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Nucleus accumbens lesions decrease sensitivity to rapid changes in the delay to reinforcement

Ashley Acheson[a], **Andrew M. Farrar**[b], **Michele Patak**[c], **Kathryn A. Hausknecht**[d], **Artur K. Kieres**[e], **Seulgi Choi**[d], **Harriet de Wit**[a], and **Jerry B. Richards**[d,*]

[a]University of Chicago, Department of Psychiatry, Chicago, IL 60637, United States

[b]Department of Psychology, University of Connecticut, Storrs, CT 06269-1020, United States

[c]Center for Biobehavioral Health, Columbus Children's Research Institute, Columbus, OH 43205, United States

[d]Research Institute on Addictions, The State University of New York at Buffalo, Buffalo, NY 14203, United States

[e]Department of Psychology, Tufts University, Medford, MA 02155, United States

Abstract

Both humans and non-humans discount the value of rewards that are delayed or uncertain, and individuals that discount delayed rewards at a relatively high rate are considered impulsive. To investigate the neural mechanisms that mediate delay discounting, the present study examined the effects of excitotoxic lesions of the nucleus accumbens (NAC) on discounting of reward value by delay and probability. Rats were trained on delay (n = 24) or probability discounting (n = 24) tasks. Following training, excitotoxic lesions of the NAC were made by intracranial injections of 0.5 μl 0.15 M quinolinic acid (n = 12) or vehicle (n = 12) aimed at the NAC (AP +1.6, ML ±1.5, DV −7.1). NAC lesions did not alter performance in animals tested with a constant delay (4 s) or probability (0.4) of reinforcement. However, when tested with between session changes in the delay (0, 1, 2, 4, and 8 s) of reinforcement, the lesioned rats had flatter discount curves than the sham group, indicating that they were less sensitive to frequent changes in the delay to reward. In contrast, the NAC lesions did not affect discounting of probabilistic rewards. NAC lesions impaired the ability to adapt to frequent between session changes in the delay to reward but did not increase or decrease discounting when the delay was held constant across sessions. NAC lesions may disrupt the ability of the animals to predict the timing of delayed rewards when the delay to reward is changed frequently.

Keywords

Timing; Operant; Reward; Rat; Impulsivity; Decision-making; Learning

* Corresponding author at: Research Institute on Addictions, University at Buffalo, The State University of New York, 1021 Main Street, Buffalo, NY 14203, United States. Tel.: +1 716 887 2211. jrichard@ria.buffalo.ed (J.B. Richards).

1. Introduction

Impulsivity is an important component of psychiatric conditions such as Attention Deficit Hyperactivity Disorder (ADHD), Antisocial Personality Disorder, Borderline Personality Disorder and Substance Abuse [1]. One operational definition of impulsivity is the degree to which an individual discounts the value of a delayed reward, known as delay discounting [2–6]. Increased discounting of delayed rewards has been observed in children with ADHD, impulsive psychiatric patients, and substance abusers [7–12]. Although delay discounting is an accepted operational definition of impulsivity, little is known about its underlying neurobiological substrates.

One brain area thought to be important in mediating delay discounting is the nucleus accumbens (NAC). In a previous study Cardinal et al. [13] reported that in rats, lesions of the NAC core decreased choice of a larger reward presented after variable delays (0–60 s) over a smaller, immediate reward and concluded that integrity of the NAC is necessary for tolerating delays to appetitive reinforcement. However, these findings were complicated by the observation that lesioned rats had a low preference for the “large” reward even when there was no delay, suggesting that the lesions generally impaired choice behavior rather than directly affecting delay discounting. Because the NAC is part of a circuit involved in predicting the occurrence of delayed rewards [14–26], it is possible that the lesioned rats in the Cardinal study were less able to track the within session changes in the delay associated with the large reinforcer and generally avoided this option without affecting delay discounting.

In the present study, we examined the role of the NAC in delay and probability discounting using the adjusting amount procedure [27]. In this procedure the rat makes repeated choices between a fixed delayed amount of water and a variable amount of immediate water. The amount of the immediate water is systematically adjusted until an indifference point is reached where the rat chooses both the fixed delayed amount of water and the immediate amount with equal frequency. The immediate amount of water at the point of indifference is used as an objective measure of how much the rat values the delayed reward. This procedure is sensitive to the acute effects of drugs and acute (single session) changes in the delay to the large reward and the amount of the delayed reward [6,8,27–29]. In addition, the same indifference point is reached regardless of the amount of water available on the immediate side at the beginning of a test session [27]. In the delay discounting version of the task, the value of the reward decreases as the delay to that reward increases. In the probability discounting task version, the value of a reward decreases as probability of obtaining that reward decreases.

The delay discounting task used in the present study employed shorter delays with less frequent delay changes than the task used by Cardinal et al. [13], a potentially important difference if NAC lesions impair the ability to adapt to changes in delay to reinforcement. Testing the effects of NAC lesions on both delay and probability discounting with the same adjusting amount procedures allowed us to determine the specificity of the NAC lesion-induced impairments. The specificity of these impairments was further investigated by parametric manipulations assessing sensitivity to reward delay, probability, and magnitude.

2. Materials and methods

2.1. Subjects

Forty-eight male Holtzman Sprague–Dawley rats (Harlan Inc., Indianapolis, IN) were used. The rats were 3 months old and weighed 250 g at the beginning of the experiment. They were housed in pairs in plastic cages (42.5 cm×22.5 cm×19.25 cm). Lights were on in the colony room from 07:00 to 19:00. All behavioral testing occurred during the light phase of the light/dark cycle. Food (Harlan Teklad Laboratory Diet #8604, Harlan Inc., Indianapolis, IN) was continuously available. Access to water was restricted to 20 min per day given immediately after testing sessions. The rats were tested 7 days per week. Twenty-four rats were trained on delay discounting, while the remaining 24 were trained on probability discounting. Within each condition, half the animals received excitotoxin lesions, while the rest were given sham lesions. This study was conducted in accordance with the guidelines set up by the Institutional Animal Care and Use Committee of The University at Buffalo, The State University of New York.

2.2. Apparatus

2.2.1. Adjusting amount procedure apparatus—Sixteen locally constructed experimental chambers were used. These chambers have been described in detail previously [27]. The chambers had stainless-steel grid floors, aluminum front and back walls, and Plexiglas sides and top. The test panel had two water dispensers located on either side of a centrally located snout-poke hole. Stimulus lights were mounted above the two water dispensers and the center snout-poke hole. The water-dispenser stimulus lights were arranged so that they were level with the rat's eyes when the rat's snout interrupted an infrared beam in the center snout-poke hole. A Sonalert tone generator (Model #SC628, Newark Electronics, Chicago, IL) with a frequency of 2900 Hz was mounted above the left stimulus light. Snout pokes and head entries into the water dispensers were monitored with infrared detectors. Water was presented to the rats in the feeder holes via syringe pumps (MED Associates, PHN-100, St. Albans, VT), which pushed 60 ml syringes (Becton Dickinson and Company, Franklin Lakes, NJ). The entire apparatus was computer controlled through a MED Associates interface with MED-PC (version 4). The temporal resolution of the system was 0.01 s.

2.2.2. Activity monitors—Locomotor activity was recorded by an infrared motion-sensor system (Hamilton-Kinder, Poway, CA) fitting outside a standard cage tub (42.5 cm×22.5 cm×19.25 cm). Infrared motion sensors set at 5.5 cm above the cage floor were used to detect horizontal movement (locomotion) and sensors set at 15.5 cm above the floor were used to detect vertical movements (rearing). One month after surgery, subjects were placed in the activity monitors 1 h post-session for a 2 h period. The total distance traveled during the activity monitor exposure was used as the measure of locomotor activity.

2.3. Surgery

Subjects were randomly assigned to receive excitotoxin or sham lesions aimed at the NAC. Rats were anesthetized with Avertin (2% [w/v] 2,2,2-tribromoethanol, 1% [w/v] 2-methylbutan-2-ol, and 8% [v/v] ethanol in phosphate-buffered saline, 10 ml/kg ip) and

placed in a stereotaxic frame (Stoelting CO, Wood Dale, IL). The skull was exposed, and a Dremel tool (Dremel, Mount Prospect, IL) was used to remove the bone directly above the injection sites. The dura mater was broken with the tip of a needle to avoid damaging the underlying venous sinuses. Lesions were performed in accordance with the atlas of Paxinos and Watson [30] using bregma as the origin, with the incisor bar set to ensure the surface of the skull was level.

Fiber-sparing excitotoxic lesions aimed at the NAC were made with 0.15 M quinolinic acid (Sigma, St. Louis, MO) in 0.1 M phosphate buffer (final pH = 7.2–7.4) injected through a 30-gauge cannula mounted on a stereotaxic frame. At each site, 0.5 μl of toxin was infused over 3 min, after which 2 min was allowed for diffusion before the injector was removed. Lesion coordinates for the NAC (in millimeters from the skull surface at bregma) were AP +1.6, ML ±1.5, DV −7.1. The cannula was connected by a polythene tube to a 10 μl Hamilton syringe (Hamilton Company, Reno, NV). Sham lesions were made in the same manner, except that vehicle was infused. After surgery the rats were given 1 week to recover with free access to food and water and were not tested. During this period, rats were weighed daily. Rats showing signs of dehydration were given subcutaneous injections of lactated Ringer's solution (Webster Veterinary Supply Inc., Sterling, MA).

