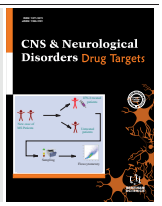
CNS & Neurological Disorders - Drug Targets, 2018, *17*, 184-192

REVIEW ARTICLE



Physiological and Morphological Principles Underpinning Recruitment of the Cerebellar Reserve

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ARTICLE HISTORY

Received: July 31, 2017
Revised: December 25, 2017
Accepted: December 27, 2017

DOI:
10.2174/1871527317666180315164429

Abstract: ***Background***: In order to optimize outcomes of novel therapies for cerebellar ataxias (CAs), it is desirable to start these therapies while declined functions are restorable: *i.e.* while the so-called cerebellar reserve remains.

Objective: In this mini-review, we tried to define and discuss the cerebellar reserve from physiological and morphological points of view.

Method: The cerebellar neuron circuitry is designed to generate spatiotemporally organized outputs, regardless of the region. Therefore, the cerebellar reserve may be defined as a mechanism to restore its proper input-output organization of the cerebellar neuron circuitry, when it is damaged. Then, the following four components are essential for recruitment of the cerebellar reserve: operational local neuron circuitry; proper combination of mossy fiber inputs to be integrated; climbing fiber inputs to instruct favorable reorganization of the integration; deep cerebellar nuclei to generate reorganized outputs.

Results: We discussed three topics related to these resources, 1) principles of generating organized cerebellar outputs, 2) redundant mossy fiber inputs to the cerebellum, 3) plasticity of the cerebellar neuron circuitry.

Conclusion: To make most of the cerebellar reserve, it is desirable to start any intervention as early as possible when the cerebellar cell loss is minimal or even negligible. Therefore, an ideal future therapy for degenerative cerebellar diseases should start before consuming the cerebellar reserve at all. In the meantime, our real challenge is to establish a reliable method to identify the decrease in the cerebellar reserve as early as possible.

Keywords: Adventitiousness, asthenia, B/K ratio, cerebellar reserve, direct pathway, error-related potential, indirect pathway, redundancy.

1. INTRODUCTION

Patients with partial cerebellar lesions induced by strokes or head injuries frequently show exceptional recovery. At first, their movements could be highly ataxic. Nevertheless, the symptoms quickly disappear, sometimes even in weeks, leaving little or no sign of remaining complications. On the other hand, we cannot generally expect comparable recoveries for lesions in the other parts of the central nervous system such as the cerebral cortex, the basal ganglia, the thalamus, the brainstem or the spinal cord.

Judging from the relatively short latent time to restore the cerebellar function, the functional recovery appears to occur without regeneration of lost neurons or damaged connectivity. In other words, the recovery is probably due to reorganization of the remaining cerebellar neuron circuitry [1]. Therefore, a critical question is why the cerebellum, if not alone, has so much room to reorganize the neuron circuitry and restore its original functions, *i.e.* the cerebellar reserve [1]. Of course, resources for the cerebellar reserve are not unlimited. For instance, the cerebellar reserve in patients with spinocerebellar degeneration is most probably running out when the cerebellar ataxia is developing. Then another critical question may be how to evaluate the cerebellar reserve to determine the timing of treatment before the cerebellar reserve runs out.

In this mini-review, we will discuss the resources for the cerebellar reserve, from physiological and morphological points of view, more specifically at the level of cerebellar

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neuron circuitry. We will also discuss candidates of methods to evaluate the cerebellar reserve non-invasively.

2. RESOURCES FOR THE CEREBELLAR RESERVE

From a functional point of view, the cerebellar reserve could be defined as potential for restoration of proper input-output organization of the cerebellum. Then, at least four components are essential for recruitment of the cerebellar reserve: operational local neuron circuitry; proper combination of mossy fiber (MF) inputs to be integrated; climbing fiber (CF) inputs to instruct favorable reorganization of the integration; deep cerebellar nuclei to generate reorganized outputs. It should be noted that these components are not independent to each other. Rather, the cerebellar reserve thrives only when they work together. In the following, we are going to address three topics related to these components, 1) principles of generating organized cerebellar outputs, 2) redundant mossy fiber inputs to the cerebellum, 3) plasticity of the cerebellar neuron circuitry.

