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Neuronal Activity in Monkey Ventral Striatum Related to the Expectation of Reward

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Projections from cortical and subcortical limbic structures to the basal ganglia are predominantly directed to the ventral striatum. The present study investigated how the expectation of external events with behavioral significance is reflected in the activity of ventral striatal neurons. A total of 420 neurons were studied in macaque monkeys performing in a delayed go–no-go task. Lights of different colors instructed the animal to do an arm-reaching movement or refrain from moving, respectively, when a trigger light was illuminated a few seconds later. Task performance was reinforced by liquid reward in both situations. A total of 60 ventral striatal neurons showed sustained increases of activity before the occurrence of individual task events. In 43 of these neurons, activations specifically preceded the delivery of reward, independent of the movement or no-movement reaction. In a series of additional tests, these activations were time locked to the subsequent reward, disappeared within a few trials when reward was omitted, and were temporally unrelated to mouth movements. Changes in the appetitive value of the reward liquid modified the magnitude of activations, suggesting a possible relationship to the hedonic properties of the expected event. Activations also occurred when reward was delivered in a predictable manner outside of any behavioral task. These data suggest that neurons in the ventral striatum are activated during states of expectation of individual environmental events that are predictable to the subject through its past experience. The prevalence of activations related to the expectation of reward suggests that ventral striatal neurons have access to central representations of reward and thereby participate in the processing of information underlying the motivational control of goal-directed behavior.

The ventral striatum of the mammalian brain may be involved in evaluating the hedonic properties of external stimuli and in sustaining behavioral reactions toward goals of primary interest. The anatomical substrate underlying these functions may consist in the conjunction of afferents from limbic structures and mesencephalic dopamine neurons. Major limbic structures in monkeys, such as the anterior cingulate gyrus, orbitofrontal cortex, and amygdala, project to the ventral striatum, including the nucleus accumbens, in a particularly dense and interdigitating fashion, whereas their projections to the dorsal striatum are more sparse and scattered (Baleydier and Mauguière, 1980; Parent et al., 1983; Russchen et al., 1985; Selemon and Goldman-Rakic, 1985). The amygdala is involved in the association of external stimuli with primary and secondary reinforcers for sustaining performance in learning tasks (Gaffan and Harrison, 1987; Gaffan et al., 1988). Interactions in the ventral striatum between afferents from the amygdala and from dopamine neurons appear to be necessary for mediating the effects of stimulus–reward associations on behavior (Cador et al., 1989). The reinforcing effects of electrical brain stimulation and of major drugs of abuse apparently involve the dopaminergic neurotransmission in the ventral striatum (Fibiger and Phillips, 1986; Wise and Bozarth, 1987). For example, the reinforcing effects of heroin are reduced by 6-hydroxydopamine–induced lesions of dopaminergic fibers in nucleus accumbens of rats (Spyraki et al., 1983).

Few studies have investigated the neurophysiological substrates underlying the behavioral role of the primate ventral striatum. Recent investigations showed that dorsal and ventral caudate neurons are activated when different kinds of food morsels are shown to the animal (Nishino et al., 1984) and that ventral striatal neurons respond to external stimuli associated with reward through prior conditioning (Williams, 1989). Neurons in both the ventral and dorsal parts of the striatum respond to the delivery of primary liquid reward at the animal's mouth, these responses being unrelated to mouth movements (Apicella et al., 1991b). These reward responses occur twice as frequently in ventral as compared to dorsal parts of striatum and suggest that information about the reception of reward reaches preferentially the ventral striatum.

Single-neuron studies in behaving monkeys reported that dorsal striatal neurons show sustained changes in activity selectively during the expectation of external signals of behavioral significance, during the preparation of limb or eye movements, and during the expectation of reward (Alexander, 1987; Schultz and Romo, 1988; Hikosaka et al., 1989; Alexander and Crutcher, 1990; Apicella et al., 1992). Thus, striatal neurons have access to central representations of environmental events that are predictable to the subject through its past experience. These activities may constitute important components of neuronal processes underlying the organization of behavioral output by the

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basal ganglia. The objective of the present study was to investigate whether expectation- and preparation-related activity could also be found in the ventral striatum, to which external signals and behavioral events such activity could be related, and how the activity could contribute to the proposed motivational functions of the ventral striatum. Monkeys performed in a behavioral task composed of separate time periods during which external signals were expected, behavioral reactions were prepared, and reward as the common outcome of different behavioral reactions was expected. This task structure allowed discrimination of distinct expectation-related activities among the different task components.

Materials and Methods

The study was performed on three male *Macaca fascicularis* monkeys (3.5–3.8 kg weight). Animals performed under computer control in several variations of a go–no-go task for obtaining liquid reward. Activity of single neurons was recorded during task performance with moveable microelectrodes while monitoring arm and mouth muscle activity through chronically implanted electrodes. Upon termination of recording, electrode positions were histologically reconstructed on brain sections. Methods were similar to those employed previously (Schultz and Romo, 1990; Apicella et al., 1991b).

Behavioral procedures. The behavioral apparatus was positioned in the right half of the frontal wall of a completely enclosed primate chair. It contained an immovable, touch-sensitive key upon which the animal rested its right hand (elbow joint at approximately 90°). Key release was detected by a frequency-sensing circuit that converted a change in electrical capacity induced by the touch of the animal's hand into a digital signal. A yellow, rectangular light-emitting diode (11 × 11 mm) served as stimulus for triggering behavioral reactions. It was mounted in front of the animal at eye level and at 27° lateral to the midsagittal plane. A small lever (7 × 15 mm) was placed 40 mm below the trigger light at reaching distance (250 mm from the animal's shoulder). The lever protruded by 20 mm from the frontal wall and made electrical contact upon downward movement of 1 mm. One bicolor, round, light-emitting diode of 3 mm diameter was located 10 mm above the lever and served as instruction cue before the trigger light was shown. A drop of 0.15 ml of diluted apple juice delivered by an electronically controlled solenoid valve served as reward. The lights and the valve were driven by the digital output of a computer that also controlled the behavioral performance. Two closed-circuit video systems served to supervise the animal's behavior continuously. One camera was directed from above to the animal's forearms, whereas the other one provided a close-up view of its face. Monkeys were deprived of fluid during weekdays. They were released into their home cages after each daily experiment of 3–4 hr and received water ad libitum during the subsequent 1 hr.

The animal kept its right hand relaxed on the resting key. In the delayed go–no-go task, the instruction light was illuminated for 1 sec with a green or red color, indicating a "go" or "no-go" situation, respectively. After a randomly varying interval of 2.5–3.5 sec after instruction onset, the yellow trigger light was illuminated for 400 msec. In the go situation, the animal released the resting key in response to the trigger signal, reached out, and touched the lever. Liquid reward was delivered upon lever touch or after a fixed interval of 1, 2, or 3 sec afterwards. In the no-go situation employing the red instruction light, the animal remained on the resting key for a predetermined duration of mostly 2 or 3 sec after trigger onset in order to receive the same reward (symmetrically reinforced go–no-go task). Only one fixed delay of reward delivery after lever touch in go and after trigger onset in no-go trials was used in any given block of trials, which became apparent to the animal in the first trial. Trials lasted 9–12 sec; intervals between reward and the instruction of the subsequent trial varied from 4 to 7 sec. Go and no-go trials alternated randomly, the successive occurrence of same situations being limited to three trials. Thus, the task contained an instructed delay period during which the trigger signal was expected and the appropriate behavioral reaction (go or no-go, respectively) was prepared. A second period began with the trigger stimulus and terminated with the delivery of reward. Thus, the trigger light was the last externally generated signal in each trial after which the delivery of reward was to be expected in successful trials. A third, temporally less well-defined period began with reward delivery and ended with the instruction light of the subsequent trial.

In the simultaneous go–no-go task, instruction and trigger lights were illuminated at the same time. The animal received the information about the go or no-go situation (green or red instruction light, respectively) together with the trigger signal that elicited the appropriate behavioral reaction. This eliminated the preparatory period between instruction and trigger while maintaining the period of expectation of reward after the trigger. Similar to the delayed go–no-go task, reward was delivered after a delay following lever touch in go trials and trigger onset in no-go trials, respectively. This task was only used on neurons that were activated during the delayed go–no-go task.

Additional tests were occasionally employed. In a variation of the delayed go–no-go task, reward was delivered simultaneously with illumination of the trigger stimulus. This eliminated the period of reward expectation after the trigger stimulus. In another test, the tube conducting reward liquid to the spout at the animal's mouth was shut off. This eliminated the delivery of reward while maintaining the noise of the solenoid valve. This modification was only noticeable to the animal by the absence of liquid arrival. In a further test, we determined whether neuronal activations would continue when the trigger stimulus was kept present before reward delivery. The trigger light remained illuminated until lever touch (go trials) or reward delivery (no-go), instead of being turned off 400 msec after its illumination. This test served to assess whether neuronal activity was driven by sensory input or was possibly related to visual working memory. In another test, the animal received a drop of liquid reward once every 8 sec without being engaged in any specific task, the resting key being removed and lights unused.

Data acquisition and analysis. After a training period of 5–6 months, animals were implanted under general pentobarbital anesthesia with cylinders for head fixation, a microelectrode base, and thin EMG wires in different muscles. The dura was kept intact. Activity of single neurons was recorded extracellularly with movable tungsten microelectrodes that were passed each day together with and inside a guide cannula of 0.6 mm outer diameter vertically into the brain. Arm movements were monitored through the implanted EMG wires from the extensor digitorum communis and biceps brachii muscles during all neuronal recordings. We were particularly interested to record mouth movements during the entire period of 6–8 months of neuronal studies. This was done by recording EMGs from the right masseter muscle, which is sufficiently solid in small macaques to sustain chronic implantation with wire electrodes over the entire 6–8 month period and is reliably activated during orofacial movements (Luschei and Goldberg, 1981; Huang et al., 1989; Murray et al., 1991). As a more global indicator of licking movements, the animal's lingual contact with the liquid-delivering spout was monitored by an electronic touch detector connected to the spout. Mouth movements were also monitored by one of the video cameras focused on the animal's mouth. Filtered neuronal discharges and rectified and filtered EMG activity were converted into standard digital pulses by means of adjustable Schmitt triggers. Data obtained simultaneously from stimuli and behavioral events, neuronal impulses, EMGs, and licks were collected at a sampling rate of 2 kHz, displayed in the form of raster displays and histograms, and stored in original form on computer disks.

