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

I. Preparatory activity in the anterior striatum

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Summary. The purpose of these studies was to investigate neuronal activity in the basal ganglia and frontal cortex in relation to the internal generation of goal-directed movements. Monkeys performed goal-directed arm movements at a self-chosen moment in the absence of phasic stimuli providing external temporal reference. They were rewarded with a small morsel of food for each movement, although automatic or repetitive behavior was not reinforced. For reasons of comparison, animals were also trained in a delayed go no-go task in which visual cues instructed them to perform or refrain from an arm movement reaction to a subsequent trigger stimulus. This report describes the activity of neurons in the head of the caudate nucleus and rostral putamen preceding self-initiated arm movements and compares it with instruction-induced preparatory activity preceding movements in the delay task. A total of 497 caudate and 354 putamen neurons were tested in the delay task. Two types of preparatory activity were observed: (1) transient responses to the instruction cue, and (2) sustained activity preceding the trigger stimulus or movement onset. Transient responses were found in 48 caudate and 50 putamen neurons, occurring twice as often in movement ('go') as compared to no-movement ('no-go') trials, but rarely in both. These responses may code the information contained in the instruction relative to the forthcoming behavioral reaction. Sustained activity began after instruction onset and lasted until the trigger stimulus or the arm movement occurred, this being for periods of 2–7 s, 12–35 s, or up to 80 s, depending on the task requirements. This activity was seen in 47 caudate and 45 putamen neurons, was largely confined to go trials, and was unrelated to the preparation of saccadic eye movements. In some cases, this activity began as direct responses to the instruction stimulus, but in the majority of cases developed more gradually before the movement. Thus, both transient and sustained activations appear to be related to the preparation of movements. A total of 390 caudate and 293 putamen neurons were tested during self-initiated movements. Activity preceding earliest movement-related muscle activity was found in 32 caudate and 42 putamen neurons. This premovement activity began 0.5–5.0 s before movement onset (median 1160 ms), increased slowly, reached its peak close to movement onset, and subsided rapidly thereafter. It was unrelated to the preparation of saccadic eye movements. Comparisons between the two tasks were made on 53 neurons. Only one third of the task-related neurons showed premovement activity before both self-initiated and instructed movements, whereas in two thirds such activity was restricted to only one of the tasks. Peak premovement activity occurred significantly closer to movement onset with self-initiated as compared to instructed movements, whereas the magnitudes varied insignificantly. These data show that single neurons in caudate and putamen were activated up to a few seconds before self-initiated movements that were performed, within the constraints of the experimental situation, with a considerable degree of temporal choice due to the absence of explicit external instructive or imperative stimuli. Two thirds of these neurons were exclusively activated before self-initiated movements and not when the movement was prepared by explicit external cues. Thus, both caudate and putamen appear to be involved in setting and maintaining central preparatory states related to the internal generation of individual behavioral acts on the basis of information about the environmental situation (task contingencies, position of movement targets, and reward). Since comparable premovement activity occurs simultaneously in frontal cortical areas closely associated with striatum, neuronal processes underlying the internal generation of behavior may engage cortico-basal ganglia loops.

Key words: Basal ganglia – Behavior – Preparation – Movement – Monkey

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Introduction

Despite the recent progress in unraveling many of the mechanisms contributing to the control of goal-directed movements, little is known about the neuronal processes underlying their internal generation. The investigation of this topic has been stimulated by the demonstration that the subjective perception of internal motor commands can be objectively studied in the temporal domain (McCloskey et al. 1983). One startling result was the finding that brain activity related to the initiation of individual movements in a prepared experimental setting may begin before the subject's conscious awareness of the urge to move (Libet et al. 1983; Libet 1985). While these studies addressed the qualities and conditions of the generation process, the understanding of underlying neuronal mechanisms could be advanced by investigating the activity of single neurons in relation to individual movements that are performed in the absence of external stimuli likely to evoke responses in sensory systems. Neuronal activity preceding these self-initiated movements would provide a biological correlate for a central generation process of individual movements. Representational aspects such as the expectation, preparation, and knowledge about the goal of action may crucially contribute to this process and help to activate the subsequent motor programs in which individual movement parameters are computed.

Neurological studies of movement disorders suggest that certain brain structures may be prominently involved in the internal generation of goal-directed behavior, notably the frontal cortex and the basal ganglia. Degeneration of caudate and putamen in human chorea leads to an exuberance of involuntarily generated distal limb movements. Destruction of nigrostriatal and mesocortical dopamine neurons in parkinsonian patients and experimentally lesioned animals induces particularly severe reductions of spontaneous movements, whereas reactions to external stimuli are less affected. Parkinsonian patients are impaired in internally guiding and adapting behavioral reactions to changing environmental situations (Cools et al. 1984; Brown and Marsden 1988; Canavan et al. 1990) and have difficulties in performing arm movements that require the use of stored representations of movements in the absence of external feedback (Flowers 1976, 1978). In addition to the basal ganglia, the supplementary motor area of the frontal cortex appears to be involved in the internal generation of movements (Eccles 1982; Goldberg 1985), as suggested by the effects of lesions in man (Talairach et al. 1973; Laplane et al. 1977), by the readiness potential observed preceding spontaneous movements in man and monkey (Kornhuber and Deecke 1965; Hashimoto et al. 1979) and by the activity of single neurons in behaving monkey (Okano and Tanji 1987; Romo and Schultz 1987; Kurata and Wise 1988; Thaler et al. 1988). The frontal cortex and the basal ganglia are linked through closed loops (Künzle 1978; Schell and Strick 1984; Percheron et al. 1984; Ilinsky et al. 1985; Selemon and Goldman-Rakic 1985; Alexander et al. 1986; Nambu et al. 1990), which would allow these two brain regions to cooperate in the internal control of various forms of behavioral processes. In particular, the heavy projections from the frontal cortex to the associational parts of caudate and putamen suggest that single neurons in the anterior striatum may be activated during the generation of self-initiated movements.

The aim of our recent experiment was to investigate neuronal mechanisms in the basal ganglia and frontal cortex contributing to the internal generation of movements. Because the behavioral deficits in parkinsonian patients and dopamine-depleted animals suggest a prime involvement of nigrostriatal dopamine neurons, we investigated the activity of midbrain dopamine neurons in monkeys performing self-initiated movements (Romo and Schultz 1990). Although responding to appetitive stimuli encountered during these movements, dopamine neurons lacked major premovement activations. Therefore, in the present experiments we investigated regions in the basal ganglia and the frontal cortex that are influenced by dopamine neurons.

Monkeys were trained to perform self-initiated movements in which they released a resting key at a self-chosen moment in the absence of any phasic external cues and reached into a small box in front of them in order to collect a hidden morsel of food. Although the animal was restrained by the experimental situation, it had sufficient liberty in the time domain to choose the moment of movement, and care was taken to avoid automatic or stereotyped task performance. Animals also performed, in separate blocks of trails, in a delayed go no-go task in which different instruction lights served as preparatory stimuli for executing or refraining from an arm movement reaction in response to a subsequent trigger stimulus. These two tasks allowed us to investigate the specificity of neuronal activity for internally generated movements by comparing the activity between the different tasks. The present report describes neuronal activity in caudate and putamen preceding self-initiated movements. This activity is compared to that observed in the same neurons in the delay task, in which the instruction set up an internal preparatory state that lasted for several seconds until the trigger stimulus occurred. Portions of these data have been briefly reported (Schultz and Romo 1988; Schultz et al. 1989a). The second report on caudate and putamen neurons compares the activity preceding self-initiated movements with movement-related activity during stimulus-guided movements in the delay task, in which the imperative trigger stimulus serves to immediately elicit an arm movement (Romo et al. 1992). This report, furthermore, describes activity during the execution of self-initiated movements and again compares it with activity related to stimulus-triggered movements. The third report (Romo and Schultz 1992) describes the activity of neurons in the supplementary motor area during self-initiated and stimulus-guided movements and compares it with activity in the striatum.

Materials and methods

The study was performed on three *Macaca fascicularis* monkeys (3.0-kg female, 3.5-kg and 4.3-kg males), two of which had also been used for studying dopamine neurons (Romo and Schultz 1990). Activity of

single neurons was recorded from the left striatum with movable microelectrodes during contralateral performance of behavioral tasks while monitoring electromyographic activity and eye movements in the same trials through chronically implanted electrodes. Recording positions were reconstructed from histological sections at the end of the experiment.

Behavioral procedures

The behavioral apparatus was positioned in the right half of the frontal wall of a completely enclosed primate chair (Fig. 1). It contained an immovable, touch-sensitive resting key (elbow joint at approximately 90°) and two food boxes with a frontal opening of 40 × 40 mm located at reaching distance (250 mm from the animal's shoulder) and eye level of the animal. Centers of medial and lateral boxes were located at 15° and 27° to the right of the midsagittal plane, respectively. A cover mounted in front of each box prevented sight of the interior while giving a 40-mm-wide and 50-mm-deep access from below to the animal. One green light-emitting diode was located 40 mm above each box. Small pieces of apple or cookie or a raisin (each about 1 g) served as rewards. Limb and mouth movements were continuously supervised by two closed-circuit video systems. Animals were food- and mildly fluid-deprived during weekdays but received a limited quantity of standard monkey cubes and free water during 1h after each daily experiment.

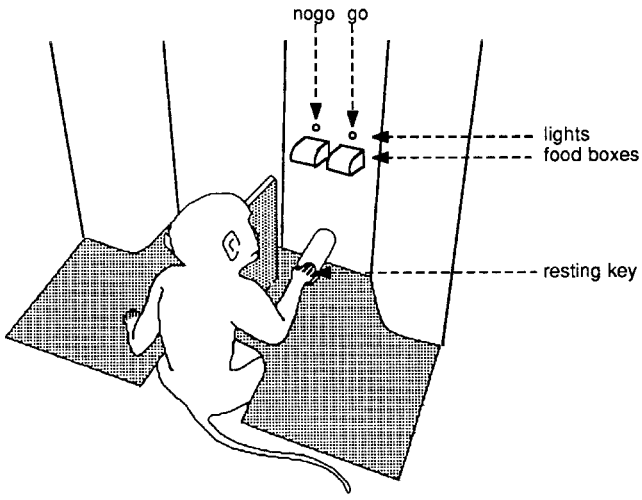


Fig. 1. Behavioral task. The animal sits in a completely enclosed primate chair and faces a response panel with a touch-sensitive, immovable resting key and two food boxes. The cover mounted in front of each box prevents vision into the interior while permitting manual access from below. Before trial initiation, the animal's hand rests on the key. In the delayed go no-go task, an instruction light above one of the food boxes comes on and, a few seconds later, the door of the respective box opens audibly but invisibly behind the cover. In go trials, the animal releases the key, enters the lateral box, collects the food and brings it to the mouth. In no-go trials, the animal keeps its hand on the resting key for several seconds longer and receives no reward. Thus, the instruction light prepares the animal for the upcoming movement or no-movement reaction, whereas opening of the food boxes does not provide information about the go or no-go situation and only serves to indicate the moment of reaction (trigger stimulus). The lateral and medial boxes are invariably associated with go and no-go situations, respectively. For self-initiated movements, the animal releases the resting key without any phasic external instruction or trigger stimuli and performs the same reaching movement toward the food box for obtaining reward. Only the lateral box is used in this task, and its door is kept open during the whole block of trials

Each animal was first trained in the delayed go no-go task. When the animal kept its right hand relaxed on the resting key, the lateral or medial light came on as instruction, indicating a go or no-go situation, respectively. In go trials, the door of the lateral food box opened several seconds later, and the animal released the key, reached into the box, collected a small morsel of food reward and brought it to the mouth. In no-go trials, the medial box opened and the animal's hand remained on the resting key for 3 s or more; no reward was given. Door opening required 20–22 ms and produced a low-intensity sliding noise that was identical for both boxes. Animals could not determine which box had opened without the preceding instruction light. Intervals between instruction light onset and door opening varied from 2 to 3 s, 4 to 7 s, or up to 80 s during different phases of experimentation. The instruction light was extinguished either 1 s after its onset in go and no-go trials (short instruction), or, in separate blocks of trials, upon key release in go trials and 5–10 s after its onset in no-go trials (continuous instruction). Thus, the instruction light served as preparatory signal for the upcoming behavioral reaction to door opening, whereas door opening was a trigger stimulus that only determined the time of reaction. The box was closed and refilled with a reward morsel 800–1000 ms after opening in go trials and closed after 7–8 s in no-go trials. Intervals between door closing and instruction light onset in the following trial varied between 3 and 5 s. Go and no-go trials alternated randomly. The rerun procedure was employed after erroneous behavioral reactions in both go and no-go situations. Thus, the animal needed to refrain from moving in the unrewarded no-go trial before it could perform a rewarded go trial. An accompanying paper describes results from additional neurons studied in a direct reaction go no-go task in which food boxes opened visibly and without preceding instructions (Romo et al. 1992).

