EXPLORING THE ROLE OF THE NUCLEUS ACCUMBENS CORE IN COCAINE SATIETY IN GOAL-DIRECTED VERSUS HABITUAL RESPONDING

An Undergraduate Research Scholars Thesis

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ABSTRACT

Exploring the Role of the Nucleus Accumbens Core Plays in Cocaine Satiety in Goal-Directed Versus Habitual Responding

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When an animal is conducting instrumental behavior (e.g., pressing a lever to earn food), responding can be guided by two different response strategies: goal-directed or habitual. Experimenters are able to determine an animal's response strategy based on their sensitivity to outcome devaluation. Methods for assessing habitual behaviors with food rewards have been established, but there is no accepted method for assessing habitual cocaine seeking. Recently, my lab has developed a novel method that can be used to identify habitual responding for cocaine. Preliminary data and previous studies show that animals will maintain a stable level of cocaine responding and will adjust their pressing to account for changes in dosage; this is thought to similarly reflect food satiety when an animal has eaten enough. This study aimed to investigate the role of dopaminergic activity within the nucleus accumbens core (NAc core) which has been previously implicated in cocaine satiety. To determine if dopaminergic activity in NAc core is sufficient to drive cocaine satiety, we used a within subjects design in which rats underwent, in separate trials, both outcome devaluation via non-contingent cocaine infusions and an extinction session in which D1- and D2-type agonists were administered directly into the NAc core

beforehand. We hypothesized that agonism of D1- and D2-type receptors in the NAc core is sufficient to drive cocaine satiety, reflected by a decrease in cocaine-seeking behavior.

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CHAPTER I

INTRODUCTION

Instrumental behavior and habit learning

Instrumental behavior refers to actions an animal takes to receive an outcome such as obtaining a reward or avoiding aversive stimuli. This results in the outcome being contingent on the response or action of the animal (Fragaszy and Liu, 2012). Two neural systems have been identified that influence the strategy an animal uses when performing an instrumental action. The goal-directed system guides flexible behaviors that are driven by the current value of the outcome, and is guided by response-outcome (R-O) associations, making the animal sensitive to variations in outcome value (Dickinson and Balleine, 1994). Contrasting this, stimulus-response (S-R) associations underlie the habitual system, which guides behaviors that are driven by prior experience with rewarding outcomes rather than the current outcome value thus making them insensitive to changes in this value (Balleine and Dickinson, 1998a; Dickinson, 1985; Colwill and Rescorla, 1986).

It has been hypothesized that the formation of instrumental behavior initially begins as an R-O association that, with enough experience, gradually shifts to an S-R association (Yin and Knowlton, 2006). The same is thought to occur when the habitual system is experimentally deactivated, leading to a shift from habitual to goal-directed responding (Leblanc et al., 2013; Zapata et al., 2010). In order to observe this shift, methods have been established to discern whether a behavior is goal-directed or habitual as both systems can be used to drive the same observable response. One of the methods that has been developed to discern between these two

systems involves devaluing the outcome of an action and is known as outcome devaluation (Balleine and Dickinson, 1998a).

Identifying habitual versus goal-directed actions

Goal-directed behavior is sensitive to changes in outcome value, so by devaluing an outcome, it is possible to distinguish the R-O association driving this behavior from that of an S-R association. Devaluation is a method used to decrease the outcome value associated with food rewards by allowing the animal *ad libitum* access before placing them in an operant chamber in which they perform an action to receive a food pellet. An animal exhibiting goal-directed behavior is less likely to seek food after devaluation because the subjective value of the food has decreased and it is assumed that the animal has satiated its hunger (Adams and Dickinson, 1981; Adams, 1982). Balleine and Dickinson (1998a) further explored this concept by designing an experiment in which rats were trained to press a lever for a sugar solution (R_1-O_1) and to pull a chain for food pellets (R_2-O_2) in separate sessions. After training, each rat was given one hour of unlimited access to either food pellets or sugar solution in their home cage. These rats were then tested under extinction conditions in which lever presses or chain pulls had no consequence (i.e., did not produce a reward). Rats that were devalued by the sugar solution were able to decrease their responding for sugar while continuing to press for food. Similarly, food devalued rats continued pressing the lever for the sugar solution while decreasing their food response. (Balleine and Dickinson, 1998b). These results indicate that this method induces satiety that is specific for the devalued reward, resulting in a decrease in incentive value and response behavior. Goal-directed animals display sensitivity to outcome devaluation while habitual animals are insensitive to this satiety and will continue to respond.

