DISSOCIABLE ROLES FOR NUCLEUS ACCUMBENS CORE AND SHELL IN REGULATING RISK-BASED DECISION MAKING

by

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ABSTRACT

Decision making under conditions of risk and uncertainty constitutes a fundamental aspect of society. Few routine cost/benefit decisions are independent of any consideration of risk and uncertainty, from investing and financial matters to simple assessments of time management and resource allocation. Neuropsychological studies with brain-damaged patients gave initial insights into the cortical contributions to risk-based decision making. Subsequent imaging work has allowed for an understanding of the neural functioning of patients afflicted by disorders which impair risk-based decision making and has also implicated various subcortical structures, including the nucleus accumbens, in these types of decisions. Recent research in humans has shown that nucleus accumbens activation precedes risk-taking or risk-seeking on a financial decision making task. Additionally, animal research has determined that lesions of the nucleus accumbens bias choice away from larger but riskier rewards. The current experiments expand upon these findings by demonstrating that inactivation of a subregion of the accumbens, the shell, is responsible for this bias while the other subregion, the core, mediates the speed at which these decision are made. The effects of accumbens inactivation on risky choice appeared to be due to a reduced tendency to choose the riskier option following trials where rats chose risky and received reward (i.e., reduced win-stay performance), suggesting reduced reward sensitivity. Additionally, this set of experiments demonstrates that instead of inducing risk-aversive tendencies, inactivation of the nucleus accumbens interferes with general value judgments. Specifically, accumbens inactivation induces a slight reduction in preference for the larger reward when the risk/uncertainty component is eliminated. Additionally, inactivation only shifts choice preference away from the more valuable option when it is larger and probabilistic. These data suggest that in addition to effort- and delay-based decision making, the nucleus accumbens also mediates risk-based decision making. In addition to decisions under risk, the nucleus accumbens also seems to play a smaller, yet significant role in judgments of overall value and utility.

PREFACE

Research for this thesis was approved by the UBC Animal Care Committee, application number A06-0300.

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I would like to thank the faculty and fellow students at UBC. I owe particular gratitude my supervisor, Dr. Stan Floresco for his continual guidance with regard to my research and otherwise. I also offer thanks to my fellow lab-mates Maric Tse, Takeshi Enomoto, Jennifer St. Onge, Anna Cantor, Naghmeh Shafiei, Sarvin Ghods-Sharifi, Shahin Khayambashi, Davis Kelly, and Emily Green for their support and assistance. I am thankful to the Canadian Institutes of Health Research and the UBC Graduate Research Fellowship for financial support. Finally, special thanks to my parents and sister for their enduring love and support.

DEDICATION

For Kate

I. INTRODUCTION

The capacity to make advantageous decisions is dependent the ability to evaluate the relative benefits and costs associated with different choices to estimate which option may yield outcomes of greater value. Costs associated with certain rewards may take multiple forms, including delaying the delivery of the reward, requiring more effort to obtain it, or making the reward probabilistic or "risky". Decisions under risk typically involve choice between a smaller but more certain reward and a larger, probabilistic reward. In humans, examples of risk-based decision making generally are observed with regard to financial matters, such as gambling at a casino or playing the stock market. Functional imaging studies employing laboratory tasks that share similarities to these types of everyday decisions have repeatedly implicated the nucleus accumbens (NAc) region of the ventral striatum in contributing these types of judgments. For example, Kuhnen and Knutson (2005) conducted a financial risk task in human subjects who were asked to choose between two risky stocks which yielded either a large gain or loss, or a safe bond that always yielded a small gain. Increased NAc activation preceded risky choices and risk-seeking mistakes. Similar results have been observed in numerous other studies employing various risk-based decision tasks, suggesting that NAc activation may bias choice towards riskier options associated with larger magnitudes of rewards (Matthews et al., 2004; Knutson et al., 2008; Rao et al., 2008; Samanez-Larkin et al., 2010)

The notion that the NAc plays a critical role in cost/benefit decision making is further supported by studies employing experimental animals. Many of these studies have focused on the contribution of this nucleus to effort- or delay-related judgments. Thus, lesions or inactivations of the NAc core reduce an animal's preference to work harder or wait longer for larger rewards (Cardinal et al., 2001; Ghods-Sharifi and Floresco 2010; Hauber and Sommer, 2009; Pothuizen et al., 2005). These forms of decision making are also altered by manipulations of the basolateral amygdala (Ghods-Sharifi et al., 2009; Winstanley et al., 2004) or different regions of the prefrontal cortex (Mobini et al., 2002, Rudebeck et al., 2006, Winstanley et al., 2004). However, in comparison, there has been substantially less research looking at the contribution of the NAc to risk/reward judgments in experimental animals. Cardinal and Howes (2005) utilized a probabilistic discounting task conducted in operant

chambers, where rats were given a choice between a small/certain lever that always delivered one pellet and a large/risky lever that delivered four pellets with probability of 100, 50, 25, 12.5, or 6.25 percent, decreasing across trial blocks. Normal animals adjusted their lever choice over the trial blocks accordingly, selecting the large/risky lever in early trial blocks and biasing response toward the small/certain lever during later trial blocks. Permanent, excitotoxic lesions to the NAc following training initially caused rats to be relatively indifferent to the two alternatives, choosing the large/risky option close to 50% of the time across all probability blocks. With extended training, lesioned animals eventually biased their choice toward the small/certain lever primarily during the earlier trial blocks, when the large/risky option was more advantageous. However, a control experiment revealed that lesions of the NAc did not reduce choice of a larger reinforcer when the probability of reinforcement on the large reward lever was fixed at 100%. These findings led to the conclusion that the NAc is involved specifically in the processing of different valued rewards under conditions of uncertainty.

It is now well-established that the NAc can be subdivided into core and the shell subregions, based on a variety of neurochemical and anatomical characteristics. (Floresco et al., 2001; Groenewegen et al., 1991; Ikemoto and Panksepp, 1999; Mogenson et al., 1993; Oades, 1985; Pennartz et al., 1994). Accordingly, lesions of the NAc core or shell have been reported to produce dissociable effects on a variety of behaviors, including instrumental action, latent inhibition, set shifting, and cue-induced reinstatement of food-seeking behavior (Corbit et al., 2001; Weiner, 2003; Floresco et al., 2006; Floresco et al., 2008). Studies of cost/benefit decision making using subregion selective manipulations of the NAc have also identified dissociations between the core and shell, with the core appearing to be more play a more critical role than the shell in mediating both delay- and effort-based decision making (Cardinal et al., 2001; Ghods-Sharifi et al., 2010; Hauber and Sommer, 2009; Pothuizen et al., 2005). With respect to risk-based decision making, Cardinal and Howes (2005) lesioned the more lateral portions of the NAc core, but these lesions also included considerable damage to the more medial portions of the shell. Thus, it is unclear whether the reduced preference for larger, probabilistic rewards induced by lesions of the NAc in this experiment was attributable primarily to cell loss in the NAc core or shell (or both).

To more clearly understand the NAc's role in mediating risk-based decision making, procedures were employed that have been used to understand the role of the PFC, BLA, and dopamine in this form of decision making (Ghods-Sharifi and Floresco, 2010; St. Onge and Floresco, 2009; St. Onge and Floresco, 2010). An initial experiment employed relatively large inactivation of the entire NAc, and subsequent experiments used more discrete inactivaitons to determine which subregion (core or shell) seems to be mediating risk-based decision making. This was accomplished using a risk discounting task in which animals choose between a small/certain reward and a larger but probabilistic reward as the odds on this lever change throughout the session. Additionally, the risk discounting task with fixed probabilities helped in understanding if the effect was genuinely due to risk aversion or if it was more attributed to the change of probabilities within a session. Finally, whereas Cardinal and Howes (2005) had used lesions, the current experiments utilized reversible inactivation. The benefit of this is two-fold; it allowed for increased power with small sample sizes and afforded the ability to manipulate the NAc only during the testing session in animals well-trained on the task.

