

## Organization of Cerebellar Outputs to Primary Motor Cortex and Prefrontal Cortex

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### Abstract

Most theories of cerebello-cortical pathway have assumed that the prefrontal cortex receives input from cerebellar Purkinje cells of crus II while the motor cortex receives cerebellar input from those of crus I. Here we discuss that, in this neural connection, cerebellar outputs to cerebral cortex are complex, and there is marked disagreement regarding the possibility that these projections might overlap within cerebellar Purkinje cells.

The cerebellum receives massive inputs from widespread areas of the cerebral cortex through cortico-pontine-cerebellar projections [1-4]. The major output from the cerebellum is directed toward the frontal lobe through cerebello-thalamo-cortical pathways. In this review, my discussion targets on cerebellar output to the primary motor cortex and prefrontal cortex. It has been known that the motor cortex and prefrontal cortex receive cerebellar inputs that originate from the neurons located in the dorsal and ventral portions of cerebellar Dentate Nucleus (DN) respectively [5-7]. This has been confirmed by using of retrograde transneuronal transport of rabies virus to identify multisynaptic neurons in the motor cortex and prefrontal cortex [8-11].

Using the same technique, prefrontal areas were demonstrated to be the main targets of crus II of the cerebellar cortex while the motor cortex receives cerebellar projections from the lobules and crus I [12]. Since these involve diverse capabilities, in particular, higher cognitive functions in the prefrontal cortex, it has been thought that the cerebello-prefrontal projections mediated by the ventral portion of the DN (VDN) of the cerebellar nucleus and crus II of the cerebellar cortex contribute to higher cognitive functions, often called the "nonmotor channel" [11, 12]; whereas the projections from the cerebellar cortex to motor cortex are mediated by the dorsal portion of the DN (DDN) and lobule III-crus I are involved in motor control, often called the "motor channel". However, there are marked disagreements regarding this theory of crus I being specific for motor cortex and crus II being specific for the prefrontal cortex for several reasons.

First, it has been reported that there is no projection relationship like Purkinje cells of crus I to the DDN or those of crus II to the VDN in the cerebellum. In fact, at the dorso-ventral level of the DN, the middle aspect of the DN, including both dorsal and ventral parts, receives inputs from Purkinje cells located in crus I and throughout crus II. At the rostrocaudal level, the aspect of DN that receives inputs from crus I was anterior to that of crus II [13-16].

Second, we have recently performed two experiments to identify neurons in the cerebellar cortex that project via the thalamus to area 46 of the prefrontal cortex and the motor cortex of macaques using retrograde transneuronal transport of rabies virus [10,17,18]. As results of experiment 1, Purkinje cells labeled from area 46 were equally observed in crus I and crus II [Lu et al. unpublished observations]. Moreover, in experiment 2, after viral injections into the motor cortex, although Purkinje cells labeled from the forelimb representation, including the proximal and distal regions, were observed in lobules IV-VI and crus I but not in crus II, Purkinje cells labeled from the orofacial representation were observed in lobule VI, crus I, and crus II [Lu et al. unpublished observations]. These data suggest that these cerebello-cortical pathways originating from the Purkinje cells to prefrontal

cortex (nonmotor channel) and the motor cortex (motor channel) are overlapped in crus I and/or crus II of the cerebellar cortex, rather than completely separated.

The reason to focus on the issue of cerebellar outputs to area 46 of the prefrontal cortex is that area 46 is characterized by cognitive functions, such as reward [19], spatial working memory [20], temporal processing [21, 22], evaluation of self-generated decision-making [23], categorization [24], and motor learning of classical conditioned action [25]. However, the possibility that neurons in the cerebellum are involved in cognitive functions has been a controversial subject. Thus, our recent studies provide new anatomical evidence for the involvement of cerebellar output in cognitive functions.

Third, physiological and clinical studies have reported that both crus I and crus II are involved in cognitive functions. For example, crus I has been thought to be involved in judgment of spatial orientation [26], language perception [27], complex visual functions like encoding parameters of target motion [28], pain-related processes like grimacing, fear, and startle reactions [29], pleasant feelings [30], emotional processes like evaluating facial expression and empathizing [31]. Furthermore, crus I and crus II have been known to be crucial to verbal working memory [32, 33], episodic memory/self-reflection and salience detection [34], eyeblink conditioning [35, 36]. Given such diverse capabilities of crus I and crus II, it may not be surprising that cerebellar outputs to prefrontal cortex actually originates from cerebellar Purkinje cells located in crus I and throughout crus II.

In summary, this review discusses that the so called motor and cognitive channels from Purkinje cells to prefrontal cortex and motor cortex overlap in crus I and crus II of the cerebellar cortex. This challenges the theory that crus I outputs to the motor cortex, and crus II to the prefrontal cortex independently. Last, the questions of how this special overlapping structure of cerebellar Purkinje cells relates to behavioral function, and why crus I and crus II project to orofacial

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representation rather than limbic representation of the motor cortex, remain to be answered.

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