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SEQUENTIAL ORGANIZATION OF MULTIPLE MOVEMENTS: Involvement of Cortical Motor Areas

Jun Tanji
Department of Physiology, Tohoku University School of Medicine, Sendai 980, Japan, and The Core Research for Evolutional Science and Technology Program, Kawaguchi 332-0012, Japan; e-mail: tanjij@mail.cc.tohoku.ac.jp

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■ **Abstract** Much of our normal behavior depends on the sequential execution of multiphased movements, or the execution of multiple movements arranged in a correct temporal order. This article deals with the issue of motor selection to arrange multiple movements in an appropriate temporal order, rather than the issue of constructing spatio-temporal structures in a single action. Planning, generating, and controlling the sequential motor behavior involves multiple cortical and subcortical neural structures. Studies on human subjects and nonhuman primates, however, have revealed that the medial motor areas in the frontal cortex and the basal ganglia play particularly important roles in the temporal sequencing of multiple movements. Cellular activity observed in the supplementary and presupplementary motor areas while performing specifically designed motor tasks suggests the way in which these areas take part in constructing the time structure for the sequential execution of multiple movements.

INTRODUCTION

In performing motor tasks, in order to attain our objective we usually need to execute more than one movement. Multiple single movements must be linked in a variety of spatial and temporal configurations for purposeful motor behavior. Thus, the generation and control of a sequence of movements is of crucial importance in many aspects of our life (Rosenbaum 1991). Lashley (1951) called the problem of coordinating constituent actions into organized sequential temporal patterns the "action syntax" problem. This article reviews current knowledge of how cortical structures are involved in arranging the voluntary limb movements of primates in a variety of temporal structures; it does not deal with more automated motor

behavior, such as occurs in locomotion, respiration, or mastication. Needless to say, the performance of complex motor actions, such as throwing a ball or swinging a tennis racket, requires sequential motor control. Although the issues of motor coordination and combining movement segments into a unified single action are of great interest (Soechting & Flanders 1992, Mussa-Ivaldi 1999), I do not go into that aspect of neural mechanisms. Rather, in this paper, I focus on the issue of selecting appropriate movements sequentially in a purposeful manner. At the end of this review, I propose a hypothesis to explain the cortical mechanism for sequencing multiple movements in temporal order.

CNS STRUCTURES INVOLVED

Overview

Although multiple cortical and subcortical structures are doubtlessly involved in planning, generating, and controlling sequential motor behavior, each area appears to be involved selectively in different aspects of sequential motor control. The primary motor cortex, known to be active during the execution (Evarts 1981) and preparation of movements (Tanji & Evarts 1976), appears to increase its activity when subjects perform sequential movements (Shibasaki et al 1993, Karni et al 1995, Catalan et al 1998). This increase in activity can be explained largely in terms of enhanced demand for signals specifying activation and suppression of motor apparatus to determine multiple motor parameters (Kettner et al 1996a), or additional requirements for preparatory processes (Kettner et al 1996b). A putative role of the primary motor cortex in some cognitive aspects may, in part, influence this activity (Georgopoulos 2000).

The cerebellum, which is essential for motor coordination as well as adaptive and predictive motor control (Ito 1984), is inevitably involved in programming and executing sequential movements. It is not yet known, however, whether the cerebellar activation observed during performance of sequential motor tasks (Seitz & Roland 1992, Doyon et al 1998) indicates its extensive involvement in coordinating or stabilizing movements (Thach et al 1992) or whether it suggests possible cerebellar involvement in more cognitive aspects of motor control (Middleton & Strick 1998, Imamizu et al 2000). The involvement of the basal ganglia in sequential motor tasks should also be considered (Middleton & Strick 2000) and is discussed in later sections.

On the other hand, posterior parietal areas, which have been implicated in visuospatial guidance of movements (Sakata et al 1995, Jeannerod et al 1995, Batista et al 1999), are active during sequential motor tasks (Catalan et al 1998, Grafton et al 1998). Because sequential motor tasks call for particularly elaborate spatial control of limb movements or spatial patterning of actions, it is understandable that enhanced parietal activation would follow. The premotor cortex is also thought to be involved in spatial guidance of movements (di Pellegrino & Wise

1993, Kurata 1994, Rizzolatti et al 1998, Binkofski et al 1999b), and this is likely to be a dominant factor causing activation of the premotor cortex while subjects perform sequential movements (Catalan et al 1998, Harrington et al 2000). The role of premotor cortex in temporal ordering of multiple movements has not been studied precisely under behavioral conditions minimizing spatial factors, although an interesting observation of premotor neurons during preparation for sequential movements was made (Kettner et al 1996b). Which areas are of particular importance in temporal, rather than spatial, sequencing? The following sections deal with this issue.

Involvement of Cortical Areas in Temporal Organization of Movements

Clinical Reports By the 1930s, it was known that lesions in the frontal "premotor cortex" could impair the serial organization of movements without causing problems in performing single movements or producing defects in spatial motor control. Luria (cf Luria 1966) explicitly described disturbances in organizing movements in correct temporal sequences in patients with lesions in the "parasagittal division of the premotor cortex." A decade later, Laplane et al (1977) reported that patients with circumscribed ablations of the supplementary motor area (SMA), as defined by Penfield & Welch (1951), had a deficiency in performing alternating serial movements with both hands. Subsequently, a number of clinical reports have hinted at the involvement of the SMA in temporal sequencing of limb movements and speech (for review, see Goldberg 1985). In a systematic functional analysis of a patient with an SMA lesion, Dick et al (1986) reported a deficit in programming sequential limb movements. More recently, Halsband et al (1993) reported that patients with lesions in the SMA (and adjacent areas) had poor temporal control of finger movements. For oculomotor controlling regions, Pierrot-Deseilligny et al (1995) reported that patients with lesions in the supplementary eye field (located anterolateral to the SMA) were poor at performing sequential saccades, particularly in the absence of visual guidance. These reports all point to the importance of medial motor areas in the temporal sequencing of motor behavior.

There are few reports of involvement of premotor areas in the lateral hemisphere in temporal sequencing of motor behavior. This may be because of a paucity of clinical cases with circumscribed lesions limited to the lateral premotor cortex, or it may suggest that the lateral premotor cortex is not crucial to temporal organization.

The involvement of the prefrontal cortex in motor sequencing is well known (Kolb & Milner 1981, Kimura 1982). In temporal organization, however, the involvement of the prefrontal cortex is primarily in the aspect of structuring general patterns of behavior, making use of purposeful processing of perception and memory (Goldman-Rakic 1996, Shallice & Burgess 1996, Fuster 1997). The timekeeping function of the prefrontal cortex covers a whole range of behavioral aspects and is beyond the scope of this review.

Lesion Studies in Subhuman Primates Only a small number of lesion studies have specifically looked for the involvement of particular areas of the brain in sequential motor performance. Brinkman (1984) made the first detailed report of the effects of lesions in the SMA on the motor sequence. Preoperatively, monkeys removed bait from slots in a Perspex plate in a systematic manner, proceeding from one slot to the next. Postoperatively, the systematic sequence for bait retrieval was lost. Passingham and his coworkers compared the effects of lesioning the lateral premotor cortex (PM) and the SMA. They showed that PM lesions impaired the monkey's ability to associate visual information with particular movements (Halsband & Passingham 1982). This finding is in line with a proposal that the PM plays a crucial role in the visual guidance of movements (Wise 1985, di Pellegrino & Wise 1993, Kurata 1994, Rizzolatti et al 1996, 1998). However, the ability of monkeys with PM lesions to perform different manipulations to an object in a particular sequence was not impaired (Halsband & Passingham 1982, Passingham 1985). Subsequently, they found that the ability of monkeys with SMA lesions to perform a sequence of movements to an object without visual cues was impaired (Halsband & Passingham 1987, Chen et al 1995).

