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Effect of Social Peers on Risky Decision Making in Male Sprague Dawley Rats

Virginia Weiss
University of Kentucky, vwe222@g.uky.edu

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Virginia Weiss, Student

Dr. Michael T. Bardo, Major Professor

Dr. Mark Fillmore, Director of Graduate Studies

EFFECT OF SOCIAL PEERS ON RISKY DECISION MAKING IN MALE SPRAGUE DAWLEY RATS

THESIS

A thesis submitted in partial fulfillment of the
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By

Virginia Graham Weiss

Lexington, Kentucky

Director: Dr. Michael T. Bardo, Professor of Psychology

Lexington, Kentucky

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ABSTRACT OF THESIS

EFFECT OF SOCIAL PEERS ON RISKY DECISION MAKING IN MALE SPRAGUE DAWLEY RATS

Adolescence is a time associated with increased risk taking and peer relations. Research has shown that adolescents are more vulnerable to peer pressure compared to adults, leading to exacerbated risk taking. Preclinical research suggests that these findings may also be applicable to adolescent rodents, which find social interaction rewarding and are prone to risky behavior. There is, however, little research on the effect of social interaction on rodent models of risky decision-making. This thesis utilized social chambers, which consisted of adjacent operant chambers separated by wire mesh. Adolescent rats performed a risky decision-making task in which they had a choice between a small and large reward (associated with a mild footshock, which increased in probability across the session). Experiment 1 determined if the presence of peer altered performance on the task after stability. Experiment 2 determined if the presence of a peer altered performance on the task during acquisition. Results of Experiment 1 revealed no significant changes. Results from Experiment 2 revealed a significant increase in preference for the risky reward in the group of rats that had daily exposure to a social peer. These results provide evidence that social influence on risk taking can be modeled in rodents.

KEYWORDS: Adolescents, Rodents, Risk-taking, Social Interaction

Virginia Graham Weiss

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By

Virginia Graham Weiss

_____Michael T. Bardo_____
Director of Thesis

_____Mark Fillmore_____
Director of Graduate Studies

_____May 21, 2015_____

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CHAPTER 1

Introduction

Adolescence is a time associated with maturation of both neuronal and peripheral body systems. During this age period, peer interactions are typically extensive due to school and extracurricular activities. These peer interactions also are apparent with crimes and antisocial behaviors committed by adolescents, which typically occur in a group setting (McCord et al., 2005). This contrasts with adults, who often act alone. It is unknown, however, why there are age differences related to crimes. One possibility is that because adolescents are in the presence of peers more often than adults, they are simply showing increased odds that if they commit a crime, it will be within a group context.

The phenomenon of social facilitation of disruptive behaviors is not solely associated with crimes such as robbery, destruction of property, or vandalism. In particular, the initiation of drug use during adolescence also generally happens in a group setting. Research has found that for most drugs, initiation of use begins around age 18 (being a little younger for nicotine and a little older for prescription opiates) and discontinuation often occurs around age 21 (Kandel et al., 1984). These findings confirm that while most adolescents experiment with illicit substances, relatively few continue use to the point where a substance use disorder becomes manifest. Therefore, the focus of research on drug use should not be exclusively on targeting the elimination of initiation of use, but rather finding risk factors that are associated with those persons who go on to develop substance use disorders.

The purpose of the current thesis was to evaluate whether or not social risk taking can be modeled in rodents, both before and after acquisition of behavior, and observe

whether or not behavioral changes in rodents mimic those seen in humans following peer interaction.

Sensation and Novelty Seeking

Human and animal research has begun to determine individual differences in behavioral and personality traits are correlated with substance abuse later in life. Among the various individual difference traits used to predict drug use, sensation seeking or novelty seeking has been shown to be one of the most reliable predictors in both humans and animals (Zuckerman, 1986; Franques, 2003; Belin et al., 2011; Marusich et al., 2011; Gancarz et al., 2011).

In humans, sensation seeking is measured via a paper survey called the Sensation Seeking Scale, with a large number of items that include information about thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. Those individuals who rank higher on these traits are also more likely to be current drug users (Zuckerman, 1986). A newer survey has also been created to assess sensation seeking, namely the UPPS, which measures urgency (U), premeditation (P), perseverance (P), and sensation seeking (S) (Whiteside et al., 2005). This scale is commonly used and involves choosing an answer that most accurately matches how you act in situations on a Likert scale. In a study that compared performance on a gambling task to levels of sensation seeking and urgency (as measured by the UPPS), it was found that there was a link between sensation seeking and urgency to disadvantageous decisions during the gambling task (Bayard et al., 2011).

To test for sensation seeking or novelty seeking in rats, the experimenter places the animal into a large, novel, chamber and measures the amount of horizontal movement for

a set period of time (Jodogne et al., 1994). Alternatively, novelty seeking may be tested in a conditioned place preference (CPP) chamber, which is made up of 3 separate compartments that can be blocked off from one another and differ in appearance. On the first three sessions, the animal is confined to one end compartment of the chamber for a set period of time (typically 30 minutes). On the next session, the animal is allowed to explore all of the compartments. The measurement of novelty seeking is defined by the percentage of time spent in the novel compartment compared to the total time. If the animal is high in novelty seeking, they will spend more than 50% of their time in the novel chamber. Spending time exploring novel environments is predictive of increased rates of acquisition of stimulant self-administration in drug naïve rats compared to their low novelty- or sensation-seeking cohorts (Belin, 2011; Gancarz, 2011).

Impulsivity

Delay Discounting

A commonly used task for measuring impulsive behavior in both humans and animals is the delay-discounting task. In humans, delay discounting is measured by asking participants to choose between the possibility of receiving a set amount of money after a set delay, compared to a lesser amount of money immediately. The amount of time the participant would have to wait steadily increases until they reach a break point, which is defined as having no preference between the money available after the delay, and the amount that would be available immediately (Reynolds, 2006). Regular use of nicotine, cocaine, marijuana, and alcohol are all associated with steeper discounting than controls (Businelle et al., 2010; Washio et al., 2011; Peters et al., 2013; Andrade et al., 2013). However, it is not clear if this change in discounting precedes or results from drug use.

In preclinical models, the animal is given the choice to respond for a small reward, which is delivered immediately preceding a response, or a large reward, which is delivered after a set amount of time elapses preceding a response (Cardinal, 2006). The question that this task asks is whether the animal is willing to wait for a reward of greater magnitude. Larger discounting rates (choosing the small reward over the large reward) are associated with higher rates of drug use. For example, Marusich and Bardo (2009) found that rats that were highly impulsive on the delay discounting task self-administered more methylphenidate at low doses than rats that were low in impulsivity. Furthermore, it has also been shown that impulsive rats will show greater escalation of cocaine self-administration compared to non-impulsive rats when tested on a 6-hr long-access paradigm (Anker et al., 2009). Not are individual differences in delay discounting associated with subsequent stimulant self-administration, chronic drug use can increase impulsive choice. For example, research has shown that pre-exposure to stimulants (particularly amphetamine and cocaine) causes increased discounting in this task, indicating that rats with a history of stimulant exposure become more impulsive than rats with no drug exposure (Mendez et al., 2010; Gipson and Bardo, 2009). Thus, there is a reciprocal relationship between impulsive choice and stimulant use.

Cued Go/No Go Task

Another human task designed to measure impulsivity is the cued go/no go task (Fillmore, 2003). This task has a "go" cue that is associated with the requirement for the participant to make a response 80% of the time and a "no go" cue that is associated with the need for a participant to withhold a response 80% of the time. This means that on 20% of trials in which a "go" cue is shown, it will be followed by a "no go" target, and the

participant needs to withhold a response. Based on the data from these trials, researchers are able to sort participants into high or low impulsivity groups, with those who are unable to inhibit responding falling into the high impulsivity group. Individuals who are dependent on substances such as cocaine and methamphetamine are highly impulsive based on results of this task (Pike et al., 2013). That is, cocaine users who are given a cocaine image for a "go" signal have much higher rates of inhibitory failures than participants who are either assigned a neutral "go" signal or non-cocaine users who are assigned a cocaine "go" signal. Alcohol has also been shown to affect performance on this task. Participants who received a moderate dose of alcohol before completing the task had significantly higher rates of inhibitory failures compared to participants who received a placebo drink (Weafer and Fillmore, 2012).

