Shaping action sequences in basal ganglia circuits

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Many behaviors necessary for organism survival are learned anew and become organized as complex sequences of actions. Recent studies suggest that cortico-basal ganglia circuits are important for chunking isolated movements into precise and robust action sequences that permit the achievement of particular goals. During sequence learning many neurons in the basal ganglia develop sequence-related activity — related to the initiation, execution, and termination of sequences — suggesting that action sequences are processed as action units. Corticostriatal plasticity is critical for the crystallization of action sequences, and for the development of sequence-related neural activity. Furthermore, this sequence-related activity is differentially expressed in direct and indirect basal ganglia pathways. These findings have implications for understanding the symptoms associated with movement and psychiatric disorders.

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''Action may not always bring happiness; but there is no happiness without action.''

- Benjamin Disraeli (1804–1881)

Animals survive and reproduce by behaving, that is, by interacting with, adapting to and changing the environment around them. Many of the behaviors animals generate are innate, genetically determined, and pre-wired during development [1]. Although these behaviors may be modulated by an animal's experience or internal state, they are essentially fixed action patterns produced by either reflex-like stimulus-response circuits [2], or by central pattern generators (CPGs) — intrinsic neuronal networks capable of generating organized motor activity [3,4]. However, we and other animals have the extraordinary capacity of developing novel, sophisticated action skills to communicate with each other, seek resources and build new environments. This amazing ability raises several interesting challenges in neuroscience. One is to understand the mechanisms by which an organism can generate novel actions. Another is to understand how these new actions are organized through experience into precise sequences of movements to produce complex skills that are accurately performed. Still another challenge is to understand how the brain then executes different motor sequences and switches between them, for example, how each sequence is initiated and terminated in a given situation. Dissecting the molecular and circuit mechanisms underlying these processes will greatly advance our understanding of how neural circuits generate novel complex behavior [5], and hopefully give important insights into a wide range of neurological and psychiatric diseases [6–8].

There is increasing evidence that cortico-basal ganglia circuits, including the mesencephalic dopamine system, play a critical role in generating, shaping, and executing action sequences [9–13,14[•],15[••]]. 'Chunking' in psychology was first proposed as a phenomenon to associate a collection of elements together because of the limited 'channel capacity' in memory systems [16]. The sequential organization of behavior may result from a sensorimotor form of 'chunking', and has been proposed to include a hierarchical representation of actions [17,18]. Numerous studies in humans, non-human primates, rodents, pigeons, etc., show that something akin to 'chunking' takes place during action learning, as revealed by the systematic decrease in response times following the training of motor sequences, and by the increase in precision and accuracy [14[•],19–21,22[•]]. The basal ganglia, an ancient set of circuits streaming through a series of interconnected nuclei functionally conserved in virtually all vertebrates [5,23], has been proposed to be critically involved in 'chunking' of sequences of actions [9,13,14[•],24]. In this review, we discuss how basal ganglia circuits contribute to the shaping of action sequences, focusing heavily on recent genetic and physiological studies in mice.

Taming variability and shaping action sequences

Learning new actions often starts from trying. Selection from variability has been proposed as a general feature contributing to a wide range of biological phenomena, from evolution to gene expression, to development, and behavior and learning [25–28]. Although generation of action variability is essential for new learning, the