Special attention was paid to control for untimely muscle activity and premature movements, particularly during the preparatory period following instruction onset. This occurred on some occasions of the several months of experimentation. Skeletal activity was monitored with a video camera focused on the forearm and, after implantation, by additional continuous electromyographic recordings. When untimely skeletal activity occurred, the food box was not opened and the trial aborted. If this failed after a few trials, animals were submitted to go trials of the direct reaction task, or the session was interrupted and the frontal enclosure of the primate chair opened for a pause.

While learning the delay task, animals occasionally released the resting key and explored the invisible interior of the lateral food box with their hand while waiting between trials. These self-initiated movements were systematically reinforced by food reward as soon as animals were able to remain relaxed for several tens of seconds while their hand rested on the key. Due to this way of conditioning, intervals between movements initially showed large variations. During neuronal recordings they ranged from 5 to 30 s. Pauses in task performance were introduced by withdrawing the resting key. Animals would occasionally not find food in the box when higher rates of self-initiated movements occurred, a measure that was usually effective in preventing uncontrolled or repetitive motor acts. When animals were still too impatient and repeatedly performed movements at intervals of less than 4–5 s, which occasionally occurred during the first hour of daily experimentation, they were submitted to the delay task, which provided a more explicit means for controlling their behavior. When animals became satiated during a daily experiment and intervals were unsuitably long for data recording, a change of food usually increased the frequency of movements for several tens of trials. Only the lateral food box was employed for self-initiated movements. Its door was kept open, and food morsels were stuck to the end of a rigid wire and entered into the box without giving visual or auditory cues.

Self-initiated movements in this situation occurred in the absence of external cues that could provide temporal reference for the behavior of the animal, and with minimal externally imposed time limits. Although biased in their behavior by the presence of primary reward, animals were free to choose whether to move, remain

motionless, or occasionally perform task-unrelated movements for postural adjustments. Although highly practiced, movements were not rhythmically paced and were devoid of automatic or involuntary character. Movements were directed to a known and stable target under visual guidance, with the purpose of exploring a known object for food reward and obtaining that food. The behavior involved a limited uncertainty about the availability of food, because animals were unable to see the interior of the box. Animals were not free to choose between different tasks or rewards, although their incorrect performance usually resulted in switching to the delay task or a change of reward.

Behavior was electronically monitored from standard digital pulses generated by the different events of the task. Onset of door opening activated an infrared light beam switch. Key release was directed by a frequency-sensing circuit, which reacted to a change in electrical capacity induced by the touch of the animal's hand. Interruption of an infrared light beam across the entrance of each food box detected the time at which the animal's hand entered and left the box (onset and end of beam interruption, respectively).

Electrophysiological techniques

Animals underwent surgery after proficiency in all behavioral tasks was attained. Under deep sodium pentobarbital anesthesia and aseptic conditions, 2 cylinders for head fixation and a stereotaxically positioned, stainless steel chamber for microelectrode recordings were mounted on the skull. The dura was left intact. Polytetrafluoroethylene-(Teflon)-coated, multistranded, stainless steel wires were implanted into musculi extensor digitorum communis and biceps brachii on both sides in all three monkeys and, in addition, into the right triceps, anterior deltoid, and lateral deltoid in one monkey. Ag-AgCl electrodes were implanted into the outer, upper, and lower canthi of the orbits. All metal components, including plugs for periorbital and muscle electrodes led subcutaneously to the head, were imbedded in dental cement, and fixed to the skull with surgical grade stainless steel screws.

The activity of single neurons was recorded extracellularly with glass-insulated, platinum-plated tungsten microelectrodes (exposed tips of 5–10 μm length and 1.8–3.5 μm diameter), which were passed into the brain each day inside a rigid guide cannula of 0.6 mm outside diameter. Microelectrodes were moved in parallel tracks oriented vertically in the stereotaxic plane and conforming to a 1-mm grid. Signals from the microlectrode were conventionally amplified, filtered (>100Hz pass), and monitored with oscilloscopes and earphones. Somatodendritic discharges were discriminated against those originating from fibres using earlier established criteria, in particular the very short durations of fiber impulses (0.1–0.3 ms; Hellweg et al. 1977). Neuronal discharges were converted into standard digital pulses by means of an adjustable Schmitt trigger, the output of which was continuously monitored on a digital oscilloscope together with the original waveform.

Electromyograms (EMGs) were collected during all neuronal recordings through both implanted and acutely inserted wire electrodes from several arm flexor and extensor muscles, and from shoulder, neck, trunk, dorsum, and upper and lower leg muscles, both contra- and ipsilateral to the moving arm. EMG activity was filtered (10–250 Hz band pass; -12 dB at 1 kHz), rectified, displayed on conventional oscilloscopes, and converted into digital pulses by an adjustable Schmitt trigger.

Horizontal and vertical electrooculograms (EOGs) were systematically collected during neuronal recordings from the implanted periorbital electrodes. The gain of ocular electrodes and the eye positions were calibrated by having the food-deprived animal fixate on small morsels of food presented at several known horizontal and vertical eccentricities. We did not specifically search for neuronal activity in relation to eye movements during the experiment. Such activity has been found in the head of the caudate neurons (Hikosaka et al. 1989a). However, we have referenced neuronal activity during off-line evaluations to the onsets of saccades in order to detect possible eye movement relationships.

Data acquisition and analysis

All behavior-related digital signals and pulses and neuronal discharges were sampled on line as bits in parallel at a rate of 2 kHz by a laboratory computer. Analog signals from EOGs were sampled after 12-bit digital conversion at a rate of 2 kHz by the computer. Eight consecutive analog values were averaged to obtain a final temporal resolution of 4 ms (0.25 kHz) for data storage. Rectified EMG activity was sampled both as digital pulses delivered from a Schmitt trigger and as analog signals using the 12-bit converter. Data were collected during individual trials lasting up to 32 s (usually 8–15 s), which were triggered by the animal's contact with the resting key or by an experimenter. Thus, for the delay task, the instruction came on 1 or 2 s after trial start. With self-initiated movements, where arm movements began at times unforeseeable to the experimenters, data were only accepted and stored when the movement began more than 5 s after trial start and more than 3 s before trial end. Thus, approximately 30–50% of trials were rejected, which was unnoticeable to the animal. Raster dots representing neuronal discharges and EMG activity referenced to three behavioral events were displayed on the computer screen after each trial, together with analog displays of EMG activity and EOGs. All data from neurons suspected to covary with some behavioral event, and occasionally from apparently unmodulated neurons, were stored uncondensed on computer disks. Only neurons tested with at least 15 trials of a given go or no-go situation or ten trials with self-initiated movements are reported.

Off-line data inspection was performed on the basis of raster dots, perievent time histograms, and cumulative frequency distributions of neuronal impulses and EMGs, and with displays of single-trial or averaged analog data, in reference to each behavioral event. Onset and offset times of saccades were determined off line by single trial analysis using a movable cursor on a computer screen. Onset, duration, magnitude, and statistical significance of increases in neuronal activity were assessed with a sliding window procedure on the basis of the non-parametric one-tailed Wilcoxon matched-pairs signed-ranks test. This procedure takes the activity of single trials into account, rather than the summed perievent time histogram, and does not require normal distribution of data, which would be unsuitable for the low-impulse activity in striatum. The numbers of impulses in two time epochs, normalized over time, were considered as a pair in each trial. One epoch was the control period, while the second epoch consisted of a time window that was moved in steps through the period of a suspected change, with the Wilcoxon test being performed at each step. Onset of activation was determined as the mid-window-time of the first of a number of consecutive steps showing an activation at $P<0.01$. The time comprised in this number of consecutive steps was 70% of the length of the moving time window. Offset of activation was determined in analogy by searching for the loss of statistically significant increase. Subsequently, a Wilcoxon test was performed over the total duration of activation to test against $P< 0.005$. Neurons not showing an onset of activation or failing in the total duration test were considered as unmodulated. The magnitude of activation was assessed by counting neuronal impulses between onset and offset of response and expressed as percentage above background activity during the control period. After extensive testing, the following parameters were found to be robust for the relatively slow time courses of changes: (1) for activity after instruction onset, 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) – step size 8 ms, time window 48 ms; (2) for self-initiated movements, 400-ms control period before the presumed activation, as judged from visual inspection, step size 20 ms, time window 200 ms; (3) for offset of activation in the delay task and with self-initiated movements relative to door opening (delay task only), key release, enter box, or

leave box, 1- or 2-s control period before instruction, step size 20 ms, time window 200 ms moving backwards. A few neurons with slowly increasing preinstruction activity were excluded from the analysis. Only activations evaluated with the sliding window procedure with at least 15 go or no-go trials or ten self-initiated movements are reported.

Results obtained with the sliding window procedure were compared with parametric procedures occasionally employed in other studies. A measure of control activity (mean + 2 standard deviations) was used as threshold for at least three consecutive bins on perievent time histograms with bin widths of 8, 20, or 25 ms, corresponding to the sliding window steps. The obtained onset and offset times of strong activations coincide well with results from the sliding window procedure. However, the parametric procedure resulted in proportionately more unreliable results with increasing intertrial variations or decreasing trial numbers. Similar deviant results were obtained with the 0.1% confidence interval (CI) on perievent time histograms (CI = mean $\pm$ student's $t \times$ standard error of the means). Therefore, the two parametric procedures were abandoned.

Peak activity was determined from the 500-ms interval showing the highest activity in the perievent time histogram of neuronal impulses. Peak latency was taken to be 250 ms after onset of this interval. The peak interval of 500 ms was sufficiently short to limit latency distortion due to temporally asymmetric activity and sufficiently long to allow a reasonable integration over time.

Results from evaluations were stored and classed using specifically written procedures on a relational data base management system. Because of skewed distributions, the median (50th percentile) was determined as single numerical value for each set of data. Differences in distributions were assessed with two-way analyses of variance (Anovas), and with two-tailed versions of the Mann-Whitney *U*-test for unpaired and the conventional Wilcoxon test for paired data.

Histological reconstruction

During the last recording sessions with each animal, small marking lesions were placed by passing negative currents (5–10 μA for 5–20 s) through the microelectrode at a few positions in each of several tracks. This produced distinct patterns of vertically aligned histological marks. Animals were deeply anesthetized with pentobarbital and conventionally perfused with formaldehyde through the heart. Guide cannulas were inserted into the brain at known coordinates of the implant system in order to delineate the general area of recording. The tissue was cut in 50-μm-thick serial coronal sections on a cryotome and stained with cresyl violet. All histological sections were projected on paper, and marks from lesions and recent electrode tracks were drawn on outlines of brain structures. Recording positions in tracks marked by electrolytic lesions were reconstructed by using distance to lesions according to protocolled micrometer readings. Positions in parallel neighboring tracks were reconstructed at comparable vertical levels.

