

Cerebellar Internal Models: Implications for the Dexterous Use of Tools

Hiroshi Imamizu · Mitsuo Kawato

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Abstract Humans have remarkable abilities in the dexterous use of tools to extend their physical capabilities. Although previous neuropsychological and functional neuroimaging studies have mainly focused on the contribution of frontal–parietal cerebral networks to skills for tool use, dense anatomical and functional connections are known to exist between the frontal–parietal regions and the lateral cerebellum, suggesting that the cerebellum also supports the information processing necessary for the dexterous use of tools. In this article, we review functional and structural imaging studies reporting that the cerebellum is related to the learning acquisition of neural mechanisms representing input–output properties of controlled objects, including tools. These studies also suggest that such mechanisms are modularly organized in the cerebellum corresponding to the different properties of objects, such as kinematic or dynamic properties and types of tools, and that they enable humans to flexibly cope with discrete changes in objects and environments by reducing interference and combining acquired modules. Based on these studies, we propose a hypothesis that the cerebellum contributes to the skillful use of tools

by representing the input–output properties of tools and providing information on the prediction of the sensory consequences of manipulation with the parietal regions, which are related to multisensory processing, and information on the necessary control of tools with the premotor regions, which contribute to the control of hand movements.

Keywords Tool use · Cerebellar internal models · Frontal–parietal cerebral networks · Modularity · Sensorimotor learning

Introduction

Humans are unique in having remarkable abilities of manual dexterity and conceptual knowledge of tool use in comparison to other animals. Many neuropsychological studies of patients with brain lesions have suggested two distinct types of functional components in the human faculties for tool use: One is the skill necessary for manipulating tools, and the other is the semantic/conceptual knowledge about tools representing the relationships between tools and their functions [1, 2] (for a recent review, see [3]). Although the brain regions related to each type of component cannot be uniquely determined, a meta-analysis of a large number of functional neuroimaging studies (35 studies including 64 paradigms) has shown that the brain network consisting of the premotor and parietal regions supports the skills for tool use while the network consisting of the inferior frontal gyrus and the middle temporal gyrus contributes to the semantic/conceptual knowledge about tools [4]. Neurophysiological studies in monkeys found activity changes in parietal neurons after acquisition of the skills needed to

H. Imamizu
National Institute of Information and
Communications Technology (NICT),
Kyoto, Japan

H. Imamizu · M. Kawato
Advanced Telecommunications Research
Institute International (ATR),
Kyoto, Japan

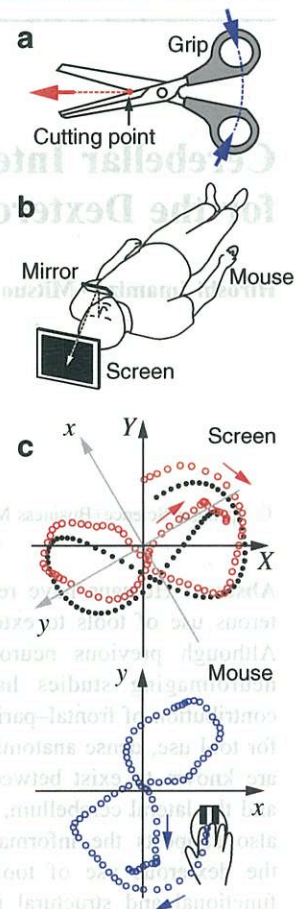
H. Imamizu (✉)
2-2-2 Hikaridai,
Keihanna Science City, Kyoto 619-0288, Japan
e-mail: imamizu@gmail.com

use a rake to retrieve food rewards (for a recent review, see [5]). The frontal–parietal network is known to be involved in generating and mediating skilled movements associated with tool use as well as other behaviors that do not involve external objects (e.g., gestures). Although many neuropsychological and neuroimaging studies on tool use have focused on neocortical regions, some works have proposed the existence of dense anatomical and functional connections between the premotor or the parietal regions and the lateral cerebellum [6–8], suggesting that the cerebellum also contributes to the skilled behavior in using tools.

It has been suggested that the neural mechanisms representing input–output properties of controlled objects, including our own bodies, enable us to skillfully manipulate objects in a predictive fashion, and such mechanisms are called internal models. The central nervous system (CNS) is thought to use two forms of internal models: an inverse internal model and a forward internal model. In the context of arm reaching movements, forward models transform efference copies of motor commands into the resultant trajectory or sensorimotor feedback [9–11]. Inverse models transform an intended motion of the arm into the motor commands used to realize the motion [9].

Although inverse and forward models were originally proposed in studies on the control of muscle–skeletal systems such as the arms and the eye movement system, many behavioral studies have suggested that the CNS applies such models to the manipulation of external objects [12] as well as tools [13]. In the case of external objects, forward models predict how the object will move from one's manipulation of the object while the inverse models predict the manipulation necessary to realize the intended motion of the object. For example, skilled manipulation of a computer mouse requires the ability to predict how the cursor will move on the screen if the mouse is moved in a particular direction (forward model) and how the mouse should be moved in order to move the cursor to a particular position on the screen (inverse model). Namely, we have to learn the input–output properties of tools for these to be used skillfully. Learning such properties is necessary for using more common and simple tools than a computer mouse, such as scissors. The movement direction of the grips of scissors is different from that of the cutting point (Fig. 1a, blue and red arrows), and the movement distance of the grips is also different from that of the cutting point. Therefore, we have to learn the kinematic relationship (input–output property) between the motion of the grips and that of the cutting point for a skillful use of scissors. Of course, learning the kinematic properties of tools is not likely to be the sole component needed for the skillful use of tools, but it is an important component for various kinds of tools.

Fig. 1 **a** Movement directions of grips (blue arrows) and the cutting point (red arrow) of scissors. **b** Posture of subjects during a tracking task using a computer mouse in the magnetic resonance scanner (the scanner is not drawn in the figure). The subjects moved a mouse using their right hand while viewing a screen through a mirror. A target and a mouse cursor were projected onto the screen. **c** *Upper panel*, examples of target (black-filled circles) trajectories, whose vertical and horizontal components were the sum of sinusoids with different amplitude and frequency, and cursor (red open circles) trajectories in the screen coordinates (X, Y) for 1.5 s. Circles indicate the position of the target and cursor every 16.7 ms (60 Hz). *Lower panel*, a mouse trajectory in the hand coordinates (x, y) corresponding to the above cursor trajectory. Red and blue arrows indicate moving direction. Data from [14]



We have been conducting functional imaging studies on how the internal models of such kinematic properties of tools are acquired in the cerebellum as well as studies on the models' modular organization, which is important for the flexible use of tools. In the following, we review a series of our studies on the cerebellum and the issues related to learning the kinematic and dynamic properties of tools.

