Behavioral and Pharmacological Validation of the Differential Reinforcement of Low-Rate Behavior Paradigm in Non-Human Primates

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ABSTRACT

The development of novel antidepressants is hindered by limited predictive validity of preclinical models. The Differential Reinforcement of Low-Rate (DRL) task is a classic rodent assay with strong sensitivity to antidepressants, but its translational potential remains unexplored in non-human primates (NHPs). Here, we adapted the DRL task for use in cynomolgus macaques (*Macaca fascicularis*) and evaluated its pharmacological sensitivity, specificity, and clinical utility across 19 compounds spanning diverse drug classes. Antidepressants, including SSRIs, SNRIs, NRIs, NDRIs, TCAs, MAOIs, and PDE4 inhibitors, consistently improved DRL performance, increasing reinforcers earned and inter-response times while decreasing response rates. In contrast, benzodiazepines, antipsychotics, and psychostimulants without serotonergic or noradrenergic engagement failed to enhance performance. Critically, the primate DRL task identified antidepressant-like efficacy of PDE4 inhibitors, while also capturing emesis, a dose-limiting side effect not observable in rodent models. These findings validate the primate DRL task as a pharmacologically selective and translationally relevant platform for screening novel antidepressant therapies. By modeling core cognitive domains implicated in depression, impulse control and internal timing, this assay offers a unique opportunity to bridge preclinical and clinical development with improved sensitivity to both therapeutic efficacy and tolerability.

INTRODUCTION

Depression remains a leading cause of disability worldwide, yet translating promising preclinical findings into effective clinical therapies is still challenging (Willner, 1984; Wang et al., 2017; Lee et al., 2023; Moncrieff et al., 2023). While many benefit from current antidepressants, a significant subset remains treatment-resistant. Clinical failures of new compounds often stem from limited efficacy, poor tolerability, or both, reflecting a key bottleneck: lack of behavioral assays with strong predictive validity and translational relevance for novel therapeutic screening.

The Differential Reinforcement of Low-Rate Behavior (DRL) task is a classic preclinical assay used in rodents for identifying antidepressant-like effects of therapeutics (McGuire and Seiden, 1980; O'Donnell and Seiden, 1983, 1984; Seiden et al., 1985; Richards and Seiden, 1991; O'Donnell et al., 2005). In the DRL, subjects are rewarded for withholding responses for a minimum, un-signaled delay interval. Premature responses reset the interval and forfeit reward. This task requires precise timing, response inhibition, and sustained attention—functions often impaired in depression (Fales et al., 2009; Ma, 2015; Hsu et al., 2019). These behaviors are subserved by a distributed neural circuit involving the prefrontal cortex, striatum, and hippocampus, brain regions consistently implicated in the pathophysiology of depression (Cho and Jeantet, 2010; Liu et al., 2017; Hamilton et al., 2018; Belleau et al., 2019; Liao and Pattij, 2022). In addition, performance on the DRL task is modulated by serotonergic signaling, aligning it with the pharmacological targets of many clinically effective antidepressants (Liao and Pattij, 2022).

In rodents, the DRL paradigm has demonstrated strong predictive validity for antidepressant efficacy (Marek and Salek, 2020; Marek et al., 2016). Compounds across several pharmacological classes including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), consistently improve DRL performance. These improvements are reflected by increasing the number of reinforcers obtained, decreasing inter-trial response rates, and increases in inter-response intervals compared to control animals (McGuire and Seiden, 1980; O'Donnell and Seiden, 1983; Richards and Seiden, 1991; O'Donnell et al., 2005). In contrast, other psychotropics such as anxiolytics, sedatives, and stimulants do not enhance performance, supporting the specificity of DRL for antidepressant screening (Marek et al., 1993; O'Donnell and Seiden, 1982).

Despite this, the DRL paradigm has not yet been validated in non-human primates (NHPs). This is a significant gap, given that rodents differ significantly from humans in terms of genetics, neuroanatomy, pharmacokinetics, and behavioral complexity. NHPs share closer

homology in cortical organization and neurotransmitter systems (Nestler et al., 2002; Liu et al., 2017; Hamilton et al., 2018). Importantly, NHPs exhibit depressive-like phenotypes under naturalistic conditions, enhancing their translational relevance (Xu et al., 2015; Deng et al., 2019; Price et al., 1994). Moreover, NHPs display clinically relevant side effects, including emesis, which rodents cannot. This is a significant limitation when evaluating the tolerability of drug candidates such as phosphodiesterase-4 (PDE4) inhibitors (Robichaud et al., 2001; McDonough et al., 2020).

Here, we adapted the DRL paradigm for macaque monkeys and conducted a comprehensive pharmacological validation of the model. The primary objectives were to (1) evaluate the sensitivity of NHP DRL performance to established antidepressants, (2) assess the specificity of the task using psychotropic control compounds, and (3) determine whether the model could detect emesis and other side effects relevant to clinical translation. We tested 19 pharmacotherapies from multiple classes, including SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenergic reuptake inhibitors (NRIs), a norepinephrine-dopamine reuptake inhibitor (NDRI), a TCA, a MAOI, a benzodiazepine (BZD), an atypical antipsychotic, several psychostimulants, and several phosphodiesterase-4 (PDE4) inhibitors for activity in the DRL task. This allowed us to evaluate the specificity and translational validity of the NHP DRL model for distinguishing antidepressant-like effects from those of other psychoactive compounds. By establishing the validity, specificity, and translational utility of the DRL paradigm in macaques, this study provides a foundation for its use in preclinical evaluation of novel antidepressant therapeutics, particularly for mechanistically distinct or side-effect-prone drug classes.

MATERIALS AND METHODS

Subjects

Eight adult male cynomolgus macaques (*Macaca fascicularis*) weighing 6-10 kg, were used in this study. Animals were housed in a same-sex colony room maintained on a 12-hour light/dark cycle and at 21 ± 2 ºC, 40 ± 10% humidity. Monkeys were pair-housed except for during drug administration, feeding, nights, and weekends. Water was available *ad libitum*, and animals were fed a standard diet (Purina High Protein #5045) at the end of each day. Enrichment, including toys and fresh fruits and vegetables was provided. All procedures were approved by the Institutional Animal Care and Use Committee at Roche Palo Alto and SRI International and adhered to the USDA Guide for the Care and Use of Laboratory Animals.

Apparatus

Behavioral testing was conducted in a sound-attenuated chamber (30”W, 30”D, 59”H; Med Associates, St. Albans, VT), equipped with a light, exhaust fan, and a white-noise generator. Subjects were seated in a standard Plexiglas restraint chair. A panel inside the chamber contained a retractable lever and indicator light that were activated at the beginning of the session and inactivated and retracted at the end. Reinforcers (300mg banana flavored pellet; TestDiet, Dean’s Animal Feed, Redwood City, CA) were delivered to the lower right of the chair from a feeder mounted on top of the chamber. The task and data acquisition were controlled using Graphic State software (Coulbourn Instruments, Allentown, PA).

