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REVIEW

PREFRONTAL DOPAMINE IN ASSOCIATIVE LEARNING AND MEMORY

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Abstract—Learning to associate specific objects or actions with rewards and remembering the associations are everyday tasks crucial for our flexible adaptation to the environment. These higher-order cognitive processes depend on the prefrontal cortex (PFC) and frontostriatal circuits that connect areas in the frontal lobe with the striatum in the basal ganglia. Both structures are densely innervated by dopamine (DA) afferents that originate in the midbrain. Although the activity of DA neurons is thought to be important for learning, the exact role of DA transmission in frontostriatal circuits during learning-related tasks is still unresolved. Moreover, the neural substrates of this modulation are poorly understood. Here, we review our recent work in monkeys utilizing local pharmacology of DA agents in the PFC to investigate the cellular mechanisms of DA modulation of associative learning and memory. We show that blocking both D1 and D2 receptors in the lateral PFC impairs learning of new stimulus–response associations and cognitive flexibility, but not the memory of highly familiar associations. In addition, D2 receptors may also contribute to motivation. The learning deficits correlated with reductions of neural information about the associations in PFC neurons, alterations in global excitability and spike synchronization, and exaggerated alpha and beta neural oscillations. Our findings provide new insights into how DA transmission modulates associative learning and memory processes in frontostriatal systems.

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Abbreviations: BG, basal ganglia; BLA, basolateral amygdala; CN, caudate nucleus; DA, dopamine; dlPFC, dorsolateral aspect of the PFC; GPe, globus pallidus pars externus; GPi, globus pallidus pars internus; LFP, local field potential; LTD, long-term depression; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SR, stimulus–response; vlPFC, ventrolateral aspect of the PFC; VTA, ventral tegmental area.

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INTRODUCTION

Learning to identify and remember rewarding and aversive stimuli in our environment is key to our advanced cognitive abilities and to our survival. Associative learning and memory processes are not only crucial for a simple classification of food as appetitive or unpleasant but also to know what outcomes will follow our actions. This type of goal-directed associative learning and memory depend heavily on the prefrontal cortex (PFC) and interactions between the PFC and other subcortical structures such as the striatum (Fuster, 2001; Miller and Cohen, 2001; Graybiel, 2008). Neurophysiological studies show changes in PFC neural activity during learning and memory tasks (Asaad et al., 1998; Pasupathy and Miller, 2005; Histed et al., 2009; Benchenane et al., 2010; Antzoulatos and Miller, 2011, 2014; Puig and Miller, 2012, 2014), and

damage to the PFC elicits profound learning, memory, and other cognitive deficits (Godefroy, 2003; Robbins, 2007; Kehagia et al., 2010). Furthermore, learning and memory impairments are found in psychiatric and neurological disorders associated with abnormalities in PFC transmission such as schizophrenia (Park and Holzman, 1992; Elvevåq and Goldberg, 2000).

The PFC is innervated by dopamine (DA) axons originating in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) (Levitt et al., 1984; Fallon, 1988; Goldman-Rakic et al., 1992; Lewis, 1992; Williams and Goldman-Rakic, 1998; Björklund and Dunnett, 2007; Yetnikoff et al., 2014), that modify PFC function via the D1 and D2 families of receptors (D1R and D2R, respectively) (Seamans and Yang, 2004). Selective DA depletion in the PFC of macaque monkeys produces deficits in executive function (Brozoski et al., 1979). In fact, disruption of PFC DA transmission is suspected to underlie a number of psychiatric conditions including schizophrenia, depression, and attention-deficit hyperactivity disorder (Grace, 1991; Robbins, 2000a,b; Winterer and Weinberger, 2004; Arnsten, 2009; Arnsten et al., 2010).

Studies conducted in non-human primates have revealed that DA neurons carry out computations that support associative learning and memory. More specifically, they compute reward prediction errors that allow them to keep track of stimuli associated with rewards. However, the functional connection between PFC DA and learning is not straightforward considering that the PFC is an associational area that integrates information from numerous cortical and subcortical structures and receives axons from other neuromodulatory cores such as the serotonergic and noradrenergic systems (Clarke et al., 2004; Ramos and Arnsten, 2007; Robbins and Arnsten, 2009; Puig and Gulledge, 2011; Celada et al., 2013). Therefore, the exact role of PFC DA signals during associative learning and memory awaits full elucidation.

