Ventral Striatum Lesions Enhance Stimulus and Response Encoding in Dorsal Striatum

Amanda C. Burton, Gregory B. Bissonette, Nina T. Lichtenberg, Vadim Kashtelyan, and Matthew R. Roesch

Background: The development of addiction is thought to reflect a transition from goal-directed to stimulus-response driven behavior, functions attributed to ventral (VS) and dorsal striatum (DS), respectively. In line with this theory, neuroadaptations that occur during prolonged drug use progress from VS to DS. Here we ask if VS dysfunction alone, independent of drug use, can affect neural selectivity in DS.

Methods: To address this issue, we recorded from single neurons in DS while rats performed an odor-guided choice task for differently valued rewards in rats with and without unilateral VS lesions. In a separate group of animals, we used bilateral VS lesions to determine if VS was critical for performance on this task.

Results: We describe data showing that unilateral lesions of VS enhance neural representations in DS during performance of a task that is dependent on VS. Furthermore, we show that VS is critical for reward-guided decision-making initially, but that rats regain function after several days.

Conclusions: These results suggest that loss of VS function, independent of chronic drug use, can trigger stronger encoding in DS in a reward-guided decision-making task and that the transition from VS to DS governed behavior observed in addiction might be due, in part, to initial loss of VS function.

Key Words: Nucleus accumbens, rat, single unit, stimulus-response, striatum, value

Ventral striatum (VS) and dorsal striatum (DS) perform critical roles in reward-guided decision-making and reinforcement learning, but it is still unclear how they interact. Together with midbrain dopamine neurons, they form a circuit commonly referred to as the actor–critic model (1–12). In this model, VS and dopamine neurons function to generate reward predictions and prediction errors, which modify action policies in DS so that desired outcomes can be obtained. This circuit is thought to be critical for drug seeking and is affected by chronic drug use (13–17).

Many behaviors, including drug seeking, are initially goal-directed but eventually become stimulus driven or habitual with repetition. The transition away from goal-directed behavior toward stimulus driven habits is thought to depend on a switch in control from VS to DS (18,19), which is amplified by drugs of abuse (18,20). Because many structural and functional alterations occur with extended drug use, it is still unclear what might initiate this change. Importantly, VS appears to be one of the earliest brain regions to be affected by administration of drugs of abuse, suggesting that its disruption might be enough to initiate changes in downstream areas critical for stimulus driven behaviors. Here, we ask if loss of VS function alone, independent of drug use, might increase encoding in DS.

From the Department of Psychology (ACB, GBB, NTL, VK, MRR), and Program in Neuroscience and Cognitive Science (ACB, MRR), University of Maryland, College Park, Maryland.

Authors ACB and GBB contributed equally to this work.

Address correspondence to Matthew Ryan Roesch, Ph.D., Program in Neuroscience and Cognitive Science, 1147 Biology-Psychology Building, University of Maryland, College Park, MD 20742; E-mail: mroesch@umd.edu.

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Consistent with this hypothesis, stimulus and response encoding in DS was enhanced after VS lesions during performance of a task that was dependent on VS. After several days of postsurgery training, lesioned rats were able to make accurate reward-guided decisions, suggesting that enhanced encoding in DS might compensate for loss of VS function. These results demonstrate that disruption of decision-making with lesions to VS is enough to amplify signals in DS. This suggests that the main locus through which prolonged drug use transitions behavior away from goal-directed to stimulus–response (S-R) driven might reflect initial neuroadaptations in VS and that this alone is enough to initiate changes in DS and enhance S-R learning.

Methods and Materials

Subjects

Twenty-six male Long-Evans rats were obtained at 175 to 200 g from Charles River Labs (Wilmington, Massachusetts). Rats were tested at the University of Maryland, College Park, in accordance with the university and National Institutes of Health guidelines.

