

Spring 2013

# Examining the effects of d-amphetamine on discounting in spontaneously hypertensive rats (SHR)

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EXAMINING THE EFFECTS OF D-AMPHETAMINE ON DISCOUNTING IN  
SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

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A thesis submitted to the Graduate Faculty of

JAMES MADISON UNIVERSITY

In

Partial Fulfillment of the Requirements

for the degree of

Master of Arts

Psychological Sciences

May 2013

## Acknowledgements

This project could not have been completed without the full support of the graduate psychology faculty at James Madison University. I would like to thank my advisor, Dr. Jeff Dyche, for allowing me to keep the animal research lab open during a time filled with much uncertainty and for his very generous track changes during the thesis writing process. Secondly, I would like to thank Dr. Daniel Holt for his countless hours of support with Med-PC programming and feedback during the data collection. I most certainly can't forget Dr. Bryan Saville or he'll be sure to say something about it. Dr. Saville's feedback and Sigma Plot expertise were very helpful and I'm forever grateful for their support. None of this would have been possible were it not for devoted undergraduate assistants: Teri Corbett, Tiffany Crosby, Maddie Munday and Sancho Sequeria. Last but not least, I thank my brother from another mother Curtis Bradley. Thanks for doing the shifts that nobody else wanted to do and keeping me company during those long fluorescent light filled afternoons in the lab.

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## Abstract

This experiment examined d-amphetamine's effect on discounting of delayed and probabilistic outcomes in spontaneously hypertensive rats (SHRs), a purported animal model of Attention Deficit/Hyperactivity Disorder (ADHD), with two control strains. Stimulants such as d-amphetamine are commonly administered in humans diagnosed with ADHD, thus resulting in increases in self-controlled responding on delay tasks. However, very little has been done examining the effects of d-amphetamine on delay tasks using the SHR strain, a purported animal model of ADHD. Recent research has also suggested that responses on delay and probability discounting procedures are mediated by the same underlying mechanism in animal models (Green, Myerson & Calvert, 2010). However, this equivalence is not observed when using human participants in similar choice procedures. The current experiment used an adjusting amount procedure to measure the subjective value of delayed and probabilistic reinforcers and the effects of d-amphetamine on choice behavior. The standard reinforcer varied across 8 conditions (5 pellets, each evaluated at two delays: 2 and 16-s and across two probabilities: VR-2 and VR-10. Each condition was run with both d-amphetamine [1.0mg/kg] and a saline vehicle.). The current results suggest non-equivalence as d-amphetamine appears to have differential effects on the choice behavior across different strains of rats. The current findings suggest that d-amphetamine appears to have differential effects on subjective values in the delay and probability discounting tasks.

## Background

The *DSM-IV TR* defines impulsivity as an inability to tolerate delays and inhibit responses (American Psychiatric Association, 2000). It is commonly diagnosed when behaviors such as inappropriate overactivity, inattention and an inability to delay gratification are persistent in a person's repertoire (Tripp et al., 2009). Although the inability to attend is considered a defining feature of Attention Deficit Hyperactivity Disorder (ADHD), according to the *DSM-IV TR*, many characteristics (e.g., hyperactivity) are also observed in increased levels of motor activity and impulsivity. For example, lack of attending and inability to inhibit responses are illustrated by continuous performance tasks (CPT) in individuals diagnosed with ADHD (Losier et al., 1996).

Recent research has shown that children diagnosed with ADHD exhibit an inability to delay gratification on certain behavioral tasks. For example, in an experiment involving children diagnosed with ADHD, Tripp and Alsop (2001) examined whether children would exhibit impulsive behavior (preference for the more immediate reward) when presented with a choice between a reinforcer delivered immediately and another reinforcer delivered after some delay. Thirty-six children diagnosed with ADHD were compared with 36 neurotypical children who served as controls. In this study, a matching-to-sample procedure was used in which the children had to respond on one of two keys that corresponded with faces that had been presented earlier. Matching one of the faces always resulted in an immediate delivery of a token, whereas matching the other face resulted in tokens after a short (3.5 s) delay. Incorrect responses were not reinforced, and a brief 50-s timeout followed. Results indicated that children who had been



diagnosed with ADHD typically made more responses on the more immediate key even when the face associated with that key was not presented. These data support the notion that individuals diagnosed with ADHD are very sensitive to delays of reinforcement when compared to neurotypical individuals. In other words, an individual is said to behave impulsively when one exhibits an inability to delay gratification. Using this behavioral definition of impulsivity, psychologists have been able to examine the effects of delays to reinforcement on individuals with impulse disorders such as ADHD.

Many tasks have been developed in the laboratory to examine impulsive behavior in both general and clinical populations (Winstanley et al., 2006). For example, two measures used to study this behavioral phenomenon are the go/no-go and stop-signal reaction time tasks (SSRTs). In a typical go/no-go task, the participant learns to emit a response when a stimulus associated with “go” is presented. In the following trials, a no-go stimulus is typically presented concurrently or just prior to the presentation of the “go” stimulus. During these trials, participants are to withhold their responses. Typically, children diagnosed with ADHD tend to make more errors than do typically developing peers on the same task (Winstanley et al., 2006). However, one of the issues with these tasks is the inability to measure the latency to a response that is withheld. In the SSRT, the inhibition of a response that has already been initiated is measured. That is, the latency to stopping a response. However, the ability to inhibit responses is calculated as an estimation of the time taken to inhibit a response and thus cannot be measured directly.

A behavioral choice task involving delayed outcomes seems to map onto both non-human animal and human research better than the other previously mentioned

methods (i.e. tasks involving two outcomes in which one is delivered immediately but smaller in magnitude compared to a concurrently available larger outcome after some delay). Delay tasks are able to capture changes in behavior as a function of delay to the arrival of the reward. It is a common procedure used to examine choice behavior in children as well as adults (Tripp & Alsop, 2001; Winstanley et al., 2006).

### **Neurobiology of ADHD**

At the neurobiological level, there is evidence suggesting that ADHD is the result of abnormal dopamine (DA) and serotonin (5-HT) functioning (Sagvolden et al. 2005; Zeeb et al., 2009). Though the effects of dopamine on prefrontal functioning are quite complicated, the general consensus is that dopamine exerts a strong regulatory effect on prefrontal neuronal activity (Sagvolden et al. 2005). The effect of dopamine depends on the state of the prefrontal cells (e.g., hyperpolarized non-firing or depolarized firing state). Dopamine (DA) has been postulated to mediate the value of delayed rewards (Wade et al., 2000). When comparing patients who have had injuries or diseases of the prefrontal cortex to individuals clinically diagnosed with ADHD, there are similarities in attention deficiencies and distractibility (Winstanley et al., 2006). Additionally, there are data from functional magnetic resonance imaging (fMRI) that show atypical fronto-striatal activity during go/no-go tasks with ADHD (Tripp & Wickens, 2009).

