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Role of primate basal ganglia and frontal cortex in the internal generation of movements

III. Neuronal activity in the supplementary motor area

Ranulfo Romo* and Wolfram Schultz

Institut de Physiologie, Université de Fribourg, CH-1700 Fribourg, Switzerland

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Summary. This study is a part of a project investigating neuronal activity in the basal ganglia and frontal cortex and describes externally and internally induced preparatory activity in the supplementary motor area (SMA), which forms a closed neuronal loop with the striatum. Monkeys made self-initiated arm reaching movements toward a constant target in the absence of phasic external stimuli. In separate blocks of trials, animals performed in a delayed go no-go task in which an instruction cue prepared for subsequent movement or no-movement to a trigger stimulus. A total of 328 neurons were tested in the delay task. Of these, 91 responded transiently to the instruction light with a median latency of 262 ms. Three quarters of these responses were restricted to the instruction preparing for arm movement, as opposed to withholding it, and thus may be involved in movement preparation processes. Sustained activation during the instruction-trigger interval was found for 67 neurons and occurred nearly exclusively in movement trials. Activation usually increased gradually after the cue and ended abruptly upon movement onset and thus could be related to the setting and maintenance of processes underlying the preparation of movement. Time-locked responses to the trigger stimulus were found in 38 neurons and were usually restricted to movement trials (median latency 80 ms). Activity time-locked to movement execution occurred in 67 neurons, beginning up to 252 ms before movement onset. A total of 266 neurons were tested with self-initiated arm movements. Of these, 43 showed premovement activity beginning 610–3030 ms before movement onset (median 1430 ms). The activity increased slowly and reached its peak at 370 ms before movement onset. It ended before movement onset or continued until the arm began to move or reached the target. This activity appears to reflect neuronal processes related to the internal generation of movements. Two thirds of activations preceding self-initiated movements occurred in neurons not activated before externally instructed movements, suggesting a selectivity for the internal generation process. Activity related to the execution of self-initiated movements occurred in 67 neurons: it began during and up to 420 ms before movement onset and was usually not associated with premovement activity. Most of these neurons were also activated with stimulus-triggered movements, suggesting a lack of selectivity for the execution of self-initiated movements. In comparison with the striatum, more SMA neurons showed preparatory activity preceding externally instructed movements (transient 27% vs 16%, sustained 20% vs 12%) and self-initiated movements (16% vs 11%). Whereas transient responses showed similar latencies and durations in the two structures, sustained preparatory activity preceding externally instructed or self-initiated movements began and reached its peak earlier in SMA compared to striatal neurons. However, due to the long durations, sustained activation largely overlapped in the two structures, and thus essentially occurred simultaneously. Instruction-induced or internally generated preparatory activity may originate outside of the SMA and striatum or may derive from activity reverberating in cortico-basal ganglia loops, possibly in conjunction with other, closely associated cortical and subcortical structures. These data would favor a conjoint role for SMA and striatum in the internal generation of individual behavioral acts and the preparation of behavioral reactions.

Key words: Behavior – Movement – Go no-go task – Basal ganglia – Monkey

Introduction

Several lines of evidence suggest that the supplementary motor area (SMA) at the medial surface of area 6 is involved in the internal generation of voluntary movements (Eccles 1982; Goldberg 1985). Patients with

* Present address: Institute of Cellular Physiology, National Autonomous University of Mexico, Box 70-600, Mexico 04510

Correspondence to: W. Schultz

extensive SMA lesions suffer from a predominant lack of internally initiated, intentional behavioral actions, including limb movements and speech, whereas behavioral reactions to external stimuli are less impaired (Talairach et al.1973; Laplane et al.1977; Goldberg et al. 1981). Well-controlled bilateral lesions of SMA in monkeys lead to impairments in self-generated movements requiring an internal representation of the target (Thaler and Passingham 1989), whereas unilateral SMA removal does not result in similar deficits (Brinkman 1984). Electrophysiological studies investigating the intentional aspect have revealed a negative voltage shift over the SMA and other frontal and parietal cortical areas which preceded by about 1 s the onset of spontaneously initiated arm movements (readiness potential, Kornhuber and Deecke 1965). Illustrative examples of the role of the SMA in the internal representation of movements are the increased blood flow occurring during the mental rehearsal of complex sequences of finger movements (Roland et al. 1980) and the neuronal activity specifically preceding particular sequences of arm movements (Mushiake et al. 1990).

The different areas of frontal cortex are intimately linked with the basal ganglia through closed neuronal loops (Alexander et al. 1986). In one of these loops, the SMA projects to striatum, particularly lateral putamen and dorsolateral caudate (Künzle 1978; Selemon and Goldman-Rakic 1985), which in turn connects, via globus pallidus and ventroanterior thalamus, back to the cortex at the level of SMA and motor cortex (Percheron et al. 1984; Schell and Strick 1984; Nambu et al. 1988). Thus, this loop links two major centers involved in the internal generation of voluntary movement, the SMA and the basal ganglia. A major participation of the basal ganglia in the generation of movements is suggested by the deficits occurring after destructions of nigrostriatal dopamine neurons in parkinsonian patients and experimentally lesioned animals, and after lesions of the globus pallidus in patients suffering from Wilson's disease.

The two preceding studies in this series dealt with the activity of striatal neurons during the preparation and execution of self-initiated and stimulus-guided arm movements (Romo et al. 1992; Schultz and Romo 1992). In order to further elucidate the role of cortico-basal ganglia loops in the internal generation of movements, the present study investigated the activity of SMA neurons in the same behavioral contexts using the same monkeys and compared this with that obtained in the striatum. Animals performed in a delayed go no-go task in which an instruction signal prepared the animal to perform or refrain from an arm movement reaction to a subsequent trigger stimulus. Activity of the same neurons was examined during self-initiated arm movements that animals performed in the absence of any phasic external stimuli. Whereas self-paced movements in previous studies of SMA neurons were considerably associated with external stimuli (Okano and Tanji 1987; Kurata and Wise 1988), we were particularly interested to employ a minimum number of temporal constraints without any reference to external signals and to avoid automatically paced task performance. Some of these data have been presented before in preliminary form (Romo and Schultz 1987; Schultz et al. 1989).

Materials and methods

The study was performed on the same three *Macaca fascicularis* monkeys used in the preceding reports, in which all experimental procedures are described in detail (Romo et al. 1992; Schultz and Romo 1992). Activity of single neurons in the left SMA was recorded with movable microelectrodes during contralateral performance of a delayed go no-go task and during self-initiated arm movements.

