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Neuronal Activity in Monkey Striatum Related to the Expectation of Predictable Environmental Events

PAUL APICELLA, EUGENIO SCARNATI, TOMAS LJUNGBERG, AND WOLFRAM SCHULTZ
Institut de Physiologie, Université de Fribourg, CH-1700 Fribourg, Switzerland

SUMMARY AND CONCLUSIONS

1. This study investigated neuronal activity in the striatum preceding predictable environmental events and behavioral reactions. Monkeys performed in a delayed go-nogo task that included separate time periods during which animals expected signals of behavioral significance, prepared for execution or inhibition of arm reaching movements, and expected the delivery of reward. In the task, animals were instructed by a green light cue to perform an arm reaching movement when a trigger stimulus came on ~3 s later (go situation). Movement was withheld after the same trigger light when the instruction cue had been red (nogo situation). Liquid reward was delivered on correct performance in both situations.

2. A total of 1,173 neurons were studied in the striatum (caudate nucleus and putamen) of 3 animals, of which 615 (52%) showed some change in activity during task performance. This report describes how the activity of 193 task-related neurons increased in advance of at least 1 component of the task, namely the instruction cue, the trigger stimulus, or the delivery of liquid reward. These neurons were found in dorsal and anterior parts of caudate and putamen and were slightly more frequent in the proximity of the internal capsule.

3. The activity of 16 neurons increased in both go and nogo trials before the onset of the instruction and subsided shortly after this signal. These activations may be related to the expectation of the instruction as the first signal in each trial.

4. The activity of 15 neurons increased between the instruction and the trigger stimulus in both go and nogo trials. These activations may be related to the expectation of the trigger stimulus independent of an arm movement. Further 56 neurons showed sustained activations only when the instruction requested a movement reaction. Activations were absent in trials in which the movement was withheld. Twenty-one of these neurons were tested with 2 different movement targets, 5 of which showed activity related to the direction of movement. These activations may be related to the preparation of movement or expectation of the specific movement triggering signal. The activity of an additional 20 neurons was unmodulated before the trigger stimulus in movement trials but increased in the interval between the no-movement instruction and the trigger stimulus for withholding the movement. These activations may be related to the preparation of movement inhibition as specific nogo reaction.

5. The activity of 87 neurons increased immediately before or soon after the trigger stimulus and continued until a drop of liquid reward was delivered, independent of the movement being executed or withheld. Activations were prolonged when reward was delayed. These activations may be related to the expectation of reward, which was the common external event in both situations. They do not appear to reflect the preparation of mouth movements, which also occurred without reward consumption.

6. The activity of 11 neurons increased only between the no-movement trigger stimulus and the delivery of reward, a period during which the movement was being withheld. These neurons were not activated during movement trials. These activations may be related to the inhibition of movement as nogo reaction, rather than to the expectation of reward.

7. These data show that striatal neurons are activated in relation to the expectation and preparation of individual environmental and behavioral events that are known to the animal through prior conditioning. These activations may reflect neuronal processes in which information acquired through past experience may be used for guiding the behavior of the subject. The neuronal activations preceding predictable environmental events suggest that the striatum has access to stored informations about individual external events that may serve to perform behavioral tasks consisting of a sequence of individual components.

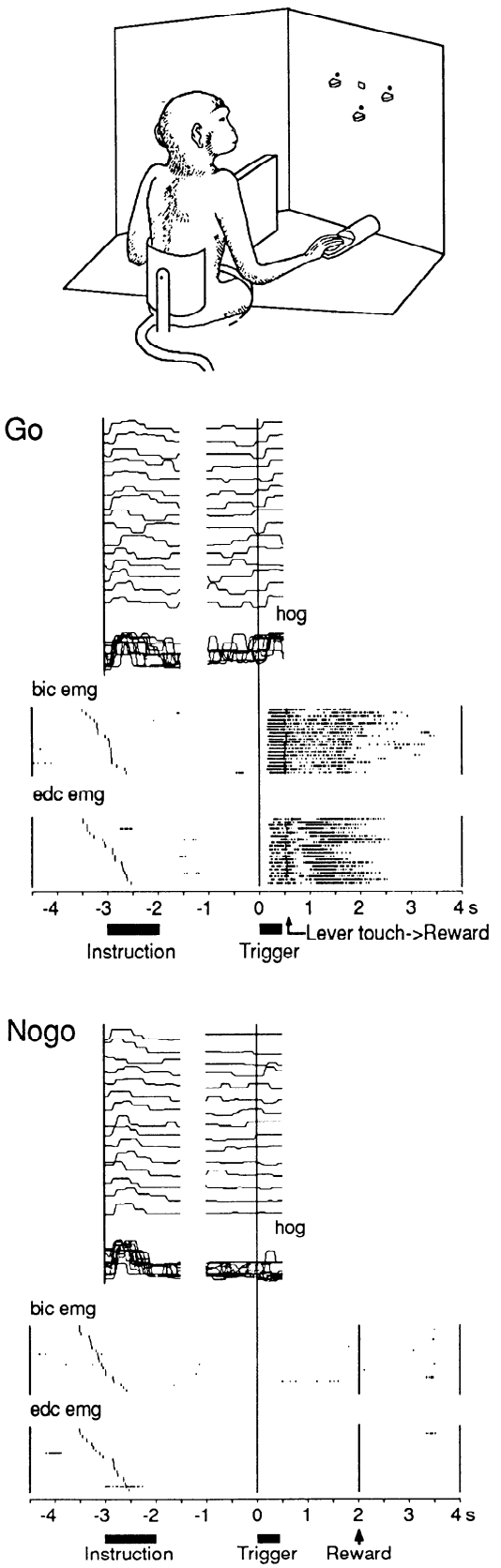
INTRODUCTION

The obvious motor disturbances in neurological diseases such as Parkinsonism, chorea, and hemiballism apparently point to a predominantly motor role of primate basal ganglia. Electrophysiological studies reveal that neurons in most structures of the basal ganglia are phasically modulated in relation to the execution of limb and eye movements. These structures include the caudate nucleus (Hikosaka et al. 1989a), putamen (Crutcher and Alexander 1990; Crutcher and DeLong 1984; DeLong 1973; Liles 1985), pallidum (Anderson and Horak 1985; DeLong 1971; Mink and Thach 1991), subthalamic nucleus (Georgopoulos et al. 1983), and pars reticulata of substantia nigra (Hikosaka and Wurtz 1983; Schultz 1986).

Whereas these data underline the involvement of the striatum in various aspects of motor activity and are in general agreement with the proposed motor role of basal ganglia, accumulating evidence from deficits occurring in human Parkinsonism and after experimental lesions of individual basal ganglia structures in animals demonstrate an involvement in functions extending beyond a mere role in movement execution (Schultz 1989). Electrophysiological studies on single neurons suggest that the basal ganglia may be involved in the preparation and initiation of individual limb and eye movements, in the expectation of external signals and in reward-related processes. Neurons in the striatum respond to external stimuli under the condition that they elicit arm and eye movements (Aldridge et al. 1980; Hikosaka et al. 1989b; Kimura 1990; Rolls et al. 1983). They are also activated for several seconds during the preparation phase of externally triggered or internally generated arm and eye movements (Alexander 1987; Alexander and Crutcher 1990a; Hikosaka et al. 1989a; Niki et al. 1972; Schultz and Romo 1988; Soltysik et al. 1975). The closer investigation of apparent motor preparatory activity

in putamen revealed a relationship to the expectation of task-relevant events, such as the impending motion of a target (Alexander and Crutcher 1990b). In various oculomotor tasks, caudate neurons were activated in advance of different expected stimuli, before acquisition of targets for eye movement, and during the expectation of task reinforcement (Hikosaka et al. 1989c). In short-term memory tasks, striatal neurons showed activity during the preparation of movements that was specific for the modality of the preparatory stimulus (Johnstone and Rolls 1990). Thus striatal activity appears to be involved in several processes contributing to the organization of behavioral responses beyond a strict relationship to motor control.

The purpose of the present experiments was to obtain a more comprehensive knowledge about the relationship of striatal neurons to predictable environmental events and subsequent behavioral reactions in larger areas of both caudate and putamen and in a larger variety of behavioral events than so far investigated. Striatal neurons were studied in delayed conditional motor tasks in which movement or no-movement reactions were performed depending on the color of a memorized instruction light and in which correct task performance led to the predictable obtainment of reward. These go-nogo tasks allowed to study the neuronal relationships to the expectation of environmental events independent of a movement reaction being performed. Through the training procedure, individual task-related signals gained predictive value for subsequent signals, behavioral reactions, and attribution of reward. External stimuli and behavioral acts were temporally separated by delays of several seconds, thus allowing to investigate the expectation of behaviorally significant external stimuli, the preparation for execution and inhibition of movements, and the expectation of reward. Parts of these data were presented in preliminary form (Apicella et al. 1990).



METHODS

The study was performed on three male *Macaca fascicularis* monkeys (3.5–3.8 kg weight). Two of these animals were also subjects of a study on dopamine neurons (Ljungberg et al. 1992). Animals performed in several variations of a behavioral task for obtaining liquid reward under computer control. Activity of single neurons was recorded with moveable microelectrodes while monitoring arm and mouth muscle activity and eye movements through chronically implanted electrodes. On termination of re-

FIG. 1. Behavioral task, eye movements, and muscle activity. The monkey keeps its hand relaxed on an immovable resting key and faces a panel with a central trigger light and 3 lever-light combinations. In the delayed go-nogo task, the light above the lower, central lever is illuminated for 1 s with either green or red color. The green light instructs the animal to release the resting key, reach forward, and touch the lower lever when the central trigger light is illuminated ~3 s after the instruction (go situation). A drop of liquid reward is delivered on touching the lever. The red light indicates a nogo trial in which the animal remains motionless until 2 s after onset of the trigger light, at which time reward is delivered. The 2 horizontally arranged lever-light combinations are used in the spatial delayed response task, in which illumination of the green instruction light in go trials also indicates the lever to be touched. Below the task are shown consecutive and superimposed traces of horizontal components of eye movements referenced to instruction (*left*) and trigger lights (*right*). Vertical eye movements were of less appreciable extent because the response panel was mounted at eye level. The electromyographic (EMG) recordings obtained from the biceps (BIC) and extensor digitorum communis (EDC) are shown as dots representing rectified activity above a preset level. All data were collected during neuronal recordings in which go and nogo trials alternated randomly within each block of trials and were separated for analysis. The sequence of trials during the experiment is shown downward.

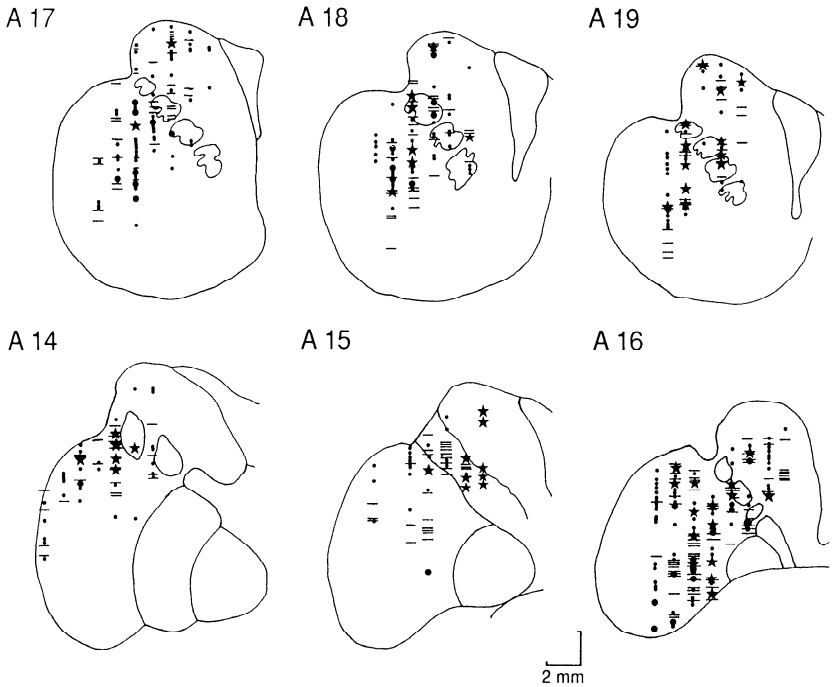


FIG. 2. Positions of recorded striatal neurons. Different symbols show positions of neurons unmodulated in the task (small dots), neurons activated before the trigger stimulus (in only go, only nogo, or both go and nogo trials; stars), neurons activated before reward (in both go and nogo trials; heavy dots), and neurons with activity modulated in the task without being related to expectation or preparation (bars). Coronal sections from the left hemisphere of 1 monkey are labeled according to the distances from the interaural line (A14–A19).

cording, electrode positions were reconstructed on histological brain sections.

