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Parallel neural networks for learning sequential procedures

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Recent studies have shown that multiple brain areas contribute to different stages and aspects of procedural learning. On the basis of a series of studies using a sequence-learning task with trial-and-error, we propose a hypothetical scheme in which a sequential procedure is acquired independently by two cortical systems, one using spatial coordinates and the other using motor coordinates. They are active preferentially in the early and late stages of learning, respectively. Both of the two systems are supported by loop circuits formed with the basal ganglia and the cerebellum, the former for reward-based evaluation and the latter for processing of timing. The proposed neural architecture would operate in a flexible manner to acquire and execute multiple sequential procedures.

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THERE ARE a variety of learned actions, such as lacing shoes, writing words with a pencil, riding a bicycle and using a computer that make our lives more efficient. When we learn a new action, we pay full attention to carrying it out; but after repeating it, the action becomes nearly automatic[1,2]. We can then concentrate on learning a new action while performing previously learned actions skilfully. Thus, as we learn to do a new action, a neural code or memory for carrying it out is created in our brain, which is generally called 'procedural memory', in that it encodes procedures, rather than facts[3]. Learned actions can then be combined in sequence to achieve a new goal. Accordingly, learning of sequential procedures can be regarded as a key element of voluntary

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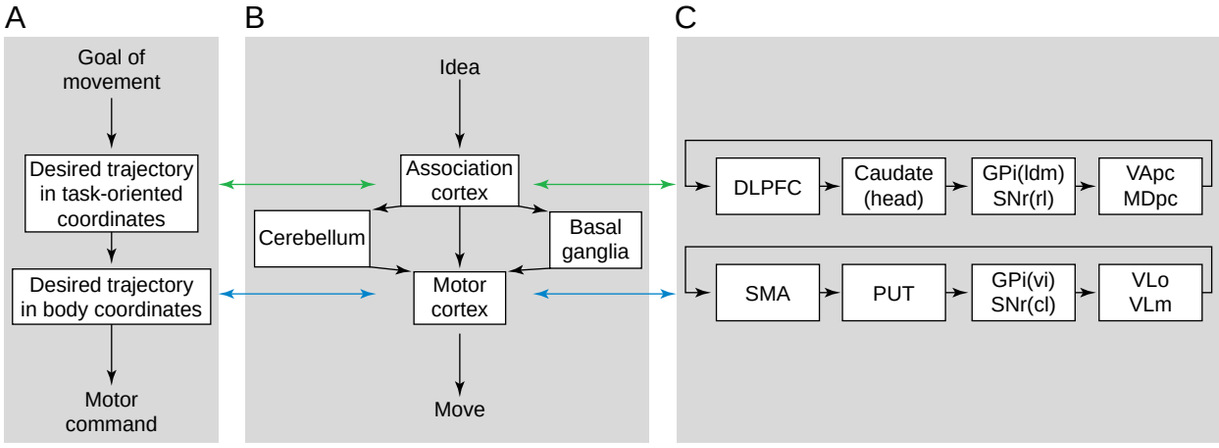

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Fig. 1. ***Schemes for motor control.*** *Only the parts of their schemes that are relevant to our arguments are shown. Green and blue arrows indicate two functional modules that are represented differently in the three schemes. Note that information is transmitted across the functional modules in* **(A)** *and* **(B)** *(serial processing), whereas it is processed separately in each module in* **(C)** *(parallel processing). Abbreviations: DLPFC, dorsolateral prefrontal cortex; GPi (ldm, vi), globus pallidus, internal segment (latero–dorso–medial part, ventro–inferior part); MDpc, nucleus medialis dorsalis, pars parvocellularis; PUT, putamen; SMA, supplementary motor area; SNr, substantia nigra, pars reticulata; VApc, nucleus ventralis anterior, pars parvocellularis; VLm, nucleus ventralis lateralis, pars medialis; VLo, nucleus ventralis lateralis, pars oralis.* (A) modified, with permission from Ref. 13, (B) modified, with permission from Ref. 10, and (C) modified, with permission, from Ref. 12.

behavior[4–6]. Furthermore, it has been suggested that procedural skill provides a basis for intelligent behaviors, such as logical thinking and language[7,8].

A number of studies have been carried out recently to elucidate the neural mechanism for procedural learning (see Ref. 9 and references therein). On the basis of these results, this article proposes a neural-network scheme for the acquisition, memory storage and execution of sequential procedures.

Previous concepts of motor control

Many neuroscientists have proposed hypothetical schemes for motor control[10–14], three of which are shown in Fig. 1. They can be classified into two groups, one stressing serial information processing and the other stressing parallel information processing. The former can be seen in the conceptual model of Kawato *et al.*[13] (Fig. 1A), which illustrates the sensorimotor processes that are minimally required for a simple movement, such as reaching. Here, the location of the target is first encoded by the visual system in eye-centered (retinotopic) coordinates. The spatial information must then be converted into information suitable for the motor system, in terms of kinematics and dynamics.