Off-line data inspection was performed on the basis of dot displays, perievent time histograms, and cumulative frequency distributions of neuronal impulses referenced to any of the behavioral events. Onset, duration, magnitude, and statistical significance of increases of neuronal activity were assessed with a sliding window procedure on the basis of the nonparametric one-tailed Wilcoxon matched-pairs test. This procedure takes into account the activity of single trials, rather than the summed perievent time histogram, and does not require normal distribution of data unsuitable for the low striatal background activity. The numbers of impulses in two normalized time epochs were considered as a pair in each trial. One epoch was a 2 sec control period before the instruction, while the second consisted of a time window of 250 msec that was moved in steps of 25 msec through the time period of a suspected change, the Wilcoxon test being performed at each step. Onset of activation was determined as the mid-window time of the first of seven consecutive steps showing an activation at $p < 0.01$. In analogy, offset of activation was determined by the loss of statistically significant increase over seven steps. A Wilcoxon text was subsequently performed over the total duration between onset and offset 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 mag-

nitude of activation was assessed by counting neuronal impulses between onset and offset of activation and expressed as percentage above control activity. Peak magnitude was determined in the 500 msec interval containing maximal activity, and peak latency denotes the center of this interval. Only the statistical significance was determined for activations preceding the instruction. Here, the control period was placed individually for each neuron toward trial end where obvious neuronal changes were absent. Only neurons showing statistically significant increases of activity assessed with at least 15 trials in a given task situation were considered to be activated.

Histological reconstruction. During the last recording sessions with each animal, several small marking lesions were placed by passing negative currents (20 μA for 20 sec) through the microelectrode. 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 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 the noted micrometer readings from the microelectrode drive. Positions in parallel neighboring tracks were reconstructed at comparable vertical levels.

Results

General

The explored region of the ventral striatum was predominantly defined by its known connections with cortical and subcortical structures, because neither nucleus accumbens nor the ventral striatum was separated from the other striatal territories by well-defined anatomical boundaries in the cresyl violet–stained sections. As in our previous study (Apicella et al., 1991b), the explored area was located rostral to the anterior commissure and comprised the ventral caudate and the ventromedial putamen. It is innervated by the amygdala (Russchen et al., 1985) and orbitofrontal and cingulate limbic cortex (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985) (Fig. 1). It lies anterior, ventral, and medial to the area of putamen receiving somatotopically organized afferents from motor and somatosensory cortex in the same species (Künzle, 1975, 1977; Jones et al., 1977). In particular, it is situated rostral and ventromedial to the face area of putamen, as defined by anatomical and electrophysiological criteria (Künzle, 1975; Crutcher and DeLong, 1984; Apicella et al., 1991b). Nucleus accumbens forms the most medial portion of the ventral striatum without being clearly separated from it in the monkey. In accordance with a recent anatomical description in the same primate species (Russchen et al., 1985), we assumed that the dorsolateral border of nucleus accumbens extended from the ventral tip of the lateral ventricle to the mediolateral center of the ventral border of putamen.

The recording sites in the ventral caudate and ventromedial putamen are shown in Figure 2, in which neurons activated before individual task events are marked by large symbols. The dorsal border of the explored area extends from the ventral part of the lateral ventricle to the internal capsule and farther laterally descends toward the inferior tip of putamen. The caudal border was defined by the anterior commissure and the dorsal pallidum, which provided reliable electrophysiological landmarks during the experiment, these showing characteristically short fiber impulses in the commissure and elevated background discharge rates in the pallidum.

Mouth movements were not a part of the task contingencies. Contacts of the tongue at the spout had already begun sporadically before and with variable delays after instruction onset, occurred systematically after reward delivery, and were occasionally repeated thereafter (Fig. 3, top; see Fig. 11*C*). There was occasionally a tendency for later onsets of licking after the instruction when trigger–reward intervals were increased. The masseter muscle showed irregular and variable activity in most trials and was occasionally active before the instruction and often during the trigger–reward interval (Fig. 3, bottom; see Figs. 5, 7, 9, 11*A,B*, 12, 13). Short peaks of intense activity occurred systematically in response to reward delivery. Both lingual contact and masseter activity continued for >1 sec after reward

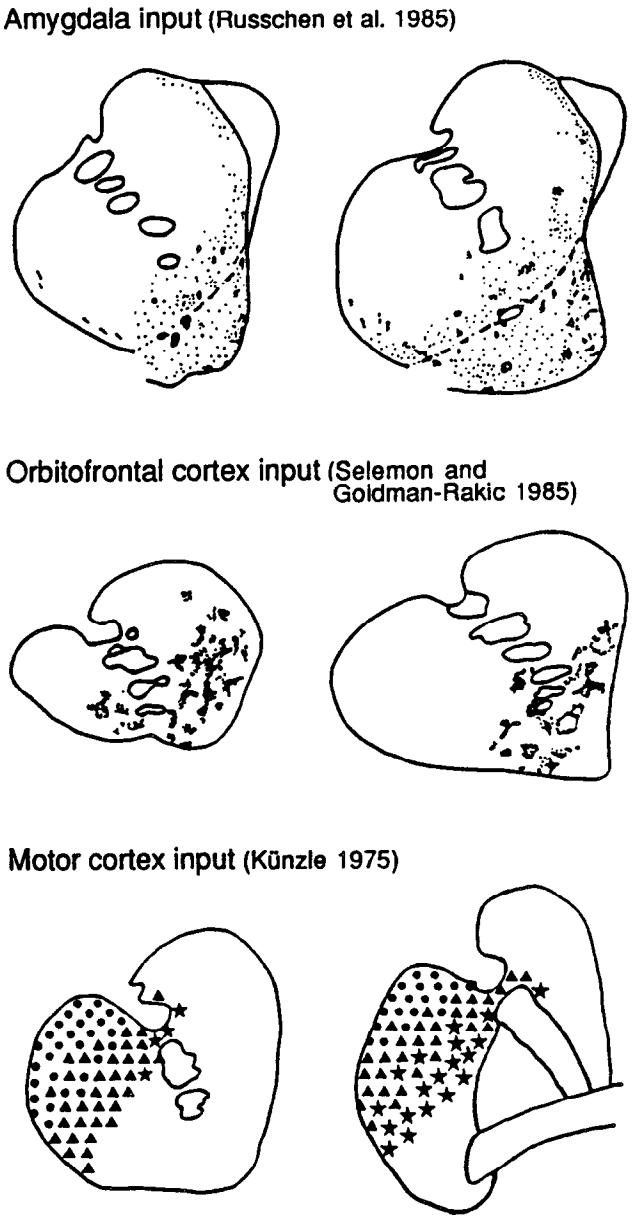

Figure 1. Definition of ventral striatum as area receiving common inputs from limbic cortical and subcortical structures. This region is devoid of sensorimotor cortical afferents. *Top,* Terminal fields of projections from basal and accessory basal nuclei of amygdala (Russchen et al., 1985). The *broken line* indicates the dorsal border of nucleus accumbens. *Middle,* Inputs from lateral orbitofrontal cortex (Selemon and Goldman-Rakic, 1985). *Bottom,* Somatotopic afferents from different parts of motor cortex (*circles,* leg area; *triangles,* arm area; *stars,* face area) (Künzle, 1975).

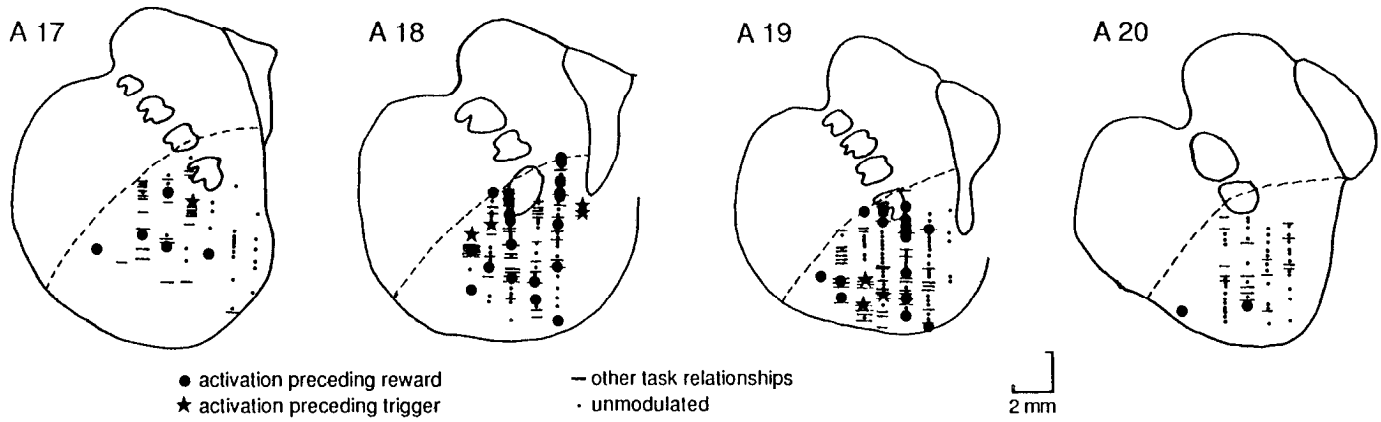

Figure 2. Positions of ventral striatal neurons with activations preceding predictable task events. Activations preceding reward occurred in both go and no-go trials and are indicated by *large circles.* Activations preceding the trigger stimulus refer to activity occurring only in go trials or in both go and no-go trials and are shown by *stars.* Responses to stimuli and reward are indicated by *short horizontal lines.* Unmodulated neurons are represented by *small dots.* The demarcation of the ventral striatum is shown by an *interrupted line.* Data from all three monkeys are drawn at corresponding positions on coronal sections of the left brain from one monkey labeled according to distances to the interaural line (A17–A20).

delivery. Thus, mouth movements occurred irregularly and over relatively long periods in each trial, with a maximum after reward delivery.

A total of 420 slowly discharging neurons (median of 1.7 impulses/sec; range, 0.1–3.8/sec) were recorded during contralateral task performance in the ventral striatum, of which 117 were in nucleus accumbens. Tonically discharging neurons (4.5–9.0 impulses/sec) were not included and are reported elsewhere (Apicella et al., 1991a). Transient responses to task-related signals were seen in 57 of the 420 neurons (14%) (19 of them in accumbens). Of these, responses to reward delivery were most numerous (n = 46; Apicella et al., 1991b), whereas responses to instruction (n = 12) or trigger stimuli (n = 6) occurred less frequently. Seven of these neurons responded to two of these signals. Examples of combined responses to instruction and trigger stimuli are shown in Figure 4*A*.

