MESOCORTICAL DOPAMINERGIC REGULATION OF CUE-GUIDED RISK/REWARD DECISION MAKING

by

Jackson Schumacher

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the thesis entitled:

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Examining Committee:

Stan Floresco, Professor, Psychology, UBC
Supervisor

Catharine Winstanley, Professor, Psychology, UBC
Supervisory Committee Member

Luke Clark, Professor, Psychology, UBC
Supervisory Committee Member

Abstract

When seeking reward, we are often faced with decisions between options that pay out often but yield low rewards and those that are relatively riskier but more profitable when they pay off. Human behavioral paradigms used to study this type of decision making often give participants explicit cues associated with the probability of reward. Conversely, rodent decision-making paradigms generally require the animal to develop internal representations of reward contingencies to guide decision-making in the absence of explicit cues. Human and rodent studies have uncovered a role for dopamine transmission in the medial prefrontal cortex (mPFC) in risky decision making, however, it is unclear if cortical dopamine serves the same purpose in cue-guided and non-cue-guided decision-making contexts. Our group has recently developed a rodent decision-making assay to bridge this gap named the "Blackjack task". In this task, rats choose between a small/certain option that delivers 1 sugar pellet 100% of the time and a large/risky option that delivers 4 sugar pellets, probabilistically. The chance of the large/risky option being rewarded is signaled by two distinct auditory cues (signaling either 50% or 12.5% chance of reward). Previously, using this task, we have shown that the dorsal mPFC facilitates risk taking when the odds are favorable whereas the ventral mPFC inhibits risk taking when the odds are poor. Our lab has also demonstrated dissociable roles for cortical dopamine D1 and D2 receptors during un-cued risk reward decision making, however, the role for dopamine receptors in the mPFC during cued risk/reward decision making remains unknown. Here, we assess the effect of blockade of dopamine D1 and D2 receptors in the dorsal and ventral mPFC in male rats. Dopamine D2 (but surprisingly, not D1) receptors in the dorsal mPFC promote risky choice when the odds are favorable by promoting flexible responding to dynamically changing reward contingencies. Cue-guided risk/reward decision making in the ventral mPFC, however, is not

dependent on D1 and D2 receptors. These data highlight a role for prefrontal dopamine receptors in cue-guided risk/reward decision making that is distinct from other types of risk/reward decision making, sub-region dependent and specific to D2 receptors.

Lay Summary

Sometimes when making decisions, it's better to play it safe. Other times, it's better to risk it for the biscuit. To make the best decision, we must use information in our environment to gauge if a gamble is likely to pay off. In order to understand the brain mechanisms that allow us to make good decisions, we developed a risky decision-making task in rats called the Blackjack task. Here, rats press levers for sugar pellets and choose to either risk not getting anything for a large reward or play it safe for a small reward. We then play tones that tell the rat if the odds of getting a large reward are good or bad. By blocking the neurotransmitter dopamine in the prefrontal cortex while rats play this game, we show that prefrontal dopamine promotes risky decisions when the odds are good and allows rats to switch between betting strategies.

Preface

I am the primary author of the work presented in this thesis. Dr. Floresco and I identified the research question and designed the experiment. I led data collection. Mieke van Holstein taught me the necessary techniques to perform the experiment. Christina Wong, Vaishali Bagrodia, Farah Charania and Kavya Kaluarachi assisted with data collection. I was responsible for data analysis and manuscript writing. Dr. Floresco acted as supervisory author, providing guidance and feedback on data analysis, interpretation and drafting the manuscript. All experiments were conducted in accordance with the Canadian Council for Animal Care and were approved by the Animal Care Committee of the University of British Columbia – protocol number A18-0242.

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Mesocortical Dopaminergic Regulation of Cue-Guided Risk/Reward Decision Making, J.D. Schumacher, M. van Holstein, S.B. Floresco

Table of Contents

List of Tables

List of Figures

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Introduction

Optimal decision-making hinges on the ability to weigh costs and benefits of different actions. Evaluation of costs and benefits, in the context of reward seeking, requires integration of information about reward magnitude, probability of reward and potentially other costs (delay, effort) associated with different rewards. This information can be garnered from the environment or constructed over time through trial and error learning. We know that this diverse decision-making landscape is altered in individuals suffering from many psychiatric disorders, including substance use and gambling disorders. Thus, translational neuroscience represents a key step in understanding the systems that govern cost-benefit decision making processes in health in order to treat their dysfunction in disease.

Parallel lines of research in humans and animals have shown a critical role for the prefrontal cortex in cost-benefit decision making. Seminal research from Antoine Bechara and colleagues was the first to develop assays to test decision making with uncertainty surrounding the probability of reward and punishment. In their task - later named the Iowa Gambling Task (IGT) – participants were given a starting sum of money to play with and asked to select cards from 4 decks. The 4 decks varied in terms of reward magnitude as well as the magnitude and probability of monetary punishment such that, over many turns, the decks with lower reward magnitude had higher utility due to smaller magnitude and risk of financial loss. Through trial and error, participants had to learn to inhibit choice of decks associated with large reward magnitude to avoid their associated punishments and maximize utility over many turns. Patients with ventromedial frontal lobe damage, unlike controls and patients with damage to non-frontal lobe areas, did not adopt this optimal response strategy and continued to choose decks with high initial gains but ultimately larger losses over time (Bechara et al. 1994). Subsequent PET

imaging studies in healthy participants identified activation throughout the prefrontal cortex during performance of the IGT including the dorsolateral prefrontal cortex (DLPFC) or Brodmann areas (BA) 6 & 8-10, the orbital frontal cortex (OFC) or BA 11 & 47 and the right anterior cingulate cortex (AC) or BA 24 & 32 (Ernst et al. 2002).

Following these discoveries, Rob Rogers, Trevor Robbins and colleagues developed a cue-guided, risk/reward decision making task (later named the Cambridge Gambling Task or CGT) in which participants were given explicit information about the odds of a particular bet paying out and were given the opportunity to choose how much they wanted to wager, accordingly. PET imaging of healthy participants performing this task demonstrated cortical activation in areas including middle frontal gyrus (BA 10) and the inferior frontal gyrus (BA 47) and the OFC (BA 11) (Rogers et al. 1999). Furthermore, studies of patients with prefrontal lesions replicated observations of impairments on IGT performance and demonstrated that patients with prefrontal damage picked the optimal option in the CGT at similar rates to controls but tended to bet more (Manes et al. 2002; Rogers et al. 1999).

Follow up studies using larger patient pools and more specific lesion sites discovered functional differences in cortical subregions with both ventromedial and dorsolateral lesions contributing to poor IGT performance but with only ventromedial lesions contributing to reversal learning deficits (Fellows and Farah 2005). Furthermore, IGT (but not CGT) impairments were correlated with total lesion volume and lesion volume lateral of the ventromedial PFC - demonstrating differential involvement of cortical subregions in different forms of risk/reward decision-making (Clark et al. 2003). Cumulatively, these results demonstrate that different subregions of the human prefrontal cortex are critical to mediating different aspects of optimal cost-benefit decision making involving risks and rewards.

In rodent research, studies have highlighted a role for the medial prefrontal cortex (mPFC) and its subregions (infralimbic – IL, prelimbic – PL, and anterior cingulate – AC) in choosing between small rewards and large rewards associated with various types of costs, including reward uncertainty. While rodent-human cortical homologies remain contentious, evidence from corticolimbic projection mapping in rodents and non-human primates (NHP) points towards similarities between the rodent IL and NHP BA 25 and rodent PL and NHP BA 32 (Heilbronner et al. 2016). In addition to anatomical similarities, these regions serve complementary functions in risk/reward decision making as their human counterparts. For example, in probabilistic discounting, inactivation of the PL mPFC impairs rats ability to flexibly adjust to changing reward probability contingencies (St. Onge and Floresco 2010). Bulk fiber photometry recordings in PL during the probabilistic discounting task show activity ramps up during deliberation and decreases during trial outcomes. Furthermore, these transient increases and decreases in activity are modulated by trial and outcome type, respectively – showing that cortical neurons track multiple task parameters at the population level (Braunscheidel et al. 2019). Similar to the response profile seen following mPFC inactivation during probabilistic discounting, mPFC inactivation in the risky decision making task (RDT) - where rats choose between a safe, small reward and a punished large reward with probability of punishment changing over blocks of trials – impaired rats ability to adapt to changing likelihoods of punishment (Orsini et al. 2018). In the rat gambling task (RGT) patterned after the human Iowa gambling task, rats choose between 4 static options that vary in terms of magnitude and probability of reward and magnitude and probability of a timeout punishment. Similar to the IGT, low reward magnitude options had significantly higher utility in the long term. Inactivation

of either the IL or PL mPFC decreased choice of optimal options and increased choice of disadvantageous high risk/high reward options (Zeeb et al. 2015).

Different regions of the frontal lobes implicated in risk/reward decision making receive dopaminergic innervation from the midbrain, and evidence human studies suggests a role for mesocortical dopamine transmission in modulating these functions. Early evidence for this link came from treatment strategies for Parkinson's disease (PD) that employ D2 dopamine receptor agonists, showing heighted rates of pathological gambling and impulse control disorders in medicated PD patients (Dodd et al. 2005; Weintraub et al. 2006). Research in non-clinical populations has demonstrated that depletion of dopamine via ingestion of branched-chain amino acids that interfere with tyrosine metabolism impairs performance on the IGT (Sevy et al. 2006) and administration of a D1 receptor agonist increased willingness to expend physical effort, reduced preference for risky options and had no effect on preference for delayed rewards (Soutschek et al. 2020). Subjects with homozygous Met alleles in the catechol-o-methyltransferase (COMT) gene (and likely greater cortical dopamine availability) showed increased prefrontal reward anticipatory activity (Yacubian et al. 2007). Finally, a pilot study using the COMT inhibitor tolcapone to semi-selectively increase dopamine availability in the prefrontal cortex in problem gamblers showed significant symptom reduction and augmented fronto-parietal BOLD activation (Grant et al. 2013). However, another pilot study found seemingly contradictory evidence showing that tolcapone increased risky choice among problem gamblers on the IGT (Peters et al. 2019).