Procedure

Monkeys were trained to press a lever for food reinforcement during 60-minute test sessions, conducted 4-5 times per week. Initial training used a fixed-ratio 1 (FR1) schedule where each lever press delivered one pellet. The schedule was then transitioned to a Differential Reinforcement of Low-Rate (DRL) schedule, where subjects were required to withhold responding for a delay interval between lever presses to obtain reinforcement. The delays were individualized to each monkey to standardize performance baselines. Therefore, each animal was titrated to an individualized delay that resulted in 2-6 reinforcers per session at baseline (80-240 second delay interval), typically within 10-15 sessions. If a response occurred before the end of the delay interval, the interval was reset and no reinforcement was delivered. Behavioral metrics recorded included the total number of reinforcers obtained (total number correct; RF); the response rate (responses per minute; RR); and the time, in seconds, between successive responses (inter-response time; IRT). Sessions with fewer than 10 total lever presses were excluded from analysis.

Drugs

Drug doses and pretreatment times were selected based on available literature and internal pharmacokinetic data to target clinically relevant exposure levels. Paroxetine (0.3,1,3 mg/kg), fluoxetine (1,3,10 mg/kg), duloxetine (0.03,0.1,0.3,1mg/kg), atomoxetine (1,3 mg/kg), desipramine (1,3,10 mg/kg), reboxetine (1,3,10 mg/kg), and bupropion (0.3,1,3 mg/kg), were all dissolved in water. Sibutramine (0.1,0.18,0.3,0.56 mg/kg), moclobemide (0.3,1,3 mg/kg), chlordiazepoxide (1,3,10,30 mg/kg), nicotine (0.03, 0.1, 0.18, 0.3 mg/kg), cocaine (0.03,0.1,0.3 mg/kg), methylphenidate (0.1,0.18 mg/kg), and modafinil (0.1,0.3,1 mg/kg), were dissolved in saline. Citalopram (1, 3, 10 mg/kg), was dissolved in fruit punch. Olanzapine (0.1, 0.3 mg/kg), was dissolved in 0.3% tween 80. Roflumilast (0.1, 0.3,1 mg/kg), rolipram (0.01, 0.03, 0.1, 0.3 mg/kg), and cilomilast (1, 3 mg/kg), were dissolved in 10% cremophor. All drugs were

administered through the intramuscular (i.m.) route with an injection volume of 0.1 ml/kg, with the exception of citalopram and atomoxetine, which were dosed orally (p.o.) at a dose volume of 2.5 ml/kg. Pretreatment times were 1 hour except for citalopram at 4 hours, duloxetine at 5 hours, reboxetine, methylphenidate, roflumilast, rolipram, and cilomilast at 30 minutes, and olanzapine and nicotine at 15 minutes. Drug details are summarized in Table 1.

Data Analysis

Behavioral performance on the DRL task was evaluated across multiple pharmacological manipulations using three dependent variables: number of reinforcers obtained (RF), response rate (RR), and inter-response time (IRT). Performance under each drug dose was normalized to the corresponding vehicle condition on a per-animal basis to control for individual variability in performance, yielding percent-of-control values for each metric. In the rare case that Vehicle condition RF performance was equal to zero, we assigned 0.1 as the value so that the percent of control value was not infinity. To account for repeated measures within subjects, non-normality of the data, and small sample sizes, we conducted rank-based linear mixed effects models for each drug and dependent variable. Models were fitted using the lmer() function in the lmerTest package in R (version 4.5.0), with Dose as a fixed effect and Monkey as a random intercept. Significance of the Dose effect was assessed via F-tests using Satterthwaite's approximation for degrees of freedom. For pairwise post-hoc comparisons between doses, we used estimated marginal means and Tukey-adjusted contrasts via the emmeans package. Results are reported both for overall model significance (main effect of Dose) and for pairwise contrasts between doses and vehicle conditions. Significance was defined by $\alpha = 0.05$.

RESULTS

Pharmacological Validation of the NHP-DRL Assay

To evaluate the sensitivity of the primate DRL model to antidepressant compounds, we first examined drugs across mechanistically diverse antidepressant classes. These included SSRIs, SNRIs, selective norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, TCAs, and MAOIs.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Paroxetine (0.3-3 mg/kg; n = 8) produced a dose-dependent increase in RF (Figure 1a; ($F(3, 17.3) = 6.92$, $p = 0.003$) and IRT ($F(3, 17.5) = 13.61$, $p < 0.001$), along with a significant decrease in RR ($F(3, 17.5) = 9.70$, $p < .001$). Post-hoc analyses revealed that each of the doses administered (0.3, 1, and 3 mg/kg) significantly increased RF and IRT and decreased RR (all $p < 0.05$). Similarly, citalopram (1-10 mg/kg; *n* = 7) significantly increased RF (Figure 1b; $F(3, 24) = 3.48$, $p = 0.031$) and IRT ($F(3, 18) = 7.74$, $p = 0.002$), and decreased RR ($F(3, 18) = 10.61$, p

< 0.001). These effects were dose-dependent, with RF significantly increased at 10 mg/kg, and RR significantly decreased and IRT significantly increased at both 3 mg/kg and 10 mg/kg (all p < 0.05). Acute fluoxetine treatment (1-10 mg/kg; n = 4) also produced significant increases in RF (Figure 1c; F(3, 9) = 10.62, p = 0.003) and IRT (F(3, 9) = 5.56, p = 0.019), and a significant decrease in RR (F(3, 9) = 7.54, p = 0.008). Post-hoc analyses revealed that highest dose (10 mg/kg) significantly altered performance compared with vehicle administration for all three dependent variables (all p < 0.05).

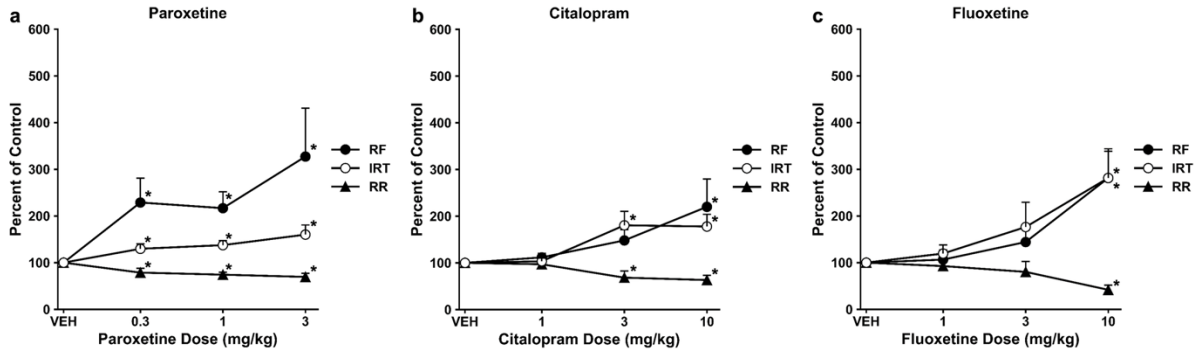

Figure 1. Effects of SSRIs on DRL task performance. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following acute administration of (a) paroxetine, (b) citalopram, and (c) fluoxetine. All three SSRIs produced dose-dependent increases in RF and IRT, and decreases in RR. Data represent group means ± SEM. *p < 0.05 vs vehicle.

