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A Novel Behavioral Paradigm to Measure Addiction in Rats

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The following study examined the addictive nature of Coca-Cola® by providing either diet, caffeine free Coca-Cola® or Coca-Cola® for two weeks to rats. On day 15, rats were given 10% apple juice followed by a 0.15M lithium chloride. On day 16, the controls was given a choice between 10% apple/diet caffeine free Coca-Cola® vs. Coca-Cola® with the experimental group given 10% apple/Coca-Cola® vs. diet caffeine free Coca-Cola®. The study found that the experimental rats continued to drink Coca-Cola®, despite it being paired with the illness producing apple juice, and preferred it over a non-illness producing substance, as similarly observed in addiction. Equally important, this experiment also provides a novel behavioral paradigm for measuring addiction in animals.

Key Terms: *Addiction, Soft Drink, Caffeine, Dependence, Conditioned Taste Aversion, Rats*

Studies of drugs of abuse have recognized the emotional and financial strain to the individual suffering from dependence, but also those affected such as family, friends, employers and government programs utilized for the treatment of drug dependency. To be classified as a drug of abuse, the drug must fulfill three out of the seven criteria set by the American Psychological Association in the current Diagnostic and Statistical Manual (DSM-IV-TR, 2000). The criteria are: (1) tolerance, (2) withdrawal, (3) taking more of the substance or for longer periods of time than intended, (4) inability to reduce or control the use of the drug, (5) spending considerable time obtaining, using and/or recovering from the drug, (6) significant impact on social, occupational and/or family activities, (7) continued use despite adverse effects, either physical or psychological. Researchers have spent much time measuring dependency (referred to as addiction when studied in animals) based on the first four criteria, with most focusing on tolerance and withdrawal.

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Animal Models of Addiction

To date the primary animal models of addiction consists of operant intravenous drug self-administration, drug discrimination, brain stimulation reward, and place preference (Koob, 1994; Willner, 1997). While these models have been shown to be reliable, valid, and widely accepted tools used to investigate drug-taking behavior in humans (Koob, 1994; Willner, 1997), there are many disadvantages to using these currently accepted animal models. First, individuals must be trained in surgical procedures or involve extensive animal behavioral training. Secondly, the equipment costs may be prohibitive for a number of research laboratories. Third, the drug delivery methods may not mimic those of humans and finally.

While self-administered drug testing is often used in animal research with drugs of abuse due to the reinforcing qualities of many drugs (Grigson, 1997), there is limited use of behavior models of addiction such as the use of lithium chloride (LiCl) induced conditioned taste aversion (CTA) drug testing. Conditioned taste aversion relies on some of the principles of Plavlovian or classical conditioning. In Pavlov's classic experiment (1927), food (Unconditioned Stimulus:US) produced the reflexive response of salivation (Unconditioned Response) in

dogs. Upon repeated pairing of a neutral stimulus (metronome) with the food (US), the neutral stimulus was then able to produce salivation (CR) when food was not present, therefore resulting in the metronome transitioning from the neutral to the conditioned stimulus (CS).

Conditioned taste aversion, or the Garcia Effect (Garcia, Kimeldorf, & Koelling, 1955) uses saccharin (Neutral stimulus-CS) paired with radiation or more commonly LiCl (US) to produce illness (UR/CR) in rats. However, there are two significant advantages of CTA over classical conditioning. One is that learning can occur in only one trial or pairing of the CS-US and, second, there can be a significant time delay (i.e. hours) between the CS and US pairing, both of which are not always possible in other examples of classical conditioning.

However, the addiction research using CTA uses the drug of abuse in place of LiCl to induce a CTA, which has been found to be ineffective if the drug of abuse has positive reinforcing effects (Grigson, 1997). There are other advantages to using a CTA animal model of drug addiction, besides one-trial learning and CS-US delay. CTA testing is efficient and inexpensive; there is little training time required for the animals and no expensive surgeries or equipment required to perform testing. Another advantage to using a CTA model is drugs, such as caffeine, can be ingested orally, mimicking human consumption.