Despite a robust human literature, methodological limitations make it difficult to make causal claims about the role of dopamine in specific regions of cortex. Furthermore, rodent studies that mirror human studies by using systemic administration of dopaminergic drugs have

uncovered a role for dopamine in a diverse array of behaviors and provided evidence for the translational relevance of these procedures. In rats performing the RGT, amphetamine impaired performance and DAT inhibition had no effect on choice (Baarendse, Winstanley, and Vanderschuren 2013; Zeeb, Robbins, and Winstanley 2009). Furthermore, in the RGT, administration of the D2 antagonist eticlopride improved performance whereas the D1 antagonist SCH-23390 had no effect (Zeeb et al. 2009). A study using the probabilistic discounting task, however, showed administration of either D1 or D2 antagonists induced risk aversion (St. Onge and Floresco 2009).

Other preclinical rodent studies more specifically examined PFC DA transmission in risk/reward decision making by using local administration of receptor antagonists. Studies using intracortical infusions of a D2 receptor antagonist in either PL, IL, AC or OFC during the RGT found no effect of infusion into any subregion (Zeeb et al. 2015). On the other hand, during performance of a probabilistic discounting task in which rats must use action/outcome history to adjust choice biases, PL D1 blockade reduces preference for the large/risky option while PL D2 blockade impaired adjustments in decision biases in response to changes in reward probabilities (St Onge, Abhari, and Floresco 2011). Using microdialysis to track dynamic fluctuations in mPFC DA efflux in rats performing the probabilistic discounting task or in reward-yoked controls showed that dopamine levels tracked reward probabilities with no differences between task performing or yoked control animals (St. Onge et al. 2012). This suggests that cortical dopamine levels track reward rates on slow timescales and act differently on D1 or D2 receptors to bias behavior towards the optimal option.

Real world risk/reward decision making requires individuals to integrate information about reward probabilities from multiple sources to guide action selection. In some instances,

this information comes from internal representations of reward contingencies generated from past experience (as modeled in the probabilistic discounting task). In other situations this information may come from explicit cues in the environment. In this regard, a considerable amount of human research on the topic employs tasks that model both these "cue-guided" or "representation-guided" decision making strategies (the CGT vs IGT, for example) whereas most rodent tasks focus on the latter. A relatively novel procedure, colloquially termed the "Blackjack" task was designed to fill this gap in the literature by requiring rats to attend to explicit cues to obtain information about reward probabilities. Specifically, rats choose between a small/certain option that delivers 1 sugar pellet 100% of the time or a large/risky option that delivers 4 sugar pellets probabilistically. The "odds" associated with the large/risky option are signaled by two distinct auditory tones that indicate either a 50% or 12.5% probability of reward. Over training, rats adopt an optimal response strategy in which they preferentially choose the large/risky option on good odds trials and the small/safe option on poor odds trials (Floresco et al. 2018).

Like other forms of risk/reward decision making, choice on the Blackjack task is dependent on the integrity of the mPFC, although different subregions play dissociable roles in biasing choice. Specifically, inactivation of the PL mPFC reduces choice of the large/risky option on good odds trials whereas inactivation of the IL mPFC has the diametrically opposed effect – increasing choice of the large/risky lever on poor odds trials (van Holstein and Floresco 2020). Furthermore, PL inactivation induced choice effects that were associated with a decrease in win-stay behavior on good odds trials whereas infralimbic inactivation did not have any effect on feedback sensitivity. This data supports the idea that the dorsal and ventral mPFC bias decision making in different, but complimentary ways – promoting advantageous risky choice

and suppressing disadvantageous risky choice, respectively. These results contrast those described earlier from probabilistic discounting studies where PL inactivation impaired the ability to adapt to changing reward contingencies or from RGT studies where PL and IL inactivation shift response strategies from optimal low risk/low reward options to suboptimal high risk/high reward options (St. Onge and Floresco 2010; Zeeb et al. 2015). Collectively, these findings indicate that the type of information that is used to guide risk-reward decision making can markedly alter the manner in which different subregions of the mPFC contribute to choice.

As noted above, previous preclinical studies on how mesocortical DA modulates risk/reward decision making have primarily used procedures where choice was guided by internally-generated estimates of reward probability and choice/outcome contingencies. However, it remains unknown how dopaminergic signaling in the mPFC regulates cue-guided risk/reward decision making. To address this, the present study assessed the role of dopamine D1 or D2 receptors in the PL or IL mPFC during cue-guided risk/reward decision making using intra-cortical micro infusions of D1 or D2 antagonists in rats performing the Blackjack task.

Methods

Animals

Male Long Evans rats (225-275g) were initially group housed and allowed 1 week to habituate to the colony room after arrival. They were then pair housed until surgery and singly housed for the rest of the experiment. The colony room had a 12h light/dark cycle (Light 7am-7pm) and was maintained at a temperature of 21 degrees Celsius. All training and experiments were performed in the light phase of the cycle. Five days prior to the start of training, rats were food restricted to 15-18g of food per day (LabDiet 5053, PicoLab) which initially reduced their body weights to ~90% of their free feeding weight but allowed for age-typical weight gain thereafter. All experiments were conducted in accordance with the Canadian Council for Animal Care and were approved by the Animal Care Committee of the University of British Columbia.

Apparatus

Rats were trained and tested in operant chambers (30.5 × 24 × 21 cm; Med-Associates, St Albans, VT, USA) enclosed in sound-attenuating boxes. Internal fans served to regulate temperature and mask external noise. Each chamber contained two retractable levers on either side of a food port that allowed for delivery of 45 mg sweetened reward pellets (Bioserv Frenchtown, NJ, USA) via a pellet hopper. Chambers were equipped with one 100mA house light. Auditory stimuli were presented using a speaker in the wall opposite the levers that was connected to a programmable sound generator (ANL-926, Med Associates).

Behavioral training

Initial lever press training and Reward Magnitude Training

Details of training are diagramed in Figure 1A. On the first day, rats received one day of magazine training, where 30 pellets were delivered into the food port over 30 minutes on a 60 s

variable interval. The next day, rats were trained to lever press on a fixed ratio-1 schedule of reward. One lever was inserted into the chamber, baited with reward pellet dust and remained extended until 60 presses were made or 30 minutes had elapsed. The next day, rats repeated this training with the other lever extended. Rats were trained for a minimum of 2 days and continued training (levers alternating each day) until they reached a criterion of 50 presses in 30 minutes (requiring 2-3 days).

After reaching FR1 criteria, rats were trained to press retractable levers. Each session consisted of 90 trials. Every 40 s, the house light illuminated and 3 s later, one lever extended into the chamber (randomized in pairs). Rats had 10 s to press the lever after its insertion, otherwise it would retract, and the trial was scored as an omission. A lever press was rewarded with 1 pellet with a 50% probability. Rats continued retractable lever press training until they made less than 10 omissions on a session (requiring 2-3 days)

After lever press training, rats underwent additional training procedures to associate one reward option with a larger reward. First, they were trained on a reward magnitude discrimination task, consisting of 4 blocks made up of forced-choice and free-choice trials. Every 40 s, one or both levers were inserted into the chamber. Pressing one lever within 10 s of insertion delivered 4 pellets, and the other 1 pellet (right and left lever counterbalanced between rats). The large/small reward levers assigned to each rat remained consistent for the duration of the experiment. On the first session (48 trials; 2 forced and 10 free-choice trials/block), both the large and small reward was delivered with 100% probability. On the second and third sessions (72 trials; 8 forced and 10 free-choice trials/block) the large reward was delivered with a 50% probability.

Blackjack Task

Rats were then trained on the Blackjack task (Fig. 1B). One lever was designated as the small/certain option (delivering 1 pellet with 100% certainty) and the other as the large/risky option (delivering 4 pellets with varying probabilities) in line with the lever associations made during reward magnitude training. Trials occurred every 40 s with illumination of the house light and the initiation of one of two distinct auditory cues (3 kHz pure tone or white noise) that signaled the probability of obtaining the large/risky reward on that trial. One cue signaled a "good-odds" trial, where a risky choice would be rewarded with a 50% probability. The other tone signaled a "poor odds" trial, where risky choices were only rewarded with a 12.5% probability. Both cues were presented an equal number of times over the session (randomized in pairs). Choosing the large/risky option was more advantageous on good-odd trials, whereas on poor-odd trials, the small/certain option had greater utility. Auditory cues associated with good vs poor odd trials were counterbalanced across rats and remained consistent over the duration of the experiment. Choice of either lever caused both levers to retract. If the rat chose the large/risky option and received a reward, the auditory cue and house light remained on during the delivery of the four pellets and turned off 3 s after choice. Large/risky choices that did not deliver reward extinguished the house light immediately and the auditory cue was terminated 2 s after the choice. The extended presentation of the auditory cue was intended to facilitate learning of their predictive value and the likelihood of the different outcomes associated with these choices. Following an omission, both levers were retracted, and the house light and auditory cue were extinguished.

Initially, rats were trained on a forced-choice version of the task consisting of 32 forced-choice trials followed by 20 free-choice trials. On forced-choice trials, when the large/risky

lever was extended, the auditory cue indicated the respective probability of obtaining the large reward on that trial (50% or 12.5%). On forced-choice trials where the small/certain lever was inserted, an equal number of each auditory cue was presented over the course of the session, such that rats could learn that a response on this lever always delivered one pellet, irrespective of the cue presented. After 12-17 days of training on the forced-choice version, rats displayed stable choice behavior and were moved to the final version of the task which consisted of 40 free-choice trials. Choice behavior was determined to be stable over a period of 3 days if a 2 x 3 repeated measures ANOVA with days and odds as within-subject factors had a non-significant main effect of days and a non-significant days x odds interaction ($p > 0.1$) as well as a significant main effect of odds ($p < 0.05$). Rats were trained on the free-choice version of the task for at least 5 days and until they were again determined to be stable at which point, they underwent surgery.

