Title: Dopamine and norepinephrine differentially mediate the exploration-exploitation tradeoff

Abbreviated title: Dopamine and norepinephrine mediate exploration

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Abstract

The catecholamines dopamine (DA) and norepinephrine (NE) have been implicated in neuropsychiatric vulnerability, in part via their roles in mediating the decision making processes. Although the two neuromodulators share a synthesis pathway and are co-activated, they engage in distinct circuits and roles in modulating neural activity across the brain. However, in the computational neuroscience literature, they have been assigned similar roles in modulating the exploration-exploitation tradeoff. Revealing how each neuromodulator contributes to this explore-exploit process is important in guiding mechanistic hypotheses emerging from computational psychiatric approaches. To understand the differences and overlaps of the roles of dopamine and norepinephrine in mediating exploration, a direct comparison using the same dynamic decision making task is needed. Here, we ran mice in a restless bandit task, which encourages both exploration and exploitation. We systemically administered a nonselective DA antagonist (flupenthixol), a nonselective DA agonist (apomorphine), a NE beta-receptor antagonist (propranolol), and a NE beta-receptor agonist (isoproterenol), and examined changes in exploration within subjects across sessions. We found a bidirectional modulatory effect of dopamine receptor activity on exploration - increasing dopamine activity decreased exploration and decreasing dopamine activity increased exploration. The modulation of exploration via beta-noradrenergic activity was mediated by sex. Computational model parameters revealed that dopamine modulation affected exploration via decision noise and norepinephrine modulation via outcome sensitivity. Together, these findings suggested that the mechanisms that govern the transition between exploration and exploitation are sensitive to changes in both catecholamine functions and revealed differential roles for NE and DA in mediating exploration.

Significance Statement

Both dopamine (DA) and norepinephrine (NE) has been implicated in the decision making process. Although these two catecholamines have shared aspects of their biosynthetic pathways and projection targets, they are thought to exert many core functions via distinct neural targets and receptor subtypes. However, the computational neuroscience literature often ascribes similar roles to these catecholamines, despite the above evidence. Resolving this discrepancy is important in guiding mechanistic hypotheses emerging from computational psychiatric approaches. This study examines the role of dopamine and norepinephrine on the explore-exploit tradeoff. By testing mice, we were able to compare multiple pharmacological agents within subjects, and examine source of individual differences, allowing direct comparison between the effects of these two catecholamines in modulating decision making.

Introduction

Dysfunctions in cognitive processes, particularly within the domain of executive function, are implicated in numerous neuropsychiatric disorders (Elliott, 2003; Malloy-Diniz et al., 2017; Grissom and Reyes, 2019). One essential aspect of executive function is value-based decision making. Decision making involving exploring and learning in an uncertain environment has been a focus in computational neuroscience, which has developed approaches for discovering latent structures in decision making strategies (Rothenhoefer et al., 2017; Ebitz et al., 2018; Chen et al., 2021a, 2021b). Many computational models for value-based decision making distinguish two essential latent processes: exploration and exploitation (Sutton and Barto, 1998; Niv et al., 2002; Daw et al., 2006; Jepma et al., 2020; Wilson et al., 2021). Exploration is the ubiquitous learning process across species that allows the discovery of the best action to take in an uncertain environment (Ebitz et al., 2018; Gershman, 2019; Chen et al., 2021b; Wilson et al., 2021). Once a favorable action or option is discovered, exploitation, i.e. repeating a rewarding action, is necessary to obtain the best rates of reward. However, exploitation must be balanced with continued exploration as environments and their reward probabilities change. Dysregulation in this exploration-exploitation tradeoff is implicated in the phenotypes of numerous neuropsychiatric disorders and challenges, including schizophrenia, autism spectrum disorders, addictions, and chronic stress (Kim et al., 2007; Mussey et al., 2015; Morris et al., 2016; Addicott et al., 2020; Kaske et al., 2022). Understanding the fundamental mechanisms impacting the computations in our brain that underlie the balance between exploration and exploitation could help identify critical circuits that are associated with differential risk factors for neuropsychiatric disorders and open avenues for novel interventions for executive function challenges.

Many neuropsychiatric challenges are associated with dysfunction in the catecholamines dopamine and norepinephrine (Kobayashi, 2001; Ressler and Nemeroff, 2001; Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Money and Stanwood, 2013; Addicott et al., 2020; Williams et al., 2021). These neuromodulators are well-positioned to carry information about the state of the environment and influence behavior outputs via downstream control of action selection (Cohen et al., 2007; Wilson et al., 2021). Indeed, dopamine and norepinephrine have each separately been implicated in mediating the exploration-exploitation tradeoff (Seamans and Yang, 2004; Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Cohen et al., 2007; Redish et al., 2007; Wilson et al., 2021; Cremer et al., 2022). While dopamine and norepinephrine share biosynthetic pathways and are co-activated under states of arousal, they act through partially separable circuits and have distinct neural targets (Ranjbar-Slamloo and Fazlali, 2019). However, in the computational neuroscience literature, dopamine and norepinephrine have largely been ascribed similar or even identical roles in mediating the explore-exploit tradeoff despite of the distinct pharmacological profiles.

We have previously shown that multiple latent cognitive processes, such as the reinforcement learning model-derived parameters of learning rate and decision noise, can describe differences in the level of exploration between groups (Chen et al., 2021b). Dopamine has often been implicated in mediating reward prediction errors and value-based learning (Schultz, 1998, 2013; Daw et al., 2006; Niv, 2009) while norepinephrine in modulating arousal, attention, and value assessment (Aston-Jones and Cohen, 2005; Yu and Dayan, 2005; Amemiya et al., 2016), but more recently both neuromodulators have been implicated in the process of action selection (Humphries et al., 2012; Warren et al., 2017). Therefore, it is unknown whether dopamine and norepinephrine govern this exploration-exploitation tradeoff via distinct or similar

latent cognitive processes because they have been largely studied in this context in isolation (Cremer et al., 2022).

To uncover the distinct roles of dopamine and norepinephrine in the exploration-exploitation tradeoff, we conducted within-subjects pharmacological manipulations for these two neuromodulators to examine their effect on exploration and the latent cognitive parameters that influence exploration, in the same restless bandit task. We pharmacologically up- and down-regulated dopaminergic and noradrenergic receptor activity and compared the modulatory effects on exploration in the same dynamic decision making task, a spatial restless two-armed bandit (Ebitz et al., 2018; Chen et al., 2021b). We found a bidirectional modulatory effect of dopamine receptor activity on the level of exploration. Increasing dopamine activity decreased exploration and decreasing dopamine activity increased exploration. Beta-noradrenergic receptor activity also modulated exploration but the modulatory effect was mediated by sex. Contrary to dopamine modulating choice solely by changing value-based learning for outcomes, via reinforcement learning modeling we find that dopamine mediates exploration by changing decision noise, i.e. the precision of value-based choice selection. In contrast, noradrenergic activity surprisingly influenced exploration by changing value-based learning for outcomes in a sex dependent manner. These data suggest differential roles of dopamine and norepinephrine in mediating exploration, and complex roles for both catecholamines in signaling reward.

Materials and Methods

Animals. Thirty-two BL6129SF1/J mice (16 males and 16 females) were obtained from Jackson Laboratories (stock #101043). Mice arrived at the lab at 7 weeks of age and adapted to 0900-2100 hours reversed light cycle throughout the testing phase. Mice were housed in groups of four with ad libitum access to water while being mildly food restricted (85-95% of free feeding weight) before the start of the experiment (12 weeks) and during the experiment. All animals were cared for according to the guidelines of the National Institution of Health and experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota.

Apparatus. Sixteen identical triangular touchscreen operant chambers (Lafayette Instrument Co., Lafayette, IN) were used for training and testing. Two walls were black acrylic plastic. The third wall housed the touchscreen and was positioned directly opposite the magazine. The magazine provided liquid reinforcers (50% Ensure) delivered by a peristaltic pump, typically 7ul (280 ms pump duration). ABET-II software (Lafayette Instrument Co., Lafayette, IN) was used to program operant schedules and to analyze all data from training and testing.

Behavioral task. *Two-armed spatial restless bandit task.* Animals were trained to perform a two-armed spatial restless bandit task in the touchscreen operant chamber. Each trial, animals were presented with two identical squares on the left and right side of the screen. Nose poke to one of the target locations on the touchscreen was required to register a response. Each location is associated with some probability of reward, which changes independently over time. For every trial, there is a 10% chance that the reward probability of a given arm will increase or decrease

143 by 10%. All the walks were generated randomly with a few criteria: 1) the overall reward
144 probabilities of two arms are within 20% of each other, preventing one arm being overly better
145 than the other, 2) the reward probability cannot go down to 0% or go up to 100%, 3) there are no
146 30 consecutive trials where the reward probabilities of both arms are lower than 20% to ensure
147 motivation.

148 Animals ran for 6 control sessions and 6 drug sessions for each pharmacological
149 manipulation. The wash-out period between each drug condition is 3 days. Each session
150 consisted of 300 trials. Within each session, animals completed either 300 trials or spent a
151 maximum of two hours in the operant chamber. On average across all sessions, animals
152 performed 276.5 trials with a standard deviation of 8.6 trials (male average: 253.7 trials, std =
153 15.4; female average 299.3 trials, std = 0.74. Data were recorded by the ABET II system and was
154 exported for further analysis. All computational modeling was conducted using python.
155

156 Drug administration. To assess the effect of norepinephrine and dopamine receptor activity on
157 explore behaviors, we used the following four different drugs to increase or decrease beta-
158 noradrenergic or dopaminergic receptor activity systemically: a beta-noradrenergic receptor
159 agonist isoproterenol (0.3mg/kg), a beta-noradrenergic receptor antagonist propranolol (5mg/kg),
160 a non-selective dopamine receptor agonist apomorphine (0.1mg/kg), and a non-selective
161 dopamine receptor antagonist flupenthixol (0.03mg/kg).

162 All drugs were fully dissolved in 0.9% saline and protected from light. Animals received
163 intraperitoneal (IP) injection of drug or saline (control) at an injection volume of 5ml/kg right
164 before the experiment with the exception of apomorphine being administered 20 minutes before
165 the experiment due to the immediate drug influence of locomotor behaviors. Drug and saline

were administered in alternating sessions using a within-subject so that every animal received each of the four drugs. The dopamine receptor agonist and antagonist were administered counterbalanced across animals. Half of the animals (n = 8) were randomly selected to receive apomorphine first, the other received flupenthixol first. Since this experiment prioritized using a within-subject design to understand the effect of each drug within individual animals and the source of individual differences, the length of study only limited us to test one dose for each of the four drugs. Therefore, dosage chosen was based on previous studies on the effect of drugs on cognitive functions (Fernandez-Tome et al., 1979; Cabib et al., 1984; Goldschmidt et al., 1984; Ichihara et al., 1988; Nakamura et al., 1998; Grigoryan, 2012; Cinotti et al., 2019). Doses for each drug were chosen from previous studies as the lowest doses necessary to produce alterations in cognitive functions including decision making, learning and exploration with minimal influence on locomotion.

Data Analysis

General analysis techniques. Data were analyzed with custom PYTHON, and Prism 8 scripts. Generalized linear mixed models (GLMMs), ANOVA, and t-test were used to determine the fixed effects of drug, sex, and interaction term, accounting for random effects of animal identity and session, unless otherwise specified. P values were compared against the standard $\alpha = 0.05$ threshold. The sample size is n = 32 (16 males and 16 females) for all statistical tests. No animal was excluded from the experiment. All statistical tests used and statistical details were reported in the results. All figures depict mean ± SEM.