II. MATERIALS AND METHODS

Animals

Male Long Evans rats (Charles River Laboratories, Montreal, Canada) weighing 250-300 g at the beginning of training were used. On arrival, rats were given 1 week to acclimatize to the colony and food restricted to 85-90 % of their free feeding weight for 1 week before behavioral training and given ad libitum access to water for the duration of the experiment. Feeding occurred in the rats' home cages at the end of the experimental day and body weights were monitored daily. All testing was in accordance with the Canadian Council on Animal Care and the Animals Care Committee of the University of British Columbia.

Apparatus

Behavioral testing was conducted in twelve operant chambers (30.5 X 24 X 21 cm; Med Associates, St Albans, VT, USA) enclosed in sound attenuating boxes. The boxes were equipped with a fan that provided ventilation and masked extraneous noise. Each chamber was fitted with two retractable levers, one located on each side of a central food receptacle where food reinforcement (45 mg; Bioserv, Frenchtown, NJ, USA) was delivered by a pellet dispenser. The chambers were illuminated by a single 100-mA house light located in the top center of the wall opposite the levers. Four infrared photobeams were mounted on the side of each chamber, and another photobeam was located in the food receptacle. Locomotor activity was indexed by the number of photobeam breaks that occurred during a session. All experimental data were recorded by personal computers connected to the chambers through an interface.

Lever Press Training

Our initial training protocols were identical to those of St. Onge and Floresco (2009a), as adapted from Cardinal et al. (2000). On the day before their first exposure to the operant chamber, rats were given approximately 25 food reward pellets in their home cage. On the first day of training, 2-3 pellets were delivered into the food cup and crushed pellets were placed on a lever before the animal was placed in the chamber. Rats were first trained under a fixed ratio 1 schedule to a criterion of 60 pellets in 30 min, first for one lever, and then repeated for the other lever (counterbalanced left/right between subjects). They were then trained on a simplified version of the full task. These 90 trial sessions began with the levers

retracted and the operant chamber in darkness. Every 40s, a trial was initiated with the illumination of the house light and the insertion of one of the two levers into the chamber. If the rat failed to respond on the lever within 10s, the lever retracted and a single pellet was delivered with 50% probability. This procedure was used to familiarize the rats to the probabilistic nature of the full task. In every pair of trials, the left or right lever was presented once, and the order within the pair of trials was random. Rats were trained for approximately 3-5 days to a criterion of 80 or more successful trials (i.e. < 10 omissions).

Decision making tasks

Risk Discounting Task. The primary task used in these studies has been described previously (Floresco and Whelan, 2010; Ghods-Sharifi et al., 2009; St. Onge and Floresco, 2009a; St. Onge and Floresco, 2010; St. Onge et al., 2010), which was originally modified from that described by Cardinal and Howes (2005) (Fig. 1). Rats received daily sessions consisting of 72 trials, separated into four blocks of 18 trials. The entire session took 48 min to complete, and the animals were trained 5-7 days per week. A session began in darkness with both levers retracted (the intertrial state). A trial began every 40s with the illumination of the house light and the insertion of one or both levers into the chamber. One lever was designated the large/risky lever, the other the small/certain lever, which remained consistent throughout training (counterbalanced left/right). If the rat did not respond within 10s of lever presentation, the chamber was reset to the intertrial state until the next trial (omission). When a lever was chosen, both levers retracted. Choice of the small/certain lever always delivered one pellet with 100% probability; choice of the large/risky lever delivered four pellets but with a particular probability (see below). After a response was made and food delivered, the house light remained on for another 4s, after which the chamber reverted back to the intertrial state until the next trial. Multiple pellets were delivered 0.5 s apart. The larger reinforcer probability was varied systematically across the session as follows. The four blocks consisted of eight forced choice trials where only one lever was presented (four trials for each lever, randomized in pairs) permitting animals to learn the amount of food associated with each lever press and the respective probability of receiving reinforcement over each block. This was followed by 10 free-choice trials, where both levers were presented and the animal had to decide whether to choose the small/certain or the large/risky lever. The probability of obtaining four pellets after pressing the large/risky lever varied

across the four blocks: it was initially 100%, then 50, 25, and 12.5%, respectively. Thus, when the probability of obtaining the 4-pellet reward was 100% or 50%, this option would be more advantageous. At 25%, it is arbitrary which lever the animal chooses, and at 12.5%, the small/certain lever would be the more advantageous option in the long term.

Rats were trained on the task until as a group, they (1) chose the large/risky lever during the first trial block (100% probability) on at least 80% of successive trials, (2) chose the large/risky lever during the final trial block (12.5% probability) on at most 60% of successive trials, and (3) demonstrated stable baseline levels of choice. Infusions were administered after a group of rats displayed stable patterns of choice for 3 consecutive days, assessed using a procedure similar to that described by Winstanley et al. (2005) and Floresco et al. (2008). In brief, data from three consecutive sessions were analyzed with a repeated-measures ANOVA with two within-subjects factors (day and trial block). If the effect of block was significant at the $P<0.05$ level but there was no main effect of day or day x block interaction (at the $P>0.1$ level), animals were judged to have achieved stable baseline levels of choice behavior.

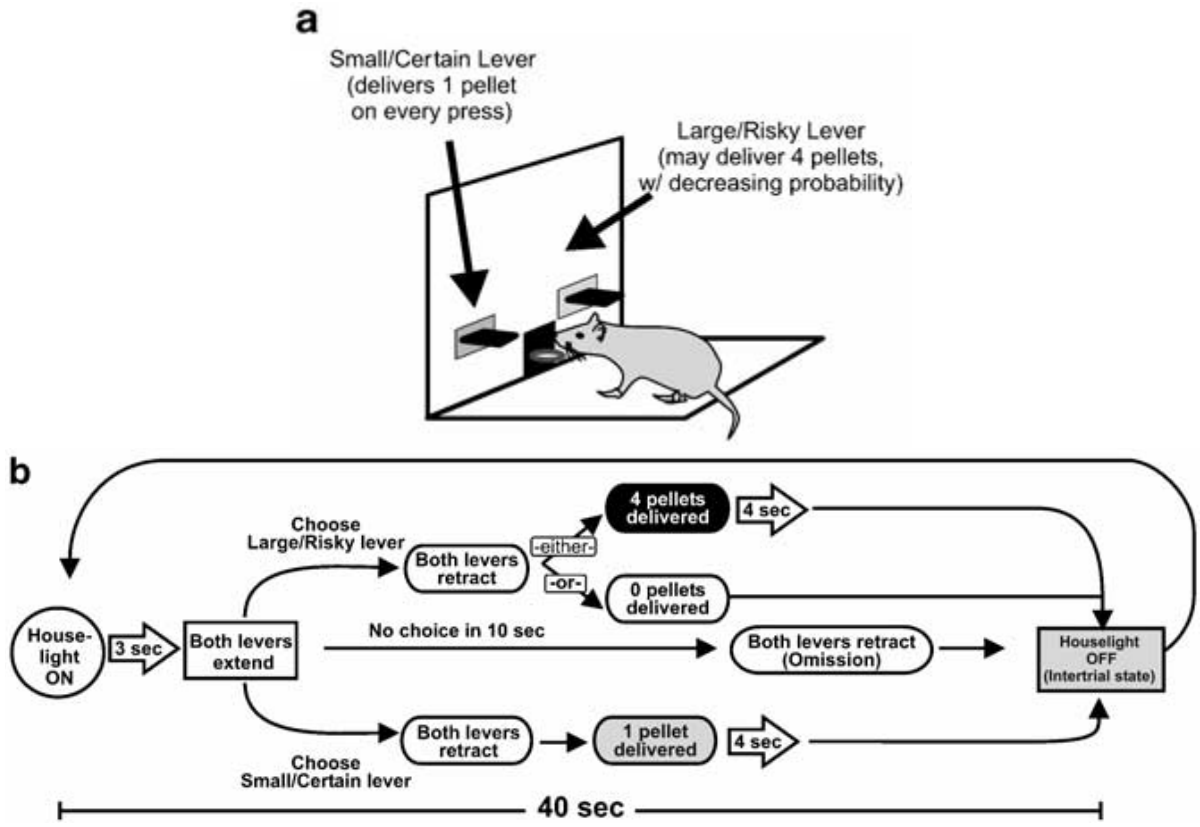

Figure 1. Risk discounting task design. (a) Cost/benefit contingencies associated with responding on either lever and (b) format of a single free choice trial

