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Role for cells in the presupplementary motor area in updating motor plans

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ABSTRACT **Two motor areas are known to exist in the medial frontal lobe of the cerebral cortex of primates, the supplementary motor area (SMA) and the presupplementary motor area (pre-SMA). We report here on an aspect of cellular activity that characterizes the pre-SMA. Monkeys were trained to perform three different movements sequentially in a temporal order. The correct order was planned on the basis of visual information before its execution. A group of pre-SMA cells ($n = 64, 25\%$) were active during a process when monkeys were required to discard a current motor plan and develop a plan appropriate for the next orderly movements. Such activity was not common in the SMA and not found in the primary motor cortex. Our data suggest a role of pre-SMA cells in updating motor plans for subsequent temporally ordered movements.**

On the basis of physiological and anatomical criteria, it has recently been established that two separate areas exist in the medial frontal lobe of the cerebral cortex of primates, termed the pre-supplementary motor area (pre-SMA), and the supplementary motor area (SMA) (1). Although differences in their functional roles have been suggested, not enough experimental findings have revealed their differential activity in relation to performance of actual motor behavior. Rizzolatti *et al.* (2) reported that neurons in the medial part of the cortical area 6aβ (equivalent to pre-SMA) were characterized as being active throughout the period of arm reaching–grasping movements. In their report, however, neuronal activity in the SMA was not examined. Matsuzaka *et al.* (3) reported that pre-SMA cells were more frequently related to preparation of forthcoming reaching movements than SMA cells, whereas more SMA cells were related to the execution of reaching movements. Because the preparatory activity before impending movements has been observed in multiple motor areas, the abundance of the preparatory activity may not sufficiently characterize the pre-SMA activity. Therefore, it seemed necessary to study cellular activity in more demanding motor tasks to find differences in the pre-SMA and SMA.

In a previous study we reported that cells in the SMA exhibit two different types of activity that seem useful for preparing or coding multiple movements arranged in various temporal orders (4). In that study, monkeys were required to perform three different movements in four different sequential orders. We found that a group of SMA cells were active specifically before performing the three movements temporally arranged in a particular order (like push, pull, and turn a handle). Another group of SMA cells were tonically active after performance of a particular movement and before initiation of another specific movement (e.g., push followed by turn). We proposed a hypothesis that the activity of these cells constitutes necessary elements for planning and time-linking of multiple movements. What then are the properties of cells in the pre-SMA during performance of such multiple movements in a planned order? We report here a type of cellular activity that characterizes the pre-SMA, and that is only infrequently found in the SMA and not at all in the primary motor cortex (MI).

MATERIALS AND METHODS

We trained two monkeys (*Macaca fuscata*) to perform three movements (push, pull, or turn a manipulandum) in four different orders with their right arm. Monkeys, sitting in a primate chair, were required to place a manipulandum to a neutral position and wait 2.5–4.5 s for the first movement-trigger signal (a high-pitched tone). When the animal performed the first movement, a mechanical device returned the manipulandum to the neutral position. While keeping the manipulandum in this position, the animal had to wait 1–1.4 s for the second, and then another 1–1.4 s for the third movement-trigger signal. A series of three correct movements was rewarded with delivery of apple sauce 500 ms later. The average time interval between motor sequences was 7–8 s. Initially, the correct movement was indicated with green (for turn), red (for push), and yellow (for pull) lights. The lights came on individually at the time of each of the movements, together with the movement-triggering tone signal. During this period of visually guided five trials, the animal had to learn the correct sequence, after which the sequential motor task was performed on the basis of memory. Under this condition of memory-guided trials, only the tone signal was given as the movement trigger, without any lights. After completion of the six trials of the memorized sequential task, random flashing of lights (for 2 s) signaled the end of current sequence, and the beginning of the next sequence. After the flash of lights, the wait period (2.5–4.5 s) for the subsequent trial started. Thus, a particular sequence of movements was performed in blocks. Each block consisted of 11 trials with a particular sequence of the 3 movements, 5 trials under visual guidance and 6 with no visual cues, followed by the next block with a different sequence of movements. The order of appearance of different sequences was unpredictably varied. Electromyographic analysis showed that the forelimb muscles exhibited changes of activity for a brief period during the execution of individual movements, but not during the period when animals were waiting for the next movement-trigger signal. Although the area examined did not include the supplementary eye field (5, 6), vertical and horizontal eye movements were also monitored by electrooculographic recordings with a resolution of 2° at 20° from the primary position of the eye. Standard electrophysiological techniques for single-cell recording were used (3, 7) to record from the left pre-SMA, SMA, and the primary motor cortex. At least two blocks of trials of each sequence of movements were included in a data file while recording from individual cells.