Generalized Linear Mixed Models (GLMMs). In order to determine whether drug and sex

predicted the reward acquisition performance, response time, probability of win-stay, probability of lose-shift, outcome sensitivity, probability of exploration, we fitted a series of generalized linear mixed model to examine the fixed effects of drug, sex, and interaction term, with animal identity and sessions as random effects.

$$Y = \beta_0 + \beta_1(drug) + \beta_2(sex) + \beta_3(drug)(sex) + u_1(animal\ ID) + u_2(session) \quad \textbf{[1]}$$

,where Y is the dependent variable (obtained reward, response time, win-stay, lose-shift, outcome sensitivity, exploration). In this model, β1 describes the main effect of drug and β2 describes the main effect of sex. β3 captures any interaction effect between drug and sex. u1 and u2 capture the random effect of animal identity and session respectively.

Outcome Sensitivity. In order to examine how much of the switching behavior was sensitive to reward outcome, we calculated the difference between switching given no reward and switching given reward control by the total amount of switching. If switching behavior was not affected by the outcome at all, the outcome sensitivity should be close to zero.

$$outcome\ sensitivity = \frac{p(switch|no\ reward) - p(switch|reward)}{p(switch)} \quad \textbf{[2]}$$

Hidden Markov model (HMM).

In order to identify when animals were exploring, we fit a Hidden Markov model (HMM) to the animals' choice sequence. Our model consisted of two hidden states - explore state and exploit state, which are defined by the probability of making each choice (k, out of N_k possible options) and the probability of transitioning from one state to another. When an HMM model is fitted to animals' choices, it estimates a transition matrix, which is the mapping between every state at one time point and every state at some future point of time. The HMM model fitting is the

process of estimating how the distribution over states will evolve over time. The transition matrix estimates the probability of each type of transition between states. The HMM models exploration as a uniform distribution over choices, i.e. the emissions model for the explore state was uniform across options. This is the maximum entropy distribution of a categorical variable, which makes the few assumptions of true distribution of choices during exploration and therefore does not bias the model towards or away from any particular type of high-entropy choice period. In the exploitation state, subjects repeatedly sample the same choice, therefore the exploit states only permit one choice, i.e. exploit-left state only emits left choices and exploit-right state only emits right choice.

The latent states in this model are Markovian, meaning that they are time-independent. They depend only on the most recent state. The HMM model estimates a transition matrix to fit the behavior by mapping of past and future states. This matrix is a system of stochastic equations describing the 1-time-step probability of transitioning between every combination of states. In our model, there were 3 possible states (2 exploit states and 1 explore state). The parameters were tied across exploit states such that each exploit state had the same probability of beginning (from exploring) and of sustaining itself. Transitions out of the exploration, into exploitative states, were also tied. The model also assumed that the mice had to pass through exploration in order to start exploiting a new option, even if only for a single trial. Through fixing the emissions model, constraining the structure of the transmission matrix, and tying the parameters, the final HMM had only two free parameters: one corresponding to the probability of exploring, given exploration on the last trial, and one corresponding to the probability of exploiting, given exploitation on the last trial.

The model was fit via expectation-maximization using the Baum Welch algorithm

(Bilmes, 1998). This algorithm finds a (possibly local) maxima of the complete-data likelihood. A complete set of parameters θ includes the emission and transition models, discussed already, but also initial distribution over states, typically denoted as PI. Because the mice had no knowledge of the environment at the first trial of the session, the initial distribution started with p (explore state) = 1. The algorithm was reinitialized with random seeds 10 times, and the model that maximized the observed (incomplete) data log likelihood across all the sessions for each animal was ultimately taken as the best. To decode latent states from choices, we used the Viterbi algorithm to discover the most probable posteriori sequence of latent states.

Reinforcement learning (RL) models. We fitted five reinforcement learning (RL) models that could potentially characterize animals' choice behaviors, with the structure of each RL model detailed below. AIC weights were calculated from AIC values across all treatment groups and compared across models to determine the best model with the highest relative likelihood. Model agreement was calculated as the probability of choice given model to demonstrate how well the best fit model captures actual choices.

The first model (random) assumes that animals choose between two arms randomly with some overall bias for one side over the other. This choice bias for choosing left side over right side is captured with a parameter *b.* The probability of choosing left side on trial *t* is:

$$p_t^L = b \qquad [3] \quad \text{“random”}$$

The second model is a noisy win-stay lose-shift (WSLS) model that adapts choices with regards to outcomes. This model assumes a win-stay lose-shift policy that is to repeat a rewarded choice and to switch to the other choice if not rewarded. Furthermore, this model includes a parameter ϵ that captures the level of randomness, allowing a stochastic application of the win-

stay lose-shift policy. The probability of choosing arm k on trial t is:

$$p_t^k = \begin{cases} 1 - \frac{\epsilon}{2}, if\ (c_{t-1} = k\ and\ r_{t-1} = 1\ OR\ c_{t-1} \neq k\ and\ r_{t-1} = 0) \\ \frac{\epsilon}{2}, if\ (c_{t-1} \neq k\ and\ r_{t-1} = 1\ OR\ c_{t-1} = k\ and\ r_{t-1} = 0) \end{cases} \quad [4]\ \textit{“noisy WSLS”}$$

, c_t indicates the choice on trial t and r_t is a binary variable that indicates whether or not trial t was rewarded.

The third model (RL) is a basic delta-rule reinforcement learning (RL) model. This two-parameter model assumes that animals learn by consistently updating Q values, which are values defined for options (left and right side). These Q values, in turn, dictate what choice to make next. For example, in a multi-armed bandit task, Q_t^k is the value estimation of how good arm k at trial t, and is updated based on the reward outcome of each trial:

$$Q_{t+1}^k = Q_t^k + \alpha(r_t - Q_t^k) \quad [5]\ \textit{”RL”}$$

In each trial, $r_t - Q_t^k$ captures the reward prediction error (RPE), which is the diffe-rence between expected outcome and the actual outcome. The parameter a is the learning rate, which determines the rate of updating RPE. With Q values defined for each arm, choice selection on each trial was performed based on a Softmax probability distribution:

$$p(a_{t+1} = k) = \frac{e^{\beta Q_t^k}}{\sum_j e^{\beta Q_t^j}}$$

, where inverse temperature β determines the level of random decision noise.

The fourth model (*RLCK*) incorporates a choice updating rules in addition to the value updating rule in model 3. The model assumes that choice kernel, which captures the outcome-independent tendency to repeat a previous choice, also influences decision making. The choice kernel updating rule is similar to the value-updating rule:

$$CK_{t+1}^k = CK_t^k + \alpha_c(a_t^k - CK_t^k) \quad [6]\ \textit{“RLCK”}$$

, where a_t^k is a binary variable that indicates whether or not arm k was chosen on trial t and a_t is

choice kernel updating rate, characterizing choice persistence. The value and choice kernel term were combined to compute the probability of choosing arm *k* on trial *t*:

$$p_t^k = \frac{e^{\beta(Q_t^k + CK_t^k)}}{\sum_j e^{\beta(Q_t^j + CK_t^j)}}$$

, where β is the inverse temperature, capturing the decision noise outside value and choice bias.

The fifth model (*RLγ)* is an asymmetrical learning model that incorporates an asymmetric learning scalar parameter that scales the learning rate on the trials where there is no reward. The choice selection is also based on a Softmax probability distribution where the inverse temperature determines the decision noise in the system.

$$Q_{t+1}^k = \begin{cases} Q_t^k + \alpha\left(r_t - Q_t^k\right), r_t = 1 \\ Q_t^k + \gamma \times \alpha\left(r_t - Q_t^k\right), r_t = 0 \end{cases} \qquad [7]\ \text{“}RL\gamma\text{”}$$

The sixth model (*RLCKγ*) is the combination of the fourth and the fifth model, incorporating both asymmetrical learning and choice kernel. This model included a learning rate, an asymmetric learning scalar, a choice kernel, and an inverse temperature parameter.

293 **Results**

294 Aged-matched adult male and female wildtype mice (n = 32, 16 males and 16 females,
295 strain B6129SF1/J) were trained to perform a restless two-armed spatial bandit task in touch-
296 screen operant chambers (**Figure 1A**). In this task, animals were presented with two identical
297 visual targets (squares) on the left and right side of the screen during each trial. They indicated
298 their choices by nose poking at one of the two target locations, each of which provided some
299 probability of reward that changed independently and randomly over time (**Figure 1B)**. The
300 dynamic reward contingency of this task naturally encourages the animal to balance between
301 exploiting a favorable option when it is found and exploring to gain information about potential
302 better alternatives. This task has been employed in rodents and primates as well as human
303 subjects to understand learning and exploration and have successfully revealed divergent
304 exploration strategies (Ebitz et al., 2018; Grossman et al., 2020; Chen et al., 2021b). In this
305 study, we adopted this task to understand the modulatory effect of catecholamine receptor
306 activity on the transition between exploration and exploitation.

307 To examine the distinct and/or overlapping roles of dopamine and norepinephrine in
308 modulating exploration, we tested the systemic effect of a non-selective dopamine receptor
309 agonist apomorphine (0.1mg/kg), a non-selective dopamine receptor antagonist flupenthixol
310 (0.03mg/kg), a beta-noradrenergic receptor agonist isoproterenol (0.3mg/kg), and a beta-
311 noradrenergic receptor antagonist propranolol (5mg/kg) on exploration. The experiment used a
312 within-subject design, where all animals received each of the four drugs tested. This design
313 allowed us to directly compare the effect of each drug within individual animals and dissociate
314 drug effects from potential cohort differences. Since each animal received all four drugs, the
315 length of study did not allow us to test multiple doses for each drug. Therefore, we selected the

316 dosages of the drugs based on numerous previous studies on the role of dopamine and
317 norepinephrine in cognitive processes (Fernandez-Tome et al., 1979; Cabib et al., 1984;
318 Goldschmidt et al., 1984; Ichihara et al., 1988; Nakamura et al., 1998; Grigoryan, 2012; Cinotti
319 et al., 2019). Animals were intraperitoneally (IP) administered either saline (control) or treatment
320 with 5 mg/kg of propranolol, 0.3mg/kg of isoproterenol, or 0.03 mg/kg of flupenthixol
321 immediately prior to the bandit task or 0.1mg/kg of apomorphine 30 minutes prior to the bandit
322 task. Saline and drug treatments were administered interleaved by session (**Figure 1C, 2A**). Mice
323 performed 12 sessions under each pharmacological condition (6 control and 6 drug treatment
324 sessions). Each drug effect was compared to its own vehicle control collected in the interleaved
325 sessions.

