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The Role of the Nucleus Accumbens Core in Impulsive Choice, Timing, and Reward Processing

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Abstract

The present series of experiments aimed to pinpoint the source of nucleus accumbens core (AcbC) effects on delay discounting. Rats were trained with an impulsive choice procedure between an adjusting smaller sooner reward and a fixed larger later reward. The AcbC-lesioned rats produced appropriate choice behavior when the reward magnitude was equal. An increase in reward magnitude resulted in a failure to increase preference for the larger later reward in the AcbC-lesioned rats, whereas a decrease in the larger later reward duration resulted in normal alterations in choice behavior in AcbC-lesioned rats. Subsequent experiments with a peak timing (Experiments 2 and 3) and a behavioral contrast (Experiment 4) indicated that the AcbC-lesioned rats suffered from decreased incentive motivation during changes in reward magnitude (Experiments 2 and 4) and when expected rewards were omitted (Experiments 2 and 3), but displayed intact anticipatory timing of reward delays (Experiments 2 and 3). The results indicate that the nucleus accumbens core is critical for determining the incentive value of rewards, but does not participate in the timing of reward delays.

Keywords

nucleus accumbens; impulsivity; delay discounting; timing; rats

Impulsive choice is often measured in the context of temporal discounting tasks, in which individuals are presented with choices between a smaller reward delivered after a shorter delay (the smaller sooner reward) and a larger reward delivered after a longer delay (the larger later reward). An over preference for the smaller sooner reward is viewed as indicative of poor self-control, or impulsive choice. A compelling interpretation of behavior in this paradigm is that impulsive choice emerges from a temporal discounting process, whereby the value of a reward is discounted over time (Mazur, 1987). If the temporal discounting rate is higher, then this will lead to a rapid decrease in reward value over time, and this in turn will cause an increased preference for more immediate rewards.

Temporal discounting has been frequently invoked to explain impulsive choice behavior in both humans (Dixon, Jacobs, & Sanders, 2006; Dixon, Marley, & Jacobs, 2003; Green, Myerson, & Ostaszewski, 1999a, 1999b; Johnson & Bickel, 2002) and nonhuman animals (Green & Estle, 2003; Ito & Asaki, 1982; Kobayashi & Schultz, 2008; Madden, Smith, Brewer, Pinkston, & Johnson, 2008; Mazur, 1987; Mazur, 2007a, 2007b; Rodriguez &

Logue, 1988). Higher discounting rates have been implicated in impulsive choice in gamblers (Dixon et al., 2006; Dixon et al., 2003), cigarette smokers (Bickel, Odum, & Madden, 1999), drug addicts (Kirby, Petry, & Bickel, 1999; Madden, Petry, Badger, & Bickel, 1997), and children with attention-deficit hyperactivity disorder (ADHD; Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Kuntsi, Oosterlaan, & Stevenson, 2001; Luman, Oosterlaan, & Sergeant, 2005; Schweitzer & Sulzer-Azaroff, 1995; Solonto et al., 2001; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Tripp & Alsop, 2001). Differences in discounting rates are also linked with higher levels of impulsive choice in pigeons (Mazur, 2005; Mazur, 2007b), and certain strains of rats (Madden et al., 2008).

The present set of experiments sought to examine the source of impulsive choice induced by nucleus accumbens core (AcbC) lesions. The nucleus accumbens (Acb) has been identified as a potentially key contributor to impulsive choice and temporal discounting for a number of reasons. The Acb is known to play an important role in regulating incentive motivation (Belin, Jonkman, Dickinson, Robbins, & Everitt, 2008; Olsson et al., 2006; Robbins & Everitt, 1996; Zhang, Balmadrid, & Kelley, 2003) and in sustaining goal-directed behavior (Carelli, 2004; Everitt & Robbins, 2005; Goto & Grace, 2005; Yun, Nicola, & Fields, 2004). In addition, the spontaneously hypertensive rat, a popular model of ADHD, suffers from abnormal dopamine release and gene expression in the Acb (Carey et al., 1998; Russell, 2000; Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1995, 1998). The mesocorticolimbic dopamine system, which projects to the striatum, nucleus accumbens, limbic areas, and frontal cortex appears to play an important role in ADHD, and overactivity in this system may contribute to the altered reward processing that has been associated with the disorder (Castellanos & Tannock, 2002; Johansen, Aase, Meyer, & Sagvolden, 2002; Sagvolden, Aase, Zeiner, & Berger, 1998). The AcbC is rich in the neurotransmitter dopamine that appears to play an important role in regulating clock and attention processes in interval timing (e.g., Buhusi, 2003; Maricq & Church, 1983; Meck, 1996) and amphetamine, a dopamine agonist, increases impulsive choice in a discounting paradigm (Cardinal, Robbins, & Everitt, 2000) in a similar manner to AcbC lesions. Finally, the Acb has been directly implicated in impulsive choice (Doya, 2008; Gregorios-Pippas, Tobler, & Schultz, 2009), with AcbC lesions resulting in increased preference for smaller sooner rewards in temporal discounting tasks (Bezzina et al., 2007; Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Winstanley, Theobald, Dalley, & Robbins, 2005).

Despite these links, little research has attempted to pinpoint the source of the Acb involvement in impulsive choice. Cardinal and colleagues (Cardinal et al., 2001; Cardinal, Winstanley, Robbins, & Everitt, 2004) suggested that the AcbC was critical for tolerating delays to reinforcement and Acheson et al. (2006) indicated that AcbC-lesioned rats could not adjust to changes in delays. Wakabayashi, Fields, and Nicola (2004) examined the effect of Acb dopamine depletion on a progressive delay task. Rats were required to produce a sustained response in the reward receptacle for a progressive delay that began at 0 s and incremented by 1.75 s until the rats reached a fail point. Infusion of a D1 receptor antagonist *R*-(+)-SCH23390 hydrochloride into the Acb had no effect on the fail point, suggesting that the Acb was not involved in the ability of rats to wait for the reward. These results would seem to conflict with the purported role of the AcbC in withstanding delays to reward. However wait time and effort were confounded in this study, so it is difficult to determine whether the effects were definitively due to delay tolerance. Meck (1996, 2006) found no evidence of any timing deficits in Acb-lesioned rats, but the rats could not determine the relative reward value of a signal. Specifically, the Acb-lesioned rats failed to show differential response rates to a short (10 s) versus long (60 s) signal, indicating that the 10-s delay to reward was not valued higher than the 60-s delay to reward. Thus, it seems that the Acb may play a role in reward value determination when delays are involved even though it does not seem to be directly implicated in timing of delays.

Because delay and reward magnitude are usually confounded in impulsive choice tasks, it is difficult to discern the possible sources of impulsive choice. Increases in impulsive choice could occur due to preferences for shorter delays, which could emerge from deficits in delay perception or due to problems in waiting for longer durations. Alternatively, impulsive choice could emerge due to a failure to prefer the larger amount or a failure to discriminate amounts. Finally, differences in choice patterns could be due to a more general reward discounting deficit, whereby the delay and amount information are incorrectly integrated. Thus, as a starting point, one needs to begin to isolate the source of differences in impulsive choice by separately testing control by delays and amounts (Roesch, Calu, & Schoenbaum, 2007).

The present set of experiments sought to assess the effect of AcbC lesions on impulsive choice using a discounting choice procedure (Experiment 1), a peak timing procedure (Experiments 2 and 3), and a reward magnitude contrast procedure (Experiment 4). Changes in the delay to reward and magnitude of reward were conducted separately to attempt to isolate the source of AcbC lesion effects on impulsive choice.

Experiment 1

Previous procedures using a choice between two opposing schedules of reinforcement have tended to comprise a small fixed magnitude reward available immediately versus a larger reward that varies in delay over trials (e.g., Cardinal et al., 2001; Mazur, 1987; Rodriguez & Logue, 1988). This type of adjusting delay procedure is effective for discounting functions to be determined, but it is not possible to measure timing of the delay to reward in this procedure as the small reward usually occurs after zero delay and the delay to the larger reward changes regularly.