Whereas the transient responses *followed* the external signals and usually terminated well before a subsequent event occurred, a different type of activity was observed that *preceded* individual task events. This was seen in 60 of the 420 neurons (14%) and

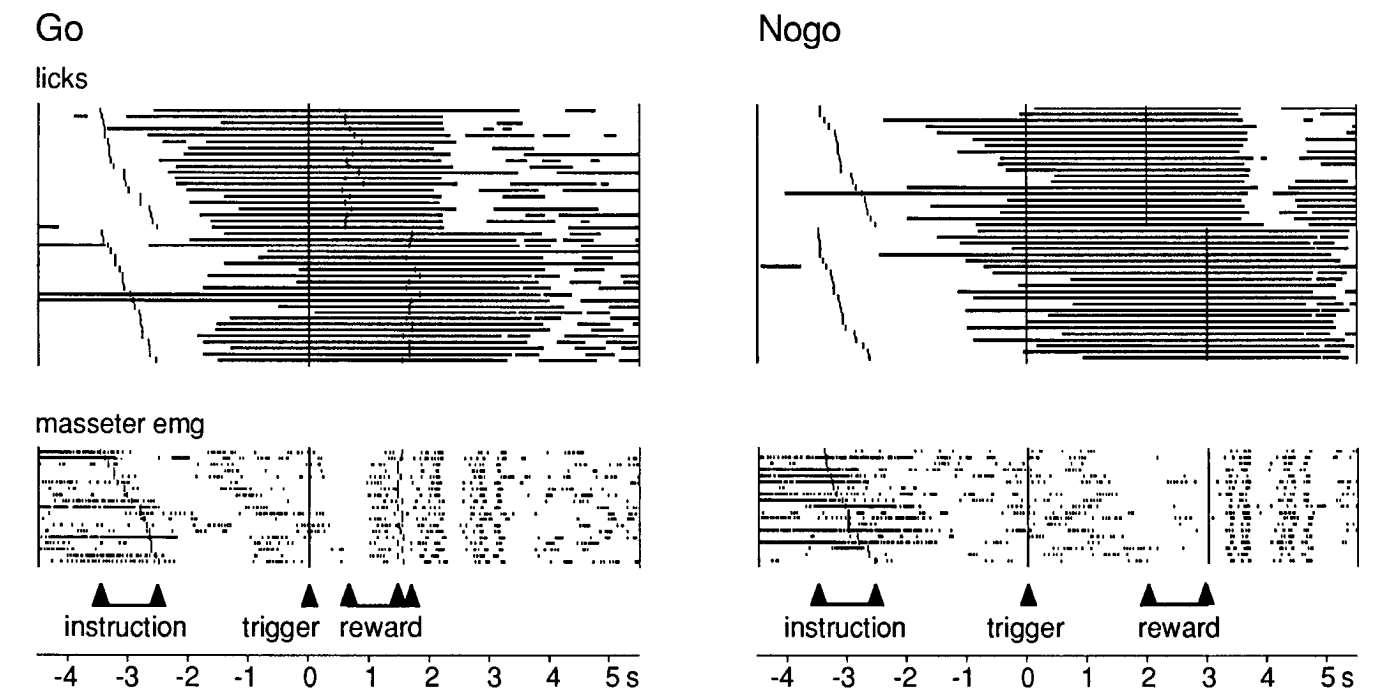

Figure 3. Mouth movement records during performance of the delayed go–no-go task. The color of an instruction light illuminated for 1 sec determined whether to execute or inhibit an arm movement in response to a yellow trigger light (green = go, red = no-go, respectively). Liquid reward was delivered from a spout at the animal's mouth at 0 or 1 sec after lever touch in go trials, and 2 or 3 sec after the trigger in no-go trials. *Top, Horizontal lines* indicate the timing of licking movements in each trial, as determined by contact of the animal's tongue with the spout. Two reward delays were employed in separate blocks of trials. *Bottom,* Rectified activity of masseter muscle exceeding a preset level is shown as *dots.* Each *line of dots* shows one trial. In *top* and *bottom, small vertical bars* to the left and right of the central reference line indicate onset of instruction light and onset of reward delivery, respectively. Go and no-go trials alternated randomly during the experiment and were separated and ordered according to instruction–trigger intervals for analysis.

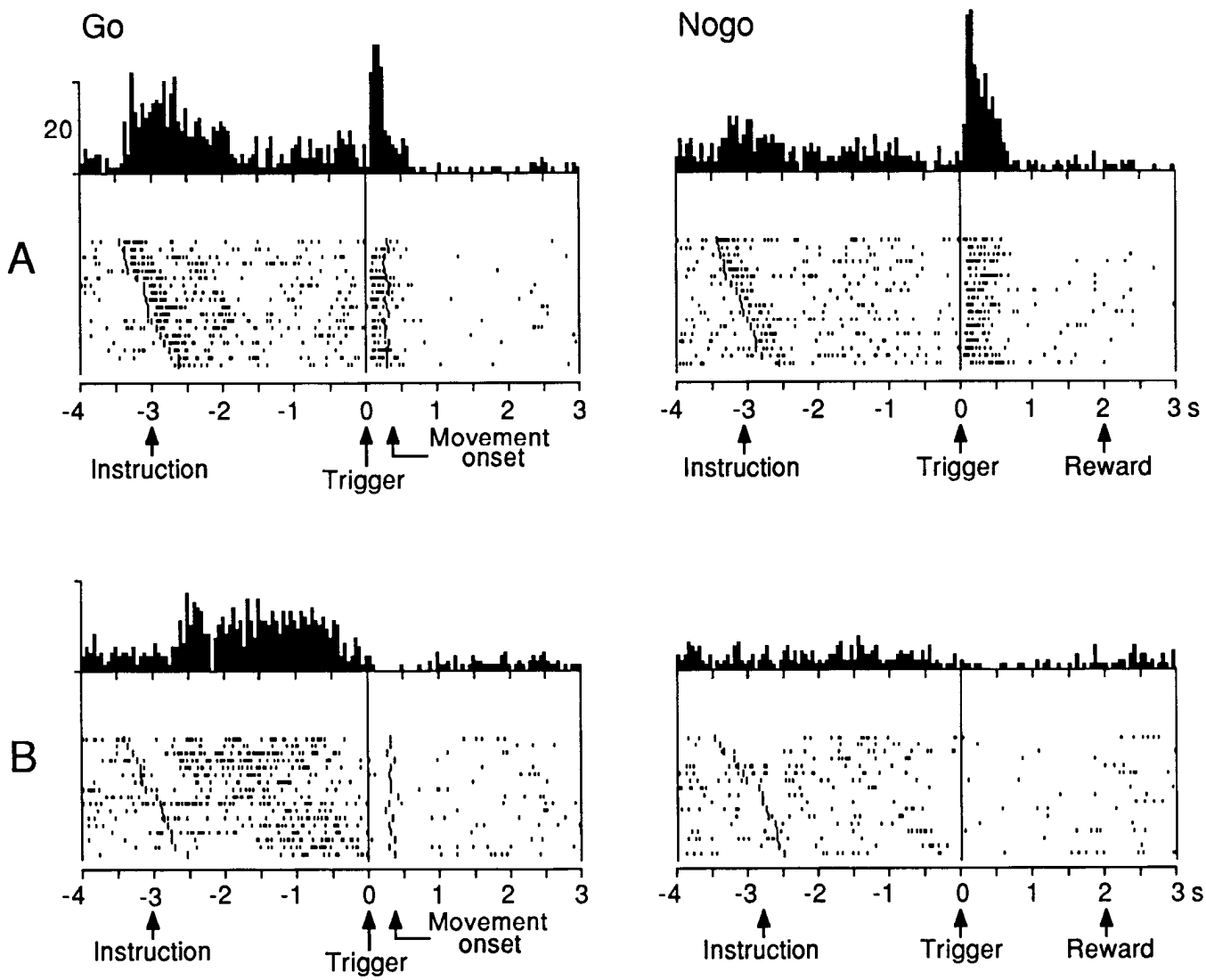

Figure 4. Task-related activation of two ventral striatal neurons. *A,* Phasic responses to onset of instruction and trigger stimuli in both go and no-go trials. *B,* Sustained activation during the preparatory period for arm movement between instruction and trigger: lack of activation during the corresponding interval in no-go trials in which the animal refrained from movement. In *A* and *B,* perievent time histograms are composed of neuronal impulses shown in rasters below. Each *dot* indicates a neuronal impulse, their distances to task components corresponding to real-time intervals. Each *line of dots* shows one trial. *Small vertical lines* in rasters denote onsets of instruction, movement, and reward, respectively. Go and no-go trials were separated and ordered according to instruction–trigger intervals for analysis. Vertical calibration is 20 impulses/bin for all histograms.

was related to one of the three events defining the different task periods: instruction cue, trigger stimulus, and reward delivery (Table 1). Activations occurring before instruction or trigger stimuli were occasionally found. Figure 4*B* shows an activation that occurred before the trigger in go trials and thus may reflect the preparation of arm movement. Neuronal activity preceding reward constituted the largest fraction of ventral striatal activations preceding external events and is the main subject of this report.

Activations preceding reward

A total of 43 ventral striatal neurons were activated before the delivery of reward in both go and no-go trials of the delayed go–no-go task. Of these, eight neurons were located in nucleus accumbens. The activation of a ventral striatal neuron before reward is shown in Figure 5, left. Activity began in both go and no-go trials after trigger onset and slowly increased until reward delivery, after which it rapidly subsided. Neuronal activity was unrelated to activity in the masseter muscle, which occurred before, during, and after the period of neuronal activation. This neuron was equally activated in the simultaneous go–no-go task in which the preparatory period for go and no-go reactions between instruction and trigger stimuli was absent (Fig. 5, right). All nine neurons activated in the delayed go–no-go task and tested in the simultaneous go–no-go task showed comparable activations in both situations.

Activations preceding reward were independent of the duration of the trigger light. Although a duration of 400 msec was usually employed, activations remained present in all 18 neurons tested when the trigger light was maintained until reward was delivered (Fig. 6). This suggests that activations were unrelated to possible mnemonic processes occurring in the absence of task-specific information during the delay between trigger offset and reward. Conversely, the continuation of activations

