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Psychedelics produce enduring enhancement of reward responsiveness in male rats

Christopher W. Thomas[1], Kayleigh S. LaMalfa[2], Tobias P. Whelan[3], Thomas Blackmore[1], Caroline T. Golden[1], Diego A. Pizzagalli[4], Jack Bergman[2], Gary Gilmour[1] and Brian D. Kangas[2]✉

Anhedonia, the blunted responsiveness to previously rewarding stimuli, is a core symptom of several psychiatric disorders. Ketamine and psilocybin have shown promising evidence in ameliorating anhedonic symptoms in clinical trials. The Probabilistic Reward Task (PRT) was developed to objectively quantify reward responsiveness in clinical populations and laboratory animals. Here, the PRT was used to explore acute and sustained effects of several psychedelics and relevant pharmacological comparators on reward responsiveness in rats ($n = 12$/group, $n = 84$/total). Reward responsiveness was significantly increased following administration of psilocybin (0.1–1 mg/kg) or ketamine (10 mg/kg) acutely, and the effect persisted 24 hours after dosing. The effects of psilocybin, but not ketamine, on reward responsiveness were blocked in a dose-dependent manner by pretreatment with the 5-HT_{2A} receptor antagonist volinanserin. Both the 5-HT_{2A}-non-selective psychedelic DMT (1–10 mg/kg) and the relatively 5-HT_{2A}-selective psychedelic (±)-DOI (0.3–3 mg/kg) produced significant dose-related increases in reward responsiveness acutely; however, these effects were not sustained 24 hours later. Neither the non-psychedelic 5-HT_{2A} agonist lisuride (0.1–1 mg/kg) nor the SSRI fluoxetine (0.3–3 mg/kg) exerted positive effects in the PRT. These results suggest that psychedelics can produce acute and enduring increases in reward responsiveness and that this effect depends, at least in part, on the 5-HT_{2A} receptor. While positive effects on reward responsiveness may be common across psychedelics, differences in time course suggest that their enhancement of hedonic function may vary. The PRT is a useful tool to comparatively assess the effects of potential treatments for anhedonia, although the clinical implications of these data require further validation.

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INTRODUCTION

Anhedonia, the loss of pleasure or lack of reactivity to previously rewarding stimuli, is a core symptom of several psychiatric disorders, including major depressive disorder [MDD [1], bipolar disorder [2], post-traumatic stress disorder [3], schizophrenia [4], and substance use disorders [5]. Despite its transdiagnostic manifestations and relevance to overall patient well-being [6], there are no approved pharmacological treatments specifically for anhedonia. While conventional medications such as selective serotonin reuptake inhibitors (SSRIs) have broad utility in many psychiatric disorders [7], they too often fail to reduce anhedonia and may even exacerbate it, leading to a generalized blunting of emotional responses following continued treatment [8, 9].

Newer pharmacotherapeutic approaches, such as the N-methyl-D-aspartate (NMDA) antagonist and rapid-acting antidepressant ketamine [10], show promise in ameliorating anhedonia and may do so independently of reductions in other depressive symptoms [11–14]. Serotonergic psychedelics, such as psilocybin and dimethyltryptamine (DMT), also have yielded preliminary evidence of efficacy in the treatment of psychiatric disorders in which anhedonia is a major component, for example, MDD [15–18]. In this regard, psilocybin treatment has been reported to diminish anhedonia for up to 3 months in patients with MDD [19, 20] and, in a direct comparison, showed potential for a significantly greater reduction in anhedonia than observed with the SSRI escitalopram [21].

While serotonergic psychedelics derive from several chemical classes, they are thought to act principally via agonism at the 5-HT_{2A} receptor [22]. However, it is also clear that psychedelics differ both in terms of their broader pharmacological profiles and in terms of the quality of subjective experiences they occasion [23, 24]. It is unknown at present what implications this may have for the therapeutic potential of different psychedelics across different domains of function. With regard to reward responsiveness and hedonic capacity, there is a clear opportunity to clarify the relationship between pharmacology, behavioral substrates, and ultimately clinical outcomes using translational rodent models.

Reward responsiveness and aspects of hedonic capacity can be readily assessed in both animals and humans using the Probabilistic Reward Task (PRT). The PRT is an RDoC-recommended task for studying positive valence, specifically the subdomain of reinforcement learning [25]. The task was first developed clinically to quantify patient deficits in reward responsiveness [26]; modified after [27], and has since been adapted, parametrically optimized, and validated for use in several

[1]Compass Pathways, London, UK. [2]Harvard Medical School, McLean Hospital, Belmont, MA, USA. [3]King's College London, London, UK. [4]University of California, Irvine, CA, USA. ✉email: bkangas@mclean.harvard.edu

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nonhuman species, including the rat [28], marmoset monkey [29], and mouse [30]. The task involves the subject discriminating between two lines of different lengths by responding to one of two touchscreen options. Importantly, during test sessions, correct responses on one alternative are three times more likely to result in reward (rich contingency) than correct responses on the other alternative (lean contingency). In healthy subjects, these asymmetric probabilistic contingencies readily generate an adaptive response bias towards the more richly rewarded contingency. In anhedonic humans [31–33] and chronically stressed rodents [34, 35], a blunted response bias is commonly observed. Blunted response bias may therefore be postulated to be one mechanism underpinning the presentation of anhedonia in subjects.

Crucially, response bias within the context of the PRT is sensitive to acute pharmacological manipulations, and effects appear to be translational between humans and animals [36, 37]. For example, recent studies of ketamine [29, 38, 39] and MDMA [40] have shown that these pharmacologically distinct drugs produce significant dose-dependent increases in reward response bias in this task. Such effects appear consistent with the clinical value of ketamine as a fast-acting antidepressant [10] and the efficacy of MDMA in PTSD clinical trials [41].

The present studies characterized the effects of serotonergic psychedelics and relevant comparator compounds using the rat PRT. Independent cohorts of adult male rats ($n = 12$/group, $n = 84$/total) were used to obtain dose-response and time course functions following treatment with ligands including: a) the serotonergic psychedelics psilocybin (0.1–1 mg/kg), DMT (1–10 mg/kg), and (±)-DOI (0.3–3 mg/kg); b) psilocybin (1 mg/kg) and ketamine (10 mg/kg) after treatment with the selective 5-HT_{2A} receptor antagonist volinanserin (0.03–0.3 mg/kg); c) the mixed-action serotonergic/dopaminergic agonist lisuride; d) the non-psychedelic NMDA antagonist ketamine (10 mg/kg); and e) the typical SSRI antidepressant fluoxetine (0.3–3 mg/kg).

METHODS

Subjects

Each of the seven studies was conducted in an independent group of adult male Long Evans rats ($n = 12$/group, $n = 84$ total) obtained from Charles River Laboratories (Wilmington, MA, USA). Upon arrival, rats were approximately 10 weeks of age and weighed between 175 and 200 grams. They were group-housed 3 to a home cage with unrestricted access to water in a climate-controlled vivarium with a 12-h light/dark cycle (lights on at 7 am). 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. Sessions were conducted 5 days a week (Mon-Fri). The study protocol was approved by the Institutional Animal Care and Use Committee at McLean Hospital in accordance with established guidelines [42].

