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The Impact of Monoamine Transport Inhibitors in the Rat Gambling Task

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THE IMPACT OF MONOAMINE TRANSPORT INHIBITORS IN THE RAT GAMBLING TASK

By

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I dedicate this thesis to my friends, family and colleagues.

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ABSTRACT

Dysfunctional decision-making is characteristic of numerous psychiatric disorders including schizophrenia, mood disorders, ADHD, eating disorders, pathological gambling and substance abuse. The rodent Gambling Task (rGT) is analogous to the Iowa Gambling Task (IGT) and models risky decision-making in rodents. The rGT has unique response options that range from high probability of small rewards and lower probability of penalty to responses that result in low probability of larger reward and higher probability of penalty. Similar to the IGT, the optimal rGT strategy is exclusive choice of an intermediate reward/penalty response option. Importantly, similar baseline behavior exists between human and rodent subjects and supports the validity of the rGT in examining different behavioral phenotypes. In addition to strong face and construct validity, the rGT measures motor impulsivity and decision-making behaviors and integration- or dissociation- of these two behaviors is essential to characterizing the impact of different neurobiological or pharmacological manipulations. Due to monoamines' (dopamine, serotonin and norepinephrine) integral role in the modulation of reward assessment and impulsivity, we examined the impact of several monoaminergic-altering drugs: *d*-amphetamine, eticlopride, cocaine, methylphenidate (Ritalin), and bupropion (Wellbutrin). Although each drug differed in mechanism of action and affinity for specific monoamine transporters, only slight behavioral differences were observed in the rGT. Interestingly, all monoamine-enhancing drugs increased selection of the lowest risk option and significantly shifted behavior away from the optimal response.

INTRODUCTION

Individuals are faced with the complex task of resolving uncertainty on a daily basis. A careful examination of the advantages and consequences associated with each option leads to a decision-making strategy. Dysfunction in this process is a hallmark of both frontal lobe damage and several psychiatric illnesses including: Attention-Deficit/Hyperactivity Disorder (ADHD) (Malloy-Diniz et al., 2007), schizophrenia (Struglia et al., 2011), bipolar disorder (Adida et al., 2011), substance abuse (Bechara and Martin, 2004), and pathological gambling (PG) (Cavedini et al., 2002). Moreover, cognitive impairments in neuropsychiatric disorders are frequently predictive of long-term community outcome (Green et al., 2004) Therefore, a better understanding of the fundamental neural mechanisms involved in decision-making is critical for the development of new treatment strategies to more effectively treat these debilitating symptoms.

The Iowa Gambling Task (IGT) is a well-established metric of human decision-making and has been used in clinical settings (Bechara et al., 1994). The IGT is a computerized task that presents subjects with the goal of winning money using four virtual decks of playing cards on a computer screen. Two of the decks are associated with small rewards and penalties whereas the other two decks are associated with large rewards and penalties. Importantly, consistent selection of a lower reward/lower penalty response represents the optimal strategy to maximize rewards. Most healthy individuals discern the optimal strategy quickly, in contrast to individuals with damage to their orbitofrontal cortex (oFC) (Bechara et al., 2004) or who are diagnosed with schizophrenia (Shurman et al., 2005), Parkinson's disease (Mimura et al., 2006), substance abuse (Rogers, 1999), or PG (Comings et al., 1996) and respond more on 'bad decks' in a suboptimal manner. Individuals who fail to appropriately assess the risks and rewards may be classified as poor decision-makers and this non-optimal performance may be an indication of frontal lobe damage (Bechara 2004b; Fellows and Farah, 2005), compromised integrity of neurotransmitter systems involving dopamine (DA) (Sevy et al., 2006) or serotonin (5-HT) (de Visser et al., 2011). Additionally, both DA and 5-HT are key modulators of personality traits (e.g., harm avoidance, novelty-seeking and impulsivity) associated with decision-making designating them prime targets for investigation (Homberg et al., 2011; Krugel et al., 2009; Paloyelis et al., 2010).

Numerous pharmacological experiments have identified possible roles for monoamines like 5-HT and DA in mediating IGT-related behaviors. Users of the serotonergic agonist, 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") performed poorer than control subjects in the IGT (Hanson et al., 2008) while OCD patients receiving chronic treatment with the atypical antipsychotic risperidone (5-HT_{2A} and DA D_2 receptor antagonist effects), improved performance (Cavedini et al., 2002). Thus, there appears to be an inverse relationship between increased 5-HT signaling and IGT performance. With regards to DA, effort- and delay-based decision-making has been historically the focus of DA's behavioral regulation (Berridge and Robinson, 1998; Salamone et al., 2007; Niv, 2007; Floresco et al., 2008). However, several recent studies have highlighted DA's role in risk-based decision-making. Foremost, patients who suffer from psychiatric conditions linked to DA disruption (e.g., schizophrenia, drug addiction, Parkinson's disease and PG) exhibit a propensity for risky choices in the IGT. Yet, in contrast to 5-HT, a directional agreement of DA to IGT performance remains unclear. For example, there is evidence for iatrogenic PG in patients being treated with DA agonists for Parkinson's disease (Pagonabarraga et al., 2007; Poletti et al., 2011), but haloperidol (DA D_2 antagonist) increased the drive to play slot machines in PG (Zack and Poulos, 2007). Although the IGT has been integral to progress in the field of risky decision-making, the limitations of clinical studies (e.g., comorbid psychiatric diagnoses, frequency of drug use, ethics) hinder ascertaining certain critical relationships. Thus, examining these research questions with a preclinical model allows for the experimental manipulations of variables that would not be possible in clinical work with human subjects and provide environmental and genetic control that could be particularly valuable for assessing individual differences and manipulating monoaminergic systems (Kalenscher and van Windergerden, 2011).

