Published in final edited form as:

Behav Brain Res. 2017 March 15; 321: 130–136. doi:10.1016/j.bbr.2017.01.001.

Effects of nucleus accumbens amphetamine administration on performance in a delay discounting task

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Abstract

Chronic administration of cocaine can cause pronounced and enduring cognitive alterations such as increases in impulsive choice. Chronic cocaine can also result in enhanced dopamine (DA) release in the nucleus accumbens (NAc) in response to reward-related cues. It is possible that this enhanced DA release in the NAc is a mechanism by which cocaine increases impulsive choice. To date, however, the specific role of DA in the NAc in impulsive choice is unclear. To begin to address this, rats received acute microinjections of the indirect DA agonist amphetamine directly into the NAc prior to testing in a delay discounting task in which rats chose between a small, immediate and a large, delayed food reward. When delays to the large reward increased within test sessions, amphetamine increased choice of the large reward. When delays decreased within test sessions, however, amphetamine decreased choice of the large reward. These findings suggest that, rather than specifically mediating impulsive choice, DA neurotransmission in the NAc is necessary for flexible adaptation of choice strategies in the presence of shifting reward contingencies. These results further indicate that enhancements in NAc DA release likely do not account for lasting increases in impulsive choice caused by chronic cocaine.

Keywords

impulsive choice; delay discounting; intertemporal choice; nucleus accumbens; amphetamine; dopamine

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Introduction

Substance use disorders are associated with cognitive and neurobiological impairments that can persist long after cessation of substance use [1]. One facet of cognition that is severely impacted is intertemporal decision making. Substance users typically display an exaggerated preference for immediate rewards, such as substances themselves, over delayed, but more beneficial rewards, such as prolonged abstinence, health and employment. Such preference for smaller, sooner over larger, more delayed rewards, or “impulsive choice,” is commonly assessed with delay discounting procedures in which subjects choose between two options, one which yields a small immediate reward and the other which yields a large reward that is delivered after varying delays [2]. All subjects decrease their choice of large rewards as the delays to their delivery increase; however, chronic users of alcohol, cocaine, and opioids, among other substances, show a steeper decrease in preference for large, delayed rewards than nonusers (i.e., steeper delay discounting, or increased impulsive choice; [3–5]). Despite numerous demonstrations of this phenomenon, the mechanisms by which chronic substance, and particularly cocaine, use increases impulsive choice remain poor elucidated.

Aside from cognitive deficits, another consequence of chronic cocaine, either passively or self-administered, is enhanced dopamine (DA) release in the nucleus accumbens (NAc) in response to rewards and reward-related stimuli [6, 7]. Studies in rodents have shown that this sensitized DA release is associated with increases in non-drug reward-directed behavior [8] as well as cocaine-dependent behaviors such as psychomotor sensitization [9]. Given the co-occurrence of increased impulsive choice and sensitized NAc DA release following chronic cocaine administration, changes in NAc DA release may be a mechanism by which these cocaine could cause increased impulsive choice. Evidence for this hypothesis includes the fact that both sensitized NAc DA release and cocaine-induced increases in impulsive choice are long-lasting phenomena (they can persist for months if not longer) [7, 10]. Additionally, artificially augmented NAc DA release enhances other aspects of reward-directed behavior, such as Pavlovian-instrumental transfer [11, 12]. Berridge [13] proposed that enhancements in DA release in the NAc may augment the incentive salience attributed to smaller, more immediate rewards over larger, delayed rewards, thus biasing choice toward more immediate gratification. Indeed, human neuroimaging data show that greater activity in the NAc is associated with choice of smaller, more immediate over larger, delayed monetary rewards [14], possibly reflecting greater salience ascribed to the immediate rewards. Together, these lines of evidence suggest that enhanced DA activity in the NAc may play a causal role in increased impulsive choice caused by chronic cocaine, possibly by enhancing the salience of more immediate gratification.