Risk Discounting with Fixed Probabilities In a subsequent experiment, we employed a fixed probability risk task we have used previously to investigating the contribution of the medial prefrontal cortex to this form of decision making (St. Onge and Floresco, 2009b). Rats were trained to press retractable levers as in the risk discounting task, and then trained on a variant of the risk discounting task. Each daily session started with 20 forced choice trials, followed by 20 free choice trials. As with the risk discounting task, the Small/Certain lever always delivered 1 pellet with 100% probability. However, the probability of obtaining the larger 4-pellet reward after selection of the Large/Risky lever remained constant over the entire session. For the first phase of this experiment, this probability was set at 40%. Rats were trained until they displayed stable levels of choice, after which they received their first round of counterbalanced microinfusions of saline and baclofen/muscimol. They were then, retrained on the task with the probability of the large/risky reward set to 10% for 14 days, after which they received a second round of counterbalanced microinfusions.
Reward magnitude discrimination task. A priori, we determined that if a manipulation decreased preference for the Large/Risky lever on the risk discounting task, separate groups of animals would be trained and tested on a reward magnitude discrimination task to determine if this effect was due to impairment in discriminating between reward magnitudes of the two levers. In these experiments, rats were trained to press retractable levers as in the risk discounting task, after which they were trained on the reward magnitude discrimination task. Here, rats chose between one lever that delivered one pellet and another that delivered four pellets. Both the small and large rewards were delivered immediately after a single response with 100% probability. A session consisted of four blocks of trials, with each block consisting of 2 forced-choice followed by 10 free-choice trials. After ~15 days of training, rats displayed a strong preference for the four-pellet option. They were implanted with guide cannulae and recovered for at least 7 d. After ~5 d of retraining, their choice behavior stabilized, and they received counterbalanced infusions on separate test days.

Surgery and microinfusion protocol
Rats were trained on their respective tasks until they displayed stable levels of choice, after which they were provided food ad libitum for 1-3 days later, and were then subjected to surgery. Rats were anaesthetized with 100 mg/kg ketamine hydrochloride and 7 mg/kg

xylazine and implanted with bilateral 23 gauge stainless steel guide cannulae aimed at one of three coordinates using standard stereotaxic techniques. Some rats received implants aimed at the central portion of the NAc along the core/shell border, to inactivate both subregions (flat skull: anteroposterior = 1.5 mm; medialateral = 1.4 mm; dorsoventral = -5.9 mm from dura). For studies employing subregion specific microinfusions, guide cannuale were aimed at either the NAc core (flat skull: anteroposterior = 1.5 mm; medialateral = 1.8 mm; dorsoventral = -5.9 mm from dura) or shell (flat skull: anteroposterior = 1.6 mm; medialteral = 1.0 mm; dorsoventral = -5.9 mm from dura). Guide cannulae were held in place with stainless steel screws and dental acrylic. 30 gauge obdurators flush with the end of guide cannulae remained in place until the infusions were made. Rats were given at least 7 d to recover from surgery before testing. During this period, they were handled at least 5 min each day and were food restricted to 85% of their free-feeding weight.

Rats were subsequently trained on their respective task for at least 5 d until the group displayed stable levels of choice behavior for 3 consecutive days. One to two days before their first microinfusion test day, obdurators were removed, and a mock infusion procedure was conducted. Stainless steel injectors were placed in the guide cannulae for 2 min, but no infusion was administered. The day after displaying stable discounting, the group received its first microinfusion test day.

A within-subjects design was used for all experiments. Inactivation was achieved by microinfusion of a solution containing the $GABA_B$ agonist baclofen and the $GABA_A$ agonist muscimol (Sigma Aldrich). Both drugs were dissolved in physiological saline, mixed separately at a concentration of 500 ng/µl, and then combined into equal volumes so that the final concentration of each compound in solution was 250 ng/µl. For inactivation of the entire NAc, drugs or saline were infused at a volume of 0.5 µl so the final dose of baclofen and muscimol was 125 ng/side. For subregion specific inactivation of the core or shell, drugs or saline were infused at a volume of 0.3 µl so that the final dose of baclofen and muscimol was 75 ng/side. Infusions of GABA agonists or saline were administered bilaterally via 30 gauge injection cannulae that protruded 0.8 mm past the end of the guide cannulae, at a rate of 0.4 µl/min by a microsyringe pump. Injection cannulae were left in place for an additional 1 min to allow for diffusion. Each rat remained in its home cage for an additional 10 min period before behavioral testing. Previous studies using similar infusions have observed

dissociable effects on behavior when GABA agonists have been infused into adjacent brain regions separated by ~1 mm (Floresco et al. 2006; Marquis et al., 2007; Moreira et al., 2007), suggesting that functional spread of these treatments is unlikely to be much more than 1 mm in radius.

On the first infusion test day, half of the rats in each group received saline infusions, and the other half received baclofen/muscimol. The next day, they received a baseline training day (no infusion). If, for any individual rat, choice of the large/risky lever deviated by >15% from its preinfusion baseline it received an additional day of training before the second infusion test. On the following day, rats received a second counterbalanced infusion of either saline or baclofen/muscimol.

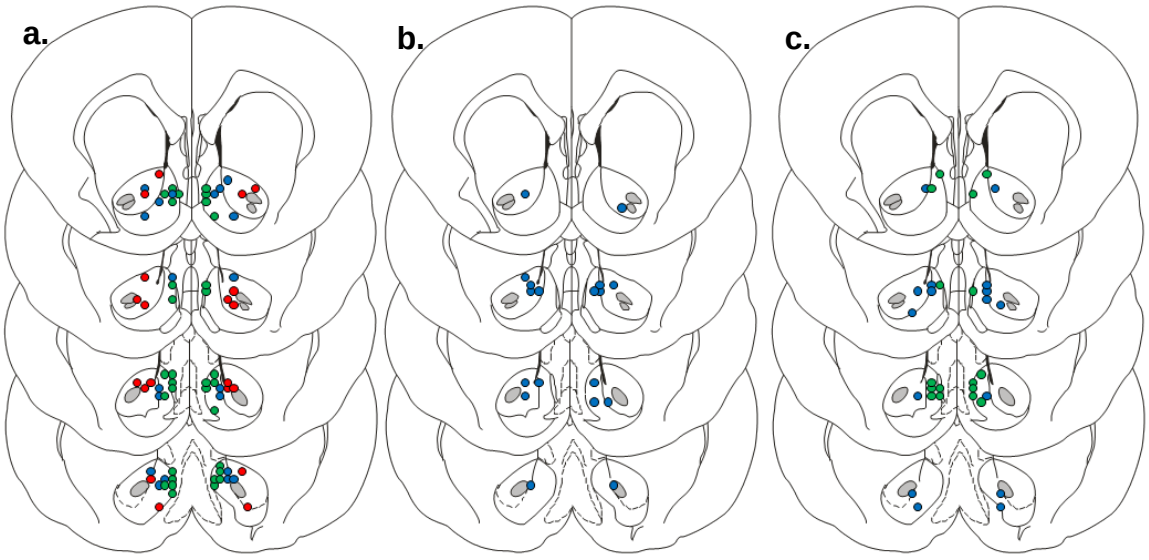

Figure 2. Cannulae/injector placements for (a) the risk discounting task, (b) the risk discounting with fixed probabilities task, and (c) the reward magnitude discrimination task. Blue dots denote entire NAc placements, green dots denote shell placements, and red dots denote core placements

Histology

After completion of behavioral testing, rats were euthanized in a carbon dioxide chamber. Brains were removed and fixed in a 4% formalin solution. The brains were frozen and sliced in 50 µm sections before being mounted and stained with Cresyl Violet. Placements were verified with reference to the neuroanatomical atlas of Paxinos and Watson (1998). Data from rats whose placements were outside the borders of the NAc core or shell, or encroached into the lateral ventricle, were removed from the analysis. Core and shell placements were confined to their respective regions, with no evidence of diffusion into the other. Placements

in the more central portion of the NAc were located along the border of the core and shell, which would permit diffusion across portions of both subregions (Fig. 2).