Outcome devaluation with cocaine satiety

While outcome devaluation for food rewards has been established, it is unclear whether cocaine can be devalued in the same manner. Previous work has suggested that it may be possible to induce cocaine satiety through the administration of cocaine by an experimenter prior to measuring responses for cocaine (Markou, 1999; Tsibulsky and Norman, 1999). Studies have also shown that trained rats will maintain relatively stable responding rates for drugs and will adjust their pressing behavior to account for changes in dosage, indicating a preferred level of cocaine or a satiety threshold (Pickens and Thompson, 1968; Yokel and Pickens, 1974; Norman and Tsibulsky, 2006). Rats have also been shown to pause between infusions of cocaine even when given unlimited access. It is thought that this is similar to the satiety that is experienced between meals (Gerber and Wise, 1989; Wise et al., 1995).

This gap in methodology prompted my lab to develop a novel outcome devaluation method to assess response strategy for cocaine seeking. With this method, rats that have been trained to self-administer cocaine are placed in an operant chamber and receive non-contingent cocaine infusions. These infusions are administered by the experimenter and do not require any action from the rat to be received. Afterwards, levers are presented and an extinction session begins in which pressing the levers has no consequence. Response strategy for cocaine seeking is assessed based on the rat's sensitivity to the prior non-contingent infusions. Data from our lab indicates that this method can be used to assess response strategy for cocaine seeking. Neural mechanisms underlying satiety for cocaine are not well understood however previous work has suggested that the nucleus accumbens core may play some role in this phenomenon.

Investigating the neural mechanism underlying cocaine satiety

Suto et al. (2009) found that antagonism of D1- and D2-type receptors within the nucleus accumbens (NAc) core shortened the interval between lever responses in a dose-dependent manner. This indicates that dopaminergic activity in the NAc core may be involved in satiety. A follow-up study similarly found that agonism of both D1- and D2-type receptors simultaneously in the NAc core significantly decreased the number of lever presses during a self-administration session (Suto and Wise, 2011). These results suggest that cocaine-induced dopaminergic action within the NAc core may be modulating the rate of drug intake during a cocaine self-administration session. The aim of this study was to determine if dopaminergic activity in the NAc core is sufficient to drive cocaine satiety. We hypothesized that agonism of D1- and D2-type receptors in the NAc core is sufficient to drive cocaine satiety, and will thus cause a decrease in cocaine responding in goal-directed behavior. We also sought to determine if agonism of D1- and D2-type receptors in the NAc core can decrease cocaine responding in the same manner as observed with noncontingent IV cocaine during outcome devaluation.

CHAPTER II

METHODS

Animals

Male Sprague Dawley rats (Charles River, Raleigh, NC) were single-housed under a 12-hour reverse light/dark cycle and had *ad libitum* access to food and water. Rats were housed in a temperature- and humidity-controlled animal facility at Texas A&M University (AAALAC-accredited). The experiment was approved by the Institutional Animal Care and Use Committee at Texas A&M University and conducted according to specifications of the National Institutes of Health as outline in the Guide for the Care and Use of Laboratory Animals.

