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Dissociable contribution of nucleus accumbens and dorsolateral striatum to the acquisition of risk choice behavior in the rat

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ABSTRACT

While a growing body of research has suggested that the mesocorticolimbic dopamine systems play a key role in decision making under risk, how the nucleus accumbens (NAC) is involved in the acquisition of risk choice behavior remains unclear. This study used a T-maze task to assess risk-based decision making in which the rat was required to assess the risk by choosing to enter either a small and certain reward arm or a large but uncertain reward arm of the maze. The latter option, when chosen, resulted in provision of 2, 4, or 8 sweeten pellets with a probability (p) of 0.5, 0.25, or 0.125, respectively. Thus the latter arm provided three different conditions of reward ratio, compared to the choice of former arm, which always provided 1 pellet with $p = 1$. This risk choice task was then run with the expected value being equality between the binary choice options. The experimental rats first received an excitoneurotoxic lesion affecting either the NAC or the dorsolateral striatum (DLS) and this was followed by post-lesion behavioral examination. The sham lesion control rats acquired a stable risk choice with regard to each reward ratio over a 10-day test. The pattern of choice behavior appeared in risk-seeking when $p = 0.5$ to obtain 2 pellets, and was risk-averse when larger reward resulted in lower p. The NAC lesion significantly disrupted the acquisition of the aforementioned risk choice behavior and apparently shifted the choice into a risk-averse style for all three reward ratios. No such effect was observed in the rats with DLS lesions. Neither the gross motor action nor the discrimination of different reward magnitudes was impaired by the lesions affecting either the NAC or DLS as assessed by an additional experiment. These findings suggest that firstly there is heterogeneity between NAC and DLS with respect to risk-based decision making, and that secondly the NAC is involved and critical to the acquisition of behavioral choice under risk, specially when the expected value of the reward under the two choice options is equal.

1. Introduction

Animals including humans often make decisions that involve components of risk or uncertainty (Balci, Freestone, & Gallistel, 2009; Paglieri et al., 2014; Trimmer et al., 2011). The individual is not entirely sure about the future reward to be obtained. As a result, both a risk and an expected reward are associated with each choice option to be considered for the engendering action outcomes with respect to the more valuable that should lead to optimal survival. Thus the expected reward value of an action during risk-based decision making can be represented by the product of the value of an outcome and its relative probability of occurrence. The phenomenon of probability discounting occurs when the subject responds toward in a risk-averse manner, due to a decrease in the probability of obtaining a reward that has the appearance of risk (Cardinal, 2006; Green & Myerson, 2004). Recently, aberrant or maladaptive risk-related decision making has been observed in a number of psychiatric populations including those with drug addiction, mood disorders, and schizophrenia (Jentsch et al., 2014; Paulus, 2007; Stopper & Floresco, 2015). However, the causal relationship between psychiatric disorders and maladaptive decision making remains unclear. Thus, it is important to delineate the underlying neural substrates and mechanisms associated with risk decision making; this will assist our understanding of this phenomenon and help with the development of treatments for these brain/mental disorders (Lee, 2013).

In order to probe the underlying neural mechanisms, several types of animal model used to test risk-related decision making

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have been developed in the past two decades (see a review by Orsini, Moorman, Young, Setlow, & Floresco, in press). Of particular interest, when testing risk-based decision making, a typical binary choice task can be set up for a rodent subject during which there is choice between either a small but certain reward (probability; $p = 1$) and a larger reward that is obtained with a degree of uncertainty (e.g. $0 < p < 1$). Accumulating evidence from lesion and psychopharmacological studies has indicated that the midbrain dopamine (DA) systems are involved in modulating risk-based decision making. Using systemic drug treatments, amphetamine (an indirect DA agonist) and flupenthixol (a non-selective DA receptor antagonist) have been shown to increase and decrease, respectively, the preference for taking the risky large reward option when carrying out a probabilistic discounting task (Floresco & Whelan, 2009; Mai, Sommer, & Hauber, 2015; St. Onge, Chiu, & Floresco, 2010). The risk-prone response induced by amphetamine can be partially reversed by treatment with the selective DA D1 and D2 receptors antagonists, SCH23390 and eticlopride, respectively (St. Onge & Floresco, 2009). Further evidence for an involvement of the nucleus accumbens (NAC) in risk associated choice has been obtained through studies that have used brain lesions, microinjection, and neurochemical measurements. For example, the enhancement of DA release in the NAC has been found to be correlated with the individual differences in a risk-taking behavior as monitored by voltammetry (Sugam, Day, Wightman, & Carelli, 2012). Similarly, risk choice in relation to a probability discounting task has been measured by using a microdialysis approach (St. Onge, Ahn, Phillips, & Floresco, 2012). When intra-NAC microinjection of drugs that can selectively activate or block DA subtype receptors is carried out, it was found that NAC D1 receptors would seem to play a more important role in the modulation of the risk choice on a probability discounting task than NAC D2/D3 receptors (Stopper, Khayambashi, & Floresco, 2013). While the roles of DA receptor subtypes may not be clearly dissected yet, it would seem that the subareas of the NAC were thought to be in the control of risk choice behavior are heterogeneous in nature. The D1/D2 receptors in the core, but not the shell, subarea of the NAC would seem to be involved in the risk-based decision making; this has been validated by locally infusing flupenthixol into the NAC core, which was found to suppress a preference for the large/risky choice with respect to a probability discounting task (Mai et al., 2015). Several excitotoxic lesion studies have shown the involvement of NAC in risk choice behavior, but with the mixed results. That rats with a NAC lesion were found to display a risk-averse pattern of choice behavior with respect to a probability discounting task was initially reported by Cardinal and Howes (2005); however, Acheson et al. (2006) reported that a NAC lesion slightly, but not reach the statistical significance, affected the discounting of probabilistic rewards. Despite these inconsistent results, a more recent study has reported that inactivation of NAC by local infusion of GABA agonists was able to produce risk-averse response (Stopper & Floresco, 2011). These findings, when taken together, support a notion that the NAC or brain DA is involved in the modulation of risk-based decision making. It is important to note that all of the NAC-related data were collected when the experimental treatment was given after behavioral training (namely, they involved post-training lesions). Up to now, very few studies have used pre-training lesions when carrying out such behavioral task (Mai & Hauber, 2012). Thus, it remains to be determined whether the mesoaccumbens DA system makes a critical contribution to the acquisition/development of risk choice behavior when a pre-training lesion approach is used.

Risk, in a sense, can be defined as the variance in the desired reward outcome. If we take this into account, the level of risk can be directly manipulated by holding the overall reward or payoff constant while changing only the variance. If not, the reward magnitude is likely to be confounded by the risk. This concern, however, has been rarely given attention during the experimental design of the aforementioned studies. The previous studies as described above, namely those with a probability discounting task, were carried out by manipulating the reward probabilities and holding the reward magnitude of the risky option as a constant. With this set up, the expected value (EV) is shifted across each of the different reward probabilities. In other words, the binary choices options set in those previous studies yield unequal payoff and this will have caused the risk to vary, but not to increase along with a reward probability decreased. Thus, it is worth to disentangle the differences that potentially existed between a test associated risk as a behavioral choice and those of the reward probability discounting.