One theory of ADHD involves dysfunction in serotonin (5-HT) levels. For example, when tryptophan, an amino acid precursor to serotonin production, is depleted, increases in impulsive responding in stop-tasks as well as in go/no-go tasks in human participants is observed (Tripp & Wickens, 2009). However, depleting 5-HT in the same

manner has no effect on choice procedures such as delay and probability discounting tasks (Tripp & Wickens, 2009). In rats, however, 5-HT depletion increases impulsive behavior on both 5-choice serial reaction time task (5CSRT) and go/no-go tasks (Winstanely et al., 2006; Bizot et al., 1999). As for humans, 5-HT depletion seems to have both increased and decreased impulsive choice behavior on delay discounting tasks (i.e. tasks involving two outcomes in which one is delivered immediately but smaller in magnitude compared to a concurrently available larger outcome after some delay) (Winstanely et al., 2006; Bizot et al., 1999). Based on these results, the consensus seems to be that there is an interaction between both 5-HT and dopamine (DA) that may contribute to behavioral symptoms associated with ADHD.

Another hypothesis, the dopamine transfer deficit theory (DTD), attributes ADHD to alterations in the magnitude and timing of anticipatory dopamine cell firing (Tripp & Wickens, 2008). In positive reinforcement procedures, dopamine neurons are activated in response to rewards. The same effects are observed in both non-human primates and in rats (Hyland et al., 2002). According to the DTD, the efficacy of conditioned reinforcers is attenuated due to reduced dopamine levels. Some evidence suggests that dopamine enhancing stimulants work because they increase the value of conditioned reinforcers that are paired with the delayed reward (Robbins 1978; Robbins et al., 1983). A more recent study (Cardinal et al., 1999) examined the effects of amphetamine on delay discounting when the cue was present with the delay and when no cue was presented. When the cue was present, amphetamine increased choosing of the delayed alternative. When the cue was absent, choosing of the immediate alternative increased. Although the etiology of ADHD is still currently unknown, the previous findings have shown that DA agonists

seem to have an effect on behavior on certain behavioral tasks. Similar findings have been observed in clinical populations, leading to DA agonists being commonly prescribed to treat ADHD (Tripp & Alsop, 2001).

### **Stimulants as a Treatment**

The most common treatment for ADHD is the administration of stimulants such as dextroamphetamine (d-amphetamine) or methylphenidate (American Psychiatric Association, 2000). These drugs implicate a dysregulation of the monoaminergic neurotransmitters with marked increases in both norepinephrine and dopamine and mild increases in serotonin (Winstanley et al., 2006). Administrations of d-amphetamine appear to enhance performance in stop-tasks in both humans and rodents (de Wit et al., 2002). Administrations have also reduced discounting in delayed tasks in humans (i.e., lowering responses for the smaller outcome) (de Wit et al., 2002). However mixed results are observed on the five-choice serial reaction time task (5CSRT). Typically, d-amphetamine results in an increase in premature responses. This is indicative of increased impulsive behavior. The reason for this differential effect of d-amphetamine on behavior in varying impulsivity tasks is unknown, but these data suggest that behaviors that may be labeled as impulsive may have different neural origins (Winstanley et al., 2006).

To date, no single etiology of ADHD has been identified and the mechanisms underlying the disorder are not well described. While there is little evidence supporting abnormal dopamine levels as the sole cause of ADHD, the behavioral deficiencies (e.g., impulsivity) seem to be reduced with the use of psychostimulants such as methylphenidate and d-amphetamine, implying a role in the monoamine system. For this

reason, the further development of an animal model of ADHD would aid researchers in better understanding the behavioral mechanisms of ADHD.

### **Spontaneously Hypertensive Rat**

One of the commonly used non-human animal models of ADHD is the spontaneously hypertensive rat (SHR) (Sagvolden, 2000). Numerous studies have demonstrated that SHRs display behavioral characteristics analogous to the behaviors of individuals diagnosed with ADHD. Research assessing the validity of the SHR across measures of sustained attention (Aase & Sagvolden, 2006), increased motor activity and behavioral variability (Wultz & Sagvolden, 1992; Mook, Jeffrey, & Neuringer, 1993; Saldana & Neuringer, 1998), and impulsiveness (Hand, Fox, & Reilly, 2009) has shown that SHRs demonstrate behavior analogous to that of individuals with ADHD.

To better examine behavior in the SHR strain, Hand et al., (2006) examined the effects of delayed reinforcement on the acquisition of lever pressing. In this study, SHRs and the control rats, Wistar Kyoto (WKY), responded under a tandem fixed ratio (FR 1), differential reinforcement of other behavior (DRO 15-s) schedule. During the FR component, each lever press triggered the DRO component. The DRO was a 15-s un signaled interval that reset if the rat made another response prior to the completion of the interval. If no response occurred during the 15-s interval, the rat received a food pellet. The average rate of lever pressing was significantly lower for the SHRs than the WKYs. In addition, relative to the WKYs, the SHRs were slower to acquire lever pressing under the tandem schedule. SHRs were also more likely to continue responding once the DRO had begun and therefore they earned fewer reinforcers per session than the

WKYs. As an animal model of ADHD, the SHRs demonstrated a response rate with respect to delayed reinforcement similar to individuals with ADHD (Saldana & Neuringer, 1998; Hand et al., 2006).

In a study by Fox et al., (2008), SHRs were compared to a control strain (WKY) across a series of delays ranging from zero to 24 seconds. The delays were presented in both ascending and descending order to the two strains. During the ascending condition, there was an equally high preference for the larger, delayed alternative in both strains in the 0 through 6-s phases. However, in the 12-s and 24-s phase, SHRs chose fewer of the larger alternatives whereas the WKYs maintained the same proportion of response for the larger alternative (Fox et al., 2008). In the descending phase (e.g. 24-s, 12-s...), SHRs displayed a preference for the more immediate alternative at all delays. SHRs response latency in reverting back to the larger delayed alternative was much higher than WKYs. The SHR strain seems to display a preference for the more immediate reinforcer versus the larger delayed alternative (Fox et al., 2008).