SNRI, NRI, NDRI, TCA and MAOi Antidepressants

We tested the effects of two serotonin-norepinephrine reuptake inhibitors (SNRIs): duloxetine and sibutramine. Duloxetine (0.03-1 mg/kg; n = 6) administration resulted in a marked increase in RF (Figure 2a; F(4, 18.2) = 7.17, p = 0.001) and IRT (F(4, 18.4) = 7.16, p = 0.001), and a decrease in RR (F(4, 18.6) = 6.31, p = 0.002). These effects were dose-dependent, with the 1.0 mg/kg dose reaching significance for each of the dependent variables (all p < 0.05). Administration of the SNRI sibutramine (0.1-0.56 mg/kg, n = 7) also significantly affected each of the dependent variables. There was a significant increase in RF (Figure 2b; F(4, 24.0) = 6.73, p < 0.001) and IRT (F(4, 24) = 5.22, p = 0.004), and a significant decrease in RR (F(4, 24) = 5.48, p = 0.003). Post-hoc analyses revealed that the 0.3 and 0.56 mg/kg doses significantly altered performance compared with vehicle administration for each of the three dependent variables (all p < 0.05).

We tested the effects of two selective norepinephrine reuptake inhibitors (NRIs): reboxetine and atomoxetine. Reboxetine (1-10 mg/kg; n = 6) elicited a significant main effect of treatment on RF (Figure 2c; $F(3, 15.0) = 3.93$, $p = 0.030$), IRT ($F(3, 15.0) = 17.34$, $p < 0.001$), and RR ($F(3, 15.0) = 13.37$, $p < 0.001$). For RF, there was a significant effect of the 10 mg/kg dose compared to vehicle performance ($p < 0.05$). All three doses (1, 3, 10 mg/kg) significantly increased IRT and decreased RR compared to vehicle treatment (all $p < 0.05$). Acute atomoxetine treatment (1-3 mg/kg; n = 8) had an overall significant effect on RF (Figure 2d; $F(2, 11.4) = 4.13$, $p = 0.045$), but post-hoc tests failed to reach significance (Vehicle vs 1 mg/kg: $p = 0.066$; Vehicle vs 3 mg/kg: $p = 0.084$). There were no significant overall effects of atomoxetine treatment on either IRT ($F(2, 12.7) = 2.01$, $p = 0.175$) or RR ($F(2, 12.7) = 2.03$, $p = 0.171$).

The norepinephrine-dopamine reuptake inhibitor (NDRI), bupropion (0.3-3 mg/kg, n = 7) significantly increased IRT ($F(3, 15.4) = 7.76$, $p = 0.002$) and decreased RR ($F(3, 21) = 6.63$, $p = 0.003$), but did not significantly alter RF (Figure 2e; $F(3, 15.6) = 3.09$, $p = 0.058$). Post-hoc analyses revealed that 3 mg/kg bupropion significantly increased IRT relative to vehicle and significantly decreased RR at the same dose (all $p < 0.05$).

The tricyclic antidepressant (TCA), desipramine (1-10 mg/kg; n = 8) significantly increased RF (Figure 2f; $F(3, 21) = 14.23$, $p < .001$) and IRT ($F(3, 21) = 3.62$, $p = 0.030$), but did not significantly affect RR ($F(3, 21) = 2.06$, $p = 0.136$). The significant overall effects of desipramine on RF and IRT were driven by significant increases in DRL performance at the 10 mg/kg dose ($p < 0.05$).

The monoamine oxidase inhibitor, moclobemide (0.3-3 mg/kg; n = 6) produced significant increases in both RF (Figure 2g; $F(3, 18.0) = 8.35$, $p = 0.001$) and IRT ($F(3, 13.2) = 8.24$, $p = 0.002$), and a significant decrease in RR ($F(3, 13.2) = 6.62$, $p = 0.006$). Significant increases in RF and were observed specifically at the 1 and 3 mg/kg doses (all $p < 0.05$). Significant increases in IRT and significant decreases in RR were observed at all three doses tested (0.3, 1, 3 mg/kg; all $p < 0.05$).