The present study used a T-maze set up to evaluate the risk choice behavior. As the task, the rat was required to assess the risk by choosing entry to either a risky large reward arm of the maze or to a certain small reward one. The former option was set up with a p of 0.5, 0.25, or 0.125 correspondingly being given 2, 4, or 8 sweeten pellets as the different reward ratio conditions, whereas the latter option was provided as a choice outcome that always gave 1 pellet ($p = 1$). Accordingly, this risk choice task was run under a condition with the EV being equal for these binary options. The present study investigated the role of the NAC on the acquisition of risk choice behavior by conducting excitotoxic lesions prior to behavioral training. A counterpart experiment where there were lesions of the dorsolateral striatum (DLS) conducted for a comparative purpose. The dorsal striatum is thought to be important to reward-mediated decision making (Balleine, Delgado, & Hikosaka, 2007), but how this region or its subareas are involved in behavioral choice under risk has not yet been examined. We expected to find differences in the profiles with respect to behavioral choice under risk for the rats with pre-taring lesions of NAC and DLS compared to the sham lesion controls.

2. Methods

2.1. Subjects

Male Wistar rats (BioLASCO Taiwan Co., Ltd.) were used that averaged approximately 200 g of body weight on arrival. The rats were housed individually. After 10 days of adaptation to the food and water provided *ad libitum*, the rats were maintained on a food-restriction regimen such that about 15 g of laboratory rodent pellets were provided in their home cage no sooner than 30 min after the end of each daily experimental session. The rats were monitored and kept at 85% of their pre-restriction body weight. Water was continuously available in each home cage. Training and/or test sessions were conducted daily at the same time (9:00–16:00) each day during the light portion of the vivarium's 12/12-h light/dark cycle (light on at 7:30 a.m.). The temperatures of the colony and the behavioral test room were kept constant around 22 ± 2 °C. Following the NIH Guide for the Care and Use of Laboratory Animals, the experimental procedures were approved by the Animal Care and Use Committee of National Cheng-Chi University.

2.2. Apparatus

The testing of the risk choice task was conducted in an acrylic-made T-maze that consisted of one start arm (55 × 15 × 25 cm) and two goal arms (55 × 15 × 25 cm each). Chocolate-flavored sweeten pellets (~0.15 g each; Chawkolo Co., Ltd., Taichung, Taiwan) were used as the reward in this task with the amount of reward varying according to the experimental protocol. Prior to

each testing trial, the specific chocolate reward was put in a small disk groove (3.5 cm in diameter) located at the end of the appropriate goal arms. The T-maze was set up in a behavioral test room separate from animal colony.

For locomotor activity test, an open field arena consisting of an acrylic box (35 × 35 × 55 cm, black) was set up in another behavioral test room with a dim light. Locomotor activity was recorded via a video camera positioned 150 cm above the central point of box floor and the imaging data collected were used to measure the traveling distance of each subject; this was calculated by commercial software (SINGA Real-Time Trace System, ver. 1.17, Taipei, Taiwan). The discrimination test was conducted in an acrylic rectangle box (80 × 25 × 35 cm), one end of which was separated by an opaque plate (35 × 25 cm) into two compartments. Different amounts of reward (one pellet vs. two pellets) were baited in small dishes located at the end of the compartment.

2.3. Surgery

For the striatal lesion, rats were first anaesthetized by intraperitoneal injection of Zoletil 50 (Virbac, Carros, France) using 1 ml/kg and positioned in a stereotaxic frame (DKI-900, David Kopf Instruments, Tujunga, CA, USA). After the scalp was incised, the scalp muscle was reflected from the skull. Bilateral burr holes were drilled in the cranium to permit lowering of the 23-gauge guide cannula in order to reach the required specific stereotaxic coordinates. For excitotoxic lesion, ibotenic acid (Tocris Cookson, Bristol, UK) was dissolved in phosphate buffer saline to a concentration of 10 mg/ml (pH = 7.4). The dose of ibotenic acid was as previously described (Castane, Theobald, & Robbins, 2010; Liao & Lin, 2008). A volume of 0.5 μl ibotenic acid solution was delivered over 75 s into each site through a 31-guage microinjector attached to a 2-μl syringe (Hamilton, NV, USA) connected with a polyethylene PE20 tube (Plastics One, Roanoke, VA, USA). The tips of injection needles extended 1 mm from the end of guide cannula (Shineteh, Taipei, Taiwan). The microinjectors were left in place for 3 min after the completion of neurotoxin infusion so that the compound could diffuse away from the tip of needle. Bilateral lesions were made at the following injection coordinates: anteroposterior (AP) = +1.2 mm; mediolateral (ML) = ±2.0 mm; dorsoventral (DV) = −7.1 mm, relative to bregma, for the NAC; AP = +0.7 mm, ML = ±3.6 mm, DV = −5.0 mm, for the DLS. The coordinates were based on the atlas of Paxinos and Watson (2004). For the sham lesion group, the surgical procedure was identical except that vehicle only was infused. After neurotoxin infusion had been completed and after the removal of guide cannula, the incision skin was push together and stapled with clips. At the end of surgery, penicillin (50,000 I. U.) was administered intramuscularly to reduce the likelihood of postoperative infection. The subjects were allowed at least 7 days before testing so that they could recover from surgery. During this time, food and water were provided in *ad libitum* for the first 3–4 days. Rats were then gradually placed back on the food deprivation regimen before the post-operation behavioral testing started. The rats were handled daily during their recovery.

2.4. Risk choice

After surgical recovery, each rat underwent a procedure to acquire the risk choice behavior. One day prior to the start of risk choice tests, a habituation session was conducted that involved placing each rat into the T-maze and along it to freely explore the whole arena for 15 min. There was no reward available during this session. Next, as the major part of the risk choice task, each subject was placed in the start arm and allowed to access to either one of the goal arms; one with a certain small reward option and the other one with a large reward and uncertain. The choice outcome of the former option was 1 reward pellet given for every time the rat entered that reward arm. By way of contrast, with regard to the choice outcome for the latter option, a reward of magnitude 2, 4, or 8 pellets was presented at corresponding with probabilities of 0.5, 0.25, or 0.125, respectively. Thus, there were three conditions in terms of the risk choice and these had different reward ratios (1:2, 1:4, and 1:8) set in between the small/certain and large/risky arms (Fig. 1). As noted above, the EV was kept constant and equal to 1 in the present risk choice task across all three conditions with different reward ratios. The arms used for the choice options were assigned in randomly across rats, but the assignment for each individual rat was kept constant throughout the experiment.