If the SHR is an effective animal model of ADHD, then it seems reasonable that drugs that reduce impulsive behavior in humans should also reduce impulsivity in the SHR. In order to test this, Hand et al., (2009) administered d-amphetamine to both SHR and WKY rats in a delay discounting task at varying dosages (1.0, 3.2 & 5.6mg/kg). No difference in choice behavior among the SHRs between saline and d-amphetamine was reported. The WKYs however, displayed a marked decrease in preference for the larger alternative in the drug conditions at all delays. There was a major potential shortcoming with that experiment involving the initial baseline preference for the immediate reinforcer. That is, the effects of d-amphetamine on preference may have been masked by

a lever bias, due to a lack of counterbalancing of the levers. Still, although these results question the validity of the spontaneously hypertensive rat as an animal model of ADHD, another study observed marked increases in preference for the larger alternative under d-amphetamine (Wade et al., 2000). Early research on impulsive behavior and the SHR strain have primarily focused on impulsive choice. However, risky behavior (e.g., drug seeking in humans) is highly comorbid in individuals diagnosed with ADHD (Tripp & Wickens, 2008).

### **Impulsive Behavior versus Risky Behavior**

Initially, Green et al, (2004) suggested that both inability to delay gratification and risky behavior are both mediated by the same underlying mechanism of impulsivity examined in both delay and probability-discounting tasks (i.e., two concurrent outcomes that differ in magnitude but also in the likelihood of their presentation following a response). In other words, if performance on both delay and probability tasks are affected by an inability to delay gratification, one would expect large devaluation of rewards as a function of time on delay and probability tasks when compared to a control group (Holt et al., 2003).

One can see the clinical relevance in such a statement if individuals diagnosed with ADHD exhibit a heightened inability to delay gratification. This relation would also provide corollary evidence for such high levels of comorbidity observed in ADHD and other maladaptive behaviors (e.g., gambling). One study of interest (Holt et al., 2003) examined whether this inability to delay gratification also mediated choice behavior on tasks involving probabilities by examining correlations on discounting tasks using

probabilistic and delayed rewards across two hypothetical amounts of money (\$1,000 and \$50,000). In this study, 18-24 year-old undergraduate students were asked to fill out the south oaks gambling screen (SOGS) and a revised version of the Eysenck Personality Questionnaire. On the delay tasks, participants were asked to choose between a small amount immediately and a larger amount after a certain period of time. On probability tasks, participants were asked to choose between hypothetical amounts for certain or a larger amount with some probability. When comparing the rates at which the onset of a larger delayed amount increases, or becomes less probable (i.e., discounting), Holt et al. found that gamblers discounted probabilistic rewards less steeply than non-gamblers. However, gamblers did not discount delayed rewards more steeply than non-gamblers.

These results suggest that sensitivity to delays may not be controlling the discounting in tasks involving probabilities. However, it should be noted that a high score on the SOGS does not necessarily mean that one behaves “impulsively” on choice tasks. These data suggest that impulsive behavior on a delay task does not necessarily predict risky behavior on a probability task.

Another study, (Green et al., 2010) examined pigeons’ discounting of delayed and probabilistic reinforcers. In this experiment, pigeons were exposed to an adjusting-amount procedure that consisted of both a delay-discounting task and a probability-discounting task. In the delay task, pigeons were exposed to 20 pellets after delays of 1, 2, 4, 8, 16, and 32 s versus a smaller amount immediately. The order of delays was random for each pigeon. The probability task was similar except instead of delays, the standard (e.g. 20 pellets) was delivered after VR 1, 2, 4, 8, and 16 were met. Variable ratios were used to assess the probabilities because the probability of the next response



resulting in reinforcement is the reciprocal of the VR schedule. In other words, on a VR-10, the odds of the next response being reinforced are 1/10 or .1%.

Green et al.'s experiment demonstrated that the same mathematical function, the hyperbolic function, does seem to describe subjective values in both delay-discounting and probability-discounting tasks. These data suggest that variable delays to reinforcement are functionally equivalent to repeated gambles (Green et al., 2010). However, this is not the case humans. In humans, the comparison of delay and probability actually suggest non-equivalence. For example, amount seems to have different effect on the rates at which money is discounted (Green & Myerson, 2004). This pattern is not typically observed in probability tasks (Green & Myerson, 2004). The current study also seeks to examine whether the two are functionally equivalent by introducing a stimulant in a particular strain of rat. In comparing the two previously mentioned studies, results seem to be mixed as to whether the two processes are functioning differently. By using both delay and probability tasks, this study will examine whether the two are truly functionally equivalent while examining the efficacy of the SHR strain as an animal model of ADHD.

### **Research Question**

The Green et al., (2010) findings with rats and pigeons are of interest in the current study and to the clinical population of ADHD. These data suggest that individuals that delay outcomes may also engage in risky behavior as a function of the same underlying mechanism, a finding inconsistent with many published studies. According to this theory, individuals that are unable to delay gratification should also be more likely to

engage in risky behavior. However, this is not the case in humans. In humans, a comparison of delay and probability data actually suggests non-equivalence. For example, the amount of money seems to have different effect on the rates at which money is discounted in humans (Green & Myerson, 2004). The current study also seeks to examine whether the two are functionally equivalent by introducing a stimulant. In comparing the Green et al., (2010) and the Holt et al., (2003) studies, results seem to be mixed as to whether the two processes are functioning differently. By using both delay and probabilities, this study will also examine whether the two are truly functionally equivalent while examining the efficacy of the SHR strain as an animal model of ADHD. The rationale behind using varying strains is quite simple. If the two processes are indeed functionally equivalent, then responding on both delay and probability tasks should be equally affected by the introduction of d-amphetamine. The SHR strain should also respond similarly to that of the ADHD population when administered d-amphetamine on delay tasks.

The purpose of this study is then twofold. The primary question being asked is whether d-amphetamine affects choice behavior in a purported animal model of ADHD as it does in humans on delay-discounting tasks. A secondary question was to examine the effects of d-amphetamine on choice behavior in tasks involving probability discounting and therefore determining if d-amphetamine, which is known to increase responding to the delayed outcome, would also reduce responding on the more risky (less probable) outcome. In other words, if the same underlying mechanism is affecting both tasks, would a known treatment of delay sensitivity influence behavior on the probability task.

## Method

### **Subjects**

The subjects were four Spontaneously Hypertensive Rats (SHR), four Wistar Kyoto (WKY) and four Wistar rats (WI). At the beginning of the study, all rats were approximately 150 days old. After three weeks of habituation, rats were housed individually in smaller plastic laboratory cages (23cm x 20.5cm) in the Miller Hall Animal Research Facility at James Madison University. All of the rats were maintained at 80% of their free feeding body weight. The colony room was maintained at approximately 24 degrees Celsius on a 12:12-hr light: dark cycle. Water was available in the home cage at all times, and each rat received 12 - 15 g of food per day, which included 45mg pellets (Bio-Serv, Frenchtown, NJ; TestDiet, Richmond, IN) earned during experimental sessions. If a rat did not earn the maximum daily food allotment during a session, it received Harlan (Madison, WI) rodent diet (8604) in the home cage 3 hr after the experimental session.