To determine whether enhanced NAc DA release could account for increased impulsive choice observed following chronic cocaine administration, we microinjected the indirect DA agonist amphetamine acutely into the NAc of rats prior to testing in a delay discounting task. This manipulation has been shown to increase incentive salience attributed to reward cues [8] in a manner similar to that produced by chronic cocaine administration [15]. Further, acute (although not chronic) systemic amphetamine has been shown to alter impulsive choice in a rodent delay discounting task [16–23]. However, the effects of amphetamine

directly into the NAc on impulsive choice have yet to be tested. Based on previous work, we predicted that intra-NAc amphetamine would increase impulsive choice, and that this would be due to enhancement of the salience of the small, immediate reward.

Methods

Subjects

Male Long-Evans rats ($n = 73$; 70 days old upon arrival; Charles River Laboratories, Raleigh, NC) were individually housed in a temperature controlled vivarium and kept on a 12 h light/dark cycle. Rats received free access to food and water except as noted. During behavioral training, rats were maintained at 85% of their free-feeding weight, with target weights adjusted upward by 5 g/week to account for growth. All animal procedures were conducted in accordance with the University of Florida Institutional Animal Care and Use Committee and followed the guidelines of the National Institutes of Health.

Apparatus

Behavioral testing was conducted in eight computer-controlled operant test chambers (Coulbourn Instruments, Harvard Apparatus). Each chamber was housed in a sound-attenuating cabinet and was equipped with a recessed foot pellet delivery trough with a photobeam to detect nose pokes and a 1.12 W lamp to illuminate the food trough. The food trough was located in the center of the front wall of the chamber, 2 cm above the floor. Two retractable levers were positioned to the left and right of the trough, 11 cm above the floor of the chamber. An additional 1.12 W lamp served as the houselight and was located on the back wall of the sound-attenuating cabinet. The floor of the chamber consisted of stainless steel rods and an activity monitor was positioned on the ceiling chamber to record locomotor activity during the test session. This monitor consisted of an array of infrared (body heat) detectors focused over the entire test chamber; movement in the chamber (in x , y , or z planes) was defined as a relative change in the infrared energy falling on the different detectors. The operant test chambers were interfaced with a computer running Graphic State 3.0 software (Coulbourn Instruments, Harvard Apparatus), which recorded task events and controlled the components of the chamber (e.g., lever insertion, food pellet delivery) based on the task parameters.

Surgical procedures

After a week of acclimation on a free feeding regimen, rats were anesthetized with isoflurane gas (1–5% in O_2) and were administered buprenorphine (0.05 mg/kg), Meloxicam (1 mg/kg) and sterile saline subcutaneously (10 mL). After being placed into a stereotaxic apparatus (David Kopf), the scalp was cleaned with a chlorohexidine/isopropyl alcohol swab and an adhesive surgical drape was placed over the rat's body. The scalp was then incised and retracted. Three small burr holes were drilled into the skull for jeweler's screws such that one screw would be anterior to the guide cannulae and two would be posterior to the guide cannulae. Prior to implanting guide cannulae, the skull was leveled to ensure that bregma and lambda were in the same horizontal plane. Finally, two additional burr holes were drilled for bilateral implantation of guide cannulae (22 gauge; Plastics One) above the NAc (AP: +1.7, ML: ± 1.8 , DV: -6.0 from skull). Cannulae were anchored in place with

dental cement, and sterile stylets were inserted into the cannulae. After surgery, rats were given additional sterile saline subcutaneously (10 mL) and placed on a heating pad to recover prior to being returned to their home cage. Rats were given one week for recovery before food restriction in preparation for behavioral testing.