Behind this idea is an anatomical scheme by Allen and Tsukahara[10] (Fig. 1B). The association cortex and the motor cortex would subserve the two-stage sensorimotor processes shown in Fig. 1A. Although the scheme indicates the presence of collateral pathways (via cerebellum and basal ganglia), the information would flow essentially in a serial fashion.

The second type of scheme, which stresses parallel information processing, has been proposed by Alexander *et al.*[12] and is based on the anatomical relationships between the cerebral cortex and the basal ganglia (Fig. 1C). Here, the flow of information is separated among multiple closed-loop circuits; two such circuits are shown, corresponding to the two stages in sensorimotor transformation in Fig. 1A,B.

The serial sensorimotor process (Fig. 1A,B) is suitable for generating a simple movement, such as reaching. However, it requires a series of coordinate transformations that involve a large amount of computation. Especially for more-complex actions, it would be extremely demanding if the brain carried out the serial sensorimotor process precisely for every movement. We propose a new scheme in which the serial sensorimotor process is replaced gradually with parallel processes (such as those in Fig. 1C) as the subject learns a complex sequential procedure.

New concept of motor control and procedural learning

Our concept is illustrated in Fig. 2, in which we outline the process of learning a sequential procedure (Acts 1–3). Evidence supporting this concept is described in the following section and summarized in Boxes 1 and 2.

Initially, the serial sensorimotor process is executed in a discrete manner for each elementary action (vertical connections in Fig. 2A). As the subject repeats the actions in a fixed order, new connections are formed between the mechanisms for individual actions (Fig. 2B and C), thus enabling the subject to perform the actions sequentially without strictly relying on the serial sensorimotor processes for each action. A unique feature of our scheme is that there are two parallel connections to support the sequential procedure (horizontal connections in Fig. 2B and C). Each of these parallel processes operates in a single coordinate system (spatial or motor coordinates) to form the spatial and motor sequences, respectively, so that the cost for computation is minimized.

By comparing the schemes in Figs 1 and 2, we can speculate that the loop circuits comprising the cerebral cortex and the basal ganglia (Fig. 1C) are the neural correlates of the parallel processes shown in Fig. 2B,C. The spatial sequence process corresponds to the loop circuit comprising the association cortex (especially the prefrontal cortex) and the anterior portion of the basal ganglia (especially the head of the caudate), while the motor sequence process corresponds to the loop circuit comprising the premotor–motor cortex [especially the supplementary motor area (SMA)] and the middle portion of the basal ganglia (especially the putamen). Thus, each of the horizontal connections shown in Fig. 2 is included in a cortico–basal ganglia loop.

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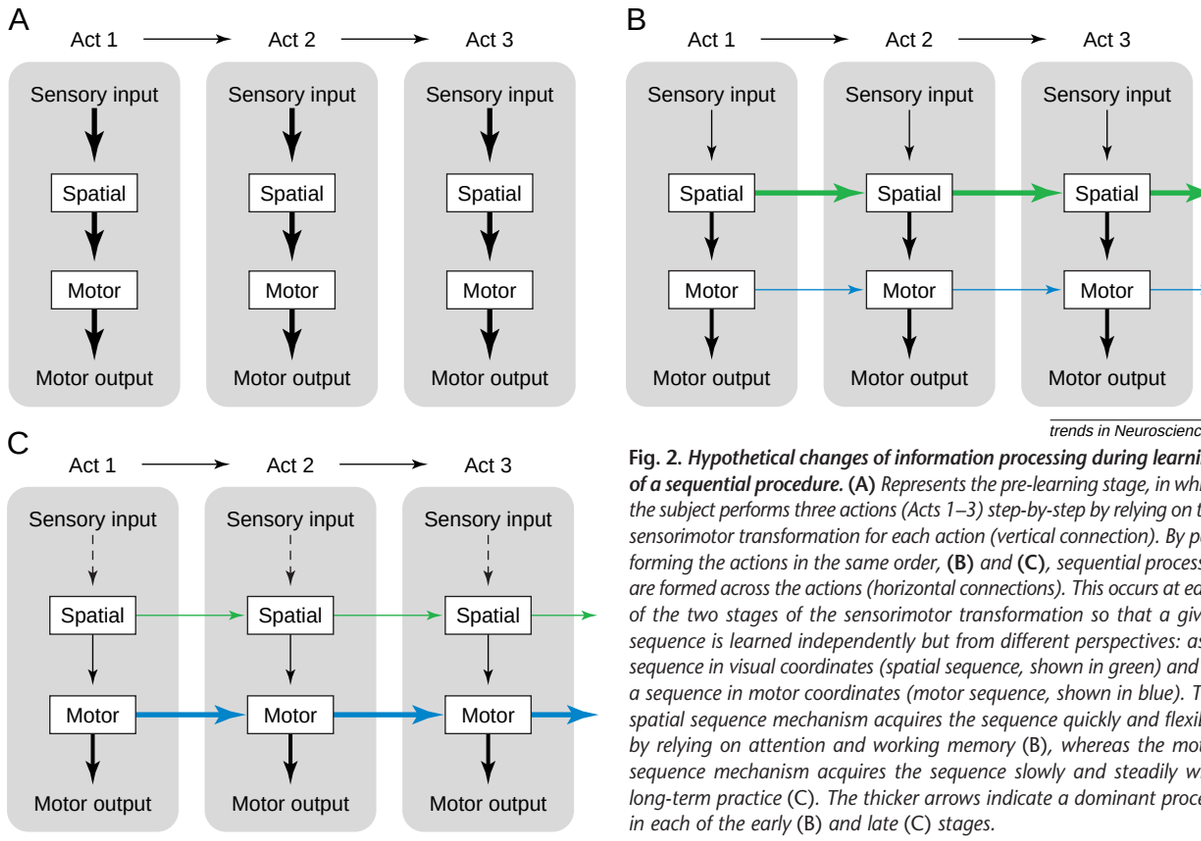

