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Cerebellar internal models: implications for dexterous use of tools

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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 dexterous use of tools. In this article, we review functional and structural imaging studies reporting that the cerebellum is related to 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 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 skillful use of tools by representing the input-output properties of tools and providing information on prediction of sensory consequences of manipulation done 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.

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 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 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 skills for tool use while the network consisting of the inferior frontal gyrus and the middle temporal gyrus contribute to semantic/conceptual knowledge about tools [4]. Neurophysiological studies in monkeys found activity changes in parietal neurons after acquisition of skills to use a rake to retrieve food rewards (for a recent review, see [5]). The front-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 skilled behaviors

using tools.

It has been suggested that 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 control of muscle-skeletal systems such as arms and the eye-movement system, many behavioral studies have suggested that the CNS applies such models to manipulation of external objects [12] as well as tools [13]. In the case of external objects, forward models predict how the object will moves from ones manipulation of the object while the inverse models predict manipulation necessary for realizing 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 input-output properties of tools for skillful use of them. Learning such properties is necessary for use of 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) as well as the movement distance of the grips is 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 skillful use of scissors. Of course, learning kinematic properties of tools is unlikely a unique component for skillful use of tools, but it is an important component for various kinds of tools.

We have been involved in functional imaging studies on how internal models of such kinematic properties of tools are newly acquired in the cerebellum as well as studies on the models' modular organization, which is important for flexible use of tools. We will review a series of our studies on the cerebellum and issues related to learning 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]. Subjects manipulated a computer mouse in an 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 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):

$$\left(\begin{array}{c} X \\ Y \end{array} \right) = \left(\begin{array}{cc} \cos 120^{\circ} & \sin 120^{\circ} \\ -\sin 120^{\circ} & \cos 120^{\circ} \end{array} \right) \left(\begin{array}{c} x \\ y \end{array} \right),$$

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 joint angles of the wrist and the

elbow. Thus, subjects are expected to learn this relationship as external but not intrinsic

one. Actually, our previous behavioral study investigated how learning use of the

rotated mouse using one hand affects use of the same mouse using the other hand

(inter-manual transfer of learning), and suggested that 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 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 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 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 activity changed during learning in 1) regions

where significant activity was identified in the error-equalized experiment (regions

enclosed by blue lines in Figs. 2B and 2C), and 2) regions where great activity was

observed in the initial stage of the learning (regions enclosed by red lines in Figs. 2A

and 2C). We also conducted correlation analysis between tracking error and brain

activity during learning, and found that regions where significant correlation was

identified was 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 Figs. 2B and 2C) in the lateral cerebellum.

Physiological correspondences to learning acquisition of internal models

Many studies have suggested that Purkinje cells play an important role in motor learning. Purkinje 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 feedforward 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, while the simple spike activated by parallel fiber inputs reflects motor-command outputs [22, 23]. In light of the uniform structure of neuronal circuitry in the cerebellum, we speculate that the above learning schema also supports learning acquisition of internal models for tools and external objects.

A hypothesis about 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 increases local cerebral blood flow, which is reflected in increase in fMRI signal [24-27]. Several studies indicated that the most energy-demanding process 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 at 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 efficacy of the parallel fiber-Purkinje cell synapse is well known as a form of synaptic plasticity [30]. Intracellular calcium ion (Ca^{2+}) and influx of Ca^{2+} into Purkinje cells in response to climbing fiber input have been suggested to play an important role in inducing LTD [31, 32]. However, it is important for cells to maintain 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 need energy consumption, which is expected to increases local oxygen consumption, blood flow and fMRI signals. It has also been suggested that 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 a reference [35] for review). Such sustained activation of intracellular pathways may be another factor of energy consumption related to synaptic plasticity.

The other types of synaptic plasticity than LTD are also known such as a long-term potentiation (LTP) [36, 37] and rebound potentiation [38]. Recently, plasticity at parallel fiber-stellate/basket cell synapses leads to change in feedforward inhibition onto Purkinje cells, and decreases excitatory postsynaptic potentials of Purkinje cells evoked by parallel fiber inputs [39, 40]. A study indicated that a pair of climbing fiber input and inhibitory input from interneurons induces LTP. This study suggests that a balance between excitatory inputs from parallel fibers and inhibitory inputs from interneurons plays a crucial role in 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 above mentioned, are probably related to intense 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 increase in fMRI signals as learning proceeds.