Several procedures to assess risky decision-making have been developed, including IGT analogues (Van Den Bos et al., 2006; Rivalan et al., 2009; Zeeb et al., 2009), probability discounting paradigms (St Onge and Floresco, 2009; Jentsch et al., 2010), and a "slot machine task" (Zeeb and Winstanley, 2011). Each task differs slightly in design and reinforcement schedules, but given the complex nature of risk ascertainment, each procedure uniquely contributes to the field of decision-making. For example, subjects examined under the probability-discounting paradigm choose between small/certain rewards and larger/uncertain rewards. In these experiments, animals that received acute doses of d-amphetamine (which

stimulates the direct release of DA out of the nerve terminal) or bromocriptine (DA D_2 receptor agonist), displayed a preference for larger/uncertain rewards (St. Onge and Floresco, 2009). Conversely, d-amphetamine administration increased risk-averse choices and the DA D_2 receptor antagonist, eticlopride, decreased risky-decisions in the rGT (Zeeb et al., 2009). Interestingly, acute administration of d-amphetamine also decreased risky decisions when a strong negative stimulus (foot shock) was employed during a probability-discounting task (Simon et al., 2009).

Dopamine nerve terminals have high-affinity DA uptake sites that are critical to terminating the neurotransmitter signal and generally aid in maintaining homeostasis. Dopamine uptake is facilitated by a specific membrane carrier protein, the dopamine transporter (DAT), which moves DA into and out of the terminal depending on the concentration gradient (Iversen et al., 2009) Regional distribution of DAT has been found in areas of the brain with established dopaminergic circuitry including nigrostriatal, mesolimbic, and mesocortical pathways (Ciliax et al., 1999). In a manner similar to that observed with DA agonists and antagonists, equivocal evidence exists in the realm of DATs as well. Over-expression of DAT in the rat nucleus accumbens led to a significant increase of suboptimal responding in a risk-prone phenotype (Adriani et al., 2009), yet DAT knockdown mice also show an increase in risky behavior (Young et al., 2011). Taken together, these suggest some critical questions remain unresolved about the role of DAT-mediated activity in risk-based decision-making.

Thus, the goal of these experiments was to investigate the specific contributions of three compounds having DAT-mediated activity: cocaine, methylphenidate (Ritalin), and bupropion (Wellbutrin), on risky decision-making using the rGT. Interestingly, these compounds also vary in affinity for norepinephrine transporters (NET) and serotonin transporters (SERT). For example, cocaine exhibits relatively high affinities for all three transporters while methylphenidate and bupropion predominantly bind to DAT and NET (Ferris and Cooper, 1983). These compounds each inhibit the action of DAT and, to a lesser extent, the other monoamine transporters, but their effects are mediated by independent mechanisms that are thought to underlie the pleasurable feelings elicited by these substances (Schultz ,1998). Previous research has demonstrated that both cocaine and methylphenidate increase impulsivity, which may impact decision-making (Fletcher et al., 2011). Interestingly, bupropion does not appear to share this characteristic (Acheson and de Wit, 2008). Although the impact of bupropion and methylphenidate in a rodent paradigm of probabilistic decision-making has not been examined

previously, Simon and colleagues (2009) determined there was no shift in suboptimal responses after acute administration of cocaine in an analogous rGT model using foot shock as punishment. Given the collection of human and rodent studies on the various monoaminergic effects on decision-making, we hypothesized that given its differences in binding affinities, cocaine would affect choice selection in a manner specific from both methylphenidate and bupropion, yet all three would negatively affect performance on the rGT.

METHODS

Subjects

Adult male Long-Evans rats (Harlan) served as subjects (n=11) in these experiments. Animals were approximately 250-275 g upon arrival in lab and individually housed in standard shoebox-style polycarbonate cages. The colony room was temperature and humidity controlled with a 12-h light/dark cycle (lights on between 7 a.m. and 7 p.m.) Subjects were weighed daily and food restricted to 85-90% of their free-feeding weight by manipulating their post-session feeding allotments. Water was available *ad libitum* when animals were in their home cage. All experimental protocols were approved by the Institutional Animal Care and Use Committee and were performed in accordance with the guidelines of the NRC Guide for Care and Use of Laboratory Animals (2011). In addition, all animal facilities were accredited by the Association for Assessment and Accreditation for Laboratory Animal Care International (AAALAC).

Apparatus

Testing was conducted in commercially available 5-hole operant chambers, each located within ventilated sound-attenuating enclosures (Med Associates, St. Albans, VT). Each chamber was equipped with a house light and stainless steel bar floor. The nose-poke holes were located on the left chamber wall with a food delivery receptacle centrally located on the opposite wall. Both the nose-poke holes and receptacle were fitted with 3 W stimulus lights and infrared beams in order to signal and detect response behavior, respectively. Control of the operant chambers and data collection were performed by MED-PC software version (IV) and adapted from operant software programs described previously (Zeeb et al., 2009)

Behavioral Procedure

Training

Animals were initially trained to nose-poke for sucrose pellet reinforcement (45 mg pellets; Bio-Serv, Frenchtown, NJ) in the illuminated food receptacle to initiate a 100-trial session. The extinguishment of the backlight and subsequent illumination of nose-poke hole 1, 2, 4, or 5 (the middle aperture was not used in these experiments) indicated a proper nose-poke response. Within 5-12 days of daily sessions the animals learned to initiate the session and make a nose-

poke response in the appropriate aperture within 10 s and retrieve one sucrose pellet in the food receptacle. Criterion for advancing to the second phase was completion of greater than 80% of trials with fewer than 20% omissions during daily training sessions. During the second phase, each of the four response choices was assigned a unique probability of consequences. In order to ensure every animal received a similar experience with the characteristic probabilities of each choice, each aperture was illuminated an approximately equal number of times during the 30-min session. Two different program versions will be created in order to counterbalance the assignment of reinforcement consequences to nose-poke holes and control for spatial biases. After completing 8 total sessions, animals then began free choice testing sessions.