2.1. Principles of Generating Organized Cerebellar Outputs

In humans and primates, the cerebellum generates its vast amount of output to the cerebral cortex through the dentate nucleus (DN). In fact, DN cells (DNCs) generate burst activity prior to limb movement [2-8], and inactivation of DNCs results in cerebellar ataxia, a destruction of finely coordinated movement [9]. There are three sources of inputs to DNCs that may contribute in the generation of their burst activity: MF collaterals, CF collaterals and Purkinje cells (PCs). MF collaterals and CF collaterals provide excitatory inputs, but neither can explain the burst activity of DNCs. MF collaterals are very poor in DN [10-15]. Discharge of the CF (~1Hz) is too infrequent to explain the burst activity of DNCs. The remaining inputs from PCs are even more enigmatic because they are inhibitory and exert tonic suppression of DNCs. To explain the excitation of DNCs or more generally the deep cerebellar nuclear (dCN) cells without effective excitatory drive, there are two proposed mechanisms. First, some researchers proposed recruitment of a post-inhibitory rebound excitation [16-19]. They observed a short burst of dCN cells after current-induced strong hyperpolarization or synchronous activation of a large number of PCs. However, such synchronous activation of PCs is not realistic in physiological conditions especially in behaving animals [16-18, 20, 21]. Second, suppression of PC activity could generate burst activity of dCN cells by disinhibition [11, 22-25]. Indeed, Heiney *et al.* (2014) [26] demonstrated that a transient suppression of PC activity was capable of activating dCN cells.

To address how DNCs become activated during voluntary limb movements, we compared the temporal patterns of movement-related changes in activity for PCs and DNCs recorded from the same monkeys during step-tracking movements of the wrist [27]. If rebound excitation works, phasic excitation of PCs and a concomitant inhibition of DNCs should precede excitation of DNCs. On the other hand, if disinhibition plays a primary role, phasic suppression of PCs and activation of DNCs should be observed at the same timing. We found that the majority of PCs in the cerebrocerebellum were suppressed prior to the onset of wrist movements (Fig. **1**, PC) [27]. At the same time, the majority of DNCs were activated without prior suppression (Fig. **1**, DNC) [27]. Taken together, our observations demonstrated that the movement-related activation of DNCs occurs when they are released from tonic inhibition by PCs, *i.e.* disinhibition.

Figure **2** summarizes these results. MF inputs to the cerebellar cortex are relayed by granule cells (GCs) and then processed in two parallel pathways to PCs. The direct pathway activates PCs directly, while the indirect pathway uses inhibitory interneurons (INs) to suppress PCs. Dean *et al.* (2010) [28] proposed that the parallel pathways work in a cooperative way to suppress or facilitate the activity of PCs in the cerebellar cortex. Based on the above observations, we extend their idea to explain the role of the parallel pathways for generation of cerebellar output from DN. The parallel pathways provide two modes for transforming MF inputs to DNC outputs though PCs (Fig. **2**). In fact, movement-related suppressions of simple spike (SS) activity dominated before movement onset, and movement-related excitations dominated after movement onset in our population of PCs (Figs. **8A** and **9A** of [27]). Therefore, the indirect pathway plays the leading role in initiating cerebellar outputs for limb movements, while the direct pathway plays an essential role in terminating the cerebellar outputs to stabilize the limb.

The differential recruitment of the two pathways is organized not only temporally but also spatially [27]. A large proportion of PCs, with somatosensory receptive fields (RFs) in the distal arm (*i.e.* around the wrist joint), was strongly suppressed before movement onset, while the majority of DNCs with the same RFs showed concurrent burst of activity. In contrast, PCs with RFs in the proximal arm demonstrated marked and simultaneous increase in activity, while DNs with the same RFs were strongly suppressed. Our observation suggests that activation of DNCs generated by reduced inhibition from PCs, *i.e.*, disinhibition, facilitates the execution of wrist movement, while suppression of the DNCs by increased PC activity contributes to the stabilization of proximal muscles and improves task performance.

The spatiotemporal organization of the two modes of cerebellar outputs reminds us overlooked Holmes' clinical signs (*i.e.* asthenia and adventitiousness) as malfunctions of the two output modes [29]. Namely, deficits of disinhibition and inhibition of DNCs could be the physiological counterparts of asthenia and adventitiousness, respectively (Fig. **3**). In conclusion, it is likely that asthenia and adventitiousness observed in cerebellar ataxia reflect deficits in the control of disinhibition and inhibition that determines spatiotemporal patterns of cerebellar outputs.

2.2. Redundant MF Inputs to the Cerebellum

In order for the cerebellar reserve to be recruited in a short period (*i.e.* a week or two), the MF inputs to the cerebellum must be organized redundantly. Otherwise, it would take much longer time for rewiring in the cerebellum. Indeed, in the cerebellar cortex, there are evidences that multimodal (*i.e.* motor and sensory) inputs are integrated to make an output based on combinations of those inputs. There are some morphological substrates for this integration.

