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Research report

Effects of striatal lesions on components of choice: Reward discrimination, preference, and relative valuation

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HIGHLIGHTS

- Lesions to dorsal and ventral striatum and free choice were examined.
- Lesion effects were observed on free choice and not serial reward responses.
- Ventral striatal lesions led to impaired optimal preference and risk aversion.
- Dorsal striatal lesions led to altered appetitive actions but minimal choice deficits.
- Striatal function is crucial to optimal free choice expression and involves diverse components of reward processing.

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ABSTRACT

The striatum is a key structure involved in reward processing and choice. Recently, we have developed a paradigm to explore how components of reward processing work together or independently during choice behavior. These components include reward discrimination, preference and relative valuation, and the goal of the present study was to determine how the striatum is involved in these dissociable components during this novel free choice paradigm. We tested choice utilizing two different outcome series with one being a more straightforward single-option discrimination anchored by a 0 reward outcome, and the other as a multi-option outcome discrimination of greater difficulty. We compared the free choice reward task to a sequential reward task and an extinction task. Striatal lesions impaired responding only in the free choice version with alterations in both appetitive and consummatory measures. Ventral striatal lesions had greater impact altering discrimination, preference and relative valuation in both the single and multi-option week studies. A major factor involved in these deficits was a significant aversion to the multi-option that contained a larger outcome option but with a longer delay to reward. Dorsal striatal lesions caused less impairment even leading to enhanced choice behavior compared to control animals during the more difficult multi-option free choice series. Overall, the results suggest that the context of action is crucial when linking striatal function to choice behavior and its diverse components. The implications include the idea that striatal involvement in decision-making is increased when responses are self-paced and diverse in a more naturalistic environment.

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1. Introduction

When exploring the brain basis for choice, the basal ganglia has been one region of intense research as the labeled 'motivation-to motor interface' of the central nervous system [40,20]. These ganglia at the base of the brain house several structures all placed in a prime position to perform dense interactions with diverse inputs from all regions of the cortical mantle and many subcortical regions [2,56]. The striatum is the main input center within the basal ganglia, and striatopallidal circuits can be divided into dorsal and ventral subsections (DS & VS) which are believed to play dissociable roles in diverse functions including movement sequencing, choice and decision-making [24,23,14,55]. Recently, we have developed a new behavioral paradigm to explore the different components of choice in a relatively free 'foraging' environment [45]. The different components of choice explored included discrimination, preference and relative valuation. Each component interacts with the

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others depending upon the choice context. Most interestingly, the different components can be dissociated from one another suggesting that the neural basis for the components could vary. This strategy of parsing complex motivation processes has worked well in prior research [11,10,29] as it can lead to new ways to explore the neurobiology of motivation and novel translational approaches to mental impairment.

Previous work has linked DS and VS to distinct functional roles involved in discrimination, preference or relative valuation but no study has explored how lesions to these specific regions could impact these diverse but interactive aspects of choice during the same task. Numerous perspectives have provided insight into how the DS and VS would differentially be involved in these components of choice. In order to optimally decide between multiple options, the "critic" must be able to discriminate between the available outcomes before the "actor" is to perform the action [30]. Quantitative and qualitative discrimination, which involves the ability to distinguish between different outcomes, is a crucial task most likely dependent upon the "critic". Populations of neurons in the DS and VS may discriminate rewards through evaluation of separate criteria. When comparing firing of neurons based on encoding of temporal value versus the overall hedonic value, neurons in the DS and VS show increased activation respectively [14]. Discrimination based upon factors such as timing and magnitude of reward must be efficiently and accurately integrated for optimal decision making [53].

Once an animal develops the ability to discriminate between outcomes, it can then establish preference. Preference has historically been defined as when an "... animal consistently takes one food instead of another when equal opportunity is given to eat both." [58]; p. 309). Work in motivation has systemically examined determinants of preference using highly controlled studies focused on internal or external factors [59,41]. Recent work based on reinforcement theory, optimal foraging or behavioral economics has focused on outcome properties such as reward magnitude [52], quality [18], or timing of reward delivery [36,18]. One possible role proposed for VS function is that this brain region actively assigns value to rewards through its role of the "critic" [42], which would be the underlying factor in the preference-forming process. This framework includes the idea that once preference has been established by the VS, the DS then takes over for performance of the newly-acquired behavior of choice [44]. Dopamine manipulations of the VS lead to mixed results related to alterations in preference and choice [46,38]. For example a recent set of studies found that dopamine depletion of the nucleus accumbens spared risk-based decision-making [37,39]. This work was done using the two-lever choice task which is a valid and well-established measure of choice. Despite its usefulness, this task could be limited in how choice behavior could be expressed in a flexible way. The need for expanding our paradigms to examine choice that utilize more self-paced, open environments could reveal connections between VS, dopamine and choice masked by the use of particular behavioral choice situations.

Experiences with alternative outcomes can also influence the incentive value of an already preferred outcome [19,27,9]. Relative reward valuation occurs when the value of a reward that has already been experienced is altered based upon an interaction with a new reward. The valuation of a reward can be subjectively altered if experienced with different alternative outcomes even though its objective value remains constant [45]. Neurons in the VS will show activational patterns consistent with this behavior [21]. Balleine and Killcross [4] demonstrated that animals can maintain sensitivity to an upshift or downshift in reward value even after lesions to the nucleus accumbens (NAc), a subsection of the VS. This sensitivity remains although lesioned animals performed less lever presses than shams, possibly due to an impairment in instrumental behavior. This holds true when there is a shift in motivational state as well, as shown by effects of shifts in food deprivation level on lever pressing [4]. These findings of reduced instrumental behavior without a reduction of sensitivity to reward shift have been shown elsewhere [33]. Animals with NAc lesions will show reduced contrast effects through altered instrumental behavior when rewards are downshifted, which may indicate a role of this brain area in reward valuation as it relates to instrumental behavior [33]. The exact role of the striatum in all three aspects of choice behavior has yet to be determined.

Understanding how these three components are interwoven to influence choice can help further our understanding for neural representations of choice components in the brain. Our lab has designed a paradigm that provides us with the opportunity to fractionate the three components of choice behavior, thus providing a more definitive profile of the decision-making process. This paradigm consists of three boxes connected to each other by tunnels, creating a relatively large, free-choice environment [45]. Rats will be confronted with the option to choose between rewards of different magnitudes within a one-week session, while magnitude shifts between weeks (see Table 1). The shifting reward values in the current paradigm lead rats to make comparisons of discrimination, preference, and relative valuation. This paradigm has also been designed to permit for the recording of multiple dependent measures, also which could allow for a clearer understanding of choice behavior. Finally, it has also been designed to overcome the confound of overtraining which has been shown to lead to the formation of habits [1], thus resulting in inaccurate reflections of outcome valuation.

In the current set of experiments, we used excitotoxic lesions to investigate the roles of the VS and DS in the decision-making process. A parametric pattern of prediction (Fig. 2A) has been proposed as a guideline for optimal choice behavior. It is our hypothesis that animals without an intact VS or DS will exhibit behaviors that do not fit these predictions, thus not providing them with the capacity to maximize on the opportunity to gain optimal reward. We divided the study into two, three-week experiments. The first experiment uses a varying single options (i.e. 0 pellets in the first week, 1 in the second week) to examine discrimination. This allows us to explore free choice when the changing outcome was simpler with a clear reference to an anchor (0 pellets). A stable multi-option was used to examine relative valuation and differences between the two options in a single session reflected preference. The second experiment used a multi-option (i.e. 0 or 5 pellets in the first week, 0 or 3 in the next) variation for discrimination with the alternative being a single option outcome (1 pellet each week). Results could boost the understanding of striatal functional heterogeneity and the role of striatal functioning in diverse components of typical and abnormal choice behavior.