Testing

A nose-poke in the food receptacle initiated the beginning of the 20-min session and was followed by a 5 s inter-trial interval (ITI) before the response apertures (1, 2, 4, 5) were illuminated. Each subject had 10 s to make a choice or the trial was scored as an omission and a new trial would begin. Each nose-poke hole was associated with a unique set of positive (sucrose pellets) and negative (session timeout) consequences that varied in both probability and magnitude (see Table 1 for details). For example, if a subject responded correctly in aperture 1, there was a high probability (p=0.9) of receiving a small food reward (one sucrose pellet) and a low probability (p=0.1) of incurring a short time out (5 s). Alternatively, if the rat chose aperture 2, there was a lower probability (p=0.4) of receiving a larger reward (4 sucrose pellets) and a higher probability (p=0.6) of incurring a longer time out (40 s). If a time-out (TO) was incurred no further trials could be initiated during that period (signaled by 5-Hz flashes during TO period in chosen aperture). Premature responses (responding at aperture during ITI) resulted in a 5 s TO. Perseverative responses were recorded both after the reward period and during TO, but not associated with any negative consequence. Given the constraint of session-length, an optimal choice was the two-pellet option (P2). Exclusive choice of P2 would produce the maximum amount of pellets earned (see Table 2). Choice preference was calculated as overall percent and animals received daily testing sessions until a stable pattern of choice behavior was observed. Stable baseline behavior was defined as no increasing or decreasing trends in choice selection percentage over five days.

Drugs

All drugs were obtained from commercial sources (SigmaAldrich, St. Louis MO). Bupropion HCl (0, 10.0, 20.0, 30.0 mg/kg), d-amphetamine HCl (0, 0.3, 1.0, 1.5 mg/kg), eticlopride HCl (0, 0.003, 0.01, 0.03 mg/kg), methylphenidate HCl (0, 1.0, 3.0, 5.7 mg/kg) and cocaine HCl (0, 5.0, 10.0, 15.0 mg/kg) were administered 15-30 min before test sessions via ip injection in a volume of 1ml/kg. Dose selection was chosen from pilot experiments and previous literature (Zeeb et al., 2009; Simon et al., 2011; Adriani et al., 2003, Evenden and Ko, 2006; Budzynska et al., 2011) Saline served as vehicle for all drugs with the exception of bupropion, which was dissolved in water.

Statistical Analyses

All statistical analyses were performed using Prism 5.0c software (GraphPad, San Diego CA). Data from pharmacological manipulations were analyzed using a two-way ANOVA with drug dose and choice selection (P1-P4) as main effects. An arcsine transformation was performed before analysis of variables expressed as proportion to limit the effect of an artificially imposed ceiling. In the case of a significant F test, a Bonferroni *post hoc* test was used to assess for significant group differences. Criterion for statistical significance was set *a priori* at $p<0.05$. Behavioral measurements of motor impulsivity were first calculated by the following equations Perseverative responses during time out (PerTO) = the number of responses/duration of time out incurred * 100. Perseverative responses during a reward period (PerRe) = responses/number of rewarded trials * 100. Premature responses = responses/number of completed trials. The data were further analyzed using a repeated measures one-way ANOVA.

Table 1. rGT response choices and consequences. Positive (sucrose pellets) and negative (session time out) outcomes ranged in both probability and magnitude (adapted from Zeeb et al., 2009).

	Response Choice			
	P1	**P2**	**P3**	**P4**
Reward	1 pellet	2 pellets	3 pellets	4 pellets
Probability	*p=0.90*	*p=0.80*	*p=0.50*	*p=0.40*
Time Out	5 sec	10 sec	30 sec	40 sec
Probability	*p=0.10*	*p=0.20*	*p=0.50*	*p=0.60*

Table 2. Optimal rGT performance. Numbers represent the maximum total number of pellets that could be theoretically obtained if each option was chosen exclusively in a 20-min session. Total maximum pellets were calculated using the minimum trial length (5 s).

	Response Choice			
	P1	**P2**	**P3**	**P4**
Maximum Pellets	196	274	90	66

RESULTS

d-Amphetamine

Amphetamine significantly increased the "risk averse" choice (least reward/least penalty), P1, at medium (1.0 mg/kg) and high doses (1.5 mg/kg). Responding increased at the low dose (0.3 mg/kg) (t = 2.184), but failed to reach significance. Optimal responding, P2, was also significantly decreased at all doses. This data is consistent with previous reports in Zeeb et al., 2009, however, no significant increase in suboptimal, P4, responding was observed at the 1.5 mg/kg dose (Figure 2; Dose X Choice: $F_{12,165}$= 4.70, p <0.0001; sal *vs* 0.3 mg/kg: P2 t(10) = 5.193 p<0.001; sal *vs* 1.0 mg/kg: P1: t(10) = 3.379, p <0.05; P2: t(10) = 5.333 p <0.001; sal *vs* 1.5 mg/kg: P1: t(10) = 3.269 p <0.05; P2: t(10) = 4.334 p <0.01). No significant changes in choice selection were observed at the high reward/high risk options (P3, P4) at any dose. Although increasing amphetamine dose appeared visually to impact omissions (Om), no significant difference from vehicle was observed.

Measurements of motor impulsivity Consistent with previous research (Cole and Robbins 1987; Baarendse et al., 2012) all doses of amphetamine increased premature (Prem) and perseverative responding. However, only the high dose (1.5) resulted in a significant difference in premature responses (q = 2.517 p <0.05; sal Prem *vs* 0.3 Prem q = 1.489 p > 0.05; sal Prem *vs* 1.0 Prem q = 2.178, p > 0.05). Perseverative responses during time out periods (PerTO) were significantly increased when compared to vehicle at medium and high doses (sal PerTO *vs* 0.3 PerTO q = 1.310, p > 0.05; sal PerTO *vs* 1.0 PerTO q = 3.384, p <0.01; sal PerTO. *vs* 1.5 PerTO q = 3.793, p <0.01). No significant differences in perseverative responses during reward (PerRe) were observed.

