PROCEDURAL LEARNING IN THE MONKEY

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SUMMARY

We devised a behavioral paradigm (sequential button press task) for monkeys in order to test the hypothesis that the basal ganglia are crucial for procedural learning. Upon pressing of a home key, two of 16 (4x4) LED buttons (called 'set') were illuminated and the monkey had to press them in a predetermined order which he had to find by trial and error. A total of 5 sets (called 'hyperset') were presented in a fixed order for completion of a trial.

To examine whether the monkey learned the hyperset as a whole or remembered the individual sets, we generated hypersets that were the same as the learned hypersets except that the sequence of the sets was reversed. The performance of these 'reversed hypersets' was much worse than for the original learned hypersets, indicating that the monkey learned the whole hyperset.

To examine whether the memory was specific to the hand used for learning, we had the monkey use one side of the hand throughout the learning, and switched the hand to the unexperienced side. The performance was worse than for learned hypersets but better than for new hypersets, suggesting that the memory was partially specific to the hand used for learning.

Basal ganglia control innate and learned behaviors

In the last decade we have learned so much detail of the anatomy and physiology of the cerebral cortex and the basal ganglia. It is now clear that the mutual interplay between these structures is so intimate that any kinds of neural signals found in the cerebral cortex are almost invariably found in the basal ganglia (Alexander and Crutcher 1990). They include movement-related activity, sensory responses, and preparatory activity. Many of them are dependent on behavioral contexts, some contingent on sensory guided behavior and others selective for memory-guided behavior. In the end what do we know? How different are the cerebral cortex and the basal ganglia? They may be hierarchically different? What would it mean?

We feel that we need to gain a new perspective to understand the real functions of both the basal ganglia and the cerebral cortex. Let us start with a simplified scheme indicating that the basal ganglia have two kinds of target: one is the brainstem motor region and the other is thalamus (Hikosaka 1994). These two outputs are conceptually different. The brainstem projection would select motor signals by inhibiting or disinhibiting the target neurons, as typically revealed for the oculomotor system(Hikosaka and Wurtz 1989) . The thalamic projection would exert a similar selective effect which however is further processed in the vast area of the cerebral cortex (Deniau and Chevalier 1985; Nambu et al. 1991).

The two kinds of basal ganglia outputs may have different functions. With the projections to the midbrain/pontine motor regions the basal ganglia can select innate actions. These midbrain areas have crucial control over a variety of movements, such as locomotion, vocalization, mastication, respiration, vomiting, eye blinks, which are thought to be genetically determined in a species-specific manner (Garcia-Rill 1986; Holstege 1991) .

The other target of the basal ganglia is the thalamus which is mutually connected with frontal cortical areas (Hoover and Strick 1993; Tokuno et al. 1992). In contrast to the midbrain projections, this pathway would control learned movements (Aizawa et al. 1991; Gemba and Sasaki 1984; Jenkins et al.; Seitz et al. 1990; Mitz et al. 1991). However, this function should be much more complex,

requiring the mutual interaction with the cerebral cortex. Obviously, the learned movements must be learned and the memory must be created. But we do not know how and where learning takes place and how and where the memory is created.

This is what we would like to know. This is what we believe is crucial for understanding the functions of the cerebral cortex and the basal ganglia. First we would like to propose a hypothesis on the neural mechanism of procedural learning, and then propose a behavioral method to test the hypothesis.

How basal ganglia might contribute to the procedure formation?