In the delayed go no-go task, an instruction light was illuminated above one of two small food boxes positioned in a mediolateral arrangement in front of the animal and at eye level. Covers in front of each box prevented viewing of opening doors and interiors. In go trials, the lateral box opened audibly 2–3 s or 4–7 s after illumination of the lateral light, and the animal immediately reached from the resting key to the box and collected a small morsel of apple, cookie or raisin. In no-go trials, which alternated randomly with go trials, the medial food box opened after illumination of the medial instruction light, but animals remained motionless until 3 s after box opening and received no reward. The noises of door opening were so similar for the two boxes that animals could not use them as cues. This was verified by occasionally opening a door without the preceding instruction light. The instruction light was either extinguished after 1 s (short instruction), or after 5–10 s in no-go trials and upon key release in go trials (continuous instruction). Thus, the instruction served as preparatory signal for the subsequent behavioral reaction, whereas the trigger stimulus determined the time of reaction without providing information about the expected behavioral reaction. Self-initiated arm movements were performed in separate blocks of trials in which the instruction lights were extinguished and food boxes were not operated. The animal released the resting key and reached in the permanently open lateral food box behind a cover at a self-chosen moment and in the complete absence of phasically changing external cues. There was no special signal indicating the transition between tasks and animals realized the task to be run from the result of the first trials. Animals regularly reached toward the lateral food box when the delay task had not been employed for a few tens of seconds.

Electromyographic (EMG) activity was monitored during all neuronal recordings from at least two muscles of the arm, dorsum, trunk and leg, ipsi- and contralateral to the moving arm. Principal muscles for the reaching movement were the extensor digitorum communis and biceps and, to a varying extent, the anterior and lateral deltoid. Some dorsum muscles were bilaterally active during, but rarely before, the movement (Schultz and Romo 1992). Particular care was taken to ensure muscular relaxation before movement-related activity. In addition, the animal's behavior was continuously monitored by two video cameras mounted above and in front of the animal in order to detect movements not involving the recorded muscles. Neuronal activity in the delay and self-initiated movement tasks was studied only in the absence of untimely muscle activity and premature movements during the preparatory phases preceding movement-related muscle activity.

Horizontal and vertical components of eye movements were recorded during neuronal recordings with electrooculographic (EOG) electrodes implanted in the orbits. In the delay task, the eyes made a saccade to the instruction signal, fixated the light for an initial period of about 1 s and subsequently moved to other targets (Schultz and Romo 1992). The trigger stimulus elicited a saccadic eye movement toward the food boxes, both in go and no-go trials (Romo et al. 1992). Ocular reactions were absent when the eyes incidentally fixated the instruction and trigger stimuli when they appeared. In the self-initiated movement task, saccades toward the food box occurred at 200–800 ms before movement onset. The eyes fixated the food box until the animal's hand left the box 500–600 ms after movement onset. Because food boxes were located at eye level, saccades were more prominent in the horizontal than the vertical plane. Onsets and offsets of saccadic eye movements were determined off-line by single-trial analysis using a movable cursor on a computer screen.

After the experiment, animals were deeply anesthetized with pentobarbital and brains were fixed by transcardiac perfusion with formaldehyde. The x–y movable electrode-holding microstage was mounted, and four steel cannulas were introduced vertically into the brain in order to delimit the recording area. The brain was cut into 50-μm-thick coronal sections which were stained with cresyl violet. Positions of neurons were graphically reconstructed by projecting brain sections on paper. Outlines of the cortex were drawn and electrode tracks and small electrolytic lesions made during the last recording sessions were marked.

Timing, magnitude and statistical significance of all behavior-related increases of neuronal activity were assessed with the sliding window procedure using the Wilcoxon test. Magnitude of activation was calculated by counting neuronal impulses between onset and offset of activations and expressed as the percentage above background activity during the control period. Parameters for determining activation after instruction onset were: a 1 or 2 s control period before instruction, step size 25 ms, time window 250 ms, except for sharp responses (latencies <250 ms with durations <350 ms), where step size was 8 ms and the time window was 48 ms. Offsets of activation referenced to box opening, key release, enter box and leave box, respectively, were measured with the same control period, step size 20 ms, and time window 200 ms moving backwards. Activity preceding self-initiated movements was evaluated with a 400 ms control period before the presumed activation, as judged from visual inspection, step size 20 ms and a time window of 200 ms. Relations to execution of movements were assessed with step size 8 ms and a time window of 80 ms. The latency, duration and statistical significance of responses to box opening were assessed from the inflections of the cumulative frequency distribution referenced to box opening against a line representing control activity, followed by a Wilcoxon test over the duration of the activation against a 250–500 ms control period before box opening. Peak latency was taken to be 250 ms after onset of the 500 ms interval showing the highest activity in the peri-event time histogram of neuronal impulses. Only data from neurons evaluated quantitatively with at least 10 trials in a given situation are reported. The median (50th percentile) was determined as single numerical value for distributions of data. Differences in distributions were assessed with the two-tailed Mann-Whitney U-test.

Results

Recordings were obtained from 454 SMA neurons, of which 328 were recorded during performance of the delay task and 266 during self-initiated movements; 140 neurons were studied during both tasks. The investigated area did not contain the giant pyramidal cells of layer V typical for area 4 (Wise and Tanji 1981; Macpherson et al. 1982) and was located in the medial wall of the frontal cortex up to 3 mm lateral to the midline and extended from about 1.5 mm posterior to 5.5 mm anterior to the posterior border of the arcuate sulcus (Fig. 1). It therefore comprised large parts of the medial agranular area 6 (the rostral part of area 6aα and most of area 6aβ of Vogt and Vogt 1919). This region is generally referred to as SMA, on the basis of anatomical connections (Muakkassa and Strick 1979; Godschalk et al. 1984), electrophysiological recordings (Tanji and Kurata 1982) and microstimulation (Mitz and Wise 1987; Huerta and Kaas 1990). However, recent investigations emphasize the differences between subdivisions 6aα and 6aβ, suggesting a functional dichotomy within SMA or, alternatively, a restriction of SMA proper to area 6aα (Luppino et al. 1990). Neurons were sampled from both subdivisions in approximately equal proportions. They are considered together because of similar activity in the paradigms used.

Occasional intracortical microstimulation in area 6 with the fine tipped electrodes used for single neuron recordings failed to consistently evoke movements with currents up to 100 μA, in agreement with earlier studies (Smith 1979; Wise and Tanji 1981; Mitz and Wise 1987). Movements of the lower extremities were evoked with much lower currents from the posteriorly adjoining motor cortex.

