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Monoaminergic modulation of decision making under risk of punishment in a rat model

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Abstract

The ability to decide advantageously among options that vary in both their risks and rewards is critical for survival and well-being. Previous work shows that some forms of risky decision making are robustly modulated by monoamine signaling, but it is less clear how monoamine signaling modulates decision making under risk of explicit punishment. The goal of these experiments was to determine how this form of decision making is modulated by dopamine, serotonin, and norepinephrine signaling, using a task in which rats choose between small, “safe” food rewards and large food rewards associated with variable risks of punishment. Preference for the large, risky reward (risk taking) was reduced by administration of a D2/3 dopamine receptor agonist (bromocriptine) and a selective D2 agonist (sumanirole). The selective D3 agonist PD128907 appeared to attenuate reward discrimination abilities, but did not affect risk taking *per se*. In contrast, drugs targeting serotonergic and noradrenergic signaling had few if any effects on choice behavior. These data suggest that in contrast to other forms of risky decision making, decision making under risk of punishment is selectively modulated by dopamine signaling, predominantly through D2 receptors.

Keywords

risk taking; decision making; monoamine; dopamine; serotonin; norepinephrine; rat

Introduction:

Many of life’s decisions involve choices between options that vary in both the magnitude of possible benefits and the potential for adverse outcomes accompanying those benefits. The ability to choose adaptively when faced with such “risky” decisions is critical for financial, social, and medical well-being. Unfortunately, adaptive risky decision making can be

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impaired in a number of psychiatric and neurological conditions (Chandler et al. 2009, Ha et al. 2012, Guillaume et al. 2015, Koob 2015, Xi et al. 2015). For example, substance use disorders are characterized by an enhanced preference for rewards and a concomitant discounting of accompanying costs, leading to greater choice of risky options (Tomassini et al. 2012, Stout et al. 2004, 2005, Thompson et al. 2012). In contrast, anorexia nervosa is characterized by pathological risk aversion (Cavedini et al. 2004, Guillaume et al. 2015, Compan et al. 2015). Importantly, maladaptive risk taking in these conditions is evident in both laboratory and real world settings, suggesting that it could contribute to disease morbidity (Lejuez et al. 2002, 2003, Wallsten et al. 2005). Hence, it is important to investigate both the mechanisms of maladaptive risky decision making and potential strategies by which it can be optimized.

Research in both human and non-human animal subjects shows that risky decision making is robustly modulated by monoamine systems, including dopamine, serotonin, and norepinephrine. Across species, acute administration of amphetamine or methylphenidate, which enhance monoamine availability through interactions with monoamine transporters, can either increase or decrease preference for probabilistic vs. certain rewards, depending on task design and study population (St Onge and Floresco 2009, Zeeb et al. 2009, DeVito et al. 2008, Rogers 2011). Comparable results have been obtained with more selective pharmacological manipulations. For example, augmentation of dopamine availability in human subjects via administration of its precursor L-DOPA enhances preference for probabilistic over certain rewards with equivalent expected values (Rigoli et al. 2016). Administration of selective dopamine receptor agonists and antagonists has a range of effects on risky decision making, depending on both the receptor subtype and behavioral task employed (Di Ciano et al. 2015, St Onge and Floresco 2009, Barrus and Winstanley 2016, Rogers 2011, Zalocusky et al. 2016, Milienne-Petiot et al. 2017, Norbury et al. 2013, van Enkhuizen et al. 2013). Serotonin and norepinephrine signaling have been less well investigated than dopamine in the context of risky decision making. Systemic manipulation of serotonergic signaling via acute tryptophan depletion (which reduces brain serotonin levels), reuptake inhibitors, or direct agonists/antagonists has been shown to have a variety of effects on performance in risky decision making tasks, depending on the drug, task, and species studied (Adams et al. 2017b, Macoveanu et al. 2014, Macoveanu et al. 2013, Long et al. 2009, Zeeb et al. 2009). Finally, in the few studies in which it has been assessed, noradrenergic reuptake blockade or direct agonists/antagonists have been shown to shift rats' preference for certain vs. uncertain rewards (Yang et al. 2016, Montes et al. 2015).

Despite the extensive evidence for modulatory actions of all three major monoamine systems on risky decision making, much of it comes from laboratory tasks in which subjects choose between certain and uncertain rewards, which are often equivalent in expected value, and in the absence of truly adverse outcomes. In contrast, "risk" as colloquially defined usually refers to a potential for consequential loss or harm; indeed, the Oxford English Dictionary (2018) defines risk as "the possibility that something unpleasant or unwelcome will happen". To model decision making in which the "risk" involves the potential for truly adverse outcomes (i.e., punishment), our laboratory developed a "risky decision-making task" in which rats make discrete-trial choices between a small, "safe" food reward and a large food reward accompanied by varying probabilities of mild footshock (Simon et al.

2009). Using this task, we found that acute amphetamine administration robustly and dose-dependently decreases risk-taking behavior (i.e., shifts rats' choices away from the large, risky reward toward the small safe reward) in a manner that is not easily accounted for by effects of the drug on reward motivation or cognitive flexibility (Simon et al. 2009, Orsini et al. 2016, 2018). Additional experiments showed that the effects of amphetamine are partially attenuated by co-administration of a dopamine D2/3 (but not D1) receptor antagonist, and mimicked by administration of a D2/3 (but not D1) agonist, suggesting that actions at D2/3 receptors are at least in part responsible for the effects of amphetamine on risk taking behavior (Simon et al. 2011).

In light of these data, there were two main goals of the current experiments, both of which were addressed using a systemic behavioral pharmacological approach. The first was to build on our previous work to evaluate the specific roles of D2 vs. D3 receptor signaling in decision making under risk of punishment. The second was to begin to evaluate the role of serotonin and norepinephrine signaling in this form of decision making. It is important to note that although all three monoamine systems have been previously (and in some cases extensively) evaluated in other rodent risky decision making contexts (St Onge and Floresco 2009, Baarendse et al. 2013, Zeeb et al. 2009, Adams et al. 2017a, Homberg et al. 2008, Ishii et al. 2015, Montes et al. 2015), the effects of both behavioral pharmacological and neurobiological manipulations can differ substantially depending on the type of risky outcome (e.g., probability of reward omission vs. probability of punishment). Thus, a thorough evaluation of the latter is important for determining optimal strategies for normalizing risk-taking behavior (Orsini et al. 2015, Anselme 2015).

Methods:

Subjects:

Male Long-Evans rats ($n = 125$; 275–300 g upon arrival from Charles River Laboratories, Raleigh, NC) were individually housed and maintained on a 12 hour light/dark cycle (lights on at 08.00 h) with free access to food and water except as noted. Rats were maintained at 85% of their free-feeding weight during behavioral testing, with target weights adjusted upward by 5 g every week to account for growth. All behavioral testing was performed during the light cycle. All procedures were conducted in accordance with the Institutional Animal Care and Use Committees of Texas A&M University or University of Florida, and followed NIH guidelines.

Apparatus:

Rats were tested in operant chambers housed in sound attenuating cabinets (Coulbourn Instruments). Each cabinet was fitted with a 1.12 W house light mounted on the interior back wall. The operant chambers contained a food pellet delivery trough that was located 2 cm above the floor on the front wall. The trough contained a photobeam that detected nose pokes and a 1.12 W light bulb for illumination. Each operant chamber also contained two retractable levers located 11 cm above the floor on either side of the trough. The floor of the operant chamber was made of stainless steel rods that were connected to a scrambled shock generator (Coulbourn Instruments). An activity monitor was mounted on the ceiling of the

chamber to detect locomotor activity through the use of an array of infrared detectors. The operant chambers were interfaced with a computer running Graphic State 3 or 4 software (Coulbourn Instruments) for experiment control and data collection.

Shaping:

Rats underwent several stages of shaping prior to the start of testing in the risky decision making task. Each shaping stage began on the day after rats reached criterion on the previous stage. Prior to the first shaping session, rats received 5 of the food pellets used to reward task performance in their home cage, in order to reduce food neophobia. Shaping began with magazine training, during which 45 mg food pellets (either grain-based or soy free, obtained from TestDiet; 5TUM and 5TUL, respectively) were dispensed every 100 +/- 40 sec into the food-pellet delivery trough during a 64 min session. In order to progress to the next shaping phase, rats were required to meet a criterion of 100 nose pokes into the food trough during a session. Once this criterion was met, rats were trained in sessions in which one lever (either left or right, randomized across rats) was extended into the operant chamber while the other stayed retracted. During these sessions, rats received a food pellet each time the lever was pressed (FR1 schedule). The rats had to meet a criterion of 50 lever presses in a 30 min session in order to move on to the next stage, in which the opposite lever was presented (but the procedures were otherwise identical). Once rats learned to reliably press both levers, they were trained on a protocol that required them to nosepoke into the trough upon illumination of the trough light. A nosepoke extinguished the light and caused one lever (left or right) to extend into the chamber. A press on this lever resulted in food pellet delivery and extinguished the house light. Criterion in this final stage was a minimum of 30 lever presses on each lever in a 60 min session.

Risky decision making task:

After shaping was complete, rats proceeded to testing in the risky decision-making task (Simon et al. 2009, 2011). Each test session was 60 min in duration and consisted of five blocks of 18 trials each. Each 40 s trial started with illumination of the house and food trough lights. A nosepoke into the food trough extinguished the trough light and triggered extension of either a single lever (on forced choice trials) or both levers simultaneously (on free choice trials). If rats failed to nosepoke within 10 s, both lights were extinguished and the trial was counted as an omission. A press on one lever always resulted in delivery of a small food reward (1 pellet; small "safe" reward), whereas a press on the other lever always resulted in delivery of a large food reward (two food pellets in Experiments 1 and 3, and three food pellets in Experiment 2; prior work from our lab indicates that the number of pellets composing the large reward does not influence choice behavior (Shimp et al. 2015)). The large reward was accompanied by a possible footshock (1 s, 0.20–0.55 mA). The probability of footshock was set at 0% in the first block and increased across the five successive blocks of trials (25, 50, 75, and 100%). The large food reward was delivered upon every choice of the risky lever, regardless of shock delivery. The association of reward type (small safe or large risky) with the position of the lever (left or right) was randomized across rats, but for each rat the association of reward type and lever position remained the same throughout testing. Each block of trials began with eight forced choice trials (only one lever present) in which the punishment contingencies in effect for that block were established (4

presentations of each lever, randomly presented). Forced choice trials were followed by 10 free choice trials, in which rats were free to choose between both levers. If rats did not press a lever within 10 s, the levers were retracted and the lights extinguished, and the trial was scored as an omission. Food delivery was accompanied by re-illumination of the house light and food trough light, which were then extinguished after rats retrieved the food pellets. On the forced choice trials, the probability of shock following a press on the large reward lever was dependent across the four trials in each block [i.e., in the 25% risk block, one and only one of the four forced choice trials (randomly selected) always resulted in shock, and in the 75% risk block, three and only three of the four forced choice trials always resulted in shock]. In contrast, the probability of shock on the free choice trials was independent of other trials in that block, such that the shock probability on each trial was the same irrespective of shocks delivered on previous trials in that block. For rats in Experiments 1 (dopamine) and 3 (norepinephrine), the shock intensities were adjusted individually for each rat to attempt to maintain their performance roughly in the center of the parametric space. For rats in Experiment 2 (serotonin), shock intensities were adjusted identically for the whole cohort of rats, again to attempt to maintain performance roughly in the center of the parametric space. Rats were trained on the task until stable performance was achieved (see Data Analysis below; (Simon et al. 2009, 2011)).

Drug administration:

For all experiments, drug administration (always at a volume of 1.0 ml/kg) was performed using a randomized, within-subjects design such that each rat received each dose of the drug and vehicle, with at least a 48 h washout period between successive administrations (Table 1). In cohorts of rats that were tested with more than one drug, rats were retrained until stable performance was achieved (at least 1 week between drugs). The drugs and dose ranges used were selected from previously-published studies in which they were behaviorally active in tasks with comparable physical and cognitive demands (in the absence of significant effects on locomotion or motivation). See Table 1 for a full list of drugs and doses.

Experiment 1 (dopamine): All drugs were administered i.p. except L-741,626 which was administered s.c. Rats were tested in 3 cohorts of $n = 16$ each. Cohort 1 ($n = 16$) received bromocriptine (D2/3 dopamine receptor agonist; Tocris Bioscience), which was prepared in 50:50 DMSO and 0.9% saline. Cohort 2 ($n=16$) received PD128907 (selective D3 receptor agonist; Tocris Bioscience), which was prepared in 0.9% saline. Cohort 3 ($n=16$) received L-741,626 (selective D2 receptor antagonist), SB-77011-A (selective D3 receptor antagonist) and sumanirole (selective D2 receptor agonist). L-741,626 (Sigma-Aldrich) was prepared in 51.67% DMSO and 48.33% saline. SB-77011-A (Tocris Bioscience) was prepared in 50:50 DMSO and 0.9% saline. Sumanirole (Sigma-Aldrich) was prepared in 0.9% saline. The drug doses and timing of injections prior to testing were based on previous studies that used these drugs in comparable behavioral tasks (Fernando et al., 2011; Koffarnus et al., 2011; Simon et al., 2011; St Onge and Floresco 2009)..