326 To examine whether mice had learned to perform the task and were able to sustain
327 reward, we first calculated the average probability of obtaining reward across sessions in all
328 control and drug groups. It's worth noting that in this task, there is no asymptotic performance
329 because the animals need to constantly adapt to the changing reward contingency and any one
330 option is not always the best choice to make. At any given time, an animal could decide to repeat
331 a favorable option or to explore the options. The performance is best measured by the amount of
332 reward acquired. Because reward schedules were dynamic and stochastic, sessions could differ
333 slightly in the amount of reward that was available. We therefore compared the probability of
334 actual obtained reward against the probability of reward if chosen randomly (chance). In the
335 dopamine modulation condition, both control groups (saline) and treatment groups (apomorphine
336 and flupenthixol) were able to obtain reward more frequently than chance (**Figure 1D, E**, one-
337 sample t test, vehicle control (apomorphine): $t(31) = 13.96$, $p<0.0001$; apomorphine: $t(31)=$
338 17.24, $p<0.0001$; vehicle control (flupenthixol): $t(31)=12.36$, $p<0.0001$; flupenthixol:

339 t(31)=16.48, p<0.0001). When modulating beta-noradrenergic receptor activity, both control
340 groups (saline) and treatment groups (isoproterenol and propranolol) were able to obtain reward
341 more frequently than chance (**Figure 2B, D**, one-sample t test, vehicle control (isoproterenol):
342 t(31)=10.01, p<0.0001; isoproterenol: t(31)=13.84, p<0.0001; vehicle control (propranolol):
343 t(31)=10.60, p<0.0001; propranolol: t(31)=20.08, p<0.0001). These results suggested that
344 animals were not choosing randomly. The animals demonstrated a strong understanding of the
345 task and were able to effectively obtain rewards above chance under baseline (vehicle control)
346 and all drug treatments.

347 Next, we asked whether manipulating dopaminergic receptor activity influenced their
348 reward acquisition performance. We used a generalized linear mixed model (GLMM) to estimate
349 effects and interactions of drug treatments and sex, with session and animal identity as random
350 effects **(Equation 1**, see methods). Increasing dopamine receptor activity with apomorphine
351 administration did not significantly alter their reward acquisition performance (**Figure 1D**,
352 GLMM, main effect of drug, p= 0.11, β1 = -0.017**)**. Antagonizing dopamine receptor activity
353 with flupenthixol administration also did not significantly alter reward acquisition performance
354 (**Figure 1E**, GLMM, main effect of drug, p= 0.28, β1 = -0.008). Increasing beta-noradrenergic
355 receptor activity with isoproterenol administration did not affect the amount of reward obtained
356 (**Figure 2B**, GLMM, main effect of drug, p= 0.93, β1 = -0.0005). However, when decreasing
357 beta-noradrenergic receptor activity with propranolol administration, animals obtained
358 significantly more reward (**Figure 2D**, GLMM, main effect of drug, p < 0.0001, β1 = -0.497).
359 Even though manipulating dopamine receptor activity and increasing beta-noradrenergic receptor
360 activity did not affect how much overall obtained reward, we considered the possibility that the
361 tuning of catecholamine receptor activity affected latent exploration strategies underlying choice

362 patterns, but not an observable change in the level of accuracy. Our previous study demonstrated
363 that similar reward acquisition performance can be achieved via divergent explore strategies
364 (Chen et al., 2021b).

365 Pharmacological manipulations of both dopaminergic and noradrenergic receptor activity
366 have been shown to have a dose-dependent effect on motor functions (Goldschmidt et al., 1984;
367 Weed and Gold, 1998). In this study, dosage selection was based on previous literature
368 examining cognitive functions and a low dose was used to have influence on cognition but avoid
369 motor function impairment (Nakamura et al., 1998; Cinotti et al., 2019). One commonly used
370 behavioral metric to examine motor function in a cognitive task is response time. Therefore, we
371 calculated the response time, which was the time elapsed between the onset of choices and nose
372 poke response to make a choice, as recorded by the touchscreen operant chamber. If the
373 administration of drugs impaired motor function, we would expect to see longer response time in
374 the drug group compared to vehicle control. Upregulating dopamine receptor activity with
375 apomorphine did not significantly influence the response time (GLMM, main effect of drug,
376 $p=0.77$, $\beta1 = 0.10$). Similarly, downregulating dopamine receptor activity with flupenthixol did
377 not significantly alter animals' response time (GLMM, main effect of drug, $p=0.96$, $\beta1 = -0.01$).
378 Modulating beta-noradrenergic receptor activity resulted in bidirectional changes in response
379 time. When increasing beta-noradrenergic receptor activity with isoproterenol, both males and
380 females took significantly longer to respond (**Figure 2C,** GLMM, main effect of drug, $p<0.0001$,
381 $\beta1 = -3.51$). Decreasing beta-noradrenergic receptor activity with propranolol significantly
382 decreased the response time (**Figure 2E,** GLMM, main effect of drug, $p=0.04$, $\beta1 = 0.51$),
383 primarily driven by response time reduction in females under propranolol compared to vehicle
384 controls (GLMM, interaction term, $p<0.009$, $\beta3 = -0.57$). Faster response time under propranolol

385 could be associated with more reward obtained - propranolol was the only drug treatment that
386 altered reward acquisition performance among the four drugs tested. Previous studies have
387 linked response time with the complexity of the strategy used (Kool et al., 2010; Filipowicz et
388 al., 2019; Chen et al., 2021b). Faster response time under propranolol might also point to the
389 possibility that decreasing beta-noradrenergic receptor activity brought on changes in strategies
390 that took shorter time to execute. Isoproterenol was a highly significant predictor for lower
391 response time in both male and female mice, implicating the potential drug effect on motor
392 behaviors.
393
394 **Opposing modulatory effect of dopamine and norepinephrine receptor activity on win-stay**
395 **lose-shift behaviors**
396 The role of dopamine has been heavily studied and shown to be a key contributor to
397 value-based decision making and reinforcement learning (Seamans and Yang, 2004; Redish et
398 al., 2007; Niv, 2009; Floresco, 2013). Although modulating dopamine receptor activity did not
399 significantly influence the overall amount of reward obtained or the response time, it is possible
400 that apomorphine and flupenthixol exerted influence on how animals adapted their choices to
401 reward outcome. To understand how increasing and decreasing dopamine activity influenced
402 animals' reward-driven choice behaviors, we examined the probability of win-stay (repeating a
403 choice when it was rewarded on the previous trial) and the probability of lose-shift (switching to
404 the other choice when not rewarded). We found that when increasing dopamine receptor activity
405 with apomorphine administration, both males and females had increased win-stay behavior
406 (**Figure 1F,** GLMM, main effect of drug, $p=0.011$, $\beta1= -0.02$) and decreased lose-shift behavior
407 (**Figure 1G,** GLMM, main effect of drug, $p=0.016$, $\beta1= 0.034$). This result suggested that

408 apomorphine increased the overall "stickiness" or inflexibility of choice and more stay behaviors
409 regardless of the outcome.

410 There was no significant change in the probability of win-stay when the animals were
411 administered flupenthixol (**Figure 1H,** GLMM, main effect of drug, p=0.27, β1= -0.001). It's
412 worth noting that there was main effect of sex in the probability of win-stay, with females having
413 a higher probability of win-stay, in both DA agonist and antagonist manipulations (GLMM, main
414 effect of sex, apomorphine: p=0.065, β2 = -0.054; flupenthixol: p=0.01, β2 =-0.05). The results
415 also revealed an opposing effect from dopamine agonist that antagonizing dopamine receptor
416 activity with flupenthixol administration increased the probability of lose-shift (**Figure 1I,**
417 GLMM, main effect of drug, p=0.04, β1 = -0.014).

418 To control for the total amount of switching, we calculated outcome sensitivity
419 (**Equation 2,** see Methods) to understand how much of the switching behavior was outcome-
420 sensitive. The result suggests that there were no significant changes in outcome sensitivity when
421 animals were administered apomorphine (GLMM, main effect of drug, p=0.22, β1 = -0.08).
422 However, administration of flupenthixol significantly increased outcome sensitivity across both
423 sexes (**Figure 1-1A,** GLMM, main effect of drug, p=0.006, β1= -0.06) and there was more
424 increase in outcome sensitivity in males (GLMM, interaction term, p=0.027, β3= -0.10).

425 Modulating beta-noradrenergic receptor activity also influenced win-stay and lose-shift
426 behaviors. Increasing beta-noradrenergic activity with isoproterenol administration decreased the
427 probability of win-stay compared to vehicle control (**Figure 2F,** GLMM, main effect of drug,
428 0.009, β1=0.007). Isoproterenol administration also decreased the probability of lose-shift in
429 both sexes (**Figure 2G,** GLMM, main effect of drug, p=0.0007, β1=0.083), primarily driven by
430 significant decrease in lose-shift in females under isoproterenol (**Figure 2G inset,** GLMM,

interaction term, p=0.004, β3=-0.077). Outcome sensitivity analysis revealed a significant decrease in outcome sensitivity when administer isoproterenol compared to vehicle control (**Figure 1-1B,** GLMM, main effect of drug, p=0.021, β1 = 0.134). In contrast, decreasing beta-noradrenergic activity with propranolol administration increased the probability of win-stay compared to vehicle control (**Figure 2H,** GLMM, main effect of drug, p<0.0001, β1 = -0.023). There was also a significant interaction between sex and drug that males showed a greater increase in win-stay on propranolol compared to females (**Figure 2H inset,** GLMM, interaction term, 0.02, β3=-0.036). Interestingly, propranolol administration also decreased the probability of lose-shift but only in males (**Figure 2I,** GLMM, main effect of drug, 0.45, β1 = -0.01, interaction term, p= 0.002, β3 =0.08). Outcome sensitivity analysis revealed a significant increase in outcome sensitivity with propranolol administration (**Figure 1-1C,** GLMM, main effect of drug, 0.003, β1 = -0.186). Together, these results suggested an opposing role of dopamine and norepinephrine in modulating reward-driven decision making. Increasing dopamine or decreasing norepinephrine activity resulted in increased win-stay and decreased lose-shift but this effect is more sex-different in the noradrenergic manipulations.

A Hidden Markov model (HMM) identifies distinct patterns of exploration and exploitation associated with modulation of dopamine and norepinephrine activity.

The changes in the reward-driven behaviors such as win-stay and lose-shift could be a manifestation of strategic changes in how animals explored the changing environment. To understand how modulation of dopamine and norepinephrine affect the balance between exploration and exploitation, we used a Hidden Markov model (HMM) that modeled exploration and exploitation as two latent goal states to infer which choices were exploratory or exploitative

454 (**Figure 3A)**. The HMM model has previously been used in rodents, primates and humans (Ebitz
455 et al., 2018, 2020; Chen et al., 2021b) to infer explore-exploit state from choices and has shown
456 robust correlation with neural activity as well as other behavioral metrics, including response
457 time, value function, and reinforcement learning. We have previously established fast-switching
458 (putatively explore) and slow-switching (putatively exploit) regimes in mice choice behavior
459 (Chen et al., 2021b). This HMM method produces explore/exploit labels that better track neural
460 activity and choice behavior across species than reinforcement learning (RL) models (Ebitz et
461 al., 2018; Chen et al., 2021b). Figure 3A showed an example of HMM labeling of choices of an
462 animal in the restless bandit task. The shaded area indicates exploratory trials inferred by the
463 HMM. The animal displayed mixtures of exploratory bouts where choices were distributed
464 across two choices and exploitative bouts where one choice was repeated.