Risk Taking

Iowa Gambling Task

In humans, risk taking is assessed using the Iowa Gambling Task (Bechara et al., 1998), which is now generally performed on a computer. The participant is shown 4 decks of cards and is told that each deck contains cards that are worth money, and some that take money away, with the goal of gaining as much money as possible. What they are not told is that 2 decks contain cards that give high gains, but also high losses, and the other 2 decks contain cards that give lower gains, but also lower losses. The most efficient way to maximize winnings is to pick from the 2 decks with the smaller gains. Cocaine dependent individuals perform poorly on the Iowa Gambling Task, preferring to choose from the two disadvantageous decks more often than the two advantageous ones (Vadhan et al., 2009; Kjome et al., 2010). Disadvantageous choices in this task have also been associated with

social dysfunction (Cunha et al., 2011), suggesting real world validity of this task. Due to methodological barriers, the Iowa Gambling task is not used in preclinical models of risk-taking.

Probabilistic Discounting Task

Preclinical models use adaptations of clinical tasks in order to test behaviors of interest. One task often used to measure risk taking in animals is the probabilistic discounting task, which is functionally similar to the Iowa Gambling Task in humans. This task allows animals to choose between a small, safe reward, where a single food pellet is delivered immediately following a response, or a large, risky reward, where the probability of multiple food pellets delivered immediately following a response decreases across a session (Cardinal, 2006). Unlike delay discounting, which measures the willingness to wait for a guaranteed reward, the probabilistic discounting task measures risk taking that is more closely associated with gambling behavior. Studies have shown that stimulants (particularly amphetamine and cocaine) increase risk taking in the probabilistic discounting task (Floresco and Whelan, 2009; Mendez et al., 2010). Chronic experimenter-administered amphetamine also increases choice of the large, risky reward compared to baseline behavior in the same animals. Similarly, chronic self-administration of cocaine also increases the choice of the large, risky reward compared to drug-naïve animals.

Risky Decision Making Task

Real life gambling is associated with both rewarding gains *and* aversive losses when making a risky choice. Unfortunately, the probabilistic discounting task does not utilize aversive stimuli directly. Thus, a new preclinical task has been designed that adds an aversive stimulus to the risky option, namely the risky decision making task, developed

by Setlow and colleagues (Simon and Setlow, 2009). In this task, rats are given a choice between a small, safe reward of a single food pellet that is delivered immediately following a response, and a large, risky reward of three food pellets that are delivered immediately following a response; however, the large reward is also associated with a mild footshock, with the probability of the shock increasing across the session by block.

Performance on the risky decision making task is altered by a variety of drugs of abuse. Acute administration of morphine or diazepam increases choice of the large, risky reward, whereas acute administration of nicotine or amphetamine decreases risky choice (Mitchell et al., 2011). Similar to the probabilistic discounting task, chronic experimenter-administered cocaine exposure increases choice of the large, risky reward compared to drug naïve animals (Simon et al., 2009).

More interestingly, this task predicts self-administration of cocaine, both in adolescent and adult rats (Mitchell et al., 2013). Rats inclined to choose the risky option more, regardless of the probability of shock are also more likely to self-administer cocaine at higher rates compared to their more risk adverse cohorts. The self-administration of cocaine, in turn, leads to choice of the risky reward more often in an intake-dependent manner. This suggests that not only does risk taking behavior lead to higher rates of drug use, but also that any drug use will lead to an increase in risk taking behavior, which can lead to a vicious escalation of drug use.

Social Influence on Behavior

Among the various tasks mentioned above, almost all have been conducted in a context where there is only one human or rat participant. Significantly less work has focused on the effects of peer influences. Since problem behaviors typically occur in a

group setting, especially among adolescents, it is important to know the effects that cohorts have on decision-making.

Social Influences in Risk Taking

The field of social psychology has contributed to our understanding of social risk taking. This work has shown that adolescents are more vulnerable to peer pressure and advice compared to adults (Gardner and Steinberg, 2005). In addition, peers typically advise friends to make riskier decisions than they would choose for themselves (Beisswanger et al., 2003). This latter finding appears to be true for only relationship and social situations, and does not generalize to risky decisions about financial situations (Stone et al., 2002).

Recent work by Gardner and Steinberg (2005) has shown that younger individuals exhibit more risk taking than older individuals, and this risk behavior is exacerbated when in a social setting among peers. In that study, examination of gender differences showed that males give greater weight to benefits of a risky decision and less weight to the negative consequences compared to females, suggesting that males are more likely to engage in these risky behaviors. When asked about the same risk taking situations in a group setting, males further increased the perceived weight of the benefits as compared to the negative consequences. When ethnicity is taken into account, non-white adults were slightly more risky than white adults, while white adolescents were slightly more risky than non-white adolescents when tested individually. For the adolescents in a peer setting, increased risk preference was seen in the non-white participants more than the white participants.

Rewarding Properties of Social Interaction

Preclinical research has suggested that social interaction during the adolescent period is a rewarding event. Douglas and colleagues (2004) investigated the rewarding properties of social interactions in both adolescent and adult male and female rats that were housed in either individual or pair-housed conditions. Testing for social place preference was conducted in a CPP chamber, where two main compartments were attached with a third, smaller compartment. Rats were exposed to each end of the compartment on alternating days, with a social partner placed in one compartment and no partner placed in the opposite compartment. On the test session, individual rats were then allowed access to all three compartments and the duration in each compartment was recorded.

Results from that study showed that the rewarding effect of social interaction was dependent not only on gender, but also the housing condition of the subjects (Douglas et al., 2004). Adolescents that were in isolated conditions found social interaction rewarding, especially in males. In contrast, animals that were in social housing did not find social interaction rewarding, although adolescents eventually began to show a preference for the chamber previously paired with a partner following multiple test sessions. Interestingly, if a socially housed animal was paired with an animal that was housed in isolation, the socially housed animal found the interaction aversive; this effect was stronger for the adolescent than the adult rats.

In a recent CPP study from our laboratory (Yates et al., 2013), it was found that adolescent male rats preferred a compartment previously paired with an age- and sex-matched conspecific relative to a compartment paired with amphetamine. This effect was not seen in adolescent females, who showed no preference for either compartment. In

addition, adult rats of either gender showed preference for the amphetamine compartment compared to the social-paired compartment.

Social Influence on Drug Use

Research shows that members of various social groups will either reinforce or punish the use of drugs based on the norms that have been decided upon by that group (Kandel, 1986). In fact, the easiest way to predict whether or not an adolescent will initiate drug use is whether or not their friends use drugs (Bahr et al., 2005). Within most social groups, the status of the leader is a critical determinant of substance use norms within the group (Jones et al., 2007). However, while group affiliation can determine drug use norms for individual members, there is also evidence that individuals who possess traits that increase risk for drug use will seek each other out in order to form peer clusters (Donohew et al., 1999), thus suggesting that predisposing individual differences in biological risk may precede peer group identification. In this regard, preclinical research may be useful for assessing social x biological interactions involved in drug use.

Many studies are able to relate social housing to drug use. For example, animals reared in an enriched environment self-administer drugs at lower rates than rats that are reared in an isolated environment (Alvers et al., 2012; Puhl et al., 2012). However, this demonstration may not have much real world application in the setting of drug use because those rats were tested for self-administration in a non-social condition (operant conditioning chamber), whereas substance use in humans typically occurs in a group setting. Therefore, it is necessary to look into the intricate dynamics of self-administration in a social context in rats as well.

Until recently, there has been little work examining drug-taking behavior in laboratory animals while in a social group. Since intravenous drug self-administration requires a catheter attached to an infusion system, placing two catheterized rats into the same operant chamber is not practical from a logistical point of view. In addition, even with orally administered drugs, putting two rats into an operant chamber simultaneously would lead to responses made by both individuals, with no accountability for which rat was making each response. To avoid these logistical problems, a novel apparatus has been devised that consists of two standard operant chambers, connected by removing one side on each and replacing it with wire mesh (Smith, 2012). This allows the animals to have limited tactile, olfactory, auditory, and visual contact with one another, but prevents one rat from interfering with the responses made by the other. Thus, these social chambers allow for two animals to run at the same time and allow the experimenter to collect data from the influence of social interaction during task performance.