Cerebellar Activity During Acquisition of an Internal Model for a New Tool

We examined whether activities reflecting an internal model of kinematic properties of a new tool and its acquisition process could be visualized in the human cerebellum by functional magnetic resonance imaging (fMRI) [14]. The subjects manipulated a computer mouse in a magnetic resonance (MR) scanner so that the corresponding cursor followed a randomly moving target on a screen (Fig. 1b). By changing the relationship between the mouse motion and the corresponding cursor motion, we made the subjects learn a novel input–output property of the mouse in a test

condition. That is, the cursor appeared in a position that was rotated 120° around the center of the screen (a *rotated mouse*; Fig. 1c):

$$\begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} \cos 120^\circ & \sin 120^\circ \\ -\sin 120^\circ & \cos 120^\circ \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix},$$

where (X, Y) is a cursor position in the screen coordinates and (x, y) is a mouse position in the hand coordinates. This novel relationship between the mouse and cursor is defined in external coordinates (the screen coordinates and the hand coordinates) that are different from intrinsic (body) coordinates such as the joint angles of the wrist and the elbow. Thus, the subjects are expected to learn this relationship as an external but not an intrinsic one. Actually, our previous behavioral study investigated how learning the use of the rotated mouse with one hand affects the use of the same mouse when using the other hand (inter-manual transfer of learning), and the results suggested that the subjects learn this property as that of an external object rather than that of their own body [15].

A baseline condition, where the mouse was not rotated (*normal mouse*), was also tested. Each subject's performance was measured by tracking errors, i.e., the distance between the cursor and the target. We subtracted cerebellar activity in the baseline condition from that in the test condition and found that the subtracted activity became smaller as the tracking error in the test condition decreased (Fig. 2a). Based on this result and on previous functional imaging studies reporting decreasing cerebellar activity with learning [16, 17], we hypothesized that the activity was evoked by the error. To test this hypothesis, we conducted a control experiment in which the target velocity was increased in the baseline condition so as to equalize the error in this condition to that in the test condition (an error-equalized experiment; Fig. 2b). This experiment was done after training sessions (Fig. 2a). We could still identify a significant activity when we subtracted the baseline condition activity from the test condition activity in the error-equalized experiment, suggesting that it was evoked not only by the error but also by other factors.

Therefore, we investigated how the activity changed during learning in (1) regions where significant activity was identified in the error-equalized experiment (regions enclosed by blue lines in Fig. 2b, c) and (2) regions where great activity was observed in the initial stage of the learning (regions enclosed by red lines in Fig. 2a, c). We also conducted a correlation analysis between tracking error and brain activity during learning, and we found that the regions where significant correlation was identified were almost the same as those where great activity was observed in the initial stage (regions enclosed by red lines). The activity in these regions markedly decreased as learning

proceeded (middle panel of Fig. 2c). However, activity in the former regions did not decrease so drastically (left panel) in comparison to the activity in the latter regions, and its correlation with the error was not statistically significant, confirming that the former regions contain activity evoked by factors other than the error. By subtracting an activity time course in the latter regions from that in the former regions, we found that the activity unrelated to the error increased at the beginning and remained high during the training sessions (right panel). This activity was thought to reflect the acquired internal model representing the input–output property of the rotated mouse. The remaining activity was mainly found around the posterior superior fissure (broken lines in Fig. 2b, c) in the lateral cerebellum.

Physiological Correspondences to the Learning Acquisition of Internal Models

Many studies have suggested that Purkinje cells play an important role in motor learning. Purkinje cells receive major inputs from parallel fibers and climbing fibers and then send the output signals from the cerebellar cortex. A computational theory proposes that the cerebellum represents inverse internal models of musculoskeletal systems, which calculate the necessary feed-forward motor commands from the desired trajectory's information [18, 19]. In this theory, climbing fiber inputs carry motor command errors, which are derived from the performance errors between the desired and actual movements, and guide the learning acquisition of internal models by changing synaptic efficacy. Purkinje cells are thought to learn to transform parallel fiber inputs into appropriate feedforward motor commands [20, 21]. Thus, the complex spike of Purkinje cells activated by climbing fiber inputs reflects error signals [22, 23], while the simple spike activated by parallel fiber inputs reflects motor command outputs [20, 21]. In the light of the uniform structure of neuronal circuitry in the cerebellum, we speculate that the above learning schema also supports the learning acquisition of internal models for tools and external objects.

Hypothesis on Physiological Correspondence to Changes in fMRI Signals During Learning

The brain's almost exclusive source of energy is glucose. Since most of the glucose is oxidatively metabolized, local oxygen consumption is proportional to local brain activity, and it increases local cerebral blood flow, which is reflected in the increase in fMRI signal intensity [24–27]. Several studies indicated that the most energy-demanding process