2.4. Histology

At the end of the experiments, subjects were deeply anesthetized with Fatal Plus (pentobarbitone sodium, 200 mg/ml, >1.5 ml ip) and perfused transcardially with 0.01 M phosphate-buffered saline followed by 4% (w/v) paraformaldehyde in phosphate-buffered saline. Their brains were removed and post-fixed in paraformaldehyde overnight before being cryoprotected in 20% (w/v) sucrose; they were sectioned coronally at 50 μm thickness on a freezing microtome, and every fifth section was mounted and allowed to dry. Sections were then passed through a series of ethanol solutions of descending concentration (3 min in each of 100%, 95%, and 70% [v/v] ethanol in water) and stained for ~5 min with cresyl violet (0.05% [w/v] aqueous cresyl violet, 2mM acetic acid, and 5 mM formic acid in water). After staining, sections were rinsed in water and 70% ethanol before being differentiated in 95% ethanol. Finally, they were dehydrated and delipidated in 100% ethanol and Citrisolve (Organic Specialties Inc., East Providence, RI) before being cover-slipped and allowed to dry.

2.5. Immunocytochemistry

A one-in-five series adjacent to the cresyl violet stained sections was used for NeuN immunostaining. Free-floating sections were rinsed in 0.1 M phosphate-buffered saline (PBS) and treated with 0.5% H_2O_2 in 0.1 M PBS for 30 min to suppress endogenous peroxidase activity. Sections were then incubated for 30 min with blocking solution consisting of 10% normal horse serum (Sigma, St. Louis, MO) and 0.3% Triton X-100 (Sigma, St. Louis, MO) in PBS (PBST). The sections were then incubated for 24 h at 4°C in the monoclonal anti-NeuN serum (1:5000, Chemicon, Temecula, CA) diluted in PBST. After rinsing in PBST, sections were incubated for 1 h at room temperature in biotinylated horse antimouse serum (1:1000, Vector Laboratories, Burlingame, CA) in PBST. After more rinses in 0.1 M PBST, sections were incubated for 1 h in avidin-biotin-horseradish

peroxidase complex (1:200, ABC-Elite, Vector Laboratories) in PBST. Sections were then rinsed in 0.1 M PBS followed by rinses in 0.1 M tris buffered saline (TBS) and placed in a chromagen solution consisting of 0.05% diaminobenzidine (Sigma, St. Louis, MO) and 0.01% H_2O_2 for approximately 5 min. The reaction was visually monitored and stopped in rinses of 0.1 MTBS, and the sections were mounted and dried on gelatin-coated slides.

2.6. Procedures

2.6.1. Delay discounting task—The adjusting amount procedure used to measure delay discounting has been previously described [27]. Each session consisted of 60 discrete choice trials and a variable number of forced trials. Trials were separated by a minimum intertrial interval (ITI) of 15 s (although see the ITI challenge described below). The total time between the start of one trial and the start of the next trial was 15 s plus the time taken for the rat to make a choice response. During the ITI, all of the stimuli in the chamber were off. The onset of the light above the center snout-poke hole signaled the start of each trial. The first response (snout poke) to the center hole after the beginning of a trial caused the stimulus light above the center hole to be turned off and the stimulus lights above the left and right water dispensers to be turned on. The rat was then required to choose between the left and right water dispensers. The standard alternative was always presented on the left side, and inserting the head into this dispenser resulted in the delivery of 150 μl water delayed by a constant interval. The immediate adjusting amount of water was always presented on the right side. Inserting the head into this dispenser resulted in the immediate delivery of a variable amount of water.

When the rat chose the standard alternative, the lights above both the standard and immediate adjusting alternatives turned off and a tone was presented during the delay to reward period. At the end of the delay period a 150 μl drop of water was delivered and the tone turned off for the remainder of the 15 s trial. Note that when the rat chose the standard, the ITI duration was 15 s minus the delay associated with that reinforcer. When the rat chose the immediate adjusting alternative, the ITI duration was 15 s.

When the rat chose the immediate adjusting alternative, an amount of water was delivered immediately, and the stimulus lights above the left and right water dispenser holes were turned off for the remainder of the 15 s trial. During each session, the amount of water available on the immediate adjusting alternative was systematically varied. If the rat chose the standard alternative, the amount delivered on the immediate adjusting alternative was increased by 15% on the next trial. Choosing the same condition twice in succession resulted in a forced trial in which only the stimulus above the opposite alternative was turned on and only responses to the indicated alternative had a consequence. The next trial was not presented until that animal responded to the forced alternative. Forced trials ensured the rat was sampling both alternatives. The amount of water on the immediate adjusting alternative was not changed after forced trials.

The immediate adjusting side was set at high (150 μl) and low (25 μl) starting amounts on alternate days for Phases 1 and 2. Intact rats reach the same indifference points regardless of the starting amount, indicating they adjust the amount available on the immediate side based on the relative value of the delayed reward [27]. In the present experiment, if lesioned rats

had not been able to reach the same indifference points regardless of the starting point, it would have indicated that they were generally impaired on performing the adjusting amount task.

The dependent measure used to measure discounting was the indifference point (i.e., the value of the delayed reinforcer). The indifference point was defined as the median amount of water available on the immediate adjusting alternative during the last 30 choice trials of each 60-trial session. Using the last 30 trials of the session ensured that the rats had reached the point of indifference. During the last 30 trials the rats chose the immediate adjusting alternative approximately 50% of the time indicating indifference between the immediate and delayed amounts of water. At this point the reinforcing value of delayed alternative was equal to the value of the immediate adjusting amount. Sometimes the rats failed to complete all 60 trials. In these cases the median amount was calculated for those trials completed after the 30th trial. Only test sessions in which a rat completed at least 40 trials were included in the data set. Forced trials were not included in this calculation. Lower indifference points, indicating greater discounting of the delayed reward, indicated greater impulsivity.

2.6.2. Probability discounting task—The adjusting amount procedure used to measure probability discounting was in most respects identical to that described above for delay discounting. However, instead of the standard reward being delayed, it was delivered immediately at a set probability. When the rat chose the standard alternative and it received the reward on that trial, a brief tone was presented simultaneously with immediate delivery of 150 μl of water, and the stimulus lights above the left and right water dispenser holes were turned off for the 15 s ITI. When the rat chose the standard and did not receive the reward on that trial, no tone was presented, and the lights above both the standard and immediate adjusting alternatives were turned off for the 15 s ITI. Water was always delivered after choice of the immediate adjusting side. The immediate adjusting side was set at high (150 μl) and low(25 μl) starting amounts on alternate days for phases 1 and 2, as in the delay discounting task. Lower indifference points on this task, indicating greater discounting of the probabilistic reward, indicated risk aversion. Higher indifference points indicated risk proneness.

2.6.3. Training—delay discounting—The 24 rats tested on delay discounting were initially trained using an auto-shaping procedure. In the auto-shaping procedure, the center stimulus light was turned on, and rats were required to make a center snout poke. This caused the center stimulus light to turn off and the stimulus lights over both the left and right water dispensers to turn on. A response to either of the two dispensers resulted in the delivery of a 75 μl water reward. The left (standard) side remained fixed while the right (immediate adjusting alternative) varied based on rats' choices as described above. Two consecutive choices to the same side initiated a forced trial to the opposite side. If the rat did not respond to the center stimulus light by initiating a snout poke within two minutes, the center light flashed for 30 s, and the left and right stimulus lights were turned on. A response to either side was then reinforced. The ITI was initially set at 0.01 s and increased to 15 s over successive days once the rats were reliably responding for both sides. The standard reinforcer was then set at 150 μl with a 4 s delay. Once the rats were responding for this, the

auto-shaping procedure was no longer used. Rats were then trained on delay discounting with a 4 s delay to 150 μl of water with alternating high (150 μl) and low (25 μl) starting amounts on the immediate adjusting alternative (i.e. Day 1—high start, Day 2—low start, Day 3—high start, etc.). Once indifference points were determined to be similar week to week, with no upward or downward trend for 4 weeks, rats were divided into matched groups based on their indifference points and assigned to receive excitotoxin or sham lesion conditions.

2.6.4. Training—probability discounting—Rats on probability discounting underwent similar training. Subjects were initially trained on the same auto-shaping procedure as described above for rats on delay discounting. As with the delay discounting task, once the rats were reliably responding to both sides, the ITI was increased to 15 s over successive days. Once subjects were reliably responding to both sides with the ITI set at 15 s, the standard reinforcer was set at 150 μl with a 0.4 probability of occurrence. After the rats were reliably responding on this procedure, the auto-shaping procedure was no longer used. Rats were then trained on probability discounting with a 0.4 probability of receiving 150 μl of water with alternating high (150 μl) and low (25 μl) starting amounts on the immediate adjusting alternative, as described above for delay discounting.