Behavioral procedures

The behavioral apparatus was positioned at reaching distance (250 mm from the animal's shoulder) in the right half of the frontal wall of a completely enclosed primate chair (Fig. 1). A yellow, rectangular light-emitting diode (11 × 11 mm) was mounted at 27° lateral to the midsagittal plane and at eye level of the animal. Three small Plexiglas levers (7 × 15 mm) were placed 40 mm medial to, lateral to, and below the yellow light, respectively. Levers protruded by 20 mm from the frontal wall and made electrical contact on downward movement of 1 mm. Depending on the task used, either the one central or the two mediolaterally arranged levers were continuously illuminated from a rear dim light source. One bicolor, round light-emitting diode of 3 mm diam was located 10 mm above each lever. Two closed-circuit video systems served to continuously supervise limb and mouth movements.

DELAYED GO-NOGO TASK. At least 2 s before the first task-related event, the fluid-deprived animal was required to keep the right hand relaxed on an immovable, touch-sensitive key (elbow joint at ~90°). Then the central bicolor light-emitting diode was illuminated for 1 s with a green or red color that served as instruction signal indicating a "go" or "nogo" situation, respectively. After a randomly varying interval of 2.5–3.5 s, the yellow rectangular light was illuminated for 400 ms as trigger stimulus. In the go situation the animal released the resting key, touched the continuously illuminated central lever below the central instruction light, and received a drop of apple juice (0.15 ml). In the nogo situation the animal remained on the resting key for a fixed duration of 2 s to receive the same amount of apple juice (symmetrically reinforced delayed go-nogo task). Thus the instruction light served as preparatory signal for the upcoming reaction (what: go or nogo), whereas the trigger light determined the time of the behavioral reaction (when) without providing information about the nature of the required reaction. The trigger light was the last externally generated signal after which the delivery of reward could be expected in successful trials. Trials lasted 9–12 s, intervals between reward and the instruction of the following trial varied between 4 and 7 s. Go and nogo trials alternated randomly, with the exception that the alternate situation was imposed if one situation had occurred for three successive trials.

DELAYED REWARD. This modification of the delayed go-nogo task served to increase the time interval between the trigger stimulus and the delivery of reward in go trials to durations comparable with those in nogo trials. The delivery of reward after lever touch was delayed by a fixed interval of 1 s, occasionally 2–3 s. This did not affect reaction and movement times in the trained animal (cf. Figs. 10 and 14). In particular, the animal touched the response lever and moved back to the resting key in the way it did when reward was delivered instantaneously on lever touch.

SPATIAL DELAYED RESPONDING. Spatial components of signal presentation and movement target were varied by using the medial and lateral instruction lights and levers instead of the single central light and lever. Both medial and lateral levers were continuously illuminated, instead of the central lever. The instruction light situated above one of the two levers was illuminated for 1 s. In go trials the animal released the resting key in response to the yellow trigger light and touched the lever indicated by the green instruction. The spatial information was not used in nogo trials in which the animal remained motionless on the resting key after illumination of the trigger stimulus (red instruction light). A variation of this task investigated the relative contributions of the spatial positions of the instruction cues and levers by varying the position of the instruction while keeping a single and spatially constant movement target. The medial or lateral instruction light was illuminated, but the animal reached toward the continuously lit central lever.

Data acquisition

Behavioral performance was controlled by a suitably interfaced laboratory computer. The different lights and the solenoid for reward delivery were controlled by output pulses from the computer. All behavior-related digital signals were sampled as bits in parallel at a rate of 2 kHz. Key release was detected by a frequency-sensing circuit that reacted to a change in electrical capacity induced by the touch of the animal's hand. Errors in behavioral

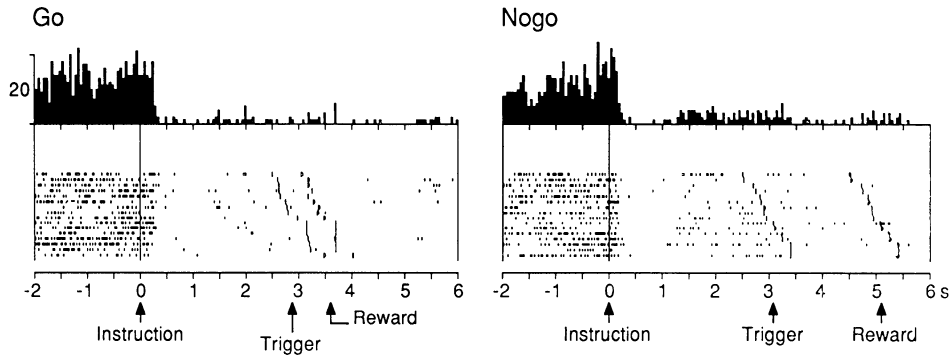


FIG. 3. Expectation of instruction signal in a putamen neuron. The activation occurred both in go and nogo trials. This neuron discharged at very low rates in the absence of task performance, as shown after reward delivery. Perievent time histograms are composed of the neuronal impulses shown as dots below. Each dot indicates a neuronal impulse, horizontal distances corresponding to real-time intervals. Each line of dots shows 1 trial. Small vertical lines in dot displays indicate onsets of trigger and reward, respectively. Go and nogo trials alternated randomly during the experiment. They were separated and ordered off-line according to intervals between instruction and trigger stimuli. Vertical calibration is 20 impulses/bin for all histograms.

performance either led to cancellation of all further signals in a given trial, including reward, or to immediate trial restart.

Animals underwent surgery under deep pentobarbital sodium anesthesia and aseptic conditions. Two cylinders for head fixation and a stereotaxically positioned, stainless steel chamber were fixed to the skull to permit vertical access with microelectrodes to the left striatum. The dura was kept intact. Teflon-coated, multistranded, stainless steel wires were implanted into the left and right extensor digitorum communis and biceps brachii muscles and into the right masseter and led subcutaneously to the head. The masseter was chosen to monitor mouth movements, because it is reliably activated during orofacial movements (Luschei and Goldberg 1981; Murray et al. 1991) and is sufficiently solid in small macaques to sustain chronic implantation with wire electrodes. Ag-AgCl electrodes were implanted into the outer, upper, and lower canthi of the orbits. All metal components, including plugs for the muscle and periorbital electrodes, were imbedded in several layers of dental cement and fixed to the skull with surgical grade stainless steel screws.

The activity of single neurons was recorded extracellularly with sterilized glass-insulated, platinum-plated tungsten microelectrodes (stem of 180 μm OD, tapered down over 4–5 mm to exposed tips of 1.8–3.5 μm diam and 5–10 μm length). They were passed each day together with and inside a rigid stainless steel guide cannula of 0.6 mm OD into the left brain. Microelectrodes were moved in parallel tracks vertically in the stereotaxic plane and conforming to a 1-mm grid. Postmortem histological inspections revealed that the tips of all guide cannulas ended >2.5 mm above the level of the dorsal surface of caudate. Although the guide cannulas damaged more tissue in the cortex than microelectrodes, they permitted to use thin microelectrodes causing very little damage to the nuclei investigated. Signals from the microelectrode were conventionally amplified, filtered (100 Hz lower cutoff at −3 dB), and monitored with oscilloscopes and earphones. Somatodendritic discharges were discriminated against those originating from fibers using earlier established criteria, in particular the very short durations of fiber impulses (0.1–0.3 ms) (Hellweg et al. 1977; Schultz and Romo 1987). Data obtained from fiber impulses are not reported. 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 neuronal recordings with the chronically implanted electrodes and occasionally with acutely inserted wire electrodes. EMG activity was filtered (10- to 250-Hz band pass; −12 dB at 1 kHz), rectified, and

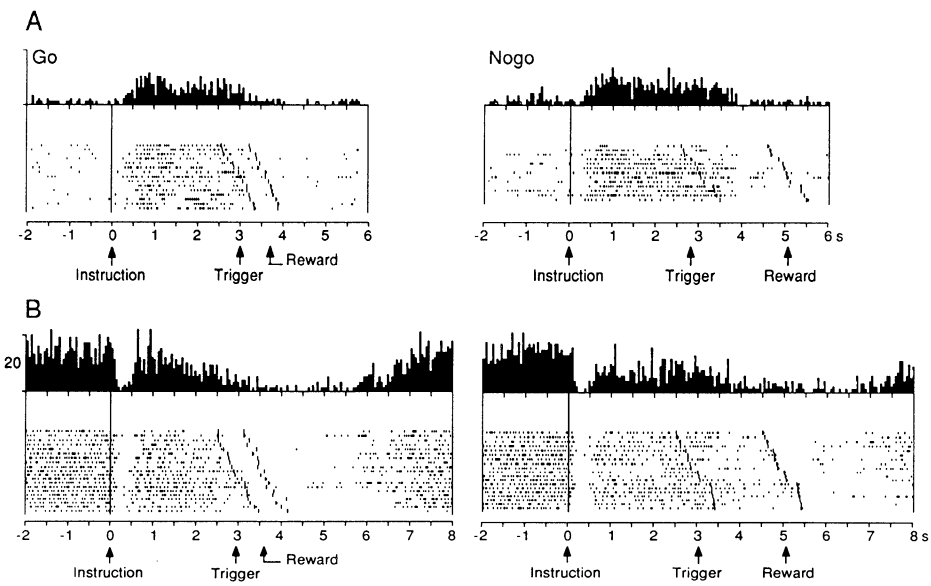


FIG. 4. *A*: activation of a putamen neuron related to the expectation of the trigger stimulus. Activation begins after instruction onset and lasts beyond onset of the trigger stimulus in both go and nogo trials. *B*: convergence of separate activations related to the expectation of instruction and trigger stimuli, respectively. Activity related to the expectation of the instruction begins after reward delivery and continues until instruction onset in both go and nogo trials. A 2nd, well-separated activation begins after instruction onset and subsides with the trigger stimulus. Neuron recorded in putamen.

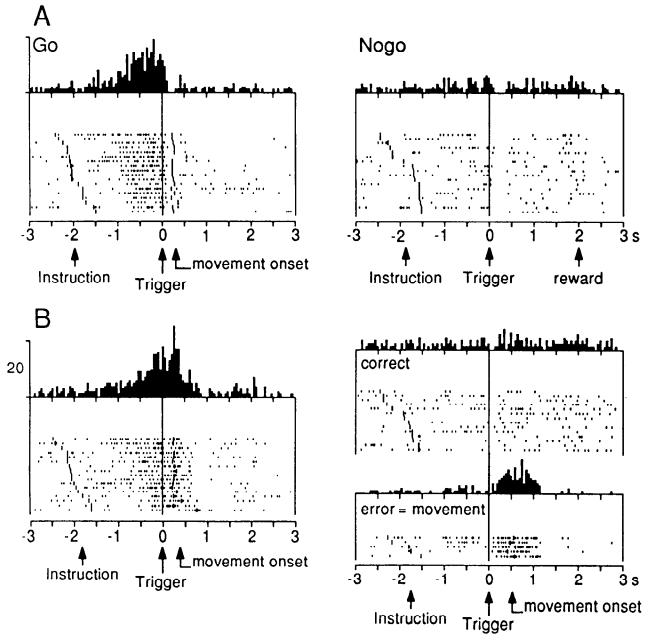


FIG. 5. Activation occurring during the preparation of arm movements in neurons of putamen (*A*) and caudate (*B*). Nogo trials, in which the animal refrains from arm movement, are devoid of activation. Separation of trials according to correct performance in *B* demonstrates movement-related activity without preparatory activity with erroneous arm movements in nogo trials. Both neurons were recorded with an exceptionally short instruction-trigger interval of 2 ± 0.5 s.

monitored on conventional oscilloscopes. Horizontal and vertical electrooculograms (EOGs) were collected during neuronal recordings from the implanted periorbital electrodes. The gain of ocular electrodes and positions of the eyes were calibrated by having the animal fixate small morsels of food presented at several known horizontal and vertical eccentricities while the frontal enclosure of the primate chair was kept open. Licking movements were recorded as digital pulses by the computer after detection by a touch-sensitive circuit connected to the mouth tube delivering liquid reward.