Transient Chemical Inactivation Two recent studies attempted to inactivate the portions of the medial frontal cortex now defined as the presupplementary motor area (pre-SMA) (see Matsuzaka et al 1992; cf Luppino et al 1991) and the newly defined SMA (Tanji 1996) transiently. Shima & Tanji (1998) locally injected muscimol into these areas while monkeys were performing a variety of motor tasks. Monkeys were not impaired in performing a simple target-reaching task with the arm after bilateral injection of muscimol into either the SMA or pre-SMA. The reaction time and movement time were not altered. However, when monkeys were required to perform three different arm movements separately in a remembered order (the task is outlined below), they were unable to perform the task. Nevertheless, at that stage of inactivation, the monkeys were still able to select and perform the three movements if instructed with a visual signal. Nakamura et al (1999) injected muscimol while monkeys performed a sequential button-pressing task. Injection into either the SMA or pre-SMA barely affected the performance of a well-learned, sequential button-pressing task, although the reaction time was slightly prolonged. The seemingly discrepant results from the two laboratories can be explained as follows. The sequential button-pressing task required continuous execution of limb manipulation, following a variety of trajectories in space, where the spatial factor was the critical control element. In contrast, the task of Shima & Tanji required the temporal arrangement of three discrete movements that were performed separately at variable intervals. Moreover, spatial factors were minimized and temporal sequencing was critical. Combining the results of the two studies indicates that the SMA and pre-SMA are not essential for performing movements involving simply reaching out to a target or a very well-learned, continuously performed motor task, even if it has multiple phases. In

contrast, both areas are critically involved in sequencing multiple, separately performed movements over time. Furthermore, Nakamura et al showed that after the pre-SMA injection, there were more errors in performing a novel sequence of button presses. This may suggest a role of the pre-SMA in acquiring a novel motor sequence (Shima et al 1996) or its role in motor learning (Hikosaka et al 1999).

Brain Imaging Numerous studies measuring regional changes in cerebral blood flow or metabolism have found active foci in the cerebral cortex associated with the performance of a variety of sequential movements by human subjects. Early studies that attempted to measure regional cerebral blood flow changes with ^{123}Xe injections reported focal activation of the medial frontal cortex, presumably covering the traditionally defined SMA (Orgogozo & Larsen 1979, Roland et al 1980). Since then, a large number of studies using positron emissions tomography techniques have looked at activation foci when subjects perform sequential movements. The literature on these studies is too large to overview, but I mention some typical findings. Excluding the primary motor and somatosensory areas, active foci related to sequential motor performance are found primarily in four cortical regions: the medial frontal cortex, including the SMA and cingulate cortex; the lateral premotor cortex; the lateral prefrontal cortex, including areas 9 and 46; and the parietal cortex (Deiber et al 1991, Grafton et al 1998). Selection or guidance of movements in space seems to be the most prominent factor calling for activation of the parietal cortex and lateral premotor cortex (Hazeltine et al 1997, Binkofski et al 1999b) whereas a high demand for cognitive behavioral control seems to require prefrontal activity. On the other hand, self determination of a movement sequence or complexity in the temporal structure leads to activation of the medial motor areas (Deiber et al 1991, Sergent et al 1992, Anderson et al 1994, Jenkins et al 1994, Picard & Strick 1996). This view is supported by reports of event-related cortical potentials (Lang et al 1992) and by a report using functional magnetic resonance imaging (Deiber et al 1999). Some studies have reported increased regional cerebral blood flow in the primary motor cortex, as well as in the SMA, while performing sequential hand movements (Shibasaki et al 1993). It needs to be clarified whether this increase merely reflects the elevated demand for sending excitatory or inhibitory output to produce appropriate muscular activity, or whether it is associated with planning and generating temporal structure for sequential motor output.

Magnetic Stimulation A technique of transcranial magnetic stimulation that produces temporary functional lesions has been applied to human subjects for 15 years (Pascual-Leone et al 2000). Gerloff et al (1997) performed a systematic study in which multiple regions of the cerebral cortex were stimulated while human subjects performed sequential finger movements of differing complexity. They found that stimulation over the mesial frontal cortical areas (including the

SMA) induced errors only in the complex sequence whereas stimulation over the primary motor cortex induced errors in both the complex and the simple sequences. Stimulation over the lateral frontal or parietal areas did not interfere with the sequential performance at all. These findings indicate the critical role of the medial frontal cortex in organizing movements in complex motor sequences. This view is also supported by an earlier report (Muri et al 1995) that transcranial magnetic stimulation targeted at the cortical region, including the supplementary eye field, caused frequent errors in performing memory-guided sequential saccades.

Involvement of Subcortical Areas

Basal Ganglia Basal ganglia exert their control functions on motor behavior through (*a*) the thalamocortical networks and (*b*) the brainstem networks (DeLong & Georgopoulos 1981). The modern concept of basal ganglia functions has been greatly advanced by the discovery of two principles. First, the main circuit of the basal ganglia, composed of serial inhibitory connections, links discrete sections of the basal ganglia with separate cortical areas (Parent & Hazrati 1995). Second, basal ganglia neurons exhibit behaviorally context-dependent activity during the execution of learned motor and cognitive tasks, as well as during learning of novel motor behavior (Hikosaka et al 2000). It is within this conceptual framework that the participation of the basal ganglia in organizing sequential motor actions is to be understood.

It is well established that each part of the basal ganglia is intimately connected with multiple areas in the cerebral cortex, forming cortico-basal ganglia loops (Alexander et al 1986, Middleton & Strick 2000). Given that cortical motor areas are involved in the performance of sequential motor behavior, it is reasonable to postulate that the basal ganglia that are intimately connected to them (Takada et al 1998) are also involved. Indeed, Benecke et al (1987) found a disturbance of sequential movements in patients with Parkinson's disease, using a task in which two hand/arm movements were performed sequentially in rapid succession. They found that not only were the individual movements slower, the interval between movements was also prolonged, and sometimes the switch from the first to the second movement could not be made. Later studies (Harrington & Haaland 1991, Agostino et al 1992, Martin et al 1994) also found impairments of sequential motor tasks in Parkinsonian patients and in patients with Huntington's disease (Thompson et al 1988).

These clinical studies on human subjects are supported by animal lesion studies. Berridge (Berridge & Whishaw 1992, Cromwell & Berridge 1996) reported that typical rule-governed sequential behavior seen in rat grooming behavior was impaired by the ablation of the striatum, but not by ablation of the neocortex or cerebellum. In primates, carbachol and atropine injection in the caudate nucleus affected the performance of sequential behavior (Van den Bercken & Cools 1982).