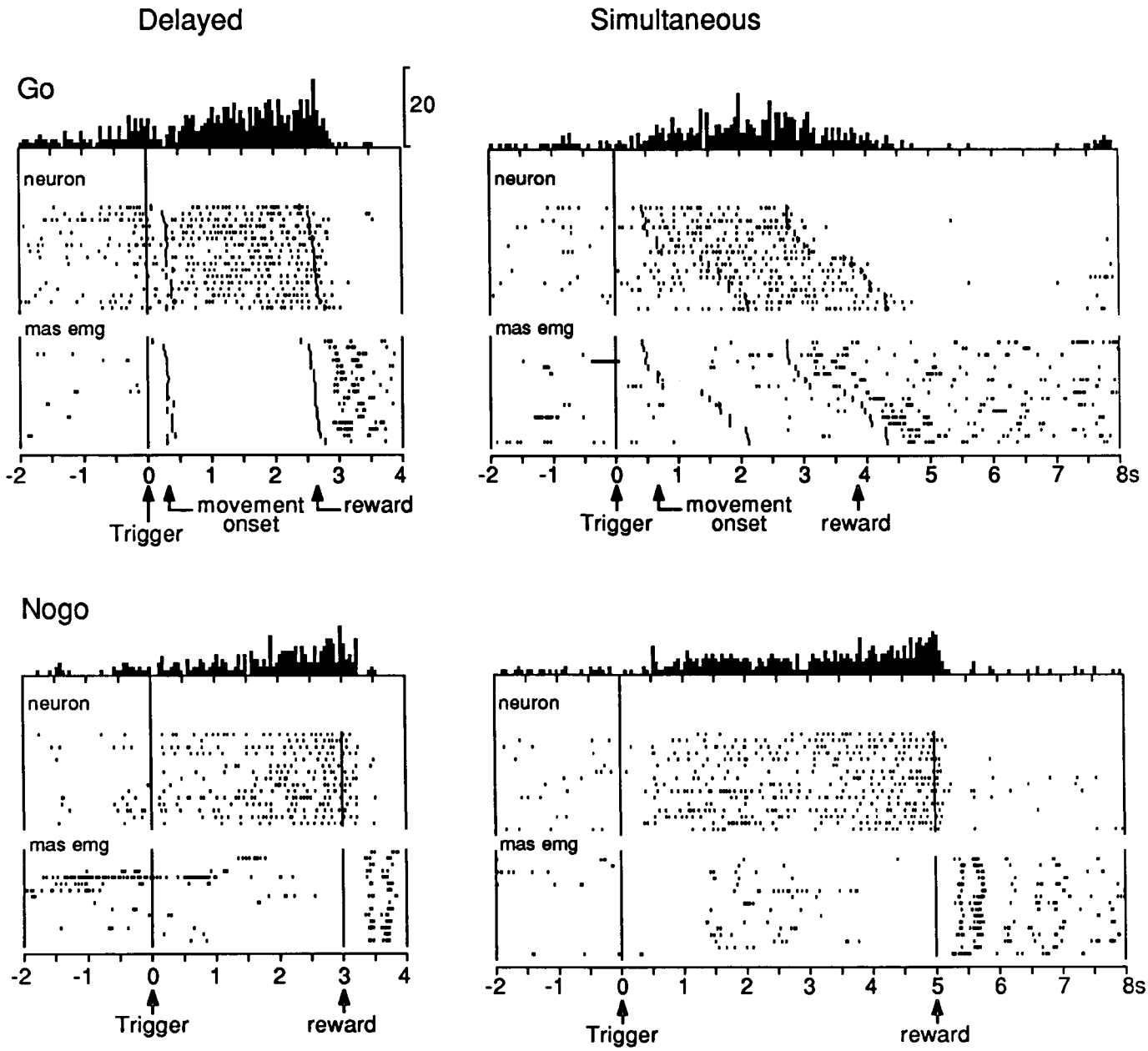

Figure 5. Activation of a ventral striatal neuron before reward. Activation occurred in both go and no-go trials and was independent of the presence or absence of a preparatory period preceding the trigger signal, as shown during the delayed go–no-go task (*left*) and the simultaneous go–no-go task (*right*) in separate blocks of trials. Each panel shows rasters and perievent time histograms of neuronal activity above rasters from simultaneously recorded masseter muscle activity (*mas emg*). *Small vertical lines* to the right of the reference line indicate movement onset (go trials) and reward delivery, respectively. Go and no-go trials were separated for analysis. Go trials are ordered according to trigger–reward intervals, whereas no-go trials are shown in original sequence downward.

after offset of the short trigger light demonstrates that activations preceding reward were not sensory responses to the light.

Activations began at different time periods before reward. The longest activations began before trigger onset in the delay task (Fig. 7*A*) (10 neurons). However, most activations began after trigger onset (33 of the 43 neurons; Fig. 7*B–D*), and some of them developed late during the trigger–reward interval immediately preceding the moment of reward delivery (Fig. 7*D*). The different onsets of neuronal activations were unrelated to activity in the masseter muscle, which varied unsystematically between trials and blocks of trials.

Quantitative evaluations were done on no-go trials with constant trigger–reward intervals of 2 sec. Activations preceding reward began at a median time of 312 msec after trigger onset. The peak of activation was reached in most neurons close to reward (median of 1825 msec after trigger onset) and consisted of a median increase of 929% over control activity before instruction onset. Activations terminated in 3 neurons before and in 40 neurons after reward (median offset time of 487 msec after no-go reward).

Temporal variations of reward delivery

The properties of neuronal activations preceding reward were further investigated by systematically varying the moment of reward delivery in relation to the preceding trigger stimulus. The interval between the trigger signal and reward was increased

Table 1. Numbers of ventral striatal neurons with expectation-related activations

	n (*n* in accumbens)
Preceding instruction signal	
Go and no-go	5 (3)
Preceding trigger signal	
Go and no-go	1
Go only	8
Subtotal	9
Preceding reward	
Go and no-go	43 (8)
No-go only[a]	3
Subtotal	46 (8)
From instruction to reward	3
−Multiple relations	3
Total	60 (11)

Neurons in nucleus accumbens are included in numbers of ventral striatal neurons given before parentheses. All activations were statistically significant at $p < 0.005$ against control activity.

[a] These activations were not considered as being related to reward expectation because of their absence before reward in go trials.

in steps of 1 sec between blocks of trials, such that the interval to reward after lever touch in go trials and after trigger onset in no-go trials became apparent to the animal during the first trial of each block.

Activations in go trials often only occurred when reward was delayed by at least 1 sec after lever touch (Fig. 8). Delays of 2 or 3 sec invariably resulted in a further prolongation of elevated activity subsiding after reward delivery in all 20 neurons tested (Fig. 8, left). The delayed arrival of reward did not affect reaction times, movement times, and muscle activity, suggesting that the activations were unrelated to arm movement (Fig. 8, right). Delaying the delivery of reward in neurons with premovement activations occasionally revealed a separate activation preceding reward (Fig. 9, left). In no-go trials, displacement of reward resulted in an analogous prolongation of activation (Fig. 9, right).

Onset times of activations remained unchanged in 12 neurons when reward delivery was delayed by 1 sec (Fig. 10*A*). The remaining eight neurons showed significantly later onsets of activation with delayed reward (>400 msec; $p < 0.01$, Wilcoxon test). An illustrative example is shown in Figure 10*B* from a neuron that seemed to be activated in relation to the trigger signal. Introduction of a 1 sec delay in reward delivery after correct lever touch revealed that the activation was in fact related to the subsequent reward, demonstrating the resolution power of sufficiently long intervals between separate task events.

A more important displacement occurred when reward was delivered simultaneously with illumination of the trigger stimulus. This condition eliminated the trigger–reward interval and abolished the predictive nature of the trigger for reward. Of 11 neurons tested in this situation, 3 lost their activations (Fig. 11*A*), whereas 8 showed activations with earlier onset times (Fig. 11*B,C*). None of these neurons showed activations lasting during the period that originally preceded reward. Recordings of lingual contacts occasionally revealed an earlier onset time of oral activity in parallel with a displacement of neuronal activation, although these two measures were not closely related (Fig. 11*C*). This indicates a temporal correspondence between the animal's anticipatory behavior and ventral striatal activity.

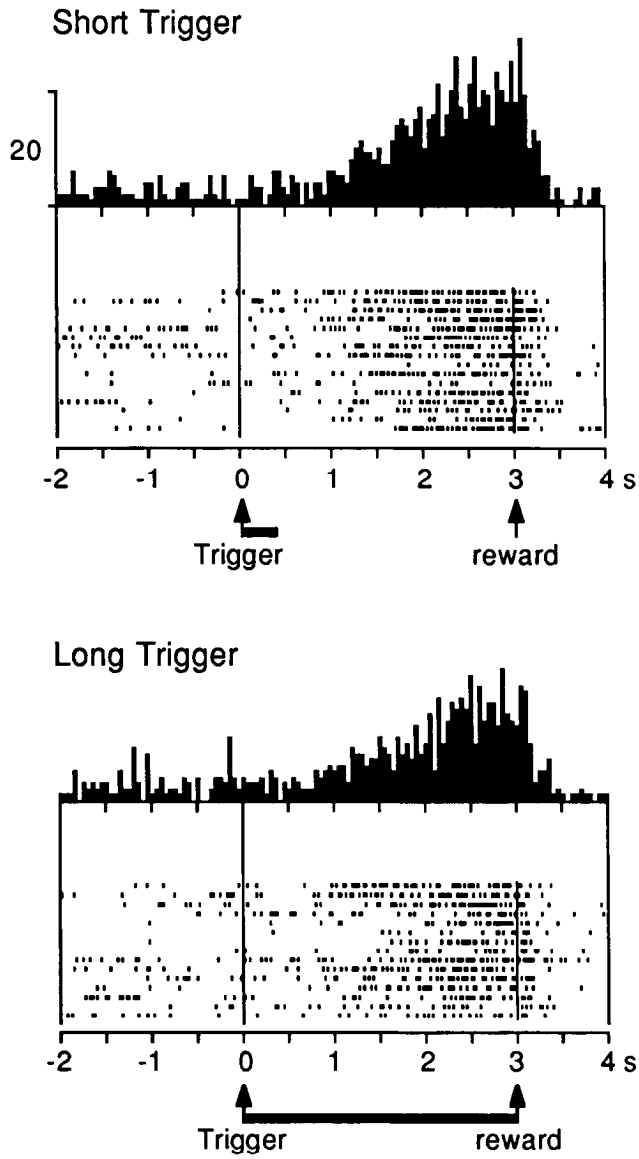

Figure 6. Activation of a ventral striatal neuron before reward occurred independently of the duration of the trigger stimulus. Only no-go trials are shown. *Horizontal bars* below each dot display denote duration of trigger. The original sequence of trials is shown from top to bottom.