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Fig. 2. ***Hypothetical changes of information processing during learning of a sequential procedure.*** **(A)** *Represents the pre-learning stage, in which the subject performs three actions (Acts 1–3) step-by-step by relying on the sensorimotor transformation for each action (vertical connection). By performing the actions in the same order,* **(B)** *and* **(C)***, sequential processes are formed across the actions (horizontal connections). This occurs at each of the two stages of the sensorimotor transformation so that a given sequence is learned independently but from different perspectives: as a sequence in visual coordinates (spatial sequence, shown in green) and as a sequence in motor coordinates (motor sequence, shown in blue). The spatial sequence mechanism acquires the sequence quickly and flexibly by relying on attention and working memory* (B)*, whereas the motor sequence mechanism acquires the sequence slowly and steadily with long-term practice* (C)*. The thicker arrows indicate a dominant process in each of the early* (B) *and late* (C) *stages.*

Box 1. Behavioral experiments using the 2 × 5 task and brain areas implicated in the early and late stages of learning.

Learned procedure is effector-dependent: when the monkeys are asked to use the hand that has not been used for long-term practice for a given sequence, their performance becomes very poor[a]. However, this is not true for a newly learned sequence (M.K. Rand *et al.*, unpublished observations). These results suggest that the memory for a visuo–motor sequence, which is accessible to both the trained hand and the untrained hand in the early stage of learning, becomes largely inaccessible to the untrained hand in the late stage of learning.

The sequence, rather than the individual elements, is learned: when the order of component elements of a well-learned sequence is reversed, the performance becomes very poor, as if the monkeys are performing completely new sequences[a]. The result suggests that the monkeys acquired the memories for the whole sequences, rather than memories for individual elements separately. This was not true in the early learning stage (M.K. Rand *et al.*, unpublished observations).

Anticipatory movements emerge with long-term practice, which means the performance is much faster in the late learning stage[b].

Long-term retention of memory: the monkeys' performance of well-learned procedures, especially speed of performance, is maintained without further practice for a long time (for example, one year)[c,d].

To summarize, the early and late learning stages are characterized by dichotomies shown as 'classification' (Table I). Brain areas are grouped into three (Table II), relating to the early or late learning stage, and another (SMA, precuneus, IPS) judged to be intermediate.

TABLE I. Learning stages in 2 × 5 task and their classification

	Early	Late
Stage		
Specific to hand?	No	Yes
Specific to order?	No	Yes
Quick performance	No	Yes
Anticipatory movements?	No	Yes
Forget?	Yes	No
Classification	Declarative	Procedural
	Controlled	Automatic
	Explicit	Implicit
	Knowledge	Skill

TABLE II. Brain areas involved in early and late stages of learning

	Early	Late
Brain areas		
'Cerebral cortex'	Pre-SMA	SMA
	DLPFC	Precuneus
		IPS
'Basal ganglia'	Anterior striatum	Putamen
'Cerebellum'		Dentate nucleus

Abbreviations: DLPFC, dorsolateral prefrontal cortex; IPS, intraparietal sulcus region; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area.

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Box 2. Physiological experiments using the 2 × 5 task with animal subjects

Table I shows data from several animal studies. These studies examined neural activity, hand preference and inactivation in several regions of the brain during acquisition of the 2 × 5 task.

Medial frontal cortex SMA and pre-SMA: single unit studies

We found that many neurons became active preferentially while the monkeys were trying to learn new sequences[a]. Such 'new-preferring' neurons were more prevalent in the pre-SMA (supplementary motor area) than in the SMA. The activation of new sequences was unrelated to the side of the hand performing the task: it occurred when either the contralateral or ipsilateral hand was used.