Data Analysis

The primary dependent measure of interest was the proportion of choices directed towards the large/risky lever for each block of free-choice trials, factoring in trial omissions (an index of risky choice). For each block, this was calculated by dividing the number of choices of the large/risky lever by the total number of successful trials. Choice and response latency data were analyzed using two-way, within-subjects ANOVAs, with treatment and trial block as the within-subjects factors. In each of these analyses, the effect of trial block was always significant ($p < 0.001$) and will not be reported further. Locomotor activity (i.e. photobeam breaks) and the number of trial omissions were analyzed with one-way repeated-measures ANOVAs. Pairwise comparison tests (Dunnett's) were used when appropriate.

When inactivation of the NAc or one of its subregions induced a significant effect on choice on the standard risk discounting task, we conducted a supplementary analysis to further clarify whether changes in choice behavior were due to alterations in sensitivity to reward (win-stay performance) or negative feedback (lose-shift performance) (Bari et al., 2009). Animals' choices during the task were analyzed according to the outcome of each preceding trial (reward or non-reward) and expressed as a ratio. The proportion of win-stay trials was calculated from the number of times the rat chose the Large/Risky lever after choosing the risky option on the preceding trial and obtaining the large reward (a win), divided by the total number of free-choice trials where the rat obtained the larger reward. Conversely, lose-shift performance was calculated from the number of times they shifted choice to the Small/Certain lever after choosing the risky option on the preceding trial and were not rewarded (a loss), divided by the total number of free-choice trials resulting in a loss. Changes in win-stay performance were used as an index of reward sensitivity, whereas changes in lose-shift performance served as an index of negative feedback sensitivity.

III. RESULTS

Experiment1: Effects of inactivation of the NAc and its subregions on risk-discounting.
NAc inactivations. In our first experiment, we infused a larger dose and volume of baclofen/muscimol aimed at the border between the core and shell, in order to induce a broader inactivation of both subregions of this nucleus. Rats in this experiment were trained on the risk discounting task for an average of 26 days prior to being implanted with guide cannulae into the central NAc, retrained on the task and receiving counterbalanced microinfusions. Analysis of choice behavior following bilateral infusions of baclofen/muscimol or saline into the NAc (n=10) revealed a significant main effect of treatment ($F(1,9) = 12.87$, $P < 0.01$; Fig 3a) but no significant treatment x block interaction ($F(3,27) = 1.76$, n.s.). NAc inactivation caused a significant decrease in the proportion of choices directed toward the Large/Risky lever relative to saline infusions. Inspection of Figure 4a reveals that this effect was apparent during the first, 100% probability block, and persisted through the next two blocks. Although there was no significant treatment x block interaction, this observed difference in the first three blocks prompted an exploratory analysis. A paired sample t-test comparing an average of choice behavior over the first three blocks was conducted between saline and inactivation. The same analysis was conducted comparing the last block choice data between the two treatment conditions. These analyses revealed a significant effect of treatment on the first three blocks ($t(9) = 3.324$, $P < 0.01$) but no effect on the final block ($t(9) = 0.254$, n.s.) Inactivation of the NAc also induced a significant increase in response latencies ($F(1,9) = 8.45$, $P < 0.05$; Table 1). Locomotion was significantly decreased following infusion of baclofen/muscimol relative to saline ($F(1,9) = 23.71$, $P < 0.005$; Table 1). Omissions were significantly increased following infusion of baclofen/muscimol relative to saline ($F(1,9) = 7.98$, $P < 0.05$; Table 1).

We conducted a supplementary analysis on the proportion of “win-stay” and “lose-shift” trials after inactivation and control treatments to determine whether inactivation of the NAc altered reward or negative-feedback sensitivity, respectively. Analysis of win-stay trials revealed a significant effect of treatment ($F(1,9) = 9.77$, $P < 0.05$; Fig 3d). Specifically, inactivation of the NAc decreased the probability of choosing the risky option following a “win” on the large/risky lever relative to saline treatment. In contrast, lose-shift performance was not altered following inactivation of the NAc ($F(1,9) = 0.00$, n.s). Thus, these results

indicate that inactivation of the NAc reduces preference for the larger, uncertain rewards most prominently when it would be more advantageous to do so when compared to smaller/certain rewards. Furthermore, this effect appears to be due primarily to a decreased sensitivity to reward. NAc inactivation made rats less likely to select the risky option following receipt of the large reward on the previous trial, as opposed to an exaggerated tendency to shift to the small/certain option after reward omission.

NAc shell inactivations. Eighteen rats with accurate placement within the NAc shell were used in the analysis. These rats were trained on the risk discounting task until showing stable and normal discounting behavior after an average of 24 days prior to implantation with cannulae in the NAc shell followed by retraining and counterbalanced infusions. Analysis of choice behavior following baclofen/muscimol or saline into the NAc shell revealed a significant main effect of treatment ($F(1,15) = 4.771$, $P < 0.05$; Fig. 3b) but no treatment x block interaction ($F(3,45) = 0.978$,n.s.). As was observed following larger infusions of baclofen/muscimol into the central NAc, inactivation of the NAc shell also lead to a decreased preference for the Large/Risky lever, although this effect was somewhat smaller than that observed in the previous experiment. In contrast, these treatments did not alter response latencies ($F(1,15) = 0.353$,n.s.; Table 1), locomotor activity ($F(1,15) = 3.055$, $P > 0.05$; Table 1), or trial omissions ($F(1,15) = 0.374$, n.s; Table 1).

The effect of treatment in the NAc shell on win-stay performance trended toward significance ($F(1,15) = 4.01$; $p=0.06$, Fig 3e). The nature of this trend was similar to that observed after inactivation of the entire NAc, such that inactivation of the NAc shell decreased the probability of choosing the risky option following a win on the large/risky lever relative to saline treatment. In contrast, lose-shift performance was not altered following inactivation of the NAc shell ($F(1,15) = 1.11$, n.s). The trend of these data suggest that similarly to the entire NAc, inactivation of specifically the NAc shell decreases sensitivity to reward.

These data suggest that the reduced preference for the Large/Risky option induced by larger inactivation of the NAc were attributable primarily to suppression of neural activity within the NAc shell.