Contingencies of activations preceding reward

Further experiments served to determine the conditions in which activity preceding reward occurred. Delivery of reward was prevented by closing the liquid tube leading to the animal's mouth. This manipulation maintained the noise of the solenoid normally controlling liquid flow. On one of the first occasions tested in an animal, neuronal activation continued beyond the usual time of reward delivery and remained present beyond the recording duration of individual trials (Fig. 12*A*). The continued activity was seen immediately with the first trial in which reward failed to arrive and ended with the last such trial. Thus, activations remained present when the animal erroneously expected reward. After 12 similar blocks of testing with the same animal, activations were completely absent during the period that usually preceded reward (Fig. 12*B*). Here, activations only occurred during the first few trials without reward. They reappeared after

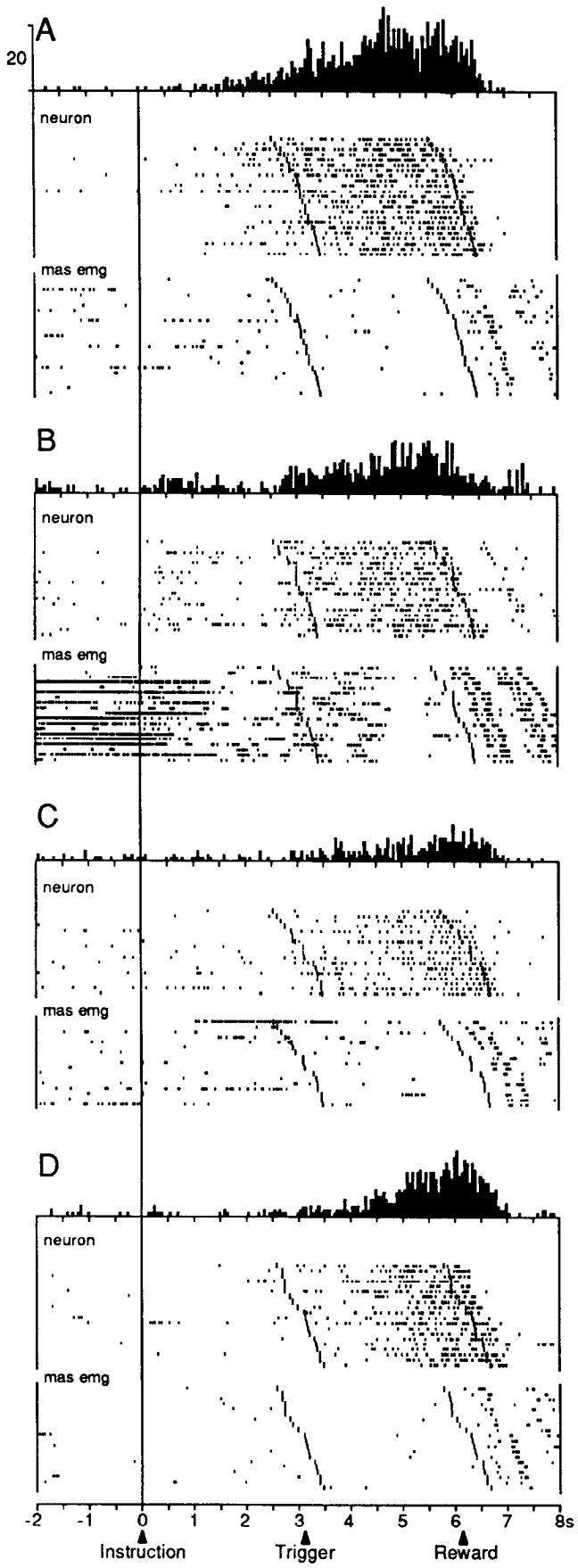

Figure 7. Different onset times of activations preceding reward in four ventral striatal neurons. *A*, Activation beginning before trigger signal. *B* and *C*, Activation restricted to trigger–reward interval. *D*, Activation developing immediately before reward. Rasters and perievent time histograms of neuronal activity are shown above rasters from simultaneously recorded masseter activity (*mas emg*). Only no-go trials are shown. Trials are ordered according to instruction–trigger intervals.

the first few rewarded trials. Thus, activations were related to the expected delivery of reward and not to the occurrence of the solenoid noise associated with reward.

Activations preceding reward were tested with different liquids in three neurons whose recordings were sufficiently stable to permit extensive testing. The administration of water instead of the usual apple juice invariably reduced the activations preceding reward (Fig. 13). These reductions in activation occurred in spite of correct task performance and maintained behavioral reactions to reward delivery, as evidenced by the reliable occurrence of peaks in masseter muscle activity (Fig. 13, right). These data demonstrate an appetitive component in neuronal activations preceding reward.

Three neurons activated before reward were also tested while reward was delivered at regular intervals of 8 sec outside of a specific behavioral task. All of these neurons were equally activated before reward delivery in this situation (Fig. 14). This suggests that these activations preceding reward were related to the delivery of liquid and not to the role of the juice as task reinforcer.

Discussion

Nature of activations related to the expectation of reward

The delayed go–no-go task comprised two well-defined periods that were delimited by external events. These were the instructed delay period beginning with instruction onset and ending with trigger onset, and the reaction period beginning with trigger onset and ending with reward upon correct task performance. Through the conditioning procedure, the sequentially occurring stimuli of the task were well known to the animal, and each signal could serve as a predictor for the subsequent event. The instruction would predict the trigger stimulus and prepare for the behavioral reaction (execution or withholding of arm movement). As first signal in each trial, it would ultimately also predict reward, albeit in a less immediate manner. By contrast, the subsequently occurring trigger stimulus was the last externally imposed stimulus to which the animal needed to react correctly in each trial in order to obtain reward. Thus, the trigger stimulus constituted the main predictor for the availability of reward in this task. It would induce a state of reward expectation and in this function sustain behavioral responding (Bindra, 1968).

Very few ventral striatal neurons showed sustained activations during the instructed delay period preceding the trigger stimulus. These activations began early after the instruction, terminated usually with trigger presentation, and rarely lasted until the delivery of reward. According to the structure of the task, these activations should reflect the preparation for behavioral reaction or the expectation of the associated trigger stimulus. They should not be directly related to the expectation of reward because they terminated well in advance of reward delivery. By contrast, a considerable number of ventral striatal neurons showed sustained activations during the delay period preceding reward delivery. These activations were independent of the behavioral reaction (execution or withholding of arm movement) and may be related to the common outcome of correct task performance, the delivery of reward. This interpretation is supported by the fact that activations occurred in the

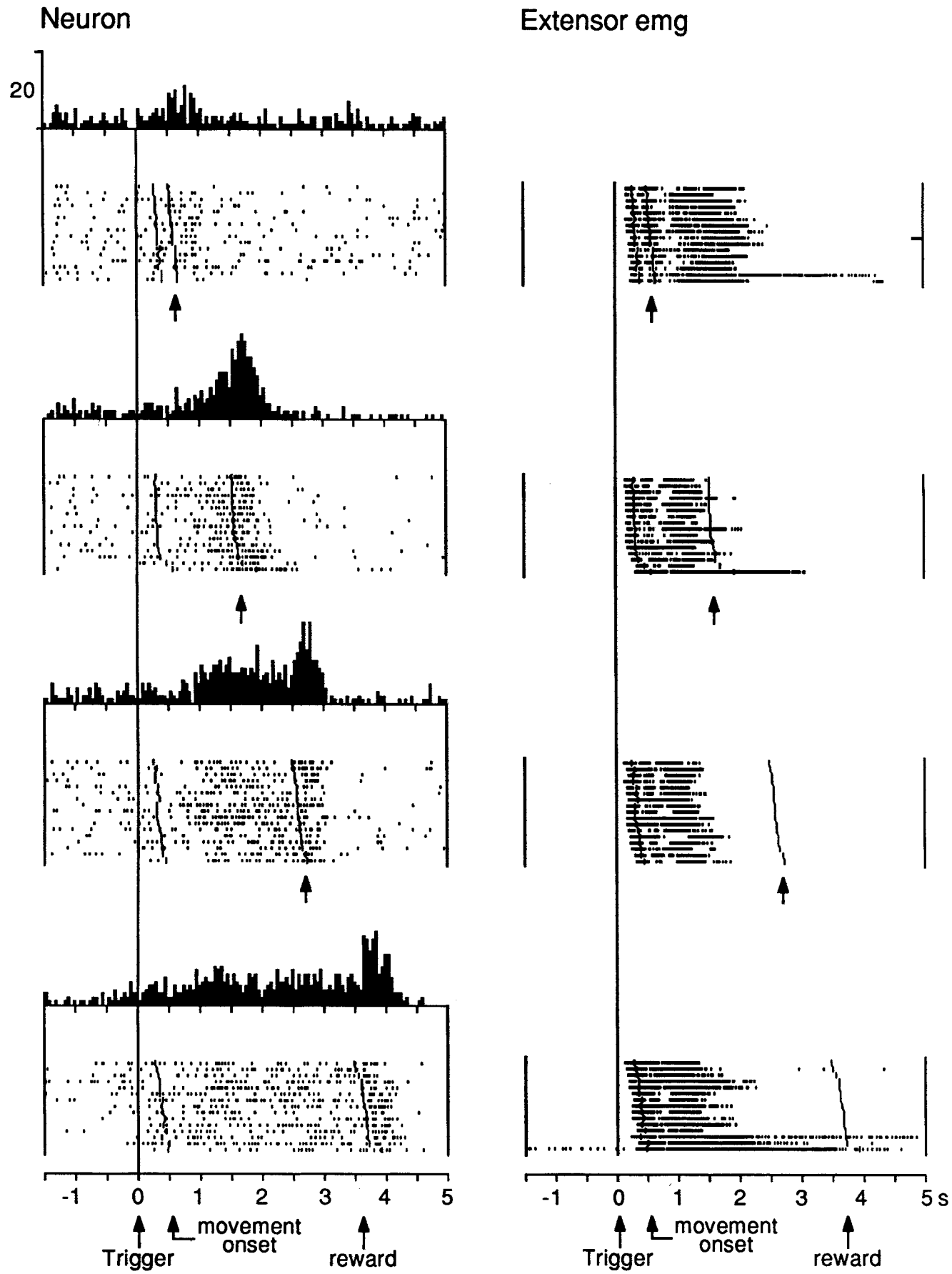

Figure 8. Activation preceding reward was prolonged when delivery of reward was delayed. In four separate blocks of trials shown, from the top, reward was delivered at intervals of 0, 1, 2, and 3 sec after lever touch while recording from the same neuron. Simultaneous recordings of extensor digitorum communis muscle activity showed largely unchanged movement-related muscle activation. Trials are ordered according to reaction time. The delivery of reward is indicated by *arrows* below rasters. This neuron also responded phasically to reward delivery. Only go trials are shown.