Pulses from neuronal discharges were sampled together with behavior-related digital signals on-line at a rate of 2 kHz by the 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 an adjustable Schmitt-trigger and as analog signals by the use of the 12-bit converter. Raster dots representing neuronal discharges and EMG activity referenced to different task components were displayed on the computer screen after each trial, together with analog displays of EOGs. Only results from neurons sampled by the computer with at least 10 go and nogo trials are reported. All data from neurons suspected to covary with some task component, and occasionally from unmodulated neurons, were stored uncondensed on computer disks.

Data analysis

Off-line data inspection was performed on the basis of raster dots, perievent time histograms, and cumulative frequency distributions of neuronal impulses, and with displays of single-trial or averaged analog data, in reference to any of the task components, with the use of both automatized and interactive evaluation programs.

Onset, duration, magnitude, and statistical significance of increases of neuronal activity were assessed with a specially implemented sliding window procedure on the basis of the non-parametric one-tailed Wilcoxon signed-rank test. This test takes the activity of single trials into account, rather than the summed perievent time histogram, and does not require normality tests, which would be unsuitable for the low impulse activity in the striatum. In each trial, two epochs were determined, and the numbers of impulses contained in each epoch were normalized over time and considered as a matched pair. One epoch was the 2-s control period before the instruction, and the second epoch consisted of a time window of 250 ms that was moved in steps of 25 ms through the time period of a suspected change. The Wilcoxon test was performed at each step of 25 ms, with the use of the signed difference from each matched pair over all trials as input. Onset of activation was determined as the midwindow time of the first of seven consecutive steps showing an increase at $P < 0.01$. Offset of activation was determined in analogy by searching for the loss of statistically significant increase over seven steps. Subsequently, the Wilcoxon test was performed to test the total duration between onset and offset of activation against the control period ($P < 0.005$). Neurons not showing an onset of activation or failing in the total duration test were considered as unmodulated. After preliminary tests, these parameters were found to be the most adequate for the relatively slow time courses of activations between instruction and trigger signals, and between the trigger and reward. Only the statistical significance was determined for activations preceding the instruction. Here, the control period was placed individually for each neuron toward trial end at a position without obvious neuronal changes. The magnitude of activation was assessed by counting neuronal impulses between onset and offset of activation and expressed as percentage above background activity measured during the control period. Activations are defined as statistically significant increases of activity in neurons tested in at least 10 go or nogo trials.

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

Results from evaluations were stored and classed by the use of 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-tailed versions of the Mann-Whitney *U* test ($P < 0.01$).

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, while larger lesions (20 μA for 20 or 60 s) were positioned at a few locations above in the same track. This produced distinct patterns of vertically oriented 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 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 outlines of brain structures and marks from lesions and recent electrode tracks were drawn. Recording positions in tracks marked by electrolytic lesions were reconstructed by using distances to lesions according to micrometer readings entered into the protocol. Positions in parallel neigh-

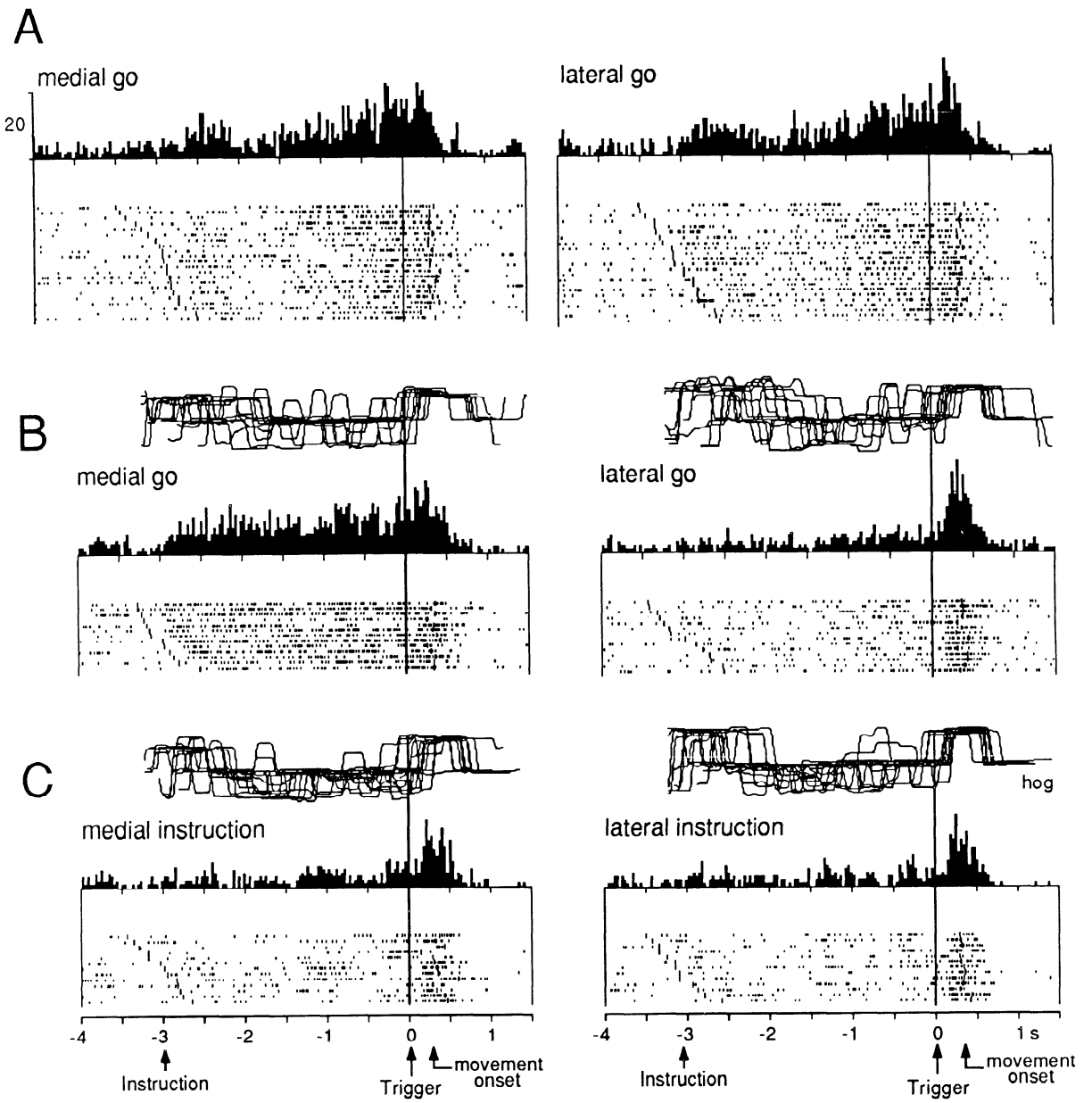


FIG. 6. Investigation of spatial selectivity of activations preceding arm movement to 2 distinct targets. *A*: lack of directional activity in a caudate neuron tested with 2 horizontally arranged targets. Medial and lateral instruction lights were located in the space contralateral to the neuron and were horizontally separated by 80 mm. Each lever to be touched was located immediately below the corresponding instruction light. *B*: directional preparatory activity preceding arm movement toward the medial lever in another caudate neuron. The neuron is not activated before movement to the lateral lever. This neuron also shows separate movement-related activity lacking directional preference. Same lever-instruction light arrangement as in *A*. *C*: neuron shown in *B* lacks directional activity when the instruction lights were illuminated at spatially distinct positions, but the single central lever was the common target for reaching. Thus the directional preference of this neuron is related to the target of reaching and not to the position of the instruction signal. Only activity from go trials is shown in *A*–*C*. Hog, horizontal eye movements.

boring tracks were reconstructed at comparable vertical levels. In the internal capsule, no attempts were made to reconstruct the recording positions of neurons in reference to individual fiber bundles. The discrimination between neuronal and fiber impulses relied on the electrophysiological criteria described above.

RESULTS

Movement parameters and muscle activity

The arm reaching movement toward the response levers and muscle activity were similar to those studied in the previous food box tasks (Schultz et al. 1989; Schultz and Romo 1992). Reaction times were 250–350 ms in individual blocks of trials. Movement times (from key release to lever press) showed values of 250–350 ms, which were substantially longer than the 130–190 ms seen in the food box task. This was probably due to the additional time required for pressing the lever at the end of the reaching trajectory. Prime mover muscles were the extensor digitorum communis, biceps, and anterior deltoid, which lifted the hand off the resting key and moved the forearm upward (Fig. 1,

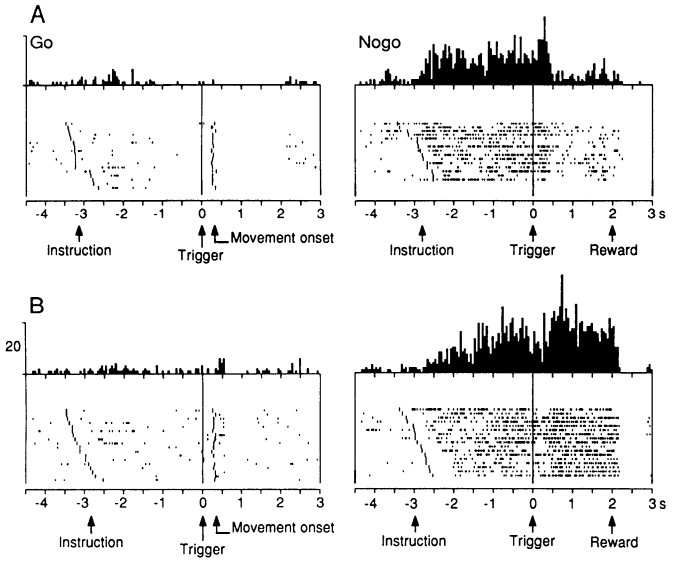


FIG. 7. Activation during the preparation for nogo responding. Animal withholds the arm movement in nogo trials to receive reward. Go trials, in which the animal executes a reaching movement after the trigger stimulus, are devoid of activation. *A*: activation terminating after trigger onset in a caudate neuron. *B*: activation lasting until delivery of reward in a putamen neuron.

middle). Activity in these muscles began at 100–140 ms before key release. 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 glutaeus maximus, quadriceps femoris, biceps femoris, and lateral gastrocnemius. Performance in nogo trials was not accompanied by muscle activity (Fig. 1, *bottom*). Contralateral to the moving arm, the infrascapular trapezius and upper paraspinal muscles were activated during but rarely before the movement. During all neuronal recordings the continuous EMG recordings and the video camera focused on the forearm were used to assure the absence of untimely isometric muscle activity or overt movements during all periods of task performance, notably the 2-s period preceding and the preparatory period after the instruction cue in both go and nogo trials, as well as the nogo reaction period after the trigger stimulus.