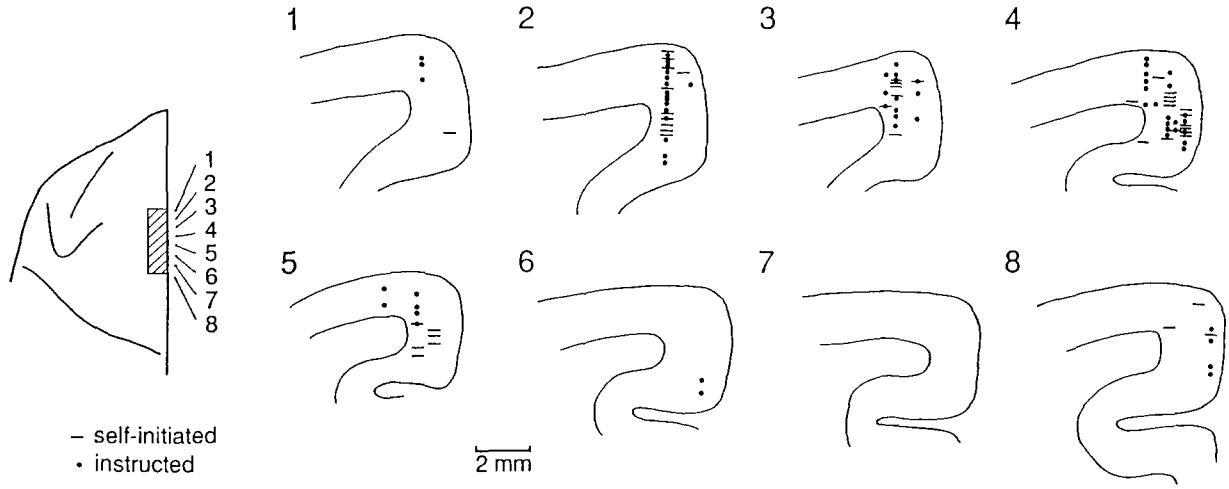

Fig. 1. Reconstruction of recording positions of SMA neurons according to different types of premovement activity. Positions in all three monkeys are projected on brain sections from one animal, using the posterior border of the arcuate sulcus as common reference. The recording area is indicated by the *hatched pattern* on the cortical surface (*left*). *Numbers* at coronal sections correspond to the coronal planes of 1 mm anteroposterior distance indicated on the surface view. *Scale* (2 mm) applies to coronal sections only. Neurons activated before self-initiated movements (*bars*) are indicated separately from neurons showing sustained activity during the instruction-trigger interval (*dots*)

We did not specifically search for neuronal activity in relation to eye movements. Such activity has been found in the corresponding region of the medial agranular frontal cortex (Schlag and Schlag-Rey 1987; Schall 1991). However, we have related neuronal activity off-line to the onset and offset of saccadic eye movements that were systematically sampled during neuronal recordings and found that none of the observed activity was related to ocular saccades.

Instruction-induced preparatory activity

Of the 328 neurons tested in the delay task, 205 were studied with ≥ 10 trials in each of the go and no-go situations. Only data from go trials will be described for the remaining 123 neurons recorded during <10 no-go trials.

Transient responses. Responses following the instruction signal and terminating before the trigger stimulus were found for 91 neurons (28%). Responses occurred in 72 neurons only in go trials, in 8 neurons in both go and no-go trials, and in 11 neurons only in no-go trials. Responses were independent of short or continuous instructions. Responses to the offset of the short instruction were not observed. Quantitative evaluation revealed median latencies, durations and magnitudes of 262 ms, 400 ms and 218% in go trials ($n=80$), and of 237 ms, 275 ms and 256% in no-go trials ($n=19$), respectively. The differences between go and no-go trials were insignificant ($P>0.01$). These values are similar to those of striatal neurons in the same animals (Schultz and Romo 1992), and show no significant difference ($P>0.03$).

Sustained activations. Activity following instruction onset and lasting beyond the trigger stimulus were found in 67 neurons (20%). Responses were restricted to go trials in 65 neurons, and only 2 neurons were activated in no-go trials. None of the neurons were activated in both go and no-go trials. A typical example is shown in Fig. 2, which also illustrates how activity continued when the trigger signal was delayed. Activity began with a median latency of 450 ms after instruction onset. Peak activity was reached in most neurons during later periods of the instruction-trigger interval, at a median of 1700 ms after instruction onset. Magnitude of peak activity amounted to an increase of 269% above background. Sustained activation was independent of the use of short or continuous instruction lights [38 of 207 (18%) and 36 of 171 neurons (21%), respectively, were activated]. Onset latencies, peak latencies and peak magnitudes differed insignificantly between the two varieties of task ($P>0.04$). Most activations in go trials terminated sharply after the trigger stimulus and before movement onset (34 neurons) (Fig. 3A). In other neurons they lasted beyond movement onset (Fig. 3B, C), ending before the animal's hand entered the food box (9 neurons), between entering and leaving the box (3 neurons), or after leaving the box (9 neurons). (Ten neurons with additional trigger responses were excluded from this analysis.) Onset and peak latencies were significantly shorter in SMA neurons than in striatum (caudate and putamen pooled; 450 vs 1137 ms, 1700 vs 2337 ms), and the magnitude lower (269% vs 415%) (all $P<0.01$).

