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The Cerebellum and Cerebello-Thalamo-Cortical Channels Contribute to New Learning and Long-Term Memory of Motor Skill

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Abstract

Why do we have a cerebellum, a little brain? Although the cerebellum contains as many neurons as there are in the cerebral cortex, we are curiously poorly informed about the finer details of its function. Recent anatomical studies have revealed cerebellar projections from the separate portions of the interpositus nuclei into the primary motor cortex (M1) and prefrontal cortex. These findings suggest that the cerebellum might not only play a role in motor control but also in cognitive domains. In particular, we discuss here that these new neural pathways provide a neural substrate for acquisition and retention of motor learning.

Lu and his research team used the retrograde transneuronal transport of rabies virus to identify neurons in the cerebellar nuclei that project via the thalamus to the cerebral cortex of macaques. In particular, projections from deep cerebellar nuclei to area 46 of the prefrontal cortex were compared with projections to the primary motor cortex (M1). They found that, after viral injections into area 46, many labeled neurons were observed in the ventral aspect of the Posterior Interpositus Nucleus (PIN), whereas no neuron labeling was found in the Anterior Interpositus Nucleus (AIN). In contrast, a number of labeled neurons were found in the dorsal portion of the PIN after viral injections into the M1. Additionally, neurons labeled from the M1 injections were also observed in the AIN [1-3]. These findings demonstrate that the cerebellar interpositus nuclei possess distinct outputs to the prefrontal cortex versus the M1, which potentially contribute to different aspects of behavioral functions such as different stages of the motor learning.

Medial cerebellar outputs from the interpositus nuclei have been thought to be crucial for the associative motor learning. McCormick and Thompson have reported that lesions of the interpositus nuclei abolished the memorized eyeblink response; recordings from these nuclei have revealed neuronal activity to response learning [4]. Yet, clinical studies have reported that initial stage of trace eyeblink conditioning learning was impaired in patients with lesions in the PIN [5]. Imaging studies have also shown that the cerebellum play a key role in eyeblink conditioning [6-8]. Moreover, significant changes of positron emission tomography and regional cerebral blood flow in several areas, including the cerebellum and the prefrontal cortex, were observed during performance of associative motor learning task [9]. The above, taken together with the new medial cerebellar channels from the posterior interpositus nucleus to area 46 of the prefrontal cortex, it is reasonable to hypothesize that the cerebellum and cerebello-thalamo-cortical channels contribute to motor learning.

The medial cerebellar output from the ventral PIN and the dorsal PIN/AIN play differential roles in various steps of the motor learning [5,10,11]. The dorsal aspect of the PIN has been thought to contribute to performance of memorized motor responses such as eyeblink and saccadic eye movements rather than to their initial learning [10, 11]. If this is the case, then impairment in the acquisition of the new learning by lesions of the PIN could be due to functional blockade of the ventral rather than dorsal portion of the PIN [5].

Furthermore, previous studies have shown evidence that the expression of representative motor memory formation genes was increased selectively in the AIN, but not in the PIN [12]. This finding strongly suggests that the AIN is involved in the storage and/or retrieval of long-term memory of motor learning. Moreover, many studies have indicated that the AIN is the site for long-term memory rather than new learning during practice of the eyeblink conditioning response. Examples include lesion [13-17]; inactivation [18,19]; electron microscopy [20]; functional magnetic resonance imaging [21]. Given the above, it is natural to raise a theory that the medial cerebellar output from the ventral PIN and the dorsal PIN/AIN plays a critical role in the new learning and long-term memory, respectively, during the motor learning processing.

Interestingly, different cortical areas have been thought to be involved in these various steps of motor learning. A considerable theory for motor learning indicates that new learning is an explicit process originating in the prefrontal cortex, and that the long term memory for the learned motor skill becomes automatic and an implicit process formed in the motor cortex [22-24]. Thus, the disynaptic pathway from the ventral aspect of the PIN to area 46 may be involved in the initiation of the association of motor learning. After repeated practice, cerebellar channels to the M1 originating from the dorsal PIN/AIN turn to play a key role in the storage and/or retrieval of long-term memory, which makes the association automatic.

Last, neuropsychological testing of patients with cerebellar lesions has revealed specific deficits in different faculties, including visual perception [25-31], short-term memory [32,33], or verbal fluency [34]. Moreover, clinical studies have shown that, in the brains of subjects with autism, the most consistent abnormalities are found in cerebellar Purkinje cells [35]. Accordingly, the questions of whether and how these cerebello-thalamo-cortical channels and their involvements in

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different stages of learning relate to those cerebellar deficits remain to be answered.

Conclusion

In conclusion, this review discusses fundamental neural mechanisms for the involvement of medial cerebellar output from the interpositus nuclei in cognitive functions such as acquisition and retention during motor learning. This provides useful information for understanding the processing of cerebellar outputs to cognitive function.

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