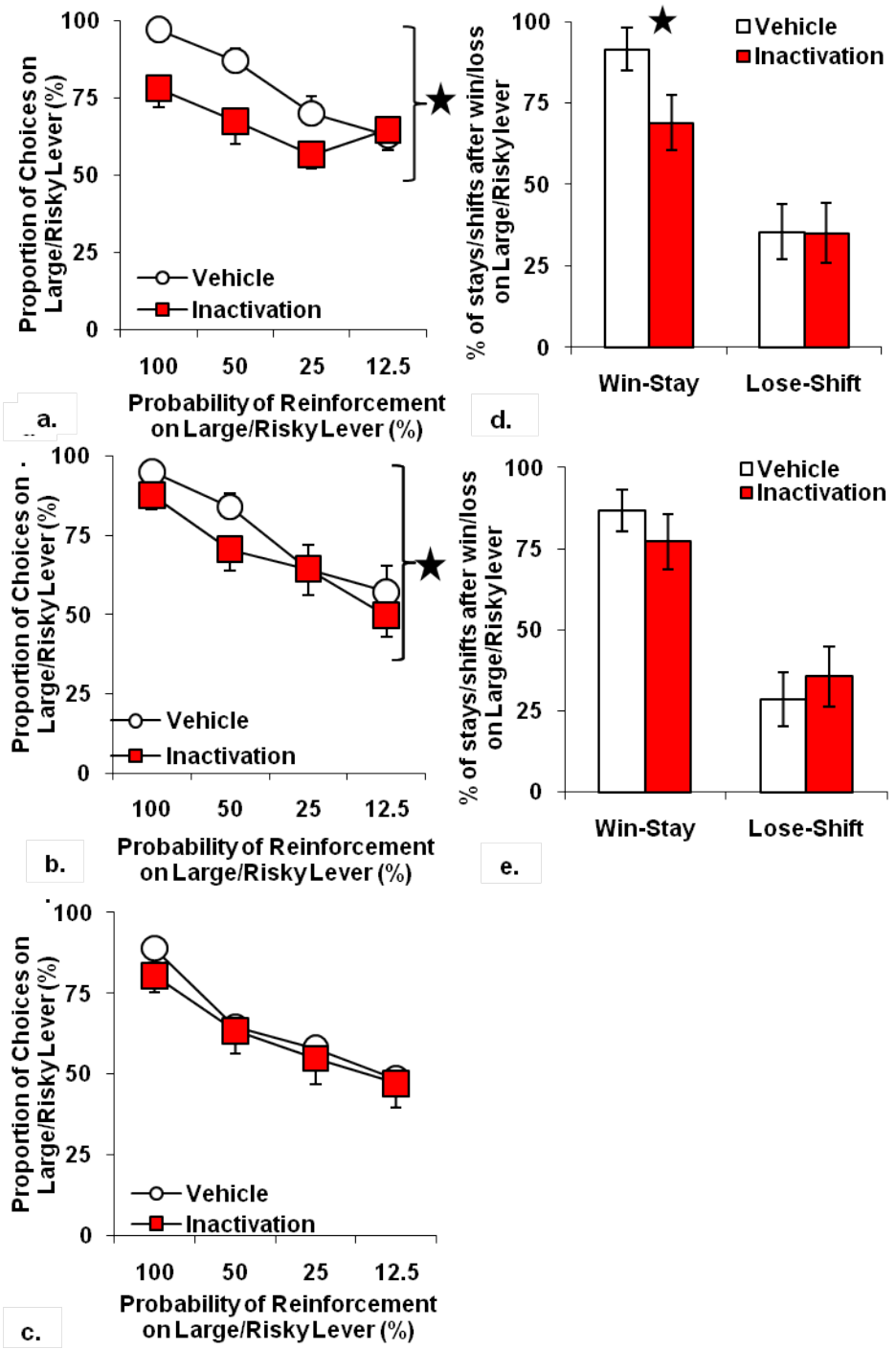

Figure 3. Choice data for the risk discounting task following inactivations of the (a) entire NAc, (b) NAc shell, and (c) NAc core. Data are displayed as the proportion of choices on the Large/Risky lever during free choice trials on each of the four different probability blocks. Also presented are win-stay and lose-shift data for the (d) entire NAc and the (e) NAc shell. Win-stay data is displayed as the proportion of choices on the large/risky lever following rewarded trials on the large/risky lever. Lose-shift data is displayed as the proportion of choices on the small/certain lever following unrewarded trials on the large/risky lever. Stars denote a significant main effect of treatment on choice behavior at the 0.05 level. Inactivation of the NAc, or more selective inactivation of the shell, but not core, reduced preference for the Large/Risky lever.

Entire NAc.	Vehicle	Inactivation
Latency (ms)	721 +/-113	1314** +/-265
Locomotion	1976 +/-135	1375*** +/-163
Omissions	0.40 +/-0.31	5.30* +/-0.02

NAc Shell.	Vehicle	Inactivation
Latency (ms)	791 +/-117	919 +/-209
Locomotion	1476 +/-162	1713 +/-170
Omissions	1.88 +/-1.07	3.50 +/-0.55

NAc Core.	Vehicle	Inactivation
Latency (ms)	729 +/-91	1392* +/-198
Locomotion	1878 +/-215	1182** +/-187
Omissions	0.60 +/-0.31	6.30 +/-3.11

Table 1. Risk discounting auxiliary data for inactivations of the entire NAc, the NAc shell and the NAc core. Locomotion counts are measured in photobeam breaks. Values are displayed as means +/- SEM * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.005$ between vehicle and inactivation.

NAc core inactivations. Data from ten rats with accurate placements within the NAc core were included in the analysis. In stark contrast to what was observed following inactivation of the NAc, or more specific inactivation of the NAc shell, infusions of baclofen/muscimol into the NAc core did not induce a significant change in choice behavior relative to saline infusions (main effect of treatment: $F(1,9) = 0.28$, n.s.; treatment x block interaction: $F(3,27) = 0.34$, n.s.; Fig. 3c). However, as was observed following NAc inactivation, these treatments did significantly increase response latencies relative to saline ($F(1,9) = 5.84$, $P < 0.05$; Table 1c) and decreased locomotion ($F(1,9) = 13.40$, $P < 0.01$; Table 1). There was no significant effect of treatment on omissions ($F(1,9) = 3.11$, $P > 0.05$; Table 1). These data suggest that the increased response latencies and decreased locomotion induced by larger inactivation of the NAc were attributable primarily to suppression of neural activity within the NAc core.

Experiment 2: Effects of inactivation of the NAc on risk-discounting with fixed probabilities.

Experiment 1 revealed that inactivation of the NAc reduced preference for the Large/Risky option, with this effect being most prominent when this option was more advantageous than the Small/Certain option. Experiment 2, employed a simplified version of the risk discounting task to determine if inactivation of the NAc induced a general decrease in preference for Large/Risky rewards, or more selective effect under conditions when the risky option was more advantageous.

Rats were trained on a simplified risk task where the probability of reinforcement on the Large/Risky lever was fixed at 40% over the entire session. Using these probabilities, selection of the Large/Risky lever would have a greater long-term value (4 pellets @ 40%) relative to the Small/Certain lever (1 pellet @ 100%). Accordingly, after 12 days of training, rats displayed stable bias towards the Large/Risky lever, selecting this option on ~75% of free-choice trials. They subsequently received their first round of counterbalanced infusions of saline and baclofen/musimol. Analysis of choice behavior revealed a significant main effect of treatment ($F(1,8) = 5.88$, $P < 0.05$; Fig. 4, left). NAc inactivation caused a small but significant decrease in the proportion of choices directed to the Large/Risky lever relative to saline infusions. There was no significant effect of treatment on latencies ($F(1,8) = 0.01$,n.s.; Table 2) or trial omissions ($F(1,8) = 0.760$, n.s.; Table 2). Locomotor activity was reduced following NAc inactivation, but this effect only approached statistical significance ($F(1,8) = 4.56$, $P =0.06$.; Table 2)

Rats were subsequently retrained on the task, with the probability of reinforcement on the Large/Risky lever fixed to 10%. Under these conditions, the Small/Certain option would yield more reward in the long-term, and after 15 days of training, rats shifted their bias away from the Large/Risky lever, selecting it on <30% of free-choice trials. They subsequently received a second round of counterbalanced microinfusions. In contrast to the above-mentioned findings, under these conditions, inactivation of the NAc had no significant effect on choice ($F(1,8) = 0.041$,n.s.; Fig. 4 right). Similarly, there were no significant effects of treatment on latencies ($F(1,8) = 0.030$, $P > 0.05$; Table 2) or omissions ($F(1,8) = 0.100$, $P > 0.05$; Table 2). However, infusion of bacolfen/muscimol into the NAc was still effective at decreasing locomotor activity compared to saline ($F(1,8) = 5.600$, $P < 0.05$; Table 2b).

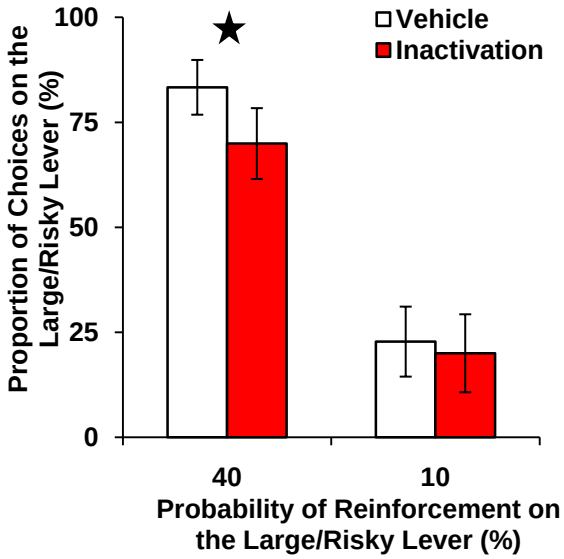

Figure 4. Choice data for the fixed probability risk task following inactivations of the entire NAc. Data are displayed to compare treatments within each of the fixed probability sessions. Stars denote a significant main effect of treatment on choice behavior at the 0.05 level.