The risk choice test for each of the three conditions with a specific reward ratio was carried out over eleven daily sessions, which were divided into one-day forced choice and ten-day free choice. Each daily session consisted of 16 discrete trials with an inter-trial interval of approximately 30 s. In the forced choice session, a barrier was used to block one of the goal arms and as a result, the rat was then forced to choose the other goal where there was no barrier in order to obtain reward. The initial 8 trials were set to allow choosing of the small reward arm, and the subsequent 8 trials were set to allow choosing of the large reward arm. The chance to obtain a reward was set at $p = 1$ for both arms during the forced choice session. A pilot experiment showed no satiety effect occurred when the rat consumed the total amount of chocolate reward during and after the forced choice given at any of the reward ratios. Subsequently, in the ten-day free choice phase, the rat was allowed to freely choose to enter either of the two goal arms. During this phase, the large/risky and small/certain arms were set up in accordance with the details described above. The procedure of forced or free choice lasted no longer than 30 min for each subject during one certain session. After the completion of the ten-day free choice test, the rats remained in the home cage for three days before being subjected to be run for another condition of risk choice sessions with a different reward ratio. Thus, each rat was repeatedly tested by three conditions of different reward ratio in 39 days: (11 days × 3 conditions) + (3 inter-condition days × 2 breaks).

2.5. Experimental protocols

Experiment 1 was designed to evaluate the effects of an excitotoxic lesion of the NAC on the risk choice task, whereas Experiment

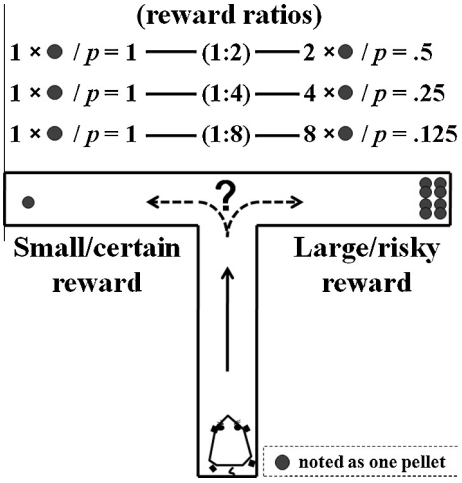

Fig. 1. The T-maze risk-dependent task; a graphical representation of a rat in a free-choice trial able to choose either a small/certain reward (1 pellet given with $p = 1$) or a large/risky reward (2, 4, or 8 pellets given, respectively, with $p = 0.5$, 0.25, or 0.125). A case of 8 pellets given with $p = 0.125$ is drawn in the T-maze of this diagram.

2 was designed to investigate the effects of excitotoxic lesion of the DLS on the risk choice task. Two cohorts of rats ($n = 20$ each) were used as the subjects for these two experiments. Before either of the behavioral experiments begun, the rats were randomly assigned to either the excitotoxic lesion group ($n = 11$) or sham lesion control group ($n = 9$). Following surgical recovery, the effect of each lesion on the risk choice task was assessed across 39 daily sessions following the protocols described above. The procedure was such that the rats from each group were tested under three conditions with reward ratios (of 1:2, 1:4, and 1:8) following a pseudorandom order; this was an attempt to minimize any potential carry-over confounding effect from carrying out the tests using reward ratios in either increasing or decreasing order. The number of events in which each rat entered the small/certain arm or the large/risky arm was recorded for each subject as the postoperative testing. The time to complete each trial, from leaving the start point to the end of the goal arm, was also recorded by a stopwatch manually. A trial was counted as an omission if a rat stayed within the start arm for more than 2 min from the initiation of the trial.

A separate group of twenty-four rats were recruited for Experiment 3, which was designed to check whether the excitotoxic lesion that had been induced in the NAC or DLS impaired the locomotor activity of the rat and discrimination of reward magnitude by the rats. The rats were randomly assigned into four subgroup ($n = 6$ each) to receive the NAC lesion or the DLS lesion or either of the corresponding sham lesion controls following the surgical protocols described above. After recovery from surgery, a post-lesion test of the rat's locomotor activity in an open field was carried out for 30 min. Subsequently, the discrimination test was conducted a day after the locomotion test. The rat was first placed at one end of the box to begin the discrimination trial. The subject was free to move and enter either one of the two compartments that had been baited with either 1 or 2 reward pellets, which were the same type as those used in the risky choice task. The rat was picked up at the end of each trial and placed in a holding cage until next trial (~20 s). The criterion set for each rat to perform this basic discrimination capability test that it entered the large reward compartment in successive 10 trials. And, the number of trials before reaching this criterion was accumulatively counted and used to determine the discrimination capability for each rat. To minimize a potential confounding effect of place preference, the placement of large reward with 2 pellets given in one of the two ends was arranged in a counterbalancing order across the subjects of each group.

2.6. Histology

A day or two after completion of the behavioral tests, each of the rats was deeply anesthetized with overdose of chloral hydrate (WS Simpson Ltd., England) administered intraperitoneally. Next perfusion was conducted by intracardial infusion of normal saline followed by 24% formalin solution. The brain was removed and post-fixed in a sucrose/formalin mixture solution for at least 48 h. The brain was then sectioned into 40 μm sections with a freezing microtome, which was followed by mounting the sections on Polysine slides (Menzel-Glaser, Berlin, Germany). These sections were then stained with cresyl violet. To verify the lesion area, the brain sections were examined by a microscope after referring to a rat brain atlas (Paxinos & Watson, 2004). Only data from the subjects with appropriate lesions were included in the data analysis.

2.7. Data analysis

The main dependent variable of interest is the percentage of events when the rat choose large/risky arm as part of the risk choice test. All the data were analyzed by two-way or three-way analysis of variance (ANOVA) in a mixed design with the between-subject factor being the lesion and the within-subject factors being the reward-ratio and/or the test day. *Post hoc* comparison tests were conducted when appropriate. The Student's *t*-test was used to analyze the effect of two types of lesion on locomotor activity and reward magnitude discrimination. All tests used a level of statistical significance of $p < 0.05$. All statistical analyses were conducted using commercial software (SPSS version 18.0, SPSS Inc., Chicago, IL, USA). The data are presented as means ± S.E.M.

3. Results

3.1. Histology

A schematic representation (Paxinos & Watson, 2004) of the bilateral lesions in the NAC and DLS are presented in Fig. 2. The lesion areas were identified by the presence of extensive cell collapse and gliosis within the brain samples examined by microscopy. Among the NAC lesion group, the area of damage was mainly located in the core subarea and did not extended into the lateral ventricle or the shell subarea. The NAC lesion areas were present from 1.56 mm to 0.84 mm anterior to bregma. Two subjects assigned for the NAC lesion in Experiment 1 were excluded from the analysis due to unilateral lesion or asymmetry of bilateral lesions. Among the DLS lesion rats, the damage areas were typically located at the dorsal and lateral edge of the striatum and extended from 1.08 mm to 0.36 mm anterior to bregma. Two subjects assigned for the DLS lesion in Experiment 2 were excluded from the analysis due to incomplete lesion. The final numbers of subjects with lesion areas in the desired regions were nine for the NAC lesion group of Experiment 1 and nine for the DLS lesion group of Experiment 2. From the cohort of Experiment 3, all six rats assigned for the NAC lesion group had specific lesion as targeted, and so were those six assigned for the DLS lesion.