Experiment 2 (serotonin): Rats were tested in 2 cohorts. With the exception of WAY 100635, which was administered subcutaneously, all drugs targeting the serotonergic system

were injected i.p.. Cohort 1 (n = 16) received citalopram hydrobromide (selective serotonin reuptake inhibitor), M100907 (5-HT_{2A} receptor antagonist), and SB242,084 (5-HT_{2C} receptor antagonist). Citalopram (Tocris Bioscience) was prepared in 0.9% saline. M100907 (Sigma Aldrich) was prepared in 0.9% saline with the pH adjusted to 6.5 with acetic acid. The vehicle for SB 242,084 (Tocris Bioscience) consisted of 240 mg of anhydrous citric acid and 4 g of cyclodextrine dissolved in 50 mL of 0.9% saline to yield an 8% cyclodextrin in 25 mM citric acid solution. The pH of this solution was then adjusted to 6.4 by adding 5 mL of 0.1 M NaOH. Cohort 2 (n = 18) received WAY-100635 (5-HT_{1A} receptor antagonist) followed by 8-OH-DPAT (5-HT_{1A} receptor agonist). WAY-100635 (Sigma Aldrich) was prepared in phosphate-buffered saline (PBS). 8-OH-DPAT (Sigma Aldrich) was prepared in 0.9% saline. The drug doses and timing of injections prior to testing were based on previous studies that used these drugs in comparable behavioral tests (Winstanley et al. 2004); (Bari et al. 2009); (Boulougouris, Glennon and Robbins 2008, Zeeb et al. 2009).

Experiment 3 (norepinephrine)—A single cohort of rats (n = 11) was used to test the effects of atomoxetine (selective norepinephrine reuptake inhibitor). Atomoxetine (Tocris Bioscience) was prepared in 50:50 DMSO and 0.9% saline and administered i.p. (Baarendse et al. 2013).

Data analysis:

Data files were either exported from Graphic State 3 and organized using a custom macro written for Microsoft Excel (Dr. Jonathan Lifshitz, University of Kentucky) or the raw data files were analyzed using a custom analysis template within Graphic State 4. Statistical analyses were performed using SPSS 24. The primary measure of analysis was the percentage of free choice trials in each block on which rats chose the large, risky reward. Stable performance on the task was assessed using a repeated-measures ANOVA (session X trial block) on data from 3 consecutive sessions. Stability was defined by the absence of both a main effect of session and session X trial block interaction, as well as the presence of a main effect of trial block. Drug effects were assessed using a repeated-measures ANOVA, with both drug dose and trial block as within-subjects variables. If this parent ANOVA revealed a significant main effect of dose and/or a significant dose X trial block interaction, additional repeated-measures ANOVAs were used to compare individual doses with vehicle. To determine whether drug effects were dependent on baseline choice performance, a median split was performed based on choice behavior under vehicle conditions for each drug. High risk-taking rats were those with a mean percent choice of the large, risky reward above the median, and low risk-taking rats were those with a mean percent choice of the large, risky reward below the median. Drug effects were then analyzed using a repeated measures ANOVA within each risk-taking group. Latencies to press each lever during the forced choice trials were calculated as the time between the nosepoke to initiate a trial and the subsequent lever press (excluding omitted trials). These latencies were analyzed using a three factor repeated-measures ANOVA, in which lever identity, dose, and trial block were within-subjects factors. Locomotor activity was assessed using a repeated measures ANOVA on the average activity across all intertrial intervals (i.e., in the absence of lights or levers). Shock reactivity was assessed as locomotor activity during the 1 s shock delivery periods, averaged across the test session and compared across drug doses using a repeated measures

ANOVA. This measure has been shown previously to be sensitive to pharmacological manipulation (Orsini et al. 2016). Trial omissions were compared across drug doses using a repeated-measures ANOVA. In the case of significant drug effects on omissions, the omissions were divided into failures to nosepoke and failures to lever press (after nosepoking). Each omission type was then analyzed using a repeated-measures ANOVA. For all statistical comparisons, p values equal to or less than 0.05 were considered significant. For post hoc comparisons, a Bonferroni correction was applied to control for multiple comparisons. Using this correction all p values equal or less than 0.02 were considered significant. Non-significant results are depicted in Tables 2.1, 2.2, and 2.3.

Results:

Experiment 1:

Dopaminergic modulation of risky decision-making

Cohort 1 (n = 16)

Bromocriptine: The D2/D3 dopamine receptor agonist bromocriptine was administered to replicate previous findings from our lab (Simon et al. 2011). Analyses of choice behavior revealed that bromocriptine significantly reduced choice of the large, risky reward [decreased risky choice; main effect of dose: $F(3, 36) = 8.54, p < 0.01$], particularly at higher probabilities of punishment [dose X trial block interaction: $F(12, 144) = 2.05, p = 0.02$] (Figure 1A). Follow-up comparisons between vehicle and each dose condition separately revealed that this effect was evident at the medium [dose: $F(1, 14) = 11.72, p < 0.01$] and the high [dose: $F(1, 12) = 16.43, p < 0.01$] doses, but not at the low dose. When rats were split into high and low risk-taking groups, analyses revealed that bromocriptine decreased choice of the large, risky reward in high risk-taking rats [dose: $F(3, 27) = 10.81, p < 0.01$; dose x trial block: $F(12, 108) = 2.26, p < 0.01$] but not in low risk-taking rats (Table 3). Post hoc comparisons showed bromocriptine caused a significant decrease in choice of the large, risky reward in the high risk-taking group at the medium [dose: $F(1, 7) = 15.86, p < 0.01$; dose x trial block: $F(4, 28) = 9.10, p < 0.01$] and high [dose: $F(1, 7) = 13.97, p < 0.01$] doses but not the low dose. Analyses of latencies to press levers during forced-choice trials revealed a significant main effect of dose [$F(3, 45) = 4.51, p < 0.01$], although there were no significant interactions between dose and lever identity, dose and trial block or dose, lever identity and trial block. Post-hoc analyses showed that there were no significant differences between vehicle and the low or medium doses. The high dose of bromocriptine, however, increased latencies to press the small, safe lever relative to vehicle [dose: $F(1, 15) = 9.66, p < 0.01$]. Mean lever-press latencies for each dose are displayed in Table 4. Finally, there was a significant main effect of trial block as well as a lever X trial block interaction on response latencies for bromocriptine as well as for the other dopaminergic drugs. Because these effects were not related to drug administration, however, these statistics will not be reported further.

In addition to the effects described above, there was a significant main effect of drug dose on locomotor activity [$F(3, 45) = 3.45, p < 0.02$] whereby both the low [$t(15) = 4.84, p < 0.01$] and high dose [$t(15) = 3.06, p < 0.01$] decreased locomotor activity during the task. Bromocriptine had no effect on shock reactivity but did cause an increase in the number of

omissions on free choice trials [$F(3, 45) = 6.88, p < 0.01$]. Follow up tests showed that the medium and high doses of bromocriptine increased omissions relative to vehicle [medium: $t(15) = -4.55, p < 0.01$ high: $t(15) = -3.49, p < 0.01$]. Omissions were further divided into failures to nose poke and failures to lever press after nose poking. Bromocriptine increased lever -press omissions [$F(3, 45) = 6.01, p < 0.01$] but had no effect on nose-poke omissions. Further post hoc analysis revealed that bromocriptine caused a significant increase in failures to lever press at the medium [$t(15) = -2.69, p < 0.02$] and high [$t(15) = -2.83, p < 0.01$] doses but not the low dose. Locomotor activity, shock reactivity and omissions data for bromocriptine as well as all other drugs are displayed in Table 5. Considered together, these data suggest that activation of D2/D3 receptors decreases risky choice by shifting rats' preference toward the small, safe reward.

Cohort 2 (n = 16)

PD128907: To determine whether the effects of bromocriptine are specifically mediated through D3 receptors, rats were tested in the task with the selective D3 receptor agonist PD128907. Analyses of choice performance revealed a significant main effect of dose [$F(3, 45) = 4.25, p = 0.01$] but no significant dose X trial block interaction (Figure 1B). Follow-up comparisons between vehicle and each dose condition separately showed that choice of the large, risky reward was reduced by the high dose [$F(1, 15) = 9.56, p = 0.01$] but not by the medium or low doses. Given that the magnitude of the reduction in choice of the large, risky reward was equivalent across all probabilities of punishment (particularly in the first block of trials when there was no possibility of punishment), these results suggest that PD128907 impaired rats' ability to discriminate between the large and small reward, or otherwise reduced preference for the large reward. When rats were split into high risk-taking and low risk-taking groups, PD128907 had no effect on low risk-taking rats. In high risk-taking rats, although there was a significant main effect of dose [$F(3, 21) = 6.27, p < 0.01$, Table 3] in decreasing choice of the large, risky reward, there was no significant dose x trial block interaction. Post hoc comparisons revealed that PD128907 decreased choice of the large, risky reward in high risk-taking rats at the high dose [dose: $F(1, 7) = 8.46, p < 0.02$] but not the other doses. These data suggest that PD128907 is more effective in impairing reward discrimination in rats that prefer the large, risky option. In addition to its effects on choice performance, PD128907 increased latencies to press both levers [dose: $F(3, 45) = 8.48, p < 0.01$; dose X lever identity X trial block: $F(12, 180) = 1.90, p < 0.05$; Table 4]. Follow-up comparisons showed that this effect was only evident at the high dose [dose: $F(1, 15) = 16.36, p < 0.01$] but not at the medium or low dose. PD128907 also decreased locomotor activity [$F(3, 45) = 3.09, p < 0.05$] but post hoc analyses revealed no significant difference between vehicle or any of the doses individually. Finally, PD128907 had no significant effect on shock reactivity or free choice trial omissions (Table 5). Collectively, these data suggest that, rather than risky choice *per se*, D3 receptor activity is involved in the ability to discriminate between rewards of different magnitudes.

Cohort 3 (n = 16)

L-741,626: To determine whether blockade of D2 receptors would have effects opposite of those caused by bromocriptine, a separate cohort of rats received the selective D2 receptor antagonist L-741,626. Analyses of task performance revealed no significant effects of

L-741,626 on choice performance, either as a whole group (1C) or when divided into high and low risk-taking groups (Table 3). There were also no significant effects on locomotor activity, shock reactivity, response latencies on forced-choice trials, or omissions during free-choice trials (Table 5). These data indicate that D2 receptor blockade is not sufficient to alter risky decision making.

SB-277011-A: To further evaluate the role of D3 receptor signaling, rats received the selective D3 receptor antagonist SB-277011-A. Analyses of task performance showed that SB-277011-A had no significant effect on risky choice, either in the group as a whole (Figure 1D) or when split into high and low risk-taking groups (Table 3). There were no significant effects of SB-277011-A on latencies to press levers in forced-choice trials (Table 4). There were also no significant effects of SB-277011-A on locomotor activity, shock reactivity, or omissions during free-choice trials (Table 5). Together with the fact that PD128907 had no effect on risky choice, these results suggest that modulation of D3 receptor activity alone is not sufficient to regulate risky decision making.

Sumanitrole: The fact that drugs targeting D3 receptors appeared to have no specific effects on risk taking suggests that bromocriptine may preferentially interact with D2 receptors to reduce risky choice. To test this hypothesis, rats received the selective D2 receptor agonist sumanitrole. Analyses of choice behavior revealed that sumanitrole decreased choice of the large, risky reward, particularly in the blocks in which the risk of punishment was the greatest [dose X trial block: $F(12, 180) = 1.91, p < 0.05$] (Figure 1E). Follow-up comparisons between vehicle and each dose separately revealed that the low dose caused a near-significant decrease in risky choice [dose: $F(1, 15) = 4.16, p = 0.06$] but that the medium and high doses were without effect on choice behavior. When rats were split into high and low risk-taking rats, sumanitrole had a selective effect in the high risk-taking rats, causing a significant decrease in risky choice [Dose: $F(3, 21) = 4.08, p < 0.02$; dose x trial block: $F(12, 94) = 2.21, p < 0.02$]. In contrast, there were no significant effects of sumanitrole in low risk-taking rats (Table 3). Further post hoc analysis in the high risk taking group revealed a significant decrease in choice of the large, risky reward at the low dose [dose: $F(1, 7) = 9.31, p < 0.02$] but not at the other doses. Sumanitrole had no significant effect on latencies to press levers in forced choice trials (Table 4). Finally, sumanitrole did not affect locomotor activity, shock reactivity, or omissions during free choice trials (Table 5). Collectively, these data provide additional evidence that activation of D2 receptors, particularly in those rats that prefer the risky option, shifts preference away from the large, risky reward (reduced risky choice).