Fig. 1 shows our hypothesis on the mechanism of procedural learning (Hikosaka 1994). Suppose there are neurons A and B in the cerebral cortex which send outputs independently. After mutual

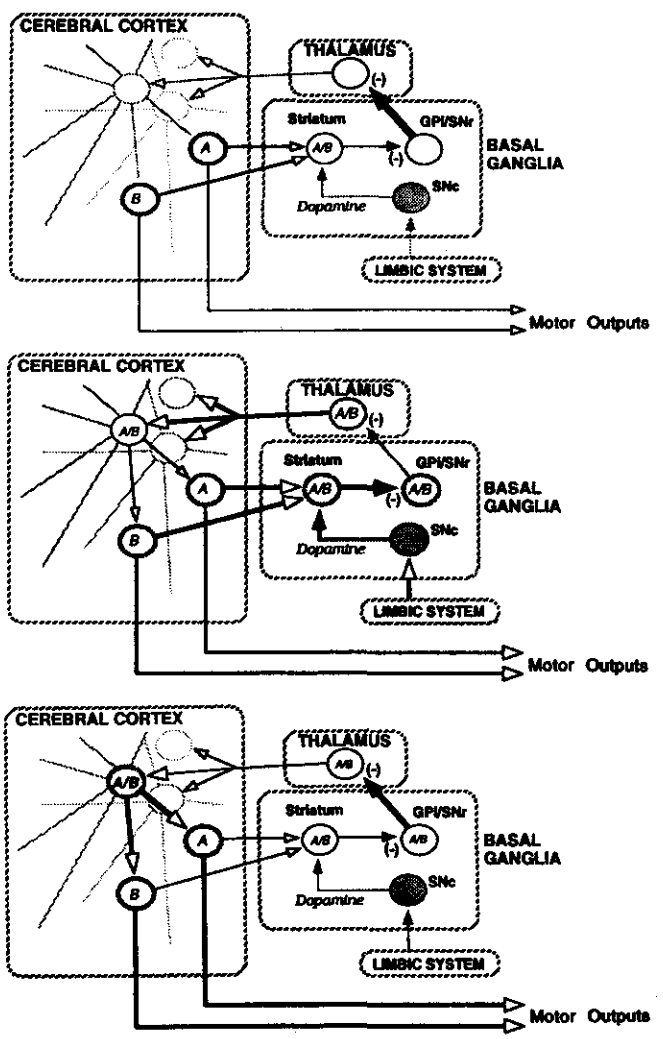

Fig. 1. Hypothetical process of procedural learning.

interplay with the basal ganglia emerge a new set of cortical neurons that control both A and B. The process would proceed as follows.

It is known that there is an extensive convergence in cortico-striatal connections (Parthasarathy et al. 1992). Thus it is conceivable that the signals A and B converge onto single neurons in the striatum (Fig. 1, top). The neurons may at first not respond, because the striatum is probably one of the quietest areas in the brain(Hikosaka et al.1989). But if the combination of A & B is repeated and if the action produces reward, the combined signals may be enhanced and become able to activate the striatal neurons. The reward value might be transmitted by dopaminergic neurons based on the limbic inputs (Romo and Schultz 1990; Ljungberg et al. 1992), and might be used to modify the strength of the cortico-striatal synapses (Gerfen et al. 1990; Garcia- Munoz et al. 1991; Calabresi et al. 1992).

Once the combined signal is put through the gateway of the basal ganglia, it would allow some of the thalamo-cortical circuits to be active by means of disinhibition (Fig. 1, center). Note that the cortical neurons are free to be active only under the condition of A/B. In other words, when the new set of cortical neurons become active, both the neuron A and B also are likely to be active. This is exactly the situation in which these synapses become potentiated which have been just fortuitous and scanty. If the attempt of A/B is repeated, these cortical neurons would acquire strong connections with the output neurons (Fig. 1, bottom).

In short, the basal ganglia would retain the memory of behavioral procedures during learning. The cerebral cortex would create procedural memory based on such a neural template. An important feature is that the basal ganglia can not only combine different cortical signals but also test the validity of the combination through their outputs and the returning evaluating signals.

The basal ganglia system is a dominant structure in the lower species of animals. It would act to select motor programs based on the reward-contingent inputs from the limbic system. The motor programs are still innate and thus their patterns are largely fixed. Such animals must learn, however, to associate particular environmental signals with particular motor programs. The attempted behavioral sets are first formed in the basal ganglia, and the cerebral cortex learns to create procedural memory based on the template. As the animal's behavior becomes more complex, the motor program itself must also be learned. Here again, the basal ganglia may play an instructive role so that motor memory is created efficiently in the motor cortical areas and the cerebellum.

