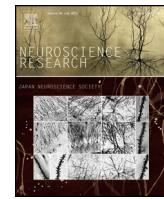




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Review article

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

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ABSTRACT

It is widely accepted that the cerebellum acquires and maintains 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 maintains 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 pre-frontal 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; Prevost 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 corticoponto-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 (Kakei 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 (Kakei 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 (Kakei 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 cerebroponto-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 (Kakei 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.

2.3. Integration of efferent and afferent signals

In a forward model, motor and sensory inputs need to be integrated to make an output based on combinations of those inputs. There are some morphological substrates for this integration. Branching patterns of individual MFs are intensively divergent especially along the medio-lateral axis (Shinoda et al., 1992; Wu et al., 1999; Jörntell and Ekerot, 2002; Voogd, 2014), despite the largely topographic projection of the MF inputs to the cerebellar cortex (Kelly and Strick, 2003; Lu et al., 2007; Hashimoto et al., 2010; Prevosto et al., 2010; Lu et al., 2012). In other words, MF inputs are highly convergent to each region of the cerebellar cortex (see also Jörntell and Ekerot, 2002). Indeed, Huang et al. (2013) recently demonstrated the convergence of inputs from the external cuneate nucleus and the basilar pontine nucleus (BPN) onto individual GCs in the paramedian lobule in mice. They also demonstrated that BPN neurons projecting to the paramedian lobule receive putative motor inputs from M1. These results indicate that efference copies and somatosensory afferent inputs are indeed integrated into single GCs in this region of the cerebellum. Large numbers of GCs allow huge number of combinations of efferent and afferent inputs. This morphological organization seems suitable for integrating the inputs from M1 and somatosensory feedback signals on individual GCs. Integration of the efferent and afferent inputs proceed even further on Purkinje cells (PCs), because (1) axons of GCs (i.e., parallel fibers [PFs]) runs more than several millimeters mediolaterally along the folium, and (2) each PC receives inputs from numerous ($\sim 10^4$) PFs in primates (summarized in Ito, 1984). Indeed, we found that almost all PCs showing pre-movement modulation, which presumably originated from M1, were also highly responsive to somatosensory stimuli (Ishikawa et al., 2014b; Tomatsu et al., 2015). That is, these PCs were *multimodal* in the sense that they are responsive to both motor and sensory inputs.

It should be noted that receptive fields (RFs) of the wrist-movement-related MFs and PCs were confined to a small part of the forearm (Ishikawa et al., 2014b), and they were not responsive to stimuli in other body parts. In contrast, non-task-related neurons that were active for movements of other body parts such as the leg or trunk had RFs in the corresponding parts of the body. Those cells are topographically organized, and therefore, there is a somatotopical map in the cerebellar cortex. The somatotopical organization was confirmed by morphological (Lu et al., 2007) and physiological (Sasaki et al., 1977; Shambes et al., 1978) studies. These observations suggest that the cerebellar neural circuit is organized into a number of modules and each module is in charge of a relatively small part of the body. This organization of the cerebro-cerebellum may make the cerebellum suitable for fine-tuning of limb movements.

3. Output signals

Thus far, the M1 region of the cerebro-cerebellum seems to satisfy the requirements for a forward model in terms of its inputs organization. However, to identify the function of the M1 region of the cerebro-cerebellum as a forward model, its output also needs to be identified. A forward model is presumed to output an estimate of the sensory consequence of the ongoing motor command. Therefore, as long as the forward model functions properly, its output is expected to resemble sensory feedback signals induced in the motor apparatus during the execution of the motor command. It is highly likely that the difference between the temporal patterns of output of a forward model and sensory feedback signals is minor in overtrained animals whose performance is stable. As Wolpert and Miall (1996) have already discussed, it is generally difficult to distinguish the efference copy, the predictive output from

the forward model and the external sensory feedback because of a causality between them. A possible way to identify the output from the cerebro-cerebellum may be by examining the timing of neuronal activity in relation to movement kinematics.