The present experiment sought to implement a different procedure for studying impulsive choice, timing, and reward processing all within the context of the same procedure in AcbC-lesioned rats. Rats were given a choice between a small reward that was available after a progressive-interval (PI) schedule and large reward that was available after a fixed-interval (FI) schedule (Hackenberg & Hinson, 1992). The reward magnitude on the PI remained constant but the delay to reward increased as a function of the successive PI choices. The FI was the anchor in this task and the PI was the comparison. Keeping the FI schedule constant over several successive sessions allowed for the insertion of nonreinforced peak trials to determine the temporal behavior of the rat. By the addition of occasional peak trials, it was therefore possible to assess timing on the FI lever within the context of the impulsive choice task. The peak trials allow measurement of response rates both prior to and following the usual time of food delivery. Typically in peak trials, response rates increase up to and peak around the usual time of reward and then gradually decrease after the expected time of food has passed. In addition to measuring choice and timing behavior, Experiment 1 sought to assess the effect of between-session changes in FI reward magnitude and FI duration on choice behavior to determine the AcbC involvement in sensitivity to reward magnitude and delay.

Method

Subjects—The animals were 12 male hooded Lister rats (Harlan, United Kingdom) approximately 12 weeks old and with a mean ad libitum weight of 309 g (range = 300 – 350 g). Prior to experimental testing and surgery the rats' weights were reduced to 85% of their original ad libitum weight by restricted feeding of 10 g of standard laboratory chow per day (Lab Diet, 2002, IPS, United Kingdom). After surgery, each rat was maintained on a restricted diet of 20 to 25 g during the postsurgery recovery period. This was reduced to 15 g per rat during experimental testing. During the experiment, the rats gained approximately 10

g per week through controlled feeding until normal adult weights under restriction were reached and then maintained. The rats were housed in pairs with free access to water in a vivarium that was maintained on a 12-hr light–dark cycle. The majority of the experimental testing was carried out during the dark portion of the cycle.

Apparatus—All phases of the experiment were conducted in a set of 12 operant chambers (Med Associates, Vermont). Each of the 12 chambers measured 25 × 30 × 30 cm and was housed inside of a ventilated, noise attenuating box measuring 74 × 38 × 60 cm. The chambers were located in two separate rooms, with six chambers in each room. Each chamber was equipped with a speaker for delivering auditory stimuli, two levers, a house light, a food cup, and a water bottle. The speaker was located on the right side of the back wall of the chamber, on the opposite wall from the food cup. The house light was positioned in the top center of the back wall. Two retractable levers (ENV–122CM, Med Associates, Vermont) were situated on either side of the food cup at approximately one third of the total height of the chamber; lever presses were recorded by a microswitch. A magazine pellet dispenser (ENV–203, Med Associates, Vermont) delivered 45-mg food pellets (MLab rodent tablet, TestDiet, Richmond, IN) into the food cup. Each head entry into the food cup was transduced by an LED photocell. The water bottle was mounted outside the chamber; water was available through a metal tube that protruded through a hole in the lower center of the back wall. Med-PC for windows (Tatham & Zurn, 1989), running on two Pentium III 800-mHz computers (one for each set of six chambers), controlled experimental events and recorded the time of events with a 2-ms resolution.

Procedure

Surgery: Six rats (AcbC-lesioned) received neurotoxic lesions of the AcbC using 0.09 M quinolinic acid; a further six rats (sham control) received a sham control lesion. Quinolinic acid was used as it effectively destroys cells within the AcbC, while largely sparing the nucleus accumbens shell (AcbS; Parkinson, Olmstead, Burns, Robbins, & Everitt, 1999).

Each rat was anesthetized using 4% Halothane, delivered in O₂ and N₂O gas (approximately 1 L/min of each) in an induction chamber (IMS Ltd., United Kingdom). Following induction (approximately 3 min) the chamber was scavenged of Halothane. The rat was then placed on a stereotaxic frame (Stoelting, Inc, Kiel, WI). Anesthesia was maintained with delivery of 2% halothane in O₂ and N₂O gas (approx 0.8 L/min of each), delivered through a facemask (IMS Ltd., United Kingdom). The depth of anesthesia was monitored by assessing the pedal withdrawal reflex and mild tail pinch response.

A 1.5-cm incision was made along the top of the skull and then the skin was parted to reveal bregma. Burr holes were drilled in the skull above the lesion site using a dental hand piece (QuDent, United Kingdom) mounted on the stereotaxic frame. One infusion per side was made using a 30-gauge needle (SMS) attached by polythene tubing to a 1- μ l SGE syringe, which was controlled by an infusion pump (Harvard). The infusions were made at the following coordinates relative to bregma: lateral $\pm$ 1.8 mm; anterior-posterior + 1.2 mm; ventral –7.1 mm. Each infusion was made over the course of a 4-min period, and then the needle was left in place for an additional 2 min to allow the neurotoxin to diffuse. Following the infusion, the skin was closed with suture. The rats were returned to the vivarium after a period of observed recovery and allowed to rest for a minimum of 14 days prior to recommencing experimental testing.

The sham control procedure was identical except no neurotoxin was delivered during the infusion stage.

Pretraining: Prior to surgery, all rats received one session of pretraining consisting of an introductory adaptation period of 30 min and then four training blocks with a 90-min break between blocks. In the first block, the rats received 40 single-pellet food deliveries on a variable time (VT) 180-s schedule. The second block comprised four subblocks within which the rats received a one-pellet food delivery for each lever press (continuous reinforcement; CRF). Both left and right levers were trained independently in alternating blocks for a total of 15 food deliveries per subblock. The remaining two blocks followed a similar structure; however, delivery of food followed a variable ratio schedule with a mean of three and five lever presses per food delivery, respectively, and with 10 food deliveries per subblock.

PIFI choice procedure, presurgery baseline: Prior to surgery, the rats received 30 sessions of training on the PIFI choice procedure to ensure any deficits in learning the basic task were not contributing to the results postsurgery. Sessions lasted until 220 food pellets had been delivered, or for a maximum of 14 hr, whichever occurred first. Each session was split into four blocks. There was an initial adaptation period of 30 min prior to the start of the first block and a 90 min interval between each block. Each block contained 22 PIFI choice trials and a maximum of two peak trials. The intertrial interval (ITI) was 120 s.

Figure 1 displays the structure of the individual PIFI trials. Each trial began with the insertion of both levers. The rat was then allowed to make a choice by depressing one of the levers. This led to the immediate withdrawal of the other lever and initiation of the schedule of reinforcement on the chosen lever. Once the FI or PI duration had timed out, food was primed and the next lever press resulted in the withdrawal of the lever, food delivery, and the initiation of the ITI. The prime was not signaled in any way to the rat. The delay to reinforcement on the PI lever began at 0 s at the start of a block and increased with each consecutive PI choice in increments of 15 s; the reward on the PI lever was a single food pellet. An FI lever choice resulted in a delay of 60 s until a single food pellet was primed and also reset the PI to 0 s. Although the rat could potentially reset the PI after each trial, they would have to wait through the 60-s FI and the 120-s ITI before the next opportunity for a 0-s PI trial. The reset of the PI duration was signaled by briefly inserting and withdrawing the PI lever at the beginning of the following PIFI choice trial. The allocation of the PI and FI schedules to the left and right levers was counterbalanced and remained consistent for each rat throughout the experiment.

Nonreinforced peak trials were intermixed with the PIFI trials. The peak trials occurred after the second and fourth choice of the FI lever in each subblock. On peak trials, the FI lever was inserted and responses were recorded for 180 s. The lever was then withdrawn and an ITI was initiated. There were no food deliveries during peak trials.

PIFI choice procedure, postsurgery baseline: Following recovery from surgery, all rats were re-exposed to the PIFI choice procedure from the presurgery phase with a 60-s FI duration, a 15-s incremental PI, and a single food pellet delivery on both levers. The postsurgery baseline phase lasted for 20 sessions.

PIFI choice procedure, FI reward magnitude manipulation: During the FI reward magnitude manipulation, the reward on the FI lever increased to four food pellets. All other aspects of the procedure were the same as during the baseline phases. The reward magnitude manipulation phase lasted for 27 sessions.

PIFI choice procedure, FI duration manipulation: During the FI duration manipulation, the FI duration was reduced to 30 s and the peak trials were reduced to 90 s for 20 sessions.

The reward magnitude on the FI remained at four pellets. All other aspects of the PIFI procedure remained the same as in the previous phases.

In all phases, the decision to progress to a new phase occurred when the mean group choice performance during the previous phase varied by less than 20% over three subsequent sessions. One rat from the sham control group was removed from the study due to a failure to learn the original baseline task.