Apparatus

Details and schematics of the rodent touch-sensitive experimental chamber have been previously published [43]. Briefly, a custom-built Plexiglas chamber (25x30x35 cm) was situated in a sound- and light-attenuating enclosure. A 17" touch-sensitive screen (1739L, ELO TouchSystems, Menlo Park, CA) comprised the inside right-hand wall of the chamber. An infusion pump (PHM-100-5, Med Associates, St. Albans, VT) outside the enclosure was used to deliver sweetened condensed milk solution into the reservoir of an aluminum receptacle. A speaker bar (NQ576AT, Hewlett-Packard, Palo Alto, CA) mounted above the touchscreen was used to emit audible feedback. All experimental events were programmed in E-Prime Professional 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA).

PRT training

Using published protocols [28], modified response-shaping techniques were used to train rats to engage with the touchscreen by rearing on their hind legs and using their paw to make a touchscreen response to a 5 × 5 cm blue square on a black background. Each response was reinforced with 0.1 mL of 30% sweetened condensed milk, and its delivery was paired with an 880 ms yellow screen flash and 440 Hz tone, followed by a 5-sec intertrial interval (ITI) blackout period. After responses with latencies <5 sec following stimulus presentation were reliably observed, line-length discrimination training commenced. Discrete trials began with the concurrent presentation of a white line presented 5 cm above left and right blue response squares. The width of the line was always 7 cm, but the length of the line was either 30 cm or 15 cm and varied in a quasi-random fashion across 100-trial sessions (50 trials of each length) that took approximately 20–30 minutes to complete, depending on the subject. Subjects learned to respond to the left or right response square depending on the length of the white line (i.e., long line = respond left, short line = respond right, or vice versa, counter-balanced across subjects). A correct response was reinforced as described above and followed by a 5 sec ITI, whereas an incorrect response immediately resulted in a 10 sec ITI. A correction procedure [44] was implemented during initial discrimination training—each incorrect trial was repeated until a correct response was made—and discontinued after session-wide trial repeats were <5 in each trial type. Discrimination sessions continued without correction until the accuracy for both line lengths was >75% correct for 3 consecutive sessions. Thereafter, PRT testing commenced.

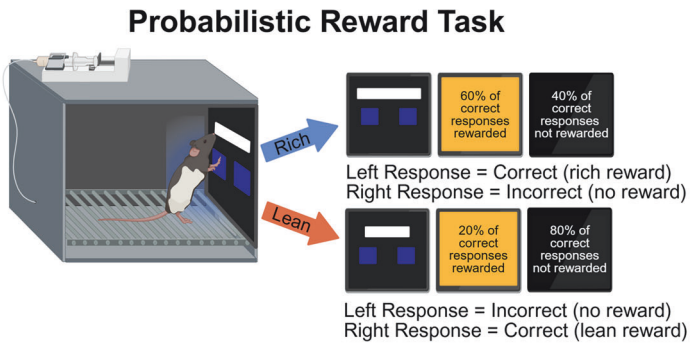
PRT testing

Following PRT line-length discrimination training, drug testing was conducted. In all experiments, the vehicle and each drug dose were studied across weekly 100-trial testing sessions (Monday-Friday) that took approximately 20-30 minutes to complete, depending on the subject. Specifically, on Monday and Tuesday, training conditions were in place as described above, in which correct responses to both long and short line trial types were reinforced. This was followed by three sessions (Wednesday-Friday) in which probabilistic reinforcement schedules were introduced. Specifically, based on the human task protocol [26], and as illustrated in Fig. 1, a 3:1 rich/lean probabilistic schedule was arranged such that 60% of correct responses to one of the line lengths (e.g., long line = rich alternative) and 20% of correct responses to the other line length (e.g., short line = lean alternative) are rewarded. For each subject, the line length with a higher mean accuracy during the Monday and Tuesday training sessions was designated as the stimulus to be rewarded on the lean contingency for each subject in subsequent PRT sessions. This was designed to examine the ability of vehicle or drug treatment to produce a response bias rather than simply amplifying a preexisting inherent bias resulting from uncontrolled variables. Drug or vehicle doses were administered on Thursday, with a defined pretreatment interval detailed below. PRT performance was also evaluated on Friday to examine drug effects 24 hours post-administration. In the psilocybin and ketamine study, a second 5-session testing condition was included to determine PRT outcomes 7-day post dosing, given the persistent effects of these drugs at the 24-hour time point.

Drugs

Psilocybin (COMP360, Compass Pathways' proprietary formulation of synthetic crystalline psilocybin) was provided by Compass Pathways (London, UK). Ketamine hydrochloride, volinanserin, (±)-DOI hydrochloride, and fluoxetine hydrochloride were purchased from Sigma-Aldrich (St. Louis, MO). DMT fumarate was purchased from Cayman Chemical (Ann Arbor, MI). Lisuride maleate was purchased from Tocris (Minneapolis, MN). Psilocybin, ketamine, DMT, (±)-DOI, lisuride, and fluoxetine were dissolved in 0.9% saline solution. Volinanserin was dissolved in a vehicle comprised of 30% DMSO and 70% saline. All drugs were delivered subcutaneously.

As depicted in Fig. 1, a within-subjects design was arranged in which vehicle and drug doses were studied across PRT test weeks (detailed above) using a Latin square counterbalanced treatment order for the 12 subjects of each group. Doses of drugs and pretreatment intervals were based on previous behavioral studies in rats or, if not available, were informed by mouse head twitch response data. They were: psilocybin 0.1–1.0 mg/kg, 1 hr pretreatment [45]; ketamine 10 mg/kg, 2 hour pretreatment [38]; DMT 1-10 mg/kg, 20 min pretreatment [46]; (±)-DOI 0.3–3 mg/kg, 1 hr pretreatment [47]; lisuride 0.1–1 mg/kg, 1 hour pretreatment [48]; fluoxetine 0.3–3 mg/kg, 1 hour pretreatment [49]. Antagonism studies were conducted by administering volinanserin (0.03–0.3 mg/kg) 15 minutes prior to 1 mg/kg psilocybin [50].