TABLE I. Summary of animal experiments

	Area	
Medial frontal cortex	**pre-SMA**	**SMA**
Neural activity	New > learned	New = learned
Inactivation (number of errors)	New only, strong	New only, weak
Hand preference	Bilateral	Contralateral and bilateral
Striatum	**Anterior striatum**	**Posterior putamen**
Neural activity	New > learned	Learned > new
Inactivation (number of errors)	New > learned	Learned only
Cerebellar nuclei	**Dentate nucleus**	**Other nuclei**
Inactivation (number of errors)	Learned only	No effect
Hand preference	Ipsilateral	Ipsilateral

Abbreviations: pre-SMA, pre-supplementary motor area; SMA, supplementary motor area.

Reversible inactivation

We inactivated different portions of the pre-SMA and SMA locally and reversibly by injecting a small amount of muscimol unilaterally[b]. After a muscimol injection, the number of errors (sequence errors) increased for new sequences, but not for learned sequences. This effect was stronger after pre-SMA injections than SMA injections. The effect was present when either the contralateral or ipsilateral hand was used, particularly after the pre-SMA injections.

Anterior and middle basal ganglia

The inactivation of the anterior striatum led to substantial increases in the number of errors for new sequences and smaller, but significant, increases for learned sequences. The inactivation of the middle putamen led to a significant increase in the number of errors for learned sequences, but not for new sequences[c]. Consistent with this observation, neurons in the anterior striatum tended to be more active for new sequences, whereas neurons in the middle putamen tended to be more active for learned sequences[d].

Cerebellar nuclei

When the dorsal or central part of the dentate nucleus was inactivated, the number of errors increased significantly for learned sequences, but not for new sequences; inactivation of the lateral or ventral region of the dentate nucleus, interpositus nucleus or fastigial nucleus produced no effect on learning or memory[e]. Furthermore, the effect was present only when the hand ipsilateral to the injection was used.

References

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e **Lu, X., Hikosaka, O. and Miyachi, S.** (1998) *J. Neurophysiol.* 79, 2245–2254

We postulate further that: (1) the acquisition usually occurs earlier in the spatial sequence process (green connections in Fig. 2B,C) than in the motor sequence process (blue connections in Fig. 2B,C); (2) the information, once acquired, is usually temporary in the spatial sequence process, but is nearly permanent in the motor sequence process; and (3) the acquired information (memory) is accessible to any body part (effector-nonspecific) in the spatial sequence process, but is specific to the body part used for practice (effector-specific) in the motor sequence process. This conceptual scheme has been derived on the basis of a series of experiments with monkeys and humans.

Experimental evidence obtained from trial-and-error learning of a sequence

We used a sequential button-press task with trial-and-error processes ('2 × 5 task' for monkeys and '2 × 0 task' for humans)[15] (Fig. 3). Monkeys learned a set of sequences repeatedly until they could perform the sequences highly skilfully. This allowed us to study the neural mechanisms that are involved in memory storage and retrieval processes. The 2 × 5 task also allowed us to study the neural mechanisms that are involved in the learning of new procedures because we could always generate a new sequence for the monkey to learn. There are other types of sequence-learning task[16–19]. For example, a serial reaction-time task[16] requires the subject to respond to targets one at a time as they are presented in a fixed sequence (of which the subject might be unaware). Although they have not been studied during learning, neural correlates of learned sensorimotor sequences have been studied extensively[20,21].

In behavioral experiments with monkeys, we have found that sequence learning is composed of at least two stages[22]: an early (short-term) stage and a late (long-term) stage. Furthermore, we found clear changes in learned behavior depending on these learning stages (Box 1). These results provided evidence for the hypothesis shown in Fig. 2: that memory becomes specific to the trained hand only in the late learning stage, indicating that the motor sequence process is effector-specific. The memory becomes specific to the order of sequence in the late stage, indicating that the serial sensorimotor processes for individual actions (vertical connections in Fig. 2) are gradually replaced by parallel sequential processes (horizontal connections in Fig. 2). The performance becomes quick, with anticipatory movements, owing to the establishment of sequential processes, especially for the motor sequence. The memory for a given sequence becomes robust and stable in the late learning stage, indicating that the motor sequence process acquires the sequence slowly but nearly permanently.

In physiological experiments with monkeys, we found that multiple brain areas contribute to the early and late learning stages differentially (Box 2). Thus, the pre-SMA and the anterior part of the striatum contribute to the learning of new sequences (early learning stage), while the middle part of the putamen and the cerebellar dentate nucleus contribute to the performance of well-learned sequences (late learning stage).