2.7. Phase 1: the effects of NAC lesions on discounting with constant delay and probability

2.7.1. Pre versus post surgery testing—delay discounting—Once indifference points were determined to be similar from week to week, with no upward or downward trend for 4 weeks, rats were divided into matched groups based on their indifference points and assigned to receive excitotoxin or sham lesion conditions. Following the 1-week recovery period from surgery, water restriction was then resumed, and rats were tested on delay discounting with a 4 s delay to 150 μl of water with alternating high (150 μl) and low (25 μl) starting amounts on the immediate adjusting alternative for 14 days.

2.7.2. Pre versus post surgery testing—probability discounting—The post-lesion treatment of the rats trained on the probability discounting task was similar to that of the delay discounting rats. Once indifference points were determined to be similar from week to week, rats were divided into matched groups based on their indifference points and assigned to receive excitotoxin or sham lesion conditions. Following the recovery period, water restriction was resumed, and rats were tested on probability discounting with a 0.4 probability of receiving 150 μl of water with alternating high (150 μl) and low (25 μl) starting amounts on the immediate adjusting alternative for 14 days.

2.8. Phase 2: the effects of NAC lesions on delay and probability discount curves

2.8.1. Delay—Following the post surgery testing at the constant 4 s delay, rats on the delay discounting task were tested with delays of 0, 1, 2, 4, and 8 s to obtain delay discounting curves while still using the alternating high and low starting amounts for 2 months. As described previously in Richards et al. [27], in normal rats the curves derived can be well-described by the hyperbolic function of Mazur [31]:

$$V = bA/(1+kD)$$

where *V* is the value of the delayed reinforcer, *A* the amount of the delayed reinforcer, *D* the length of the delay, *k* is a free parameter that describes the steepness of the discount function, and *b* is a free parameter representing bias for either the standard or immediate adjusting alternative independent of the delay associated with the standard reinforcer. Larger *k* values indicate that the delayed rewards are being discounted more steeply and indicates greater impulsivity. A 1.0 *b* value indicates the absence of bias; values greater than 1.0 indicate a bias for the standard alternative and values less than 1.0 indicate a bias for the immediate adjusting alternative. The rats were exposed to each of the 5 delays every 5 test sessions in a pseudorandom order with the condition that no delay was tested 2 days in a row.

2.8.2. Probability—Following post surgery testing at the constant 0.4 probability, discount curves were derived for rats tested on the probability discounting procedure in a similar fashion to the delay discount functions described above except that, instead of delays, probabilities of 1.0, 0.7, 0.4, 0.2 and 0.1 were varied. The curves derived from this procedure can also be fitted to a hyperbolic discount function previously described by Rachlin et al. [32] and Richards et al. [2]. In this model:

$$\text{value} = bA/(1+hO), O = 1/p - 1$$

where*p* is the probability of reward and *O* indicates odds against. *A* is the amount of the probabilistic reinforcer. The value of *h* indicates how rapidly the value of a reward decreases as the probability of its occurrence decreases, analogous to *k* in the hyperbolic discount function described above. Higher *h* values indicate steeper discounting. Again, *b* values indicate bias for either the standard or immediate adjusting alternative independent of the probability associated with the standard reinforcer. The rats were exposed to each of the 5 probabilities every 5 test sessions in a pseudorandom order with the condition that no probability was tested 2 days in a row.

2.9. Phase 3: the effects of NAC lesions on responsiveness to changes in reward parameters

2.9.1. Parametric challenges—Following determination of the delay and probability discount curves, the rats were rebaselined on the adjusting amount task with either a 4 s delay or a 0.4 probability for 14 days. The starting immediate adjusting amount was set individually for each rat at its average adjusted amount determined on non-challenge test days. The rats were then tested with a series of 3 acute challenges outlined below with a minimum of 2 days between changing each parameter. In each challenge, the order of increasing and decreasing the manipulated parameter was counterbalanced. Rats received the following challenges:

1. For rats on delay discounting, the 4 s delay to the 150 μl water reinforcer was increased to 8 s and decreased to 2 s.

2. For rats on probability discounting, the probability of occurrence of the standard alternative 150 µl water reinforcer was decreased to 0.2 and increased to 0.7.
3. The magnitude of the 150 µl standard alternative was decreased to 75 µl and increased to 300 µl on both the delay and probability tasks.
4. The 15 s ITI was decreased to 5 s and increased to 60 s on both the delay and probability tasks.

3. Results

3.1. Histology

Lesion damage was confirmed by areas devoid of NeuN staining, indicating no neurons were present [33]. Lesioned animals showed enlargement of the lateral ventricles and general reduced volume of the ventral portion of the brain around the lesion site, indicating major tissue loss and subsequent reduction in brain volume. All rats included in the analysis showed significant damage to both the NAC core and shell (Fig. 1). In the delay condition, four rats that did not meet these criteria were excluded from the analysis. Additionally, one sham lesioned rat that showed substantial enlargement of the lateral ventricles with no clear evidence of localized lesion damage was dropped from the analysis. In the probability discounting group one rat did not learn the discounting task and was dropped from the experiment prior to surgery. In addition, one rat that did not have bilateral NAC core and NAC shell damage and two that had extensive damage to the dorsal striatum were dropped from the analysis. In the rats retained for the analysis, a wide range of lesion damage was detected with the NeuN staining, a highly sensitive technique for detecting excitoxin damage months after lesion induction [33,34]. In some cases, as indicated in Fig. 1, lesion damage was observed to extend beyond the NAC to the ventral pallidum, medial septum, and striatum. Half of the rats in the delay and probability groups had minor lesion damage to the ventral pallidum. One rat in the delay group had damage that extended into the striatum above the NAC. In the probability group, two rats had minor damage to the striatum above the NAC and one rat had damage to the medial septum. The only areas of lesion damage common to all animals were the NAC core and shell and damage in other areas was not related to the behavioral impairments described below.

3.2. Phase 1: the effects of NAC lesions on discounting with constant delay and probability

The purpose of phase 1 was to determine the effects of NAC lesions on how much rats valued delayed and probabilistic rewards when the delay and probability were held constant. The rats were trained and tested with a single delay (4 s) or a single probability (0.4) of reward. Training the animals prior to surgery reduced the likelihood that any observed lesion effects would be the result of impaired task acquisition.

3.2.1. Delay—No differential effect of the lesion was observed on rats tested on delay discounting. Both the sham and lesioned groups discounted less following surgery [Fig. 2 upper panel; $F(1,16)= 11.274$, $p= 0.004$]. Rats in both the lesion and control groups performed similarly during the last 30 trials of the test session with both groups showing a downward trend in the indifference points during the last 30 trials of the test session (Fig. 3).

Ideally the indifference points would have been flat during the last 30 trials of the test session indicating no changes in preference and that a stable indifference point had been achieved. The animals' performance was not affected by the starting amount on the immediate adjusting alternative (25 or 150 μl) in either group (Fig. 3), indicating that the NAC lesions did not produce a general impairment in task performance.

3.2.2. Probability—No differential effect of the lesion was observed on rats tested on probability discounting. Both the sham and lesioned groups discounted less following surgery [Fig. 2 lower panel; $F(1, 18) = 4.409$, $p = 0.050$] and both groups reached stable indifference points during the last 30 trials of the session regardless of the high or low starting amount (Fig. 4).

3.3. Phase 2: the effects of NAC lesions on delay and probability discount curves

In phase 2 we tested a range of delays or probabilities to derive discount curves which could be quantitatively characterized using the hyperbolic discount function [27,31,32].

3.3.1. Delay—When rats were tested with several delays across sessions, lesioned rats had higher indifference points (were *less* impulsive) than the sham rats (Fig. 5). There was a significant main effect of delay on indifference points [$F(4, 56) = 43.256$, $p < 0.001$] and a delay by group interaction [$F(4, 56) = 4.001$, $p = 0.006$]. Post-hoc tests revealed lesioned rats had significantly higher indifference points at the 8 s delay [$t(16) = 2.700$, $p = 0.016$].

Not surprisingly, the k values were significantly lower in NAC lesioned rats [$t(16) = 2.513$, $p = 0.023$] (Table 1). Interestingly, the discount curves of lesioned rats did not fit the hyperbolic discount function as well as shams [$t(16) = 2.106$, $p = 0.051$], suggesting that the lesion may have disrupted performance rather than specifically affecting discounting (Table 1). There were no significant differences in b values, indicating there were no differences in bias for the delayed or immediate reward between sham and lesioned rats (Table 1). There were no significant effects of the high and low starts on indifference points (data not shown).