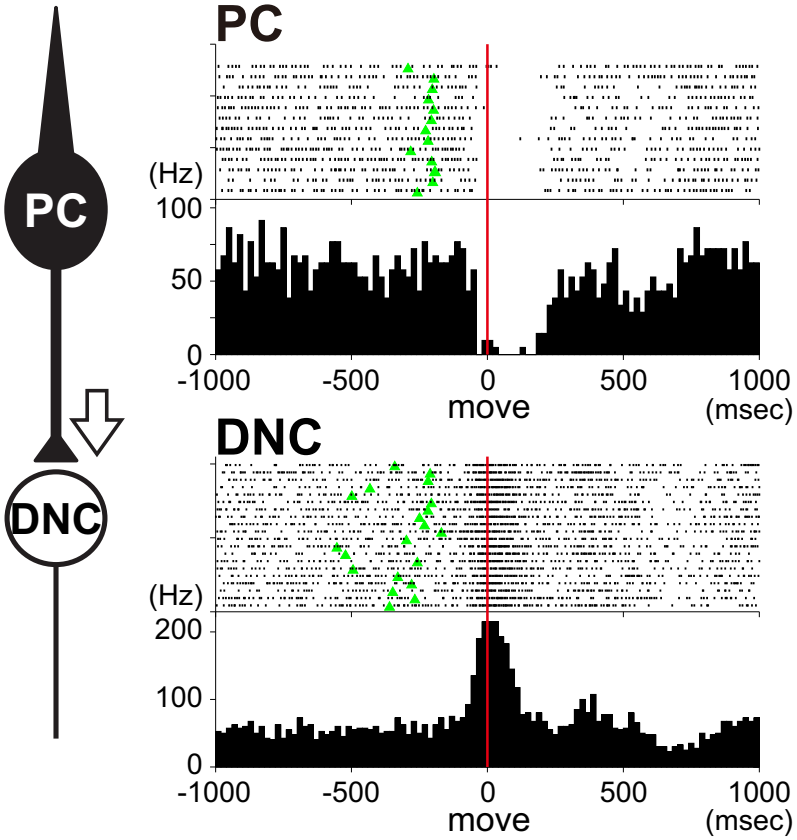

Fig. (1). Activation of dentate nucleus cell (DNC) with disinhibition in monkeys performing step-tracking movement of the wrist joint. *Left inset*: presumed connectivity between a task-related Purkinje cell (PC) and a task-related DNC. Due to strong spontaneous activity of PCs, activities of DNCs are suppressed tonically. *Top*: Raster plots and histograms of simple spike (SS) activity for a typical PC. *Bottom*: Raster plots and histograms of activity for a typical DNC. Both neurons had their receptive fields (RFs) in the distal part of the arm. "move": movement onset of the wrist joint. Green triangles: timing of the GO signal for each trial. Modified from Ishikawa *et al.* [27].

Branching patterns of individual MFs are intensively divergent especially along the medio-lateral axis [11, 14, 30, 31], despite the largely topographic projection of the MF inputs to the cerebellar cortex [32-36]. In other words, projection of individual MFs is highly divergent to various regions of the cerebellar cortex, and each region of the cerebellar cortex receives highly convergent projection from various modalities of MFs (also [30]). Namely, MF inputs to the cerebellar cortex are organized highly redundantly, allowing integration of multimodal inputs. Indeed, Huang *et al.* (2013) [37] recently demonstrated multimodal 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 integrated in single GCs of the cerebellum. Huge numbers of GCs allow also huge number of combinations of various MF inputs. Integration of the multimodal inputs proceed even further on 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 (~10^5) PFs in primates (summarized in Ito (1984) [38]). Indeed, we found that almost all PCs showing pre-movement modulation, which presumably originated from cortical motor areas, were also highly responsive to somatosensory stimuli [27, 39]. That is, these PCs were multimodal in the sense that they are responsive to both motor and sensory inputs. It is suggested that the divergent and convergent organization of the MF inputs to the cerebellar cortex provides one of the most essential resources of the cerebellar reserve. It should be noted that the multimodal organization of the MF inputs to the cerebellar cortex is not special for the cerebrocerebellum. Rather, it is common for the entire cerebellum, as shown in standard textbooks of neuroscience (*e.g*. p964 in [40]).