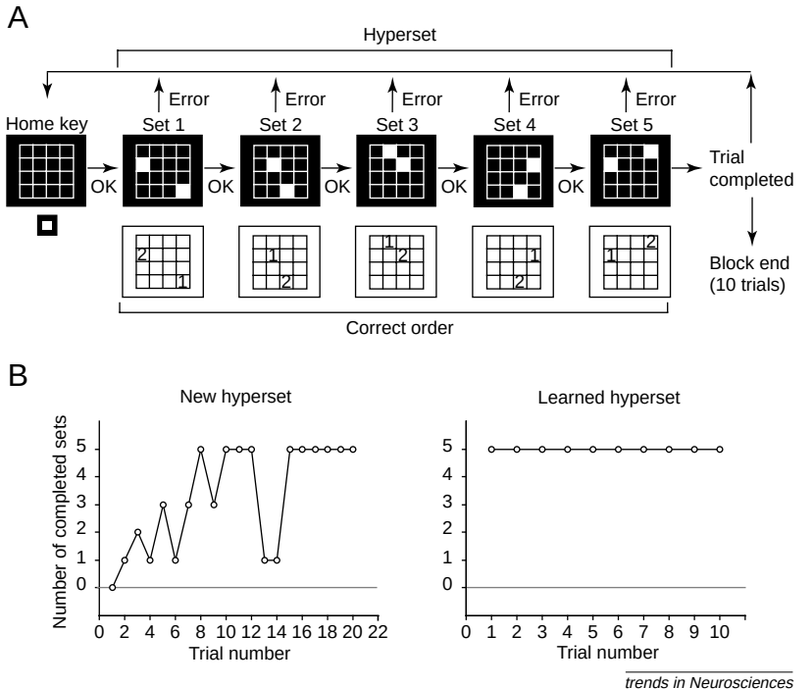

Fig. 3. ***Procedure of 2 × 5 visuo–motor sequence task.*** **(A)** *In front of the subject (monkey) is a panel on which 16 LED buttons are arranged in a 4 × 4 matrix. When the monkey presses a home key beneath the panel, two of the 16 LED buttons are illuminated simultaneously. The monkey has to press them in a correct (predetermined) order, which he has to find out by trial-and-error. This is called 'set'. If successful, the LED buttons turn off sequentially and another pair of LEDs, a second set, is illuminated, which the monkey has to press again in a correct order. A total of five sets are presented in a fixed order for completion of a trial, which we call 'hyperset'. If the monkey presses a wrong button, the trial is aborted and the monkey has to start again from the home key as a new trial. Each hyperset is presented repeatedly in a block until 10–20 successful trials have been performed. A different hyperset is then used for the next block.* **(B)** *An example of a block of practice trials using a new hyperset (left) and a learned hyperset (right). The numbers of completed sets (y-axis) are shown for consecutive trials (x-axis). In the learned hyperset, the monkey completed the block (ten successful trials) with no error. In the new hyperset, the same monkey made errors initially at the first or second set, but the number of completed sets increased gradually.*

We applied virtually the same paradigm to human subjects in functional MRI experiments[23]. We found stage-dependent activation in cortical regions: there was a global transition of activity from the two frontal regions (dorso–lateral prefrontal cortex and pre-SMA) to the two parietal regions (precuneus and intraparietal sulcus region). Note, however, that both the frontal and parietal activations were observed within the early learning stage. On the basis of the results of physiological experiments, together with the conceptual scheme shown in Fig. 2, we now propose a more-detailed scheme for procedural learning (Fig. 4B), together with its anatomical correlates (Fig. 4A). The scheme might also account for the results obtained with other behavioral tasks, such as the serial reaction-time task[16].

Neural correlates of the spatial and motor sequence mechanisms

Our scheme (Fig. 4B) is similar to that proposed by Allen and Tsukahara[10], with subtle but important modifications: the connections between the cerebral cortical areas, and the basal ganglia and the cerebellum are now bi-directional, thus forming loop circuits. These loop circuits can be classified into two groups, one using spatial coordinates and the other using motor coordinates. In this article, we refer only to eye- or head-centered coordinates for spatial representation, although there are other forms of spatial representation (such as body part-centered or world-centered coordinates)[24,25]. For motor representation, we consider joint-angle coordinates[26], although other coordinate systems are possible. The subdivision of the basal ganglia and cerebellum in relation to the association and motor cortices is roughly consistent with anatomical findings[27,28]. The memory for a sequential procedure would then be distributed in these loop circuits, which would be the neural correlates of the horizontal connections shown conceptually in Fig. 2.

We emphasize that the way in which this system works changes, depending on the stage of learning. Before learning, the correct performance relies on the serial sensorimotor information flow from the association cortices to the motor cortices (which corresponds to the vertical connections in Fig. 1 and 2) through the premotor cortex (as a translator; see below). In the early stage of learning, the procedure is acquired predominantly (not exclusively) as a spatial sequence by the loop circuit comprising the association (prefrontal and parietal) cortices[23,29–31] and the anterior basal ganglia[32,33]. After long-term practice, the procedure is now acquired predominantly as a motor sequence, depending on the motor cortices[17,34,35] and the middle basal ganglia[36]. The functional differentiation of the anterior and mid-posterior striatum is supported further by human imaging studies[37]. Theoretical schemes have been proposed recently to explain how the cortico–basal ganglia circuits might encode or produce sequences[38–40].