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

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RESULTS

We recorded activity of 251 task-related cells from the part of the medial frontal cortex defined as the pre-SMA, using combinations of physiological criteria established before (1, 3). In this report, we will concentrate on 64 of these cells that exhibited preferential activity during a specific portion of the entire task-performance period. A striking finding in these cells was the occurrence of activity increase primarily when the animal was required to perform the 1st trial in any of the renewed sequence. A typical example of this type of cellular activity is shown in Fig. 1. When the animal performed the sequential motor task of push–pull–turn under the visual guidance (SEQ 1, top panel), the cell was active at the 1st trials in the five blocks of trials (indicated with arrows). At the 2nd trials in the visual block, the cell was not very active, and remained inactive at later trials. Thereafter, the same sequence of movements was performed on the basis of memory. During

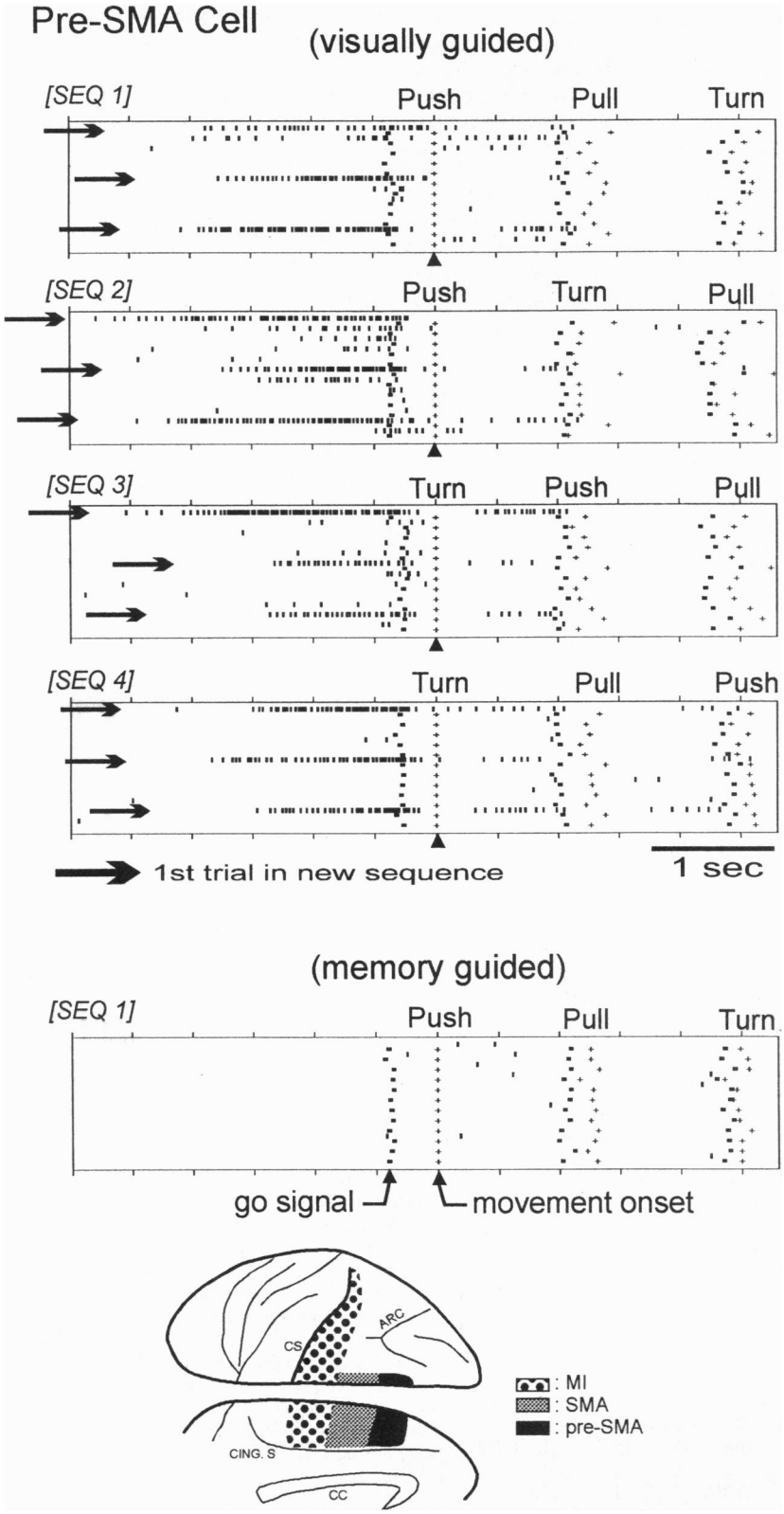

FIG. 1. Activity of a cell in the pre-SMA exhibiting discharge increase primarily at the first trial in individual sequences of visually guided three movements. This cell is active each time the animal is required to start a new sequence, regardless of the order of appearance of the three movements (SEQ 1 through SEQ 4). The activity increase starts at 1.7 s (mean lead times) before the appearance of the first visual signal, and ceases before initiation of the first movements. The cell is not at all active during performance of the three movements at any order, when the motor task is guided by memory. In raster displays, each row represents a trial, and dots represent individual discharges of this cell. Small squares and crosses denote the times of occurrence of the trigger signal and movement onset. Rasters are aligned at the onset of the first of the three movements (arrowheads). Each horizontal arrow denotes the beginning of the first trial in a series