3.2. Risk choice test

3.2.1. Experiment 1: Effects of the NAC lesion on risk choice

Fig. 3 shows the effects of the NAC lesion on the acquisition of behavioral choice under risk. The results of a three-way ANOVA revealed significant main effects for the lesion ($F_{(1,16)} = 8.954$, $p < 0.01$), for the reward ratio ($F_{(2,32)} = 20.568$, $p < 0.001$), and for the day ($F_{(9,144)} = 28.026$, $p < 0.001$). As for the two-way interaction test, the reward-ratio-by-day and the lesion-by-day interactions were found to be significant ($F_{(18,288)} = 10.023$, $p < 0.001$ and $F_{(9,144)} = 2.441$, $p < 0.05$, respectively). However, the lesion × reward-ratio × day interaction was not significant ($F_{(18,288)} = 1.242$, $p > 0.05$). The sham lesion control rats acquired a risk choice for each reward ratio over a 10-day test. The pattern of choice behavior was risk-seeking when $p = 0.5$ to obtain two pellets (1:2), as shown by a rapid preference of large/risky reward in the first 3 days of testing and remained in a higher percentage ($\geqslant 75\%$) of large/risky reward chosen under this condition over the last 7 days of testing. Conversely, the behavioral choice shifted to a risk-averse choice pattern when a larger reward was given with a higher risk as tested by $p = 0.25$ given with 4 pellets (1:4) or $p = 0.125$ given with 8 pellets (1:8). In these two conditions, the control rats gradually decreased the choices of large/risky reward over the test days, and they had a low percentage of large/risky reward on the last day of testing, 12.5 ± 4.03% for the condition of 1:4 and 9.72 ± 3.14% for the condition of 1:8. Relative to the sham control, the NAC lesion significantly produced a different pattern of behavioral choice under risk over the test days. The subjects of NAC lesion apparently chose fewer large/risky rewards in each

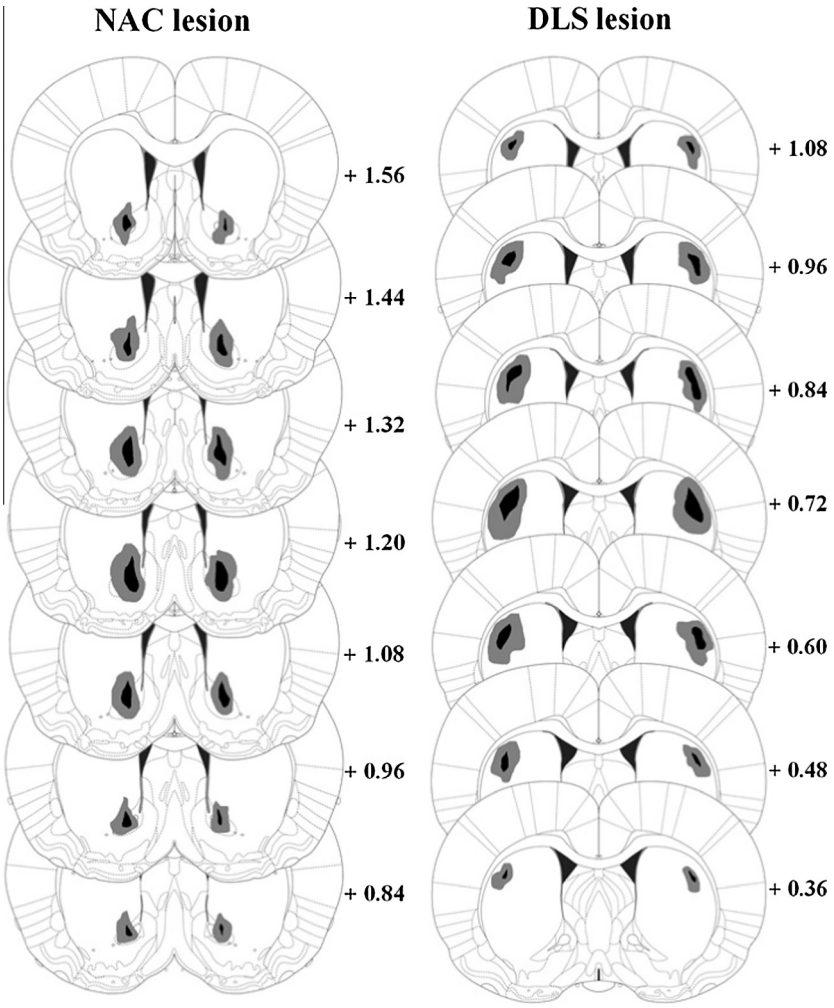

Fig. 2. Histological reconstruction of the range of the damage associated with the lesions in the nucleus accumbens (NAC) and the dorsolateral striatum (DLS). The extent of the damage in subjects bearing the maximum and minimum volume of damage in each group is represented by the black and light grey areas, respectively. The atlas plates are adapted from Paxinos and Watson (2004). The numbers beside the coronal section plates correspond to the distance in mm relative to bregma.

condition of three reward ratios, while the differentiation for reward ratios of 1:2 vs. 1:4 or 1:2 vs. 1:8 is generally remained. The NAC lesion group, in comparing to the sham control, profoundly decreased the large/risky reward choices in the condition of 1:2 over the test days.

Regarding to the mean time to complete a trial during the free choice, the NAC lesion group (3.00 ± 0.08 s) did not differ from the sham control group (2.90 ± 0.06 s), $p > 0.05$.

3.2.2. Experiment 2: Effects of the DLS lesion on risk choice

Fig. 4 shows the effects of the DLS lesion on the acquisition of behavioral choice under risk. The shame control subjects showed a similar pattern of behavioral choice under risk to that of the control subjects in the Experiment 1. When assessed visually, the DLS lesion seemed to have produced a subtle change with respect to the post-lesion test as compared to the sham control. A three-way ANOVA yielded statistical significances for the main effects of the reward ratio ($F_{(2,32)} = 24.687$, $p < 0.001$) and the day ($F_{(9,144)} = 18.684$, $p < 0.001$), but not for that of the lesion ($p > 0.05$). As for the interaction tests, only the two-way interaction of reward-ratio-by-day was significant ($F_{(18,288)} = 18.487$, $p < 0.001$).

The mean times to complete a trial over all the free choice tests was longer for the DLS lesion group (3.41 ± 0.11 s) than for the sham lesion group (2.60 ± 0.04 s), which difference reached a statistical significance, $p < 0.01$.