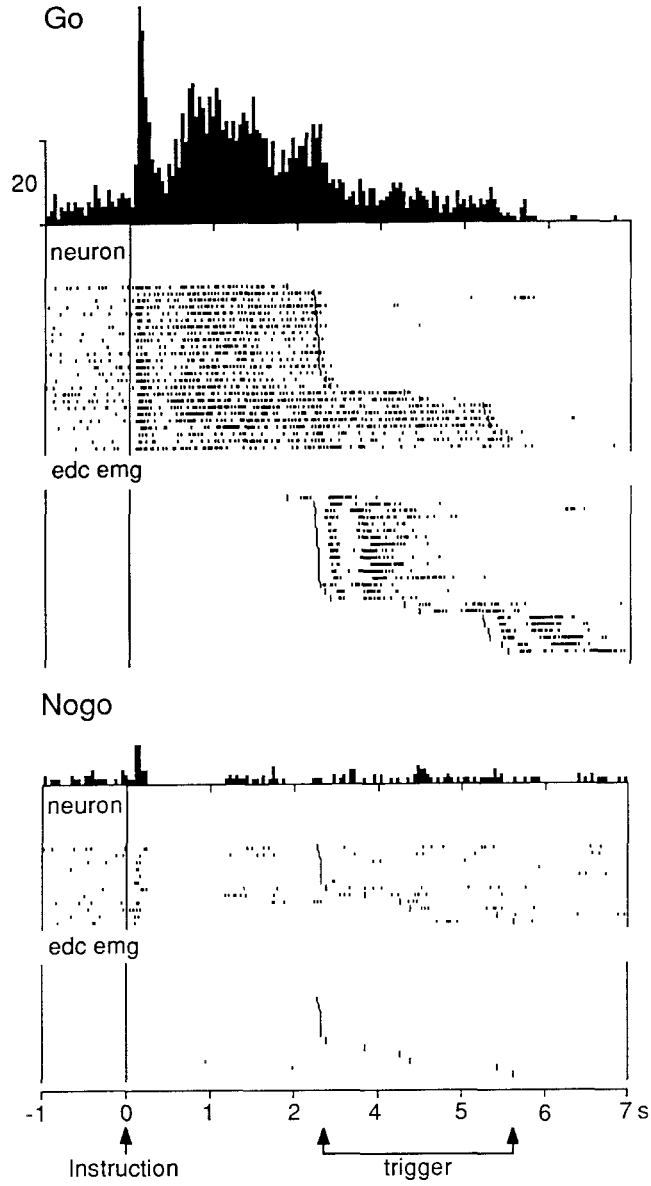

Fig. 2. Sustained activation during the instruction period in go trials (*Go*), lack of sustained activity in no-go trials (*Nogo*). An additional transient response to instruction onset is more prominent in go than in no-go trials. Peri-event time histograms in top and bottom are composed of neuronal impulses shown as dots below. Rectified electromyographic activity from extensor digitorum communis muscle (*edc emg*) exceeding a preset level was converted into digital pulses and is shown as separate raster below neuronal dots. EMGs were recorded in the same trials as neuronal impulses. Each raster dot denotes a neuronal impulse or EMG pulse, and distances to instruction onset correspond to real-time intervals. The trigger stimuli are indicated by *small vertical bars* in rasters. Each line of dots shows one trial. Go and nogo trials alternated randomly during the experiment and were separated off-line (top and bottom, respectively). The sequence of trials is rearranged according to the length of instruction-trigger intervals. Continuous instruction. *Vertical calibration* is 20 impulses/bin for histograms (bin width 40 ms)

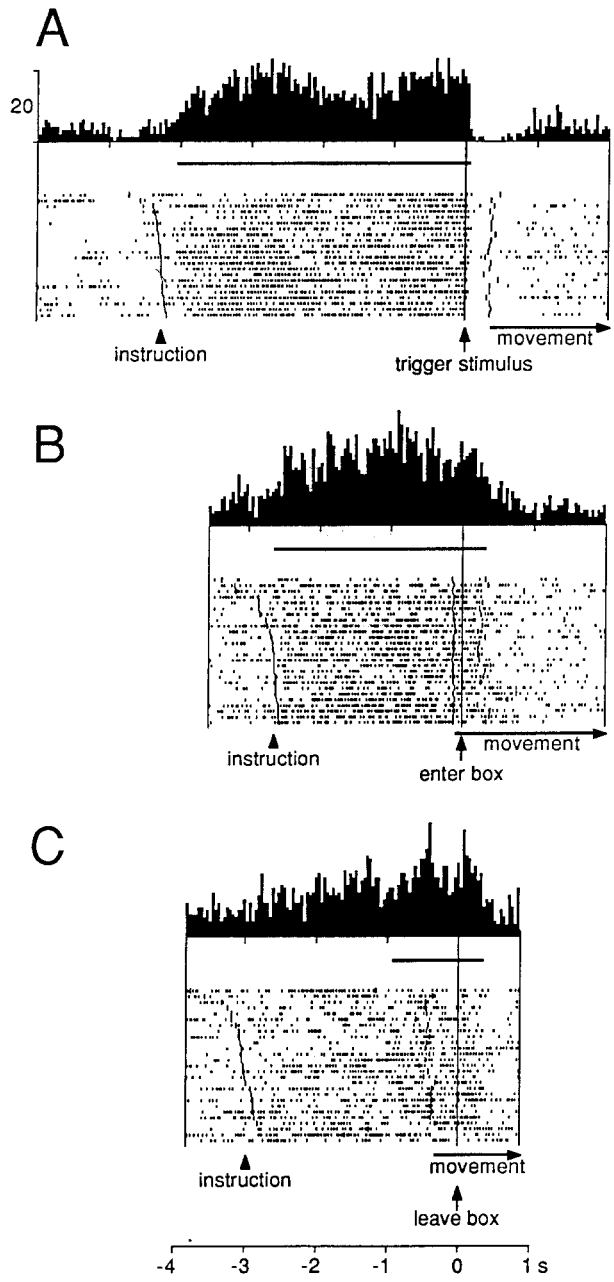

Fig. 3A–C. Relationships of offset of sustained activations to trigger stimulus and movement onset for three neurons. Histograms and raster displays are aligned to trigger stimulus **(A)**, entering the food box **(B)**, and leaving the food box **(C)**. *Horizontal arrows* below rasters indicate the period of movement, its onset (key release) being marked by *small vertical lines* in rasters. Leaving the box in **B** is indicated by *small vertical lines* in rasters to the right of the reference line. *Horizontal bars* below histograms mark durations of neuronal activation determined with the sliding window procedure. Onset and offset times in relation to the respective reference events were: **A** −4030 and +110 ms; **B** −2650 and +230 ms; **C** −970 and +410 ms

Activity following the trigger stimulus

Door opening in go trials triggered the arm movement with reaction times of 250–330 ms. The activity of 36 neurons (11%) increased in response to this stimulus, as judged from visual inspection of the temporal relationship to the trigger stimulus and the lack of a relationship to onset of EMG activity and movement in individual trials (Fig. 4). Four of these neurons also responded to the trigger stimulus in no-go trials, in which arm movement and EMG activity were absent (Fig. 4B). Only two neurons responded exclusively in no-go trials. Trigger responses in go trials occurred at median latencies of 80 ms. Latencies did not differ significantly from those of striatal neurons ($P > 0.1$).

Activity in 67 neurons (20%) began after movement onset or showed better temporal relations to movement onset than to the trigger stimulus. These movement-related neurons were not activated in no-go trials. Movement-related activity began at a median time of 84 ms before movement onset (range −252 ms to +556 ms relative to movement onset) and lasted for 272 ms.

Self-initiated movements

Premovement activity. Statistical evaluation with the time window method revealed significant increases in activity of 43 from 266 neurons (16%) which began more than 500 ms before onset of self-initiated arm movements and thus well before earliest task-related muscle activity (Fig. 5). None of these activations showed reliable trial-by-trial relationships to onset or offset of saccadic eye movements. Onset of activation was statistically detected between 610 and 3030 ms before key release, with a median of 1430 ms. Activity usually increased slowly and reached its peak at a median of 370 ms before movement onset. Peak magnitude amounted to 487% increase over background. Activations terminated before movement onset in 16 neurons (Fig. 5B). For the remaining neurons, activity fell off rather sharply at or after movement onset (Fig. 5A, C, D), ending before the animal's hand entered the food box (5 neurons), between entering and leaving the box (19), or after leaving the box (3). Median offset time of activations in all 43 neurons was 230 ms after movement onset.