Using these social chambers, Smith (2012) assessed peer influences on cocaine self-administration. Rats lived in the chambers throughout the experiment, with one rat in each chamber. Half of the rats were paired with a partner that also had access to cocaine, and the other half had a non-drug paired partner. Results showed that self-administration was facilitated in rats if both partners had access to cocaine, but was inhibited if only one had access. These findings indicate that it is not simply the presence of a peer that is important for initial acquisition of drug self-administration, but that the peer must also have access to the drug for use to occur.

In another experiment using a social chamber apparatus, Gipson et al. (2011) first trained rats to self-administer amphetamine in the absence of any social partner. After

stable responding was established, a novel same-sex partner was introduced into the adjacent chamber during the self-administration session; the social partner did not have access to drug. Results showed that amphetamine self-administration of the trained rat was increased in the presence of the partner, but that this social facilitation did not occur past the first self-administration session. Importantly, social facilitation of responding for sucrose pellets did not occur, indicating that the effect was specific to amphetamine. Overall, these findings parallel the human literature showing an increase in drug use in the presence of peers and further suggest that animal models may be useful for studying social influences on drug use.

Statement of Hypothesis

Based on the existing literature, a next logical step in the field of social drug abuse research is to compare behavior on risk taking tasks in an isolated and social situation. In this study, we made use of the social chamber and trained one animal on the risky decision making task. Following acquisition, we then introduced an age, weight, and gender matched social peer in the adjacent chamber to assess the changes in risk taking behavior. It was hypothesized that animals would increase risk taking when in the presence of an age- and weight-matched conspecific. Furthermore, acquisition of risk taking in adolescence is also a question of interest. Therefore, in a second experiment, we introduced a social peer during every session of the risky decision making task, and compared risk-taking behavior of these animals to controls, which did not have exposure to a social peer. As with the first experiment, it was predicted that the presence of a social peer would increase risk taking.

CHAPTER 2

Methods

Subjects

In total, 48 male Sprague-Dawley rats were used for two experiments (n=12 for Experiment 1, with n=12 social peer cage mates; n=16 for Experiment 2, with n=8 social peer cage mates). Animals arrived from Harlan Industries (Indianapolis, IN) on postnatal day (PND) 21. Upon arrival, rats were pair housed in a colony room that was on a 12-hr light-dark cycle, and all experimentation occurred in the light cycle. During behavioral testing, rats were maintained at 85% of their free-feeding weight, but had free access to water in their home cage. All animals were cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the Institutional Animal Care and Use Committee at the University of Kentucky approved experimental protocols.

Apparatus

A custom built social operant chamber (see Figure 2.1), made up of two connected standard operant chambers, was used (Med Associates, St. Albans, VT). The front and back walls of the operant chambers were made of aluminum, outside walls were made of Plexiglas, and the partition was a wire screen panel. A wire screen allowed for visual, auditory, olfactory, and limited tactile contact between partners, but prevented rats from interfering with the levers in the adjacent chamber. The entire apparatus measured 69.8 cm x 53.3 cm x 60.9 cm (length x width x height). Each individual chamber measured 34.9 cm long. The responder chamber included a food receptacle, located in the bottom-center of the front wall and two retractable response levers that were located on the front wall,

one on either side of the food receptacle. There were three 28-V white cue lights located on the front wall, one 6 cm over each retractable lever, and the third over the food receptacle. A houselight was mounted on the back wall of each chamber. The adjacent chamber for the social peer was identical, except the levers were retracted. Each of the floor grids were equipped with a harness that was connected to a Smartctrl interface (Med Associates, St. Albans, VT) which allowed for the delivery of shock, of which the intensity and duration could be controlled. All programs were controlled and recorded by a computer interface using Med-PC software.

Shaping

Shaping procedures for the responder rat followed those used previously (Cardinal et al. 2000; Simon et al. 2007, 2009; Mitchell et al. 2011). Following magazine training, rats were trained to press a single lever (either the left or the right, counterbalanced across groups; the other lever was retracted during this phase of training) to receive a single food pellet. After reaching a criterion of 50 lever presses in 30 min, rats were then trained on the opposite lever under the same criterion. This was followed by further shaping sessions in which both levers were retracted and rats were shaped to nose poke into the food receptacle during simultaneous illumination of the cue light above the food receptacle and house lights. When a nose poke occurred, a single lever was extended (left or right), and a lever press resulted in immediate delivery of a single food pellet. Immediately following the lever press, the receptacle light was extinguished and the lever was retracted. Rats were trained to a criterion of 30 presses on each lever within 60 min.

Risky Decision-Making Task (RDMT)

Testing procedures followed Simon et al. (2009) and Mitchell et al. (2011). Sessions were 60 min in duration and consisted of five blocks of 14 or 18 trials each. Each 40-s trial began with a 10-s illumination of both the food receptacle light and house lights. A nose poke into the food receptacle extinguished the receptacle light and triggered extension of either a single lever (forced choice trials) or of both levers simultaneously (choice trials). If rats failed to nose poke within the 10-s time window, the lights were extinguished and the trial was scored as an omission.

A press on one lever (either left or right, balanced across animals) resulted in one food pellet (the small, safe reward) delivered immediately following the lever press. A press on the other lever resulted in immediate delivery of three food pellets (the large, risky reward). However, selection of this lever was also accompanied immediately by a possible 1-s footshock contingent on a preset probability specific to each trial block. The large reward was delivered following every choice of the large reward lever, regardless of whether or not the footshock occurred. The probability of footshock accompanying the large reward was set at 0% during the first trial block. In subsequent trial blocks, the probability of footshock increased to 25%, 50%, 75%, and 100%. The intensity of the footshock began at 0.15 micro-amps and was increased by 0.05 micro-amps following tolerance, ending at 0.3 micro-amps for Experiment 1 and 0.25 micro-amps for Experiment 2; all data were collected at the highest shock values for each experiment. Each trial block began with forced choice trials (4 trials during the 0- and 100% probability blocks, and 8 trials during all other blocks) in which only a single lever was extended and which was used to establish the punishment contingencies in effect for that block (four for each lever),

followed by 10 choice trials (St. Onge and Floresco 2009). Once either lever was pressed, both levers were immediately retracted. Food delivery was accompanied by re-illumination of both the food receptacle and house lights, which were extinguished upon entry to the food receptacle to collect the food or after 10 s, whichever occurred sooner. Fewer forced choice trials were used during the first and last blocks (where there was no probability of shock, or where shock would always occur) in an attempt to decrease satiety in adolescent animals. On the forced choice trials (in which only one lever was present) the probability of shock following a press on the large reward lever was dependent across the four trials in each block. For example, 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 (in which both levers are present) was entirely independent, such that the probability of shock on each trial was the same, irrespective of shock delivery on previous trials in that block.

Experiment 1: Influence of social peer after acquisition of RDMT

Following stability of behavior in the RDMT in rats trained without a social peer in the adjacent compartment, a social peer (the cage mate of the responder rat) was placed into the adjacent chamber throughout the session. Each subject was exposed to a social peer on three different sessions. There were four sessions between pairings, where the subjects were alone in the social chamber to ensure that behavior returned to baseline responding. Before test sessions with a social peer, animals were placed into the operant chambers (social peer followed by the responding rat) and allowed to acclimate for 2 min prior to starting the task, in an effort to decrease omissions due to distraction.

Experiment 2: Influence of social peer during acquisition of RDMT

Following shaping procedures, half of the rats (n=8) performed in the RDMT alone, while the other half of the rats (n=8) were paired with a social peer (the cage mate of the responder rat) during every session. As with Experiment 1, social peers were always placed into the operant chambers prior to the responding rat, and animals were allowed to acclimate for 2 min before the session began.

Data Analysis

Statistical analyses were conducted in SPSS 22.0. Stable behavior was defined by the absence of a main effect of session, the absence of an interaction between session and trial block, and the presence of a main effect of trial block over five consecutive sessions, using a two-way repeated measures ANOVA (Winstanley et al. 2006; Simon et al. 2009, 2010). The effects of partner manipulations were assessed using two-way ANOVA. In each experiment, a median-split was used to categorize rats into high and low responders, as this procedure is commonly used in preclinical research (e.g. Piazza et al. 1989). In all cases, *p*-values less than 0.05 were considered significant.