2.3. Plasticity of the Cerebellar Neuron Circuitry

In the previous sections, we focused on MF inputs or resulting modulation of SS activity of PCs. In this section, we will focus on CF inputs (*i.e*. inputs from the inferior olive (IO)). We cannot overemphasize importance of the CF inputs, because they are assumed to instruct the cerebellum how to recruit the cerebellar reserve.

It is generally accepted that CF inputs have reciprocal effects on PF inputs to INs and PCs (Fig. **2**) [30, 41-44]. Stimulation of a PF input paired with CF activity induces long term potentiation (LTP) of PF-IN synapses and LTD of

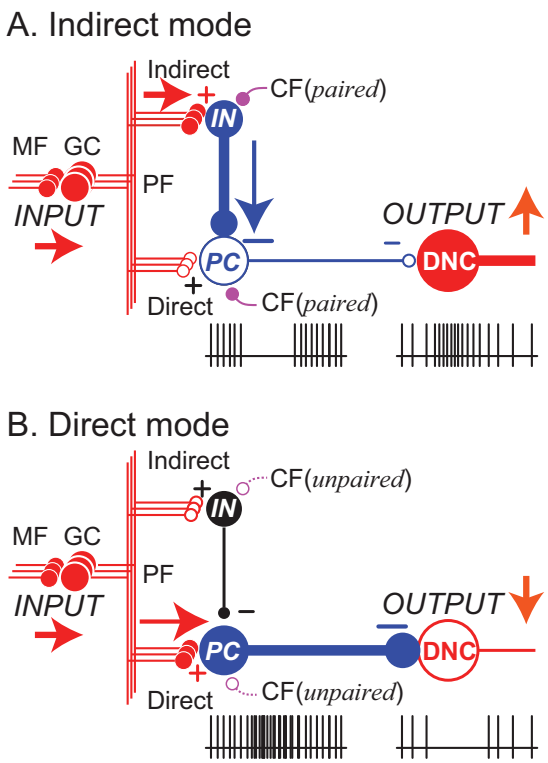

Fig. (2). Parallel pathways in the cerebellar cortex determine two modes of DNC output. **A**. Indirect mode. **B**. Direct mode. In the cerebellar cortex, mossy fiber (MF) inputs (INPUT) are relayed by granule cells (GCs) and are processed differently through two parallel pathways, an indirect pathway (Indirect) and a direct pathway (Direct). In the indirect pathway, parallel fiber (PF) inputs activate interneurons (INs) that suppress PCs. Because PC activity provides a tonic suppression of DNCs, the suppression of PC activity facilitates DNCs through disinhibition (A, OUTPUT ↑). In the direct pathway, PF inputs excite PCs directly. Because PCs are inhibitory, their activation suppresses the DNCs (B, OUTPUT ↓). The balance between the two pathways determines the final output patterns of individual PCs. In this way, inhibitory PCs are able to exert bidirectional effects on DNCs and enable a variety of cerebellar output patterns. CF: climbing fiber. Paired: CF activity paired with PF inputs. Unpaired: CF activity unpaired with PF inputs. Pluses (+) represent excitatory synapses, and minuses (-) represent inhibitory synapses. Note that, in this diagram the PC and the IN share inputs from the same PFs. This is meant to show the basic connectivity of the cerebellar cortex in the simplest form. In reality, a PC and an associated IN may or may not have common PF inputs. Modified from Ishikawa *et al.* [27].

PF-PC synapses (Fig. **2A**). Therefore, it is likely that decreases in SS activity are developed by repetitive paired activation of PF and CF inputs. In contrast, stimulation of a PF input unpaired with CF activity induces LTD of PF-IN synapses and LTP of PF-PC synapses (Fig. **2B**). Therefore, it is likely that increases in SS activity are developed by repetitive unpaired activation of PF and CF inputs. For this reciprocity in development of plasticity to occur, PCs showing decreases in SS activity and PCs showing increases in SS activity concurrently should be innervated by distinct CFs with a low or even negative correlation. Several prior studies have provided strong support for the reciprocity between CS activity and SS activity of a PC. For instance, CS activity and SS activity in individual PCs showed reciprocal activities during ocular following [45], smooth pursuit [46] and limb movements [27, 47-49]. Furthermore, during saccadic adaptation, adaptive changes of CS activity and SS activity demonstrated a negative correlation [50].

It should be noted that, in striking contrast to the highly redundant MF input, there is no redundancy for the CF input [51, 52]. One PC receives only one CF. Therefore, the CF input could be the Achilles tendon of the cerebellar reserve, in a sense that there is no reserve for it.