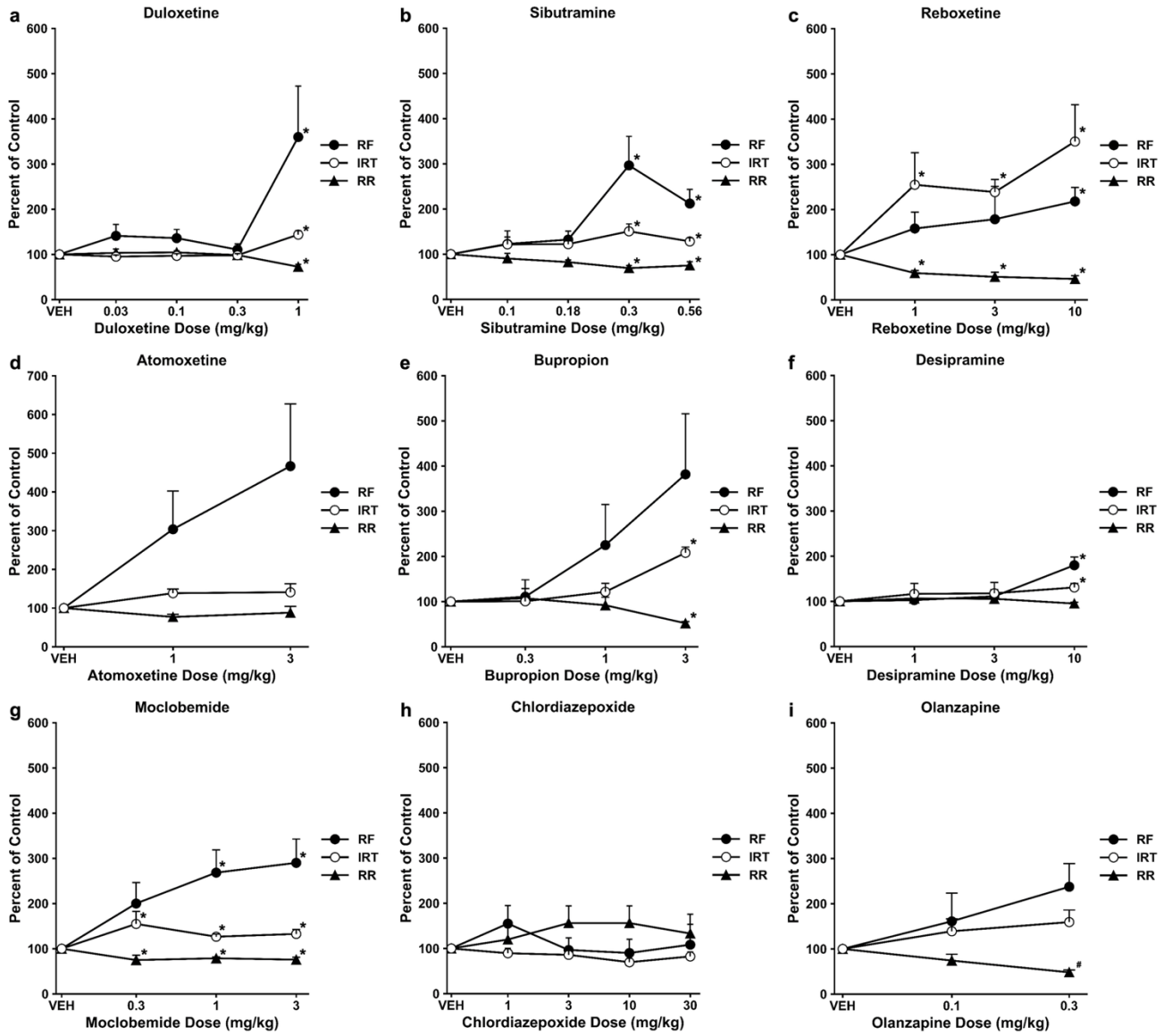

Figure 2. Behavioral effects of non-SSRI antidepressants and control compounds in the primate DRL task. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following administration of (a) duloxetine, (b) sibutramine, (c) reboxetine, (d) atomoxetine, (e) bupropion, (f) desipramine, (g) moclobemide, (h) chlordiazepoxide, and (i) olanzapine. Antidepressants across multiple classes including SNRIs (a-b), NRIs (c-d), NDRIs (e), TCAs (f), and MAOIs (g), produced dose-dependent increases in RF and IRT, and decreases in RR consistent with antidepressant-like profiles. Atomoxetine and control compounds chlordiazepoxide and olanzapine did not significantly improve DRL performance. Data represent group means ± SEM.*$p < 0.05$ vs vehicle. #$p < 0.06$ vs vehicle.

Pharmacological Specificity of the NHP-DRL Assay

To test the pharmacological specificity of the DRL task, we evaluated a set of compounds not primarily classified as antidepressants, including a benzodiazepine, an atypical antipsychotic, and psychostimulants. With a few exceptions, the overall resulting behavioral profiles were inconsistent with antidepressant-like improvements in DRL performance.

The benzodiazepine chlordiazepoxide (1-30 mg/kg; n = 6) did not significantly affect RF (Figure 2h; $F(4, 16) = 0.96$, $p = 0.455$) or RR ($F(4, 19) = 1.81$, $p = 0.168$). Although IRT approached significance ($F(4, 19.3) = 2.82$, $p = 0.054$), the change was in the opposite direction as expected of drugs with an antidepressant-like profile.

The atypical antipsychotic olanzapine (0.1-0.3 mg/kg; n = 7) produced significant main effects on RF (Figure 2i; $F(2, 9.9) = 4.26$, $p = 0.046$), RR ($F(2, 14) = 3.99$, $p = 0.043$), and IRT ($F(2, 9.7) = 4.40$, $p = 0.044$). Despite these effects, no individual dose significantly differed from vehicle in post-hoc testing (all $p > 0.05$), though the 0.3 mg/kg dose approached significance for RR ($p = 0.055$).

To evaluate whether stimulant compounds could mimic antidepressant-like effects in the DRL task, we tested four psychostimulants with diverse mechanisms of action: nicotine, cocaine, methylphenidate, and modafinil.

Nicotine (0.03-0.3 mg/kg; n = 7) significantly affected all behavioral outcomes, with main effects on RF (Figure 3a; $F(4, 23.3) = 3.15$, $p = 0.033$), RR ($F(4, 23.1) = 4.37$, $p = 0.009$), and IRT ($F(4, 23.1) = 4.99$, $p = 0.005$). Post-hoc analyses revealed several dose-specific effects compared to vehicle treatment. At 0.3 mg/kg, nicotine significantly increased RF and IRT, and decreased RR (all $p < 0.05$). Similarly, at 0.03 mg/kg, nicotine significantly increased IRT ($p < 0.05$) and approached significance for decreased RR ($p = 0.058$). Finally, the 0.18 mg/kg dose approached significance for increasing IRT ($p = 0.056$). Overall, this pattern of behavioral results shares features typically associated with antidepressant-like activity.

Cocaine (0.03-0.3 mg/kg; n=7) produced robust, dose-dependent effects across all behavioral measures, with significant main effects on RF (Figure 3b; $F(3, 15.1) = 37.32$, $p < 0.001$), RR ($F(3, 15) = 16.22$, $p < 0.001$), and IRT ($F(3, 14.9) = 20.56$, $p < 0.001$). Post-hoc comparisons revealed significant increases in RF at all doses tested relative to vehicle (all $p < 0.05$). The 0.1 and 0.3 mg/kg doses significantly decreased RR and increased IRT compared to vehicle administration (all $p < 0.05$).

In contrast to nicotine and cocaine which significantly changed DRL performance in a pattern similar to antidepressants, the stimulants methylphenidate and modafinil did not. Methylphenidate (0.1-0.18 mg/kg; n = 8) did not significantly alter performance on any DRL

measure. There were no significant main effects of dose on RF (Figure 3c; $F(2, 9.8) = 0.28$, $p = 0.760$), RR ($F(2, 9.8) = 0.78$, $p = 0.486$), or IRT ($F(2, 9.8) = 0.78$, $p = 0.486$).

Similarly, modafinil (0.1-1 mg/kg; n = 7) failed to produce significant effects on any behavioral measure in the DRL task. There were no significant main effects of dose on RF (Figure 3d; $F(3, 18) = 1.51$, $p = 0.246$), RR ($F(3, 18) = 1.25$, $p = 0.322$), or IRT ($F(3, 18) = 1.13$, $p = 0.363$).