selection of movements and improvement of motor accuracy, speed, and efficiency as actions are repeated is critical for survival. There are plenty examples of decreased action variability during sequence learning — handwriting and computer keyboard typing are among those experienced by most in everyday life. Songbirds, like humans, crystallize their songs into a precise, stable template after learning [11,29]. This is also evident in monkeys trained to perform a visuomotor sequence task [9,24]. Furthermore, it appears that this decrease in motor variability and organization of behavior as action sequences is commonly observed during skill learning, even if there are no explicit rules dictating that behavior should be organized into sequences [14•,19]. Rather it appears that the statistics of the interaction with the environment are essential for the selection of the appropriate elements in a sequence, the order in which they should be executed, the speed, the pauses, eventual division into subsequences, etc. [28]. For example, if animals are trained in self-paced operant tasks where they obtain a sucrose reinforcer after pressing a certain number of times (e.g. eight times, with no explicit signal indicating when reward is available. And no specific need of doing theses presses in sequences or bouts) they eventually start pressing in bouts or clusters of presses of about the number of presses needed for reward delivery [14•] (Figure 1). With training animals execute the sequences better and faster by decreasing sequence duration and inter-sequence interval (ISI), while increasing within-sequence press rate, indicating that performance speed increased with training. Most importantly though, the within-animal variability (measured for example by coefficient of variation) for all the behavioral features decreases with training (Figure 1), indicating that an individual but robust structure of lever-pressing behavior emerges with training [14•]. If the training rule is different, for example with animals being reinforced for faster and faster sequences of presses the variability of the press rate decreases [15••].

What are the neural mechanism underlying the decrease in variability and increased speed during sequence learning? Again, theoretical and experimental studies have suggested that changes in basal ganglia circuits are critical for the decrease in variability and improvement in performance observed in sequence learning [9,13,14•,24,30]. Clinical observations in human patients with basal ganglia disorders, like Parkinson's and Huntington's diseases, have also revealed a critical role of basal ganglia in sequence learning [31–33].

A natural prediction from the above findings is that variability in neuronal activity activity patterns in cortico-basal ganglia circuits is critical for the generation of action diversity, and that the decrease in behavioral variability observed during sequence learning may result from a reduction in the variability of neuronal activity

patterns in these circuits. Measurements of the variation in neural activity of motor cortex and dorsal striatum ensembles throughout learning of a novel skill strongly supported these predictions [34,35]. It was found that early training there was a large variability in neuronal ensemble activity between trials in both striatum and motor cortex. This variability decreased substantially with training as the skill was consolidated [34,35] and it appears to be correlated with reduction of behavioral variability in task-related dimensions [36]. It is interesting to note that this training-related decrease in neuronal ensemble variability can occur in the absence of any detectable changes in average firing rate modulation of the same neuronal ensembles [34], suggesting that coordinated, network-wide plasticity in corticostrital circuits may have taken place. These data suggest that as skills are crystallized there is a selection of particular activity patterns in particular ensembles of cortico-basal ganglia circuits, which form circuits akin to reflexive stimulus-response type circuits, which may contribute to faster and more accurate motor performance after learning.

Sequence learning and corticostriatal plasticity

What mechanisms could mediate the selection of particular activity patterns in specific neuronal ensembles? A somewhat obvious answer would be that synaptic plasticity in cortico-basal ganglia circuits could select some subcircuits/patterns and dismiss others. There is increasing evidence of synaptic plasticity in cortico-basal ganglia circuits during skill or sequence learning [37–39,40••].

In the striatum, learning an operant task where rodents pressed a lever for intracranial self-stimulation induced long-term potentiation of glutamatergic inputs onto striatal medium spiny projection neurons, and the changes in synaptic efficacy were correlated with behavioral learning and performance [37]. It has been also been shown that skill learning on an accelerating rotarod leads to long-term potentiation of glutamatergic inputs onto striatal projection neurons [38]. Additionally, genetic deletion of NMDA receptors in dopaminergic neurons, which selectively disrupts the burst firing of dopamine neurons, resulted in impairments in action learning and formation of habit [41–43].

Is this plasticity of glutamatergic inputs onto striatal projection neurons (SPN) necessary for the reduction in behavioral variability observed during the 'chunking' of sequences? Long-term potentiation of glutamatergic inputs onto striatal projection neurons is NMDA receptor-dependent [44,45]. Selective deletion of NMDA receptors in striatal projection neurons [46] severely impairs the ability of mutant animals to consolidate precise behavioral sequences and reduce behavioral variability with training (Figure 1, comparison between mutant and littermate controls) [14•]. Importantly, the ability