2. Methods

2.1. Experiment 1

2.1.1. Subjects

Thirty-two male Sprague-Dawley rats (*Rattus norvegicus*) weighing 275–415 g at the time of surgery were used for this experiment. All animals were housed in 65 × 24 × 15 cm cages with corncob bedding. They were food deprived Monday through Friday to no less than 85% of their free-feeding, baseline weight with *ad libitum* access to water in their home cages. From the end of testing Friday until approximately 24 h prior to testing on Monday, they had *ad libitum* access to food (Harlan Teklad Rat Chow #8604). The colony room was set on a 12-h reverse light/dark cycle (lights off at 8:00 a.m.) with the temperature maintained at 70 ° Fahrenheit and approximately 56% humidity. All procedures were approved by the

Table 1
Schedule of outcome shifts for experiments 1 and 2.

	Experiment 1			Experiment 2		
	W1	W2	W3	W1	W2	W3
Single-Outcome Box	0 pellets	1 pellet	2 pellets	1 pellet	1 pellet	1 pellet
Mixed-Outcome Box	0/3 pellets	0/3 pellets	0/3 pellets	0/5 pellets	0/3 pellets	0/1 pellets

Note: Table 1 shows the schedule of outcome shifts that rats are exposed to throughout the course of each experiment. In experiment 1, the shifting outcome occurs in the single-outcome box, while in experiment 2, the shift occurs in the mixed-outcome box.

Bowling Green State University Institutional Animals Care and Use Committee (Protocol 12-012). All efforts were made to keep animal suffering to a minimum.

2.1.2. Apparatus

The 3-box setup is made of three 25.40 × 30.48 × 40.64 cm cast acrylic boxes. The middle "decision" box consists of a door located in the middle of the front side and a cast acrylic tunnel (9 cm diameter) on the left and right side that connects to the other two boxes which are approximately 117 cm apart. All 3 boxes are located in separate closets and connected only by the tunnel passageways. The entrance of each box is surrounded by infrared (IR) beams to monitor and record each time the rat left or entered the box, as well as to trigger the closing of guillotine doors. A food cup is placed directly across from the entrance to each "reward" box. Rewards (45 mg dustless plain sucrose pellet; Bio-Serve, NJ) are dispensed from a connected pellet dispenser located just outside of the cast acrylic box. IR beams are also located at the bottom of the food cup to record any time the rat checks it and also to serve as a signal to the program that a new reward is to be dispensed. A lever is located next to each food cup to record superstitious behaviors. Water nozzles are located to the left of the door of each reward box for *ad libitum* access throughout testing. Sound attenuating chambers encase each reward box and a white noise generator is used to mask extraneous noises. Houselights are located above each box for illumination during outcome exposure sessions, but they only remain lit until the rat enters the respective box. MED-PC programming (Med. Associates Inc, VT) is used to run med-associated hardware that is connected to the apparatus. Behavior is monitored but not recorded via cameras located at the top of each box.

2.1.3. Surgery

All animals underwent surgery after reaching at least 2.5 months of age. Prior to surgery, rats were injected subcutaneously with Metacam (Boehringer Ingelheim Vetmedica, Inc., St. Jospeh, MO, USA) (5 mg/mL) and Buprenex (Reckitt Benckiser Healthcare (UK) Ltd., Hull, England) (3 mg/mL). After approximately ten minutes, animals were anesthetized with isoflurane using a small animal anesthesia system and placed in a stereotaxic device. The skull was exposed and standard stereotaxic procedures were used for surgery. 0.09 M quinolinic acid dissolved in 0.1 M phosphate buffer with pH adjusted to 7.4 using 0.1 M NaOH was used to create lesions. Sham animals received injections of phosphate buffered saline. All animals received 0.5 microliters of their respective injection over the course of seven minutes. Locations for bilateral lesions relative to bregma were as follows: VS (A + 0.7–1.2, M ± 0.7–1.2, D − 7.0–7.5 mm); DS (A +0.7–1.2, M ± 2.9, D − 4.7 mm) according to the standard rat stereotaxic atlas [43].

2.1.4. Recovery

Animals were given seven days to recover from surgery. For two days following surgery, they received a dose of Metacam every twenty-four hours and Buprenex every twelve hours. Animals also received one dose per day (orally) of Doxycylcine (Pfizer Labs, New York, NY) (5 mg/mL) for three weeks post-surgery.

2.1.5. Histology

After completion of the six-week testing period, animals were deeply anesthetized via intraperitoneal injection of sodium pentobarbital (100 mg/kg) and perfused intracardially using 0.9% saline solution followed by 10% formalin in a phosphate buffered saline solution. Brains were immediately removed and stored in 4% paraformaldehyde for approximately 24 h, followed by 30% sucrose solution (10% formalin) for a period of 2 − 4 days. Brains were then blocked, frozen, and sliced in 30 μm slices using a sliding microtome. Brain slices were fixed to slides and stained using cresyl violet. Lesions were classified by cell loss and gliosis (Fig. 1).

2.1.6. Schedule of outcome shifts

The current experiment exposed rats to reward outcomes that shifted between weeks. Table 1 shows the schedule of outcome shifts and magnitude of pellet delivery for each box for *Experiment 1*. Between-week outcome shifts occurred in the single-outcome box during *Experiment 1* with the outcome increasing as the weeks progressed. Pellet magnitudes were delivered no more than two consecutive times in the mixed-outcome box, resulting in a 50% chance of obtaining either reward.

2.1.7. Outcome exposure or forced choice

Animals were run through behavioral training on Monday and Tuesday of each week. Once the MED-PC program had been started, animals were placed in the "decision" box and allowed to enter either reward box from there. Guillotine doors were lowered and a ten-minute timer was started once the IR beam to a reward box was broken. Five seconds later, a sugar pellet reward was delivered to the food cup and continued to be delivered on an FI-5 schedule for every break of the food cup IR beam. After the ten-minute Outcome Exposure period, the guillotine door would lift. When the IR beam was broken upon reentering the decision box, the guillotine door to the first box would shut. This forced the rat to enter the opposite box while prohibiting re-entry into the already experienced box. Training ended once this procedure was completed in both reward boxes.

2.1.8. Free choice tests

Free choice behavior was assessed on Wednesday (Free Choice 1) and Thursday (Free Choice 2) of each week (W). The same procedure was used to start this task as was used for Outcome Exposure except the rat was free to explore the entire apparatus for thirty minutes. When entering a box, the IR beam was broken causing a pellet to be delivered to the food cup. Pellet retrieval caused an IR beam break to signal the next reward delivery. Reinforcement occurred on an FI-5 schedule. The guillotine doors would lower at the end of every thirty-minute session to keep the rat in its current box.

2.1.9. Extinction

Extinction occurred on Friday each week. The exact same procedures were ran on extinction days as were ran on Free Choice days with the exception that there was no reward delivery.