Miyachi et al (1997) studied the role of the basal ganglia in learning and executing sequential movements by training monkeys to perform a sequential button-press task (a 2×5 task) and examining how it was affected by muscimol injection. They found that injections in the anterior caudate and putamen affected the learning of new sequences, whereas injections in the middle-posterior putamen disrupted the execution of well-learned sequences. Recently, Matsumoto et al (1999) injected a neurotoxin, MPTP, into the caudo-putamen of monkeys and concluded that the nigrostriatal dopamine system was necessary for both learning and executing a sequential motor task.

Brain-imaging studies in human subjects have confirmed the involvement of the basal ganglia in sequential motor behavior. For instance, Boecker et al (Petersen et al 1985) found (with $H_2\ ^{15}$OPET) an active focus in the anterior globus pallidus when subjects performed sequential finger movements, and the increase in rCBF was correlated with increasing sequence complexity. Jueptner & Weiller (1998) reported that the anterior striatum and globus pallidus were active during learning of new motor sequences whereas the posterior putamen was more active during performance of prelearned sequences. Stimulus properties and attentional constraints influenced activation of the basal ganglia and cortical areas (Hazeltine et al 1997).

Cerebellum Thach (1998) proposed recently that the role of the cerebellum is to provide a substrate for the combination of single-response elements into larger groupings, so that the occurrence of a sensory or experiential context automatically triggers a combined response, reviewing the key contribution of parallel fibers to this function. According to this view, the cerebellum is likely to be involved in sequencing of multiple movements, in addition to its role in coordinating and combining movements into single actions. Computational frameworks that describe how the cerebellum executes its role in such operations have also been provided (Wolpert & Kawato 1998). However, despite numerous neuroimaging studies of the cerebellum in task-performing subjects (Desmond & Fiez 1998), its involvement in temporal sequencing of actions (and not in spatial patterning) has not been unequivocally demonstrated with this technique. On the other hand, the cerebellum has been implicated in learning sequential movements (Sanes et al 1990, Molinari et al 1997, Lidow et al 1989, Jenkins et al 1994, Jueptner & Weiller 1998). Unfortunately, results of an experimental study in monkeys did not accord with the brain-imaging data. Muscimol injection into any of the three cerebellar nuclei of monkeys failed to affect learning of new motor sequences (Lu et al 1998). Instead, injections into the dorsal and central part of the dentate nucleus increased the number of errors in performing learned motor sequences, and movements were slower. Mushiake & Strick (1993) analyzed neuronal activity in the dentate nucleus of monkeys performing a sequential button-pressing task, under remembered-sequence and visual-tracking condition. Neurons in the ventrolateral dentate were preferentially more active during the tracking condition, whereas

other dentate neurons did not show a preference. These studies indicate the involvement of cerebellar structures in generating spatial trajectories or in developing the motor skill necessary to exert visuospatial control. More work is necessary to examine the role of cerebellum in performing, or learning to perform, multiple movements in a correct temporal order.

LEARNING

The learning of sequential processes is a very important aspect that must be studied to understand the neural mechanisms for generating and controlling the sequential performance of motor behavior. This subject was reviewed and discussed recently in excellent review articles (Hikosaka et al 1998, 1999). Mechanisms both for procedural learning to acquire skills in performing continuous execution of multiphased actions and for learning to perform visuospatial sequences have been studied. On the other hand, neural mechanisms for learning to organize multiple actions in temporal sequences have scarcely been studied.

CELLULAR ACTIVITY DURING SEQUENTIAL TASK PERFORMANCE

Barone & Joseph (1989) trained monkeys to perform a delayed spatial sequencing task, in which they had to move their eyes and an arm in complex sequences. A visual target appeared in various spatial sequences, and after a delay the animal followed the sequence with saccades and then arm reaching. They found two types of cellular activity related to the task sequence in the prefrontal cortex. First, visual-tonic type cells were active selectively depending on the spatial sequence of illumination of the visual target. Second, context-dependent type cells were active during visual fixation of a given spatial target, but only selectively in a context that depended on which other targets had been or were going to be presented. The first type of activity appeared to be useful for memorizing spatial sequences of events. The authors interpreted the second type of context-dependent activity as the neural trace of a representation of the state of the sequence constructed from cognitive information. That report did not describe sequence-selective saccade-related or reaching-related activity.

In contrast to activities reflecting sequences of sensory and cognitive information, cellular activity selective for the spatial sequence of planned movements was reported in the traditionally defined supplementary motor area (Mushiake et al 1990). For instance, Mushiake et al found cellular activity before initiating a motor task that involved pressing buttons in the sequence top-bottom-right. The activity was not observed when the motor sequence was top-right-bottom or top-left-right. Subsequently, the same authors compared cellular activity in the supplementary, premotor, and primary motor areas during visually guided and internally

determined sequential movements (Mushiake et al 1991). Monkeys were trained to push three buttons sequentially under two conditions. In one condition, three button presses were individually guided and triggered with illumination of the buttons. In the other, three sequential presses were guided by memorized information. More than half of the SMA cells were preferentially active during the sequential task based on memory. In contrast, more than half of the cells in the lateral premotor cortex were more active during the visually guided sequential task. Although a simple dichotomy was ruled out, the sequence-selective SMA activity relied more on memory-based information whereas the premotor activity relied more on visual information. In the primary motor cortex, cellular activity occurred during both motor preparation and motor execution. Most of the activity in this area was not affected by whether the motor sequence was memory based or visually guided.

Early studies on neuronal activity in the basal ganglia have hinted at its participation in sequential motor behavior (Kimura 1990, Brotchie et al 1991, Kimura et al 1992). In 1995, studies of neuronal activity in the caudate nucleus (Kermadi & Joseph 1995) and the pallidum (Mushiake & Strick 1995) revealed two interesting aspects of activity related to sequential motor performance. One was activity selective to a particular spatial sequence of target-reaching arm movements or saccades (sequence-selective activity). The other was movement-related activity selective to a particular serial position in the sequence (rank-order-selective or phase-selective activity). In addition, a variety of context-dependent activities were found among caudate neurons.

PLANNING AND EXECUTING MULTIPLE MOVEMENTS IN A SEQUENCE

In the single-cell studies described above, animal subjects performed sequential reaching movements where the spatial sequence was crucial. In these studies, selection of spatial trajectories in successive reaching was inevitably critical to control. On the other hand, selection of multiple movements performed separately, but in succession, is a separate issue from trajectory determination. When we intend to drink beer, we place a glass on a table, use a bottle opener, and pour beer into the glass. When we select the three movements in the correct sequence, we plan the time sequence of discrete movements performed separately, rather than the trajectories of the movements.