TABLE 1. *Numbers of striatal neurons with expectation-related activity*

	Caudate	Putamen	Total
Preceding instruction cue			
Go and nogo	8	8	16
Preceding trigger stimulus			
Go and nogo	4	11	15
Go only	29	27	56
Nogo only	7	13	20
Subtotal	40	51	91
Preceding reward			
Go and nogo	36	51	87
Nogo only	3	8	11
Subtotal	39	59	98
From instruction to reward	3	3	6
Multiple relations	6	12	18
Total	84	109	193

Eye movements

Illumination of the instruction signal was regularly followed by a horizontal saccade, both in go and nogo trials (Fig. 1). Ocular fixation remained on the instruction for ~1 s and subsequently became irregular until the trigger light occurred. This stimulus was usually followed by a saccade in go trials and less systematically in nogo trials (Figs. 1, 6, and 12). Delivery of reward was neither preceded by particular ocular fixation patterns nor followed by a saccade (Fig. 12).

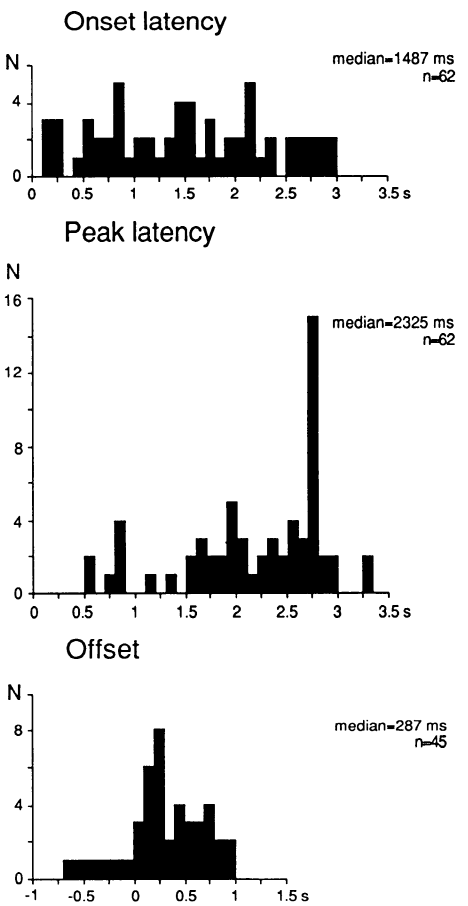


FIG. 8. Temporal characteristics of neuronal activations preceding the trigger stimulus. Only data from go trials are shown. Peak latency is at 250 ms after onset of the 500-ms interval containing peak activity. Onset and peak latencies are given in reference to instruction onset, whereas offset times refer to trigger onset. Data are pooled over caudate nucleus and putamen because of insignificant differences ($P > 0.1$). Medians for onset latency, peak latency, and offset time in caudate neurons are as follows: 1,712 ($n = 31$), 2,275 ($n = 31$), and 437 ms ($n = 23$), respectively; for putamen: 1,437 ($n = 31$), 2,350 ($n = 31$), and 224 ms ($n = 22$). Neurons with additional activations related to other task events interfering with the quantitative analysis are excluded. In nogo trials (not shown), medians for onset latency, peak latency, and offset time in caudate neurons are as follows: 1,537 ($n = 10$), 2,775 ($n = 10$), and 537 ms ($n = 7$), respectively; for putamen: 1,537 ($n = 18$), 2,390 ($n = 18$), and 512 ms ($n = 17$); for both structures: 1,537 ($n = 28$), 2,490 ($n = 28$), and 524 ms ($n = 24$). Differences of all 3 parameters between go and nogo trials are statistically insignificant ($P > 0.08$). All values were obtained from evaluations with the sliding window procedure.

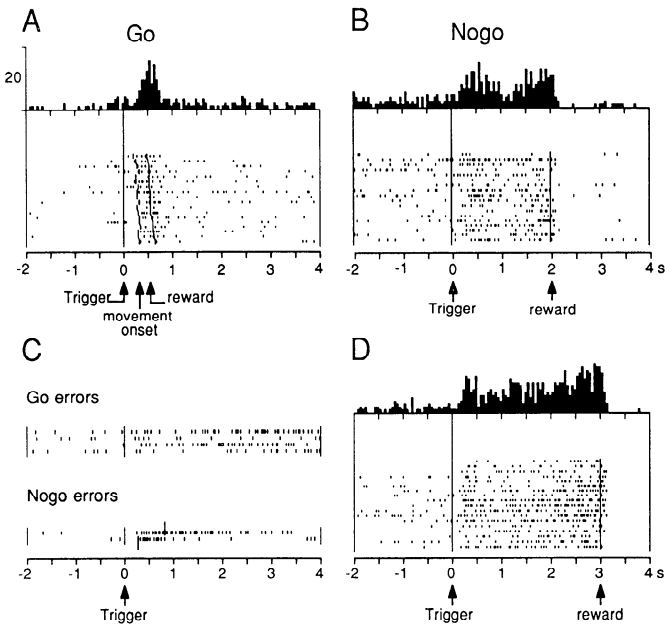


FIG. 9. Activation of a putamen neuron preceding delivery of reward in both go and nogo trials. The activation began after trigger onset and terminated on reward. In go trials the activation coincided with the reaching movement. In nogo trials the activation lasted during the total duration of movement inhibition (*B*, 2 s; *D*, 3 s). Go and nogo trials in *A* and *B* alternated randomly during the experiment and were separated for analysis, whereas data in *D* were recorded in a separate block of trials. *C*: error trials recorded in the same block of trials as *A* and *B*. Here, the animal made no movement in go trials (*top*) or made an erroneous movement in nogo trials (*bottom*).

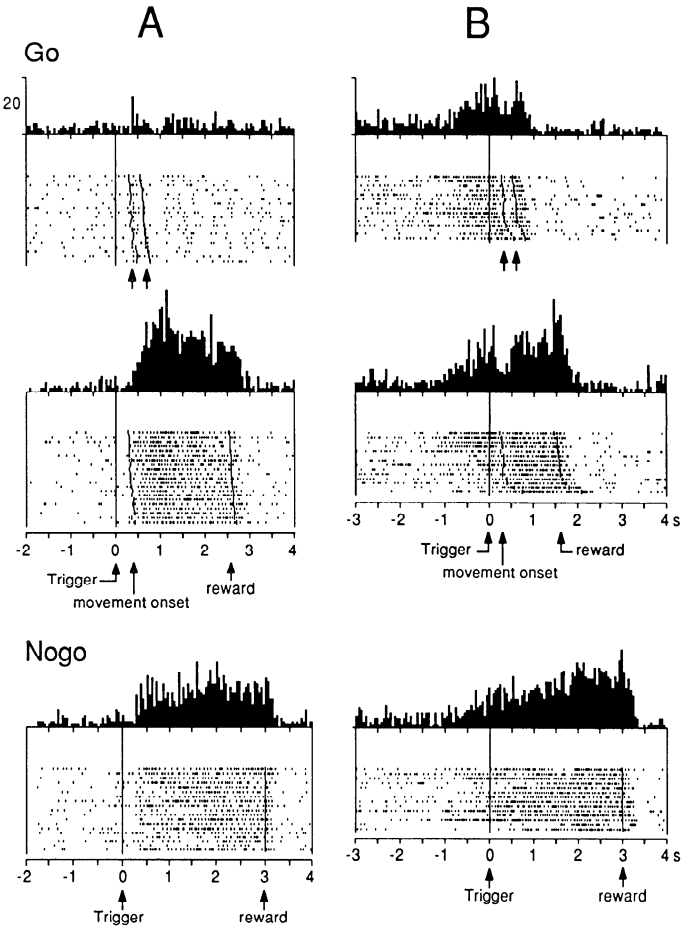


FIG. 10. *A*: activation preceding reward in go trials with delayed delivery of reward. Reward was given on correct lever touch in trials shown in *top*, whereas it was delayed by 2 s after lever touch for *middle display* (data recorded in separate blocks of trials). Arm movements were similar independent of the delay between lever touch and reward. This demonstrates the absence of relationship to movement execution and illustrates the slow time course of activity related to the expectation of external events. Neuron recorded in caudate. *B*: activation preceding reward begins gradually before the trigger stimulus in go and nogo trials. This activity was not influenced by the delayed delivery of reward in go trials (*middle*). Neuron recorded in putamen.

Data base for neurons

The activity of 1,173 striatal neurons was tested during contralateral performance of the go-nogo task (475 in caudate, 698 in putamen). Neurons were located between 4 mm anterior and 2 mm posterior to the anterior commissure. They were distributed over the mediolateral extent of mostly dorsal parts of striatum (Fig. 2). Investigated neurons had low spontaneous activity, as measured during task performance before instruction onset (median of 1.7 imp/s). An additional 396 striatal neurons with tonically elevated discharge rates (median of 5.8 imp/s) are not included in this report and are described elsewhere (Apicella et al. 1991b). Some of them were phasically depressed by instructions and reward.

Of the 1,173 striatal neurons, 615 (52%) showed changes in activity in relation to one or more task components (215 in caudate, 400 in putamen). This report describes the activity of 193 striatal neurons (84 in caudate, 109 in putamen) that showed statistically significant sustained activations that preceded and subsided in close temporal relation to at least one of the following task components; onset of the instruction cue, onset of the trigger stimulus, and delivery of reward (Table 1). The remaining 433 neurons were activated after the delivery of reward (Apicella et al. 1991a), responded phasically to instruction and trigger stimuli similar to those found in another study (Schultz and Romo 1992), or showed phasic activations during various periods of the arm movement. We have not particularly searched for neuronal activity related to eye movements, but all neuronal data saved on computer media were tested off-line for oculomotor relationships.

Histological reconstructions of recording positions of neurons showing various types of activations or being un-

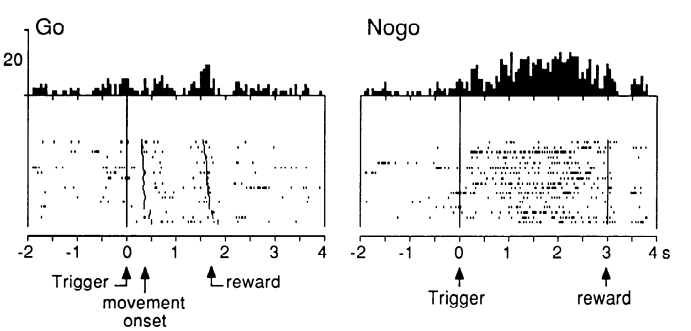


FIG. 11. Selective activation during withholding of movement in nogo trials between the trigger stimulus and reward delivery. The activation preceding reward was absent in go trials in spite of a sufficient delay before delivery of reward. Neuron recorded in putamen.