of renewed sequences of the three movements (five visual trials followed by six memory-guided trials). Occurrences of blocks of SEQ 1 through SEQ 4 were intermixed during actual task performance, but in raster displays, trials of the same sequence were rearranged together. A cortical map at bottom shows locations of the SMA and pre-SMA in the surface of the hemisphere viewed from the top and from the inside. Rostral is to the right. CS, central sulcus; ARC, arcuate sulcus; CING. S, cingulate sulcus; CC, corpus callosum.

that period, the cell was not at all active (Fig. 1, bottom panel). When the animal was to perform the sequence of push–turn–pull (SEQ 2), the cell was again active at the first of the five visually guided trials. The same cell was also active at the 1st trials of other sequences (SEQ 3 and SEQ 4), but not active during any sequences under memory guidance. To demonstrate more clearly the specificity of the cellular activity to the renewal of sequences, the cellular activity was rearranged and summated according to the order within blocks (1st through 5th) of visually-guided trials, combining the data at the performance of all sequences. As apparent in Fig. 2, activity was strongest at the 1st trials, only modest at 2nd trials, and almost nonexistent at the 4th and 5th trials. This trend of specificity was quantified (Fig. 2, bottom) where the mean discharge frequency of the cell is plotted against the trial number in individual sequences (the 6th through 11th trials were memory guided).

In a majority of the 64 cells, the activity started more than 1 s (mean lead time = 1.6 s) before the appearance of the first of the three visual signals, and mostly ceased before the initiation of the first movement in the sequence. In other cells (33%), however, the activity was also observed until the onset of the second movement of the three. An example of such activity is shown in Fig. 3. In these cells, the activity was also the strongest at the 1st trials and much weaker at later trials. Interestingly, none of the 64 cells were strongly active after the second movement.