To study how neurons in the medial motor areas participate in performing sequential multiple movements that are individually separated in time, we analyzed neuronal activity in two areas (Tanji & Shima 1994, Shima & Tanji 2000): the pre-SMA and the newly defined SMA (Matsuzaka & Tanji 1996). Monkeys were trained to perform three different movements, separated by a waiting time, in six different orders. Initially, each series of movements was learned during five trials guided by visual signals that indicated the correct movements. The monkeys subsequently executed the three movements in the memorized order without the

visual signals. Three types of neuronal activity were of particular interest and appeared to be crucially involved in sequencing the multiple motor tasks in different orders. First, we found activity changes that were selective for a particular sequence of three movements that monkeys were prepared to perform (Tanji & Shima 1994). Figure 1 shows a typical example of this sequence-selective activity. The

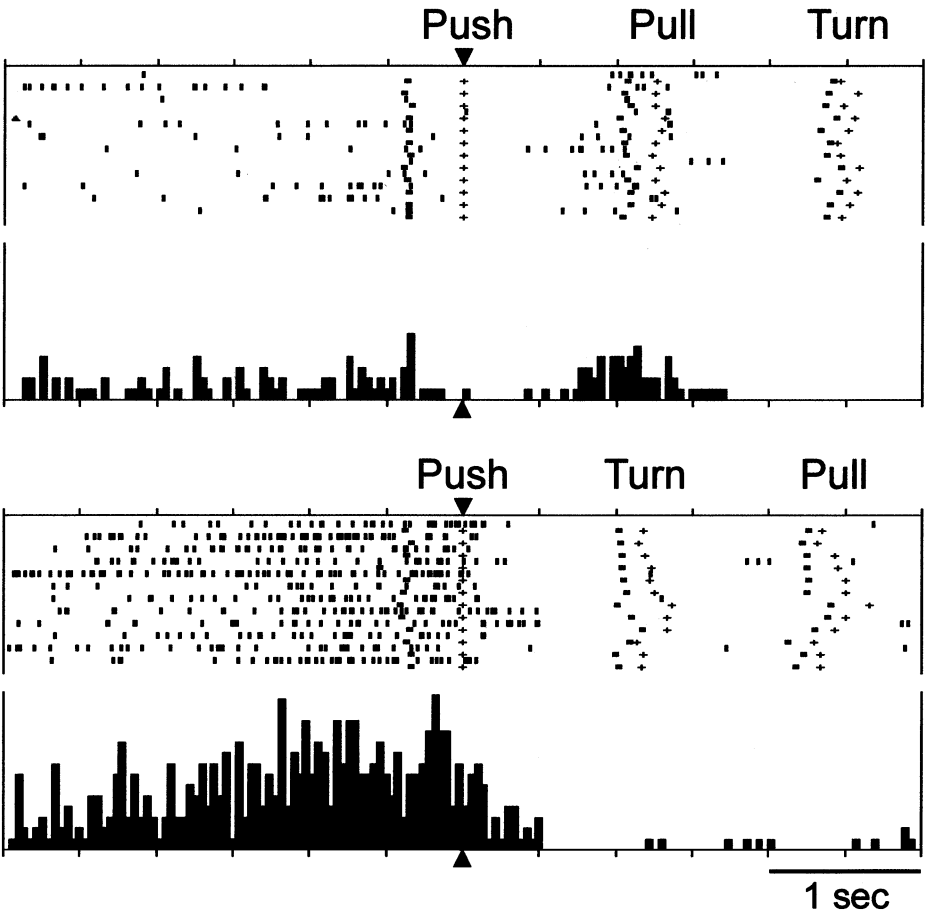

Figure 1 Activity of a neuron in the presupplementary motor area exhibiting preferential relation to a specific order of three movements performed without sensory guidance. This neuron is active during a waiting period before initiating the first movement, but only if the sequence of upcoming movements is in the order of PUSH, TURN, PULL (bottom). (Top) PUSH-PULL-TURN sequence. In raster displays, each row represents a trial, and dots represent individual discharges of this neuron. Small crosses denote the time of occurrence of the movement onset. In histograms, discharges over 12 trials are summated. Bin width for the display purpose is 40 ms. Triangles at the top of each raster indicate the start of the first movement.

neuronal activity recorded in the SMA increased before the animal initiated the first movement, PUSH, only when the second movement was TURN, and the third movement was PULL. The selective activity was not observed when the sequence was PUSH-PULL-TURN or any four of others. The sequence-selective activity ceased when the monkeys initiated the first movement. Second, we found interval-selective activity that appeared in the interval between one particular movement and another particular movement. In the SMA neuron shown in Figure 2, the activity was most prominent during the interval after the execution of PULL and before the execution of PUSH. Third, we found neuronal activity representing the rank-order of three movements arranged chronologically; that is, the activity differed selectively in the process of preparing the first, second, or third movements in individual trials. An example of rank-order–selective preparatory activity is shown in Figure 3. The pre-SMA neuron was active only during the third preparatory period, irrespective of the sequence of the three movements. Interval-selective activity was more prevalent in the SMA, whereas rank-order–selective activity was more frequently recorded in the pre-SMA. These results suggest how the neurons in both the SMA and pre-SMA are involved in sequencing multiple movements over time.

Our previous study inactivating the SMA and pre-SMA (Shima & Tanji 1998) indicated that the neuronal activities described above play a number of crucial

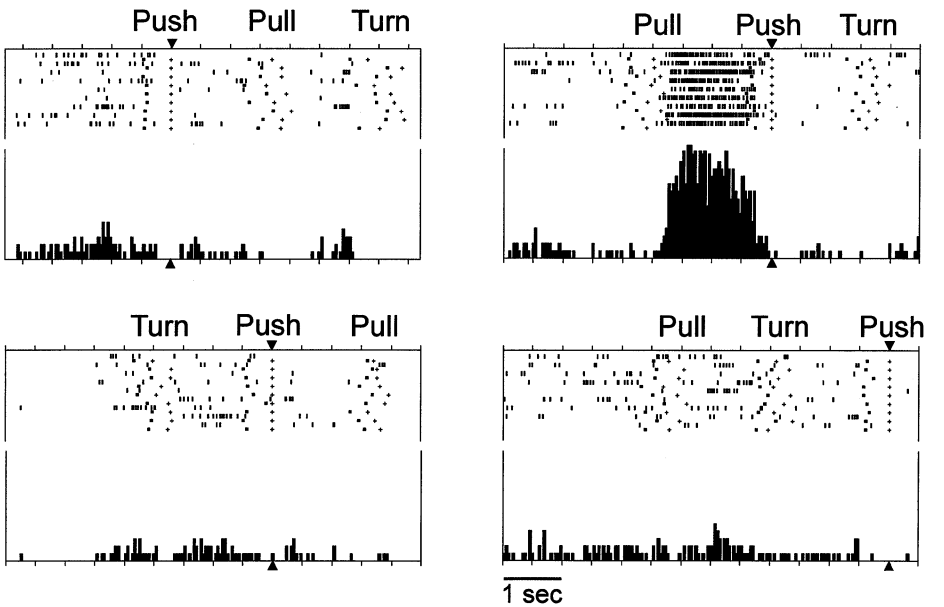

Figure 2 Discharges of a supplementary motor area neuron whose activity increased selectively during the interval after completion of a particular movement, PULL, and before the initiation of another particular movement, PUSH. Display format is the same as in Figure 1.