Histology—After the completion of behavioral testing, the animals were anesthetized with a lethal overdose of sodium pentobarbital (Euthatal, 1 ml ip, per animal) and perfused via the ascending aorta with 0.1 M phosphate buffered saline pH 7.4, followed by 4% paraformaldehyde. The brains were then removed and postfixed in 4% paraformaldehyde solution before being transferred into 20% sucrose solution. The brains were frozen using CO₂, before coronal sections (60 μ m) were cut on a freezing microtome throughout the full extent of the lesioned area. Every second section was taken and mounted on a gelatin coated glass slide, and then stained with cresyl violet. Slides were cover slipped, dried, and then examined under a microscope to assess the extent and nature of neuronal damage. Areas of neuronal loss were mapped onto standardized sections of the rat brain (Swanson, 1998), without reference to the behavioral data.

Data analysis—All analyses were conducted on the last five sessions of each phase.

Change-over time: Change-over time was calculated as an index of indifference between the two choices and was determined by the duration of the PI during the trial before an FI choice reset the PI schedule.

Delay discounting: The hyperbolic value addition (HVA) model (Mazur, 2001) was used to determine the delay discounting rate for the FI schedule: $V_d = \frac{A}{1+kD}$, where V_d is the discounted value of the reward as a function of delay, A is the undiscounted value of the reward, D is the delay to reward, and k is the discounting rate. We calculated k by setting the value of A according to the magnitude of reward on the FI schedule (0.1 or 0.4 representing the one and four pellet rewards) and D according to the delay to reward on the FI schedule (30 or 60 s). Also, k_{FI} was taken at the point that the value of the FI (V_{FI}) and the value of the PI (V_{PI}) was equal to the observed change-over time (the crosspoint of the FI and PI discount functions).

Response rate functions: The response rate in responses per minute as a function of time was determined by computing the frequency of responses in successive 5-s bins during each trial and summing those frequencies across trials. The frequency of response in each bin was divided by the total number of trials included in the analysis to give a metric of responses per second and then finally multiplied by 60 produce a metric of responses per minute.

Single-trial analysis: Responding on individual peak trials is typically characterized by a low-high-low pattern, in which responding early and late in the trial is characterized by a low rate, but responding around the expected time of reinforcement is characterized by a high rate. To identify high-rate periods of responding, a low-high-low analysis was conducted on each peak trial (Church, Meck, & Gibbon, 1994; Galtress & Kirkpatrick, 2009). This involved an exhaustive search for the best fitting low-high-low model that maximized the value of the index: $A = d_{L1}(r - r_{L1}) + d_H(r_H - r) + d_{L2}(r - r_{L2})$, where r was the mean response rate over the whole trial and r_{L1} , r_H , and r_{L2} were the response rates in the first low, the high, and the second low states, respectively, and d_{L1} , d_H , and d_{L2} were the durations of those states. The only constraint on the analysis was that the end time had to be

later than the start time, and that the $\mathcal{R}^2$ (metric of the goodness of fit of the low-high-low model to the data) for the trial had to exceed 0.05. This latter constraint was to remove trials in which the rat did not exhibit a clear response burst, which is indicative of poor temporal control over behavior. The time of the transition from a low to high rate was recorded as the start (s) time and the time of the transition from a high to low rate was recorded as the end (e) time, respectively. The high state duration (d) was determined as $e - s$ and the middle time was $s + (d/2)$. The response rate in the high state was the number of high state responses divided by the high state duration.

Statistical analyses: All statistical analyses were conducted in SPSS (v 16). Greenhouse–Geisser corrections were conducted where necessary. The criterion for significance was set at $p < .05$ in all cases. Specific F - and t -test values are only reported for significant results.

Results

Histology—Histological analysis revealed that all six AcbC-lesioned rats had extensive bilateral damage to the AcbC whereas the AcbS and surrounding areas remained intact. All five sham control rats had intact AcbC and AcbS areas. As such all six AcbC-lesioned and all five sham control rats were included in the analysis. Figure 2 provides photomicrographic representation of a sham control (top left panel) and an AcbC-lesioned (bottom left panel) brain section and displays the extent of the smallest and largest AcbC lesions (right panel).

Change-over time

FI reward magnitude manipulation: Figure 3 displays the change-over time for the AcbC-lesioned and sham control rats as a function of phase. During the postsurgery baseline phase, change-over times were near 60 s in both groups, which is the expected result given that both the FI and PI choices were yielding only a single pellet. A change-over time of 60 s would produce local maximizing of reward earning rates. A one-sample t test performed separately on each group indicated that the change-over times did not differ significantly from 60 s. A comparison of the postsurgery baseline phase (60S–1P) and the FI reward magnitude manipulation phase (60S–4P) indicates that both groups displayed a decrease in change-over time during the shift from one to four pellets, but the decrease was much larger in the sham control rats. An analysis of variance (ANOVA) was conducted with the variables of group (lesion vs. sham) and magnitude (one vs. four pellets). This revealed a significant effect of magnitude, $F(1, 9) = 20.5$, and a Magnitude $\times$ Group interaction, $F(1, 9) = 5.3$. Tukey's post hoc tests on the interaction indicated that there was a significant shift in change-over times in the sham control group when the reward magnitude increased, but not in the AcbC-lesioned group. Moreover, the two groups differed significantly during the reward magnitude manipulation (60S–4P), but not during the baseline phase (60S–1P).

FI duration manipulation: The change in FI duration from 60 s to 30 s appeared to have an effect in both groups (see Figure 3, 60S–4P vs. 30S–4P). An ANOVA with the variables of group and duration revealed only a significant main effect of duration, $F(1, 9) = 18.2$, indicating that the decrease in FI duration resulted in an increased preference for the FI lever in both groups. There was a trend toward a significant group difference, but this did not reach statistical significance.

Delay discounting

FI reward magnitude manipulation: Figure 4 displays the computed discounting rate (see Data Analysis section) for the two groups of rats as a function of phase. The shift from one to four pellets (60S–1P vs. 60S–4P) resulted in a large increase in the discounting rate in the

AcbC-lesioned rats, but a much smaller increase in the discounting rate in the sham control rats. An ANOVA revealed significant effects of magnitude, $F(1, 9) = 17.8$, and Magnitude $\times$ Group, $F(1, 9) = 5.3$. Tukey's post hoc tests revealed that the discounting rate in the AcbC-lesioned group increased significantly when the reward magnitude increased, but the discounting rate did not change in the sham control group. Moreover, the groups differed during the reward magnitude manipulation (60S–4P) but not during baseline (60S–1P).

FI duration manipulation: The discounting rate remained stable in both groups when the delay to reinforcement on the FI schedule was reduced from 60 to 30 s (Figure 4, 60S–4P vs. 30S–4P). This pattern was verified by an ANOVA that revealed only an effect of group, $F(1, 9) = 5.7$, which reflected the difference that emerged in the FI reward magnitude manipulation and was maintained during the FI duration manipulation.

Response rate functions—Figure 5 displays the peak response functions during the FI reward magnitude (60S–1P vs. 60S–4P) and duration (60S–4P vs. 30S–4P) manipulations for both the sham control (top panel) and AcbC-lesioned (bottom panel) rats. The increase in reward magnitude resulted in a leftward shift in the location of the peak coupled with an increase in response rate in the sham control rats. The decrease in FI duration shifted the function further to the left. For the AcbC-lesioned rats, the reward manipulation had little or no effect on the response function, whereas the decrease in FI duration produced a leftward shift in the response function.

Single-trial analysis

FI reward magnitude manipulation: Figure 6 shows the start time, middle time, end time, the high state duration, and the high state response rate for both groups of rats during peak trials as a function of phase of training. In examining the effect of the reward magnitude manipulation (60S–1P vs. 60S–4P), it appears that the increase from one to four pellets produced a slight decrease in start, middle, and end times, and a slight increase in high state response rate, particularly in the sham control rats. This was also seen in the response rate functions in Figure 5 in which the response rate increased and the peak sharpened and moved earlier. In addition, the AcbC-lesioned rats displayed later end times and longer high state durations in both 60S–1P and 60S–4P phases (see also Figure 5 in which the peak functions are flatter on the right side in the AcbC-lesioned group). Separate ANOVAs were conducted on each of the five measures of the peak with the variables of magnitude and group, revealing the following: there was a significant effect of group, $F(1, 9) = 8.7$ on the end times, and on the high state duration, $F(1, 9) = 15.6$, and there was a significant effect of magnitude, $F(1, 9) = 5.4$, on the high state response rate. There were no significant group or magnitude effects on the start times or middle times.