Surgery

Rats were anesthetized with vaporized isoflurane (induced at 5%, maintained at 1-2%), given the analgesic ketoprofen (2 mg/kg, s.c.), and were implanted with a chronic indwelling intravenous jugular catheter. Immediately following catheter implantation, rats were placed in a stereotaxic frame (Kopf, Tujunga, CA) to implant intracranial guide cannulae (26 gauge, 15 mm length, Plastics One, Roanoke, VA) aimed at the NAc core of both the left and right hemisphere. For stereotaxic surgery, a skin incision was made over the skull, small screws were secured to each skull plate, and holes were drilled in the skull over the target sites. Cannulae were inserted 2 mm above NAc core (surgical coordinates: AP +1.3, ML +2.3, DV -5.3 from bregma, 6° angle) and secured in place with orthodontic acrylic. Stainless steel dummy wires were inserted into the guide cannulae to prevent clogging. Beginning 3 days after surgery, intravenous catheters were flushed once daily with 0.1 ml of cefazolin (100 mg/ml) and 0.05 ml of heparin (10 units/ml).

Self-administration sessions began at least 5 days after surgery. Catheters were flushed with 0.1 ml saline before each self-administration session to test for proper flow, and then flushed with cefazolin and heparin after the session.

Cocaine self-administration

After recovery from surgery, rats were trained to self-administer cocaine in operant chambers housed in sound-attenuating cubicles and controlled by a MED-PC IV program (Med-Associates, St. Albans, VT). Rats learned to self-administer cocaine in daily 2-hour sessions on a fixed ratio (FR) 1 schedule of reinforcement in which a press on the active lever led to an infusion of intravenous cocaine (0.5 mg/kg/infusion; cocaine HCl powder was provided by the NIDA Drug Supply Program). Each infusion was paired with a compound light/tone cue (white LED light above the active lever; 78 dB, 2900 Hz tone) and followed by a 20-s timeout. The inactive lever in the chamber had no programmed consequences. Once the rats had reached a stable level of responding on the active lever during the FR1 schedule, they were introduced to a a seeking-taking paradigm in which a seeking lever was presented at the start of each trial. Activating the seeking lever caused it to retract and then presented the taking lever which would give an infusion of cocaine on an FR1 schedule when pressed. This paradigm dissociates the actions of drug-seeking and drug-taking as evidence suggests that these are separate behavioral processes and can develop separate response strategies as a result (Balleine et al., 1995; Olmstead et al., 2000). A 4 minute timeout was introduced between each trial. Rats were assigned to either an RR or RI schedule in a counterbalanced manner, because it has been shown that differing these schedules can bias the use of a particular response strategy. Ratio schedules tend to bias towards goal-directed behavior whereas interval schedules bias for habitual

responses (Derusso, 2010; Dickinson, 1985; Dickinson et al., 1983). The goal was to have a roughly equivalent number of both habitual and goal-directed rats. The rats were required to progress through several RR or RI schedules before they underwent the microinjection extinction procedure and non-contingent cocaine devaluation. The final RR schedule required the rat to press the seeking lever on average 20 times (RR20) in order to start a trial and gain access to the taking lever. The RI final schedule required animals to wait on average 60 seconds regardless of seeking lever presses in order to start a trial and gain access to the taking lever.

Microinjection and devaluation procedure

One day prior to the first microinjection, sham microinjectors were inserted 2 mm beyond guide cannulae while rats were acclimated to the gentle towel restraint used for the microinjection procedure. Prior to the microinjection extinction session, injector cannulae were inserted into NAc core (33 gauge; extending 2 mm beyond guide cannulae). The injection was a cocktail of the D1-type agonist SKF-81297 and the D2-type agonist quinpirole (10 and 33 mM, 0.3 µl/hemisphere; Tocris, Minneapolis, MN; doses based on Schmidt et al., 2006a; Schmidt and Pierce, 2006b). The vehicle used for all drugs was sterile-filtered phosphate buffered saline (PBS). Microinjections occurred over 60 seconds and then microinjectors were left in place for an additional 60 seconds to allow for diffusion. To determine if microinjection of D1- and D2-type receptor agonists produces devaluation of cocaine via satiety, we used a within-subject design in which rats experienced outcome devaluation via non-contingent cocaine infusions and an extinction session with D1- and D2-type receptor agonists. For the microinjection extinction sessions, animals were counterbalanced to receive either the drug cocktail or vehicle before being placed under extinction conditions in which pressing the active lever had no consequences.