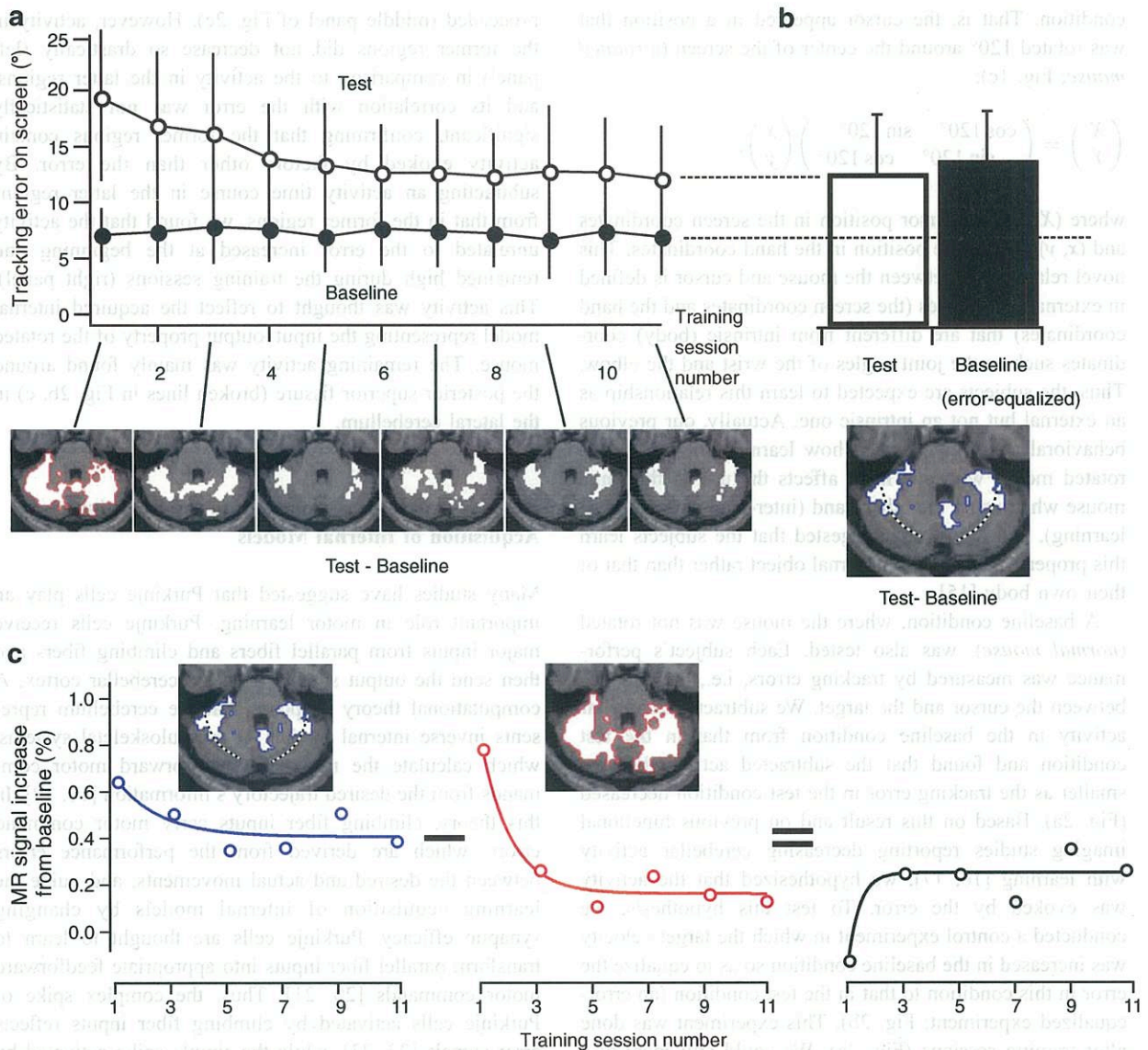


Fig. 2 **a** The upper panel shows the tracking error (mean ± SD) averaged across subjects as a function of the number of training sessions. The images below show the activation maps when the activity in the baseline periods was subtracted from that in the test periods (test – baseline). **b** The upper panel indicates the tracking error (mean + SD) in the error-equalized session (see main text). The image below shows the activation map when the activity in the error-equalized baseline periods was subtracted from that in the test periods in the same session (test – baseline). **c** The left panel shows the change in activity (test – baseline)

across training sessions averaged within the regions enclosed by blue lines in **b**. The middle panel shows the change in activity (test – baseline) across training sessions averaged within the regions where strong activity was observed in the initial stage of the learning (regions enclosed by red lines in **a**). The right panel shows the subtraction of the activity change in the middle panel from that in the left panel. Each curve indicates the exponential function fitted to the circles. Broken lines in the activity maps indicate the posterior superior fissure. Figure modified, with permission, from [14]

in the cerebellar cortex is the restoration of ionic equilibrium after a complex spike with wide plateau potentials [28, 29]. Therefore, strong activity in the broad cerebellar regions in the early stage of learning (middle panel of Fig. 2c) may reflect local energy consumption due to a complex spike activated by climbing fiber inputs.

On the other hand, the increase in fMRI activity with learning (right panel of Fig. 2c) may reflect processes inducing various types of synaptic plasticity related to learning acquisition of internal models. Long-term depression (LTD) of the efficacy of the parallel fiber–Purkinje cell synapse is well known as a form of synaptic plasticity [30].

High intracellular calcium ion (Ca^{2+}) concentration produced by Ca^{2+} -induced Ca^{2+} release from intracellular calcium stores (endoplasmic reticula), which is triggered by the influx of Ca^{2+} into Purkinje cells in response to climbing fiber inputs, has been suggested to play an important role in inducing LTD [31, 32]. However, it is important for cells to maintain a low concentration of Ca^{2+} for proper cell signaling. Therefore, it is necessary to employ calcium pumps to remove the Ca^{2+} , and the pumps necessitate energy consumption, which is expected to increase local oxygen consumption, blood flow, and fMRI signal intensity. It has also been suggested that the sustained activation of intracellular signaling pathways is required for LTD: a theoretical [33] and an empirical [34] study indicated that a positive feedback loop, in which mitogen-activated protein kinase and protein kinase C mutually activate each other, plays a pivotal role in LTD (see [35] for a review). Such sustained activation of intracellular pathways may be another factor of energy consumption related to synaptic plasticity.

Known types of synaptic plasticity other than LTD include long-term potentiation (LTP) [36, 37] and rebound potentiation [38]. Besides the plasticity of parallel fiber–Purkinje cell synapse, the plasticity at parallel fiber–stellate/basket cell synapses leads to a change in feedforward inhibition onto Purkinje cells and decreases the excitatory postsynaptic potentials of Purkinje cells evoked by parallel fiber inputs [39, 40]. A study found that a pair of excitatory climbing fiber input and inhibitory input from interneurons induces LTD, and it suggested that a balance between excitatory inputs from parallel fibers and inhibitory inputs from interneurons plays a crucial role in the change in outputs from Purkinje cells [41]. So far, the most detailed studies, including bioinformatics, have been conducted on mechanisms for LTD. However, the other types of synaptic plasticity, as mentioned above, are probably related to intensive energy consumption processes such as influx and pumping out of Ca^{2+} , activation of intracellular signaling pathways, gene expressions, and morphological changes. Such energy consumption may be related to the increase in fMRI signal as learning proceeds. Additionally, the simultaneous use of fMRI, microstimulation, and electrophysiology in the rat hippocampus demonstrated that LTP induces an increase in fMRI signal [42].

Ogasawara and colleagues pointed out that the local concentration of nitric oxide (NO) is critical for the induction of LTD and for its input specificity [43]. They suggested that the NO concentration contributes to the regional specificity of internal models in the cerebellum depending on the context of behavior. On the other hand, Akgoren and colleagues found that NO dilates blood vessels and increases blood flow in the cerebellum [44]. In the late stage of learning, NO is expected to concentrate

in restricted regions where appropriate internal models are acquired and updated. Therefore, blood flow and thus fMRI signal increase in those regions.

The above hypothesis on physiological and chemical correlates for changes in fMRI signals during learning is based on results from various studies using different animals and experimental methods, including computer simulations. Therefore, it should ideally be examined in a unified experimental setup that can simultaneously measure fMRI and the electrophysiological and chemical signals of animals during learning.