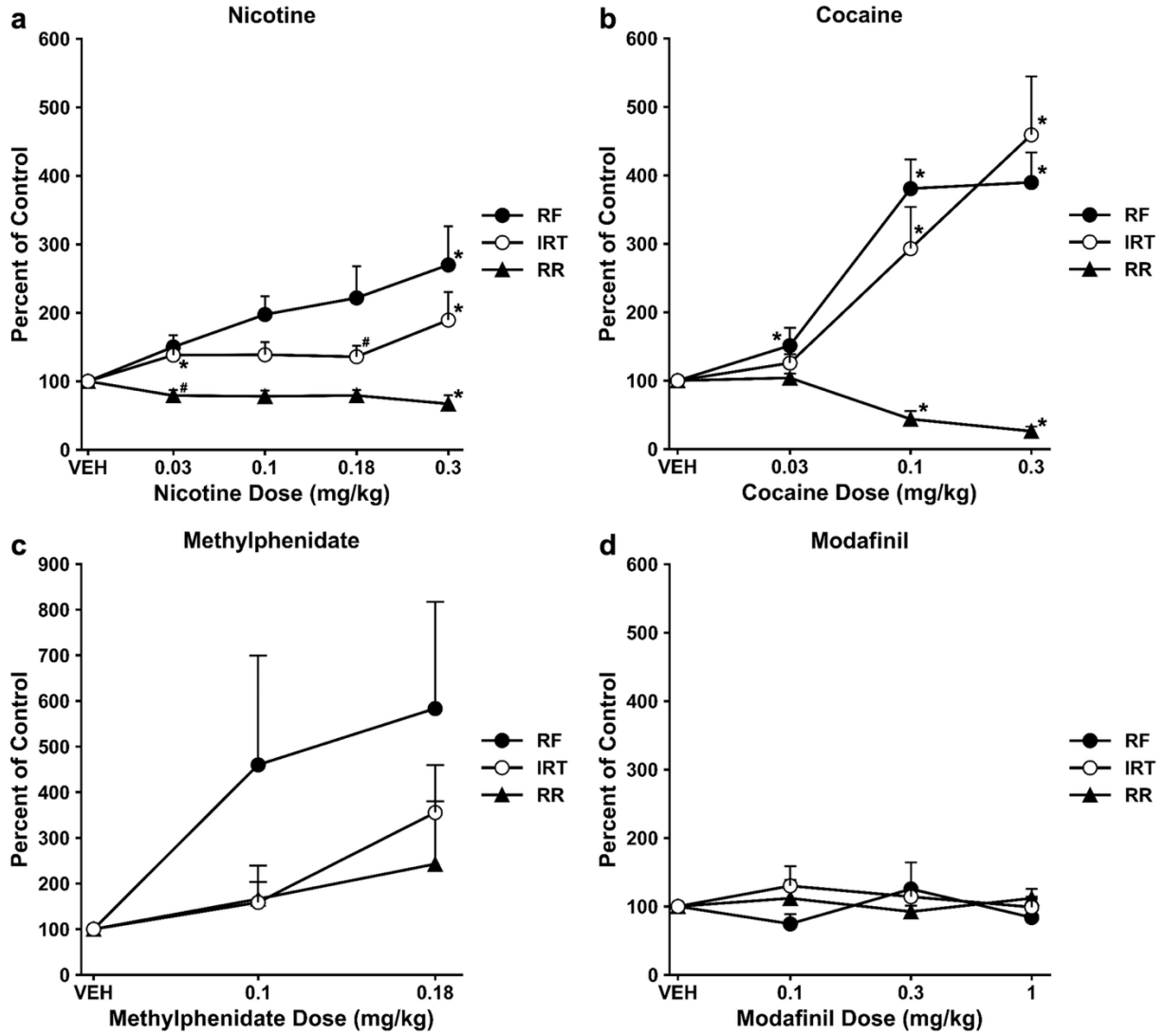

Figure 3. Effects of psychostimulant compounds on DRL task performance. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following administration of (a) nicotine, (b) cocaine, (c) methylphenidate, and (d) modafinil. Nicotine and cocaine produced robust antidepressant-like profiles with increases in RF and IRT and decreases in RR. Methylphenidate and modafinil produced no significant effects. Data represent group means ± SEM.*$p < 0.05$ vs vehicle. #$p < 0.06$ vs vehicle.

Evaluation of PDE4 Inhibitors

Given growing interest in PDE4 inhibitors as potential antidepressants, and their challenging side effect profile in clinical development, we tested three compounds with distinct selectivity and tolerability profiles: roflumilast, rolipram, and cilomilast. Each compound produced measurable effects on DRL performance, with emesis observed at higher doses across all agents.

Roflumilast (0.1-1 mg/kg; n = 7) produced significant effects on all three behavioral measures, with main effects on RF (Figure 4a; $F(3, 15.5) = 4.72$, $p = 0.016$), and IRT ($F(3, 15.3) = 9.32$, $p < 0.001$), and decreased RR ($F(3, 15.9) = 3.83$, $p = 0.031$). Post-hoc analyses revealed significant behavioral changes at 0.3 mg/kg and 1 mg/kg. Specifically, IRT was significantly increased at both of these doses and RR was significantly increased at the 1.0 mg/kg dose (all $p < 0.05$. Finally, the 1 mg/kg dose approached significance for increased RF ($p = 0.053$). Emesis was observed in six of the seven animals at this dose.

Rolipram (0.01-0.3 mg/kg; n = 6) significantly increased RF (Figure 4b; $F(4, 19) = 4.23$, $p = 0.013$) and IRT ($F(4, 18.1) = 8.09$, $p < 0.001$), but did not significantly affect RR ($F(4, 18.5) = 2.79$, $p = 0.057$). Post-hoc comparisons revealed that rolipram significantly increased IRT at both 0.1 and 0.3 mg/kg, and significantly increased RF at 0.3 mg/kg (all $p < 0.05$). Notably, the 0.1 and 0.3 mg/kg doses were associated with emesis in all subjects.

Cilomilast (1-3 mg/kg; n = 7) administration had a significant main effect on IRT (Figure 4c; $F(2, 9.7) = 35.00$, $p < 0.001$), with significant increases following the 1 and 3 mg/kg doses compared to vehicle (all $p < 0.05$). Cilomilast did not significantly alter RF ($F(2, 9.5) = 1.21$, $p = 0.339$) or RR ($F(2, 9.5) = 2.52$, $p = 0.132$). All subjects exhibited emesis at 3 mg/kg cilomilast.

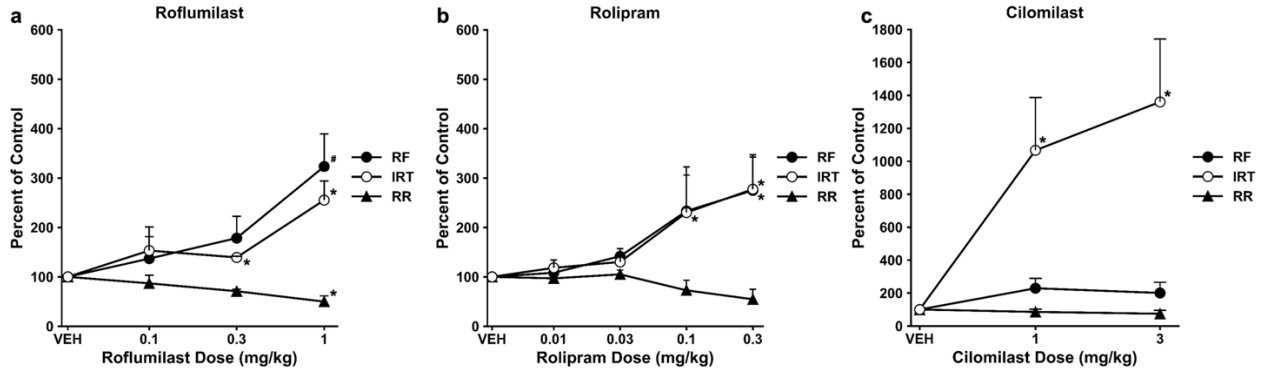

Figure 4. Effects of PDE4 inhibitors on DRL task performance. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following acute administration of (a) roflumilast, (b) rolipram, and (c) cilomilast. Roflumilast and rolipram produced antidepressant-like behavioral profiles, but cilomilast did not. Data represent group means ± SEM. *$p < 0.05$ vs vehicle. #$p < 0.06$ vs vehicle.

