REVIEW

K.M. Turner et al. – Synaptic neurotransmission

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. We can then concentrate on learning a new action while performing previously learned actions skillfully. Thus, as we learn to do a new action, a neural code or memory for carrying it out is created in 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. The proposed neural architecture would operate in a flexible manner to acquire and execute multiple sequential procedures.


Parallel neural networks for learning sequential procedures

Okihide Hikosaka, Hiroyuki Nakahara, Miya K. Rand, Katsuyuki Sakai, Xiaofeng Lu, Kae Nakamura, Shigehiro Miyachi and Kenji Doya

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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behavior. Furthermore, it has been suggested that procedural skill provides a basis for intelligent behavior, such as logical thinking and language.

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, 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.11 (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 Tsukahara12 (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.13 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.

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.

**A**. Initial learning

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

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<thead>
<tr>
<th>TABLE I. Learning stages in the 2 × 5 task and their classification</th>
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<td>Stage</td>
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<td>Specific to hand?</td>
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<td>Specific to order?</td>
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<td>Quick performance</td>
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<td>Anticipatory movements?</td>
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<td>Forget?</td>
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<th>TABLE II. Brain areas involved in early and late stages of learning</th>
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<td>Brain areas</td>
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<td>Basal ganglia</td>
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<td>Cerebellum</td>
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References

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.
We postulate further that: (1) the acquisition usually occurred earlier in the sequential 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 (effectort-nonspecific) in the motor sequence process. This conceptual scheme has been derived on the basis of a series of specific learning stages differentially (Box 2). Thus, the pre-SMA and the anterior part of the striatum contribute to the early and late stages of the motor sequence process. The memory for a given behavior depending on these learning stages becomes specific to the body part used for practice (effectort-specific) in the motor sequence process. This conceptual scheme has been derived on the basis of a series of experimental observations 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) (Fig. 3). Monkeys learned a set of sequences repeatedly until they could perform the sequences highly skillfully. 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 task14,15. For example, a serial reaction-time task16 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 early sensory-motor sequences have been studied extensively16,17. In behavioral experiments with monkeys, we have found that sequence learning is composed of at least two stages19,20: 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 effectort-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).
We applied virtually the same paradigm to human subjects in functional MRI experiments\textsuperscript{25}. We found stage-dependent activation in cortical regions; there was a global transition of activity from the two frontal regions (dorsolateral 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\textsuperscript{26}.

**Neural correlates of the spatial and motor sequence mechanisms**

Our scheme (Fig. 4B) is similar to that proposed by Allen and Tsukahara\textsuperscript{27}, with subtle but important modifications: the connections between the cerebral cortical areas, and the basal ganglia and the cerebellum are now bidirectional, 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\textsuperscript{28}). For motor representation, we consider joint-angle coordinates\textsuperscript{29}, 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\textsuperscript{30,31}. 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 cortex to the motor cortices (which corresponds to the vertical connections in Fig. 1 and 2) through the pre-motor 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\textsuperscript{32} and the anterior basal ganglia\textsuperscript{33,34}. After long-term practice, the procedure is now acquired predominantly as a motor sequence, depending on the motor cortices\textsuperscript{33,34} and the middle basal ganglia\textsuperscript{35}. The functional differentiation of the anterior and mid-posterior striatum is supported further by human imaging studies\textsuperscript{36}.

**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 of the motor loop**

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\textsuperscript{36,37}. 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).
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 learning8,9, and their inactivation leads to deficits in the learning of new sequences10. The pre-SMA is activated when the motor output must be determined each time by an incoming sensory input11—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 updated12,13. 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)14,15 and projects to the SMA (part of the motor cortices in Fig. 4B)16.

Motivational value is attached by the basal ganglia

Using evidence from recent studies16–20, we propose that the basal ganglia have a key role in motivating procedural learning based on reward. Specifically, a corticostriatal input is reinforced if it is associated with dopaminergic input, which signals the upcoming reward21,22. The reinforced signal is used either to select the ongoing behavior or to be retained as a memory. Our experimental data23 and model24 suggest that reinforcement might occur independently in separate loop circuits involving the basal ganglia. The pre-SMA is active during procedural learning of the 2 × 3 task. They are indicated in different colors that correspond to the scheme in (B). Gray areas (SMA, IPS, pre-SMA) are not readily classified into the functional groups.

Quick and accurate performance might be achieved by the cerebellum

Skilled 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)25,26. This is consistent with a common view on the function of the cerebellum27.

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 rhythm28,29. Motor symptoms following cerebellar lesions (such as dysmetria) could be attributed, at least partly, to the incorrectly timed activation of agonist and antagonist muscles30,31. Patients with cerebellar disorders are poor at recognizing or reproducing this timing. 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 timing32 or perception of time duration33. These processes might be particularly important in the early stages of learning.

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, since these sequences are orga-
nized in a parallel fashion, either of these mechanisms
could be the initial step to learn a sequential procedure.
If explicit trial-and-error processes are not involved (as
in a serial reaction-time task19), learning might be ini-
tiated by the motor sequence mechanism, rather implicit-
ly20. The motor sequence mechanism could then guide
the spatial sequence mechanism27. 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 spatial and sequential information in one di-
(5) (for example, spatial) will eventually spread to
the other dimensions (for example, motor). In the case
of spatial and motor-spatial cortical areas, it will
be compiled into a skill; in the case of motor-to-spatial
spread, knowledge might emerge out of habitual acts.
Emergence of complex behavior
The development of the spatial sequence mechanism
at the beginning of learning requires attention and work-
ning 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. suggested22, 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 experi-
ments on trained monkeys and humans, we propose
a scheme for the learning of sequential procedures.
According to our scheme, the sensorimotor transfor-
mations 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 pro-
voke 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
actions is thought to be an important clue to this question.
However, we still do not know how the mem-
ories implemented in different brain areas, such as the
SMA, M1 and parietal cortical areas, are.

sequence execution and implementation of sequential information
Our network model is particularly robust in the ex-
ception of learned sequences, owing to the cooperative
relationships between different dimensions. For exam-
ple, even if the motor sequence mechanism is disrupted
sooner, so that it is unable to reproduce the infor-
mation 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.

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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, 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, as the HIV-1-related cognitive–motor complex, such as the 'AIDS dementia syndrome' or the HIV-1 related cognitive–motor complex. Therefore, it is clear that many types of cell in the brain possess chemokine receptors, which might regulate neuronal functions physiologically. However, the importance of this direct interaction 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. AIDS-related neurological problems have been variously described as the ‘AIDS dementia syndrome’ or the HIV-1-related cognitive–motor complex. 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.

Neuropsychological and imaging studies have demonstrated a variety of complex changes in the brain that 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 chemokines that act at these same receptors. However, the importance of this direct interaction 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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