Stereotaxic surgery

Rats received surgery after their group performance had reached stability in the final phase of behavioral training. They were initially sedated with a subanesthetic intraperitoneal dose of ketamine (50 mg/kg) and xylazine (4 mg/kg) and were maintained on a surgical plane of anesthesia with isoflurane for the duration of surgery. They were then implanted with bilateral stainless steel cannula (23-gauge, beveled at the tip) in either the PL (AP = + 3.4 mm; ML = +/− 0.7; DV = − 2.8 mm from dura) or IL mPFC (AP = + 2.8 mm; ML = +/− 0.7; DV = − 4.1 mm from dura). Cannula were held in place with stainless steel skull screws and dental acrylic. Obdurators (30 G) were inserted into the cannula and were checked daily to ensure they remained in place until microinfusion test days. All rats were given at least 1 week to recover

before beginning food restriction and behavioral retraining. Rats were retrained after surgery until their group performance reached stability, after which they began micro infusion testing.

Micro infusions

Prior to the first microinfusion test day, rats received a mock infusion to familiarize them with the procedure. On these days, obdurators were removed and 30 gauge wires attached to tubing were inserted into the guide cannulae for 2 minutes. They were then placed in their home cage for 10 minutes prior to being placed in the operant chamber for their training session. Most rats received their first microinfusion test day 1-4 days after the mock injection, with the exception of 2 rats with prelimbic placements (5-6 days retraining) and 5 rats with infralimbic placements (5-8 days retraining)

For all groups, saline and 2 doses of drug (counterbalanced) were infused at a volume of 0.4 μl over 90 seconds (0.27 μl/min) using a Sage instruments model 341 syringe pump. D1 dopamine receptor blockade was achieved using a solution of the D1/D5 receptor antagonist SCH-23390 (0.1 μg or 1.0 μg per hemisphere) dissolved in saline. D2 dopamine receptor blockade was achieved using a solution of the D2/D3 receptor antagonist eticlopride (0.1 μg or 1.0 μg per hemisphere) dissolved in saline. Infusions were delivered via a 30-gauge injector that protruded 0.8 mm past the end of the guide cannula. After the 90 second infusion period, pumps were turned off and the injector remained in place for 60 s to allow for diffusion. Rats were then returned to their home cage for 10 minutes before being placed in the chamber for their test session.

A within subjects design was used for all experiments such that each rat received saline and all doses of either SCH-23390 or eticlopride. After each test session, rats were retrained

daily until they met their pre-test baseline performance (1-11 days of retraining) before receiving their next, counterbalanced micro infusion.

Histology

After completion of behavioral experiments, animals were anesthetized with isoflurane and euthanized with CO2. Brains were removed and post fixed in 4% formalin for at least 24 hours before sectioning. Brains were rapidly frozen and cryosectioned at 50 um, mounted to gelatin coated slides and Nissl stained with Cresyl Violet dye. Placements were verified with reference to the Paxinos and Watson (2005) neuroanatomical atlas. Rats with placements residing outside the border of the mPFC as well as those on the border of the IL and PL mPFC were removed from the analysis (6 rats with prelimbic placements 13 rats with infralimbic placements). The *n*s reported for each experiment represent the final number of animals with acceptable placements within the mPFC. The location of all acceptable infusion placements is displayed in Figure 2.

Statistical Analysis

The primary dependent measure was percentage choice of the large/risky option calculated separately for good- and poor-odds trials. We also compared choice latencies and the number of trail omissions across treatments.

Choice data from the Blackjack task was analyzed using a two-way repeated measures ANOVA with treatment (saline, low dose, high dose) and odds (good vs. poor) as within-subject factors. In these analyses, the main effect of odds was always significant ($p<0.01$), and will not be reported further. The majority of rats utilized optimal choice strategies, showing a strong bias (>50%) towards the large/risky option on good-odds trials, and selecting it more often on good vs poor-odds trials. However, some rats (3 in the PL D1 group, 3 in the PL D2 group, 1 in the IL

D1 group and 2 in the IL D2 group) failed to develop an optimal strategy over training, and instead chose the large/risky option on fewer than 50% of *both* good and poor odds trials. As we have done previously (van Holstein et al., 2020; Bryce et al., 2020), these rats were classified as "poor players". Our analyses of the choice data focused on the subset of "good players", although inclusion of the data from the poor players did not qualitatively change the results of the analysis.

Following a significant main effect or interaction on choice data, supplementary analyses (Fig. 1C) were conducted to determine how mPFC D1 or D2 receptor blockade altered sensitivity to reward or negative feedback (i.e.; reward omission). Specifically, we calculated the proportion of trials where rats were rewarded after choosing the large/risky option on the previous trial and chose the large/risky option again on the next trial (win-stay behavior) as well as the proportion of trials when a rat was not rewarded for a risky choice and then switched to the small/certain option on the next trial (lose-shift behavior). Win-stay ratios were calculated for each session by dividing the number of large/risky choices made after obtaining the large reward on the preceding trial, by the total number of large/risky wins. Similarly, lose-shift ratios were calculated by dividing the number of small/certain choices following a non-rewarded risky choices, by the total number of non-rewarded risky choices.

Feedback sensitivity data was analyzed with a two-way ANOVA with treatment (saline, low dose or high dose) and feedback type (win-stay vs lose-shift) as within-subjects factors. This analysis was only conducted on "good players" as the "poor players" did not have a sufficient number of large/risky wins and losses to compute win-stay/lose-shift ratios. Feedback sensitivity by trial type (good/poor odds) was analyzed using a two-way ANOVA with treatment (saline, low dose or high dose) and feedback type (win-stay vs lose-shift) as within-subjects factors.

Further supplementary analyses (Fig. 1C) were conducted following a significant main effect or interaction on choice data to determine how mPFC D1 or D2 receptor blockade altered the ability to adjust choice bias following shifts in the trial odds. Specifically, looking at just trials where the odds had changed from the previous trial (odds-switch trials), we calculated the proportion of trials where the rat chose the same response option that was chosen in the previous trial (lever-stay) or the option that is had not been chosen in the previous trial (lever-shift). We also calculated the proportion of both lever-shift and lever-stay trials where the rat stayed on or shifted to the "optimal" or "suboptimal" response option given the current trial odds. Finally, we looked at the proportion of optimal or suboptimal lever-shifts or stays separately for the set of trials where the odds switch from good-to-poor or poor-to good. All analyses were done on the ratios of these types of responses to the total number of odds-switch trials on that session.

The basic lever-shifts and lever-stays are perfectly inversely related, so we only analyzed lever-shifts with a one-way ANOVA. We analyzed optimal shifts, optimal stays, suboptimal shifts and suboptimal stays with 4 separate one-way ANOVAs with a Bonferroni corrected alpha of 0.0125. We used the same analysis strategy for these measures on good to poor and poor to good switch trials, separately.

Latency data for the Blackjack task was analyzed using a one-way repeated measures ANOVA. Finally, the number of omissions for all tasks were compared with a one-way repeated measures ANOVA.

In conditions where we observed significant effects of treatment we ran supplementary analysis to assess the effect of cannula placement on drug effects. Specifically, we ran a linear regression with the dependent variable set as the difference between risky choice on saline and the risky choice on the average of low and high drug doses for trial types (good or poor odds)

that showed sensitivity to drug effects. We set the predictors as the coordinate of the cannula placement along the anterior-posterior and dorsal-ventral axis of the brain. In these analyses we included good players with both PL and IL placements as well as rats with placements that fell on the border between PL and IL.

To allow for direct comparisons to be made between the role of D1 and D2 receptors within a region we ran additional analysis with an expanded model in regions that were sensitive to dopaminergic manipulations. Specifically, we used a 3 way, mixed ANOVA with dose (high, low, saline) and odds (good, poor) as within subjects factors and drug (D1 antagonist, D2 antagonist) as a between subjects factor.

Following significant drug effects, multiple comparisons were conducted using Dunnett's tests to assess dose effects. All repeated measures ANOVAs were assessed for sphericity violations using a Mauchly's test. All analyses were performed using SYSTAT and R.

Results

Prelimbic D1 blockade

Data from 17 rats with acceptable placements were included in the analysis. As displayed in Figure 3A, the majority of rats were classified as "good players" under control conditions, showing a strong bias towards the large/risky option on good odds trials. A total of 6 rats met criteria for being classified as poor players on their saline test session, however, only 3 of those rats consistently met this criteria during baseline training and were excluded from subsequent analysis of good players. A two-way ANOVA on choice data from all rats revealed no significant main effect of treatment ($F(2,32) = 0.06$, $p = 0.939$) or treatment by odds interaction ($F(2,32) = 0.20$, $p = 0.158$). However, these treatments were not without effects, as analysis of the response latency data revealed that D1 blockade slowed reaction time ($F(2,32) = 3.66$, $p = 0.037$, Table 1) but did not affect trial omissions ($F(2,32) = 2.09$, $p = 0.141$, table 1). A Dunnett's test revealed that the decrease in reaction times was driven by a significant difference between saline and the high dose ($p = 0.018$) but not the low dose. Moreover, a similar analysis of choice data obtained from just "good players" (n=14), plotted in Figure 3B, yielded similar results with no significant main effect of treatment ($F(2,26)=0.17$, $p = 0.845$) or treatment by odds interaction ($F(2,26) = 2.07$, $p = 0.147$). Thus, blockade of PL D1 receptors did not alter cue-guided risk/reward decision making, but did increase deliberation times.

Prelimbic D2 Blockade

Data from 17 rats with acceptable placements were included in the analysis. As displayed in Figure 3C, the majority of rats (n=14) were classified as "good players". A two-way ANOVA on choice revealed that D2 blockade significantly reduced choice of the large/risky option ($F(2,32) = 6.48$, $p = 0.004$). A similar analysis in just good players also revealed a significant

main effect of treatment ($F(2,26) = 4.27$, $p = 0.025$, Fig. 3D) and a non-significant treatment by odds interaction $F(2,26) = 2.96$, $p = 0.069$). Despite the lack of a significant interaction, exploratory, follow-up analysis revealed that the decrease in overall risky choice induced by PL D2 receptor antagonism was primarily driven by choice on good odds trials ($F(2,26) = 4.83$, $p = 0.016$) as opposed to poor odds trials ($F(2,26) = 0.10$, $p = 0.902$). Although both doses qualitatively reduced good odds risky choice, Dunnett's tests on good-odds risky choice found a significant reduction following treatment with the low dose ($p = 0.004$), whereas the effect of the high dose did not achieve statistical significance.

