future work, especially in light of the greater prevalence of stress-induced major depression diagnoses in women (Hyde and Mezulis, 2020) and, as well, emerging evidence suggesting that females are more sensitive than males to ketamine, with regard to both dosage and magnitude of antidepressant response (Ponton et al, 2021). Second, although rodent studies examining the effects of ketamine on antidepressant-like behavior most often use subcutaneous or intraperitoneal routes of administration, it should be noted that they differ from those used clinically (ie, intranasal for esketamine and slow intravenous infusion for racemic ketamine). It is unclear whether resulting differences in onset or duration of action are clinically meaningful. Third, anhedonic phenotypes within the context of the PRT were produced by chronic stress, and it is presently uncertain whether these findings extend to an anhedonic syndrome induced by nonstress-related variables. This is particularly relevant in view of the known heterogeneity of depression and why studying anhedonia as an endophenotype might inform the likelihood of response to pharmacotherapeutic treatment (Pizzagalli, 2014). An ancillary but related issue pertains to the use of a thermal stressor given the fact that ketamine is known to lower body temperature (Lin et al, 1978). Although thermal support (eg, heat lamp) was intentionally withheld in these studies to maximize stress effectiveness, a potential role of ketamine's ability to further reduce body temperature following chronic ice water stress on PRT outcomes was not examined.

In summary, the study findings indicate that environmental determinants (ie, stressful vs nonstressful conditions) produce remarkable differences in the behavioral effects of ketamine. Notwithstanding potential differences in the underlying neurobiological mechanisms of action, this was most apparent behaviorally in ketamine's time course of action. The relatively short duration of ketamine's prohedonic efficacy appears consistent in time with its relatively short duration of action when used as an anesthetic agent or recreational drug. Likewise, the persistent antianhedonic effects documented in this study under conditions of chronic stress are remarkably consistent with the duration of ketamine's medicinal effects in patients with TRD. These environmentally determined outcomes provide additional evidence that an important feature of ketamine's therapeutic value in TRD may be its efficacy in attenuating anhedonia.

Abbreviations

FDA, Food and Drug Administration; PRT, probabilistic reward task; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression.

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Conflict of interest

Daniela B. Radl and Thomas J. Kornecook are employees of Neurocrine Biosciences, Inc, and own stock or stock options in Neurocrine Biosciences. Over the past 3 years, Diego A. Pizzagalli has received consulting fees from Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Sage Therapeutics, Sama Therapeutics, and Takeda; he has received honoraria from the American Psychological Association, Psychonomic Society, and Springer (for editorial work) and from Alkermes; he has received research funding from the BIRD Foundation, Brain and Behavior Research Foundation, Dana Foundation, DARPA, Millennium Pharmaceuticals, National Institute on Mental Health, and Wellcome Leap MCPsych; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. At the time of this work, Derek L. Buhl and Patricio O'Donnell were full-time employees and shareholders of Takeda Pharmaceuticals, Inc. During the past 3 years, Brian D. Kangas has received sponsored research agreements with BlackThorn Therapeutics, Compass Pathways, Delix Therapeutics, Engrail Therapeutics, Neurocrine Biosciences, and Takeda Pharmaceuticals.

All other authors declare that they have no disclosures to report. All views expressed are solely those of the authors.

Data availability

All individual subject and group data presented in this article can be obtained upon request to the corresponding author.

Authorship contributions

Participated in research design: Jenkins, Radl, Kornecook, Pizzagalli, Bergman, Buhl, O'Donnell, Kangas.

Conducted experiments: Jenkins.

Performed data analysis: Jenkins, Kangas.

Wrote or contributed to the writing of the manuscript: Jenkins, Radl, Kornecook, Pizzagalli, Bergman, Buhl, O'Donnell, Kangas.

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