3.2.3. Effects of the NAC and DLS lesions on the last 3 daily sessions of risk choice

The results of the sham control groups described above indicate that the subject could acquire a risk dependent choice based on the reward ratio used. The change of behavioral choice appeared in the succession of 10-day test for each reward ratio reflected an acquisition of this behavior. The data collected in the last few days to compare from those of earlier days could be informative, so could the comparisons of different reward ratios made for the last few days of test. To further evaluate whether the presence of a lesion involving either the NAC or the DLS affected the acquisition of behavioral choice under risk, the data sets from the first three days (the days 1–3), the middle four days (the days 4–7), and the last three days (the days 8–10) were analyzed for exploring the lesion effects on each of three reward ratios. The results of these analyses for the last three days by two-way ANOVA are presented in Fig. 5. However, only the data sets of the last three days are reported, because the main effect of lesion was not significantly yielded from ANOVA's for the other two data sets. For the NAC lesion (Fig. 5A), the main effects of lesion ($F_{(1,16)} = 6.939$, $p < 0.05$) and reward-ratio ($F_{(2,32)} = 32.539$, $p < 0.01$) were significant, but not the interaction test. For the DLS lesion (Fig. 5B), the main effect of reward

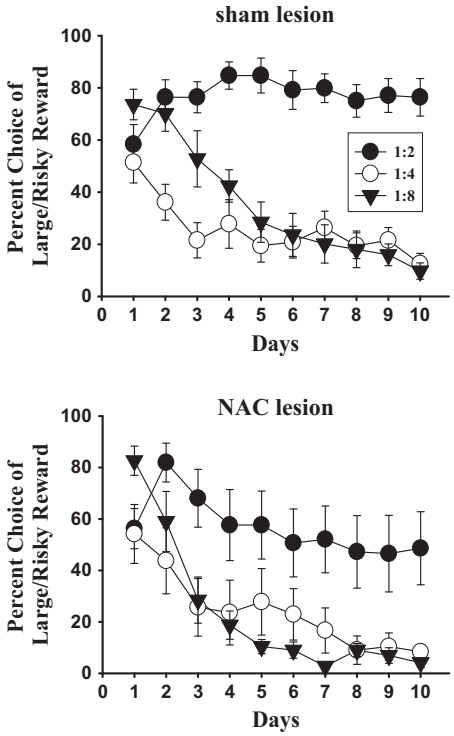

Fig. 3. Effects of the nucleus accumbens (NAC) lesion on the acquisition of behavioral choice under risk (Experiment 1) as measured by the percentage of choosing the large/risky reward arm under the three conditions with different reward ratio (1:2, 1:4, and 1:8). Behavioral choices of each reward ratio were recorded from a ten-day post-lesion test for the NAC lesion group ($n = 9$; bottom panel) and its sham lesion control group ($n = 9$; top panel).

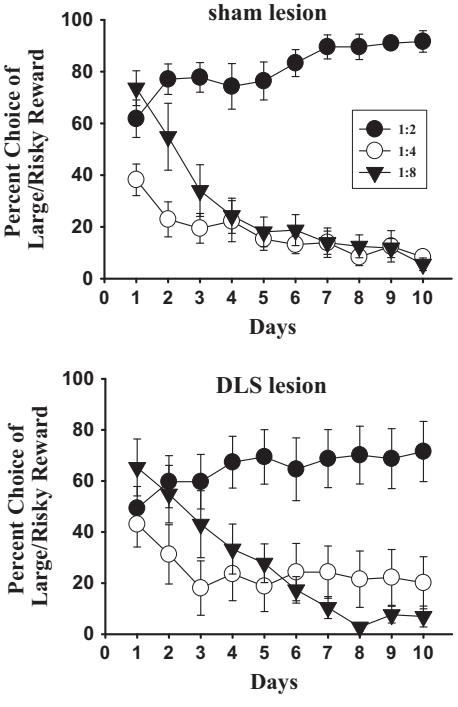

Fig. 4. Effects of the dorsolateral striatum (DLS) lesion on the acquisition of behavioral choice under risk (Experiment 2) as measured by the percentage of choosing the large/risky reward arm under the three conditions with different reward ratio (1:2, 1:4, and 1:8). Behavioral choices of each reward ratio were recorded from a ten-day post-lesion test for the DLS lesion group ($n = 9$; bottom panel) and its sham lesion control group ($n = 9$; top panel).

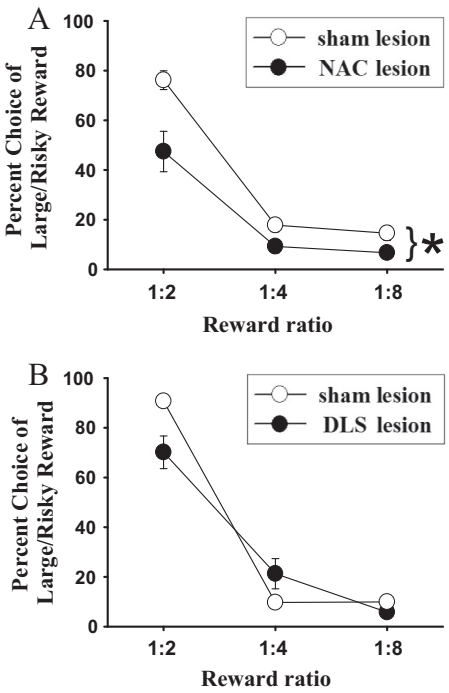

Fig. 5. Behavioral choices for the last three days of the free-choice test for each reward ratio in the rats with the nucleus accumbens (NAC) lesion and the sham controls in Experiment 1 (A), and the rats with the dorsolateral striatum (DLS) lesion and the sham controls in Experiment 2 (B). * denoted of a significant main effect of lesion treatment at $p < 0.05$.

ratio was significant ($F_{(2,32)} = 48.346$, $p < 0.01$), but that of the lesion was not significant ($F_{(1,16)} = 2.935$, $p = 0.106$). Collectively, the results indicate that the rats with a NAC lesion, but not with a DLS lesion, show an effect on the acquisition of the risk choice task. The NAC lesion group decreased the rate at which the large/risky choice was made for all three reward ratios throughout the 10-day test. This indicates that a risk-averse pattern of choice behavior was acquired by these rats.

3.3. Experiment 3: Locomotor activity and discrimination tests

The effects of the NAC and DLS lesions on locomotor activity and discrimination are shown in Fig. 6. The present NAC lesion did not produce any gross locomotive impairment; in contrast, as shown in Fig. 6A, the locomotion of the NAC lesion group was significantly higher than that of the sham lesion control group ($t_{(11)} = 2.94$, $p < 0.05$). The DLS lesion had no effect on locomotor activity as compared to its control ($t_{(11)} = 0.349$, $p > 0.05$, Fig. 6C). The capability to discriminate one pellet from two pellets (1-to-2) was not impaired by a lesion affecting the NAC (Fig. 6B) or the DLS (Fig. 6D) as compared to its sham control group (both $p > 0.05$). The numbers of trials presented in Fig. 6B and D include the last ten trials that counted for the criterion; the subject successively entered into the end baited with two pellets. All the subjects, regardless of lesion, reached the criterion no more than 40 trials within one daily session. And, the rat alternately entered into the end of either compartment during the first few trials. If a rat with lesion is able to detect the difference between one and two pellets, then it is assumed that this lesion subject is able to discriminate reward magnitude differences when there is a larger contrast (e.g. 1-to-4 pellets and 1-to-8 pellets). These findings from Experiment 3 collectively demonstrated that excitotoxic lesions affecting the NAC or DLS that were used in this study do not impair locomotor activity or discrimination capability of the experimental rats.