Follow-up analysis of feedback sensitivity in good players revealed no main effect of treatment ($F(2,24) = 0.15$, $p = 0.862$, Table 2) or treatment by feedback type interaction ($F(2,21) = 0.79$, $p = 0.468$, Table 2). Similar analysis on feedback sensitivity within just good odds or just poor odds trials revealed no main effect of treatment (good odds: $F(2,24) = 2.10$, $p = 0.144$, poor odds: $F(2,24) = 0.75$, $p = 0.483$, Table 3) or treatment by feedback type interaction (good odds: $F(2,24) = 1.26$, $p = 0.301$, poor odds: $F(2,24) = 0.38$), $p = 0.687$, Table 2). Thus, the effect of PL D2 receptor antagonism on cue-guided risk/reward decision making was not driven by alterations in how recently rewarded or non-rewarded actions influenced subsequent choice.

Given the significant treatment effect on choice, we also conducted follow-up analysis to ascertain if the choice effect was accompanied by alterations in the ability to flexibly adapt to dynamic changes in reward contingencies. Specifically, a one-way ANOVA on the proportion of lever-shifts on odds-switch trials revealed a significant decrease in this measure following D2 receptor blockade ($F(2,26) = 11.08$, $p < 0.001$, Fig. 4A). Similar to the effect on choice, a Dunnett's test revealed significant differences between saline and low dose ($p < 0.001$) but not high dose ($p = 0.127$) sessions. A more granular analysis of lever-shifts and stays by their utility

(Fig. 4B) using one way ANOVAs with a Bonferroni correction revealed significant increases in optimal ($F(2,26) = 14.11$, $p < 0.001$) and suboptimal lever stays ($F(2,26) = 5.29$, $p = 0.012$) and a significant decrease in optimal ($F(2,26) = 5.86$, $p = 0.008$) but not suboptimal lever-shifts ($F(2,26) = 0.30$, $p = 0.742$). A Dunnett's test revealed that all effects were driven by the difference between saline and low dose (all $p < 0.002$) and not saline and high dose (all $p > 0.100$) test sessions. A similar analysis targeting only odds switch trials where the odds switch from poor to good (Fig. 4C) revealed a significant decrease in optimal ($F(2,26) = 6.30$, $p = 0.006$) but not suboptimal lever-shifts ($F(2,26) = 0.17$, $p = 0.844$) and a significant increase in suboptimal ($F(2,26) = 5.29$, 0.012) but not optimal ($F(2,26) = 0.08$, $p = 0.925$) lever-stays. A Dunnett's test revealed both effects were driven by differences between saline and low (both $p < 0.003$) but not the high dose test sessions. Conversely, analysis of just odds-switch trials where the odds switch from good to poor (Fig. 4D) revealed a significant increase in optimal stays ($F(2,26) = 10.43$, $p < 0.001$) but not suboptimal stays ($F(2,26) = 0.06$), $p = 0.938$) , optimal shifts ($F(2,26) = 4.95$, $p = 0.015$) or suboptimal shifts ($F(2,26) = 1,68$, $p = 0.205$). Like all previous Dunnett's tests for PL D2 blockade results, the effect on optimal stays was driven by differences between saline and low ($p < 0.001$) but not high dose test sessions.

With respect to other performance measures, intra-PL infusions of eticlopride altered decision latency ($F(2,32) = 3.67$, $p = 0.037$) and had no effect on omissions ($F(2,32) = 1.00$, $p = 0.379$) (Table 1). However, a Dunnett's test revealed that neither the low ($p = 0.655$) or high ($p = 0.110$) dose were significantly different from saline. Latencies on high dose test sessions were longer than those on saline test sessions whereas the opposite was true for response latencies on low dose test sessions. Therefore, the latency effect here is qualitatively different from that seen following D1 blockade and also harder to interpret.

Collectively, these results demonstrate that dopamine D2 receptors in the PL mPFC bias choice towards more profitable risky options and facilitate the flexible adaptation to rapidly changing reward contingencies.

Infralimbic D1 Blockade

Data from 12 rats with acceptable placements were included in the analysis. As displayed in Figure 5A, all but one rat exhibited optimal choice patterns and were classified as good players under control conditions. A 2 way ANOVA on choice data revealed no main effect of treatment ($F(2,22) = 1.45$, $p = 0.256$) or treatment by odds interaction ($F(2,22) = 0.16$, $p = 0.856$). These treatments also did not affect response latencies ($F(2,22) = 0.40$, $p = 0.677$) or omissions ($F(2,22) = 1.88$, $p = 0.177$; Table 1). An analysis of choice data from just "good players" (n=11, Fig. 5B) yielded similar results with no significant main effect of treatment ($F(2,20) = 1.46$, $p = 0.256$) or treatment by odds interaction ($F(2,20) = 0.09$, $p = 0.912$). Thus infralimbic D1 blockade had no effect on choice or deliberation time.

Infralimbic D2 Blockade

Data from 8 rats with acceptable placements were included in the analysis. As shown in Figure 5C, 6 out of 8 rats exhibited optimal choice patterns under control conditions and were classified as good players. A 2-way ANOVA on choice data revealed no main effect of treatment ($F(2,14) = 0.53$, $p = 0.60$) or treatment by odds interaction ($F(2,14) = 0.78$, $p = 0.478$). Similarly, response latencies ($F(2,14) = 1.04$, $p = 0.379$) and omissions ($F(2,14) = 0.84$, $p = 0.452$) were unaffected by these treatments (Table 1). An analysis of choice in just "good players" (n=6, Fig. 5D) yielded similar results with no significant main effect of treatment

(F(2,10) = 0.34, p = 0.723) or treatment by odds interaction (F(2,10) = 1.28, p = 0.321). Thus, infralimbic D2 blockade had no effect on choice or deliberation time.

Correlations Between Cannula Placement and D2 Blockade Effects

Additional linear regression analyses examined whether there was any relationship to the location of infusion of the D2 antagonist in the PL or IL mPFC and the effect on choice. This revealed that neither dorsal-ventral placement (p = 0.610, Fig. 6A), anterior-posterior placement (p = 0.579, Fig. 6B), or their interaction (p = 0.665) significantly predicted differences between good odds risky choice on D2 blockade test sessions and saline test sessions. Furthermore, an ANOVA on choice data from good players in the D2 group with cannula placements within the mPFC (PL, IL or the PL-IL border) revealed a significant reduction in risky choice (main effect: F(2,56) = 3.84, p = 0.027). Simple main effects analysis demonstrates this effect is primarily driven by a significant reduction in risky choice on good odds trials (F(2,56) = 4.12, p = 0.021) but not poor odds trials (F(2,56) = 1.26, p = 0.291). Thus, the placement of the cannula along the anterior-posterior or dorsal-ventral axis did not predict the magnitude of D2 blockade effects on choice.

Comparison of Prelimbic D1 vs D2 blockade

Data from 14 good players in the PL D1 group and 14 good players in the D2 group was included in the analysis. A 3-way ANOVA on choice data revealed a significant dose x drug x odds interaction (F(2,52) = 4.80, p = 0.012). Follow up simple main effects analysis revealed this effect was driven by a significant reduction in risky choice in the D2 group on good odds trials (F(2,26) = 4.83, p = 0.016) but not poor odds trials (F(2,26) = 0.10, p = 0.902) nor either good (F(2,26) = 0.77, p = 0.472) or poor odds trials (F(2,26) = 0.44, p = 0.648) in the D1 group.

Discussion

This work provides evidence for a role of dopaminergic transmission – acting on D2 receptors – within the PL, but not IL mPFC in promoting optimal cue-guided risk/reward decision making. D2 receptor activation within PL mPFC appears to bias choice towards risky, high reward options when the utility is relatively higher than certain, low reward options. They also appear to mediate dynamic shifts in response strategy in response to rapidly changing reward probability contingencies.

Prelimbic D1 receptor blockade

One of the most curious findings of the present set of studies is that D1 receptor blockade had no effect on choice. This is in contrast to a vast literature showing that blockade or supranormal stimulation of prefrontal D1 receptors impairs performance on a variety of spatial working memory or delayed response tasks in rodents and non-human primates (Floresco and Phillips 2001; Romanides, Duffy, and Kalivas 1999; Sawaguchi and Goldman-Rakic 1991; Seamans, Floresco, and Phillips 1998; Zahrt et al. 1997) and that dopaminergic modulation of working memory performance is widely thought to follow an inverted U relationship (Seamans and Yang 2004; Vijayraghavan et al. 2007). Cortical D1 receptors have also been shown to modulate behavioral flexibility (Ragozzino 2002), appetitive trace and trace fear conditioning (Pezze, Marshall, and Cassaday 2015; Runyan and Dash 2004), effort and probabilistic discounting (Schweimer and Hauber 2006; St Onge et al. 2011), and even more rudimentary behaviors such as instrumental associative learning (Baldwin, Sadeghian, and Kelley 2002; Puig and Miller 2012) and reinstatement of cocaine or heroin seeking (Sanchez et al. 2003; See 2009). Given how ubiquitous the role of prefrontal D1 receptor activity is in cognition, the lack of an effect on the highly complex Blackjack task was initially surprising. However, closer examination of the

cognitive demands of tasks that are impaired by D1 receptor manipulations provides insight into this otherwise paradoxical finding. All the tasks described above require the animal to form, switch between and, most importantly, stabilize internal representations of task-relevant contingencies. Spatial working memory, delayed response and trace conditioning tasks all require maintenance of task related information in working memory. Set-shifting and effort or probabilistic discounting assays require animals to stabilize new response strategies following changes to reward contingencies in the presence of competing obsolete strategies. Associative learning tasks require animals to form novel task representations and drug reinstatement after extinction relies on the stabilization of previously suppressed action-outcome contingencies. The fact that these tasks are sensitive to D1 receptor manipulations may reflect a broader role for D1 receptors in facilitating enduring representations of task contingencies in the absence of task relevant cues as has been hypothesized previously (Seamans and Yang 2004). Conversely, in the Blackjack task, rats receive explicit, external information that signals the probability of reward from trial onset until after their response has been made. Furthermore, reward magnitude information - that is not explicitly signaled - is well learned and does not change over training or the course of a session. Therefore, when performing the Blackjack task, despite its complex design, the specific burden placed on working memory may be relatively light and thus D1 receptor activation may be less critical to optimal performance.

