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Bridging the gap between striatal plasticity and learning

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The striatum, the main input nucleus of the basal ganglia, controls goal-directed behavior and procedural learning. Striatal projection neurons integrate glutamatergic inputs from cortex and thalamus together with neuromodulatory systems, and are subjected to plasticity. Striatal projection neurons exhibit bidirectional plasticity (LTP and LTD) when exposed to Hebbian paradigms. Importantly, correlative and even causal links between procedural learning and striatal plasticity have recently been shown. This short review summarizes the current view on striatal plasticity (with a focus on spike-timing-dependent plasticity), recent studies aiming at bridging *in vivo* skill acquisition and striatal plasticity, the temporal credit-assignment problem, and the gaps that remain to be filled.

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Introduction

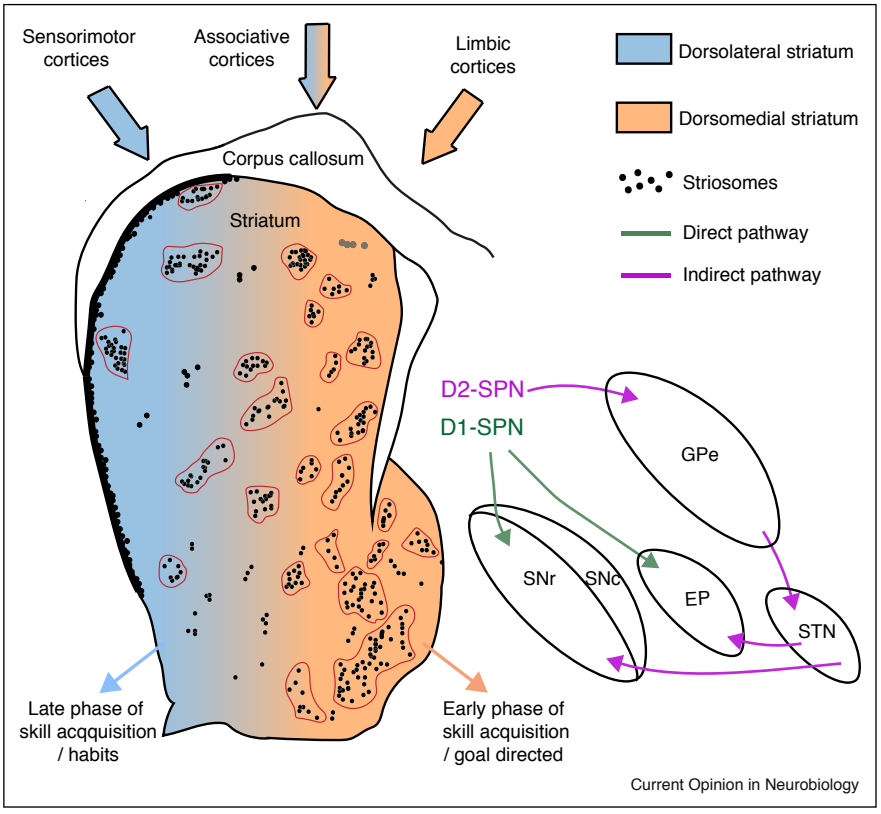
The striatum receives topographic glutamatergic afferents from all cortical areas and from some thalamic nuclei [1] (Figure 1). It is an important site for action selection and procedural memory formation [2]. Since the demonstration by Yin and coll. [3•] of striatal plasticity following acquisition of a procedural skill, several studies have extended this pioneering work by assessing striatal plasticity across various learning tasks. This review aims at giving the current view on *ex vivo* striatal plasticity in the light of recent studies evidencing correlative or causal link between *in vivo* learning and striatal plasticity, in a physiological context. Here, '*ex vivo*' refers to brain slice recordings from animals subjected to training or treatment, as opposed to studies in which brain slices are examined in naïve animals to reveal plasticity mechanisms. Striatal plasticity has been a controversial field for at least two decades because of its great variety of results (reviewed in Refs. [4–8]) and the rise of back-and-forth investigations between *in vivo* and *ex vivo* bring a unique opportunity for a better understanding of striatal plasticity, and most importantly for bridging the gap between learning and striatal plasticity.

