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Sharon Lin 04/12/2011

Intravenous Self-Administration (IVSA) with Psychostimulants in a Rodent Model of Depression

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A thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Depressive symptoms and psychostimulant abuse are frequently comorbid conditions. The presence of both conditions in a patient makes it more difficult to treat either one. Despite the prevalence, there are few animal models examining psychostimulant abuse behaviors in depression, and none that incorporate hereditary aspects of depression and drug abuse. The purpose of this investigation was to examine the intravenous self-administration behaviors of two rat lines in fixed ratio-1 (FR-1), progressive ratio (PR), extinction, and reinstatement schedules. These two rat lines have been selectively bred for high and low activity on the forced swim test. The low active line (Lo) is used as a model of atypical depression, and the high active line (Hi) is said to show a depression resistant phenotype. Because atypical depression is the most common depressive subtype comorbid with drug abuse, we predicted that the Lo rats would show higher response rates in progressive ratio and reinstatement schedules. Instead, we found that the Hi, or depression resistant, rats generally responded more for both cocaine and amphetamine than the Lo rats in the self-administration paradigm. The Hi rats were also found to have a greater increase in locomotor activity than the Lo rats in response to intraperitoneal (IP) administration of amphetamine. These results show that self-administration studies with SwLo and SwHi rats using psychostimulants may be affected by differences in baseline activity and sensitivities of each line to the rewarding and aversive aspects of the drug.

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Introduction

Many clinical studies have focused on the comorbidity of depression and psychostimulant abuse (Pagliaro, Jaglalsingh, & Pagliaro, 1992; Rounsaville, 2004; Schmitz et al., 2000). A NIAAA (National Institute on Alcohol Abuse and Alcoholism) national survey found that adults with depression were 6.19 times more likely to abuse amphetamine, and 4.96 times more likely to abuse cocaine when compared to non-depressed adults (Grant, 1995). A common explanation for the comorbidity is that patients are self medicating for anhedonic, or loss of pleasure, symptoms of depression (Moss & Werner, 1992; R. D. Weiss & Mirin, 1986). Similarly, depressed patients may be more motivated to administer psychomotor stimulants, such as cocaine or amphetamine, because they experience a more euphoric high from cocaine than non-depressed users (Newton, Kalechstein, Tervo, & Ling, 2003; Uslaner, Kalechstein, Richter, Ling, & Newton, 1999). Another possible explanation is that depression may include neurobiological abnormalities that predispose patients to substance abuse (Markou, Kosten, & Koob, 1998).

Depression has been associated with substance abuse both as a cause and result (Pagliaro, et al., 1992). Although there are no FDA-approved therapies for cocaine or amphetamine abuse, it has been shown that treatment with certain antidepressants (most notably, tricyclics) may reduce stimulant abuse in depressed users (Gawin et al., 1989; Kosten, 1989). In the cases where antidepressants were effective in attenuating drug use, they were found to be more effective in drug users with depressive symptoms than non-depressed patients (Nunes et al., 1995; Nunes, Quitkin, Brady, & Stewart, 1991; Nunes et al., 1998). However, most animal models used to examine both conditions focus on

depressive behaviors as a result of psychostimulant withdrawal (D'Souza & Markou, 2010; Newton, et al., 2003; Perrine, Sheikh, Nwaneshiudu, Schroeder, & Unterwald, 2008). Because treatment of either condition is more difficult in patients with both psychostimulant dependence and depression than in patients who are only affected by one of the disorders, it is important to have an animal model of the comorbidity to test potential treatments that can target both conditions (Regier et al., 1990). Olfactory-bulbectomized (OBX) rats show depression-like symptoms and self-administer more amphetamine than control rats (Holmes et al., 2002). However, major depression and drug abuse have both been shown to be affected by genetic risk factors, a finding which is not accounted for by the OBX model (Duaux, Krebs, Loo, & Poirier, 2000; Stevens, 1999; Sullivan, Neale, & Kendler, 2000; Tsuang & Faraone, 1990). Thus, to further understand the underlying genetic factors and neurobiological underpinnings in the comorbidity of depressive symptoms and drug abuse, it is necessary to utilize a model that incorporates the heritability of such traits. In this study, we examine addiction-relevant behaviors of two rodent lines that are selectively bred based on a depression-like phenotype, activity in the forced swim test activity.

The forced swim test is a validated and widely used test for antidepressant screening, in which the floating behavior of a rat (interpreted as a state of learned helplessness) is decreased and struggling behavior (interpreted as active attempts for escape) is increased as a result of antidepressant treatment (Porsolt, Le Pichon, & Jalfre, 1977). Dr. Jay Weiss and colleagues have selectively bred rats for dozens of generations to generate two lines with robustly different baseline swim scores in this test (Weiss, Cierpial, & West, 1998). The Swim High-active (SwHi) line exhibits high swim activity

(much more struggling than floating), and the Swim Low-active (SwLo) line has very low activity scores (less struggling and much more floating) (Weiss, et al., 1998). Importantly, the low swim activity of SwLo rats can be reversed by chronic, but not acute, antidepressant drug treatment, similar to clinical depression (West & Weiss, 1998). SwLo rats are considered to be a model of atypical depression, characterized by lethargy and anhedonia (West & Weiss, 1998). For example, in addition to their low swim test scores, they also have decreased preference for sucrose, a "natural" reward, and have an increased intracranial self-stimulation threshold, both indicative of anhedonia (Weiss, Boss-Williams, Ritchie, & West, 2009). Because the most common type of depression seen in cocaine users is atypical depression (Nunes, Quitkin, & Klein, 1989), these characteristics make the SwLo rat a particularly good subject to study the comorbidity of drug abuse and depression. SwHi rats, showing the opposite phenotypes of the SwLo rats, have depression-resistance characteristics (Weiss, et al., 1998). SwLo rats have also been found to show increased oral ingestion of amphetamine and cocaine and increased preference for the drug-paired chamber in conditioned place preference tests in comparison to SwHi and non-selectively bred (SwNS) rats, making them a promising model of drug abuse and depression comorbidity (Weiss et al., 2008).