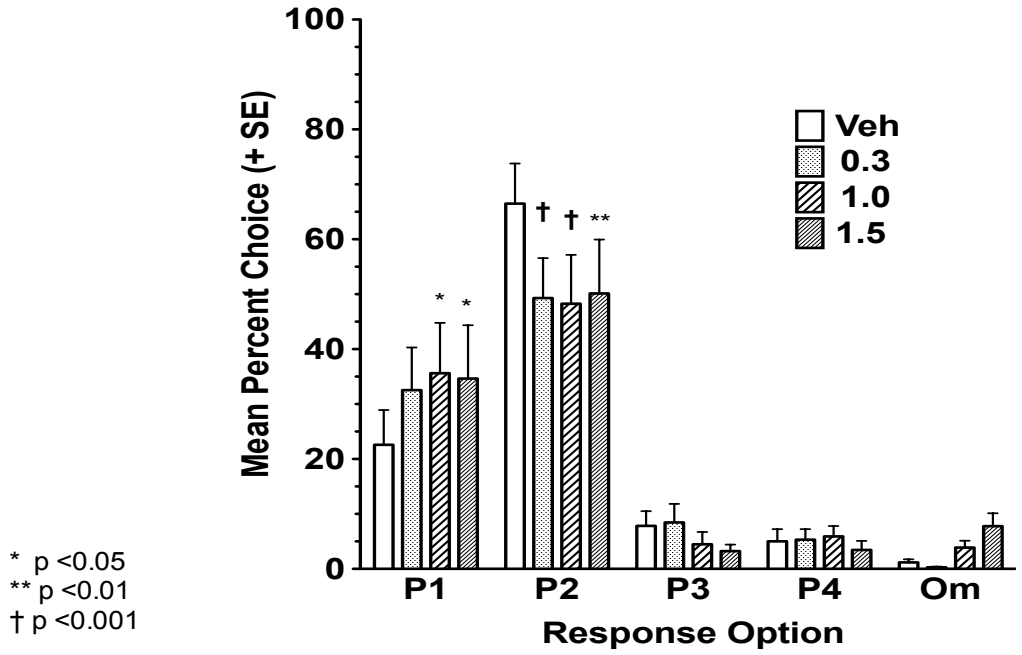

Figure 1 Mean percent choice (± SEM) is plotted as a function of each response option for doses of *d*-amphetamine examined (0-1.5 mg/kg) in the rGT. Acute administration significantly shifted choice selection to the lowest risk/reward option, P1, at 1.0 mg/kg and 1.5 mg/kg. Optimal choice, P2, was significantly decreased at 0.3, 1.0, and 1.5 mg/kg. (Note: asterisks and dagger represent statistical significance compared to vehicle control).

Eticlopride

Consistent with previous reports (Zeeb et al., 2009), the DA D_2 receptor antagonist, eticlopride, significantly decreased responses on suboptimal choice, P3 (50% chance of 3 pellet reward, 50% chance of 30 sec. TO) at the 0.01 mg/kg dose. However unlike Zeeb and colleagues (2009), no significant decrease in P4 or increase in P2 optimal choice was observed. Importantly, only seven of the eleven animals reached criterion for trials within the rGT session at the 0.03 mg/kg dose. Animals that reached criterion showed a significant increase in omissions and were therefore not viable for analysis. (Figure 3; Dose X Choice: $F_{6, 80} = 2.58$, $p = 0.0247$; sal *vs* 0.01 mg/kg: P3: $t(10) = 3.478$, $p < 0.01$). Eticlopride did not significantly affect perseverative, premature responses or omissions (all ps >0.05).

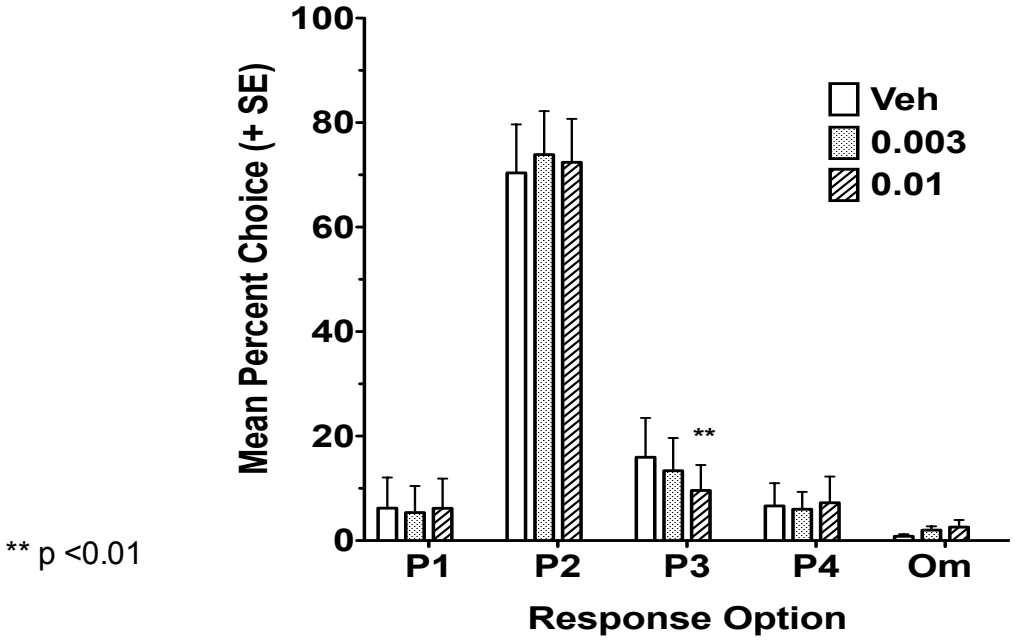

Figure 2 Mean percent choice (± SEM) is plotted as a function of each response option for doses of eticlopride (0-0.01) in the rGT. Acute administration significantly decreased suboptimal choice, P3, at 0.01 mg/kg. (Note: asterisks represent statistical significance compared to vehicle control).

Cocaine

The main behavioral impact of cocaine was decreased optimal responding. Responses at the P2 choice were numerically decreased across all doses, but this reached statistical significance only at medium (10.0 mg/kg) and high (15.0 mg/kg) doses (Figure 4; Dose X Choice: $F_{9,120}$= 3.31, p =0.0012; sal *vs* 10.0 mg/kg: P2: t(10) = 4.921, p <0.001; sal *vs* 15.0 mg/kg: P2: t(10) = 3.309, p <0.01). Similar to d-amphetamine, a dose-dependent upward numeric trend in risk averse or P1 responding was observed at moderate and high doses of cocaine, however these data did not reach statistical significance at any dose examined. In addition, no significant effect was observed at the riskier choices, P3 and P4, despite an overall shift away from optimality.

Measurements of motor impulsivity. In addition to its effect on choice behavior, cocaine significantly altered PerTO responding at the 10.0 mg/kg dose (q = 4.044, p <0.001). Although the highest dose (15.0 mg/kg) did not yield a significant increase in PerTO, an increasing trend in

PerRe responses was observed and nearly reached significance at the high dose (q = 2.231, p >0.05). Premature and omitted responses were not affected at any dose.