3.3.2. Probability—The lesion did not affect probability discounting (Fig. 6). There was a significant main effect of probability on indifference points [$F(4, 64) = 172.279$, $p < 0.001$], but the lesion did not affect h values, bias for the probabilistic or certain rewards or how well the probability discount curves were fit by the hyperbolic function (Table 2). Indifference points were generally higher under the low start condition (data not shown), with a significant main effect of the high and low starts on indifference points [$F(1, 16) = 4.968$, $p = 0.041$] but no differential effect of lesion.

3.4. Phase 3: the effects of NAC lesions on responsiveness to changes in reward parameters

The purpose of phase 3 was to assess the animals' sensitivity to acute changes in parameters associated with reward delivery. The results of phase 2 may have been related to an inability to adapt to changes in the delay conditions, rather than specifically decreasing delay

discounting. To test this, we assessed the animals' sensitivity to changes in reinforcer delay, probability, magnitude and intertrial interval (ITI).

The rats were first tested daily for 4 weeks with either a 4 s delay to reward (delay discounting rats) or a 0.4 probability of reward (probability discounting rats). Training with constant delay and probability of reward lasted for 4 weeks and followed the phase of training in which the discount curves were obtained. No differences in discounting were found at the baseline values (4 s delay to reward, and 0.4 probability of reward).

3.4.1. Rats trained with a 4 s delay and challenged with delays of 2 and 8 s— Lesioned rats were less sensitive to acute changes in the delay (Fig. 7, panel A). There was a significant main effect of delay on indifference points [$F(2, 30) = 15.659$, $p < 0.001$] and a significant delay by group interaction [$F(2, 30) = 5.541$, $p = 0.009$], with the lesioned rats being less responsive to the delay challenges. Post-hoc tests revealed that lesioned rats had significantly higher indifference points than shams when challenged with an 8 s delay [$t(15) = 2.666$, $p = 0.018$].

3.4.2. Rats trained with a 0.4 s probability and challenged with 0.2 and 0.7 probabilities—The lesion did not affect sensitivity to acute changes in the probability of reward (Fig. 7, panel B). There was a significant main effect of probability on indifference points [$F(2, 34) = 43.855$, $p < 0.001$]. Both groups discounted more when probability decreased and less when probability increased.

3.4.3. Magnitude challenges

3.4.3.1. Delay: Lesioned rats were less sensitive to acute changes in the amount of delayed rewards (Fig. 7, panel C), There was a significant main effect of magnitude on indifference points [$F(2, 28) = 120.874$, $p < 0.001$] and a significant magnitude by group interaction [$F(2, 28) = 4.985$, $p = 0.014$]. Post-hoc *t*-tests revealed that lesioned rats discounted significantly less than shams when challenged with 75 μl of water [$t(15) = 2.878$, $p = 0.011$].

3.4.3.2. Probability: The lesion did not change sensitivity to variations in the amounts of probabilistic rewards (Fig. 7, panel D). There was a significant main effect of magnitude on indifference points [$F(2, 36) = 171.901$, $p<0.001$]. Both groups discounted less with increasing reinforcer magnitude.

3.4.4. ITI challenges

3.4.4.1. Delay: Increasing the ITI caused rats to discount delayed rewards more, with no differential effects of lesion (Fig. 7, panel E) [$F(2, 24)= 18.935$, $p<0.001$]. There was a significant main effect of ITI on indifference points [$F(2, 24)= 18.935$, $p<0.001$]. Follow up paired samples *t*-tests revealed that increasing the ITI to 60 s significantly lowered indifference points [$t(13) = 5.596$, $p < 0.001$].

3.4.4.2. Probability: Decreasing the ITI caused rats to discount probabilistic rewards more, while increasing the ITI tended to cause them to discount less (Fig. 7, panel F). There was a significant main effect of ITI on indifference points [$F(2, 34) = 9.522$, $p = 0.001$]. Follow-up

paired samples *t*-tests revealed that decreasing the ITI to 5 s significantly lowered indifference points [$t(18) = 5.455$, $p < 0.001$], and there was a trend for indifference points to be increased when the ITI was increased to 60 s [$t(18) = -1.958$, $p = 0.066$].

3.5. Effects of NAC lesions on bodyweight and locomotor activity

NAC lesioned rats exhibited more activity in the activity monitors (lesion 6052 ± 721.13 cm versu sham 4861.23 ±254.39 cm) [$t(37) = 1.766$, $p = 0.042$] and had significantly lower bodyweights at the conclusion of the experiment (lesion 601.42 g ± 18.68 versus sham 673.5± 12.31 g) [$t(37) = 3.417$, $p < 0.001$]. Increased locomotor activity and decreased rates of weight gain are behavioral indicators of NAC core damage [35].

4. Discussion

This study examined the role of the NAC in delay and probability discounting in two separate groups of rats using an adjusting amount procedure. In animals trained with delay discounting, NAC lesions did not affect delay discounting when the delay of reward was held constant, but made animals appear less impulsive when delays were changed daily. Further investigation with parametric challenges revealed that lesioned rats were less responsive to acute changes in both delay and the magnitude of delayed rewards, whereas probability discounting was unaffected. The lack of effects on responsiveness to changes in the magnitude of probabilistic reinforcers indicates that the overall sensitivity to the magnitude of reinforcers was not disrupted. Taken together these results suggest that the lesions generally impaired the animals' ability to adapt to changes in reward outcomes that are delayed, rather than specifically enabling rats to tolerate longer delays to reward. NAC lesions did not affect task performance in the animals trained on the probability discounting task, indicating that the impairment induced by NAC lesions was specific to delayed reinforcement.

4.1. Impairment specific to delay

The absence of an effect on probability discounting indicates that NAC lesions did not cause a general impairment in the ability of the animals to perform the adjusting amount procedure. Both the delay and probability versions of the adjusting amount procedure require the rats to track the changing value of the immediate reward across the session, compare its value to the delayed or probabilistic large reward, and then make a decision about which alternative has the greatest value. Furthermore, there was no evidence that the lesion caused rats to generally per-severate in responding for either option on either the delay or probability discounting versions of this task. Because both the delay and probability versions of the task had the same general performance requirements and the NAC lesioned rats were not impaired on the probability version of the task, it does not seem likely that NAC lesions generally disrupted performance on the adjusting amount procedure.

The overall lack of effects on probability discounting observed in the present study contrasts with Cardinal and Howes [36] findings in which NAC core lesions decreased choice of uncertain larger rewards over smaller certain rewards on a different probability discounting task. Although we found no significant effects of lesions on probability discounting, there

was a tendency for lesioned rats to discount slightly more in all phases of the study, therefore providing some supportive evidence that the NAC may play some role in probability discounting. Undoubtedly this is a matter that warrants further investigation.

The differential effects of NAC lesions on delay and probabilistic reinforcement suggest that these processes require different underlying neural circuits. Previously it has been suggested that delay and probability discounting are governed by similar mechanisms. In natural settings, rewards that are delayed for long periods are often less certain and consequently may be perceived as less likely than rewards delivered immediately [37–39]. Conversely, it has been hypothesized that a series of probabilistic rewards is experienced as a series of delayed rewards [40]. The finding that NAC lesions affected only delayed reinforcement provides evidence that perception of delay and probability are governed by dissociable processes. Further evidence for the hypothesis that delay and probability discounting are separate processes is provided by the fact that varying the ITI in the current experiment had opposite effects with decreasing ITI durations resulting in higher indifference points on the delay task and lower indifference points on the probability task.

4.2. Relation of present study to Cardinal et al. [13]

While the effects of NAC lesions on delay discounting in the present study appear opposite to those reported by Cardinal et al. [13], there are actually strong similarities between the findings of the two studies. The findings of Cardinal et al. [13] could also be explained by an effect of NAC lesions on responsiveness to changes in delay within the test sessions. In that study, lesioned animals showed a strong bias toward the immediate small reward, choosing it approximately 70% of the time even when there was no delay to the larger reward. Cardinal et al. interpreted their findings as indicating that NAC core lesions decreased the ability of rats to tolerate delays to appetitive reinforcement. However in the present study NAC lesions appeared to *increase* the ability of rats to tolerate delays to appetitive reinforcement when the delay to reward was varied between sessions. It does not appear that we truly affected delay discounting as we found no changes in discounting when delay to reinforcement was held constant across sessions. In contrast, the discounting procedure used by Cardinal et al. always involved varying the delay within a single session and animals were never tested with a reward held to a constant delay across sessions. Based on our results that NAC lesions affected performance only when the delay was changed across sessions and not when the delay was held constant, it appears that lesions of the NAC may impair learning about or adapting to changes in delayed reinforcement but do not affect the ability to tolerate delays to appetitive reinforcement.