For non-contingent cocaine devaluation, animals were counterbalanced to receive either 3 infusions of cocaine or no cocaine in the operant chamber before being placed under extinction conditions in which pressing the active lever had no consequence. The microinjection extinction and devaluation sessions lasted for 10 minutes and were followed by a typical 2 hour cocaine self-administration session.

Punishment

After the first microinjection extinction and non-contingent cocaine devaluation sessions, we found that many of the rats were insensitive to outcome devaluation and DA agonists. We hypothesized that many of the rats were habitually responding and were insensitive to devaluation. To induce a shift from habitual to goal-directed responding, these rats underwent 3 days of footshock punishment (0.6 mA on day 1, 0.7 mA on days 2 and 3). Shock was given following completion of seeking requirements on one-third of trials in a random manner, with each shock lasting 0.3 seconds. Preliminary data from our lab found that punishment of drug seeking leads to a shift from habitual to goal-directed drug seeking behavior. The rats were given several days after punishment to once again stabilize self-administration before undergoing both another microinjection extinction procedure and non-contingent cocaine devaluation.

Histology

Rats were deeply anesthetized with isoflurane and then transcardially perfused with 0.9% NaCl followed by 10% neutral-buffered formalin via a peristaltic pump (Cole Parmer, Vernon Hills, IL). Brains were collected, post-fixed in 10% formalin overnight, placed in 20% sucrose with 0.02% sodium-azide for ≥2 days, frozen in dry ice, and then sectioned at 40 μm using a

cryostat. To assess cannula placements, sections were mounted onto glass slides, Nissl stained (0.045% thionin), and coverslipped with Permount (Fisher Scientific, Fair Lawn, NJ). NAc core and shell borders were defined according to Paxinos et al. (2007).

Data analysis

When analyzing data, raw lever presses were normalized by creating a ratio of the number of lever presses during a devalued session (3 infusions of cocaine or DA agonists) over the total number of lever presses during both devalued and non-devalued (no cocaine or vehicle) sessions. Punishment trials were normalized by dividing the number of trials in a given punishment session over the average number of trials in a session before the first outcome devaluations (averaged from 3 sessions at the animal's final schedule). Linear regressions and figures were produced using GraphPad Prism.

CHAPTER III

RESULTS

To determine whether dopaminergic activity in the NAc core is sufficient to drive cocaine satiety, we microinjected the D1-type receptor agonist SKF-81297 and the D2-type receptor agonist quinpirole in to the NAc core. Initial microinjection extinction and non-contingent cocaine outcome devaluation produced varied response rates. Only two animals appeared to respond in a goal-directed manner during the outcome devaluation sessions (Fig. 1a) and only one animal displayed sensitivity to DA agonists during the microinjection extinction session; the animal that displayed sensitivity to the DA agonists responded in a habitual manner during outcome devaluation (Fig.1b). This may indicate that the DA agonists were not inducing satiety in this animal, but were instead decreasing motivation for cocaine through another mechanism, given that the responding of habitual animals is insensitive to satiety. Because only two animals were sensitive to outcome devaluation, we hypothesized that the other three animals were responding in a habitual manner. In an effort to make all of the animals sensitive to outcome devaluation, and possibly to the DA agonists, footshock punishment was administered over three consecutive days. Our lab has observed that when habitually responding animals are presented with a negative consequence (e.g., footshock), these animals will decrease their responding for cocaine and will also shift response strategies back to goal-directed control.