FI duration manipulation: The FI duration manipulation (60S–4P vs. 30S–4P) produced stronger effects on the timing of the high state response burst in both groups, consistent with the changes that were observed in the response rate functions (see Figure 5). The start, middle, and end times decreased in both groups, and the high state duration decreased. These trends were verified by an ANOVA including the variables of duration and group. There was a significant effect of duration on start times, $F(1, 9) = 79.1$, and middle times, $F(1, 9) = 289.1$. The analysis of end times revealed effects of duration, $F(1, 9) = 565.5$, group, $F(1, 9) = 17.3$, and Duration $\times$ Group, $F(1, 9) = 10.3$. The interaction was due to a significant group difference during the 60S–4P phase, but not during the 30S–4P phase. The same pattern was seen in the high state duration analysis: duration, $F(1, 9) = 396.3$, group, $F(1, 9) = 60.3$, Duration $\times$ Group, $F(1, 9) = 17.4$. Again, the interaction was due to the convergence of the two groups during the 30-s FI condition. There were no effects of FI duration on the high state response rate.

Discussion

For the sham control rats, change-over time decreased in response to the shift from one to four pellets on the FI schedule (see Figure 3), leading to a stable delay discounting rate (see Figure 4). This is the expected pattern from rats sensitive to an increase in reward magnitude. However, the AcbC-lesioned rats displayed a different pattern of behavior. Their willingness to increment the PI lever; although initially the same as the sham control rats, was not significantly altered by the shift in reward magnitude on the FI lever (see Figure 3). As a result, the AcbC-lesioned rats failed to maximize reward intake and instead earned fewer rewards than the sham controls due to their persistence in responding on the PI lever. As the discounting rate calculation is determined by absolute reward magnitude, the failure to adjust choice behavior led to an increase in discounting rate when reward magnitude was increased (see Figure 4). This increase in delay discounting, and therefore a relatively enhanced preference for the smaller reward when compared to sham controls, is consistent with previous research (Bezzina et al., 2007; Cardinal et al., 2001; Cardinal et al., 2004), but in terms of performance, the AcbC rats' behavior did not change and as such could reflect a lack of sensitivity to the increase in reward magnitude.

During the shift from an FI 60-s to an FI 30-s schedule, changeover times decreased and discounting rates remained stable in both the AcbC-lesioned and the sham control rats. This suggests that there is sufficient change in value through the reduction of the FI duration to induce a change in choice behavior and so the preference for the PI lever was reduced. The change in the behavior of both the AcbC-lesioned and the sham control rats indicates that both groups were sensitive to the decrease in the delay to reinforcement. The change-over time in the AcbC-lesioned rats during the 30S–4P phase was consistent with what would be expected from 30-s FI, but with a one-pellet reward. This further indicates that the AcbC-lesioned rats did not appropriately value the FI reward following the magnitude increase.

The intact sensitivity to reward delay in the AcbC-lesioned rats is further evidenced by the temporal measurements taken from the FI peak trials throughout the experiment. Both the sham controls and the AcbC-lesioned rats showed a decrease in the start, middle, and end times and duration of the high response state as a result of the shift from the FI 60-s to the FI 30-s schedule. The present experiment suggests that AcbC-lesioned rats are not intrinsically impulsive and that increased delay discounting in these rats is a result of a lack of sensitivity to reward magnitude whereas the sensitivity to temporal cues remains intact.

However, one possible alternative explanation for the failure to shift behavior under the reward magnitude change may have been due to dynamics of the choice situation and not to a lack of sensitivity to reward magnitude. For example, the lesion rats may have shown stronger perseveration of responding on the PI schedule in the reward magnitude manipulation phase and this might then have reduced their ability to learn about the reward increase on the FI schedule. However, this argument does not explain the shift in choice behavior demonstrated by the AcbC-lesioned rats when the FI duration decreased. Moreover, the increased high state response rate as a result of the magnitude increase in both the AcbC-lesioned and sham control rats would suggest that there is some sensitivity to magnitude, although this did not result in altered choice behavior in the AcbC-lesioned group. A second possibility is that the AcbC-lesioned rats might have experienced more generalization between the FI and PI choices, which would have decreased their sensitivity to changes on the FI schedule. Because the reward magnitude manipulation occurred first, and then the FI duration manipulation, the reward magnitude manipulation might have been more susceptible to the effects of generalization across schedules. If the AcbC-lesioned rats demonstrated more perseveration of generalization across the schedules, then this would have affected the initial reward magnitude manipulation more strongly than the duration manipulation. The sham group also appears to have generalized across the schedules in the

first phase given their poor timing of the FI duration (see Figure 5), so it is clear that generalization was a factor in the experiment.

Both of the above concerns indicate that it is essential to examine sensitivity to reward magnitude and delay to reward outside of the more complex choice environment. Experiment 2 will examine sensitivity to magnitude and timing in a simpler single-response paradigm, the peak procedure.

Experiment 2

The peak procedure (Roberts, 1981) is commonly used to measure timing behavior. This procedure involves training on a discrete-trials FI schedule in which the first instrumental action (e.g., lever press or nose poke) after a target interval results in food delivery. Intermixed with these FI trials are nonreinforced peak trials, typically three or four times the length of the FI duration. The peak procedure is virtually identical to the procedure delivered on the FI lever in Experiment 1, but in the absence of any alternative choice.

The present experiment used the peak procedure to measure the timing behavior of AcbC-lesioned rats when required to wait 60 s for a single food pellet. This reward was then increased to four pellets and then subsequently the FI duration was decreased to 30 s. Thus, the same manipulation as Experiment 1 was conducted, but in the absence of the alternative PI choice. The responding of the AcbC-lesioned rats was then compared against sham controls to assess whether the AcbC-lesioned rats remained sensitive to changes in the delay to reward, but not to changes in reward magnitude. The peak procedure also allowed for more precise measurement of timing responses due to the usage of a single interval, and avoided any problems with generalization between the two options.

Method

Subjects—The animals were 24 male hooded Lister rats (Harlan, United Kingdom) approximately 12 weeks old prior to surgery and with a mean ad libitum weight of 333 g (range = 310–375 g). Other aspects of housing and husbandry were as Experiment 1.

Apparatus—The apparatus were identical to Experiment 1.

Procedure

Surgery: Twelve rats (AcbC-lesioned) received neurotoxic lesions of the AcbC using 0.09 M quinolinic acid; the other 12 rats (sham control) received a sham control lesion. All aspects of the surgical procedure were identical to Experiment 1. In this case the surgery was carried out prior to any experimental training.

Pretraining: All rats were given magazine and instrumental lever training prior to the implementation of the peak procedure. Magazine training involved one-pellet food deliveries on a VT 60-s schedule. Instrumental lever training was carried out over 3 days. Day 1 consisted of a CRF schedule. On Days 2 and 3, food deliveries occurred on a variable interval (VI) 15-s and VI 30-s schedule, respectively, with the first lever press after the variable interval resulting in food delivery. All rats received 30 one-pellet food deliveries per session. Each rat was randomly assigned to receive either the left or right lever throughout training and testing.

Peak procedure training: In Phase 1, the rats were given initial peak procedure training on an FI 60-s schedule resulting in the delivery of a single food pellet following each FI trial. Each session consisted of 15 reinforced FI 60-s trials that were randomly intermixed with

five nonreinforced 180-s peak trials and the ITI was 120-s throughout. Lever insert signaled the start of a trial; food delivery and lever withdrawal were contingent on the first lever press after the FI schedule had timed out. The lever remained withdrawn throughout the ITI. Phase 1 lasted for 40 sessions.

FI reward magnitude manipulation: In Phase 2, the reward magnitude increased to four pellets with trial durations remaining consistent with Phase 1. Phase 2 lasted for 20 sessions.

FI duration manipulation: In Phase 3, the reward magnitude remained at four pellets, while the FI duration decreased to 30 s and the peak trial duration decreased to 90 s. Phase 3 lasted for eight sessions. Due to constraints imposed by laboratory renovation, only half the rats (six AcbC-lesioned, six sham control) completed Phase 3.