Experiment 2: Serotonergic modulation of risky decision making

Cohort 1 (n = 16)

Citalopram: To determine whether serotonergic signaling modulates decision making under risk of punishment, the selective serotonin reuptake inhibitor citalopram was administered prior to testing. Analyses of choice behavior (Figure 2A) revealed that there was neither a significant main effect of dose nor a significant dose X trial block interaction, indicating that blockade of serotonin reuptake (resulting in an increase in serotonin availability) had no effect on choice of the large, risky reward. There also was also no significant effect of

citalopram on choice performance when rats were divided into high and low risk-taking groups (Table 3). Consistent with this, there was no effect of citalopram on latencies to press levers on forced choice trials (Table 4). Notably, for citalopram, as well as the other drugs targeting the serotonergic system, there was no significant difference in latencies to press the small, safe lever vs. the large, risky lever [lever identity: $F(1, 8) = 1.49$, *NS*; lever identity X trial block: $F(4, 32) = 1.19$, *NS*] and therefore these statistics will not be reported further. Finally, a repeated-measures ANOVA revealed that citalopram had no significant effect on locomotor activity, shock reactivity or omissions during free choice trials. Locomotor activity, shock reactivity and omissions for citalopram and the other serotonergic drugs, are displayed in Table 5.

M100907: Rats received systemic injections of M100907, a 5-HT_{2A} receptor antagonist, prior to testing. Similar to citalopram, a repeated-measures ANOVA revealed no significant effect of M100907 on risky choice (Figure 2B), including when rats were divided into high and low risk-taking groups (Table 3). There were no significant effects of M100907 on latencies to press levers in forced-choice trials (Table 4). Additional analyses showed that M100907 did not significantly affect locomotor activity, shock reactivity or omissions during free-choice trials (Table 5). Collectively, these results indicated that blockade of 5-HT_{2A} receptors had no effect on risky choice.

SB 242,084: Rats received systemic injections of SB 242,084, a 5-HT_{2C} receptor antagonist, prior to testing. Using a two-factor repeated-measures ANOVA, analyses showed that there was neither a significant main effect of dose nor a significant dose X trial block interaction (Figure 2C). There also was no significant effect of SB 242,084 on choice performance when rats were divided into high and low risk-taking groups (Table 3). In contrast, when effects of SB 242,084 on latencies to press levers on forced choice trials were analyzed, there was a significant main effect of dose [$F(3, 27) = 4.60$, $p = 0.01$; Table 4]. There were, however, no significant interactions between dose and trial block, dose and lever identity or dose, lever identity and trial block. Subsequent post-hoc analyses comparing each dose with vehicle showed that the high dose of SB 242,084 decreased lever -press latencies [dose: $F(1, 9) = 11.84$, $p < 0.01$], but that neither the low nor or medium doses had any effect. Analysis of locomotor activity also revealed a significant main effect of dose [$F(3, 45) = 4.48$, $p < 0.01$; Table 5] although there were no significant differences between vehicle and any of the doses. Finally, SB 242,084 had no effect on shock reactivity or omissions during free choice trials (Table 5). Collectively, these results indicate that SB 242,084 had no effect on risky choice, but the highest dose did cause a decrease in latencies to press levers on forced choice trials and an increase in locomotor activity.

Cohort 2 (n = 18)

WAY-100635: In a separate cohort of rats, the effects of WAY-100635, a 5-HT_{1A} receptor antagonist, on risky decision making were assessed. A two-factor repeated-measures ANOVA showed no significant main effect of dose and no significant dose X trial block interaction, indicating that blockade of 5-HT_{1A} receptors had no effect on risky choice (Figure 2D). There also was no significant effect of WAY-100635 on choice performance when rats were divided into high and low risk-taking groups (Table 3). Similarly,

WAY-100635 had no significant effect on latencies to press levers on forced-choice trials (Table 4). Additionally, there were no significant effects of WAY-100635 on locomotor activity, shock reactivity or omissions during free choice trials (Table 5).

8-OH-DPAT: Rats received systemic injections of 8-OH-DPAT, a 5-HT_{1A} receptor agonist, prior to testing. Although there was no significant main effect of dose on risky choice, there was a significant dose X trial block interaction [$F(12, 180) = 3.86, p < 0.01$]. As depicted in Figure 2E, this significant interaction manifested as a decrease in risky choice, particularly in the first block, which was largely driven by the high dose. Post hoc analyses comparing vehicle to the high dose confirmed this with a significant interaction between dose and trial block [dose X trial block: $F(4, 68) = 4.24, p < 0.01$]. There were, however, no significant differences in risky choice between vehicle and the low or medium doses. Given that the high dose decreased choice in the first block of trials in which there was no risk of punishment, these data suggest that rather than risky choice *per se*, 8-OH-DPAT may have instead affected reward discrimination. When rats were divided into high and low risk-taking groups, there was a significant main effect of dose [$F(3, 18) = 3.74, p < 0.053$] and a significant dose x trial block interaction [$F(12, 72) = 2.95, p < 0.01$] in high risk-taking rats. In low risk-taking rats, there was a significant dose x trial block interaction [$F(12, 96) = 2.31, p < 0.02$] but no significant main effect of dose (Table 3). Further post hoc analysis revealed that 8-OH-DPAT caused a significant dose x trial block interaction in the low risk-taking group at the high dose [$F(4, 32) = 3.37, p < 0.02$] but no significant effects with the other doses. In the high risk-taking group, post hoc analyses revealed no significant main effects or interactions in comparisons between vehicle and each dose individually. These effects on choice behavior were accompanied by significant effects of 8-OH-DPAT on lever press latencies in forced-choice trials (Table 4). Although there was neither a significant main effect of dose nor a significant interaction between dose, lever identity and trial block, there were significant interactions between dose and lever identity [$F(3, 18) = 3.51, p < 0.05$] and dose and trial block [$F(12, 72) = 6.18, p < 0.01$]. Given these interactions, subsequent post hoc analyses focused on the effects of 8-OH-DPAT on each lever separately. For the small, safe lever, there was a significant main effect of dose [$F(3, 39) = 2.83, p < 0.05$] and a significant interaction between dose and trial block [$F(12, 156) = 3.51, p < 0.01$]. While there were no significant differences in latencies for the small, safe lever for the low and medium doses compared to vehicle, the highest dose increased latencies to press this lever [dose X trial block: $F(4, 60) = 6.92, p < 0.01$]. Similar to choice performance, the most dramatic effect of the high dose on latencies was in the first block, after which latencies decreased and became comparable to those under vehicle conditions. For latencies to press the large, risky lever, there was also a significant main effect of dose [$F(3, 21) = 3.40, p < 0.05$] and a significant interaction between dose and trial block [$F(12, 84) = 4.09, p < 0.01$]. In contrast to the small, safe lever, however, the medium and high doses but not the low dose of 8-OH-DPAT caused a significant decrease in latencies to press the large, risky lever [medium: dose X trial block, $F(4, 32) = 4.63, p < 0.01$; high: dose X trial block, $F(4, 36) = 10.08, p < 0.01$]. Given that 8-OH-DPAT decreased choice of the large, risky reward and increased latencies to press the small, safe lever predominantly in the first block, it appears that this 5-HT_{1A} receptor agonist may have affected the ability to discriminate between small and large rewards rather than affecting decision making *per se*.

With respect to other behavioral measures, there was a significant main effect of dose on locomotor activity [$F(3, 51) = 6.94, p < 0.01$], with the highest dose decreasing locomotor activity relative to vehicle [$t(17) = 2.89, p < 0.01$]. There were, however, no significant effects of 8-OH-DPAT on shock reactivity or omissions during free choice trials (Table 5).

Noradrenergic modulation of decision making

To begin to investigate whether norepinephrine modulates risky decision making, a separate cohort of rats ($n = 11$) received systemic injections of atomoxetine, a norepinephrine reuptake inhibitor, prior to testing (Figure 3). There was neither a significant main effect of dose nor a significant interaction between dose and trial block. There was also no significant effect of atomoxetine on choice performance when rats were divided into high and low risk-taking groups (Table 3). There were no significant effects of atomoxetine on latencies to press levers on forced-choice trials (Table 4). Finally, atomoxetine had no significant effect on locomotor activity, shock reactivity or omissions during free-choice trials (Table 5). Thus, similar to the drugs targeting the serotonergic system, atomoxetine did not appear to alter risky decision making.

Discussion:

Dopamine, serotonin, and norepinephrine signaling are implicated in several forms of decision making, but their roles in decision making under risk of punishment are less clear. To this end, the current study investigated the role of each of these neurotransmitter systems in a decision-making task in which the risk associated with the large reward is that of footshock punishment (Simon et al. 2009, Orsini et al. 2015). Replicating previous work (Simon et al. 2011), acute administration of the D2/D3 dopamine receptor agonist bromocriptine decreased choice of the large, risky reward (decreased risky choice), an effect that was also observed (albeit to a lesser extent) with the more selective dopamine D2 receptor agonist sumanirole (Table 5). In contrast, although the selective D3 dopamine receptor agonist PD128907 also reduced choice of the large, risky reward, its effects seemed to be due to impairments of reward discrimination, in that preference for the large reward was reduced even in the absence of punishment. Finally, although the 5-HT1A receptor agonist 8-OH-DPAT also appeared to have a small, yet significant, effect on reward discrimination, there were otherwise no effects of any serotonergic-targeting drugs or the norepinephrine reuptake inhibitor atomoxetine (Table 5). The fact that many of the drugs had few if any effects on behavior could indicate that the doses tested were sub-effective. However, these doses have been shown to alter behavioral performance in other tasks that have comparable cognitive and motor demands (Fernando et al. 2012; Koffarnus et al. 2011; Simon et al. 2011; St Onge and Floresco 2009; Winstanley et al. 2004; Bari et al. 2009; Boulougouris et al. 2008, Zeeb et al. 2009, Baarendse et al. 2013), suggesting that the absence of drug effects instead indicates a lack of significant role of the receptor systems involved. This notion is consistent with previous work showing that the neuropharmacology of decision making depends on the “cost” associated with the large reward. For example, stimulation of dopamine D1 receptors increases risky choice when the cost associated with the large reward is that of reward omission (St Onge and Floresco 2009). When the cost

involves risk of punishment, however, stimulation of D1 receptors has no effect (Simon et al. 2011).

Collectively, these data suggest that decision making involving risk of explicit punishment is modulated by dopaminergic, but not serotonergic or noradrenergic, neurotransmission and that these effects are mediated predominantly through D2 receptors. On the surface, this conclusion appears to conflict with the fact that there were no effects of the selective D2 receptor antagonist L-741,626. One mechanistic explanation for this discrepancy is that the D2 receptor agonist-induced decrease in risky choice may arise from activation of presynaptic D2 autoreceptors, resulting in a decrease in synaptic dopamine levels. If true, this would be consistent with previous work showing that dopamine levels in the nucleus accumbens decrease upon presentation of aversive stimuli (Badrinarayan et al. 2012; Oleson et al. 2012). Binding of a D2 receptor antagonist to autoreceptors, however, would not result in a decrease in dopamine levels, and thus would not be expected to cause shifts away from (or toward) aversive or risky options. Finally, it is worth noting that there is precedence in the literature for such differences in the effects of D2 receptor agonists and antagonists. Porter-Stransky et al. (2013) reported that intra-accumbens administration of the D2 receptor agonist quinpirole altered behavior in a choice task, whereas a D2 receptor antagonist was without effect. In addition, in our previous work with the risky decision-making task, we found that, like systemic bromocriptine, intra-accumbens quinpirole reduces choice of the large risky reward (Mitchell et al. 2014), whereas systemic administration of eticlopride has no effect on choice behavior (Simon et al. 2011). It will be important to perform follow up experiments to determine whether D2 receptor tone (particularly in the nucleus accumbens) is key to optimal risk taking behavior.

Dopaminergic signaling in risky choice

The decrease in risky choice produced by bromocriptine administration stands in contrast to the effects of bromocriptine in other risk-based decision-making tasks. Using a probabilistic discounting task in which the risk associated with the large reward is that of reward omission, St. Onge and Floresco (2009) found that bromocriptine increased risky choice. To complicate matters further, bromocriptine had no effect on choice performance in a rat gambling task. In this task, rats choose between four different options, each of which is associated with different reward sizes and punishment time outs-. While this task was sensitive to modulation by amphetamine [as is the risky decision making task (Simon et al. 2009)], Zeeb et al. (2009) did not observe any changes in decision making after acute bromocriptine. Such discrepancies in the effects of dopamine receptor-targeting drugs, however, are not without precedent. For example, while the D2 receptor antagonist eticlopride decreases risky choice in the probability discounting task (St Onge and Floresco 2009), it has no effect on risky choice in the risky decision-making task (although co-administration of eticlopride does attenuate amphetamine-induced decreases in risky choice (Simon et al. 2011). Thus, it appears that, unlike in other risk-based decision-making tasks, D2 receptors play a modulatory but not necessary role in punishment-based decision-making. Unlike with non-selective D2/D3 ligands, the effects of administration of more selective drugs appears to be more consistent across studies. St. Onge and Floresco (2009) also found that acute systemic administration of PD128907 (D3 agonist) reduces choices of

large risky rewards in a manner consistent with impaired reward discrimination, although this same drug had no effect in the rat gambling task (Ciano et al., 2015). In addition, as in the current study, neither D2 nor D3 antagonists affected choice behavior in either the probability discounting task or the rat gambling task (St Onge and Floresco 2009, Di Ciano et al. 2015)).