465 The HMM allows us to make statistical inferences about the probability that each choice
466 was due to exploration or exploitation by modeling explore/exploit as the distinct latent goal
467 states underlying choices. To evaluate the face validity of the HMM labels, we next examined
468 whether HMM-labeled exploration matched the normative definition of exploration. First, by
469 definition, exploration is a pattern of non-reward-maximizing choices whose purpose is to gain
470 information. A non-reward maximizing goal would produce choices that are orthogonal to
471 reward value. Therefore, we examined the probability of choosing a choice with regards to its
472 relative value. In all control and dopamine treatment conditions, HMM-labeled exploratory
473 choices were non-reward-maximizing: they were orthogonal to reward value, whereas exploit
474 choices were correlated with relative reward value (**Figure 3B, E)**. The probability of choosing a
475 target choice across bins of reward value was not different from chance ($t(43) = 0.39$, $p = 0.70$),
476 which means that choice behavior was not driven by reward value during exploration. During

477 exploration, animals chose both high-value choices and low-value choices at around chance level
478 (mean = 49.8% ± 3.4% STD across all value bins). During exploitation, animals were much
479 more likely to choose a high value choice over a low value choice (mean probability of choosing
480 high value choice = 75.8% ± 10.0% STD, mean probability of choosing low value choice =
481 23.3% ± 10.1% STD). Second, prior research has shown that exploratory choices are more
482 computationally expensive thus take longer than exploitative choices (Kool et al., 2010;
483 Filipowicz et al., 2019; Chen et al., 2021b). We calculated the response time across HMM-
484 inferred states and demonstrated that across all treatment conditions, HMM-inferred exploratory
485 choices had longer response time than exploit choices (**Figure 3C, D, F, G,** paired t test, vehicle
486 control (apomorphine): $t(31) = 4.48$, $p<0.0001$; apomorphine: $t(31)= 4.42$, $p<0.0001$; vehicle
487 control (flupenthixol): $t(31)=2.27$, $p=0.03$; flupenthixol: $t(31)=4.49$, $p<0.0001$). Together, these
488 results suggested that HMM produced meaningful and robust labeling of explore/exploit choices
489 that match the normative definition of exploration and were able to explain variances in value
490 selection and response time. Because this approach to infer exploration is agnostic to the
491 generative models and depends only on the temporal statistics of choices (Ebitz et al., 2018,
492 2020; Chen et al., 2021b), it is particularly ideal for circumstances like this one, where we
493 suspect that the generative computations may differ across treatment groups.
494

495 **Modulating dopamine receptor activity bidirectionally affected the level of exploration**

496 To examine how much animals were exploring, we calculated the average number of
497 exploratory choices inferred from HMM. The results revealed a bidirectional modulatory effect
498 of dopamine receptor activity on the level of exploration. When animals were administered
499 apomorphine, we found that animals on average had fewer exploratory trials than when they

500 were on vehicle control, with 55.5% ± 12.6% STD of trials labeled as exploratory on
501 apomorphine and 72.3% ± 13.6% STD of trials labeled as exploratory on vehicle (**Figure 3H, J,**
502 GLMM, main effect of drug, $p<0.0001$, $\beta1 = 0.174$). This is also consistent with our findings in
503 the win-stay lose-shift analysis that apomorphine increased the stickiness or repetitiveness of
504 choice behaviors. In contrast, when decreasing dopamine receptor activity with flupenthixol
505 administration, animals explore more compared to vehicle control, with 58.2% ± 12.0% STD of
506 trials being exploratory on flupenthixol and 52.1% ± 12.3% STD of trials being exploratory on
507 vehicle control (**Figure 3H, J**, GLMM, main effect of drug, 0.002, $\beta1 = -0.062$). This result
508 suggested that manipulating dopamine receptor activity bidirectionally affected the level of
509 exploration across both sexes (**Figure 3I, Figure 3-1)** - increasing dopamine receptor activity
510 decreased exploratory choices and decreasing dopamine receptor activity increased exploratory
511 choices.
512

513 **The effect of beta-noradrenergic receptor activity on exploration was sex-modulated**

514 First, we conducted an HMM model validation by examining the value selection and
515 response time during HMM-labeled explore and exploit state. Same as our findings in the
516 dopamine treatment conditions, we found that in all norepinephrine conditions, HMM-inferred
517 exploratory choices were also orthogonal to reward and exploit choices proportional to relative
518 reward value (**Figure 4A, D)**. The probability of choosing a target choice across bins of reward
519 value was not different from chance ($t(43) = 0.85$, $p = 0.398$). During exploration, animals chose
520 both high-value choices and low-value choices at around chance level (mean = 49.8% ± 1.8%
521 STD across all value bins). During exploitation, animals were much more likely to choose a high
522 value choice over a low value choice (mean probability of choosing high value choice = 74.5% ±

523 8.6% STD, mean probability of choosing low value choice = 24.2% ± 9.3% STD). Response
524 time during HMM-labeled exploratory choices were also longer than exploitative choices across
525 all control conditions and propranolol condition (**Figure 4B, C, E, F,** paired t test, vehicle
526 control (isoproterenol): $t(31)=3.01$, $p=0.005$; isoproterenol: $t(31)=1.48$, $p=0.15$; vehicle control
527 (propranolol): $t(31)=1.93$, $p=0.06$; propranolol: $t(30)=5.70$, $p<0.0001$). With confidence in the
528 approach to infer exploration, we next examined the effect of propranolol and isoproterenol on
529 the level of exploration.

530 Modulating beta-noradrenergic receptor activity also influenced the probability of
531 exploration and the modulatory effect on exploration was associated with sex. Decreasing beta-
532 noradrenergic receptor activity with propranolol significantly decreased the level of exploration
533 (**Figure 4G-I**) but only in males (**Figure 4J, Figure 3-1**, GLMM, interaction term, 0.0001, $\beta 1$ =
534 0.138). Increasing beta-noradrenergic receptor activity with isoproterenol administration
535 significantly decreased exploration in females (**Figure 3K, Figure 3-1**, interaction term, p=
536 0.002, $\beta 3$=-0.103). Together these results suggested a sex-linked neuromodulatory effect of beta-
537 noradrenergic receptor on exploration - increasing beta-noradrenergic activity decreased
538 exploration in males and decreasing beta-noradrenergic activity decreased exploration in
539 females. One possibility is that this sex-differentiated modulatory effect reflected sex-dependent
540 ceiling/floor effects of noradrenergic signaling.

541

542 **Reinforcement learning (RL) models revealed changes in distinct parameters under**
543 **modulation of dopamine and epinephrine**

544 The results of the HMM suggested that both dopamine and norepinephrine modulation
545 influenced the level of exploration. However, it is unclear whether changes in exploration were

546 due to changes in similar or distinct latent cognitive parameters. Does dopamine and
547 norepinephrine modulate exploration via distinct or overlapping mechanisms? To address this
548 question, we fitted a series of reinforcement learning (RL) models to understand the effect of
549 pharmacological manipulation on the latent cognitive parameters that could influence exploration
550 and exploitation (Ishii et al., 2002; Daw et al., 2006; Pearson et al., 2009; Jepma and
551 Nieuwenhuis, 2011).

552 To make inferences about changes in the RL model parameters, we first identified the
553 best-fitting RL model for the animals' behaviors. The majority of RL model parameters can be
554 categorized in three ways: value-dependent learning terms, value-independent bias terms, and
555 decision noise/randomness terms (Katahira, 2018). Previous studies demonstrated the effect of
556 various RL parameters on value-based decision making, including value-dependent terms such as
557 learning rate and asymmetrical learning rate (Frank et al., 2007; Gershman, 2016; Cinotti et al.,
558 2019; Chen et al., 2021b), value-independent terms such as choice bias (Katahira, 2018; Wilson
559 and Collins, 2019; Chen et al., 2021b), and noise terms such as inverse temperature and lapse
560 rate (Economides et al., 2015; Cinotti et al., 2019; Wilson and Collins, 2019). Here, we
561 compared six reinforcement learning models that incorporated one or more of the above
562 parameters (learning rate, bias, noise) and had different assumptions about the latent cognitive
563 processes that animals might employ during exploration (**Figure 5A, Equations 3-7)**. These
564 models included: (1) a "random" model with some overall bias for one choice over the other, (2)
565 a "noisy win-stay lose-shift" model (WSLS) that assumes a win-stay lose-shift policy with some
566 level of randomness, (3) a two-parameter "RL" model with a consistent learning rate and some
567 inverse temperature that captures decision noise, (4) a three-parameter "RLCK" model that
568 captures both value-based and value-independent decision with two parameters for learning rate

569 and choice bias, and an overall decision noise parameter, (5) a three-parameter "RLγ" model that
570 captures asymmetrical learning with a learning rate parameter and a scaling parameter for
571 negative outcome learning and a decision noise parameter, and (6) a four-parameter "RLCKγ"
572 asymmetrical learning and bias model that includes a choice bias term on top of the "RLγ" (see
573 methods). We fitted these models to each individual animal and compared the likelihood of each
574 of the six models under four vehicle control conditions and four drug conditions.

575 In dopamine modulation conditions, the RLCK model (learning + choice kernel,) and the
576 RLCKγ (asymmetrical learning and bias) model best fit the behaviors (**Figure 5B,** average AIC
577 across DA conditions: model 1 random: 73838.03; model 2 WSLS: 55843.26; model 3 RL:
578 58133.45; model 4 RLCK: 54652.02; model 5 RLγ: 57545.47; model 6 RLCKγ: 54612.56).
579 Since the RLCKγ model did not significantly improve the model fitting, we decided to use the
580 more parsimonious RLCK model that has three parameters (learning rate, choice bias, and
581 decision noise). To examine how well the best fit RLCK model was at actually predicting
582 animals' choices, we measured the model agreement for each model, which was calculated as the
583 probability of choice correctly predicted by the optimized model parameters for each model
584 (**Figure 5C**). In dopamine agonist condition, the RLCK model predicted over 66% of animals'
585 actual choices (vehicle: 66.1% ± 5.3% STD, APO: 67.6% ± 5.0%). In the dopamine antagonist
586 condition, the RLCK model also predicted over 66% of animals' actual choices (vehicle: 66.4%
587 ± 6.4%, FLU: 67.3% ± 5.4%). Figure 5D and 5E showed the model simulation, actual choice,
588 and reward probability of the same animal. This also visually demonstrated that the RLCK
589 model was able to accurately predict animal's changing choice behaviors. Additionally, this also
590 demonstrated that animal choice behaviors were following the reward contingency.

591 Then we examined how the reinforcement learning model parameters changed with

592 dopamine modulation. Previous study has shown that both learning rate and inverse temperature
593 parameters could induce changes in the overall level of exploration (Chen et al., 2021b).
594 Therefore, we asked whether the bidirectional changes in exploration when up- or down-
595 regulating dopamine receptor activity were due to changes in learning rate or decision noise. The
596 results revealed a bidirectional effect of dopamine modulation on the inverse temperature
597 parameter (**Figure 5F-H**). Because RL model data can be non-normally distributed, the Shapiro-
598 Wilk test of normality was conducted to determine whether the RL parameters were normally
599 distributed. The result suggested that the parameters were not always normally distributed
600 (decision noise: vehicle: $p= 0.85$, APO: $p<0.0001$; vehicle: $p<0.0001$, FLU: $p=0.09$), therefore
601 we will report both parametric and non-parametric statistics results for RL parameters.
602 Increasing dopamine receptor activity with apomorphine administration increased inverse
603 temperature and decreased random noise (**Figure 5F**, Wilcoxon matched-pairs test, $p= 0.0165$;
604 paired t-test, $p= 0.053$). Decreasing dopamine receptor activity with flupenthixol administration
605 decreased inverse temperature and increased random noise (**Figure 5G**, Wilcoxon matched-pairs
606 test, $p= 0.0253$; paired t-test, $p= 0.053$). Neither dopamine agonist (apomorphine) nor dopamine
607 antagonist (flupenthixol) significantly influenced learning rate or choice kernel compared to
608 vehicle controls.