Despite having no effect on choice performance, D1 blockade did slow decision latency in the Blackjack task. This is consistent with previous reports that cortical D1 receptor blockade impairs performance on a simple reaction time task as well as the more complex 5 choice serial reaction time task (Granon et al. 2000; Parker et al. 2013). These studies indicate that in addition to D1 blockade induced deficits in working memory, these treatments may impair timing,

attention and task engagement. Furthermore, the effect on response latency serves as a positive control or manipulation check in lieu of a direct effect on choice. Thus, even though D1 receptor activity in the PL does not appear to influence the direction of choice in cue-guided risk/reward decision making, tone on these receptors can influence how rapidly these decisions are initiated.

Prelimbic D2 receptor blockade

D2 blockade in the prelimbic mPFC reduced choice of the large/risky option selectively on trials where the odds were advantageous, an effect similar to that observed following inactivation of this region (van Holstein & Floresco, 2020). Superficially, this effect could be interpreted simply as a deficit in the ability to use arbitrary cues to guide behavior. However, this is unlikely as PL inactivation had no effect in an auditory conditional discrimination task, wherein rats were instructed by the same auditory cues to select a left or right lever to obtain reward delivered in a deterministic manner (van Holstein and Floresco 2020). Furthermore, auditory discrimination performance elicited no detectable change in cortical dopamine efflux as measured with microdialysis and administration of the D1/D2 antagonist α-flupenthixol had no effect on auditory discrimination performance (Dunn and Killcross 2007; George, Jenkins, and Killcross 2011). Finally, a pure impairment in auditory conditional discrimination would be expected to affect performance on good and poor odds trials as was seen following inactivation of the nucleus accumbens core after which rats adopted random response patterns on the Blackjack task and an auditory conditional discrimination task (Floresco et al. 2018).

The effect of PL D2 blockade on choice was not accompanied by any change in sensitivity to reward or negative feedback. This lack of effect stands in contrasts to the effect of PL inactivation, which reduced risky choice *and* reward sensitivity on good-odds trials (van Holstein and Floresco 2020). This suggest that even though the PL may keep track of recent action

outcomes to influence choice during cue-guided risk/reward decision making, DA transmission does not appear to play a role in modulating these functions. However, additional analyses of how these treatments altered the propensity to shift responses following changes to the probability of large/risky reward showed marked treatment effects. Overall, D2 receptor blockade reduced the tendency to shift lever choice from trial to trial and increased the tendency to repeat choices on trials where the odds had changed from the previous trial. Lever shifts or stays can be advantageous or disadvantageous depending on the odds of the current trial and the response made on the previous trial. Accordingly, we also parsed out these shifts or stays by their utility. This more detailed analysis revealed that reducing D2 tone within the PL caused rats to make fewer advantageous shifts, but did not alter disadvantageous shifts (although the total number of these type of response at baseline or in any treatment condition was relatively low). Conversely, rats showed increases on advantageous *and* disadvantageous stays (i.e., repeating the same choice) following drug administration. When viewed collectively, it suggests that under these conditions, the alterations in choice on the Blackjack task induced by D2 receptor blockade was driven by a reduced ability to shift response selection upon changes in cued risk/reward probabilities. This notion is consistent with a well-established role of prefrontal dopamine D2 receptors in cognitive flexibility. PL D2 blockade impaired rats ability to shift between egocentric and cued response strategies in an operant set-shifting task and also impaired the ability to adapt to changing risk/reward contingencies in a probabilistic discounting task (Floresco et al. 2006; St Onge et al. 2011).

It is important to highlight that if the effect of PL D2 blockade on Blackjack performance results purely from an impairment in cognitive flexibility, it is unclear why effects on choice would only be observed on good-odds trials. Targeted analysis of lever-shifts and stays on poor-

to-good odds switch trials (which informs us about performance on good-odds trials) revealed a decrease in optimal shifts and an increase in suboptimal lever stays. In this context, optimal lever shifts are those from the small/certain to large/risky lever and suboptimal stays are repeated responses on the small/certain lever. Thus, the decrease in optimal shifts and increase in suboptimal stays on these trials will cumulatively result in more small/certain responses on good-odds trials - as is reflected in the choice data. On the other hand, examining shifts on good-to-poor odds-switch trials (which informs us about performance on poor-odds trials), showed that D2 blockade increased optimal stays, though notably, there is still a sizable reduction in optimal shifts though it does not achieve statistical significance at an adjusted alpha of 0.0125. Optimal stays on these good-to-poor odds switch trials are repeated choices of the small/certain lever and optimal shifts are those from the large/risky to small/certain option. Thus, a qualitative increase in optimal stays and a decrease in optimal lever-shifts would have opposing effects on choice of the large/risky option such that no overall change is observed on choice of the large/risky lever, despite the marked changes on the propensity to shift to or stay on a lever following D2 blockade. Cumulatively, what these results suggest is that PL D2 blockade reduced the tendency of animals to make optimal lever-shifts regardless of the type of switch or trial odds (small/certain → large/risky when odds switch from poor → good; large/risky → small/certain when the odds switch from good → poor). However, rats are more likely following D2 blockade to make consecutive responses on the small/safe option on odds switch trials regardless of if this is optimal (on good → poor odds switch trials) or suboptimal (on poor → good odds switch trials). Thus, D2 receptor activation in the PL mPFC promotes lever-switches in general and inhibits repeated responses made on the small/safe option.

When taking these additional observations into account, this pattern of effects could suggest that in addition to causing deficits in flexibility, PL blockade could induce heightened risk aversion. This is partially supported by several studies showing that systemic administration of a D2/D3 agonist reverses stress induced risk aversion (Morgado et al. 2015), systemic administration of a D2 antagonist improved RGT performance (shifting choice towards less risky options) (Zeeb et al. 2009), and D2 mRNA expression in the mPFC predicted risk preference in a punished risky decision making task (Simon et al. 2011). However, intracranial administration of the D2 antagonist eticlopride in the PL mPFC at the same doses used in the present study had no effect on risky choice in the RGT (Zeeb et al. 2015) and *increased* choice of the large/risky lever in the probabilistic discounting task when the odds of getting a large/risky reward transition from high to low over the course of the session (Jenni, Larkin, and Floresco 2017; St Onge et al. 2011). Thus, unlike their role in other forms of risk-reward decision making, PL D2 receptor activity appears to aid in biasing choice towards larger risky options when the external cues signal that odds of obtaining larger rewards are relatively high.

This effect of PL D2 receptor blockade may also reflect a disruption of top down regulation of subcortical regions that promote choice of the large/risky lever. Previous work shows that PL D2 receptors serve to modulate a neuronal ensemble that interfaces with the basolateral amygdala (BLA) to facilitate flexible decision making (Jenni et al. 2017; St Onge et al. 2011). In this regard, inactivation of the BLA produces similar decreases in good odds risky choice on the Blackjack as that observed following PL D2 receptor blockade (van Holstein and Floresco 2020; van Holstein, MacLeod, and Floresco 2020). Therefore, it is possible that D2 receptors play modulatory roles in the descending cortico-amygdala pathway that promotes choice of the large/risky option. It follows that cortical D2 receptor blockade may have induced perturbations

in top-down signaling from the PL to the BLA, lessened bias towards the large/risky option and increased repeated choices of the small/certain option.

Infralimbic D1 and D2 Receptor Blockade

In contrast to the effects of DA receptor blockade in the PL mPFC, we did not observe any effects of either D1 or D2 receptor blockade specifically within the IL mPFC. However, there are certain caveats to take into account when interpreting these null effects. First, the IL D2 blockade group had a smaller sample size than all other groups (n=8) and even fewer good players (n=6). Furthermore, an ANOVA of all rats in the D2 antagonist group with PL, IL or PL/IL border cannula placements revealed qualitatively identical choice affects compared to the analyses of the data obtained from just animals with PL placements. Finally, a linear regression using the dorsal/ventral and anterior/posterior cannula coordinates as predictors revealed no effect of cannula coordinate along either axis on the magnitude of D2 antagonist drug effects.

These caveats aside, evidence for IL dopaminergic contributions specifically to risk/reward decision making is sparse compared to the numerous studies examining DA function within the PL and many studies that collapse analysis of these two regions. Among these few studies, IL D2 blockade had no effect on RGT overall choice performance although it did reduce the number of perseverative choices (Zeeb et al. 2015). It is important to emphasize that IL inactivation in rats performing the Blackjack task *increased* risky choice on poor odds trials – the diametrically opposed effect from PL inactivation (van Holstein and Floresco 2020). Yet, the present results suggest that the role of the IL mPFC in suppressing disadvantageous risky choice during cue-guided decision making is dopamine independent.

Theoretical Role of Prefrontal Dopamine in Risk Reward Decision Making

Seamans and Yang (2004) outlined an influential theory for the principle mechanisms of dopaminergic modulation of prefrontal network activity and working memory. In this model, based on behavioral pharmacology, electrophysiology and computational modeling, they propose prefrontal networks alternate between two states: in State 1, neurons exhibit low spontaneous activity levels and in State 2 neurons exhibit stimulus evoked, sustained high activity levels. State 1 is theorized to allow for flexible - although unstable - representation of multiple items during working memory updating or strategy switching whereas State 2 facilitates a single enduring representation in working memory. When the ratio of D1 to D2 receptor activation is high, State 2 is dominant, whereas, when the ratio of D1 to D2 receptor activation is low, the prefrontal network shifts into state 1 (Seamans and Yang 2004).

