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Review article

The cerebro-cerebellum: Could it be loci of forward models?

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ABSTRACT

It is widely accepted that the cerebellum acquires and maintain internal models for motor control. An internal model simulates mapping between a set of causes and effects. There are two candidates of cerebellar internal models, forward models and inverse models. A forward model transforms a motor command into a prediction of the sensory consequences of a movement. In contrast, an inverse model inverts the information flow of the forward model. Despite the clearly different formulations of the two internal models, it is still controversial whether the cerebro-cerebellum, the phylogenetically newer part of the cerebellum, provides inverse models or forward models for voluntary limb movements or other higher brain functions. In this article, we review physiological and morphological evidence that suggests the existence in the cerebro-cerebellum of a forward model for limb movement. We will also discuss how the characteristic input-output organization of the cerebro-cerebellum may contribute to forward models for non-motor higher brain functions.

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1. Introduction

It is widely accepted that the cerebellum acquires and maintain internal models for motor control (Ito, 1970; Wolpert and Miall, 1996; Wolpert et al., 1998). An internal model simulates mapping between a set of causes and effects. There are two candidates of cerebellar internal models, forward models and inverse models.

A forward model transforms a motor command into a prediction of its outcome in terms of the sensory reafference the movement will generate, i.e., the sensory consequences of the movement. In contrast, an inverse model computes the motor command that is required to achieve the desired state change of the body. Thus, in terms of information flow, the inverse model is the inversion of the forward model. For eye movements, such as the vestibulo-ocular reflex, optokinetic response or ocular following response, there is physiological evidence showing that parts of the cerebellum represent inverse models (reviewed in Wolpert et al., 1998; Kawato, 1999; Ito, 2013) and output directly to the controller. In contrast, it is still controversial whether the cerebro-cerebellum, the phylogenetically newer part of the cerebellum, provides inverse models

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or forward models for voluntary limb movements or other higher brain functions.

A number of cortical areas, most notably the primary motor cortex (M1), premotor cortex (PM), parietal cortex (PAC) and prefrontal cortex (PFC), contribute to the voluntary control of arm movement, and these cortical areas form parallel loops between individual regions of the cerebro-cerebellum (Kelly and Strick, 2003; Lu et al., 2007; Hashimoto et al., 2010; Prevosto et al., 2010). Given the functional specialization of these cortical areas, it is most likely that each region of the cerebro-cerebellum plays a unique functional role by means of a common computational operation performed on an almost uniform neuron circuitry. Among others, the communication loop between the M1 and the corresponding region of the cerebro-cerebellum (i.e., lateral part of lobules IV–VI in monkeys, Kelly and Strick, 2003; Lu et al., 2007) has been studied most intensively for decades since the pioneering work by Allen and Tsukahara (1974). It is generally assumed that this M1 loop plays an essential role in voluntary limb movements. On the other hand, the other loops, i.e., PM, PAC, and PFC loops, are most likely to contribute to higher brain functions (reviewed in Ramnani, 2006; Ito, 2008) and motor control; however, little physiological data are available to explain the nature of their inputs and outputs, and the transformation between them in the cerebellum. Recently, a number of studies in human (Miall et al., 2007; Nowak et al., 2007; Izawa et al., 2012) and primates (Popa et al., 2013) suggested that the cerebellum is a locus of the forward model, although these studies do not necessarily exclude the possibility of the cerebellum working as an inverse model. The aim of this paper was to review physiological and morphological evidences that suggest the existence in the cerebro-cerebellum of a forward model for limb movement. To serve as a forward model, a neural substrate must satisfy at least the following two conditions: (1) receiving an efference copy as well as direct somatosensory afferent input, and (2) becoming active later than the controller but earlier than the movement itself and an accompanying sensory feedback. We will also discuss how the cerebro-cerebellum may contribute to non-motor higher brain functions with the common neuron circuitry of the cerebellum.