Another significant advantage to using CTA to measure addiction in animals is that it can be used to investigate the 7th criteria of the DSM-IV-TR 's definition of dependency, continued use of the drug despite adverse effects. This is important to the field of psychopharmacology as it provides an additional measure for researchers to use, especially when tolerance and withdrawal effects are most measured. In order to classify a drug of abuse, it must satisfy three out of the seven criteria, and this method gives researchers additional options to meet that criteria. If the drug of choice were paired with the CS (i.e. apple juice) following illness, it stands to reason that the animal is still choosing the drug, despite its pairing with a substance that previously made them ill. The current experiment will test this using caffeine as the drug, delivered via the soft drink Coca-Cola.

Caffeine Addiction

There is much debate about whether caffeine should be considered a drug of abuse (Griffiths & Mumford, 1994; Satel, 2006). In fact, the current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) of the American Psychological Association (DSM-IV-TR, 2000) states

> "some individuals who drink large amounts of coffee display some aspects of dependence on caffeine and exhibit tolerance and perhaps withdrawal. However, the data are insufficient at this time to determine whether these symptoms are associated with clinically significant impairment that meets the criteria for Substance Dependence or Substance Abuse" (p. 231).

Therefore, the DSM-IV-TR does not classify caffeine as a drug of dependence or abuse, but instead gives it an intoxication status. This is based on the fact that caffeine does not definitively fulfill three out of the seven criteria set by the APA in the DSM-IV-TR.

Part of the problem has been the inconsistencies and problems with studies that have investigated caffeine addiction (For a Review, See Nehlig, 2004). For example, problems for the human data have included, but not limited to, possible unreliable subjective reports of withdrawal, tolerance, etc, small sample sizes, and individual differences as they relate to caffeine sensitivity and metabolism. In addition, there are problems in interpretation as different coffees and they way they are prepared yield different caffeine concentrations.

In animal studies, the major concerns are that to measure tolerance and withdrawal symptoms, high doses are required beyond that of human consumption (67 mg/kg in animals vs. 2.4-4.0 mg/kg in humans) and the drug is usually administered via injection and thus, not mimicking how humans typically consume caffeine (Nehlig, 2004). Therefore, this suggests that an additional measure would be useful to study drugs that are typically orally consumed in humans, and to increase the external validity, it might be helpful to use a substance (i.e. soft drinks) consumed regularly, without huge variances in caffeine concentrations based on preparation.

Health Concerns with Soft Drinks

Despite the intoxicant status, the argument for classifying caffeine as a drug of abuse has gained momentum due to the vast increases in childhood obesity and type-two diabetes (Schulze, et al., 2007) and their positive correlation with increased soft drink consumption over the last three decades (French, Lin, & Guthrie, 2003). While much of the research surrounding soft drinks examines the health effects of the beverage, little research has been done to identify any addictive qualities of soft drinks, despite the mean intake of soft drink consumption within the population more than doubling within a twenty-year span (French, Lin, & Guthrie, 2003). In

fact, most research dealing with caffeine dependence has studied coffee, which has higher concentrations than soft-drinks.

One study that examined the reinforcing and subjective effects of caffeinated colas found that 22% of adolescent participants reliably self-administered caffeine during a choice period, choosing caffeinated over non-caffeinated colas (Hale, Hughes, Oliveto, & Higgins, 1995). However, this result alone does not conclusively demonstrate psychological and/or physical dependence. Further complicating research studying the reinforcing qualities of caffeine consumption, especially coffee, are the smells and social environments associated with consumption.