With this in mind, how does cortical dopamine interact with risk-reward decision making? We know that cortical dopamine levels (as measured by microdialysis) reflect the probability of reward following choice of the large/risky lever in rats performing the probabilistic discounting task and reward yoked controls – suggesting that cortical dopamine levels track relative reward rates on slow timescales (St. Onge et al. 2012). The fact that tonic dopamine tracks reward rate has been interpreted as a mechanism to signal the utility of a given choice strategy (St. Onge et al. 2012). Initially, high reward rates in the high probability blocks increase dopamine levels and stabilize choice strategy via action on D1 receptors whereas declining reward rates (and therefore declining extra synaptic dopamine) during latter blocks destabilize the network and allow for shifts in response strategy. Cortical D1 antagonism decreases choice of the large/risky option during probabilistic discounting. Furthermore, associated changes in feedback sensitivity suggest that D1 receptors guide action selection by

supporting the effect of reinforcements and suppressing shifts in choice direction after reward omission (St Onge et al. 2011). This is perhaps due to the slow decay of dopamine in the extra synaptic space (and thus prolonged D1 receptor activation) that stabilizes the prefrontal network and allows animals to persist in a behavioral strategy in the absence of temporally proximal reward. Conversely, D2 blockade in this task impairs adjustments to changing reward contingencies such that rats choose the large/risky option more when the odds decrease over a session and less when they increase (Jenni et al. 2017; St Onge et al. 2011). This effect is parsimoniously explained by the inability of the cortical network to transition into the more labile State 1 in the absence of D2 activation. In the RGT, neither D1 or cortical D2 receptors seem to be critical for normal choice performance (Zeeb et al. 2015, 2009). This is perhaps due to the fact that reward contingencies in this task are well learned and stable – mitigating a strong requirement for maintenance of reward representations in working memory or the flexible switching between choice strategies. In the Blackjack task, reward contingencies change on fast timescales but are signaled by external cues. This means that, like the RGT, there is a low requirement for the active maintenance of reward representations as they can be observed from the environment through learned associations. Furthermore, slowly changing tonic dopamine levels (on the scale of minutes) during the task do not signal meaningful information about reward probabilities as the task contingencies change every 40 seconds. These observations are in line with the lack of effect of D1 antagonism on choice performance. However, flexible switches to response strategy are highly advantageous in the Blackjack task which is in line with the finding that D2 antagonism in PL (which likely blocks transition to prefrontal State 1) reduces optimal choice behavior on good-odds trials and decreases the propensity to switch response strategy following changes to the odds of reward.

Implications for Human Research and Biological Psychiatry

The ability to integrate risk/reward information from external cues allows us to make adaptive decisions. Dysfunction in reward associated cue processing is a hallmark of substance and behavioral addictions. Thus, understanding how reward probability predictive cues are processed in healthy individuals and laboratory animals can lend insight into the systems that may be dysfunctional in those suffering from disordered decision making. PET and fMRI imaging studies have consistently shown abnormalities in cortical metabolism and D2 receptor function in individuals with substance use disorders (Volkow et al. 2002). Furthermore, reductions in cortical D2 receptors in detoxified cocaine and methamphetamine abusers correlated with reductions in OFC and AC glucose metabolism and, furthermore, cocaine dependent individuals show blunted amphetamine induced cortical dopamine release (Narendran et al. 2020; Volkow et al. 2002). Conversely, in active cocaine users, cortical metabolism is increased and correlates with intensity of craving (Volkow et al. 2002). Similar PET studies in Parkinson's disease patients taking dopamine agonists to combat motor symptoms showed that patients with problem gambling behavior had lower dopaminergic tone in the AC and that D2/D3 receptor binding in this region correlated with trait impulsivity (Ray et al. 2012). In non-Parkinsonian patients with gambling disorders, delay discounting associated activation of the right inferior frontal cortex correlated with greater tolcapone mediated reductions in delay discounting behavior and tolcapone administration increased cortico-striatal connectivity (Kayser et al. 2017). Finally, a genetic study of over 200 patients with varying degrees of problem gambling showed that individuals with the val/val COMT genotype (and presumably increased cortical dopamine metabolism) had the highest rates of pathological gambling and worse performance on the CGT (specifically, impaired risk adjustment to varying probabilities of

reward) (Grant et al. 2015). Collectively, these results implicate cortical D2 receptor function in substance and behavioral addiction and cue-guided decision making in humans. The findings presented in this thesis establishes a causal association between cortical D2 receptor function and the ability to adjust risk preference to varying probabilities of reward in a cue-guided setting. This provides further motivation to study the mesocortical dopamine system in the context of addiction and the therapeutic potential of drugs that target cortical dopamine levels (namely COMT inhibitors) in the treatment of disorders of addiction.

Conclusion

Here we present evidence that D2 receptors in the PL mPFC (but not PL D1 receptors or IL D1 or D2 receptors) promote choice of risky options when external cues signal that the odds of reward are high. Furthermore, these receptors facilitate flexible adjustment of choice strategy to quickly changing reward contingencies. These findings are consistent with a role of cortical D2 receptors in mediating flexible updating of reward value representations within working memory. This work builds on a larger literature of prefrontal dopaminergic contributions to risk reward decision making and points towards prefrontal dopaminergic transmission as a potential target in the treatment of disorders of decision making.

Table 1

Summary of Omissions and Response Latencies. * denotes $p<0.05$ vs Saline.

Experiment	Saline	Low dose	High Dose
Prelimbic			
D1 (SCH-23390)			
Locomotion	1257 (114)	1361 (159)	965 (68)
Trial omissions	0.06 (0.06)	0.24 (0.14)	0.53 (0.26)
Response latency	0.55 (0.05)	0.60 (0.07)	0.74 (0.10) *
D2 (Eticlopride)			
Locomotion	1210 (156)	1310 (195)	1202 (165)
Trial omissions	0.06 (0.06)	0.06 (0.06)	0.18 (0.10)
Response latency	0.80 (0.11)	0.74 (0.11)	0.97 (0.15)
Infralimbic			
D1 (SCH-23390)			
Locomotion	903 (134)	763 (106)	795 (101)
Trial omissions	0.25 (0.13)	0.08 (0.08)	0 (0)
Response latency	0.66 (0.07)	0.63 (0.09)	0.69 (0.10)
D2 (Eticlopride)			
Locomotion	922 (130)	851 (169)	914 (159)
Trial omissions	0.13 (0.13)	0.38 (0.18)	0.63 (0.42)
Response Latency	0.71 (0.18)	0.76 (0.15)	0.66 (0.13)

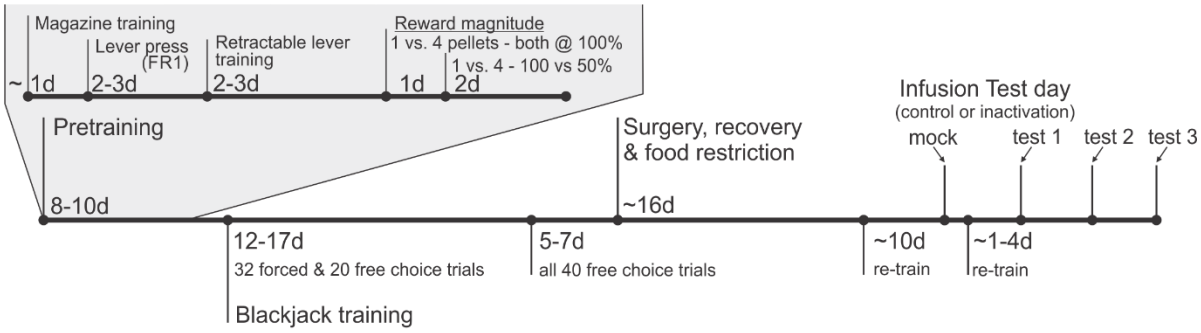
Table 2

Summary of Win Stay and Lose Shift Analysis by Trial Type for Prelimbic D2 blockade

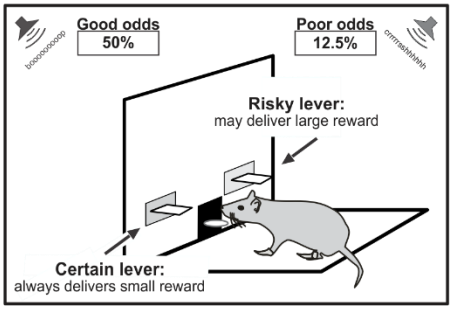
Feedback Type	Saline	Low dose	High Dose
Win-Stay Ratio (all trials)	0.51 (0.09)	0.47 (0.10)	0.55 (0.07)
Good Odds Trials	0.26 (0.04)	0.17 (0.04)	0.27 (0.03)
Poor Odds Trials	0.25 (0.06)	0.31 (0.07)	0.28 (0.07)
Lose-Shift Ratio (all trials)	0.54 (0.07)	0.56 (0.09)	0.54 (0.08)
Good Odds Trials	0.09 (0.02)	0.16 (0.06)	0.19 (0.06)
Poor Odds Trials	0.45 (0.07)	0.41 (0.09)	0.35 (0.08)