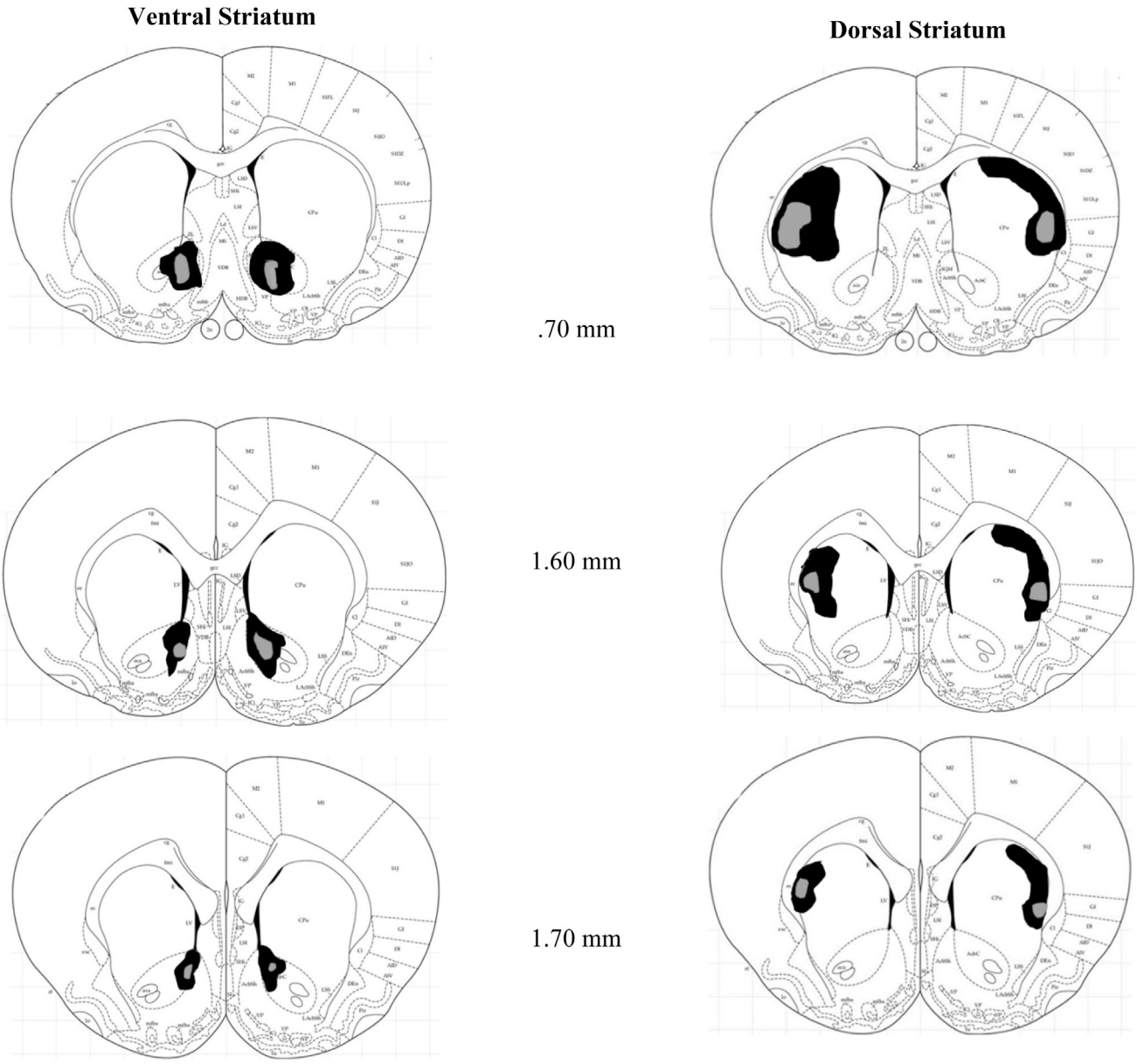

Fig. 1. Schematic representation of lesion locations. Pictures represent areas of maximum (black) and minimum (gray) excitotoxic damage for each lesion group.

2.2. Behavioral measures

The current paradigm permits for the measurement of multiple variables to aid in the process of distinguishing the multiple aspects of reward choice. All dependent measures have been described elsewhere [45]. We have broken down all of our measures to fit into one of three categories: measures of consumption (trials and total reward), measures of place conditioning (total time in box and average time in box), and measures of approach (food cup checks, entries, and latencies). Measures of consumption refer to the amount of pellets that have been consumed throughout the task. Measures of place conditioning measure time spent in each box. Measures of approach measure the animal's seeking behavior. Correlational analyses were run within groups to determine any relationship between variables within the same category. Due to high levels of correlation, total reward is reported for measures of consumption (significant r ranged from 0.641 to 1.000, $p < 0.033$) and total time in box is reported for measures of place conditioning (significant r ranged from 0.641 to 0.926, $p < 0.0046$). Measures of approach did not correlate significantly.

2.3. Data analysis

All data analysis was performed on these measures using IBM SPSS statistics version 20 (IBM corp., Armonk, NY). One rat died during surgery, reducing the overall number of subjects to 31. There were three instances of data lost due to technology failure for measures other than total reward. The overall N's for each group were: sham lesion = 9, ventral lesion = 8, dorsal lesion = 10. Preference was analyzed in both experiments by a $3 \times 2 \times 3$ mixed ANOVA and is defined as the animal's behavior indicating that it favors either the single-outcome or mixed-outcome box. A one-way analysis of variance was performed on the single-outcome box to analyze reward discrimination as the outcome shifted between weeks. A one-way analysis of variance was also performed on the mixed-outcome box to assess the relative reward effect when the outcome remained the same over the three weeks. Significant main effects

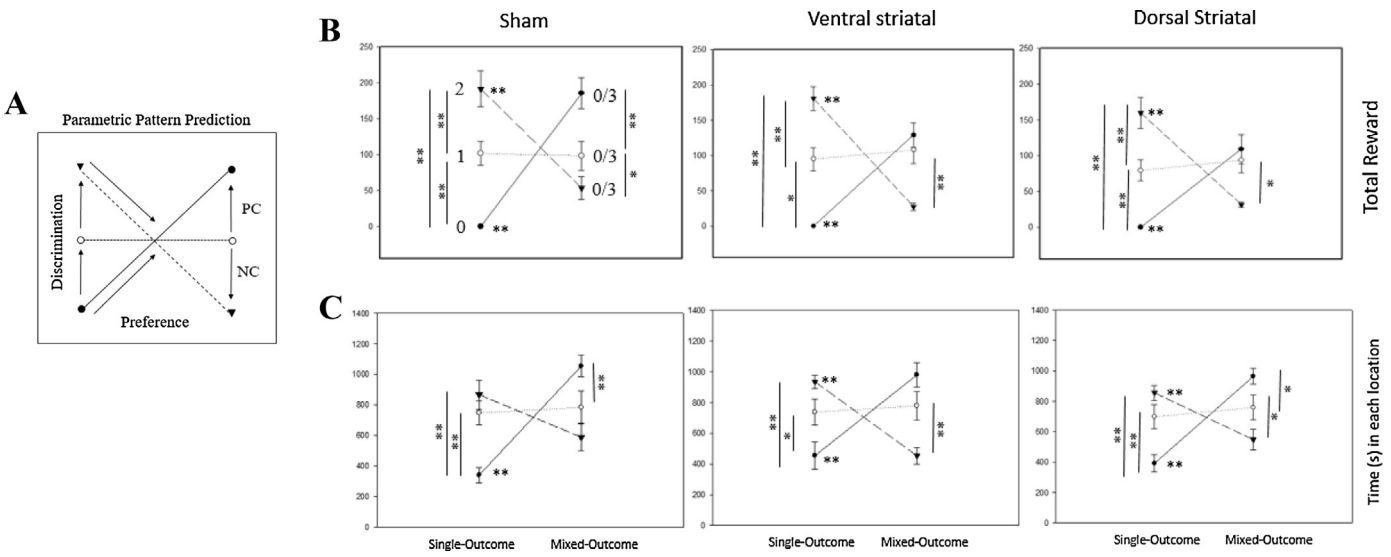

Fig. 2. Measures of consumption and place preference as related to parametric pattern predictions (Experiment 1). (A) The parametric pattern predictions exhibit what are considered optimal preference based upon the outcome magnitude available between boxes within each week of testing, discrimination between weeks within the box where outcome magnitude shifts between weeks, and contrast when the magnitude remains consistent. All three groups showed behavior similar to predictions for total reward (B) and total time in box (C). Data presented are from the entire 30-min session on free choice day 2. Values are mean ± standard error. * = $p < 0.05$. ** = $p < 0.01$.

or interactions were further assessed using pair-wise comparisons. P-values that were less than 0.05 were considered statistically significant. Bonferroni and Greenhouse-Geisser corrections were made for multiple comparisons and any violations of sphericity, respectively.