Drug	Drug Class	Doses (mg/kg)	RF Effect	RR Effect	IRT Effect
Paroxetine	SSRI	0.3, 1, 3	↑	↓	↑
Citalopram	SSRI	1, 3, 10	↑	↓	↑
Fluoxetine	SSRI	1, 3, 10	↑	↓	↑
Duloxetine	SNRI	0.03, 0.1, 0.3, 1	↑	↓	↑
Sibutramine	SNRI	0.1, 0.18, 0.3, 0.56	↑	↓	↑
Reboxetine	NRI	1, 3, 10	↑	↓	↑
Atomoxetine	NRI	1, 3	--	--	--
Bupropion	NDRI	0.3, 1, 3	--	↓	↑
Desipramine	TCA	1, 3, 10	↑	--	↑
Moclobemide	MAOI	0.3, 1, 3	↑	↓	↑
Chlordiazepoxide	BZD	1, 3, 10, 30	--	--	--
Olanzapine	Atypical	0.1, 0.3	--	↓*	--
Nicotine	Stimulant	0.03, 0.1, 0.18, 0.3	↑	↓	↑
Cocaine	Stimulant	0.03, 0.1, 0.3	↑	↓	↑
Methylphenidate	Stimulant	0.1, 0.18	--	--	--
Modafinil	Stimulant	0.1, 0.3, 1	--	--	--
Roflumilast	PDE4	0.1, 0.3, 1	↑*	↓	↑
Rolipram	PDE4	0.01, 0.03, 0.1, 0.3	↑	--	↑
Cilomilast	PDE4	1, 3	--	--	↑

Table 1. Drug administration and results summary. Abbreviations: SSRI - Selective serotonin reuptake inhibitor; SNRI - serotonin-norepinephrine reuptake inhibitor; NRI - norepinephrine reuptake inhibitor; NDRI - norepinephrine-dopamine reuptake inhibitor; TCA - tricyclic antidepressant; MAOI - monoamine oxidase inhibitor; BZD - benzodiazepine; PDE4 - phosphodiesterase-4 inhibitor; IM - intramuscular; PO - per oral; RF - reinforcers obtained; RR - response rate; IRT - inter-response time. *approached significance ($p < 0.06$)

DISCUSSION

In this study, we adapted the DRL paradigm for use in NHPs and systematically evaluated its predictive validity, pharmacological specificity, and translational utility for detecting antidepressant-like effects. Antidepressants from multiple mechanistic classes elicited significant and consistent improvements in DRL performance. These effects were not broadly replicated by non-antidepressant compounds, underscoring the translational potential of the DRL as a platform for detection of effective antidepressants. Critically, we extended the application of this model to evaluate PDE4 inhibitors, a mechanistically novel antidepressant class whose clinical development has been limited by a narrow therapeutic window and emetic liability. The NHP model allowed us to assess both behavioral efficacy and emetic liability in the same subjects, offering a translational bridge between preclinical screening and clinical development. Together, these findings validate the NHP DRL paradigm as a robust translational platform for preclinical evaluation of novel antidepressant therapies.

Interpreting Antidepressant-Like Effects in the DRL Model

Selective Serotonin Reuptake Inhibitors (SSRIs)

Consistent with prior rodent studies, the NHP DRL model demonstrated strong sensitivity to classical antidepressants across multiple pharmacological classes. All SSRIs (paroxetine, citalopram, and fluoxetine) produced dose-dependent increases in RF and IRT and decreased RR. These results closely align with prior studies in rodent DRL models, which have repeatedly demonstrated that SSRIs elicit antidepressant-like behavioral changes (Danysz et al., 1988; van Hest et al., 1992; Olivier et al., 1993; Seiden et al., 1985; Marek et al., 1989; Sokolowski and Seiden, 1999; Cousins and Seiden, 2000; Cousins et al., 2000; Richards et al., 1993a; Dekeyne et al., 2002). The consistency of these effects across species reinforces the primate DRL task's validity as a translational tool that captures antidepressant efficacy.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Although SNRIs are widely prescribed for the treatment of depression in humans, the rodent DRL literature has largely failed to demonstrate antidepressant-like effects with this class. For example, venlafaxine failed to produce antidepressant-like effects in rodent DRL, even at does that produce clear effects in other antidepressant-sensitive assays (Dekeyne et al., 2002). In contrast, our findings demonstrate that the primate DRL model is sensitive to SNRI treatment. Both duloxetine and sibutramine significantly improved performance, increasing RF and IRT while decreasing RR.

These species differences may reflect broader pharmacological or neurobiological divergences in monoaminergic regulation of response inhibition and interval timing. They may

also highlight distinctions between individual drugs within the SNRI class. For instance, duloxetine has a 10-fold selectivity for serotonin over norepinephrine, while venlafaxine exhibits a 30-fold preference (Montgomery, 2008), potentially explaining duloxetine's more balanced noradrenergic contribution to DRL performance. Clinically, duloxetine has been shown to outperform SSRIs in some populations, particularly individuals with treatment-resistant depression (Mallinckrodt et al., 2007; Pitchot et al., 2010; Rodrigues-Amorim et al., 2020). However, other findings indicate that duloxetine may not be as effective as venlafaxine (Schueler et al., 2011).

Sibutramine, while structurally and mechanistically similar to antidepressants, was originally developed as an appetite suppressant and is not approved for depression (Araujo & Martel, 2012; Bray et al., 1999). Nonetheless, its dual blockade of serotonin and norepinephrine reuptake mirrors that of traditional SNRIs (Stahl et al., 2014). Our results show that sibutramine robustly improves DRL performance across doses, suggesting that its underlying pharmacology is sufficient to engage the same cognitive processes targeted by approved antidepressants. This supports the utility of the primate DRL model in detecting compounds with dual reuptake inhibition, even when their primary clinical indication lies outside of depression.