Requirements for the behavioral paradigm

Having extended our thought to this end, we are aware that there is no firm evidence to support this hypothesis, although we have been greatly encouraged by the recent elegant studies by Kimura, Schultz, Carabresi (this volume) and other groups in addition to clinical neuropsychological evidence. We have felt a great urge to develop an experimental paradigm to test our hypothesis which can be applied to monkeys and humans.

There are at least two important questions we have to ask. First, where are procedural/motor memories stored? Second, which brain areas are necessary for learning? These mechanisms may well be different and the responsible brain regions may well be separate, as our hypothesis predicts. More specific questions may be raised for each issue. Are the memories distributed or localized? Is there a hierarchical organization for the memory storage? Are there different stages in learning to which different brain regions contribute? In what aspect are they necessary?

The experimental paradigm to solve these problems must be easy to learn so that a new task can be tested while a single cell is recorded or a brain region is blocked reversibly. The paradigm must be able to provide many different sets sets or combinations so that we can examine the neural mechanisms necessary for different stages of learning.

Given these requirements, we can have specific predictions. If the instrumental mechanism is destroyed or shut down, the learning of new tasks will become deficient while the performance of learned tasks will remain intact. If the storage mechanism is destroyed, the performance of learned tasks will become deficient while the learning of new tasks will remain intact.

Procedure of 2x5 task

To investigate the acquisition process of procedural learning, we trained two monkeys to perform a sequential button press task (Rand et al.). As shown in Fig. 2, 16 LED buttons were arranged 4x4. When the monkey pressed a home key, two of the 16 LEDs were illuminated simultaneously. The monkey had to press the illuminated buttons in a correct order which he had to find by trial and error. If successful, another pair of LEDs, which we call 'set', were illuminated which the monkey had to press again in a predetermined order. A total of 5 sets were presented in a fixed order for completion of a trial, which we call 'hyperset'. An error at any set aborted the trial and a new trial was started over from the first set. So we call this task '2x5 task'.

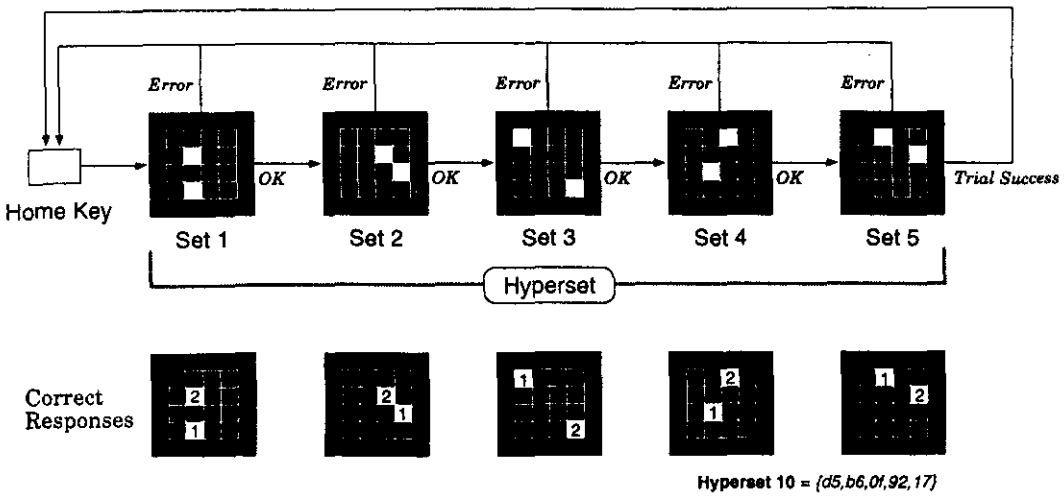

Fig. 2. Procedure of 2x5 task.