We also use a measure of optimal preference that has been used previously [45]. Briefly, this score represents the percentage of trials performed in the box with the higher overall outcome. The score was obtained by dividing the number of trials performed in the box with the higher overall magnitude by the total number of trials performed (e.g. mixed-outcome trials in W1/S.O + M.O trials in W2) and multiplied by 100. For comparisons between Outcome Exposure, Free Choice, and Extinction, only data from the first twenty minutes of Free Choice and Extinction sessions were analyzed.

2.4. Experiment 2

2.4.1. Subjects, apparatus, surgery, recovery, histology, outcome exposure, free choice, and extinction

The subjects, apparatus, surgery, recovery, histological procedures, outcome exposure, free choice, and extinction procedures used for *Experiment 2* were all the same as those that were used in *Experiment 1*.

2.4.2. Schedule of outcome shifts

The key difference between *Experiment 1*and *Experiment 2* was the schedule of outcome shifts. As opposed to *Experiment 1, Experiment 2* consisted of shifting outcome magnitudes in the mixed-outcome box. Table 1 shows the schedule of outcome shifts and magnitude of pellet delivery for each box for *Experiment 2*. The program was written to deliver the same pellet magnitude no more than two consecutive times in the single-outcome box, resulting in a 50% chance of obtaining either reward.

2.4.3. Data analysis

Data analysis for *Experiment 2* was the same as *Experiment 1* with the exception of how reward discrimination and the relative reward effect were analyzed. Reward discrimination was analyzed by a one-way analysis of variance performed on the mixed-outcome box. Relative reward effects were assessed by a one-way analysis of variance on the single-outcome box. Optimal preference scores were also obtained for this experiment.

3. Results

3.1. Experiment 1

3.1.1. Forced choice testing

Animal responding was measured during the 'forced choice' day when they enter into each chamber in series and are restricted from moving out of the chamber for 10 min. We explored preferences using the measure of reward consumption among weeks and between boxes. A main effect of week, F (2,48) = 55.46, $p < 0.01$, and a box by week interaction, F(2,48) = 15.65, $p < 0.01$, was found that followed our parametric prediction pattern (Fig. 2A). There were no lesion effects on the behavior in this sequential responding for the different outcomes demonstrating that in this context without alternatives all the animals displayed similar discrimination, preference and relative reward effects. Optimal preference was significantly decreased in the forced choice compared to the free choice testing (week by day interaction, F (4,92) = 10.69, $p < 0.01$). Animals chose optimally more during the Free Choice Session than Forced Choice or Extinction in W1 (87.31% ± 2.73 vs 57.30% ± 3.55 and 74.15% ± 1.50 respectively) and W3 (76.58% ± 3.15 vs 57.27% ± 3.42 and 53.77% ± 2.46 respectively) and no difference between sessions during W2.

3.1.2. Free choice: between group differences

Ventral striatal lesions: We examined optimal preference in the ventral lesion group (main effect of week, F(2,48) = 38.24, $p < 0.01$). Post-hoc analyses found that the ventral lesions disrupted the formation of a preference for the more advantageous choice across the three-week experiment, yet this preference remained for the groups with dorsal and sham lesions (Fig. 3). While all groups showed a decrease in optimal preference during W2 when choice would be most ambivalent, those with ventral lesions were impaired in their decision making in W1 and W3. No significant between-group differences were observed for testing on Extinction days.

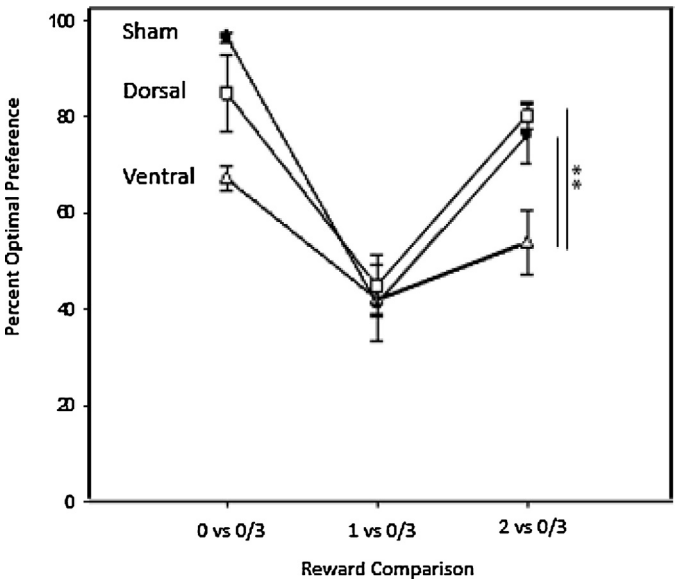

Fig. 3. Optimal preference scores (Experiment 1). Ventral lesion animals showed significantly less optimal choice when compared to both dorsal and sham lesion animals across the entirety of Experiment 1. Data presented are from the entire 30-min session on free choice day 2. Values are mean ± standard error. * = p < 0.05. ** = p < 0.01.

Dorsal striatal lesions: Lesions to the dorsal striatum led to deviations from the parametric pattern predictions as was shown by differences in speed of retrieval. A 3 × 2 × 3 mixed ANOVA found a significant box by lesion interaction for the relative reward effect, $F(2,24) = 5.67$, $p < 0.01$. LSD comparisons found that the dorsal lesion group was retrieving pellets faster than both the sham lesion ($M = 659.19 \pm 33.49$ vs 818.61 ± 35.30 milliseconds, $p < 0.01$) group and ventral lesion group ($M = 659.19 \pm 33.49$ vs 769.42 ± 37.44 milliseconds, $p < 0.05$) over the three-week period in the mixed-outcome box. There were no significant differences between groups for measures of consumption or measures of place conditioning.

3.1.3. Free choice: within group differences

Ventral striatal (VS) lesions: All deviations from the parametric predictions (Fig. 2A) were obtained from appetitive actions (food pellet retrieval latency or food cup checks) or place conditioning and not consummatory responses. VS significantly reduced discrimination for the single-option outcome between the 1 and 2 pellet options ($F(2,14) = 11.32$, $p < 0.01$). Similar lack of discrimination was seen in control animals ($F(1.138, 9.106) = 16.28$, $p < 0.01$). Animals with VS lesions had faster latencies to retrieve food for the single option in week 3 and this supports the general strategy of aversion for the multi-option outcome in this group. Incentive contrast was significantly impaired as well after VS lesions. There was no positive contrast for the multi-option outcome when pitted against the 0 pellet option when measured using food reward consumption, time in box or food cup checking. Negative contrast remained intact with each of these measures (Fig. 2B and C).