Selective norepinephrine reuptake inhibitors (NRIs)

NRIs offer an important test of the DRL model's sensitivity to noradrenergic modulation independent of serotonergic mechanisms. We evaluated two NRIs, reboxetine and atomoxetine that differ in clinical application and efficacy (Kobayashi et al., 2010; Holm & Spencer, 2012; Ding et al., 2014). Reboxetine produced dose-dependent improvements on DRL performance across all behavioral endpoints. These results are consistent with previous literature utilizing this compound in the rodent DRL model (Dekeyne et al., 2002; Wong et al., 2000), but contrast with the questionable efficacy of reboxetine as an antidepressant in humans (Cipriani et al., 2009). In contrast, atomoxetine had minimal effects on DRL performance. While a main effect of treatment on RF was detected, post-hoc comparisons were nonsignificant, and no effects emerged for IRT or RR. These findings alight with the fact that atomoxetine is approved for clinical use in attention-deficit/hyperactivity disorder, not depression (The Atomoxetine ADHD and Comorbid MDD Study Group et al., 2007; Michelson et al., 2003). It is likely that its relatively weak affinity for the norepinephrine transporter compared to other NRIs explains the lack of robust behavioral modulation (Aldosary et al., 2022). The divergence between reboxetine and atomoxetine emphasizes that not all NRIs exert equivalent effects in the DRL task. These results also suggest that norepinephrine reuptake inhibition can modulate DRL behavior, but only under specific neurochemical or receptor engagement conditions.

Norepinephrine-dopamine reuptake inhibitor (NDRI)

The NDRI bupropion significantly improved DRL performance by increasing IRT and reducing RR, though the increase in reinforcers earned did not reach statistical significance.These effects were most pronounced at the highest dose tested, however, the magnitude of these effects was relatively mild compared to other antidepressants. This parallels the rodent literature where bupropion has produced weak and inconsistent effects on DRL tasks (Dekeyne et al., 2002; Seiden et al., 1985, Zhang et al., 2024). This relatively limited efficacy may reflect bupropion's pharmacological profile, which includes weaker inhibition of norepinephrine and dopamine transporters compared to classic NRIs or stimulants, and an absence of serotonergic activity (Stahl et al., 2004). While clinically effective for some individuals, especially those with atypical or treatment-resistant depression, bupropion is also often used as an adjunctive therapy, suggesting that its modest behavioral impact in the DRL task may be pharmacologically appropriate (Raju et al., 2025; Nasr et al., 2014).

Tricyclic antidepressant (TCA)

Tricyclic antidepressants are among the earliest pharmacologic treatments for depression (Kamp et al., 2024). Although their clinical use has declined due to unfavorable side effect profiles, their mechanisms, primarily inhibition of norepinephrine reuptake, remain relevant for evaluating antidepressant efficacy in preclinical models. In the present study, the TCA desipramine significantly increased RF and IRT, supporting its antidepressant-like behavioral profile.

These findings are consistent with rodent literature demonstrating desipramine-induced improvements in DRL performance (O'Donnell and Seiden, 1983; Danysz et al., 1988; Britton and Koob, 1989; Dekeyne et al., 2002; Richards and Seiden, 1991; Richards et al., 1993b; O'Donnell and Seiden, 1984, Jackson et al., 1995, Richards et al., 1993a). There are, however, some differences between our results and those from rodents. In rats, desipramine typically produces robust increases in RF and IRT along with decreases in RR. While our primate data mirrored the increased RF and IRT, we saw no effect of desipramine on RR. Additionally, whereas primates showed an increase in RF following desipramine treatment, one rodent study found no effect of desipramine on RF (Jackson et al., 1995). Finally, whereas in primates, increases in RF and IRT were driven by the highest dose tested, rodent studies have frequently reported broader dose responsiveness. In primates, effects were dose-dependent and driven by the highest dose, whereas rodents often show broader dose responsiveness. These discrepancies may reflect species-specific sensitivity or suggest that higher doses are required

to elicit full effects in macaques. Overall, while broadly concordant with rodent data, the primate DRL model may provide a more conservative or selective measure of TCA efficacy.

Monoamine Oxidase Inhibitor (MAOI)

MAOIs were among the first antidepressants developed but are less commonly prescribed today due to safety concerns related to medication and dietary tyramine interactions (Brown et al., 1989; Edinoff et al., 2022). Nonetheless, MAOIs remain mechanistically informative and are particularly useful for treatment-resistant depression (Yamada and Yasuhara, 2004). In the present study, the reversible MAOI moclobemide produced a robust antidepressant-like profile in the primate DRL model. These effects were dose-dependent and consistent across all three measures. Importantly, these findings align with rodent DRL studies using irreversible MAOIs such as phenelzine, iproniazid, and isocarboxazid (O'Donnell and Seiden, 1982, 1983). However, our results extend this literature by demonstrating that a reversible, MAO-A-selective inhibitor can produce similar behavioral improvements. This is clinically relevant because reversible MAOIs like moclobemide have a more favorable safety profile than irreversible agents, yet still may preserve the therapeutic benefit seen in classical MAOI compounds (Nair et al., 1993). The efficacy of moclobemide in this primate model suggests that enhancing monoaminergic tone through selective MAO-A inhibition is sufficient to produce antidepressant-like effects, and further supports the use of primate DRL as a translational tool to evaluate mechanistically diverse antidepressants.

Benzodiazepines (BZD) and Antipsychotic therapies

To assess the pharmacological specificity of the DRL paradigm, we included compounds not traditionally considered antidepressants. The benzodiazepine chlordiazepoxide failed to improve DRL performance producing no significant changes in RF or RR, and a marginal, non-significant change in IRT in the opposite direction of an antidepressant-like effect. This aligns with prior rodent DRL studies demonstrating that benzodiazepines often either impair performance or increase impulsivity, likely due to their sedative and disinhibitory effects (van Hest et al., 1992; Richards et al., 1993b; O'Donnell and Seiden, 1982).

The atypical antipsychotic olanzapine elicited significant main effects on all three behavioral measures, but post-hoc comparisons failed to reveal statistically significant differences at any dose. Although RR approached significance at the highest dose tested, the overall behavioral pattern did not match the profile typically observed with antidepressants. Olanzapine has yet to be tested in the rodent DRL model, but clozapine, which is structurally and pharmacologically similar, has been tested a handful of times. Specifically, (Seiden et al., 1985) found that clozapine decreased RR and RF, which is similar to the primate olanzapine

results reported here. Similarly, acute clozapine failed to rescue deficits in DRL produced by administration of phencyclidine (Compton et al., 2001).

Psychostimulants

We tested four stimulant compounds with distinct pharmacological mechanisms to evaluate whether behavioral activation alone is sufficient to enhance DRL performance, or whether antidepressant-like effects depend on specific neuromodulatory engagement (Pary et al., 2015; Hai et al., 2022). Both nicotine and cocaine produced robust antidepressant-like profiles on the task. Although their primary mechanisms differ, with nicotine acting via nicotinic acetylcholine receptors, and cocaine blocking monoamine reuptake transporters, both increase extracellular levels of dopamine, norepinephrine, and serotonin (Ruiz et al., 2021; Beer, 2016; Wignall & de Wit, 2011). This shared profile of broad monoaminergic activation may account for their convergent behavioral effects.