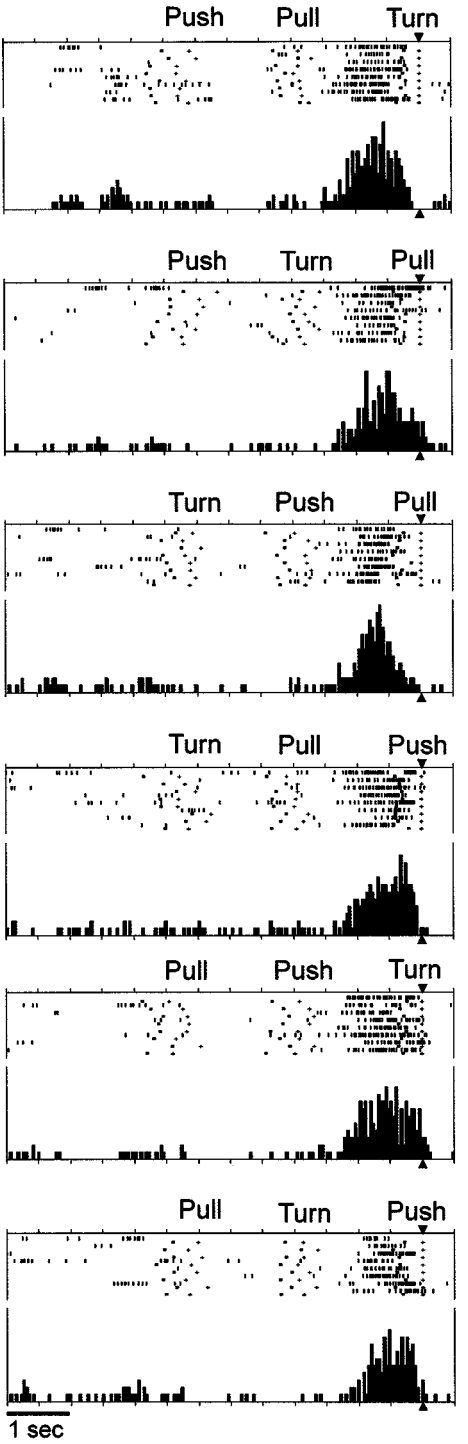

Figure 3 Discharges of a presupplementary motor area neuron whose activity increased while the monkey was preparing to initiate the third movement, irrespective of the sequence of three movements.

roles in organizing multiple movements in the correct temporal order. Therefore, in the next section, we hypothesize how each of these types of neuronal activity can be used to accomplish the sequencing task.

How Neuronal Activity Arranges Multiple Movements in the Correct Temporal Order—A Hypothesis

Let us consider how the neuronal activities in the SMA and pre-SMA described above might work together to provide the signals necessary to perform movements *A*, *B*, and *C*, in that order (Figure 4 shows the processes and actions necessary to perform the sequence). What kinds of neural components, with what properties, are required to provide the necessary signals? First, we need a component that retrieves and carries the information that the currently required sequence is *A*-*B*-*C*. The sequence-selective, preparatory activity found in the SMA and pre-SMA serves this function. We also found plenty of preparatory activity selective for the upcoming movement. This neuronal activity would make the preparations to start the first movement, *A*. The addition of a trigger signal following this preparatory process automatically starts the first movement, *A*. Once movement *A* is accomplished, the sequence information carried in the sequence-selective, preparatory neurons ceases, as seen in the neuronal activity exemplified in Figure 1. What mechanism (*a*) indicates that the next movement is movement *B* and (*b*) holds that information during the waiting period until receiving the signal to start the second movement? This requires an element that carries information to connect the occurrence of movement *B* after the occurrence of movement *A*. We propose that the interval-selective neuronal activity we observed serves as the element linking the occurrence of *B* after *A*, because this activity starts after movement *A* has occurred and ends before the initiation of movement *B*. This tonic signal is useful for feeding information to the neural component involved in the preparatory process before initiating movement *B*. Alternatively, the tonic signal may continuously activate a neural component that triggers a command to initiate movement *B* after receiving an external signal. When movement *B* is executed, the next step is to connect the occurrence of movement *C* after movement *B*. This can be done by a linking element that is activated after movement *B* and lasts until the initiation of movement *C* (see Figure 2). This linking element feeds tonic input to the next element, which produces the output to initiate movement *C*. When the third movement is complete, neuronal activity after the third movement might be an "end" signal, reporting completion of the sequence. We observed such activity predominantly in the pre-SMA.

If this hypothesis is correct, then it follows that the linking elements described should be involved in the process as follows. To perform the sequence *A*-*B*-*C*, elements linking $A \rightarrow B$ and $B \rightarrow C$ should be activated. The element linking $A \rightarrow B$ should come into play after the end of the first movement in the sequence and long before the initiation of the second movement. The element linking $B \rightarrow C$ should come into play after completion of the second movement in the sequence and long

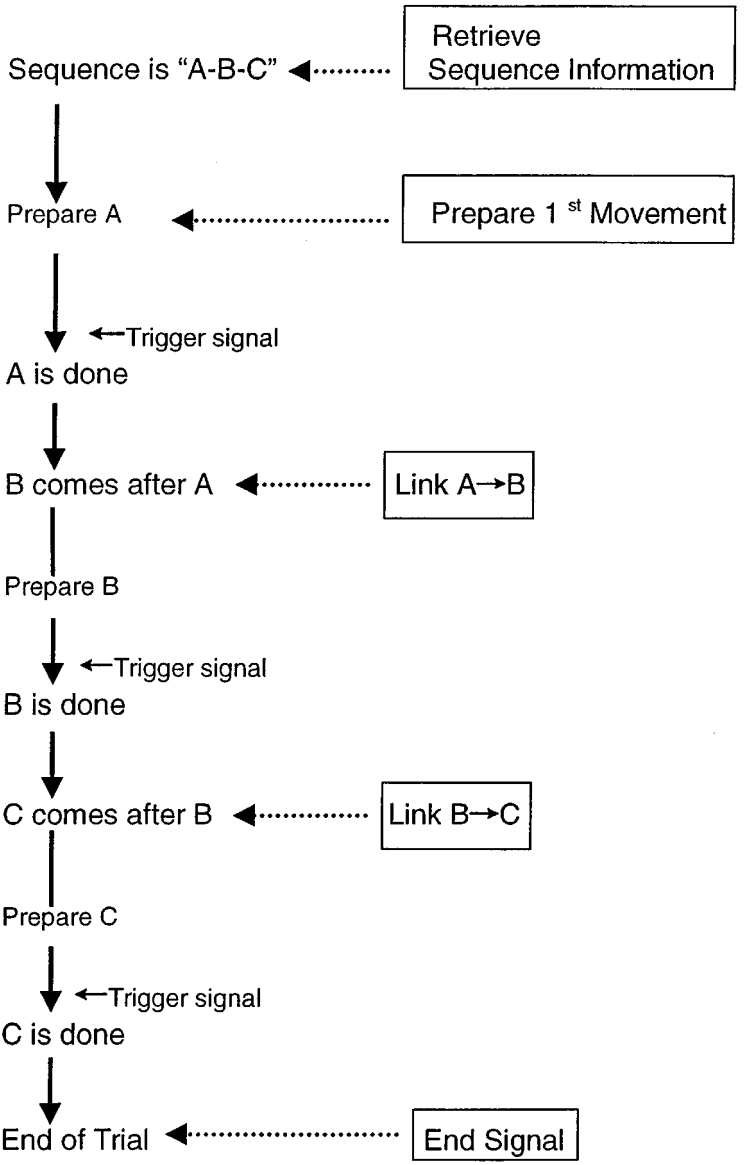

Figure 4 Processes and necessary actions for the orderly performance of three movements with time intervals when the sequence is in the order of *A*, *B*, and *C*. The information for the correct sequence should lead to a chain of events that gives rise to orderly delivery of output signals appropriate for commanding three movements in a correct sequence. The timing of initiation of each movement is externally determined with a trigger signal. [Adapted from Shima & Tanji (2000).]