Results

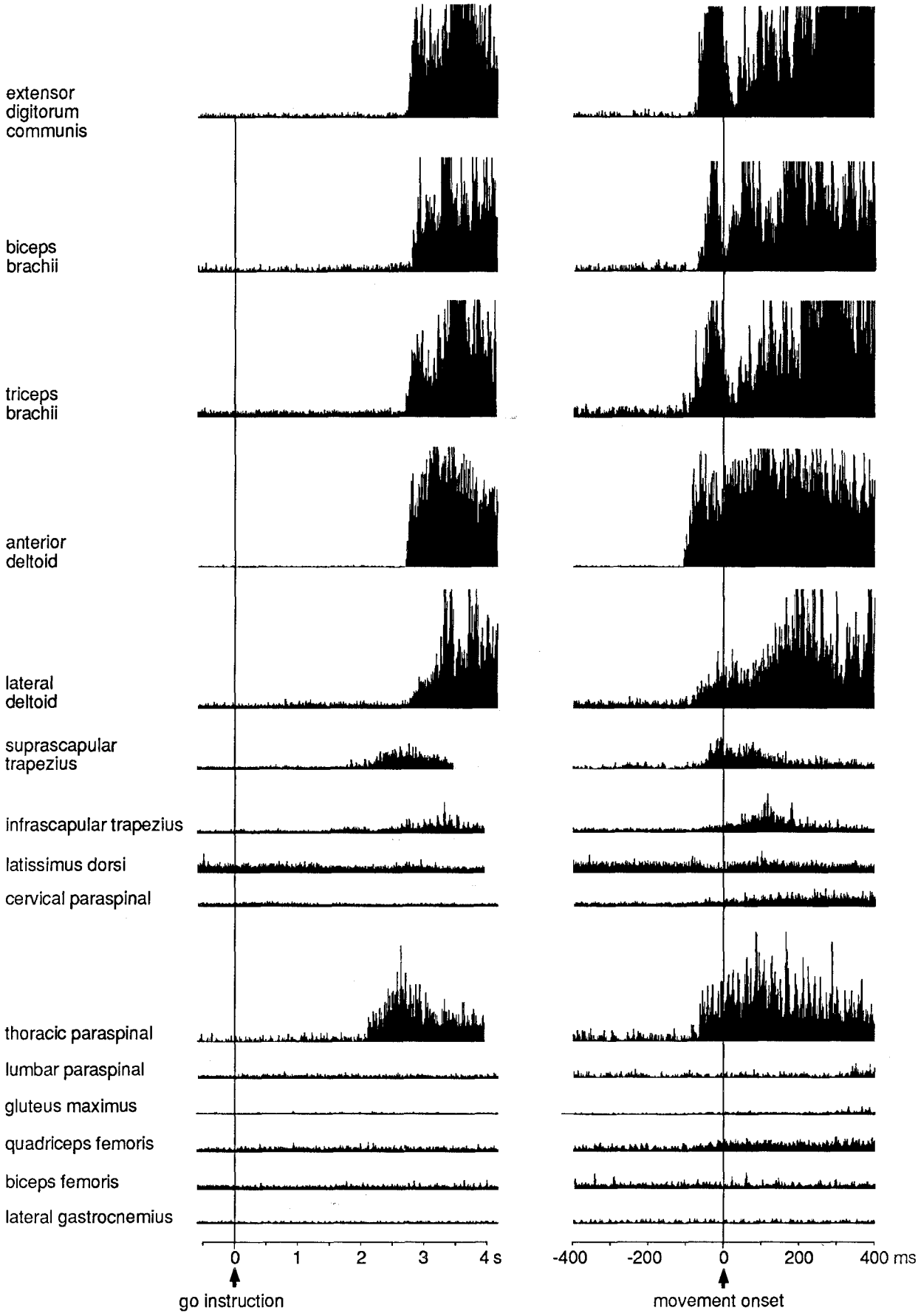
General

Muscle activity. Systematic recordings of EMGs during all neuronal recordings served as controls for the absence of muscle activity during the preparatory periods preceding arm movements in both tasks (Figs. 2–4). The prime mover muscles of the reaching movement were the extensor digitorum communis, the biceps of the arm, and the anterior deltoid (Fig. 2A). In the delay task, earliest activity was seen in the prime mover muscles with median latencies of 97–200 ms after the trigger stimulus, this being 114–141 ms before movement onset. Less consistent activity was observed in shoulder and trunk muscles, such as the lateral deltoid, the suprascapular part of trapezius, and the thoracic paraspinal group. Task-related activity was absent in paraspinal lumbar and in leg muscles such as gluteus maximus, quadriceps femoris, biceps femoris, and lateral gastrocnemius. Performance in no-go trials was not accompanied by muscle activity (Fig. 3, top). Contralateral to the moving arm, the infrascapular trapezius and upper paraspinal muscles were activated during but rarely before the movement (Fig. 3, bottom). With self-initiated movements, the pattern of muscle activity was very similar (Fig. 4). Occasionally, the initial peak and the subsequent trough in prime mover muscle activity were less pronounced, as compared to stimulus-triggered movements. Onset of activity in the prime mover muscles was consistently (two monkeys) or occasionally (one monkey) earlier and more variable than in the delay task (up to 300–500 ms before movement onset, see Figs. 12, 15).

Neuronal database. Activity was recorded from 923 slowly discharging neurons of the left striatum (Table 1). The head of the caudate nucleus and the anterior putamen were explored in two monkeys at coronal planes A15–A20 (see Fig. 6) and in one monkey at planes A16–A19, although the majority of penetrations in all animals were made rostral to the anterior commissure (anterior to plane A16, the levels being labeled according to the atlas of Shanta et al. 1968). A total of 851 neurons were tested in the delay task with continuous or short instruction lights, and 683 neurons were studied with self-initiated movements, of which 611 were investigated in both tasks. The spontaneous discharge rate was higher in two monkeys in which neurons were sought while animals sat still without performing in any task (median 2.5 impulses per second), as compared to one animal in which task performance aided the additional detection of rather silent neurons (1.3 impulses per second). An additional 361 striatal neurons were recorded in the direct-reaction go no-go task and are reported separately (Romo et al. 1992). The present reports do not include tonically discharging striatal neurons (4.5–9.0 impulses per second; see Kimura et al. 1984), some of which were phasically depressed by instructions and resembled those reported in another study (Apicella et al. 1991).

Table 1. Numbers of neurons tested

	Caudate	Putamen	Sum
Delayed go no-go task	497	354	851
Self initiated movements	390	293	683
Both delay task and self-initiated movements	348	263	611
Total	539	384	923


extensor digitorum communis
biceps brachii
triceps brachii
anterior deltoid
lateral deltoid
suprascapular trapezius
infrascapular trapezius
latissimus dorsi
cervical paraspinal
thoracic paraspinal
lumbar paraspinal
gluteus maximus
quadriceps femoris
biceps femoris
lateral gastrocnemius
0
1
2
3
4 s
go instruction
-400
-200
0
200
400 ms
movement onset

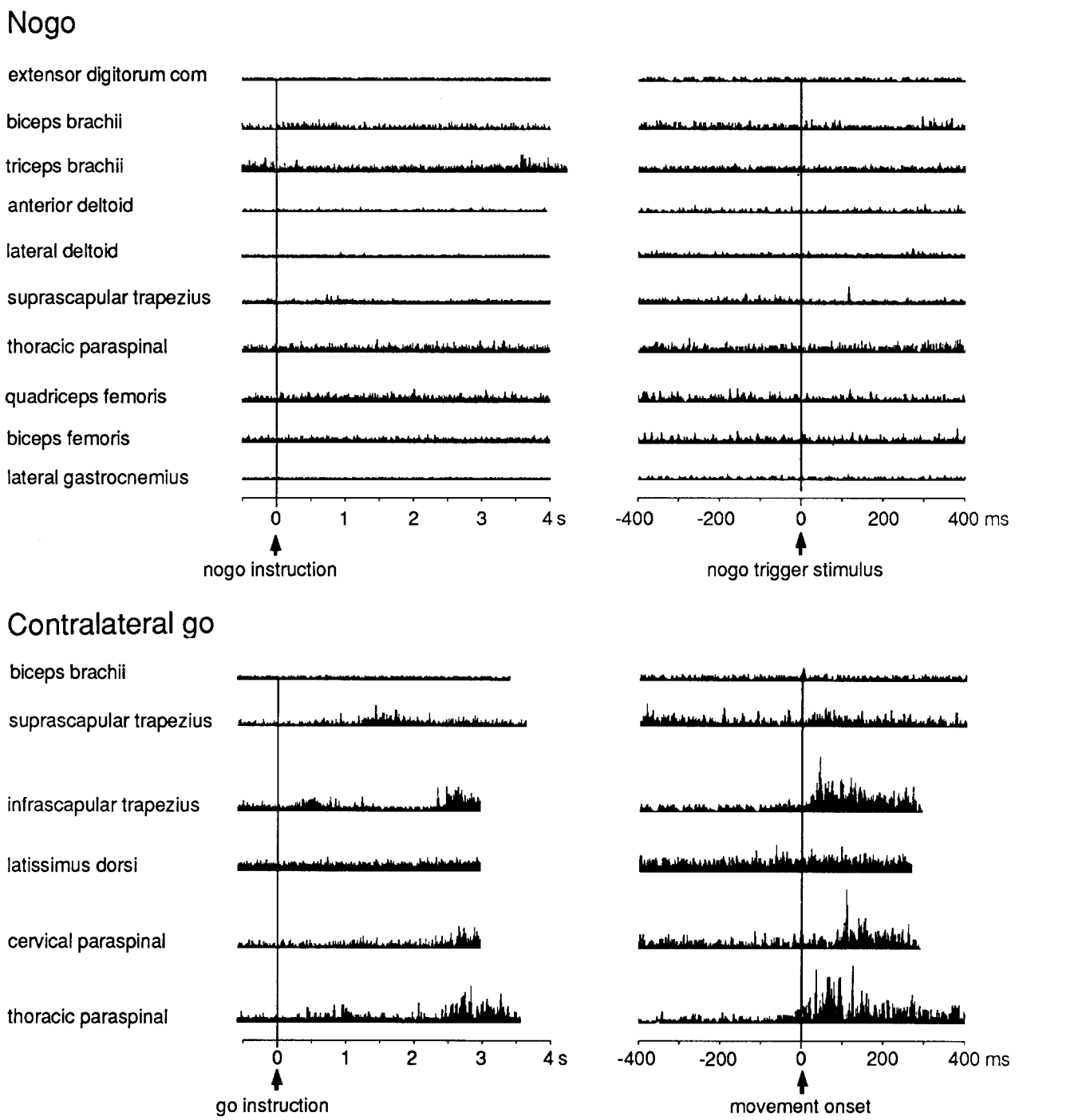


Fig. 3. *Top*: electromyographic activity in no-go trials of the delay task; *bottom*: activity in muscles contralateral to the arm moving in go trials

Fig. 2. Electromyographic activity in different arm, shoulder, neck, dorsum, and leg muscles during performance of go trials of the delay task. Each display shows superimposed rectified activity from 13–35 trials sampled after 12-bit analog-to-digital conversion. This display method reveals the maximum of muscular activity over all trials without modification by averaging. Traces were filled to the bottom for display. Due to high-gain amplification, peaks of activity during the movement were cut. Data shown to the *left* and *right* were recorded in the same trials from each muscle, respectively, and are presented with different temporal resolution in reference to two task components. *Movement onset* refers to release of the resting key. Most muscles were recorded simultaneously with striatal neurons

Delayed go no-go task

Transient responses to instructions. A total of 133 striatal neurons showed activating responses to instruction onset that ended before the trigger stimulus (Table 2). Most neurons responded in go trials ($n=98$), fewer were activated in no-go trials ($n=49$), and very few showed responses in both situations ($n=14$). Responsive neurons were distributed with similar frequencies over the anterior parts of caudate and putamen and occurred equally well with continuous as with short instructions. None of the

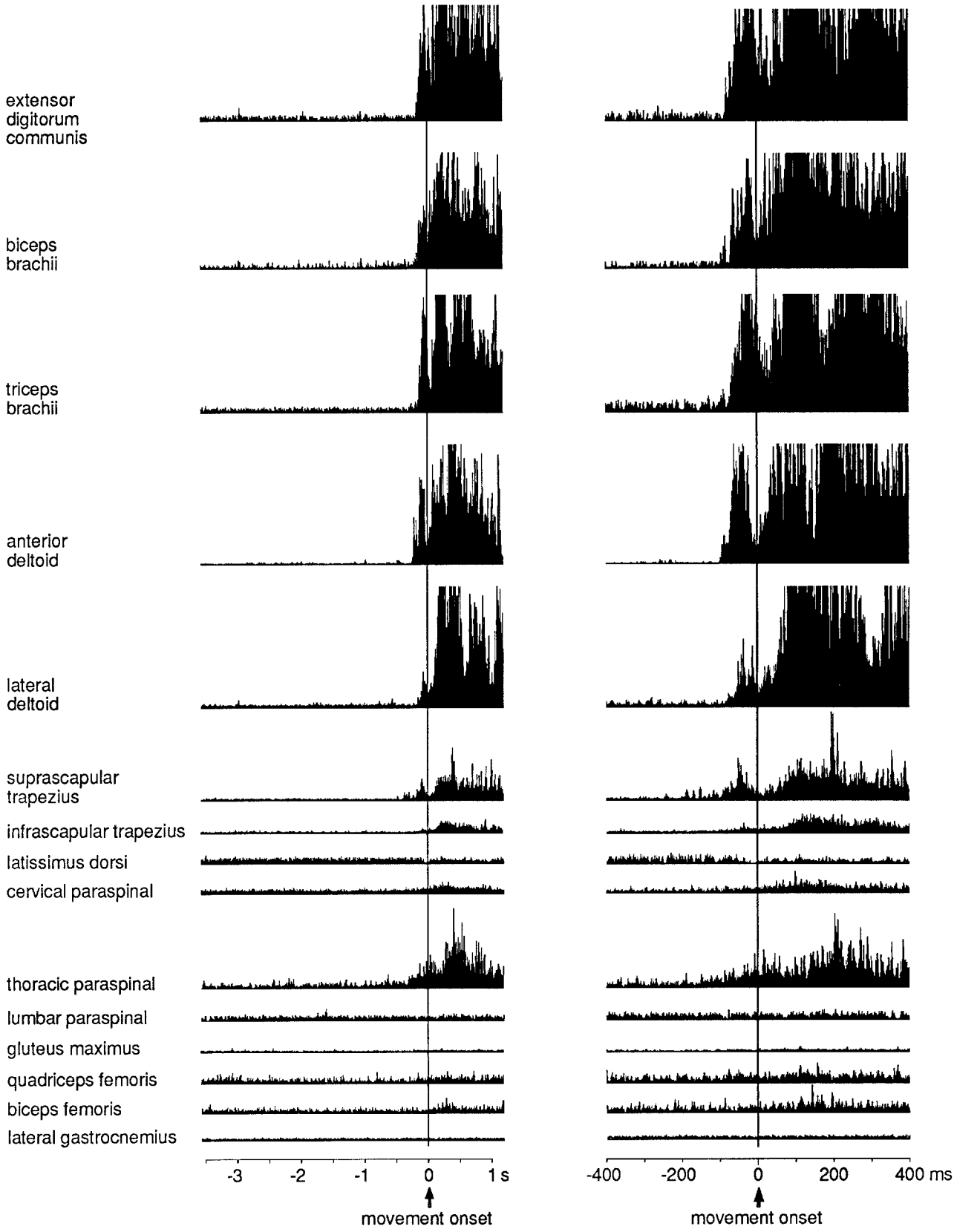


Fig. 4. Electromyographic activity in different arm, shoulder, neck, dorsum, and leg muscles in relation to self-initiated arm movements. Each display shows superimposed activity from 19–36 trials. Data in the *left column* show premovement activities; those to the *right* are shown from the same trials with higher time resolution to reveal the onset of activation. Most muscles were recorded simultaneously with striatal neurons

neurons responded to offset of the short instruction light. Transient depressant responses to instruction onset were seen in 14 neurons.