Modular Organization of Internal Models for the Kinematic Properties of Tools

We further examined whether the remaining activity reflects the input–output properties of controlled objects by investigating whether the activity pattern changes depending on the properties [45]. We asked the subjects to learn another relationship between the cursor motion and the mouse motion. The relationship was also kinematic, but the cursor velocity (\dot{X}, \dot{Y}) was proportional to the mouse position (a *velocity control mouse*):

$$\begin{pmatrix} \dot{X} \\ \dot{Y} \end{pmatrix} = k \begin{pmatrix} x \\ y \end{pmatrix}.$$

Here, k is a constant value determined so as to equalize the difficulty of manipulation, measured by tracking errors, to that of the rotated mouse. Newly recruited subjects sufficiently learned the manipulation of both the rotated mouse and the velocity control mouse. Then, we measured their cerebellar activity when they manipulated each mouse (test condition) in comparison to when they manipulated the normal mouse (baseline condition). Tracking error in the baseline condition was equalized to that in the test condition by increasing the target velocity. By subtracting the activity in the baseline condition from that in the test condition, we derived a map specific to each type of mouse. Figure 3 shows the activity map averaged across subjects for the rotated mouse (magenta regions) and that for the velocity control mouse (cyan regions). Both types of activity were found near the superior posterior fissure, but the rotated mouse activations tend to be located more anteriorly and laterally than the velocity control mouse activations. Because Fig. 3 shows the activity averaged across subjects, a significant overlap between the two types of activity can be observed. However, the overlapping volume was only 2.1% of the total activated volume when we measured the volume in each subject's activity map and then averaged the results. This suggests that the different tools evoked activities in distinct locations, demonstrating

that the activity pattern changes depending on the input–output properties of controlled objects. By showing that distinct regions in the lateral cerebellum help to represent different input–output properties, this result suggests the modularity and multiplicity of internal models [46, 47].

Modular Organization of Cerebellar Internal Models: Kinematics Versus Dynamics

Although learning kinematic properties is important for the dexterous use of tools, dynamic properties such as mass, moment of inertia, and rigidity should be learned for the use of common tools such as scissors and a wrench, which dynamically interact with external objects. To explore brain activity related to internal models that contribute to the manipulation of an object with complex dynamics, we measured the activity when the subjects grasped a weighted

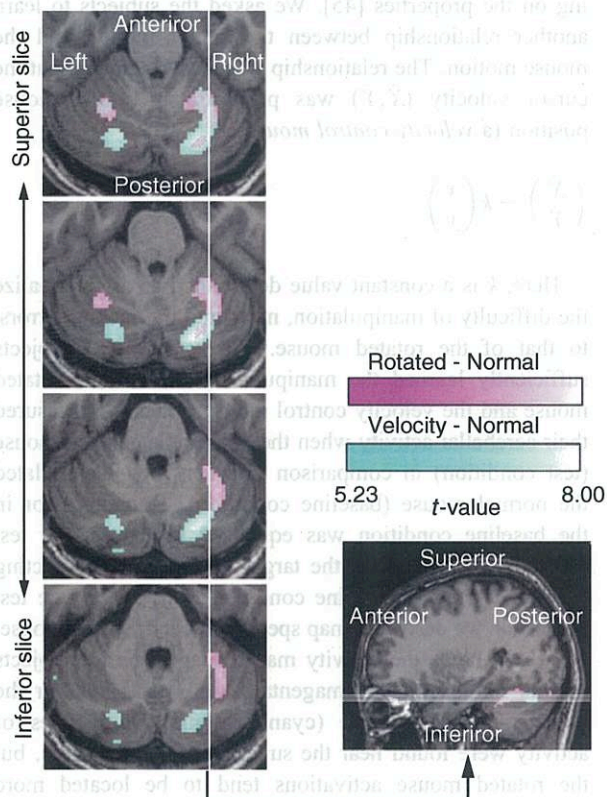


Fig. 3 Cerebellar activity averaged across subjects in transverse sections in the order from the superior (top panels) to inferior (bottom panels) sections. The magenta and cyan regions were significantly activated when the subjects manipulated a rotated mouse and velocity mouse, respectively, in comparison to when the subjects manipulated the normal mouse (error-equalized). White lines in the bottom-right figure indicate vertical levels of the sections in the sagittal plane whose sagittal position is indicated by white vertical lines in the left figures. Data from [45]

flexible ruler and balanced it in an unstable equilibrium position (Fig. 4a) as an archetype of grasping an object with complex dynamics [48]. In a baseline condition, the subjects squeezed a foam ball (Fig. 4b) as an archetype of grasping an object with simple dynamics. The subjects were instructed to compress the ball to a point where the force was equal to the force applied to the ruler. This amounted to compressing the ball until the thumb was close to the fingers. By measuring electromyogram, muscle activation was carefully matched between the two conditions in amplitude and frequency. Extensive training was not required to perform these tasks successfully. All subjects were given sufficient practice under each condition prior to the experiment in order to master the control of each object. First, we contrasted activity when the subjects grasped an object (with complex or simple dynamics) with that in a rest condition and found activity in the primary motor cortex, Brodmann area 6, and the cerebellum among motor-related regions. Then, we investigated the difference in intensity of activation in these regions between the two grasping conditions. We found a statistically greater activation in the complex condition than in the simple condition only in the cerebellum, suggesting that the cerebellum represents an internal dynamics model necessary for balancing the flexible ruler.

The cerebellar activity was mainly found in the anterior and posterior lobules of the ipsilateral hemisphere to the grasping hand. More specifically, the activated regions in the anterior lobule were near the primary fissure (lobules V/VI) and more anterior to the posterior superior fissure around which the activity related to internal models for the kinematic properties were found. The activated region in the posterior lobule is the inferior part of the cerebellum (lobule VIII) and also significantly different from the regions related to the internal kinematic models. These results suggest that distinct regions in the cerebellum contribute to representing internal kinematic or dynamic models.

Cerebellar activity in the anterior lobule associated with learning dynamic properties was also found in previous studies as follows. Adaptation to force field as well as rotated (displaced) visual feedback is often used to investigate the mechanisms for sensorimotor learning. Using positron emission tomography and a robot manipulandum that exerts force to the subjects' hands during reaching movements, Shadmehr and Holcomb [49] investigated how the brain activity changes as learning proceeds. They found that activity shifts from prefrontal regions to the premotor, posterior parietal, and cerebellar regions when skills for interacting with the manipulandum become consolidated and less fragile with respect to behavioral interference. The cerebellar activity reported by their study was also near the primary fissure in the anterior part of the cerebellum ipsilateral to the moving hands.