Histology—All aspects of histology were identical to Experiment 1.

Results

Histology—Histological analysis confirmed that 10 of the 12 AcbC-lesioned rats had extensive bilateral damage to the AcbC area; with one rat having additional damage to the AcbS area. Thus, nine of the original 12 AcbC-lesioned rats were included in the analysis for the baseline and magnitude manipulation phases of the experiment. Of those, four were included in the analysis of the FI duration manipulation phase of the experiment. All 12 sham control rats were included in the analysis for the magnitude manipulation and of those six were included in the FI duration manipulation phase of the experiment. Figure 7 displays the extent of the smallest and largest AcbC lesions.

Response rate functions

FI reward magnitude manipulation: Figure 8 (top panel) displays the peak response functions for the phases of the experiment resulting in a reward magnitude shift from one to four pellets (60S–1P and 60S–4P) in the AcbC-lesioned (L) and sham control (S) rats. The sham control group showed an increase in early responses and an increase in the height of the response function when the reward magnitude increased. The AcbC-lesioned rats showed a different pattern of responding, with a greater tendency to respond after the usual time of reinforcement in the baseline phase (60S–1P L), but this effect was diminished during the magnitude manipulation (60S–4P L).

FI duration manipulation: Figure 8 (bottom panel) displays the peak response functions for the FI duration manipulation (60S–4P vs. 30S–4P) for both the sham control (S) and AcbC-lesioned (L) rats. The decrease in the delay to reward had a similar effect on both groups of rats with a leftward shift in the response function in both cases.

Single-trial analysis—To conduct statistical analyses on the response timing functions, single-trial analyses were completed using a low-high-low algorithm (see Data Analysis, Experiment 1).

FI reward magnitude manipulation: Figure 9 displays the five different measures of the high state response burst for both groups of rats as a function of five-session blocks of training during the baseline (60S–1P) and reward magnitude manipulation (60S–4P) phases. The reward magnitude manipulation produced a shortening of the start, middle, and end times in the sham control group, mirroring the effects on the response rate functions, particularly in promoting early responses (see Figure 8). The AcbC-lesioned rats displayed later middle and end times throughout training, and a lower high state response rate. They also demonstrated some decrease in middle and end times during the reward magnitude

manipulation phase. Separate ANOVAs were conducted on each measure with the variables of magnitude, block, and group. For the start times, there were significant effects of magnitude, $F(1, 19) = 8.5$, group, $F(1, 19) = 11.7$, and Magnitude $\times$ Group, $F(1, 19) = 6.9$. The Magnitude $\times$ Group interaction was due to a significant decrease in start times in the sham control group during the reward magnitude manipulation, but not in the AcbC-lesioned group, as verified by Tukey's post hoc analyses. For the middle and end times there were significant effects of magnitude: middle times, $F(1, 19) = 29.2$, end times, $F(1, 19) = 27.3$; block: middle times, $F(3, 57) = 7.0$, end times, $F(3, 57) = 7.0$; and group: middle times, $F(1, 19) = 32.9$, end times, $F(1, 19) = 33.2$. The high state duration analysis revealed effects of magnitude, $F(1, 19) = 13.8$, Magnitude $\times$ Group, $F(1, 19) = 9.5$, block, $F(3, 57) = 3.4$, and group, $F(1, 19) = 19.7$. The Magnitude $\times$ Group interaction was due to a significant decrease in the high state duration in the AcbC-lesioned group during the reward magnitude manipulation. Finally, the measure of high state response rate was affected by the variables of magnitude, $F(1, 19) = 25.6$, and group, $F(1, 19) = 5.9$.

FI duration manipulation: The results of single-trials analysis conducted on the FI duration manipulation are displayed in Figure 10. This figure shows the last five-session block of each phase (an analysis by blocks was not possible due to the small number of sessions included in the FI duration manipulation). As seen in the figure, both groups displayed a clear sensitivity to the duration manipulation, exhibiting decreased start, middle, and end times, decreased high state durations and increased high state rates when the FI duration decreased to 30 s (30S–4P). This was verified by an ANOVA, which disclosed a main effect of duration in the analysis of all five measures of responding, smallest $F(1, 8) = 67.8$. There was no effect of group on any of the measures.

Discussion

The increase in reward magnitude on the peak procedure led to a decrease in start, middle, and end times in the sham rats. This behavioral pattern is consistent with recent findings that changes in reward magnitude and/or value alter timing with increases in magnitude/value producing earlier response times and decreases in magnitude/value producing later response times (e.g., Galtress & Kirkpatrick, 2009; Ludvig, Conover, & Shizgal, 2007; Roberts, 1981). These results have been interpreted as due to motivational effects operating on one or more elements of the interval clock process. On the other hand, the AcbC-lesioned rats did not show such sensitivity to the increase in reward magnitude, further suggesting a potential deficit in motivational processes.

In contrast to the reward magnitude deficits, the AcbC-lesioned rats displayed normal anticipatory timing and adjusted their timing behavior when the FI duration decreased to 30 s (Figures 8 and 9). However, their timing behavior was not entirely normal as they did show later middle and end times during the baseline and reward magnitude manipulation phases. A comparison of the peak functions from both groups (see Figure 8) indicates a failure of the AcbC-lesioned rats to mediate responding after the omission of an expected food delivery that resulted in the later middle and end times. In the peak procedure, learning to stop responding following the omission of an expected food delivery on peak trials has been reported to occur independently from learning to start to respond prior to the expected time of an upcoming food delivery (Cheng, Westwood, & Crystal, 1993; Gibbon & Church, 1990; Kirkpatrick-Steger, Miller, Betti, & Wasserman, 1996). Therefore, it is possible that the AcbC-lesioned rats in Experiment 2 suffered from a deficit in the ability to stop responding, but no effect on the ability to initiate responding. The middle and end times did decrease over the course of training indicating that the AcbC-lesioned rats were gradually adjusting the right side of their peak, but this adjustment was impaired relative to shams. Alternatively, AcbC-lesioned rats have been shown to respond inappropriately when

required to withhold responding on DRL schedules (Pothuizen, Jongen-Relo, Feldon, & Yee, 2005) and omitting rewards has been shown to modulate neuronal activity in the Acb (Janak, Chen, & Caulder, 2004) and so these factors could be responsible for elevating the postpeak response rates.

Experiment 3

Experiment 2 indicated that AcbC-lesioned rats were deficient in their timing on peak trials following the omission of an expected reward. The results are somewhat puzzling given that the AcbC-lesioned rats were sensitive to temporal manipulations and showed intact anticipatory timing. It is possible that the effect on timing after the peak is related to deficits in the ability to withhold responding on DRL schedules (Pothuizen et al., 2005). The AcbC-lesioned rats may have been less able to learn to stop responding, even though their ability to initiate responding appeared normal. On the other hand, the impairment may have emerged from a decreased sensitivity to reward omission as the Acb has been implicated in encoding reward omission (Janak et al., 2004). Experiment 3 sought to disentangle these two possibilities by training the rats until peak response curves were obtained before performing the AcbC surgery to measure effects on responding. This would determine whether the deficits were in learning or performance.

Method

Subjects—The animals were 20 male hooded Lister rats (Harlan, United Kingdom) approximately 12 weeks old prior to the start of experimental testing and with a mean ad libitum weight of 350 g (range 325–380 g). Prior to experimental testing this was reduced to 85% of ad libitum weight through controlled feeding. After surgery each rat was maintained on a diet of 20 to 25 g of laboratory chow per day for a 14 to 21 day recovery period. During experimental testing this was reduced to 15 g per rat. All other aspects of their housing and husbandry were as Experiments 1 and 2. Testing occurred during the light portion of the cycle.

Apparatus—The apparatus were identical to Experiments 1 and 2.

Procedure

Surgery: After initial training, 12 rats (AcbC lesioned) received neurotoxic lesions of the AcbC using 0.09 M quinolinic acid; the other eight rats (sham control) received a sham control lesion. All aspects of the surgical procedure were identical to Experiment 1.

Pretraining: Pretraining progressed in the same manner as in Experiment 2.

The peak procedure: Prior to surgery, the rats were trained on an FI 60-s peak procedure (see Experiment 2); 15 FI trials were randomly intermixed with five nonreinforced 180-s peak trials. A single food pellet was delivered on FI trials throughout. The presurgery phase lasted 25 sessions. This procedure was repeated for 15 sessions after AcbC and sham control lesions were administered.