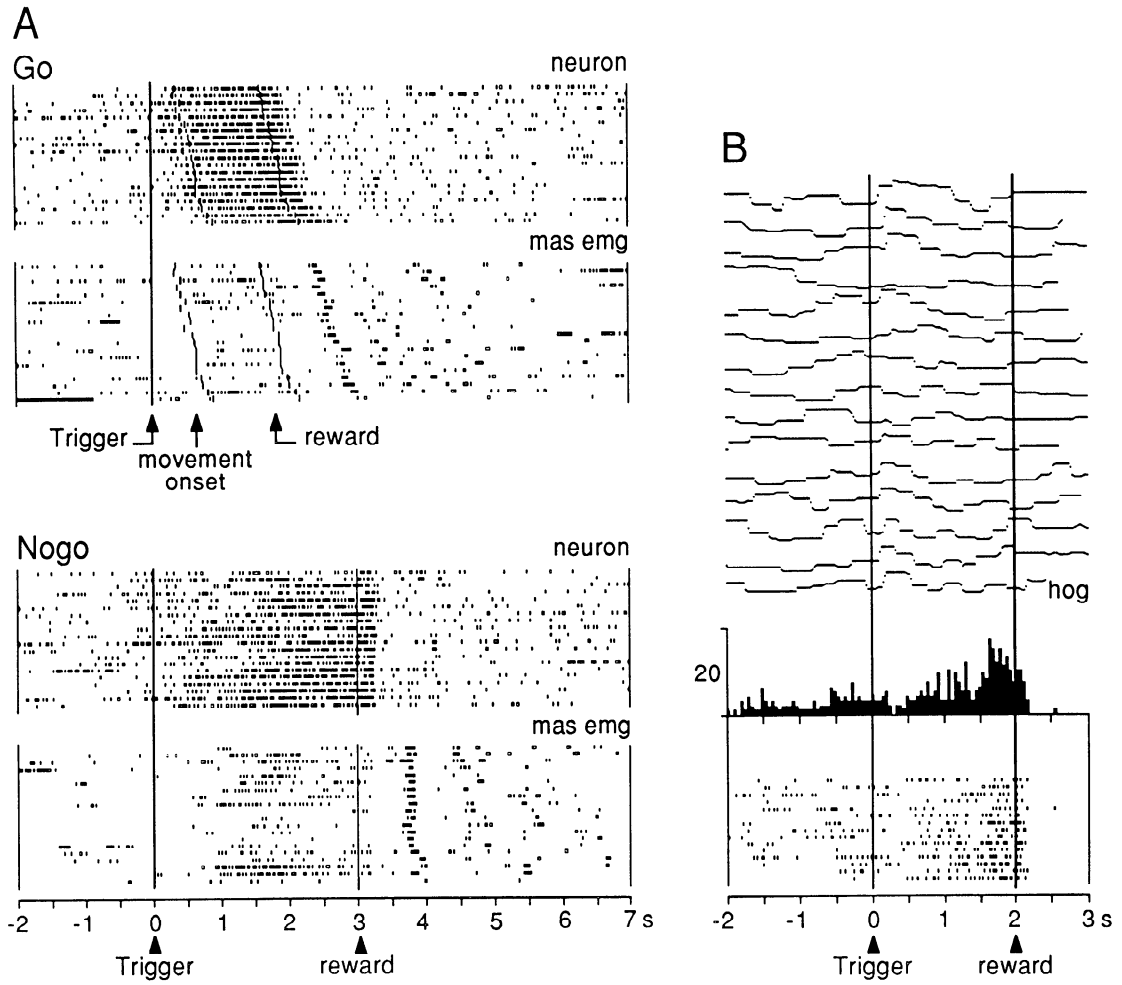


FIG. 12. Lack of relationships of reward expectation-related activity to mouth and eye movements. *A*: activity in a putamen neuron is unrelated to the preparation of mouth movements. The electromyogram (EMG) of the masseter shows irregular activity over the whole trial, an increased activity between the trigger stimulus and reward, and a marked phasic activity after reward delivery. Offset times of neuronal activation are not related to onset of phasic EMG activity, as best seen in nogo trials (*bottom*). Go trials are rank ordered for reaction times, whereas in nogo trials the original sequence of trials is preserved downward, both for neuronal and muscle activity. *B*: activity in a putamen neuron is unrelated to saccadic eye movements. Horizontal components of electrooculograms are shown above the histogram and raster display of simultaneously recorded neuronal activity. The sequence of trials during the experiment is shown downward, and only nogo trials are displayed.

modulated during task performance are shown in Fig. 2. The two major groups of activations, those preceding the trigger stimulus and those preceding the delivery of reward, show a considerable overlap in the distribution in anterior parts of both caudate and putamen without clear regional preferences. A number of modulated neurons were located in close proximity to the fiber bundles in the internal capsule.

Activations preceding the instruction cue

The instruction was the first task-specific signal in each trial. It was preceded by delivery of reward in the previous trial, with intervals of 4–7 s. Activity preceding the instruction and terminating in close temporal relation to its onset was seen in 16 striatal neurons (8 each in caudate and putamen). It occurred in both go and nogo trials (Fig. 3) and was unrelated to arm or mouth movements that occurred at other times during the task. Activations began at some time after the reward of the preceding trial (Fig. 4*B*) and thus appeared as high-frequency activity immediately before instruction onset. Activations preceding the instruction were specific for this stimulus in nine neurons not activated before other task components, whereas seven neurons showed additional activations between instruction and trigger signals in go and/or nogo trials (Fig. 4*B*). Four of the 16 neurons showed an additional phasic response to instruction onset, similar to those described elsewhere (Schultz and Romo 1992).

Activations preceding the trigger stimulus

A total of 91 striatal neurons (40 in caudate, 51 in putamen) showed sustained activations in the interval between instruction and trigger signals. Activations occurred in both go and nogo trials in 15 neurons (Fig. 4*A*). Activations usually lasted beyond onset of the trigger stimulus, and in only one putamen neuron terminated before the trigger in

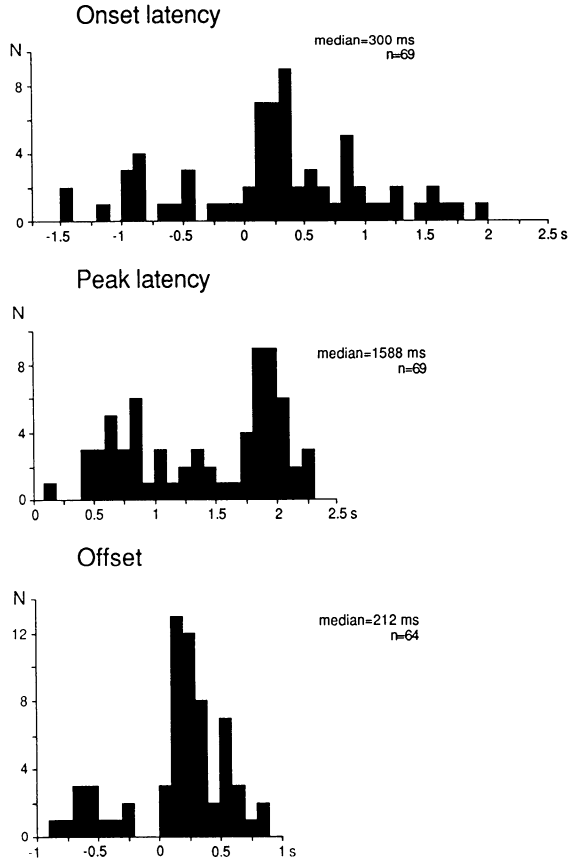


FIG. 13. Temporal characteristics of neuronal activations preceding the delivery of reward. Only data from nogo trials are shown. Peak latency is at 250 ms after onset of the 500-ms interval containing peak activity. Onset and peak latencies are given in reference to trigger onset, whereas offset times relate to reward onset. Only data obtained with a fixed trigger-reward interval of 2 s are shown. Data are pooled over caudate and putamen because of largely insignificant differences ($P > 0.07$, except offset time: $P > 0.025$). Medians for onset latency, peak latency, and offset time in caudate neurons are as follows: 312 ($n = 33$), 1,275 ($n = 33$), and 162 ms ($n = 29$), respectively; for putamen: 212 ($n = 36$), 1,825 ($n = 36$), and 237 ms ($n = 35$). Neurons with additional activations related to other task events interfering with the analysis are excluded.

both go and nogo trials. Only two neurons were also activated before the instruction (Fig. 4*B*), indicating the stimulus specificity of most of the activations.

Activations restricted to go trials were seen in 56 neurons of caudate and putamen. Activations terminated before the trigger stimulus in 8 neurons, between trigger stimulus and movement onset in 27 neurons (Fig. 5*A*), and after movement onset in 21 neurons (Fig. 5*B*). A separate phasic component related to the execution of movement was revealed in some neurons with late activation offset when erroneous movements in nogo trials were inspected (Fig. 5*B, right*). Separate phasic responses to the trigger stimulus were seen in 9 neurons, whereas phasic responses to the instruction were not seen in these 56 neurons. Two neurons were also activated before the instruction cue.

The spatial version of the delayed go-nogo task containing two instruction-target positions served to investigate whether reaching toward different targets or spatially separated presentation of instruction lights would influence the activations preceding the trigger stimulus. We tested 21 neurons that were activated only in go trials (18 neurons) or in both go and nogo trials (3). The activations in 16 of these neurons were independent of the lateral or medial light-lever combinations (Fig. 6*A*). By contrast, activations in the remaining five neurons were dependent on the lever used (2 in caudate, 3 in putamen; Fig. 6*B*), all of them occurring before reaching to the medial lever. This relationship was not explained by particular ocular fixation patterns during the instruction-trigger interval (Fig. 6*B*). We then determined whether this spatial preference was due to the target for reaching or the position of the instruction by using the two horizontally arranged lights as instruction cues and the lower central lever as single target for reaching. None of the five neurons showed a preferential or exclusive activation dependent on the position of the instruction light. Neurons were either not activated during the instruction-trigger interval (Fig. 6*C*), or their activations lacked conspicuous differences. Thus some striatal neurons were activated in a spatially differentiating manner before the execution of arm movements toward targets in the contralateral space. This differential activity was not due to the spatial position of the instruction cue.

Activations restricted to nogo trials were seen in 20 striatal neurons. Activations terminated in 7 neurons before and in 13 neurons after the trigger stimulus (Fig. 7*A*). They lasted in three of these neurons until the delivery of reward (Fig. 7*B*). Separate phasic responses to the trigger stimulus were seen in four neurons. Three neurons also showed sustained activations before the instruction cue.

Quantitative evaluations revealed that some activations began immediately after instruction onset, whereas others developed later, in some cases immediately preceding the trigger stimulus (Fig. 8, *top*). The peak of activation was reached in most neurons toward the end of the instruction-trigger interval and thus appeared to precede the trigger stimulus, rather than follow the instruction (Fig. 8, *middle*). Offset of activations occurred in most neurons shortly

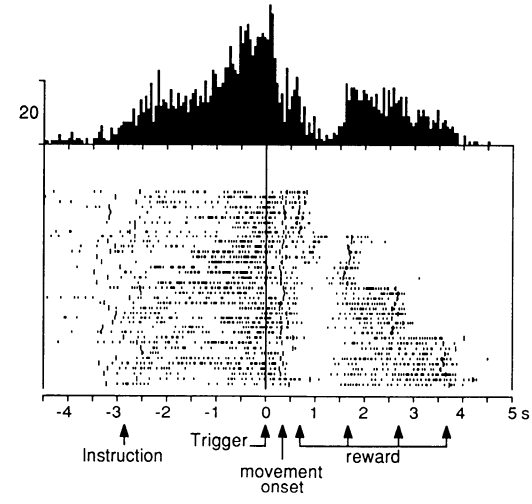


FIG. 14. Convergence of activations related separately to the expectation of the trigger stimulus and reward delivery. A 2nd, well-separated activation developed before reward after the activation preceding the trigger terminated. This is only apparent when reward is sufficiently separated in time from the trigger stimulus. The original sequence of trials is shown downward. Neuron recorded in putamen.

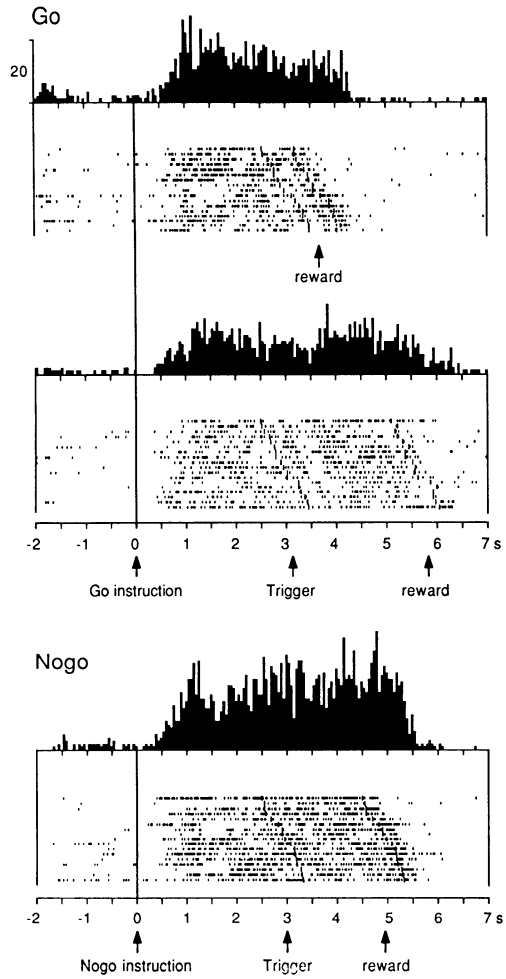


FIG. 15. Activation spanning the total task duration in a putamen neuron. Each trial began with the instruction cue and terminated with the delivery of reward. The activation occurred in both go and nogo trials and was independent of the delay between lever touch and reward in go trials.

after the trigger stimulus (Fig. 8, *bottom*). The slight differences in onset latency, peak latency, and offset times between caudate and putamen, and between go and nogo trials were insignificant (see legend to Fig. 8 for details).