2. Input signals

2.1. Efference copy

The basic idea of a forward model in motor control is that the model predicts the behavior of the motor apparatus for a motor command. Therefore, a forward model requires the following two inputs: (1) an efference copy (copy of a motor command) from the controller and (2) an afferent sensory signal that describes current state of the motor apparatus (Shadmehr and Krakauer, 2008). Given that the motor command is generated in M1, a highly plausible scenario may be that a region of the cerebro-cerebellum that is connected with M1 serves as a forward model. In general, the cerebro-cerebellum receives its primary input through the cortico-ponto-cerebellar pathway. Layer V corticofugal neurons in M1 send collateral projections to the pontine nuclei (Ugolini and Kuypers, 1986). Therefore, the region of the cerebro-cerebellum connected with M1 is presumed to receive an efference copy of the motor command through the pathway, and monitors the recently issued motor command with minimum delay (probably less than 10 ms). However, only a few studies have investigated the activities of the ponto-cerebellar projection, i.e., mossy fibers (MFs), in the cerebellar cortex during voluntary limb movements. By definition, the efference copy inputs are assumed to show movement-related activities that lag slightly behind those of M1 neurons. van Kan et al. (1993) demonstrated that MFs in the intermediate part of the cerebellum in monkeys were highly active during a limb movement, and

the modulation onset of the activity preceded the movement onset in many MFs (the mean lead time was about 80 ms). Recently, we reported similar movement-related MF activities for wrist movements in the cerebro-cerebellum (Ishikawa et al., 2014a). In our experiment, monkeys were trained to perform a step-tracking wrist movement for eight directions, and we recorded the task-related activities of MFs in the hemispheric parts of lobules V and VI, which are most strongly connected with M1 (Kelly and Strick, 2003; Lu et al., 2007). We found that most of MFs showed modulation onset before movement onset, and the modulation onsets lagged slightly behind those of M1 neurons recorded in the same experimental setup (Takei et al., 1999). In addition, we also found that directional tuning of those MFs demonstrated a significant shift in the preferred direction (PD) for different forearm postures (Tomatsu et al., 2015) just as *muscle-like* neurons in M1 (Takei et al., 1999). Thus, the activities of these MFs seemed to represent intrinsic information rather than extrinsic information. Overall, it is more likely that the MF inputs to this region of the cerebellum convey an efference copy of motor commands. The later onset of the MF activities than that of M1 neurons almost exclude the possibility that this region of the cerebro-cerebellum serves as an inverse model (or a part of an inverse model) for M1. On the other hand, MF inputs that encode extrinsic information may be represented heavily in a region of the cerebro-cerebellum that is more lateral to the M1 region, where PM that represents spatial or visual information of movement (Takei et al., 2001) projects (Hashimoto et al., 2010). However, this region is not likely to comprise a part of the inverse model that serve for M1, because its output does not return to M1, but to PM (Kelly and Strick, 2003; Lu et al., 2007; Hashimoto et al., 2010).

2.2. Afferent sensory signals

As mentioned above, forward models also require sensory feedback signals from the periphery that provide the current state of the body. Indeed, the cerebellum receives strong muscle (proprioceptive) and cutaneous (exteroceptive) afferents directly through the cuneocerebellar and rostral spinocerebellar tracts from the arm and through the dorsal and ventral spinocerebellar tracts from the leg (Oscarsson, 1965; Cooke et al., 1971; Ekerot and Larson, 1972). These afferents terminate as MFs in lobules IV and V mainly in the intermediate part of the cerebellum (summarized in Ito, 1984). Although detailed experiments on these pathways have not been conducted in primates, it is plausible to presume that primates also have the same sensory pathway to the cerebellum. The somatosensory inputs should enable the cerebellum to monitor the current state of the body with minimal delay. In fact, according to Jörntell and Ekerot (2006), electrical skin stimulation evokes excitation of granule cells (GCs) in no more than 6–8 ms in decerebrated cats. In conscious monkeys, we confirmed that most MFs in the hemispheric part of lobules V and VI responded vigorously to manual somatosensory stimuli such as gentle palpation of muscles, extension/flexion of joints or light touch to the skin (Ishikawa et al., 2014b). In addition, the cerebro-ponto-cerebellar input from the primary somatosensory cortex (S1), which was demonstrated in cats (Tolbert, 1989), may provide another path for the somatosensory input to the M1 region of the cerebro-cerebellum in monkeys. Alternatively, MFs derived from M1 may be activated by somatosensory stimuli, because almost all M1 neurons are strongly responsive to somatosensory stimuli (Takei et al., 1999). In either case, the part of the cerebro-cerebellum that forms a loop connection between M1 appeared to receive both the efference copy and somatosensory inputs required for a neuronal substrate to serve as a forward model.

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