Histology—All aspects of histology were identical to Experiment 1.

Results

Histology—Of the 12 AcbC-lesioned rats, two rats became ill postsurgery and so were euthanized; of the remaining 10 rats in this group, nine had extensive bilateral damage to the AcbC; one of these rats had additional damage to the AcbS and ventral pallidum and as such was excluded. In total, eight AcbC-lesioned animals and eight sham control animals were

included in the data analysis. Figure 11 displays the extent of the smallest and largest AcbC lesions.

Response rate functions—Figure 12 displays the peak response functions for the pre- and postsurgery training sessions. The sham control rats (S Pre vs. S Post) showed no change in the peak location or height or any change in shape of the response function. The AcbC-lesioned rats, however, increased their tendency to respond after the usual time of reinforcement in the postsurgery phase when compared to the presurgery phase (L Pre vs. L Post).

Single-trial analysis—Figure 13 displays the results of the single-trial analysis for both groups of rats as a function of five-session blocks of training during the presurgery and postsurgery phases of the experiment. Both groups appear comparable in their timing of the delay to reinforcement prior to surgery, and the sham control group maintained presurgery performance after surgery. On the other hand, the AcbC-lesioned rats increased the middle and end time of the high state of responding while also decreasing the high state response rate. This is consistent with the observation that response rates remained relatively high following the peak (see Figure 12), indicating a failure to react to the omission of reward on peak trials.

An ANOVA comparing both the AcbC-lesioned and sham control rats with the variables of phase, block, and group revealed a significant Phase $\times$ Group interaction in analyzing the measures of middle time, $F(1, 14) = 6.1$, end time, $F(1, 14) = 6.4$, and high state response rate, $F(1, 14) = 15.3$. The interaction in all cases was due to a change in responding in the AcbC-lesioned group after surgery, but not in the sham control group. The middle and end times increased, and the high state response rate decreased following surgery. There were a few additional effects: middle times, Phase $\times$ Block, $F(2, 28) = 8.8$; end times, Phase $\times$ Block, $F(2, 28) = 5.0$ and high state response rate, phase, $F(1, 14) = 5.0$, block, $F(2, 28) = 17.4$.

Discussion

The present study indicated that the AcbC lesions induced a performance deficit in the timing function following reward omission, but anticipatory timing remained intact. The postsurgery timing functions in the present experiment are highly similar to the baseline (postsurgery) timing data from Experiment 2. The results indicate that the AcbC contributed to performance of the timed response following reward omission as these same rats had fully acquired their peak response prior to surgery.

Pothuizen et al. (2005) found evidence that, when compared to sham controls, AcbC-lesioned rats showed an increased tendency to respond early on a DRL task, suggesting a lack of behavioral inhibition. Although behavioral inhibition could possibly account for the present results, one would expect to see increases in early responses prior to the expected time of food as well. The DRL results could, however, relate to the reported role of the AcbC in processing reward omission (Janak et al., 2004). Successful DRL learning requires, in part, a sensitivity to reward omission in discriminating between successful and unsuccessful IRTs. If AcbC-lesioned rats are poorer at detecting reward omission, then this could interfere with DRL performance as they would be less sensitive to the consequences of producing overly short IRTs.

The results of Experiments 2 and 3 appear to be most consistent with a performance-based effect of AcbC lesions on timing following omission of an expected reward rather than an effect on the ability to learn to inhibit responding. A deficit in processing reward omission might emerge from the same mechanism that produced a deficit in detecting a change in

magnitude in Experiments 1 and 2. In other words, the AcbC-lesioned rats may have a general deficit in detecting changes in the magnitude of an expected reward and this may have caused the impairments in choice behavior under the reward magnitude manipulation (Experiment 1), timing behavior under the reward magnitude manipulation (Experiment 2), and timing behavior following reward omission (Experiments 2 and 3).

One factor that requires some further consideration, however, is whether the reward magnitude and/or reward omission processing deficit is due to perception or to motivation. In other words, are the deficits in timing following changes in reward magnitude due to a poor ability to detect those changes or to a deficit in incentive motivation? A deficit in incentive motivation would impair the ability to appropriately respond to the perceived value of the reward by altering choice behavior or increasing response rate even though the individual correctly distinguished the two options. For example, an individual might recognize that option **B** is better, but may not be sufficiently motivated to alter their behavior in favor of option **B**. On the other hand, a perceptual deficit would impair the ability to distinguish between the two options, which would result in a failure to alter behavior because of a failure to recognize the difference in reward value. Experiment 4 aimed to answer this question by using a behavioral contrast procedure.

Experiment 4

A role for the Acb in processing reward magnitude and/or value changes is supported by previously published results. For example, Corbit, Muir, and Balleine (2001) found that rats with lesions of the AcbC are insensitive to sensory-specific reductions in reward value. Cardinal et al. (2001) also found that AcbC-lesioned rats showed a reduced preference for a larger reward compared to shams even when the delay to reward was 0 s for both the larger and the smaller reward. However, there is some evidence that AcbC lesions may not be sufficient to fully disrupt reward value sensitivity. The rats in the Corbit et al. study reduced overall response rates in accordance with a global sensitivity to reward value adjustment, while Balleine and Killcross (1994) found that rats with Acb lesions remained sensitive to both satiety and an increase in the hedonic value of a reward. Here, the rats reduced responding for a reward with which they had been prefed and also increased responding for a higher concentration of sucrose solution. It therefore seems that the role of the Acb in reward processing requires further clarification.

With regard to the present series of studies, Experiments 1 through 3 implicated the AcbC in the processing of reward magnitude changes and the omission of an expected reward. However, those experiments did not indicate whether the lesioned rats were incapable of perceiving the changes in reward, or if the deficits were due to a poor ability to adjust incentive motivation following a change in expected reward.

The present experiment employed a simultaneous contrast procedure. All rats received discrete trials during which reinforcement was available on one of two levers on a VI schedule. In the baseline phase, both levers yielded a single pellet. During the contrast phase, one of the levers yielded four pellets while the opposing lever continued to deliver one pellet. The contrast procedure will allow for an assessment of both an induction and a contrast response. If the AcbC lesions produce a deficit in the ability to detect a change in reward magnitude then neither induction nor contrast should be present because they would not distinguish between the two options. However, if the rats have a deficit in positive incentive motivation, then one would expect to observe a contrast response, but no induction response for the increased reward magnitude. This is because the rat would notice the difference in the two magnitudes, but would not be positively motivated to increase their response rate toward the more valued option. They would, however, still demonstrate

contrast because they would recognize that the contrast lever is relatively less valuable and would be less motivated to work on that lever.

Method

Subjects—The animals were 24 experimentally naïve male hooded Lister rats (Harlan, United Kingdom) approximately 12 weeks old and with a mean ad libitum weight of 320 g (range = 305–340 g). Their weights were reduced to 85% of the ad libitum weight prior to the start of experimental testing and maintained at this weight until surgery. Postsurgery, each rat was maintained on a restricted diet of 20 to 25 g of laboratory chow per day for a 14 to 16 day recovery period. During experimental testing this was reduced to 15 g per rat. All other aspects of their housing and husbandry were as in previous experiments (see Experiment 1). The experiment occurred during the light portion of the cycle between 8:00 and 12:00.

Apparatus—The apparatus was identical to previous experiments.

Procedure

Surgery: After initial training, 12 rats (AcbC-lesioned) received neurotoxic lesions of the AcbC using 0.09 M quinolinic acid; the other 12 rats (sham control) received a sham control lesion. All aspects of the surgical procedure were identical to previous experiments.

Histology: All aspects of histology were identical to previous experiments.

Pretraining: The rats received magazine and lever training on both the left and right levers. Magazine training involved delivering one food pellet per trial on a VT 60-s schedule. Instrumental lever training was carried out over 4 days. Days 1 and 2 consisted of a CRF schedule on each lever separately with the order of presentation counterbalanced. On Days 3 and 4, food was delivered on a VI 15-s and VI 30-s schedule, respectively, with the first lever press after the variable interval resulting in food delivery. The total amount of food was shared equally between the two levers and when the rat had received the total food available on one lever it was withdrawn until the remaining food was collected on the opposite lever. All rats received 30 one-pellet food deliveries per session.