Behavioral Procedures

Rats were first shaped to perform the different components of the task (lever pressing for food, nosepoking into food trough) as described previously [24]. They then began training in the delay discounting task, which consisted of five 12-trial blocks and lasted 60 min in duration. Each 40 s trial was initiated by the illumination of both the houselight and trough light. A nosepoke into the trough extinguished the trough light and triggered extension of either a single lever (forced choice trials) or both levers (free choice trials) into the chamber. If rats failed to nosepoke within 10 s, both lights were extinguished and the trial was scored as an omission. A press on one lever (left or right; randomized across rats) always delivered 1 food pellet immediately and a press on the other lever delivered 3 pellets after a variable delay. In one group of rats ($n = 15$), the delay to the large reward increased across successive blocks of trials ("ascending" group; 0, 4, 8, 16, and 32 s). In a second group of rats ($n = 11$), the delay decreased across successive blocks of trials ("descending" group; 32, 16, 8, 4, and 0 s). The identity of the two levers remained fixed across all testing sessions. Each block of trials began with 2 forced choice trials in which the delay contingencies for that block were established (1 presentation of each lever). Forced choice trials were followed by 10 free choice trials. If rats failed to lever press within 10 s, the levers were retracted, the lights extinguished and the trial scored as an omission. Upon pressing a lever, both the houselight and food trough light were reilluminated and food was delivered. Rats were trained in the task until stable behavior emerged (30–45 days in the ascending group; 20–30 days in the descending group), at which point they were ready for microinjections.

Prior to microinjections, rats received dummy injections, in which the injectors were inserted into the cannulae but no drug was microinjected. Immediately after dummy injections, rats were tested to ensure that this mock procedure had no lasting effects on choice behavior. Twenty-four hours later, rats received intra-NAc microinjections (0.3 μ L at a rate of 0.3 μ L/min) of amphetamine (0, 10 and 20 μ g/hemisphere in 0.9% saline vehicle) in a randomized, counterbalanced order such that each rat received each dose of amphetamine, with a 48 h washout period between successive microinjections. During microinjections, the injection needles (28 gauge, Plastics One) were attached to 10 μ L Hamilton syringes mounted on an infusion pump (Harvard Apparatus) via polyethylene tubing. After microinjection of amphetamine or saline, the injection needles were kept in place for an additional 1 min to allow for diffusion of the drug. Sterile stylets were then inserted into the guide cannulae and after ten minutes, rats were placed in the chambers for testing.

Drugs

d-amphetamine sulfate (0, 10 and 20 μ g/hemisphere; Drug Supply Program at the National Institute on Drug Abuse) was dissolved in 0.9% saline vehicle and microinjected into the NAc 10 min prior to behavioral testing.

Histology

At the conclusion of the experiment, rats were overdosed with Euthasol and perfused across the heart with 0.1M PBS followed by 4% paraformaldehyde. Brains were immediately extracted and post-fixed in 4% paraformaldehyde for 24 h before being transferred into a 20% sucrose in 0.1M PBS solution. Brains were sectioned (35 μ m) on a cryostat maintained at -19°C . Brain sections were mounted on electrostatic slides (Fisherbrand) and subsequently stained with 0.25% thionin to verify cannulae placements.

Data analysis

Raw data files were extracted from Graphic State software and compiled using a custom macro written for Microsoft Excel (Dr. Jonathan Lifshitz, University of Kentucky). Subsequent data analyses were conducted with SPSS 22.0. Choice performance in the delay discounting task was measured as the percentage of free choice trials in each delay block on which rats chose the large, delayed reward. To determine when rats reached stable performance (prior to drug administration), a repeated measures analysis of variance (ANOVA) was conducted on free choice trials from 5 consecutive sessions. Stable behavior was defined as an absence of both a main effect of session and an interaction between session and delay block [18, 25]. To determine the effects of amphetamine on impulsive choice and whether this effect differed depending on the direction in which the delays were presented, a three-factor repeated measures ANOVA was used to analyze choice performance. In this analysis, dose and delay were within subjects factors, and direction group (ascending vs. descending) was the between subjects factor. Upon obtaining significant main effects or significant interactions in this three-factor parent ANOVA, additional repeated measures ANOVAs were conducted within each direction group to determine whether the low and high doses differed significantly from vehicle. Omissions were calculated as the percentage of free choice trials on which rats did not lever press, out of the maximum number of choice trials (50) in the task. A repeated measures ANOVA was used to test whether amphetamine affected trial omissions, with dose as the within subjects factor and group as the between subjects factor.