609 In norepinephrine modulation conditions, the RLCK model (learning + choice kernel,)
610 and the RLCKγ (asymmetrical learning and bias) model also best fit the behavioral data (**Figure**
611 **5I,** average AIC across NE conditions: model 1 random: 66898.83; model 2 WSLS: 56061.3;
612 model 3 RL: 53194.59; model 4 RLCK: 50035.02; model 5 RLγ: 52664.48; model 6
613 RLCKγ:50027.82). However, since the RLCKγ model did not significantly improve the model
614 fitting, we decided to use the more parsimonious RLCK model for the NE condition as well. The

615 model agreement was calculated for all NE modulations. In the noradrenergic agonist condition,
616 the RLCK model predicted over 65% of animals' actual choices (**Figure 5J,** vehicle: 65.7% ±
617 5.9% STD, ISP: 66.4% ± 5.7%). In the noradrenergic antagonist condition, the RLCK model also
618 predicted over 65% of animals' actual choices (vehicle: 65.5% ± 3.9% STD, PRO: 69.8% ±
619 4.5%). Figure 5K and 5L showed the model simulation, actual choice, and reward probability of
620 the same animal as Figure 5D and 5E.

621 We found that modulating beta-noradrenergic receptor activity also resulted in changes in
622 the reinforcement learning model parameter. Up-regulating norepinephrine activity with
623 isoproterenol significantly decreased the learning rate (**Figure 5M**, Wilcoxon matched-pairs test,
624 p= 0.0001; paired t-test, p= 0.0008). This result is consistent with the decreased win-stay and
625 decreased lose-shift behaviors when administered isoproterenol because the lower learning rate
626 under isoproterenol resulted in reduced outcome sensitivity (**Supplementary figure 1C**), which
627 means learning less from either a rewarded or a non-rewarded outcome. There were no
628 significant changes in other parameters when administered isoproterenol compared to vehicle
629 control. We did not find any significant changes in any reinforcement learning parameters when
630 administered propranolol compared to vehicle control. Together, these results suggested distinct
631 roles of dopaminergic drugs in modulating exploration via decision noise and isoproterenol in
632 modulating exploration via outcome sensitivity.
633

634 **Discussion**

635 In this study, we pharmacologically up- and down-regulated dopamine and beta-
636 noradrenergic receptor activity and examined the modulatory effects of the manipulations on
637 exploration in an explore/exploit task. We used a combination of computational modeling
638 approaches to characterize changes in the level of exploration and latent cognitive variables that
639 could contribute to exploration. Modulating dopamine receptor activity revealed a bi-directional
640 modulatory effect on exploration - increasing dopamine receptor activity decreased the level of
641 exploration and decreasing dopamine receptor activity increased the level of exploration.
642 Modulation of beta-noradrenergic receptor activity also influenced how much animals explored -
643 beta-noradrenergic receptor antagonist (propranolol) decreased the level of exploration.
644 However, when examining the modulatory effect of beta-noradrenergic receptor activity on
645 exploration across sexes, we found that modulatory effect was sex-different: isoproterenol
646 selectively decreased exploration in females whereas propranolol decreased exploration in males.
647 Previously, the role of dopamine and norepinephrine in mediating exploration were often
648 examined in isolation with different task designs. This study allowed the direct comparison of
649 the modulatory effect of dopamine and norepinephrine on the transition between exploration and
650 exploitation in the same task across the same animals.

651 Dopamine's function as a neuromodulator has been described in two key ways. First, the
652 phasic activation of midbrain dopamine neurons is thought to be a key contributor to
653 reinforcement learning (Barto, 1995; Montague et al., 1995, 1996; Schultz et al., 1997; Schultz,
654 1998). Numerous studies across species have shown that dopamine neurons encoded the reward
655 prediction error (RPE) (Schultz, 1998; Niv, 2009). Ventral tegmental dopamine neuronal activity
656 and release in ventral striatum is proposed to reflect this error, which is used to update action

values (Schultz, 1998, 2013; Niv, 2009). Consistent with this view, some previous pharmacological investigations in human decision making have observed changes in model-derived learning rates that directly correlate with dopamine synthesis agonism via L-DOPA (Frank et al., 2004; Rutledge et al., 2009) and dopamine receptor D2/D3 antagonism via amisulpride (Cremer et al., 2022). However, this framework does not necessarily account for a large body of literature describing a second way to view dopamine's neuromodulatory function, as tonic levels influencing motivation, vigor, and cognitive flexibility (Floresco, 2013; Beeler et al., 2014), especially when pharmacologically targeted in the frontal cortex. Because pharmacological agents are by definition modulating receptor activity over long periods of time, this role for tonic dopamine is poised to be computationally described. Indeed, when pharmacologically or genetically modulating tonic dopamine function, many studies have noted profound changes in the decision "noise" (inverse temperature) or perseverative errors - consistent with a role for dopamine modulation in cognitive flexibility in earlier work (Beeler et al., 2010; Humphries et al., 2012; Eisenegger et al., 2014; Lee et al., 2015; Cinotti et al., 2019; Ebitz et al., 2019). Two prior examples combining pharmacological manipulation and computational modeling in animal tasks explicitly testing the explore-exploit tradeoff particularly highlight this. Cinotti et al. found that systemic dopamine blockade with flupenxithol increased the amount of random exploratory choices without affecting learning rate in a rat three-arm bandit task (Cinotti et al., 2019), particularly in situations where uncertainty was manipulated. Similarly, Ebitz et al. reported that systemic cocaine, which blocks dopamine reuptake, reduced flexibility and regulated tonic exploration in rhesus macaques (Ebitz et al., 2019). Likewise, we find that systemic activation of dopamine receptors significantly decreased exploration as defined by our Hidden Markov model and decision noise as described by our

680 reinforcement learning model, while antagonism of these receptors increased these
681 computational parameters measuring flexible behavior. Our data thus provide additional support
682 for the idea that dopamine modulation across the brain provides more than a learning signal, but
683 also a key signal tuning the precision or flexibility of behavior.

684 As noted in our introduction, the roles of dopamine and norepinephrine are sometimes
685 conflated in the computational neuroscience literature. This is in part because modulation of
686 these systems can be correlated, and noninvasive measures of catecholamine function, for
687 example blink rate and pupil diameter, could be ascribed to the endogenous activity of either
688 neuromodulator (although pharmacological action may target one or the other) (Jepma and
689 Nieuwenhuis, 2011; Ebitz and Moore, 2018; Sescousse et al., 2018; Findling et al., 2019; Cremer
690 et al., 2022). This is further complicated by the fact that some studies examining the relationship
691 between dopamine and exploration have used pharmacological manipulations which
692 simultaneously influence both tonic dopamine and norepinephrine levels, such as
693 psychostimulants or L-DOPA (Pessiglione et al., 2006; Rutledge et al., 2009; Orsini et al., 2016;
694 Ebitz et al., 2019; Chakroun et al., 2020). This makes it challenging to dissociate the modulatory
695 roles of dopamine and norepinephrine in exploration i.e. how dopamine and norepinephrine
696 distinctively contribute to changes in reinforcement learning model parameters, and addressing
697 this challenge was a major goal of our study.

698 Surprisingly, we found that when modulating beta-noradrenergic receptor activity
699 changed the level of exploration, it did so via changes in outcome sensitivity. Previous studies
700 have proposed the locus coeruleus-norepinephrine (LC-NE) system to regulate exploration by
701 changing decision noise. Kane et al. chemogenetically stimulated locus coeruleus activity in rats
702 and found that increased LC tonic activity increased in increased exploration, best explained by

703 an increase in decision noise (Kane et al., 2017; Wilson et al., 2021). Other studies have echoed
704 the findings that norepinephrine levels predicted the level of random exploration, or decision
705 noise, in the system (Jepma and Nieuwenhuis, 2011; Ebitz and Moore, 2018; Joshi and Gold,
706 2020). However, in this study we did not find any changes in the noise parameter (inverse
707 temperature, or how closely you adhere to your value rule) associated with up- and down-
708 regulation of beta-noradrenergic activity. Instead, the results revealed some learning rate changes
709 when increasing beta-noradrenergic receptor activity. Model-free analysis on outcome sensitivity
710 suggested that increasing or decreasing beta-noradrenergic receptor activity bi-directionally
711 changed outcome sensitivity. Propranolol increased outcome sensitivity and decreased
712 exploration, which means the animals were more likely to switch choice after loss and more
713 likely to repeat rewarded choices. In contrast isoproterenol decreased outcome sensitivity, as
714 seen in reduced win-stay and lose-shift behavior. This is consistent with the decreased learning
715 rate when administered isoproterenol because a decrease in learning rate is associated with
716 decreased value learning from each outcome. Where might this strange association between
717 noradrenergic modulation, exploration, and outcome sensitivity emerge from? We have
718 previously shown that exploration as defined by our Hidden Markov model can be driven by
719 either changes in learning rate or changes in inverse temperature (Chen et al., 2021b), supporting
720 the idea that the exploration we see here could be driven by long-term changes in the influence
721 of outcomes. Work focused on beta noradrenergic signaling in the context of aversive learning
722 has highlighted a role for noradrenergic signaling in extinction (Iordanova et al., 2021), over a
723 phasic timeframe of minutes to hours. This suggests the intriguing possibility that the effect of
724 noradrenergic blockade here may be to prevent extinction of learned values. In short, although
725 the most common associations in the computational neuroscience literature are between

726 dopamine and reward learning versus norepinephrine and decision noise, our current data
727 suggests a more nuanced role for each of these modulators.

728 Adding an additional layer of nuance to these findings, we find that sex differences are a
729 major axis of variability in the effect of beta-noradrenergic receptor modulation on the explore-
730 exploit tradeoff. Increasing NE receptor activity with the beta agonist isoproterenol decreased
731 exploration only in males, while decreasing NE receptor activity with the beta antagonist
732 propranolol decreased exploration especially in females. One possible explanation is that the
733 relationship between exploration and NE receptor activity was nonlinear but instead, followed an
734 inverted U-shape. Such inverted U-shape correlation has been suggested between cognitive
735 performance and NE level (Aston-Jones and Cohen, 2005; Redish et al., 2007; Mäki-Marttunen
736 et al., 2020). Since females have been reported to have higher tonic NE levels due to both
737 function and structural differences (Pinos et al., 2001; Bangasser et al., 2016), it is possible that
738 the baseline difference in tonic NE level across sexes could posit individuals on different parts of
739 the inverted U-curve, where increasing or decreasing NE could affect exploration in one sex
740 without impacting the other.

741 Taken together, this study demonstrates the distinct role of dopamine and norepinephrine
742 in tuning the exploration-exploitation tradeoff when learning about an uncertain environment.
743 Dopamine modulated exploration via decision noise and norepinephrine modulated exploration
744 via outcome sensitivity. The systemic manipulation of dopamine and norepinephrine receptor
745 activity did not allow for more precise modulation of phasic changes in catecholamine levels.
746 However, the computational tool that we presented here can complement higher resolution
747 neural recording techniques to examine for phasic changes in dopamine and norepinephrine
748 activity on a trial-by-trial basis. Finally, this study also highlighted that the modulatory effects of

catecholamine on exploration-exploitation tradeoff are strongly influenced by sex and sex-linked mechanisms. Therefore, future research should take into account sex-correlated individual variability when examining the neural correlates of exploration.