Striatal complexity

Three main reasons account for the diversity of results concerning striatal plasticity: the induction protocols (rate-coded versus time-coded and Hebbian versus non-Hebbian), the striatal heterogeneity, and some technical issues. Some critical technical issues are the age of the animals, the slice orientation (coronal versus sagittal versus horizontal), the location of the stimulation electrode (cortex versus corpus callosum versus striatum) and the rate of the extracellular and intracellular component washout (LTP being optimally observed under sufficient rates of superfusion and high resistance whole-cell recordings). Intermingled anatomo-functional compartments and neuronal units constitute the basis of the striatal heterogeneity: dorsolateral and dorsomedial striatum (DLS and DMS), and direct and indirect trans-striatal pathways, just to cite the main ones which can be assessed during recordings (Figure 1). DMS and DLS receive inputs from associative and sensorimotor cortices and encode for goal-directed behavior and skill acquisition, respectively [3•,9]. In rodents, striatal projection neurons (SPNs) belong either to the direct (d-SPNs) or indirect (i-SPNs) trans-striatal pathways and show distinct dopaminergic receptor expression, D_1-class and D_2-class receptors, respectively [10]. Recent studies show that d-SPNs and i-SPNs are engaged in a complementary and coordinated manner for action initiation and execution [11–13]. DMS/DLS and d-SPNs/i-SPNs are distinguished in the majority of the plasticity studies. Nevertheless, the third level of striatal structuration, the striosomes (patch)/matrix compartments [14], remains to be more documented for striatal plasticity expression. Another compartment has been recently added, the annular compartments, surrounding the striosomes [15] (Figure 1). Functionally, substance P increases dopamine release within the striosomes but decreases it in the annular compartment, and leaves dopamine unmodified in the matrix [15,16] suggesting distinct neuromodulation of striatal plasticity among these compartments.

Here, instead of recapitulating the plasticity observed in brain slices with the signaling pathways at play (reviewed in Refs. [4,6–8]), we opt for another angle: we first present recent *in vivo* studies establishing correlative and causal

Figure 1



Schematic representation of the striatal heterogeneity and the anatomo-functional compartments of the dorsal striatum. Schematic representation of the direct and indirect trans-striatal pathways of the basal ganglia. Striosomes are shown with black dots distributed between the dorsolateral striatum (blue) and the dorsomedial striatum (orange). Grouped black dots represent striosomes surrounded by the annular compartment (red line, [15]), whereas isolated black dots illustrate the exo-patch [14]. Striosomal SPNs mainly project to SNc whereas SPNs from the matrix belong to the direct or indirect pathway, identified respectively by the expression of D1 and D2 receptors. The direct and indirect pathways are represented, respectively, in green and purple. GPe, external segment of the globus pallidus; EP, entopeduncular nucleus; STN: subthalamic nucleus; SNr, substantia nigra *pars reticulata*; SNc, substantia nigra *pars compacta*.

links between learning and striatal plasticity, and then from these studies we discuss the conditions of emergence of bidirectional striatal plasticity.

From learning to striatal plasticity

Striatal plasticity has been assessed during goal-directed behavior, and across the early and late phases of procedural learning. The analysis of various parameters, used as proxies for synaptic plasticity, has been achieved either *in vivo* during behavioral tasks (analysis of the firing rate and activity coherence [9,13,17,18,19••,20]; measurement of opto-induced LFP [21••]), or *ex vivo* after behavioral training (NMDAR/AMPAR ratio [3•,22•,23]; spontaneous-EPSCs: [24]; saturation/occlusion plasticity tests [25•,26]) (Figure 2). The link between the acquisition/consolidation of procedural learning and striatal plasticity was first shown by the combined analysis of *in vivo* firing rate and *ex vivo* NMDAR/AMPAR ratio from mice subjected to an accelerating rotarod [3•]. *In vivo* analysis shows that DMS, but not DLS, displays increased activity during the early phases of skill acquisition whereas the reverse picture is obtained during the consolidation phases, that is DLS displays increased firing activity while DMS is back to naïve levels. Interestingly, NMDAR/AMPAR ratio varies only in DLS for the consolidation phase [3•], pointing to the non-NMDAR nature of the corticostriatal plasticity in DMS for the early phases. *Ex vivo* saturation/occlusion experiments after extended training show LTP at i-SPNs but not at d-SPNs, suggesting that LTP is induced at d-SPNs for the consolidation phase [3•]. *Ex vivo* AMPAR/NMDAR ratio analysis revealed that during T-maze task, LTP is engaged (but not LTD) in DMS in the early phase while LTD (but not LTP) is involved in the late phase, whereas in DLS, LTD is involved only in the late phase (but LTP in DLS was not explored) [25•]. After habit learning using the lever-pressing task (corresponding to the late phase described in [3•,25•]), *ex vivo* spontaneous-EPSC are specifically decreased in DLS i-SPNs (indicative of a postsynaptic LTD) [24]. In a serial order task, learning