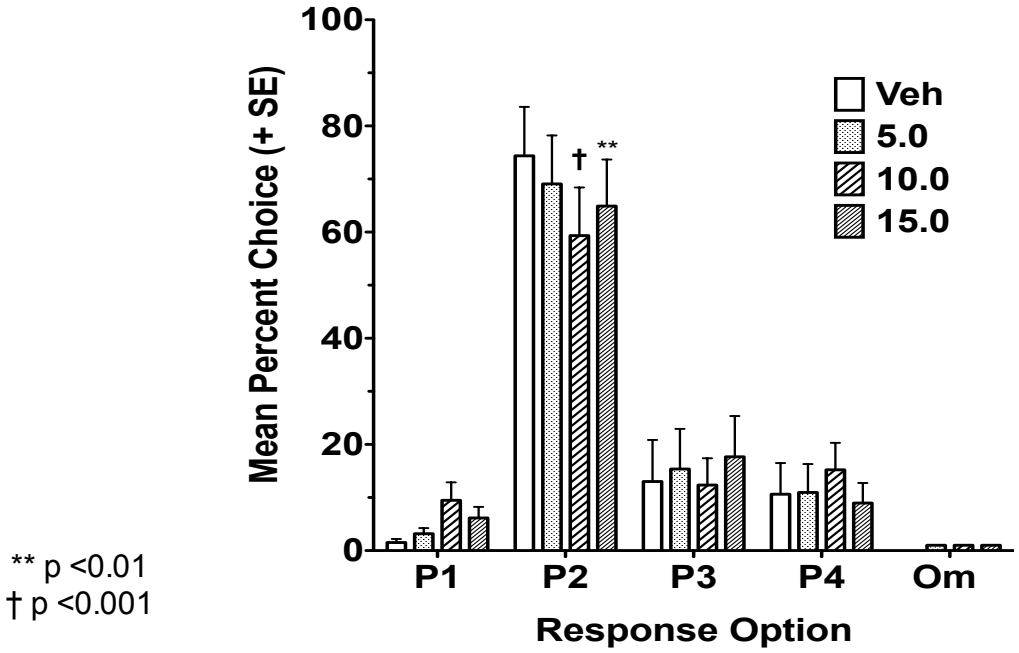

Figure 3 Mean percent choice (± SEM) is plotted as a function of each response option for doses of cocaine examined (0-15.0 mg/kg) in the rGT. Acute administration significantly decreased optimal choice, P2, at 10.0 mg/kg and 15.0 mg/kg. (Note: asterisks and dagger represent statistical significance compared to vehicle control).

Methylphenidate

Methylphenidate administration dose-dependently decreased optimal responding. Responses at the P2 choice were significantly decreased at moderate (3.0 mg/kg) and highest (5.7 mg/kg) doses. Similar to d-amphetamine, a dose-dependent upward trend in risk averse or P1 responding was observed, however significance was not reached at any dose (Figure 5; Dose X Choice: $F_{9,120}$= 4.44, p <0.0001; sal *vs* 3.0 mg/kg: P2: t(10) = 4.282, p <0.001; sal *vs* 5.7 mg/kg: P2: t(10) = 3.983, p <0.001). Significance was nearly reached at P1 after administration of the high dose (t(10) = 2.317, p >0.05). No change in omissions was observed at any dose.

Measurements of motor impulsivity In addition to its affect on choice behavior, methylphenidate administration significantly altered PerTO responding at the 3.0 mg/kg

dose (q = 2.675, p <0.05). Similar to cocaine, all perseverative (PerTO and PerRe) responses were increased compared to saline but only the medium dose had a significant affect on responding during time out periods. Premature responses increased as dose increased, but were not significantly affected at any dose. Furthermore, no significant effect was observed at the riskier choices, P3 and P4, yet overall choice shifted away from optimality.

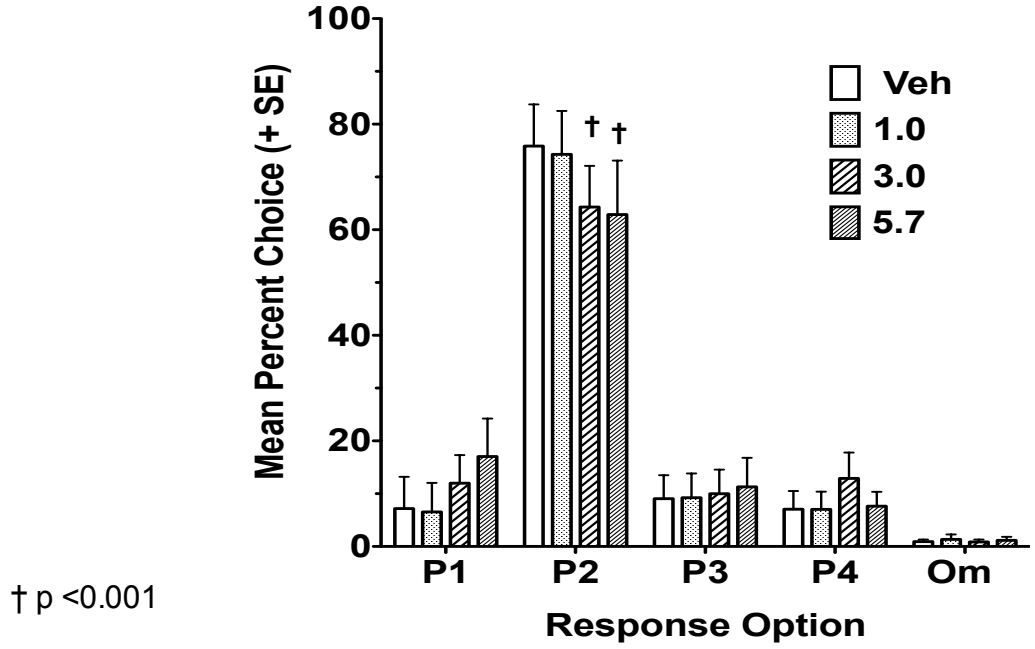

Figure 4 Mean percent choice (± SEM) is plotted as a function of each response option for doses of methylphenidate examined (0-5.7 mg/kg) in the rGT. Acute administration of significantly decreased optimal choice, P2, at 3.0 mg/kg and 5.7 mg/kg. (Note: daggers represent statistical significance compared to vehicle control).