Baseline phase: All rats received discrete trials on both levers, with one lever inserted per trial. Trials were presented in a pseudorandom order, with a restriction of no more than two successive presentations of each lever. Food delivery occurred on an exponential VI 30-s schedule. The first lever press after the VI timed out resulted in food delivery and lever retraction. The ITI was 120 s. During the baseline phase, a single food pellet was delivered on all trials. Sessions lasted for 60 min. The initial baseline phase lasted for 20 sessions, after which the surgeries were conducted as in previous experiments. Following recovery, the rats were returned to the baseline procedure for a further 20 sessions.

Contrast phase: The contrast phase lasted for 20 sessions and was identical to the initial baseline phase except the induction lever now delivered four pellets; the opposing contrast lever continued to deliver one food pellet. The purpose of the contrast phase was to induce a negative contrast effect on the contrast lever by increasing the value of the induction lever. Thus, although the contrast lever did not change in actual value, there might be a change in subjective value of the one-pellet reward due to a contrast effect from the increase in reward on the induction lever. The assignment of the contrast versus induction lever to the left and right levers was counterbalanced.

Results

Histology—Histological analysis revealed that of the 12 AcbC-lesioned rats, nine had extensive bilateral AcbC damage and as such nine AcbC-lesioned and 12 sham control rats were included in the analysis. Figure 14 shows the extent of the smallest and largest AcbC lesions.

Responses per session—Figure 15 displays the mean lever press responses per session during the baseline and contrast phases in the two groups. The response on the induction lever (top panel) was similar in the two groups in the baseline phase, but the sham control rats displayed an increase in responding on this lever during the contrast phase when the induction lever now resulted in the delivery of a four-pellet reinforcer. The AcbC-lesioned rats did not show an induction response during the contrast phase, but instead continued to respond at approximately the same rate as in the baseline phase. These trends were confirmed by an ANOVA on the induction lever response with the factors of phase and group. This revealed significant effects of phase, $F(1, 19) = 11.1$, and Phase $\times$ Group, $F(1, 19) = 6.5$. The interaction was due to the increase in responding on the induction lever in the sham control group during the contrast phase, but not in the AcbC-lesioned group.

The response on the contrast lever disclosed a different pattern. Here, both groups displayed a decrease in response on the contrast lever compared to baseline. An ANOVA on the contrast lever response disclosed a significant effect of phase, $F(1, 19) = 10.1$, indicating that a significant contrast effect had occurred in both groups. There was no group effect or any interaction.

Discussion

The results indicate that the sham control group increased responding on the induction lever when it yielded a four-pellet reinforcer in the contrast phase. This group also displayed a behavioral contrast effect in that the response rate decreased on the opposing contrast lever, which remained at one pellet throughout. The AcbC-lesioned group displayed a different result in that they showed a significant contrast effect, but no significant induction response. Thus, the AcbC-lesioned rats were sensitive to the increase in reinforcer magnitude, but that change failed to elicit sufficient positive incentive motivation to produce an induction effect.

The failure to find an induction effect is unlikely to be due to an inability of the AcbC-lesioned group to increase their response rate as a consequence of the change in reward. Although dopamine depletions within the Acb have been shown to affect instrumental response rate, particularly on high-requirement or ratio schedules, performance on VI schedules is largely unimpaired (Correa, Carlson, Wisniecki, & Salamone, 2002; Salamone, Correa, Mingote, & Weber, 2003). In addition, in both Experiments 1 and 2, an increase in reward magnitude led to an increase in response rate akin to that of sham controls. Finally, the lean VI task resulted in moderate response rates in both groups during the baseline phase, so one would not expect any ceiling effects to occur here. The rather large increase shown by the shams provides further evidence indicating that response rates were far from any ceiling. Accordingly, these results support those of Corbit et al. (2001) and clarify those of Balleine and Killcross (1994), by indicating that the AcbC appears to be involved in anticipation of the incentive value of upcoming instrumental outcomes and the associated mediation of performance. The effect appears to be motivational in origin rather than due to a perceptual deficit, which would reduce the ability to discriminate the two magnitudes because the AcbC-lesioned rats were able to display a significant contrast effect indicating that they did indeed detect the change in reward magnitude.

General Discussion

Previous research into the AcbC has shown that rats with lesions of this region tend to be impulsive, both in demonstrating a lack of ability to withhold inappropriate behavior (Pothuizen et al., 2005), and also in displaying an increased preference for a shorter delayed smaller reward over a longer delayed larger reward when compared to controls (e.g., Cardinal et al., 2001). This pattern of choice behavior has been termed impulsive and has been described as a result of increased delay discounting, which is the rate of reduction in the value of reward as a function of delay. However, previous research did not pinpoint the possible cause of the increase in delay discounting in AcbC-lesioned rats.

In the present Experiment 1, the PIFI procedure was developed to separately manipulate reward magnitude and delay, while also assessing timing and choice behavior. The results of Experiment 1 indicate that the AcbC is necessary for altering choice behavior in response to a change in the FI reward magnitude, but that sensitivity to the changes in the delay to reward (on the FI schedule) remained intact. In fact, the lack of an intact AcbC does not result in impulsivity as a matter of course, at least in terms of delay discounting, as when the reward magnitude was equal on both schedules of reinforcement, AcbC lesion rats behaved appropriately (see Figure 3). The results of Experiment 1 suggest that it is the lack of a change in behavior following a change in reward magnitude that results in the increased rate of delay discounting in the AcbC-lesioned rats. Support for this can be found in previous investigations into AcbC discounting. Specifically, Cardinal et al. (2001) found that when the delay to two rewards was equal, rats with lesions of the AcbC chose the larger magnitude reward significantly less often than the controls even with extended training on the task. Gierler, Bohn, and Hauber (2003) also found that AcbC-lesioned rats did not alter responding appropriately during a shift in reward magnitude. In addition, infusions of the NMDA antagonist DL-2-amino-5-phosphonovaleric acid into the Acb also disrupted appropriate responding to reward magnitude shifts (Hauber, Bohn, & Gierler, 2000). Finally, fMRI investigations in humans have shown Acb activity when monetary reward magnitude is varied (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005) and when expected reward value is altered (Gregorios-Pippas et al., 2009) or an expected reward is omitted (Spicer et al., 2007).

The results of Experiment 2 are also consistent with the previous research on AcbC involvement in reward processing. In a simpler peak procedure, the AcbC-lesioned rats failed to demonstrate the expected pattern of responding when the reward magnitude was manipulated, whereas the sham control group exhibited behavior similar to that reported in previous investigations of reward magnitude/value shifts on timing (e.g., Galtress & Kirkpatrick, 2009; Ludvig et al., 2007; Roberts, 1981). This further indicates a lack of adjustment to the change in reward magnitude. The AcbC-lesioned rats did, however, demonstrate a change in timing behavior when the delay to reward was reduced, but their timing was not completely intact as they failed to suppress responding following the expected time of reinforcement (see also Pothuizen et al., 2005). This was further supported by Experiment 3—rats that were previously trained on the peak procedure before the destruction of the AcbC subsequently showed increased postpeak responding; these effects were most likely due to poor sensitivity to the omission of an expected reward (see also Janak et al., 2004).

Experiment 4 sought to further clarify the nature of the deficit in adjustment of behavior to reward magnitude shifts shown in Experiments 1 and 2 by utilizing a behavioral contrast procedure. The results of this experiment indicated that AcbC-lesioned rats were sensitive to a change and/or disparity in reward magnitude, but this was insufficient to result in appropriate modification of behavior. Thus it may be the failure to modify choice behavior

that resulted in increased delay discounting in Experiment 1 rather than a failure to detect the reward magnitude change. This finding is consistent with previous research implicating the AcbC involvement in incentive motivation (Balleine & Killcross, 1994; Corbit et al., 2001).