Results

Experiment 1: Influence of a social peer after acquisition of RDMT

Results revealed no significant effect of social peer presence (see Figure 2.2). Rats were then assigned to a "high risk taker" or "low risk taker" group, based on a median split (see Figure 2.3). A 2-way ANOVA revealed a significant main effect of block ($F(4,40) = 75.84$, $p < 0.001$), significant main effect of risk group ($F(1,10) = 50.03$, $p < 0.001$), and a significant block x group interaction ($F(4,40) = 4.675$, $p = 0.003$). Tukey's t-tests revealed

significant differences at the 25% ($t(10) = 3.104$, $p = 0.011$), 50% ($t(10) = 5.625$, $p < 0.001$), 75% ($t(10) = 2.667$, $p = 0.024$), and 100% ($t(10) = 3.094$, $p = 0.011$) risk blocks. Further analysis with a 2-way ANOVA comparing the effect of the presence of a social peer on risk taking within the high risk takers and low risk takers revealed no significant changes in either group (see Figure 2.4).

Experiment 2: Influence of social peer during acquisition of RDMT

Results of a 2-way ANOVA revealed a significant main effect of block ($F(4,56) = 13.98$, $p < 0.001$) and significant main of group ($F(1,14) = 6.228$, $p = 0.015$), such that rats that were paired with a social peer showed greater preference for the large, risky reward than rats in the control group (see Figure 2.5). There was, however, no significant block x group interaction. Rats were then divided into "high risk takers" and "low risk takers" within their groups based on a median split, as Experiment 1. A 3-way ANOVA revealed a significant block x group x risk interaction ($F(4,48) = 6.647$, $p = 0.002$). In the control group, there was a significant main effect of block ($F(4,24) = 18.85$, $p < 0.001$), significant main effect of risk group ($F(1,6) = 58.03$, $p < 0.001$), and significant block x risk-group interaction ($F(4,24) = 5.402$, $p = 0.002$), such that rats in the high risk taking group showed greater preference for the large, risky reward than rats in the low risk taking group (see Figure 2.6). Tukey's t-tests revealed significant differences between risk groups at the 25% ($t(6) = 3.364$, $p = 0.015$), 50% ($t(6) = 4.434$, $p = 0.004$), 75% ($t(6) = 5.459$, $p = 0.002$), and 100% ($t(6) = 2.474$, $p = 0.048$) risk blocks. In the social group, there was a significant main effect of block ($F(4,24) = 28.48$, $p < 0.001$), a significant main effect of risk group ($F(1,6) = 10.16$, $p = 0.003$), and significant block x risk-group interaction ($F(4,24) = 5.674$, $p = 0.002$), such that rats in the high risk taking group showed greater preference for the

large, risky reward than rats in the low risk taking group (see Figure 2.7). Tukey's t-tests only revealed a significant difference at the 100% risk block ($t(6) = 7.798$, $p < 0.001$). When comparing high and low risk takers across the control and social groups, there were no significant differences between the high risk-takers in the control group compared to the social group. When comparing low risk-takers, however, there was a significant main effect of block ($F(4,24) = 33.59$, $p < 0.001$), a significant main effect of group ($F(1,6) = 24.88$, $p < 0.001$), and a significant block*group interaction ($F(4,24) = 3.766$, $p = 0.0134$), such that that low risk taking rats in the social group showed a greater preference for the large, risky reward than low risk taking rats in the control group (see Figure 2.8). Tukey's t-tests revealed a significant difference at the 25% ($t(6) = 3.481$, $p = 0.013$) and 50% ($t(6) = 3.563$, $p = 0.012$) risk blocks.

Figure 2.1. Representation of social chamber used in both experiments. Two operant chambers were separated by a wire mesh barrier. Floor grid equipped with shock was only connected to the compartment where responding rats were placed.

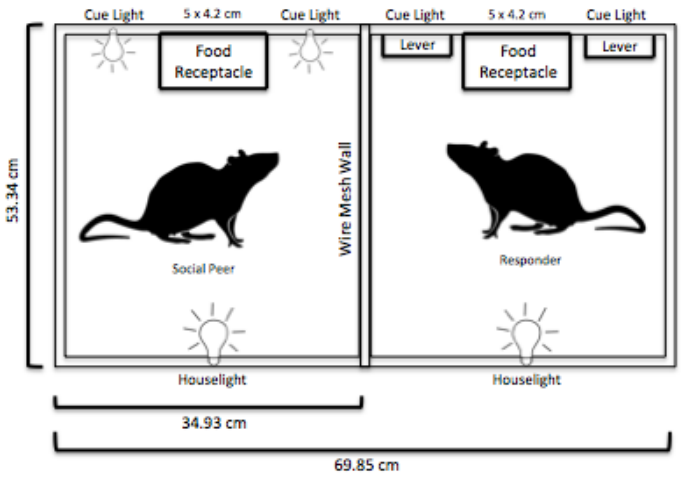


Figure 2.2. Choice of the large, risky reward across blocks 1-5 in all rats in Experiment 1 in which the baseline was compared to the average of three test sessions with a social peer. Analysis revealed no significant difference between baseline and behavior following introduction of a social peer.

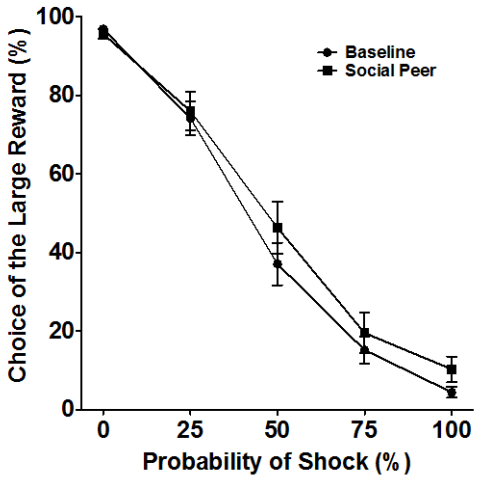


Figure 2.3. Rats in Experiment 1 divided into high and low risk-takers, based on a median-split. Choice of large, risky lever across blocks 1-5. *Significant difference compared to low risk takers at the same probability, $p < 0.05$

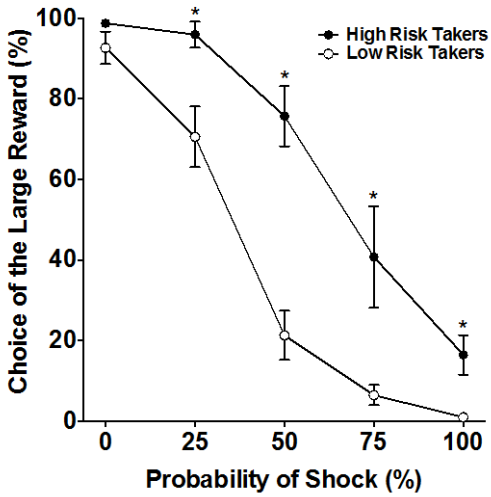


Figure 2.4. Comparing effect of social peers on high and low risk takers in Experiment 1 as choice of the large, risky reward changes across blocks 1-5. Analysis revealed no significant differences in behavior following introduction of a social peer in either the high or low risk takers.

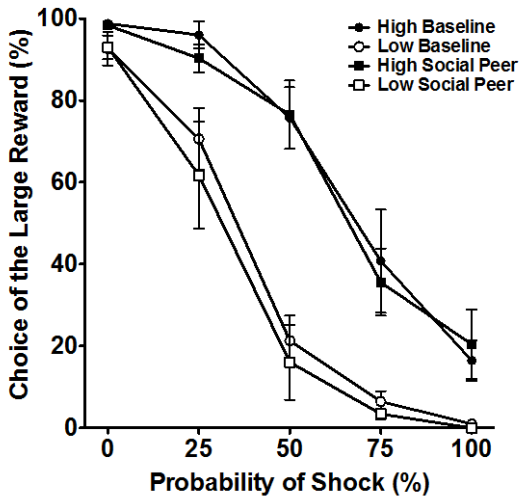


Figure 2.5. Average choice of large, risky lever across blocks 1-5 in all rats in Experiment 2 in which control (no social peer) and social peer groups were compared. Analysis revealed a significant main effect of group, such that rats in the social group showed increased preference for the large, risky reward compared to controls ($p = 0.015$).