Results

Histology

Of the initial 48 rats in the ascending group, 13 were excluded due to illness or death during surgery and 20 were excluded due to cannulae misplacements. In the descending group, 11 out of the initial 25 rats were excluded due to cannulae misplacements. In this same group, three additional rats were excluded due to illness during the experiment. Locations of cannulae placements for rats included in the study (ascending, $n = 15$; descending, $n = 11$) are depicted in Figure 1.

Effects of intra-accumbens amphetamine on delay discounting task performance

Rats were trained in the delay discounting task until stable behavior was obtained (ascending group, 30–45 days; descending group, 20–30 days). A repeated measures ANOVA was used to analyze the effects of amphetamine on choice performance, with dose and delay as within

subjects factors and direction as a between subjects factor. This analysis revealed that there was no main effect of dose on choice performance [$F(2, 48) = 0.83, p > 0.05$], but there was a significant main effect of direction [$F(1, 24) = 4.5, p = 0.04, \eta^2p = 0.16$]. Further, there were significant dose X direction [$F(2, 48) = 6.9, p < 0.01, \eta^2p = 0.22$], delay X direction [$F(4, 96) = 84.0, p < 0.01, \eta^2p = 0.78$] and dose X delay X direction [$F(8, 192) = 3.1, p < 0.01; \eta^2p = 0.11$] interactions. Together, these results indicate that amphetamine differentially affected choice performance depending on the direction of the delays (Figure 2). On the basis of the significant dose X delay X direction interaction, follow-up analyses were conducted to evaluate the effects of amphetamine in each direction group. In the ascending delays group, a repeated measures ANOVA (dose X delay) comparing the low dose to vehicle revealed a significant main effect of dose [$F(1, 14) = 5.2, p = 0.04, \eta^2p = 0.27$] and a trend toward a dose X delay interaction [$F(4, 56) = 2.3, p = 0.07, \eta^2p = 0.14$]. When comparing the high dose to vehicle, there was both a significant main effect of dose [$F(1, 14) = 7.7, p = 0.02, \eta^2p = 0.35$] and a significant dose X delay interaction [$F(4, 56) = 4.0, p < 0.01, \eta^2p = 0.22$]. Together, these results indicate that while both doses caused an overall mean increase in choice of the large reward relative to vehicle, the high dose also caused a significant shift in the rate at which rats chose the large reward as delays increased. A similar repeated measures ANOVA was performed to determine whether each dose of amphetamine affected impulsive choice in the descending delays group. These analyses revealed that the high dose, but not the low dose, significantly increased impulsive choice relative to vehicle [high: dose, $F(1, 10) = 9.4, p = 0.01, \eta^2p = 0.49$; dose X delay, $F(4, 40) = 2.1, p = 0.09, \eta^2p = 0.18$; low: dose, $F(1, 10) = 1.2, p > 0.05$; dose X delay, $F(4, 40) = 1.1, p > 0.05$]. An additional analysis (repeated measures ANOVA) comparing performance in the ascending and descending groups under vehicle conditions revealed neither a main effect of direction [$F(1, 24) = 0.02, p > 0.05$] nor a direction X delay interaction [$F(4, 96) = 0.72, p > 0.05$] suggesting that baseline differences between the two direction groups likely do not account for the differences in the effects of amphetamine. Finally, a repeated measures ANOVA revealed that there was neither a main effect of dose nor a dose X direction interaction effect on trial omissions [Table 1; dose, $F(2, 48) = 0.84, p > 0.05$; dose X direction, $F(2, 48) = 0.01, p > 0.05$].