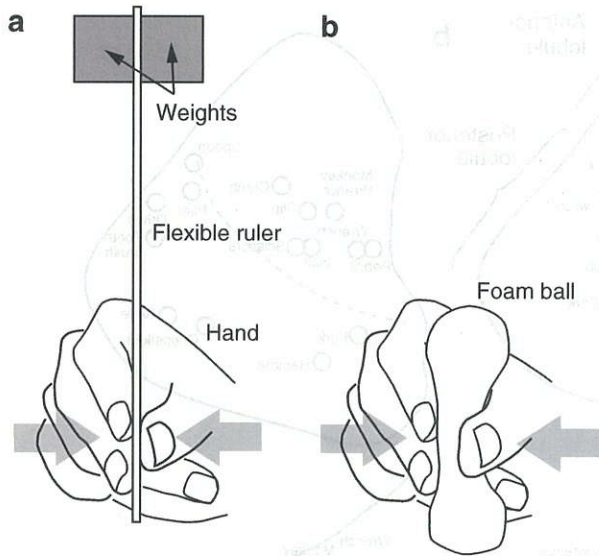


Fig. 4 The objects chosen as archetypes of complex and simple dynamics are illustrated. *Arrows* indicate the directions of forces generated by subjects. Figure modified, with permission, from [48]

Recently, a neuropsychological study [50] investigated the relationships between regions of atrophy in a large number of patients with cerebellar degeneration and their performance during adaptation to kinematic perturbation (visuo-motor rotation of hand-position feedback) and dynamic perturbation (force field). Their results indicated that atrophy in the anterior lobule is correlated more with impairment in adaptation to dynamic perturbation while that in the posterior lobule is correlated more with adaptation deficit in kinematic perturbation, suggesting that the adaptation to kinematic or dynamic perturbation is processed independently and relies on different cerebellar structures. Consistent with the above findings, a behavioral study has reported that humans can independently learn the dynamic properties of their own arms altered by weights and kinematic properties altered by the rotation of visual feedback of their hand position, with little interference of each other [51, 52].

Modular Organization of Cerebellar Internal Models: Common Tools

We measured the cerebellar activity of subjects using 16 common tools (scissors, a hammer, chopsticks, and so on) to investigate internal models for those tools [53]. Because it was impossible to create baseline conditions in which muscle activation was precisely matched with that during the manipulation of each tool, we asked the subjects to mentally imagine using the tools without actual hand movements. The subjects lied in a supine position in an MR scanner and looked at their own hands and the tool through an

arrangement of two mirrors. In an actual use condition, the subjects were asked to use one of the 16 common tools along with an appropriate object (e.g., using scissors to cut a sheet of paper). In an imaginary use condition, the subjects were asked to imagine using a tool without making actual hand movements while holding the tool. In a rest condition, the subjects held the tool in their hand and looked at the object without moving the hand or imagining using the tool.

Activity in the actual use condition in comparison to the rest condition was found in both the anterior and posterior lobules of the cerebellum across the tools, but activity in the anterior lobule was generally stronger than that in the posterior lobule. By contrast, activity in the imaginary use condition in comparison to the rest condition was observed laterally in the posterior lobule. That is, the activity in the actual use condition was overlapped with that in the imaginary condition in the posterior lobule. Strong activities found in the anterior lobule are probably evoked by activities of limb muscles and sensory feedbacks. This speculation is consistent with the existence of somatotopic representations in the anterior lobule (e.g., [54]). By contrast, the activities observed mainly in the posterior lobule during the imaginary use conditions may reflect the internal models for using the tools.

To characterize the distribution of activity, we calculated the *t*-value weight centroids of activation for individual tools in both actual use and imaginary use conditions. Figure 5 shows the calculated centroids when the subjects actually used individual tools (Fig. 5a) or when they imagined using the tools (Fig. 5b) in comparison to the rest condition. Some of the centroids during the imaginary use are also found in the anterior lobule (e.g., wrenches and a pencil). However, the centroids in the imaginary use condition tend to be distributed more posteriorly and laterally than those in the actual use condition. It was difficult to determine how the locations of the centroids are organized in the cerebellum, but the distribution of the centroids in the imaginary use condition suggests that the internal models contributing to the skillful use of common tools are modularly organized, that is, different parts of the lateral cerebellum contribute to the use of different tools.

Combination of Acquired Internal Models

A benefit of modular organization of internal models is that it facilitates the initial learning of objects and environments by combining stored modules. Many situations that we encounter are derived from combinations of previously experienced contexts. By modulating the contribution of the outputs of the internal models to the final motor command, an enormous repertoire of behaviors can be generated. In our previous behavioral study, we made the subjects learn a kinematic