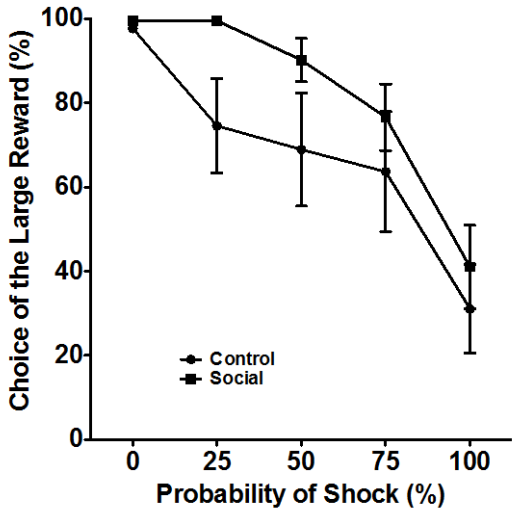


Figure 2.6. Control group of Experiment 2 divided into high and low risk takers. *Significant difference from low risk takers at same probability of shock, $p < 0.05$

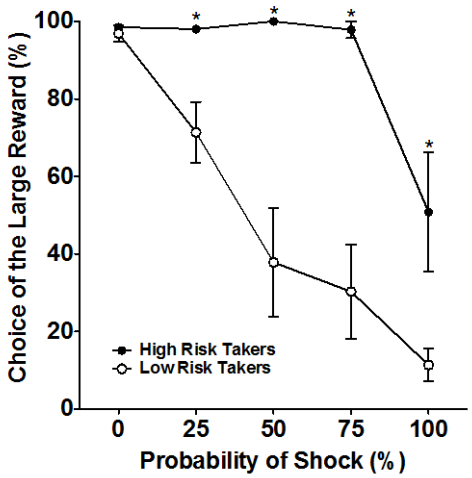


Figure 2.7. Social group of Experiment 2 divided into high and low risk takers. *Significant difference from low risk takers at the same probability of shock, $p < 0.05$

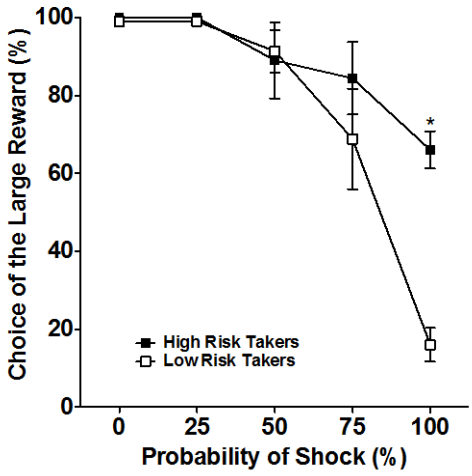
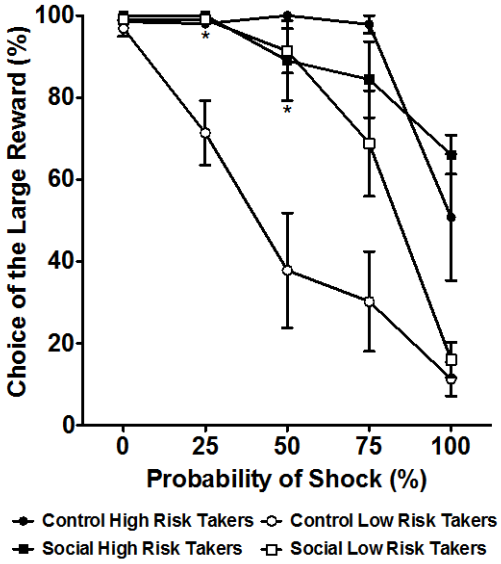


Figure 2.8. Comparison of high and low risk takers in the control and social groups from Experiment 2. *Significant difference from control low risk takers at same probability of shock, $p < 0.05$



CHAPTER 3

Discussion

This thesis provides evidence that a social peer can have influence risky decision-making, given the appropriate social conditions. Although periodic exposure to a social peer did not have an effect on risky behavior that was already established, daily exposure to the same social peer during acquisition lead to an increase in preference of the large, risky reward compared to controls.

In Experiment 1, acute, intermittent exposure to a social peer had no significant effect on risky decision-making. Although significant differences were found between animals labeled as "high" and "low" risk takers, this was due to the arbitrary median-split approach, and thus it was to be expected. Even within the two risk-taking groups, social peer exposure had no differentiating effects. Given that responder rats were cage mates with the social peer they were exposed to during test sessions, it is possible that there was not enough novelty in the peer manipulation to lead to behavioral changes in responder rats tested after performance was stable.

In contrast, in Experiment 2, repeated, daily exposure to a social peer during the acquisition phase led to a significant increase in risk-taking behavior. Rats that were exposed to a social peer (their cage mate) during every session of the risky decision-making task showed a significantly higher preference for the large, risky reward, compared to controls, which were not exposed to a social peer. Furthermore, when rats in both groups were subdivided into "high" and "low" risk-takers, controls showed significant differences in their choice of the large, risky reward in all risk blocks except when there was a 0% chance of punishment. This finding contrasts to rats in the social group, who only showed

significant differences in preference for the large, risky reward at the 100% risk block. When comparing high and low risk-takers across groups, there were no significant differences between high risk-takers in the control and social groups. There were, however, significant differences between the low risk-takers, such that animals in the social group showed a greater preference for the large, risky reward at both the 25- and 50% risk blocks. This latter finding suggests that social peers have a greater influence on rats that are predisposed to be low in risk-taking. It is possible, however, that differences were not found between the high risk taking groups because of a ceiling effect, such that animals could not choose the large, risky lever more than 10 out of 10 times within each free-choice trial block, leaving no possibility of showing further increases in risk-taking behavior.

There is abundant literature from humans to support the findings of Experiment 2. Beisswanger and colleagues (2003) have found that peers typically advise friends to make riskier decisions than they would choose for themselves. Encouraging risk-taking was more prevalent for social and relationship situations, but was not commonly found with financial decisions. Items included on surveys that participants commonly said they would encourage a friend to do included: (1) introducing themselves to an attractive member of the opposite sex, (2) giving someone attractive their phone number, (3) going home with a member of the opposite sex after a party, and (4) moving in with a significant other.

In another study, social influence on risk-taking was evaluated using a computer task called "Chicken," in which the participants were controlling when a car going along a course should stop (Gardner and Steinberg, 2005). In the task, subjects gained points based on the distance their car traveled. However, if a brick wall appeared in front of their car, causing a crash, the subject lost all points for that trial. In this task, adolescents were

significantly more risky than adults, such that they would allow the car to travel further before stopping it. Furthermore, adolescents were more influenced by social peers to travel further along the course than adults, who showed no significant increases in risk taking in the presence of peers. Importantly, all participants in the study knew the other members of the group to which they were assigned prior to participating. This may be an important factor for enhancing the effect of social influence, as friends tend to pressure others more than acquaintances (McPhee, 1996).

In animal research (particularly rodents), prosocial interactions typically involve the presentation of familiar peers in order to avoid aggressive fighting. In particular, adult males are more likely to engage in aggressive behavior towards novel males. In the absence of aggressive fighting, adolescent rodents find social interaction to be highly rewarding (Calcagnetti et al., 1992; Douglas, 2004). Thus, the novelty associated with an unknown social peer may confound data collected, particularly if behavioral changes following repeated prosocial interaction is the measure of interest.