Finally, close inspection of Figure 1 suggests that in the ascending group, the cannula placements are distributed across both the core and shell subregions of the NAc whereas in the descending group, the placements appear to be predominantly located in the core. Previous work has shown that manipulations of the core and shell can have different effects on behavior, including impulsive choice [27–31]. To address this issue, rats were divided into two groups: those with shell placements and those with core placements. The effects of amphetamine were then analyzed within each placement group using a repeated measures ANOVA, with both dose and delay as within subject factors and direction as a between subjects factor. If the results diverged from those obtained when core vs. shell placements were combined, it could suggest that the subregional placement of the amphetamine microinjections accounted for the different effects in the two directions. Consistent with the combined data, however, there was a significant dose X direction interaction [$F(2, 28) = 4.0, p = 0.03, \eta^2p = 0.22$] and a significant dose X delay X direction interaction [$F(8, 112) = 2.3, p = 0.02; \eta^2p = 0.14$] in rats with core placements. Similarly, there was a significant

dose X direction interaction [$F(2, 16) = 14.1, p < 0.01, \eta^2 p = 0.64$] and a strong trend toward a significant dose X delay X direction interaction [$F(8, 64) = 2.0, p = 0.06, \eta^2 p = 0.20$] in rats with shell placements (although the presence of only one rat with a shell placement in the descending group renders this latter result more challenging to interpret). As an additional argument against microinjection placement accounting for the effect of direction, a repeated measures ANOVA with dose and delay as within subject factors and direction and cannula placement as between subjects factors revealed no main effect of placement [$F(1, 22) = 0.02, p > 0.05$] and no placement X direction interaction [$F(1, 22) = 3.1, p > 0.05$]. Further, there was neither a dose X direction X placement interaction [$F(2, 44) = 2.3, p > 0.05$] nor a dose X delay X direction X placement interaction [$F(8, 176) = 0.9, p > 0.05$]. Thus, the results of these additional analyses suggest that the different effects of amphetamine in the ascending and descending groups cannot be easily attributed to differences in core vs. shell placements between these two groups.

Discussion

Taken together, the data show that acute intra-NAc amphetamine administration affects delay discounting task performance, but that the direction of the effect depends upon the order in which the delays are presented. These findings are consistent with previous work demonstrating that the effects of systemic amphetamine may depend on several different factors, such as the parameters of the delay discounting task and baseline levels of impulsivity. For example, as with the current findings, Tanno et al. [16] showed that acute systemic amphetamine administration decreased impulsive choice when delays were ascending, but increased impulsive choice when delays were descending. Others have shown that the effects of systemic amphetamine on impulsive choice depend on whether the delay is signaled by a discrete cue: amphetamine decreased impulsive choice when a cue was presented during the delay, but increased impulsive choice in the absence of a cue [19]. Finally, the effects of amphetamine on impulsive choice can be influenced by baseline levels of impulsivity, with systemic amphetamine decreasing impulsivity in rats that are more impulsive at baseline and increasing impulsivity in rats that are less impulsive at baseline [20]. The current data extend this previous work with systemic amphetamine and show that monoamine neurotransmission within the NAc may mediate the effects of amphetamine on delay discounting task performance.

Considerable evidence implicates the NAc in impulsive choice. Lesions of the NAc increase impulsive choice, although the behavioral mechanisms by which this occurs are not entirely clear [31, 32]. The role of NAc dopamine in impulsive choice is also unclear. Although NAc DA depletion alone does not affect impulsive choice [18], other studies have shown that NAc DA release in intact animals tracks the subjective value of delayed rewards [33]. Regardless of the direction of the delays, the current data provide support for a role of NAc DA in delay discounting task performance. Surprisingly, and in contrast to our original prediction, enhanced DA availability in the NAc increased choice of the large, delayed reward in the ascending delays condition [which contrasts with the lasting effects of chronic cocaine in the same task design [24]]. When delays descended across the session, however, amphetamine reduced choice of the large, delayed reward. Together, these data suggest that, rather than altering impulsive choice *per se*, intra-NAc amphetamine impairs behavioral

