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Molecular substrates of action control in cortico-striatal circuits

Michael W. Shiflett [a], Bernard W. Balleine [b,*]

[a] Department of Psychology, Rutgers University, Newark, USA
[b] Brain and Mind Research Institute, University of Sydney, 100 Mallett St, Camperdown, NSW 2050, Australia

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ABSTRACT

The purpose of this review is to describe the molecular mechanisms in the striatum that mediate reward-based learning and action control during instrumental conditioning. Experiments assessing the neural bases of instrumental conditioning have uncovered functional circuits in the striatum, including dorsal and ventral striatal sub-regions, involved in action–outcome learning, stimulus–response learning, and the motivational control of action by reward-associated cues. Integration of dopamine (DA) and glutamate neurotransmission within these striatal sub-regions is hypothesized to enable learning and action control through its role in shaping synaptic plasticity and cellular excitability. The extracellular signal regulated kinase (ERK) appears to be particularly important for reward-based learning and action control due to its sensitivity to combined DA and glutamate receptor activation and its involvement in a range of cellular functions. ERK activation in striatal neurons is proposed to have a dual role in both the learning and performance factors that contribute to instrumental conditioning through its regulation of plasticity-related transcription factors and its modulation of intrinsic cellular excitability. Furthermore, perturbation of ERK activation by drugs of abuse may give rise to behavioral disorders such as addiction.

Contents

Abbreviations: AC, adenylyl cyclase; Cdk5, cyclin dependent kinase 5; CREB, cAMP response element binding protein; CS, conditioned stimulus; DA, dopamine; D1, dopamine D1 receptor; D2, dopamine D2 receptor; DARPP-32, dopamine- and camp-regulated phosphoprotein; DMS, dorsomedial striatum; DLS, dorsolateral striatum; ERK, extracellular signal regulated kinase; GPe, globus pallidus external; GPi, globus pallidus internal; IMD, intermediodoral nucleus of the thalamus; LTD, long term depression; LTP, long term potentiation; MD, mediodorsal thalamus; mGLUr, metabotropic glutamate receptors; MSK1, mitogen- and stress-activated protein kinase 1; MSN, medium spiny neuron; NAc, nucleus accumbens; pDMS, posterior dorsomedial striatum; PIT, Pavlovian-instrumental transfer; PKA, protein kinase A; PL, prelimbic region of the medial prefrontal cortex; PO, posterior nucleus of the thalamus; PP, protein phosphatase; R-O, response-outcome; Rsk, ribosomal s6 kinase; S-R, stimulus–response; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STEP, striatal-enriched phosphatase; STN, subthalamic nucleus; VA/VL, ventroanterior/ventrolateral nucleus of the thalamus; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area.

* Corresponding author. Tel.: +61 2 91144011; fax: +61 2 91144034.
E-mail address: bernard.balleine@sydney.edu.au (B.W. Balleine).

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1. Introduction

The basal ganglia are a network of subcortical nuclei that have long been known to exert a strong coordinating influence on the motor system, particularly on the feed-forward and feedback processes involved in action initiation and execution. More recent research has, however, significantly broadened our understanding of basal ganglia anatomy and the functions with which it is concerned. Although there have been many attempts to paint it as a network serving a single homogeneous function, recent evidence suggests that the basal ganglia are involved in heterogeneous motor functions ranging from simple reflexive, sensorimotor habits to deliberated, goal-directed actions. The latter function is of particular interest given recent advances in our understanding of the nature of the learning and motivational processes involved in the control of actions, in choice between actions and in decision-making more generally.

Much of this recent work has focused on the striatum, which is the largest of the basal ganglia nuclei and serves as the entry point for cortical and thalamic inputs into basal ganglia circuitry. Human and primate research has found evidence of striatal involvement in the learning and performance processes engaged by reward-related actions during decision-making tasks and disorders that affect the striatum, such as Parkinson's disease, Huntington's disease and substance abuse, produce impairments in these kinds of action (Balleine et al., 2007; Balleine and O'Doherty, 2010; Bechara et al., 2002; Cohen and Frank, 2009; Delgado, 2007; Hikosaka, 2007). Parallel research in rodents using paradigms derived from instrumental conditioning has identified sub-regions within the striatum that mediate distinct forms of action control based on an assessment of the learning and performance processes (Balleine et al., 2008, 2009; Balleine and Ostlund, 2007; Yin et al., 2008). In similar fashion to the primate research, rodent research has identified a network involving the dorsomedial striatum mediating the role of reward-related learning in the cognitive control of action and that has been dissociated anatomically and functionally from a more lateral network engaged during the learning and performance of habits.