Activations preceding reward

A total of 87 striatal neurons (36 in caudate, 51 in putamen) showed sustained activations in the interval between the trigger stimulus and delivery of reward in both go and nogo trials. The example shown in Fig. 9, *A* and *B*, demonstrates how the activation in go trials occurring during the movement is typically paralleled by an increase in activity in nogo trials, which terminates in close temporal relation to the delivery of reward, suggesting that the activation in go trials was not related to the execution of movements. Prolongation of the trigger-reward interval to, e.g., 3 s invariably extended this activation (Fig. 9*D*). When the animal erroneously refrained from moving in go trials, the activation after the trigger stimulus remained present for several seconds (Fig. 9*C*). In view of the frequently employed delays between correct lever touch and reward delivery, this might indicate that the animal was still waiting for reward in the absence of an indication of error. Comparable activations occurred with erroneous movement in nogo trials. Activations in correct go trials became more prominent and reached an extent comparable with that of nogo trials when sufficient time for their development was allowed by introducing a delay of 1 or 2 s between lever touch and delivery of reward (Fig. 10*A*). Twelve of the 87 neurons showed an additional phasic response to the delivery of reward in both go and nogo trials.

Activations in 68 neurons began after onset of the trigger stimulus, and in 19 neurons up to 1.5 s before this stimulus (4 in caudate, 15 in putamen). In these early onset neurons, activity slowly increased during the instruction-trigger interval and invariably reached its peak close to reward (Fig. 10*B*). Activations preceding reward in nogo trials always lasted >1 s. They terminated in 16 neurons immediately before the delivery of reward (11 in caudate, 5 in putamen) and in 71 neurons after this event (25 in caudate, 46 in putamen).

In contrast to this activity occurring in both go and nogo trials, activations in 11 neurons were restricted to nogo trials (3 in caudate, 8 in putamen; Fig. 11). These occurred although the length of the interval between trigger and reward in go trials was sufficiently long to allow an activation.

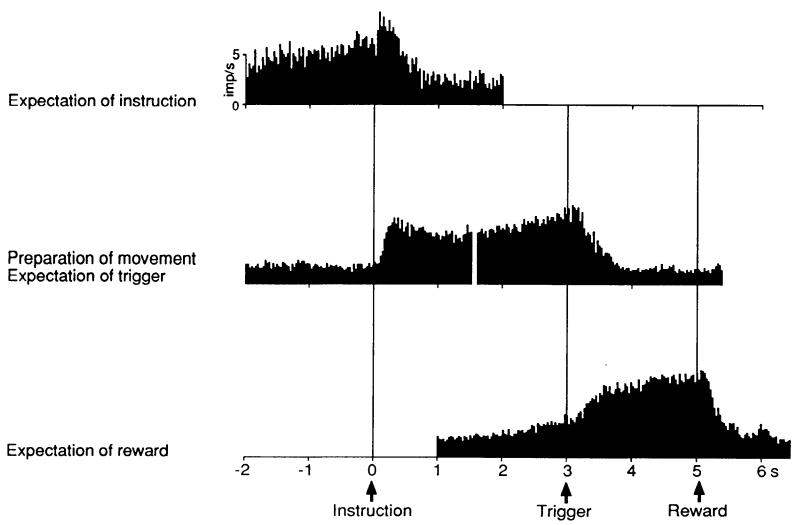


FIG. 16. Population activity of expectation- and preparation-related striatal neurons. *Top*: activation of 16 neurons preceding instruction onset (total of 341 go trials). *Middle*: activation of 44 neurons preceding the trigger stimulus in go trials (total of 1,254 trials). Because of varying intervals, the histogram is split, and its 2 parts are separately referenced to onset of instruction and trigger stimuli, respectively. Neurons responding to the trigger stimulus, activated during movement or activated before instruction or reward, are excluded. *Bottom*: activation of 68 neurons preceding reward in nogo trials (total of 1,315 trials). Only data obtained with a trigger-reward interval of 2 s are used. In each display, histograms from each neuron normalized for trial number are added and the resulting sum is divided by the number of neurons.

Three of these neurons were activated over the whole time span between instruction and reward in nogo trials (Fig. 7*B*). None of the 1,173 striatal neurons exclusively showed activations in go trials that lasted until reward delivery. Neurons that were activated after the trigger stimulus and during the arm movement were considered as being related to the execution of movement and were not further evaluated. Visual inspection of histograms and rasters indicated that their activity began at different times before or after movement onset and terminated during or at the end of the reaching movement.

Regular assessment of masseter muscle activity and of licks at the mouth tube during neuronal recordings revealed that monkeys performed mouth movements in a repeated, exploratory fashion after instruction onset and more so after trigger onset, whereas a series of more vigorous mouth movements occurred in response to the delivery of reward (Fig. 12*A*). Neuronal activations preceding reward thus occurred in the occasional presence of mouth movements, but a trial-by-trial relationship was not observed. Neuronal activations terminating after reward delivery lacked temporal correspondence to onset of the more vigorous muscle activity at this period (Fig. 12*A*). These data suggest that activations preceding reward were not specifically related to the preparation or execution of mouth movements. Activations preceding reward equally lacked relationships to eye movements, which during this period occurred irregularly and were devoid of particular fixation patterns (Fig. 12*B*).

Quantitative evaluations showed that activations preceding reward in nogo trials began up to 1.5 s before trigger onset, immediately after trigger onset, or later and closer to reward delivery (Fig. 13). The peak of activation was reached in most neurons close to reward and thus appeared to precede this event rather than follow the trigger stimulus. Offset of activations occurred in most neurons after reward. Differences in these parameters between caudate and putamen were insignificant.

A total of 11 neurons showed additional separate activations preceding the trigger stimulus (2 in caudate, 9 in putamen). This became particularly apparent when reward was sufficiently separated in time from the trigger, like in Fig. 14, in which two separate activations appeared when reward was delayed by >1 s after lever touch in go trials. These neurons provide evidence for a convergence of activations that were separately related to two different task components.

Rather than individually preceding separate components, some activations lasted over the whole duration of the task. These activations began after instruction onset and continued without interruption until reward delivery in both go and nogo trials (3 neurons in caudate and putamen each; Fig. 15).

Overall evaluations

Although single neuron recordings provide individual examples of brain activity with high resolution, they give less clear descriptions of the properties of the whole population of neurons. We therefore assessed the population activity for each of the three classes of activations by averaging the perievent time histograms from all activated neurons. Figure 16, *top*, shows how the activity of 16 neurons gradually increased before onset of the instruction stimulus, which was the first external signal in each trial of the task. The population histogram of all neurons activated before the trigger stimulus is shown in Fig. 16, *middle*, which reveals an early response component to instruction onset followed by a continuously elevated discharge rate terminating when the trigger stimulus occurred. Temporal characteristics of the activations preceding reward are shown in Fig. 16, *bottom*. The activation began to a modest extent already before trigger onset, gained increasingly in amplitude after this stimulus and reached its peak when reward was delivered. The population histograms suggest slightly higher magnitudes of activations preceding reward delivery, as compared with those preceding the trigger stimulus. Comparisons of individual magnitudes substantiated these differences but revealed a lack of statistical significance ($P > 0.03$ for peak activity; Fig. 17).

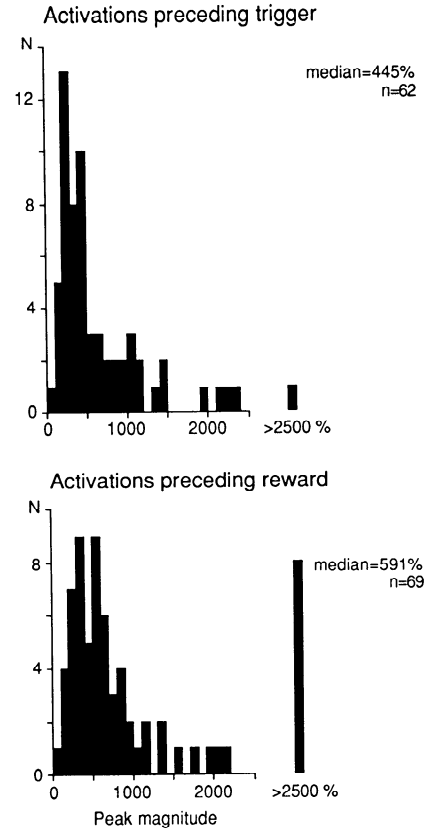


FIG. 17. Comparison of peak magnitudes of activations preceding trigger and reward. Peak activity was determined during intervals of 500 ms in reference to trigger onset. Differences in peak magnitude between trigger and reward are not significant for neurons of caudate ($P > 0.09$), putamen ($P > 0.25$), or both parts of striatum ($P > 0.03$). Data are pooled over caudate nucleus and putamen because of insignificant differences ($P > 0.36$). Medians for peak magnitudes for activations preceding the trigger stimulus are 402 ($n = 31$) and 529% ($n = 31$) for caudate and putamen neurons, respectively. Values for activations preceding reward are 620 ($n = 33$) and 551% ($n = 36$) for caudate and putamen. Only data obtained with a trigger-reward interval of 2 s are used for the *bottom histogram*. Neurons with activations preceding both the trigger stimulus and reward are excluded, as are neurons with additional activations related to other task events interfering with the analysis.

DISCUSSION

The present task employed a sequence of external signals with different behavioral significances. Through the past experience of the subject, each signal or sequence of signals has gained the capacity to predict the occurrence of a subsequent task component. The instruction cue would inform about the subsequent trigger stimulus and induce a state of expectation of this stimulus. It equally informs about the required reaction to the trigger stimulus and thus may serve to prepare for the reaction, this being the execution of movement in go and the withholding of movement in nogo trials. In both go and nogo trials, the trigger stimulus as last externally imposed imperative signal is able to set a state of expectation of reward. Delivery of reward terminates a trial and, because of repeated trial performance, may evoke the expectation of the instruction cue as first signal of the next trial.

Neurons in rostral parts of caudate and putamen were activated in advance of these predictable individual task components. Two principal types of activity were found. *1*) Activations specific for a behavioral reaction may reflect the preparation of action, as seen with activity preceding the trigger stimulus that depended on the subsequent execution or withholding of movement. *2*) Activations occurring in both go and nogo trials before the instruction cue, the trigger stimulus, or the delivery of reward may reflect event-specific internal states of expectation related to the occurrence of subsequent individual signals of behavioral significance. Because behavioral tasks that allow the discrimination between these two types of neuronal activity are difficult to design, part of the following discussion is devoted to elucidating some of the factors that may contribute to the differences between these types of activity.