	Treatment	Time Points	Sample Size
Study 1	0.1-1 mg/kg psilocybin, 10 mg/kg ketamine	Acute, 24hr, 7-day	n=12
Study 2	0.03-0.3 mg/kg volinanserin + 1 mg/kg psilocybin	Acute, 24hr	n=12
Study 3	0.3 mg/kg volinanserin + 10 mg/kg ketamine	Acute, 24hr	n=12
Study 4	1-10 mg/kg DMT	Acute, 24hr	n=12
Study 5	0.3-3 mg/kg (±)-DOI	Acute, 24hr	n=12
Study 6	0.1-1 mg/kg lisuride	Acute, 24hr	n=12
Study 7	0.3-3 mg/kg fluoxetine	Acute, 24hr	n=12

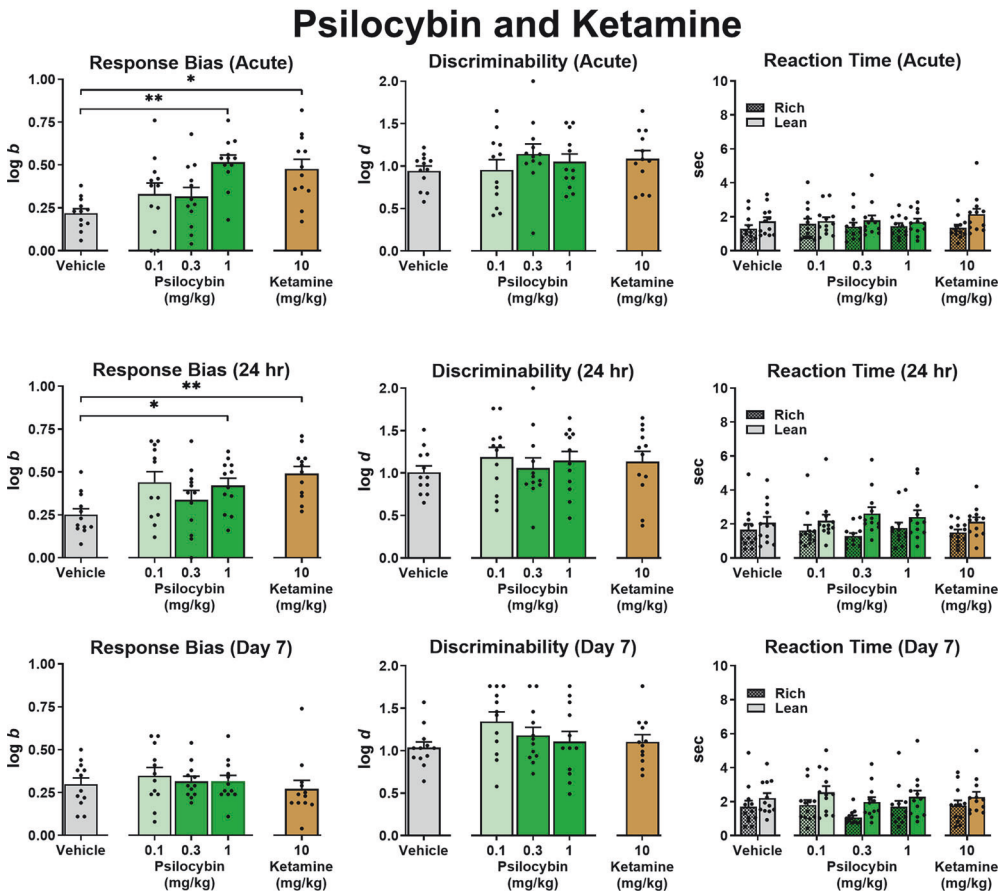


Fig. 1 Task schematic, drug table, and effects of psilocybin and ketamine. Upper: Probabilistic Reward Task schematic and table outlining pharmacological treatments, time points, and sample sizes across independent cohorts of animals. Lower: Effects of vehicle (saline), psilocybin (0.1-1.0 mg/kg), and ketamine (10 mg/kg) on response bias (log *b*, left panels), discriminability (log *d*, middle panels), and reaction time (sec, right panels). PRT outcomes were assessed following acute treatment (1 hour for vehicle and psilocybin and 2 hours for ketamine, top panels), 24 hours later (middle panels), and 7 days later (bottom panels). $n = 12$, $^{*}p < 0.05$, $^{**}p < 0.01$.

Data analysis

The implementation of probabilistic contingencies in the context of the PRT yields two primary dependent measures: Response Bias (log *b*) and Task Discriminability (log *d*), which are quantified by examining the number of correct and incorrect responses during rich and lean trial types using equations derived from signal detection theory [51]. Specifically, response bias is calculated as follows:

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

High log *b* values are produced by high numbers of correct responses during rich trials and incorrect responses during lean trials, which increase the log *b* numerator, both of which are expected and adaptive psychophysical responses under these asymmetric probabilistic contingencies [52]. Task discriminability is calculated as follows:

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

High log *d* values are produced by high numbers of correct responses during both rich and lean trials, which increase the log *d* numerator, similar to standard percent correct accuracy measures, but on traditional signal detection logarithmic coordinates. In both equations, 0.5 is added to all parameters to avoid instances where no errors are made on a given trial type, which would make log transformation impossible [53]. Reaction time during PRT performance was also calculated by averaging across trials the time (secs) from line length presentation to the response (visual discrimination) during each of the two trial types (i.e., rich vs. lean).

PRT outcomes following treatment with vehicle and drug doses were subject to one-way repeated measures analysis of variance (ANOVA) and a Greenhouse-Geisser correction. When appropriate, ANOVAs were followed by Dunnett's multiple comparisons post-hoc tests to examine the statistical significance of PRT outcomes following drug treatment relative to vehicle control. The criterion for significance was set at $p < 0.05$. Statistical analyses were performed using GraphPad Prism 10 (Boston, MA).

RESULTS

Psilocybin and ketamine enhance reward responsiveness acutely and after 24 hours

Figure 1 presents the effects of vehicle (saline), psilocybin (0.1-1 mg/kg), and ketamine (10 mg/kg) on PRT outcomes of response bias (left column), task discriminability (middle column), and reaction time (right column). Data are presented for acute effects (first row), 24 h (second row), and 7 days (third row) later. Overall, response bias was significantly higher following drug treatment ($F[3.1,34] = 5.30$, $p = 0.004$) than saline administration (0.22 ± 0.03). These effects were most pronounced after 1 mg/kg psilocybin (0.52 ± 0.04; $d = 1.49$; $p < 0.01$) and 10 mg/kg ketamine (0.48 ± 0.06; $d = 1.08$; $p < 0.05$). Log *b* values also were elevated during PRT test sessions conducted 24 hours later ($F[2.3,25] = 3.80$, $p = 0.03$), with significant increases observed again in subjects treated with 1 mg/kg psilocybin (0.42 ± 0.04; $d = 0.96$; $p < 0.05$) and 10 mg/kg ketamine (0.49 ± 0.04; $d = 1.33$; $p < 0.01$). (Log *b* increases at the individual subject level following treatment with psilocybin and ketamine, acutely and 24 hours later, are presented in Supplementary Fig. 1 and Table 1.) For all doses of psilocybin and for ketamine, response bias 7 days after drug administration had returned to a level observed with saline ($F[3.5,38] = 0.47$, $p = 0.73$). Critically, and highlighting specificity, increases in response bias were not accompanied by significant changes in task discriminability at either the acute ($F[3.0,33] = 0.85$, $p = 0.48$) or 24-hr ($F[2.9,32] = 0.50$, $p = 0.68$) timepoints; log *d* values were approximately 1.0 during all test sessions. Similarly, reaction time (approximately 1 and 2 sec during rich and lean trial types, respectively) was unaffected by psilocybin or ketamine acutely ($F[3.0,65.1] = 0.36$, $p = 0.78$) and at the 24-hr ($F[3.1,67.9] = 0.40$, $p = 0.76$) and 7-day ($F[3.6,80.1] = 1.53$, $p = 0.21$) timepoints.