A study by Harnack, Stang, and Story (1999) examining children ages 2 to 18 years, found that soft drink users consumed more dietary calories per day than non-soft drink users, and that children rated as high soft drink users consumed less milk and fruit juice when compared to non-soft drink users. These findings suggest that children consuming soft-drinks decrease their intake of other more nutritious options, possibly decreasing the amount of nutrients consumed during childhood development; this could have strong health implications for children later in life. Other studies have positively correlated soft-drinks and other sugar-sweetened beverages with childhood obesity, weight gain, and type 2 diabetes in young and middle aged women (Ludwig, Peterson, & Gortmaker, 2001; Schulze, Manson, Ludwig, et al., 2007). A range of other studies have linked consumption of soft-drinks and other sugar-sweetened beverages to negative health outcomes such as hypocalcemia, decreased bone mineral density, increase risk of bone fractures, dental caries, kidney stones, increased risk of hypertension, and most consistently associated with increased energy intake of which individuals do not adequately compensate (Vartanian, Schwartz, & Brownell, 2007).

However, there is a lack of studies that have examined soda addiction in animals. Similar health risks have been identified in animal studies examining soft-drink consumption in rats. Belpoggi and colleagues (2006) found statistically significant increase of body weight, malignant mammary tumors in female rats, exocrine ademonas of the pancreas in males and females, as well as a non-significant increase of rare pancreatic carcinomas in female rats administered Coca-Cola® as a substitute for drinking water. Other animal studies examining soft-drink consumption in rats found evidence of hypocalcemia and lower femoral mineral density (García-Contreras, Paniagua, Avila-Díaz, et al., 2000) as well as dental caries, hyperuresis, diarrhea, and decreased hair gloss (Tamura, Fujii, & Kusaba, 1979). Such a large number of studies finding evidence of negative health outcomes associated with soft-drink consumption strengthens the need for further investigations into the addictive nature of soft drinks.

The purpose of this study was two-fold: first, to test a new behavioral animal model of addiction, with many advantages over other methods described above, using a LiCl-induced CTA to see if animals would still orally consume a drug that was mixed with a substance that previously made them ill. This method differs from previous models in that it examines the 7th DSM-IV-TR criteria of: continued use, despite adverse consequences. As stated previously, the DSM-IV-TR classifies a drug of abuse based on satisfying 3 out of the 7 criteria listed previously. Therefore, the development of an additional method to measure addiction in animals will only add to the current methods that typically only measure tolerance and withdrawal. The second purpose was to apply the method to study the addictive qualities of soft drinks, a substance that is readily available to children, and despite one property (caffeine) not classified as a drug of abuse, has serious enough health concerns that might require another look at the data or a separate classification in combination with caffeine, based on its sugar content.

Method

Subjects

The study used 16 Long-Evans (Harlan) rats 60 days old. Eight rats were assigned to one of two groups: group one was the control group, which received diet, caffeine free Coca-Cola® and group two was the experimental group, which received the treatment of Coca-Cola® containing caffeine at 23mg/8fl oz. Coca-Cola® and the diet, caffeine free Coca-Cola® were self-administered daily via test tubes with drinking spouts for 14 days. The animals were housed in the animal vivarium where the lights were kept on a 15:9 light/dark cycle, starting at 7AM. Rats were housed in Plexiglas cages and were given free access to food and water unless otherwise noted. IACUC approval was obtained before the start of the experiment.

Procedure

The control group received 10mls of the control medium (diet, caffeine-free Coca-Cola®), the treatment group received 10mls of regular Coca-Cola® (containing 23mg of caffeine/8 fl ounces) daily for 14 days. However, the first four days, the diet, caffeine-free Coca-Cola® was flat. Starting day 5 the diet, caffeine-free Coca-Cola® was once again

carbonated. The amounts of control or treatment solutions ingested were recorded daily. After administration of control and treatment on day 14, rats were water deprived for 23 hours. On the 15th day, all animals were given a 30-minute exposure to 10% apple juice (Walmart) followed by a 0.15 M lithium chloride (Carolina Biological Supply) IP injection, which served as the unconditioned stimulus (US), 10 minutes later to provoke a CTA. On day 16 of the study, the control group was given 30-minute access to a 10% apple juice/control medium mixture vs. regular Coca-Cola®, while the rats in the treatment group were given 30-minute access to a 10% apple juice/Coca-Cola® mixture vs. diet, caffeine-free Coca-Cola® (See Figure 1).