To confirm and extend the SwLo rats as a model of depression and addiction comorbidity, our study examined their substance abuse behavior using the widely accepted paradigm of substance abuse, intravenous self-administration. This operant paradigm of drug self-administration allows the animals to directly work to obtain the drug, and controls for non-pharmacological aspects of the oral self-administration model, such as drug taste. We tested SwLo and SwHi rats on fixed ratio-1, progressive ratio,

extinction, and reinstatement schedules to determine the rate at which both lines acquired stable drug self-administration, how hard each line would work for the drug, and the rate of relapse resulting from re-exposure to the drug after a period of abstinence. Because of the prevalence of depressive symptoms in psychostimulant abusers and vice versa, as well as the increased oral drug-self-adminsitration previously observed in SwLo rats (Weiss, et al., 2008), we predicted that SwLo rats would work harder to obtain the drug and relapse at a higher rate than the SwHi rats.

Materials and Methods

Subjects

Male SwHi-a, SwHi-b, SwHi-c, SwLo-a, SwLo-b, and SwLo-c rats of 2-4 months of age at the start of the experiments were used. The Swim-a lines were selectively bred from an original stock of outbred rats based on previously mentioned criteria. The Swim-b lines were derived from the Swim-a lines in generation 13 and have been bred in parallel using the same selection criteria (swim scores in the forced swim test). The Swim-c lines were created more recently by breeding SwHi-a rats with SwHi-b rats and SwLo-a rats with SwLo-b rats. Because they all exhibit similar swim activity phenotypes, it was assumed they would show similar behavioral characteristics in addiction paradigms. Swim-a, -b, and -c rats were used for the amphetamine locomotor study and cocaine self-administration study, while Swim-a rats only were used for the amphetamine self-administration study. The determination of which rats to use for each study was based on the availability of each rat line at the time of the experiment. SwHi-a and SwLo-a rats will simply be referred to as SwHi and SwLo rats. High-active rats are collectively termed Hi rats, and Low-active rats are referred to as Lo rats.

All subjects were singly housed and received *ad libitum* access to food and water unless otherwise noted. Rats were maintained in a temperature-controlled environment on a 12 hour reverse light/dark cycle with the lights on from 1900 to 0700 hours for self-administration experiments. For the amphetamine locomotion experiments, rats were maintained on a 12h/12h light/dark cycle with the lights on at 0700 hours.

Rats used for the self-administration experiments were acclimated to the vivarium for 1 week prior to food training. All self-administration sessions occurred during the dark cycle following standard methods with minor alterations (Fuchs, Branham, & See, 2006). All animals were treated in accordance with NIH policy, and experiments were approved by the Emory IACUC committee.

Food Training

Prior to catheterization surgery, rats were trained to lever-press on a fixed ratio-1 (FR1) schedule for food (45 mg pellets) in standard rat operant chambers (Med Associates, St Albans, VT) as described (Fuchs, et al., 2006). Each chamber was equipped with a house light, two retractable levers (active and inactive), stimulus lights above both levers, and a food pellet dispenser. Inactive lever presses had no consequence. A computer with MED-PC software (MED Associates) controlled the program and recorded data. Food training sessions lasted for 8 h, or until the animal obtained at least 100 food pellets with a 70% selection for the active lever. Some rats required a few days of training before meeting this criteria.

Surgery

Rats were anesthetized with isoflurane and implanted with intravenous jugular catheters using standard methods. Catheters were inserted into the right jugular vein and

anchored with suture material. The catheters were also anchored between the shoulder blades using surgical staples. Catheters were flushed twice daily with 0.05 ml gentamicin (4 mg/ml) and 0.1 ml heparin solution (30 U/ml in sterile saline) for three days following surgery, then once daily. Catheter patency was verified by infusing methohexital sodium (20 mg/ml, IV), which results in rapid muscle tone loss when administered intravenously. The calculation for the amount infused was the following (Bondy et al.):

$$\textit{Infusion Volume} = 0.25\ \textit{ml/kg} * [\textit{rat weight(kg)}] + 0.04\ \textit{ml}$$

Rats were allowed at least 5 days of recovery time before commencing self-administration experiments.

Cocaine Self-Administration

Fixed Ratio-1. Daily self-administration sessions on a FR1 schedule lasted for a maximum of 2 h or until rats received 40 drug infusions. At the beginning of each session, rats received a non-contingent infusion of cocaine (0.5 mg/kg). During the sessions, each active lever press resulted in a cocaine infusion (0.5 mg/kg in a volume of 167 μl/kg) and illumination of a stimulus light above the lever. A timeout period of 20 s followed the infusion, in which active lever presses had no programmed consequences. After the timeout period, the stimulus light was extinguished. Inactive lever presses were recorded, but had no programmed consequences.

Once rats met the criteria for a stable response level (a minimum of 5 total days of cocaine self-administration, and 3 consecutive days where: active lever responses varied by <20% of the mean, active lever preference was at least 75%, and active lever response was at least 20) they moved onto the progressive ratio schedule.

Progressive Ratio. After rats completed the FR1 maintenance paradigm of cocaine self-administration, rats were moved to a progressive ratio (PR) schedule in which each subsequent infusion of cocaine (0.5 mg/kg) required a greater number of active lever presses than the last, as described (Richardson & Roberts, 1996). The equation used for the number of active presses for each infusion was:

$$\textit{Response Requirement (rounded to nearest integer)} = [5e^{(\textit{injection number}*0.2)}] - 5$$

Thus, response requirements for infusions would be: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, etc. Obtained infusions were followed by the same programmed consequences as seen in the FR-1 schedule. Sessions lasted until rats reached breakpoint, defined as the number of infusions received prior to a 1 h period in which no rewards were obtained, or for a maximum of 6 h. Rats were considered to have reached a stable response level using the same criteria as the FR1 schedule, but for a minimum of 3 total days on the PR schedule.