Bupropion

The effect of bupropion on choice selection was nearly identical to methylphenidate. A significant decrease in optimal responding (P2) was observed at medium (20.0 mg/kg) and high (30.0 mg/kg) doses. Again, a slight increase in P1 responding at medium and high doses and no differences in choice behavior at P3, P4 or omissions were observed (Figure 6; Dose X Choice:

$F_{9,120}$= 3.93, p <0.0002; sal *vs* 20.0 mg/kg: P2: t(10) = 2.845, *p* <0.05; sal vs 30.0 mg/kg: P2: t(10) = 4.609, *p* <0.0001).

Measurements of motor impulsivity. Compared to vehicle, increases in perseverative responses were positively correlated to dose. Specifically, PerTO responses were significantly higher at the highest dose (*q* = 3.870, *p* <0.01) however PerRe responses were not significantly higher than chance at any dose. Interestingly, all doses increased premature responses and significantly at the medium dose (*q* = 2.694, *p* <0.05).

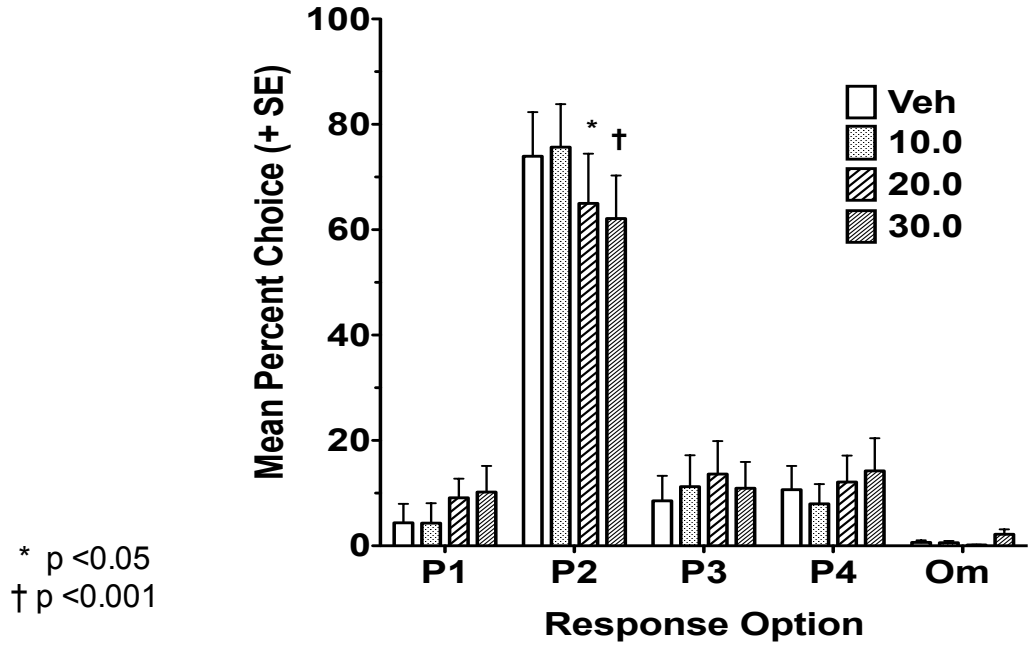

Figure 5 Mean percent choice (± SEM) is plotted as a function of each response option for doses of bupropion examined (0-30 mg/kg) in the rGT. Acute administration of bupropion significantly decreased optimal choice, P2, at 20 mg/kg and 30 mg/kg. (Note: asterisk and dagger represent statistical significance compared to vehicle control).

DISCUSSION

We examined the effect of monoamine transporters (MATs) with unique binding affinities for DAT, NET, and 5-HTT on probabilistic decision-making in the rGT. The role for dopamine in the rGT has been previously established (Zeeb et al., 2009), however the contributions of specific MATs to these behavioral processes were unknown. Importantly, two previously genetic studies reported conflicting findings in that both reduction (Young et al., 2011) and over-expression (Adriani et al., 2009) of DAT led to increased proneness for risky decision-making. Most interestingly, despite varying binding affinities for DAT, NET, and 5-HTT, behavioral responses observed in our study were largely consistent across drug manipulations. Cocaine dose-dependently decreased optimal (P2) responses and contributed to an increasing trend of the risk-averse (P1) selection in a similar fashion to methylphenidate (MPH) and bupropion (BUP). Consistency in the behavioral results following MPH and BUP was expected given the analogous nature of their physiological action (DAT/NET). However, it was hypothesized that because cocaine has a binding affinity distinct from MPH and BUP (i.e., active at all MATs), that this would distinguish it from both MPH and BUP. Although no robust difference in response behavior existed among drugs, it is interesting that each ligand examined in the present study is DAT-dependent, which may highlight the role of DAT in probabilistic decision-making. Thus, inhibition of DAT may be a critical mechanism that underlies these behavioral processes.

Administration of cocaine significantly decreased the optimal choice behavior after acute administration of medium (10 mg/kg) and high doses (15mg/kg). Inhibition of 5-HTT is the distinguishing property in cocaine's pharmacological profile. Humans who carry an allelic variation of the common serotonin 5-HTT linked polymorphic region exhibited maladaptive IGT performance (Homberg et al., 2011). Furthermore, 5-HTT knockout rats perform poorly on a comparable rodent version of the IGT (Homberg et al., 2008). These data partially support our observed decrease in optimal choice after cocaine administration in the rGT. Alternative metrics of decision-making often focus on measures of impulsivity. Some have reported an increase in premature responses after acute dosing (15 mg/kg) in a five-choice serial reaction task (5-CSRTT), suggesting increased motor impulsivity (Fletcher et al., 2011). We did not observe an increase in premature responses at any dose examined, but we did observe an increase in an alternative measurement of impulsivity, perseverative responses. However, perseverative

responses were not penalized in our experiments and both trial number and omissions remained consistent across doses, suggesting motor impulsivity did not affect choice behavior. Recent investigation of specific monoamine reuptake inhibitors report 5-HT or norepinephrine reuptake inhibitors actually work to decrease impulsive action, while DA reuptake inhibitors enhance impulsive action (Homberg et al., 2007; Baarendse et al., 2011). Such evidence may elucidate the moderate, yet insignificant effects of cocaine-induced motor impulsivity in the rGT. Surprisingly, there is a relative paucity in probabilistic measurements of decision-making after administration of cocaine. A study conducted by Simon and colleagues (2009) used varying probabilities and magnitudes of foot shock as punishment. Although they failed to observe a dose-dependent shift in choice behavior, selection of the optimal reward (i.e., large reward during 0% chance of shock) was decreased. Similarly, maladaptive behavior was perpetuated not necessarily by a shift to risk-averse or risky options, but by a ubiquitous decrease of the optimal choice.