The cerebellum would also contribute to the early and late stages of learning. Our data[41] suggest that the dorsal part of the dentate nucleus contributes to the late stage of learning. This subregion is connected with the anterior lobe of the cerebellum and the primary motor cortex (M1; Ref. 42). In addition, human imaging studies have shown activation of the cerebellum in the early stage of learning[43,44], although it is unclear whether this function is localized to the cerebellum.

Similar hypotheses, with multiple stages of learning to which different brain regions contribute, have been proposed by other investigators[37,45–48].

Communication between the parallel mechanisms

We have suggested that a sequential procedure is acquired independently by the two different sequence mechanisms (spatial sequence mechanism and motor sequence mechanism). However, in order to acquire and execute a sequence adequately and efficiently, these mechanisms must cooperate or compete with each other. In these processes, the premotor area and the pre-SMA might have important roles.

Translation: role of the premotor area

At the beginning of learning, information in visual coordinates must be translated into information in motor coordinates for each elementary action (Fig. 2A). It is assumed that such coordinate transformation occurs somewhere in the connections between the parietal cortex and the premotor cortex[24,25,49]. The translation mechanism is also important in promoting interactive learning between the two sequence mechanisms. For example, if the spatial sequence mechanism has acquired a sequence, it can guide the motor sequence mechanism to learn the same sequence (Fig. 2B).

Coordinator: role of the pre-SMA

Given their independent nature, the spatial and motor sequence mechanisms might generate inconsistent signals. Such a disagreement would happen frequently in

the early stage of learning, in which one of the sequence mechanisms, especially the motor sequence mechanism, might generate incorrect signals. It is then desirable to rely on the spatial sequence mechanism by suppressing the output of the motor sequence mechanism (while allowing it to learn the sequence). This might be a major function of the pre-SMA.

This hypothesis is based on two pieces of experimental evidence. First, it has been shown that pre-SMA neurons tend to become active during the early stage of learning[23,31] and their inactivation leads to deficits in the learning of new sequences[50]. The pre-SMA is activated when the motor output must be determined each time by an incoming sensory input[51] – the situation that occurs at the beginning of learning (Fig. 2A). Second, Tanji and his colleagues have shown that pre-SMA neurons are activated particularly when subjects encounter a new context that requires motor plans to be updated[52,53]. The scheme shown in Fig. 4B is also supported anatomically: the pre-SMA receives inputs predominantly from the dorso-lateral prefrontal cortex (part of the association cortices in Fig. 4B)[54,55] and projects to the SMA (part of the motor cortices in Fig. 4B)[56].

Motivational value is attached by the basal ganglia

Using evidence from recent studies[57–60], we propose that the basal ganglia have a key role in motivating procedural learning based on reward. Specifically, a cortico–striatal input is reinforced if it is associated with dopaminergic input, which signals the upcoming reward[57,60]. The reinforced signal is used either to select the ongoing behavior or to be retained as a memory.

Our experimental data[36] and model[40] suggest that reinforcement might occur independently in separate loop circuits for the spatial sequence mechanism (via the anterior striatum) and for the motor sequence mechanism (via the middle striatum). This is probably the key mechanism that makes the model system extremely robust and adaptable because these sequence mechanisms can learn a sequence independently and, therefore, either one of them can take the initiative, depending on the behavioral context (as described below).

Quick and accurate performance might be achieved by the cerebellum

Skilful performance after long-term practice involves quick and coordinated movements of multiple joints and requires fine-tuning of movement parameters (such as velocity, force and timing). Our data suggest that such a learned motor skill depends on the loop circuit formed by the motor cortices and the anterior cerebellum (including the dorsal dentate nucleus[41]). This is consistent with a common view on the function of the cerebellum[61].

According to our scheme (Box 1; Fig. 2), individual movements that comprise a well-learned action are carried out independently by the mechanisms specific to the body parts. It is then crucial to organize these movements with correct timing. We speculate that the cerebellum (specifically its anterior lobe) performs this role by sending the trigger signal to the motor cortices.

Previous studies support this hypothesis. The acquisition of a motor skill is usually associated with the acquisition of timing or rhythm[5,62,63]. Motor symptoms following cerebellar lesions (such as dysmetria) could be attributed, at least partly, to the incorrectly timed activation of agonist and antagonist muscles[64,65]. Patients with cerebellar disorders are poor at recognizing or reproducing this timing[66].