Typical examples of transient activations are shown in Fig. 5. These include 31 rather rapid responses of short latency (< 300 ms) and short duration (< 400 ms), some of which also occurred in no-go trials (Fig. 5A). The remaining neurons showed longer-lasting activations at somewhat longer latencies, which could also occur preferentially in no-go trials (Fig. 5B; Table 2). A total of 25

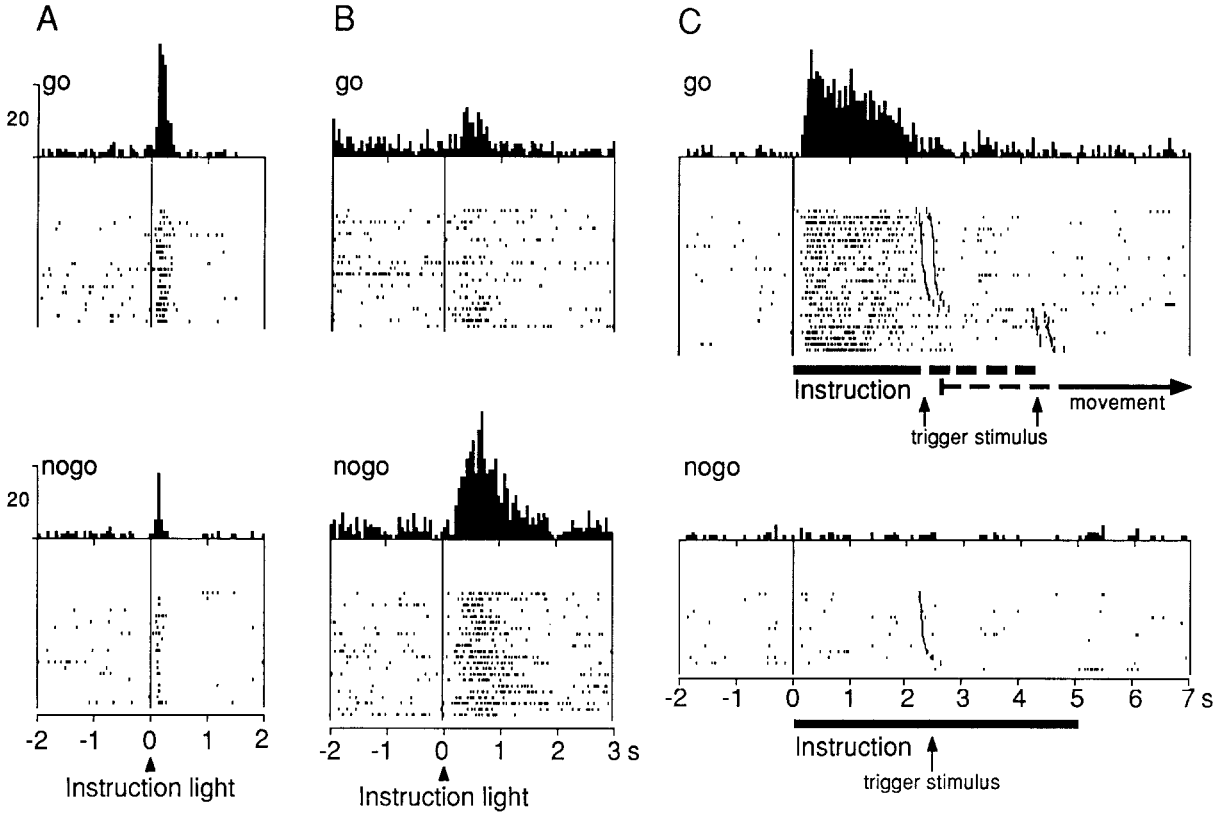


Fig. 5A–C. Transient responses to onset of instruction light. **A** Short response of a caudate neuron (short instruction). Response is stronger in go as compared to no-go trials. **B** Putamen neuron responding preferentially in no-go trials (continuous instruction). **C** Prolongation of the instruction period reveals the transient character of a rather long response in a caudate neuron (bottom lines of dots in go trials). Trials were rank-ordered off line according to instruction-trigger intervals. *Horizontal bars* below rasters indicate duration of the instruction light, which was turned off upon key release in go trials and 5 s after its onset in no-go trials. The *pairs of small vertical bars* among the *dots* denote the trigger stimulus and movement onset, respectively. Perievent time histograms in **A–C** are composed of neuronal impulses, shown as *dots* below. Each *dot* denotes the time of a neuronal impulse, and distances to instruction onset correspond to real-time intervals. Each *line of dots* shows one trial. Go and no-go trials alternated randomly during the experiment and were separated off line. Otherwise, the original sequence of trials is preserved downward, except in C. Vertical calibration is 20 impulses per bin for all histograms

Table 2. Transient responses to instruction onset

	Neurons	Neurons responding				Latency (ms)		Duration (ms)		Magnitude (%)	
	Tested	Go	No-go	Both	Sum	Go	No-go	Go	No-go	Go	No-go
Caudate	497	48(10%)	28(6%)	8	68(14%)	175	132	513	308	302	214
Putamen	354	50(14%)	21(6%)	6	65(18%)	162	156	500	304	190	235
Total	851	98(12%)	49(6%)	14	133(16%)	162	156	500	304	238	217

Latency, duration, and magnitude values were obtained with the sliding window procedure and are shown as medians. The differences in latency, duration, and magnitude were insignificant between caudate and putamen, and between go and no-go trials ($P > 0.1$ in two-way Anova with two structures and two task situations as factors; $P > 0.01$ in Mann-Whitney test on caudate vs putamen and on go vs no-go trials). All calculations were done on responses to continuous instructions (go 72, no-go 36 neurons) and short instructions (go 26, no-go 13 neurons). Data were pooled because of largely insignificant differences between the two task variations (all $P > 0.1$, except go durations, $P < 0.02$). The responses to continuous instructions were used when neurons responded to both continuous and short instructions (go 24, no-go 8 neurons).

responses lasted for more than 1 s and appeared to be of sustained nature when short instruction-trigger intervals were used. However, their transient response character was revealed with slightly longer intervals (Fig. 5C). Systematic analysis of eye movements demonstrated that the responses to the instruction light occurred independent of the presence or absence of saccadic reactions to the instruction signal. Median latencies, durations, and magnitudes of responses in go and no-go trials are shown in Table 2.

Sustained preparatory activity. Increases in neuronal activity beginning after instruction onset and lasting beyond the trigger stimulus were found in 98 striatal neurons (Table 3). They were scattered over the whole striatal region explored (Fig. 6). Activations occurred mostly in go

Table 3. Sustained activations in the delayed go no-go task

	Neurons	Neurons activated				Go activations		
	Tested	Go	No-go	Both	Sum	Latency (ms)	Peak latency (ms)	Peak magnitude (%)
Caudate	497	47(9%)	4(1%)	1	50(10%)	1262	2500	298
Putamen	354	45(13%)	5(1%)	2	48(14%	1037	2600	618
Total	851	92(11%)	9(1%)	3	98(12%)	1137	2337	415

Latency, peak latency and peak magnitude data were obtained from activity referenced to instruction onset in go trials and are given as medians. Caudate and putamen differed insignificantly in all three parameters ($P > 0.1$, Mann-Whitney test). All calculations were done on activations with continuous or short instructions (76 and 16 neurons, respectively). Data were pooled because of largely insignificant differences between the two task variations ($P > 0.1$, except peak magnitude, $P < 0.02$). The activations with continuous instructions were used when neurons were activated with both continuous and short instructions (32 neurons).

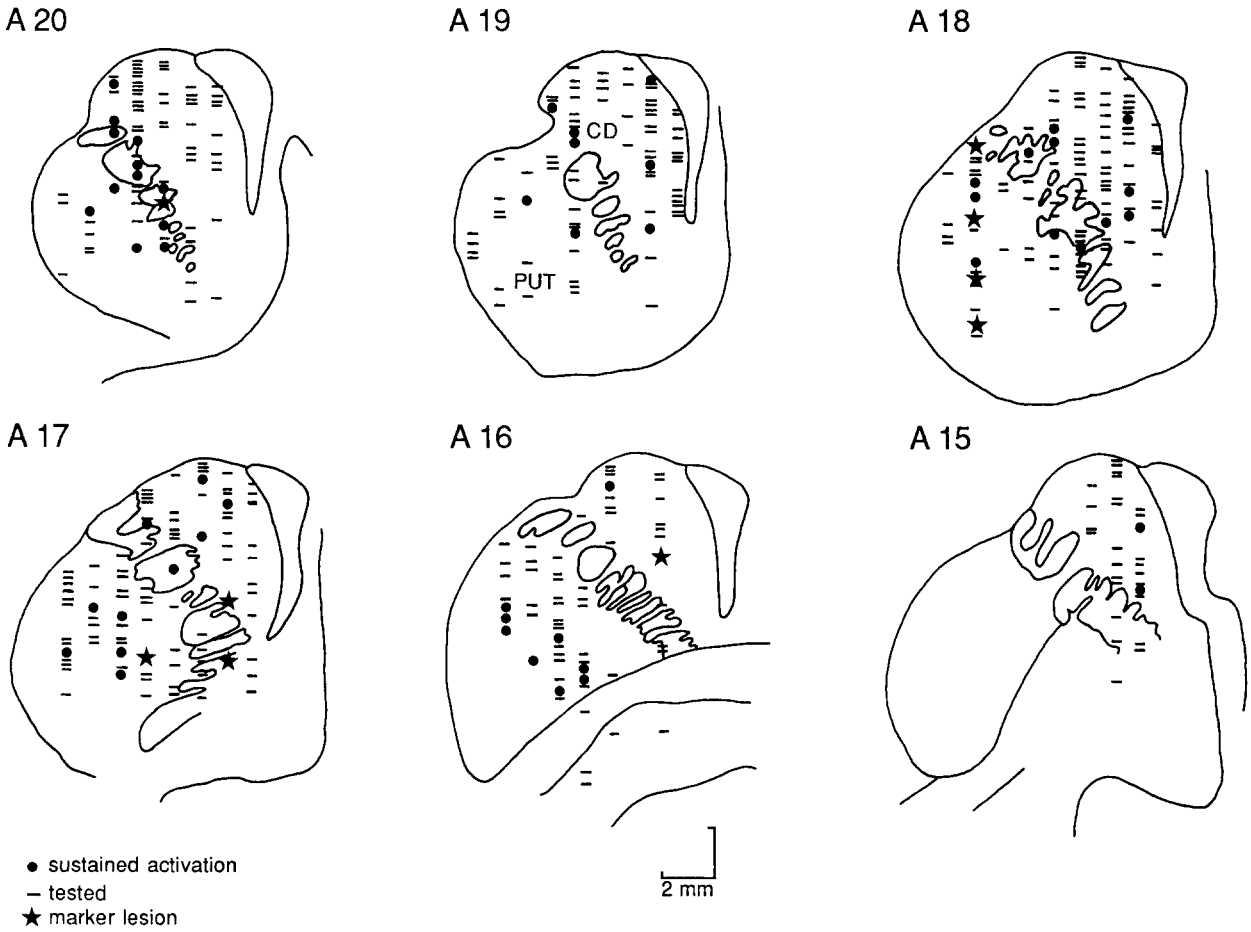


Fig. 6. Plots of recording sites in the striatum of one monkey. Positions of striatal neurons with sustained activations in the instruction-trigger interval of the delay task are shown by *heavy dots*. Coronal sections from the left hemisphere are labeled in coronal stereotaxic planes according to the distances from the interaural line (*A15–A20*)