In contrast, methylphenidate and modafinil failed to improve DRL performance. Both compounds lack meaningful serotonergic activity (Repantis et al., 2010), which may limit their ability to enhance inhibitory control and internal timing required for optimal DRL performance. Methylphenidate primarily blocks dopamine and norepinephrine reuptake, but its dopaminergic predominance may increase arousal and motor output without improving response regulation (Schrantee et al., 2016). This is consistent with rodent data showing that methylphenidate increases impulsivity and disrupts performance on tasks requiring response inhibition (Navarra et al., 2008; Richards et al., 1993b). Modafinil promotes wakefulness via orexin and dopamine systems but has minimal impact on serotonin or norepinephrine and does not engage the cognitive mechanisms that underlie antidepressant-like performance (Gerrard & Malcolm, 2007; Mereu et al., 2014). Together, these findings highlight the specificity of the primate DRL paradigm in distinguishing compounds that enhance goal-directed behavioral restraint from those that merely increase general behavioral output.

Effects of Phosphodiesterase-4 (PDE4) Inhibitors

Having validated the primate DRL model as both sensitive and specific to compounds with antidepressant-relevant monoaminergic activity, we next applied it to a novel drug class. Phosphodiesterase-4 inhibitors, including roflumilast, rolipram, and cilomilast have shown promising antidepressant properties in preclinical studies (Wang et al., 2015, 2020; Yu et al., 2021). However, their clinical development has been hindered by dose-limiting side effects. We used the primate DRL model to evaluate both the antidepressant-like efficacy and tolerability of these compounds in a translationally relevant context.

Importantly, NHPs offer a distinct advantage over rodents for evaluating PDE4 inhibitors. While rodents are widely used for early antidepressant screening, they lack a gag reflex and cannot vomit, limiting their utility in detecting dose-limiting side effects such as emesis, a major development of clinical PDE4 compounds. The primate DRL model thus offers a unique opportunity to simultaneously assess efficacy and tolerability in a single behavioral paradigm, improving predictive validity for human clinical trials.

Two of the compounds, roflumilast and rolipram exhibited classic antidepressant-like profiles in the DRL task. These effects mirror prior rodent studies showing that PDE4 inhibitors improve DRL performance (Zhang et al., 2006; O'Donnell, 1993; O'Donnell and Frith, 1999; Zhang et al., 2005; O'Donnell and Zhang, 2004). In contrast, cilomilast only increased IRT, and failed to affect RF or RR, yielding a weaker and incomplete antidepressant-like profile.

Despite these drug efficacy signals, tolerability remains a major limitation. Emesis was observed in all monkeys administered rolipram at 0.1 or 0.3 mg/kg, in all subjects given 3 mg/kg cilomilast, and in six of seven animals treated with 1 mg/kg roflumilast. These side effects closely resemble clinical experiences with PDE4 inhibitors, where nausea and vomiting curtailed further development despite clear antidepressant potential (Zeller et al., 1984; Burnouf et al., 1998). Thus, while the DRL model detects antidepressant efficacy for PDE4 inhibitors, it also recapitulates their dose-limiting side effect profile, emphasizing the need for improved tolerability in this drug class.

Cognitive Processes Underlying DRL Performance

In the DRL task, subjects are reinforced for responding only after withholding behavior across an un-signaled delay interval, making the task sensitive to both impulsivity and timing precision. All animals were first trained to a stable baseline, which, under vehicle treatment, was marked by moderate response rates, short inter-response times, and few reinforcers earned, reflecting impulsive responding and imprecise timing. Improvement from this baseline requires two key processes: (1) enhanced inhibitory control to suppress premature responses, and (2) improved internal time estimation to better align responses with the delay requirement. Optimal DRL performance, therefore, is defined by low response rate, long inter-response times, and a high number of reinforcers earned, indicating infrequent, well-timed responding. Most antidepressants produced simultaneous improvements across all three behavioral measures, suggesting coordinated engagement of both inhibitory control and timing. This pattern provides a clear and interpretable behavioral signature of antidepressant-like efficacy and reinforces the utility of the DRL task as a translational model for probing core cognitive processes disrupted in depression.

Conclusion

The present findings establish the delayed reinforcement task as a powerful, translationally relevant model for evaluating antidepressant-like effects in non-human primates. The DRL paradigm reliably differentiated antidepressants from non-antidepressants based on a clear and consistent behavioral signature: increased reinforcement, lengthened inter-response times, and reduced response rates. These effects were observed across diverse antidepressant classes, including SSRIs, SNRIs, NRIs, NDRIs, TCAs, MAOIs, and PDE4 inhibitors, but not on other drug classes, such as and anxiolytics, antipsychotics, or psychostimulants. Critically, the primate DRL model not only captured therapeutic effects but also revealed side effect liabilities, such as emesis with PDE4 inhibitors—an outcome not detectable in rodent models. By enabling simultaneous evaluation of efficacy and tolerability, this model provides a robust framework for antidepressant drug discovery and development. Taken together, these results position the primate DRL task as a highly sensitive, pharmacologically specific, and clinically relevant platform for identifying and characterizing novel treatments for depression.

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FIGURE LEGENDS

Figure 1. Effects of SSRIs on DRL task performance. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following acute administration of (a) paroxetine, (b) citalopram, and (c) fluoxetine. All three SSRIs produced dose-dependent increases in RF and IRT, and decreases in RR. Data represent group means ± SEM. *$p < 0.05$ vs vehicle.

Figure 2. Behavioral effects of non-SSRI antidepressants and control compounds in the primate DRL task. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following administration of (a) duloxetine, (b) sibutramine, (c) reboxetine, (d) atomoxetine, (e) bupropion, (f) desipramine, (g) moclobemide, (h) chlordiazepoxide, and (i) olanzapine. Antidepressants across multiple classes including SNRIs (a-b), NRIs (c-d), NDRIs (e), TCAs (f), and MAOIs (g), produced dose-dependent increases in RF and IRT, and decreases in RR consistent with antidepressant-like profiles. Atomoxetine and control compounds chlordiazepoxide and olanzapine did not significantly improve DRL performance. Data represent group means ± SEM.*$p < 0.05$ vs vehicle. #$p < 0.06$ vs vehicle.

Figure 3. Effects of psychostimulant compounds on DRL task performance. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following administration of (a) nicotine, (b) cocaine, (c) methylphenidate, and (d) modafinil. Nicotine and cocaine produced robust antidepressant-like profiles with increases in RF and IRT and decreases in RR. Methylphenidate and modafinil produced no significant effects. Data represent group means ± SEM.*$p < 0.05$ vs vehicle. #$p < 0.06$ vs vehicle.

Figure 4. Effects of PDE4 inhibitors on DRL task performance. Percent-of-control performance for reinforcers earned (RF), inter-response time (IRT), and response rate (RR) following acute administration of (a) roflumilast, (b) rolipram, and (c) cilomilast. Roflumilast and rolipram produced antidepressant-like behavioral profiles, but cilomilast did not. Data represent group means ± SEM. *$p < 0.05$ vs vehicle. #$p < 0.06$ vs vehicle.