REGIONALLY DISTINCT PHASIC DOPAMINE RELEASE PATTERNS IN THE STRIATUM DURING REVERSAL LEARNING

MARIANNE KLANKER, LISANNE FELLINGER, MATTHIJS FEENSTRA, INGO WILLUHN AND DAMIAAN DENYS

a Netherlands Institute for Neuroscience, Institute of the Royal Netherlands Academy of Arts and Sciences, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands

b Department of Psychiatry, Academic Medical Center, University of Amsterdam, Postbus 22660, 1100 DD Amsterdam, The Netherlands

Abstract—Striatal dopamine (DA) plays a central role in reward-related learning and behavioral adaptation to changing environments. Recent studies suggest that rather than being broadcast as a uniform signal throughout the entire region, DA release dynamics diverge between different striatal regions. In a previous study, we showed that phasic DA release patterns in the ventromedial striatum (VMS) rapidly adapt during reversal learning. However, it is unknown how DA dynamics in the dorsolateral striatum (DLS) are modulated during such adaptive behavior. Here, we used fast-scan cyclic voltammetry to measure phasic DA release in the DLS during spatial reversal learning. In the DLS, we observed minor DA release after the onset of a visual cue signaling reward availability, followed by more pronounced DA release during more proximal reward cues (e.g., lever extension) and execution of the operant response (i.e., lever press), both in rewarded and non-rewarded trials. These release dynamics (minor DA after onset of the predictive visual cue, prominent DA during the operant response) did not change significantly during or following a reversal of response-reward contingencies. Notably, the DA increase to the lever press did not reflect a general signal related to the initiation of any motivated motor response, as we did not observe DA release when rats initiated nose pokes into the food receptacle during inter-trial intervals. This suggests that DA release in the DLS occurs selectively during the initiation and execution of a learned operant response. Together with our previous results obtained in the VMS, these findings reveal distinct phasic DA release patterns during adaptation of established behavior in DLS and VMS. The VMS DA signal, which is highly sensitive to reversal of response-reward contingences, may provide a teaching signal to guide reward-related learning and facilitate behavioral adaptation, whereas DLS DA may reflect a ‘response execution signal’ largely independent of outcome, that may be involved in initiation and energizing of operant behavior.

Key words: spatial reversal learning, dopamine, fast-scan cyclic voltammetry, dorsolateral striatum, cognitive flexibility.

INTRODUCTION

Corticostriatal circuits are important for the regulation of motivated behavior and cognitive functioning. These circuits consist of converging input from different cortical areas and midbrain dopamine (DA) neurons to projection neurons in the striatum. The projections from the cortex to the striatum are organized topographically, where sensory and motor cortical areas dominate inputs to the dorsolateral striatum (DLS) and limbic areas constitute the majority of the cortical projection to the ventromedial striatum (VMS) (Webster, 1961; McGeorge and Faull, 1989). DA is an essential neuromodulator that regulates activity in corticostriatal circuits. Loss of the modulatory role of DA in these circuits leads to impairments in motor performance, motivated behavior and executive functioning (Cools et al., 2001; Sawamoto et al., 2008). One of the executive functions that is affected by compromised DA function is cognitive flexibility, the ability to adapt behavior in response to changes in the environment (Klanker et al., 2013).

Successful adaptation of behavior requires the use of negative feedback to switch behavior and sensitivity to positive feedback to acquire a new response. Previously, we showed that DA signaling in the VMS is associated with positive feedback during reversal learning (Klanker et al., 2015), consistent with the idea of a quantitative reward prediction error (Schultz et al., 1997; Steinberg et al., 2013). However, several studies suggest that DA in the dorsal striatum might also be important for the regulation of this type of behavior. For example, dorsal DA is not just involved in the acquisition and execution of operant actions and habit formation (Amalric and Koob, 1987; Robbins et al., 1990; Beninger and Ranaldi, 1993; Faure et al., 2005; Robinson et al., 2007), but also in cognitive flexibility (Cools et al., 2001; Sawamoto et al., 2008; Clarke et al., 2011). In other words, dorsal striatal DA may invigorate both flexible and inflexible behavior.
Although electrophysiological studies suggest that all midbrain DA neurons behave similarly during conditioning tasks (Schultz et al., 1997), more recent findings reported differences between the characteristics of the VMS and DLS DA systems (Bromberg-Martin et al., 2010; Lemer et al., 2015). However, not only are VMS and DLS innervated by separate populations of DA neurons (Beckstead et al., 1979; Bjorklund and Dunnett, 2007), that are under excitatory influence of somewhat distinct afferent projections (Watabe-Uchida et al., 2012; Lemer et al., 2015), these regions also differ in DA receptor density (Dubois and Scatton, 1985; Savasta et al., 1986), DA uptake kinetics (Missale et al., 1985; Stamford et al., 1988; Garris et al., 1994) and local mechanisms influencing DA release (Rice et al., 2011).