Dorsal striatal (DS) lesions: Animals with lesions to the DS showed more mild impairments. Discrimination between the 1 and 2 pellet weeks was reduced when measured by appetitive actions ($F(2,18) = 16.84$, $p < 0.01$; 0 pellets < 1 pellet: $M = 15.30 \pm 4.10$ vs. 315.20 ± 66.79, $t(9) = -4.57$, $p < 0.01$; 0 pellets < 2 pellets: $M = 15.30 \pm 4.10$ vs. 442.10 ± 91.10, $t(9) = -4.77$ $p < 0.01$; Fig. 4). The latencies to retrieve food pellets were not significantly different between the 2 and 0/3 options deviating from the parametric prediction. Contrast effects in both directions were absent when monitored using appetitive responding but spared when measured with reward consumption or place conditioning measure. This latter measure was impaired in control animals making the DS group unique in retaining contrast with the time spent in box measure across weeks.

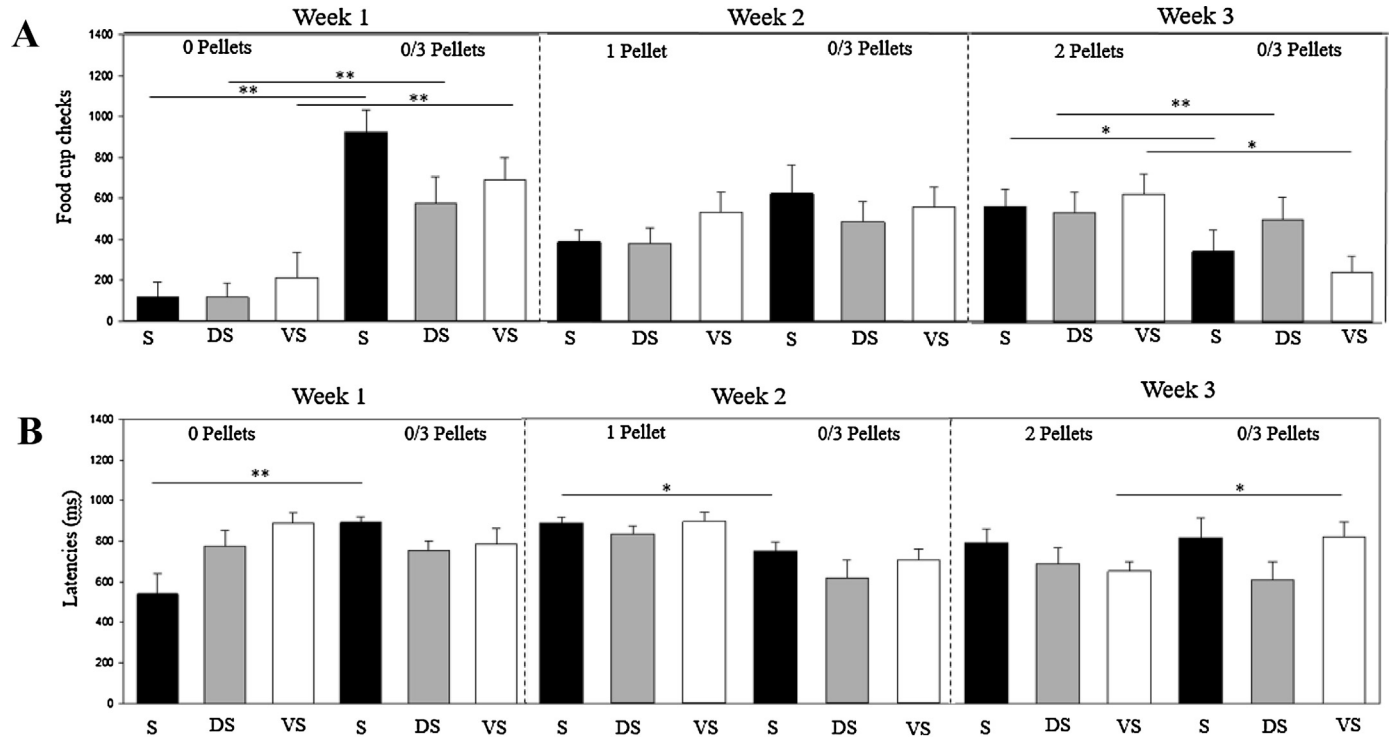

Fig. 4. Measures of approach (Experiment 1). All three groups showed a different behavioral profile for latencies (B) across the three-week session in experiment 1; however they all showed a similar profile with within group differences existing in W1 and W3 for food cup checks (A). Data presented are from the entire 30-min session on free choice day 2. Values are mean ± standard error. * = p < 0.05. ** = p < 0.01.

3.2. Experiment 2

3.2.1. Forced choice testing

Experiment 2 differed from 1 in that the option that shifted among weeks was the multiple-option and the option that remained the same was identical (1 pellet). As in *Experiment 1*, main effects of week, $F(2,44) = 23.93$, $p < 0.01$, and box, $F(1,22) = 43.33$, $p < 0.01$, with no lesion effect indicates similar performance between all groups during the forced choice testing phase of the experiment. A $3 \times 3 \times 3$ ANOVA revealed no interaction between lesion groups when looking across all days and weeks of *Experiment 2*; however, there was a week by day interaction, $F(4,96) = 7.87$, $p < 0.01$. Animals failed to show differences in optimal preference until W6 where they exhibited higher optimal preference during Free Choice as compared to Forced Choice and Extinction (86.04% ± 1.94 vs 60.59% ± 3.02 and 60.26% ± 1.89 respectively; Fig. 5).

3.2.2. Free choice testing: between group differences

Ventral striatal lesions: This subgroup continued to display an aversion to the multi-option outcome with significantly higher overall food consumption ($F(2,27) = 3.95$, $p < 0.05$, $M = 160.7 \pm 11.1$ vs. 119.2 ± 10.6 (dorsal) and 128.26 ± 11.7 (sham) pellets eaten, Fig. 6) and time spent in the single option box ($F(2,24) = 3.76$, $p < 0.05$, 414.45 ± 62.38 vs 638.61 ± 55.79 (dorsal) seconds, Fig. 6). As expected given these results, the vs subgroup had a significant difference in optimal preference compared to the other groups (ventral = 44.29% ± 3.86, dorsal = 56.13 ± 0.345). They showed a significant reduction in the preference score highlighting their aversion to the 0/5 and 0/3 boxes compared to the single-option 1 pellet box. This was observed even when the multi-option box outcome was 2x more food compared to the single-option outcome. No VS lesion effects were found for extinction day when animals were tested in free choice with the food pellets removed.

Dorsal striatal lesions: In contrast to VS lesions, DS lesions did not lead to significant aversion to the multi-option outcome nor a change in optimal preference compared to the control group. Additionally, there were no significant lesion effects for the Extinction day of testing compared to controls.