Results

The independent variable of this study was whether animals received Coca-Cola® (treatment group) or diet, caffeine-free Coca-Cola® (control) previous to CTA. The dependent measures were Pre-test/Post-test difference score and preference for the two different solutions at test.

There was no significant difference ($t(24) < 1.00$, $p > .10$) in mean consumption, measured in milliliters, of either the diet, Coca-Cola® or diet, caffeine-free Coca-Cola® across the last three days of the two-week exposure, nor was there a significant difference ($t(14) < 1.00$, $p > .10$) for the 10% apple juice solution consumption before the LiCl injection between the experimental and control rats (See Table 1).

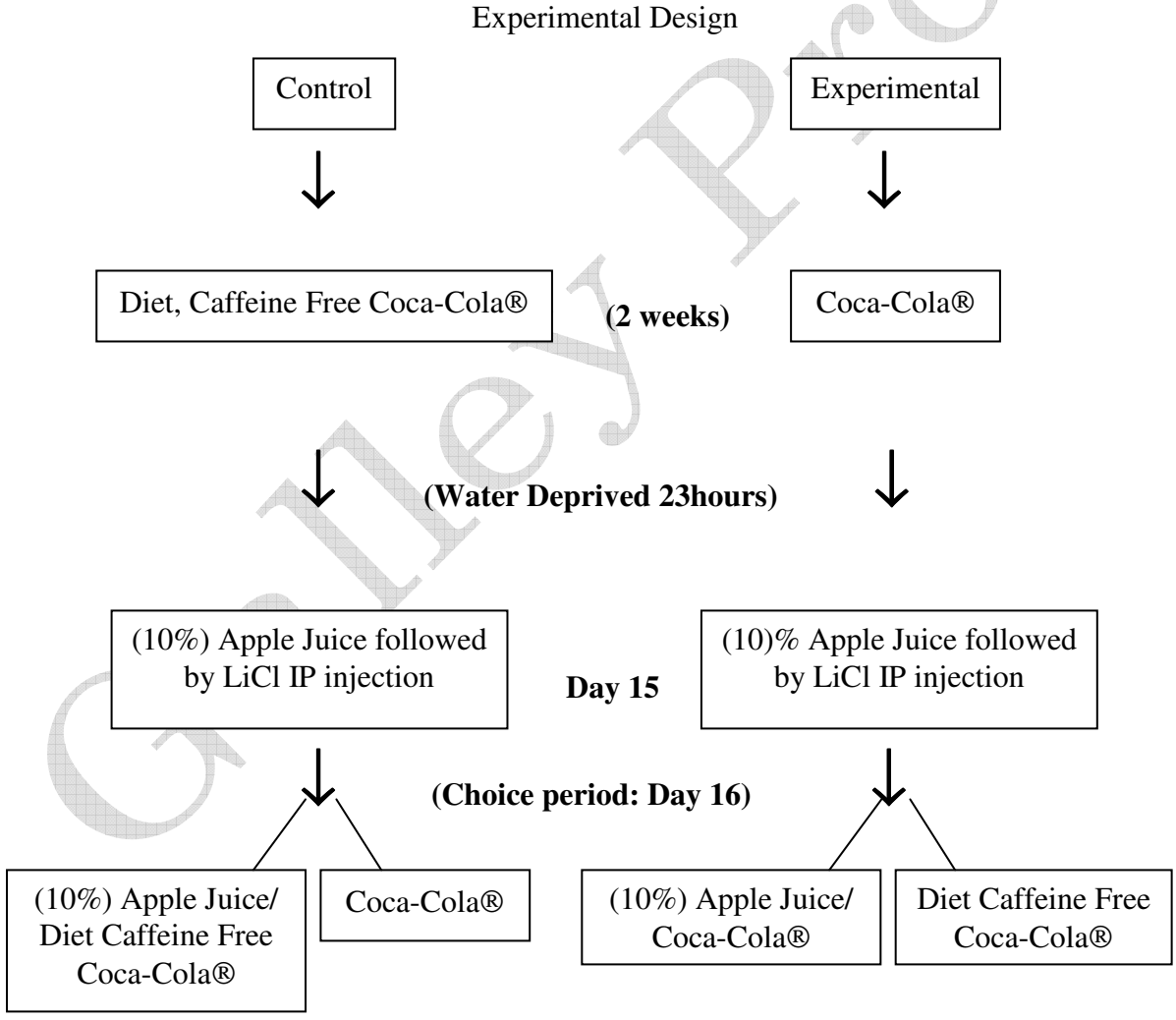

Figure 1: Schematic of the experimental design, differentiating between the experimental (Coca-Cola®) and control (diet, caffeine free Coca-Cola®) groups.

Table 1

	Day							
	1*	2*	3*	4*	5	6	7	8
Experimental (Coke®)	8.20 (1.81)	9.29 (0.05)	9.14 (0.74)	9.06 (0.70)	8.98 (0.96)	8.25 (1.65)	7.11 (1.51)	8.05 (1.36)
Control (Diet Caffeine Free Coke®)	4.14 (2.91)	1.88 (1.18)	2.51 (1.72)	1.65 (1.48)	8.13 (1.58)	6.40 (0.94)	7.34 (0.68)	7.45 (0.84)

	Day								
	9	10	11	12	13	14	15 Apple CTA	16 Apple Mix	16 Cont.
Experimental (Coke®)	7.48 (1.78)	6.33 (1.01)	7.31 (1.79)	9.00 (1.17)	7.85 (1.49)	8.03 (1.72)	10.00 (0.00)	8.09 (1.69)	3.08 (1.20)
Control (Diet Caffeine Free Coke®)	6.41 (0.51)	6.68 (0.84)	6.35 (0.30)	9.04 (1.08)	7.88 (1.33)	7.85 (1.69)	10.00 (0.00)	5.33 (0.61)	8.74 (1.47)

Table 1. Mean consumption (in mls) of beverage across exposure (Days 1-14), training (Day 15) and retention/preference (day 16). *On Days 1-4 control rats were given flat, noncarbonated diet, caffeine free Coca-Cola®