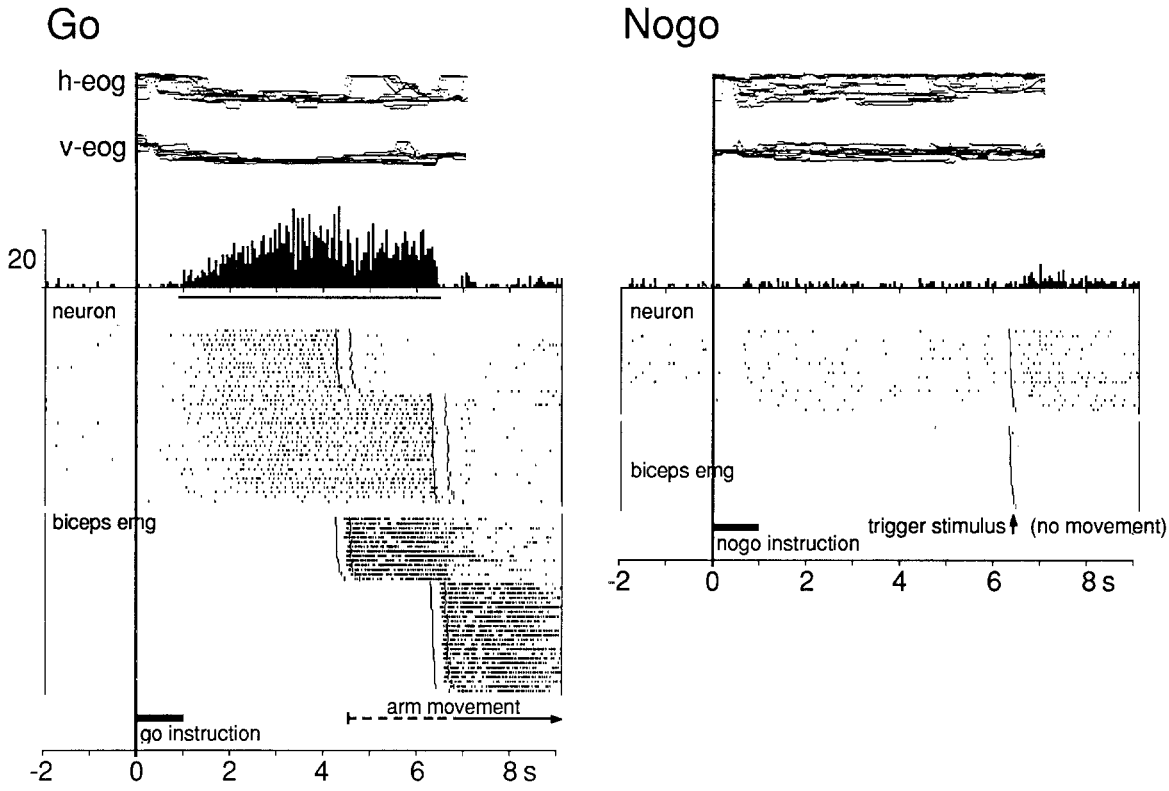


Fig. 7. Sustained activation in a putamen neuron after the instruction cue. Increased activity occurred only during the instruction preparing for arm movement (go trials, *left*). Horizontal and vertical electrooculograms (*h*-and v-*eog*) from the first ten go and no-go trials, respectively, are shown superimposed on top of perievent time histograms and rasters of neuronal impulses. Rectified biceps activity (*emg*) converted into digital pulses is shown in separate rasters below neuronal impulses. EMGs were recorded in same trials as neuronal impulses. The *horizontal bar below* the *left* histogram marks the period of neuronal activation, as assessed with the sliding window procedure on the basis of coherent changes in individual trials (onset time 900 ms, duration 5496 ms, magnitude 3679%). In each *row of dots* of neuronal and EMG activity, *two vertical lines* to the *right* of the reference line denote the time of the trigger stimulus and, in go trials, onset of arm movement (key release), respectively. Go and no-go trials alternated randomly during the experiment and were separated off line. The sequence of trials is rearranged according to instruction-trigger intervals

trials ($n=92$) and were rarely observed in no-go trials alone ($n=9$) or in both situations ($n=3$). Separate transient responses to the instruction cue were seen in 5 of these 98 neurons. Sustained depressions were found in 35 neurons in both parts of striatum. They occurred in go or no-go trials, but rarely in both, and were seen with continuous and short instructions.

A typical sustained activation is shown in Fig. 7. The activity of this putamen neuron increased slowly after instruction onset and remained elevated until the trigger stimulus for the arm reaching movement occurred. No such activation was seen in no-go trials in which the animal refrained from moving. The relationship of the activation to the subsequent behavioral response became further apparent when the behavioral plan was changed during the instruction period. For example, presentation of a go instruction immediately following a no-go instruction resulted in the appearance of an activation that only subsided with movement onset (Fig. 8). Sustained activations occurred equally with continuous as well as with short instructions in all 32 neurons so tested, suggesting

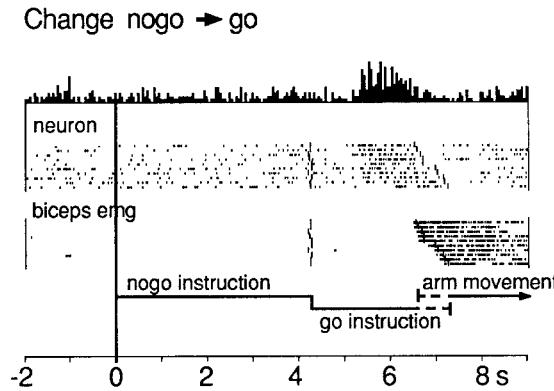


Fig. 8. Change of preparation for behavioral reaction induces a change in sustained preparatory activity in a putamen neuron. The change of the no-go to the go instruction prepared an arm movement reaction and induced a neuronal activation typical for go trials. This neuron displayed sustained activity over several seconds very similar to that shown in Fig. 7. *Small vertical lines* in the *right* part of the raster display denote the onset of arm movement (key release). Trials are rank ordered according to instruction-movement intervals

that sustained activations were neither sensory responses nor specifically related to mnemonic aspects of the task. Activations were unrelated to particular ocular fixation patterns, since the eyes usually fixated the instruction light only for an initial period of less than 1s and subsequently moved to other targets (Fig. 7, top).

Sustained activations were typically maintained during delays of several seconds until the trigger stimulus occurred, despite considerable and irregular variations of instruction-trigger intervals (Fig. 9). When the requirements for muscular relaxation were reduced, animals cooperated for delay periods as long as 80 s but occasionally showed brief uncontrolled muscle contractions at 30–50 s after instruction onset. Activations invariably continued during the maximal testable durations while subsiding shortly during the intervening muscle activity. This was observed in all 16 caudate and putamen neurons tested with these long durations in go trials and in 1 caudate neuron activated in no-go trials.

Quantitative evaluations revealed that activity in some neurons began in response to instruction onset (go latencies of <500 ms in 26 neurons), whereas in others it developed toward the end of the instruction period (go latencies of >1.5 s in 38 neurons). The analysis of peak activity revealed that most activations culminated toward the middle or end of the preparatory period, whereas only seven neurons reached their peak activity in <500 ms after instruction onset (Table 3). Onset times, offset times, and magnitudes of neuronal activations varied insignificantly between continuous and short instructions and were pooled.

In order to further investigate to which task component the sustained activity was related, we determined the temporal relationships to subsequent behavioral events by assessing the offset times of activations relative to each task event with the sliding window procedure in 67 neurons not responding to the trigger stimulus or covarying with movement execution. Most sustained activations terminated during the reaction time period, i.e., between the trigger stimulus and the onset of arm movement (38 neurons; Figs. 7–9A, 10A), whereas fewer ended after movement onset (12 neurons; Fig. 9B), after entering the box and contact with food (14 neurons) or after leaving the box (3 neurons). This resulted in a median offset time of 50 ms before movement onset, the difference between caudate and putamen being insignificant (10 and 110 ms, respectively; $P>0.05$). Offset times in relation to the different task events are shown in Fig. 11.

The animal's first reactions to the trigger stimulus in most trials consisted of a saccadic eye movement toward the food boxes (Fig. 10A). Although occasionally terminating close to the onset of saccades, activations were equally present in the few go trials lacking sccades. Eye movements also occurred in no-go trials during which the same neuron lacked sustained activity (Fig. 10B, C). Thus, the observed sustained activations were not specifically related to the preparation of saccadic eye movements.

Self-initiated movements

Significant increases in activity beginning more than 500 ms before onset of self-initiated arm movements were

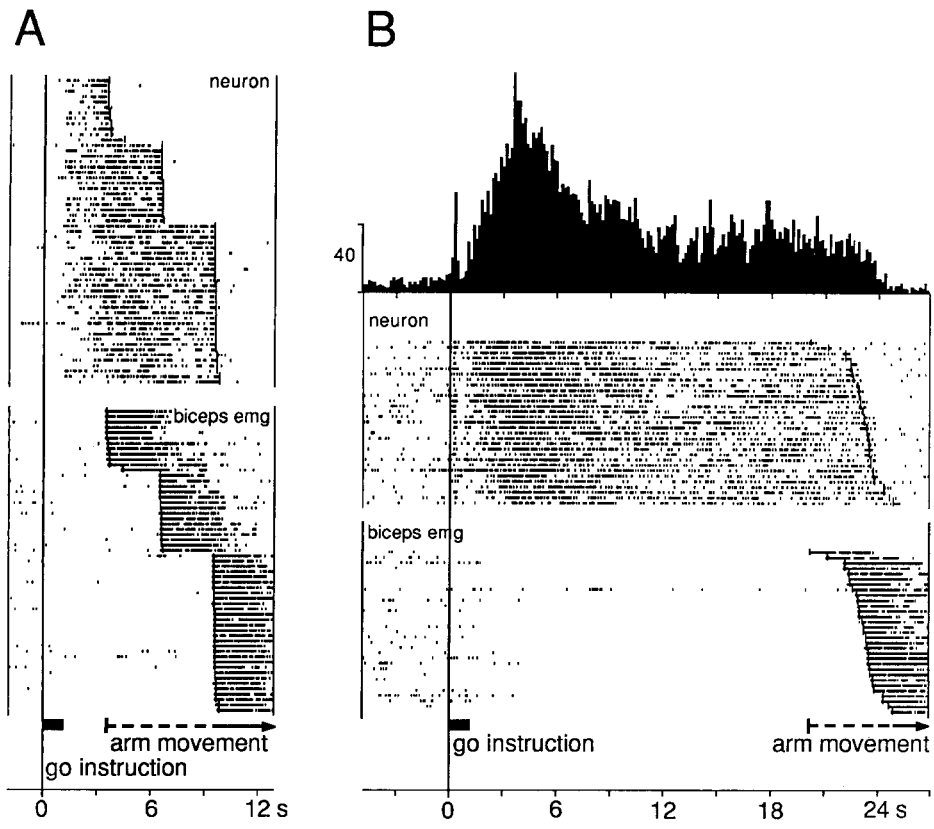


Fig. 9A, B. Sustained activations during long delays. **A** Caudate neuron. Various instruction-trigger stimulus intervals were used in irregular sequence and were regrouped after the experiment according to length of delay. **B** Putamen neuron. Short instructions were used in **A** and **B**. Thus information about forthcoming demanded behavioral reactions (movement vs no movement) was absent between instruction offset and trigger stimulus. Only data from go trials are shown

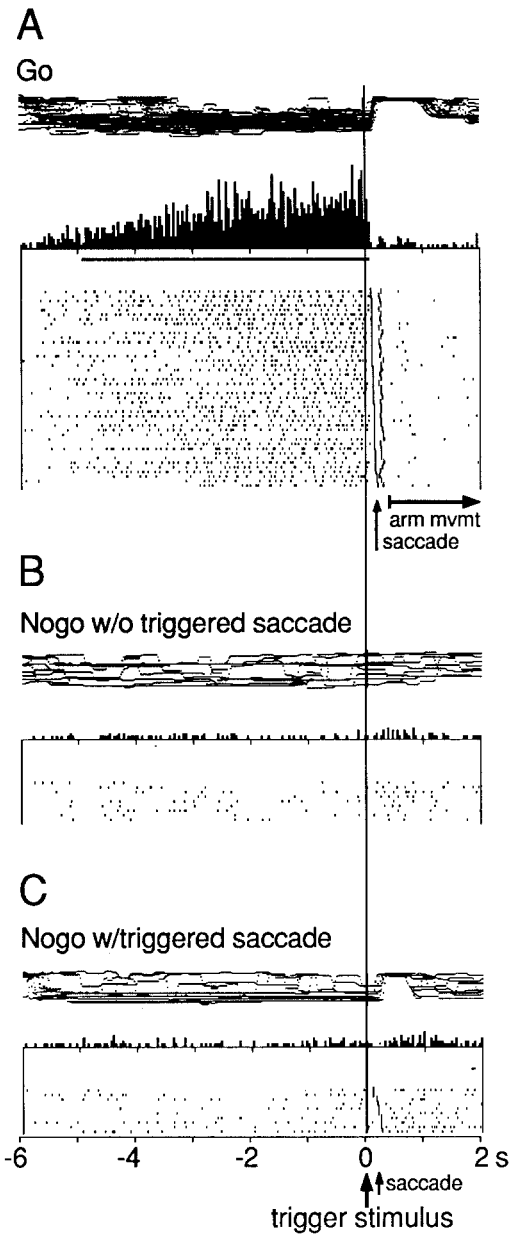


Fig. 10A–C. Sustained activity is unrelated to eye movement onset in a putamen neuron during performance of the delay task. **A** The activity in go trials terminates after the trigger stimulus and before the onset of saccadic eye movement. **B, C** In no-go trials, the neuron is not activated, independent of the absence (**B**) or presence (**C**) of saccades (*horizontal components*). This demonstrates a lack of relationship to the preparation of saccadic eye movements. Data were recorded in one block and separated according to go and no-go situations and, within no-go trials, according to the absence or presence of saccadic eye movements. *Small vertical lines* in rasters indicate saccade onset and key release. The *horizontal bar* below the histogram in **A** marks the periods of neuronal activation determined with the sliding window procedure (onset 4910 ms before, offset 110 ms after the trigger stimulus). *w/o*, without; *w*, with; *mvmt*, movement

found in 74 neurons (32 in caudate and 42 in putamen). The time limit of 500 ms was chosen for ruling out any overlap with occasionally occurring very early muscle activity (see Figs. 12, 15). This limit had little influence on the results; reducing it to 400 ms would only increase the sample of modulated neurons by two. Several examples of premovement activations are shown in Fig. 12. This activity began slowly, barely exceeding the low background activity, and only several hundred milliseconds later attained a statistically significant level. Significant onsets occurred occasionally as early as 5 s but usually less than 3 s before movement onset (median for caudate 940 ms, putamen 1359 ms, total 1160 ms; $P > 0.05$). The peak of activity was reached before movement onset in 55 neurons (Fig. 12A, B) and occurred within 300 ms after movement onset in the remaining 19 neurons (Fig. 12C, D; median 270 ms before movement). Subsequently, the activations declined rapidly and terminated before movement onset (31 neurons; Fig. 12A, B), after movement onset (9 neurons), at the end of the reaching movement after the hand entered the food box (31 neurons; Fig. 12C) or immediately thereafter (3 neurons). Median offset time was 120 ms after movement onset, the difference between caudate and putamen being insignificant (200 and 89 ms, respectively; $P > 0.05$). Onset and offset times in relation to the different task events are shown in Fig. 13.