### **Apparatus**

Experimental sessions occurred in Med-Associates (Georgia, VT) rodent operant chambers (ENV-008CT) housed in ventilated, sound and light-attenuated cubicles (ENV-018MD). The operant chambers contained two retractable response levers (ENV-122CM) located on the front wall, on either side of an opening through which pellet delivery occurred. A third retractable lever was located on the back wall across from the feeder opening. Above each lever were three colored LED cue lights (red, yellow, and green, left to right). A house light was located at the top of the back wall of the operant chamber

above the lever and a 4.0 KHz (80 db) speaker, controlled by a Med Associates Audio Stimulus Generator (ANL-926), was located above the pellet dispenser. A computer using Med-state MED-PC IV programming language controlled the operant chambers.

### **Procedure**

**General Procedure.** Training sessions occurred 5 – 7 days a week throughout the study. Fifteen min prior to each session, each rat received an intraperitoneal injection of d-amphetamine or saline and was placed in the operant chamber. The type of injection was dependant on the current phase each rat was on in the experiment (see Table 1). Each session began with the illumination of the houselight. Each session ended after 50 min or the completion of 10 trial blocks, whichever came first. At the end of each session, all levers were retracted and the house light extinguished.

**Pretraining.** During pretraining sessions, the house light remained illuminated throughout the session. For the first habituation session, the food receptacle was baited with 25 food pellets. No levers were extended, and there were no pellets delivered from the hopper during this session. For the second habituation session, the food receptacles again were baited with 25 pellets prior to the session and pellets were delivered on a random time (RT) 30-s schedule with a probability of delivery of .3 every 10-s. An audible, 500-ms 2000-Hz tone accompanied each pellet delivery throughout pretraining. Each habituation session ended when the rat received 100 pellets or 110 min elapsed.

Following habituation, autoshaping began. This involved extending one of the front levers (counterbalanced across rats) into the chamber according to a RT 30-s schedule with a probability of delivery of .3 every 10-s. During the lever extension, all three LED lights above the lever were illuminated. If the rat made a response on the

extended lever, the lever retracted, the LED lights terminated, and a pellet delivery occurred immediately. If the rat failed to make a response on the extended lever within 10-s, the lever retracted and a pellet was delivered. Once the rat made 10 responses on the extended lever during a session, lever pressing was placed under an operant contingency such that the lever remained extended and the LED lights remained illuminated until the rat responded. A response on the extended lever resulted in the lever retracting, termination of the LED lights, and pellet delivery. Once lever pressing was established, the extended lever varied systematically across days; each rat received seven sessions with left lever extension, eight sessions with right lever extension, and two sessions with rear lever extension.

**Discounting Measured Using An Adjusting-Amount Procedure.** The experimental conditions of the adjusting-amount procedure were similar to Green et al. (2010). Each session included 40 trials arranged in 10 four-trial blocks and terminated after all 40 trials were completed, 50 min had elapsed, or 200 pellets (13.5 g) were delivered. Each block included one larger, later (standard) sample trial and one smaller (adjusting) sample trial in random order, followed by two choice trials. Each trial began with the illumination of the house light and the center light above the rear lever accompanied by extension of the rear-wall lever. When the rat pressed the lever, it retracted and the center light terminated. Adjusting lever assignment was counterbalanced across rats, and it remained constant throughout the experiment.

During sample trials, one of the levers on the front wall extended into the chamber accompanied by illumination of a LED light. Once the rat pressed the lever, it retracted and the house light terminated. The LED light remained illuminated during the

requirements imposed by the current contingency but was extinguished once food delivery began.

Food delivery was signaled by a 10-s, 2000-Hz tone. Each intertrial interval (ITI) began with the illumination of the house light. The duration of each ITI varied in order to keep the time between trials at 70 s. During choice trials, both front-wall levers extended into the chamber and the LED lights associated with each alternative illuminated. When the rat pressed one of the levers, both levers retracted and only the chosen alternative's LED light remained illuminated. Following the contingency associated with the chosen alternative, the reinforcer associated with that alternative was delivered, and the ITI followed in the same manner as during sample trials. The larger standard reinforcer was five pellets, and there were two delay conditions and two probability conditions: 2-s and 16-s delays and a VR-2 and VR-10 for probabilities.

Throughout the study, each rat's response during the choice trials determined the number of reinforcers associated with the adjusting alternative during each session. Selection of the standard alternative on both choice trials resulted in the adjusting alternative increasing by one pellet for the next block of trials up to a maximum of five. Selection of the adjusting alternative on both choice trials resulted in the adjusting alternative decreasing by one pellet for the next block of trials (to a minimum of zero pellets). Selection of the adjusting alternative on one choice trial and the standard alternative on the other choice trial, regardless of the order of the choices, resulted in no change in the adjusting amount for the next block of trials. For the first session of both the delay and probability condition, the amount of the adjusting reinforcer began at one pellet, and for all subsequent sessions in the condition, the choices made in the last block

of trials of the preceding session determined the amount of the adjusting reinforcer at the beginning of the session.

To determine stability, the last five sessions were divided into half sessions, and the mean number of pellets earned from the adjusting alternative during each half was compared to the overall mean number of adjusting reinforcers earned across the full sessions. Each condition terminated when the mean number of reinforcers earned from the adjusting alternative during each half-session was within two pellets of the overall mean number of reinforcers earned from the adjusting alternative. Data for the WKY drug condition are incomplete due to laboratory repairs that occurred while the experiment was being conducted

## **Results**

As conditions change, there appears to be a systematic change in subjective values across strains. This change in subjective values is seen in drug and saline conditions as well as both delay and probability. The change in subjective values as a function of condition manipulation is important to the experiment because the changes in subjective values as delays and probabilities changed effectively produced discounting. Each rat's individual subjective values are plotted as dots on each graph. The same color dot represents the same rat in each strain. Individual data are plotted for illustrative purposes.

Figure 1 shows the subjective values during the VR-2 in both the drug and saline phase. The SHR strain's median subjective value is 4.84 pellets in the saline condition. Under the influence of d-amphetamine, the median subjective value is 4.67 pellets. The WKY's subjective value under saline is 4.49 pellets in the saline condition.

During the drug phase, the subjective is 3.89 pellets. The WI's subjective value under saline is 4.7 pellets and changes to 4.61 pellets during the drug phase. In looking at the individual data points, there seems to be very little variability, less than one pellet difference, within the SHRs and the WIs but much variability in the WKY strain.