Aside from the 64 cells that had specific relationship to the 1st of the renewed sequences, we observed other pre-SMA cells that were active in relation to movement execution during waiting periods before initiation of movements or in relation to sensory signals. Some pre-SMA cells also showed activity properties that were similar to those of SMA cells that were recently reported (4). A detailed account of these activities will be discussed elsewhere.

We have recorded 385 task-related cells in the SMA from the same two monkeys, of which only 6 (1.6%) exhibited similar activity specific to the 1st trials in new sequences. None of 258 task-related cells in the primary motor cortex exhibited this type of activity. Electromyographic analysis confirmed that there were no changes in muscle activity during the transition period between the sequences. The electrooculogram showed that eye movements during the transition period were not different from those observed in other periods. The frequency

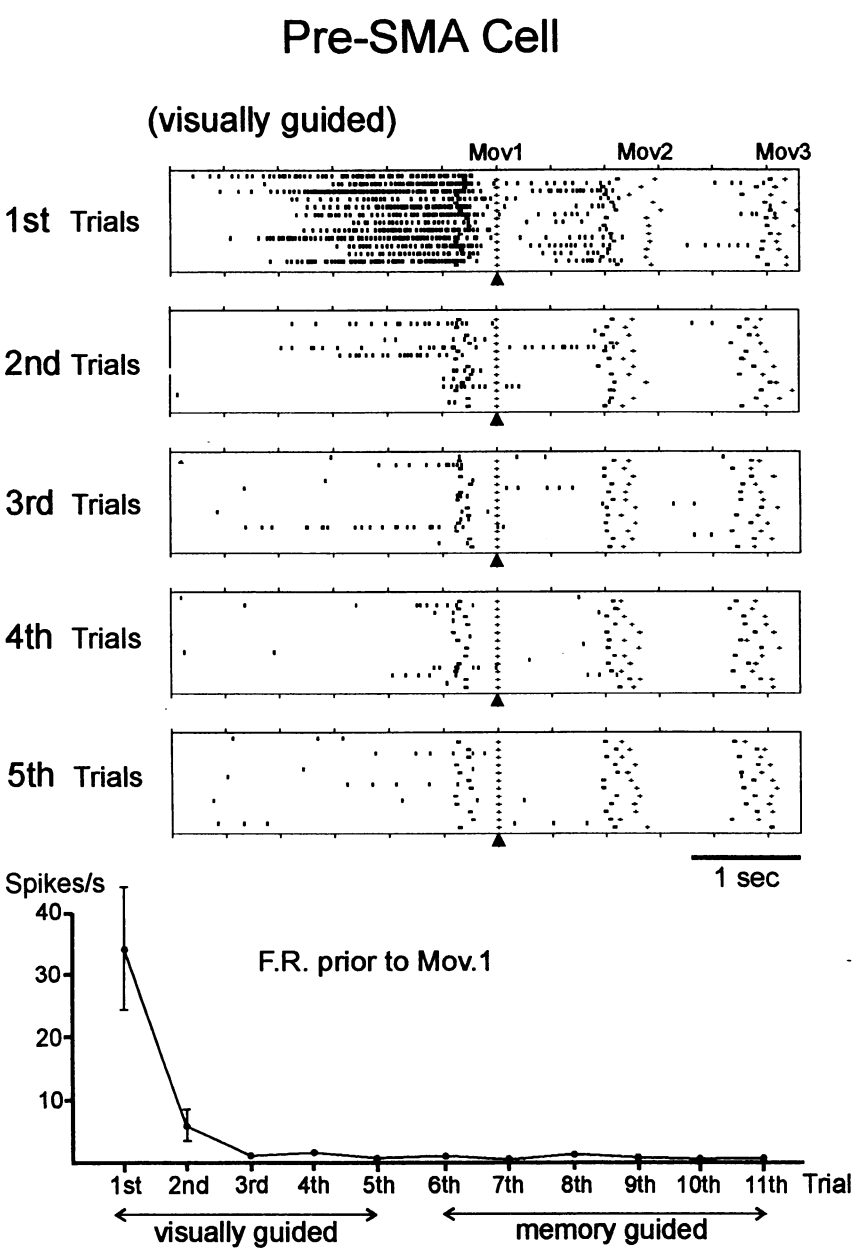

