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Dissociable effects of dopamine on learning and performance within sensorimotor striatum

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ABSTRACT

Striatal dopamine is an important modulator of current behavior, as seen in the rapid and dramatic effects of dopamine replacement therapy in Parkinson disease (PD). Yet there is also extensive evidence that dopamine acts as a learning signal, modulating synaptic plasticity within striatum to affect future behavior. Disentangling these "performance" and "learning" functions is important for designing effective, long-term PD treatments. We conducted a series of unilateral drug manipulations and dopamine terminal lesions in the dorsolateral striatum of rats highly trained to perform brief instructed head/neck movements (two-alternative forced choice task). Reaction times and accuracy were measured longitudinally to determine if task behavior changed immediately, progressed over time, and/or persisted after drug withdrawal. Enhanced dopamine signaling with amphetamine caused an immediate, nonprogressive, and bilateral decrease in reaction times (RT). The altered RT distributions were consistent with reduced distance to threshold in the linear approach to threshold with ergodic rate (LATER) model of decision-making. Conversely, the dopamine antagonist flupenthixol caused experience-dependent, persistent changes in RT and accuracy indicative of a "learning" effect. These RT distributions were consistent with a slowed rate of approach to decision threshold. Our results show that dopaminergic signaling makes dissociable contributions to current and future behavior even within a single striatal subregion, and provide important clues for both models of normal decision-making and the design of novel drug therapies in PD.

Introduction

Difficulty initiating movements is a core symptom of Parkinson disease (PD) that is markedly improved by dopamine replacement therapy [1]. However, the precise mechanisms by which striatal dopamine loss interferes with, and dopamine replacement improves, movement initiation remain unclear.

The short duration response (SDR) to levodopa is an acute improvement in motor function correlated with plasma levodopa levels [2,3]. In the standard "rate" model of the basal ganglia (BG) [4,5], the SDR arises from dopaminergic effects on striatal medium spiny neuron (MSN) firing rates, leading to reduced activity of BG output neurons that tonically suppress behavior. Alternatively, levodopa may help restore normal patterns of BG activity [6–9], instead of the excessive bursting [10], synchrony [11], and oscillations [12] precipitated by dopamine loss. Whether dopamine influences firing rates or patterns, the speed with which levodopa and other dopaminergic drugs affect behavior is consistent with a critical role for the BG in online motor performance [13,14]. Indeed, behavior can be rapidly altered by optogenetic [15], electrical [16], or pharmacologic [17–19] manipulations of BG circuits.

The long duration response (LDR) is persistent motor improvement after levodopa elimination [20]. It may arise through dopamine-modulated synaptic plasticity that normally supports reinforcement learning [21–25]. With decreased striatal dopamine signaling, normal learning of motor skills is impaired [26], aberrant learning can occur [27], and established performance of various

Abbreviations: aCSF, artificial cerebrospinal fluid; AMPH, amphetamine; BG, basal ganglia; DLS, dorsolateral striatum; FLU, flupenthixol; LATER, linear approach to threshold with ergodic rate; LDR, long duration response; mfb, medial forebrain bundle; PD, Parkinson disease; RAC, raclopride; RT, reaction time; SC, superior colliculus; SDR, short duration response; SNr, substantia nigra, pars reticulata.

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operant tasks may be initially preserved but decline with practice (“experience-dependent” effects; [28,29]). BG output is important for the acquisition of motor sequences [30], but may not be required to perform previously learned sequences [31,32]. Some therefore argue that striatal circuitry with dopamine-dependent plasticity acts primarily as a trainer for other subregions [33] or different brain regions altogether [34,35].

Intracerebral infusions are a powerful means of dissecting the contributions of specific neurotransmitter systems in specific brain regions to behavior. For example, bilateral inactivation of striatal subregions with muscimol can force rats to transition between goal-directed and habitual behavior [36,37], and bilateral intrastriatal infusion of dopamine antagonists reproduces the catalepsy induced by systemically administered neuroleptics [38–41]. Bilateral intrastriatal infusions of amphetamine post-training have been found to improve retention for certain types of tasks [42]. Unilateral putaminal dopamine receptor blockade in nonhuman primates induces contralateral parkinsonism [43]. Finally, intra-caudate infusion of D1 or D2 antagonists modifies the apparent effects of reward expectation on reaction time (RT) [44]. Most of these studies have not investigated striatal contributions to action selection, and none have attempted to distinguish the contributions of striatal dopaminergic signaling to skill acquisition/maintenance vs acute performance.