Extinction. Following the completion of stabilized PR response, lever pressing was extinguished in daily 2 h sessions that had the same contingencies as the FR1 schedule, but cocaine was replaced with 0.9% sterile saline. Behavior was considered extinguished when active lever presses over 3 consecutive days were <25% of the average number of active lever presses during the last 3 days of progressive ratio.

Drug-Primed Reinstatement. The day after rats reached extinction criteria, they were pretreated with cocaine (1 mg/kg or 10 mg/kg, IP) immediately before a 2 h session using the extinction conditions. Rats were then re-extinguished and reinstated using the second dose of cocaine. Dose order was counterbalanced between subjects.

Amphetamine Self-Administration

Separate groups of rats were used for amphetamine self-administration experiments, and conditions were similar to those used for cocaine self-administration. Rats were first run on FR1 with 0.1 mg/kg amphetamine. After maintaining a stable active lever response rate of the same criteria as the FR1 maintenance criteria for cocaine but without a minimum number of active lever presses, rats were trained on a FR1 schedule with 0.25 mg/kg amphetamine.

After reaching criteria for the second FR1 paradigm, rats were moved to a PR schedule with 0.1 mg/kg and then 0.25 mg/kg amphetamine until reaching the identical criteria as for PR cocaine self-administration.

Lever pressing for amphetamine was extinguished after rats stabilized in responses for PR in an extinction program in which an active lever press resulted in no consequence.

After extinguishing, rats were reinstated with 0.5 mg/kg amphetamine (IP) immediately before the session and run on the extinction program.

Food Self-Administration

Separate groups of drug-naive rats were used in the food self-administration experiments. Rats were placed on restricted diets of 16g of normal rat chow per day, which was given at least 1 h after the end of self-administration sessions. Food self-administration for FR1, PR, and extinction parameters and criteria were identical to the cocaine self-administration experiments, except rats received a 45mg food pellet instead of a cocaine infusion per active lever press, and sessions lasted for 1h or ended when 60 pellets were obtained.

Food-Primed Reinstatement. Following extinction, rats were reinstated for food as we have described previously (Schroeder et al., 2010). At the beginning of the session, 3 food pellets were non-contingently delivered in the first 10 s and levers were presented. Reinstatement sessions ran for 2 h, in which a food pellet was delivered non-contingently every 3 minutes, and lever responses had no programmed consequence.

Amphetamine Locomotor Activity

The Swim-b and Swim-c rats used in this experiment were separate from the self-administration groups. The Swim-a rats were used again in the amphetamine self-administration experiment. Animals were tested using a modified version of a published protocol (West, Bonsall, Emery, & Weiss, 1999). Rats were individually housed in clear acrylic cages in an activity-monitor room with *ad libitum* access to food and water. Movement was tracked using eight parallel infrared beams positioned at 5-cm intervals along the length of the cage. To exclude repetitive movements in a small area, each beam break that was different from the previous four breaks was recorded by a computer as a unit of "ambulatory activity." Rats were allowed to habituate to the room for 3 days and were handled for several minutes each day. All animals received a vehicle injection (0.9% saline) and, 2 days later, an injection with amphetamine (0.5 or 1.0 mg/kg in a volume of 0.05 ml/100 g of rat body weight). Ambulatory activity was measured in 2 min bins for 1 h immediately following injection. Each animal was only tested with one dose of amphetamine.

RESULTS

Cocaine Self-Administration

There was no significant difference between lines in cocaine fixed ratio-1 active and inactive responses and reward numbers (Fig. 1a-c). Both Hi and Lo lines received the maximum number of rewards and showed a similar active lever preference over the inactive lever.

In the PR schedule for cocaine self-administration, a t-test revealed that Hi rats had a significant increase in active lever response, $t(13) = 2.79$, $p = 0.0154$ (Fig. 1d) and breakpoint, $t(13) = 2.37$, $p = 0.0342$ (Fig. 1f). Hi and Lo rats showed similar amounts of inactive response during PR testing (Fig. 1e).

The reinstatement and extinction data show that there was no significant difference between lines for active lever presses during extinction training or the low dose (1 mg/kg) of cocaine-primed reinstatement (Fig. 2a). However, a two-way ANOVA revealed a significant interaction between rat line and dose, $F(2, 31) = 3.31$, $p = 0.0498$. A Bonferroni posttest showed a significant difference between lines in the higher reinstatement dose, $t = 3.456$, $p < 0.01$. The post hoc test also showed the high dose of cocaine significantly reinstated active lever pressing compared to extinction in Hi rats, $t = 5.319$, $p < 0.001$, but not Lo rats. The post hoc also revealed that the high dose of cocaine significantly reinstated active lever pressing compared to the low dose of cocaine in both Hi rats, $t = 5.583$, $p < 0.001$ and Lo rats, $t = 2.86$, $p < 0.05$. The inactive lever presses for extinction and reinstatement showed no significant difference between lines.

Fig. 3 shows the average number of days it took each line to reach the stable response criteria for each schedule. Although there was no significant difference

between lines, there seemed to be a trend for Hi rats to take slightly longer than Lo rats to stabilize in their responses.

Amphetamine self-administration

Both lines of rats had similar active responses, inactive responses, and drug infusions on the FR1 schedule (Fig. 4). Although there were no significant differences between lines, rats generally had fewer responses and infusions at the higher dose of amphetamine, as expected for the typical inverted-U dose response for psychostimulants.

When the PR schedule was used to determine how hard the animals would work for the drug, the SwHi rats generally showed higher response rates than SwLo rats for the PR schedule (Fig. 5). A t-test showed that, SwHi rats pressed the active lever significantly more than SwLo rats in the higher dose of amphetamine PR, $t(4) = 3.598$, $p = 0.0228$ (Fig. 5d). The breakpoint reached was also shown to be significantly lower in SwLo rats for both the 0.1mg/kg dose (Fig. 5c), $t(7) = 2.89$, $p = 0.0232$, and the 0.25mg/kg dose (Fig. 5f), $t(4) = 3.307$, $p = 0.0297$ of amphetamine. There were no significant differences between lines or doses for inactive responses (Fig. 5b, e).