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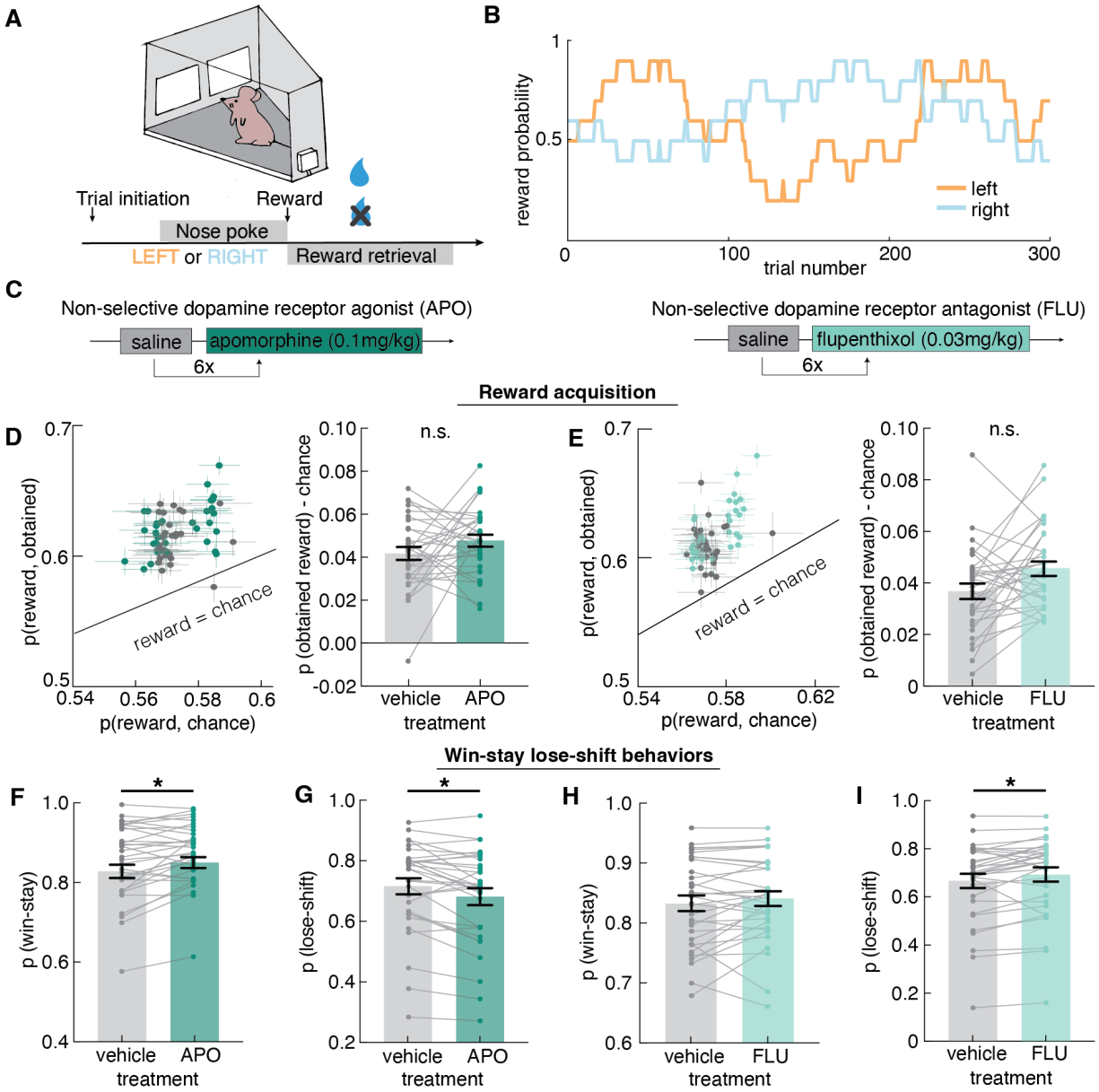
994 **Figures and figure legends**



995

996 **Figure 1. Modulation of dopamine receptor activity affected reward-directed behaviors.**

997 **Up-regulating dopamine activity increased stickiness in choice behaviors regardless of**

998 **outcomes.**

999 **A)** Schematic of the mouse touchscreen chamber and the trial structure of the two-armed spatial

1000 restless bandit task. **B)** An example of the dynamic reward contingency showing the changing

1001 reward probabilities associated with each option over 300 trials. **C)** The dopaminergic drug
1002 administration schedule and drug dosage used to modulate dopamine receptor activity. A non-
1003 selective dopamine receptor agonist apomorphine (0.1mg/kg) and a non-selective dopamine
1004 receptor antagonist flupenthixol (0.03mg/kg) were systemically administered to respectively up-
1005 and down-regulate dopamine receptor activity. 0.9% saline was used as the vehicle control.
1006 Control and drug sessions were interleaved and repeated for six sessions each. **D)** (left) Average
1007 probability of obtaining reward compared to the chance level probability of reward for each
1008 animal under apomorphine (APO) and vehicle (dot). Error bars depict mean ± SEM across
1009 sessions for each animal. (right) probability of obtaining reward over chance level across vehicle
1010 and APO condition. **E)** (left) Average probability of obtaining reward compared to the chance
1011 level probability of reward for each animal under flupenthixol (FLU) and vehicle (dot). Error
1012 bars depict mean ± SEM across sessions for each animal. (right) probability of obtaining reward
1013 over chance level across vehicle and FLU condition. **F)** Average probability of win-stay on
1014 vehicle and APO condition. **G**) Average lose-shift on vehicle and APO condition. **H)** Average
1015 probability of win-stay on vehicle and FLU condition. **I**) Average lose-shift on vehicle and FLU
1016 condition. * indicates $p < 0.05$. Graphs depict mean ± SEM across animals unless specified
1017 otherwise.
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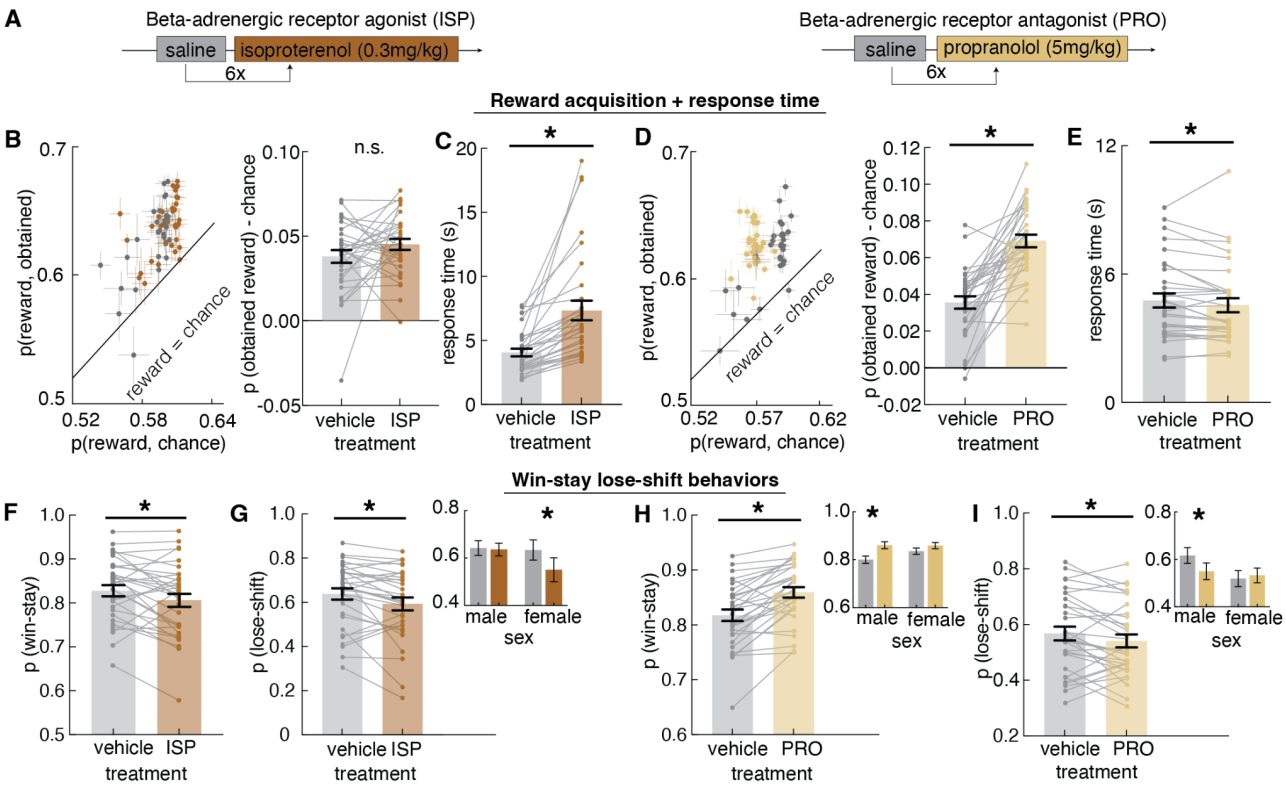

Figure 2. The modulatory effects of beta-noradrenergic receptor activity on reward-directed behavior was also influenced by sex.

A) The noradrenergic drug administration schedule and drug dosage used to modulate noradrenergic receptor activity. A beta-noradrenergic receptor agonist isoproterenol (0.3mg/kg) and a beta-noradrenergic receptor antagonist propranolol (5mg/kg) were systemically administered to respectively up- and down-regulate norepinephrine activity. 0.9% saline was used as the vehicle control. Control and drug sessions were interleaved and repeated for six sessions each. **B)** (left) Average probability of obtaining reward compared to the chance level probability of reward for each animal under isoproterenol (ISP) and vehicle (dot). Error bars depict mean ± SEM across sessions for each animal. (right) probability of obtaining reward over chance level across vehicle and ISP. **C)** Average response time under ISP and vehicle. ISP significantly increased response time. **D)** (left) Average probability of obtaining reward