3. EVALUATION OF THE CEREBELLAR RESERVE

So far, the cerebellar reserve is a conceptual framework inferred from physiological and morphological organization of the cerebellum. In order to utilize it for treatment of cerebellar ataxia, it is necessary to develop a method to evaluate or even quantify the cerebellar reserve. In this section, we are going to introduce our novel analysis of ataxic movements (Mitoma *et al.* 2016) that appears to capture existence of the cerebellar reserve in patients with immune-mediated CA, whose symptoms are partially reversible.

3.1. Reversibility of Immune-mediated Cerebellar Ataxia

When we make a reaching movement, there are infinite combinations of muscle activities that could produce the same movement, due to the redundancy of the musculoskeletal system (*e.g.* [53]). Nevertheless, muscle activities are usually stereotyped, suggesting that there is a hidden constraint why the controller chooses a particular pattern of muscle activities. The constraint or the recipe of muscle activities, if identified in both health and neurological disorders, could provide valuable information to allow pathophysiological explanations for movement disorders. Therefore, it is desirable to develop a method to functionally characterize patterns of muscle activities.

Recently, we developed a novel method to characterize patterns of muscle activities in terms of their similarities to components of movement kinematics [54, 55]. Using a canonical correlation analysis, we determine a symmetric relationship between the linear sum of activities of the four wrist prime movers and the second-order linear equation of motion for the wrist joint in terms of the joint torque. The analysis determines a set of parameters that characterize the muscle activities by quantifying their similarity to the components of movement kinematics. Recently, we applied this method to compare functional characteristics of muscle activities of immune-mediated CAs, degenerative CAs and age-matched normal controls [56].

The six patients with immune-mediated CAs (3 patients with anti-GAD Ab associated CA, 2 with gluten ataxia, and 1 patient with cerebellar type of Hashimoto's encephalopathy) included 3 males and 3 females, with a mean age of 66.6±7.2 years (±SD), with a mean disease duration of 6.2±6.4 years. With regard to activities of daily living, three patients walked without assistance while the others used walkers. Importantly, these patients showed clinical improvement following immunotherapy. In fact, the ICARS of

23.4±15.5 improved to 14.8±13.6. Two patients exhibited distinct cerebellar atrophy, whereas three patients showed mild cerebellar atrophy and the cerebellum was normal in one patient. Furthermore, the latter four patients showed no obvious atrophy of the white matter on MRI voxel-based morphometry. The study also included eight patients with degenerative CAs (5 patients with MSA and 3 patients with SCA6; 4 males and 4 females, mean age, 64.2±10.5 years), with a mean disease duration of 4.8±2.3 years. Five of these patients walked without assistance, two used walkers, and one was wheel chair-dependent. Our study also included nine normal control subjects (6 males and 6 females, mean age, 61.9±X years) free of neurological abnormalities.

We asked the subjects to perform a smooth tracking movement of the wrist joint with a manipulandum (Fig. **1a** in [54]). The subjects were required to maintain the position of the cursor within a target moving smoothly along a path of the Fig. (**2**) at a constant slow speed [54, 55]. We evaluated accuracy of movement with a tracking score. The tracking score represents how much time (in %) the subject keeps the cursor within the target from start to the end of a trial. During the task, we recorded the wrist position (X and Y) and surface EMG signals of four wrist prime movers (ECR, ECU, FCU, FCR) at 2 kHz.

We assumed a causal relationship between EMG signals of the four wrist prime movers and movement kinematics with the equation (1)

$$\tau(t) = \sum_{i=1}^{4} a_i T_i(t) = M\ddot{\theta}(t) + B\dot{\theta}(t) + K\theta(t) \qquad (1)$$