Ogasawara and colleagues pointed out that local concentration of nitric oxide (NO) is critical for induction of LTD and for its input specificity [42]. They suggested that the NO concentration contributes to regional specificity of internal models in the cerebellum depending on context of behavior. On the other hand, Akgoren and

colleagues found that NO dilates blood vessels and increases blood flow in the

cerebellum [43]. At 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 about physiological and chemical correlates for changes in

fMRI signals during learning is based on results from various studies using different

animals, experimental methods including computer simulations. Therefore, it should be

ideally examined in a unified experimental setup that can simultaneously measure fMRI,

electrophysiological and chemical signals of animals during learning.

Modular organization of internal models for 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 [44]. We asked 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 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 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 Figure 3 shows activity averaged across subject, a significant overlap between the two types 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. 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 [45, 46].

Modular organization of cerebellar internal models: kinematics versus dynamics

Although learning kinematic properties is important for dexterous use of tools, dynamic properties such as mass, moment of inertia, and rigidity should be learned for 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 manipulation of an object with complex dynamics, we measured activity when subjects grasped a weighted flexible ruler and balanced it in an unstable equilibrium position (Fig. 4A) as an archetype of grasping an object with complex dynamics [47]. In a baseline condition, subjects squeezed a foam ball (Fig. 4B) as an archetype of grasping an object with simple dynamics. 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 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 with each condition prior to the experiment to master the control of each object. First, we contrasted activity when 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 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, activated regions in

the anterior lobule were near the primary fissure (lobules V/VI) and more anterior to the posterior superior fissure around which 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 regions related to 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 mechanisms for sensorimotor learning. Using positron emission tomography and a robot manipulandum that exerts force to subjects' hands during reaching movements, Shadmehr and Holcomb [48] investigated how 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.

Recently, a neuropsychological study [49] investigated the relationships between regions of atrophy in a large number of patients with cerebellar degeneration and their performance during adaptation to kinematic perturbation (visuomotor 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 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 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 [50, 51].

Modular organization of cerebellar internal models: common tools

We measured cerebellar activity of subjects using sixteen common tools (scissors, a hammer, chopsticks and so on) to investigate internal models for those tools [52]. Because it was impossible to create baseline conditions in which muscle activation was precisely matched with that during manipulation of each tool, we asked subjects to mentally imagine using the tools without actual hand movements. Subjects lied in supine position in an MR scanner and looked at their own hand and the tool through an arrangement of two mirrors. In an actual-use condition, subjects were asked to use one of the sixteen common tools along with an appropriate object (e.g., using scissors to cut a sheet of paper). In an imaginary-use condition, subjects were asked to imagine using a tool without making actual hand movements but while holding the tool. In a rest condition, 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 the 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., [53]). By contrast, activities observed mainly in the posterior lobule during the imaginary-use conditions may reflect internal models for use of the tools.

To characterize distributions of activity, we calculated t-value-weight centroids of activation for individual tools in both actual-use and imaginary-use conditions. Figure 4 shows the calculated centroids when subjects actually used individual tools (Fig. 4A) or when they imagined using the tools (Fig. 4B) 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 distribute more posteriorly and laterally than those in the actual-use condition. It was difficult to find how locations of the centroids are organized in the cerebellum but distribution of the centroids in the imaginary-use condition suggest that internal models contributing to 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 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 subjects learn a kinematic perturbation (visuomotor rotation), a dynamic perturbation (force field), and a combination of these perturbations [51]. When the subjects learned the combined transformation, reaching errors were 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 [54] also suggests the ability of the CNS to combine output signals from internal models. Subjects sufficiently learned to use 60º and 160º rotated joysticks, where the cursor appeared in a position rotated 60º or 160º around the center of the screen. Then we investigated brain activity when subjects learned to use a 110º rotated joystick (an intermediate angle between 60º and 160º). In the early and late stages of learning the 110º joystick, we measured cerebellar activity specific to the 60º, 110º or 160º joystick according to the same method we used when measuring 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 60º and 160º joysticks to cope with the novel 110° joystick in the early stage, while in the late stage an internal model for the 110º joystick had been acquired, and activity of internal models for 60º and 160º joysticks decreased due to the decreased necessity for these models. We investigated activated volumes in the lateral cerebellum separately for 60º, 110º and 160º conditions across subjects (Fig. 6). Consequently, volumes for both 60º and 160º conditions were larger than that for the 110º condition in the early stage, suggesting that internal models for 60º and 160º joysticks largely contribute to subjects' performance. However, the volumes for 60º and 160º conditions in the late stage became small in comparison to the initial stage, and the volume for the 110º 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 performance levels of subjects, which were measured by a tracking error, in the 60º and 160º conditions did not significantly change after the training for 110º condition from those before the training despite decreased activity for the 60º and 160º conditions. This may suggest that processing for the 60º and the 160º conditions became more effective and need smaller regions after 110º training. Such reorganization of internal models is necessary for effective use of limited volumes of the cerebellum but mechanisms for the reorganization are unknown and need further