Table 1. Effect size (Cohen's *d*) of drug treatments relative to vehicle control tests on response bias (log *b*) using established conventions: small ($d = 0.20$), medium ($d = 0.50$), and large effect ($d > 0.80$).

Effect Size (Cohen's *d*) Relative to vehicle	Acute	24 hr	Day 7
0.1 mg/kg Psilocybin	0.47	0.70	0.25
0.3 mg/kg Psilocybin	0.47	0.44	0.08
1 mg/kg Psilocybin	1.49	0.96	0.11
10 mg/kg Ketamine	1.08	1.33	-0.12
Vehicle + 1 mg/kg Psilocybin	1.13	0.86	
0.03 mg/kg Volinanserin + 1 mg/kg Psilocybin	0.52	0.43	
0.1 mg/kg Volinanserin + 1 mg/kg Psilocybin	0.19	0.69	
0.3 mg/kg Volinanserin + 1 mg/kg Psilocybin	0.29	0.15	
Vehicle + 10 mg/kg Ketamine	1.19	1.81	
0.3 mg/kg Volinanserin + 10 mg/kg Ketamine	0.95	1.98	
1 mg/kg DMT	0.72	0.38	
3 mg/kg DMT	0.72	0.58	
10 mg/kg DMT	1.05	0.46	
0.3 mg/kg (±)DOI	0.35	0.03	
1 mg/kg (±)DOI	0.55	-0.10	
3 mg/kg (±)DOI	1.02	0.10	
0.1 mg/kg Lisuride	-0.90	-0.12	
0.3 mg/kg Lisuride	-0.05	-0.09	
1 mg/kg Lisuride	0.004	0.23	
0.3 mg/kg Fluoxetine	0.03	-0.10	
1 mg/kg Fluoxetine	-0.07	-0.17	
3 mg/kg Fluoxetine	0.02	-0.02	

5-HT_{2A} antagonism blocks psilocybin's (but not ketamine's) enhancement of reward responsiveness

The top two rows of Fig. 2 show the effects of 1 mg/kg psilocybin, alone and after treatment with the 5-HT_{2A} antagonist, volinanserin, on PRT outcomes. Response bias values following acute treatment with 1 mg/kg psilocybin (0.53 ± 0.05; $d = 1.13$; $p < 0.01$) were significantly higher ($F[3.4,37] = 4.10$, $p = 0.01$) than those obtained following vehicle (0.27 ± 0.04), closely replicating the psilocybin findings presented in Fig. 1 in an independent group of subjects. The highest dose of volinanserin (0.3 mg/kg), followed by saline, did not alter log *b* values (0.24 ± 0.04) but, administered prior to 1 mg/kg psilocybin, dose-dependently blocked psilocybin-associated increases in response bias [log *b*: 0.03 (0.41 ± 0.06), 0.1 (0.33 ± 0.07), and 0.3 (0.34 ± 0.05) mg/kg]. The highest dose of volinanserin (0.3 mg/kg) followed by saline or 1 mg/kg psilocybin, did not alter task discriminability ($F[3.2,35] = 1.80$, $p = 0.17$) or reaction time ($F[3.2,70.3] = 0.95$, $p = 0.43$). During PRT test sessions conducted at the 24 hr timepoint, reduced elevations in response bias relative to acute treatment of 1 mg/kg psilocybin were observed in a manner that, unlike parallel findings in Fig. 1, did not meet statistical criteria ($F[3.2,35] = 1.90$, $p = 0.14$); however, log *b* values (0.43 ± 0.07) remained higher than those relative to vehicle (0.21 ± 0.06) at the 24 hr time point with a large effect size ($d = 0.86$). Volinanserin blockade of psilocybin-associated increases in log *b* also persisted at the 24-hr timepoint following 0.03 (0.32 ± 0.05), 0.1 (0.32 ± 0.05), and 0.3 (0.25 ± 0.06) mg/kg of the antagonist. As with acute determinations, 0.3 mg/kg volinanserin followed by saline or psilocybin failed to modify task discriminability ($F[3.2,36] = 0.45$, $p = 0.74$) or reaction time ($F[3.3,71.5] = 1.41$, $p = 0.25$) at the 24 hr timepoint.