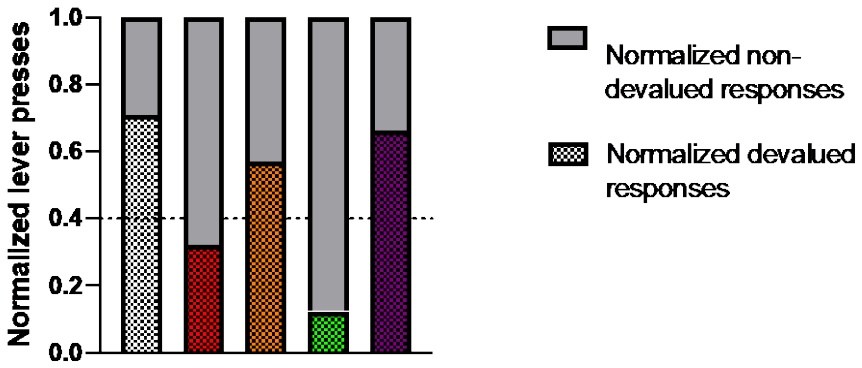

Figure 1a. Pre-punishment sensitivity to outcome devaluation. Only two animals displayed sensitivity to outcome devaluation which indicates goal-directed responding. The dotted line indicates our cutoff point at 0.4; all animals whose normalized devalued response is lower than this are considered goal-directed.

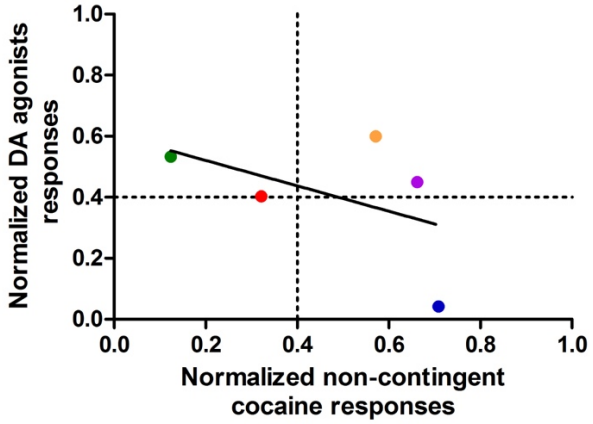

Figure 1b. Pre-punishment comparison of sensitivity to outcome devaluation versus DA agonists. A weak correlation was observed between DA agonist and outcome devaluation sensitivity (R= 0.480).Only one animal was sensitive to the DA agonists; interestingly, this animal was insensitive to outcome devaluation.

The three days of footshock punishment decreased cocaine taking in all animals (Fig. 2), but only one rat showed a shift from a habitual to a goal-directed response strategy during post-punishment outcome devaluation (Fig. 3a). One animal was excluded from the study after punishment because one of its cannulae was bent and we were unable to administer another microinjection extinction session. Two of the animals appeared to be more resistant to punishment as indicated in Fig. 2; however another animal that also appeared to be more resilient to punishment was sensitive to outcome devaluation before and after punishment.

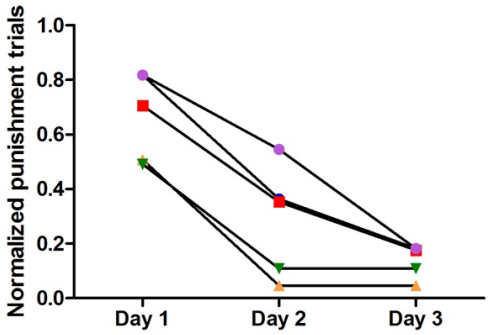

Figure 2. Punishment decreased responding for cocaine. Note that two of three animals that maintained the highest responses for cocaine on Day 3 were insensitive to outcome devaluation. Interestingly, one of these animals was sensitive to the DA agonists.

Only one animal that initially displayed habitual responding during the first outcome devaluation session showed a shift to a goal-directed response strategy during the second outcome devaluation session. Despite punishment only showing a change in cocaine response strategy in one animal, three of the four animals tested showed sensitivity to the DA agonists compared to only one animal before punishment. One of the animals that displayed sensitivity to the DA agonist microinjections remained insensitive to outcome devaluation for cocaine (Fig. 3b).