Extinction and reinstatement data show that both lines had similar active and inactive responses in extinction (Fig. 6a, b). Although there was no significant difference between lines for reinstatement, there was a trend for increased lever pressing in SwHi rats.

Although it took both lines a similar number of days to reach stable response criteria in FR-1 and PR schedules (Fig. 7a, b), a t-test showed that the SwHi rats took significantly longer time than SwLo rats to extinguish, $t(3) = 3.573$, $p = 0.0375$ (Fig. 7c).

Food Self-administration

To test operant responding for a non-drug reward, rats were tested for food self-administration. While there were no significant differences between lines for any measure during FR1 or PR responding, Hi rats tended to have higher response rates than Lo rats (Fig. 8). Both lines reached the maximum number of obtainable rewards in the FR-1 schedule.

A two-way ANOVA for active responses in extinction and reinstatement revealed no significant interaction. However, there was a significant line effect, $F(1, 15) = 6.805$, $p = 0.0198$ (Fig. 9a). There does seem to be a trend that the Hi rats responded more in reinstatement conditions than the Lo rats. Both lines show similar inactive responses for both schedules (Fig. 9b). No differences between lines were found for days to reach criteria for each schedule (Fig. 10a-c).

Amphetamine-induced locomotor activity

Amphetamine-induced locomotor activity was previously shown to be higher in Hi rats compared to Lo rats (West, et al., 1999). We replicated this finding in the SwHi and SwLo rats (Fig. 11). A two-way ANOVA found significant interaction between rat line and dose, $F(2, 26) = 4.084$, $p = 0.0287$. Bonferroni post hoc tests for ambulatory activity 1 hour after an IP injection of amphetamine resulted in a significant difference between SwHi and SwLo rats at the 0.5 mg/kg dose, $t = 3.937$, $p < 0.01$, and the 1.0 mg/kg dose of amphetamine, $t = 2.57$, $p<0.05$ (Fig. 11a). SwHi-b and SwHi-c rats had a trend towards a greater increase in ambulation following amphetamine administration, but it was not significantly different from SwLo-b and SwLo-c rats.

DISCUSSION

The main finding from this study was that, contrary to our prediction, Lo rats did not show increased drug-taking or drug-seeking behavior compared to Hi rats. Indeed, in some cases, the opposite was true. While Hi and Lo rats self-administered similar amounts of cocaine and amphetamine on the FR1 schedule, Hi rats showed higher response rates and breakpoint on the PR schedule, indicating more motivation to obtain the drug. Furthermore, Hi rats also had higher response rates during the reinstatement phase, suggesting that they are more prone to relapse provoked by re-exposure to drug. How can we explain these results, given that Lo rats consume much more drug in oral self-administration experiment?

One possible explanation is that the operant behavior of intravenous self-administration has a learning component that may differ between lines. However, FR1 self-administration schedule data show that even though Hi rats have slightly higher active response rates, both lines acquire the task equally (Fig. 1a-c, 4a-c, 7a-c).

It is possible that the higher response rates in Hi rats can be accounted for by general increased activity and motivation. Although the food self-administration studies show a lack of significant difference in baseline self-administration response between lines for FR1 and PR (Fig. 7), the Hi rats do show a trend towards higher rates of active and inactive responding. More importantly, the Hi rats reinstate at higher rates than Lo rats, which could partially account for the increase in activity for drug self-administration. However, this could also be explained as the Lo rats showing decreased preference for non-drug related reward compared to Hi rats, which was determined in a previous study on sucrose solution preference (Weiss, et al., 2009).

Because Hi rats were shown to have a greater locomotor response to psychostimulants in this experiment (Fig. 10) and a previous study (West, et al., 1999), the drug they received in PR self-administration and reinstatement sessions may have driven the Hi rats to be more active in lever pressing. The trend for increased response in Hi rats can be seen in both active and inactive lever presses in all self-administration schedules. In addition, the stress experienced by Lo rats in the absence of drug when they expect its presence in PR and reinstatement schedules may enhance their lethargic "helpless" behavior, resulting in less response.

It is possible that the discrepancy in oral and intravenous administration of drug is caused by the Lo rats preference for the taste of drug-spiked water. However, when West et. al. presented rats with a sucrose solution containing amphetamine, SwLo rats still showed a greater preference than SwHi and non-selectively bred rats (2008). Because SwHi rats showed decreased sucrose preference compared to SwLo rats (Weiss, et al., 2009), one would expect that the addition of sucrose might result in an increase in consumption in SwHi rats and a decrease in consumption by SwLo rats had their preference been based on taste. Another experiment to control for the bitter taste of amphetamine solution tested consumption of quinine solution in SwLo and SwHi rats (Weiss, et al., 2008). They found no difference in preference between lines, but quinine may not fully mimic the taste of amphetamine.

It has also been reported that depressed cocaine users experience a higher state of euphoria than non-depressed patients (Newton, et al., 2003; Uslaner, et al., 1999). If the Lo rats also experienced a greater reward, they may require less drug than Hi rats for the same effect, and thus have decreased responses. Although this was not seen in oral

consumption of psychostimulants, it is important to note that oral self-administration slowly delivers drug to the brain over a longer period of time, whereas intravenous self-administration (IVSA) almost instantaneously affects the brain. The difference in pharmacokinetics and pharmacodynamics for both paradigms may result in different effects on the rewards system. It is possible that although Lo rats have been shown to be less sensitive to orally consumed psychostimulants (Weiss, et al., 2008), they may actually be more sensitive to intravenously administered psychostimulants than Hi rats, and thus respond less to achieve a similar level of reward as Hi rats. Intracranial self-stimulation (ICSS) studies on the Swim rats may argue against this possibility, because SwLo rats reached a higher current threshold than SwHi rats, and thus have a decreased sensitivity to the reinforcing effects of the reward (Weiss, et al., 2009). However, only baseline ICSS thresholds were measured. It would be interesting to see what effects psychostimulants had on ICSS in the Swim lines.