When contrasting the results of Cardinal et al. [13] with the present study, differences in the behavioral test procedures need to be taken into account. The adjusting amount procedure used in the current study was designed to measure the value of delayed or probabilistic rewards. Rats are given a choice between a delayed or probabilistic constant volume of water and an immediate adjusting amount of water. The value of the adjusting alternative is increased after a choice of the delayed or probabilistic alternative and decreased following a choice of the immediate, certain adjusting alternative. When the rat chooses the delayed or probabilistic alternative and the adjusting immediate alternative with equal frequency we

infer that the subjective value of the amount of water on the adjusted alternative matches the subjective value of the standard alternative. This is referred to as the indifference point. Smaller indifference points indicate delayed rewards are valued less and are thought to indicate increased impulsivity. The primary measure in the procedure developed by Evenden and Ryan [41] and used in the Cardinal et al. study is percent choice of the larger delayed alternative. The delay to the large alternative is set at zero at the beginning of the test session and is systematically incremented to 10, 20, 40 and 60 s during the session. Theoretically, the point at which the animals in the Evenden and Ryan procedure choose the delayed alternative 50% of the time is equivalent to the indifference point measure used in the adjusting amount procedure. However, it is notable that in the Cardinal et al. study no such indifference point was obtained because the lesioned animals chose the large alternative approximately 30% of the time even when it was not delayed. Whether this bias toward the immediate alternative was due to an “intolerance of delayed reward” or an inability to discriminate between varying delays and adapt behavior to changes in delay is debatable.

In support of their interpretation of the data, Cardinal et al. [42], subsequently, reanalyzed their data to include only those animals that chose the large reward at least 90% of the time when retrained with no delays to this option. When these selected animals were tested with varying delays in subsequent test sessions, steeper discount functions were obtained. However it was notable that the NAC lesioned animals still appeared to make fewer choices of the immediate large reward than control animals when the delays were varied. It is difficult to reconcile the Cardinal et al. interpretation of hypersensitivity to the effects of delaying reinforcement with the seeming insensitivity to the effects of delay observed in the present study. However, an inability to discriminate between varying delays and adapt behavior to changes in delay may explain both of these effects.

Both the findings of the present study and those of Cardinal et al. [13] could be the result of the NAC lesioned rats’ being less sensitive to changes in delay. In the present study, during the determination of the delay discount curve three shorter delays were added (0, 1, and 2 s) but only one longer delay was added (8 s). The lesioned rats may have formed an association that the delayed reward was now available sooner and adapted their behavior accordingly. However, in the Cardinal et al. study it appears that intact subjects preferred the large reinforcer over the smaller immediate reinforcer at 0 and 10 s and not the three other delays (20, 40 and 60 s). Consequently, lesioned animals in the Cardinal et al. study may have associated that the large reinforcer with an unappealing delay and consequently were biased away from this option.

While an insensitivity to changes in delays is a plausible explanation for the results of the present study as well as those observed by Cardinal et al. [13], it is necessary to consider other alternatives. It is possible that the NAC lesion did in fact make rats more tolerant to delays to reward, and that the 4 s delay used in phase 1 was simply not long enough to observe this effect. It is notable that a significant effect of delay was found only at 8 s in both the discount curve analysis and in the acute challenge data. This interpretation seems less likely because it would be completely opposite the results observed by Cardinal et al. [13], which used delays much longer than 8 s. Alternatively, as all the delays tested in the present study were shorter than those used by Cardinal et al., it is possible that we would

have observed different or even opposite effects had we tested animals on longer delays. Further studies with longer delays using the adjusting amount procedure will be needed to conclusively rule out these interpretations.

It is also important to emphasize that both the core and shell regions of the NAC were damaged in the present study while the Cardinal et al. study reported that only the core region was damaged. It cannot be ruled out that the additional NAC shell damage in the present study may have played a role in the results observed in the present study. However, a recent study by Pothuizen [43] reported no effect of shell lesions on preference for immediate uncertain versus delayed certain rewards, suggesting that the shell is not important for choosing between immediate and delayed reinforcement. Clearly further studies are needed to clarify these issues.

4.3. Supporting evidence for a role of the NAC in adapting to temporal contingencies

More evidence for a major role of the NAC in delayed reinforcement can be obtained from previous studies on the effects of NAC lesions on operant responding in rats [44–46]. NAC core lesions impaired the acquisition of responding for delayed but not immediate reinforcement [46]. In another study, NAC lesions prevented the increases in latency to resume responding on a progressive ratio schedule, as work requirements and consequently delay to reinforcement increased [44]. This finding is consistent with insensitivity to changes in delay to reinforcement. Finally, NAC lesions prevented decreases in run speeds that are normally observed when reinforcers were omitted on a T-maze [45], also suggesting insensitivity to changes in delayed reinforcement contingencies. These reports, considered in the context of the present study, suggest that the NAC may be important for adapting behavior in response to delayed consequences, when these relationships are initially learned or when contingencies of delayed reinforcement are changed.

Numerous electrophysiological and imaging studies on rodents, humans and non-human primates have implicated the NACas part of a neural circuit responsible for predicting delayed rewards [14–26]. The results of the present study provide strong behavioral evidence that the NAC is an essential part of this reward prediction circuit. The NAC may be necessary for precise temporal prediction of delayed rewards, although impaired temporal prediction would not necessarily increase or decrease delay discounting.

4.4. Potential implications

NAC dysfunctions could potentially be an important component in impulsive disorders. An intact NAC appears to be necessary for behavior to be well-governed by delayed reinforcement, not by differentially affecting the discounting of delayed rewards but by acting as part of the neural substrate for temporal associations. Therefore, dysfunctions in the NAC could be expected to lead to maladaptive behavior due to an impaired ability to learn the relationship between a behavior and delayed consequences.

Acknowledgments

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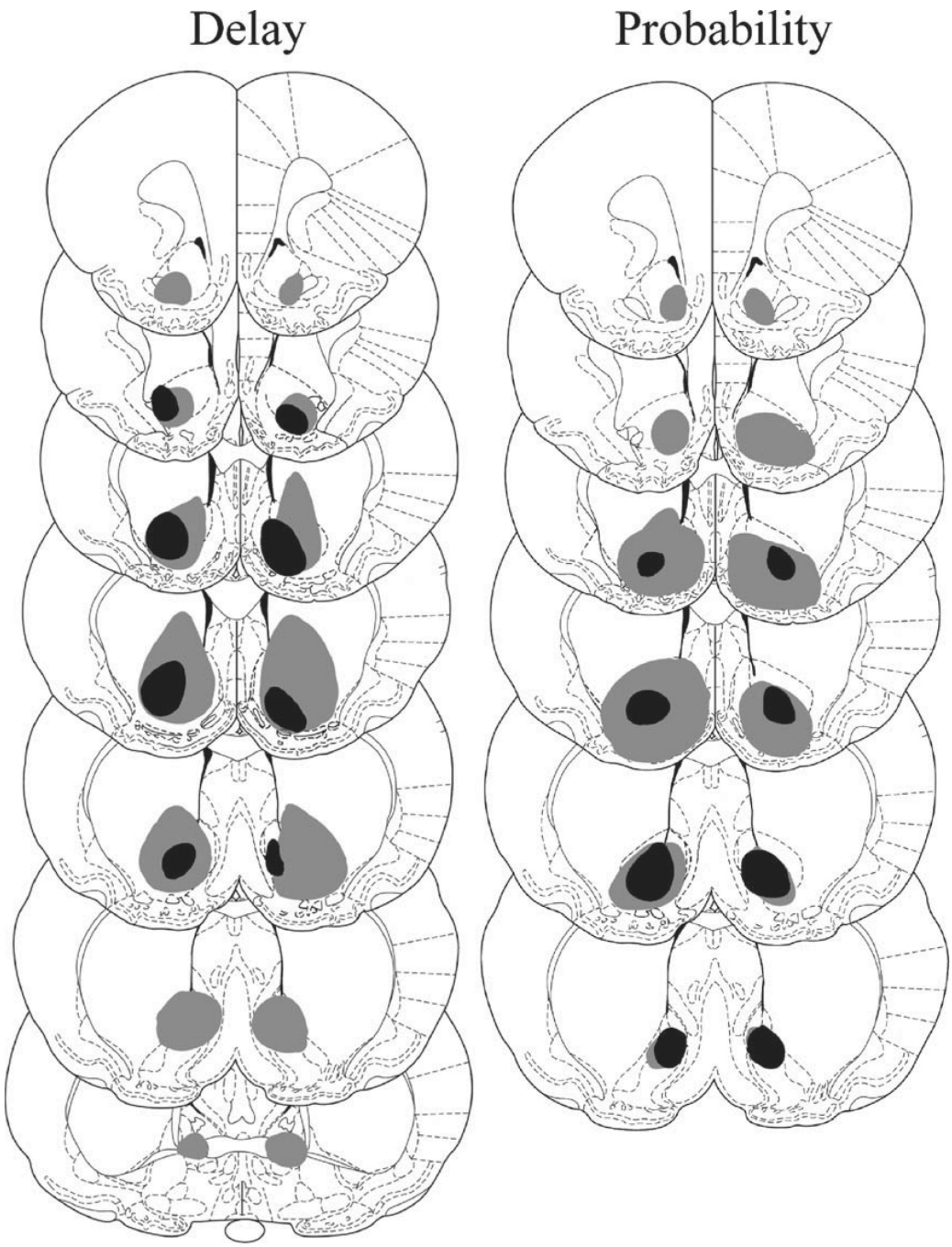

Fig. 1.