studies.

Discussion

We comprehensively reviewed functional neuroimaging studies investigating how

internal models for tools are acquired in the cerebellum. First, we succeeded in

visualizing 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 changes in 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 multiplicity and modularity of

internal models from several aspects: differences in kinematic properties, whether

properties are kinematic or dynamic, and types of common tools used. We believe 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 behavioral 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 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 [48] or when a screen controlled by a computer program kinematically

alters visual feedback of hand position [55] or joystick position [56]. 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 internal models representing input-output properties of controlled objects are likely acquired.

Recent advances in structural imaging of the brain support a contribution of the cerebellum to dexterous use of tools. Using MRI and voxel-based morphometry, Quallo and colleagues [57] investigated changes in brain structure in Japanese macaque monkeys trained for six 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 activity related to kinematic internal models of new tools. Another structural imaging study found correlation between rate of learning the use of a new tool and white-matter microstructure in the human cerebellum: Della-Maggiore and colleagues [58] used diffusion-weighted MRI to estimate the fractional anisotropy (FA) reflecting 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 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 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 control of a tool to realize desired performance and the sensory consequences of that control play crucial roles in skillful use of tools. This is because 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 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 control of movements.

However, the above hypothesis about global networks contributing to skillful use of tools is mainly based on studies of ours and others investigating of correlation between behavioral and neuroimaging data. Such studies have limitations in

examination of 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., [59-61]). Future studies that can extract neural information simultaneously from multiple regions will enable us to elucidate the outlines of the brain network supporting skillful use of tools as well as the functional differences among the regions, and to examine validity of the above hypothesis.

Acknowledgements

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Figure legends

Figure 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 (MR) scanner (scanner is not drawn in the figure). 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 (small red circles) trajectories, whose vertical and horizontal components were the sum of sinusoids with different amplitude and frequency, and cursor (small open circles) trajectories in the screen coordinates (X, Y) for 1.5 s. Circles indicate positions of the target and cursor every 16.7 ms (60 Hz). Blue arrows indicate moving direction. (**C: lower panel**) A mouse trajectory in the hand coordinates (x, y) corresponding to the above cursor trajectory. Data from REF. [14].

Figure 2

(**A**) The upper panel shows tracking error (mean ± SD) averaged across subjects as a function of number of training sessions. The lower panels show the activation maps when activity in the baseline periods was subtracted from that in the test periods (test - baseline). (**B**) The upper panel indicates tracking error (mean + SD) in the error-equalized session (see main text). The upper lower shows the activation map when 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 change in activity (test - baseline) across training session averaged within regions enclosed by blue lines in Fig. 2B. The middle panel shows 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 Fig. 2A). 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 REF. [14] © (2000) Macmillan Magazines Ltd.

Figure 3

Cerebellar activity averaged across subjects in transverse sections in the order from the superior (top panels) to inferior (bottom panels) sections. Magenta and cyan regions were significantly activated when subjects manipulated a rotated mouse and velocity mouse, respectively, in comparison to when 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 REF. [44].

Figure 4

The objects chosen as archetypes of complex and simple dynamics are illustrated. Arrows indicate directions of forces generated by subjects. Figure modified, with

permission, from REF. [47] © (2007) Elsevier.