Surgical Procedures

All surgical procedures were performed after training on the task described subsequently. Ten rats had a drivable bundle of 10 to 25 μm diameter FeNiCr (iron, nickel, chromium) wires chronically implanted in the left or right hemisphere dorsal to DS (n = 10; 1 mm anterior to bregma, + or –3.2 mm laterally, and 3.5 mm ventral to the brain surface) (21–23). VS lesions were made with a 2-μL Hamilton syringe, beveled edge facing the posterior direction, using .11 mol/L quinolinic acid, pH 7.4 in Dulbecco's phosphate buffer saline (Sigma). Quinolinic acid (.3 μL) was delivered at .15 μL/min at coordinates: anterior–posterior +1.9, medial–lateral ±1.9, and dorsoventral −7.3. The remaining four rats served as controls, which received sham surgeries during which the Hamilton syringe loaded with saline was lowered to the same coordinates. In addition to rats that received electrodes, another group of rats only received bilateral sham (n = 6) or VS lesions (n = 8) to characterize

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behavior. Brains were removed and processed for histology using standard techniques at the end of the experiment (21).

Odor-Guided Delay/Size Choice Task

Before surgery, all rats were trained on the odor-guided delay/size choice task. On each trial, nose poke into the odor port after houselight illumination resulted in delivery of an odor cue to a hemicylinder located behind this opening (24,25). One of three odors (2-octanol, pentyl acetate, or carvone) was delivered to the port on each trial. One odor instructed the rat to go to the left to receive reward, a second odor instructed the rat to go to the right to receive reward, and a third odor indicated that the rat could obtain reward at either well. Odors were presented in a pseudorandom sequence such that the free-choice odor was presented on 7 of 20 trials and the left and right odors were presented in equal proportions.

During the first day of training, rats were first taught to simply nose poke into the odor port, then respond to the well for reward. On the second day, the free-choice odor was introduced, and rats were free to respond to either well for reward. On each subsequent day, the number of forced-choice odors increased by two for each block of 20 trials. During this time, we introduced blocks in which we manipulated the reward size and the length of the delay preceding reward. Once the rats were able to maintain accurate responding (>65%) on forced-choice trials through these manipulations, surgery was performed.

During recording, one well was randomly designated as short (500 msec) and the other long (1–7 sec) at the start of the session (Figure 1A, Block 1). In the second block of trials, these contingencies were switched (Figure 1A, Block 2). The length of the delay under long conditions abided by the following algorithm: the side designated as long started off as 1 sec and increased by 1 sec every time that side was chosen on a free-choice odor (up to a maximum of 7 sec). If the rat chose the side designated as long fewer than 8 of the previous 10 free-choice trials, the delay was reduced by 1 sec for each trial to a minimum of 3 sec. The reward delay for long forced-choice trials was yoked to the delay in free-choice trials during these blocks. In later blocks, we held the delay preceding reward delivery constant (500 msec) while manipulating the size of the expected reward (Figure 1A, Blocks 3 and 4). The reward was a .05-mL bolus of 10% sucrose solution. For big reward, an additional bolus was delivered 500 msec after the first bolus. Essentially there were four basic trial types (short, long, big, and small) by two directions (left and right) by two stimulus types (free- and forced-choice odor).

For behavior after bilateral lesions, only one manipulation varied each day. On each day, one well was randomly designated as high value (i.e., short delay or large reward depending on the day). The location of the high value outcomes switched every 60 correct trials. There were three blocks each day. Delay manipulations occurred on days 1, 3, 5, and 7. Size manipulations occurred on days 2, 4, 6, and 8. All other contingencies were the same as during recording.

Single-Unit Recording

Procedures were the same as described previously (24,26). Electrodes were advanced daily (40–80 μm). Neural activity was