Histological reconstruction of the range of lesion damage. Grey area represents the rat with the largest lesion damage. Black area represents the rat with the smallest lesion damage. Left column—eight rats tested on delay discounting and included in the analysis. Right column—nine rats tested on probability discounting and included in the analysis.

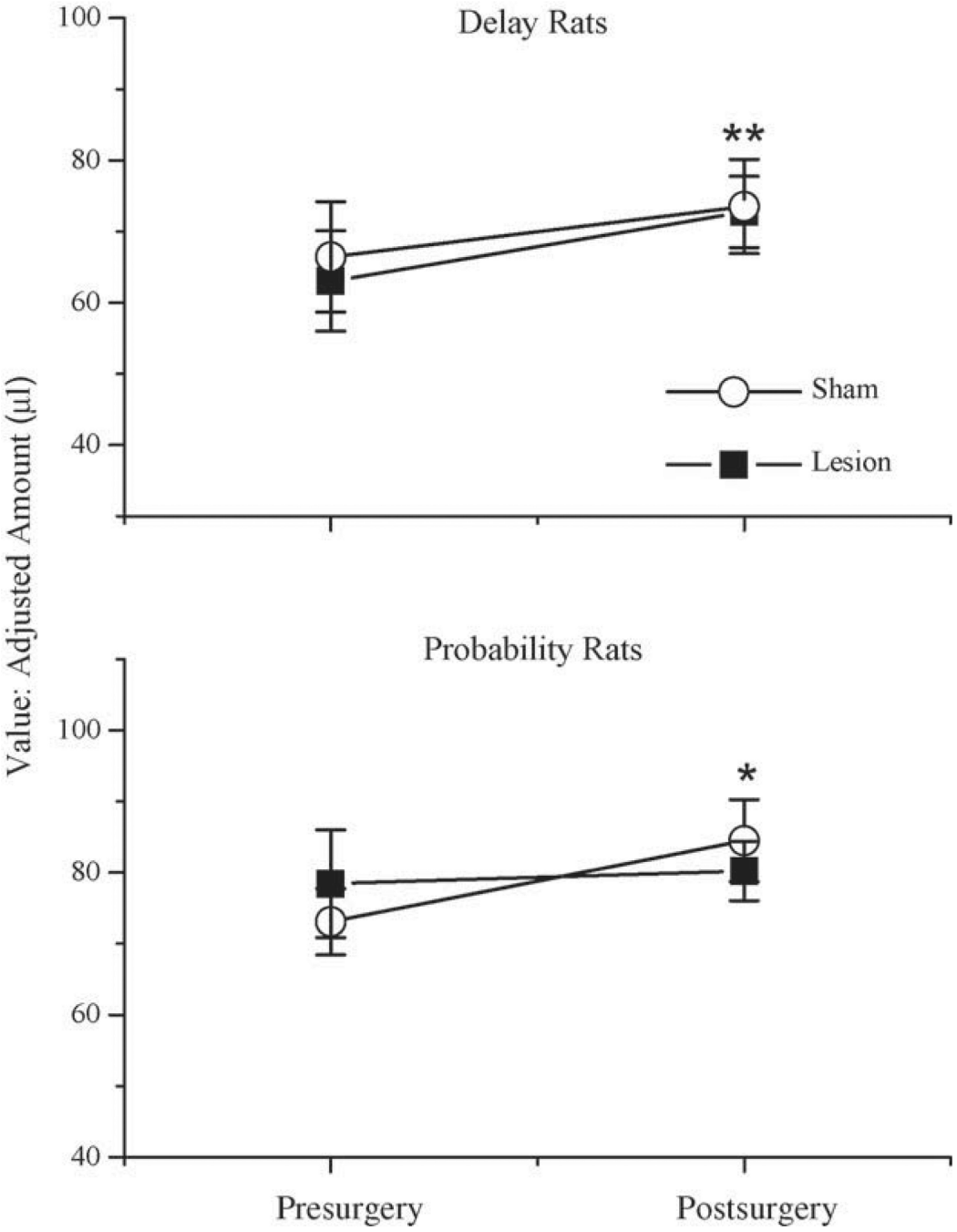

Fig. 2.

Indifference points for rats on delay discounting (upper panel) and probability discounting (lower panel) averaged across high and low start conditions for 10 days prior to surgery (5 days high start condition, 5 days low start) and the indifference points of the final 10 days of the 2 weeks of postoperative testing averaged across high and low start conditions (5 days high start, 5 days low start) for rats tested on delay discounting with a 4 second delay to the standard rein-forcer. There was a significant increase in indifference points in both sham and lesioned animals on delay discounting following surgery. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$.

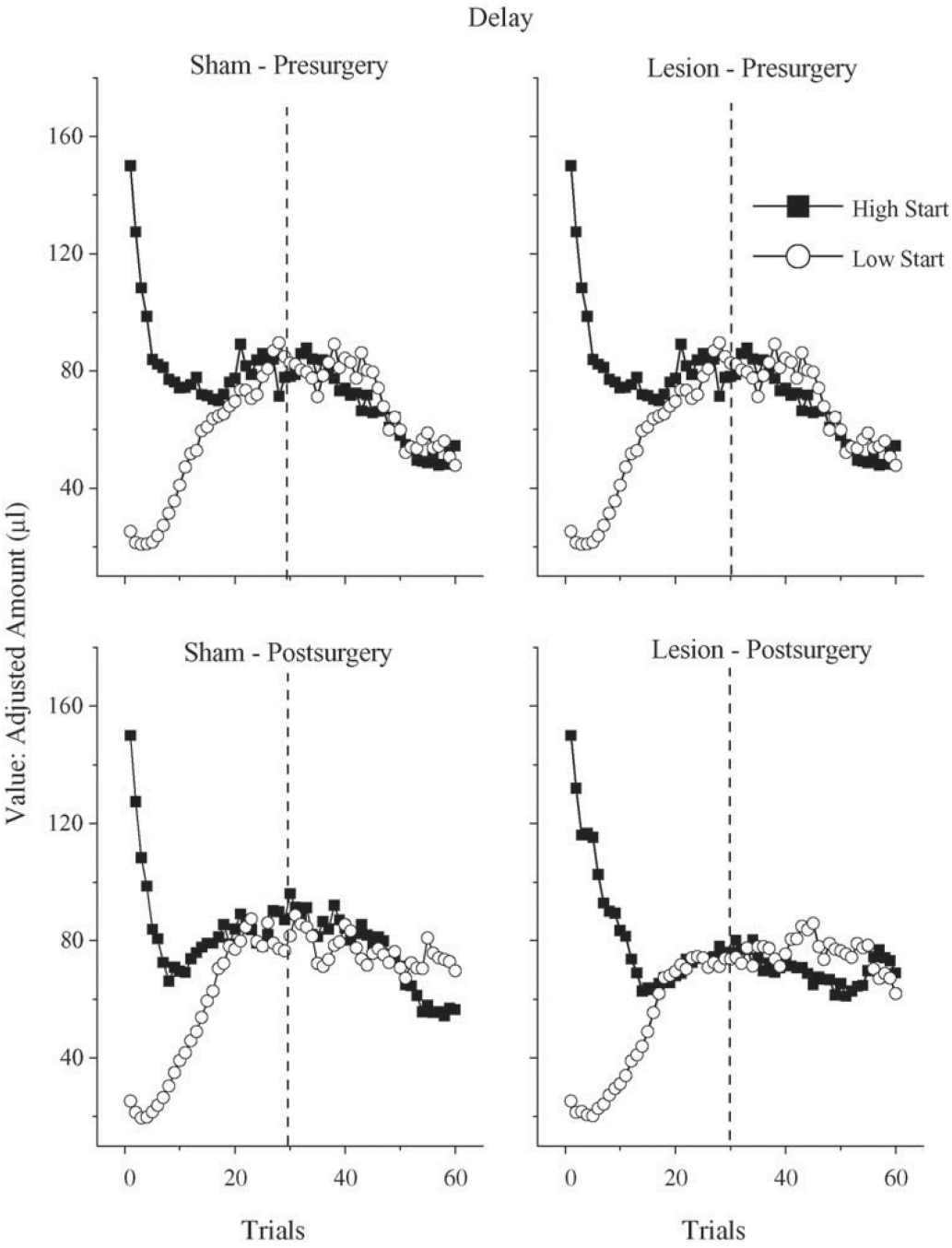

Fig. 3.

Determination of indifference points for rats tested on delay discounting before surgery (left columns) and post surgery (right columns) in shams (upper row) and lesioned rats (lower row). The dashed line indicates the point beyond which the median amount available on the adjusting alternative was used to determine indifference points. The same indifference points were reached whether the amount on the adjusting alternative is started at 25 µl or 150 µl both before and after surgery in both sham and lesioned rats.