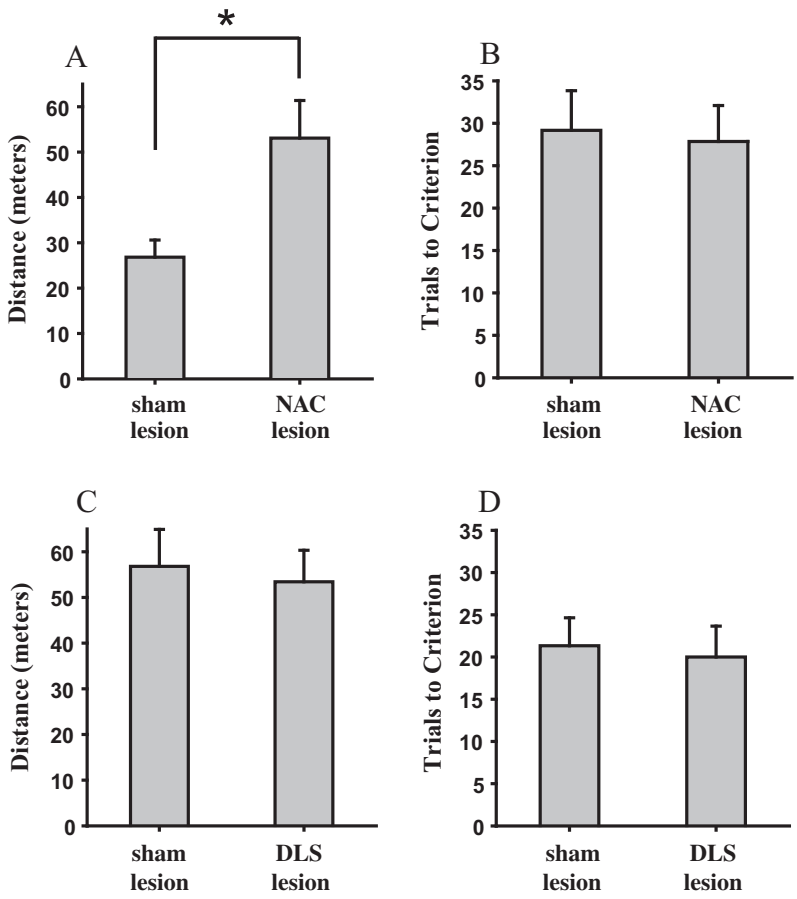

Fig. 6. Behavioral tests of locomotion activity and reward discrimination after either the nucleus accumbens (NAC) lesion or the dorsolateral striatum (DLS) lesion were induced in Experiment 3. The results of the NAC lesion and sham lesion control ($n = 6$ for each group) are shown in A and B, whereas the results of the DLS lesion and sham lesion control ($n = 6$ for each group) are shown in C and D ($^*p < 0.05$).

4. Discussion

The present study investigated the effects of pre-training lesions of the NAC or DLS on the acquisition of behavioral choice under risk. The risk choice task used in this study was designed to specifically manipulate reward risk by setting up the EV to be constantly equal between the choice options. Our results demonstrate that the control rats acquired a stable pattern of choice with respect to each of the three reward ratios over a 10-day free choice test. The pattern of choice behavior was risk dependent. Specifically, a risk-seeking performance appeared when $p = 0.5$ was available to obtain 2 pellets, while the behavioral choice shifted into a risk-averse style when a larger reward was given, but with a lower p of 0.25 or 0.125. The NAC lesion produced a risk-averse choice behavioral pattern with its most apparent effectiveness being decreases in the preference for the large/risky reward given at $p = 0.5$ to obtain 2 pellets. By way of contrast, the DLS lesion did not affect the acquisition of the risk choice. The current findings indicate that these two structures have distinct roles of the acquisition of behavioral choice under risk.

4.1. Manipulations of the risk

A novel feature of the present behavioral task is that it is designed to have an EV that is equal for binary choice option, which enables us to address the effectiveness of the risk on decision making. The risk is defined as the mathematical variance of a known probability distribution (Rothschild & Stiglitz, 1970). As noted above, an EV = 1 was set for the choice options in the present task and this was the case not only for each free-choice trial but also for all the tests run across three blocks with different reward ratios. Thus, the risk is leveled differently across the three reward ratios in the present experimental setup. Specially, the values of the risk for large/risky option are 1, 3, and 7 for the three conditions with reward ratios of 1:2, 1:4, and 1:8, respectively. For comparative purpose, if we use as an example the probability discounting task investigated by Floresco and associates (e.g. St. Onge & Floresco, 2009), the values for the risk are 4, 3, and 1.75 and these respectively represent the blocks with percentages of 50%, 25%, and 12.5% to get a constant amount of reward (4 pellets). In this situation, the block with the most risky situation was the block set at 50% ($p = 0.5$) rather than the block set at 12.5%. Therefore, it should be noted that the aforementioned probability discounting task does not fit an increase of risk as the reward probability decreased. In effect, the terms EV in the aforementioned probability discounting task, unlike the task in the present study, contains different EV's across the different probability blocks, despite the fact that the EV decreased in linear along with the reward probability decrease.

In order to determine whether a subject is risk-averse or risk-seeking, or to test for genuine risk dependent decision making with respect to reward-directed behavior, it is critical to manipulate the levels of risk by holding EV equal for a binary choice and for the EV to remain constantly equal throughout the behavioral test. We followed this tenet in designing the present behavioral task to assess risk related choice. The current results indeed show that the

behavioral choice was risk dependent. The subjects in the sham control groups of both Experiment 1 and Experiment 2 did learn a dissociable pattern of risk choice based on the risk associated with the different levels of the test. Namely, during the last three days of the free-choice test, a risk-seeking performance appeared when the risk was low ($p = 0.5$ to obtain 2 pellets), and conversely, the behavioral choice shifted into a risk-averse style when the risk was increased ($p = 0.25$ and $p = 0.125$ for 4 and 8 pellets, respectively). Before turning toward this pattern of risk-dependent choice, the subjects chose the large/risky reward for about 60 (±20)% of the time, which suggests a lack of clear risk perception at the beginning of acquisition test. Hence, the control subjects did acquire behavioral choice under risk and this accounted after an initial "lack" of risk sense, which later developed into risk-dependent choice bias.

The study of decision making in neuroscience in the past has mostly focused on the reward value rather than on the risk *per se*. The direct manipulation of the risk while holding EV in constantly equal in terms of choice options was only broached recently (Schultz et al., 2008). In neurophysiological studies, risk has been shown to be encoded separately from reward value in the orbitofrontal cortex of the primate (O'Neill & Schultz, 2010, 2013). Furthermore, from human functional imaging data, brain activity in the subcortical DA regions, including the ventral striatum (similar to the NAC of the rat) have been demonstrated to positively correlate with risk (Preuschoff, Bossaerts, & Quartz, 2006). In mice, a task specifically designed to test behavioral choice under risk was developed and this was shown to be sensitive to both the motivational state of the animal and the reward content (Leblond, Fan, Brynildsen, & Yin, 2011). Using such a task, but testing in the rat, a lesion in or the inactivation of the posterior pedunculopontine nucleus, a major source of excitatory input to the mesolimbic DA system, has been shown to abolish risk aversion during decision-making (Leblond, Sukharnikova, Yu, Rossi, & Yin, 2014). Despite this area of research is still being its early stages, brain regions in the mesolimbic and mesocortical DA systems have been argued to be essential to the processing of risk-dependent decision making (Schultz, 2010; Schultz, O'Neill, Tobler, & Kobayashi, 2011). To our knowledge, the present study is the first to report the role of rodent striatal areas (NAC and DLS) in the risk-dependent choice.