The same hyperset was used in a block of experiment which was terminated when the monkey completed 20 successful trials. If the hyperset was new or not well-learned, the monkey's performance looked hopeless but gradually stepped up until the fifth set. We gave the monkey liquid reward at each successful set and the amount of the reward was increased toward the final set.

A major advantage of the 2x5 task is that new hypersets can be generated practically as many as possible. Since the number of possible combinations for a set is ${}_{16}P_2$, the number of possible combinations for a hyperset is $({}_{16}P_2)^5$, which amounts to about 7.96×10^{11}, an astronomical value. To create a new hyperset, we had a computer generate ten sequential hexadecimal numbers; there have been no identical hypersets among a total of more than 1000 hypersets used for the two monkeys. On everyday experiment the monkey experienced about 20 to 30 hypersets; for example, 22 learned hypersets and 4 new hypersets.

Process of learning

As the monkey experienced a hyperset many times, the number of errors decreased gradually and the speed of performance became faster. The learning proceeded as follows. On the very first day the monkey failed at the first or second set for the initial several trials. The whole 5 sets were completed thereafter but only occasionally, but the rate of success became increased gradually. By the time the monkey completed 20 successful trials, the rate of success had become much higher than the chance level (1/32), indicating that learning occurred. The time spent in this process

was only about 5 min. On day 3, the monkey failed at the initial several trials, but the performance became nearly complete after trial 10 as if the memory was retrieved. On day 30, he failed only twice before completing 20 successful trials. The performance time was defined as the time between the offset of the home key and the completion of the 5th set. It was initially about 5 sec per trial but decreased to around 3.5 sec, and continued to decrease after day 60.

To evaluate the progress of learning across days, we set a criterion to 10 successful trials and determined the number of trials to reach the criterion for individual blocks of experiment, a value which will be used to assess the procedural, rather than motor, aspect of learning. Another measure we used to evaluate learning was a performance time - time spent for completion of a trial - which will be used to assess the motor, rather than procedural, aspect of learning.

How learning proceeded over the days of learning is shown in Fig. 3 for hyperset 60 using the two parameters: the number of trials to criterion (A) and the total performance time (B). The number of trials to criterion decreased rapidly over the first few days and more gradually afterwards until about day 30, approaching the minimum

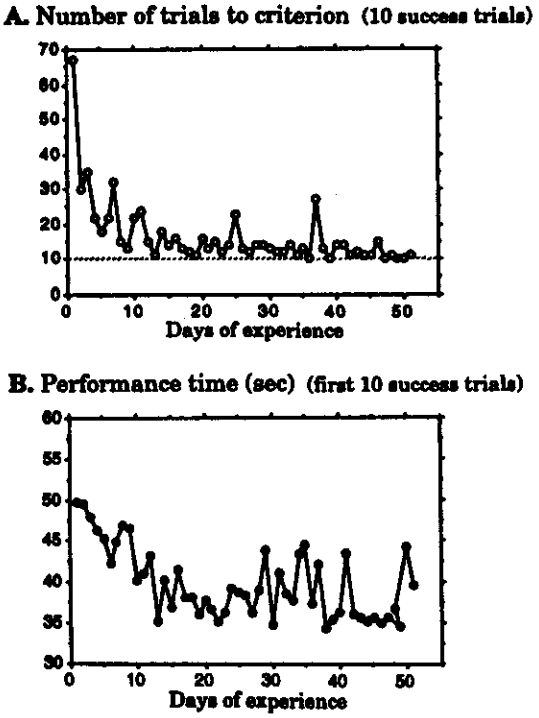

Fig. 3. Learning of procedure and speed across days of experience. The procedural learning is measured by the number of trials to criterion (10 successful trials) (A). The speed of performance is measured by the total performance time for the initial 10 successful trials (B). The data were obtained for hyperset 60 (monkey PI)

value of 10. The total performance time decreased more gradually and kept on shortening even after day 30.

It should be emphasized that the learning took place for each hyperset with similar time courses. During the course of the learning on 2x5 task, new hypersets were introduced at different stages, some of which were chosen for further extensive learning. The results showed that learning took place in a similar manner for each hyperset despite the different stages of monkey's experience. This was the case for the learning of the procedure and speed.