Lastly, Hi and Lo rats may have different sensitivities to the aversive effects of cocaine and amphetamine. Lo rats may actually be hypersensitive to both rewarding and aversive effects of the drugs. Increased sensitivity to aversive effects like anxiety would cause Lo rats to press less even though the rewarding effects are also increased. SwLo rats have been shown to have a more robust conditioned place preference (CPP) than SwNS rats, but were not compared to SwHi rats (Weiss, et al., 2009). To test sensitivity to rewarding and aversive aspects of drug without operant condition or taste interference, a future study could be conducted to examine the dose-response in CPP for cocaine and amphetamine in Hi and Lo rats.

Although a previous study on an OBX rat model of depression has shown that OBX rats lever press more for amphetamine, these rats possess irritable and aggressive dispositions with increased activity (Holmes, et al., 2002; Song & Leonard, 2005). This behavior is more reminiscent of the increase in activity seen in Hi rats, which may have some effect on lever pressing activity. Because the Lo rats exhibit lethargic characteristics of atypical depression in addition to the increased locomotor sensitivity of Hi rats to psychostimulants, it could be that the operant aspect of the self-administration is not optimal for testing cocaine and amphetamine self-administration in these lines.

To determine whether increased Hi response in cocaine IVSA could also be explained by the locomotor effects of the drug, a future study could examine the effects of cocaine-induced ambulatory activity in the two lines. It would also be beneficial to establish a dose-response curve for the Lo and Hi rats in the self-administration paradigm to determine if lines have different thresholds for cocaine and amphetamine doses. Possible future experiments could also focus on the effect of antidepressants on IVSA behavior in the Swim rat.

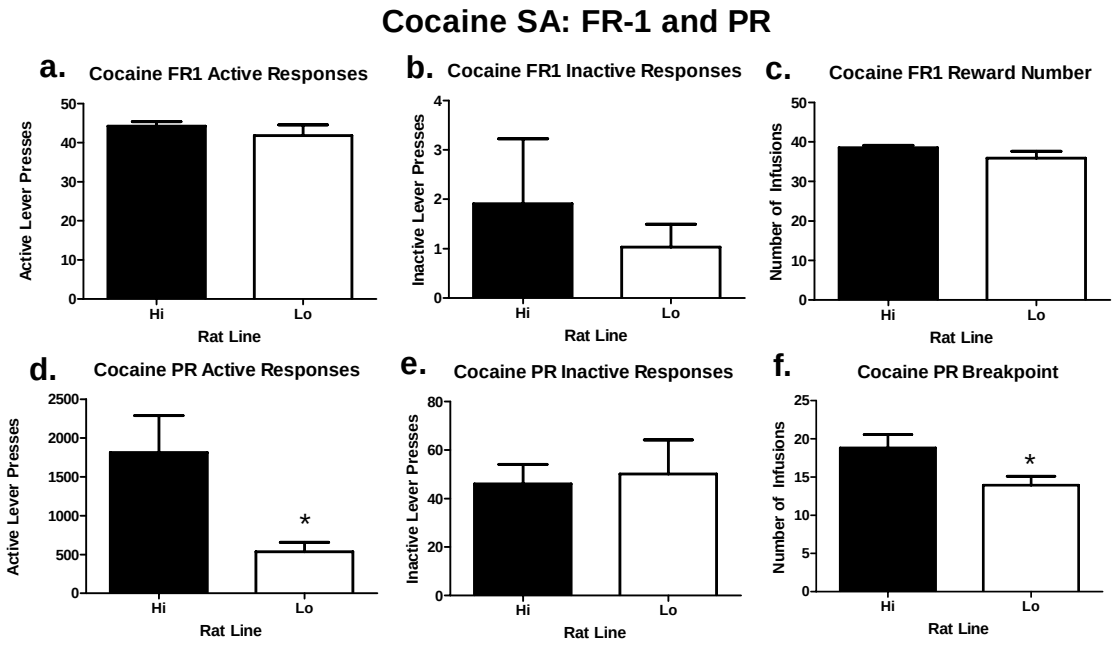

Figure 1. Active lever responses and breakpoints in PR for rats self administering 0.5 mg/kg cocaine are significantly higher in SwHi rats. Shown are the average active lever presses, inactive lever presses, and obtained infusions for the last 3 days of FR1 (a-c) and PR (d-f) schedules. *$p<0.05$ compared to Hi rats. (Active responses: Hi n=7, Lo n=8, inactive responses and rewards: Hi n=8, Lo n=9).

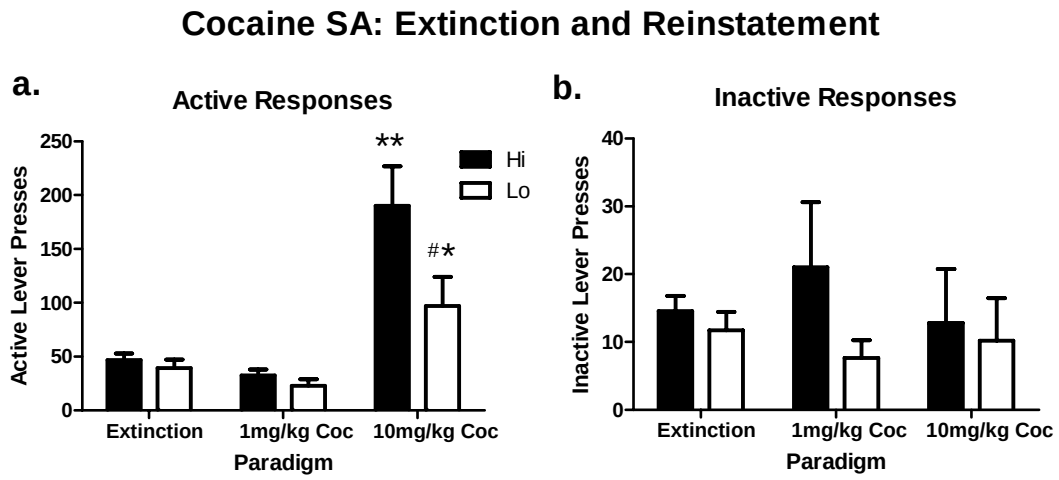

Figure 2. Hi rats reinstated and had a greater active response than Lo rats in 10 mg/kg cocaine-primed reinstatement. After reaching extinction criteria, rats were reinstated with an IP injection of cocaine prior to the session. Shown are average active lever (a) and inactive lever (b) responses. Extinction values reflect the average of the last 3 days of sessions. $^{**}p<0.001$ compared to Hi extinction and 1 mg/kg cocaine reinstatement active responses. $^{*}p<0.05$ compared to Hi active response for 1 mg/kg reinstatement. $\#p<0.01$ compared to Hi 0.25 mg/kg reinstatement active response. (Extinction Hi n=6, Lo n=7; 1mg/kg cocaine Hi n=5, Lo n=7; and 10mg/kg cocaine Hi n=6, Lo n=6).