Figure 2 shows the median subjective values for both drug and saline under the VR-10 schedule. In comparing both the VR-2 and VR-10 figures, a noticeable decrease in subjective values is observed across all strains. The SHR strain under saline is 2.57 pellets and 2.82 pellets when in the drug condition. The WKYs have the lowest subjective value in the saline phase at 1.04 pellets. During the drug condition, the subjective value more than doubles to 2.57 pellets. The WI strain's value is 2.37 pellets in the saline phases and 3.72 pellets in the drug condition. There is much more within-group variability at this VR-10. In looking at individual data, most of the rats' subjective values changed as a function of drug introduction. However, the direction of the change varies across each animal.

In Figure 3, subjective values are illustrated graphically as a function of the 2-s delay. Under the drug condition, the SHRs' median subjective value is 3.52 pellets compared to 4.95 pellets in the drug condition. The WKYs median saline subjective value is 2.08 pellets. The WKYs drug data was not analyzed due to incompleteness. The WI strain shows almost no change in subjective value as it goes from 3.5 pellets in the saline condition to 3.41 pellets in the drug condition.

Figure 4 represents the median subjective values in the 16 s delay condition. Under the 16 s delay, the SHRs subjective value is 1.29 pellets under saline and 1.4 pellets in the drug condition. The WKY and WI strain show increases in subjective



values under the drug condition. The WKY subjective value changes from 0.68 pellets to 1.37 pellets in the drug condition. The WI changes as well, increasing from 0.77 pellets to 2.27 pellets in the drug condition. At the individual level, changes in subjective values generally increase under d-amphetamine. An increase in subjective value is observed in all but one of the rats (See SHR in Figure 4

## Discussion

The current investigation served multiple functions. The primary function was to examine the efficacy of an animal model of ADHD and a commonly prescribed medication (d-amphetamine) on choice behavior using delay and probability discounting as an assessment tool. Previous findings regarding the efficacy of this strain as an ADHD model have been mixed at best (e.g., Hand et al., 2009; Sagvolden, 2000). The current investigation sought to examine the effects of the stimulant, d-amphetamine, which is often prescribed to reduce ADHD symptomatology, specifically, impulsive choice. In a clinical setting, stimulants such as d-amphetamine often result in an increase in self-controlled choice behavior (Losier et al., 1996). The animal analogue of self-controlled choice behavior is delay discounting. However, many of the previous studies have had varied results regarding the effectiveness of d-amphetamine on choice behavior (see Hand et al., 2009; Wade et al., 2000). Previous studies have also reported that risky behavior on probability tasks in animal models may be functionally equivalent to tasks involving delays (see Green et al., 2010). Another question of interest was to investigate whether or not probability and delay discounting are being mediated by the same mechanism.

The current study also employed the Wistar (WI) as a comparison strain. The SHRs are inbred from the WKY strain and share a very similar genetic makeup. Previous research has shown that the WKY and SHR strains behave similarly on some discounting tasks (Halsey, 2010). However, these effects have yet to be observed under a task involving probabilistic outcomes paired with a stimulant.

### **Effects of D-amphetamine on Behavior**

After administration of the drug, the subjective value seemed to vary as a function of the condition being run. In other words, preference for the larger but delayed outcome varied under the drug condition but not always in the direction hypothesized. These results are consistent for both the Wistar and Wistar Kyoto rats in the 16-s delay condition. It is interesting that impulsive choice behavior seems to increase in the 16-s drug condition among the SHRs. These results seem to coincide with the findings of Hand et al. (2009) in which differential effects of d-amphetamine on behavior were also observed at larger delays. Dextroamphetamine failed to reduce impulsive choice in the SHR rats once the delayed outcome increased to 16 s. One may speculate that this could be attributed to the age of the rats at the time of testing. A previous study by Bizot et al. (2007) has shown that the age of the rats seems to affect whether drugs will affect choice behavior. In the 2007 study by Bizot et al., methylphenidate resulted in an increased preference on the larger delayed reward in a T-maze in juvenile Wistar rats but not in the WKY or SHR adults. Results from this study could be confounded due to the fact that the rats' were at different ages during the various conditions. In the probability discounting task, rats in the current study began running around post natal day 150 and while each animal was run until stability criteria were reached, this process took at least two months to complete all four conditions. However, in the delay tasks, rats were at post natal day 210 at the very least.

Earlier research has shown that dopaminergic drugs may affect the strength of conditioned reinforcers in adjusting amount procedures (Robbins, 1978; Robbins et al.,

1983). Data from the Robbins et al., (1983) experiment suggests that dopamine enhancing drugs may intensify the conditioned reinforcers (e.g. the tone in this experiment). This may seem like a subtle difference but it is a very important one to note. In the current adjusting amount procedure, the tone that was associated with the delivery of the food pellets was programmed to beep just before the delivery of the pellets. These two occasions are noticeably different in a 2 s and 16 s delay. For example, during the 16 s delay sessions, if a choice was made on the larger but delayed lever, the levers would retract and a timeout would ensue. The conditioned reinforcer was also delayed whereas in both the shorter delay and the VR schedules this delay was absent. The illumination of the LEDs during both the delay-task and probability-task attempted to balance conditioned reinforcer saliency. However, it is possible that the changes in responding that are observed with the SHRs could simply be a function of conditioning.

The drug seems to be having the opposite effect on the Wistar Kyoto and Wistar rats in the 16 s delay condition. The two strains subjective values increased under the influence of d-amphetamine. A previous study done by Wade et al. (2000) showed similar increases in responding on the delayed outcomes under d-amphetamine with Sprague-Dawley rats.

One key difference between the Wade et al. and the current experiment was the introduction of varying strains of rats. By using these particular strains, this experiment sought to examine the efficacy of the SHR strain as an animal model of ADHD. A secondary question of interest was in regard to the previous use of the WKY strain as a control for the SHR (see Lowes & Howes, 1990). A study by Sanabria and Killeen (2008) found that on tasks that measured impulsivity by means on withholding

responses (DRL) the WKY and SHR rats seemed to respond comparably to one another vis-a-vis a more genetically diverse Long Evans (LE) rat strain. These results seem to be consistent when impulsive behavior is measured by choice procedures as well. In both delay and probability, the WKY strain seems to more closely resemble the SHR strain with respect to observed subjective value. These data support the argument that the WI strain may function as a better control in behavioral studies.