Although the current study employed only systemic drug administration, the loci of drug actions can be speculated on the basis of previous work. Stable individual differences in rats' preference for the large, risky reward in the risky decision-making task are negatively correlated with striatal expression of D2 receptor mRNA, such that greater risk taking is associated with lower expression (Mitchell et al. 2014). Consistent with these prior data, as well as the current results, acute administration of the D2/D3 agonist quinpirole into the ventral striatum (but not dorsal striatum) reduced choice of the large, risky reward (Mitchell et al. 2014). These findings in the context of an explicit risky decision making task mirror those from other lines of research. For example, ventral striatal quinpirole administration facilitates conditioned avoidance behavior, and knockdown of ventral striatal D2 receptors abolishes place aversion induced by optogenetic silencing of ventral tegmental area dopamine neurons (Boschen et al. 2011, Danjo et al. 2014). Considered together, these data suggest a broader role for ventral striatal D2 receptor signaling in promoting risk- and harm-avoidant behavior.

Serotonergic and noradrenergic signaling in risky choice

Although none of the drugs targeting the serotonin system had an appreciable effect on decision making, many of them have been shown to modulate other forms of risky decision making (Zeeb et al. 2009, Adams et al. 2017b, Homberg et al. 2008, Ishii et al. 2015). For example, performance in the rat gambling task is sensitive to modulation by serotonergic agents. Zeeb et al. (2009) found that the 5-HT_{1A} receptor agonist 8-OH-DPAT impaired choice performance such that rats decreased their choice of the best option (i.e., maximal reward with minimal punishment) and biased their choice toward non-optimal options, or those that resulted in larger immediate rewards but greater long-term losses. It is true that there was an effect of 8-OH-DPAT on choice behavior in the present study (Figure 2E), but it appears that this effect was a result of impaired reward discrimination given that the decrease in choice of the large, risky reward occurred in the first block of trials, in which there was no risk of punishment. In a more recent study, Adams et al. (2017) provided evidence for a role of 5-HT_{2C} receptors, but not 5-HT_{2A} receptors, in performance in the rat gambling task. Critically, however, this was dependent on the addition of audiovisual cues to the task. Administration of the 5-HT_{2C} antagonist SB 242,084 improved decision making (i.e., increased choice of the optimal option) only in a version of the rat gambling task in which cues were present. Given that serotonergic neurotransmission was recruited selectively in the cued version of the task, it is possible that the lack of effects of serotonergic agents on choice behavior in the present work was due to the absence of cues. Indeed, it is well-established that reward-paired cues can enhance motivation and drive goal-directed behavior (Robinson and Berridge 2008). Thus, serotonin may be specifically important for the ability of cues to guide behavior in the context of risky decision making,

suggesting that if cues were incorporated into the task, effects of drugs targeting the serotonergic system, or at least 5-HT_{2C} receptors, might emerge.

Another, and perhaps more parsimonious, explanation for why there were no effects of serotonergic agents is simply that, in contrast to dopamine, serotonin is not an important modulator of decision making involving risk of explicit punishment. Not surprisingly, the nature of the cost involved in decision making can dictate how different neurotransmitter systems and brain regions are engaged during decision making. Stimulation of D₂ receptors with bromocriptine, for example, decreases risky choice [present study; (Simon et al. 2011a)], has no effect in the rat gambling task (Zeeb et al. 2009) and increases risky choices in a decision making task in a probability discounting task (St Onge and Floresco 2009). Notably, there is evidence that serotonin plays an important role in punishment-induced inhibition of ongoing behavior (Crockett et al. 2009). Many of the studies that have reported such effects, however, have employed less complex tasks that do not entail weighing different punishment contingencies against potential rewards. Given the complexity of decision making (Orsini et al. 2015, Fobbs and Mizumori 2017, Rangel, Camerer and Montague 2008), it is important to consider differences such as task design and the cost involved as they may recruit different neurobiological systems.

This explanation may also extend to the role of norepinephrine in risky decision making. Systemic administration of atomoxetine had no effect on choice under risk of punishment, which contrasts with other work showing that atomoxetine increases preference for large, risky rewards in a probability discounting task (Montes et al. 2015). Instead of risk of footshock, the probability discounting task uses reward uncertainty as the cost associated with large reward, with the uncertainty of reward delivery increasing across the task. Hence, norepinephrine may differentially modulate decision making depending on the type of risk involved in the decision. There are few other studies that have examined the role of norepinephrine on risky decision making, and for those that do exist, it is still unclear how norepinephrine is involved. For example, atomoxetine impairs decision making in the rat gambling task, but only when it is co-administered with a dopamine reuptake inhibitor (Baarendse et al. 2013). Based on the present study, however, it is evident that decision making involving risk of explicit punishment is not sensitive to modulation by norepinephrine.

Limitations and concluding remarks

It is notable that the drug that produced the largest effect on choice performance (bromocriptine) was also one of the least selective. Among dopamine receptors, bromocriptine has high affinity and selectivity for the D₂ and D₃ subtypes, but its affinity for several serotonin and norepinephrine receptor subtypes is nearly equivalent (Kvernmo et al., 2006). Hence, it is possible that its greater efficacy may have been due in part to its combined actions on multiple monoamine systems. Future studies employing combinations of both agonists and antagonists will be necessary to fully explore this possibility.

An additional caveat to the findings in the present study is that only male rats were used. In recent years, it has become evident that there are clear sex differences in risky decision making (Orsini and Setlow 2017, van den Bos, Homberg and de Visser 2013). For example,

in the same task used in the present study, females are significantly more risk averse relative than males (Orsini et al. 2016). Using a rodent simulation of the Iowa Gambling Task, others have demonstrated that while females can identify the most advantageous option earlier in training than males, males overall select such options more frequently than females (Georgiou et al. 2018). Importantly, in both of these tasks, pharmacological manipulation of dopamine neurotransmission had sex-dependent effects on choice performance. In the risky decision-making task, amphetamine decreased risky choice to a greater extent in females than males (Orsini et al. 2016), suggesting that females may be more sensitive to dopaminergic modulation of decision making involving risk of punishment. In the rat Iowa Gambling Task, activation of D2 receptors impaired choice performance only in females, but blockade of these same receptors impaired choice performance only in males (Georgiou et al. 2018). In addition to such sex differences in decision making, there is a large literature documenting sex differences in amphetamine-induced dopamine release and dopamine receptor density in the striatum [for review, see (Becker and Hu 2008, Becker et al. 2012)]. Hence, it seems reasonable to hypothesize that D2 receptor activity may function differently during risky decision making in males and females, and consequently, that D2 receptor agonists such as bromocriptine and sumanirole may affect choice behavioral differently in the two sexes. Future experiments are underway to test this hypothesis.

Many disorders that feature altered dopamine neurotransmission such as Parkinson's disease and substance use are also characterized by abnormal risky decision making (Mimura et al. 2006, Rogers et al. 1999, Verdejo-Garcia et al. 2007, Dodd et al. 2005, Brand et al. 2004). A better understanding of the contributions of dopamine (as well as serotonin and norepinephrine) to risky decision making will be important for understanding the etiology of and possible treatments for these disorders.

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References

- 2018. Oxford English Dictionary. ed. O. E. Press.
- Adams WK, Barkus C, Ferland JN, Sharp T & Winstanley CA (2017a) Pharmacological evidence that 5-HT_{2C} receptor blockade selectively improves decision making when rewards are paired with audiovisual cues in a rat gambling task. *Psychopharmacology (Berl)*, 234, 3091–3104. [PubMed: 28733811]
- (2017b) Pharmacological evidence that 5-HT_{2C} receptor blockade selectively improves decision making when rewards are paired with audiovisual cues in a rat gambling task. *Psychopharmacology (Berl)*, 234, 3091–3104. [PubMed: 28733811]
- Anselme P (2015) Does reward unpredictability reflect risk? *Behav Brain Res*, 280C, 119–127.
- Baarendse PJ, Winstanley CA & Vanderschuren LJ (2013) Simultaneous blockade of dopamine and noradrenaline reuptake promotes disadvantageous decision making in a rat gambling task. *Psychopharmacology (Berl)*, 225, 719–31. [PubMed: 22968659]
- Badrinarayan A, Wescott SA, Vander Weele CM, Saunders BT, Couturier BE, Maren S, Aragona BJ (2012) Aversive stimuli differentially modulate real-time dopamine transmission dynamics within the nucleus accumbens core and shell. *J Neurosci*, 32, 15779–90. [PubMed: 23136417]

- Bari A, Eagle DM, Mar AC, Robinson ES & Robbins TW (2009) Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. *Psychopharmacology (Berl)*, 205, 273–83. [PubMed: 19404616]
- Barrus MM & Winstanley CA (2016) Dopamine D3 Receptors Modulate the Ability of Win-Paired Cues to Increase Risky Choice in a Rat Gambling Task. *J Neurosci*, 36, 785–94. [PubMed: 26791209]
- Becker JB & Hu M (2008) Sex differences in drug abuse. *Front Neuroendocrinol*, 29, 36–47. [PubMed: 17904621]
- Becker JB, Perry AN & Westenbroek C (2012) Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. *Biol Sex Differ*, 3, 14. [PubMed: 22676718]
- Boschen SL, Wietzikoski EC, Winn P & Da Cunha C (2011) The role of nucleus accumbens and dorsolateral striatal D2 receptors in active avoidance conditioning. *Neurobiol Learn Mem*, 96, 254–62. [PubMed: 21619938]
- Boulougouris V, Glennon JC & Robbins TW (2008) Dissociable effects of selective 5-HT_{2A} and 5-HT_{2C} receptor antagonists on serial spatial reversal learning in rats. *Neuropsychopharmacology*, 33, 2007–19. [PubMed: 17957219]
- Brand M, Labudda K, Kalbe E, Hilker R, Emmans D, Fuchs G, Kessler J & Markowitsch HJ (2004) Decision-making impairments in patients with Parkinson's disease. *Behav Neurol*, 15, 77–85. [PubMed: 15706051]
- Cavedini P, Bassi T, Ubbiali A, Casolari A, Giordani S, Zorzi C & Bellodi L (2004) Neuropsychological investigation of decision-making in anorexia nervosa. *Psychiatry Res*, 127, 259–66. [PubMed: 15296825]
- Chandler RA, Wakeley J, Goodwin GM & Rogers RD (2009) Altered risk-aversion and risk-seeking behavior in bipolar disorder. *Biol Psychiatry*, 66, 840–6. [PubMed: 19615669]
- Compan V, Walsh BT, Kaye W & Geliebter A (2015) How Does the Brain Implement Adaptive Decision Making to Eat? *J Neurosci*, 35, 13868–78. [PubMed: 26468187]
- Crockett MJ, Clark L & Robbins TW (2009) Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans. *J Neurosci*, 29, 11993–9. [PubMed: 19776285]
- Danjo T, Yoshimi K, Funabiki K, Yawata S & Nakanishi S (2014) Aversive behavior induced by optogenetic inactivation of ventral tegmental area dopamine neurons is mediated by dopamine D2 receptors in the nucleus accumbens. *Proc Natl Acad Sci U S A*, 111, 6455–60. [PubMed: 24737889]
- DeVito EE, Blackwell AD, Kent L, Ersche KD, Clark L, Salmond CH, Dezsery AM & Sahakian BJ (2008) The effects of methylphenidate on decision making in attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 64, 636–9. [PubMed: 18504036]
- Di Ciano P, Pushparaj A, Kim A, Hatch J, Masood T, Ramzi A, Khaled MA, Boileau I, Winstanley CA & Le Foll B (2015) The Impact of Selective Dopamine D2, D3 and D4 Ligands on the Rat Gambling Task. *PLoS One*, 10, e0136267. [PubMed: 26352802]
- Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA & Ahlskog JE (2005) Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol*, 62, 1377–81. [PubMed: 16009751]
- Fernando AB, Economidou D, Theobald DE, Zou MF, Newman AH, Spoelder M, Caprioli D, Moreno M, Hipólito L, Aspinall AT, Robbins TW & Dalley JW (2012) Modulation of high impulsivity and attentional performance in rats by selective direct and indirect dopaminergic and noradrenergic receptor agonists. *Psychopharmacology (Berl)*, 219, 341–52. [PubMed: 21761147]
- Fobbs WC & Mizumori SJ (2017) A framework for understanding and advancing intertemporal choice research using rodent models. *Neurobiol Learn Mem*, 139, 89–97. [PubMed: 28065715]
- Georgiou P, Zanos P, Bhat S, Tracy JK, Merchanthaler IJ, McCarthy MM & Gould TD (2018) Dopamine and Stress System Modulation of Sex Differences in Decision Making. *Neuropsychopharmacology*, 43, 313–324. [PubMed: 28741626]
- Guillaume S, Gorwood P, Jollant F, Van den Eynde F, Courtet P & Richard-Devantoy S (2015) Impaired decision-making in symptomatic anorexia and bulimia nervosa patients: a meta-analysis. *Psychol Med*, 45, 3377–91. [PubMed: 26497047]