A total of 140 neurons was studied during both self-initiated and instructed movements. Of these, 7 neurons showed statistically significant sustained premovement activity in both tasks, 12 neurons only with self-initiated movements (Fig. 6), and 16 neurons only in go trials of the delay task. When considering all activated neurons, activity preceding self-initiated movements ($n = 43$) showed later peaks ($P < 0.002$) but insignificantly later offsets and higher peak activity ($P > 0.01$), than before instructed movements ($n = 65$) (all values in relation to movement onset). The population histograms of Fig. 7 show the overall profiles of activity preceding movements in both tasks.

Premovement activity preceding self-initiated movements began earlier, reached its peak earlier and showed later offset times in SMA than in the striatum (Schultz and Romo 1992), although none of these differences was statistically significant (1430 vs 1160 ms before movement, 370 vs 270 ms before movement, and 230 vs 120 ms after movement onset; all $P > 0.02$).

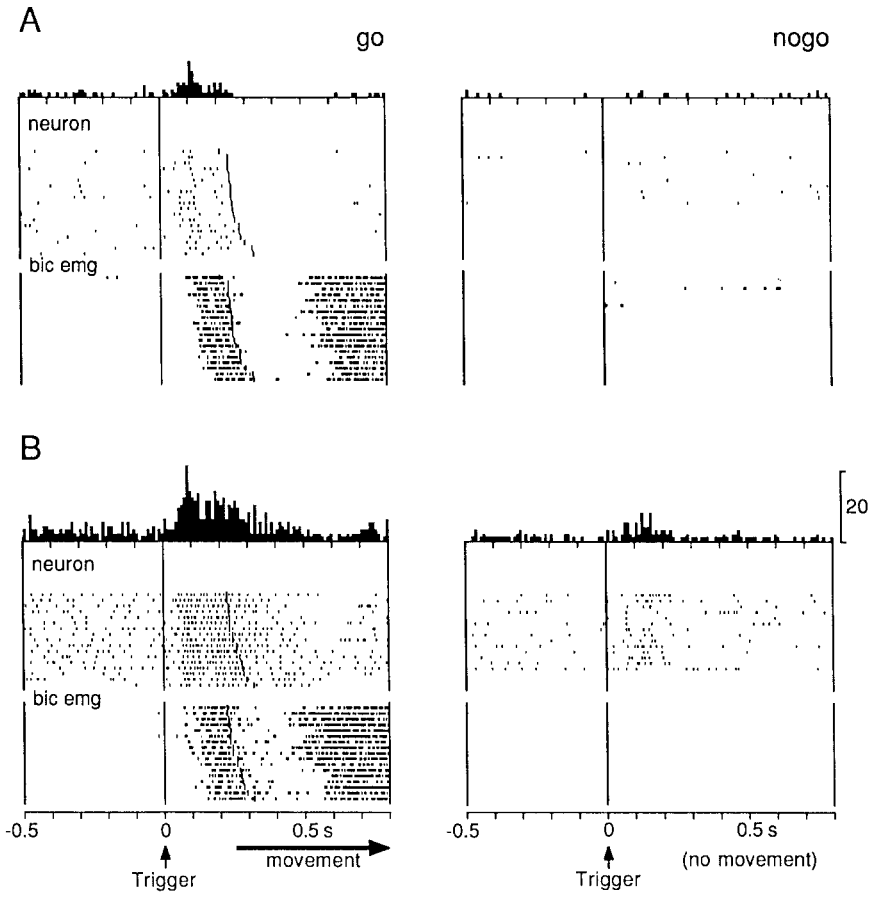

Fig. 4A, B. Activating responses in two SMA neurons to the trigger stimulus for the arm reaching movement (*left*). *Right*: Absent **(A)** and moderate **(B)** response in no-go trials without arm movement. Movement onset (key release) is indicated by *small vertical lines* in rasters. The sequence of go trials is rearranged according to the stimulus–movement interval (reaction time), whereas in no-go trials the original sequence is preserved downward

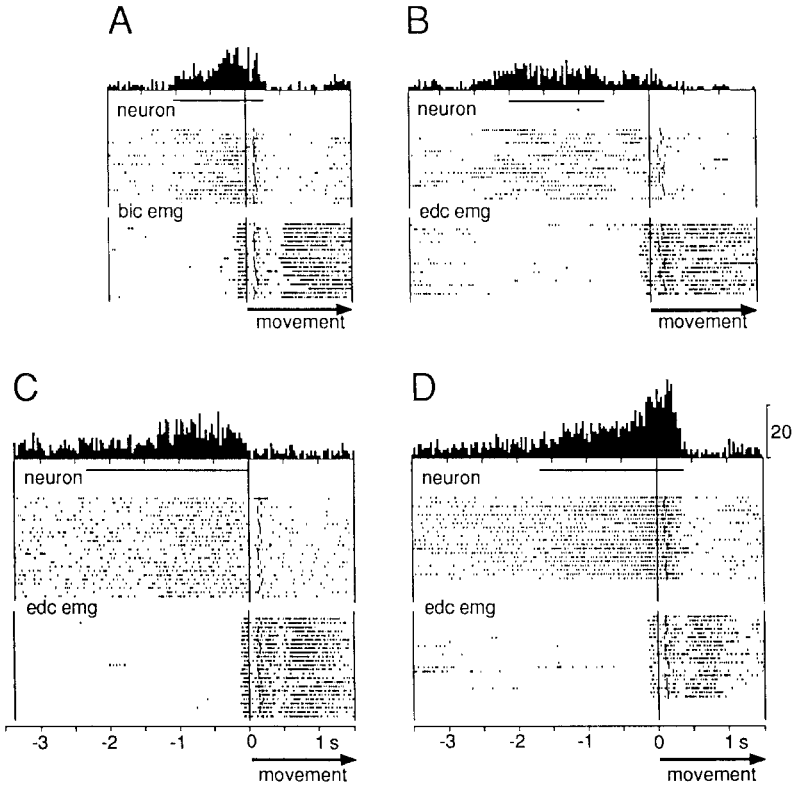

Fig. 5A–D. Premovement activity in four SMA neurons during performance of self-initiated movements. **A** Short lead activation terminating after box entry. **B** Long lead activation terminating before movement onset. Note that the statistical procedure detects only the common part of considerably varying activity (*bar* below histogram). **C** Long lead activation terminating upon movement onset (key release). **D** Long lead activation culminating after movement onset and terminating after box entry. Histograms and rasters are referenced to movement onset (key release). *Small vertical lines* in rasters indicate entering of the food box. *Horizontal bars* below histograms indicate durations of statistically significant activations determined with the sliding window procedure. The following values were obtained for onset and offset times, respectively: **A** −1010 ms and +260 ms; **B** −1970 ms and −620 ms; **C** −2370 ms and 0 ms; **D** −1640 ms and +385 ms