By introducing d-amphetamine, this study was able to more accurately mirror the human research paradigm by adding a treatment condition, administration of d-amphetamine. However, the current results, as in the extant animal literature, appear to be quite mixed. In the 2-s delay under saline, SHRs' choice behavior seems to be no different than that of the Wistar controls. Initially, this seems counterintuitive. One would expect more discounting to occur across the delays (indicative of lower bar graphs). A possible explanation for this occurrence could be due to the fact that a 2-s delay is very short, meaning that from the organism's perspective the choices may have been more difficult to discriminate. Pairing this with the fact that there was a short delay (.75 s) on the adjusting lever may have attributed to higher subjective values on delay tasks. Under the influence of the drug on the short delay, a noticeable increase is observed in the SHR strain. The increase in subjective value is indicative of fewer responses on the adjusting lever. These 2-s delay data do not support the findings of Hand et al. (2008) in which they failed to detect a decrease in impulsivity. One key difference between the current study and the Hand study was the design of the procedure. In the current study, test sessions were separated into blocks that consisted of two sample trials followed by two choice trials. Each session consisted of 10 blocks. The Hand et al. study consisted of

three blocks that consisted of two sample trials followed by 10 choice trials. The rationale for the design of the current study was to ensure that the saliency of contingencies operating on the levers didn't deteriorate over time. It is possible that these procedural differences led to differences in observed outcomes.

### **Neurobiological Evidence Supporting Psychostimulant Use and the SHR**

While the current experiment did not directly examine biological underpinnings, recent evidence (Russell, 2002) has shown that psychostimulants are very effective at alleviating all three of the symptoms associated with ADHD (inattention, impulsivity, and overactivity). Methylphenidate and d-amphetamine work by inhibiting reuptake and stimulating the release of dopamine and norepinephrine, resulting in an increase of the neurotransmitters' presence at postsynaptic receptors (Russell, 2002). In clinical trials, transcranial magnetic stimulation showed that psychostimulant use significantly enhanced intracortical inhibition and were equally effective in reducing motor activity in children diagnosed with ADHD (Russell, 2002).

One of the common criticisms against the SHR strain is that the rats develop hypertension at later stages in life. Hypertension is not associated with ADHD in children. What this means is it is possible that the dopamine deficiencies observed could be a function of hypertension and not necessarily impulsivity. To examine this disparity, Linthorst et al., (1990) examined the release of dopamine through electrical stimulation across differing ages of the SHR strain. Deficiencies in dopamine release were found in caudate slices of adolescent SHRs (4 weeks) as well as more mature SHRs (12-14

weeks). Although the rats in the current study were much older (30 weeks), previous research shows that the onset of hypertension is not the causal factor of impulsive choice behavior. Unchanged deficiencies in dopamine expression are important to the validity of the SHR strain because these deficiencies do not appear to be caused by the onset of hypertension. The deficiencies in dopamine found in the SHRs regardless of age are relevant to the current study because the rats were approximately 21 weeks old at the beginning of the study, well after the onset of hypertension has been observed (Linthorst et al., 1990). A possible extension of the current study might entail looking at differences in dopamine transporters at both pre and post adolescence. Even though the effects of d-amphetamine on behavior in the current study appear somewhat mixed, the current study examined d-amphetamine's influence on behavior in two previously deemed functionally equivalent processes.

### **Impulsive Choice Behavior versus Risky Behavior**

The purpose of the probability discounting task was to examine a paradox between human and non-human research. Probabilities and delays seemed to be functioning differently in humans and non-human animals. The current study used a stimulant, the SHR rat, and control strains as a means to investigate whether the two processes are truly related.

The probability data in the current experiment suggest that the two processes are indeed non-equivalent. The introduction of d-amphetamine had very different effects on choice behavior in the current tasks. In looking at the VR-2 saline condition, there seems to be no difference between the three strains at such a high probability. The probability at

a VR-2 is simply the reciprocal of the current schedule. That is, a VR-2 means that the likelihood of the current response being reinforced is 1/2 or 50%. Under drug conditions, the subjective value slightly decreases but the change does not appear vastly different based on a visual analysis. It is important to note that the subjective values on delays and probabilities paint two very different pictures. A higher subjective value on a delay task is indicative of a choice of the larger delayed reward. This in turn increases the adjusting value. From a clinical standpoint, higher values on delay tasks are indicative of self-control (e.g., Tripp & Alsop, 2001). One can view these higher subjective values on delays and the optimal choice. In contrast, a higher subjective value on a probability (VR) task is indicative of a gamble. With this in mind, it is possible that a VR-2 is not a large enough probability to tease out strain differences in responding. This choice behavior has been termed risky because there is a certain probability associated with each lever response.

Under the VR-10, the SHRs seem to engage in more risky behavior in the saline condition compared to the WKY strain. The WI strain also engages such behavior. This pattern is of interest for a few reasons. First, one would expect the SHR strain to persist in such behavior as this risky behavior has been observed in novel gambling tasks (Zeeb et al., 2009). The fact that the WI control was also equally high is an interesting finding, possibly suggesting that in behavioral studies the WI strain may also not be the ideal control. Secondly, the SHRs are willing to engage in that risky behavior when an immediate alternative is readily available. There is an increase in responding on the probabilistic outcome in the two control strains but not in the SHR strain. The same drug has a differential effect and it appears condition specific. When the probability data are



compared to the delay data, responding becomes more optimal in the delay but less optimal in the probabilities.

There has been some debate as to whether or not the probability task used is truly a probability task. In a human experimental session, the probabilities are set and only one response is required (i.e. a gamble). However, this is procedurally different in the animal sessions whereas the same process could be considered extinction. The current experiment required the animals to finish responding on the VR lever until reinforcers were delivered. By definition, our probability task is not a true probability based on the mathematical definition. In each session the probability is 100% and therefore arbitrary. It should also be noted that as each response is made on a VR the probability increases. This is an ongoing issue in animal research because true probability tasks would ultimately result in extinction. Although there is no way to circumvent the shortcomings with an animal model of assessing probabilities, the current study defined probabilities based on the likelihood that the very next response would produce a reinforcer and is consistent with past literature examining probability discounting in rats.

The current experiment does seem to provide some data that suggest these processes are not functionally equivalent; it does not seem to answer how d-amphetamine affected responding. The study also raises the question of whether a tolerance to such a consistent dose would develop and ultimately affect choice behavior. There is a possibility that the animals may have become habituated to the dose during the criterion requirements. It should also be noted that not all animals were able to complete the trials due to construction in the laboratory that was required due to flooding from a severe

storm. A future extension may involve examining brain structures to observe changes between adolescent and adult rats after chronic administrations of d-amphetamine.