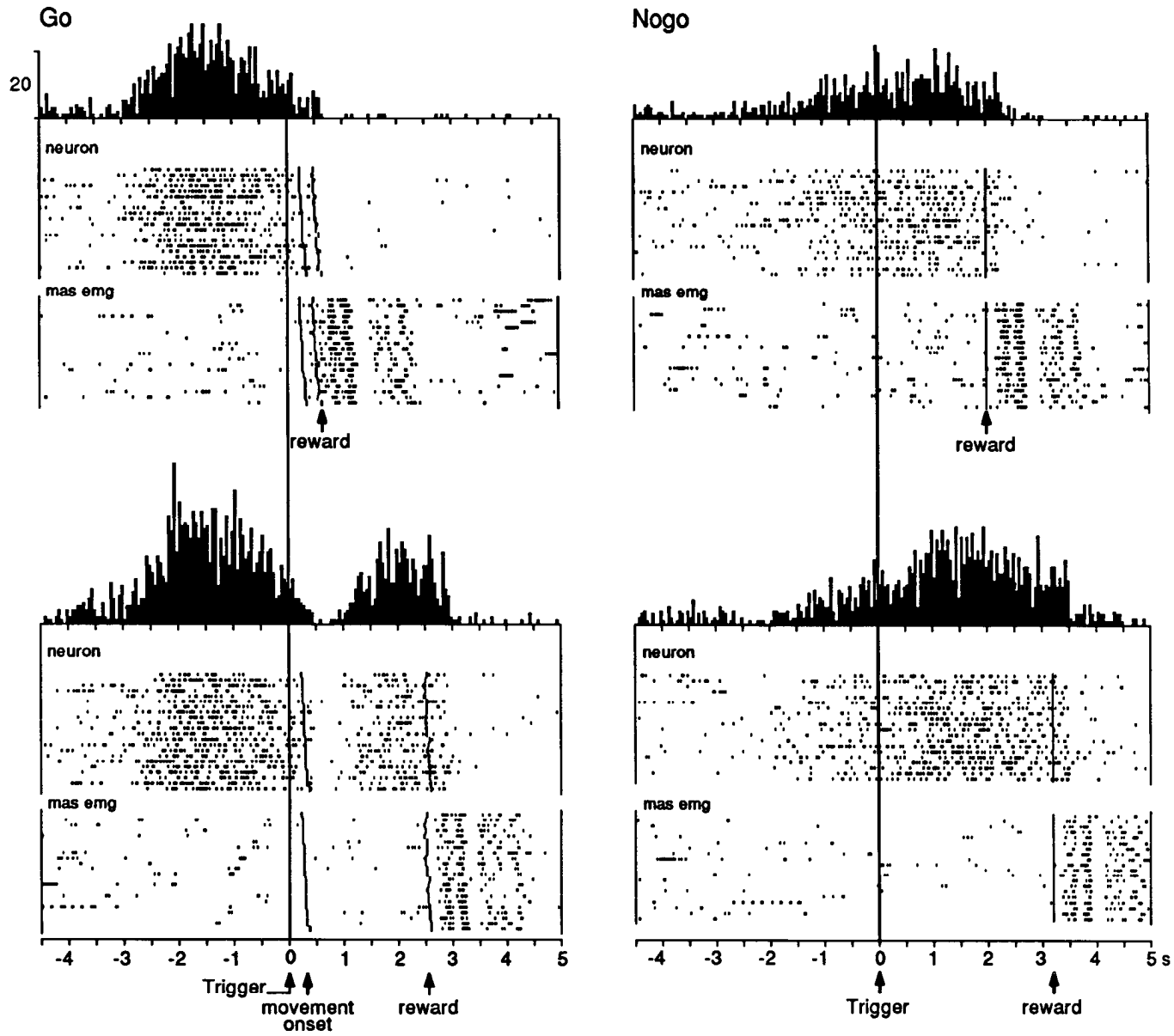

Figure 9. Separation of different sustained activations by temporal separation of behavioral events in a ventral striatal neuron. *Left* (go trials), The apparent major change in this neuron was a premovement activation (*top*). A separate activation preceding reward appeared when reward was delayed by 2 sec after correct lever touch (*bottom*). *Right* (no-go trials with same neuron), Only an activation preceding reward occurred in no-go trials. This activation continued when reward was delayed. Rasters and perievent time histograms of neuronal activity are shown above rasters from simultaneously recorded masseter activity (*mas emg*).

same manner when the instructed delay period was omitted in the simultaneous go–no-go task and only the delay period before reward remained present. Thus, the majority of sustained neuronal activations observed presently in the ventral striatum appear to be related to the expectation of reward.

Activations related to the expectation of reward usually began slowly after the trigger stimulus with a few impulses, required about 1 sec to develop to an appreciable level, and reached their peak toward the time when reward was normally delivered. In several neurons activated during the trigger–reward interval, activations began even before the trigger signal in occasional trials, suggesting that the individual signals, such as instruction and trigger, served as temporal references during task performance rather than uniquely evoking the sustained activations. This also demonstrates that activations did not constitute prolonged responses to trigger or instruction signals but were related to the subsequent event, the delivery of reward.

Neuronal activations continued when the normally employed moment of reward delivery was delayed by several seconds and terminated upon reward delivery. When the tube containing the reward liquid was closed for the first time with an animal and reward was not delivered, neuronal activity continued for many seconds, possibly in the erroneous expectation of very late reward delivery. However, with continued testing, this activity disappeared very rapidly within a few trials when the failure of reward delivery became predictable during the first trials with the tube closed. These data suggest that activations of ventral striatal neurons are related to the expectation of the occurrence of reward without predicting the exact time of arrival, at least during the initial testing of this control condition.

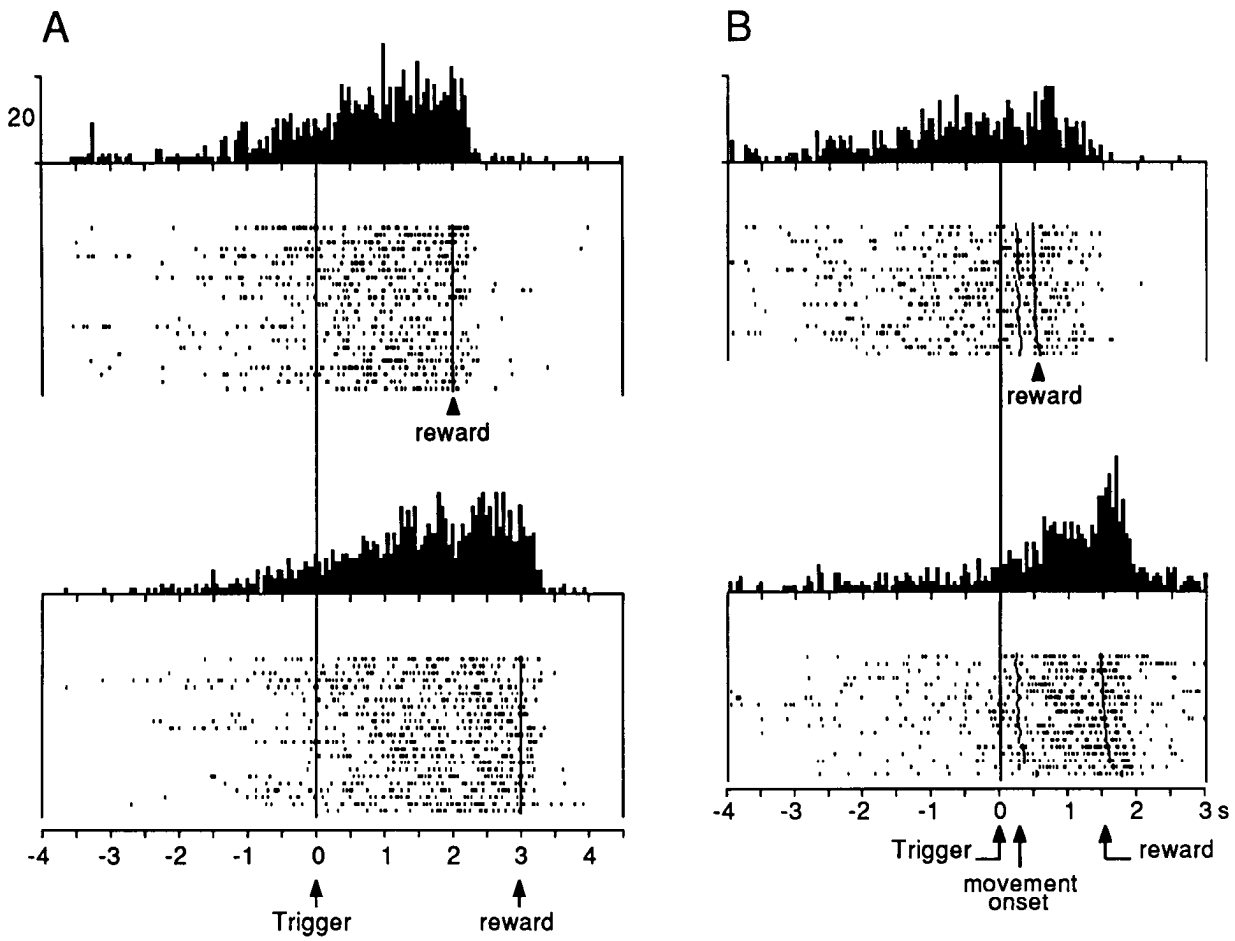

Figure 10. Influence of delayed reward delivery on the onset of expectation-related neuronal activation. *A,* Lack of change of onset time when increasing the delay by 1 sec (*top* vs *bottom*). The original sequence of trials is shown from top to bottom. Only no-go trials are shown. *B,* Temporal separation of environmental events revealed event-specific relationship of neuronal activity. *Top,* Neuronal activation preceding trigger stimulus and lasting until reward occurred when reward was delivered immediately upon correct lever touch. *Bottom,* Introduction of a delay of 1 sec demonstrates that the activation of this neuron specifically preceded reward delivery. Only go trials are shown. Trials are ordered according to trigger–reward intervals.

Onsets of activations in some neurons were displaced in parallel with displaced reward delivery. This was particularly striking when reward was delivered simultaneously with the trigger stimulus, in which case the instruction became the main stimulus predicting reward. This suggests that reward expectation–related activity may begin in reference to those stimuli of the task that serve as closest predictors of reward.

Several lines of evidence suggest that activations preceding reward were unrelated to the expectation of the acoustic stimulus of solenoid opening. Activations continued beyond the usual time of reward delivery or were completely absent when the tube conducting liquid to the animal's mouth was closed, a manipulation that left the solenoid noise present. Another argument is derived from the results obtained when the appetitive value of reward was modified. On the three neurons tested, a change from apple juice to plain water did not alter the solenoid noise but largely abolished the activity preceding reward.

Activations resembling those observed presently were seen in caudate neurons during performance of oculomotor tasks (Hikosaka et al., 1989). Through a series of control tests, the authors ruled out a relationship to ocular fixation or preparation of hand movement. The combined evidence from these oculomotor tasks and our data obtained with arm movements suggests that reward expectation may indeed constitute an important relationship of striatal activity independent of the motor system employed for reaching the goal. Whereas reward expectation–related activity has been found in the center of the head of caudate (Hikosaka et al., 1989) and in other parts of the dorsal striatum (Apicella et al., 1992), the present study reporting its occurrence in the ventral striatum suggests a relatively widespread distribution of reward expectation–related activity throughout the anterior striatum.