To help disentangle “performance” and “learning” functions, we transiently suppressed the output of, or altered dopaminergic signaling in, rat dorsolateral striatum (DLS) unilaterally. Rodent DLS is a sensorimotor subregion homologous to human lateral/posterior putamen, the earliest region affected by dopamine loss in PD [45]. The rats engaged in a lateralized reaction time task (a.k.a. two-alternative forced choice, or conditional discrimination [46,47]) in which tone cues prompt brief head/neck movements to the left or right. Behavior was assessed primarily by the fraction of correct responses and RT, including examination of full RT distributions to make inferences about specific striatal contributions to decision-making processes. Drug manipulations were considered to affect learning if behavioral changes were experience-dependent, and/or persisted after drug withdrawal. These selective, reversible interventions then informed the interpretation of more PD-like permanent destruction of dopaminergic terminals using 6-hydroxydopamine (6-OHDA) infusions into DLS.

Methods

Animals

All animal procedures were approved by the University of Michigan Committee on the Use and Care of Animals. Adult male Long–Evans rats were housed on a 12 h reversed light-dark cycle, and tested during the dark phase. Rats were food restricted to 15 g of standard laboratory chow per day, but allowed to free-feed one day per week and in the peri-operative period. Their weights were monitored to ensure that they maintained at least 85% of anticipated body weight for their age.

Behavioral task

The operant chamber (Med Associates, St. Albans, VT) and task performance are illustrated in Fig. 1 (see also the “Immediate-Go” task of Leventhal et al. [47]). One of the three central nose-ports was lit. The rat had an unlimited amount of time to poke and maintain its nose in the lit port, initiating a trial. After a variable delay (uniform distribution from 750 to 1250 ms), a 1 or 4 kHz pure tone (~60 dB) played for 250 ms, indicating that the rat should move one port to the left or right, respectively. Simultaneous with tone onset, the center port light was extinguished and both adjacent ports were lit. From the start of the tone, the rat was allowed a maximum of 1 s (the “limited hold”, Fig. 1c) to poke an adjacent port. Correct responses (the infrared beam for the correct side-port was broken first) were rewarded with a 45 mg fruit punch flavored sucrose pellet delivered at the back of the chamber. On 20% of trials, a linear summation of 4 kHz and 1 kHz tones indicated that either adjacent port would be rewarded with 50% probability (“catch” trials). Each test session lasted 1 h. Intertrial intervals were pulled from a uniform distribution between 15 and 25 s.

Trials were classified as “procedure errors” or “completed trials.” Procedure errors were “wrong starts” (poking an unlit port to initiate a trial), “false starts” (withdrawing from the center port before the cue tone played), and “failures to respond” (failure to poke a side port within 1 s of the tone). “Completed trials” included “incorrect trials” (poking the wrong lit side-port) and “correct trials.” For “catch” trials, no distinction was made between “correct” and “incorrect” completed trials, regardless of whether they were rewarded. After procedural errors, but not completed trials, the house light was lit during the intertrial interval.

Training sequence

Training before surgery lasted about 2 months. Rats were handled daily for one week prior to beginning operant testing, then habituated to the chamber for one to two test sessions during which all ports were lit and poking any port was rewarded. They were then trained to maintain their noses in a single lit port for progressively longer periods to obtain a reward, signaled by a 250 ms burst of white noise. Finally, pure tone instruction cues replaced the white noise at the end of the hold period, and the rats were allowed progressively less time to poke an adjacent port.

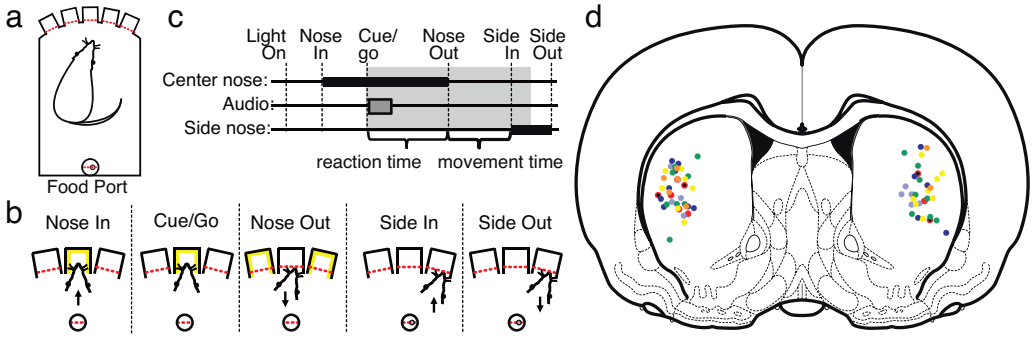

Fig. 1. Task performance and infusion sites. (a) Schematic diagram of the operant box. Red dashed lines indicate photobeams. (b) Illustration of task events. (c) Timeline of task performance. Thick black bars indicate a nose-port is occupied. The gray bar indicates the cue tone. The gray shaded area indicates the limited hold period (1 s). (d) Histologically verified infusion sites projected onto an A-P = +0.48 mm coronal atlas section (A-P range −0.72 to +1.2 mm with respect to bregma) [107]. Small black dots – MUSC, red dots – AMPH, light blue dots – LOW FLU, dark blue dots – HIGH FLU, green dots – RAC, yellow dots – SCH, orange dots – 6OHDA.

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