3.2.3. Free choice testing: within group differences

Ventral striatal lesions: The profile of these animals deviated from the parametric predictions mainly because of deviations in responses to the 0/5 and 0/3 multi-option outcome. Our initial predictions included that animals would show a significant preference for the higher magnitude 0/5 outcome and equivalent responding between the 0/3 and 1 options. VS lesion animals showed impaired discrimination between the 0/5 and 0/3 option expressed in all measures from consumption to place conditioning (105.00 ± 20.95 vs 90.56 ± 52.30 total pellets eaten; 609.22 ± 93.13 vs 410.60 ± 137.90 s; Fig. 6). They also had a lack of preference for the 0/5 option ($M = 108.13 \pm 18.85$ vs 105.00 ± 20.95 pellets; Fig. 6) and absent negative contrast for the 1 pellet when pitted against the 0/5 option (108.13 ± 18.85 vs 137.00 ± 72.75 pellets; Fig. 6). Positive contrast for the 1 pellet was spared in the 2nd week series showing that positive contrast can be produced in this group and relative valuation deficits depend upon on the outcomes more than on the specific direction of reward value shift.

Dorsal striatal lesions: Animals with DS lesions did have impaired discrimination between 0/5 and 0/3 options ($M = 391.50 \pm 63.65$ vs 405.20 ± 124.80 checks; 761.51 ± 211.86 vs 735.10 ± 304.38 milliseconds; Fig. 7) but this was restricted to food cup checks and food retrieval latencies. Preference was also absent for the 0/5 outcome when measured with these appetitive measures (315.60 ± 59.72 vs 391.50 63.65 checks; 817.95 ± 64.38 vs 761.51 ± 66.99 milliseconds) and not other measures (consumption or place conditioning).

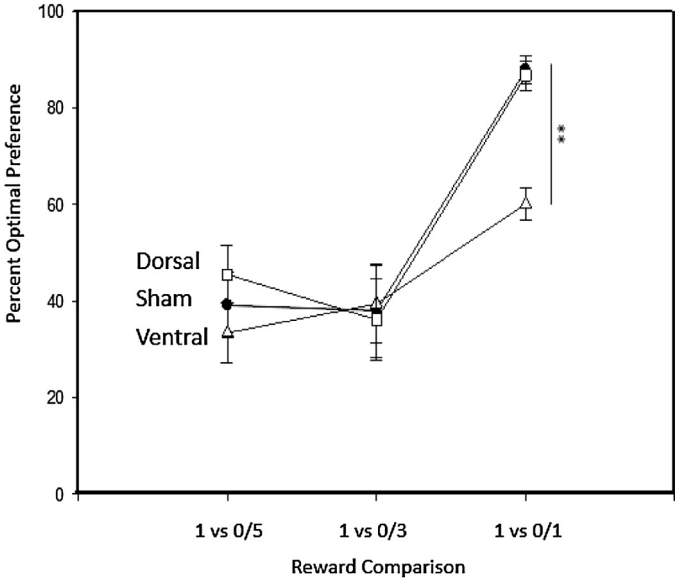

Fig. 5. Optimal preference scores (Experiment 2). The ventral group only significantly differed from the dorsal group across the entirety of the experiment. Data presented are from the entire 30-min session on free choice day 2. Values are mean ± standard error. * = p < 0.05. ** = p < 0.01.

Relative reward was mainly intact across several measures but was impaired only with the time in box showing lack of negative contrast for the 1 pellet when pitted against the 0/5 outcome alternative (609.27 ± 60.94 vs 746.18 ± 93.53 s; Fig. 6).

4. Discussion

4.1. Current experiments

The current experiment demonstrated that controlled, excitotoxic lesions were able to disrupt advantageous decision making in an open, free-choice environment. The 3-box paradigm required rats to update their reward evaluations with outcomes in the single-outcome box shifting across weeks in *Experiment 1* and outcomes in the mixed-outcome box shifting across weeks in *Experiment 2*. The parametric pattern of predictions (Fig. 2A) hypothesizes that as the reward in the single-outcome box increases across weeks in *Experiment 1*, the rats' behaviors should indicate a preference for this box by the end of this experiment that has shifted from a preference for the mixed-outcome box at the beginning of the experiment. A similar process of reward evaluation and updating of behaviors should occur for *Experiment 2*, with the reward outcomes shifting in the mixed-outcome box as opposed to the single-outcome box.

In *Experiment 1*, the sham controls exhibited behaviors consistent with those proposed by the parametric pattern of predictions, which indicates that they were making advantageous choices. They successfully chose between reward values in the single-outcome box and mixed-outcome box, showed discrimination in the single-outcome box across all three weeks, and devalued the reward in the mixed-outcome box as the weeks progressed, consistent with the relative reward effect. Lesions to the dorsal striatum had an effect on the animals' approach behavior in that the group with these lesions had shorter latencies to retrieve pellets across the entire three-week session. In comparison, the group receiving ventral lesions showed an impaired ability to choose optimally in W1 and W3, times during the time when decisions between rewards should be the least ambiguous.

In *Experiment 2*, the emergence of optimal choice was impeded for most measures in all three groups until the 1-pellet to 0/1-

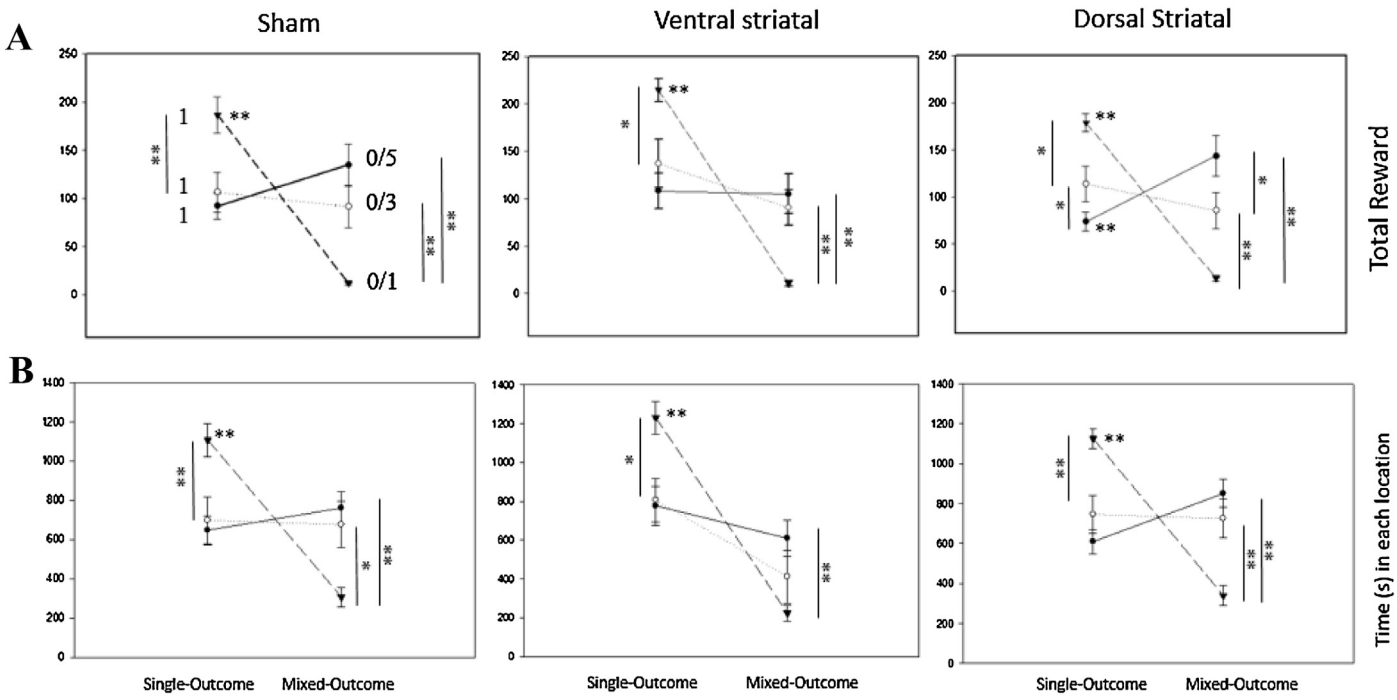

Fig. 6. Measures of consumption and place preference as related to parametric pattern predictions (Experiment 2). While there was evidence of discrimination and contrast, most animals did not show preference until W3 for both total reward (A) and total time in box (B), thus not fitting the parametric pattern predictions (Fig. 2A). Data presented are from the entire 30-min session on free choice day 2. Values are mean ± standard error. * = $p < 0.05$. ** = $p < 0.01$.