The AcbC, as part of the ventral striatum, has been shown to play an important role in impulsive control disorders such as drug addiction and ADHD. Scheres, Milham, Knutson, and Castellanos (2007) found reduced activity during reward anticipation in patients with ADHD whereas the spontaneously hypertensive rat, a potential animal model of ADHD, suffers from abnormal dopa-mine release and gene expression in the Acb (Carey et al., 1998; Russell, 2000; Russell et al., 1995, 1998). Yet, the contribution of the AcbC to the mechanisms behind impulsive behavior has yet to be determined. The present set of experiments advances the understanding of AcbC involvement in timing, reward processing, and temporal discounting by indicating that the temporal anticipation of rewards remains intact, and that the ability to modify behavior in response to a change in reward magnitude or the omission of an expected reward delivery is dependent on an intact AcbC. These results are consistent with recent research indicating that the nucleus accumbens may be the site where the computation of overall reward value occurs (Gregorios-Pippas et al., 2009; Kable & Glimcher, 2007; Kobayashi & Schultz, 2008), further underlining the importance of reward processing in impulsive choice behavior. The fact that timing abilities are spared in AcbC-lesioned rats indicates that the temporal anticipation and incentive valuation of rewards are accomplished by separate neural substrates. It appears that interval timing is mostly likely accomplished, at least in part, by the nigrostriatal dopamine pathway, which may play a role in regulating the internal clock process (see Meck, 2006, for a review). Accordingly, the results indicate that therapeutic interventions for the treatment of impulsive choice disorders should focus on timing and reward processing as separate components of impulsivity.

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Figure 1.

A diagram depicting the PIFI training trials and peak test trials during the pre- and postsurgery baseline phases. The key defines the different symbols used in the diagram. PI = progressive interval; FI = fixed interval; S = seconds; ITI = intertrial interval.

Figure 2.

Left column: Photomicrograph of a representative sham control (top) and nucleus accumbens core (AcbC)-lesioned (bottom) section from the nucleus accumbens (Acb) region of the left hemisphere. Note the gliosis evident in the left portion of the section; the enlarged ventricle near the top; and the intact area to the right of the AcbC lesion when compared to the corresponding areas of the sham control brain. Right column: The largest (light gray) and smallest (black) areas of damage to the AcbC region of rats included in the analysis for Experiment 1. From *The Rat Brain in Stereotaxic Coordinates*, 3rd ed., by G. Paxinos & C. Watson, 1996, San Diego, CA: Academic. Copyright 1996 by Elsevier Science. Adapted with permission.

Figure 3.

Change-over time as a function of phase of training for the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats in Experiment 1. Error bars are ± 1 SEM. Asterisks mark significant changes during fixed-interval (FI) reward magnitude manipulation (60S-1P vs. 60S-4P) and FI duration manipulation (60S-4P vs. 30S-4P) phases of the experiment. Ampersands mark significant group differences (AcbC lesion vs. sham) within a phase of the experiment. S = seconds; 60S-1P = 60 s, one pellet; 60S-4P = 60 s, four pellets; 30S-4P = 30 s, four pellets.

Figure 4.

Delay discounting rates (k) for the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats as a function of phase of training in Experiment 1. Error bars are ± 1 SEM. Asterisks mark significant changes during fixed-interval (FI) reward magnitude manipulation (60S-1P vs. 60S-4P) and FI duration manipulation (60S-4P vs. 30S-4P) phases of the experiment. Ampersands mark significant group differences (AcbC lesion vs. sham) within a phase of the experiment. S = seconds; 60S-1P = 60 s, one pellet; 60S-4P = 60 s, four pellets; 30S-4P = 30 s, four pellets.

Figure 5.

Response rate as a function of time since peak trial onset during the baseline (60S–1P), fixed-interval (FI) reward magnitude manipulation (60S–4P), and FI duration manipulation (30S–4P) in Experiment 1 in the sham control (top) and nucleus accumbens core (AcbC)-lesioned (bottom) groups of rats. S = seconds; 60S–1P = 60 s, one pellet; 60S–4P = 60 s, four pellets; 30S–4P = 30 s, four pellets.

Figure 6.

Results of the single-trial analyses conducted in Experiment 1: start time, middle time, end time, high state duration, and high state response rate as a function of phase of training in the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats. Error bars are ± 1 SEM. Asterisks mark significant changes during fixed-interval (FI) reward magnitude manipulation (60S-1P vs. 60S-4P) and FI duration manipulation (60S-4P vs. 30S-4P) phases of the experiment. Ampersands mark significant group differences (AcbC lesion vs. sham) within a phase of the experiment. S = seconds; 60S-1P = 60 s, one pellet; 60S-4P = 60 s, four pellets; 30S-4P = 30 s, four pellets.

Figure 7.

The largest (light gray) and smallest (black) areas of damage for the rats included in the analysis for Experiment 2. From *The Rat Brain in Stereotaxic Coordinates*, 3rd ed., by G. Paxinos & C. Watson, 1996, San Diego, CA: Academic. Copyright 1996 by Elsevier Science. Adapted with permission.

Figure 8.

Top: Response functions from the fixed-interval (FI) reward magnitude manipulation (60S–1P vs. 60S–4P) in Experiment 2 in the sham control (S) and nucleus accumbens core (AcbC)-lesioned (L) groups. Bottom: Response functions from the FI duration manipulation (60S–4P vs. 30S–4P) in Experiment 2 in the sham control (S) and AcbC-lesioned (L) groups. 60S–1P = 60 s, one pellet; 60S–4P = 60 s, four pellets; 30S–4P = 30 s, four pellets.

Figure 9.

Results of the single-trial analyses conducted in Experiment 2: start time, middle time, end time, high state duration, and high state response rate as a function five-session blocks of training in the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats during the baseline (60S–1P) and reward magnitude manipulation (60S–4P) phases. Error bars are ± 1 SEM. Asterisks mark significant changes during fixed-interval (FI) reward magnitude manipulation (60S–1P vs. 60S–4P) phases of the experiment. Ampersands mark significant group differences (AcbC lesion vs. sham) within a phase of the experiment. S = seconds; 60S–1P = 60 s, one pellet; 60S–4P = 60 s, four pellets; 30S–4P = 30 s, four pellets.

Figure 10.

Results of the single-trial analyses conducted in Experiment 2: start time, middle time, end time, high state duration, and high state response rate in the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats during the fixed-interval (FI) duration manipulation. Error bars are ± 1 SEM. Asterisks mark significant changes during the FI duration manipulation (60S-4P vs. 30S-4P) phases of the experiment. S = seconds; 60S-1P = 60 s, one pellet; 60S-4P = 60 s, four pellets; 30S-4P = 30 s, four pellets.

Figure 11.

The largest (light gray) and smallest (black) areas of damage for the rats included in the analysis for Experiment 3. From *The Rat Brain in Stereotaxic Coordinates*, 3rd ed., by G. Paxinos & C. Watson, 1996, San Diego, CA: Academic. Copyright 1996 by Elsevier Science. Adapted with permission.

Figure 12.

Response rate functions during the pre- and postsurgery phases of Experiment 3 in the sham control (S) and nucleus accumbens core (AcbC)-lesioned (L) groups. 60S-1P = 60 s, one pellet; 60S-4P = 60 s, four pellets; 30S-4P = 30 s, four pellets; pre = presurgery; post = postsurgery.

Figure 13.

Results of the single-trial analyses conducted in Experiment 3: start time, middle time, end time, high state duration, and high state response rate in the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats during the presurgery and postsurgery phases. Error bars are ± 1 SEM. Asterisks mark significant changes during pre- versus postsurgery phases of the experiment. Ampersands mark significant group differences (AcbC lesion vs. sham) within a phase of the experiment. S = seconds; 60S-1P = 60 s, one pellet; 60S-4P = 60 s, four pellets; 30S-4P = 30 s, four pellets; pre = presurgery; post = postsurgery.

Figure 14.

The largest (light gray) and smallest (black) areas of damage for the rats included in the analysis for Experiment 4. From *The Rat Brain in Stereotaxic Coordinates*, 3rd ed., by G. Paxinos & C. Watson, 1996, San Diego, CA: Academic. Copyright 1996 by Elsevier Science. Adapted with permission.

Figure 15.

Top: Responses per session on the induction lever during the baseline and contrast phases of Experiment 4 in the sham control and nucleus accumbens core (AcbC)-lesioned groups of rats. Bottom: Responses per session on the contrast lever during the baseline and contrast phases of Experiment 4 in the sham control and AcbC-lesioned groups of rats. Error bars are ± 1 SEM. Asterisks mark significant changes during the contrast (vs. baseline) phase of the experiment. Ampersands mark significant group differences (AcbC lesion vs. sham) within a phase of the experiment. The reward magnitude for each lever is indicated above each bar in the figure.