where, τ(t) denotes the wrist joint torque calculated from the wrist joint kinematics. T_i represents the tension of each muscle and a_i denotes parameters that convert the muscle tension into the wrist joint torque. The variables $\theta(t)$, $\dot{\theta}(t)$ and $\ddot{\theta}(t)$ represent angle, angular velocity and angular acceleration of the wrist joint. *M*, *B* and *K* represent the inertia [kg·m^2], the viscous coefficient [N·m·s/rad] and the elastic coefficient [N·m/rad] for the wrist joint. We used a canonical correlation analysis to determine the combination of M, *B*, *K* and a_i (i=1-4) that yielded the best match for the equation (1) (Fig. **4**). Importantly, the best symmetric relationship was obtained when *B* was in a specific ratio to *K* (Fig. **6** in [55]). Thus, we used the *B/K* ratio as a parameter to characterize the muscle activities in terms of the movement kinematics for the three groups of subjects: 1) normal controls, 2) the patients with degenerative CAs and 3) the patients with immune-mediated CAs. The control subjects were capable to follow the moving target smoothly with high accuracy (tracking score 93-100%, m ± sd = 97.8 ± 2.3, n = 8). Their *B/K* ratios ranged from 1.34 to 1.85 (m ± sd = 1.59 ± 0.18, n = 8) (Fig. **3**), suggesting that their muscle activities were weighted comparably or more for velocity control than for position control of the wrist joint. In contrast, *B/K* ratios for the degenerative CA patients were much lower (0.68-1.20, 0.83 ± 0.28, n = 8) ($p < 1.4 \times 10^{-5}$, Student's *t*-test), suggesting that the muscle activities of the degenerative CA patients contained much less component for velocity control. The lower weight for smooth velocity control may explain rough movement kinematics (Fig. **4** in [54]) and poor accuracy (Fig. **5**) (19-89%, 60.5 ± 25.6, n = 8) ($p < 0.001$) of the tracking in the patients with degenerative CAs. On the other hand, for the patients with immune-mediated CAs, accuracy of tracking was as poor as the patients with degenerative CAs (26.4-84.9%, 59.68 ± 29.4, n = 6) ($p > 0.95$) (Fig. **5**). Nevertheless, their *B/K* ratios were comparable or even higher (1.19-2.95, 1.75 ± 0.64, n = 6) ($p > 0.49$) than that of normal controls. This result suggested that the module to generate muscle activities for velocity control was more preserved in the patients with immune-mediated CAs than in the patients with degenerative CAs.

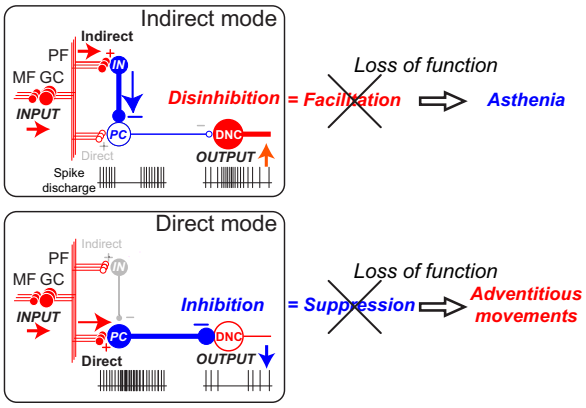

Fig. (3). Relationship between breakdown of two modes of DNC output and asthenia (top) and adventitious movements (bottom). Asthenia (top) is the consequence of breakdown of the Indirect mode while Adventitious movements (bottom) is the result of breakdown of the Direct mode. The diagram provides a summary of the functional organization of the cerebellum (Ishikawa *et al.* 2014). In the cerebellar cortex, MF inputs (INPUT) are relayed by GCs and processed through two parallel but different pathways, an indirect pathway (Indirect) and a direct pathway (Direct). In the indirect pathway (top), PF inputs activate INs that suppress PCs. Because PC activity provides tonic suppression of DNCs, suppression of PC activity facilitates DNCs through disinhibition (OUTPUT ↑). Breakdown of this output mode leads to a decrease in facilitatory output, resulting in Asthenia. In the direct pathway (bottom), PF inputs excite PCs directly. Because PCs are inhibitory, their activation suppresses the DNCs (OUTPUT ↓). Breakdown of this output mode leads to a decrease in suppression, resulting in Adventitious movements. CF: climbing fiber. (+): excitatory synapses, (-): inhibitory synapses. Modified from Ishikawa *et al.* [29].

In the task employed in this study, it was necessary to control both velocity and position of the wrist joint to track the moving target accurately. In accordance with this requirement, both velocity and position were comparably encoded in the muscle activities of the normal controls as was represented in their B/K ratios (Fig. **5**, open circles). In contrast, for the patients with degenerative CAs, B/K ratios were significantly lower than the normal controls, suggesting a relative lack of velocity control (Fig. **5**, red symbols). In fact, their tracking movement was largely replaced with a series of stepwise movements. Consequently, tracking accuracy of the degenerative CA patients was much poorer than the control subjects (Fig. **5**). On the other hand, in the case of the