- Ha J, Kim EJ, Lim S, Shin DW, Kang YJ, Bae SM, Yoon HK & Oh KS (2012) Altered risk-aversion and risk-taking behaviour in patients with Alzheimer's disease. *Psychogeriatrics*, 12, 151–8. [PubMed: 22994612]
- Homberg JR, van den Bos R, den Heijer E, Suer R & Cuppen E (2008) Serotonin transporter dosage modulates long-term decision-making in rat and human. *Neuropharmacology*, 55, 80–4. [PubMed: 18534635]
- Ishii H, Ohara S, Tobler PN, Tsutsui K & Iijima T (2015) Dopaminergic and serotonergic modulation of anterior insular and orbitofrontal cortex function in risky decision making. *Neurosci Res*, 92, 53–61. [PubMed: 25481848]
- Koffarnus MN, Newman AH, Grundt P, Rice KC & Woods JH (2011) Effects of selective dopaminergic compounds on a delay-discounting task. *Behav Pharmacol*, 22, 300–11. [PubMed: 21694584]
- Koob GF (2015) The dark side of emotion: the addiction perspective. *Eur J Pharmacol*, 753, 73–87. [PubMed: 25583178]
- Kvernmo T, Hartter S, & Burger E (2006) A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clin Ther*, 28, 1065–78. [PubMed: 16982285]
- Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, Strong DR & Brown RA (2002) Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *J Exp Psychol Appl*, 8, 75–84. [PubMed: 12075692]
- Lejuez CW, Aklin WM, Zvolensky MJ & Pedulla CM (2003) Evaluation of the Balloon Analogue Risk Task (BART) as a predictor of adolescent real-world risk-taking behaviours. *J Adolesc*, 26, 475–9. [PubMed: 12887935]
- Long AB, Kuhn CM & Platt ML (2009) Serotonin shapes risky decision making in monkeys. *Soc Cogn Affect Neurosci*, 4, 346–56. [PubMed: 19553236]
- Macoveanu J, Rowe JB, Hornboll B, Elliott R, Paulson OB, Knudsen GM & Siebner HR (2013) Serotonin 2A receptors contribute to the regulation of risk-averse decisions. *Neuroimage*, 83, 35–44. [PubMed: 23810974]
- Macoveanu J, Fisher PM, Haahr ME, Frokjaer VG, Knudsen GM & Siebner HR (2014) Effects of selective serotonin reuptake inhibition on neural activity related to risky decisions and monetary rewards in healthy males. *Neuroimage*, 99, 434–42. [PubMed: 24857827]
- Milienne-Petiot M, Geyer MA, Arnt J & Young JW (2017) Brexpiprazole reduces hyperactivity, impulsivity, and risk-preference behavior in mice with dopamine transporter knockdown—a model of mania. *Psychopharmacology (Berl)*, 234, 1017–1028. [PubMed: 28160035]
- Mimura M, Oeda R & Kawamura M (2006) Impaired decision-making in Parkinson's disease. *Parkinsonism Relat Disord*, 12, 169–75. [PubMed: 16563850]
- Mitchell MR, Weiss VG, Beas BS, Morgan D, Bizon JL & Setlow B (2014) Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. *Neuropsychopharmacology*, 39, 955–62. [PubMed: 24145852]
- Montes DR, Stopper CM & Floresco SB (2015) Noradrenergic modulation of risk/reward decision making. *Psychopharmacology (Berl)*, 232, 2681–96. [PubMed: 25761840]
- Norbury A, Manohar S, Rogers RD & Husain M (2013) Dopamine modulates risk-taking as a function of baseline sensation-seeking trait. *J Neurosci*, 33, 12982–6. [PubMed: 23926253]
- Oleson EB, Gentry RN, Chioma VC, Cheer JF (2012) Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance. *J Neurosci*, 32, 14804–8. [PubMed: 23077064]
- Orsini CA & Setlow B (2017) Sex differences in animal models of decision making. *J Neurosci Res*, 95, 260–269. [PubMed: 27870448]
- Orsini CA, Moorman DE, Young JW, Setlow B & Floresco SB (2015) Neural mechanisms regulating different forms of risk-related decision-making: Insights from animal models. *Neurosci Biobehav Rev*.
- Orsini CA, Willis ML, Gilbert RJ, Bizon JL & Setlow B (2016) Sex differences in a rat model of risky decision making. *Behav Neurosci*, 130, 50–61. [PubMed: 26653713]

- Orsini CA, Heshmati SC, Garman TS, Wall SC, Bizon JL & Setlow B (2018) Contributions of medial prefrontal cortex to decision making involving risk of punishment. *Neuropharmacology*, 139, 205–216. [PubMed: 30009836]
- Porter-Stransky KA, Seiler JL, Day JJ, Aragona BJ (2013) Development of behavioral preferences for the optimal choice following unexpected reward omission is mediated by a reduction of D2-like receptor tone in the nucleus accumbens. *Eur J Neurosci*, 38, 2572–88. [PubMed: 23692625]
- Rangel A, Camerer C & Montague PR (2008) A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci*, 9, 545–56. [PubMed: 18545266]
- Rigoli F, Rutledge RB, Chew B, Ousdal OT, Dayan P & Dolan RJ (2016) Dopamine Increases a Value-Independent Gambling Propensity. *Neuropsychopharmacology*, 41, 2658–67. [PubMed: 27149935]
- Robinson TE & Berridge KC (2008) Review. The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc Lond B Biol Sci*, 363, 3137–46. [PubMed: 18640920]
- Rogers RD (2011) The roles of dopamine and serotonin in decision making: evidence from pharmacological experiments in humans. *Neuropsychopharmacology*, 36, 114–32. [PubMed: 20881944]
- Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JF, Sahakian BJ & Robbins TW (1999) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology*, 20, 322–39. [PubMed: 10088133]
- Shimp KG, Mitchell MR, Beas BS, Bizon JL & Setlow B (2015) Affective and cognitive mechanisms of risky decision making. *Neurobiol Learn Mem*, 117, 60–70. [PubMed: 24642448]
- Simon NW, Gilbert RJ, Mayse JD, Bizon JL & Setlow B (2009) Balancing risk and reward: a rat model of risky decision making. *Neuropsychopharmacology*, 34, 2208–17. [PubMed: 19440192]
- Simon NW, Montgomery KS, Beas BS, Mitchell MR, LaSarge CL, Mendez IA, Banuelos C, Vokes CM, Taylor AB, Haberman RP, Bizon JL & Setlow B (2011) Dopaminergic modulation of risky decision-making. *J Neurosci*, 31, 17460–70. [PubMed: 22131407]
- St Onge JR & Floresco SB (2009) Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology*, 34, 681–97. [PubMed: 18668030]
- Stout JC, Bussemeyer JR, Lin A, Grant SJ & Bonson KR (2004) Cognitive modeling analysis of decision-making processes in cocaine abusers. *Psychon Bull Rev*, 11, 742–7. [PubMed: 15581127]
- Stout JC, Rock SL, Campbell MC, Bussemeyer JR & Finn PR (2005) Psychological processes underlying risky decisions in drug abusers. *Psychol Addict Behav*, 19, 148–57. [PubMed: 16011385]
- Thompson LL, Claus ED, Mikulich-Gilbertson SK, Banich MT, Crowley T, Krmpotich T, Miller D & Tanabe J (2012) Negative reinforcement learning is affected in substance dependence. *Drug Alcohol Depend*, 123, 84–90. [PubMed: 22079143]
- Tomassini A, Struglia F, Spaziani D, Pacifico R, Stratta P & Rossi A (2012) Decision making, impulsivity, and personality traits in alcohol-dependent subjects. *Am J Addict*, 21, 263–7. [PubMed: 22494229]
- van den Bos R, Homberg J & de Visser L (2013) A critical review of sex differences in decision-making tasks: focus on the Iowa Gambling Task. *Behav Brain Res*, 238, 95–108. [PubMed: 23078950]
- van Enkhuizen J, Geyer MA & Young JW (2013) Differential effects of dopamine transporter inhibitors in the rodent Iowa gambling task: relevance to mania. *Psychopharmacology (Berl)*, 225, 661–74. [PubMed: 22945515]
- Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL & Bolla KI (2007) The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug Alcohol Depend*, 90, 2–11. [PubMed: 17367959]
- Wallsten TS, Pleskac TJ & Lejuez CW (2005) Modeling behavior in a clinically diagnostic sequential risk-taking task. *Psychol Rev*, 112, 862–80. [PubMed: 16262471]

- Winstanley CA, Theobald DE, Dalley JW, Glennon JC & Robbins TW (2004) 5-HT_{2A} and 5-HT_{2C} receptor antagonists have opposing effects on a measure of impulsivity: interactions with global 5-HT depletion. *Psychopharmacology (Berl)*, 176, 376–85. [PubMed: 15232674]
- Xi C, Zhu Y, Mu Y, Chen B, Dong B, Cheng H, Hu P, Zhu C & Wang K (2015) Theory of mind and decision-making processes are impaired in Parkinson's disease. *Behav Brain Res*, 279, 226–33. [PubMed: 25435317]
- Yang FN, Pan JS & Li X (2016) Beta-adrenoreceptor blockade abolishes atomoxetine-induced risk taking. *Physiol Behav*, 153, 125–32. [PubMed: 26524512]
- Zalocusky KA, Ramakrishnan C, Lerner TN, Davidson TJ, Knutson B & Deisseroth K (2016) Nucleus accumbens D2R cells signal prior outcomes and control risky decision-making. *Nature*, 531, 642–6. [PubMed: 27007845]
- Zeeb FD, Robbins TW & Winstanley CA (2009) Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology*, 34, 2329–43. [PubMed: 19536111]

Figure 1. Dopaminergic modulation of risky decision making.

(A) Bromocriptine (D2/D3 receptor agonist) decreased choice of the large, risky reward (decreased risky choice). (B) Sumanitrole (D2 receptor agonist) caused a near-significant decrease in risky choice. (C) PD128907 (D3 receptor agonist) decreased risky choice, although this effect appeared due to an impairment in reward discrimination. (D) L-741,626 (D2 receptor antagonist) did not affect risky choice. (E) SB-277011-A (D3 receptor antagonist) did not affect risky choice. Data are represented as mean % choice of the large, risky reward $\pm$ SEM.

Figure 2. Serotonergic modulation of risky decision making.

(A) Citalopram (selective serotonin reuptake inhibitor) did not affect choice of the large, risky reward (risky choice). (B) M100907 (5-HT_{2A} receptor antagonist) did not affect risky choice. (C) SB 242,084 (5-HT_{2C} receptor antagonist) did not affect risky choice. (D) WAY 100635 (5-HT_{1A} receptor antagonist) did not affect risky choice. (E) 8-OH-DPAT (5-HT_{1A} receptor agonist) decreased risky choice, but this effect appeared largely due to an impairment in reward discrimination. Data are represented as mean % choice of the large, risky reward $\pm$ SEM.

Figure 3: Noradrenergic modulation of risky decision making.

A) Atomoxetine (norepinephrine reuptake inhibitor) did not affect choice of the large, risky reward. Data are represented as % mean choice of the large, risky reward $\pm$ SEM.