Difference scores were calculated using the 10% apple juice from training and subtracting the soft drink/10% apple solution data from test for both groups to determine differences between the groups, if any, in the amount of 10% apple juice drank at training and the amount of soft drink/10% apple solution drank at test. The study found that controls (M=4.68, SD=0.61) drank significantly less ($t(14)=-4.35$; $p=<.01$; Cohen's $d = 2.33$, $r^2 = .79$) 10% apple solution following CTA than the treatment group (M=1.91, SD=1.69). This means that the treatment rats continued to drink Coca-Cola®, even when it was paired with the apple juice that made them ill 24-hours previously (See Figure 2).

The preference at test was measured by taking the amount of the apple solution minus the control soft drink solution divided by the total amount of both liquids. Therefore, a positive number would reflect a preference for the apple/soft drink solution and a negative number, preference for the non-apple juice solution, demonstrating that they were avoiding the illness producing substance. As such, the treatment group (M = 0.46, SD = 0.17) demonstrated a significant preference ($t(14) = 9.28$; $p = < 0.01$; $d = 4.96$, $r^2 = .93$) for the apple juice solution over control animals (M = -.24, SD=0.13). Combined with the difference scores above, the preference data provide more evidence that the rats that previously consumed the Coca-Cola®, continued to do so even when paired with a solution that previously made them ill (See Figure 3).