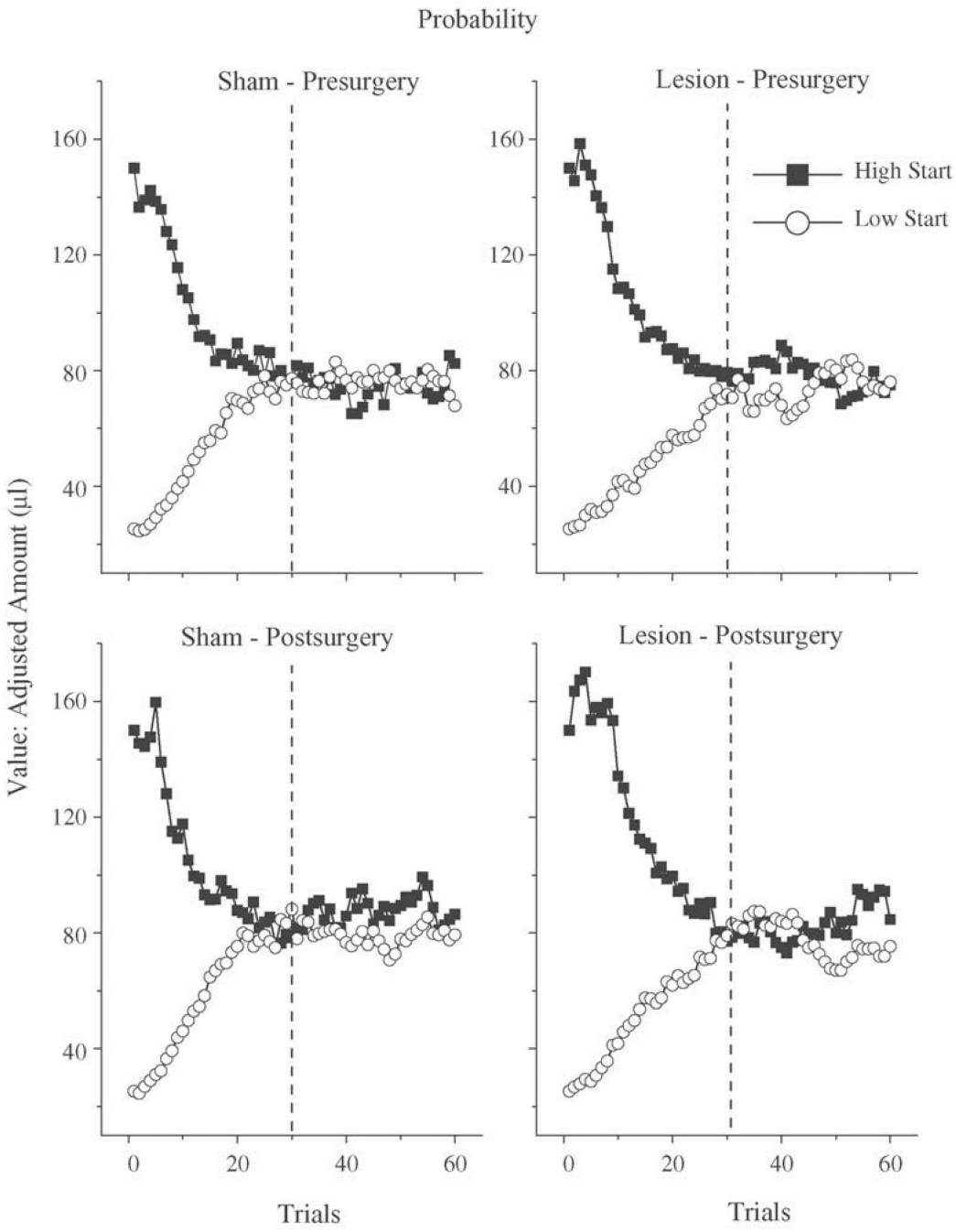

Fig. 4.

Determination of indifference points for rats tested on probability discounting before surgery (left columns) and postoperatively (right columns) in shams (upper row) and lesioned rats (lower row). The dashed line indicates the point beyond which the median amount available on the adjusting alternative was used to determine indifference points. The same indifference points were reached whether the amount on the adjusting alternative is started at 25 or 150 µl both before and after surgery in both sham and lesioned rats.

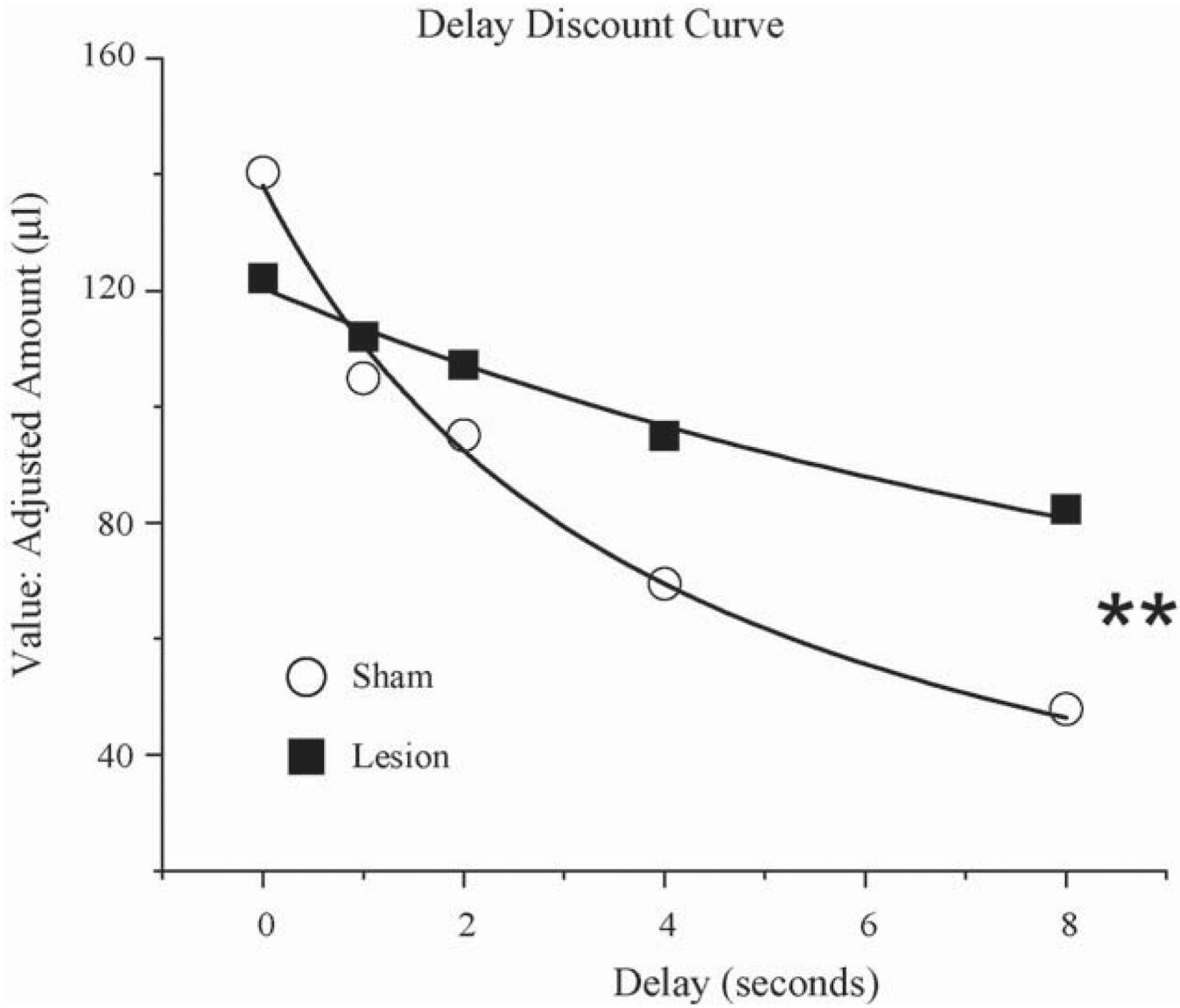

Fig. 5.

Median indifference point for rats tested with 0, 1, 2, 4, and 8 s delays to the standard reinforcer collapsed across high and low start conditions taken from the last month of the delay curve phase. Lesioned rats discounted less than shams. $^{**}p \leq 0.01$.