Fig. 1 depicts a comparison between the speed profile and the population activity of PCs recorded in the cerebro-cerebellum of three monkeys during a rapid wrist movement in our recent study (Ishikawa et al., 2014b). In this analysis, the increase and decrease of simple spike (SS) activity of all movement-related PCs were summed separately. As shown in Fig. 1, the sum of the decrease in SS activity demonstrated the highest correlation with the speed profile of the movement, when the speed profile was shifted by -60 ms. Namely, the population activity of PCs precedes the actual movement by about 60 ms. The lead times of SS activities were comparable to the average onset of movement-related muscle activities in the same animals (Tomatsu et al., 2015). On the other hand, the onset latencies of individual PCs lagged behind those of neurons in M1 and PMv reported in our previous studies (-97.0 ± 15.3 ms for 44 extrinsic-like M1 neurons, -93.6 ± 20.8 ms for 28 muscle-like M1 neurons, and -124.3 ± 30.6 ms for 55 extrinsic-like PMv neurons, Kakei et al., 1999, 2001). In other words, the SS activity of a population of PCs follows the motor command ($p < 0.001$, Mann-Whitney *U*-test). Therefore, the output of the cerebro-cerebellum is most likely to represent an estimate of the coming state of the motor apparatus rather than a motor command or external sensory feedback.

Nevertheless, our results do not necessarily mean that the temporal patterns of SS activities of individual PCs precisely reproduce movement kinematics. Rather, the correlation between SS modulation and movement kinematics at the single-neuron level is moderate or even lower for most PCs (see Fig. 4 in Ishikawa et al., 2014b). It should also be emphasized that most movement-related PCs demonstrated directionally tuned activities around movement onset, and the PDs as well as gains of their activities were significantly altered for a change in forearm postures (Tomatsu et al., 2015). These strong posture-dependent changes of PC activities indicate that the activities of those PCs encode intrinsic parameters and provide another support that this region of the cerebro-cerebellum works as a forward model to predict the state of the motor apparatus (Tomatsu et al., 2015).

It should be noted that both the PCs and deep cerebellar nuclear (DCN) cells activated before movement onset in our experiment were remarkably responsive to passive movement and/or somatosensory stimuli to a specific body part (Ishikawa et al., 2014b). Therefore, it is assumed that there are a number of forward models corresponding to each body part in the cerebro-cerebellum. However, as mentioned in Section 2, the morphological organization of the cerebellar cortex indicates that individual neurons receive diverse motor and sensory inputs, thereby enabling the generation of a variety of outputs for each specific combination of inputs. Then what is the basis for the functional specialization of each region of the cerebro-cerebellum? It is most likely that the longitudinal narrow band structure of single climbing fibers (CFs) (Sugihara et al., 2001) provides fine-tuning to select specific combinations of inputs. Therefore, we will review the character of CF inputs in the next section.

4. Evaluation signal

In order to maintain an internal model of a motor apparatus to make a suitable prediction, a forward model needs to be updated. In other words, a forward model requires a signal that informs the evaluation (i.e., goodness) of the prediction. In the cerebellum, an olivo-cerebellar projection, i.e., a CF input that originates from the inferior olive (IO), has long been established to provide an error