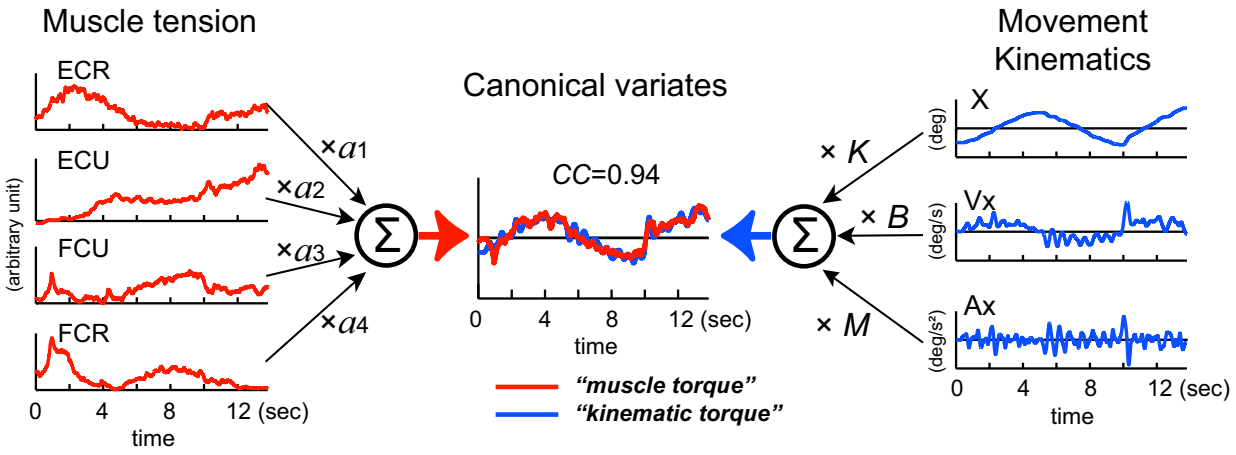

Fig. (4). Explanation of the relationship between muscle tension and movement kinematics modeled in equation (1). The left side represents the middle of equation (1). EMG activities of the four muscles (ECR, ECU, FCU, FCR) converted into *muscle tension* are linearly summed (∑) after multiplying parameter $a_1 - a_4$, respectively to obtain *muscle torque* in the center (*red line*). The right side represents the right side of equation (1). Acceleration (Ax), velocity (Vx) and position (X) of the wrist joint are summed (∑) after multiplying the inertia parameter (*M*), the viscous coefficient (*B*) and the elastic coefficient (*K*), respectively to obtain kinematic torque in the center (*blue line*) (Materials and Methods in Lee *et al.* (2015)). We used a canonical correlation analysis (CCA) to obtain values of these parameters. The two canonical variates, *muscle torque* and *kinematic torque*, were calculated by substituting the values for the fitting parameters in equation (1). Note the high canonical correlation (*CC* = 0.94) between the two canonical variates (in *Estimated torque*). This figure explains calculation of torque around the x-axis, but the same method applies to calculation of torque around the y-axis. Modified from Lee *et al.* [55].

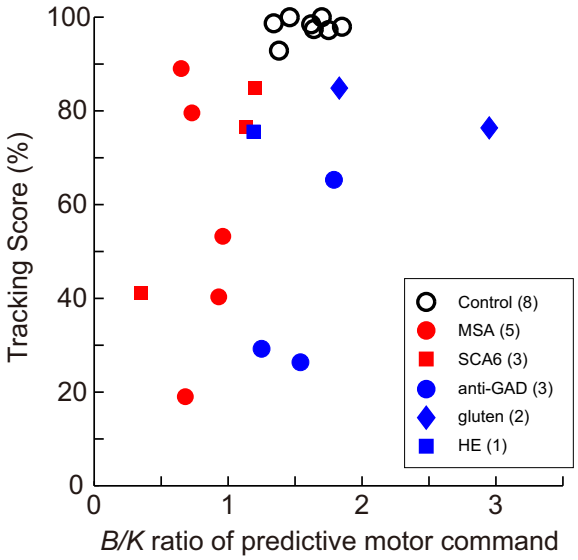

Fig. (5). Relationship between the *B/K* ratio of predictive motor command and tracking score. Circles represent the normal control subjects. Red symbols represent the patients with degenerative cerebellar ataxias (CAs). Blue symbols represent the patients with immune-mediated CAs. MSA = multiple systemic atrophy, SCA6 = spinocerebellar ataxia type 6, anti-GAD = anti-glutamic acid decarboxylase (GAD) antibody associated cerebellar ataxia, gluten= gluten ataxia, HE=cerebellar type of Hashimoto's encephalopathy. Modified from Mitoma *et al.* [56].