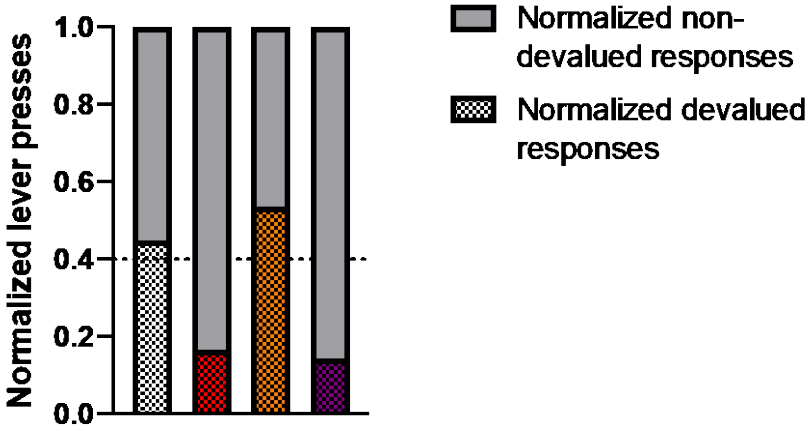

Figure 3a. Post-punishment sensitivity to outcome devaluation. Only one animal shifted its response strategy after punishment. This animal also showed sensitivity to the DA agonists after punishment.

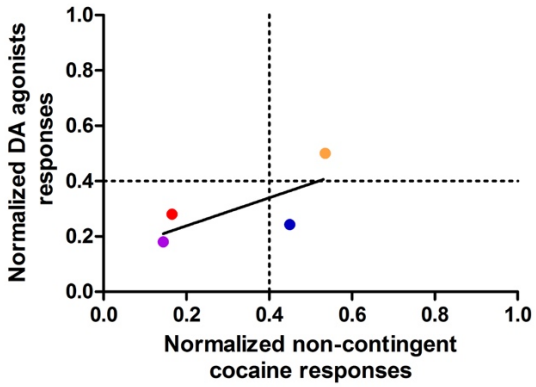

Figure 3b. Post-punishment comparison of sensitivity to outcome devaluation versus DA agonists. A moderate correlation was observed between DA agonist and outcome devaluation sensitivity (R= 0.723). A majority of the animals displayed sensitivity to the DA agonists. One of these animals still remained insensitive to outcome devaluation.

Post-mortem assessment of cannulae placements was conducted in order to determine if site of DA agonist microinjections altered behavior between individual animals. Figure 4 shows the placement of bilateral cannulae tracts for all five animals. Cannulae placement AP levels had a 2.16 mm range. Three of these placements bilaterally hit NAc core. For cannulae that did not hit NAc core, a roughly equivalent decrease in cocaine responding was still observed with both non-contingent and DA agonists. One animal with the most rostral NAc core miss (red) still displayed some sensitivity to the microinjection extinction session even though another animal with a more caudal NAc core miss (yellow) remained insensitive before and after punishment. These results indicate that another mechanism(s) separate from dopaminergic activity in NAc core may have been driving cocaine satiety. Another animal that did have a NAc core hit remained insensitive to cocaine devaluation, but showed sensitivity to microinjection extinction before and after punishment (blue). This may indicate that injection of D1- and D2-type receptor agonists into the NAc core is suppressing responding for cocaine via other means besides satiety.