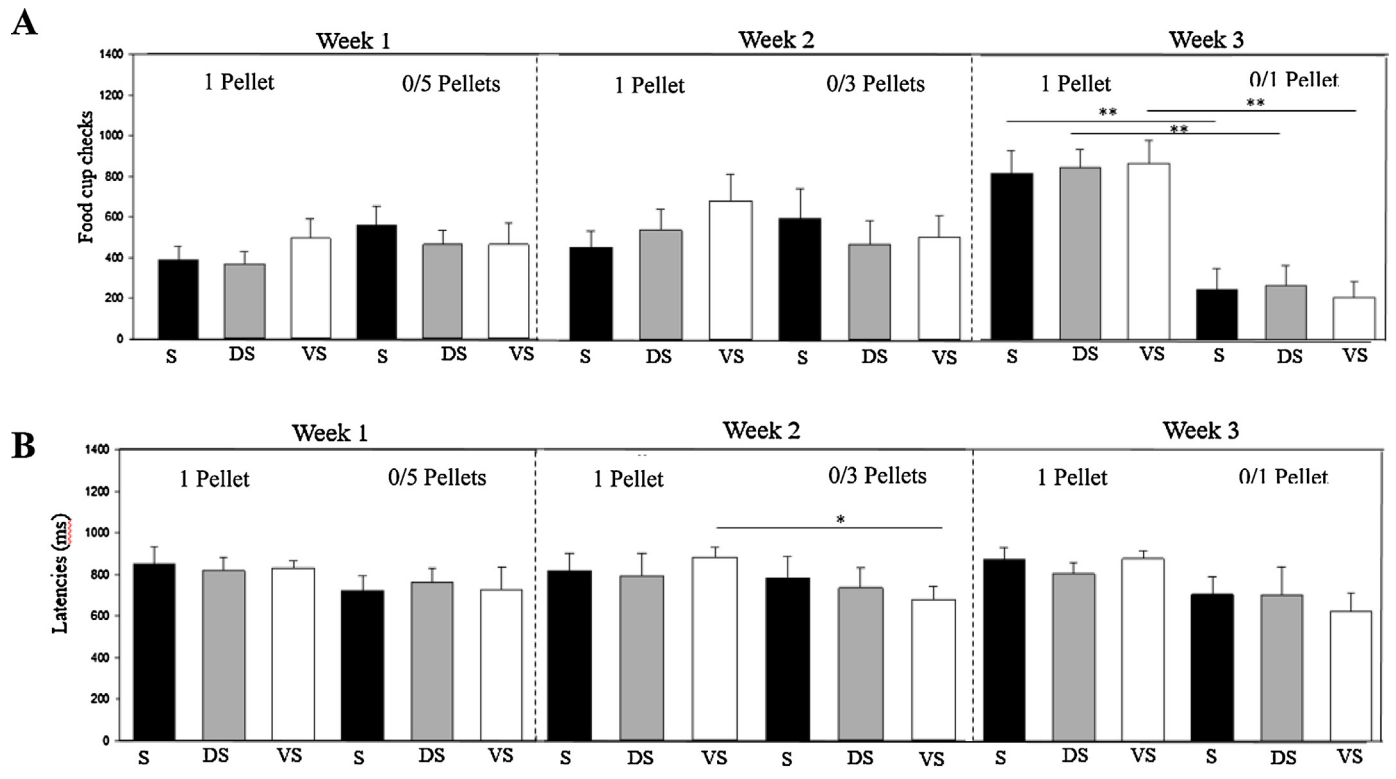

Fig. 7. Measures of approach (Experiment 2). With the exception of the ventral group in W2, there were no within-group differences for latencies (B), but all groups showed significant differences between boxes for food cup checks (A) in W3. Data presented are from the entire 30-min session on free choice day 2. Values are mean ± standard error. * = $p < 0.05$. ** = $p < 0.01$.

pellet comparison when the objective value of the single-outcome box was double that of the mixed-outcome box. The VS-lesion group showed more extreme impairment when collapsing choice across all three weeks in that they consumed significantly more pellets in the single-outcome box which is behavior indicative of disadvantageous choice. The DS-lesion group exhibited behaviors that paralleled those proposed by the parametric pattern of predictions in terms of preference (Fig. 6A). We also found that the

DS-lesion group spent more time in the mixed-outcome box over the three weeks when compared to the other two groups. The mixed-outcome box contained the reward with the higher overall magnitude for two out of the three weeks of the experiment, showing that this group may have been able to employ more advantageous choice strategies.

4.2. Impact of the vs on choice behavior

The striatum has been shown to be a crucial component in the decision making process, and the different subsections play dissociable roles in the process Ito and Doya, 2015. The VS functions in mediating impulsive choice [16]. In *Experiment 2*, the 1-pellet delivery occurred every five seconds in the single-outcome box, while in the mixed-outcome box, the delivery between pellets could take up to 15 s at times. Preference of the single-outcome box could be an indicator of the tendency for animals with lesions to this brain region to make more impulsive choices. Animals in our experiment that received lesions of the VS showed this behavioral profile. When compared to the DS-lesion group, VS-lesioned animals consumed significantly more pellets in the single-outcome box (the effect was nearly significant when compared to sham-lesions). Given that the outcome in the mixed-outcome box was larger overall in two out of the three weeks than that of the single-outcome box, this can be deemed as a disadvantageous choice and a reflection of impulsivity when the timing of delivery is taken into account.

Cardinal and Howes [15] have shown that lesions of the nucleus accumbens (NAc) shift preference away from larger, uncertain choices; however, this same experiment found when all probabilities are held equal, the ability to discriminate remains. These findings mesh with others stating that different distributions of neurons within the ventral subsection of the striatum may be responsible for other aspects that lead to choice behavior, such as value and motivation [12]. Lesions to the VS in our study seemed to have disrupted the ability of rats to discriminate. Rats did not show preference, discrimination, or relative reward valuation in line with the parametric pattern of predictions for any of our measures until the final week of testing (1-pellet to 0/1-pellet comparison). The disruption upon the decision making process is also reflected in the lower optimal preference scores shown in the VS-lesion group over the three-week testing period of *Experiment 2* when compared to the DS-lesion group. The suboptimal choice exhibited by this group may be a function of the inability to discriminate while also exemplifying impulsive tendencies or from improper valuation of already experienced rewards.