These findings are consistent with those of the risk discounting task, demonstrating that inactivation of the NAc biases choice away from the large/risky lever when that option had greater long-term value relative to the small/certain option. However, when the odds of obtaining the larger reward were relatively low (i.e., the small/certain option had greater long-term value), inactivation of the NAc did not affect choice behavior.

40% .	Vehicle	Inactivation
Latency (ms)	744 +/-140	764 +/-128
Locomotion	1205 +/-131	851 +/-96
Omissions	0.11 +/-0.11	1.00 +/-1.00

10%	Vehicle	Inactivation
Latency (ms)	582 +/-52	570 +/-85
Locomotion	1078 +/-158	889* +/-145
Omissions	0.67 +/-0.37	0.56 +/-0.38

Table 2. Fixed probabilities risk auxiliary data following inactivations of the entire NAc with the reinforcement probability of the Large/Risky lever set to 40% and 10%. Locomotion counts are measured in photobeam breaks. Values are displayed as means with SEM. * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.005$ between vehicle and inactivation.

Experiment 3 Effects of Inactivation of the NAc or NAc shell on reward magnitude discrimination

In Experiment 1, inactivation of the NAc, or more selective inactivation of the shell reduced preference for the larger, uncertain reward. In Experiment 3, a separate group of rats were trained on a simpler task, where they chose between two levers that delivered either one or four pellets, both with 100% probability.

NAc inactivations. Eight rats were trained for 10 days on this task before receiving counterbalanced microinfusions of baclofen/muscimol and saline. Following saline infusions, rats displayed a very strong bias towards the larger reward, selecting this option on nearly 100% of the trials (Fig 5a). Following infusions of baclofen/muscimol, rats continued to display a strong bias towards the four-pellet option, yet, the preference for this option was slightly reduced. Analysis of choice behavior confirmed that slight reduction in preference was statistically significant ($F(1,7) = 6.34$, $P < 0.05$). There was no significant main effect of treatment on locomotion ($F(1,7) = 1.83$, n.s.; Table 3) or omissions ($F(1,7) = 2.05$, n.s.; Table 3). The locomotion sensors malfunctioned in the chambers of four of the animals on their saline infusion day. Therefore, locomotion data for both treatments for these four animals was not included in the analysis. Similar to the standard risk discounting task and the risk discounting with fixed probabilities task, the effect of inactivation of the entire NAc on latencies approached significance ($F(1,7) = 3.94$, $P = 0.08$; Table 3a).

NAc shell inactivations. A similar profile was observed in another eight rats that received inactivation of the NAc shell. Again, rats selected the four-pellet option on almost all of the free choice trials after saline infusions. However, infusions of baclofen/muscimol into the NAc shell caused a slight, but statistically significant decrease in choice of the larger reward ($F(1,7) = 8.18$, $P < 0.05$; Fig. 5b). However, there was no significant effect on latencies, locomotion, or omissions (all $Fs < 1.9$, n.s.). Collectively, these findings suggest that natural bias towards larger versus smaller rewards is slightly blunted following inactivation of the NAc shell.

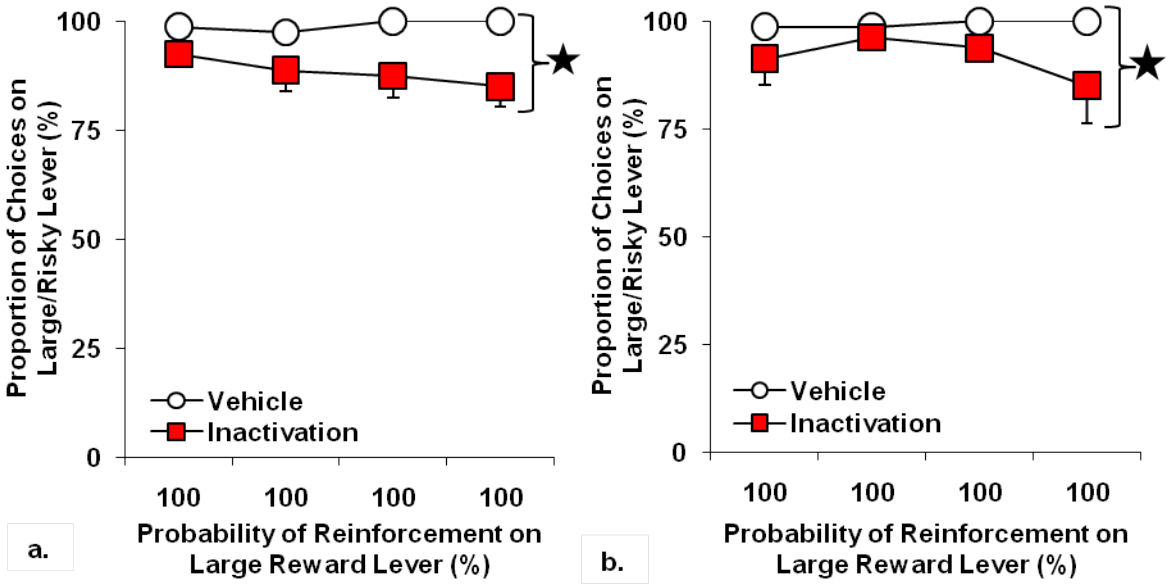

Figure 5. Choice data for the reward magnitude discrimination task following inactivations of the (a) entire NAc and (b) NAc shell. Data are displayed as the proportion of choices on the Large/Risky lever during free choice trials on each of the four different probability blocks. Stars denote a significant main effect of treatment on choice behavior at the 0.05 level.

Entire NAc.	Vehicle	Inactivation
Latency (ms)	764 +/-100	1658 +/-501
Locomotion	938 +/-103	539 +/-70
Omissions	0.00 +/- 0.00	0.88 +/-0.61

NAc Shell	Vehicle	Inactivation
Latency (ms)	793 +/-142	752 +/-126
Locomotion	1176 +/-264	1396 +/-571
Omissions	0.00 +/-0.00	0.13 +/-0.13

Table 3. Reward magnitude discrimination auxiliary data following inactivations of the entire NAc and the NAc shell only. Locomotion counts are measured in photobeam breaks. Values are displayed as means with SEM * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.005$ between vehicle and inactivation.

IV. DISCUSSION

The present data lend further support to the notion that the NAc plays a critical role in biasing the direction of choice between smaller rewards and larger, probabilistic rewards, and provides further insight into the contribution of this nucleus to this form of decision making. The nature of the data and those data of subsequent control experiments suggest that, rather than inducing a general risk aversion or disruption in reward valuation, inactivation of the NAc seems to reduce the bias towards either certain or uncertain larger rewards, when these options have greater long-term value. Furthermore, they reveal that the NAc shell, rather than the core, seems to play a more critical role in guiding this form of decision making.