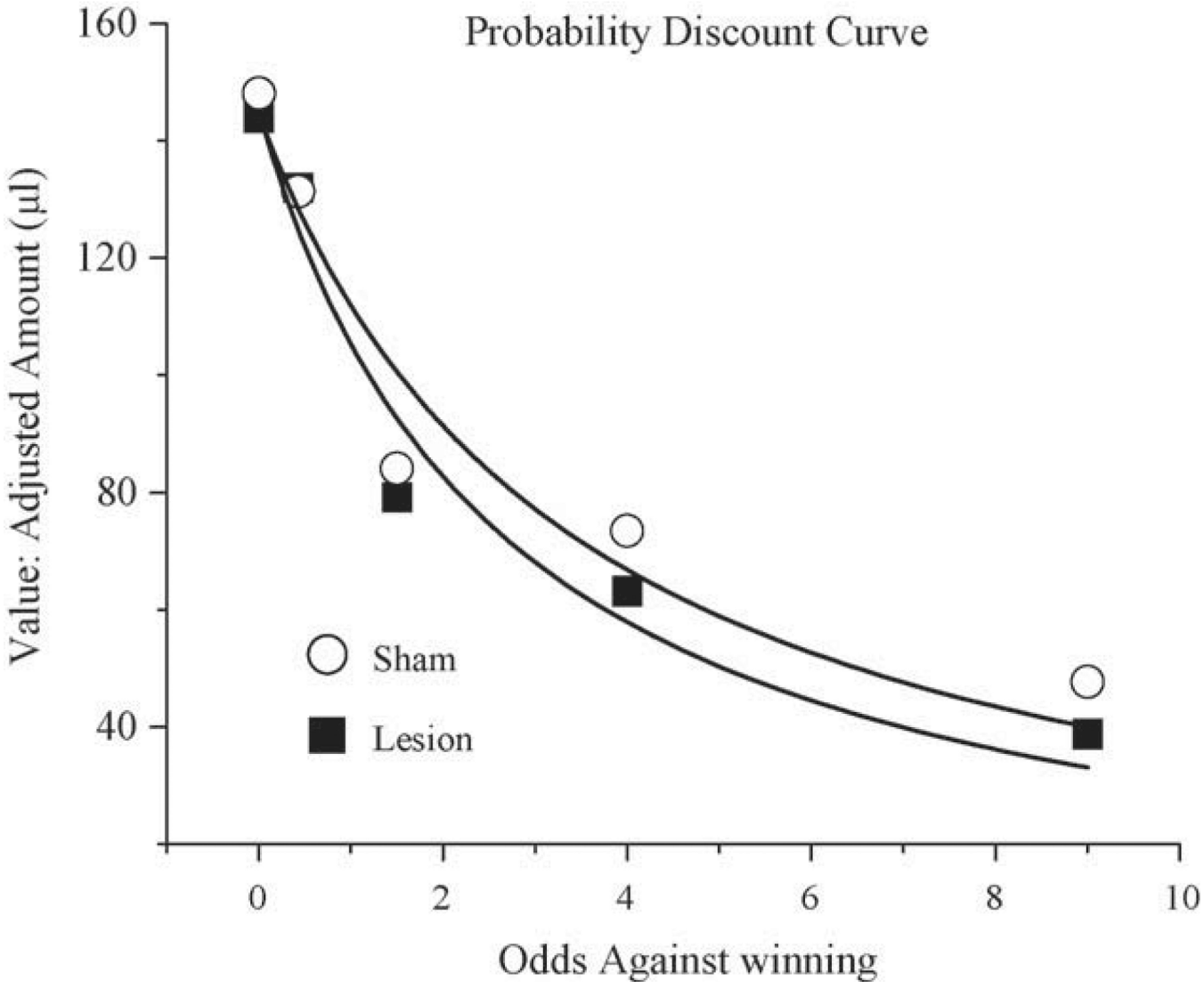

Fig. 6.

Median indifference points for rats tested with 1.0, 0.7, 0.4, 2.0, and 0.1. Probabilities of receiving the standard reinforcer, transformed as odds-against winning and collapsed across high and low start conditions taken from the last month of the probability curve phase.

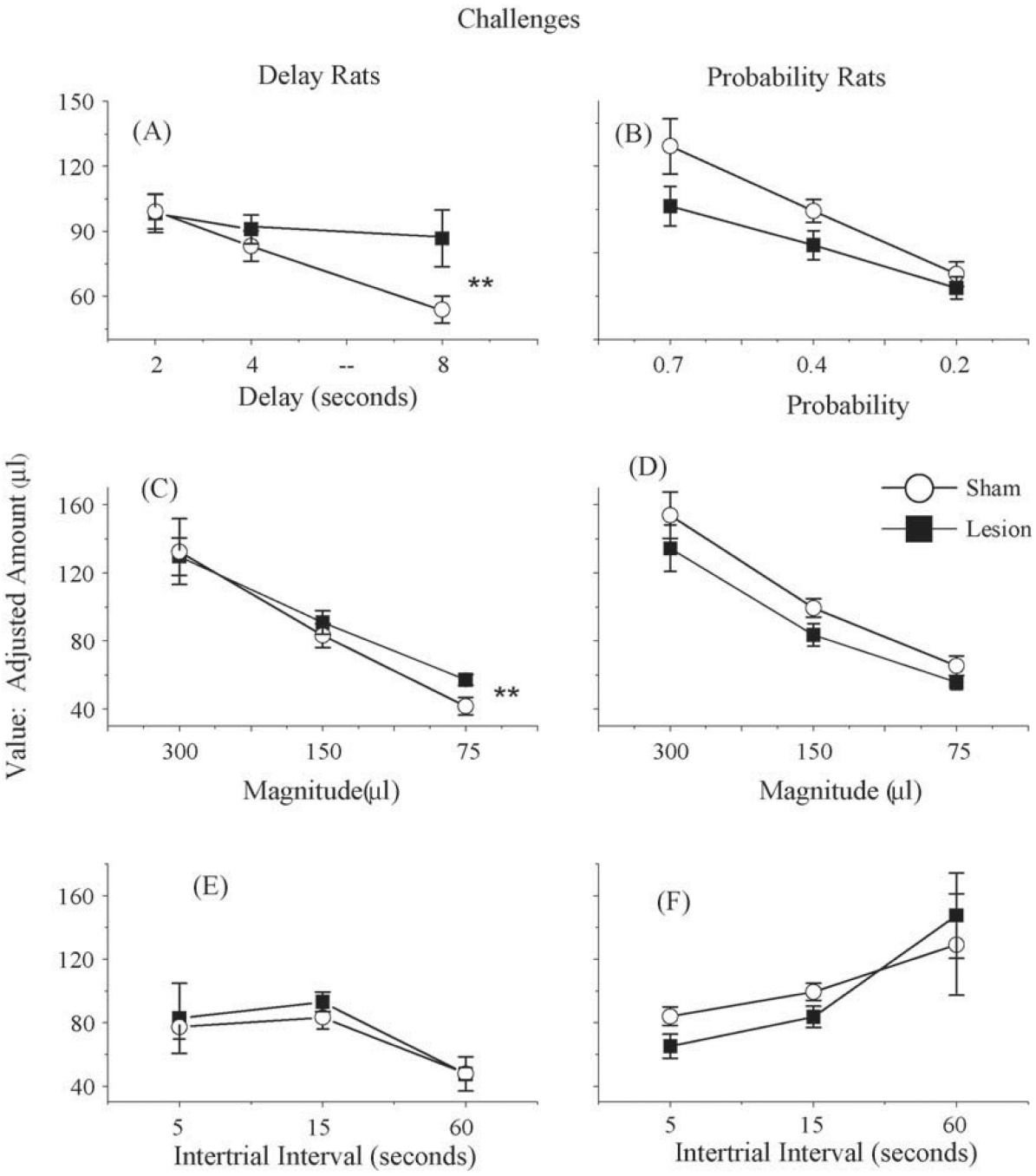

Fig. 7.

Parametric challenges. (A) Effects of challenging rats trained on delay discounting with a 4 s delay to the standard reinforcer with delays of 2 and 8 s on indifference points. Lesioned rats were significantly less responsive to the delay challenge than shams. (B) Effects of challenging rats trained on probability discounting with a 40% probability of receiving the standard reinforcer with probabilities of 20% and 70% on indifference points. (C) Effects of challenging rats on delay discounting with 75 and 300 µl delayed water rewards. Lesioned rats were significantly less responsive to the magnitude challenge than shams. (D) Effects of

challenging rats on probability discounting with 75 and 300 μl probabilistic water rewards. (E) Effects of challenging rats on delay discounting with ITIs of 5 and 60 s. Indifference points significantly decreased as ITI increased. (F) Effects of challenging rats on probability discounting with ITIs of 5 and 60 s. Indifference points significantly increased as ITI increased. $^{**}p \leq 0.01$.

Table 1

Average *k*, *b* and r^2 values determined from individual subjects' delay discount curves

	Delay discount curve		
	k	***b***	r^2
Sham	0.25 ±0.07[a]	0.96 ±0.07	0.86 ±0.04[a]
Lesion	0.12 ±0.05	0.92 ±0.08	0.63 ±0.10

[a] $p < 0.05$ significant between group difference.

Table 2

Average *h*, *b* and r^2 values determined from individual subjects' probability discount curves

	h	***b***	r^2
Sham	0.29 ± 0.04	0.97± 0.06	0.91 ±0.02
Lesion	0.48 ± 0.11	0.98± 0.06	0.88 ±0.03