The assigning of value relative to previously experienced outcomes is an aspect of choice behavior that was also disrupted in the VS-lesion group. Proper valuation is a function of expectations of forthcoming outcomes, a process which involves certain neuronal populations within the VS [22]. These expectations lead to relative valuations between outcomes which are reflected by neuronal processing in the VS [21]. Rats in our study with VS lesions failed to show relative reward valuation in any measure of approach in *Experiment 2*, nor did they show this valuation when shifting from no reward to one pellet in two of our three measures in *Experiment 1*. This may be a reflection of interrupted expectancy formations. The NAc, a subsection of the VS, plays a large role in the modulation of behavior when expectations are unmet [33]. Animals with NAc lesions show a deficit in instrumental functioning in a relative reward evaluation task; however, their ability to successfully contrast between shifted rewards remained intact. This could be a result of compensatory mechanisms (e.g. amygdala) leading to the contrast effects [6]. Lesioning certain areas of the brain, such as the VS, may open the window for other areas to take over in the decision making process, leaving the possibility for some occurrences of advantageous decision choices to be made.

4.3. Impact of the DS on choice behavior

Advantageous choices require the ability to consistently monitor and accurately evaluate reward options as they fluctuate. This capacity can become less effective as an animal becomes more familiar with outcomes, thus leading to a formation of a habitual response. The dorsal subsection of the striatum is well-known to be a key contributor to this process [57]). Our study builds upon current research suggesting that this area is also involved in certain aspects of choice behavior. The DS is necessary for both the acquisition of a task requiring discrimination of stimuli Featherstone and McDonald, 2004 and the transformation of a behavior into a habit [57]). Once behaviors have been established as a habit, the true value of a reward gained from the behavior may not be represented. The DS-lesion group was the only group of the three in the current experiment to show a pattern of preference that fit our predictions. This could be the result of a disruption in the formation of a habit. The sham lesion and VS-lesion group may have been acting on previously acquired behaviors, while the DS-lesion group was consistently and accurately able to update the reward values of the current outcomes.

Rats with DS lesions in the current study maintained the ability to discriminate between rewards in a manner similar to those with sham lesions. Previous studies in mice have shown that the ability to discriminate actions based on whether they are goal-directed or habit-directed are mediated by the dorsolateral striatum and dorsomedial striatum, respectively [28]). Featherstone and McDonald [26] showed that when the dorsolateral striatum is lesioned, animals were much less efficient at the acquisition of a CS+/CS − discrimination task. The results in our study fall in line with others that found rats with lesions to the DS maintained their ability to discriminate. Tedford et al. [49] found that task acquisition capabilities and the ability to discriminate between qualities of reward remained in animals with dorsolateral striatal lesions, and their performance was similar to those with sham lesions. Rats in the current study showed this ability as well with the exception of a lack of discrimination for measures of approach for the 1 − pellet to 2–pellet comparison in *Experiment 1* and the 0/5-pellet to 0/3-pellet comparison in *Experiment 2.*

While its role in habit formation has been well-documented, the DS is also known to have a role in motor sequencing [32], which ultimately could influence the behavioral representation of choice. It is this role integrated with that of action selection [3]) that greatly signifies the importance of the DS in the decision making process. It is possible that interfering with this process could influence an animal's ability to embody its decision-making process through behavior; however, we do not believe this is the case. In both Experiment 1 and Experiment 2, we saw the same pattern of discrimination for animals with sham, VS-, and DS-lesions in our measures of approach and place conditioning. We see the same pattern with relative reward effects between all three groups, with the exception of the sham group showing a lack of an effect later in Experiment 1 than we see with the other two groups. This signifies that motor behavior was left unimpaired for the DS-lesion group. This could be due to the simplicity of the three-box paradigm, which allows for an animal to engage in a choice task without the complexity of learning an elaborate motor sequencing or action-outcome task [3]. The DS-lesion group also retrieved pellets faster than the other two groups over the course of Experiment 1, showing that the DS-lesioned animals were not only able to perform similarly in terms of motor behaviors, but they also may have had an enhanced capability to time reward retrieval. Appropriate timing is a func-

tion of choice that builds upon the ability to discriminate between rewards.

4.4. Further neural components of choice behavior

In order to gain maximum reward in the current experiment, a properly functioning timing mechanism is essential. Previous work has shown that optimal timing relies on brain areas functioning in reward including the striatum, as well as the frontal cortex, amygdala, and midbrain dopamine (DA) neurons (for review: see Ref. [8]. DA plays a large function in the ability of an organism to optimally time the retrieval of reward or wait for a larger, more optimal reward when a smaller more immediate reward is available, an effect known as delay discounting. The effects of dopaminergic lesions or DA blockades on delay discounting have been ambiguous. Injections of the DA toxin 6-hydroxydopamine (6-OHDA) led to an exacerbation of delay discounting [49]. Other studies found no effect of DA alterations on delay discounting, whether utilizing bilateral injections of the D2 receptor antagonist eticlopride into the NAc [34] or using 6-OHDA infusions into the NAc [54]. Only the VS-lesion group in *Experiment 2* showed an aversion to the larger, delayed reward. It is possible that the way in which DA levels are interfered with could mediate and enable or disable the effects on delay discounting.

Alterations in DA levels have also been shown to affect other aspects of choice behavior which include increased risk aversion [47] and a decrease the amount of effort animals will put forth [5]). This could be related to DA's role in predicting and evaluating which reward is most optimal when a choice is presented [25]. The DA receptor being acted upon during this process also influences choice behavior, with injections of the D1 antagonist SCH-233390 and the D2 antagonist haloperidol reducing preference for a larger reward that requires more effort to obtain and injections of a D3 antagonist leaving it unaffected [5]. Effort needed to obtain reward is one factor that contributes to establishing preference, and excitotoxic lesions of the nucleus accumbens core [16] or dopaminergic lesions of the dorsolateral striatum [49] have been shown to alter choice behavior towards an originally less-preferred reward. We found this behavior to only be apparent in one instance throughout the experiment. These findings may be a function of using a free-choice task as opposed to the standard forced-choice procedure.

There were instances in the current experiment where advantageous decision making was spared. This could be a function of compensatory mechanisms being employed within the basal ganglia. Recent evidence also shows that this process could be spared by function of the ventromedial prefrontal cortex [48]. Burton et al. [13] found that when the VS is damaged unilaterally, decision-making was initially interrupted, but the animals were able to functionally adapt after a brief time period. Neural recordings revealed that firing in the DS was increased during the task normally reliant on VS function. Conversely, it has been found that the VS contains segregated groups of neurons that either encode the value of reward or the motivation to obtain the reward [12]. Finally, functional recovery from dopaminergic lesions has been shown to occur spontaneously [17]. Thus, plasticity, recovery, or redundancy within a system may permit an organism to optimally make decisions if damage has occurred in the relative area.

4.5. Future directions

Dysfunctional decision making is believed to be an element of the foundation of multiple clinical disorders, particularly of addiction. The role of the VS in impulsivity makes it an attractive target for addiction research [35,31]. The VS is part of an interwoven system in which glutamate is believed to be the key factor in the development of addictive behaviors (for review: see Ref. [50]. When comparing addiction to a pathological habit [7], it would appear as if the DS would take over as the key modulator of this behavior. This hypothesis has recently been supported using fMRI to investigate hedonic versus compulsive alcohol intake in social drinkers and alcoholics [51]. This suggests that there is a shift from prefrontal-cortical, to ventral striatal, to dorsal striatal functioning in the development of addictive behaviors. Further research investigating the role of these brain areas will provide us with information that could be valuable in developing new treatments.

5. Conclusion

There are multiple aspects of choice behavior animals must take into account in order for optimal decision-making to occur. Our novel paradigm aids in making these aspects more readily available for observation. While there were few lesion effects in either experiment, the decision-making process was disrupted between our groups of animals. Further research using our 3-box paradigm is warranted, and by altering few aspects of the paradigm could help fill the gaps of knowledge still existing in the area of reward choice and decision-making.

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