patients with immune-mediated CAs, their movement kinematics appeared as ataxic as that of the patients with degenerative CAs. Nevertheless, their B/K ratios remained comparable to those of the normal controls (Fig. **5**, blue symbols). How can we interpret the striking contrast of B/K ratios in the two groups of patients with ataxia? In degenerative CA patients, the velocity control is almost lost due to degeneration of cerebellar neurons (*i.e.* little or no cerebellar reserve). On the other hand, in patients with immune-mediated CAs, the velocity control appears to remain at least in early phase, although its accuracy is deteriorated considerably. Furthermore, a part of the deficit appears to remain reversible because they are sometimes treatable [57-61]. Overall, the contrasting changes in B/K ratios for the immune-mediated CAs and the degenerative CAs might be explained as follows. In patients with degenerative CA, outputs from PCs are largely lost due to severe loss of PCs. Therefore, there remains virtually no cerebellar reserve to be recruited. By contrast, in the patients with immune-mediated CAs, outputs from PCs are inadequately augmented, due to blockade of strong GABAergic inhibition from INs (Fig. **2**) to PCs [57]. It should be emphasized that the blockade most likely results in a temporal malfunction of the indirect mode mentioned earlier (Fig. **3**) if the blockade is reversible. In both groups of patients, the cerebellum might well generate erroneous predictions because of insertion of virtual errors [62], although in different manners. Overall, analysis of B/K ratio in ataxic patients may provide a unique and useful tool to find potentially treatable ataxias (*i.e.* ataxias with cerebellar reserve). On the other hand, to make this analysis more practical, we have to make the surface EMG recording from the four wrist prime movers easier to perform. We also have to extend the

analysis to movements of different joints such as elbow or knee to evaluate the cerebellar reserve of different body parts.

3.2. Cerebellar Related Cortical Responses

Performance monitoring, *i.e*. the ability to concurrently monitor and rapidly evaluate actions, plays a pivotal role in everyday life by enabling behavioral adaptation in response to changing environmental demands. A number of studies have shown that performance monitoring engages a widespread network of cortical and subcortical brain regions (for a recent review [63] that include the cerebellum [64, 65]). More importantly, Peterburs *et al.* (2012, 2015) [64, 65] reported changes in the error-related potential components (ERPs) in both patients with focal cerebellar lesions [64] and patients with cerebellar degenerative diseases [65], compared to the control subjects. Fortunately, analyzing ERPs is not too demanding. We can analyze ERPs noninvasively with a conventional EEG recording system and a simple experimental setup [64, 65]. Yet we need to establish relationship between changes in ERPs and CAs or the cerebellar reserve before we use them for evaluation of the cerebellar reserve.

CONCLUSION

The cerebellar neuronal machine is designed to generate spatiotemporally organized outputs. The cerebellar reserve is a mechanism to restore its output by reorganization of the neuron circuitry when it is damaged. We reviewed some of the key elements of the cerebellar reserve. It runs out when a significant number of PCs or MFs are lost. It will not be recruited when CF inputs are lost. In order to make most of the cerebellar reserve, it is desirable to start any intervention as early as possible when the cerebellar cell loss is minimal or even negligible. Therefore, an ideal future therapy for degenerative cerebellar diseases should start before consuming the cerebellar reserve at all. In the meantime, our real challenge is to establish a reliable method to identify the decrease in the cerebellar reserve as early as possible.

LIST OF ABBREVIATIONS

BPN = Basilar Pontine Nucleus

CA = Cerebellar Ataxia

CF = Climbing Fiber

dCN = Deep Cerebellar Nucleus

DN = Dentate Nucleus

DNC = DN Cell

ERPs = Error-related Potential Components

GC = Granule Cell

IN = Interneuron

IO = Inferior Olive

LTD = Long-term Depression

LTP = Long-term Potentiation

MF = Mossy Fiber

PC = Purkinje Cell

PF = Parallel Fiber

RF = Receptive Field

SS = Simple Spike

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We thank Prof. Koji Ito for his invaluable advices and discussions.

This work was supported by grants-in-aid from the Japan Science and Technology Agency (PRESTO: Intelligent Cooperation and Control) and the Ministry of Education, Culture, Sports, Science and Technology (MEXT), KAKENHI to S.K. (JP14580784, JP15016008, JP16015212, JP20033029, JP21500319, JP26120003), T.I. (JP24650224) and S.T. (JP18700492, JP20700478) and J.L. (JP21700229, JP24650304). This work was also supported by NBRP "Japanese Monkeys" through the National BioResource Project of the MEXT Japan.

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