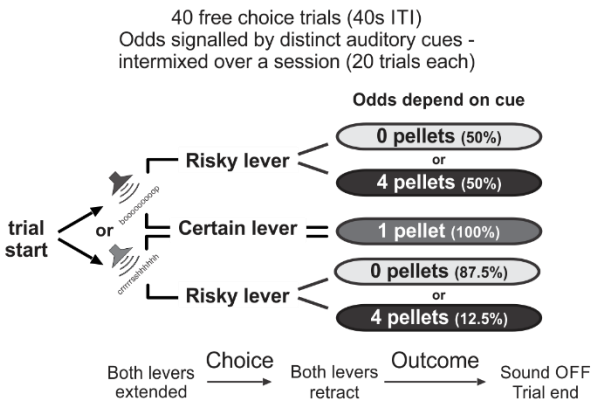
Fig 1: Experimental Design

A: Experiment Timeline

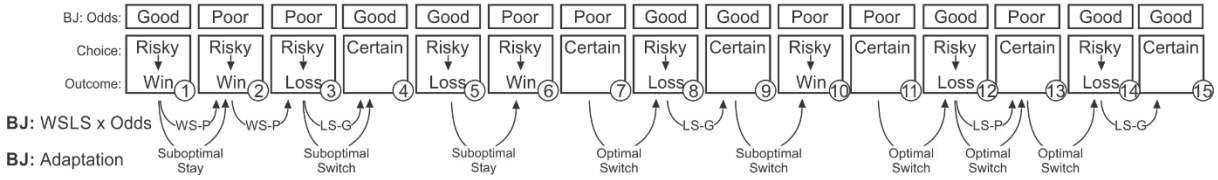


B: Trial Design



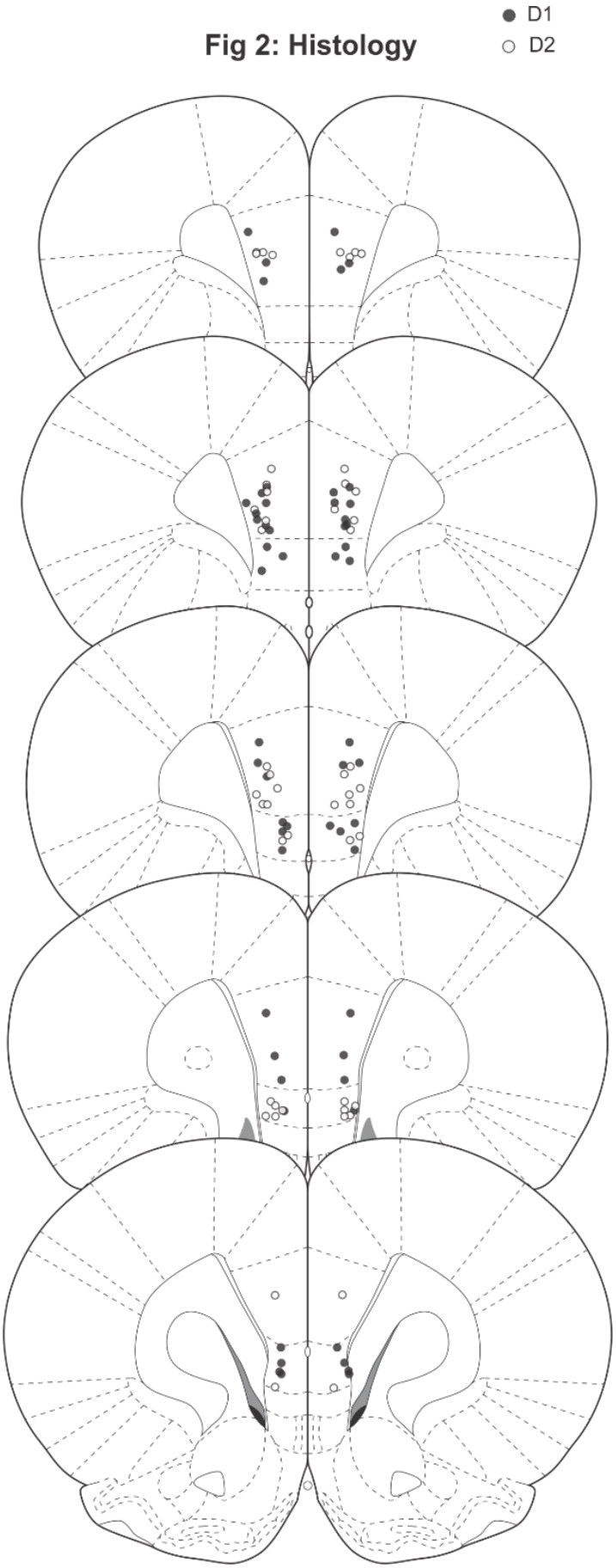


C: Switching and Feedback Sensitivity Analysis



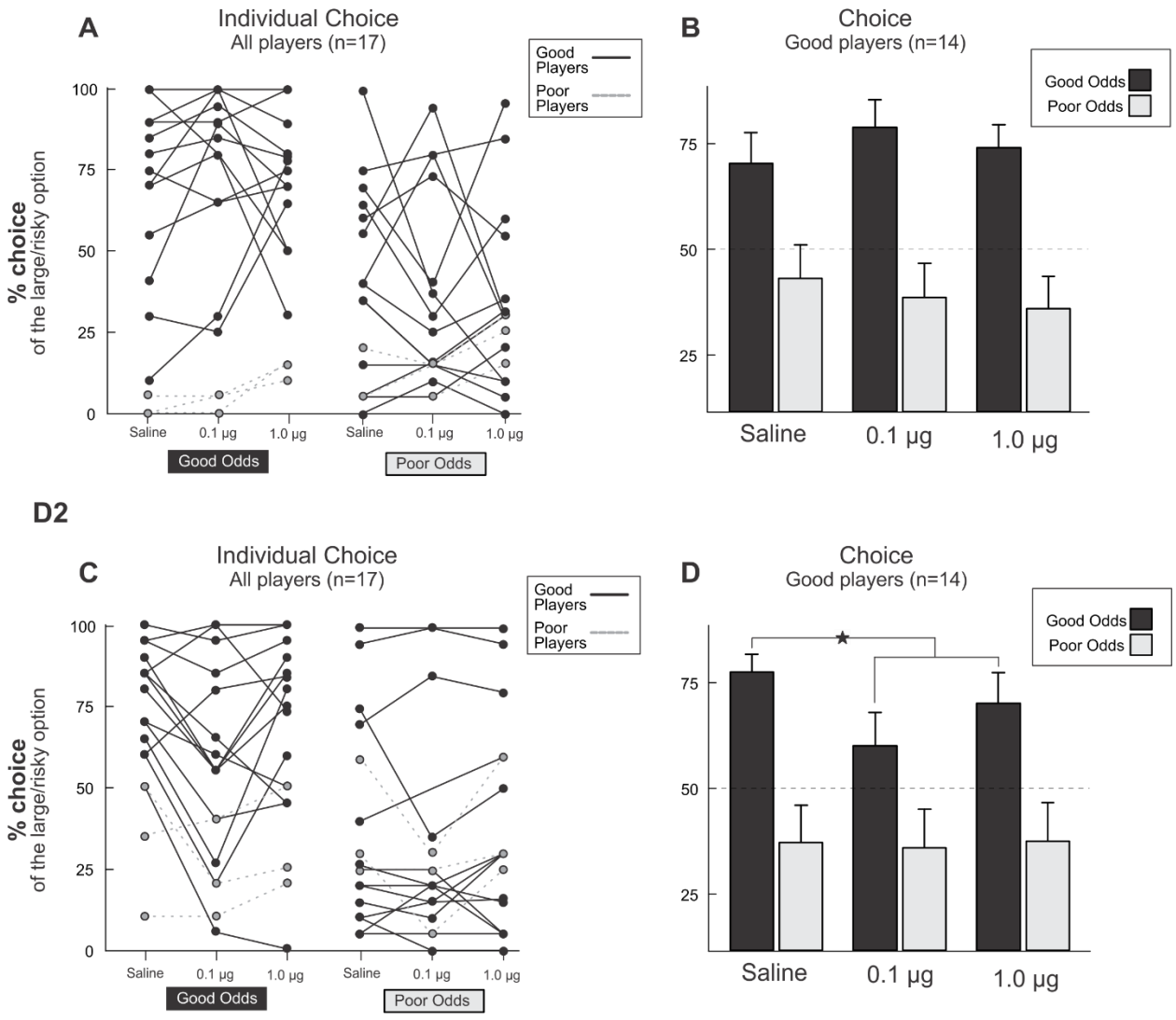
Timeline for behavioral training, surgery and testing (A), task design with cost/benefit contingencies associated with either lever on particular odds (B), and diagram of post-hoc analysis with the trial characteristics and rats performance shown in the boxes and the classification of the win-stay/ lose-shift or shift/stay behavior below (C).

Fig 2: Histology



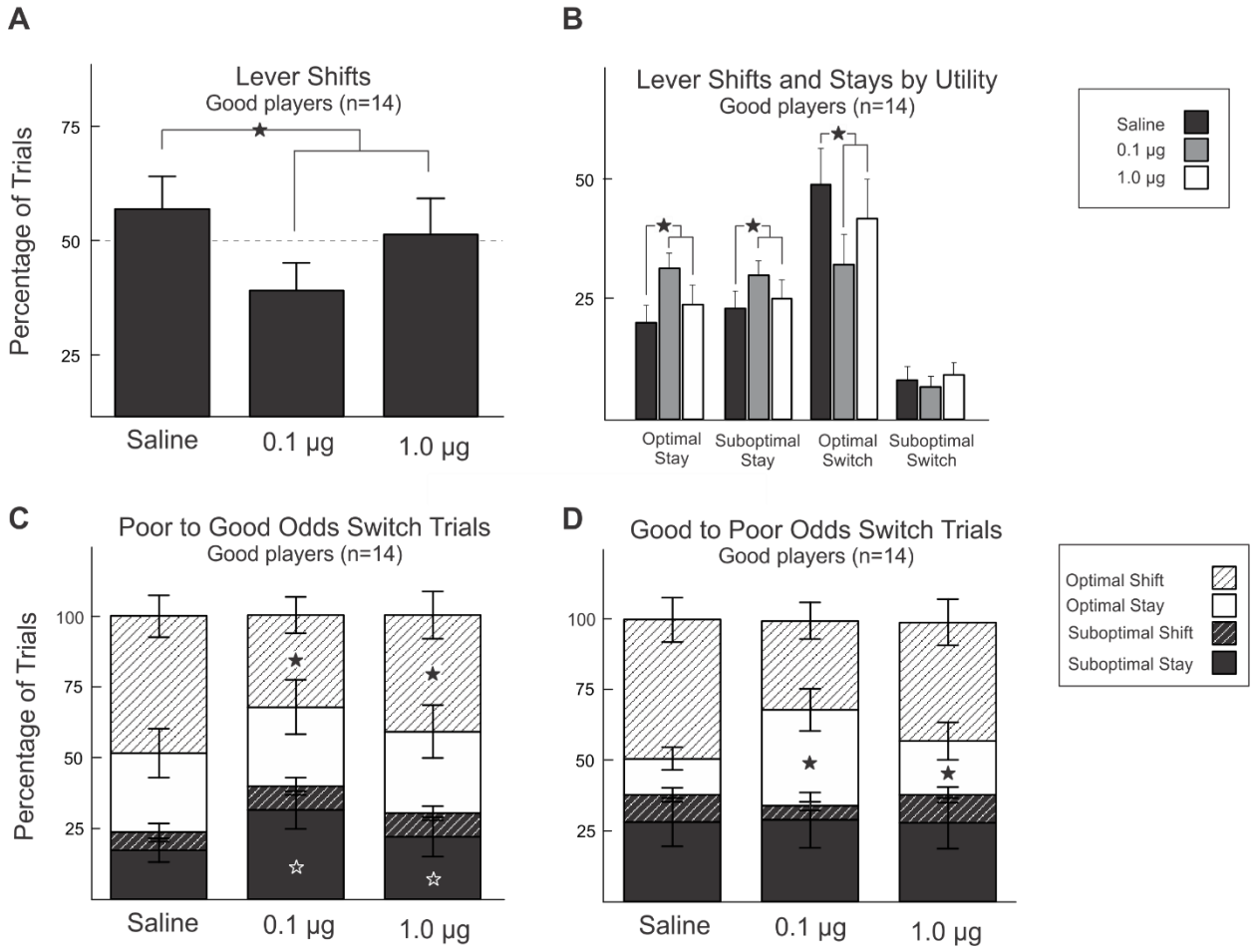
Schematic of coronal sections of the rat brain (Paxinos and Watson, 2005) showing all locations of acceptable infusions into the PL or IL mPFC. Rats receiving the D1 and D2 antagonist are shown in black and white, respectively.