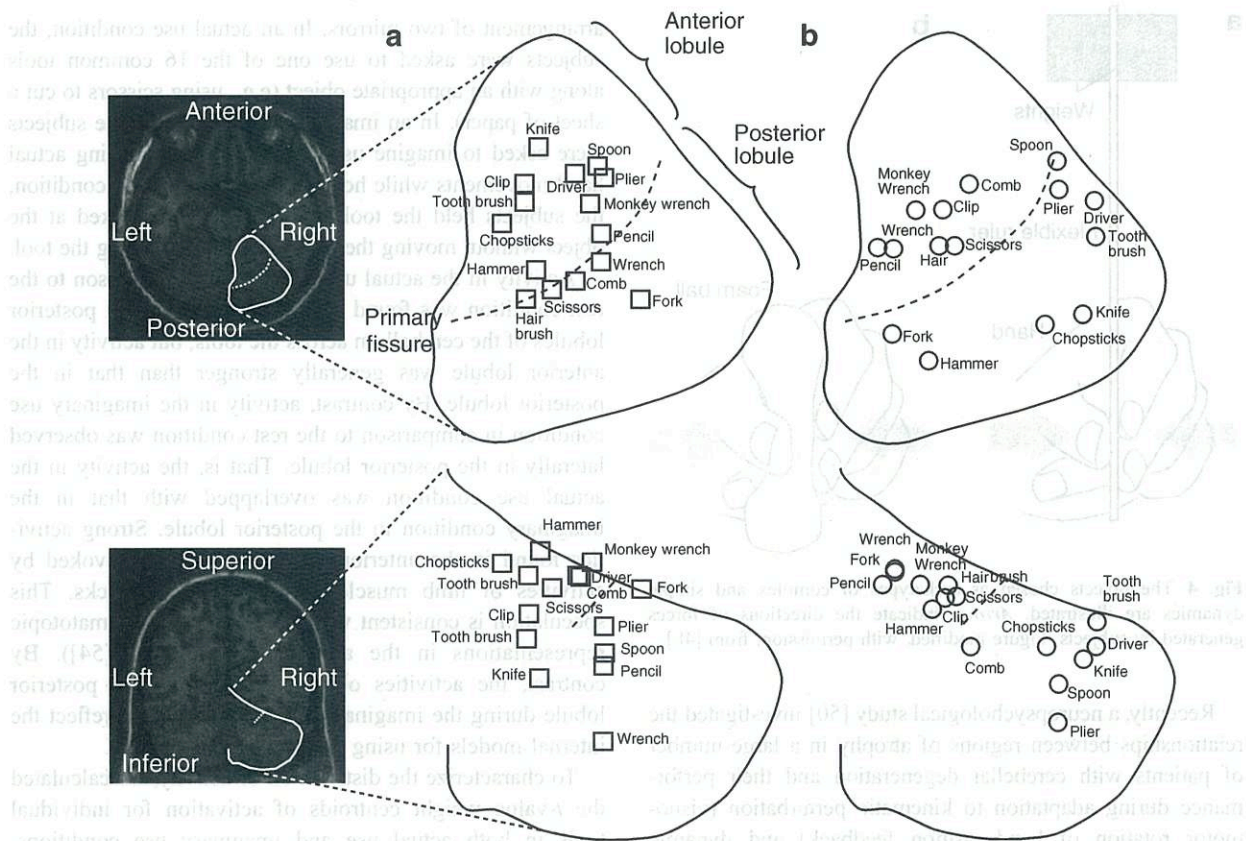


Fig. 5 Distribution of t -value-weighted centroid of activation coordinates when the subjects actually used common tools (a) or when they imagined the use of the tools (b). Centroids are projected to transverse (upper panels) or coronal (lower panels) planes as indicated by the left anatomical images. The subjects used 16 tools but one of

the tools (saw) could not evoke a significant activation ($P < 0.001$, uncorrected for multiple comparisons in random-effect analysis). Thus, the number of centroids is 15. Broken lines indicate the primary fissure. Data from [53]

perturbation (visuomotor rotation), a dynamic perturbation (force field), and a combination of these perturbations [52]. When the subjects learned the combined transformation, reaching error was smaller if the subject first learned the separate kinematic and dynamic transformations. This result suggests the ability of humans to combine internal models as needed, depending on the situation.

Our functional imaging study [55] also suggests the ability of the CNS to combine output signals from internal models. The subjects sufficiently learned to use 60° and 160° rotated joysticks, where the cursor appeared in a position rotated 60° or 160° around the center of the screen. Then, we investigated brain activity when the subjects learned to use a 110° rotated joystick (an intermediate angle between 60° and 160°). In the early and late stages of learning the 110° joystick, we measured cerebellar activity specific to the 60°, 110°, or 160° joystick according to the same method that we used when measuring the activity specific to the rotated mouse or the velocity control mouse (see above).

We hypothesized that the CNS combined output signals from internal models for 60° and 160° joysticks to cope with the novel 110° joystick in the early stage, while in the late stage an internal model for the 110° joystick had been acquired, and the activity of internal models for 60° and 160° joysticks decreased due to the decreased necessity for these models. We investigated activated volumes in the lateral cerebellum separately for 60°, 110°, and 160° conditions across subjects (Fig. 6). Consequently, volumes for both 60° and 160° conditions were larger than that for the 110° condition in the early stage, suggesting that internal models for 60° and 160° joysticks largely contribute to the subjects' performance. However, the volumes for 60° and 160° conditions in the late stage became small in comparison to the initial stage, and the volume for the 110° condition became the largest. These results support the above hypothesis and suggest that the CNS may be able to combine acquired internal models according to the degree of acquisition of a new internal model.

We confirmed that the performance levels of subjects, which were measured by a tracking error, in the 60° and 160° conditions did not significantly change after the training for the 110° condition from those before the training, despite the decreased activity for the 60° and 160° conditions. This suggests that the processing for the 60° and 160° conditions became more effective and required smaller regions after the 110° training. Such reorganization of internal models is necessary for the effective use of limited volumes of the cerebellum, but the mechanisms of this reorganization are unknown and need further studies.

Discussion

We comprehensively reviewed functional neuroimaging studies investigating how the internal models for tools are acquired in the cerebellum. First, we succeeded in visualizing the changes in cerebellar activity during the learning acquisition of a new tool. Our findings were consistent with a learning schema supported by physiological studies on the changes in the synaptic efficacy of Purkinje cells. Then, we summarized studies on differences in cerebellar regions corresponding to distinct input–output properties of controlled objects and tools. These studies suggested the multiplicity and modularity of internal models from several aspects: differences in kinematic properties, whether the properties are kinematic or dynamic, and the types of common tools used. We believe that such multiplicity and modularity enable humans to flexibly cope with discrete changes in objects and environments by reducing interference and combining acquired internal models. Our behav-

ioral and fMRI studies have found evidence indicating that the CNS can combine acquired internal models depending on the situation.

In this review article, we focused on the changes in cerebellar activity based on previous neurophysiological and computational studies. Many studies have reported changes in whole-brain activity with sensorimotor learning when a force field alters limb dynamics [49] or when a screen controlled by a computer program kinematically alters the visual feedback of hand position [56] or joystick position [57]. These studies identified different cerebral regions related to learning as a consequence of the differences in experimental methods (e.g., adaptation to a force field or altered visual feedback; different effectors such as the arm, a computer mouse, and a joystick; tracking a continuously moving target or aiming at a static target). However, their results are consistent with ours in that significant activity is found in the lateral cerebellum after learning. These results suggest that the cerebellum is one of the regions where the internal models representing the input–output properties of controlled objects are likely acquired.

Recent advances in the structural imaging of the brain support the contribution of the cerebellum to the dexterous use of tools. Using MRI and voxel-based morphometry, Quallo and colleagues [58] investigated the changes in brain structure in Japanese macaque monkeys trained for 6 weeks to use a rake to retrieve food rewards. Their analysis revealed increases in gray matter with improved rake performance of the monkeys. The effects were significant in the superior temporal sulcus, second somatosensory area, and intraparietal sulcus in the right hemisphere. They also found significant bilateral increases in the white matter of the lateral cerebellum (lobule VI near the posterior superior fissure), in which our functional imaging studies on humans reported an activity related to the kinematic internal models of new tools. Another structural imaging study found a correlation between the rate of learning the use of a new tool and white matter microstructure in the human cerebellum: Della-Maggiore and colleagues [59] used diffusion-weighted MRI to estimate the fractional anisotropy (FA) reflecting the myelination of axons, axonal diameter, and packing density of axons. According to their results, FA in regions near the posterior superior fissure positively correlated with the individual rate of adaptation to visuomotor rotation. They also found the same pattern of correlation in the superior cerebellar peduncle that contains fibers connecting the cerebellar cortex with the motor and premotor cortices.