The results of the difference scores between the apple juice consumed before the LiCL injection vs. the apple juice mixed with Coca-Cola® found that only the control animals reduced their apple juice consumption, with the treatment group continuing to consume the apple juice when mixed with Coca-Cola®. These results are further supported by the preference data, which showed that 24-hours after the LiCl injection, the treatment rats preferred the apple juice mixed with Coca-Cola® over the substance that had not previously made them ill. This study demonstrates that rats previously given Coca-Cola® for two-weeks will continue to drink the beverage (and prefer it over non-nauseating substances) even when it is mixed with a substance that previously made them ill, thus, continuing to consume a substance despite the possibility of adverse consequences.

Discussion

This study used a new, efficient, and inexpensive behavior model of addiction that

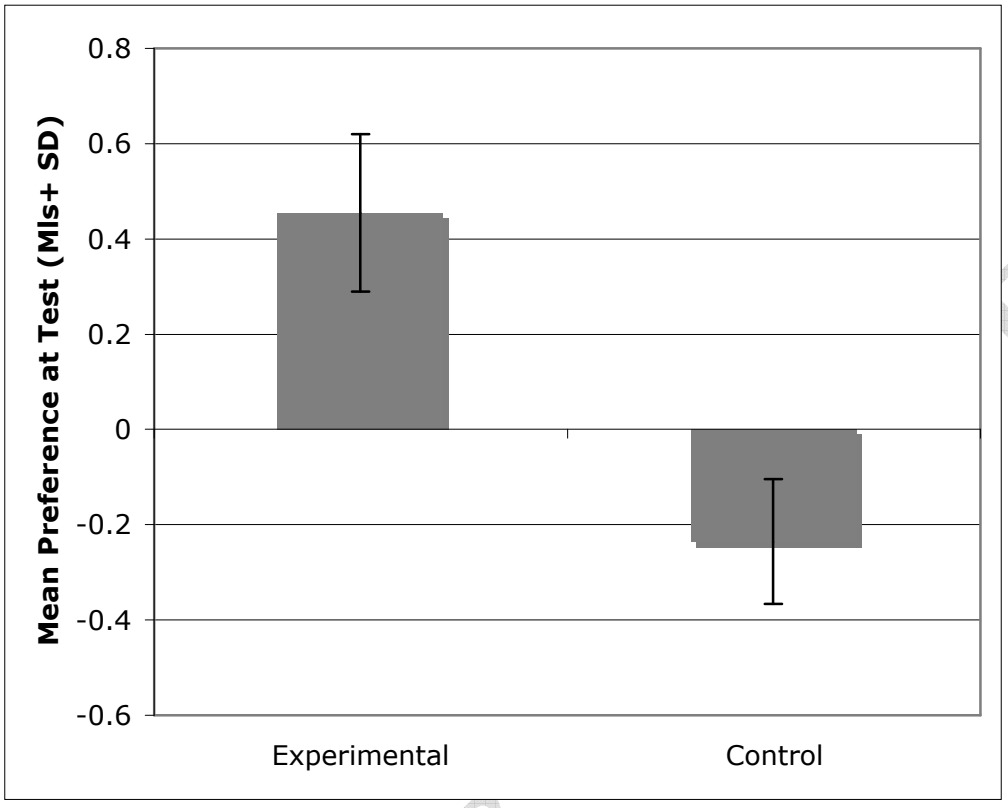

Figure 2: The mean differences (mls) between 10% apple water drank at training and 10% apple/soft drink solution drank at test for each group can be found by looking at the y-axis, with group condition on the x-axis. The error bars in this figure represents the standard deviation of the difference between the 10% apple water drank at the train condition and the 10% apple/soft drink solution drank at the test condition for each group. The study found that there was a significant reduction of drinking a 10% apple solution between controls and the treatment group, which demonstrates that the rats in the control group drank considerably less 10% apple solution at test than did the treatment group, after twenty-four hours following exposure to the LiCl injection.

examines the 7th DSM-IV-TR criteria of continued use, despite adverse effects, utilizing a LiCl-induced CTA to examine the addictive nature of Coca-Cola® in rats. The results of this study provide evidence for the notion that soft drinks, such as Coca-Cola®, may be more addictive or reinforcing to rats than previously thought, further suggesting that soft drinks that combine caffeine and sugar may need to be classified separately from other caffeine drinks, especially in light of the serious health concerns discovered with soft drink consumption in both humans and rats.