Table 1:

Methods for dopaminergic, serotonergic and noradrenergic manipulation

Drug	Cohort number within each experiment	Drug doses	Injection time (prior to testing)	Targets
Dopaminergic manipulation				
Bromocriptine	1	0.00 mg/kg 1.00 mg/kg 3.00 mg/kg 5.00 mg/kg	40 min	D2/D3 agonist
PD128907	2	0.00 mg/kg 0.10 mg/kg 0.25 mg/kg 0.50 mg/kg	10 min	D3 agonist
L-741,626	3	0.00 mg/kg 0.15 mg/kg 0.50 mg/kg 1.50 mg/kg	45 min	D2 antagonist
SB277011A	3	0.00 mg/kg 1.00 mg/kg 3.00 mg/kg 10.00 mg/kg	30 min	D3 antagonist
Sumanitrole	3	0.00 mg/kg 0.10 mg/kg 0.30 mg/kg 1.00 mg/kg	15 min	D2 agonist
Serotonergic manipulation				
Citalopram	1	0.00 mg/kg 0.10 mg/kg 0.30 mg/kg 1.00 mg/kg	20 min	Serotonin reuptake inhibitor
SB242084	1	0.00 mg/kg 0.03 mg/kg 0.10 mg/kg 1.00 mg/kg	20 min	5-HT(2C) antagonist
M100907	1	0.00 mg/kg 0.01 mg/kg 0.03 mg/kg 0.10 mg/kg	20 min	5-HT(2A) antagonist
8-OH-DPAT	2	0.00 mg/kg 0.10 mg/kg 0.30 mg/kg 1.00 mg/kg	20 min	5-HT(1A) agonist
WAY-100635	2	0.00 mg/kg 0.10 mg/kg 0.30 mg/kg 0.60 mg/kg	20 min	5-HT(1A) antagonist
Noradrenergic manipulation				Norepinephrine reuptake inhibitor
Atomoxetine	1	0.00 mg/kg 0.30 mg/kg 1.00 mg/kg 3.00 mg/kg	30 min	

Table 2.1:

Dopaminergic manipulations: non-significant data

Experiment	Choice performance	Latency (s)	Locomotor activity (locomotor units/ITI)	Shock reactivity (locomotor units/shock)	% Omitted trials
<u>Bromocriptine</u>					
Main effect		Dose $\times$ lever identity $F(3, 45) = 0.96, p = 0.42$ Dose $\times$ trial block: $F(12, 180) = 0.99, p = 0.46$ Dose $\times$ lever identity $\times$ trial block: $F(12, 180) = 0.38, p = 0.97$		$F(3, 27) = 0.76, p = 0.53$	<u>Failure to nosepoke</u> $F(93, 45) = 2.47, p = 0.07$
Low	Dose: $F(1, 15) = 0.94, p = 0.35$ Dose $\times$ block: $F(4, 60) = 0.94, p = 0.45$	Dose: $F(1, 15) = 0.31, p = 0.59$ Dose $\times$ lever identity: $F(1, 15) = 0.06, p = 0.81$ Dose $\times$ trial block: $F(4, 60) = 1.71, p = 0.16$ Dose $\times$ lever identity $\times$ trial block: $F(4, 60) = 1.33, p = 0.27$			<u>Total omissions</u> $t(15) = -2.19, p = 0.05$ <u>Failure to Nosepoke:</u> $t(15) = -1.00, p = 0.33$
Medium	Dose $\times$ trial block: $F(4, 56) = 2.58, p = 0.05$	Dose: $F(1, 15) = 2.56, p = 0.13$ Dose $\times$ lever identity: $F(1, 15) < 0.01, p = 0.99$ Dose $\times$ trial block: $F(4, 60) = 0.66, p = 0.62$ Dose $\times$ lever identity $\times$ trial block: $F(4, 60) = 1.96, p = 0.11$	$t(15) = 2.11, p = 0.05$		
High	Dose $\times$ trial block: $F(4, 48) = 2.23, p = 0.08$	Dose $\times$ lever identity: $F(1, 15) = 0.90, p = 0.36$ Dose $\times$ trial block: $F(4, 60) = 0.59, p = 0.67$ Dose $\times$ lever identity $\times$ trial block: $F(4, 60) = 0.33, p = 0.86$			
<u>PD128907</u>					
Main effect	Dose $\times$ trial block: $F(12, 180) = 0.62, p = 0.82$	Dose $\times$ lever identity: $F(3, 45) = 2.42, p = 0.78$ Dose $\times$ trial block: $F(12, 180) = 0.45, p = 0.94$		$F(3, 42) = 0.12, p = 0.95$	$F(3, 45) = 1.57, p = 0.21$
Low	Dose: $F(1, 15) = 0.5, p = 0.82$ Dose $\times$ trial block: $F(4, 60) = 0.83, p = 0.51$	Dose: $F(1, 15) = 0.31, p = 0.586$ Dose $\times$ lever identity: $F(1, 15) = 0.06, p = 0.81$ Dose $\times$ trial block: $F(4, 60) = 1.71, p = 0.16$ Dose $\times$ lever identity $\times$ trial block: $F(4, 60) = 1.33, p = 0.27$	$t(15) = 1.45, p = 0.17$		
Medium	Dose: $F(1, 15) = 0.2, p = 0.90$ Dose $\times$ trial block: $F(4, 60) = 0.70, p = 0.59$	Dose: $F(1, 15) = 2.56, p = 0.13$ Dose $\times$ lever identity: $F(1, 15) < 0.01, p = 0.99$ Dose $\times$ trial block: $F(4, 60) = 0.66, p = 0.62$ Dose $\times$ lever identity $\times$ trial block: $F(4, 60) = 1.96, p = 0.11$	$t(15) = 1.82, p = 0.09$		
High	Dose $\times$ trial block: $F(4, 60) = 0.92, p = 0.46$	Dose $\times$ lever identity: $F(1, 15) = 3.48, p = 0.08$ Dose $\times$ trial block: $F(4, 60) = 0.37, p = 0.83$ Dose $\times$ lever identity $\times$ trial block: $F(4, 60) = 1.88, p = 0.13$ $t(15) = 2.29, p = 0.04$			
<u>L-741,626</u>					
Main effect	Dose: $F(3, 45) = 1.55, p = 0.22$	Dose: $F(3, 42) = 1.85, p = 0.15$ Dose $\times$ lever identity: $F(3, 42) = 0.42, p = 0.74$	$F(3, 45) = 0.24, p = 0.87$	$F(3, 36) = 0.42, p = 0.74$	$F(3, 45) = 1.32, p = 0.28$

Experiment	Choice performance	Latency (s)	Locomotor activity (locomotor units/ITI)	Shock reactivity (locomotor units/shock)	% Omitted trials
	Dose × trial block: $F(12, 180) = 0.66, p = 0.79$	Dose × trial block: $F(12, 168) = 1.26, p = 0.25$ Dose × lever identity × trial block: $F(12, 168) = 0.81, p = 0.64$			
<u>SB277011A</u>					
Main effect	Dose: $F(3, 45) = 0.58, p = 0.63$ Dose × trial block: $F(12, 180) = 0.76, p = 0.69$	Dose: $F(3, 39) = 0.66, p = 0.58$ Dose × lever identity: $F(3, 39) = 0.34, p = 0.80$ Dose × trial block: $F(12, 156) = 0.66, p = 0.79$ Dose × lever identity × trial block: $F(12, 156) = 0.53, p = 0.89$	$F(3, 45) = 1.09, p = 0.36$	$F(3, 39) = 2.20, p = 0.10$	$F(3, 45) = 1.24, p = 0.31$
<u>Sumanitrole</u>					
Main effect	Dose: $F(3, 45) = 1.63, p = 0.20$	Dose: $F(3, 45) = 0.48, p = 0.70$ Dose × lever identity: $F(3, 45) = 0.80, p = 0.50$ Dose × trial block: $F(12, 180) = 0.83, p = 0.62$ Dose × lever identity × trial block: $F(12, 180) = 0.78, p = 0.67$	$F(3, 45) = 1.40, p = 0.26$	$F(3, 39) = 1.62, p = 0.20$	$F(3, 45) = 1.56, p = 0.21$
Low	Dose × block: $F(4, 60) = 1.23, p = 0.31$				
Medium	Dose: $F(1, 15) = 0.41, p = 0.53$ Dose × block: $F(4, 60) = 1.34, p = 0.27$				
High	Dose: $F(1, 15) = 0.22, p = 0.65$ Dose × block: $F(4, 60) = 0.78, p = 0.54$				

All post hoc comparisons are compared to vehicle

Table 2.2:

Serotonergic manipulation: non-significant data

Experiment	Choice performance	Latency (s)	Locomotor activity (locomotor units/TTI)	Shock reactivity (locomotor units/shock)	% Omitted trials
Citalopram					
Main effect	Dose: $F(3, 42) = 0.94$, $p = 0.43$ Dose x block: $F(12, 168) = 0.94$, $p = 0.51$	Dose: $F(3, 24) = 1.049$, $p = 0.24$ Dose x lever identity: $F(3, 24) = 0.80$, $p = 0.50$ Dose x trial block: $F(12, 96) = 0.63$, $p = 0.81$ Dose x lever identity x trial block: $F(12, 96) = 0.60$, $p = 0.84$	$F(3, 45) = 0.19$, $p = 0.90$	$F(3, 45) = 1.31$, $p = 0.28$	$F(3, 42) = 0.40$, $p = 0.76$
SB242084					
Main effect	Dose: $F(3, 45) = 2.04$, $p = 0.12$ Block: $F(12, 180) = 0.79$, $p = 0.66$	Dose x lever identity: $F(3, 27) = 2.83$, $p = 0.06$ Dose x trial block: $F(12, 108) = 1.35$, $p = 0.20$ Dose x lever identity x trial block: $F(12, 108) = 1.31$, $p = 0.22$		$F(3, 45) = 0.53$, $p = 0.67$	$F(3, 45) = 1.00$, $p = 0.40$
Low		Dose: $F(1, 9) = 0.6$, $p = 0.38$ Dose x trial block: $F(4, 36) = 1.60$, $p = 0.20$	$t(15) = 0.19$, $p = 0.85$		
Medium		Dose: $F(1, 9) = 3.19$, $p = 0.11$ Dose x trial block: $F(4, 36) = 1.18$, $p = 0.38$	$t(15) = -0.38$, $p = 0.71$		
High		Dose x trial block: $F(4, 36) = 3.11$, $p = 0.03$	$t(15) = 2.42$, $p = 0.03$		
M100907					
Main effect	Dose: $F(3, 39) = 0.80$, $p = 0.50$ Dose x block: $F(12, 156) = 0.94$, $p = 0.51$	Dose: $F(3, 30) = 0.71$, $p = 0.55$ Dose x lever identity: $F(3, 30) = 0.31$, $p = 0.29$ Dose x trial block: $F(12, 120) = 1.17$, $p = 0.31$ Dose x lever identity x trial block: $F(12, 120) = 1.16$, $p = 0.32$	$F(3, 45) = 0.42$, $p = 0.74$	$F(3, 45) = 1.23$, $p = 0.31$	$F(3, 45) = 0.37$, $p = 0.78$
8-OH-DPAT					
Main effect	Dose: $F(3, 45) = 1.25$, $p = 0.30$	Dose: $F(3, 18) = 1.41$, $p = 0.08$ Dose x lever identity x trial block: $F(12, 72) = 1.01$, $p = 0.45$		$F(3, 21) = 2.09$, $p = 0.13$	$F(3, 51) = 1.27$, $p = 0.29$
Low	Dose: $F(1, 17) = 3.98$, $p = 0.06$ Dose x block: $F(4, 68) = 0.31$, $p = 0.87$	Small, safe lever Dose: $F(1, 16) = 1.16$, $p = 0.30$ Dose x block: $F(4, 64) = 1.00$, $p = 0.41$ Large, risky lever Dose: $F(1, 10) = 7.11$, $p = 0.02$ Dose x block: $F(4, 40) = 1.32$, $p = 0.28$			
Medium	Dose: $F(1, 15) = 3.28$, $p = 0.09$ Dose x block: $F(4, 60) = 0.31$, $p = 0.87$	Small, safe lever Dose: $F(1, 14) = 0.05$, $p = 0.82$ Dose x block: $F(4, 56) = 0.14$, $p = 0.97$ Large, risky lever Dose: $F(1, 8) = 7.18$, $p = 0.03$			
High	Dose: $F(1, 17) = 0.05$, $p = 0.83$	small, safe lever Dose: $F(1, 15) = 5.61$, $p = 0.03$ Large, risky lever Dose: $F(1, 9) = 1.91$, $p = 0.20$			
WAY-100635					

Experiment	Choice performance	Latency (s)	Locomotor activity (locomotor units/ITI)	Shock reactivity (locomotor units/shock)	% Omitted trials
Main effect	Dose: $F(3, 51) = 0.70$, $p = 0.56$ Block: $F(12, 204) = 0.93$, $p = 0.52$	Dose: $F(3, 24) = 1.96$, $p = 0.15$ Dose x lever identity: $F(3, 24) = 1.03$, $p = 0.40$ Dose x trial block: $F(12, 96) = 0.96$, $p = 0.50$ Dose x lever identity x trial block: $F(12, 96) = 1.44$, $p = 0.16$	$F(3, 51) = 2.47$, $p = 0.07$	$F(3, 21) = 0.24$, $p = 0.87$	$F(3, 51) = 1.64$, $p = 0.19$

All post hoc comparisons are compared to vehicle

Table 2.3:

Noradrenergic manipulation: non-significant data

Experiment	Choice performance	Latency (s)	Locomotor activity (locomotor units/TTI)	Shock reactivity (locomotor units/shock)	% Omitted trials
<u>Atomoxetine</u>					
Main effect	Dose: $F(3, 30) = 1.70$, $p = 0.19$ Dose x block: $F(12, 120) = 0.45$, $p = 0.94$	Dose: $F(3, 24) = 2.23$, $p = 0.11$ Dose x lever identity: $F(3, 24) = 1.25$, $p = 0.32$ Dose x trial block: $F(12, 96) = 0.53$, $p = 0.89$ Dose x lever identity x trial block: $F(12, 96) = 1.11$, $p = 0.36$	$F(3, 27) = 2.56$, $p = 0.08$	$F(3, 27) = 0.87$, $p = 0.47$	$F(3, 30) = 1.32$, $p = 0.29$

All post hoc comparisons are compared to vehicle

Table 3:

Dopaminergic, serotonergic and noreadrenergic manipulation of high risk and low risk rats

Experiment	High risk takers	Low risk takers	Targets
Dopaminergic manipulation			
Bromocriptine	$F(3,21) = 10.59, p < 0.01$	$F(3,21) = 0.69, p = 0.57$	D2/D3 agonist
Dose	$F(12,84) = 2.66, p = 0.04$	$F(12,84) = 0.56, p = 0.87$	
Dose x Block	$F(1,7) = 3.17, p = 0.12$		
Low	$F(4,28) = 1.60, p = 0.20$		
Dose	$F(1,7) = 15.86, p = 0.01$		
Dose x Block	$F(4,28) = 9.10, p < 0.01$		
Medium	$F(1,7) = 13.97, p = 0.01$		
Dose	$F(4,28) = 2.92, p = 0.04$		
Dose x Block			
High			
Dose			D2 agonist
Dose x Block			
Sumanitrole	$F(3,21) = 4.08, p = 0.02$	$F(3,21) = 0.14, p = 0.93$	
Dose	$F(12,84) = 2.21, p = 0.02$	$F(12,84) = 0.78, p = 0.67$	
Dose x Block	$F(1,7) = 9.31, p = 0.02$		
Low	$F(4,28) = 3.07, p = 0.03$		
Dose	$F(1,7) = 5.12, p = 0.06$		
Dose x Block	$F(4,28) = 1.78, p = 0.16$		
Medium	$F(1,7) = 0.00, p = 0.96$		
Dose	$F(4,28) = 0.48, p = 0.75$		
Dose x Block			D2 antagonist
High			
Dose			
Dose x Block			D3 antagonist
L-741,626	$F(3,21) = 1.98, p = 0.15$	$F(3,21) = 0.79, p = 0.51$	
Dose	$F(12,84) = 1.20, p = 0.30$	$F(12,84) = 1.04, p = 0.42$	
Dose x Block			
SB277011A	$F(3,21) = 0.36, p = 0.78$	$F(3,21) = 1.35, p = 0.29$	D3 agonist
Dose	$F(12,84) = 0.59, p = 0.84$	$F(12,84) = 1.20, p = 0.30$	
Dose x Block			
PD128907	$F(3,21) = 6.27, p < 0.01$	$F(3,21) = 1.70, p = 0.20$	D3 agonist
Dose	$F(12,84) = 0.72, p = 0.73$	$F(12,84) = 0.64, p = 0.80$	
Dose x Block	$F(1,7) = 1.39, p = 0.28$		
Low	$F(4,28) = 2.26, p = 0.09$		
Dose	$F(1,7) = 1.36, p = 0.28$		
Dose x Block	$F(4,28) = 0.42, p = 0.79$		
Medium	$F(1,7) = 8.46, p = 0.02$		
Dose	$F(4,28) = 0.69, p = 0.61$		
Dose x Block			
High			
Dose			Serotonin reuptake inhibitor
Dose x Block			
Serotonergic manipulation			
Citalopram	$F(3,18) = 0.81, p = 0.51$	$F(3,21) = 0.68, p = 0.57$	5-HT(2C) antagonist
Dose	$F(12,72) = 0.49, p = 0.91$	$F(12,84) = 0.97, p = 0.48$	
Dose x Block			
SB242084	$F(3,21) = 1.67, p = 0.20$	$F(3,21) = 2.96, p = 0.06$	5-HT(2A) antagonist
Dose	$F(12,84) = 0.79, p = 0.66$	$F(12,84) = 0.80, p = 0.65$	
Dose x Block			
M100907	$F(3,15) = 0.47, p = 0.71$	$F(3,21) = 0.97, p = 0.42$	5-HT(1A) agonist
Dose	$F(12,60) = 1.05, p = 0.42$	$F(12,84) = 0.93, p = 0.52$	
Dose x Block			
8-OH-DPAT	$F(3,18) = 3.74, p = 0.03$	$F(3,12) = 1.35, p = 0.28$	5-HT(1A) agonist
Dose	$F(12,72) = 2.95, p < 0.01$	$F(12,96) = 2.31, p = 0.01$	
Dose x Block	$F(1,8) = 0.25, p = 0.63$	$F(1,8) = 4.52, p = 0.07$	
Low	$F(4,32) = 0.77, p = 0.55$	$F(4,32) = 0.37, p = 0.83$	
Dose	$F(1,6) = 2.40, p = 0.17$	$F(1,8) = 2.86, p = 0.13$	
Dose x Block	$F(4,28) = 0.92, p = 0.47$	$F(4,32) = 0.41, p = 0.80$	
Medium	$F(1,8) = 3.25, p = 0.11$	$F(1,8) = 1.64, p = 0.24$	
Dose	$F(4,32) = 2.56, p = 0.06$	$F(4,32) = 3.37, p = 0.02$	
Dose x Block			

Experiment	High risk takers	Low risk takers	Targets
High Dose Dose x Block			
WAY-100635 Dose Dose x Block	$F(3,24) = 0.25, p=0.86$ $F(12,96) = 0.40, p=0.96$	$F(3,24) = 0.44, p=0.72$ $F(12,96) = 1.06, p=0.41$	5-HT(1A) antagonist
Noradrenergic manipulation Atomoxetine Dose Dose x Block	$F(3,21) = 1.98, p=0.15$ $F(12,84) = 1.20, p=0.30$	$F(3,21) = 0.79, p=0.60$ $F(12,84) = 1.04, p=0.42$	Norepinephrine reuptake inhibitor

Table 4:

Effects of pharmacological manipulations of the dopaminergic, serotonergic and noradrenergic systems on latencies to press levers

Experiment	Small lever					Large lever				
	1	2	3	4	5	1	2	3	4	5
Dopaminergic manipulation										
Bromocriptine (D2/D3 agonist)										
0.00 mg/kg	0.81 (0.07)	0.82 (0.06)	0.86 (0.06)	0.87 (0.07)	0.92 (0.08)	0.66 (0.05)	1.01 (0.25)	1.23 (0.32)	1.48 (0.50)	1.52 (0.40)
1.00 mg/kg	0.90 (0.06)	0.88 (0.05)	0.99 (0.10)	1.01 (0.09)	0.97 (0.09)	0.70 (0.07)	1.08 (0.21)	1.49 (0.36)	1.95 (0.44)	2.04 (0.47)
3.00 mg/kg	0.97 (0.08)	1.03 (0.05)	1.20 (0.10)	2.00 (0.42)	1.57 (0.31)	0.87 (0.10)	1.12 (0.31)	1.16 (0.19)	2.12 (0.48)	1.77 (0.53)
5.00 mg/kg	1.45 (0.20)	1.30 (0.17)	1.90 (0.37)	1.87 (0.32)	1.85 (0.33)	1.30 (0.29)	1.12 (0.22)	1.91 (0.45)	1.68 (0.45)	2.14 (0.72)
Sumanirole (D2 agonist)										
0.00 mg/kg	0.92 (0.11)	0.82 (0.06)	0.77 (0.06)	0.80 (0.08)	0.69 (0.06)	0.76 (0.10)	0.83 (0.10)	1.51 (0.32)	1.61 (0.38)	1.64 (0.36)
0.10 mg/kg	0.80 (0.05)	0.81 (0.06)	0.75 (0.05)	0.71 (0.05)	0.73 (0.05)	0.63 (0.04)	0.88 (0.09)	1.32 (0.14)	1.58 (0.26)	2.01 (0.46)
0.30 mg/kg	0.97 (0.15)	0.89 (0.06)	0.88 (0.08)	0.78 (0.05)	0.77 (0.05)	0.75 (0.08)	0.98 (0.14)	1.43 (0.22)	1.55 (0.26)	1.91 (0.44)
1.00 mg/kg	0.87 (0.05)	0.93 (0.08)	0.83 (0.07)	0.85 (0.08)	0.78 (0.06)	0.81 (0.08)	0.86 (0.11)	1.70 (0.43)	1.28 (0.25)	1.22 (0.19)
L-741,626 (D2 antagonist)										
0.00 mg/kg	0.84 (0.06)	0.84 (0.05)	0.81 (0.04)	0.81 (0.05)	0.78 (0.04)	0.69 (0.05)	0.93 (0.07)	1.33 (0.17)	1.44 (0.18)	1.76 (0.36)
0.15 mg/kg	0.76 (0.05)	0.83 (0.06)	0.74 (0.04)	0.83 (0.07)	0.79 (0.05)	0.64 (0.04)	0.96 (0.08)	1.51 (0.23)	1.56 (0.32)	1.89 (0.36)
0.50 mg/kg	0.87 (0.07)	0.90 (0.07)	0.84 (0.05)	0.90 (0.07)	0.85 (0.06)	0.67 (0.03)	0.99 (0.09)	1.23 (0.18)	1.98 (0.47)	1.78 (0.36)
1.50 mg/kg	0.83 (0.05)	0.91 (0.10)	0.86 (0.04)	0.98 (0.08)	0.99 (0.07)	0.66 (0.05)	0.96 (0.06)	1.64 (0.31)	1.84 (0.46)	2.12 (0.42)
SB277011A (D3 antagonist)										
0.00 mg/kg	0.68 (0.03)	0.74 (0.05)	0.65 (0.03)	0.65 (0.03)	0.69 (0.04)	0.58 (0.03)	1.13 (0.16)	1.56 (0.35)	1.79 (0.30)	1.77 (0.32)
1.00 mg/kg	0.70 (0.05)	0.73 (0.06)	0.69 (0.05)	0.69 (0.05)	0.74 (0.06)	0.66 (0.06)	1.07 (0.10)	1.76 (0.33)	1.62 (0.26)	2.55 (0.53)
3.00 mg/kg	0.71 (0.04)	0.77 (0.05)	0.74 (0.06)	0.72 (0.04)	0.69 (0.04)	0.69 (0.07)	1.04 (0.10)	1.42 (0.21)	2.17 (0.49)	2.32 (0.55)
10.00 mg/kg	0.80 (0.06)	0.76 (0.06)	0.71 (0.03)	0.70 (0.04)	0.65 (0.03)	0.64 (0.05)	0.98 (0.10)	1.63 (0.31)	2.07 (0.51)	2.13 (0.34)
PD128907 (D3 agonist)										
0.00 mg/kg	1.19 (0.11)	1.03 (0.06)	1.20 (0.10)	1.28 (0.15)	1.45 (0.17)	0.64 (0.04)	0.74 (0.04)	1.13 (0.15)	1.77 (0.26)	2.41 (0.43)
0.10 mg/kg	1.21 (0.18)	1.13 (0.08)	1.25 (0.08)	1.39 (0.18)	1.50 (0.17)	0.86 (0.10)	0.99 (0.09)	1.40 (0.20)	1.75 (0.35)	1.84 (0.43)
0.25 mg/kg	1.28 (0.14)	1.24 (0.10)	1.42 (0.20)	1.30 (0.15)	2.08 (0.51)	1.28 (0.37)	0.95 (0.12)	1.78 (0.30)	1.89 (0.41)	1.97 (0.32)
0.50 mg/kg	1.96 (0.40)	1.46 (0.26)	1.42 (0.20)	1.42 (0.12)	1.64 (0.25)	1.35 (0.32)	1.24 (0.12)	2.40 (0.42)	2.79 (0.58)	3.17 (0.49)