D1 **Fig 3: Prelimbic D1 and D2 Blockade**



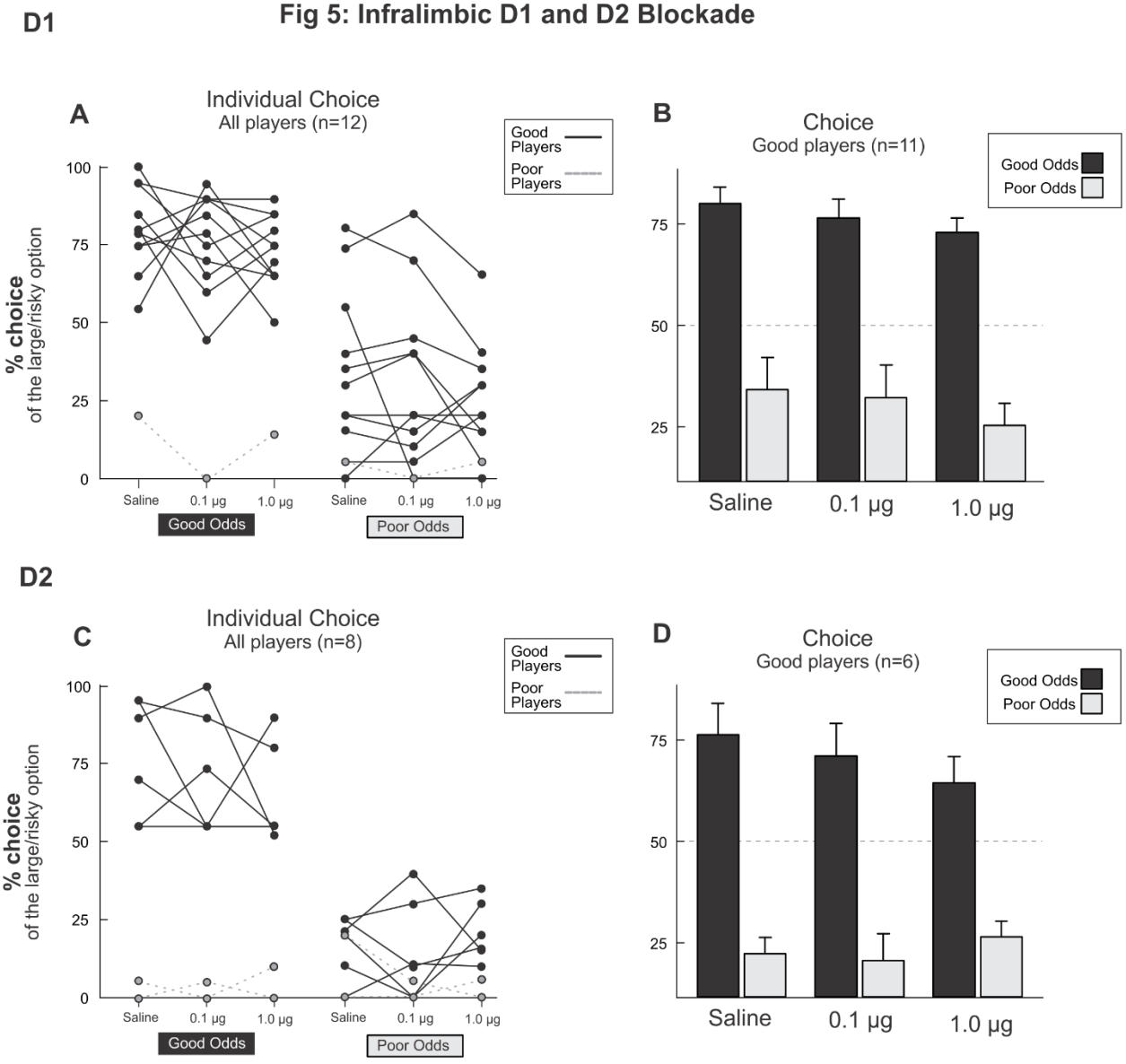
Individual choice data for all rats receiving the dopamine D1 antagonist into the PL mPFC. Dots of each line from left to right represent a rat's choice of the large/risky lever on saline, low dose and high dose test sessions. When data for good and poor players overlapped, the color of poor player dots was overplayed on that of good players (A). Mean percentage choice of the large/risky lever for just good players in the PL D1 group (B). Individual choice data for rats receiving the dopamine D2 antagonist into the PL mPFC (C). Mean percentage choice of the large risky lever for just good players in the PL D2 group (D).

Fig 4: Prelimbic D2 Blockade Lever Shift Analysis



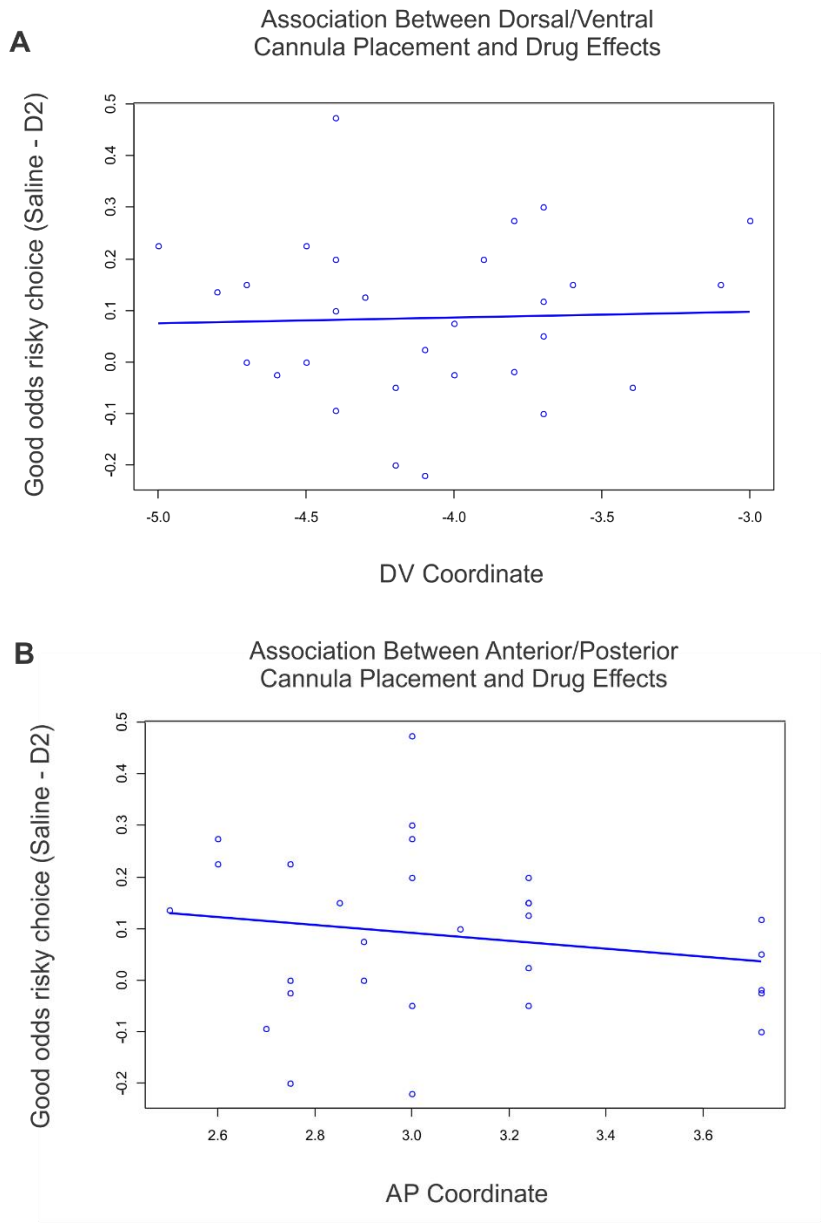
Mean percentage of all odds-switch trials in which rats made a lever-shift response (A). Mean percentage of all odds-switch trials in which rats made optimal or suboptimal stays and optimal or suboptimal shifts (B). Mean percentage of all odds-switch trials where the odds switch from poor to good in which rats made optimal or suboptimal stays and optimal or suboptimal shifts (note that the 4 response types add up to 100% of trials) (C). Mean percentage of all odds-switch trials where the odds switch from good to poor in which rats made optimal or suboptimal stays and optimal or suboptimal shifts (D).

Fig 5: Infralimbic D1 and D2 Blockade



Individual choice data for all rats receiving the dopamine D1 antagonist into the IL mPFC. Dots of each line from left to right represent a rat's choice of the large/risky lever on saline, low dose and high dose test sessions. When data for good and poor players overlapped, the color of poor player dots was overplayed on that of good players (A). Mean percentage choice of the large risky lever for just good players in the IL D1 group (B). Individual choice data for rats receiving the dopamine D2 antagonist into the IL mPFC (C). Mean percentage choice of the large risky lever for just good players in the IL D2 group (D).

Fig 6: Association Between Cannula Placement and Drug Effect



Scatter plot and associated regression line showing the difference in good odds choice of the large/risky lever on saline vs drug (average of low and high dose) test sessions vs their dorsal/ventral cannula coordinate (A). Scatter plot and associated regression line showing the difference in good odds choice of the large/risky lever on saline vs drug (average of low and high dose) test sessions vs their anterior/posterior cannula coordinate (B).

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