The ability of the NAc inactivation to reduce preference for the large/risky option appeared to be greatest in the first three trial blocks of the risk discounting task, an effect that closely mirrors that induced following permanent lesions of the NAc using a similar discounting procedure (Cardinal and Howes, 2005). During these trials, the long-term value of the large/risky option is either greater than or equal to that provided by the small/certain option. Thus, in the first block, the probability of obtaining the larger reward was 100% (i.e., no risk associated with this choice). In the second block, even though the larger reward was uncertain, this option was still advantageous, in that it delivers four pellets with a 50% probability as compared to the small/certain lever which delivers one pellet with a 100% probability, so that the overall utility of the large/risky lever is large enough such that its relative value is double that of the small/certain lever. Similarly, in the third block, with a 25% probability, the choice is an arbitrary one, as the probability on the large/risky lever is balanced by the larger reward magnitude, resulting in a choice between two levers with equal relative long-term value. In contrast, during the 12.5% block, the low reinforcement probability outweighs the benefit of potentially receiving a larger reward, which would make the small/certain reward more advantageous. Although the analysis of the data did not produce a statistically significant treatment and trial-block interaction, inspection of Fig 4a shows that the disparity between saline and inactivation in choice of the large/risky lever across blocks, so that during the 12.5% block, there was no apparent difference between treatment conditions in terms of choice, As such, even though the analysis revealed a significant overall decrease in choice of the large/risky lever, this pattern of choice does not suggest that NAc inactivation caused a uniform increase in risk aversion. One would expect

that rational risk aversion would be associated with no change in choice in the early trial blocks, where there is little or no risk, and a decrease in choice of the large/risky lever in the blocks where choices are riskier. It is unlikely that the difference between treatment groups during the last block reflects a floor effect, given that rats still selected this lever on 50-60% of the trials in the last block, and could thus continue to bias choice away from this lever. The different choice pattern observed in these data, with bias away from the large/risky option when it is advantageous but not when it is disadvantageous, suggests a different relationship between NAc function and choice behavior.

Further insight into the contribution of the NAc to risk discounting comes from a detailed analysis of choice behavior on trials following those where animals chose risky and received the larger reward (win-stay) versus those where they selected the risky option and did not receive reward (lose-shift). Under the control condition, animals chose the risky option on <85% of trials following a win after choosing the large/risky option. Thus, obtaining the larger reward had a strong impact on determining how rats chose on the next trial. Changes in choice following receipt of a probabilistic reward may be used as a measure of reward sensitivity (Bari et al., 2010). On trials following a loss on the large/risky option, animals shifted to the small/certain option 35.5% of the time. Lose-shift performance serves as a measure of hypersensitivity to reward omissions. Inactivation of the NAc or the NAc shell selectively reduced win-stay tendencies, demonstrating that obtaining a reward after a risky choice is less effective in biasing animals toward the large/risky option on a subsequent trial. Thus, the NAc functions to bias choice toward the higher magnitude reward, despite risk, when selecting the risky option proved successful on the most recent trial.

In experiment 2, rats were trained on a simpler decision making task, in which they again chose between a small/certain and large/risky option, but the probability of obtaining the larger reward remained constant over a session. When the odds on the large/risky lever were 40%, rats displayed an appropriate bias toward this option. Under these conditions, NAc inactivation decreased choice of the large/risky lever, in a manner consistent with the findings of experiment 1. However, when rats were retrained on the task where the odds of obtaining the four pellet option were fixed at 10%, they displayed a preference for the small/certain option, and inactivation of the NAc did not alter choice behavior. Thus, in this instance, inactivation of the NAc did not alter choice when the more valuable option was the

smaller, certain reward. This latter finding is in keeping with those of Cardinal and Howes (2005), where lesions of the NAc did not alter choice between a certain one-pellet option versus four pellets delivered at 6. 25%. Taken together, these findings suggest that within the context of risk-based decision making, the NAc appears to contribute to biasing the direction of choice toward more valuable rewards primarily when this option is of a larger magnitude. This reinforces the trend displayed by the risk discounting data, in that there is a decrease in large/risky choice when the odds of obtaining the larger reward are more advantageous, and no such effect when the large/risky option is disadvantageous.

In both experiments 1 and 2, inactivation of the NAc reduced choice of the option associated with the larger reward. To more clearly understand the nature of this effect we tested a separate group of animals on a reward magnitude discrimination task to determine if inactivation of the NAc causes an irrational decrease in choice of a larger reward with no associated cost. Inactivation of the entire NAc or more selective inactivation of only the shell resulted in a significant decrease in choice of the four pellet lever. Note that in this experiment, rats continued to display a prominent bias towards the larger reward after inactivation of the NAc (~90%), but this was consistently lower than that displayed after saline infusions (~99%). These results indicate that the NAc shell does make a somewhat minor contribution to the normal bias animals have towards larger versus smaller rewards. Interestingly, other researchers have failed to observe an effect of NAc lesions on reward magnitude discrimination. There may be a number of reasons. First, unlike the present study that used a within-subjects design, many of these previous studies used permanent lesions to the NAc, so only between-subjects designs were possible, resulting in a lack of statistical power to observe a statistically significant effect (Cardinal et al., 2000; Cardinal and Cheung, 2005; Cardinal and Howes, 2005). Second, animals in the lesion studies were trained for a number of days post-lesion but the data was only examined for a few days late in re-training (Cardinal and Cheung, 2005; Cardinal and Howes, 2005) compared to the present study, in which performance was examined on only one day during inactivation. Moreover, it is important to note that in at least one study (Cardinal and Howes, 2005), lesions of the NAc did cause a slight decrease in choice of the larger reward, but the observed data only trended toward significance ($p=0.13$ in that study). Finally, many of these studies utilized only manipulations to the core when examining reward magnitude discrimination (Cardinal and

Howes, 2005; Ghods-Sharifi and Floresco, 2010). The present results suggest that the shell may be a key region of the ventral striatum that may bias choice towards larger rewards. Despite these findings, it must be noted that the shift in bias away from the larger reward option after inactivation of the NAc was greater on the risk discounting task than that observed with the reward magnitude discrimination task. This suggests that while the NAc may be play a fundamental (albeit small) role in biasing choice between rewards of different magnitudes, neural activity in this nucleus makes an even greater contribution to decision making requiring integration of a variety of information, including reward magnitude, risk or other costs, etc., to bias the direction of behavior towards more favorable outcomes.

Although the NAc has been shown to influence risk-based decision making, the finding that the shell, rather than the core subregion, played a more critical role in biasing choice was somewhat unexpected based on what has been demonstrated in previous studies of other forms of cost/benefit decision making. Specifically, lesions to the NAc core, but not shell, have been shown to reduce the time animals are willing to wait for reward using a variety of tasks. Selective lesions to the NAc core induced impulsive choice on a delay-discounting task in which animals chose between a small but immediate reward and a larger reward with a delay component that varied over the course of the session (Cardinal et al., 2001). On a delayed reward choice task, rats with core lesions, but not shell lesions, shifted response from a continuously reinforced lever to a partially reinforced lever when a delay component was associated with the continuously reinforced lever (Pothuizen et al., 2005). Also, on a differential reward for low rates of responding (DRL) task, only core lesions impaired withholding the response for a fixed time period in order to receive reward (Pothuizen et al., 2005). With regard to effort-based decision making, on a T-maze task, in which animals could choose between climbing a barrier to obtain a large reward or obtain a small reward without a barrier, lesions of the NAc core decreased the tendency of animals to work harder for the larger reward (Hauber and Sommer, 2009). Ghods-Sharifi and Floresco (2010) utilized an effort discounting task to dissociate the core and shell with regard to effort-based decision making. On discrete trials, animals chose between an immediate small reward after a single press on one lever, and a large reward associated with a greater effort cost (i.e., 2-20 press). Both on the standard task and an associated equivalent delays procedure (used to isolate effort from the delay associated with increased lever pressing),

inactivation of the NAc core, but not the shell, biased choice away from the larger reward with the effort component. In these other forms of decision making, selecting the large reward option incurs a cost, but regardless of choice, the organism is always certain a reward will be received. In comparison, risk-based decision making involves a component of uncertainty not present in effort- and delay-based decision making. In other words, unlike with risk-based decision making, when animals choose a high effort or long delay option, they incur a cost, but they know as long as they fulfill the cost requirement they will always receive reward. The fact that inactivation of the shell, but not core, altered choice on the risk discounting task may be related to the proposed role of this subregion in the detection and reaction to novelty. Neural activity in the NAc shell has been proposed to be particularly important under conditions involving cognitive processing related to novelty and uncertainty on tasks involving food neophobia or novel environments (Burns et al., 1996; Rebec et al., 1997; Wood and Rebec, 2004). Though not identical, the type of uncertainty present in the current experimental paradigm (uncertainty of receipt of reward) shares similar characteristics with these novelty paradigms, in that this novelty is based on uncertainty as to the safety of the unfamiliar food or environment.