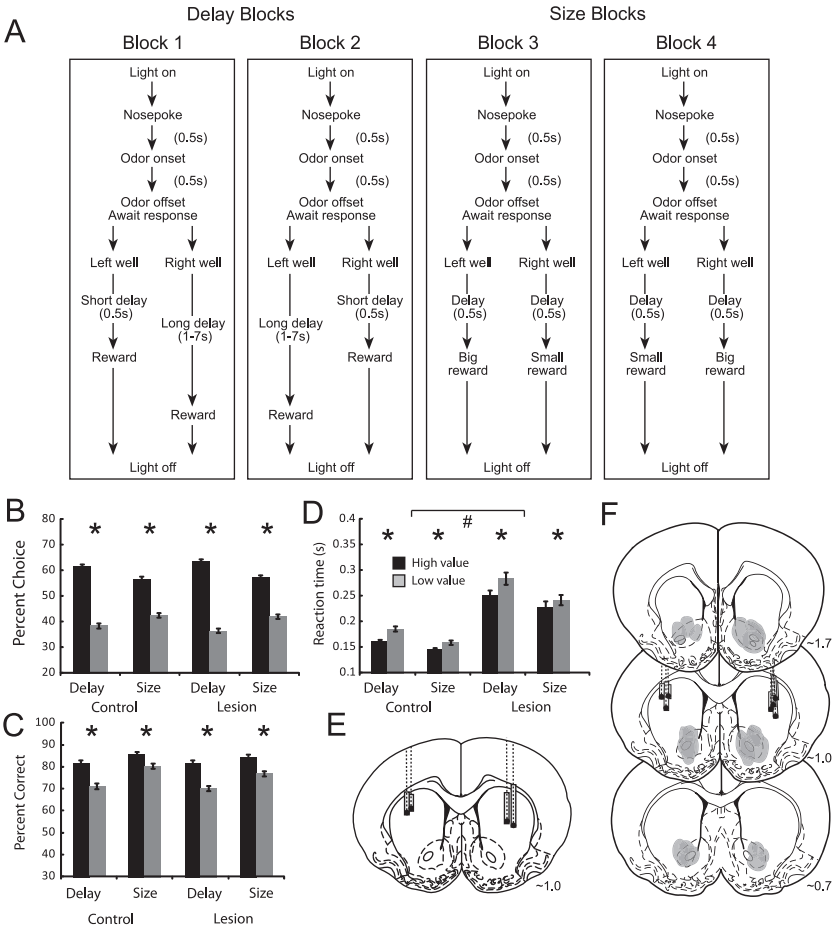

Figure 1. Task, behavior and recording/lesion locations. **(A)** An example of the sequence of events in each trial block. For each recording session, one fluid well was arbitrarily designated as short (500-msec delay before reward) and the other designated as long (1–7 sec delay before reward; Block 1). After the first block of trials (~60 trials), contingencies unexpectedly reversed (Block 2). With the transition to Block 3, the delays to reward were held constant across wells (500 msec), but the size of the reward was manipulated. The well designated as "long" during the previous block now offered two to three fluid boli, whereas the opposite well offered one bolus. The reward stipulations again reversed in Block 4. Free-choice odors signal that either well could be selected for reward, whereas forced-choice odors signaled that reward would only be delivered in the well that the rat was instructed to go to. **(B)** The impact of delay length and reward size manipulations on choice behavior during free-choice trials. Percent choice is calculated by taking the number of choices made and divided by the total number of well entries on free-choice trials, multiplied by 100. **(C)** Impact of value on forced-choice trials for short versus long delay and big versus small reward. **(D)** Reaction times (odor offset to nose unpoke from odor port) on forced-choice trials comparing short versus long delay trials and big versus small reward trials. High value = short and large. Low value = long and small. **(E, F)** Location of recording sites and unilateral lesions based on histology for sham **(E)** and lesioned rats **(F)**. Recordings and lesions were performed in the same hemisphere (three lefts, four rights). Filled gray boxes mark the locations of electrodes based on histology and initial recording site. Black dot marks the bottom of the recording tract. Transparent gray areas mark lesions for each animal. Shown are representative slices at 1.7, 1.0, and .7 anterior to bregma taken from Paxinos and Watson (reprinted from Paxinos G, Watson C. *The Rat Brain, Compact Third Edition*. London: Academic Press, 1997;11-15. With permission from Elsevier). *Planned comparisons revealing statistically significant differences (*t* test, $p < .05$). #Main effect of lesion in the analysis of variance ($p < .05$). Error bars indicate SEM.