NEUROSCIENCE

Brain's traffic lights

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The organization of behaviour as sequences of actions requires proper initiation and termination of each action sequence. The neural circuit that signals instructions to start and stop is now revealed.

Learning to execute a new action in a sequence — from start to finish — is essential for survival and subserves many routine behaviours and everyday activities, such as shifting the gear in a car or playing a musical instrument. Action sequences are learned, and eventually, with practice, are performed automatically, through an implicit learning process that involves changes in neuronal activity in specific brain structures. On page 457 of this issue, Jin and Costa¹ show that neurons in two brain structures — the nucleus striatum and the substantia nigra, constituting the nigrostriatal circuit — can signal the initiation and termination of self-paced action sequences, and that this 'start/stop' neuronal activity emerges as animals learn how to execute a specific action sequence.

This neuronal circuit in the basal ganglia — an interconnected set of neuronal clusters, in the subcortical region of the brain, that includes the nucleus striatum and the substantia nigra — contributes to the learning and execution of acquired behavioural sequences by interacting with the brain's cortex² (Fig. 1). In particular, the input structure of the circuit — the nucleus striatum — is essential in the control of behavioural outputs. This structure's activity is modulated by the neurotransmitter dopamine, which is released by neurons of the substantia nigra. The activity of the nucleus striatum is believed to have a crucial role in learning how to select actions that lead to reward and to avoiding punishment³. It is also thought to be involved in various forms of learning and memory, such as procedural learning, skill learning, habit learning and reward-associated learning⁴.

Jin and Costa's finding¹, that the neurons of the nucleus striatum and the substantia nigra make a circuit to signal the start/stop of action sequences, highlights the crucial role played by the basal ganglia, and in particular the striatum, in learning and 'crystallizing' newly acquired action sequences⁴. It also points to the potential part played by long-lasting changes in the activity of striatal neurons in motor learning and behavioural control.

The strength of the synaptic junctions that connect neurons can change with experience — a concept known as synaptic plasticity. Several mechanisms can lead to synaptic plasticity in the nigrostriatal circuit. The excitatory synapses connecting to a type of nucleus striatum neuron called a projecting spiny neuron exhibit the main forms of synaptic plasticity

Figure 1 | Learning the sequence of an action.

Jin and Costa¹ find that, in mice, neurons in the substantia nigra and in the nucleus striatum (constituting the nigrostriatal circuit) signal the initiation and termination of self-paced action sequences. This 'start/stop' neuronal activity emerges as animals learn how to execute a specific action sequence. In the circuit, glutamate released from cortical terminals acts together with dopamine to induce long-lasting changes in striatal neuronal activity. Alterations in the start/stop activity of this circuit may underlie neurodegenerative disorders such as Parkinson's disease.

— long-term depression (LTD) and long-term potentiation (LTP)⁵; these represent the molecular basis of learning and memory. In the nucleus striatum, LTD and LTP depend on the interaction between dopamine and another key neurotransmitter, glutamate. In particular, LTP depends on activation of both the D1 dopamine receptor and NMDA (*N*-methyl-D-aspartate)-type glutamate receptors⁵.

Jin and Costa¹ show that, in mutant mice carrying a striatal-specific deletion in the NMDA receptor, the percentage of neurons displaying start/stop activity is significantly lower than in normal animals, and that this percentage does not increase with training. Moreover, the mutant mice show little evidence of sequence learning. These observations suggest that a functional NMDA receptor in the striatum is essential for sequence learning, by affecting learning-related start/stop activity, and thus provides further evidence

that NMDA-dependent neuronal activity and plasticity may be essential for the brain to store learned behaviours. The start/stop activity that Jin and Costa observe in the nigrostriatal circuit can be compared to a traffic light, organizing actions by specifically signalling the initiation and termination of each action sequence during sequence learning (Fig. 1).

Initiation and termination of action sequences is usually impaired in human disorders involving the basal ganglia. Parkinson's disease, for example, is a typical basal-ganglion neurodegenerative disorder in which the activity of the nigrostriatal circuit is deeply compromised. In this disease, dopamine-releasing neurons of the substantia nigra degenerate; the nucleus striatum loses its connection to dopamine-releasing neurons; and motor and cognitive symptoms surface⁶. In parallel, striatal synapses can no longer undergo the main forms of synaptic plasticity⁵. Given the important role of the nigrostriatal circuit in motor learning and control, patients with Parkinson's disease often cannot learn new action sequences⁷ and show a selective difficulty in initiating and terminating motor sequences⁶. For instance, they usually have great difficulty in initiating gait, in rising from deep chairs or in rolling over in bed; but, at the same time, once they start to walk, their gait may rapidly and involuntarily quicken in the forward direction, making them fall.

For these reasons, Jin and Costa's results¹ in mice not only are an important step towards understanding striatal physiology, but also could have potentially significant implications for unravelling the mechanisms of disabling neurological diseases such as Parkinson's. Indeed, it could be that, in Parkinson's disease, functional alterations in the nigrostriatal circuit impair striatal start/stop activity during sequence learning. In turn, loss of a 'traffic light' organizing the initiation and termination of each action sequence might lead to the onset of deficits in sequence learning in patients, and to clinical symptoms mirroring the inability of the circuit to signal when each action sequence should start and stop. Further experiments in animal models, as well as clinical studies should explore this intriguing hypothetical possibility. ■

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