The results show that the rats in the control group drank significantly less 10% apple solution at test than did the treatment group after twenty-four hours following exposure to LiCl, and that the rats in the control group significantly avoided the 10% apple solution while the rats in the treatment group significantly preferred the 10% apple solution after the acquisition of a CTA to 10% apple juice.

These findings have many implications for the widely accepted availability and use of soft drinks, like Coca-Cola®, by children and adolescents. Recent attention has been placed on the epidemic of obesity across the nation, especially in our children, and the association between obesity and soft drink consumption (Ludwig, Peterson, & Gortmaker, 2001). While much of the research surrounding soft drinks examines the health effects of the beverage, such as its consistent positive correlation with increased energy intake (Harnack, Stang, & Story, 1999), which may also be associated with increased body mass index (BMI) and obesity (Ludwig, Peterson, & Gortmaker, 2001). However, little research has been done to identify any addictive qualities of soft drinks despite the mean intake in the

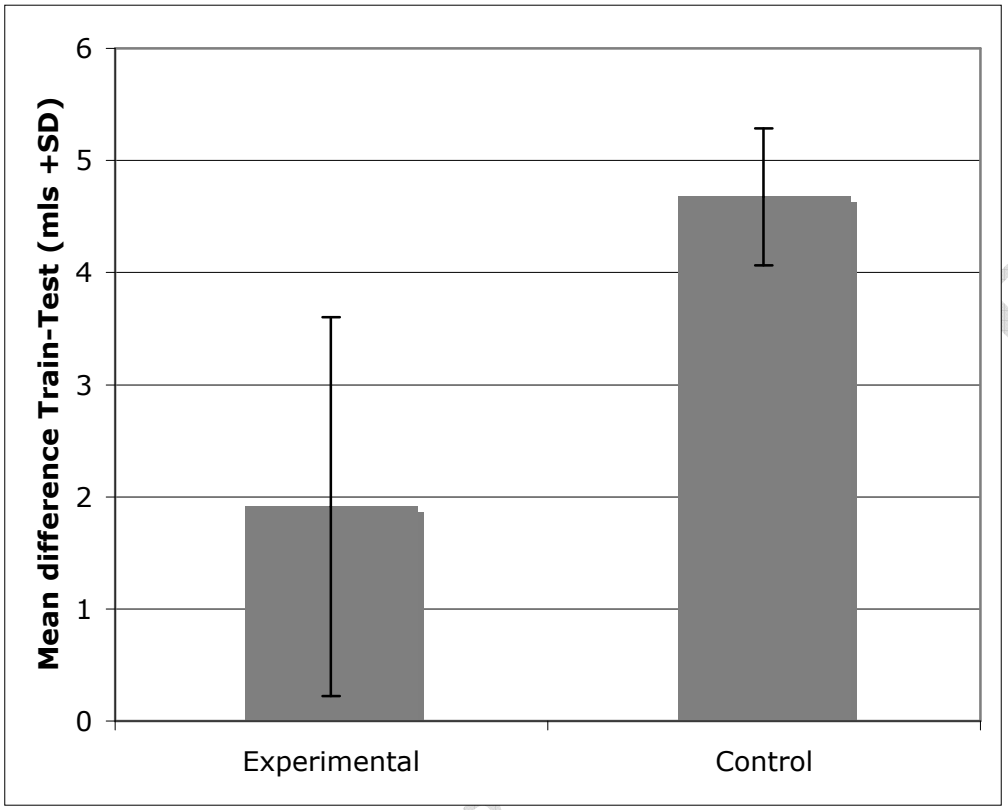

Figure 3: The mean difference (mls) between the amount of a 10% apple solution and a non-10% apple solution drank at test for each group for the purpose of showing preference, can be found by looking at the y-axis, while the group condition can be found by looking at the x-axis. The error bars in this figure represents the standard deviation of the difference between the amount of a 10% apple solution and a non-10% apple solution drank at test condition for each group. The control group demonstrated a statistically significant difference in the preference for the non-10% apple solution over the 10% apple solution, while the treatment group demonstrated a statistically significant difference in the preference of the 10% apple solution over non-10% apple solution. This shows that the rats in the control group avoided the 10% apple solution while the rats in the treatment group did not.

U.S. population more than doubling within the last 20 years (French, Lin, & Guthrie, 2003). French and colleagues (2003) further found that soft drink consumption increased 48% among American children and adolescents from 1977 to 1998.

The results of this study provide support for the addictive nature of Coca-Cola® in rats. In addition, this study calls attention to a new animal model of addiction testing that is both efficient and inexpensive, but limited to drugs that are typically orally consumed. To date there are four primary models of testing animal addiction, which include self-administered drug testing, animal place preference testing, brain stimulation testing, and drug discrimination testing. While these methods are widely accepted by the research community to investigate drug dependence behavior in humans (Koob, 1994; Willner, 1997), most of them require lengthy training times and expensive surgeries to prepare the animals for testing. Other disadvantages include the inability of the method to truly mimic drug use in humans, such as a drug being administered via catheter as opposed to oral ingestion used most often by human for certain drugs such as caffeine, and not having enough control over many variables that can impact results.