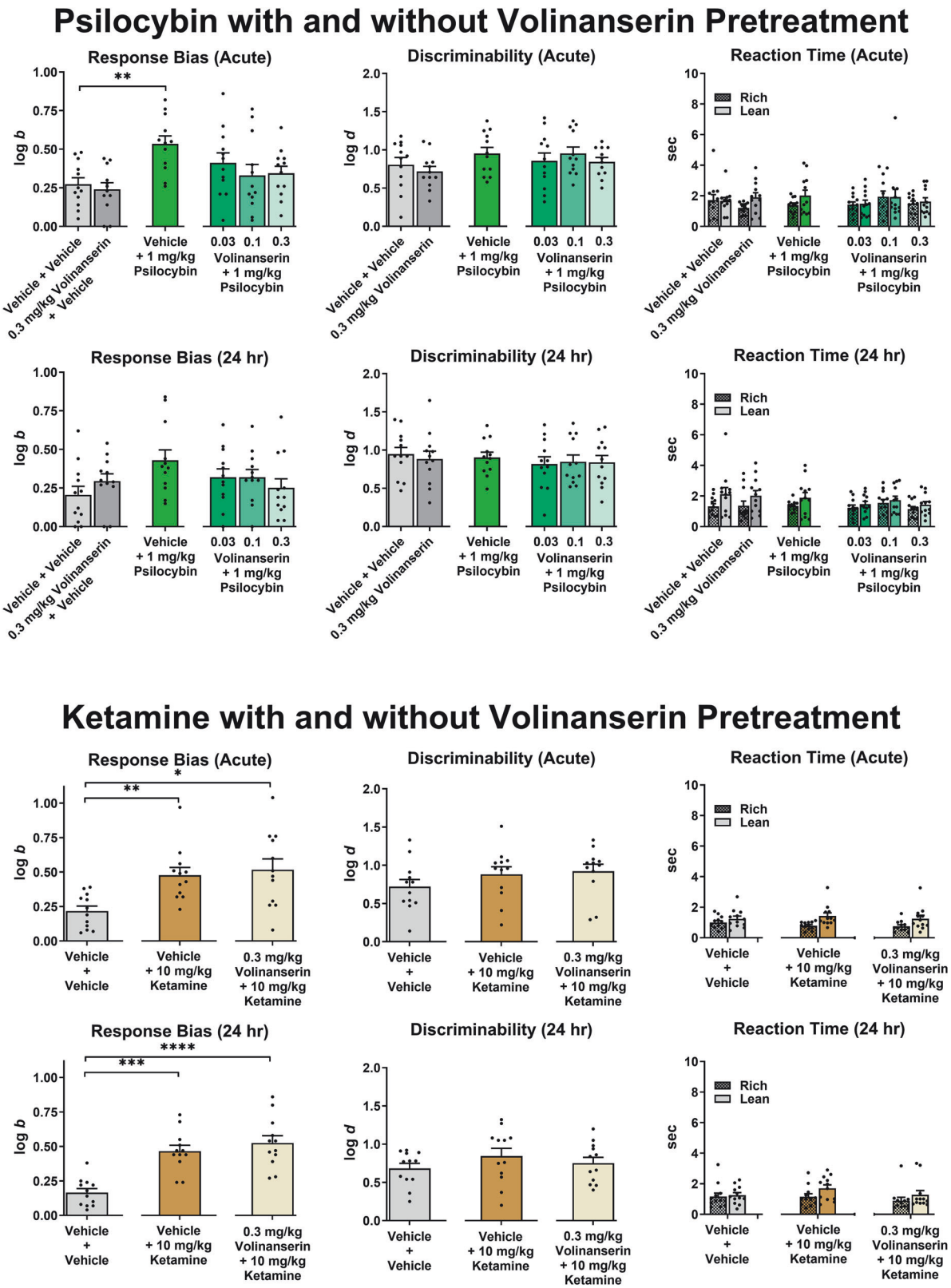


Fig. 2 Effects of psilocybin and ketamine with and without volinanserin pretreatment. Top two rows: Effects of volinanserin's vehicle (30% DMSO) + psilocybin's vehicle (saline), 0.3 mg/kg volinanserin + saline, 30% DMSO + 1 mg/kg psilocybin, and 0.03–0.3 mg/kg volinanserin + 1 mg/kg psilocybin on response bias (log *b*, left panels), discriminability (log *d*, middle panels), and reaction time (sec, right panels). PRT outcomes were assessed following acute treatment (15 min for volinanserin or its vehicle, and 1 hr for psilocybin and its vehicle, top panels) and 24 hr later (bottom panels). $n = 12$, $^{**}p < 0.01$ Bottom two rows: Effects of volinanserin's vehicle (30% DMSO) + ketamine's vehicle (saline), 30% DMSO + 10 mg/kg ketamine, and 0.3 mg/kg volinanserin + 10 mg/kg ketamine on response bias (log *b*, left panels), discriminability (log *d*, middle panels), and reaction time (sec, right panels). PRT outcomes were assessed following acute treatment (15 min for volinanserin or its vehicle, and 2 hours for ketamine and its vehicle, top panels) and 24 hr later (bottom panels). $n = 12$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

The bottom two rows of Fig. 2 present the effects of 10 mg/kg ketamine, alone and after treatment with 0.3 mg/kg volinanserin, on PRT outcomes. Ketamine significantly increased response bias, whether pretreated with 0.3 mg/kg volinanserin or vehicle ($F[1.7,19] = 8.8$, $p = 0.003$). Specifically, response bias values following acute treatment with vehicle and 10 mg/kg ketamine (0.48 ± 0.06; $d = 1.19$; $p < 0.01$) were significantly higher than those obtained following vehicle (0.22 ± 0.04), replicating the ketamine findings presented in Fig. 1 in an independent group of subjects. Pretreatment with 0.3 mg/kg volinanserin did not modify the ability of 10 mg/kg ketamine to increase response bias (0.52 ± 0.08; $d = 0.95$; $p < 0.05$). Neither task discriminability ($F[1.6,18] = 3.1$, $p = 0.08$) nor reaction time ($F[1.9,41.8] = 0.44$, $p = 0.64$) was affected by 10 mg/kg ketamine, alone or following volinanserin pretreatment. During PRT test sessions conducted at the 24 hr timepoint, ketamine-associated elevations in response bias persisted ($F[1.9,21] = 27$, $p < 0.0001$) whether volinanserin preceded ketamine treatment or not. Like acute determinations, task discriminability ($F[1.5,16] = 1.4$, $p = 0.27$) and reaction time ($F[1.3,29.3] = 1.62$, $p = 0.21$) were unaffected at the 24 hr timepoint.

DMT and (±)-DOI enhance reward responsiveness acutely but not after 24 hours

PRT outcomes following administration of DMT and (±)-DOI, both immediately after the pretreatment interval and 24 hr later, are presented in Fig. 3. As shown in the top row of panels, acute administration of DMT produced significant dose-dependent increases in response bias ($F[2.0,22] = 4.20$, $p = 0.03$), which were largest following 10 mg/kg (0.51 ± 0.06; $d = 1.05$; $p < 0.05$) relative to vehicle (0.25 ± 0.03). These increases in log *b* were not accompanied by changes in task discriminability ($F[2.1,23] = 0.92$, $p = 0.42$) or reaction time ($F[2.6,56.8] = 0.54$, $p = 0.63$). As shown in the second row of panels, although modest increases in log *b* were observed 24 hours following administration of 1 (0.43 ± 0.09), 3 (0.45 ± 0.05), and 10 (0.44 ± 0.07) mg/kg DMT relative to vehicle (0.32 ± 0.04), they did not meet statistical criteria for significance ($F[2.4,27] = 1.20$, $p = 0.32$). Task discriminability ($F[2.4,27] = 0.25$, $p = 0.82$) and reaction time ($F[2.3,50.9] = 0.47$, $p = 0.66$) remained unchanged 24 hr following DMT administration. As depicted in the third row of panels, like DMT, acute administration of (±)-DOI also produced significant dose-dependent increases in response bias ($F[2.6,29] = 4.00$, $p = 0.02$), which were largest following 3 mg/kg (0.47 ± 0.06; $d = 1.02$; $p < 0.05$) relative to vehicle (0.24 ± 0.03). Unlike psilocybin and DMT, however, (±)-DOI produced dose-dependent decreases in task discriminability that trended toward significance ($F[2.5,27] = 2.60$, $p = 0.08$) and dose-dependent increases in reaction time that were highly significant ($F[1.7,36.6] = 18.59$, $p < 0.0001$). As shown in the fourth row of panels, 24 hours following (±)-DOI administration, response bias ($F[2.3,25] = 0.15$, $p = 0.89$), task discriminability ($F[2.3,25] = 0.17$, $p = 0.87$), and reaction time ($F[2.6,57.2] = 0.71$, $p = 0.53$) all returned to levels that approximated performance following treatment with vehicle.