Figure 5

Distribution of t-value-weighted centroid of activation coordinates when subjects

actually used common tools (**A**) or when they imagined use of the tools (**B**). Centroids

are projected to transverse (upper panels) or coronal (lower panels) planes as indicated

by the left anatomical images. Subjects used 16 tools but one of the tools (saw) could

not evoke 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 REF. [52].

Figure 6

Volumes (across-subjects mean) in the cerebellar regions that were more activated when

subjects manipulated 60º, 110º or 160º rotated joystick than when subjects manipulated

normal joystick (error equalized). (**A**) Volumes measured in the initial stage of learning

how to use 110º joystick just after intensive training for use of 60º and 160º joysticks.

(**B**) Volumes measured in the late stage of learning to use 110º joystick. Diameter of

each circle is proportional to total activated volume. Threshold for activation was $t > 3.08$, $p < .05$ uncorrected for multiple comparisons. Data from REF. [54].
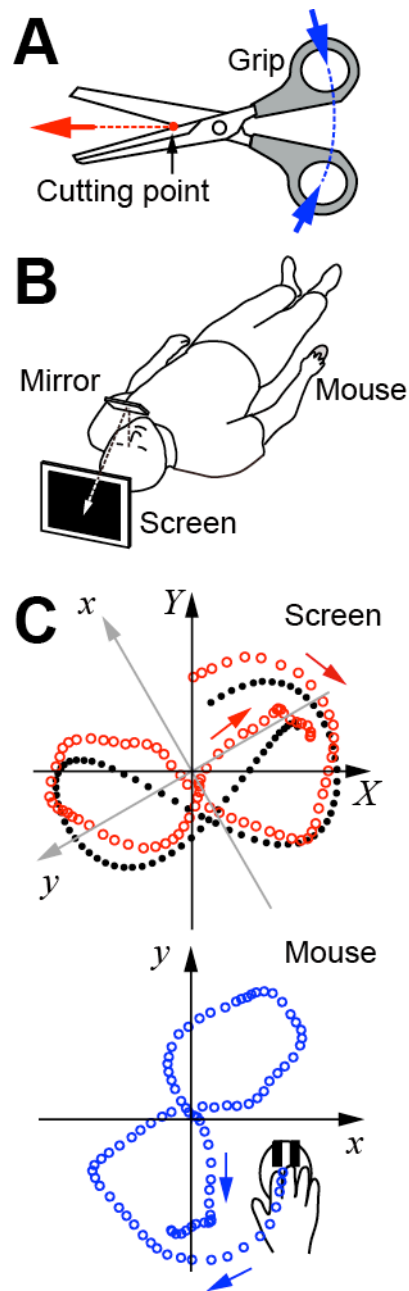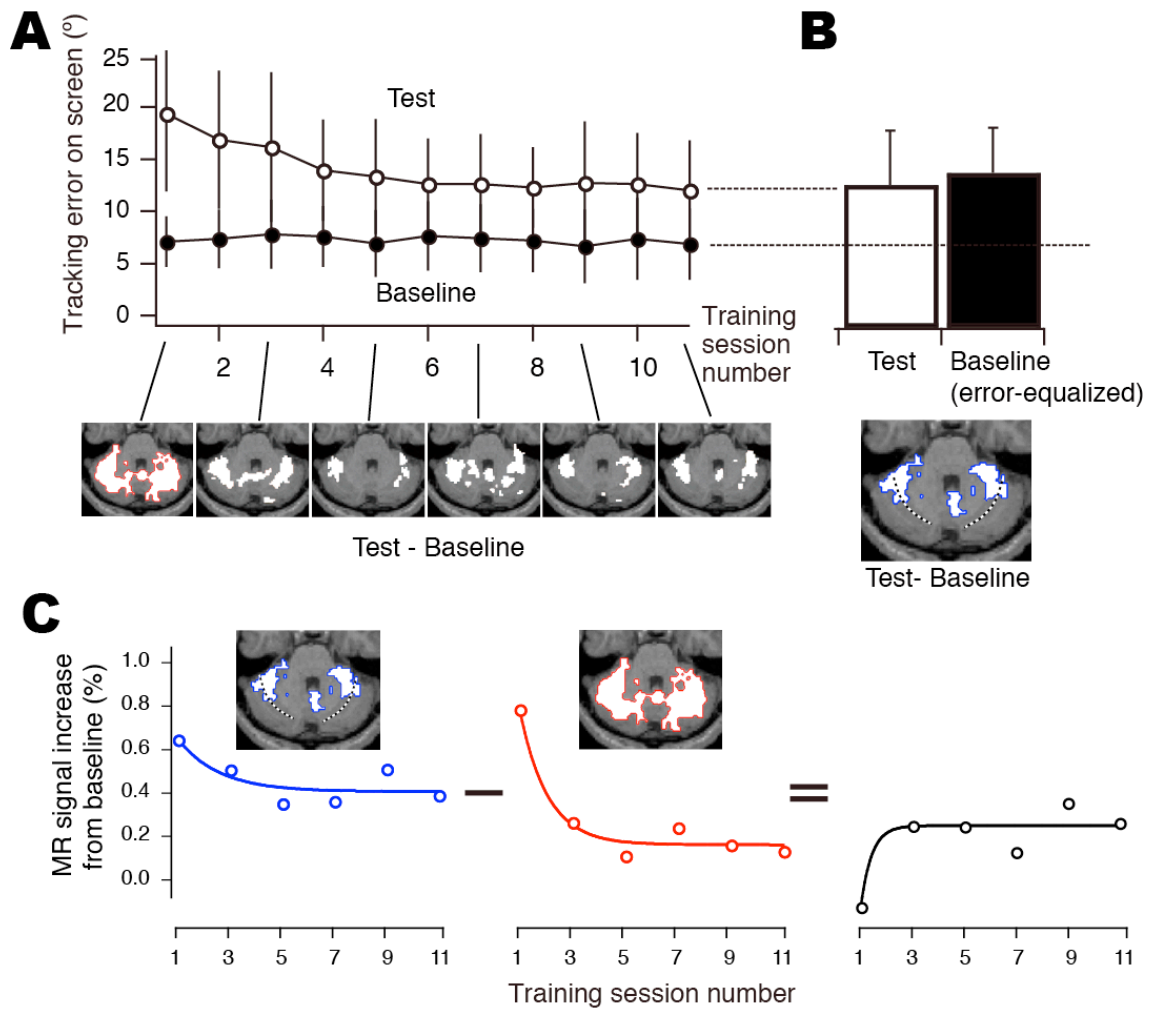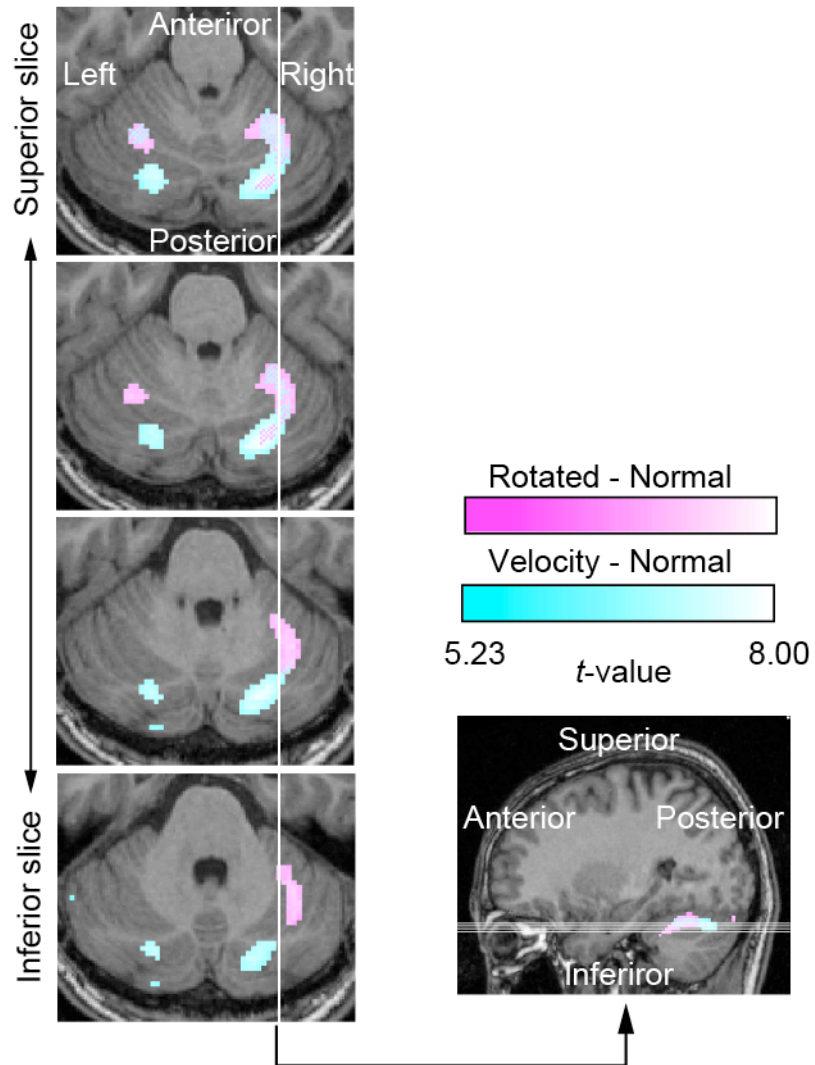
Figure 1