Besides the frequent spontaneous eye movements, each self-initiated arm movement was preceded by a single saccade toward the food box 200–800 ms before movement onset (Fig. 12D). Thus, saccades occurred together with or slightly before onset of earliest muscle activity. The eyes kept the food box fixated until the animal's hand left the box 0.5–1.0 s after movement onset. None of the premovement activity showed reliable trial-by-trial relationships to onset of the targeting saccade or the other spontaneous saccades. In particular, the offsets of premovement activity were unrelated to saccade onset in the present sample of neurons.

Histological reconstructions of recording positions revealed that neurons with premovement activity were located in the whole area of anterior caudate and putamen explored in the present experiments, the two main types of premovement activity occurring in largely similar regions (Fig. 14).

Comparison between self-initiated and instructed movements

A total of 611 striatal neurons were studied in both the self-initiated movement task and the delay task. Activations preceding self-initiated movements were seen in 53 neurons, of which 18 (34%) also showed sustained activations in the delay task (8 in caudate, 10 in putamen; Figs. 14, 15). None of these 18 neurons were activated in no-go trials of the delay task. By contrast, 35 of the 53 neurons (66%) lacked sustained activations in the delay task (17 in caudate, 18 in putamen). Sustained activations in the delay task were seen in 54 neurons tested in both tasks, of which 36 (67%) were not activated before self-initiated movements (17 in caudate, 19 in putamen). Transient responses to the instruction light were seen in an additional 8 neurons activated before self-initiated movements, of which 4 also showed sustained activations.

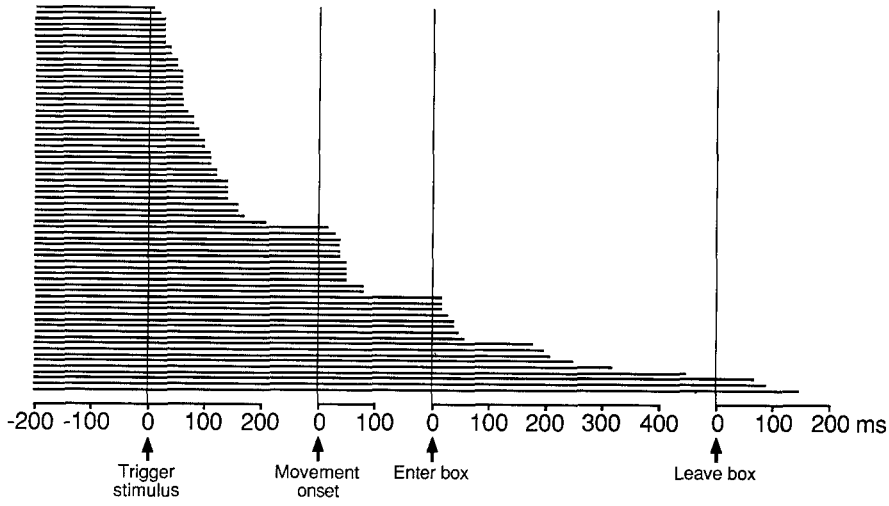


Fig. 11. Summary of offset times of sustained activity in relation to different events of the delay task. Each *horizontal bar* represents the statistically significant activation of a single striatal neuron (total of 67 neurons not responding to other task events). Bars are rank ordered according to offset times. Because of varying intervals between behavioral events, activity was evaluated by consecutively referencing impulses to trigger stimulus, movement onset, entering the box, and leaving the box, by using the sliding window procedure. The latest obtained offset value is included in the graph and drawn in temporal reference to the immediately preceding event

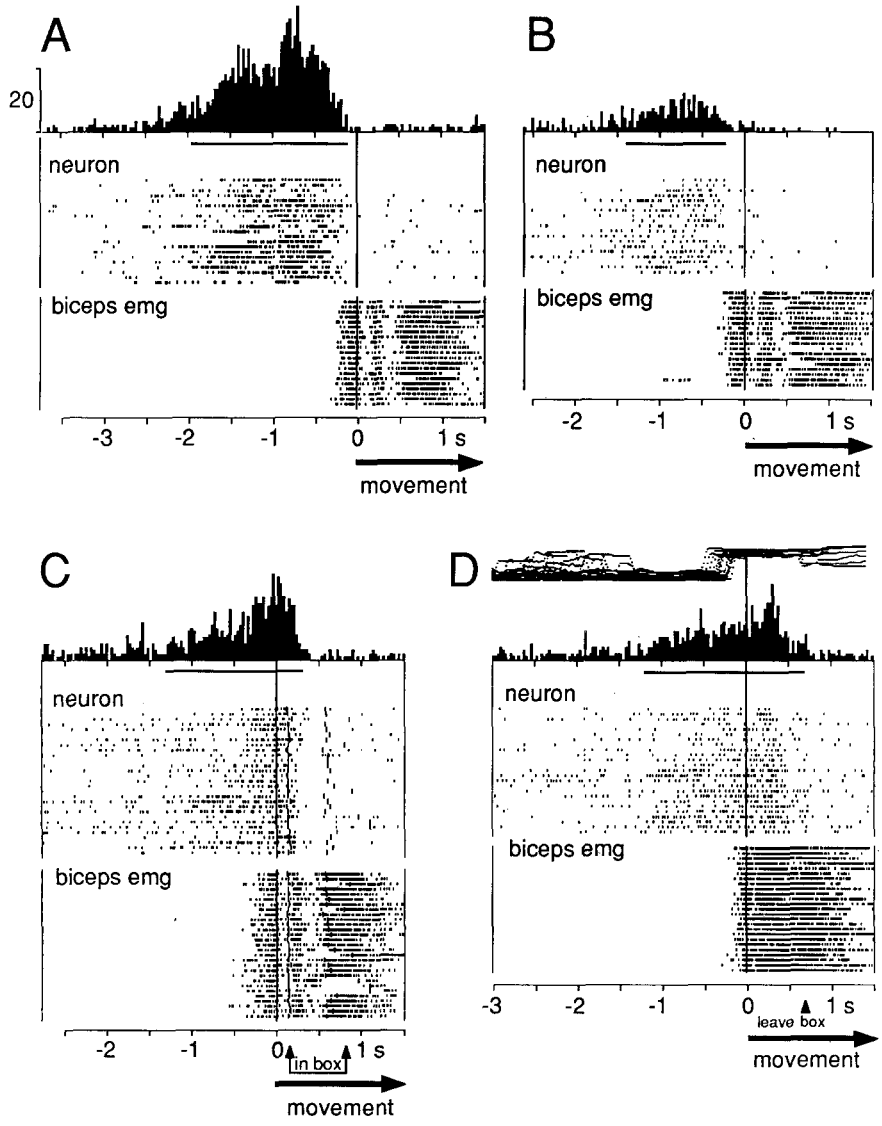


Fig. 12A–D. Activity in four putamen neurons preceding self-initiated arm movements. **A, B** Activity terminating before movement onset. **C** activity terminating after entering the food box. **D** Lack of relationship to eye movements. Superimposed traces of the horizontal component of eye movements are shown above histogram and raster of simultaneously recorded neuronal activity. The original sequence of trials is preserved downward. All data are referenced to movement onset (key release). *Horizontal bars* below histograms indicate durations of statistically significant activations determined with the sliding window procedure. Onset and offset times were: −1388 and −233 ms (**A**); −1913 and −100 ms (**B**); −1268 and 322 ms (**C**); −1248 and 667 ms (**D**) *emg*, electromyogram

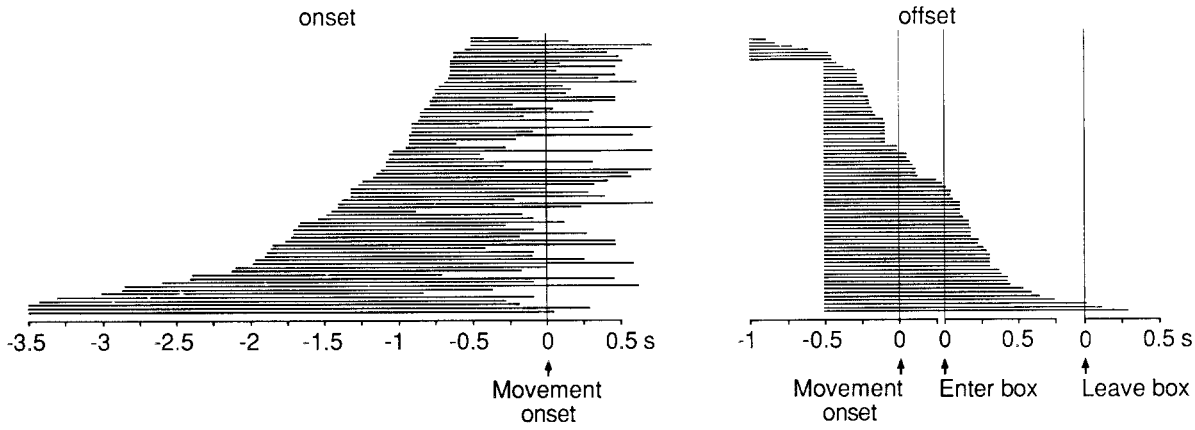


Fig. 13. Summary of temporal relationshiops of premovement activity to different components of self-initiated movements. *Horizontal bars* represent the times of increased activity of 74 individual neurons and are rank ordered according to onset (*left*) and offset times (*right*). Data are shown commonly for caudate and putamen because of insignificant differences in these parameters ($p > 0.05$)

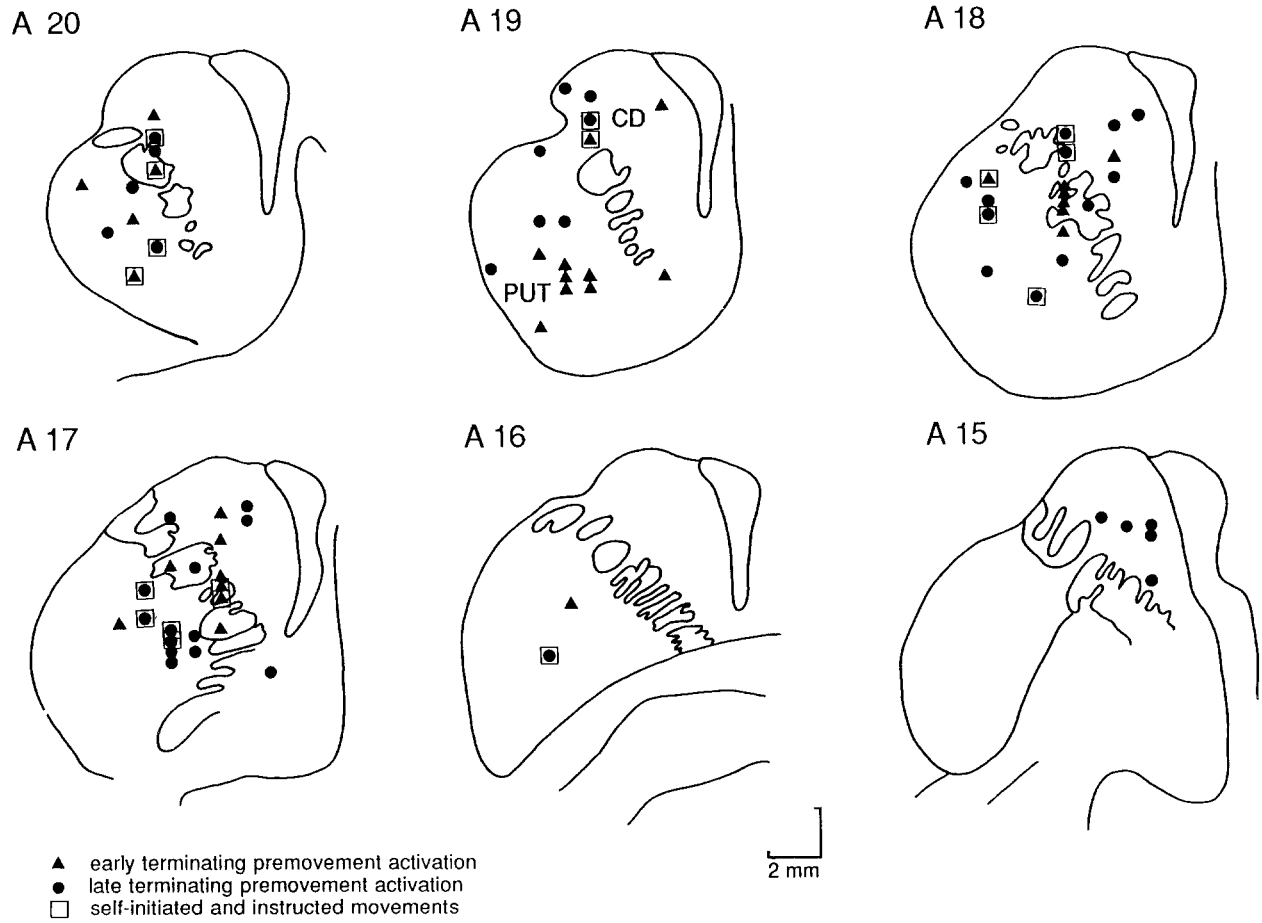


Fig. 14. Positions of striatal neurons with premovement activity preceding self-initiated arm movements by more than 500 ms. *Triangles* and *Circles* indicate neurons with activity terminating before ($n = 31$) and after movement onset ($n = 43$), respectively. Superimposed *squares* indicate neurons activated before both self-initiated and instructed movements ($n = 18$). Data from all three monkeys are drawn on representative coronal sections of the left striatum labeled in coronal stereotaxic planes (*A15–A20*). *PUT*, putamen; *CD*, caudate