Lisuride and fluoxetine fail to enhance reward responsiveness

The effects of lisuride and fluoxetine on PRT outcomes are shown in Fig. 4. Unlike psilocybin, DMT, and (±)-DOI, none of the lisuride doses increased response bias. Instead, a significant reduction in log *b* ($F[2.5,27] = 5.20$, $p = 0.008$) was observed following 0.1 mg/kg (0.003 ± 0.10; $d = -0.90$; $p < 0.05$) relative to vehicle (0.31 ± 0.06). Lisuride treatment did not modify task discriminability ($F[2.2,24] = 1.50$, $p = 0.25$) but did produce a significant ($F[1.19,26.3] = 3.90$, $p = 0.05$) increase in reaction time, most notably during the lean trial type (4.84 ± 1.69) relative to vehicle (1.59 ± 0.12). These lisuride-related effects on response bias ($F[2.5,27] = 0.56$, $p = 0.61$), task discriminability ($F[2.4,26] = 0.79$, $p = 0.48$), and reaction time ($F[2.4,53.0] = 0.27$, $p = 0.80$) were absent during PRT test sessions conducted 24 hr later (second row of panels). As shown in the third row of panels, acute treatment with fluoxetine did not significantly modify response bias ($F[1.9,21] = 0.04$, $p = 0.96$), task discriminability ($F[1.9,21] = 0.83$, $p = 0.45$), or reaction time ($F[2.3,49.4] = 0.55$, $p = 0.60$) at any of the doses tested. A similar lack of effect on response bias ($F[2.5,28] = 0.12$, $p = 0.93$), task discriminability ($F[2.6,29] = 2.30$, $p = 0.11$), and reaction time ($F[2.7,58.9] = 0.66$, $p = 0.56$) was observed again during PRT test sessions 24 hr later (fourth row of panels).

To summarize relative outcomes across the various drug treatments described above, Table 1 presents the effect sizes (Cohen's *d*) of drug treatment across time points (relative to vehicle control tests) on response bias (log *b*) for the more richly rewarded stimulus. Peak effect sizes for psilocybin, ketamine, DMT, and (±)-DOI were large by established conventions ($d > 0.80$). This can be contrasted with little-to-no effect sizes following the doses of lisuride or fluoxetine tested, save a large negative effect size ($d = -0.90$) following the low dose of lisuride (0.1 mg/kg). Taken together, these effect size outcomes are largely consistent with visual inspection of Figs. 1–4 and the associated inferential statistics detailed above.

DISCUSSION

The present study compared several psychedelic and non-psychedelic drugs in a rat Probabilistic Reward Task. Psilocybin, ketamine, DMT, and (±)-DOI produced significant dose-dependent increases in response bias (log *b*), which, under this signal detection framework, are indicative of enhanced reward responsiveness and potentially may support anti-anhedonic efficacy. Critically, despite the well-accepted psychedelic properties of psilocybin and DMT and dissociative actions of ketamine, no significant deficits in task discriminability (log *d*) or reaction time were observed following their administration, highlighting the behavioral selectivity of their effects on reward responsiveness.

Role of 5-HT_{2A} in mediating reward responsiveness

Of note, the elevation in response bias after treatment with psilocybin was blocked by pretreatment with volinanserin, a selective 5-HT_{2A} receptor antagonist. This 5-HT_{2A}-related blockade was not observed with ketamine, which is consistent with current thinking regarding ketamine's complex, but not 5-HT_{2A}-mediated, mechanisms of rapid-acting antidepressant action [54]. This suggests that despite the somewhat comparable efficacy of psilocybin and ketamine in enhancing reward responsiveness in the PRT, different mechanisms are likely responsible. 5-HT_{2A} receptor activation may be a driver of the response bias effect of psilocybin, perhaps much in the same way as it is thought to be a driver of the psychedelic experience [23, 55]. By extension, it could also be speculated that 5-HT_{2A} receptor activation is required for clinical anti-anhedonic effects, which would be consistent with previous work documenting 5-HT_{2A} mediation in long-term behavioral enhancement of other therapeutic-related functions in rodents [56–59]. One particularly relevant study characterized the ability of acute psilocybin to enhance another behavioral phenotype disrupted by major depression, cognitive flexibility, as assessed by set-shifting behavior, which was blocked by the 5-HT_{2A} receptor antagonist ketanserin [60]. However, some caution would be warranted currently in concluding this is the necessary and sufficient driver of all psychedelic-induced changes in this context, as other pharmacological factors may prove to be important [23].

In contrast to psilocybin and DMT, a relatively modest but dose-dependent decrease in discriminability and increase in reaction time accompanied increases in response bias produced by (±)-DOI. Although only reaction time increases met statistical significance, log *d* outcomes trended toward statistical criteria