A
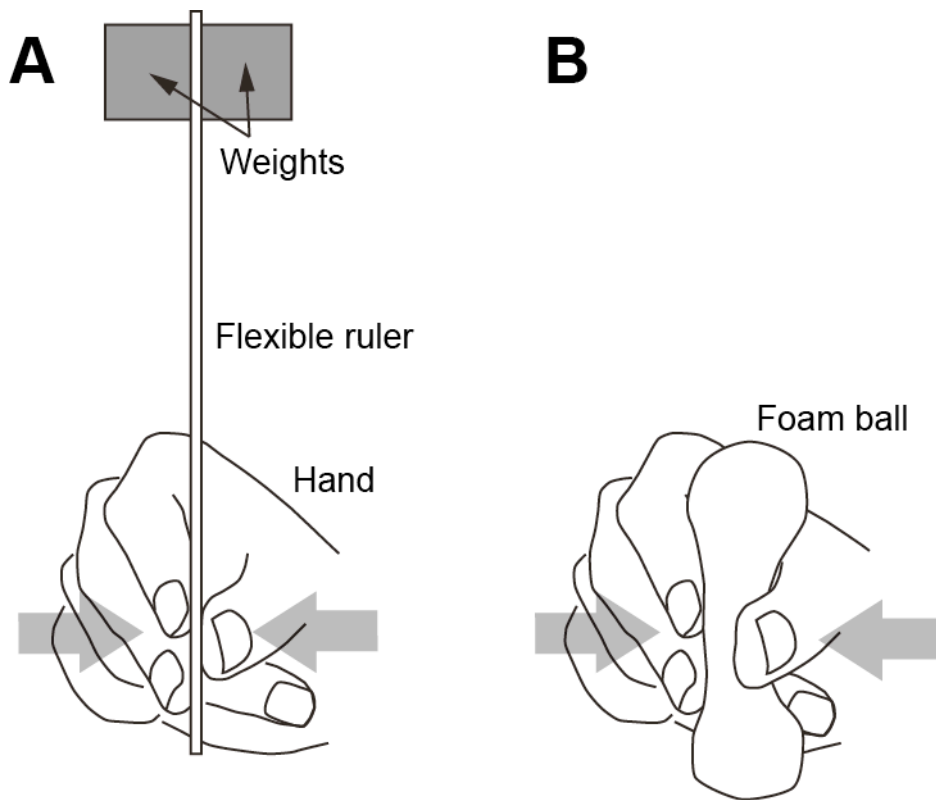
Tracking error on screen (°)

Test

Baseline

Training session number

Test - Baseline

B

Test   Baseline (error-equalized)

Test- Baseline

C

MR signal increase from baseline (%)

Training session number

Figure 2

Figure 3

A

Weights

Flexible ruler

Hand

B

Foam ball

5

Figure 4

Figure 5

A Initial stage

160 °
11.3 cm^3
60 °
7.5 cm^3
5.2 cm^3
110 °

Total: 24.0 cm^3

B Late stage

3.3 cm^3
9.3 cm^3
10.7 cm^3

Total: 23.3 cm^3

Figure 6