1032 compared to the chance level probability of reward for each animal under vehicle and
1033 propranolol (PRO). Error bars depict mean ± SEM across sessions for each animal. (right)
1034 probability of obtaining reward over chance level across PRO (light brown) and vehicle (gray).
1035 **E)** Average response time under PRO and vehicle. PRO significantly decreased response time.
1036 **F)** Average probability of win-stay under ISP and vehicle. **G)** Average probability of lose-shift
1037 under ISP and vehicle. (Inset) probability of lose-shift across treatments across sexes. Decrease
1038 in lose-shift under ISP was primarily driven by changes in females (interaction term). **H)**
1039 Average probability of win-stay under PRO and vehicle. (Inset) probability of win-stay across
1040 treatments across sexes. Increase in win-stay under PRO was primarily driven by changes in
1041 males (interaction term). **I)** Average probability of lose-shift under PRO and vehicle. (inset)
1042 probability of lose-shift across treatments across sexes. Decrease in lose-shift under PRO was
1043 primarily driven by changes in males (interaction term). * indicates $p < 0.05$. Graphs depict mean
1044 ± SEM across animals unless specified otherwise.
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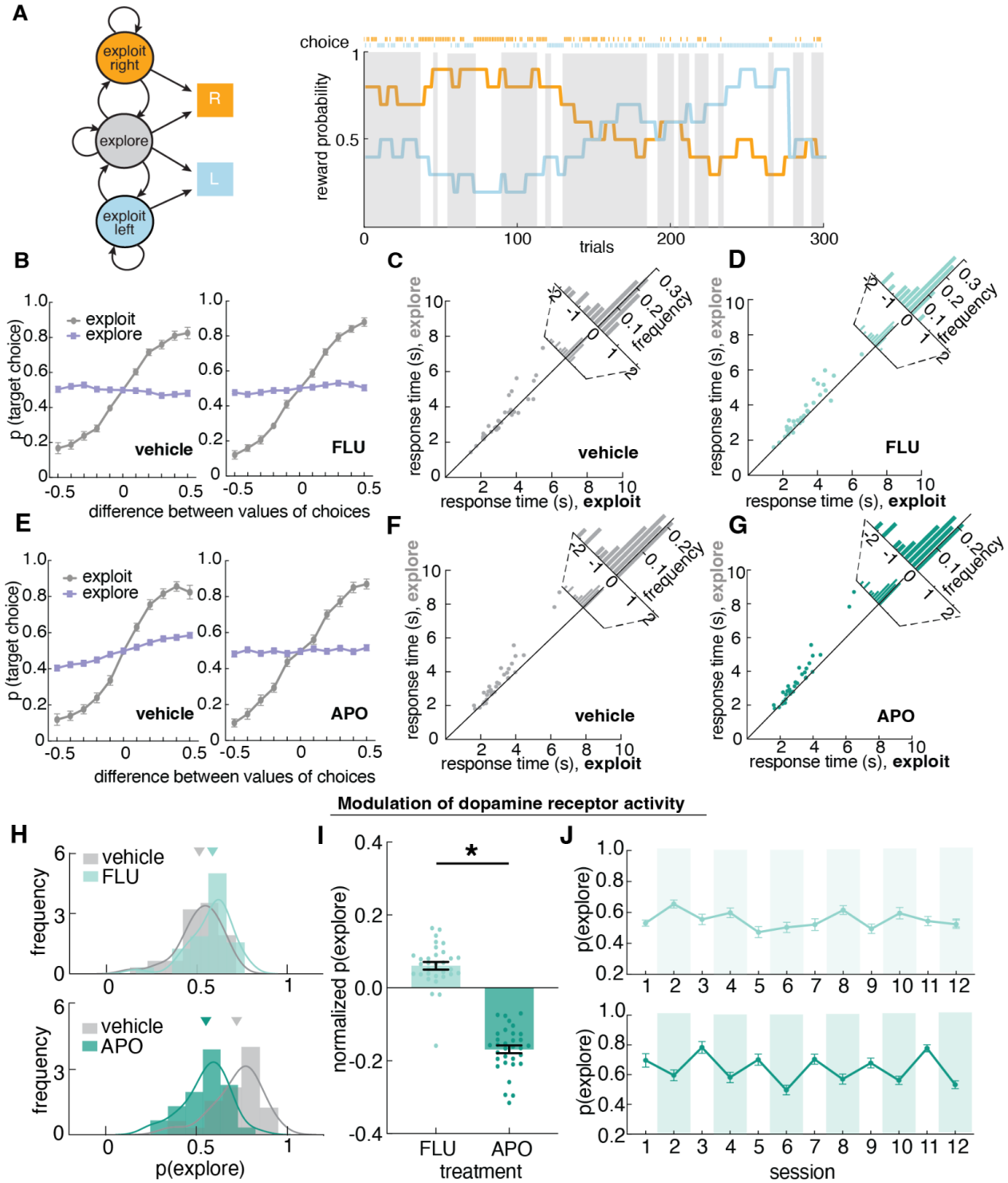


Figure 3. Up- and down-regulation of dopamine activity had bidirectional effects on the level of exploration.

A) (left) Structure of a Hidden Markov model (HMM) that modeled exploration and exploitation

as latent goal states underlying observed choices. This model incorporates two exploit states for left and right choice respectively, and one explore state where choices were uniformly distributed across options. (right) Reward probabilities, choices, and HMM labels for an example session of 300 trials for an example mouse. Shaded areas demonstrated HMM-labeled exploratory choices. **B)** Probability of choice as a function of value differences between choices for exploratory and exploitative states under vehicle (left) and flupenthixol (FLU) (right). **C, D)** Difference in response time for explore and exploit choices under vehicle and flupenthixol (FLU). **E)** Probability of choice as a function of value differences between choices for exploratory and exploitative states under vehicle (left) and apomorphine (APO) (right). **F, G)** Difference in response time for explore and exploit choices under vehicle and apomorphine (APO). **H)** Distribution of the percentage of HMM-labeled exploratory choices under flupenthixol (FLU)/ vehicle (top) and apomorphine (APO)/vehicle (bottom). **I)** Probability of exploration for dopamine antagonist (FLU) and agonist (APO), normalized by their vehicle control. Decreasing dopamine activity increased exploration and increasing dopamine activity decreased exploration. **J)** Probability of exploration by session with vehicle and drug session interleaved (flupenthixol: top; apomorphine: bottom). Drug administration sessions are in colored shades. * indicates $p < 0.05$. Graphs depict mean ± SEM across animals.

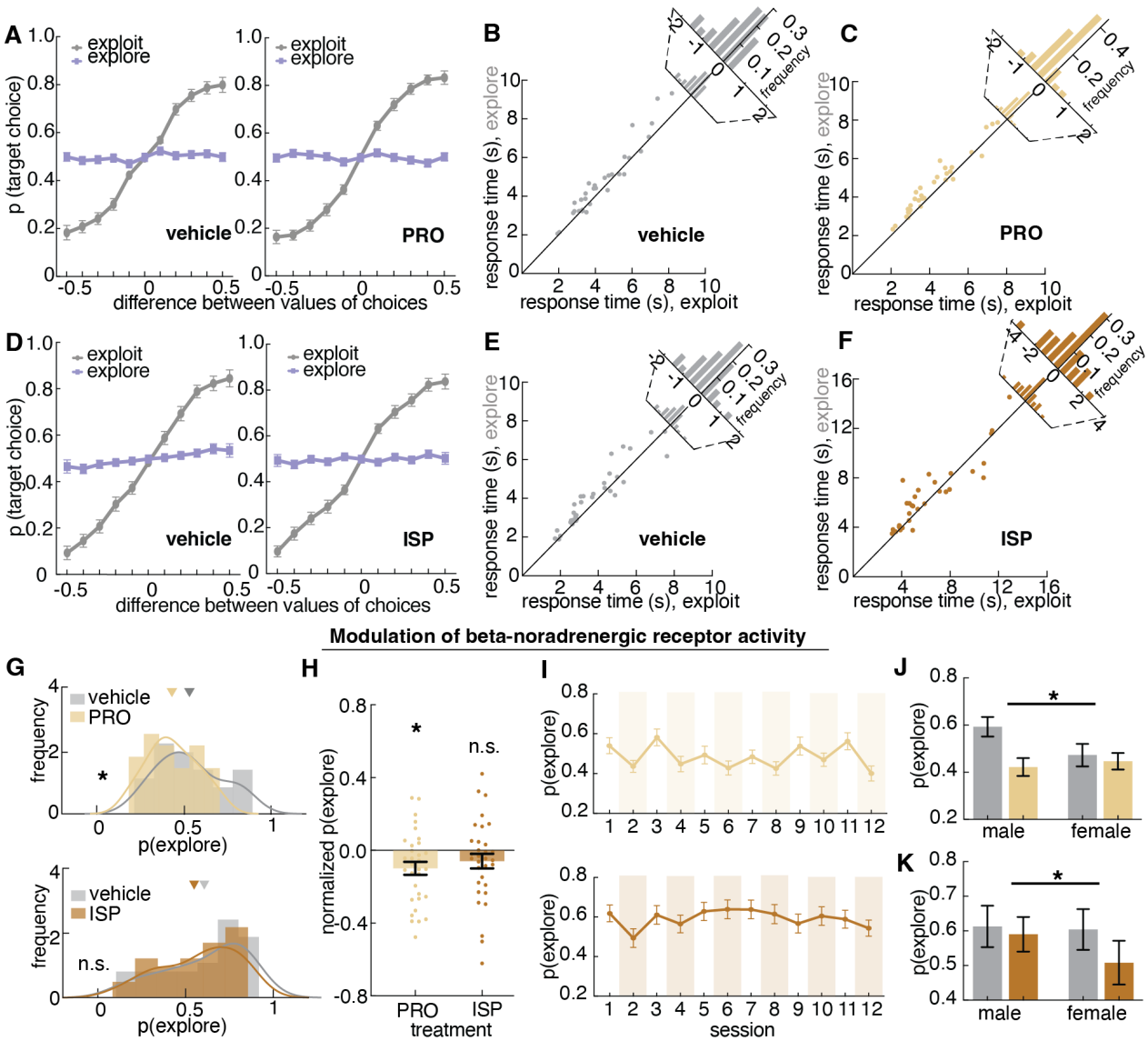


Figure 4. Downregulating norepinephrine activity influenced exploration but the effect was modulated by sex.

A) Probability of choice as a function of value differences between choices for exploratory and exploitative states under vehicle (left) and propranolol (PRO) (right). **B, C)** Difference in response time for explore and exploit choices under vehicle and propranolol (PRO). **D)** Probability of choice as a function of value differences between choices for exploratory and exploitative states under vehicle (left) and isoproterenol (ISP) (right). **E, F)** Difference in

1076 response time for explore and exploit choices under vehicle and isoproterenol (ISP).
1077 **G)** Distribution of the percentage of HMM-labeled exploratory choices under propranolol
1078 (PRO)/ vehicle (top) and under isoproterenol (ISP)/vehicle (bottom). **H)** Probability of
1079 exploration for beta-noradrenergic antagonist (PRO) and agonist (ISP), normalized by their
1080 vehicle control. Propranolol decreased the level of exploration. **I)** Probability of exploration by
1081 session with vehicle and drug session interleaved. Drug administration sessions are in colored
1082 shades. Top: propranolol (PRO) condition; bottom: isoproterenol (ISP) condition. **J)** Probability
1083 of exploration under PRO and vehicle across sexes. The effect of PRO on exploration was
1084 primarily driven by a significant decrease in exploration under PRO in males. **K)** Probability of
1085 exploration under ISP and vehicle across sexes. ISP significantly decreased exploration in
1086 females but not males. * indicates $p < 0.05$. Graphs depict mean ± SEM across animals.
1087