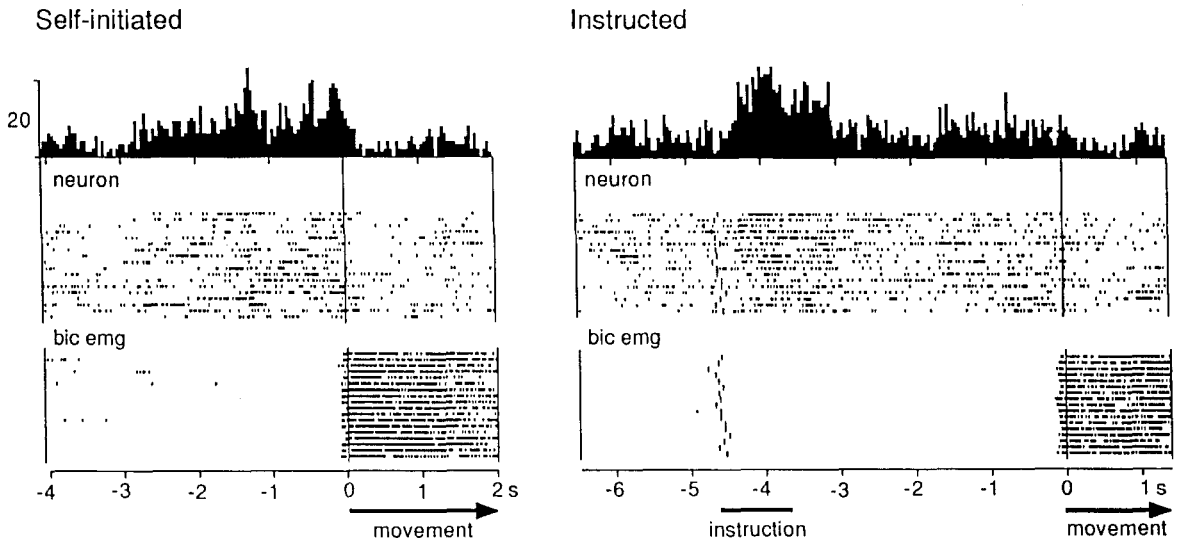

Fig. 6. Sustained premovement activity restricted to self-initiated movements. In the delay task (*right*), only a transient response to instruction onset occurred that terminated several seconds before movement onset. The two tasks were performed in separate blocks of trials while recording from the same SMA neuron. *bic emg*, Electromyographic activity from biceps muscle

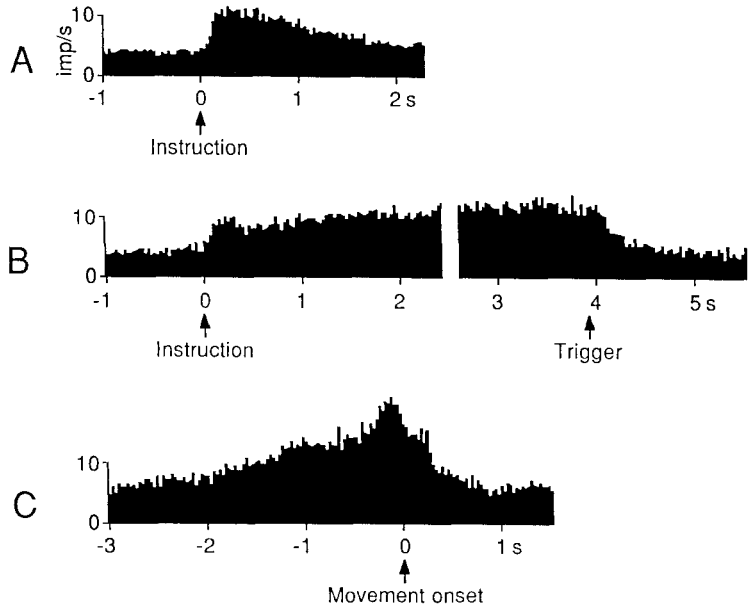

Fig. 7A–C. Population histograms of average instruction responses and premovement activity. **A** Average of transient responses to instruction onset in go trials. Instruction responses in individual neurons were defined as transient when they terminated before the subsequent trigger stimulus. **B** Sustained activations in go trials of the delay task. The time base is split because of variable intervals between instruction and trigger stimuli. **C** Premovement activity with self-initiated movements. Histograms from each neuron with statistically significant increases normalized for trial number were added and the resulting sum was divided by the number of neurons and calculated as impulses per second (*vertical scale*) **A** 1314 trials in 80 neurons responding in go trials; **B** 928 trials in 55 neurons activated in go trials without trigger responses; **C** 598 trials in 43 neurons

Movement-related activity. Neuronal activations beginning <500 ms before movement onset or during the movement were considered to be movement-related. These were found in 67 neurons (25%). They occurrred in conjunction with premovement activity (6 neurons), began immediately before movement onset together with onset of EMG activity (26 neurons), or appeared during different periods and in various forms during the movement (35 neurons). Activation of all movement-related neurons began at a median of 76 ms after movement onset (range -420 ms to $+684$ ms relative to movement onset) and lasted for 368 ms.

A total of 35 neurons showing movement-related activity with self-initiated movements were also tested during stimulus-triggered movements. Of these, 27 showed movement-related activity in both tasks (Fig. 8A), and 2 responded to the trigger stimulus (Fig. 8B).

Discussion

Externally induced preparatory activity

A sizeable proportion of SMA neurons was activated during the preparatory period of several seconds between the external instruction signal and the arm movement. The activity was specific for a movement being prepared and was absent during no-go trials in which the animal