Preparation of action

EXECUTION OF MOVEMENT. The majority of sustained activations preceding the trigger stimulus occurred selectively in go trials in which the trigger stimulus elicited an arm movement. These neurons were not activated in nogo trials in which arm movement was withheld, suggesting that activations were related to the preparation of arm movement. Comparable go-specific activity was previously found in caudate and putamen during performance of a go-nogo task with asymmetric reinforcement (Schultz and Romo 1988). The pattern of eye movements during the delay suggests that activations were not related to specific ocular fixation patterns. Extensive recordings of EMG activity of several arm and postural muscles in our present and preceding studies suggest that neuronal activations occurring before overt behavioral reactions and terminating immediately afterward can not be simply attributed to uncontrolled muscle activity. In view of the large number of muscles, however, it may not be completely ruled out that some activations could have been related to activity in one of the muscles not monitored during the recording of a particular neuron. A role in movement preparation is particularly suggested for neurons with directional delay activity in the spatial task. Similar activity in premotor and supplementary motor cortex during performance of go-nogo or directional movement tasks is usually interpreted in terms of movement preparation (Tanji et al. 1980; Wise et al. 1983). In analogy to the present task, activations related to the direction of impending reaching movements toward horizontally arranged targets were also found in monkey prefrontal cortex (Niki and Watanabe 1976). In contrast to some prefrontal neurons, activity in the presently recorded striatal cells was unrelated to the spatial position of the instruction. In the striatum, movement direction-specific activations were found in putamen of monkeys performing elbow movements (Alexander 1987; Alexander and Crutcher 1990a) and in caudate before ocular reactions (Hikosaka et al. 1989a). As an alternative to the preparation of movement, these activations might be related to the expectation of the trigger stimulus that triggers the movement reaction. Whereas the trigger stimulus is physically the same in go and nogo trials, expectation-related activity restricted to go trials could reflect the particular behavioral significance of the upcoming stimulus. Although it is unclear how neuronal activity would differ between these alternatives in the employed tasks, both relationships would reflect the predictable impending execution of movement.

INHIBITION OF MOVEMENT. The symmetrically reinforced delayed go-nogo task constitutes a conditional behavioral paradigm in which the animal performs an arm movement after the trigger stimulus under the condition that the instruction cue was green, whereas it withholds the movement after the same trigger stimulus when the instruction was red. Two principal types of activity restricted to nogo trials were observed that may be related to the withholding or inhibition of movement: activity beginning after the instruction and terminating on presentation of the trigger stimulus, and activity beginning after the trigger and terminating on reward delivery. By contrast, these neurons were not activated after both the go and nogo instructions and the trigger stimulus in nogo trials. During these periods, movement is conceivably also inhibited, which in these situations serves to assure timely and controlled performance of the task. This might imply that activations restricted to nogo trials were related to the particular aspect of movement inhibition as conditional reaction of the task, rather than to the more general process of inhibiting erroneous movements.

This tentative interpretation of the data is supported by the effects of brain lesions on nogo performance. Lesions of the orbitofrontal cortex impair go-nogo tasks because of perseverative go performance, resulting in deficient nogo responding (Iversen and Mishkin 1970). Lesions of premotor cortex lead to a deficit in go-nogo tasks only when both go and nogo trials are rewarded, whereas asymmetrically reinforced go-nogo tasks are unimpaired. This deficit in nogo performance is interpreted as an impairment in the selection of a conditional behavioral reaction (Petrides 1986), such that the reaction to the trigger stimulus in rewarded nogo trials is not simply an absence of responding but may constitute a behavioral reaction consisting of the inhibition of movement.

If the inhibition of movement in rewarded nogo trials constitutes a behavioral reaction to the trigger stimulus and not just an absence of responding, activations only ob-

served after the preparatory instruction cue in nogo trials might be related to the preparation of movement inhibition. Likewise, activations beginning after the trigger stimulus and restricted to nogo trials might be related to the actual inhibitory reaction to the trigger stimulus. Interestingly, activations restricted to nogo trials were more numerous in the present go-nogo task with rewarded nogo trials, as compared with the previous task in which nogo trials were not rewarded (Schultz and Romo 1992).

Expectation of environmental signals

Three types of activations preceding external stimuli in both go and nogo trials were observed in largely separate populations of striatal neurons (Fig. 16). *1*) Activations occurring before the instruction cue may be related to the expectation of this signal as the first event in each trial. *2*) Activations preceding the trigger stimulus may be related to the expectation of the trigger and contrast with those occurring exclusively in go or nogo situations reflecting the preparation of the appropriate behavioral reaction. *3*) Activations beginning close to or after the trigger stimulus and terminating in temporal relation to the delivery of reward may be related to the expectation of reward, which was the common event in both go and nogo situations. Further experimentation should resolve whether this last type of activity might be related to the hedonic properties of the liquid, to the role of the liquid as task reinforcer, or to the more abstract attainment of the goal of the behavioral performance in each trial. The activations preceding reward should not be related to the acquisition of the movement target, which in go trials was completed up to 3 s before reward delivery and did not exist in nogo trials. Only 18 of the 193 neurons showed sustained activations that separately preceded more than 1 task component, reflecting the convergence of different expectation-related processes in a single neuron. These neurons could be members of partly overlapping circuits, each of them subserving the expectation of different task components. The separate relationships of activations to individual task events is further suggested by the very rare occurrence of activations lasting from instruction onset to reward delivery in both go and nogo trials (6 of 193 neurons). These activations may reflect more general processes lasting over the whole trial duration, such as a higher arousal level or general attention.

Similar expectation-related activity specifically preceding target instruction cues, target appearance, or reward delivery was observed during oculomotor tasks in monkey dorsal caudate (Hikosaka et al. 1989c). Activity obviously related to the expectation of moving external stimuli was recently found in putamen neurons when the direction of impending target movement was separated from that of arm movement. Some of the apparent movement preparatory activity was indeed related to the direction of expected target movement and not to the direction of arm movement (Alexander and Crutcher 1990b). The combined evidence from these studies suggests that a considerable number of neurons in caudate and putamen show activity related to the expectation of specific environmental signals. Although occurring in the context of specific behavioral performance, these activations reflect processes that appear to be distinct from the preparation of behavioral reactions.

Many neurophysiological studies in anesthetized and behaving animals investigated neuronal responses that *followed* the occurrence of an external stimulus imposed by the experimenter or the behavioral task. By contrast, the presently described activations *preceded* events that have repeatedly occurred during the past performance of the task, such as the instruction signal, the execution or inhibition of arm movement, the trigger stimulus, and the delivery of reward. Through the experience of the subject in a particular behavioral task, each signal or series of signals had gained predictive value for the occurrence of individual subsequent task components. The reception of a known signal would lead to the recall of stored information concerning a subsequent event by evoking a central representation of the particular task component. The occurrence of expectation- and preparation-related activations indicates that striatal neurons have access to these centrally stored informations and may provide a neurophysiological correlate for the use of representations by basal ganglia neurons. This information appears to concern individual task components and not the whole task sequence as an entity, because different populations of striatal neurons were activated before each component.

It is tempting to wonder how the presently suggested access to stored informations by striatal neurons might correspond to the representational functions of the basal ganglia inferred from physiological and pathological studies. It has been proposed on the basis of deficits in Parkinsonian and choreatic patients that the striatum plays a role in procedural representations underlying habit performance (Butters et al. 1985; Heindel et al. 1988; Marsden 1982; Saint-Cyr et al. 1988). After relatively stereotyped tasks are sufficiently well trained, the information concerning external signals, required behavioral reactions, and occurrence of reward is thought to be centrally represented in a noncognitive, procedural form closely linked to the way it is used for task performance (Dickinson 1980). However, the striatum might also be involved in cognitive, declarative representations by which information about individual events is stored independent of a particular task, thus allowing context-independent use for a larger variety of behavior. Increases of oxidative metabolism in human striatum during the mental imagination of walking through familiar scenery (Roland et al. 1987) may suggest an involvement of the basal ganglia in declarative representations. It is unclear how the presently observed activations preceding individual task components at a time scale of hundreds of milliseconds might be related to the different types of representations that underlie behavioral performance involving the basal ganglia. Also, similar expectation- and preparation-related activity has been found in several cortical areas (see below), thus refuting a unique occurrence of sustained activity in the striatum that might be related to the representational deficits observed after striatal lesions.

Regional specificity in the striatum

Neurons related to the execution of arm movements are found in posterolateral putamen (Crutcher and DeLong

1984; Liles 1985), an area receiving afferents from primary motor and somatosensory cortex (Künzle 1975, 1977). Neurons activated during eye movements are located in central portions of the head of caudate (Hikosaka et al. 1989a), which receives afferents from the frontal eye fields (Künzle and Akert 1977; Stanton et al. 1988). This suggests that relationships to primary movement processes of limbs and eyes are found in circumscribed parts of striatum, in agreement with the restricted projections of somatomotor and oculomotor cortical areas to posterolateral putamen and centroanterior caudate, respectively.

By contrast, activations related to the expectation of environmental signals and preparation of arm movements were presently found in large anterior zones of both caudate and putamen. Interestingly, onset and offset times of these activations did not differ between the two structures. Although it was previously suggested that activations related to the preparation of arm movements occur predominantly in the arm area of posterolateral putamen (Alexander 1987), recent studies on larger striatal territories revealed that preparation-related activity is also present in the anterior putamen rostral to the motor area (Alexander and Crutcher 1990a). In caudate, neurons related to the preparation of eye movements tended to be located more rostrally than neurons activated during the execution of saccades (Hikosaka et al. 1989a). Thus the anterior parts of both caudate and putamen appear to be involved in neuronal processes related to the expectation of environmental events and the preparation of behavioral reactions.

Striatal expectation-related activity may be driven by input from frontal cortical structures in which comparable activity is found. Activations preceding instruction stimuli are found in monkey prefrontal cortex (Niki and Watanabe 1979; Watanabe 1986) and in premotor cortex (Mauritz and Wise 1986). Certain premotor cortex neurons appear to be activated during the expectation of the temporal occurrence of the signal rather than its significance for indicating the target of future arm movements (Vaadia et al. 1988). Activations preceding trigger stimuli in both go and nogo trials similar to those observed presently are found in prefrontal neurons (Pragay et al. 1987). Some neurons in the supplementary motor, premotor, and dorsolateral prefrontal cortex show activations specifically preceding nogo reactions (Tanji and Kurata 1985; Watanabe 1986; Weinrich et al. 1984), which strikingly resemble the present results in striatum. Some neurons in monkey prefrontal cortex show reward expectation-related activations in both go and nogo trials similar to those observed presently (Komatsu 1982; Watanabe 1986). Expectation- and preparation-related neuronal activity is also found in parietal and temporal association cortex (Crammond and Kalaska 1989; Fuster and Jervey 1982; Koch and Fuster 1989; Lynch et al. 1977; Miyashita and Chang 1988). Thus activations related to the preparation of behavioral reactions and the expectation of instructions, trigger stimuli, and reward are found in several cortical areas that project in an interdigitating fashion into the large regions of anterior caudate and putamen presently explored (Selemon and Goldman-Rakic 1985). The particular motivational components of the expectation of reward may suggest that an input from limbic structures to striatum plays a role in the observed activity. However, this route is presently difficult to evaluate in the absence of comparable studies in limbic structures.

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Present addresses: P. Apicella, Laboratoire de Neurobiologie Cellulaire et Fonctionnelle, CNRS, Marseille, France; E. Scarnati, Dept. of Biomedical Technology, Laboratory of Human Physiology, School of Medicine, University of L'Aquila, L'Aquila, Italy; T. Ljungberg, Dept. of Pharmacology, Karolinska Institute, Stockholm, Sweden.

Address reprint requests to W. Schultz.

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REFERENCES

ALDRIDGE, J. W., ANDERSON, R. J., AND MURPHY, J. T. The role of the basal ganglia in controlling a movement initiated by a visually presented cue. *Brain Res.* 192: 3–16, 1980.

ALEXANDER, G. E. Selective neuronal discharge in monkey putamen reflects intended direction of planned limb movements. *Exp. Brain Res.* 67: 623–634, 1987.

ALEXANDER, G. E. AND CRUTCHER, M. D. Preparation for movement: neural representations of intended direction in three motor areas of the monkey. *J. Neurophysiol.* 64: 133–150, 1990a.