Discrimination against mouth movement–related activity

During neuronal recordings, the temporal occurrence of mouth movements was monitored by three means, EMG recordings from the masseter through implanted wires, recordings of licks in the form of tongue contact with the liquid-delivering spout, and inspection of the image from the video camera focused on the mouth. Although EMG recordings from several muscles may give highly specific indications about the motor aspects of liquid ingestion, we limited recordings to only one muscle. The masseter is the major jaw-closing muscle that, together with the jaw-opening muscles genioglossus and digastric, is very active during rhythmic mouth movements and thus is an excellent and representative, albeit not exclusive, indicator of many aspects of

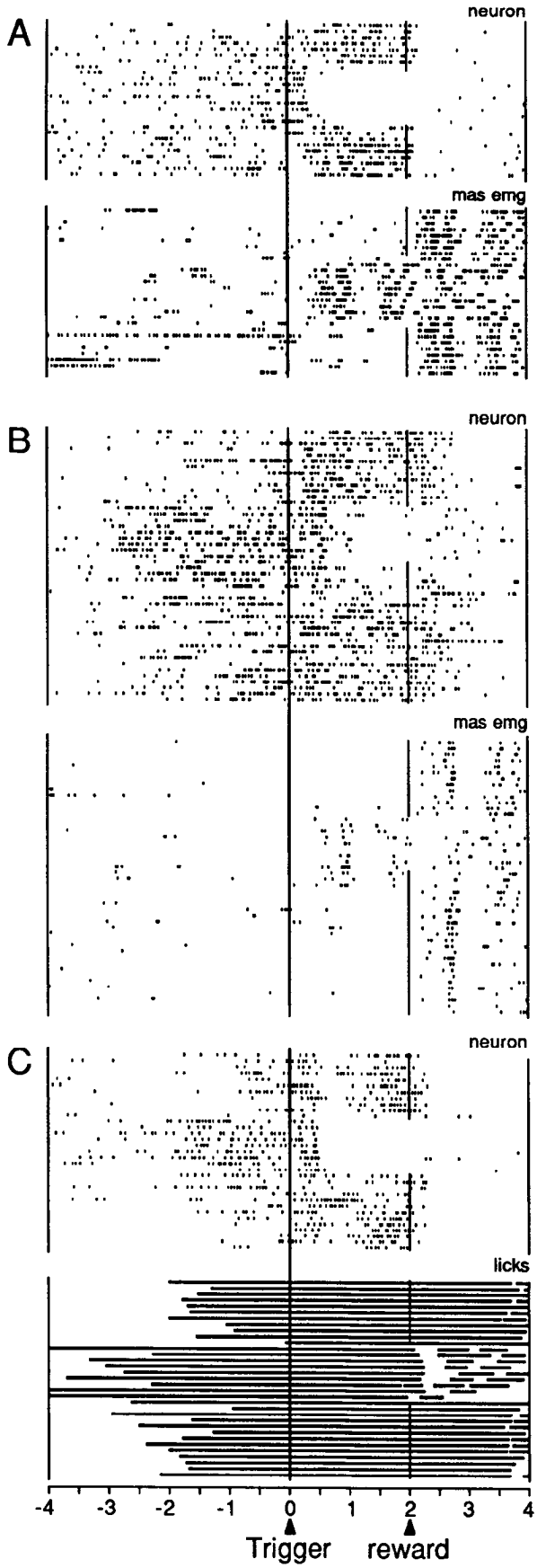

Figure 11. Influence of delivering reward simultaneously with illumination of trigger stimulus on activations preceding reward in three ventral striatal neurons. *A*, Short-stopped activation with unchanged onset. *B* and *C*, Displacement of activation toward earlier time in trial. Original sequences of trials are shown from top to bottom. Trials in *A–C* sequentially employed a regular trigger–reward interval of 2 sec, reward delivered together with trigger, and a second trigger–reward interval. Reward delivered at regular 2 sec interval after trigger is marked by *vertical lines* in rasters. Rasters and perievent time histograms of neuronal activity are shown above rasters from simultaneously recorded masseter activity (*mas emg* in *A*, *B*) or licks at the liquid-delivering tube (*C*). Only no-go trials are shown.

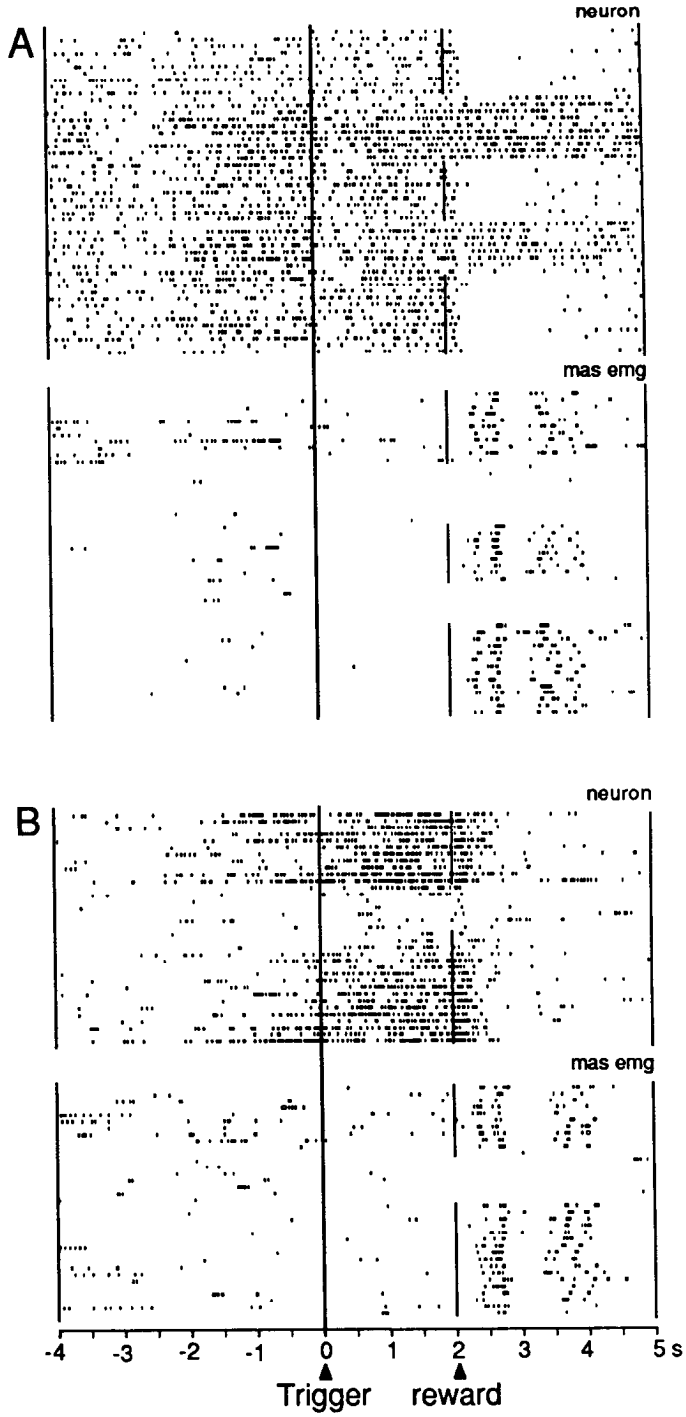

Figure 12. Modifications of activation preceding reward by interruption of liquid flow. *A*, Prolonged activation when the liquid tube was closed for the first time with this animal. *B*, Absence of activation with another neuron tested later in the same animal with an identical procedure. Original sequences of trials are shown from top to bottom. Liquid was only delivered in trials marked by *vertical lines* in rasters, whereas the liquid tube was closed otherwise. The solenoid normally controlling liquid flow opened audibly 2 sec after trigger onset in all trials. Rasters and perievent time histograms of neuronal activity are shown above rasters from simultaneously recorded masseter activity (*mas emg*). Only no-go trials are shown.

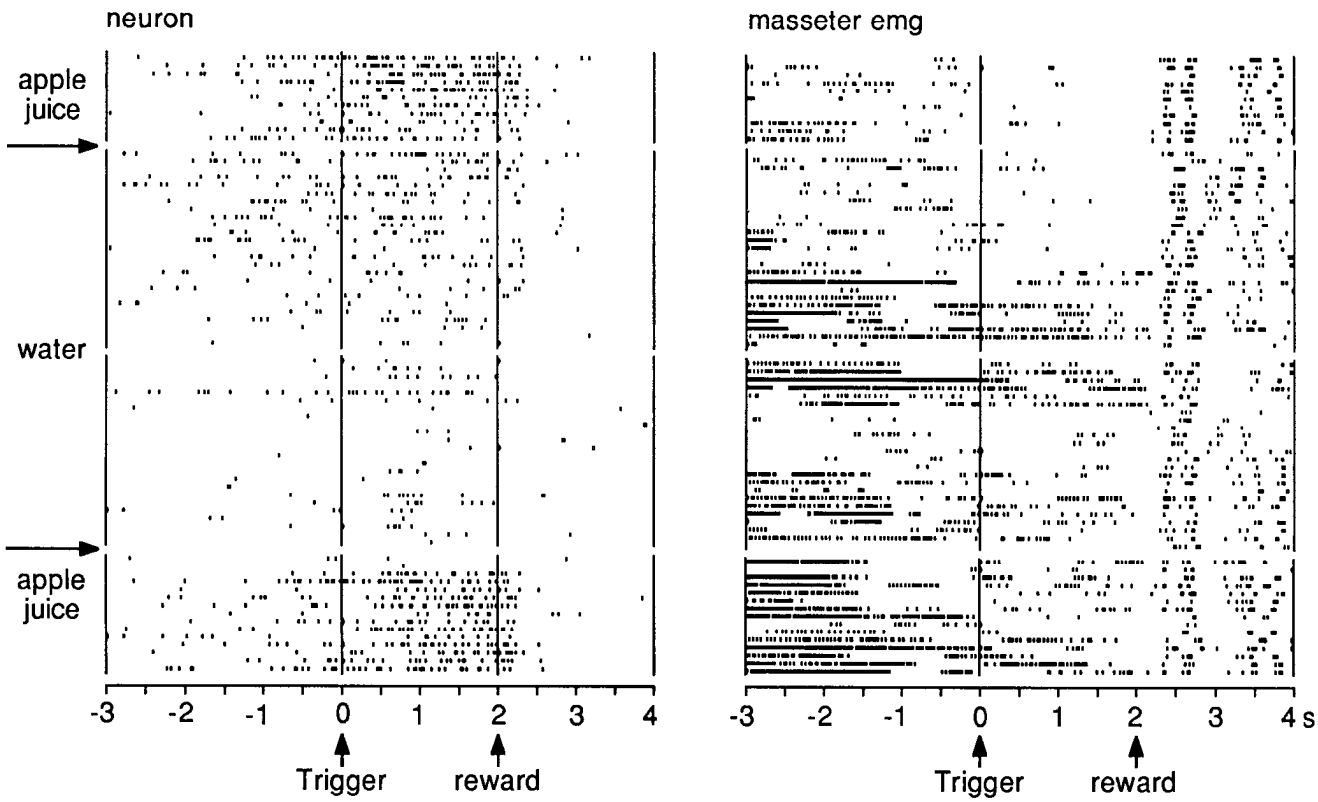

Figure 13. Influence of different reward liquids on activation preceding reward in a ventral striatal neuron. The change from the regularly used apple juice to plain water (*upper arrow*) reduced activation over successive trials. Reinstatement of apple juice (*lower arrow*) led to reappearance of activation within two trials. Original sequence of trials is shown from top to bottom. The change in neuronal activation was unrelated to mouth muscle activity (*right*).

oral activity (Huang et al., 1989; Murray et al., 1991). Since our experimental plan required functioning implanted electrodes during the entire 6–8 months, we chose this large and solid muscle for recording. Recordings from both masseter activity and licks revealed that mouth movements occurred before and after the delivery of reward and showed spontaneous variations during other task periods. This was not unexpected since mouth movements were not a part of the task contingencies and animals were not restricted in this behavior, in contrast to the arm movements, whose correct execution or withholding was the decisive factor for obtaining reward.