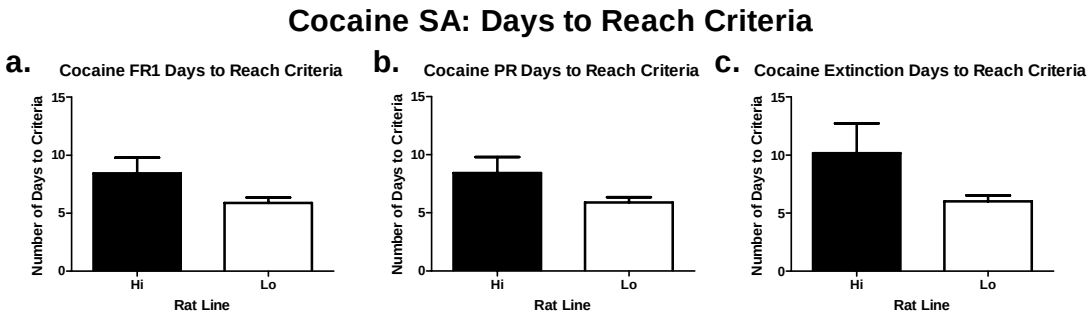

Figure 3. The number of days it took to reach criteria levels for each schedule in cocaine self-administration was not significantly different between lines. (FR1 and PR: Hi n=8, Lo n=9. Extinction Hi n=6, Lo n=7).

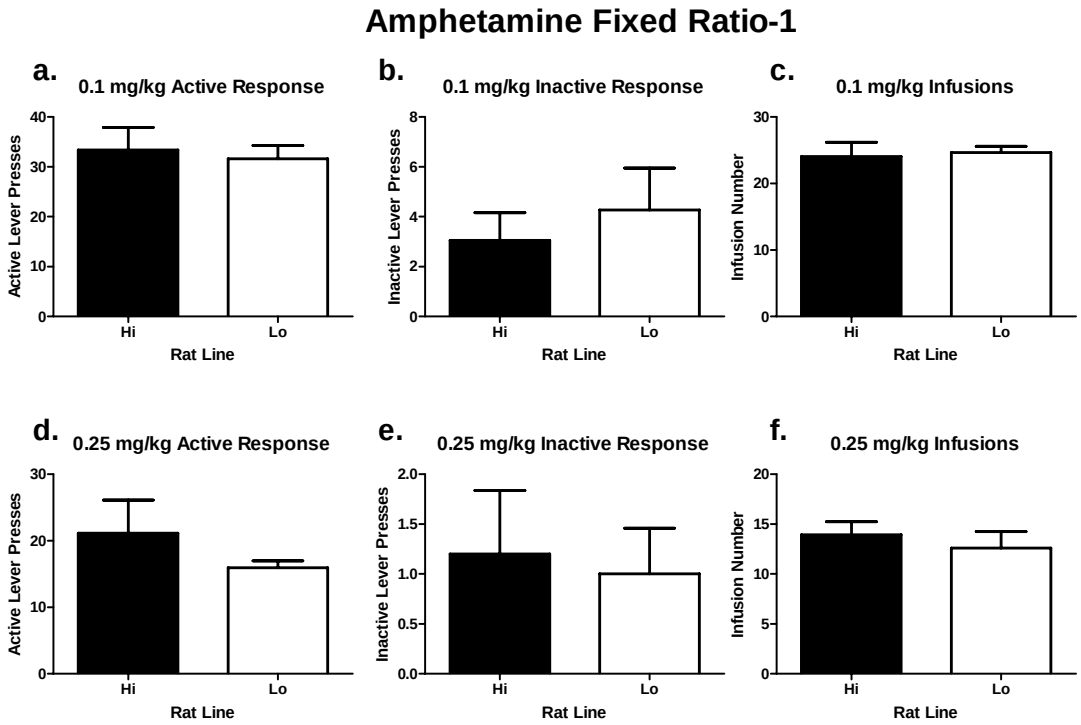

Figure 4. Average active and inactive lever responses and number of infusions obtained in the last three days of FR-1 for rats self administering 0.1 mg/kg (a-c) and 0.25 mg/kg amphetamine (d-f) are not significantly difference between lines. **p*<0.05 compared to Hi rats. (Active responses: Hi n=7, Lo n=8, inactive responses and rewards: Hi n=8, Lo n=9).