4.2. NAC lesion

The results of NAC lesion from Experiment 1 indicate this brain region is critical for the acquisition or development of behavioral choice under risk. Comparing to the experimental results to sham controls, the subjects in the NAC lesion group produced a risk-averse pattern of choice behavior that was statistically significant. This effect is more profound in the condition of reward ratio set on 1:2 which contains the lowest risk. Further analyses of win-stay and loss-shift support this finding. As compared to the sham controls, the NAC lesion rats significantly decreased the win-stay responses during the reward ratio of 1:2, but not significantly affected the loss-shift responses (dada not shown). The decrease of win-stay responses could be associated to the development of risk-averse behavior (Stopper & Floresco, 2011). Regardless of the lesion stage (pre-training vs. post-training) or the behavioral task, the present results are consistent with those reported by previous studies using excitotoxic lesions (Cardinal & Howes, 2005) and using inactivation (Stopper & Floresco, 2011) of the NAC; all these studies show risk-averse response with respect to a probability discounting task when the NAC is aberrantly affected. As noted in the Introduction, a post-training lesion approach was applied in these two previous studies, whereas the pre-training lesion paradigm was used in the present work. Thus, these consistent findings of risk-averse effects after lesion support a notion that the NAC is important for both the acquisition as well as the performance of the risk choice behavior.

The present results regarding the effects of NAC lesions on risk choice might possibly be attributed to motor deficit induced by lesion. We thought this is to be unlikely based on the following, firstly, the present excitotoxic lesion produced hyperactive, rather than hypoactive, locomotion in an open field as observed by a separate experiment of this study (Fig. 5A). Secondly, the mean times to complete a trial during the free choice were not different between the NAC lesion and the sham control groups. Thirdly, no omission trial was recorded for the subjects with NAC lesion in the present test. The lack of an omission event indicates that the lesion subjects were able to respond to the present test in the time and were not slowed down by any motor impairment. Another potential confounding factor that is related to lesion induced side effect is the rat might have lost the ability to discriminate between rewards of different magnitude. A discrimination test was therefore conducted as part of Experiment 3 and the results revealed that there was no difference between the NAC lesion group and the sham lesion group. Specifically, the rats of the NAC lesion group were still able to distinguish the magnitude of rewards from one pellet with two pellets. Thus, behavior alteration on risk choice among the NAC lesion subjects cannot be attributed to an impairment of their basic discriminative function with respect to different reward magnitudes, nor to a lesion induced motor deficit.

Interestingly, some other studies have reported findings that are comparable to the hypothesis argued here that the NAC is critical to risk-based decision making. For instance, the assessment of within-session reward probabilities and probability discounting across blocks was found not to be altered by NAC DA depletion by 6-hydroxydopamine (6-OHDA) given before behavioral training (Mai & Hauber, 2012). While this study and the present work are similar in that both applied the pre-training lesion approach to testing the acquisition of risk choice, the difference in results can be mainly attributed to the use of two neurotoxins that produce distinctly different lesion outcomes. The neurochemical results of 6-OHDA are known to be a depletion of DA from nerve terminals within the NAC, whereas the excitotoxic lesions induced by ibotenic acid, as used in the present study, most likely result in a loss of neuronal cell bodies in the NAC. Although this may seem to infer that the release of DA itself may not be fully responsible for mediating the acquisition of risk choice behavior, other neurochemical processes within the NAC need to be taken into account. For example, over-expression of the DA reuptake transporter (DAT) in the NAC, which was produced by using lenti-virus approach, has been reported to affect the acquisition of risk choice behavior in rats (Adriani et al., 2009). However, unfortunately, a contrasting result in terms of behavioral change was not observed when DAT expression was silenced in the NAC. Obviously, more work is needed before it can be concluded that DA in the NAC is involved in the *acquisition* of behavioral choice under risk. Despite this, it is noteworthy that the NAC DA transmission has been shown to be critical for the *performance* of risk choice behavior.

4.3. DLS lesion

In contrast to the effects of lesions in the NAC observed here, the lesions made in the DLS was found to produce no significant change in the present choice task as compared to the sham control group. As noted in Experiment 3, neither the locomotion activity nor the reward magnitude discrimination was affected by the DLS lesion in the present study's post-operational test. Thus it would seem that this null effect of DLS lesion on risk choice behavior observed here is not associated to deficits in either gross motor function or in reward discrimination capability that were

potentially induced by a lesion made in this region. While the DLS lesion could enhance the response latency, it did not produce any omission trial. Together, the effectiveness of DLS lesion on the present test of behavioral choice under risk is so subtle that it leaves the percentage of choosing large/risky reward unaltered in this group of rats. These findings imply that the DLS is not critical for the acquisition of the present behavioral task, at least as compared to the NAC. This notion is supported by a recent study. Rokosik and Napier (2012) developed a novel probability discounting paradigm to examine risk choice behavior, in which intracranial self-stimulation of the lateral hypothalamus served as the reward. Despite using this task for a test not primarily set to examine the neural substrate of risk choice behavior, they reported that the rats with a 6-OHDA lesion in the DLS were still able to acquire probability discounting that was similar to the controls.

To our knowledge, no other study has attempted to investigate the role of DLS on risk-based decision making in the rat. The current results indicate that the DLS may not be a critical site for the neural substrates engaged in risk decision making. Instead, it may be involved in other processes that underlie behavioral choice such as motor movement toward a goal. In fact, the DLS has been suggested to be active in the selection of the next movement segment in a behavioral sequence by linking the afferent information from the primary sensorimotor cortex with the striatal efferent outputs (Horvitz, 2009). In addition, in contrast to the involvement of dorsomedial part of the striatum in the formation of action–outcome association mediating goal-directed action, the DLS is important to the aforementioned sensorimotor connections that control the performance of habitual actions or well-trained behavior (Balleine, Liljeholm, & Ostlund, 2009; Kim, Lee, & Jung, 2013). If we accept this hypothesis whereby there is DLS involvement in habitual action, this may also provide another explanation as to why behavioral choice under risk was unaffected by the DLS lesion as was observed in the present study. The pre-training lesion approach applied in this study has led us to test the acquisition rather than the performance of behavior in the rat. In another words, the rats were not behaviorally tested under well-trained conditions. As such, the DLS might not be involved in the acquisition of behavioral choice under risk. While the dorsal striatum has been argued to be associated with decision making (Balleine et al., 2007), this has turned out to be more complicated than what was initially thought. The null effect of the DLS lesion with respect to the present task does not necessarily mean that this brain area is excluded from being part of the neural substrates associated with risk choice behavior. When considering the multi-facets of risk decision making, the DLS may contribute to another type of risk-based decision making or be involved in processing a different construct regarding risk choice behavior. More work is required to verify in what way and how the dorsal striatum and its subareas contribute to risk choice behavior.