### **Research Question Revisited**

The primary focus of the study was to further expand to a growing body of literature that supports the use of the spontaneously hypertensive rat as an effective animal model of ADHD. Results on the delay tasks at both large and short delays appear inconsistent enough to provide further validation for this strain. As seen in Figures 3 and 4, discounting does occur, but not in the expected directions for the SHR at the larger delays compared to the control strains. Although these data may be an anomalous outcome, they do not correspond with previously reported changes in discounting when using the SHR strain (See Sagvolden, 2000). These delay data, paired with the differential effects of d-amphetamine on behavior in the SHR, provide evidence that more research needs to be done examining the efficacy of using drugs commonly prescribed to treat neurobiological deficiencies associated with ADHD in humans on a rodent brain that may not exhibit similar deficiencies.

D-amphetamine appears to have differential effects on subjective values in the delay and probability discounting tasks. On probability tasks, d-amphetamine appears to cause an increase in risky behavior, as noted by increased preference for the less probable outcome in the VR-10 condition in the two control strains. This did not appear to be the case in the SHR strain. This is of particular interest because in the 16-s delay task, the controls showed increases in subjective value under the drug condition, indicative of a self-controlled response, whereas the SHRs did not. If the two processes were truly

functionally equivalent, the effect of d-amphetamine would have been similar across all three strains.

As previously mentioned, the purpose of using all three strains was to provide data based on an earlier study (Halsey, 2010) examining the use of the WKY as a control strain for SHR. The results for the WKY on both probability and delay tasks are slightly obscure in comparison to the SHR and WI. However, a recent study further clarifies the problems in using the WKY strain as a control (Sagvolden et al., 2009).

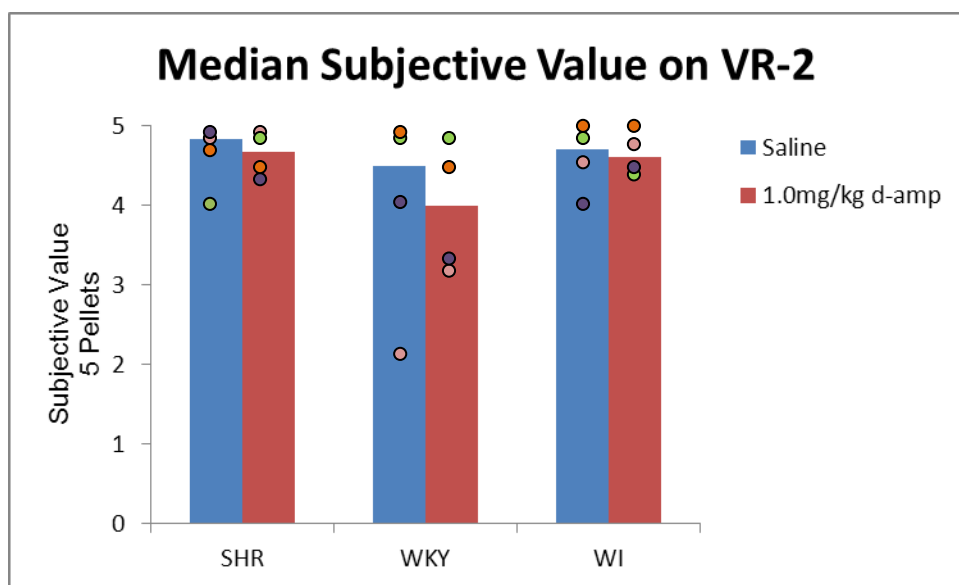
Although some results appear inconclusive, this study attempted to validate one of the animal models of ADHD, the SHR. To date, very little has been done examining whether commonly administered drugs used to treat ADHD in humans affect their non-human counterparts in a similar fashion. This study provides preliminary evidence that drug effects on purported animal models should be used to evaluate the model's validity. In attempting to establish similar effects on behavior across species, the SHR strain could potentially be further supported as an advantageous animal model of ADHD.