Experiment	Small lever					Large lever				
	1	2	3	4	5	1	2	3	4	5
Serotonergic manipulation										
Citalopram (Serotonin reuptake inhibitor)										
0.00 mg/kg	0.99 (0.08)	1.04 (0.10)	1.18 (0.13)	1.25 (0.18)	1.42 (0.22)	0.73 (0.05)	0.97 (0.11)	1.22 (0.20)	2.12 (0.62)	2.12 (0.59)
0.10 mg/kg	0.87 (0.05)	0.93 (0.10)	1.25 (0.21)	1.69 (0.45)	1.36 (0.19)	0.77 (0.06)	1.49 (0.49)	1.97 (0.53)	2.28 (0.70)	2.42 (0.60)
0.30 mg/kg	1.00 (0.08)	1.26 (0.15)	1.36 (0.21)	1.47 (0.29)	1.60 (0.31)	0.66 (0.05)	1.02 (0.10)	1.75 (0.34)	2.48 (0.69)	2.35 (0.65)
1.00 mg/kg	0.99 (0.07)	1.31 (0.19)	1.13 (0.10)	1.60 (0.22)	1.52 (0.32)	0.74 (0.04)	1.26 (0.19)	1.39 (0.20)	1.67 (0.38)	1.86 (0.57)
SB242084 [5-HT(2C) antagonist]										
0.00 mg/kg	0.85 (0.05)	1.20 (0.13)	0.92 90.05)	1.13 (0.10)	1.29 (0.19)	0.66 (0.03)	1.12 (0.27)	1.33 (0.19)	1.47 (0.21)	2.73 (0.75)
0.03 mg/kg	0.92 (0.05)	0.97 (0.09)	1.02 (0.10)	1.06 (0.17)	1.24 (0.24)	0.68 (0.05)	0.76 (0.06)	1.18 (0.13)	1.54 (0.23)	1.61 (0.27)
0.10 mg/kg	0.89 (0.07)	1.00 (0.11)	0.98 (0.09)	0.96 (0.09)	1.35 (0.28)	0.62 (0.03)	0.98 (0.26)	1.04 (0.23)	1.09 (0.05)	1.13 (0.13)
1.00 mg/kg	0.90 (0.09)	0.85 (0.06)	0.85 (0.07)	1.02 (0.14)	0.98 (0.11)	0.60 (0.05)	0.78 (0.10)	0.95 (0.08)	1.03 (0.07)	1.33 (0.25)
M100907 [5-HT(2A) antagonist]										
0.00 mg/kg	0.90 (0.07)	1.02 (0.08)	1.20 (0.14)	1.43 (0.17)	1.22 (0.14)	0.75 (0.09)	0.91 (0.11)	1.29 (0.23)	1.14 (0.18)	1.37 (0.19)
0.01 mg/kg	0.95 (0.09)	0.97 (0.08)	1.28 (0.14)	1.42 (0.20)	1.74 (0.39)	0.61 (0.03)	2.23 (0.75)	1.16 (0.17)	1.25 (0.18)	1.45 (0.23)
0.03 mg/kg	1.02 (0.08)	1.25 (0.19)	0.17 (0.10)	1.33 (0.20)	1.45 (0.19)	0.66 (0.04)	1.13 (0.21)	1.13 (0.21)	1.54 (0.40)	1.18 (0.19)
0.10 mg/kg	1.09 (0.16)	1.08 (0.09)	0.14 (0.12)	1.21 (0.14)	1.64 (0.28)	0.68 (0.06)	1.02 (0.19)	1.14 (0.17)	1.40 (0.25)	1.45 (0.31)
8-OH-DPAT [5-HT(1A) agonist]										
0.00 mg/kg	1.25 (0.09)	1.17 (0.11)	1.13 (0.11)	1.20 (0.15)	1.22 (0.11)	0.67 (0.03)	0.22 (0.41)	2.78 (0.51)	3.01 (0.65)	2.59 (0.51)
0.10 mg/kg	1.29 (0.08)	1.14 (0.11)	1.12 (0.11)	1.09 (0.11)	1.05 (0.10)	0.69 (0.03)	1.72 (0.38)	2.16 (0.38)	2.39 (0.52)	2.97 (0.64)
0.30 mg/kg	1.21 (0.11)	1.14 (0.10)	1.32 (0.17)	1.21 (0.12)	1.37 (0.24)	0.77 (0.05)	1.25 (0.16)	2.18 (0.36)	3.06 (0.68)	2.73 (0.59)
1.00 mg/kg	2.26 (0.30)	1.41 (0.13)	1.14 (0.11)	1.14 (0.10)	1.05 (0.09)	1.43 (0.23)	1.94 (0.39)	2.50 (0.53)	2.73 (0.58)	3.48 (0.75)
WAY-100635 [5-HT(1A) antagonist]										
0.00 mg/kg	1.19 (0.08)	1.24 (0.09)	1.27 (0.13)	1.32 (0.13)	1.33 (0.13)	0.75 (0.04)	1.40 (0.17)	2.49 (0.47)	2.87 (0.57)	3.93 (0.66)
0.10 mg/kg	1.30 (0.08)	1.34 (0.11)	1.24 (0.09)	1.38 (0.11)	1.35 (0.13)	0.93 (0.09)	1.54 (0.33)	3.10 (0.53)	3.67 (0.62)	4.13 (0.70)
0.30 mg/kg	1.24 (0.08)	1.47 (0.11)	1.29 (0.12)	1.42 (0.11)	1.44 (0.12)	0.89 (0.06)	1.89 (0.06)	2.33 (0.42)	3.60 (0.74)	3.90 (0.63)
0.60 mg/kg	1.24 (0.11)	1.57 (0.18)	1.41 (0.14)	1.51 (0.15)	1.44 (0.21)	0.86 (0.06)	1.69 (0.25)	3.45 (0.56)	3.19 (0.57)	3.92 (0.69)
Noradrenergic manipulation										
Atomoxetine (Norepinephrine reuptake inhibitor)										
0.00 mg/kg	0.96 (0.08)	0.96 (0.08)	0.86 (0.05)	1.01 (0.14)	0.94 (0.10)	0.75 (0.07)	1.14 (0.20)	2.00 (0.53)	2.30 (0.66)	2.60 (0.69)

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Experiment	Small lever					Large lever				
	1	2	3	4	5	1	2	3	4	5
0.30 mg/kg	0.98 (0.17)	0.97 (0.17)	0.90 (0.09)	0.98 (0.10)	0.99 (0.11)	0.74 (0.07)	0.77 (0.07)	1.23 (0.16)	2.03 (0.55)	1.46 (0.19)
1.00 mg/kg	0.96 (0.08)	1.04 (0.09)	1.08 (0.12)	1.04 (0.14)	1.02 (0.12)	0.68 (0.07)	0.90 (0.11)	1.43 (0.20)	2.11 (0.45)	1.69 (0.28)
3.00 mg/kg	1.26 (0.22)	1.24 (0.12)	1.25 (0.18)	1.14 (0.14)	1.19 (0.10)	0.91 (0.09)	1.07 (0.12)	1.59 (0.25)	3.22 (0.79)	2.78 (0.61)

Table 5:

Omitted trials, shock reactivity and locomotor activity for dopaminergic, serotonergic and noradrenergic manipulation

Drug	% Omitted trials	Shock reactivity (locomotor units/shock)	Locomotion (locomotor units/TTI)
Dopamine D2 receptors			
<i>Bromocriptine (agonist)</i>			
0.0 mg/kg	0.63 (0.51)	2.89 (0.21)	18.67 (1.68)
1.00 mg/kg	4.25 (1.59) *	2.74 (0.22)	13.20 (1.32) *
3.00 mg/kg	12.75 (2.53) *	2.96 (0.28)	14.29 (1.89)
5.00 mg/kg	16.75 (4.71) *	2.57 (0.20)	13.58 (1.99) *
<i>Sumanitrole (agonist)</i>			
0.0 mg/kg	0.13 (0.13)	2.83 (0.23)	17.97 (1.93)
0.10 mg/kg	0.25 (0.17)	3.25 (0.27)	19.00 (1.96)
0.30 mg/kg	0.88 (0.36)	2.89 (0.20)	17.23 (1.70)
1.00 mg/kg	1.13 (0.66)	2.84 (0.26)	15.67 (1.76)
<i>L741,625 (antagonist)</i>			
0.0 mg/kg	0.13 (0.13)	3.12 (0.28)	11.52 (1.32)
0.15 mg/kg	0.00 (0.00)	2.76 (0.19)	12.25 (1.70)
0.50 mg/kg	0.50 (0.29)	2.71 (0.19)	12.27 (1.07)
1.50 mg/kg	0.25 (0.17)	2.87 (0.29)	11.99 (1.21)
Dopamine D3 receptors			
<i>SB277011A (antagonist)</i>			
0.0 mg/kg	0.13 (0.13)	3.39 (0.24)	12.14 (1.30)
1.00 mg/kg	0.25 (0.17)	3.21 (0.28)	11.80 (1.30)
3.00 mg/kg	0.00 (0.00)	3.13 (0.23)	14.20 (2.58)
10.00 mg/kg	0.00 (0.00)	3.05 (0.20)	11.89 (1.39)
<i>PD128907 (agonist)</i>			
0.0 mg/kg	3.00 (0.98)	2.61 (0.24)	11.85 (1.28)
0.10 mg/kg	4.38 (1.40)	2.59 (0.21)	9.86 (0.87)
0.25 mg/kg	4.25 (1.28)	2.79 (0.25)	9.26 (0.99)
0.50 mg/kg	6.63 (1.72)	2.65 (0.30)	8.06 (1.25) *
Serotonergic			
<i>Citalopram (reuptake inhibitor)</i>			
0.0 mg/kg	2.80 (1.29)	2.10 (0.44)	42.69 (4.96)
0.1 mg/kg	5.47 (3.69)	2.28 (0.43)	42.73 (5.18)
0.3 mg/mL	2.53 (1.33)	2.56 (0.42)	43.81 (5.82)
1.0 mg/kg	3.73 (1.68)	2.46 (0.42)	41.82 (5.99)
<i>SB 242,084 [5-HT(2A) receptor agonist]</i>			
0.0 mg/kg	1.88 (0.79)	2.00 (0.47)	43.21 (6.37)

Drug	% Omitted trials	Shock reactivity (locomotor units/shock)	Locomotion (locomotor units/TTI)
0.03 mg/kg	0.88 (0.41)	1.83 (0.49)	42.57 (6.71)
0.1 mg/kg	0.88 (0.45)	1.86 (0.50)	44.39 (7.37)
1.0 mg/kg	1.00 (0.45)	2.03 (0.48)	52.03 (7.83) *
<i>M100907 [5-HT(2A) receptor antagonist]</i>			
0.0 mg/kg	3.88 (2.72)	2.26 (0.42)	42.67 (6.06)
0.01 mg/kg	2.50 (1.42)	2.25 (0.41)	40.58 (5.68)
0.03 mg/kg	3.25 (1.78)	2.11 (0.39)	40.91 (5.89)
0.10 mg/kg	1.38 (0.54)	2.25 (1.36)	39.82 (6.82)
<i>8-OH-DPAT [5-HT(1A) receptor agonist]</i>			
0.0 mg/kg	0.67 (0.46)	2.79 (0.36)	12.17 (1.50)
0.1 mg/kg	0.22 (0.15)	2.66 (0.24)	13.45 (1.43)
0.3 mg/kg	3.22 (2.13)	2.50 (0.17)	10.62 (1.68)
1.0 mg/kg	1.56 (0.66)	2.16 (0.42)	8.44 (1.37) *
<i>WAY-100635 [5-HT(1A) receptor antagonist]</i>			
0.0 mg/kg	1.89 (1.02)	2.52 (0.28)	10.88 (1.02)
0.1 mg/kg	3.67 (1.41)	2.44 (0.18)	8.89 (0.92)
0.3 mg/kg	1.22 (0.43)	2.62 (0.42)	9.73 (1.17)
0.6 mg/kg	5.44 (2.54)	2.43 (0.19)	8.42 (1.18)
<i>Noradrenergic</i>			
<i>Atomoxetine (reuptake inhibitor)</i>			
0.0 mg/kg	0.0 (0.0)	2.35 (1.68)	9.48 (1.70)
0.3 mg/kg	1.82 (1.82)	2.42 (0.50)	8.82 (1.95)
1.0 mg/kg	0.73 (0.56)	2.59 (0.52)	7.23 (1.98)
3.0 mg/kg	2.91 (1.12)	2.23 (0.45)	6.79 (2.03)

* Significant difference between vehicle and drug treated animals ($p < 0.05$). Data are represented as mean (standard error of the mean).

Table 6:

Results for dopaminergic, serotonergic and noradrenergic manipulation on the risky decision making task

Drug Target	Cohort number within each experiment	Target receptor	Overall effect on choice of large, risky reward
Dopamine	1	D2/D3 agonist	Decrease
Bromocriptine			
PD128907	2	D3 agonist	Decrease
L-741,626	3	D2 antagonist	No effect
SB277011A	3	D3 antagonist	No effect
Sumanitrole	3	D2 agonist	Decrease
Serotonin	1	Serotonin reuptake inhibitor	No effect
Citalopram			
SB242084	1	5-HT(2C) antagonist	No effect
M100907	1	5-HT(2A) antagonist	No effect
8-OH-DPAT	2	5-HT(1A) agonist	Decrease
WAY-100635	2	5-HT(1A) antagonist	No effect
Norepinephrine	1	Norepinephrine reuptake inhibitor	No effect
Atomoxetine			