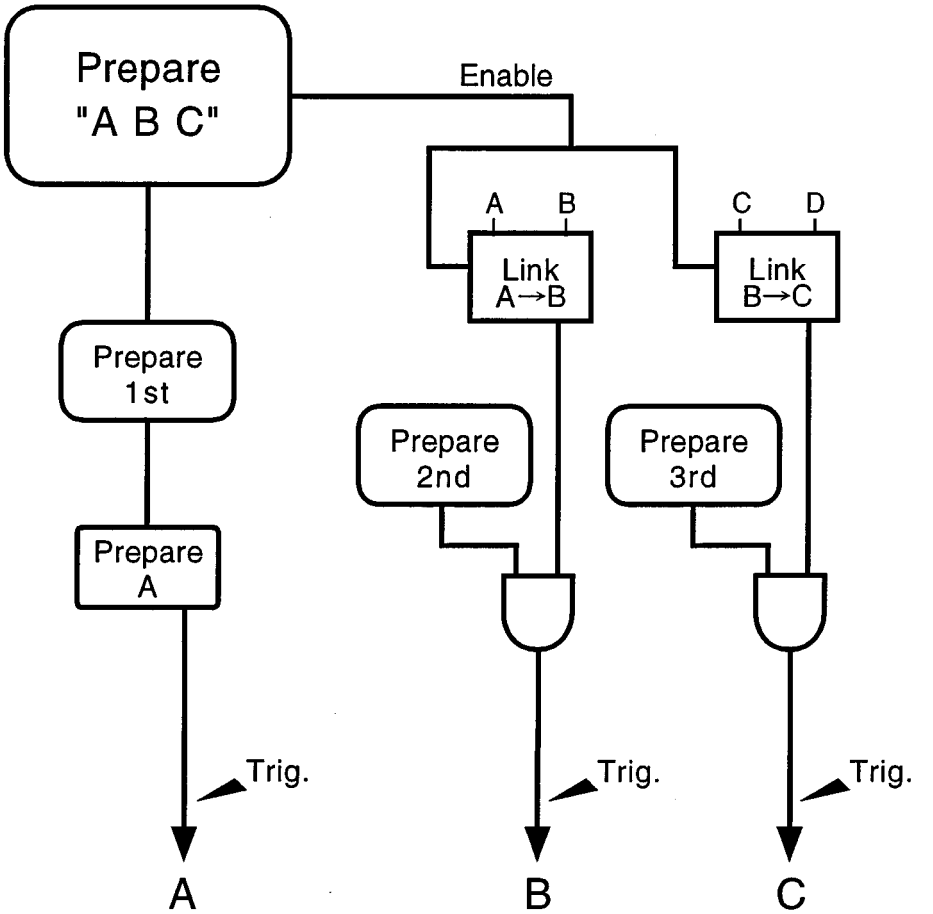

Figure 5 A diagram illustrating a hypothetical network connecting the neural elements found in medial cortical motor areas. If the preparatory elements delivering signals with four different properties feed outputs to linking elements and output elements in the way drawn, then for automatic delivery of output signals they will contribute in the order of *A*, *B*, and *C*. [Reproduced with permission from Shima & Tanji (2000).]

before initiation of the third movement. These steps require information about which of the three movements in the sequence is next. This information can be provided by the many rank-order–selective neurons that we found. If the neural system has a way of telling whether to prepare the second or third movement, the elements linking $A \rightarrow B$ and $B \rightarrow C$ should be incorporated at the appropriate times. In other words, the rank-order–selective elements serve to regulate the linking-element information. In our studies (Tanji & Shima 1994, Shima & Tanji 2000), we observed three types of interval-selective activity: activity that appeared

(*a*) nonselectively before the second and third movement, (*b*) selectively before the second movement, or (*c*) selectively before the third movement. These neurons are candidates for the linking elements that appear before and after regulatory actions by the rank-order elements. Our hypothesis on the use of neural elements found in the SMA and pre-SMA is summarized in Figure 5. The diagram illustrates the basic actions of each element, which could be hardwired to generate the signals appropriate to performing the three movements in the order *A*, *B*, and *C*. We hasten to add, however, that much study remains to determine whether the neural structures in the SMA and pre-SMA actually operate in a way similar to that proposed. Moreover, the illustration may be too simple to account for the actual operation of neuronal elements. Neural structures for the sequential control of motor behavior may include components that are not readily comprehensible intuitively. Neural components may interact in a complex manner and may undergo use-dependent alteration.

REMAINING QUESTIONS

We are beginning to understand how neural structures generate and control sequential motor behavior, but many questions remain unanswered. This article is aimed at mechanisms for temporal, rather than spatial, aspects of behavioral sequence, discussing extensively the participation of medial motor areas. We need to study more the participation of other cortical and subcortical areas. The process of learning or acquiring sequential motor acts remains a central issue. We need to study whether the neural components found to participate in a particular sequential motor behavior are used to control other sequential behaviors in a general-purpose fashion (i.e. for the sequence *X-Y-X* as well as for *A-B-C*). Moreover, it will be interesting to study the mechanisms for the control of actions with long sequences, such as the playing of musical instruments.

LITERATURE CITED

Agostino R, Berardelli A, Formica A, Accornero N, Manfredi M. 1992. Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia. *Brain* 115 (Part 5):1481–95

Alexander GE, DeLong MR, Strick PL. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9:357–81

Anderson TJ, Jenkins IH, Brooks DJ, Hawken MB, Frackowiak RS, Kennard C. 1994. Cortical control of saccades and fixation in man. A PET study. *Brain* 117(Part 5):1073–84

Barone P, Joseph JP. 1989. Prefrontal cortex and spatial sequencing in macaque monkey. *Exp. Brain Res.* 78:447–64

Batista AP, Buneo CA, Sbyder LH, Andersen RA. 1999. Reach plans in eye-centered coordinates. *Science* 285:257–260

Benecke R, Rothwell JC, Dick JP, Day BL,

Marsden CD. 1987. Disturbance of sequential movements in patients with Parkinson's disease. *Brain* 110:361–79

Berridge KC, Whishaw IQ. 1992. Cortex, striatum and cerebellum: control of serial order in a grooming sequence. *Exp. Brain Res.* 90(2):275–90

Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H. 1999a. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur. J. Neurosci.* 11(9):3276–86

Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund HJ. 1999b. A parieto-premotor network for object manipulation: evidence from neuroimaging. *Exp. Brain Res.* 128(1–2):210–13

Brinkman C. 1984. Supplementary motor area of the monkey's cerebral cortex: short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *J. Neurosci.* 4:918–29

Brotchie P, Iansek R, Horne MK. 1991. Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. *Brain* 114:1685–702

Catalan MJ, Honda M, Weeks RA, Cohen LG, Hallet M. 1998. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. *Brain* 121:253–64

Chen YC, Thaler D, Nixon PD, Stern CE, Passingham RE. 1995. The functions of the medial premotor cortex. II. The timing and selection of learned movements. *Exp. Brain Res.* 102(3):461–73

Cromwell HC, Berridge KC. 1996. Implementation of action sequences by a neostriatal site: a lesion mapping study of grooming syntax. *J. Neurosci.* 16(10):3444–58

Deiber MP, Honda M, Ibanez V, Sadato N, Hallett M. 1999. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. *J. Neurophysiol.* 81(6):3065–77

Deiber MP, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RS. 1991. Cortical areas and the selection of movement: a study with positron emission tomography. *Exp. Brain Res.* 84:393–402

DeLong MR, Georgopoulos AP. 1981. Motor functions of the basal ganglia. In *Handbook of Physiology, The Nervous System II, Part 2*, ed. VB Brooks, 23:1017–61. Bethesda, MD: Am. Physiol. Soc.