On the other hand, the posterior cerebellum might adjust the timing of a motor output in response to a sensory input. Indeed, the posterior lobe of the human cerebellum is activated in relation to the adjustment of timing[67] or perception of time duration[68]. These processes might be particularly important in the early stages of learning.

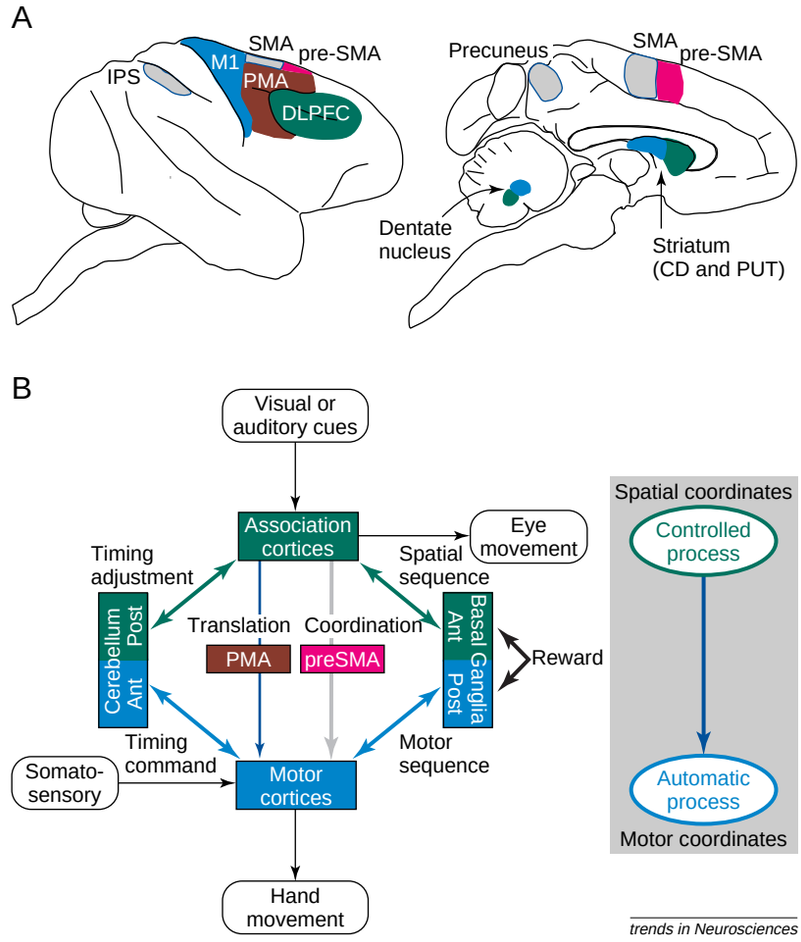

Fig. 4. ***Neural correlates of the parallel learning mechanisms.*** **(A)** *Brain areas related to learning of the 2 × 5 task. They are indicated in different colors that correspond to the scheme in* (B). *Gray areas (SMA, IPS, precuneus) are not readily classified into the functional groups.* **(B)** *The association cortices (particularly prefrontal cortex) and the anterior part of the basal ganglia comprise a loop circuit that operates as a spatial sequence mechanism (shown in green); the motor cortices (including M1 and SMA) and the middle part of the basal ganglia comprise a loop circuit that operates as a motor sequence mechanism (shown in blue). In addition, the anterior and posterior parts of the cerebellum contribute to the motor and spatial sequence mechanisms by forming loop circuits with the motor and association cortices; their functions in the control of timing (indicated here) are still speculative. The spatial and motor mechanisms are capable of operating independently, acquiring and reproducing a given sequence in different coordinates. In addition, they have their own input and output: visual and auditory inputs and oculomotor outputs for the association cortices; somatosensory inputs and skeletomotor outputs for the motor cortices. The interaction between the two learning mechanisms is made possible in two ways: (1) by translation from the spatial coordinates to the motor coordinates by the premotor area (PMA); (2) by coordination or switching by the pre-SMA. Abbreviations: CD, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; IPS, intra-parietal sulcus area; M1, primary motor cortex; pre-SMA, presupplementary motor area; PUT, putamen; SMA, supplementary motor area.*

Functional advantage of the parallel learning mechanisms

Flexible ways to acquire new sequences

We have suggested that procedural learning proceeds as a gradual transition from a spatial sequence to a motor

sequence. However, because these sequences are organized in a parallel fashion, either of these mechanisms could take the initiative to learn a sequential procedure. If explicit trial-and-error processes are not involved (as in a serial reaction-time task[15]), learning might be initiated by the motor sequence mechanism, rather implicitly[69]. The motor sequence mechanism could then guide the spatial sequence mechanism[48]. The subject would start learning without awareness, but become aware of the procedure at some point in learning.