Methylphenidate is a psychostimulant structurally similar to d-amphetamine, yet its mechanism of DA-mediated activity is more comparable to cocaine with the exception of its lack of affinity for 5-HTT (Iversen et al., 2009). MPH has been shown to improve attention deficits, hyperactivity and impulsivity in individuals diagnosed with ADHD (Schneider, 2011). Individuals with ADHD make more choices for smaller, immediate rewards (Barkley et al., 2004) and such impulsive behavior can be ameliorated by MPH (Shiels et. al., 2009). In measurements of probabilistic decision-making, a decrease in risky choice behavior was observed in patients diagnosed with ADHD or frontotemporal dementia after acute treatment of MPH (De Vito et al., 2008; Rahman et al., 2005) Furthermore, animal models of ADHD showed a similar decrease in delay discounting after acute administration of MPH, but only after an intermediate dose (Slezak and Anderson, 2011). Dose regimen of MPH has been shown to be the critical factor in attention and motor impulsivity as low doses increase accuracy in the 5-CSRTT while high doses decrease accuracy and increase premature responses (Paine et al., 2007). Our study is in agreement with existing literature in that measures of motor impulsivity and suboptimal selection increased as dose increased. However, only perseverative TO responding at the intermediate dose reached significance and trials/omissions were unaffected. Therefore, motor impulsivity may be a contributing, but not a determining factor of choice selection. Interestingly, MPH created an increasing trend of risk-averse choices that nearly reached

significance at the highest dose. The data are remarkably similar to those observed using *d*-amphetamine, yet they differ in the extent of effect. This may be due to the capacity of MPH to inhibit NET. Previous studies established that the NET reuptake inhibitor, atamoxetine, dose-dependently improved accuracy and reduced premature responses (Robinson, 2012; Baarendse, 2011). Inactivity of NETs may aid in counterbalancing the effect of DAT inhibition. Our study is the first to investigate risk-taking behavior after acute MPH administration in rats. Further behavioral analysis of NET inhibition using the rGT may be helpful in identifying its specific contribution to probabilistic decision-making.

Bupropion is an atypical anti-depressant that weakly inhibits reuptake of DA and to a slightly lesser degree, NE reuptake, but it has virtually no effect on the reuptake of 5-HT (Ferris and Cooper, 1983). It is also a noncompetitive inhibitor of nicotinic acetylcholine receptors (Slemmer et al., 2000). Bupropion has been used successfully treatment for smoking cessation, methamphetamine abuse, ADHD, and pathological gambling (Aubin, 2002; Elkashef et al., 2008; Barrickman et al., 1995; Wilens et al., 2005; Dannon et al., 2005). In one study, acute treatment in rats dose-dependently lowered reward threshold in an intracranial self-stimulation paradigm (Cryan et al., 2003). However, to our knowledge, no previous research has been done on the behavioral effect of bupropion on risk-based decision-making tasks in rodents or humans. We found the drug had markedly similar results to that of cocaine and methylphenidate, producing decreased optimal choices at intermediate (20 mg/kg) and highest doses (30 mg/kg) examined. Previous research demonstrated that a higher dose (40 mg/kg) does increase locomotor activity in rats (Santamaria and Arias, 2010). Given that total perseverative responses were significantly higher at both doses, one plausible explanation of our findings is increased locomotion. Yet, omissions, trial number and premature responses were not significantly affected, suggesting any possible increase in locomotor activity was not the basis for the change in percent choice. These data correspond with previous reports that suggest bupropion is beneficial in improving attention without affecting impulsivity (Acheson and de Wit, 2008). However, caution is warranted when generalizing effects in rats to humans as recent research demonstrated acute administration of bupropion in rats produced higher occupation of DAT in the striatum when compared to humans DA while performing a cognitive task. This difference is most likely due to species difference in that human metabolic pathways break down bupropion into its pharmacologically active metabolites, hydroxybupropion and threohydrobupropion (Egerton et

al., 2010; Schroeder, 1983).

Consistent with Zeeb et al. (2009), acute administration of *d*-amphetamine not only decreased optimal choice but significantly increased choice of the lowest risk/lowest reward option. In addition to blocking catecholamine transporters, amphetamine also induces release of both NE and DA by way of transporter reversal (Iversen et al., 2009). Humans with disruption in DA such Parkinson's disease, schizophrenia, or amphetamine abusers all perform poorly on risk-assessment tasks (Rogers et al., 1999; Mimura et al., 2006). In rodent models of probabilistic decision-making the impact of amphetamine is differential across metrics Zeeb and colleagues (2009) observed a shift toward risk-averse responses even when both probability and/or magnitude of TO was held constant. Additionally, decreased high-risk choices have been reported when a primary negative reinforcer (foot shock) was used in a similar rodent gambling task (Simon et al., 2009). This is in contrast with St. Onge and Floresco (2009) where animals chose larger, riskier options without a signaled reinforcement. The effect of amphetamine on motor impulsivity in 5-CSRT is well documented (Cole and Robbins, 1987; Fletcher et al., 2011) and supported by our data demonstrating an increase in premature and perseverative responses. Again, neither omissions nor trials were affected suggesting motor impulsivity likely was not the determining factor in choice selection. Our study adds consistency to the literature in that when a consequence (session time out) was signaled by a stimulus (flashing light), amphetamine administration shifted behavior away from optimality to a risk-averse or low reward/low penalty contingency. Such studies bolster the argument that amphetamine-induced aversion to risk may be due to a stimulus that signals the salience of negative consequences.