4.4. Functional overview of risk choice behavior

The current findings indicate that the NAC, but not the DLS, is highly involved in the acquisition of behavioral choice under risk. While the role of the NAC with respect to risk or probability decision making is unambiguous, it should be noted that the NAC is just one node of the circuitry involved in the mesocorticolimbic DA systems. Beyond this region, other DA-associated areas are involved in risk choice behavior for reward. Subareas of the prefrontal cortex, including the medial prefrontal cortex (mPFC) and the orbitofrontal cortex (OFC), have been examined for their contributions to risk-based decision making via the use of a probability discounting task. St. Onge and Floresco (2010) reported risk-seeking choice behavior induced by inactivation of mPFC, but no alternation in probability discounting performance was seen for OFC inactivation. In contrast to this negative result for OFC inactivation, excitotoxic lesion of the OFC has been shown to disrupt the acquisition of risk assessment, but with different outcomes in terms of choice pattern that are putatively task-dependent (Mobini et al., 2002; Pais-Vieira, Lima, & Galhardo, 2007). Despite some discrepancies still existing for the role of prefrontal cortex in risk decision making, the critical contribution of the mesocorticolimbic DA systems should not be neglected. Using a functional disconnection approach, the dissociable roles of mPFC, NAC and basolateral amygdala (BLA) have been identified for risky choice of probability discounting task (St. Onge, Stopper, Zahm, & Floresco, 2012). The mPFC has been suggested to play a supervisory role in monitoring action outcomes over time, whereas the BLA and NAC are thought to provide relatively fundamental processing in terms of the direction of choice. It has been suggested that the BLA and NAC may be critical to the processing of risk-based decision making for punishment and reward, respectively (Ghods-Sharifi, St. Onge, & Floresco, 2009; Orsini, Moorman, et al., in press; Orsini, Trotta, Bizon, & Setlow, 2015). While it has been known that the NAC in the mesolimbic DA systems is critically important for the reward motivation and learning, it is feasibly to infer that the NAC is involved in higher functions related to cognitive and affective processing, including reward-associated risk decision making (Floresco, 2015). This notion is supported by the present findings whereby pre-training lesions affect the acquisition of risky choice and our findings are compatible with evidence from previous studies that used post-training lesions or the inactivation of the NAC when studying the performance of probability discounting choice (Cardinal & Howes, 2005; Stopper & Floresco, 2011). As the NAC lesion was made in the location of the core subarea, the risk-averse response observed from the lesion rats in the aforementioned three studies may be a result of an impaired "go-to-it" component of action selection as suggested by Floresco (2015). Furthermore, in combination with the intact "stay-on-task" component, which is functionally driven by NAC shell, the rats with NAC core lesion would then perform in a risk-averse style.

Evidence from human studies indicates that the NAC or the ventral striatum plays a key role of reward-based learning and decision making (a review by Daniel & Pollmann, 2014). Of particular interest, this brain region of human is active in the decision making under risk in addition to processing the expected reward (Preuschoff et al., 2006; Tobler, O'Doherty, Dolan, & Schultz, 2007). With comparable evidence from neurophysiological work, human fMRI study indicates that the NAC and certain other cortical and subcortical brain areas can use the uncertainty signals to assess the risk via the learning experience of the different payoffs and their probabilities (Schultz et al., 2008). While much is known about the neural correlates that give rise to the risk sensitivity come from the studies provided with the probability and reward magnitude associated with a gamble task in human imaging study (e.g. Preuschoff et al., 2006; Tobler et al., 2007), how the "genuine" risk can be formed from the experiential learning to influence decision making is less clear. However, like the present study, particularly in examining the behavioral choice under different levels of risk with equal mean reward set for the binary choices, a recent fMRI study revealed that the risk sensitivity can be integrated to human learning on the basis of neural correlates in the NAC (Niv, Edlund, Dayan, & O'Doherty, 2012). Furthermore, the striatal DA D2/D3 receptors are reported to be positively related to fMRI signal activation modulated in the ventral striatum underlying for a risk-taking behavior (Kohno et al., 2015). In line with these findings of the NAC correlating to the risk-dependent decision making in human, the present study provides complementary data to support a causal role of the normal NAC in behavioral choice under risk.

This study, however, has some limitations. Firstly, the neural substrates of risk-dependent decision making could not be only located in the NAC. For instance, both the NAC and the OFC have been shown to correlate with the risk-dependent decision making in human, but functionally processing in dissociable time points (Tobler et al., 2007). In this regard, it is heuristic to examine whether the OFC lesion in rats, as tested by the same task used in the present study, would produce behavioral results similar to what being reported here. Secondly, based on the present findings, it is still unclear what neural inputs specifically control the risk-dependent choice in the NAC. Using the optogenetic tools enables to disentangle this puzzle. Most recently, optogenetic stimulation enhanced DA release within the NAC with the afferents selectively projected from the ventral tegmentum area has been demonstrated to alter the value-related choice in a modified delay-discounting task, but not magnitude based decision (Saddoris et al., 2015). In addition, optogenetic stimulation and inhibition prelimbic prefrontal cortex projection to dorsomeidal striatum produce the preference and the avoidance, respectively, to high-reward/high-cost option of an effort-based decision making task in the rat (Friedman et al., 2015). Surprisingly, no such a kind of study is reported in examining for the probability or risk related decision making in the rodents. In view of these findings, it is worth noting that to use optogenetic tools in the future work for the proper dissection of decision-making mechanisms including that for the present task. Thirdly, regarding to the pre-training lesion approach used in the present study, there may be compensatory processes following the lesions to compromise behaviors being tested. If the null effects of DLS lesion are due to the putative compensatory processes, then the results of the NAC lesion should have occurred in negative. However, it is not the case for the present results, at least at the behavioral level. The possibility of lesion induced compensatory processes could be detected by pharmacological challenge after the lesion in among several other approaches. Further studies are needed before conclusions can be drawn for this concerned issue.

5. Conclusion

When investigating risk decision making alteration induced by brain lesion in the rat, previous studies have relied on applying a post-training lesion/drug-test approach and the manipulation of reward probability with a variable EV. The present study was designed to investigate the role of NAC in the acquisition of behavioral choice under risk using a binary choice task in which the EVs are equal. In this behavioral task, the rat's risk choice was based on the same payoff, namely an EV = 1, for both the small/certain and the large/risky reward option within each trial, and this was also true for all three test conditions with different reward ratios. Thus, the rat was required to choose by specifically assessing the risk which was set at three levels. The control rats acquired a stable choice for each of the three reward ratios during a 10-day free choice test. The pattern of choice behavior was risk dependent. Specially, a risk-prone performance appeared when the risk is low, and this behavioral choice shifted into a risk-averse style when the risk is increased. The NAC lesion significantly altered the acquisition of the aforementioned risk choice behavior and apparently caused a move toward a risk-averse style for all three reward ratios. No such effect was observed in those rats with DLS lesions. These results suggest that firstly there is heterogeneity between the NAC and DLS with respect to risk-based decision making, and secondly the NAC is critical to the acquisition of behavioral choice under risk when the amount of reward expected to be acquired is the same for the selected options.

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