As mentioned in the “Introduction”, many neuropsychological and functional imaging studies have suggested that a brain network including the premotor and parietal regions supports the skills needed for tool use. We speculate that

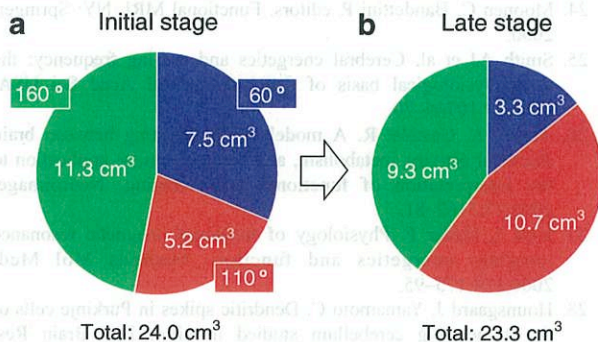


Fig. 6 Volumes (across-subjects mean) in the cerebellar regions that were more activated when the subjects manipulated 60°, 110°, or 160° rotated joystick than when the subjects manipulated normal joystick (error-equalized). **a** Volumes measured in the initial stage of learning how to use 110° joystick just after an intensive training for use of 60° and 160° joysticks. **b** Volumes measured in the late stage of learning to use 110° joystick. The diameter of each circle is proportional to the total activated volume. The threshold for activation was $t > 3.08$, $P < .05$, uncorrected for multiple comparisons. Data from [55]

the primary skills are acquired in the premotor–parietal network at an early stage of learning tool use. However, after intensive training, humans gain the ability to use a tool very rapidly and precisely in a predictive fashion. At this stage, neural mechanisms predicting the control of a tool to realize desired performance and the sensory consequences of that control play crucial roles in the skillful use of tools. This is because the sensory feedbacks of movements are inevitably delayed by many factors, including delay for transmission of motor commands from the brain to muscles, mechanical delay of a tool, and time for processing sensory information. The cerebellum contributes to the skillful use of tools by providing information about the prediction of sensory consequences with the parietal regions, which are related to multisensory processing, and about the necessary control of tools by the premotor regions, which contribute to the control of movements.

However, the above hypothesis on global networks contributing to the skillful use of tools is mainly based on studies of ours and others investigating the correlation between behavioral and neuroimaging data. Such studies have limitations for examining the information represented in specific brain regions. Recent advances in machine learning techniques made it possible to non-invasively extract information from various regions (e.g., [60–62]). Future studies that can extract neural information simultaneously from multiple regions will enable us to elucidate the outlines of the brain network supporting the skillful use of tools, as well as the functional differences among the regions, and to examine the validity of the above hypothesis.

Acknowledgements We would like to thank Miho Onizuka and Nicolas Schweighofer for helpful comments on an earlier version of the manuscript. This research is supported by the Strategic Research Program for Brain Sciences (SRPBS) to MK.

Conflicts of interest The authors declare that they have no potential conflict of interests.

References

- De Renzi E, Lucchelli F. Ideational apraxia. *Brain*. 1988;111:1173–85.
- Ochipa C, Rothi LJ, Heilman KM. Conceptual apraxia in Alzheimer's disease. *Brain*. 1992;115(Pt 4):1061–71.
- Johnson-Frey SH. The neural bases of complex tool use in humans. *Trends Cogn Sci*. 2004;8:71–8.
- Lewis JW. Cortical networks related to human use of tools. *Neuroscientist*. 2006;12:211–31.
- Iriki A. The neural origins and implications of imitation, mirror neurons and tool use. *Curr Opin Neurobiol*. 2006;16:660–7.
- Clower DM, West RA, Lynch JC, Strick PL. The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *J Neurosci*. 2001;21:6283–91.
- Dum RP, Strick PL. An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. *J Neurophysiol*. 2003;89:634–9.
- Ramnani N. The primate cortico-cerebellar system: anatomy and function. *Nat Rev Neurosci*. 2006;7:511–22.
- Kawato M, Furukawa K, Suzuki R. A hierarchical neural-network model for control and learning of voluntary movement. *Biol Cybern*. 1987;57:169–85.
- Miall RC, Weir DJ, Wolpert DM, Stein JF. Is the cerebellum a Smith predictor? *J Mot Behav*. 1993;25:203–16.
- Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. *Science*. 1995;269:1880–2.
- Flanagan JR, Wing AM. The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. *J Neurosci*. 1997;17:1519–28.
- Mehta B, Schaal S. Forward models in visuomotor control. *J Neurophysiol*. 2002;88:942–53.
- Imamizu H et al. Human cerebellar activity reflecting an acquired internal model of a new tool. *Nature*. 2000;403:192–5.
- Imamizu H, Shimojo S. The locus of visual–motor learning at the task or manipulator level: implications from intermanual transfer. *J Exp Psychol Hum Percept Perform*. 1995;21:719–33.
- Raichle ME et al. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex*. 1994;4:8–26.
- Flament D, Ellermann JM, Kim SG, Ugurbil K, Ebner TJ. Functional magnetic resonance imaging of cerebellar activation during the learning of a visuomotor dissociation task. *Hum Brain Mapp*. 1996;4:210–26.
- Kawato M, Gomi H. The cerebellum and VOR/OKR learning models [see comments]. *Trends Neurosci*. 1992;15:445–53.
- Kawato M, Gomi H. A computational model of four regions of the cerebellum based on feedback-error learning. *Biol Cybern*. 1992;68:95–103.
- Shidara M, Kawano K, Gomi H, Kawato M. Inverse-dynamics model eye movement control by Purkinje cells in the cerebellum. *Nature*. 1993;365:50–2.
- Gomi H et al. Temporal firing patterns of Purkinje cells in the cerebellar ventral paraflocculus during ocular following responses in monkeys. I. Simple spikes. *J Neurophysiol*. 1998;80:818–31.
- Kitazawa S, Kimura T, Yin PB. Cerebellar complex spikes encode both destinations and errors in arm movements. *Nature*. 1998;392:494–7.
- Kobayashi Y et al. Temporal firing patterns of Purkinje cells in the cerebellar ventral paraflocculus during ocular following responses in monkeys. II. Complex spikes. *J Neurophysiol*. 1998;80:832–48.
- Moonen C, Bandettini P, editors. *Functional MRI*. NY: Springer; 2000.
- Smith AJ et al. Cerebral energetics and spiking frequency: the neurophysiological basis of fMRI. *Proc Natl Acad Sci USA*. 2002;99:10765–70.
- Aubert A, Costalat R. A model of the coupling between brain electrical activity, metabolism, and hemodynamics: application to the interpretation of functional neuroimaging. *Neuroimage*. 2002;17:1162–81.
- Kida I, Hyder F. Physiology of functional magnetic resonance imaging: energetics and function. *Methods Mol Med*. 2006;124:175–95.
- Hounsgaard J, Yamamoto C. Dendritic spikes in Purkinje cells of the guinea pig cerebellum studied in vitro. *Exp Brain Res*. 1979;37:387–98.
- Hockberger PE, Tseng HY, Connor JA. Fura-2 measurements of cultured rat Purkinje neurons show dendritic localization of Ca^{2+} influx. *J Neurosci*. 1989;9:2272–84.
- Ito M, Sakurai M, Tongroach P. Climbing fibre induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells. *J Physiol Lond*. 1982;324:113–34.
- Doi T, Kuroda S, Michikawa T, Kawato M. Inositol 1,4,5-trisphosphate-dependent Ca^{2+} threshold dynamics detect spike timing in cerebellar Purkinje cells. *J Neurosci*. 2005;25:950–61.