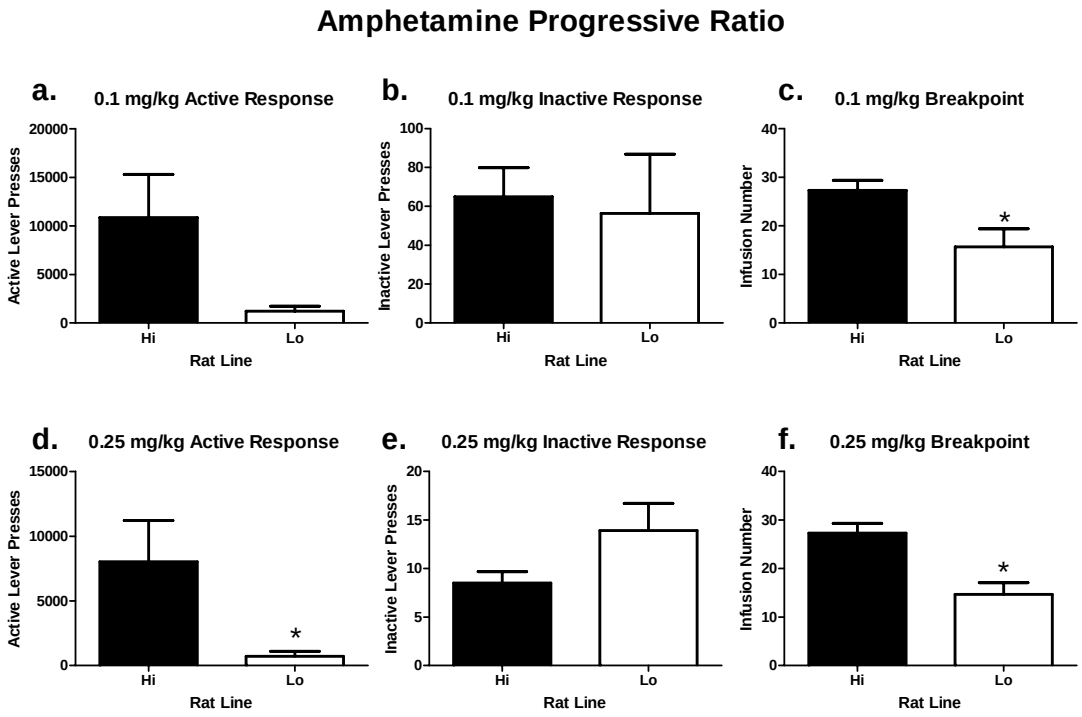

Figure 5. Average active and inactive lever responses and breakpoint obtained in the last three days of PR for rats self administering 0.1 mg/kg (a-c) and 0.25 mg/kg amphetamine (d-f) are shown. Hi rats respond significantly more than Lo rats in the active lever (d) ($p = 0.0228$). Hi rats also reach a greater breakpoint than Lo rats for the 0.1mg/kg dose ($p = 0.0232$) and the 0.25mg/kg dose ($p = 0.0297$). (Active responses: Hi n=7, Lo n=8, inactive responses and rewards: Hi n=8, Lo n=9).

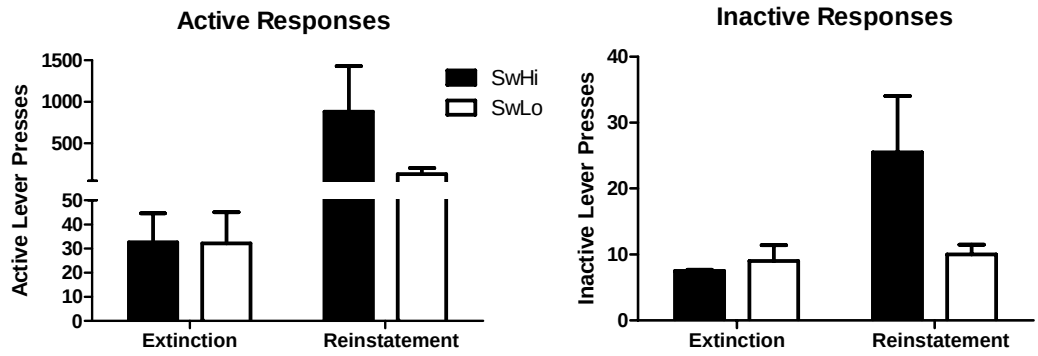

Figure 6. Lo rats press the inactive lever less that Hi rats in reinstatement. Rats were given amphetamine-primed reinstatement following extinction. Shown are the average active responses (left) and inactive responses (right) in the last 3 days of extinction and in reinstatement. (Hi n=2, Lo n=3).

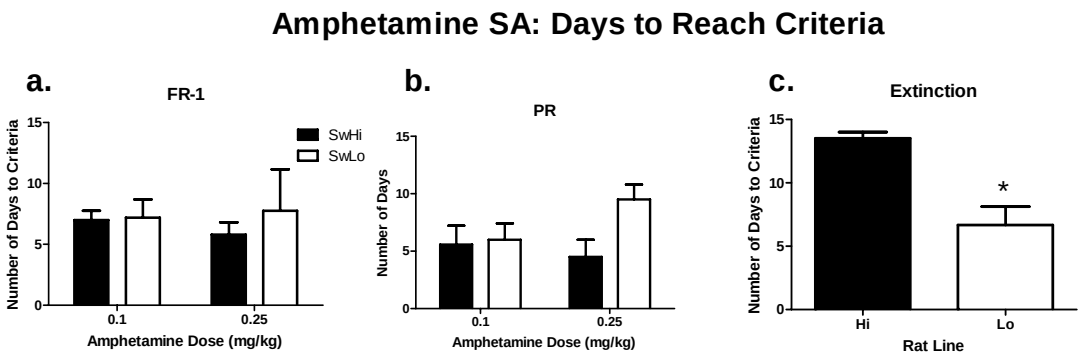

Figure 7. Hi rats take longer to extinguish than Lo rats. Shown are the average number of days for rats to reach criteria in each schedule. **p*=0.0375 compared to number of days to extinction criteria in Hi rats.