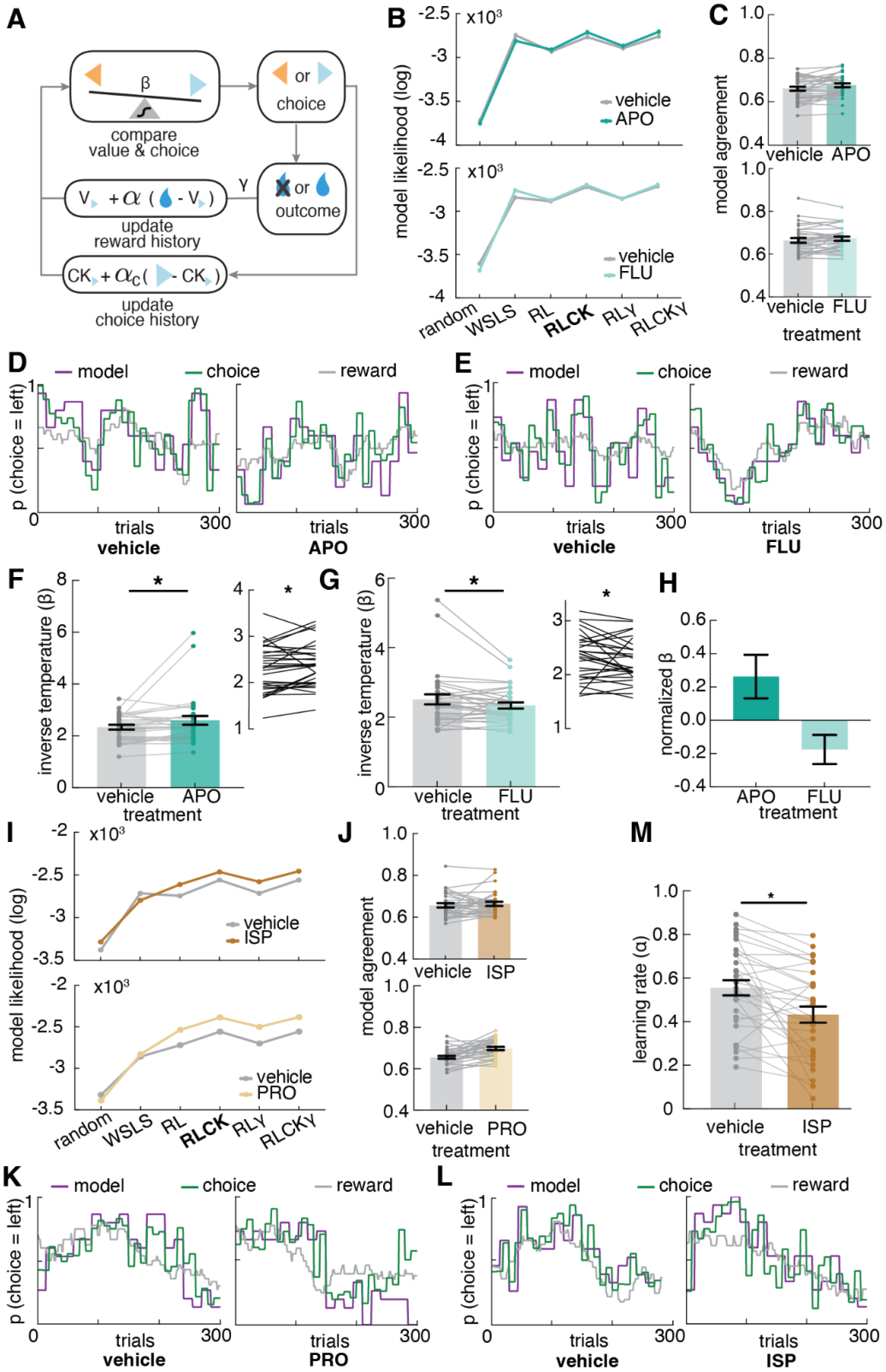


Figure 5. Modulation of dopamine and noradrenergic receptor activity led to changes in

1090 **different reinforcement learning (RL) model parameters.**

1091 **A)** A diagram of reinforcement learning (RL) parameters that capture learning rate (α),
1092 asymmetric learning (γ), choice bias (α_c), inverse temperature/decision noise (β). The RL models
1093 tested included one or more of the above parameters. **B)** Model likelihood for six RL models
1094 using log likelihood for vehicle and apomorphine (APO) condition (top), and vehicle and
1095 flupenthixol condition (bottom). The three-parameter RLCK model was the best fit and most
1096 parsimonious model for behaviors. **C)** Model agreement for the best fit model (RLCK), which
1097 measures the probability of the model predicting the actual choices of animals for vehicle and
1098 apomorphine (APO) condition (top), and vehicle and flupenthixol condition (bottom). **D, E)**
1099 Actual choices (purple) and simulated choices (green) from the best fit model (RLCK) for the
1100 same animal under vehicle/apomorphine and vehicle/flupenthixol. Grey line represents the
1101 reward probability of the left choice. **F)** Average inverse temperature (β) across apomorphine
1102 and vehicle. (inset) inverse temperature across conditions after removing two outliers. **G)**
1103 Average inverse temperature (β) across flupenthixol and vehicle. (inset) inverse temperature
1104 across conditions after removing two outliers. **H**) Agonizing (apomorphine) and antagonizing
1105 (flupenthixol) dopamine activity revealed bidirectional effect on inverse temperature, controled
1106 by their own vehicle control. **I**) Model likelihood for six RL models using log likelihood for
1107 vehicle and isoproterenol (ISP) condition (top) and vehicle and propranolol (PRO) condition
1108 (bottom). **J)** Model agreement for the best fit model (RLCK), which measures the probability of
1109 the model predicting the actual choices of animals for vehicle and isoproterenol (ISP) condition
1110 (top) and vehicle and propranolol (PRO) condition (bottom). **K, L)** Actual choices (purple) and
1111 simulated choices (green) from the best fit model (RLCK) for the same animal under
1112 vehicle/propranolol and vehicle/isoproterenol . Grey line represents the reward probability of the

1113 left choice. **M)** Average learning rate (α) across isoproterenol and vehicle. * indicates $p < 0.05$.

1114 Graphs depict mean ± SEM across animals.

1115

Supplementary figure 1

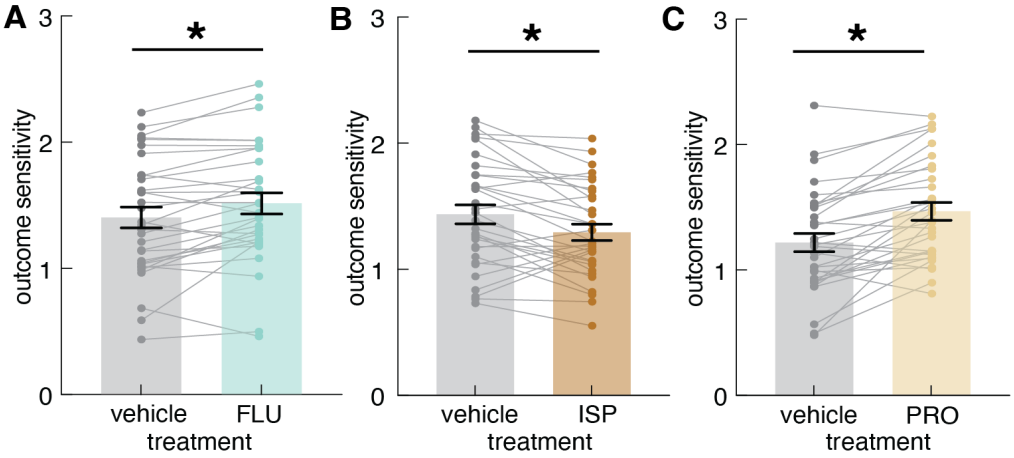
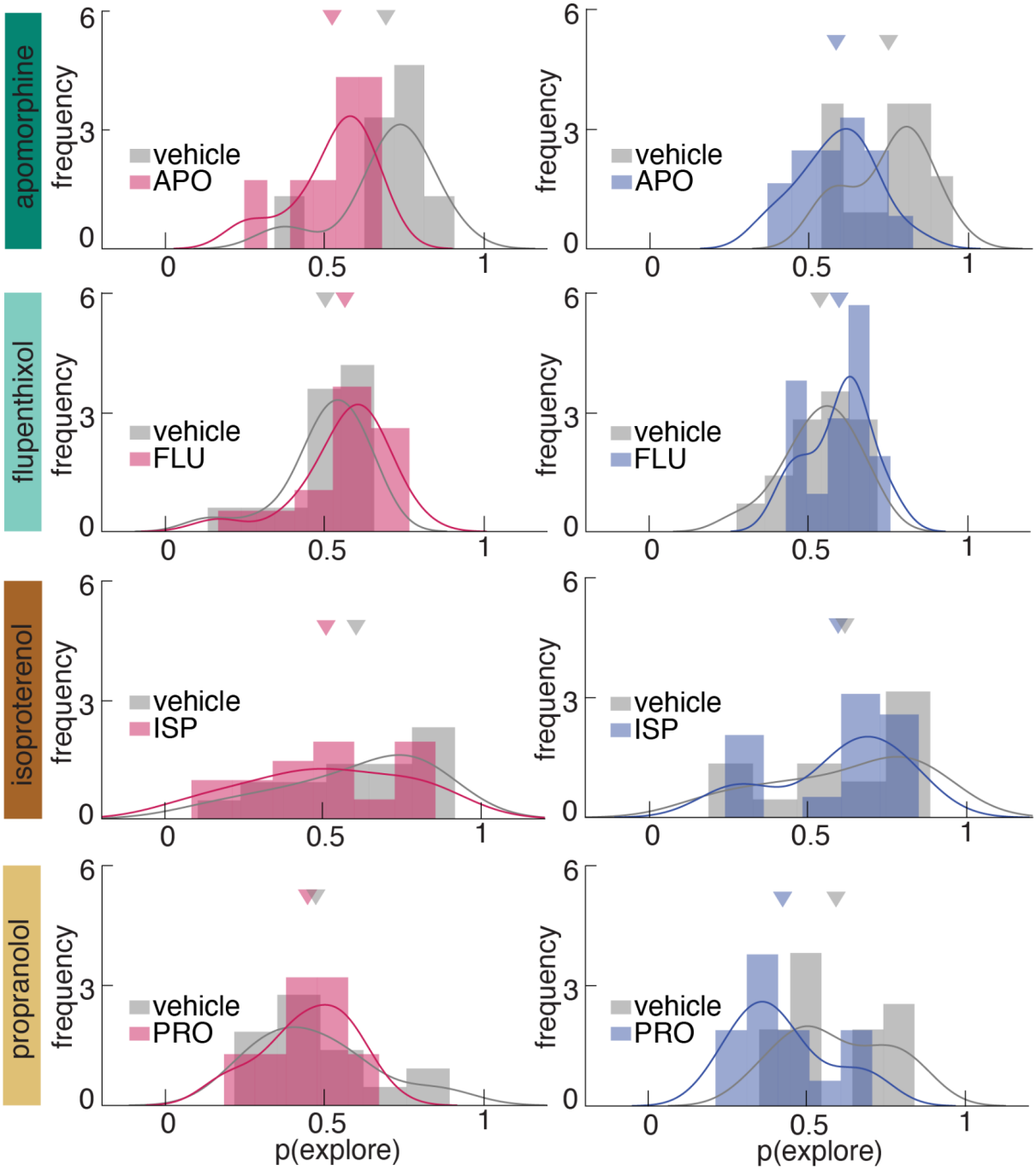


Figure 1-1. Effect of dopamine and norepinephrine modulation on outcome sensitivity. Related to Figure 1.

A) Average outcome sensitivity across flupenxithol (FLU) and vehicle. **B**) Average outcome sensitivity across isoproterenol (ISP) and vehicle. **C**) Average outcome sensitivity across propranolol (PRO) and vehicle. * indicates $p < 0.05$. Graphs depict mean ± SEM across animals.

1125 **Supplementary figure 2**

1126



1127

1128 **Figure 3-1. Effect of dopamine and norepinephrine modulation on exploration in female**

1129 **and male mice. Related to Figure 3,4.**

1130