Our data partially replicated previous findings (Zeeb et al., 2009) in that the selective D_2 receptor antagonist eticlopride decreased risky choices, however it differed in that no improvement of the optimal choice was observed. Our findings are curious in that one may expect a not only a decrease in the selection of risky options, but a compensatory increase in the optimal option. Furthermore, although there was not a significant change in motor impulsivity across doses, the highest 0.03 mg/kg dose of eticlopride examined significantly increased omissions and decreased trial number. Such evidence may support the "the inverted U" hypothesis of DA modulation in decision-making tasks. Both significant increases and decreases in DA manipulation cause deficits in optimal behavior (Sevy et al., 2006; Brozoski et al., 1979; Arnsten, 1997) thereby relating the regulatory role of DA. These data add to a history of

equivocal reports of DA receptor manipulations within measures of probabilistic reinforcement. Bromocriptine (DA D_2/D_3 receptor agonist) increased choice of larger uncertain rewards in a probability-discounting task in which the rat chose between a certain low risk/low reward and larger uncertain reward (St. Onge and Floresco, 2009). However, bromocriptine and the selective DA receptor agonists like SKF 81297 (D_1), and quinpirole (D_2/D_3) did not have an effect, although DA antagonists eticlopride (D_2) and flupenthixol (nonspecific DA) decreased the propensity to make risky choices (St. Onge et al., 2010, 2011; Zeeb et al., 2009; Ghods-Sharifi et al., 2008). In a recent study, quinpirole did increase the propensity to continue to "gamble" after "almost winning" in a Slot Machine Task (Zeeb and Winstanley, 2011). Taken together, one can reliably say D_2 –like, rather than D_1 – like, receptors are critical in maintaining performance within measures of probabilistic reinforcement. However given that D_2 antagonists can also block inhibitory autoreceptors leading to an increase in neuronal DA firing (Pucak and Grace, 1994, 1996), the specific cellular mechanisms related to gambling behavior remain unknown.

Our present study has replicated data suggesting that the rGT is a viable and highly translation model of research for investigating pharmacological modulations of probabilistic decision-making. In addition to strong face and construct validity, the rGT measures motor impulsivity and decision-making behaviors, and integration- or dissociation- of these two behaviors is essential to characterizing the impact of different neurobiological or pharmacological manipulations. Additionally, the rGT integrates probability and magnitude of negative consequences akin to the complexity inherent to the type of decisions humans are presented with every day. Here, we reported that acute administration of commonly abused psychomotor stimulants (cocaine and amphetamine) and therapeutic drugs (methylphenidate and bupropion) both effectively contributed to a behavioral phenotype—specifically decreased selection of optimal choice. Moreover, an increasing numeric trend toward risk-averse choices existed in all drugs, but most robustly in those with preference for DA/DAT-mediated mechanisms (*d*-amphetamine, methylphenidate, and bupropion). Further investigation of MAT inhibition in other decision-making tasks involving signaled negative consequences would help elucidate specific roles and address inconsistencies in the literature. Additionally, attention must be paid to repeated or chronic administration of these drugs as it may produce critical neuroanatomical changes relevant to the evaluation of risk and reward (Nestler, 2001). Finally, central delivery of genetic modulators for specific transporters in brain regions associated with

impulse control and risk evaluation would be a logical future direction to pursue. Examination of the ability to successfully perform a complicated task such as the rGT may provide an appreciable advantage in answering several experimental questions surrounding the pervasive and intricate nature of dysfunctional decision-making.

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BIOGRAPHICAL SKETCH

NAME Eckrich, Samuel Joseph	POSITION TITLE Graduate Student/Teacher's Assistant
eRA COMMONS USER NAME sje10c	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
St. John's University, Collegeville, MN	B.A.	05/07	Biology
Florida State University, Tallahassee	Ph.D.	Current	Neuroscience

A. Personal Statement

The inability of an individual to properly formulate a strategy that will lead to profitable long-term outcomes is a hallmark of nearly every mental illness. However, inherent to researching a topic as broad as decision-making is a multitude of constraints including inter-individual differences, environment and genetics. Certainly, an animal model that incorporates important economic decisions while controlling for extraneous variables is indispensable for explicating specific brain regions, circuits, neurochemical modulation and development. In collaboration with local and international investigators, our lab has adopted and validated a rodent model used to measure probabilistic decision-making and impulsivity. My first project successfully investigated the impact of monoamine transporters on rat's ability to make optimal long-term decisions. Perhaps the most exciting attribute of a viable rodent model of decision-making is its potential to impact and inspire research across several fields of science including neuroscience, biology, medicine, cognitive psychology, social psychology, behavioral economics and even the emerging field of neuroeconomics. My comprehensive background in clinical and laboratory research paired with excellent tutelage under Dr. Josh Rodefer and a supportive laboratory environment places me in a position to make important contributions to various areas of science.

B. Positions and Honors

Positions and Employment

2006-2007	Teacher's Assistant/Laboratory Technician, Biology Department, St. John's University, Collegeville, MN
2007-2010	Psychiatric Associate, University of Minnesota Medical Center-Riverside, Minneapolis, MN.
2008-2010	Laboratory Assistant, University of Minnesota, Department of Animal and Veterinary Sciences, St. Paul, MN.
2011-	Teacher's Assistant, Psychology Department, Florida State University, Tallahassee, FL.
2012-	Graduate Neuroantomy Lab Instructor, Psychology Department, Florida State University, FL

Other Experience and Professional Memberships

2010-	Member, Society for Neuroscience

Honors

2012	Selected student speaker, Florida State University's Rushton Seminar

C. Selected Peer-reviewed Publications

1. Rodefer JS, Saland SK, **Eckrich SJ** (2012). Selective phosphodiesterase inhibitors improve performance on the ED/ID cognitive task in rats. Neuropharmacology 62(3): 1182-1190.

2. **Eckrich SJ**, Saland, SK, Rodefer JS (under review). The impact of monoamine transport inhibitors in the rat gambling task**.**

D. Coursework

1. Cell and Molecular Neuroscience	A
2. Neuroscience Methods	A
3. Systems and Behavioral Neuroscience	A
4. Neuroanatomy	A
5. Research and Design Analysis	A-