Together, these factors induce regionally distinct release patterns in striatal subregions during the execution of goal-directed behavior (Brown et al., 2011; Cacciapaglia et al., 2012; Willuhn et al., 2012; Shnitko and Robinson, 2015). However, while a large body of work investigated VMS DA during reward-related learning, it is unclear how phasic DA release in the DLS is modulated during performance of instrumental actions, as previous work produced inconsistent findings (Brown et al., 2011; Shnitko and Robinson, 2015). It is also unknown how DLS DA dynamics are modulated during adaptation of response behavior to a reversal of response-reward contingencies. Our previous results showed that DA signaling in the VMS rapidly adapts to reversed response-reward contingencies and that updating of cue-evoked DA following positive feedback predicts performance of reversal learning (Klanker et al., 2015). Here, we extend these findings by describing DA release dynamics in the DLS during reversal learning.

**EXPERIMENTAL PROCEDURES**

All experiments were approved by the Animal Experimentation Committee of the Royal Netherlands Academy of Arts and Sciences and were carried out in agreement with Dutch laws (Wet op de Dierproeven, 1996) and European regulations (Guideline 86/609/EEC).

**Animals**

Male Wister rats (Charles River, n = 13) were housed socially under a reversed day-night schedule (lights on from 7 p.m. to 7 a.m.). During behavioral training, rats were food-restricted (16 grams/animal/day) with water available ad libitum. The day before and 3–4 days after surgery, unlimited access to food and water was provided. Rats were individually housed after surgery.

**Surgery**

Rats (weighing ~300 g) were anesthetized with Isoflurane (induction: 3%, maintenance: 1.8–2.5%) and received subcutaneous Metacam® (Meloxicam, 1 mg/kg, Boehringer-Ingelheim, Germany) as analgesic. Body temperature was maintained by a temperature controller and heating pad. Rats were placed in a stereotactic frame and implanted with a guide cannula (custom made, NIN mechanical workshop) above the DLS (anteroposterior +1.2 mm, lateral ±3.3 mm relative to bregma (Paxinos and Watson, 2007) and an Ag/AgCl reference electrode in the contra-lateral hemisphere. A bipolar stimulation electrode (Plastics one, Roanoke, VA, USA) was placed into the medial forebrain bundle (MFB; AP –3.6 mm, ML ±1.8 mm, DV –8.5 mm from skull). The guide cannula and electrodes were fixed to the skull with screws and dental cement. The cannula was closed with a removable stylet after surgery.

**Apparatus**

All experiments were performed in a custom-made operant chamber (40 × 40 × 40 cm, NIN mechanical workshop) with Med Associates components (Med Associates, Sandown Scientific, Hampton, UK). The operand chamber was connected to a Med-PC interface and controlled by Med-PC software (Med Associates, Sandown Scientific, Hampton, UK). One wall of the operand chamber contained two retractable levers placed left and right from a food dispenser, with a cue light above each lever. An infrared sensor detected nose-pokes made to retrieve sucrose pellets (dustless precision pellets®, 45 mg, Bio-Serv) from the food dispenser.

**Behavioral training**

Rats were habituated to the operand chamber and sucrose pellets before behavioral training (also see methods in Klanker et al., 2015). During lever-press training, rats were randomly presented with either the left or the right cue light. After a 2-s delay, the corresponding lever was presented. If a lever-press was made within 30 s, the lever was retracted, the cue light switched off and a sucrose pellet was delivered in the food dispenser. Failure to respond within 30 s ended cue light illumination and lever presentation and the trial was scored as omission. Sessions consisted of 32 trials, with variable inter-trial intervals (10/20 s). Rats received up to three training sessions per day with 2–3 h between the sessions.

During discrimination and reversal sessions, rats were presented with both cue lights simultaneously, and 2 s later both levers were presented. If a lever press was made within 10 s, the levers were retracted and the cue lights switched off. During discrimination session, lever presses on one side were always rewarded, whereas lever presses on the other side were never rewarded. Thus, the task was spatial: cue lights did not signal which side was rewarded, but indicated the potential availability of a reward. The rewarded side was counterbalanced between rats. Discrimination and reversal sessions consisted of 120 trials, with a variable inter-trial interval (15/25/35/45 s). In case of an omission, cue light and lever presentation ended after 10 s. During the reversal session, response-reward contingencies reversed between the 16th and 32nd trial in the session, so that a response to the previously rewarded lever was no longer rewarded and a response to the previously unrewarded lever was now rewarded. The reversal of response-reward contingencies was
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