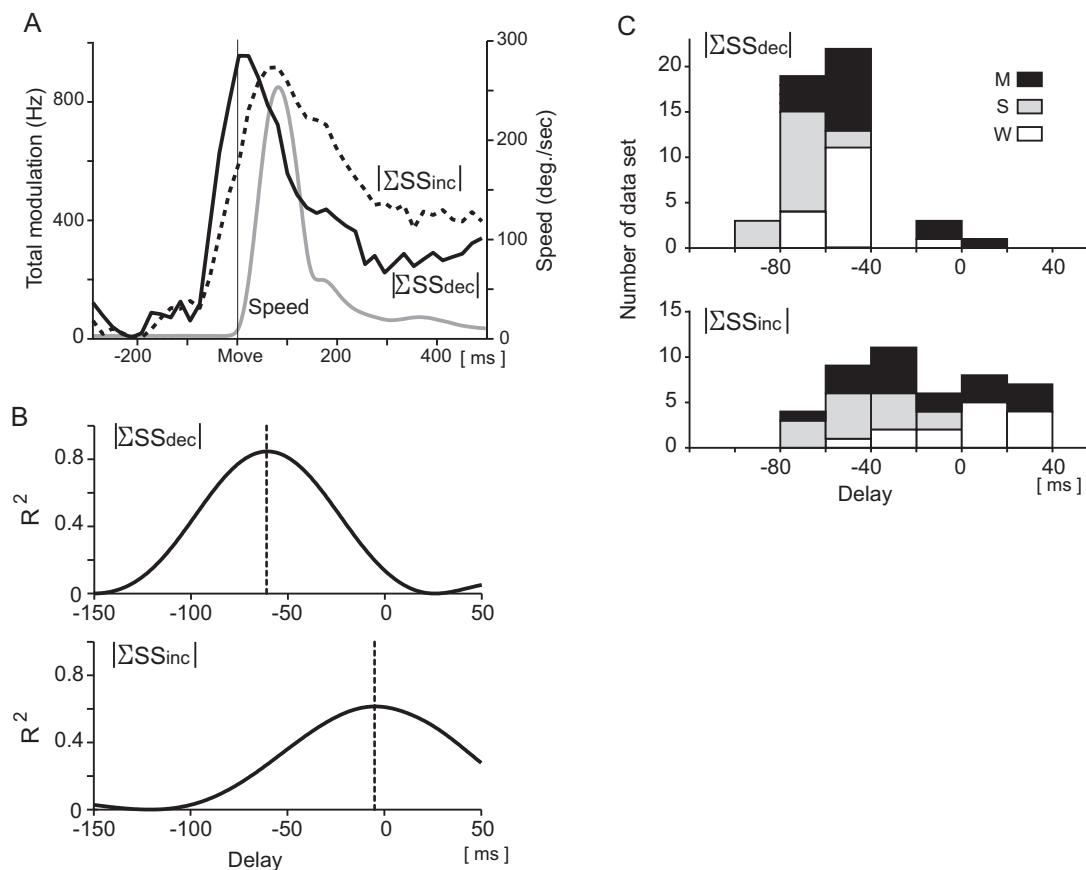


Fig. 1. Correlation between the population modulation of Purkinje cells (PCs) and movement kinematics. (A) Temporal patterns of the sum of the decrease ($|\Sigma SS_{dec}|$, solid line) and increase ($|\Sigma SS_{inc}|$, dashed line) of the simple spike (SS) activity of all movement-related PCs and the averaged speed of the wrist movement (gray line) in a monkey. To obtain $|\Sigma SS_{dec}|$ and $|\Sigma SS_{inc}|$, we summed all decreases and increases of SS activity relative to a reference period (260–200 ms before movement onset) separately in each 20 ms bin. The speed profile was calculated from a displacement range per 1 ms of the cursor on the monitor controlled by wrist joint movement. See Ishikawa et al. (2014b) for the details of the experimental procedures. (B) Optimal delay between the movement speed and $|\Sigma SS_{dec}|$ and $|\Sigma SS_{inc}|$ for the data shown in (A). We calculated the R^2 value for the correlation between them for each 1 ms shift of movement speed from -150 to 50 ms relative to movement onset. Upper panel: R^2 values between the movement speed and $|\Sigma SS_{dec}|$ for each delay. The value was the highest (=0.847) when the movement speed profile was shifted by -61 ms (i.e., optimal delay). Lower panel: R^2 values between the movement speed and $|\Sigma SS_{inc}|$ for each delay. The value was the highest (=0.732) when the movement speed profile was shifted by -7 ms. (C) Distribution of the optimal delays of $|\Sigma SS_{dec}|$ and $|\Sigma SS_{inc}|$ for 48 data sets (eight movement directions for two forearm postures in three monkeys). Data from each monkey are distinguished by black, gray and white blocks, respectively. Data with a low R^2 value (<0.1 , $n=5$) were excluded. The optimal delay did not differ significantly for the two postures for any animal.

or teaching signal to facilitate motor learning (Gilbert and Thach, 1977; Raymond et al., 1996; Kitazawa et al., 1998; Raymond and Lisberger, 1998; Ito, 2006; Medina and Lisberger, 2008; Rasmussen et al., 2008; Soetedjo et al., 2008). Therefore, the nature of the CF input is crucially important in identifying the internal models in the cerebro-cerebellum.