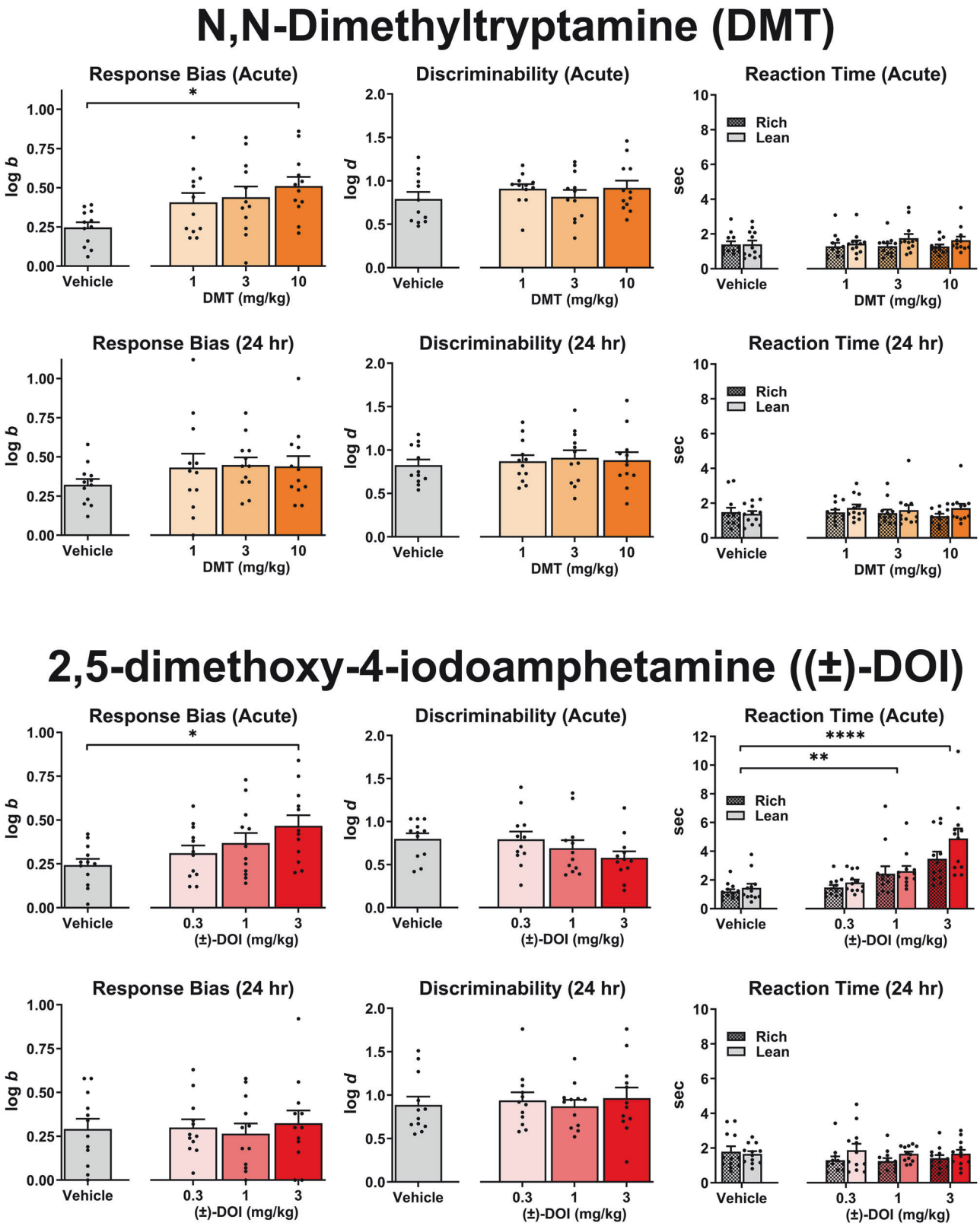


Fig. 3 Effects of DMT and (±)-DOI. Effects of vehicle (saline), DMT (1.0–10 mg/kg), and (±)-DOI (0.3–3.0 mg/kg) on response bias (log *b*, left panels), discriminability (log *d*, middle panels), and reaction time (sec, right panels). PRT outcomes were assessed following acute treatment (20 min for DMT [first row] and 1 hour for (±)-DOI [third row]) and 24 hr later (DMT [second row] and (±)-DOI [fourth row]). $n = 12$/drug, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$.

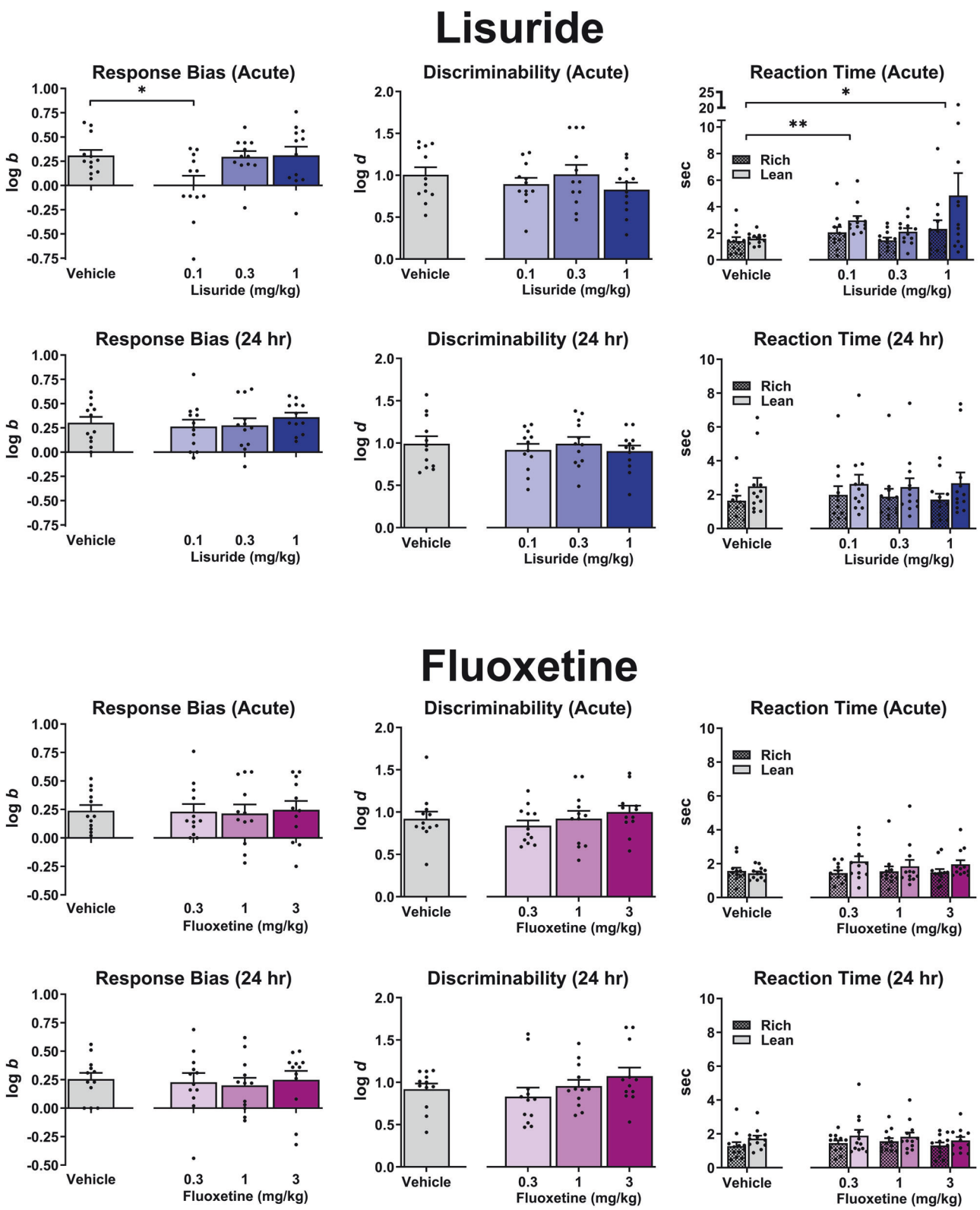


Fig. 4 Effects of lisuride and fluoxetine. Effects of vehicle (saline), lisuride (0.1–1.0 mg/kg), and fluoxetine (0.3–3.0 mg/kg) on response bias (log *b*, left panels), discriminability (log *d*, middle panels), and reaction time (sec, right panels). PRT outcomes were assessed following acute treatment (1 hour for lisuride [first row] and 30 minutes for fluoxetine [third row]) and 24 hours later (lisuride [second row] and fluoxetine [fourth row]). $n = 12$/drug, $^{*}p < 0.05$, $^{**}p < 0.01$.

($p = 0.08$) with a medium effect size ($d = 0.73$) observed at the largest dose of (±)-DOI tested. Interestingly, in the aforementioned study demonstrating the ability of psilocybin to enhance cognitive flexibility in rats, (±)-DOI also impaired that performance [60], which appears functionally similar to the present findings. The mechanistic reasons for such a difference are unclear. The dose ranges for the three agonists were selected to be approximately equivalent in an in vivo assay of 5-HT_{2A} activity (i.e., mouse head twitch response; [46]) and are most likely functionally comparable in that regard. Notably, (±)-DOI is considerably more selective than psilocin or DMT in binding to 5-HT_{2A} receptors, suggesting that a reduced contribution from other receptor actions could explain differences in the behavioral profile of (±)-DOI. Notably, both 5-HT_{1A} and 5-HT_{2C} receptor agonism in psychedelics have been suggested to modulate specific 5-HT_{2A}-receptor mediated effects [23, 48, 61–65]. Further systematic comparison of compounds with different 5-HT receptor pharmacology profiles may help to resolve key attributes that drive such differences in effect size on reward responsiveness.