ALEXANDER, G. E. AND CRUTCHER, M. D. Neural representations of the target (goal) of visually guided arm movements in three motor areas of the monkey. *J. Neurophysiol.* 64: 164–178, 1990b.

ANDERSON, M. E. AND HORAK, F. B. Influence of the globus pallidus on arm movements in monkeys. III. Timing of movement-related information. *J. Neurophysiol.* 54: 433–448, 1985.

APICELLA, P., LJUNGBERG, T., SCARNATI, E., AND SCHULTZ, W. Responses to reward in monkey dorsal and ventral striatum. *Exp. Brain Res.* 85: 491–500, 1991a.

APICELLA, P., SCARNATI, E., AND SCHULTZ, W. Tonically discharging neurons of monkey striatum respond to preparatory and rewarding stimuli. *Exp. Brain Res.* 84: 672–675, 1991b.

APICELLA, P., SCARNATI, E., SCHULTZ, W., AND LJUNGBERG, T. Neuronal activity related to expectation of external signals and reward in dorsal and ventral striatum of the monkey. *Soc. Neurosci. Abstr.* 16: 234, 1990.

BINDRA, D. Neuropsychological interpretation of the effects of drive and incentive-motivation on general activity and instrumental behavior. *Psychol. Rev.* 75: 1–22, 1968.

BUTTERS, N., WOLFE, J., MARTONE, M., GRANHOLM, E., AND CERMAK, L. S. Memory disorders associated with Huntington's disease: verbal recall, verbal recognition and procedural memory. *Neuropsychologia* 23: 729–743, 1985.

CRAMMOND, D. J. AND KALASKA, J. F. Neuronal activity in primate parietal cortex area 5 varies with intended movement direction during an instructed-delay period. *Exp. Brain Res.* 76: 458–462, 1989.

CRUTCHER, M. D. AND ALEXANDER, G. E. Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey. *J. Neurophysiol.* 64: 151–163, 1990.

CRUTCHER, M. D. AND DELONG, M. R. Single cell studies of the primate putamen. I. Functional organization. *Exp. Brain Res.* 53: 233–243, 1984.

DELONG, M. R. Activity of pallidal neurons during movement. *J. Neurophysiol.* 34: 414–427, 1971.

DELONG, M. R. Putamen: activity of single units during slow and rapid arm movements. *Science Wash. DC* 179: 1240–1242, 1973.

DICKINSON, A. *Contemporary Animal Learning Theory.* Cambridge, UK: Cambridge Univ. Press, 1980.

FUSTER, J. M. AND JERVEY, J. P. Neuronal firing in the inferotemporal cortex of the monkey in a visual memory task. *J. Neurosci.* 2: 361–375, 1982.

GEORGOPOULOS, A. P., DELONG, M. R., AND CRUTCHER, M. D. Relations between parameters of step-tracking movements and single cell

discharge in the globus pallidus and subthalamic nucleus of the behaving monkey. *J. Neurosci.* 3: 1586–1598, 1983.

HEINDEL, W. C., BUTTERS, N., AND SALMON, D. P. Impaired learning of a motor skill in patients with Huntington's disease. *Behav. Neurosci.* 102: 141–147, 1988.

HELLWEG, F. C., SCHULTZ, W., AND CREUTZFELDT, O. D. Extracellular and intracellular recordings from cat's cortical whisker projection area: thalamocortical response transformation. *J. Neurophysiol.* 40: 462–479, 1977.

HIKOSAKA, O., SAKAMOTO, M., AND USUI, S. Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movements. *J. Neurophysiol.* 61: 780–798, 1989a.

HIKOSAKA, O., SAKAMOTO, M., AND USUI, S. Functional properties of monkey caudate neurons. II. Visual and auditory responses. *J. Neurophysiol.* 61: 799–813, 1989b.

HIKOSAKA, O., SAKAMOTO, M., AND USUI, S. Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. *J. Neurophysiol.* 61: 814–832, 1989c.

HIKOSAKA, O. AND WURTZ, R. H. Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J. Neurophysiol.* 49: 1268–1284, 1983.

IVERSEN, S. D. AND MISHKIN, M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Exp. Brain Res.* 11: 376–386, 1970.

JOHNSTONE, S. AND ROLLS, E. T. Delay, discriminatory, and modality specific neurons in striatum and pallidum during short-term memory tasks. *Brain Res.* 522: 147–151, 1990.

KIMURA, M. Behaviorally contingent property of movement-related activity of the primate putamen. *J. Neurophysiol.* 63: 1277–1296, 1990.

KOCH, K. W. AND FUSTER, J. M. Unit activity in monkey parietal cortex related to haptic perception and temporary memory. *Exp. Brain Res.* 76: 292–306, 1989.

KOMATSU, H. Prefrontal activity during a color discrimination task with go and nogo responses in the monkey. *Brain Res.* 244: 269–277, 1982.

KÜNZLE, H. Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. *Brain Res.* 88: 195–209, 1975.

KÜNZLE, H. Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. *Exp. Brain Res.* 30: 481–492, 1977.

KÜNZLE, H. AND AKERT, K. Efferent connections of cortical area 8 (frontal eye field) in *Macaca fascicularis*. A reinvestigation using the autoradiographic technique. *J. Comp. Neurol.* 173: 147–164, 1977.

LILES, S. L. Activity of neurons in putamen during active and passive movements of the wrist. *J. Neurophysiol.* 53: 217–236, 1985.

LJUNGBERG, T., APICELLA, P., AND SCHULTZ, W. Responses of monkey dopamine neurons during learning of behavioral reactions. *J. Neurophysiol.* 67: 145–163, 1992.

LUSCHEI, E. S. AND GOLDBERG, L. J. Neural mechanisms of mandibular control: mastication and voluntary biting. In: *Handbook of Physiology. The Nervous System. Motor Control.* Washington DC: Am. Physiol. Soc., 1981, sect. 1, vol. II, p. 1237–1274.

LYNCH, J. C., MOUNTCASTLE, V. B., TALBOT, W. H., AND YIN, T. C. T. Parietal lobe mechanisms for directed visual attention. *J. Neurophysiol.* 40: 362–389, 1977.

MARSDEN, C. D. The mysterious motor function of the basal ganglia: the Robert Wartenberg lecture. *Neurology* 32: 514–539, 1982.

MAURITZ, K. H. AND WISE, S. P. Premotor cortex of the rhesus monkey: neuronal activity in anticipation of predictable environmental events. *Exp. Brain Res.* 61: 229–244, 1986.

MINK, J. W. AND THACH, W. T. Basal ganglia motor control. II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters. *J. Neurophysiol.* 65: 301–329, 1991.

MIYASHITA, Y. AND CHANG, H. S. Neuronal correlate of short-term memory in the primate temporal cortex. *Nature Lond.* 331: 68–70, 1988.

MURRAY, G. M., LIN, L. D., MOUSTAFA, E. M., AND SESSLE, B. J. Effects of reversible inactivation by cooling of the primate face motor cortex on the performance of a trained tongue-protrusion task and a trained biting task. *J. Neurophysiol.* 65: 511–530, 1991.

NIKI, H., SAKAI, M., AND KUBOTA, K. Delayed alternation performance and unit activity of the caudate head and medial orbitofrontal gyrus in the monkey. *Brain Res.* 38: 343–353, 1972.

NIKI, H. AND WATANABE, M. Prefrontal unit activity and delayed response: relation to cue location versus direction of response. *Brain Res.* 105: 79–88, 1976.

NIKI, H. AND WATANABE, M. Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Res.* 171: 213–224, 1979.

PETRIDES, M. The effect of periarcuate lesions in the monkey on the performance of symmetrically and asymmetrically reinforced visual and auditory go, no-go tasks. *J. Neurosci.* 6: 2054–2063, 1986.

PRAGAY, E. B., MIRSKY, A. F., AND NAKAMURA, R. K. Attention-related unit activity in the frontal association cortex during a go/no-go visual discrimination task. *Exp. Neurol.* 96: 481–500, 1987.

ROLAND, P. E., ERIKSSON, L., STONE-ERLANDER, S., AND WIDEN, L. Does mental activity change the oxidative metabolism of the brain? *J. Neurosci.* 7: 2373–2389, 1987.

ROLLS, E. T., THORPE, S. J., AND MADDISON, S. P. Responses of striatal neurons in the behaving monkey. 1. Head of the caudate nucleus. *Behav. Brain Res.* 7: 179–210, 1983.

ROMO, R. AND SCHULTZ, W. Role of primate basal ganglia and frontal cortex in the internal generation of movements: neuronal activity in the supplementary motor area. *Exp. Brain Res.* In press.

SAINT-CYR, J. A., TAYLOR, A. E., AND LANG, A. E. Procedural learning and neostriatal function in man. *Brain* 111: 941–959, 1988.

SCHULTZ, W. Activity of pars reticulata neurons of monkey substantia nigra in relation to motor, sensory and complex events. *J. Neurophysiol.* 55: 660–677, 1986.

SCHULTZ, W. Neurophysiology of basal ganglia. In: *Handbook of Experimental Pharmacology,* edited by D. B. Calne. Berlin: Springer-Verlag, 1989, p. 1–45.

SCHULTZ, W. AND ROMO, R. Responses of nigrostriatal dopamine neurons to high intensity somatosensory stimulation in the anesthetized monkey. *J. Neurophysiol.* 57: 201–217, 1987.

SCHULTZ, W. AND ROMO, R. Neuronal activity in the monkey striatum during the initiation of movements. *Exp. Brain Res.* 71: 431–436, 1988.

SCHULTZ, W. AND ROMO, R. Role of primate basal ganglia and frontal cortex in the internal generation of movements: preparatory activity in the anterior striatum. *Exp. Brain Res.* In press.

SCHULTZ, W., STUDER, A., ROMO, R., SUNDSTRÖM, E., JONSSON, G., AND SCARNATI, E. Deficits in reaction times and movement times as correlates of hypokinesia in monkeys with MPTP-induced striatal dopamine depletion. *J. Neurophysiol.* 61: 651–668, 1989.

SELEMON, L. D. AND GOLDMAN-RAKIC, P. S. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J. Neurosci.* 5: 776–794, 1985.

SOLTYSIK, S., HULL, C. D., BUCHWALD, N. A., AND FEKETE, T. Single unit activity in basal ganglia of monkeys during performance of a delayed response task. *Electroencephalogr. Clin. Neurophysiol.* 39: 65–78, 1975.

STANTON, G. B., GOLDBERG, M. E., AND BRUCE, C. J. Frontal eye field efferents in the macaque monkey. I. Subcortical pathways and topography of striatal and thalamic terminal fields. *J. Comp. Neurol.* 271: 473–492, 1988.

TANJI, J. AND KURATA, K. Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. I. Responses to instructions determining motor responses to forthcoming signals of different modalities. *J. Neurophysiol.* 53: 129–141, 1985.

TANJI, J., TANIGUCHI, K., AND SAGA, T. Supplementary motor area: Neuronal responses to motor instructions. *J. Neurophysiol.* 43: 60–68, 1980.

VAADIA, E., KURATA, K., AND WISE, S. P. Neuronal activity preceding directional and nondirectional cues in the premotor cortex of rhesus monkeys. *Somatosens. Mot. Res.* 6: 207–230, 1988.

WATANABE, M. Prefrontal unit activity during delayed conditional go/no-go discrimination in the monkey. II. Relation to go and no-go responses. *Brain Res.* 382: 15–27, 1986.

WEINRICH, M., WISE, S. P., AND MAURITZ, K. H. A neurophysiological study of the premotor cortex in the rhesus monkey. *Brain* 107: 385–414, 1984.

WISE, S. P., WEINRICH, M., AND MAURITZ, K. H. Motor aspects of cue-related neuronal activity in premotor cortex of the rhesus moneky. *Brain Res.* 260: 301–305, 1983.