How the striatum controls the influence of reward learning on the cognitive control of action selection and initiation at a cellular and molecular level is an area of active research. The primary inputs to striatum are excitatory projections from diverse regions of cortex and thalamus, and synaptic plasticity at corticostriatal synapses is thought to be critical for these aspects of action control (Costa, 2007; Di Filippo et al., 2009; Horvitz, 2002, 2009; Wickens et al., 2007). The striatum also receives dopaminergic input from the midbrain, and indeed, models of reward learning and action control emphasize the importance of dopamine signals in learning and decision making (Dayan and Balleine, 2002; Redgrave et al., 2008; Salamone and Correa, 2002; Schultz, 2007; Schultz and Dickinson, 2000). Dopamine and glutamate signaling interact through multiple cellular mechanisms to shape neural excitability and synaptic plasticity in striatal neurons (Di Filippo et al., 2009; Kreitzer, 2009; Lovinger, 2010; Surmeier et al., 2007). An important question for current research is to understand the role that these diverse cellular signaling mechanisms play in striatal-based reward learning and action control. In order to address this topic, it is important to have a framework for understanding the cognitive processes mediated by the striatum. Here we use concepts derived from instrumental conditioning in rodents as a model for examining the molecular mechanisms that underlie striatal function. We suggest that signaling molecules that are sensitive to combined dopamine and glutamate receptor signaling have a key role in learning and action control in the striatum and that alteration in the activity of these signaling molecules may underlie many of the abnormalities in these behavioral processes induced by genetic conditions, neurodegeneration and addiction.

2. Actions, habits and the striatum

As the main input nucleus of the basal ganglia, the striatum receives excitatory glutamatergic afferents from cortical, limbic and thalamic regions, as well as heavy dopaminergic input from the midbrain (Sesack et al., 2003; Smith et al., 1998). Traditionally, the striatum has been divided into dorsal and ventral subdivisions. The ventral subdivision contains the nucleus accumbens (NAc), which itself consists of core and shell sub-regions (Zahm, 2000; Zahm and Brog, 1992). The glutamatergic inputs to striatum are topographically organized, with limbic and ventral prefrontal regions projecting to the ventral striatum, sensorimotor cortical regions projecting to the dorsolateral striatum (DLS) and association areas of the prefrontal cortex projecting to the dorsomedial striatum (DMS) (Alexander et al., 1986; Groenewegen et al., 1990)—see Fig. 1A. This pattern of connectivity has lead to the idea that cortico-basal-ganglia loops are organized into functional circuits that mediate distinct components of behavior (Alexander et al., 1990; Joel and Weiner, 1994; Pennartz et al., 2009; Voorn et al., 2004). Indeed, early studies of maze task performance in animals concluded that the dorsal striatum was necessary for implementing a "response" strategy, defined in terms of a reliance on egocentric information (e.g., turn left) or simple stimulus–response associations to encode goal locations (see Packard and Knowlton, 2002; White, 2009; Yin and Knowlton, 2006 for review). In contrast, the ventral striatum, specifically the nucleus accumbens, was described as having a role in the expression of conditioned emotional responses to cues and contexts associated with appetitive (or aversive) events, such as access to mates, drugs of abuse, and food or liquid rewards (see Belin et al., 2009; Berridge, 2009; Cardinal et al., 2002; Day and Carelli, 2007 for review). Furthermore, behavior mediated by the striatum in these tasks were found to depend on glutamate and dopamine signaling (Burns et al., 1994; Cory-Slechta et al., 1999; Di Ciano et al., 2001; Packard, 1999; Packard and Teather, 1997; Packard and White, 1991; Smith-Roe and Kelley, 2000) suggesting that combined activation of these neurotransmitter systems in the striatum is necessary for normal striatal function.

More recently, the application of instrumental procedures has more precisely elucidated the various action-related functions mediated by the striatum—see Fig. 1B. One of the most important aspects of this research has been the repeated demonstration that, contrary to appearance, instrumental actions, such as lever pressing, can be controlled at different times by fundamentally distinct learning and motivational processes. In particular, various instrumental procedures and tests have been used to establish whether and when an animal's actions are deliberated or goal-directed and when they are elicited, automatic or habitual. Generally, actions are considered goal directed if it can be demonstrated both that an animal has encoded the outcome resulting from its actions and uses that information to select among potential actions. More specifically, Balleine and Dickinson (1998) argued, based on human action theory, that for any action to be labeled goal-directed it must be shown to satisfy two criteria; referred to as the goal and the contingency criteria. To satisfy the goal-criterion, performance of an action must be shown to be sensitive to changes in the encoded value of the outcome, whereas to satisfy the contingency criterion an action must be shown to depend on the contingent or causal relationship between the action its specific consequences. If the performance of an action persists in a situation where either its causal relationship to the outcome or the value of the outcome declines then it is difficult to claim it is truly goal-directed.