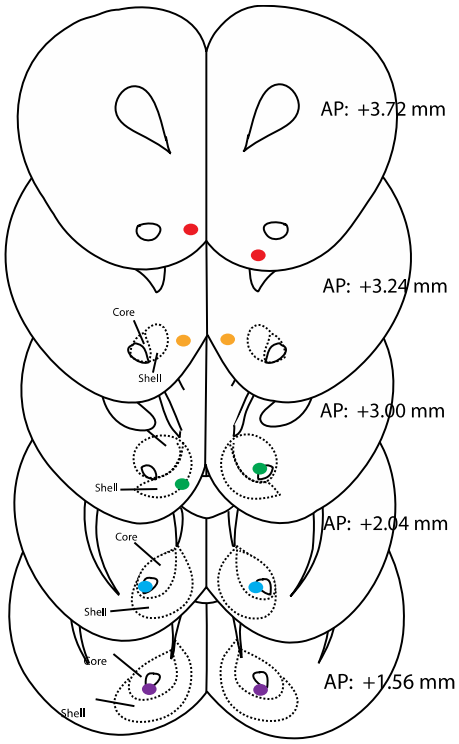

Figure 4. Histology of cannulae placements.

CHAPTER IV

DISCUSSION

The present study investigated whether dopaminergic activity in the NAc core is sufficient to drive satiety in a manner consistent with outcome devaluation. After we observed that many of the animals were insensitive to both outcome devaluation and the NAc core DA agonists, footshock punishment was used to shift response strategies. Even after punishment, only two animals showed sensitivity to outcome devaluation; however, nearly all of the animals were sensitive to the DA agonists. Although the sample size is limited, these results may indicate that stimulating dopamine receptors in the NAc core is sufficient to drive cocaine satiety.

Punishment increased the correlation between DA agonist sensitivity and outcome devaluation. Although punishment only made one animal sensitive to outcome devaluation, we also observed that there was greater correlation between DA agonist sensitivity and outcome devaluation sensitivity when compared to pre-punishment data. This moderate correlation may indicate that sensitivity to DA agonist and outcome devaluation are both similarly affected by punishment. This would support the idea that both are being driven by a similar mechanism and that the satiety that is driving outcome devaluation is dependent upon dopaminergic activity in the NAc core. Despite this, some variables were observed that may point to alternative explanations for the decrease in cocaine responding after administering the DA agonists.

After analyzing cannulae placements post-mortem, it would appear that placement had little effect on whether or not an animal would be sensitive to the DA agonists. One animal had cannulae placements that were rostral to the NAc core, yet sensitivity to the DA agonists was observed after punishment. Similarly, another animal with placements that directly hit the NAc

core was insensitive to the DA agonists both before and after punishment. One explanation for this might be that structures neighboring the NAc core were sufficient to drive cocaine satiety rather than the NAc core itself. If this were the case, then sensitivity to the DA agonists may be more dependent upon diffusion and how far off the cannulae placements were from NAc core. Alternatively, the decrease in cocaine responding may not be due to an induced state of satiety, but rather the disruption of pathways involved in motivation and reward processing within the striatum. To explore this further, future experiments could investigate the effects of varying the dosage of the DA agonists and the placements of the cannulae.

Evaluating sensitivity to the DA agonists while establishing a dose-response curve could further examine the impact that both diffusion and saturation of DA receptors in NAc core have on cocaine responding. It could be the case that our dosages were enough to observe an effect in some but not all of our animals. Our method of delivery via microinjection may also have had a different effect than previous work by Suto and Wise (2011), who used reverse microdialysis to deliver the agonists instead. Varying cannulae placements may also reveal structures in the region that may be sufficient to drive cocaine satiety. For example, investigating dopaminergic activity in the dorsomedial and dorsolateral striatum may also provide insight into the neural substrate involved in cocaine satiety and how it relates to response strategy.

In conclusion, despite a limited sample size, our results support the notion that outcome devaluation and sensitivity to DA agonists are working under a similar mechanism which suggests that dopaminergic activity within the NAc core is sufficient to drive cocaine satiety. Future studies with a larger sample size, variations in agonist dosage and cannulae placement, and the introduction of DA antagonists should be used to further pinpoint the exact mechanism that underlies cocaine satiety.

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