Desmond JE, Fiez JA. 1998. Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn. Sci.* 2:355–62

Dick JPR, Benecke R, Rothwell JC, Day BL, Marsden CD. 1986. Simple and complex movements in a patient with infarction of the right supplementary motor area. *Mov. Disord.* 1(4):255–66

di Pellegrino G, Wise SP. 1993. Visuospatial versus visuomotor activity in the premotor and prefrontal cortex of a primate. *J. Neurosci.* 13:1227–43

Doyon J, Laforce R, Bouchard G, Gaudreau D, Roy J, et al. 1998. Role of the striatum, cerebellum and frontal lobes in the automatization of a repeated visuomotor sequence of movements. *Neuropsychologia* 36:625–41

Evarts EV. 1981. Role of motor cortex in voluntary movements in primates. See DeLong & Georgopoulos 1981, pp. 1083–1120

Fuster JM. 1997. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*. Philadelphia: Lippincott-Raven

Georgopoulos AP. 2000. Neural aspects of cognitive motor control. *Curr. Opin. Neurobiol.* 10:238–41

Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. 1997. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain* 120(Part 9):1587–602

Goldberg G. 1985. Supplementary motor area structure and function: review and hypotheses. *Behav. Brain Res.* 8:567–615

Goldman-Rakic PS. 1996. The prefrontal landscape: implications of functional architecture for understanding human mentation and

the central executive. *Philos. Trans. R. Soc. London Ser.* B 351:1445–53

Grafton ST, Hazeltine E, Ivry RB. 1998. Abstract and effector-specific representations of motor sequences identified with PET. *J. Neurosci.* 18(22):9420–28

Halsband U, Ito N, Tanji J, Freund HJ. 1993. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain* 116(Part 1):243–66

Halsband U, Passingham RE. 1982. The role of premotor and parietal cortex in the direction of action. *Brain Res.* 240:368–72

Halsband U, Passingham RE. 1987. Higher distrubances of movement in monkeys (*Macaca mulatta*). In *Motor Control*, ed. GN Gantchev, B Dimitev, PC Gatev, pp. 79–85. New York: Plenum

Harrington DL, Haaland KY. 1991. Sequencing in Parkinson's disease. Abnormalities in programming and controlling movement. *Brain* 114:99–115

Harrington DL, Rao SM, Haaland KY. 2000. Specialized neural systems underlying representations of sequential movements. *J. Cogn. Neurosci.* 12:56–77

Hazeltine E, Grafton ST, Ivry R. 1997. Attention and stimulus characteristics determine the locus of motor-sequence encoding. A PET study. *Brain* 120(Part 1):123–40

Hikosaka O, Miyashita K, Miyachi S, Sakai K, Lu X. 1998. Differential roles of the frontal cortex, basal ganglia, and cerebellum in visuomotor sequence learning. *Neurobiol. Learn. Mem.* 70:137–49

Hikosaka O, Nakahara H, Rand MK, Sakai K, Lu X, et al. 1999. Parallel neural networks for learning sequential procedures. *Trends Neurosci.* 22(10):464–71. Erratum 1999. *Trends Neurosci.* 22(12):569

Hikosaka O, Takikawa Y, Kawagoe R. 2000. Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol. Rev.* 80(3):953–78

Imamizu H, Miyauchi S, Tamada T, Sasaki Y, Takino R, et al. 2000. Human cerebellar activity reflecting an acquired internal model of a new tool. *Nature* 403:192–95

Ito M. 1984. *The Cerebellum and Neural Control*. New York: Raven

Jeannerod M, Arbib MA, Rizzolatti G, Sakata H. 1995. Grasping objects: the cortical mechanisms of visuomotor transformation. *Trends Neurosci.* 18:314–20

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RS, Passingham RE. 1994. Motor sequence learning: a study with positron emission tomography. *J. Neurosci.* 14:3775–90

Jueptner M, Weiller C. 1998. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. *Brain* 121 (Part 8):1437–49

Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG. 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 377:155–58

Kermadi I, Joseph JP. 1995. Activity in the caudate nucleus of monkey during spatial sequencing. *J. Neurophysiol.* 74(3):911–33

Kettner RE, Marcario JK, Clark-Phelps MC. 1996a. Control of remembered reaching sequences in monkey. I. Activity during movement in motor and premotor cortex. *Exp. Brain Res.* 112(3):335–46

Kettner RE, Marcario JK, Port NL. 1996b. Control of remembered reaching sequences in monkey. II. Storage and preparation before movement in motor and premotor cortex. *Exp. Brain Res.* 112(3):347–58

Kimura D. 1982. Left-hemisphere control of oral and brachial movements and their relation to communication. *Philos. Trans. R. Soc. London Ser. B* 298(1089):135–49

Kimura M. 1990. Behaviorally contingent property of movement-related activity of the primate putamen. *J. Neurophysiol.* 63:1277–96

Kimura M, Aosaki T, Hu Y, Ishida A, Watanabe K. 1992. Activity of primate putamen neurons is selective to the mode of voluntary movement: visually guided, self-initiated or

memory-guided. *Exp. Brain Res.* 89:473–77

Kolb B, Milner B. 1981. Performance of complex arm and facial movements after focal brain lesions. *Neuropsychologia* 19(4):491–503

Kurata K. 1994. Information processing for motor control in primate premotor cortex. *Behav. Brain Res.* 61(2):135–42

Lang W, Beisteiner R, Lindinger G, Deecke L. 1992. Changes of cortical activity when executing learned motor sequences. *Exp. Brain Res.* 89(2):435–40

Laplane D, Talairach J, Meininger V, Bancaud J, Orgogozo JM. 1977. Clinical consequences of corticectomies involving the supplementary motor area in man. *J. Neurol. Sci.* 34:301–14

Lashley KS. 1951. The problem of serial order in behavior. In *Cerebral Mechanisms in Behavior*, ed. LA Jeffress, pp. 112–36. New York: Wiley

Lidow MS, Goldman-Rakic PS, Gallager DW, Rakic P. 1989. Quantitative autoradiographic mapping of serotonin 5-HT1 and 5-HT2 receptors and uptake sites in the neocortex of the rhesus monkey. *J. Comp. Neurol.* 280:27–42

Lu X, Hikosaka O, Miyachi S. 1998. Role of monkey cerebellar nuclei in skill for sequential movement. *J. Neurophysiol.* 79(5):2245–54

Luppino G, Matelli M, Camarda RM, Gallese V, Rizzolatti G. 1991. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J. Comp Neurol.* 311(4):463–82

Luria AR. 1966. *Higher Cortical Functions in Man*. London: Tavistokc

Martin KE, Phillips JG, Iansek R, Bradshaw JL. 1994. Inaccuracy and instability of sequential movements in Parkinson's disease. *Exp. Brain Res.* 102(1):131–40