Table 1

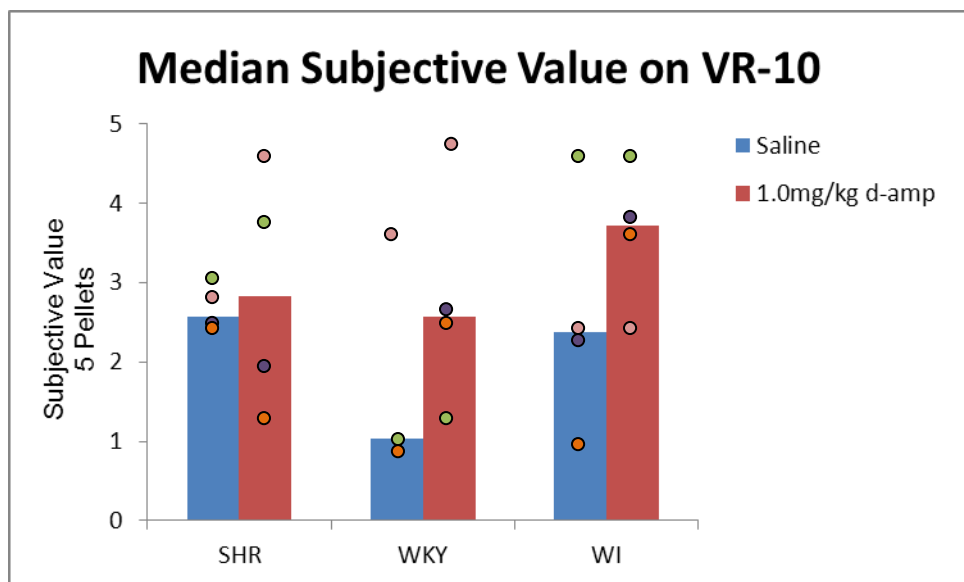
*Order of Phases Across Conditions*

Strain/Rat ID	Condition 1	Condition 2	Condition 3	Condition 4
SHR/Z $\Xi$ -1-1	VR-2 <i>d</i> -amp	VR-10	Delay 16-s	N/A
	VR-2	VR-10 <i>d</i> -amp	Delay 16-s <i>d</i> -amp	N/A
SHR/ Z $\Xi$ -1-5 s	VR-2 <i>d</i> -amp	VR-10	Delay 2-s	Delay 16-s
	VR-2 saline	VR-10 <i>d</i> -amp	Delay 2-s <i>d</i> -amp	N/A
SHR/Z $\Xi$ -1-3	VR-2	VR-10 <i>d</i> -amp	Delay 2-s <i>d</i> -amp	Delay 2-s
	VR-2 <i>d</i> -amp	VR-10	Delay 16-s <i>d</i> -amp	Delay 16-s <i>d</i> -amp
SHR/Z $\Xi$ -1-4	VR-2	VR-10 <i>d</i> -amp	Delay 16-s <i>d</i> -amp	Delay 2-s
	VR-2 <i>d</i> -amp	VR-10	Delay 16-s	N/A
SHR/Z $\Xi$ -2-1	VR-2 <i>d</i> -amp	VR-10 <i>d</i> -amp	Delay 16-s	N/A
	VR-2	VR-10	Delay 16-s <i>d</i> -amp	N/A
WKY/Z $\Xi$ -2-2	VR-2 <i>d</i> -amp	VR-10	Delay 16-s	N/A
	VR-2	VR-10 <i>d</i> -amp	Delay 16-s <i>d</i> -amp	N/A
WKY/Z $\Xi$ -2-3	VR-2	VR-10 <i>d</i> -amp	N/A	N/A
	VR-2 <i>d</i> -amp	N/A	N/A	N/A
WKY/Z $\Xi$ -2-4	VR-2	VR-10	Delay 2-s	N/A
	VR-2 <i>d</i> -amp	VR-10 <i>d</i> -amp	N/A	N/A
WI/Z $\Xi$ -3-1	VR-2 <i>d</i> -amp	VR-10	Delay 2-s	N/A
	VR-2	VR-10 <i>d</i> -amp	N/A	N/A
WI/Z $\Xi$ -3-2	VR-2 <i>d</i> -amp	VR-10	Delay 16-s <i>d</i> -amp	Delay 2-s
	VR-2	VR-10 <i>d</i> -amp	Delay 16-s N/A	N/A
WI/Z $\Xi$ -3-3	VR-2	VR-10	Delay 16-s	N/A
	VR-2 <i>d</i> -amp	VR-10 <i>d</i> -amp	Delay 2-s <i>d</i> -amp	N/A
WI/Z $\Xi$ -3-4 s <i>d</i> -amp	VR-2	VR-10 <i>d</i> -amp	Delay 2-s <i>d</i> -amp	Delay 16-s
	VR-2 <i>d</i> -amp	VR-10	Delay 2-s	N/A

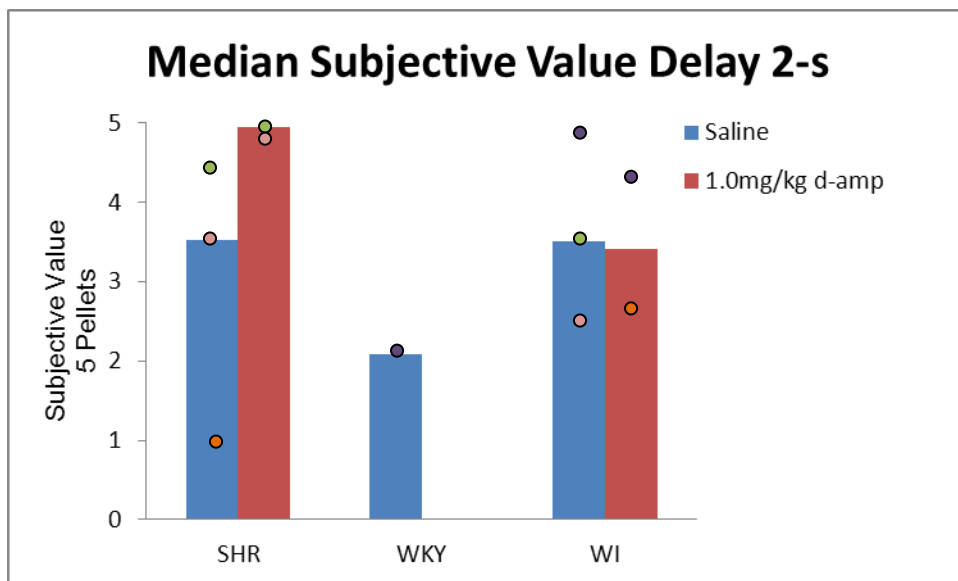
*Note.* N/A means they were unable to reach stability. The columns indicate the order in which they received the drug. A blank next to the contingency requirement indicates a saline injection phase.



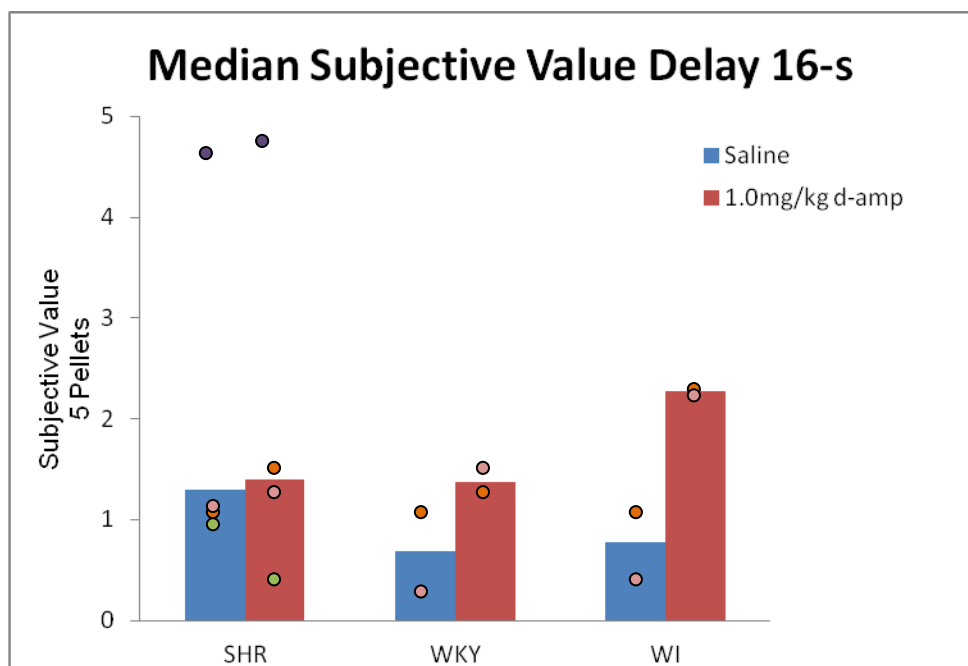
*Figure 1:* Shows the median and individual subjective value across strains under drug and saline conditions. The colored dots represent an individual rat's subjective value.



*Figure 2:* Shows the median and individual subjective value across strains under drug and saline conditions under the VR-10. The colored dots represent an individual rat's subjective value



*Figure 3:* Shows the median and individual subjective value across strains under drug and saline conditions under the Delay 2 s. The colored dots represent an individual rat's subjective value. Data for the strains are incomplete due to some rats not meeting the stability criteria.



*Figure 4:* Shows the median and individual subjective value across strains under drug and saline conditions under the Delay 16 s. The colored dots represent an individual rat's subjective value. Data for the strains are incomplete due to some rats not meeting the stability criteria.



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