In humans, social interaction has been associated with increased endogenous opioid release. Using positron emission tomography (PET), it has been shown that social acceptance leads to an increase in mu-opioid receptor activation (i.e. reduced receptor availability) in the amygdala and anterior insula, which are areas associated with emotional regulation and awareness (Hsu et al., 2013). There are also decreases in mu-opioid activation in both the thalamus and subgenual anterior cingulate cortex, areas associated with mood (particularly sadness) and memory. Interestingly, the dorsal anterior cingulate cortex and anterior insula also have implications in the expression of physical pain. Activation of these regions due to physical pain can be dampened with social support,

which also leads to a reported decrease in pain scale ratings (Eisenberger, 2012). Conversely, social rejection leads to increased mu-opioid receptor activation in the ventral striatum, amygdala, thalamus, and periaqueductal gray; all areas associated with emotion and pain (Hsu et al., 2013). These increases in activation of these areas caused by social rejection have also been show to increase sensitivity to physical pain (Eisenberger, 2012).

Additional work in humans has shown that individuals high in impulsivity have increased numbers of mu-opioid receptors, particularly in the anterior cingulate cortex, thalamus, and amygdala (Love et al., 2009). These individuals also show an increased endogenous opioid response to stress. It is possible that endogenous opioid release following stress, including stress caused by social rejection, may be an adaptive way the brain decreases pain associated with emotional changes. Alternatively, it is possible that release of endogenous opioids following positive social interaction has evolved to allow humans to form bonds, which allows for the continuation of the species. Further work is needed to determine if these opioid-mediated changes in social influence demonstrated in humans involve homologous brain structures in rats.

Some evidence suggests that mu-opioid receptors also appear to play an important role in adolescent play behavior in rats. Adolescent rats given a systemic injection of morphine, a mu-opioid receptor agonist, exhibit an increase in the number of vocalizations evoked in response to the vocalizations emitted from another rat (Wöhr and Schwarting, 2009). An infusion of morphine into the nucleus accumbens of adolescent male rats also leads to an increase in pinning and pouncing, which are commonly associated with important developmental play behaviors (Trezza et al., 2011). Conversely, systemic administration of naloxone, a mu-opioid receptor antagonist, decreases vocalizations, and

micro-infusion of naloxone into the nucleus accumbens decreases play behavior. Furthermore, these social behaviors seem to be selectively mediated by the mu-opioid receptor, as infusions into the nucleus accumbens of other opioid receptor agonists (i.e. gamma and/or kappa) yield no change in social interactions.

It is well established that opioids have analgesic properties. This includes the class of endogenous opioids known as endomorphins, which are selective for the mu-opioid receptor. Endomorphin-1 is thought to inhibit GABA neurotransmission in the periaqueductal gray, which allows for the serotonin system to have an exaggerated effect (Chen et al., 2015). Because of the location of the periaqueductal gray in the midbrain, it is a main center for pain signals entering and leaving the brainstem, and therefore, central nervous system to the peripheral nervous system. In fact, research on the placebo effect has even shown that these endogenous opioid systems are effective enough to alleviate physical pain (Abhishek and Doherty, 2013; Colloca and Grillon, 2014). Thus, alleviation of pain may be an additional factor for engaging in social activity.

Based on the extensive literature implicating endogenous opioid systems in social interaction, it is possible that rats in the social group had elevated levels of endogenous opioids while performing the risky decision-making task. Because of this socially mediated endogenous opioid release, these animals may have had a higher tolerance to the aversive effects of a mild footshock. This tolerance then lead to an increased preference for the large, risky lever in the social group, compared to controls.

In addition to endogenous opioids, the monoamine system is also heavily involved in reward and social behavior. Dopamine is commonly studied with regard to its role in reward, impulsivity, and risk taking. Mitchell et al. (2013) found a relationship between

dopamine transporters and performance on the RDMT, such that male adolescent rats with lower striatal D_2 receptor mRNA expression showed a higher preference for the large, risky reward. Others have also shown a correlation between increases in impulsivity and decreases in dopamine function (Diergaarde et al., 2008; Yates et al., 2014). Further research has shown that serotonin is also involved in impulsive action, but with the opposite relationship. Winstanley et al. (2006) discovered that there is an increase in mPFC serotonin levels during a delay-discounting task. Recent research has also found that adolescent male rats show increases in DOPAC levels following social interaction (Weiss et al., in press). The same lab also found that, following social interaction, levels of 5-HIAA in the striatum were increased. Alternatively, mice with deficiencies in brain serotonin show deficits in social communication (Beis et al., 2015).

Although both experiments involved the introduction of a social peer during the risky decision-making task, it is apparent that only daily exposure early in acquisition leads to increases in risk-taking. There are a few possible reasons for the differential effect of social influence between Experiments 1 and 2. One possibility is that this task may not be very sensitive to the effects of acute manipulations. In previous work conducted with the RDMT and with stimulants, chronic self-administration of cocaine led to a significant increase in preference for the large, risky reward (Mitchell et al., 2014). Conversely, administration of an acute dose of amphetamine prior to the session led to a decrease in preference for the large, risky reward (Mitchell et al., 2011). These results suggest that this particular task is sensitive to differences in acute compared to chronic exposure, particularly with drugs, and this sensitivity may extend to behavioral manipulations as well.

An alternative possibility for the difference between the results obtained in Experiments 1 and 2 relates to selection and socialization theories. In humans, selection theory states that individuals seek out peers whose ideals and behaviors are similar to their own. Socialization theory, on the other hand, states that we alter our behavior, and possibly our ethics, based on the social group that we are associated with. With this latter theory, the more time an individual spends with a social peer, the more influence that peer has on behavior. Extending this theory to rats, it may be that repeated exposure to the peer may have enhanced the effect of social influence. Interestingly, in humans, socialization theory seems to be the more accurate predictor of risk-taking, particularly drug use, compared to selection theory (Simons-Morton and Chen, 2006).

Finally, a third possible reason why the effects of social exposure differed between Experiments 1 and 2 related to the time at which the peer was introduced. In Experiment 1, the peer was introduced after acquiring the RDMT, whereas in Experiment 2 the peer was introduced at the beginning of the RDMT. Perhaps after the task is well-learned to stability, as in Experiment 1, the effect of social influence is minimized. Conversely, when the task is not yet learned, as in Experiment 2, the ability of social influence is more pronounced in altering performance. This may be due, in part, to the face that cage mates were used as social peers. Rats in Experiment 1 had extensive interaction with their social peer in the home cage, but very little interaction with the social peer during the specific context where risky decision-making was being measured.

Finally, future research is needed to better understand the differences in responding following both daily and intermittent interaction with a social peer during the RDMT. As for the differences observed between the social and control groups in Experiment 2, if

endogenous opioids are responsible for this effect, administration of naloxone prior to the session may be hypothesized to eliminate the differences in risk-taking. Furthermore, to the extent that socialization theory is accurate, using social peers that are not cage mates with the responding rat, or even using a novel rat every session, may lead to a decrease in risk-taking behavior.

Sex differences should also be explored in further research. Although females were not used in this study because they are less risky than males (Fattore et al., 2014; Weafer and de Wit, 2014) and do not find social interaction as rewarding as males (Douglas et al., 2004; Yates et al., 2013), it is still an important and relevant research question.

Taken together, these results are in keeping with previous clinical data on the effects that social peers have on risk-taking behavior. Repeated exposure to a familiar social peer led to significant increases in preference for the large, risky reward. However, these results are dependent on the amount of exposure, such that intermittent exposure to a social peer did not lead to these same increases in risk-taking, which is supportive of clinical research that has shown friends (or those persons whom people choose to spend a significant amount of time with) are more influential on behavior than acquaintances. As such, this thesis provides evidence that it is possible to model social risk taking behavior in rodents. This thesis also provides evidence that low risk takers are more heavily influenced by social interaction than high-risk takers, which could have implications for in-school programs that normally focus on high-risk children and adolescents. Further research should now be conducted to investigate the neurobiological mechanisms by which these behavioral changes take place.

References

Abhishek A, Doherty M. Mechanisms of the placebo response in pain in osteoarthritis. Osteoarthritis Cartilage. 2013 Sep;21(9):1229-35.

Alvers KM, Marusich JA, Gipson CD, Beckmann JS, Bardo MT. Environmental enrichment during development decreases intravenous self-administration of methylphenidate at low unit doses in rats. Behav Pharmacol. 2012 Oct;23(7):650-7. doi: 10.1097/FBP.0b013e3283584765. PubMed PMID: 22914073; PubMed Central PMCID: PMC3674782.