We have to mention, however, that the performance of new hypersets has changed as the monkey has become accustomed to the 2x5 task. Initially the monkey would spend more than 100 trials before the 10 trial success, but after more than 100 days of experience the number of trials is usually between 20 and 60. This result indicates that learning proceeds in at least 2 levels, one specific to motor sequence and the other non-specific but perhaps paradigm-specific.

Is the memory procedural or declarative?

We have assumed that what the monkeys have learned is procedural or motor memory rather than declarative memory. But is it really true? Doesn't the monkey merely remember the 1st LED out of 2 for each set, as in the object discrimination learning? If so, the memory we are pursuing might be declarative in nature. If, on the other hand, the memory is really a procedural one, we would expect that the memory exists for a whole hyperset rather than individual sets.

In order to differentiate between these possibilities, we generated hypersets which were the same as the learned hypersets

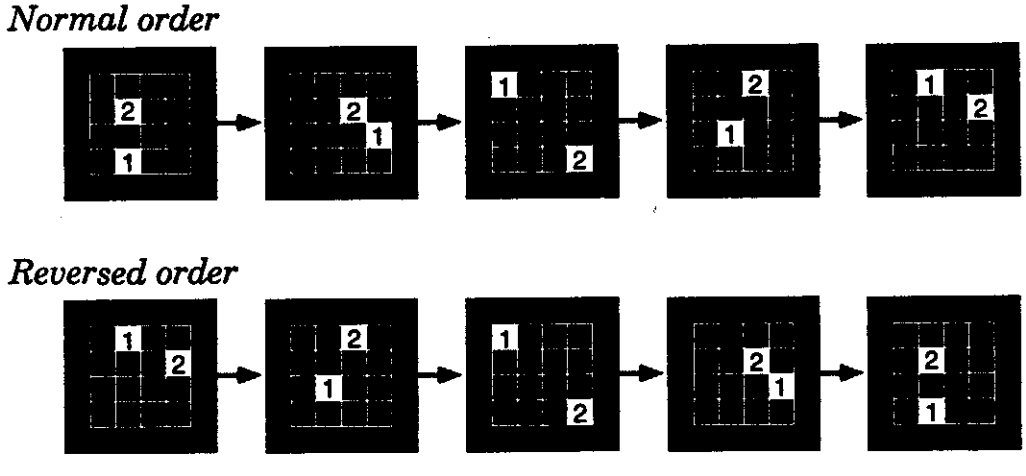

Fig. 4. Procedure for the inter-set reversal experiment.

except that the sequence of the sets were reversed; the order of button press within a set was made the same (Fig. 4).

If the individual sets are learned, the reversed hypersets should be all familiar and the performance should be no worse than the original learned ones. On the other hand, if the whole sequence is learned, the reversed hypersets should be regarded as new hypersets and the performance should be much worse than the original learned ones.

We selected 6 learned hypersets and tested their reversal. The number of trials to criterion was close to 10 (minimum value) before the reversal [mean: 13.4 (monkey PI), 13.2 (monkey BO)], indicating that the hypersets had been overtrained. The performance on the reversed experiments were clearly worse [mean: 43.2 (monkey PI), 36.4 (monkey BO)]; the number of trials reaching as many as 70 trials. The difference was highly significant in both monkeys (paired t-test, $p < 0.001$). A similar result was obtained for the performance time per trial. Compared with the pre-reversal experiments [mean: 4.2 sec (monkey PI), 4.1 sec (mokey BO)], the performance time became significantly longer after the reversal [mean: 5.2 sec (monkey PI), 5.7 sec (mokey BO)] (paired t-test, $p < 0.0001$).