The behavioral model of addiction used in this study employed the use of a CTA to (10%) apple juice solution, which was then mixed with the drug being tested for addictive qualities. This model did not require any behavioral training to test the animals; the 14 days prior to testing was used to allow the animals to orally administer the drug being tested in order to allow the animals time to

demonstrate a tolerance to caffeine (Griffiths & Woodson, 1988). Also, the method used for this study did not require any expensive equipment or surgical procedures to prepare the animals for testing.

This study is a good starting point for re-examining the addictive nature of soft drinks in animals in that this study attempted to remove two variables from the control, caffeine and sugar. While the first priority was to develop a behavioral model that measured the 7th DSM-IV-TR criteria of: continued use, despite adverse effects, the second was to investigate the reinforcing or addictive qualities of soft drinks that contain caffeine. However, the impact that sugar plays in the process cannot be minimized, especially in light of the health concerns. It would also be helpful to use a more pure and controlled concentration of caffeine to limit variability that may exist in the production of soft-drinks. That being said, Coca-Cola® was originally chosen to increase the external validity, which of course lowers the internal.

Further research should look closely at separating the three variables of soft drinks (caffeine, sugar/sugar substitute, and possibly carbonation) and controlling for each. Controlling for each variable separately would allow future studies to more thoroughly investigate which variable, or combination of variables, is responsible for the addictive nature of soft-drinks. In addition, it could be argued that the rats were simply avoiding the diet, caffeine free Coca-Cola®, so additional studies might investigate this by instead looking to see if diluted regular Coca-Cola® might yield comparable results with the diet, caffeine free Coca-Cola®, such that to the rat, 10% regular Coca-Cola® may or may not equal the results of the diet, caffeine free Coca-Cola®. Additional research is also needed to investigate if this model extends to other drugs of abuse that are typically consumed orally.

In conclusion, this study used a new, efficient, and inexpensive behavioral model of animal addiction to demonstrate the addictive nature of Coca-Cola®, based on the 7th DSM-IV-TR criteria: continued use, despite adverse consequences. As stated previously, the DSM-IV-TR classifies a drug of abuse based on satisfying 3 out of the 7 criteria listed previously. Therefore, the development of an additional method to measure addiction in animals will only add to the current methods that typically only measure tolerance and withdrawal. This new behavioral animal model of addiction is free of the many disadvantages associated with the more widely used animal models of addiction.

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