Despite the fact that inactivation of the NAc core did not alter choice, these manipulations were not without effect, as infusions of GABA agonists into this region did significantly increase response latencies and reduce general locomotor activity. The increased response latency observed following inactivation of the core indicates that a functional NAc core is necessary for making decisions under risk in a timely fashion. Inactivation of the entire NAc produced the full profile of effects: reduced choice of the large/risky lever, decreased locomotion, and increased response latency. However, there is a double dissociation between the core and shell, such that inactivation of only the shell reduced choice of the large/risky lever, while inactivation of only the core increased response latency.

The results of the current experiments support and elaborate on the findings of the imaging data regarding NAc function and risk-based decision making. In their study linking brain function to financial risk-taking, Kuhnen and Knutson (2005) found NAc activation to precede risky choices and risk-seeking mistakes. Similarly, our data show, through experimental manipulation, that inactivation of the NAc decreases risky choice. Taken

together, it appears that increased neural activity in the NAc biases selection of a risky option associated with larger reward.

As is observed from the findings of the current experiments, imaging data has also demonstrated the NAc to be involved in general value discrimination in addition to risk-taking/seeking. Various research indicates that the NAc is activated in relation to higher valued rewards based on indices of anticipated reward vs. non-reward (Knutson et al., 2001), anticipated gain magnitude (Knutson et al., 2005) and product preference (Knutson et al., 2007). These studies complement the present data by demonstrating with which cognitive processes NAc activation is associated rather than demonstrating the consequences of inactivating the NAc on decision making. This set of imaging studies also illustrates that the NAc, in addition to increasing risky choice, is responsible for general value judgments.

Recordings from the NAc indicate that the behavior of these neurons is correlated with choice during decision making. Roesch et al. (2009) utilized a choice task in which relative delay (cost) or reward magnitude was manipulated. Their findings indicate that neurons in the ventral striatum encode for overall expected value as well as the speed in which decisions were executed. Additionally, fast-scan cyclic voltametry, which measures changes in mesoaccumbens dopamine on a subsecond time-scale, has begun to elucidate the role of phasic dopamine in the NAc. Gan et al. (2010) examined the difference between cost manipulation (lever presses) and benefit manipulation (reward magnitude) with regard to NAc dopamine transmission. The NAc dopamine signal was found to be sensitive to differences in reward magnitude regardless of whether the reward magnitude of the alternative choice was less than or greater than that of the reference. However, with regard to cost manipulations, only the lower cost alternative lowered phasic dopamine transmission. No increase in dopamine transmission was observed with relation to an increase in response cost. In keeping with these findings, Day et al. (2010) conducted a study in which dopamine release was recorded as animals responded on one of two levers which differed with regard to response cost (effort or delay) but delivered equal reward magnitude. On forced choice trials, the dopamine signal following cue presentation was greater in prediction of the low cost option as compared to the high cost option. These studies indicate that the NAc encodes for an overall representation of value, including both costs and benefits, and ensures that these value judgments can be made in a timely fashion. By manipulating benefit and holding

cost constant (and vice versa), these studies also establish the notion that cost and benefit can be processed independently of one another, and NAc dopamine plays a strong role in regulating these processes.

The findings of the current experiments are consistent with, and expand upon, the findings of these electrophysiological and voltametric studies. The data support the notion that ventral striatal neurons process expected overall value as well as the speed at which decisions regarding choices between options of different value are made. Additionally, they indicate that the shell seems to be processing expected overall value while the core is responsible for processing the speed of these decisions. Gan et al. (2010) suggest that dopamine in the accumbens is responsible for processing differences in reward magnitude when cost is held constant. This agrees with our observation that inactivation of the accumbens creates a difficulty for animals in deciding between two options possessing equal cost but different reward magnitude.

When evaluating the contribution of the ventral striatum to behavior, it is important to highlight that the NAc must be viewed within the context of the cortico-limbic-striatal circuit. Two other key inputs to the NAc that reside in this circuit and have been implicated in risk-based decision making are the medial prefrontal cortex (mPFC) and the basolateral amygdala (BLA). The pattern of choice behavior observed following BLA inactivation is similar (but not identical) to that observed following NAc inactivation (Ghods-Sharifi et al., 2009), inducing a decrease in choice of the large/risky lever overall but observed mainly in the middle two trial blocks, when the relative value of the large/risky option was most ambiguous. However, inactivation of the mPFC produces a different pattern of choice, suggesting that it may exert top-down control to the BLA and NAc to fine-tune behavior as the probabilities change within a session (St. Onge and Floresco, 2010). Though further work, such as functional disconnection studies, remains to be conducted, it appears that input from the basolateral amygdala may a critical input to the NAc that aids in biasing choice towards larger, probabilistic rewards of greater long-term value. However, even though the pattern of choice behavior observed following BLA inactivation (Ghods-Sharifi et al., 2009) was similar to that observed after NAc inactivation (present study), there were differences between the two sets of findings as well. It is plausible, therefore, that fine-tuning from mPFC and other regions in the cortico-limbic-striatal circuitry may ultimately result in the

profile of choice behavior seen from NAc inactivation. A reduced preference for the large/risky option on the risk discounting task following NAc inactivation was observed in the first trial block, when the probability on the large/risky lever was 100%. This pattern of choice was not observed following BLA inactivation. Additionally, while NAc inactivation significantly decreased preference for the large reward on the reward magnitude discrimination task, no such effect was observed following BLA inactivation. Finally, unlike NAc inactivation, which decreased win-stay tendencies and did not change lose-shift tendencies, the BLA has been implicated in mediating lose-shift tendencies (De Martino et al., 2010; Dreher, 2007). Thus, while the NAc is responsible for maintaining proper sensitivity to reward, the BLA ensures normal loss aversion. Overall it seems that the BLA aids in overcoming risk aversion, biasing choice towards larger rewards only when the cost of uncertainty exists, especially following reward omission after a risky choice. Conversely, the NAc appears to play a more general role in reward value judgment, biasing choice towards larger rewards, whether receipt of those rewards is uncertain or not (though this bias is greater when uncertainty exists). This function is particularly apparent after receipt of a large/risky reward. Thus, the BLA and NAc may play distinct yet complementary roles to ensure that an organism may overcome costs such as risk to increase the likelihood of obtaining larger rewards. Further work is required to examine the functional connections between these two regions as well as connections of the NAc with other regions to precisely determine the fine-tuning taking place which designates the accumbens as a structure involved in reward value discrimination as opposed to judgments specifically of risk under uncertainty. Future studies, including, but not limited to, experiments manipulating the cost of uncertainty of options with identical benefit, will bring a more detailed understanding to the NAc with regard to processing of overall utility.

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APPENDIX A: UBC Animal Care Committee Approval

THE UNIVERSITY OF BRITISH COLUMBIA

ANIMAL CARE CERTIFICATE

Application Number: A06-0300

Investigator or Course Director: Stan Floresco

Department: Psychology, Department of

Animals:

Rats Sprague Dawley 80
Rats Long Evans 160

Start Date: **July 1, 2006** **Approval Date:** **June 25, 2008**

Funding Sources:

Funding Agency:	Canadian Institutes of Health Research (CIHR)
Funding Title:	Alternations in amygdala-prefrontal cortex circuitry by repeated psychostimulants: Electrophysiological and behavioural analyses
Funding Agency:	Parkinson Society Canada
Funding Title:	Dopaminergic mechanisms underlying risky decision-making
Funding Agency:	Canadian Institutes of Health Research (CIHR)
Funding Title:	Functional interactions between basolateral amygdala and mesocortical dopamine inputs to the medial prefrontal cortexd: electrophysiological and behavioral analyses
Funding Agency:	Dainippon Sumitomo Pharma Co., Ltd.
Funding Title:	Animal models of cognitive deficits in schizophrenia

Unfunded title: n/a

The Animal Care Committee has examined and approved the use of animals for the above experimental project.

This certificate is valid for one year from the above start or approval date (whichever is later) provided there is no change in the experimental procedures. Annual review is required by the CCAC and some granting agencies.

A copy of this certificate must be displayed in your animal facility.

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