Each PC is innervated by a single CF (Eccles et al., 1966; Schmolesky et al., 2002; Ohtsuki et al., 2009). Although each CF shows an exceptionally low firing rate (1–2 Hz) (Thach, 1970), its synaptic efficacy is exceptionally strong. In consequence, each spike of CF generates one complex spike (CS) in their target PCs. Each CF has a small RF in the periphery, and is suitable to provide a signal confined to the RF. Therefore, it is likely that the cerebellar forward model is composed of a number of modules each of which is in charge of a relatively small body part.

The CS triggers relevant synaptic plasticity not only in PCs but also in molecular layer interneurons (INs) (Jörntell and Ekerot, 2002). It should be noted that earlier investigations demonstrated that PCs and INs show opposite polarities of CF-input-induced plastic changes (Jörntell and Ekerot, 2002, 2003; Rancillac and Crepel, 2004; Smith and Otis, 2005; Szapiro and Barbour, 2007). Namely, PF inputs paired with CF inputs (i.e., concurrent increase in CS activity) induces long-term depression (LTD) of PF-PC synapses and

long-term potentiation (LTP) of PF-IN synapses. Considering the strong inhibitory effects of INs on PCs, the combined synaptic modulations produce strong suppression of SS activities for the same PF input. On the contrary, PF inputs unpaired with CF inputs (i.e., concurrent decrease in CS activity) induce LTP of PF-PC synapses and LTD of PF-IN synapses, producing marked increases of SS activities for the same PF input (see Fig. 13 in Ishikawa et al., 2014b). In fact, PCs and nearby INs in the uvula-nodulus demonstrated anti-correlated responses for natural rotatory stimulation in mice (Barmack and Yakhnitsa, 2008). Overall, CF inputs (i.e., CS) are negatively correlated with the SS activity of PCs (Barmack and Yakhnitsa, 2008; Catz et al., 2008; Ishikawa et al., 2014b). Because suppression of PC activity generates facilitation of target DCNs by disinhibition (Ishikawa et al., 2014b; Lee et al., 2015), facilitation of CF inputs increases the cerebellar output (i.e., increase in DCN activity), while suppression of CF inputs decreases the cerebellar output.

These observations question the conventional view of the CF input as an error signal. This view originates from an observation that the CS-induced LTD of the PF-PC synapse is reminiscent of a punishment for an incorrect PC response (Albus, 1971). However, this interpretation does not hold at the level of the cerebellar output, because the sign of the plasticity reverses from depression to potentiation at DCN cells because of disinhibition (Ishikawa et al.,

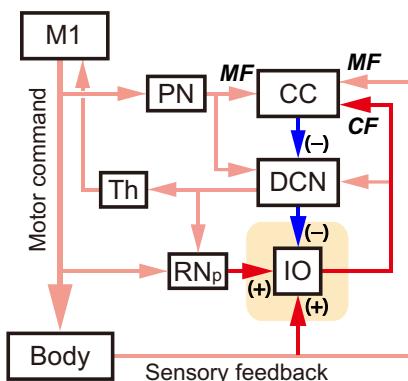


Fig. 2. Input–output organization of a region of the inferior olive (IO) that serves for the cerebro-cerebellar communication loop with M1. Red and blue arrows indicate excitatory and inhibitory inputs, respectively. The IO serves as a comparator, generating its climbing fiber (CF) output by subtracting an inhibitory input from the deep cerebellar nuclei (DCN; dark blue) from the sum of two excitatory inputs from the parvocellular red nucleus (RNp) and periphery (dark red). Then, the output from IO (CF) induces plastic changes in the cerebellar cortex (CC) and suppresses the output from PCs, resulting in the facilitation of the DCN output by *disinhibition* (Ishikawa et al., 2014b). M1, primary motor cortex; PN, pontine nuclei; Th, thalamus; MF, mossy fiber. This figure was modified from Fig. 1 in De Zeeuw et al. (1998).

2014b). In addition, the error hypothesis is not capable of explaining the spontaneous CF activity, simply because *spontaneous error* does not make sense. Overall, the interpretation of the CF input as an error signal appears to have some defects and needs reconsideration in the cerebellar physiology with a larger scope.