In contrast to the other 5-HT_{2A} receptor agonists, lisuride only decreased response bias, which was found with the lowest dose (0.1 mg/kg) tested. Notably, lisuride has prominent dopamine D_2 receptor agonist activity [66, 67], which is the basis of its clinical use in the treatment of Parkinson's disease [68, 69]. In view of evidence that other dopamine D_2 receptor agonists, such as pramipexole (at low doses, likely through presynaptic autoreceptor activation) decrease PRT response bias in both rodents and humans [36, 37], it may be that dopaminergic activity of a 0.1 mg/kg dose of lisuride accounts for the observed decrease in response bias. The lack of effect of higher doses of lisuride (0.3 and 1 mg/kg) might be interpreted as competition between an increasing 5-HT_{2A}-receptor mediated increase in reward responsiveness, overcoming a D_2-receptor mediated decrease in responsiveness. The inability of lisuride to elevate response bias above baseline values seems consistent with its lack of psychedelic [69] and anti-anhedonic [70] effects in humans.

Time course of efficacy on reward responsiveness

The time course of changes in reward responsiveness is a critical difference among the psychedelics and ketamine examined here. DMT and (±)-DOI elevated response bias only in the session directly following dose administration, whereas the effects of psilocybin and ketamine were still evident during PRT test sessions conducted 24 hours later. Such differences may imply differential activation of mechanisms downstream of serotonin receptor agonism related to enduring functional neuroplasticity [71]. Importantly, it may be difficult at present to make strong translational conclusions about the relative duration of response bias effects of drugs in rodents and what this may mean for human behavior, including among individuals with elevated anhedonia. In the present study, the positive effects of both psilocybin and ketamine notably returned to baseline 7 days after dosing. A fairly large time gap exists between PRT test sessions at 24 h and 7 days, where it is unknown whether a differential drug effect could have been detected. The antidepressant effects of ketamine typically do not last more than 1-2 weeks [72], whereas the positive effects of psilocybin on anhedonia may last for at least 3 months [20]. It could be speculated that further testing here with more resolved temporal profiling may detect a shorter effect of ketamine relative to psilocybin, although there are clear difficulties in extrapolating the temporal scaling of the drug across species. Intervening factors, such as chronic stress, may also influence the duration of ketamine effects in the PRT [38].

Caveats and considerations

The holistic expression of behavior related to hedonic capacity depends upon several substrates, of which reward responsiveness is one [73]. Other factors are clearly important, such as motivational, anticipatory, and consummatory substrates, which should all be considered in accounts of behavior related to positive valence. Thus, whereas the PRT provides an objective assessment of reward responsiveness (that is, the propensity to modulate behavior as a function of reward contingencies) across species [74], it does not explore the full range of reward-related subdomains that may or may not be involved. Accordingly, future studies across species will be needed to confirm the generality of the current findings vis-à-vis different reward-related phenotypes and conditions. It may be that different psychedelic drugs may have different profiles of effect on these substrates [75–78]. Certainly, a more predictive picture of comparative drug effects could be generated through the use of a broader battery of assays. It may ultimately be that clinical treatment outcomes depend on drug effects across a range of these parameters and not just reward responsiveness [79]. Understanding the generality of psychedelic effects on behaviors of positive valence versus more general behavioral effects is very important when considering the clinical difference between the potential to treat anhedonia versus depression more generally. In this regard, the current effects of psilocybin and ketamine on response bias without effects on discriminability and reaction time highlight some degree of behavioral specificity; nevertheless, it will be important in future studies to control for the possibility that such drug-related effects also affect attention or more general learning processes.

SSRIs continue to play a prominent role in treating depressive mood states; however, clinical observations indicate that chronic SSRI treatment does not always resolve anhedonia, even in patients who are effectively relieved of other depressive symptoms [80–82]. The present results showing no positive effects of acute fluoxetine on reward responsiveness in the PRT are consistent with this. However, further work with chronic treatment paradigms that are more aligned with efficacious treatment approaches in humans is warranted before definitive conclusions should be made here. In addition, because only male rats were used in this study, it remains to be determined whether any sex differences among these outcomes might emerge. Although sex differences have not been observed in PRT performance [28] or in studies with the atypical psychedelic MDMA [40], future work might examine these classic psychedelics in females, especially in light of the fact that diagnoses of mood disorders in which anhedonia is prominent are more prevalent in women [83]. Finally, it is also important to note that the present studies were conducted in healthy animals, that is, in subjects without histories of early-life adversity, ongoing chronic stress, or other conditions relevant to depression. As we have discussed previously [38], a distinction can be made between *prohedonic* and *anti-anhedonic* drug action. Although the reverse-translated approach used here is designed to probe the former, future studies determining whether psychedelics can also rescue anhedonic-like behavioral phenotypes produced by chronic stress [34] or early-life adversity [35], as we have documented with ketamine [38, 39], would be valuable and have high translational relevance.

CONCLUSION

The present findings show that psychedelic drugs can have sustained effects on reward responsiveness in the rat PRT that outlive the period of drug exposure and that different drugs have different magnitudes and durations of effect. While initial evidence suggests that 5-HT_{2A} receptor activation may be necessary to drive this effect, the exact pharmacological profile of individual drugs is likely to influence measured outcomes. Different psychedelic drugs are likely to possess different capacities to alter reward-related behavior, and a broader assessment of drug effects on different domains of functioning

is warranted [84]. Overall, a deeper delineation of distinctions in efficacy and underlying mechanisms among psychedelics is essential for appreciating their clinical utility in treating anhedonia, a major transdiagnostic domain that is poorly targeted by existing treatments.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

CWT, KSL, TPW, TB, CTG, DAP, JB, GG, BDK designed the research, KSL performed the research, CWT, KSL. BDK analyzed the data, and CWT, KSL, TPW, TB, CTG, DAP, JB, GG, BDK wrote the paper.

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COMPETING INTERESTS

CWT, TB, CTG, and GG were employees of Compass Pathways plc when this work was conducted; GG remains an employee of Compass Pathways plc, and all own company stock. Over the past three years, Dr. Pizzagalli has received consulting fees from Abbvie, Boehringer Ingelheim, Circular Genomics, Compass Pathways, Engrail Therapeutics, N1 BioCorp Inc., Neumora Therapeutics, Neurocrine Biosciences, Neuroscience Software Syntropic Medical, and Xenon Pharmaceuticals; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, Circular Genomics, Dana Foundation, Wellcome Leap, Millennium Pharmaceuticals, and NIMH; he has received stock options from Ceretype Neuromedicine, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. Dr. Pizzagalli retains the copyright of the Probabilistic Reward Task. Dr. Pizzagalli is also currently on the Editorial Board of Neuropsychopharmacology. Over the past three years, BDK has also received sponsored research agreements from BlackThorn Therapeutics, Delix Therapeutics, Engrail Therapeutics,

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Correspondence and requests for materials should be addressed to Brian D. Kangas.

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