Reward expectation–related neuronal activity occurred immediately before reward, predominantly during the trigger–reward interval. Since masseter activity and licks were also observed during this period, this neuronal activity might simply reflect the mouth movements. However, mouth movements were also observed during other task periods during which reward expectation–related activity did not occur. In particular, reward expectation–related neuronal activity subsided immediately after the reward, whereas mouth movements became maximal at this moment. Neurons were presently recorded in a striatal region that was situated rostrally and ventromedially from the known face region of putamen (Künzle, 1975; Crutcher and DeLong, 1984). Electrophysiological characteristics provide a fairly good separation between these regions, despite the absence of strict anatomical boundaries. Mouth movement–related activity occurring predominantly *after* reward reception and coinciding with peaks of masseter activity and mouth movements was found in the dorsally and caudally adjoining regions of putamen (Apicella et al., 1991b) but not in the presently explored regions of ventral striatum. Its temporal profile clearly contrasted with that of the present reward expectation–related activity occurring *before* the reward.

Whereas the presently observed activity was very unlikely related to the execution of mouth movements, it is more difficult to state to which particular aspect of reward delivery the activity

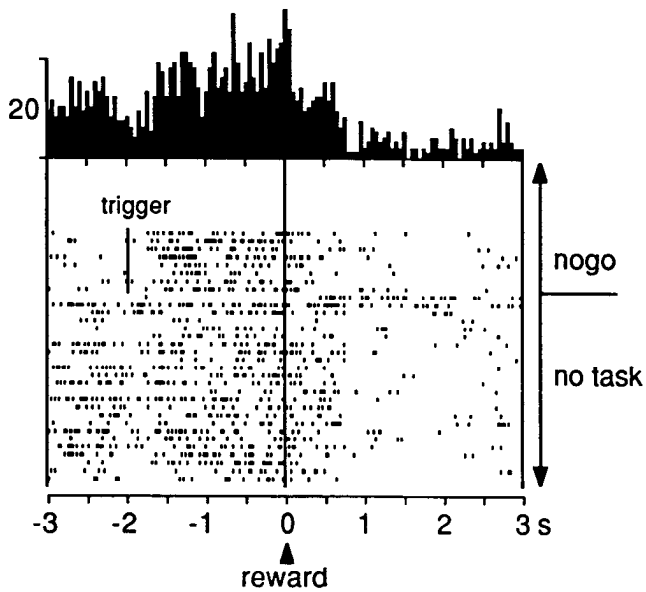

Figure 14. Maintained prereward activation when reward was delivered outside of a behavioral task. Activation preceding reward in no-go trials of task is shown on *top* (trigger onset marked by *vertical line*). Outside of the task, reward was delivered at regular intervals of 8 sec (*no task*).

could be related. Task performance was not contingent upon mouth movements performed at a particular time. These movements occurred in a rather loosely structured manner unlikely to be prepared by the animal during specific task periods. This makes a neuronal relationship to the preparation of mouth movement rather unlikely. Also, such neuronal activity should occur independently of the reward liquids used, which was not the case in the limited number of neurons tested. On the other hand, the prediction of reward delivery should induce an expectation of the particular taste of the liquid and prepare the animal to ingest the reward. A relationship to the taste or hedonic value of the reward liquid is suggested by the decreased expectation-related activity when water was used instead of apple juice. Other tests showed that reward expectation–related activity was obviously not related to visual fixation, saccadic eye movements, or the solenoid noise closely associated with reward delivery. Taken together, these arguments suggest that the observed activity should predominantly reflect motivational factors associated with expected reward delivery.

Definition of ventral striatum

The present study investigated the ventral striatum as the primary striatal recipient of afferents from the limbic system. Earlier studies have largely confined the limbic territory of the striatum to the nucleus accumbens, which in the rat can be anatomically delineated from the dorsal striatum (Heimer and Wilson, 1975). However, recent investigations showed that limbic input to the striatum of the rat and cat is not completely restricted to the nucleus accumbens and reaches the most ventral and medial parts of the rest of the striatum, which could also be included in the ventral striatum (Groenewegen et al., 1982, 1987; Heimer et al., 1982; Kelley et al., 1982). This ventral striatum in the rat does not show strict anatomical boundaries against the dorsal striatum, despite the existing cytoarchitectonic, histochemical, and hodological variations (Groenewegen et al., 1982; Heimer et al., 1991). In analogy, limbic input to the primate striatum is not restricted to the nucleus accumbens, which in addition lacks a distinctive anatomical border against the striatum proper (Russchen et al., 1985; Haber et al., 1990). In the monkey, the amygdala projects to ventral parts of the head of caudate, ventromedial anterior putamen, and nucleus accumbens, and some fibers from this structure even reach the rostral dorsal putamen and ventral parts of the body and tail of caudate (Nauta, 1961; Parent et al., 1983; Russchen et al., 1985). Orbitofrontal cortex and anterior cingulate cortex project to the very rostral parts of caudate, to ventral parts of anterior caudate and putamen, to ventral parts of the body and tail of caudate (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985; Arikuni and Kubota, 1986), and to small dorsal rims of caudate and putamen (Baleydier and Mauguière, 1980). Thus, the ventral striatum is heavily and commonly innervated by these cortical and subcortical limbic areas, although limbic inputs are to a lesser extent also directed to more dorsal and posterior striatal territories. This makes the ventral striatum, as defined in Figure 1, the predominant albeit not exclusive striatal territory with limbic input, thereby refuting a strict dichotomy of associational dorsal and motivational ventral striatum.

Reward and ventral striatum

Neurons in the dorsal caudate and putamen show sustained increases in activity during the expectation of predictable task events, including reward (Hikosaka et al., 1989; Alexander and Crutcher, 1990; Apicella et al., 1992), and the present study revealed similar activations in the ventral striatum. However, expectation-related activity in the ventral striatum was mainly related to reward, whereas only few neurons were activated before other task events, such as instruction or trigger stimuli. This preponderance changed little when the borders between dorsal and ventral striatum were drawn at slightly different levels. Placing the border 1 mm more ventrally left the fraction of reward expectation–related neurons unchanged, while placing it 1 mm more dorsally and extending it up to 1 mm posterior to the anterior commissure slightly reduced it by $<10\%$.

Less neurons with reward expectation–related activity were found in the nucleus accumbens, as compared to the rest of the ventral striatum (8 of 117, 7%, vs. 35 of 303, 12%). By contrast, about equal fractions of neurons in these two ventral striatal areas responded to the reception of reward (12% vs 11%; Apicella et al., 1991b). This may suggest a slight gradient in reward relationships between these two striatal regions, the ventral striatal region surrounding the nucleus accumbens being more active during the expectation of reward than the medially located accumbens, whereas both regions would be informed about the obtainment of reward. It is possible that neurons in the nucleus accumbens are predominantly influenced by the amgydala, where responses to reward have been found (Nishijo et al., 1988), but expectation-related activity has not yet been described. In fact, Alheid and Heimer (1988) have suggested that the most medial part of the ventral striatum might constitute a rostral component of the "extended amygdala." Further experimentation should reveal if this functional gradient also holds when other reward contingencies are used.

Neuronal activity related to the expectation of reward may be induced in the ventral striatum by a convergence of information concerning predictable external stimuli and events of motivational significance. Activity related to the expectation of external signals may be conveyed to the striatum by frontal cortical areas. In go–no-go tasks, neurons in monkey prefrontal cortex show activations similar to the present ones preceding reward in both go and no-go trials (Watanabe, 1986), which were also closely related to variations in the temporal occurrence of reward (Komatsu, 1982). Neurons in the orbitofrontal and anterior cingulate cortex are activated during delays in delayed response tasks (Niki and Wanatabe, 1976; Rosenkilde et al., 1981). A particular motivational component in reward expectation could be mediated by cortical and subcortical limbic areas projecting to striatum. Neurons in orbitofrontal cortex are selectively activated *after* the presentation of primary reward or conditioned stimuli associated with reward (Thorpe et al., 1983). Responses to external stimuli in neurons of the amygdala are modulated according to the affective significance of stimuli (Nishijo et al., 1988). Whereas these studies separately demonstrate neurophysiological correlates for the processing of affective events and the preparation of subsequent reactions, none of these limbic structures to our knowledge were investigated in tasks with a specific period of reward expectation similar to the one used presently. Thus, available data on limbic structures presently do not allow a more precise assessment of the route by which reward expectation–related activity could enter the striatum or develop in loops involving the striatum.

The present study demonstrates activity occurring *before* the expected delivery of reward. Thus, the ventral striatum is informed about the subsequent occurrence of reward during behavioral sequences. This activity constitutes a part of the in-

volvement of ventral striatum in different motivational components of behavior. We previously showed that ventral striatal neurons are activated *after* the delivery of reward and thus are informed that reward has been received (Apicella et al., 1991b). The ventral striatum receives dopaminergic afferents from areas A9 and A10. Dopamine neurons of both areas respond to primary reward during learning or in the absence of predictive stimuli, and to conditioned stimuli predicting reward in an established behavioral sequence (Romo and Schultz, 1990; Schultz and Romo, 1990; Ljungberg et al., 1992). Thus, ventral striatal neurons have direct access to information about the imminent or past delivery of primary reward and are influenced by dopamine neurons driven by main reward-related stimuli.

An intrinsically neutral stimulus that through the prior experience of the animal predicts a subsequent signal or reward sets a state of expectation by evoking a central representation of this event (Bindra, 1968; Dickinson, 1980; Fibiger and Phillips, 1986). Recent cognitive theories suggest that learning occurs through the development of central representations of the important events of a given behavioral sequence, including the representation of the occurrence of reward (Dickinson, 1980). The fact that neurons are activated *before* the occurrence of predictable environmental events may suggest that striatal neurons have access to central representations of these events. Neuronal activations possibly reflecting these representations do not concern an entire behavioral sequence but individual events. It could be that sustained neuronal activity develops when a signal evokes the representation of a specific subsequent event, for example, the trigger stimulus evoking the representation of reward. The activity continues or even increases until the expected event occurs and drops immediately thereafter. Neurons in dorsal striatum have access to representations of several task events, such as instruction stimuli, trigger stimuli, behavioral responses, and reward (Hikosaka et al., 1989; Alexander and Crutcher, 1990; Apicella et al., 1992). Representations involving ventral striatal neurons appear to concern predominantly the occurrence of reward. Thus, the striatum may receive information about predictable environmental events from association cortex, information about reward reception from subcortical limbic structures, and information about the presence of salient, incentive stimuli from dopamine neurons. Through its predominant processing of reward-related information, the ventral striatum could contribute important motivational aspects to the development of behavioral output during learning and be involved in maintaining established behavioral reactions.

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