Owing to the critical role of the CF input in the modulation of the cerebellar output, it is important to understand how activities of IO cells are generated. Oscarsson (1980) proposed the comparator hypothesis to explain the generation of output from the IO. His original idea was later modified by De Zeeuw et al. (1998) as follows (see Fig. 2). The modified comparator hypothesis assumes that IO cells receive excitatory and inhibitory inputs. The excitatory input comes from the midbrain (most notably from the parvocellular red nucleus, RNp) and the periphery (reviewed in Armstrong, 1974; Brodal and Kawamura, 1980). The other inhibitory (GABAergic) input comes from the DCN (Andersson et al., 1988; De Zeeuw et al., 1989). This hypothesis explains both the facilitation and suppression of IO neurons (i.e., CF activity) by assuming the IO as a comparator between the cortical input (via RNp, see Fig. 2) or afferent inputs, and the cerebellar output (i.e., output of the forward model) (Fig. 2). There are some experimental data to support this view. For instance, Gellman et al. (1985) demonstrated that IO cells were highly responsive to *passive* stimuli on their cutaneous RFs in the paw of cats. Nevertheless, these IO cells were inactive when the cats *actively* placed their paw on the floor. It is also well established that IO cells that project to the C3 zone are highly responsive to *passive* cutaneous stimuli (Ekerot et al., 1991a,b; reviewed by Jorntell and Bengtsson, 2015). Likewise, transdermal electrical stimulation to the radial nerve in the ipsilateral forearm reliably evoked CS in PCs during the resting state of conscious monkeys (Ishikawa et al., unpublished observation). The marked facilitation in activity of the IO neurons in these *passive* conditions may be explained as follows. For natural voluntary movements, excitatory sensory inputs to IO are accompanied by inhibitory inputs from the DCN as a prediction of the sensory consequence of movements, and the two lines of inputs cancel each other, resulting in no marked facilitation or suppression of IO activity. In contrast, for artificial sensory stimuli provided as an air puff or electrical stimulation without prior notice, the strong transient excitatory sensory input to the IO is not accompanied by a concurrent inhibitory input from the DCN owing to the lack of the cortical input to the cerebellum. The excess excitation facilitates the IO activity to inform the internal model

(more specifically, PCs) of the mismatch between the prediction and the current sensory input. Similarly, a transient increase in CF activity at onset of *rapid* limb movement in monkeys (Thach, 1970; Mano et al., 1986; Kitazawa et al., 1998; Ishikawa et al., 2014b) may also be explained with the modified comparator hypothesis. Several studies indicate that cortical inputs activate IO cells and generate CS in PCs (Provini et al., 1968; Miller et al., 1969; Allen et al., 1974; Sasaki et al., 1977). Therefore, at the movement onset, the descending motor command inputs to IO cells could inform a rapid movement, whereas the increase in cerebellar output lags behind for a short period because of the processing delay in the cerebellar neuronal circuitry. The transient mismatch might activate IO cells at the movement onset, thereby increasing CF activity at the timing.

Moreover, the comparator hypothesis may explain why IO activity shows *bidirectional* modulation of IO activity (Catz et al., 2008) as the *balance* between the *excitatory* input and the *inhibitory* input. It should be noted that an increase or decrease of IO activity would eventually result in an increase or decrease, respectively, of inhibition from DCN cells, owing to the plasticity in the cerebellar cortex (Fig. 2) (see Fig. 13 in Ishikawa et al., 2014b). In other words, the plasticity in the cerebellar cortex is organized to minimize the difference between the cortical and/or peripheral inputs and the output from the cerebellum with a negative-feedback mechanism. It may also explain why IO neurons show *spontaneous* activity (Thach, 1968; Gilbert and Thach, 1977; Raymond et al., 1996; Kitazawa et al., 1998; Raymond and Lisberger, 1998; Ito, 2006; Yamamoto et al., 2007; Medina and Lisberger, 2008; Rasmussen et al., 2008; Soetedjo et al., 2008; Ishikawa et al., 2014b). It might be necessary to maintain spontaneous activity of DCN cells by preventing PC inhibition from becoming too strong. Without the spontaneous CF input from the IO, the output from the DCN could fade away (Billard and Batini, 1991) and result in severe ataxia, as is observed following the degeneration (Koeppen et al., 1999) or lesion of the IO (Horn et al., 2013).