Andrade LF, Alessi SM, Petry NM. The effects of alcohol problems and smoking on delay discounting in individuals with gambling problems. J Psychoactive Drugs. 2013 Jul-Aug;45(3):241-8.

Anker JJ, Perry JL, Gliddon LA, Carroll ME. Impulsivity predicts the escalation of cocaine self-administration in rats. Pharmacol Biochem Behav. 2009 Sep;93(3):343-8. doi: 10.1016/j.pbb.2009.05.013. Epub 2009 May 31. PubMed PMID: 19490925; PubMed Central PMCID: PMC2734915.

Bahr SJ, Hoffmann JP, Yang X. Parental and peer influences on the risk of adolescent drug use. J Prim Prev. 2005 Nov;26(6):529-51.

Bayard S, Raffard S, Gely-Nargeot MC. Do facets of self-reported impulsivity predict decision-making under ambiguity and risk? Evidence from a community sample. Psychiatry Res. 2011 Dec 30;190(2-3):322-6. doi: 10.1016/j.psychres.2011.06.013. Epub 2011 Jul 23.

Bechara A, Damasio H, Tranel D, Anderson SW. Dissociation Of working memory from decision making within the human prefrontal cortex. J Neurosci. 1998 Jan 1;18(1):428-37.

Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia. 2001;39(4):376-89. PubMed PMID: 11164876.

Belin D, Berson N, Balado E, Piazza PV, Deroche-Gamonet V. High-novelty-preference rats are predisposed to compulsive cocaine self-administration. Neuropsychopharmacology. 2011 Feb;36(3):569-79. doi: 10.1038/npp.2010.188. Epub 2010 Oct 27. PubMed PMID: 20980989; PubMed Central PMCID: PMC3055686.

Beisswanger, Amy H., Eric R. Stone, Julie M. Hupp, and Liz Allgaier. "Risk Taking in Relationships: Differences in Deciding for Oneself Versus for a Friend." *Basic and Applied Social Psychology* 25.2 (2003): 121-35.

Businelle MS, McVay MA, Kendzor D, Copeland A. A comparison of delay discounting among smokers, substance abusers, and non-dependent controls. Drug Alcohol Depend. 2010 Dec 1;112(3):247-50. doi: 10.1016/j.drugalcdep.2010.06.010. Epub 2010 Aug 8.

Cain ME, Saucier DA, Bardo MT. Novelty seeking and drug use: contribution of an animal model. Exp Clin Psychopharmacol. 2005 Nov;13(4):367-75. PubMed PMID: 16366767.

Calcagnetti DJ, Schechter MD. Place conditioning reveals the rewarding aspect of social interaction in juvenile rats. Physiol Behav. 1992 Apr;51(4):667-72.

Chen T, Li J, Feng B, Hui R, Dong YL, Huo FQ, Zhang T, Yin JB, Du JQ, Li YQ. Mechanism Underlying the Analgesic Effect Exerted by Endomorphin-1 in the rat Ventrolateral Periaqueductal Gray. Mol Neurobiol. 2015 Apr 16.

Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. Curr Pain Headache Rep. 2014 Jun;18(6):419.

Cunha PJ, Bechara A, de Andrade AG, Nicastri S. Decision-making deficits linked to real-life social dysfunction in crack cocaine-dependent individuals. Am J Addict. 2011 Jan-Feb;20(1):78-86. doi: 10.1111/j.1521-0391.2010.00097.x. Epub 2010 Nov 12. PubMed PMID: 21175924; PubMed Central PMCID: PMC3124808.

Cardinal RN. Neural systems implicated in delayed and probabilistic reinforcement. Neural Netw. 2006 Oct;19(8):1277-301. Epub 2006 Aug 30. Review.

Donohew RL, Hoyle RH, Clayton RR, Skinner WF, Colon SE, Rice RE. Sensation seeking and drug use by adolescents and their friends: models for marijuana and alcohol. J Stud Alcohol. 1999 Sep;60(5):622-31.

Douglas LA, Varlinskaya EI, Spear LP. Rewarding properties of social interactions in adolescent and adult male and female rats: impact of social versus isolate housing of subjects and partners. Dev Psychobiol. 2004 Nov;45(3):153-62.

Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. Nat Rev Neurosci. 2012 May 3;13(6):421-34.

Fillmore MT. Reliability of a computerized assessment of psychomotor performance and its sensitivity to alcohol-induced impairment. Percept Mot Skills. 2003 Aug;97(1):21-34.

Floresco SB, Whelan JM. Perturbations in different forms of cost/benefit decision making induced by repeated amphetamine exposure. Psychopharmacology (Berl). 2009 Aug;205(2):189-201. doi: 10.1007/s00213-009-1529-0. Epub 2009 Apr 14. PubMed PMID: 19365622.

Franques P, Auriacombe M, Tignol J. [Addiction and personality]. Encephale. 2000 Jan-Feb;26(1):68-78. Review. French. PubMed PMID: 10875064.

Gancarz AM, San George MA, Ashrafioun L, Richards JB. Locomotor activity in a novel environment predicts both responding for a visual stimulus and self-administration of a low dose of methamphetamine in rats. Behav Processes. 2011 Feb;86(2):295-304. doi: 10.1016/j.beproc.2010.12.013. Epub 2011 Jan 5. PubMed PMID: 21215305; PubMed Central PMCID: PMC3045732.

Gardner M, Steinberg L. Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: an experimental study. Dev Psychol. 2005 Jul;41(4):625-35. Erratum in: Dev Psychol. 2012 Mar;48(2):589. PubMed PMID: 16060809.

Gipson CD, Beckmann JS, Adams ZW, Marusich JA, Nesland TO, Yates JR, Kelly TH, Bardo MT. A translational behavioral model of mood-based impulsivity: Implications for substance abuse. Drug Alcohol Depend. 2012 Apr 1;122(1-2):93-9. doi: 10.1016/j.drugalcdep.2011.09.014. Epub 2011 Oct 5. PubMed PMID: 21975194; PubMed Central PMCID: PMC3270200.

Gipson CD, Bardo MT. Extended access to amphetamine self-administration increases impulsive choice in a delay discounting task in rats. Psychopharmacology (Berl). 2009 Dec;207(3):391-400. doi: 10.1007/s00213-009-1667-4. Epub 2009 Sep 26. PubMed PMID: 19784636; PubMed Central PMCID: PMC3164508.

Hsu DT, Sanford BJ, Meyers KK, Love TM, Hazlett KE, Wang H, Ni L, Walker SJ, Mickey BJ, Korycinski ST, Koeppe RA, Crocker JK, Langenecker SA, Zubieta JK. Response of the μ-opioid system to social rejection and acceptance. Mol Psychiatry. 2013 Nov;18(11):1211-7.

Jodogne C, Marinelli M, Le Moal M, Piazza PV. Animals predisposed to develop amphetamine self-administration show higher susceptibility to develop contextual conditioning of both amphetamine-induced hyperlocomotion and sensitization. Brain Res. 1994 Sep 19;657(1-2):236-44.

Jones DL, Heflinger CA, Saunders RC. The ecology of adolescent substance abuse service utilization. Am J Community Psychol. 2007 Dec;40(3-4):345-58.

Kandel DB, Logan JA. Patterns of drug use from adolescence to young adulthood: I. Periods of risk for initiation, continued use, and discontinuation. Am J Public Health. 1984 Jul;74(7):660-6.

Kandel DB, Davies M, Karus D, Yamaguchi K. The consequences in young adulthood of adolescent drug involvement. An overview. Arch Gen Psychiatry. 1986 Aug;43(8):746-54.

Kjome KL, Lane SD, Schmitz JM, Green C, Ma L, Prasla I, Swann AC, Moeller FG. Relationship between impulsivity and decision making in cocaine dependence. Psychiatry Res. 2010 Jul 30;178(2):299-304. doi: 10.1016/j.psychres.2009.11.024. Epub 2010 May 15. PubMed PMID: 20478631; PubMed Central PMCID: PMC2904056.

Love TM, Stohler CS, Zubieta JK. Positron emission tomography measures of endogenous opioid neurotransmission and impulsiveness traits in humans. Arch Gen Psychiatry. 2009 Oct;66(10):1124-34.