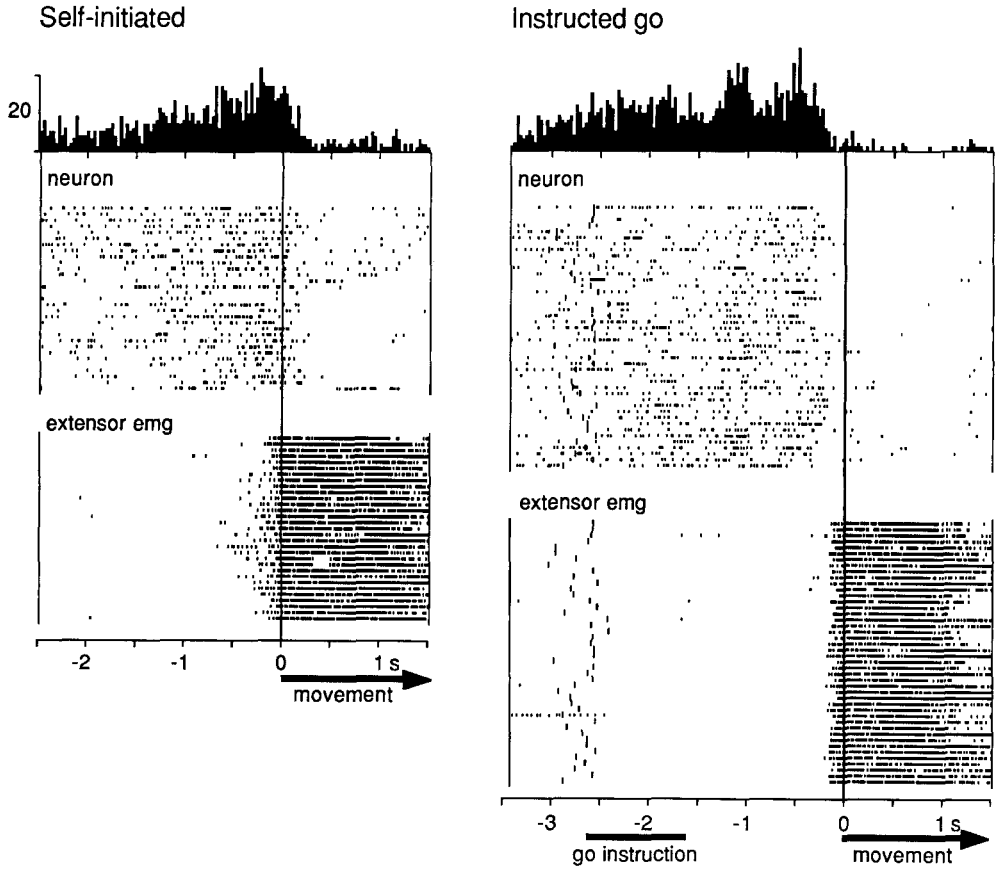


Fig. 15. Activity of a caudate neuron showing premovement activity before self-initiated and instructed movements. The premovement activity terminates after movement onset with self-initiated movements (*left*) but before the movement in the delay task (*right*)

Quantitative comparisons of all premovement activations revealed a tendency for later activation peaks and activation offsets with self-initiated as compared to instructed movements (Fig. 15; Table 4). The differences were significant for activation peaks ($P<0.001$) but insignificant for activation offsets ($P>0.1$). (The onset of the preparatory period in the delay task is explicitly defined by the instruction light, thus precluding the comparison of activation onsets between the two tasks.) Activations showed insignificantly higher peak magnitudes with self-initiated as compared to instructed movements ($P>0.1$). Paired comparisons on the 18 neurons activated in both tasks revealed only insignificant differences in these parameters ($P>0.2$). Activity preceding self-initiated movements was similar in neurons activated only with self-initiated movements as compared to those activated in both tasks in terms of offset time, peak latency, and peak magnitude ($P>0.08$).

Population histograms obtained by averaging the activity of modulated neurons give an overview of the different types of preparatory activity encountered in the striatum. Figure 16A shows the average transient response to the instruction signal in the delay task. It is particularly apparent that transient activations represent responses to the instruction. By contrast, sustained activations show only a small response component, began more gradually during the instruction-trigger interval without close temporal relation to instruction onset, and increased until the

Table 4. Comparisons of premovement activations between self-initiated and instructed movement tasks

	Caudate	Putamen	Total
Offset time (ms)			
Self-initiated	200*	89*	120*
Instructed go	−10	−110	−50
Peak latency (ms)			
Self-initiated	−290*	−260**	−270**
Instructed go	−410	−990	−650
Peak magnitude (%)			
Self-initiated	476*	733*	667*
Instructed go	330	570	391
Numbers of neurons			
Self-initiated	32	42	74
Instructed go	31	36	67

All measurements were referenced to movement onset, the results being expressed as medians. Peak activity was determined during intervals of 500 ms, its latency denoting the midpoint of the interval with maximum activity. Values for activations preceding instructed movements in the delay task were obtained from go trials of 67 neurons not covarying with other events (instructed go). Two-way Anovas on offset time, peak latency, and peak magnitude using the two structures and the two task situations as factors revealed a significant difference in peak latency between tasks ($P<0.0005$). The Mann-Whitney test located the difference in peak latency in putamen, but a similar difference between tasks was obtained when neurons from caudate and putamen were pooled (**$P<0.001$ against instructed movements, *$P>0.1$).

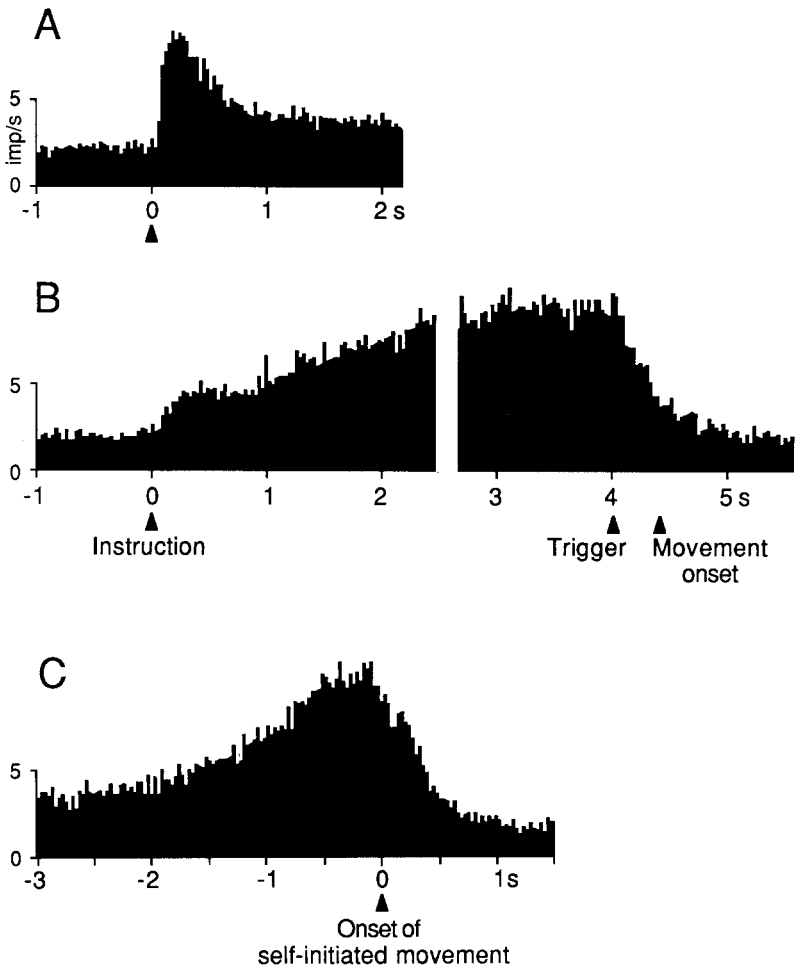


Fig. 16A–C. Population activity of striatal neurons. **A** Activity from all 98 neurons with transient responses to instruction onset in go trials (total of 1991 trials). **B** Sustained activation between instruction and trigger stimuli in go trials of the delay task. Because of varying intervals, histograms were separately referenced to instruction onset (*left*; 2192 trials from 92 neurons) and trigger stimulus (*right*; 1558 trials from 67 neurons not covarying with trigger stimulus or movement). **C** activation preceding self-initiated movements from 74 neurons (total of 1234 trials). For each display, histograms from every neuron normalized for trial number were added and the resulting sum divided by the number of neurons. *Vertical scale* denotes impulses per second (imp/s)

trigger stimulus and movement onset where they terminated rather abruptly (Fig. 16B). Average premovement activity preceded self-initiated movements by 1–2 s and increased slowly before the movement (Fig. 16C). They started to decline before movement onset and afterwards terminated rapidly. Thus, the average temporal profiles of premovement activity in the two tasks are to a considerable extent similar.

Discussion

The present study revealed that neurons in the anterior caudate and putamen of monkeys are activated up to several seconds before individual movements that are generated internally by the subject without explicit external stimuli. Two thirds of the neurons activated before self-initiated movements were not activated before movements in the delay task, thus suggesting a particular relationship to processes contributing to the internal generation of movements. For comparison, two types of activity related to the preparation of movements were observed in the delay task. Some neurons showed transient responses that followed the light instructing for a subsequent movement reaction. Other neurons showed sustained activations that began during the instruction-trigger interval and partly resembled in their time course the activity preceding self-initiated movements. These data were obtained by using the same arm reaching movement in both tasks, thus facilitating the comparison between the tasks. These tasks helped the animals to control their state of motor activity by employing movements that began from a natural, relaxed resting position maintained without muscle activity and which terminated at a distinct spatial target.

Nature of transient responses

Instruction stimuli in the delayed go no-go task served to prepare for two behavioral reactions, execution of movement and refraining from movement. Performance in the present unrewarded no-go situation involves less suppression of movement than the active inhibition required in rewarded no-go trials (Petrides 1986). Transient responses to instructions terminated before the subsequent trigger stimulus. They were specific for the behavioral situation, such that most responses were restricted to go trials, whereas fewer responses occurred in no-go trials or in both situations. These responses may be involved in neuronal processing occurring before overt behavioral reactions, such as the preparation of movement, expectation of the

trigger signal, or inhibition of movement. They may also participate in setting up selective attention and directing the attentional spotlight toward the forthcoming trigger signal. These responses may also be involved in storing information into working memory, as suggested for similar responses in pars reticulata of substantia nigra (Hikosaka and Wurtz 1983), caudate nucleus (Hikosaka et al. 1989a), and prefrontal cortex (Fuster and Alexander 1971; Funahashi et al. 1990). Some of the transient responses were of rather long duration, and their transient character was only revealed when long instruction-trigger intervals were used. This may be evidence for a transition process between transient and sustained activations involved in the generation of fully sustained activations. Similar activity has been found in premotor cortex (Wise and Kurata 1989).

Nature of sustained activity in the delay task

Through the experience obtained during conditioning, monkeys became able to use the instruction stimulus to direct their behavioral response to the trigger stimulus. Thus, the instruction gained predictive value for future events and set up an internal state of preparation for the forthcoming behavioral reaction that is maintained until the reaction occurs. In contrast to the transient responses that followed the instruction and terminated before the trigger stimulus, sustained activations lasted up to several tens of seconds during this preparatory state, until the trigger stimulus and the ensuing movement occurred. The relationships to the individual forthcoming events were quantitatively assessed by measuring the offset times of activity in relation to the different task components. Thus, activity terminating with the onset of a specific sensory or motor event should be predominantly related to that event, and less so to other events that may follow.