32. Tanaka K et al. Ca^{2+} requirements for cerebellar long-term synaptic depression: role for a postsynaptic leaky integrator. *Neuron*. 2007;54:787–800.
33. Kuroda S, Schweighofer N, Kawato M. Exploration of signal transduction pathways in cerebellar long-term depression by kinetic simulation. *J Neurosci*. 2001;21:5693–702.
34. Tanaka K, Augustine GJ. A positive feedback signal transduction loop determines timing of cerebellar long-term depression. *Neuron*. 2008;59:608–20.
35. Ogasawara H, Kawato M. Bistable switches for synaptic plasticity. *Sci Signal*. 2009;2:pe7–7.
36. Sakurai M. Synaptic modification of parallel fibre–Purkinje cell transmission in vitro guinea-pig cerebellar slices. *J Physiol Lond*. 1987;394:463–80.
37. Wang X, Chen G, Gao W, Ebner T. Long-term potentiation of the responses to parallel fiber stimulation in mouse cerebellar cortex in vivo. *Neuroscience*. 2009;162:713–22.
38. Kano M, Rexhausen U, Dreesen J, Konnerth A. Synaptic excitation produces a long-lasting rebound potentiation of inhibitory synaptic signals in cerebellar Purkinje cells. *Nature*. 1992;356:601–4.
39. Mittmann W. Feed-forward inhibition shapes the spike output of cerebellar Purkinje cells. *J Physiol*. 2004;563:369–78.
40. Brunel N, Hakim V, Isope P, Nadal J-P, Barbour B. Optimal information storage and the distribution of synaptic weights perceptron versus Purkinje cell. *Neuron*. 2004;43:745–57.
41. Mittmann W, Hausser M. Linking synaptic plasticity and spike output at excitatory and inhibitory synapses onto cerebellar Purkinje cells. *J Neurosci*. 2007;27:5559–70.
42. Canals S, Beyerlein M, Merkle H, Logothetis NK. Functional MRI evidence for LTP-induced neural network reorganization. *Curr Biol*. 2009;19:398–403.
43. Ogasawara H, Doi T, Doya K, Kawato M. Nitric oxide regulates input specificity of long-term depression and context dependence of cerebellar learning. *PLoS Comput Biol*. 2007;3:e179.
44. Akgoren N, Fabricius M, Lauritzen M. Importance of nitric oxide for local increases of blood flow in rat cerebellar cortex during electrical stimulation. *Proc Natl Acad Sci USA*. 1994;91:5903–7.
45. Imamizu H, Kuroda T, Miyauchi S, Yoshioka T, Kawato M. Modular organization of internal models of tools in the human cerebellum. *Proc Natl Acad Sci USA*. 2003;100:5461–6.
46. Wolpert DM, Kawato M. Multiple paired forward and inverse models for motor control. *Neural Netw*. 1998;11:1317–29.
47. Haruno M, Wolpert DM, Kawato M. Mosaic model for sensorimotor learning and control. *Neural Comput*. 2001;13:2201–20.
48. Milner TE, Franklin DW, Imamizu H, Kawato M. Central control of grasp: manipulation of objects with complex and simple dynamics. *Neuroimage*. 2007;36:388–95.
49. Shadmehr R, Holcomb HH. Neural correlates of motor memory consolidation. *Science*. 1997;277:821–5.
50. Rabe K et al. Adaptation to visuomotor rotation and force field perturbation is correlated to different brain areas in patients with cerebellar degeneration. *J Neurophysiol*. 2009;101:1961–71.
51. Krakauer JW, Ghilardi MF, Ghez C. Independent learning of internal models for kinematic and dynamic control of reaching. *Nat Neurosci*. 1999;2:1026–31.
52. Flanagan JR et al. Composition and decomposition of internal models in motor learning under altered kinematic and dynamic environments. *J Neurosci*. 1999;19:RC34.
53. Higuchi S, Imamizu H, Kawato M. Cerebellar activity evoked by common tool-use execution and imagery tasks: an fMRI study. *Cortex*. 2007;43:350–8.
54. Grodd W, Hulsmann E, Lotze M, Wildgruber D, Erb M. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. *Hum Brain Mapp*. 2001;13:55–73.
55. Imamizu H, Higuchi S, Toda A, Kawato M. Reorganization of brain activity for multiple internal models after short but intensive training. *Cortex*. 2007;43:338–49.
56. Krakauer JW et al. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. *J Neurophysiol*. 2004;91:924–33.
57. Graydon FX, Friston KJ, Thomas CG, Brooks VB, Menon RS. Learning-related fMRI activation associated with a rotational visuo-motor transformation. *Brain Res Cogn Brain Res*. 2005;22:373–83.
58. Quallo MM et al. Gray and white matter changes associated with tool-use learning in macaque monkeys. *Proc Natl Acad Sci USA*. 2009;106:18379–84.
59. Della-Maggiore V, Scholz J, Johansen-Berg H, Paus T. The rate of visuomotor adaptation correlates with cerebellar white-matter microstructure. *Hum Brain Mapp*. 2009;30:4048–53.
60. Kamitani Y, Tong F. Decoding the visual and subjective contents of the human brain. *Nat Neurosci*. 2005;8:679–85.
61. Miyawaki Y et al. Visual image reconstruction from human brain activity using a combination of multiscale local image decoders. *Neuron*. 2008;60:915–29.
62. Toda A, Imamizu H, Kawato M, Sato MA. Reconstruction of two-dimensional movement trajectories from selected magnetoencephalography cortical currents by combined sparse Bayesian methods. *Neuroimage*. 2011;54:892–905.