FIG. 2. (*Top*) Specificity of the activity of the pre-SMA cell to new trials. In raster displays, the activity of the same cell shown in Fig. 1 is rearranged to summate all 1st through 5th trials under visual guidance, irrespective of the order of the three movements in the motor sequence. (Data at SEQ 1 through SEQ 4 are added.) Formats for the raster display are the same as in Fig. 1. (*Bottom*) Discharge frequency of the cell at performances of the 1st through 11th trials in all sequences. Mean discharge frequencies (small dots) and SD (vertical bars) during 1 s of the preparatory period preceding the first of the three movement-trigger signals are plotted against successive trials.

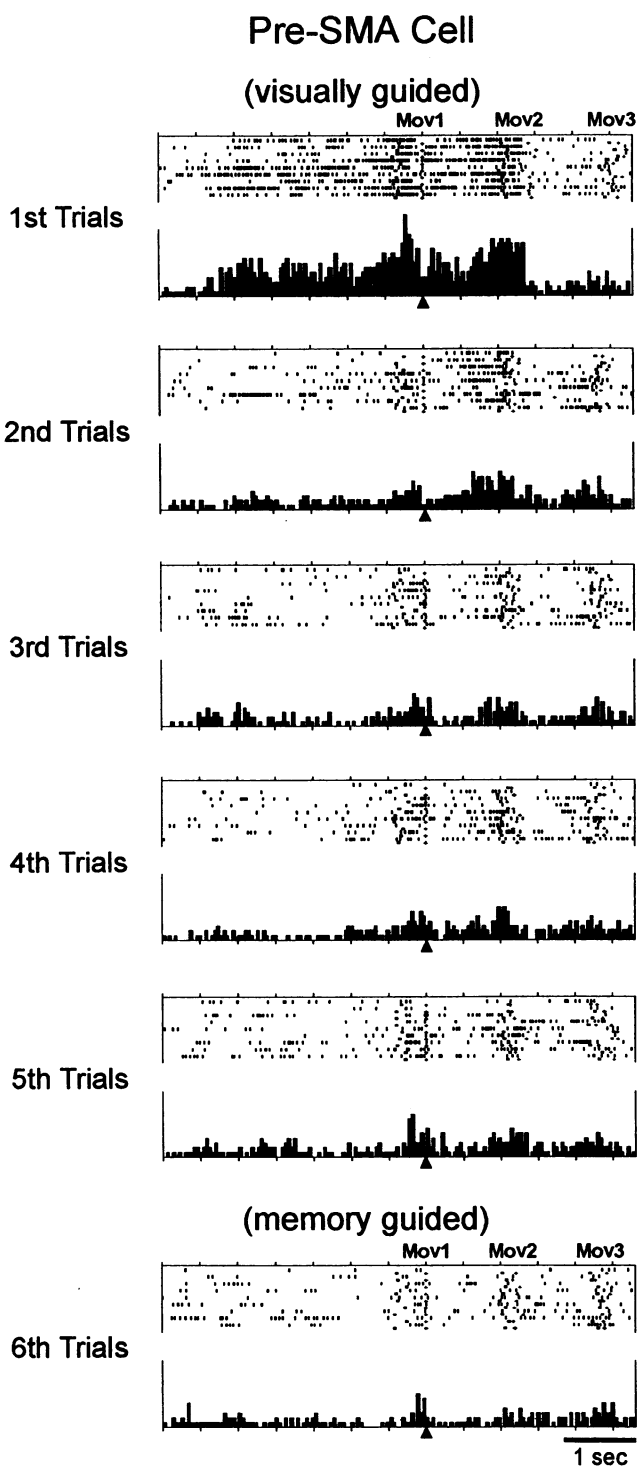

FIG. 3. Activity of a cell in the pre-SMA exhibiting activity increase, which lasts until the performance of the second (Mov2) of the three movements. In this cell, the activity is also the most intense at 1st trials under the visual guidance. The display format is the same as in Fig. 2, and trials of all sequences are combined.

of occurrences, amplitudes, and directions of saccades were not different in the 1st through 5th visually guided trials.