The large majority of sustained activations occurred exclusively in go trials and most of them terminated with the onset of movement. This activity cannot be explained by uncontrolled muscle contractions, as indicated by its offset time and by the absence of muscle activity during the period of neuronal activation. Rather, this suggests a relationship to the preparation of movements. Although the time course did not exclude a relationship to the expectation of the movement triggering signal, some of these neurons were also activated before self-initiated movements in which the expectation of external signals is eliminated. A further argument for the relation to movement-preparatory processes is the development of sustained activity when the behavioral plan changed from no-go to go during the delay period. However, the restriction of the task to arm movements does not allow us to assess whether the preparatory activity was specific for movement reactions of the arm, as opposed to other parts of the body, even though uncontrolled movements were largely ruled out. Previous studies in motor and premotor cortex have similarly interpreted directional or go-specific sustained activity to reflect the preparation of movement (Tanji and Evarts 1976; Tanji et al. 1980; Weinrich and Wise 1982).

A possible involvement in working memory was tested by keeping the instruction present beyond the trigger stimulus which made memorization unnecessary. However, all neurons maintained their activation in this situation, resembling the majority of prefrontal neurons that kept their activity in a similar task modification (Niki 1974; Kojima and Goldman-Rakic 1984). This may suggest that the tasks required little mnemonic processing and that the continuous instruction was memorized despite its maintained presence; as suggested by the only shortlived ocular fixation.

Sustained activity before arm movements was presently found in both anterior caudate and putamen and was not restricted to the arm area of posterolateral putamen as previously suggested (Alexander 1987). More recent studies reported on neurons with preparatory activity being located in the anterior putamen (Alexander and Crutcher 1990) and the center of the head of caudate (Hikosaka et al. 1989b). Thus, sustained activity preceding arm movements is apparently distributed over large areas of caudate and putamen, rather than being specific for motor putamen.

Origin of sustained activations in the delay task

Delay-related sustained activity similar to that described presently has been reported in numerous cortical areas. This type of activity has been suggested to reflect spatial short-term memory in prefrontal cortex and anterior cingulate gyrus (Fuster and Alexander 1971; Kubota and Niki 1971; Niki and Wantanabe 1976), movement preparation in supplementary motor area, premotor and motor cortex (Tanji and Evarts 1976; Tanji et al. 1980; Weinrich and Wise 1982), spatial coding, directed attention, and retention of haptic information in parietal areas 5 and 7 (Lynch et al. 1977; Kalaska et al. 1983; Crammond and Kalaska 1989; Koch and Fuster 1989), and visual memory in temporal association cortex (Fuster and Jervey 1982; Miyashita and Chang 1988). Sustained activations in striatum may well be induced by input from any or all of these cortical areas, since all of them project in an ordered, partly interdigitating fashion to the areas of striatum (Selemon and Goldman-Rakic 1985) in which the present sustained activity was found.

Alternatively, the sustained activity in striatal neurons may be triggered, via corticostriatal and intrastriatal connections, by transient responses to instructions occurring in striatal and cortical neurons. This activity may progress and be built up to sustained activity by circulating in loops involving the frontal cortex and basal ganglia (Romo and Schultz 1992). Sustained activity related to movement preparation occurs throughout major parts of cortico-basal ganglia loops, such as the supplementary motor area, motor cortex, posterolateral putamen (Alexander and Crutcher 1990), pallidum (Turner and Anderson 1989; Nambu et al. 1990), and pars reticulata of substantia nigra (Hikosaka and Wurtz 1983; Schultz 1986). Although this activity begins slightly earlier in the supplementary motor area, as compared to striatum, the large overlap suggests its largely simultaneous occurrence (Romo and Schultz

1992). At the level of individual striatal neurons, the development of activity lasting over several seconds may be facilitated by the action of slow Na^+ and K^+ channels in spiny neurons giving rise to prolonged excitatory postsynaptic potentials, slowly depolarizing ramps, and slowly inactivating K^+ conductances (Calabresi et al. 1987; Kawaguchi et al. 1989; Penartz et al. 1991; Surmeier et al. 1991). It remains to be shown whether the temporal integration provided by these slow membrane phenomena might contribute to prolonged impulse activity in the form of sustained activations.

Nature of activity preceding self-initiated movements

The time limit of 500 ms before movement onset was chosen in order to avoid conflicts with early muscle activity in occasional trials. Similar values have been used before with movements in the absence of immediately triggering stimuli (Neafsey et al. 1978; Okano and Tanji 1987; Romo and Schultz 1987; Kurata and Wise 1988). In general, premovement muscle activity began earlier with self-initiated movements, as compared to stimulus-triggered movements. This was also found in another study employing a similar degree of temporal liberty in movement initiation (Thaler et al. 1988). In contrast, comparable EMG onset times with internally and externally triggered movements were seen when movement initiation was more closely associated with external reference stimuli (Okano and Tanji 1987; Kurata and Wise 1988).

During self-initiated arm movements, activity increased up to 3–5 s before movement onset and usually subsided with movement onset. Since the self-initiated movement occurred without explicit phasic stimuli, premovement activity should be predominantly related to a state of readiness and preparedness to make a movement, referred to as motor set, as opposed to a state of readiness to receive a signal that is referred to as perceptual set in close association with selective attention (Evarts et al. 1984). Since the present task includes only a single movement without systematic variation of parameters, it is unclear whether the premovement activity is specifically related to movement parameters, such as direction, amplitude, velocity, or force, or reflects a more general motor set. By contrast, activity terminating well after movement onset might reflect the expectation of external signals generated during task performance, such as proprioceptive feedback, vision of the moving hand, somatosensory contact with the food box, or reward. Most activity terminated before contact with reward and was thus unlikely to be related to the expectation of reward or to general arousal and attention.

Animals needed to control their motor activity and inhibit an occasionally arising internal urge to move, because they were not rewarded when moving too frequently (more than once every 5 s). However, the observed steady increase in activity toward the movement is difficult to reconcile with movement inhibition operating at similar intensities during the whole delay. Also, none of the neurons showing premovement activity with self-initiated movements were activated during the preparation for no-go trials, nor in response to the no-go trigger stimulus. Thus, inhibition of movement is unlikely to contribute to a sizeable extent to the observed premovement activity.

Recordings of eye movements failed to reveal neuronal activity related to the preparation of saccades in either the delay or the self-initiated arm movement task, although such activity has been found in the part of the caudate receiving input from frontal eye fields (Hikosaka et al. 1989a). The relatively small number of neurons recorded in this restricted area in the present study might have precluded the detection of these relationships, although another important factor may have been the absence of specific task contingencies for eye movements.

Premovement activity beginning up to 1 s before self-initiated forelimb movements was previously observed in cat pallidum neurons and interpreted as being related to preparatory set (Neafsey et al. 1978). These data in general agree with those obtained presently and suggest the involvement of several basal ganglia structures in the internal generation of movements. Premovement activity was also observed in caudate and pallidum neurons of monkeys performing self-timed arm movements within a narrow time window in close temporal association with a preceding instruction signal (Soltysik et al. 1975). This situation resembles more a delayed response task, and the results are difficult to compare with those obtained here.

Degree of liberty in self-initiated movements

The assessment of factors contributing to the internal generation of individual movements needs to take into account the details of the experimental situation. The frame of this experiment was determined externally to the subjects by the experimenters. Behavioral choice was limited to a single task in which a single movement was performed toward a single target for a single purpose, the obtainment of food reward. Thus, animals were not free to generate their goal of action or to select a particular goal among different choices. Their behavior lacked telosponses (selection of goal) and thus consisted of reactions to the environmental situation (Rychlak 1981).

Animals were highly familiar with the task and had associated the various parts of the experimental apparatus with their behavioral meaning. They knew the food box, which to them represented a constantly present conditioned incentive stimulus eliciting approach behavior for obtaining food. Because of food deprivation, they were hungry and thus had a drive that in the presence of the incentive stimulus gave rise to an internal motivational state (Toates 1986) and directed their behavior toward the food box, while reducing the frequency of other competing actions. The importance of incentive stimulus properties is indicated by the reinstatement or increased frequency of self-initiated movements when food was changed (apple vs cookie vs raisin).

Thus, the liberty of animals was limited by the constraints of the externally imposed experimental situation and the motivational state. However, phasic external stimuli were completely absent and animals were free to

decide at which time to emit the approach behavior. They performed each individual movement at a self-chosen moment in the absence of explicit, stimulus-induced temporal constraints. Thus, the present study was largely concerned with the *temporal* aspects of the internal generation process of movements.

Previous studies have employed various degrees of temporal liberty with internally generated movements. Considerable temporal choice exists for humans instructed to perform movements at self-chosen moments during experimental sessions of different durations (Kornhuber and Deecke 1965; Libet et al. 1983). Work with food- or fluid-deprived animals imposes temporal pressure, because animals are naturally interested in reducing their state of deprivation as fast as possible. The ease with which animals perform eye movements allows one to study spontaneous behavior not aimed at reward (Schultz et al. 1989b), although some eye movements outside of formal tasks are known to be performed for searching reward-related signals (Schlag and Schlag-Rey 1987). Arm movements are less readily performed in a spontaneous manner and usually require reward, but may still have different degrees of temporal constraints. In the present experiments we used a natural reaching movement that animals performed whenever they liked to, but we restricted reward availability in order to avoid frequent and repetitive movements. Also, we controlled the activity of the animal using the delay task in separate blocks of trials. Other studies employed similar situations but allowed shorter intermovement intervals which makes the internal timing more automatic and considerably reduces the degree of temporal liberty. In this case, the task is more likely performed as a habit in which movements are to a lesser extent generated on an individual base, only their rhythm being controlled internally (self-paced; Neafsey et al. 1978; Hashimoto et al. 1979; Kurata and Wise 1988; Thaler et al. 1988; Turner and Andersen 1989). In another study, the animal initiated a movement if an external stimulus failed to occur after a known delay, thus involving a considerable relation to the temporal occurrence of external stimuli (Okano and Tanji 1987). A different form of temporal constraint is provided in tasks in which animals are required to wait after a external stimulus for a few seconds before starting the movement without further signals (Watts et al. 1990). This situation is also referred to as internal timing behavior (Niki and Watanabe 1979) or delayed response task (Soltysik et al. 1975), rather than self-initiation. Thus, self-initiated movements are performed within the constraints of a given experimental situation and are subject to varying temporal liberty that need to be kept in mind when interpreting the data in relation to the internal generation process.

Neuronal correlates for the internal generation of individual behavioral acts

The time course of the premovement activity observed in single neurons in the current study is in the same range as the cortical readiness potential preceding self-initiated arm movements. Recent studies have shown a temporal relation between the readiness potential and the subjective urge to move (Libet et al. 1983), further suggesting that the readiness potential reflects processes occurring during the internal generation of behavior. Depending on the experimental situation, cortical readiness potentials in man preceded movements by 1 s (Kornhuber and Deecke 1965; Libet et al. 1982) and up to 2 s (Barrett et al. 1986). Onset times of readiness potentials of only 0.6 s preceding the movement were obtained in humans reporting more spontaneous initiation with lower degrees of planning (Libet et al. 1982). Values of 0.5–1.5 s were obtained from readiness potentials recorded in the motor, supplementary motor, and premotor cortex of monkeys performing self-initiated movements (Arezzo and Vaughan 1975; Hashimoto et al. 1979; Gemba and Sasaki 1984). The present statistically measured medians of onset times before self-initiated movements of 1.2 s in individual striatal neurons thus correspond to the time courses of cortical readiness potentials. However, inspection of the population histogram obtained from all activated striatal neurons revealed an earlier onset of about 1.5 s, and some neurons were activated as early as 3–5 s before movement. A likely explanation for the earlier onsets recorded from individual neurons, as compared to the mass readiness potentials, appears to be the higher temporal resolution provided by single neuron recordings. As neuronal onset times in our monkeys were clearly longer than the 0.6 s reported in humans in the absence of planning, it may be speculated that monkeys performed the self-initiated movements with more planning and lesser degrees of temporal choice, possibly induced by the goal directedness of the individual movements. The statistical procedure does not explain the earlier onset, because it often detected onsets later but never earlier than visual data inspection. The earlier onset of premovement activity in single striatal neurons, as compared to cortical readiness potentials, does not suggest that the striatum is activated before the frontal cortex. Neuronal activity preceding self-initiated movements began slightly later in the striatum as compared to the supplementary motor area of the same animals (Romo and Schultz 1992).

The central question remains how premovement activity may develop in the absence of a stimulus-induced neuronal response. At some time the uncorrelated spontaneous neuronal activity needs to bifurcate, cross a certain threshold, and be slowly built up to the observed temporal profile of premovement activity. In analogy to the discussion on delay-related activity, above, it is possible that slow membrane processes are involved. However, in contrast to activity that develops after external stimuli, providing a temporal reference, it is unclear how and why slow channels would become operational only at specific times. The role that corticobasal ganglia loops may play in this generation process is discussed in a companion report (Romo and Schultz 1992).

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