Can reinforcement learning provide a unifying framework for the etiology of dystonia?

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A fundamental output of reinforcement learning (RL) algorithms is a mapping from states to actions (Sutton and Barto, 1998). Actions, typically expressed through motor function in the case of human agents, become disturbed in a class of neurological conditions known as movement disorders. A growing body of research in movement disorders suggests that the clinical presentation of disturbed motor function may be secondary to a disturbed sensorimotor mapping. Because sensory input is important to determining an individual's "state" information, it seems natural to characterize sensorimotor mappings as mappings from states to actions in the RL framework. In dystonia, a poorly understood movement disorder, evidence at several levels of analysis in the nervous system suggests that the disturbed sensorimotor mapping arises from maladaptive neural plasticity. Thus, the disturbed sensorimotor mapping may be the end result of a dysfunction in the brain's implementation of RL. In this proposed line of research, we suggest that RL can provide a unifying framework for uncovering the etiology of dystonia.

Dystonia is the 3rd most common movement disorder after Parkinson's disease and essential tremor. It is expressed as involuntary muscle activity producing abnormal movements and postures. It can be focal, involving only cranial, cervical, or limb musculature, or generalized, involving most of the body. Onset varies from early childhood to late adulthood. The symptoms can be functionally disabling and result in social withdrawal. Although it is not degenerative, it is chronic with a remission rate of less than 5%. There is no cure for the disease and treatments are symptomatic and only partially effective. Over 15 genes have recently been identified that may predispose one for various forms of dystonia. However, many forms of the disease have no identifiable genetic determinant, and of those that do, the penetrance is very low. Thus, non-genetically determined factors appear to be important in the etiology of dystonia. One such factor may be a dysfunctional interaction between behavior and neural plasticity instantiating how reinforcing signals are used to learn state-to-action mappings.

The basal ganglia are classically associated with reinforcement learning (Houk et al., 1994) and have been the most dominant foci of interest in dystonia research and surgical intervention. The striatum, one of the largest of the many basal ganglia nuclei, is thought to be critical for instantiating state to action mappings. Briefly, state information from a wide array of cortical areas converge on the striatum, which in turn projects (directly or indirectly) to the internal segment of the globus pallidus, the primary output of the basal ganglia influencing action via thalamic nuclei projecting to motor cortical areas. Changes in state-to-action mappings, as in the case of sensorimotor learning, involve neural plasticity, most likely predominantly in the form of synaptic plasticity. A complex but sophisticated picture is emerging about how synaptic plasticity in the striatum is mediated by the brain's neuromodulatory neurotransmitter systems. These systems have diffuse projections to widespread areas of the brain, including particularly dense projections to the striatum. Among these neuromodulatory systems, dopamine (Schultz, 2007) is perhaps the most dominant and best understood. However, there is emerging evidence that acetylcholine also influences synaptic plasticity in the striatum, and therefore how basal ganglia subserve reinforcement learning. Importantly, there is parallel evidence of dysfunction in both of these neurotransmitter systems in dystonia.

Dopamine likely plays an important role in reinforcement through its putative role of signaling reward prediction errors (Schultz et al., 1997). In principle, the errors provide information to the striatum about the discrepancy between the predicted value of the state-to-action mapping and the actual value accrued when taking the action in that state. The resultant dopamine dynamics could then mediate synaptic plasticity in the form of long term potentiation (LTP) and long term depression (LTD) in

corticostriatal synpases (Wickens et al., 2003; Shen et al., 2008). By modifying corticostriatal synapses, the dopamine system can incrementally modify the state-to-action mapping. Unlike Parkinson's disease, there is no clear degeneration of the dopamine system in dystonia. However, there are several lines of evidence that dystonia involves some abnormalities in the dopamine system. Rare forms of dystonia can be completely resolved by brief treatment with the dopamine precursor levodopa. Curiously, levodopa can also have the opposite effect, inducing hyperkinetic motor side effects resembling dystonia after chronic use as a treatment for Parkinson's disease. Such a regimen also leads to altered synaptic plasticity in striatum (Picconi et al., 2003). The MPTP primate model of Parkinson's disease, which effectively lesions the dopamine cells in the midbrain, induces a transient period of dystonia prior to onset of full Parkinson's. Collectively the basic and clinical evidence suggests that the dopaminergic influence in the striatum is both critical for signaling reinforcement and disturbed in dystonia.

Local interneurons in the striatum that release acetylcholine onto the striatal projection cells also respond to reinforcing signals but in a fashion different from the dopamine projection to striatum. Although the dopaminergic and cholinergic activity is temporally coincident, the cholinergic interneurons appear to pause rather than increase their activity in response to reinforcement signals (Morris et al., 2004). One interpretation is that acetylcholine temporally sharpens the signal-to-noise ratio of dopamine's reinforcement signals onto the striatum. This may be particularly relevant for how reinforcing signals can sequence activity (Berns and Sejnowski, 1998), and simultaneous co-contraction of specific muscles in dystonia may reflect improperly learned sequencing. Because acetylcholine also influences plasticity in the corticostriatal synapse (Pisani et al., 2007), the two systems may not only antagonistically balance striatal projection cells' ongoing activity, but also plasticity in their afferent synapses from cortex. Cholinergic neurons in the pedunculopontine nucleus, which also project to the striatum, show signs of cellular pathology in an animal model of the DYT1 genetic form of the disease (McNaught et al., 2004). The striatal influence of dopamine and acetylcholine is modulated by estrogen, and dystonia is generally more prevalent in females than in males. Thus the combined dopaminergic and cholinergic modulation of striatal synaptic plasticity may be dysfunctional in dystonia.

Reinforcement signals mediated by these neuromodulatory inputs to striatum have meaning only in the context of the structure's inputs and outputs, encoding the corresponding state and action spaces. A variety of neurological conditions can be attributed to state-to-action mappings that are used repetitively and become habitual (Graybiel, 2008). Many forms of dystonia are attributed to repetitive overuse of particular motor repertoires in particular states. For example, task-specific dystonias such as musician's dystonia arise after extensive training involving a sophisticated but relatively small portion of the body's available motor space. The "state" is defined not only by the commensurately restricted proprioceptive inputs but also by the heightened attention afforded to the task, which is known to modulate acetylcholine (Yu and Dayan, 2005). Why do only a small minority of people that undergo similarly intense regimes of motor training develop dystonia? We propose that the development of dystonia requires an excessive exploration of the state-action space in conjunction with a disturbed reinforcement system in the basal ganglia. If so, all aspects of the RL framework, including state, action, and reinforcement signal, are necessary for understanding the etiology of dystonia.

Reinforcement learning can provide a unifying framework for integrating a diverse array of empirical evidence about the neural plasticity that underlies sensorimotor learning in the basal ganglia and how its dysfunction contributes to the etiology of dystonia. Furthermore, reinforcement learning may stimulate hypotheses for principled, improved treatment strategies that employ simultaneous, coordinated pharmacological modulation of the reinforcement signaling system and physical therapy interventions that systematically control state-action space exploration.

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