DISCUSSION

In this study we found a group of pre-SMA cells that were specifically active only at a very limited period of time during the entire behavioral paradigm. The activity of interest was not simply related to occurrences of any sensory signals. The activity did not reflect preparation or execution of movements, or any sequences of motor performance. Instead, the activity was observed every time the animal started a trial in which the sequence of the three movements had to be renewed. What were behavioral requirements for the animal during the period when the specific activity was found?

Under the visual condition in the present task, the animals performed each movement in response to the three visual signals. At the same time, the animals acquired information about the temporal sequence of the three motor events. After completion of a block of five such trials, the animals were ready to perform a sequence of three movements according to the stored information that we tentatively call a motor plan. Under the memory-guided trials, the correct performance of the animals of the three movements depended on the motor plan. After the performance of six trials under that condition, the animals had to abandon that motor plan and then prepared to build another motor plan. Thus, at a transition between a current sequence to a new sequence, the animals had to update motor plans for correct performance of the three movements. It was at this particular time period when the cellular activity was specifically observed in the pre-SMA.

There exists some superficial resemblance between the presently reported activity and the activity reported as learning-selective in the premotor cortex (8) and in the supplementary eye field (9). The learning-selective activity was an activity found when monkeys learned conditional association of novel sensory signals and directions of movements. In these reports, the activity appeared during several trials while the animals acquired a correct association between the sensory and motor events. However, in the present study, no novel signals were given to the animals. All visual signals were familiar, and the animals had already established associations of the visual signals and the three movements during training sessions. Furthermore, the presently found activity appeared most intensely at the single trials where the animals had to update the motor plan. Thus, the activity is different from the learning selective activity that was previously reported. Is there a possibility that the activity in the transitional period can be explained by the increased difficulty of the task? This is not likely because the error rate in the 1st visual trials was not different from the error rate in the other trials. Is the transitional activity caused by enhanced arousal level or alertness? Two observations in the present study were relevant to this question. First, statistical analysis revealed no significant differences in reaction times (the interval between the visual cue onset and movement onset) at 1st and 2nd visual trials, despite a huge difference in neuronal activity (Figs. 1 and 2). Second, in the 43 pre-SMA cells, including the cell shown in Figs. 1 and 2, the activity increase was primarily observed in a period preceding the first of the three movements (Mov1), and much less or not at all before the second movement (Mov2). There is no reason to assume that the arousal level decreased after Mov1, because the animals still had to receive the second cue light, respond with Mov 2, and store the information about what was performed. Therefore, the increase in the arousal level cannot explain the neuronal activity in the transitional period, although its influence on the activity may not entirely be ruled out.

Recent studies have revealed differences in anatomical connectivity of the pre-SMA and SMA (10, 11). Because the pre-SMA receives direct input from the prefrontal cortex (in and around the principal sulcus), as well as from the rostral cingulate motor area, it is situated at a pivotal position to link information about the behavioral context to processes for motor performance (12, 13). This study is the first to report a striking difference in cellular activity between the pre-SMA and SMA in relationship to a behavioral aspect. The present finding seems to suggest that the pre-SMA, rather than the

SMA, is involved in updating motor plans. An interesting question is how the kind of cellular activity observed in the pre-SMA is used to achieve its functional role. A possibility is the involvement of cortical outputs to the basal ganglia and the output pathway from the basal ganglia back to the cortex, because the importance of the cortico-basal ganglia loops in motor learning (14) or in shaping motor behavior on the basis of contextual information has recently been highlighted (15). Although the question remains open, the present study provides information about the way in which the cellular activity in the pre-SMA is used in an aspect of cognitive motor control.

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