Marusich JA, Darna M, Charnigo RJ, Dwoskin LP, Bardo MT. A multivariate assessment of individual differences in sensation seeking and impulsivity as predictors of amphetamine self-administration and prefrontal dopamine function in rats. Exp Clin Psychopharmacol. 2011 Aug;19(4):275-84. doi: 10.1037/a0023897. PubMed PMID: 21574722; PubMed Central PMCID: PMC3164505.

Marusich JA, Bardo MT. Differences in impulsivity on a delay-discounting task predict self-administration of a low unit dose of methylphenidate in rats. Behav Pharmacol. 2009 Sep;20(5-6):447-54. doi: 10.1097/FBP.0b013e328330ad6d. PubMed PMID: 19696657; PubMed Central PMCID: PMC2754277.

McCord, Joan, and Kevin P. Conway. *Co-offending and Patterns of Juvenile Crime*. Washington, D.C.: U.S. Dept. of Justice, Office of Justice Programs, National Institute of Justice, 2005.

McPhee, JH. Influence strategies in young adolescent dyads. Dissertation Abstracts International: Section B: The Sciences and Engineering, Vol 57(2-B), Aug 1996, 1468.

Mendez IA, Simon NW, Hart N, Mitchell MR, Nation JR, Wellman PJ, Setlow B. Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. Behav Neurosci. 2010 Aug;124(4):470-7. doi: 10.1037/a0020458. PubMed PMID: 20695646; PubMed Central PMCID: PMC2976632.

Mitchell MR, Vokes CM, Blankenship AL, Simon NW, Setlow B. Effects of acute administration of nicotine, amphetamine, diazepam, morphine, and ethanol on risky decision-making in rats. Psychopharmacology (Berl). 2011 Dec;218(4):703-12. doi: 10.1007/s00213-011-2363-8. Epub 2011 Jun 3.

Mitchell MR, Weiss VG, Beas BS, Morgan D, Bizon JL, Setlow B. Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling. Neuropsychopharmacology. 2013 Oct 22. doi: 10.1038/npp.2013.295. [Epub ahead of print] PubMed PMID: 24145852.

Peitz GW, Strickland JC, Pitts EG, Foley M, Tonidandel S, Smith MA. Peer influences on drug self-administration: an econometric analysis in socially housed rats. Behav Pharmacol. 2013 Apr;24(2):114-23. doi: 10.1097/FBP.0b013e32835f1719. PubMed PMID: 23412112; PubMed Central PMCID: PMC3749306.

Peters EN, Petry NM, Lapaglia DM, Reynolds B, Carroll KM. Delay discounting in adults receiving treatment for marijuana dependence. Exp Clin Psychopharmacol. 2013 Feb;21(1):46-54. doi: 10.1037/a0030943. Epub 2012 Dec 17.

Piazza PV, Deminière JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science. 1989 Sep 29;245(4925):1511-3.

Pike E, Stoops WW, Fillmore MT, Rush CR. Drug-related stimuli impair inhibitory control in cocaine abusers. Drug Alcohol Depend. 2013 Dec 1;133(2):768-71. doi: 10.1016/j.drugalcdep.2013.08.004. Epub 2013 Aug 15. PubMed PMID: 24004904; PubMed Central PMCID: PMC3818419.

Puhl MD, Blum JS, Acosta-Torres S, Grigson PS. Environmental enrichment protects against the acquisition of cocaine self-administration in adult male rats, but does not eliminate avoidance of a drug-associated saccharin cue. Behav Pharmacol. 2012 Feb;23(1):43-53. doi: 10.1097/FBP.0b013e32834eb060. PubMed PMID: 22157144; PubMed Central PMCID: PMC3650841.

Reynolds B. A review of delay-discounting research with humans: relations to drug use and gambling. Behav Pharmacol. 2006 Dec;17(8):651-67. Review.

Simon NW, Setlow B. Modeling risky decision making in rodents. Methods Mol Biol. 2012;829:165-75. doi: 10.1007/978-1-61779-458-2_10. Review. PubMed PMID: 22231813; PubMed Central PMCID: PMC3305800.

Simon NW, Gilbert RJ, Mayse JD, Bizon JL, Setlow B. Balancing risk and reward: a rat model of risky decision making. Neuropsychopharmacology. 2009 Sep;34(10):2208-17. doi: 10.1038/npp.2009.48. Epub 2009 May 13. PubMed PMID: 19440192; PubMed Central PMCID: PMC2726909.

Simons-Morton B, Chen RS. Over time relationships between early adolescent and peer substance use. Addict Behav. 2006 Jul;31(7):1211-23.

Smith MA. Peer influences on drug self-administration: social facilitation and social inhibition of cocaine intake in male rats. Psychopharmacology (Berl). 2012 Nov;224(1):81-90. doi: 10.1007/s00213-012-2737-6. Epub 2012 May 16. PubMed PMID: 22588251; PubMed Central PMCID: PMC3752977.

Stone, E. R., A. J. Yates, and A. S. Caruthers. "Risk Taking in Decision Making for Others Versus the Self." *Journal of Applied Social Psychology* 32.9 (2002): 1797-824.

Trezza V, Damsteegt R, Achterberg EJ, Vanderschuren LJ. Nucleus accumbens μ-opioid receptors mediate social reward. J Neurosci. 2011 Apr 27;31(17):6362-70.

Vadhan NP, Hart CL, Haney M, van Gorp WG, Foltin RW. Decision-making in long-term cocaine users: Effects of a cash monetary contingency on Gambling task performance. Drug Alcohol Depend. 2009 Jun 1;102(1-3):95-101. doi: 10.1016/j.drugalcdep.2009.02.003. Epub 2009 Apr 5. PubMed PMID: 19346083; PubMed Central PMCID: PMC2694492.

Washio Y, Higgins ST, Heil SH, McKerchar TL, Badger GJ, Skelly JM, Dantona RL. Delay discounting is associated with treatment response among cocaine-dependent outpatients. Exp Clin Psychopharmacol. 2011 Jun;19(3):243-8. doi: 10.1037/a0023617.

Weafer J, Fillmore MT. Comparison of alcohol impairment of behavioral and attentional inhibition. Drug Alcohol Depend. 2012 Nov 1;126(1-2):176-82. doi: 10.1016/j.drugalcdep.2012.05.010. Epub 2012 Jun 4. PubMed PMID: 22673197; PubMed Central PMCID: PMC3440541.

Whiteside, Stephen P., Donald R. Lynam, Joshua D. Miller, and Sarah K. Reynolds. "Validation of the UPPS Impulsive Behaviour Scale: A Four-factor Model of Impulsivity." *European Journal of Personality* 19.7 (2005): 559-74.

Wöhr M, Schwarting RK. Ultrasonic communication in rats: effects of morphine and naloxone on vocal and behavioral responses to playback of 50-kHz vocalizations. Pharmacol Biochem Behav. 2009 Dec;94(2):285-95.

Yates JR, Beckmann JS, Meyer AC, Bardo MT. Concurrent choice for social interaction and amphetamine using conditioned place preference in rats: effects of age and housing condition. Drug Alcohol Depend. 2013 May 1;129(3):240-6. doi: 10.1016/j.drugalcdep.2013.02.024. Epub 2013 Mar 26.

Zuckerman M. Sensation seeking and the endogenous deficit theory of drug abuse. NIDA Res Monogr. 1986;74:59-70. Review. PubMed PMID: 3122054.

Vita

Virginia Graham Weiss

Bachelor of Science, University of Florida, 2012, Psychology

Mitchell, M.R, Weiss, V.G., Beas, B. S., Morgan, D., Bizon, J.L., and Setlow, B. *Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling.* Neuropsychopharmacology. 2013 Oct 22.

Mitchell, M.R., Weiss, V.G., Ouimet, D.J. Fuchs, R.A., Morgan, D., and Setlow, B. *Intake-dependent Effects of Cocaine Self-Administration on Impulsive Choice in a Delay Discounting Task.* Behavioral Neuroscience. 2014 May 19.

Weiss, V.G., Hofford, R.S., Yates, J.R., Jennings, F.C., and Bardo, M.T. *Sex Differences in Monoamines Following Amphetamine and Social Reward in Adolescent Rats.* Experimental and Clinical Psychopharmacology. In Press.