Matsumoto N, Hanakawa T, Maki S, Graybiel AM, Kimura M. 1999. Role of [corrected] nigrostriatal dopamine system in learning to perform sequential motor—tasks in a predictive manner. *J. Neurophysiol.* 82(2):978–98. Erratum 1999. *J. Neurophysiol*. 82(5):13

Matsuzaka Y, Aizawa H, Tanji J. 1992. A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. *J. Neurophysiol.* 68(3):653–62

Matsuzaka Y, Tanji J. 1996. Changing directions of forthcoming arm movements: neuronal activity in the presupplementary and supplementary motor area of monkey cerebral cortex. *J. Neurophysiol.* 76(4):2327–42

Middleton FA, Strick PL. 1998. The cerebellum: an overview. *Trends Neurosci.* 21(9): 367–69

Middleton FA, Strick PL. 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res. Rev.* 31:236–50

Miyachi S, Hikosaka O, Miyashita K, Karadi Z, Rand MK. 1997. Differential roles of monkey striatum in learning of sequential hand movement. *Exp. Brain Res.* 115(1):1–5

Molinari M, Leggio MG, Solida A, Ciorra R, Misciagna S, et al. 1997. Cerebellum and procedural learning: evidence from focal cerebellar lesions. *Brain* 120(Part 10):1753–62

Muri RM, Rivaud S, Vermersch AI, Leger JM, Pierrot-Deseilligny C. 1995. Effects of transcranial magnetic stimulation over the region of the supplementary motor area during sequences of memory-guided saccades. *Exp. Brain Res.* 104(1):163–66

Mushiake H, Inase M, Tanji J. 1990. Selective coding of motor sequence in the supplementary motor area of the monkey cerebral cortex. *Exp. Brain Res.* 82(1):208–10

Mushiake H, Inase M, Tanji J. 1991. Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. *J. Neurophysiol.* 66(3):705–18

Mushiake H, Strick PL. 1993. Preferential activity of dentate neurons during limb movements guided by vision. *J. Neurophysiol.* 70:2660–64

Mushiake H, Strick PL. 1995. Pallidal neuron activity during sequential arm movements. *J. Neurophysiol.* 74(6):2754–58

Mussa-Ivaldi FA. 1999. Modular features of motor control and learning. *Curr. Opin. Neurobiol.* 9:713–17

Nakamura K, Sakai K, Hikosaka O. 1999. Effects of local inactivation of monkey medial frontal cortex in learning of sequential procedures. *J. Neurophysiol.* 82(2):106368

Orgogozo JM, Larsen B. 1979. Activation of the supplementary motor area during voluntary movement in man suggests it works as a supramotor area. *Science* 206:847–50

Parent A, Hazrati L-N. 1995. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res. Rev.* 20:91–127

Pascual-Leone A, Walsh V, Rothwell J. 2000. Transcranial magnetic stimulation in cognitive neuroscience. *Curr. Opin. Neurobiol.* 10(2):232–37

Passingham RE. 1985. Premotor cortex: sensory cues and movement. *Behav. Brain Res.* 18(2):175–85

Penfield W, Welch K. 1951. The supplementary motor area of the cerebral cortex. *Arch. Neurol. Psychiatr.* 66:289–317

Petersen SE, Robinson DL, Keys W. 1985. Pulvinar nuclei of the behaving rhesus monkey: visual responses and their modulation. *J. Neurophysiol.* 54:867–86

Picard N, Strick PL. 1996. Motor areas of the medial wall: a review of their location and functional activation. *Cereb. Cortex* 6(3): 342–53

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Muri R, Vermersch A-I. 1995. Cortical control of saccades. *Ann. Neurol* 37:557–67

Rizzolatti G, Fadiga L, Gallese V, Fogassi L. 1996. Premotor cortex and the recognition of motor actions. *Cogn. Brain Res.* 3(2):131–41

Rizzolatti G, Luppino G, Matelli M. 1998. The organization of the cortical motor system: new concepts. *Electroencephalogr. Clin. Neurophysiol.* 106(4):283–96

Roland PE, Larsen B, Lassen NA, Skinhoj E. 1980. Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J. Neurophysiol.* 43:118–36

Rosenbaum DA. 1991. *Human Motor Control.* San Diego, CA: Academic

Sakata H, Taira M, Murata A, Mine S. 1995. Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cereb. Cortex* 5:429–38

Sanes JN, Dimitrov B, Hallett M. 1990. Motor learning in patients with cerebellar dysfunction. *Brain* 113(Part 1):103–20

Seitz R, Roland PE. 1992. Learning of sequential finger movements in man: A combined kinematic and positron emission tomograpy (PET) study. *Eur. J. Neurosci.* 4:154–65

Sergent J, Zuck E, Terriah S, MacDonald B. 1992. Distributed neural network underlying musical sight-reading and keyboard performance. *Science* 257(5066):106–9

Shallice T, Burgess P. 1996. The domain of supervisory processes and temporal organization of behaviour. *Philos. Trans. R. Soc. London Ser. B* 351(1346):1405–11

Shibasaki H, Sadato N, Lyshkow H, Yonekura Y, Honda M, et al. 1993. Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain* 116(Part 6):1387–98

Shima K, Mushiake H, Saito N, Tanji J. 1996. Role for cells in the presupplementary motor area in updating motor plans. *Proc. Natl. Acad. Sci. USA* 93(16):8694–98

Shima K, Tanji J. 1998. Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements. *J. Neurophysiol.* 80(6):3247–60

Shima K, Tanji J. 2000. Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. *J. Neurophysiol.* 84:2148–60

Soechting JF, Flanders M. 1992. Organization of sequential typing movements. *J. Neurophysiol.* 67:1275–90

Takada M, Tokuno H, Nambu A, Inase M.

1998. Corticostriatal projections from the somatic motor areas of the frontal cortex in the macaque monkey: segregation versus overlap of input zones from the primary motor cortex, the supplementary motor area, and the premotor cortex. *Exp. Brain Res.* 120(1):114–28

Tanji J. 1996. New concepts of the supplementary motor area. *Curr. Opin. Neurobiol.* 6(6):782–87

Tanji J, Evarts EV. 1976. Anticipatory activity of motor cortex neurons in relation to direction of an intended movement. *J. Neurophysiol.* 39(5):1062–68

Tanji J, Shima K. 1994. Role for supplementary motor area cells in planning several movements ahead. *Nature* 371(6496):413–16

Thach WT. 1998. A role for the cerebellum in learning movement coordination. *Neurobiol. Learn. Mem.* 70:177–88

Thach WT, Goodkin HP, Keating JG. 1992. The cerebellum and the adaptive coordination of movement. *Annu. Rev. Neurosci.* 15:403–42

Thompson PD, Berardelli A, Rothwell JC, Day BL, Dick JP, et al. 1988. The coexistence of bradykinesia and chorea in Huntington's disease and its implications for theories of basal ganglia control of movement. *Brain* 111 (Part 2):223–44

Van den Bercken JH, Cools AR. 1982. Evidence for a role of the caudate nucleus in the sequential organization of behavior. *Behav. Brain Res.* 4(4):319–27

Wise SP. 1985. The primate premotor cortex: past, present, and preparatory. *Annu. Rev. Neurosci.* 8:1–19

Wolpert DM, Kawato M. 1998. Internal models in the cerebellum. *Trends Cogn. Sci.* 2:338–47

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