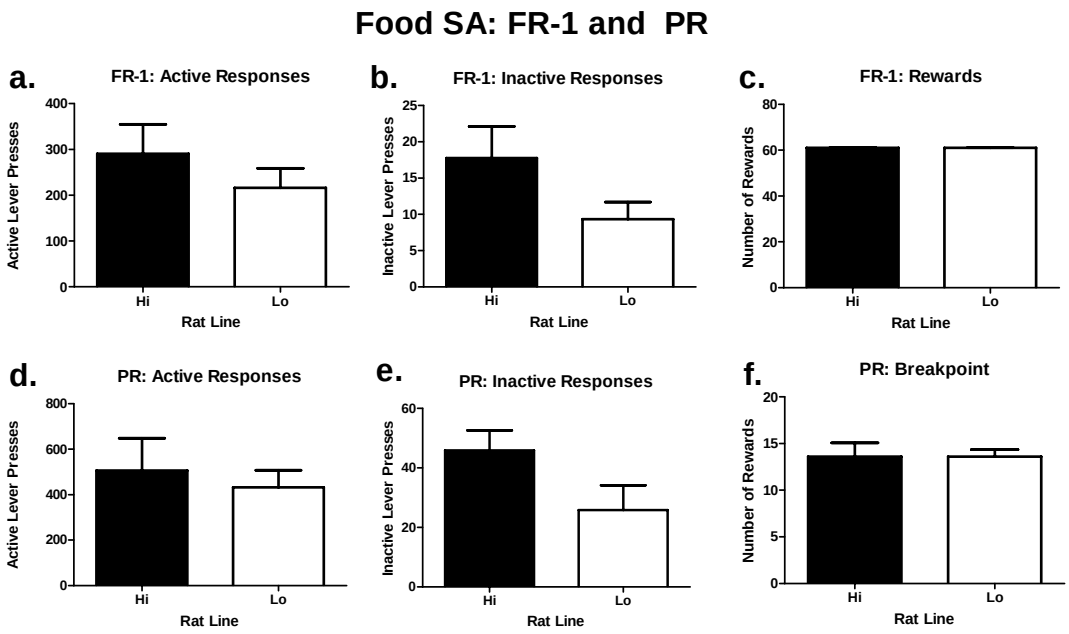

Figure 8. Hi rats seem have higher lever responses than Lo rats in food FR1 and PR schedules, but both lines obtain similar numbers of rewards. Shown are the active responses, inactive responses, and rewards obtained in FR1 (a-c) and PR (d-f) schedules. (n= 5 per group).

Figure 9. Hi rats reinstated in the food self-administration paradigm a level that seemed to be higher than that of Lo rats. Shown are active (a) and inactive (b) responses for extinction and reinstatement. Extinction values are averages of the last 3 days of the schedule. (Extinction n=5 per group, reinstatement Hi n=4, Lo n=5).

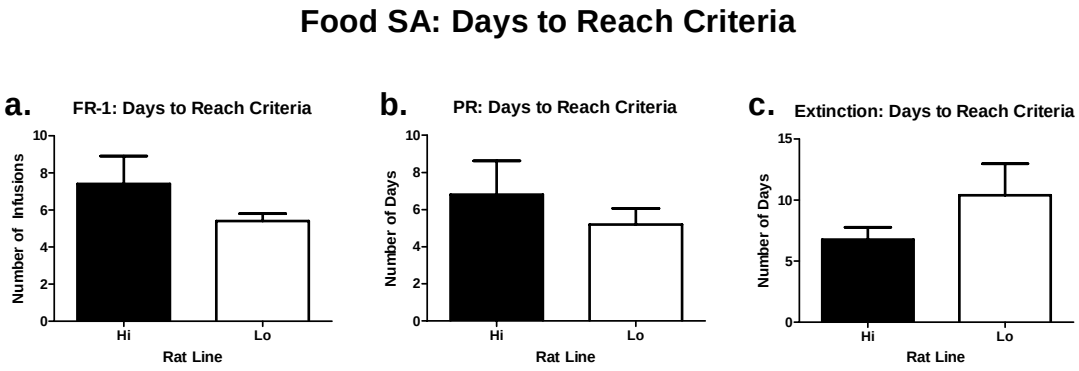

Figure 10. There is no significant difference between lines for the number of days it takes to reach criteria of each schedule, but it seems that Hi rats took slightly longer for FR-1 and PR (a,b) than Lo rats, but slightly fewer days (c) for extinction. Values are averages for each schedule.

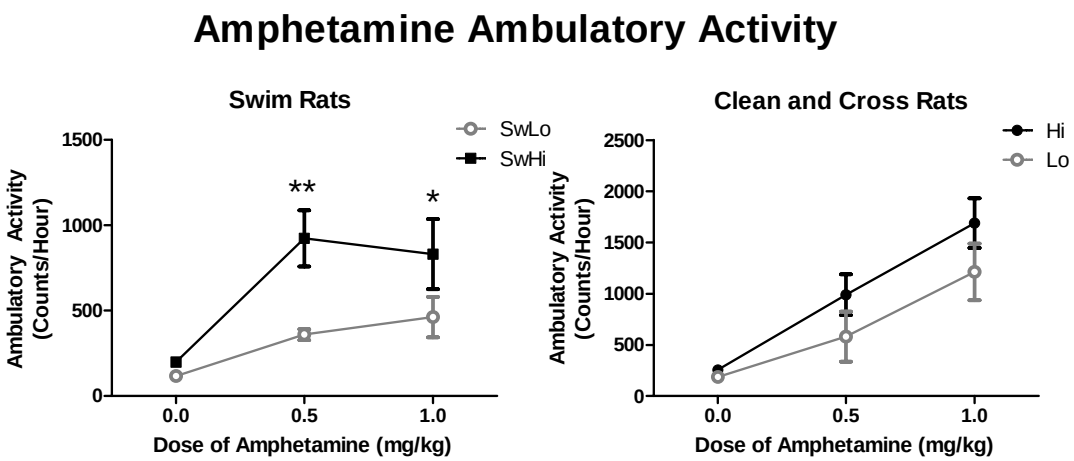

Figure 11. SwHi rats show a significantly greater amount of amphetamine-induced locomotor activity than SwLo rats. Rats were administered IP injections of amphetamine at either dose and ambulatory activity was recorded for 1 h post injection. Shown are SwHi and SwLo activity (left) and Clean/Cross Hi and Clean/Cross Lo activity (right). $^{**}p<0.01$ compared to Lo activity at 0.5 mg/kg amphetamine. $^{*}p<0.05$ comapred to Lo activity at 1.0 mg/kg amphetamine. (Swim rats:0.0mg/kg n=8 per line, 0.5mg/kg n=4 per line, 1.0mg/kg n=4 per line; Clean/Cross rats: n=4 per group per drug dose).

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