Over the last 15 years or so, sophisticated electrophysiological techniques have been developed to allow the simultaneous recording of neural activity from multiple sites in awake behaving animals. These techniques, in combination with computational approaches, have advanced our understanding of the neural substrates of complex cognitive tasks such as learning and memory. This includes the decoding of the spiking pattern of single neurons as well as the interaction of networks of neurons reflected as neural oscillations or 'brain waves'. Here, we review our recent work in monkeys on the neural substrates of learning and memory in frontostriatal systems, and the important role of DA transmission in its modulation.

THE DOPAMINERGIC SYSTEM IN FRONTOSTRIATAL CIRCUITS

Anatomy of the dopaminergic system in prefrontal microcircuits

In primates, the PFC receives inputs from DA axons originating in the VTA and the SNc that form two bands innervating superficial (II–III) and deep (IV–V) cortical layers (Levitt et al., 1984; Goldman-Rakic et al., 1992; Williams and Goldman-Rakic, 1998). The dopaminergic innervation of the PFC is very delicate and not dense, especially when compared to the striatum or motor cortex. DA modifies PFC function via D1-like receptors (D1R and D5R subtypes) and D2-like receptors (D2R, D3R, and D4R subtypes). Both families are G-protein-coupled receptors that exert slow changes of activity in the cell and act as functional neuromodulators. D1R show low affinity for DA, whereas D2R show high affinity (Seamans and Yang, 2004). PFC neurons express the D1R and D4R DA receptor subtypes, whereas D2R, D3R, and D5R are present but to a much lesser extent, especially D3R (Lidow et al., 1991; Seamans and Yang, 2004; de Almeida et al., 2008). D1R and D4R mRNAs have a widespread distribution in several cortical layers, while D2R and D5R mRNAs are preferentially confined to layer V (de Almeida et al., 2008). All receptors have been found in pyramidal neurons and inhibitory interneurons of the PFC (Mrzljak et al., 1996; Le Moine and Gaspar, 1998; Muly et al., 1998; Bordelon-Glausier et al., 2008; De Almeida et al., 2008; Glausier et al., 2009; Santana et al., 2009; De Almeida and Mengod, 2010).

In mice, separate populations of layer V pyramidal neurons of the medial PFC with unique morphological and physiological properties preferentially express only D1R or D2R (Gee et al., 2012; Seong and Carter, 2012). Interestingly, the D2R-expressing layer V pyramidal neurons project largely to the thalamus (Gee et al., 2012), suggesting a specific contribution of PFC D2R to frontostriatal circuits. We note that the mouse medial PFC is not entirely homologous with the monkey lateral PFC, indeed some of the layer V neurons in mice appear to combine properties of layer V and layer III neurons in primate. Nevertheless, this anatomical distribution of D1R and D2R in layer V of the mouse medial PFC bears some resemblance to the direct and indirect pathways in the basal ganglia (BG), where medium spiny neurons in the striatum selectively express D1R or D2R, respectively, with unique roles in associative learning (see below; Albin et al., 1989; Alexander and Crutcher, 1990; Smith et al., 1998; Gerfen and Surmeier, 2011). However, the involvement of discrete D1R- or D2R-expressing PFC networks in learning and memory has yet to be reported.

The dopaminergic system in the BG and their involvement in associative learning

A review of associative learning would be remiss without some discussion of the role of the BG. Because there have been several excellent reviews on the BG over the last few years (e.g., Gerfen and Surmeier, 2011; Lerner and Kreitzer, 2011; Seger, 2013; Calabresi et al., 2014), we will herein only present a brief overview. The BG are an evolutionarily conserved set of subcortical nuclei, which play a well-established role in motor control. Even though they do not initiate motor movements, they exert a powerful regulation of when and what motor movements will be executed. Hence, their function has been most concisely described as action selection. The action