flexibility, or the ability to shift choice behavior as contingencies (delays to the large reward) change across the test session. Thus, in both groups, intra-NAc amphetamine caused rats to perseverate on the lever that they chose in the first delay block. In the ascending delays group, rats continued to choose the large reward lever even as the cost of the large reward (delay to reward delivery) increased across the session. In the descending delays group, rats continued to choose the small reward lever even as the cost of the large reward decreased. Note that the different effects of amphetamine on choice behavior in the two direction groups rule out several alternative interpretations of the results, such as impairments in reward motivation or discrimination between reward magnitudes. These findings are also consistent with those of previous studies in which systemic amphetamine administration caused perseverative patterns of choices similar to those observed here in both probability discounting [34] and delay discounting tasks [16]. To our knowledge, no prior studies have linked intra-NAc amphetamine to impairments in behavioral flexibility; however, stimulation of DA D2 receptors in the NAc results in perseverative responding in a reversal learning task [35], lending support to this interpretation of the current data. Taken together, the current findings therefore indicate that cocaine-induced increases in NAc DA release are not likely a mechanism by which impulsive choice is increased; rather, this may underlie the behavioral inflexibility that has been reported to be a consequence of chronic cocaine administration [36].

There is growing evidence that time perception plays a role in impulsive choice and that this is mediated by an internal clock that encodes different durations with different clock values [37–40]. In a recent study, Baumann and Odom (2012) showed that the degree of discounting in a laboratory delay discounting task was positively correlated with how human participants categorized the duration of different temporal stimuli: those who were more impulsive overestimated the duration of the stimuli. The authors suggested that in these impulsive individuals, their “internal clock” was running at a faster speed, thus making it seem as though the delays were longer than they actually were. Interestingly, it has been suggested that DA can modulate this internal clock. For instance, systemic administration of methamphetamine or amphetamine in rodents increases internal clock speed, resulting in an overestimation of how much time has passed and thus, faster response times [41–43]. In the current study, intra-NAc amphetamine could have altered the rats’ perception of the delay durations; however, the fact that intra-NAc amphetamine had different effects on choice performance depending on the direction of the delays does not support this interpretation. Although the decreased choice of the delayed reward in the descending group is consistent with an amphetamine-induced increase in clock speed, the increased choice of the delayed reward in the ascending group would argue the opposite. Given that these interpretations conflict with one another, it is unlikely that alterations in timing can fully explain the effects of intra-NAc amphetamine on impulsive choice. Notably, a recent study showed that intra-NAc amphetamine had no effect on response rates and timing in a task assessing temporal perception [38]. Thus, while others have shown that DA signaling can modulate timing processes involved in impulsive choice, this mechanism does not appear to mediate changes in impulsive choice resulting from intra-NAc amphetamine.

An important limitation of the conclusion that increases in NAc dopamine release do not underlie increased impulsive choice is that intra-NAc amphetamine causes a tonic increase