We then compared the performance in the reversed hypersets with that in all new hypersets and all learned hypersets. In both monkeys the number of trials to criterion in the reversed conditions was significantly higher than that in the learned conditions (unpaired t-test, $p < 0.0001$), but was not significantly different from that in the new conditions (unpaired t-test, $p > 0.05$). Likewise, the total performance time in the reversed conditions was significantly longer than that in the learned conditions (unpaired t-test, $p < 0.0001$), but was not significantly different from that in the new condition (unpaired t-test, $p > 0.05$).

These results clearly showed that the stored memory was sequential as a whole, not concerned much with component sequences. It is interesting and rather counter-intuitive that the memory of intra-set sequence had no beneficial effect when the order of the sets was reversed.

Is the procedural memory transferred to the other hand?

This question is important if we think about where the memory is in the brain. If we learn a task using the left hand, will the memory be stored on the right hemisphere or on both hemispheres? If the memory is on the right side, is it transferred to the left side when we use the right hand at the time of execution? If

the memory resides on both hemispheres, how are the two sides coordinated?

With such questions in mind, we had the monkeys use one side of the hand for each learned hyperset; for example, the learned hypersets #7, 9, 11 were for the right hand while #8, 10, 12 were for the left hand. We then selected some of such learned hypersets and changed the hand to use to see how the performance changed. Conceptually these are the same learned hypersets, but from the standpoint of the hand they were completely new.

We found that the performance was certainly worse when the opposite hand was used, but not much. The number of trials to criterion when the opposite hand was used [mean: 21.6 (monkey PI), 29.9 (monkey BO)] was larger than when the default hand was used [mean: 12.7 (monkey PI), 13.7 (monkey BO)] (paired t-test, $p < 0.01$), but significantly smaller than for the new hypersets [mean: 46.7 (monkey PI), 71.6 (monkey BO)] (unpaired t-test, $p < 0.05$). The performance time for the opposite hand experiments was also between the learned hypersets and the new or reversed hypersets.

These results suggest that the memory can be transferred such that the mechanism for the unexperienced hand can have access to the memory, although the transfer was incomplete. Our result does not tell the physiological nature of the memory transfer, but it raises further questions and hypotheses which, we believe, can be tested experimentally.

Implication for physiological studies

Which brain areas are necessary for learning? Where and how are the memories stored? These important and unsolved questions are now testable by using the 2x5 task owing to its unique features: (1) it can produce a close-to-infinite number of procedural variations; (2) it is relatively easy to learn; (3) it has a hierarchical organization. We shall make some comments for each of them in the following.

First, by using the 2x5 task we can provide a new procedure (hyperset) under different experimental situations. A useful application would be a brain lesion or a blockade of local brain functions. If a brain region critical for the process of learning is inactivated, the learning of new hypersets would be disrupted. If the region where the memory is stored is inactivated, the performance of learned hypersets would be disrupted. The questions can be answered only if we can test, at the same period, both new procedures and learned procedures; this is the situation already provided by the 2x5 task. As another experimental manipulation,

we would be able to record single cell activities while the animal is learning new hypersets and while he is performing learned hypersets. Neurons that are critical for the learning process, for example, might become active while the animal is performing new hypersets, but not learned hypersets.

Second, the 2x5 task is easy to learn once its principle has been learned. For each set the monkey was asked to choose one target out of two and by correctly doing so he was rewarded, yet in the end he was led to perform a complex sequence of button press movements to complete 5 consecutive sets (hyperset). That the monkey in fact acquired the sequence as a whole, not for individual sets, was demonstrated by the set-reversal experiment. We had the impression that the monkeys are always motivated to perform the 2x5 task. The reason for this might be the steady growth nature of the 2x5 task: it was highly likely that they were able to obtain more reward as they continued to perform more trials especially when the hyperset was a new one. Such an easy and attractive nature of the 2x5 task would make the 2x5 task applicable widely to both animal and human studies. It might be expected, for example, that the animal continues to be motivated even when the neural mechanism for learning is disrupted by an experimental blockade or lesion; otherwise, any behavioral effects following such a manipulation would be confounded by the possible lack of motivation.

Using the 2x5 task we are now conducting physiological experiments to test the hypothesis which we proposed at the outset of this article.

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