Although the comparator hypothesis for the IO is an attractive idea and advantageous for the forward model hypothesis, it is mostly constructed on the basis of morphological data. There remain at least two fundamental unknowns: (1) activities of the rubro-olivary projection that are assumed to relay cortical inputs via the RNp to the IO (Fig. 2) (see De Zeeuw et al., 1998 for review); (2) activities of inhibitory projection neurons in the DCN (Najac and Raman, 2015). Unfortunately, their activities have never been examined in behaving animals. Moreover, this idea appears to assign too much credit to the IO, assuming it a universal teacher or a judge. To understand how an internal representation in the cerebellum could be modified by input from the IO, further studies are required.

5. Suggestions from human experiments

As mentioned already, the identification of an internal model depends on the identification of its inputs and outputs. In this regard, animal experiments are superior to human experiments, because invasive techniques are available only for animal experiments. Nevertheless, human experiments also have a great advantage, because humans are adaptive to various experimental conditions, thereby allowing the examination of various input–output relations for the presumed internal model. It should be worthwhile to review suggestions from human studies on the cerebellum in evaluating findings from animal experiments. For instance, chronic lesions (Nowak et al., 2007) or temporary disruption (Miall et al., 2007) of the cerebellum produces behavioral deficits that suggest an inability to make an accurate prediction of the sensory consequences of motor commands in humans. Izawa

et al. (2012) suggested that cerebellar integrity appears critical for learning to predict the visual sensory consequences of a motor command, whereas adaptation of motor commands can take place despite cerebellar damages. In addition, there are data from functional imaging studies (Gao et al., 1996; Jueptner et al., 1997; Inoue et al., 1998) and clinical studies (Diener et al., 1993; Nawrot and Rizzo, 1995) suggesting that the cerebellum is important for processing sensory reafference. These studies strongly support findings that the cerebellum implements a forward model for motor control. On the other hand, there are a series of studies suggesting the contribution of the cerebellum in the generation of motor commands as an inverse model (Kawato and Gomi, 1992; Wolpert et al., 1998; Kawato, 1999). It should be noted that observation of ataxic movements alone is not evidence to supporting the cerebellar contribution to either one of the two internal models. For instance, an ataxic movement could be explained as a consequence of a wrong prediction of the future state generated in a forward model. Alternatively, it could be explained as a consequence of a disorganization of activities of individual or groups (i.e., synergies) of muscles in an inverse model. At this point, it is difficult to draw a conclusion about which internal model is suitable to explain human cerebellar functions in motor control from the available evidences. At this point, it is difficult to determine which internal model is more suitable to explain human cerebellar functions in motor control from the available evidences.

Given that a number of cortical areas and corresponding regions of the cerebellum form multiple cerebro-cerebellar communication loops working in parallel (Kelly and Strick, 2003; Lu et al., 2007; Hashimoto et al., 2010; Prevosto et al., 2010; Lu et al., 2012), there is a possibility that both the forward and inverse models for motor control reside in the cerebellum but in separate regions (Wolpert et al., 1998; Haruno et al., 2001). Furthermore, the more lateral part of the cerebro-cerebellum might serve for higher brain functions, e.g., motor imagery, rather than motor control itself (Higuchi et al., 2007). These issues must be addressed in the near future with more advanced experiments that allow the identification of neuronal representation in higher spatial and temporal resolutions in the human brain.

6. Conclusion and perspectives

Morphological and physiological evidence accumulated over decades suggests that a region of the cerebro-cerebellum that forms a loop circuit with the M1 appears to satisfy the basic requirements for a forward model that generates a prediction of the sensory outcome of a motor command.

First, this region of the cerebro-cerebellum receives a putative efference copy as well as a direct somatosensory input (Fig. 3A), and these inputs are presumed to be integrated in the cerebellar cortex. Second, the activities of PCs in this region lag behind those of M1 neurons, while they precede the movement onset. In other words, this region of the cerebellum works later than M1 but earlier than the movement itself. The timing of activity is compatible with the idea that it works as a forward model that predicts a sensory outcome of the motor command. Third, CF input appears to provide an evaluation signal to update a forward model of movement to improve its prediction. As a result, the output of this region of the cerebro-cerebellum may help M1 to generate a suitable motor command for the next moment depending on the predicted sensory consequence before a feedback signal is available for the current motor command.