in DA availability [44–47], whereas it is phasic changes in NAc DA release that appear to be most closely linked to valuation and choice of delayed vs. immediate rewards [33]. Hence, although the present results argue against NAc DA-induced enhancements in incentive salience attribution (as have been demonstrated previously using similar acute amphetamine administration parameters [8]) as contributing strongly to increased impulsive choice, they do not rule out potential contributions of chronic cocaine-induced alterations in phasic DA signaling. It is also important to note that in addition to DA, amphetamine causes increases in other monoamines including serotonin (5-HT) and norepinephrine (NE) [48, 49]. Hence, it is possible that the effects of intra-NAc amphetamine are due to increases in other monoamines. In particular, there is evidence that the 5-HT system plays a role in impulsive choice. For example, both lesions of the ascending serotonergic pathways and central depletion of 5-HT cause an increase impulsive choice [50, 51]. Further, global 5-HT depletion prevents systemic amphetamine-induced decreases in impulsive choice, indicating that 5-HT signaling plays a permissive role in the effects of amphetamine [52]. Interestingly, however, this same study also showed that co-administration of flupenthixol, a DA antagonist, with amphetamine blocked the effects of amphetamine in rats with global 5-HT depletion. These data therefore suggest that DA and 5-HT interactions are important for regulating impulsive choice. In addition, there is evidence that this interaction may be particularly important in the NAc, as 6-OHDA lesions of the NAc, which decrease DA and NE levels, reduced the ability of a 5-HT agonist to block amphetamine's effect on impulsive choice [18]. Therefore, it is conceivable that in the current study, the effects of intra-NAc amphetamine were due to interactions between 5-HT and DA in the NAc. Future studies will explore this possibility.

Thus, the question as to the mechanism by which chronic cocaine causes lasting increases in impulsive choice remains unresolved. One possibility is that alterations in impulsive choice following cocaine exposure are due to cocaine-induced changes in other brain regions [53]. For example, the orbitofrontal cortex (OFC) has been shown to be involved in impulsive choice, and chronic cocaine alters gene expression and neurophysiological properties in this structure [54, 55]. Dysfunction within the basolateral amygdala has also been linked to increased impulsive choice, as chronic cocaine decreases anticipatory BLA activity during delays prior to reward delivery in a delay discounting task [10]. Finally, serotonergic neurotransmission, particularly within the prefrontal cortex, becomes dysregulated after chronic cocaine. Thus, any or all of these alternative mechanisms may be responsible for elevated impulsive choice following cocaine use. Clearly, additional work is required to gain a better understanding of the mechanisms by which chronic cocaine causes long-lasting increases in impulsive choice, and ultimately, how such increases can be attenuated to improve outcomes in substance use disorders.

Acknowledgments

We thank the Drug Supply Program at NIDA for kindly providing *D*-amphetamine. Supported by a McKnight Brain Institute Fellowship and a Thomas H. Maren Fellowship (CAO), DA033074 (MRM), and DA024671 and DA036534 (BS).

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Highlights

- Chronic cocaine can increase both impulsive choice and nucleus accumbens (NAc) dopamine (DA) release
- Thus, enhanced NAc DA release could mediate chronic cocaine-induced impulsive choice
- Intra-NAc amphetamine increased choice of large rewards in an ascending delay discounting task
- Intra-NAc amphetamine decreased choice of the large rewards in a descending delay discounting task
- NAc DA may be important for flexible decision making

Figure 1. Representation of cannula placements in the nucleus accumbens

Cannula placements in rats in the (A) ascending delay and (B) descending delay groups were verified on Nissl stained sections. The filled black circles indicate the location of the tip of the injectors used for microinjections.

Figure 2. Effects of amphetamine microinjections in the nucleus accumbens on delay discounting (A) Both doses of amphetamine increased choice of the large, delayed reward when delays increased across the session. (B) The high dose of amphetamine decreased choice of the large, delayed reward when delays decreased across the session. Data are represented as the mean $\pm$ SEM (within subjects) percent choice of the large, delayed reward. Asterisks indicate a significant difference between the indicated dose and vehicle.

Table 1

Effects of amphetamine microinjections in the nucleus accumbens on percentage of omitted choice trials in the delay discounting task. Values represent means (SEMs).

Delay Order	Veh	10 µg	20 µg
Ascending	8.1 (5.8)	10.9 (6.1)	15.2 (6.8)
Descending	1.8 (0.7)	3.6 (1.4)	8.2 (3.9)

There were no significant effects of amphetamine on the percentage of omitted choice trials in the delay discounting task, irrespective of the order of delay presentation (ascending or descending).