In short, our model network is highly adaptable, such that learning of a sequential procedure can be initiated by any kind of sequential information, either spatial or motor. The learned sequential information in one dimension (for example, spatial) will eventually spread to the other dimensions (for example, motor). In the case of spatial-to-motor spread, elementary knowledge will be compiled into a skill; in the case of motor-to-spatial spread, knowledge might emerge out of habitual acts.

Concurrent execution and implementation of sequential information

Our network model is particularly robust in the execution of learned sequences, owing to the cooperative relationships between different dimensions. For example, even if the motor sequence mechanism is disrupted somehow, so that it is unable to reproduce the information on the next element, the correct information will be provided by the spatial sequence mechanism, which is working concurrently; the reverse relationship is probably also true.

Emergence of complex behavior

The deployment of the spatial sequence mechanism at the beginning of learning requires attention and working memory. Once a sequence is acquired as a motor sequence with long-term practice, it can be carried out nearly automatically, without attention or working memory. We believe, as Schneider *et al*. suggested[70], that this initiates the emergence of complex behavior. Each of the acquired motor sequences can also be used as an element of a more-complex sequence. Thus, memories for multiple sequences should be orchestrated together by the conscious process in order to produce a complex behavior.

Concluding remarks

On the basis of behavioral and physiological experiments on trained monkeys and humans, we propose a scheme for the learning of sequential procedures. According to our scheme, the sensorimotor transformations required for individual actions (serial process) are replaced gradually with information on the sequence of actions (parallel process). Obviously, our scheme is incomplete and oversimplified, but it will certainly provoke further questions, such as those suggested below, which might be answered in future studies.

Where and how are the sequences implemented as memories?

Our scheme suggests that the memory for a given sequence is distributed in the brain in different forms (for example, spatial and motor representations). Activity of individual neurons during the performance of learned tasks has provided important clues to this question. However, we still do not know how different the memories implemented in different brain areas, such as the SMA, M1 and parietal cortical areas, are.

What are the relationships between different forms of memory?

It is thought that different types of memory have different neural correlates; for example, the prefrontal cortex for working memory[71], the hippocampal regions for declarative memory[72] and the basal ganglia for procedural memory[73]. Our scheme proposes that these memory systems cooperate to acquire and execute learned procedures. In order to prove this hypothesis, however, we also need to examine brain areas that are related to other memory systems, particularly declarative memory.

Can we simulate the learning behavior based on our scheme?

The hypothesis presented in this article is still a conceptual scheme and it remains uncertain whether our scheme operates as we have described. In order to test the validity of the scheme, we need to formulate a computational model based on this scheme and simulate the experimental results. We have obtained preliminary results for such model simulation[74].

These questions are focused on the interaction between different functional modules in the brain. We think that this is the key to the further understanding of the learning mechanisms or brain functions in general.

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AIDS and the brain: is there a chemokine connection?

Richard J. Miller and Olimpia Meucci

Many HIV-1-positive individuals suffer from a variety of neurological problems known collectively as the HIV-1-related cognitive–motor complex. However, the molecular mechanisms that underlie HIV-1-induced neuropathology are unclear. They might include a combination of indirect effects, which result from the release of neurotoxins from activated astrocytes and microglia, and the direct effects of HIV-1-related proteins, such as gp120, on neurons. As the interaction of gp120 with immune cells has been shown to require the participation of chemokine receptors, this article explores the possibility that such receptors participate in the events underlying HIV-1-induced neuropathology. It is now clear that many types of cell in the brain possess chemokine receptors, including microglia, glia and neurons, and the interaction of gp120 with neuronal chemokine receptors initiates apoptotic death of neurons *in vitro*. Such effects might be modified by the actions of chemokines that act at these same receptors. However, the importance of this direct interaction with neurons *in vivo* and its relevance in the pathogenesis of AIDS-related dementia still needs to be established. Furthermore, the existence of chemokine receptors on neurons suggests that chemokines might regulate neuronal functions physiologically.

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A VERY LARGE PERCENTAGE of patients suffering from AIDS also suffer from neurological complications. Many of these problems can be attributed to HIV-1 infection *per se* rather than being associated with subsequent opportunistic infections or malignancies. The precise characteristics of these neurological problems depend on several factors, which include the severity of the disease, the age of the patient, etc.[1,2] AIDS-related neurological problems have been variously described as the 'AIDS dementia syndrome' or the 'HIV-1 related cognitive–motor complex[3].' These names provide a reasonable description of the types of changes involved, which include subcortical dementia, memory deficits and motor problems. Neuropsychological testing and imaging techniques can sometimes detect neurological deficits in HIV-1-positive individuals, even prior to the full development of AIDS (Ref. 4). Complications of the CNS are particularly notable in children who are infected with HIV-1 perinatally and exhibit rapidly progressing disease. Up to 80% of such children display neurological symptoms, including slow development, motor deficits and impaired brain growth[5].

Neuropathological and imaging studies have demonstrated a variety of complex changes in the brain that

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