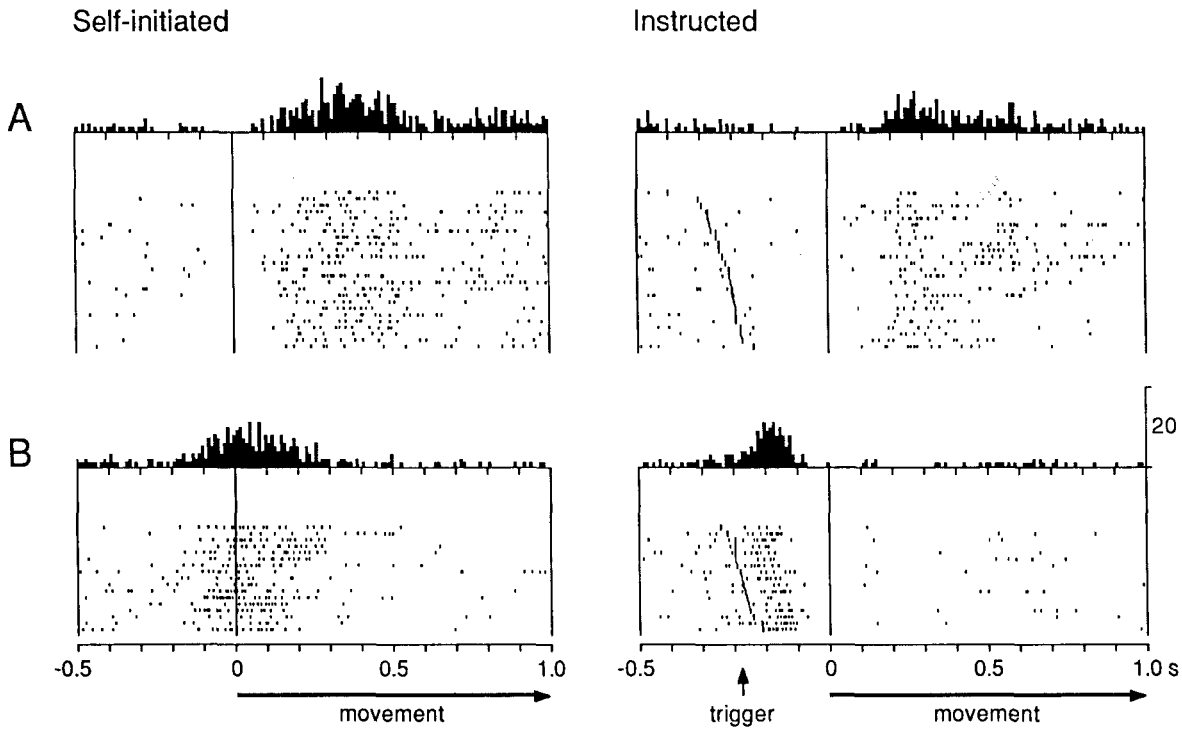

Fig. 8A, B. Comparison of movement-related activity between self-initiated and instructed movements. **A** A neuron activated during similar movement periods in both tasks. **B** A neuron with quite early activation during self-initiated movement lacks movement-related activity in the delay task but responds to the trigger. Data referenced to movement onset. Trials to the right are rank-ordered according to reaction time

refrained from moving. Extensive recordings of muscle activity suggested that the preparatory activity was not due to premature contractions. Comparable preparatory activity during go trials of similar go no-go tasks was previously observed in the premotor cortex of dorsolateral area 6 (Wise et al. 1983; Romo and Schultz 1987).

Earlier studies described similar preparatory activity in SMA neurons during performance of tasks differing in several respects from the present one. In monkeys performing push or pull arm movements, about half of task-related SMA neurons were directionally activated during the instruction period before the movement (Tanji et al. 1980), thus suggesting an involvement of SMA neurons in the preparation of an upcoming movement. Similar directionally specific instruction-related activity was observed in a task allowing the choice between two touch pads (Kurata and Wise 1988) and with wrist flexion-extension movements (Alexander and Crutcher 1990). In another task, a few SMA neurons showed instruction-related activity in anticipation of intervening stimuli not leading to movement reactions, although activity in most neurons continued until a movement-triggering stimulus occurred (Tanji and Kurata 1985). The combined evidence from these and our data suggests that activity in many SMA neurons occurs before an overt behavioral act and reflects an internal process, presumably related to the preparation of a forthcoming movement.

Although these activations may reflect preparatory processes for movements, it cannot be ruled out that they were related to the expectation of the specific movement triggering signal. A recent study on premotor cortex suggested that similar activity may be related to the information contained in the upcoming signal, rather than reflecting movement preparation (Vaadia et al. 1988). Nevertheless, movement-preparatory and signal-expecting activity are in common related to upcoming behavioral reactions to external signals. Other, less specific relationships can apparently be ruled out. The general expectation of external signals should be reflected in activity occurring in both go and no-go trials, and this was not found in the present study. General attentional mechanisms would be expected to last until the delivery of reward and thus beyond the onset of movement when most activations terminated. Activity related to the expectation of reward, which may exist in neurons of the neighboring prefrontal cortex (Watanabe 1986), should equally last until the delivery of reward. Thus, the activation appears to predominantly reflect the preparation of a behavioral response involving an overt movement.

Internally generated premovement activity

Neurons of SMA showed premovement activity preceding the onset of self-initiated movements by 0.6–3.0 s. According to our definition, premovement activity began earlier than 500 ms before movement onset and thus well in advance of the earliest electromyographic activity in all muscles of upper and lower extremities and trunk that were recorded simultaneously with neurons (Schultz and

Romo 1992). In an earlier study addressing the role of the SMA in the internal generation of movements, SMA neurons were activated 150–200 ms before a lever pulling movement (Brinkman and Porter 1979). Although activations during this relatively short lead time might reflect muscle activity preceding movement onset, the inspection of individual figures reveals onset times of up to 800 ms before movement, this being in the lower range of the premovement times observed here. Similar premovement times of 300–1000 ms were found in SMA neurons in monkeys performing wrist extension movements at 3–6 s intervals without finite targets (Thaler et al. 1988). Neurons of SMA showed premovement onset times of 1–2 s in a task in which animals performed a self-paced movement when an expected external trigger signal failed to occur (Okano and Tanji 1987), and up to 3 s when animals rather rhythmically performed a self-paced movement about every 4 s (Kurata and Wise 1988). Thus, in spite of differences in the restrictions placed on internally timed movements, premovement lead times are comparable across different studies. Premovement activity in individual SMA neurons began earlier than readiness potentials from monkey SMA (Gemba and Sasaki 1984). Since recordings were done in comparable behavioral situations, the different time courses should be explained by the lower resolution of readiness potentials which may fail to detect the usually slow and variable onset of premovement activity.

In the present study, animals performed self-initiated arm movements at a self-chosen moment and with a minimal interval of several seconds, whereas rhythmic and automatic task performance was discouraged. The movement occurred toward a well-defined, constant target and had the purpose of obtaining a reward. Although this was not a free intentional behavioral act, because of the constraining behavioral situation, the animal chose the moment of moving within a variable time interval. Although the movements were goal-directed, premovement activity terminated in about half of the activated neurons before the animal's hand reached the target. This suggests a relationship to the generation of the movement rather than to the obtaining of a reward. Interestingly, a recent study failed to find substantial activations preceding spontaneous, unrewarded and undirected saccadic eye movements (Schall 1991) in a similar part of the SMA in which such premovement activity was found with reward-related or reward-searching eye movements (Schlag and Schlag-Rey 1987). This may suggest a general relationship to the goal directedness of the movement-generation process in the activity reported here. We did not test undirected or unreward spontaneous arm movements.