In this review, we focused on reviewing the input-output organization of the M1 region of the cerebro-cerebellum (Fig. 3A and B, left). However, this organization is not limited to the M1 region. The extensive medio-lateral arborization of single MFs (Fig. 3A)

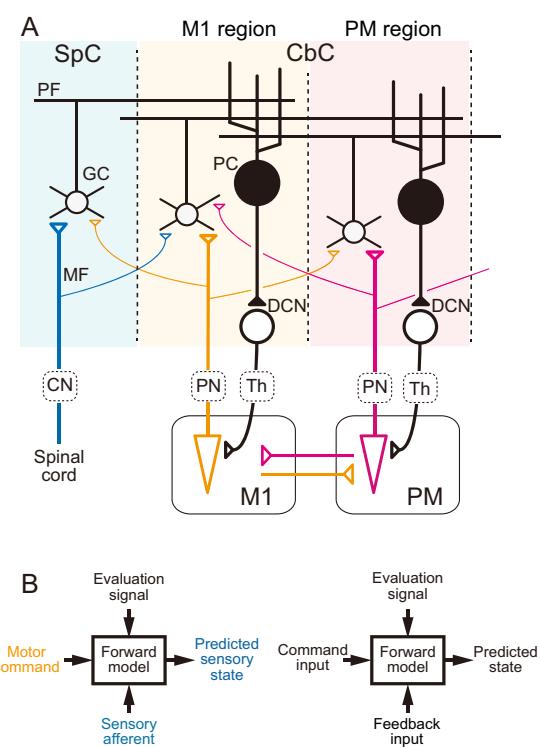


Fig. 3. Multiple communication loops with extensive overlaps. (A) Schematic diagram of the cerebellar circuit. MF inputs from the periphery, M1 and PM are represented by blue, orange and red lines, respectively. In this diagram, we assume that the sensory afferent and efference copies from the M1 are integrated into individual GCs or PCs in the M1 region of the CbC. The output from the M1 region of the CbC projects back to the M1 through the DCN and Th. MF, mossy fiber; M1, primary motor cortex; PM, premotor cortex; GC, granule cells; PC, Purkinje cells; CbC, cerebro-cerebellum; SpC, spino-cerebellum; DCN, deep cerebellar nuclei; Th, thalamus. (B) A conceptual scheme of information flow in the M1 region of the CbC (left) and a more generalized scheme in regions of the CbC specialized for higher brain functions (right).

allows vast number of combinations of multiple MF inputs at the level of single GCs, throughout the cerebellar cortex. In addition, the orthogonal, rostro-caudally oriented thin-film-like arborization of single CFs (Sugihara et al., 2001) selects or unselects a specific set of inputs in a small set of PCs (~10) depending on the correlation between activities of PFs and the CF. This morphological setup makes the cerebro-cerebellum an ideal place to integrate multi-modal information. Therefore, we propose that it is possible to apply the basic organization of the neuron circuitry (Fig. 3B left) to the other regions of the cerebro-cerebellum that form parallel loops between the PM, PAC, and PFC (Fig. 3B right), by replacing *motor command* with *command input* and *sensory afferent* with *feedback input*. For instance, in the PM region of the cerebro-cerebellum (Fig. 3A) that is located next to the M1 region (Lu et al., 2007; Hashimoto et al., 2010), it may be possible to consider a PM input as a *command input* and an M1 input as a consequence of the previous PM input (i.e., *feedback input*). In this case, the PM region is assumed to simulate a *predicted state of M1* based on the intended spatial movement representation in the PM (Kakei et al., 2001) and the current state of M1 in another representation (Kakei et al., 1999, 2003). The *predicted state of M1* could be used to update the PM activity and modify the desired movement in the next moment based on ongoing movement. In this case, the PM region of the cerebro-cerebellum seems to function as another forward model that provides a prediction in a different but closely linked movement representation. From a computational point of view, motor control may be formulated as a cascade of information transformation starting from a representation of a goal to activities of motor

neurons. The input–output organization of the cerebro-cerebellum depicted in Fig. 3 may be beneficial to update the parallel movement representations in a coordinated way during a motor execution. To identify the functional roles of the cerebro-cerebellar communication loops for the PM, PAC, or PFC, further investigations beyond motor control are needed.

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