Two thirds of neurons activated before self-initiated movements were unmodulated during instruction-induced movement preparation. This may reflect particular voluntary components in SMA activity underlying the internal movement generation process. By contrast, activity related to the execution of both types of movement was seen in the same neurons, suggesting that neuronal processes operating during ongoing movements were less dependent on the mode of movement generation. The larger separation of premovement compared to movement-related activity for the two types of movement is very similar to the situation observed in the striatum (Romo et al. 1992; Schultz and Romo 1992). A separation of premovement activity in SMA neurons according to the mode of movement generation was also found in a task using lesser degrees of liberty than the one employed here. Some neurons were only activated when animals prepared a self-paced movement when an expected external trigger signal did not occur, whereas they were not activated when the movement was triggered by a stimulus (Okano and Tanji 1987). By contrast, SMA neurons activated indiscriminately before internally and externally prepared movements were recorded in studies using a wrist extension movement without finite targets (Thaler et al. 1988) or an arm movement for contacting a touch pad in front of the animal (Kurata and Wise 1988). These differences do not appear to be derived from the considerable variations in the degree of freedom with which these movements were initiated. A further investigation of the factors determining the obvious specificity shown in some studies should shed more light on the question whether the SMA in fact contains separate neuronal populations related to different modes of preparation of movements and thus plays a particular role in 'the transformation of intent . . . into the specification of action' (Goldberg 1985).

Preparatory activity in SMA as part of cortico-basal ganglia loop activity

Premovement activity in SMA may originate from other frontal cortical areas with which the SMA has heavy, usually reciprocal connections, such as the prefrontal, premotor and anterior cingulate cortex (Jürgens 1984). Several studies have shown that neurons in these structures are activated before externally instructed movements (Fuster 1973; Niki and Watanabe 1976; Wise et al. 1983). By contrast, neurons activated before self-initiated movements were found in fewer areas. Premotor cortex neurons show activity preceding self-initiated movements (Okano and Tanji 1987; Romo and Schultz 1987; Kurata and Wise 1988), and anterior cingulate neurons are activated before movements that occur after a self-timed interval following an external signal (Niki and Watanabe 1979). However, a recent study reported a marked absence of readiness potentials in anterior cingulate cortex preceding self-initiated movements (Gemba and Sasaki 1984). Thus, it is unclear whether any of these cortical structures may constitute a single focus in which activity preceding self-initiated movements is generated and subsequently propagated to the SMA, or whether such activity might be generated within the SMA itself.

The present data suggest that preparatory activity begins earlier in SMA than in striatum, as shown by the shorter onset and peak latencies. This may imply a sequential development and processing of premovement activity from SMA to striatum and would agree with the general notion of sequentially occurring processes leading to the execution of movements in which each structure contributes unique and increasingly more specific activity to the neuronal processes underlying behavioral acts (e.g., Allen

and Tsukahara 1974; Schultz 1984; Goldberg 1985; Fischer 1987). However, the present data allow the construction of an alternative model for the development of the preparatory activity observed. The large temporal overlap of activity preceding externally and internally initiated movements suggest that this activity may not originate from a single group of neurons or a single structure. Rather, it may develop through interactions in neuronal loops linking several cortical and subcortical structures. Preparatory activity is found at several levels of cortico-basal ganglia loops, such as the frontal cortex, caudate and putamen (present study), globus pallidus (Neafsey et al. 1978; Nambu et al. 1990), and pars reticulata of substantia nigra (Hikosaka and Wurtz 1983; Schultz 1986). Dopamine neurons of substantia nigra are not components of cortico-basal ganglia loops. They do not show comparable premovement activity (Romo and Schultz 1990) and thus do not actively participate in the development of preparatory activity in loops. However, they are necessary for the generation of spontaneous movements, as suggested by the profound deficits seen in parkinsonism. This suggests that dopamine neurons exert an enabling effect on loop activity at the level of their target areas, such as the striatum and the frontal cortex (Schultz 1985). A cerebellar involvement in the internal generation of movements is suggested by the loss or reduction of readiness potentials in monkey motor and premotor cortex after cerebellectomy (Sasaki and Gemba 1981).

Instruction-induced premovement activity in SMA and striatum often began with a few impulses, slowly increased and culminated with movement onset. Activity preceding self-initiated movements showed this form to an even greater extent. The first few impulses leading to these activations may occur within one component of the loop or enter through one of the many inputs to cortex or basal ganglia. They would remain a small fluctuation of spontaneous activity and die out without further consequences unless they are conducted to the next synaptically connected component structure of the loop. A slowly and steadily increasing premovement activity could be built up through successive reverberations between cortex and striatum. Cortico-striato-pallido/nigro-thalamic-cortical loop time in macaque monkeys could be as short as 35 ms when conduction times in individual connections are summated [cortex-striatum <10 ms (Buchwald et al. 1973), striatum-pallidum/nigra <20 ms (Yoshida and Precht 1971; Levine et al. 1974; Ohye et al. 1976; Kimura et al. 1990), pallidum/nigra-thalamus <2.5 ms (Harnois and Filion 1982; Nambu et al. 1988), thalamus-cortex <4 ms (Nambu et al. 1988; for review see Schultz 1989)]. The inhibitory striato-pallidal and pallido-thalamic connection should not prevent loop transmission, since excitation in striatum results in activation in the thalamus by disinhibition (Deniau and Chevalier 1985), although the delay added by double inhibition might increase loop time to perhaps 50 ms. With activity in SMA and striatum beginning 1200–1400 ms before self-initiated movements, loop times of 35–50 ms would allow neuronal activity to reverberate about 16–25 times before onset of muscle activity and 25–40 times before onset of movement. Thus, cortico-basal ganglia loops may contain reverberating circuits suitable for the slow build-up of sustained neuronal activity preceding voluntary movements.

Besides the closed loop with frontal cortex, the basal ganglia receive information from the parietal, occipital and temporal lobes that is not directly fed back to these cortical areas (Yeterian and Van Hoesen 1978; Van Hoesen et al. 1981; Selemon and Goldman-Rakic 1985). Thus, activity containing specific information from association and limbic cortex may enter the frontal cortex-basal ganglia loops at the level of striatum, circulate in these loops and evolve into sustained activation in several areas of frontal cortex serving the preparation and initiation of the behavioral reaction. While processing in cortico-basal ganglia loops is essentially parallel and simultaneous, it is directional by ultimately serving for the production of behavioral output.

A strong argument for a functional link within SMA-basal ganglia loops is provided by the changes in cortical potentials recorded over the SMA in patients suffering from diseases of the basal ganglia. It has been repeatedly shown that various components of the readiness potential preceding spontaneous finger movements are altered in parkinsonian patients (Deecke and Kornhuber 1978; Shibasaki et al. 1978; Simpson and Khuraibet 1987), although the extent to which the potential is abnormal may be controversial and vary among different patient groups (Barrett et al. 1986; Dick et al. 1989). The cortical topography of EEG potentials preceding spontaneous finger movements is also altered in parkinsonism (Tarkka et al. 1990). Correspondingly, readiness potentials over the SMA are increased in patients suffering from tardive diskinesia, which is a disease possibly related to increased striatal dopaminergic transmission (Alder et al. 1989). Thus, the function of the SMA is compromised in diseases affecting predominantly the basal ganglia.

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