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Tonically discharging putamen neurons exhibit set-dependent responses

(striatum/globus pallidus/basal ganglia/conditioned stimulus/cholinergic neurons)

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ABSTRACT **Previous microelectrode recordings in the putamen of monkeys have revealed a class of tonically active neurons without apparent behavioral correlates. The present study shows that such neurons have responses to stimuli that trigger movement but that these responses disappear when motor responses to the stimuli are extinguished. The short latency of the responses (less than for other putamen neurons) suggests that they may play a role in linking conditioned stimuli and responses.**

The putamen is an input stage for a group of interconnected subcortical neuronal aggregates collectively referred to as the basal ganglia. It receives inputs from the cerebral cortex and thalamus, is reciprocally connected with the substantia nigra pars compacta, and projects to the globus pallidus, a basal ganglia output stage. Microelectrode recordings in monkeys have shown that relatively few putamen neurons have tonic spontaneous discharge in the absence of movement; the more numerous putamen neurons that are phasically related to voluntary movement do not exhibit tonic activity in the absence of movement and, conversely, the tonically active neurons do not appear to be related to movement (1).

The present study confirms the finding that tonic putamen neurons are unrelated to body movements *per se*, but it reveals that under certain circumstances they may exhibit highly reliable responses to external events. It was found that an auditory stimulus can elicit short-latency responses in tonic putamen neurons when the stimulus is a cue for juice delivery and consumption, but that such a stimulus fails to elicit responses when juice delivery has repeatedly failed to follow the sound, with the result that the sound no longer triggers movements associated with consuming the juice.

MATERIALS AND METHODS

Two monkeys (*Macaca mulatta*) made repeated self-paced extension–flexion movements of the elbow for a juice reward that was delivered after eight movement cycles. The delivery of the reward was preceded by the click of a solenoid valve, which came to be a trigger for movements to consume the juice. Extracellular microelectrode recordings in the putamen yielded a number of tonic neurons that were unrelated to body movements and that had action potentials of greater duration (mean ± SD, 1.2 ± 0.2 msec) than action potentials of the more numerous putamen cells (0.9 ± 0.1 msec) that were silent except during movement. On casual inspection, these tonic neurons did not appear to be related to any aspect of the behavioral situation, but in raster displays aligned on the occurrence of the solenoid click that signaled reward (Fig. 1*A*), it was apparent that there was a greatly increased probability of impulse occurrence ≈60 msec after the click. This observation led to an examination of tonic neuron responsiveness in three behavioral conditions: (*i*) self-paced movement, as already described, in which a series of elbow movements resulted in a solenoid click and a juice reward; (*ii*) free reward, in which click and juice occurred at regular intervals (every 6 sec) with arm position fixed; (*iii*) no reward, which was similar to free reward except that the tube conveying the juice was occluded so that the solenoid click was no longer followed by juice. The paradigm involved a sequence of 40 consecutive rewards during self-paced movement followed by 40 consecutive free rewards. Then, without altering the tempo of 6-sec intervals between solenoid clicks as these clicks had occurred during free reward, the no-reward sequence of 40 clicks without juice was started. The monkeys reacted to the first few unrewarded clicks following the long sequence of 80 rewarded clicks with the motor responses (head torque and sublingual EMG) that would have been appropriate for consuming the juice, but these motor responses quickly disappeared as the series of 40 consecutive unrewarded solenoid clicks proceeded. It should be noted that the monkeys had had much experience with these three sequences, and they had learned that the first unrewarded click signaled many more to come. During the experiment, there were recordings of arm position and velocity, licking movements (detected by strain gauges attached to the shaft of the spout that was licked to consume reward), head torque (detected by strain gauges), and EMGs from sublingual muscles. Conventional extracellular microelectrode recording and behavioral conditioning techniques were used.

RESULTS

Fig. 1*A* shows the responses of a tonic putamen neuron in the three behavioral conditions. There was no apparent difference between solenoid-evoked activity in self-paced movement versus free reward, showing that the presence or absence of arm movements prior to the solenoid click made little difference in the tonic neuron response.

One hundred seventy-four putamen cells with tonic discharge similar to that of the neuron shown in Fig. 1*A* were studied, and 63% of these cells exhibited characteristic responses to the solenoid click preceding the juice reward, although they lacked any apparent relation to arm or licking movements. Typically, the solenoid click was followed by one impulse with a latency of about 60 msec, and this single impulse was followed by a slightly lengthened interspike interval prior to resumption of spontaneous activity. Although related to the set of the monkey to consume the reward, the responses in the tonic neurons were not related to licking movements *per se*. Fig. 1*B* shows typical movement-related neurons that had bursts of discharge with each of the series

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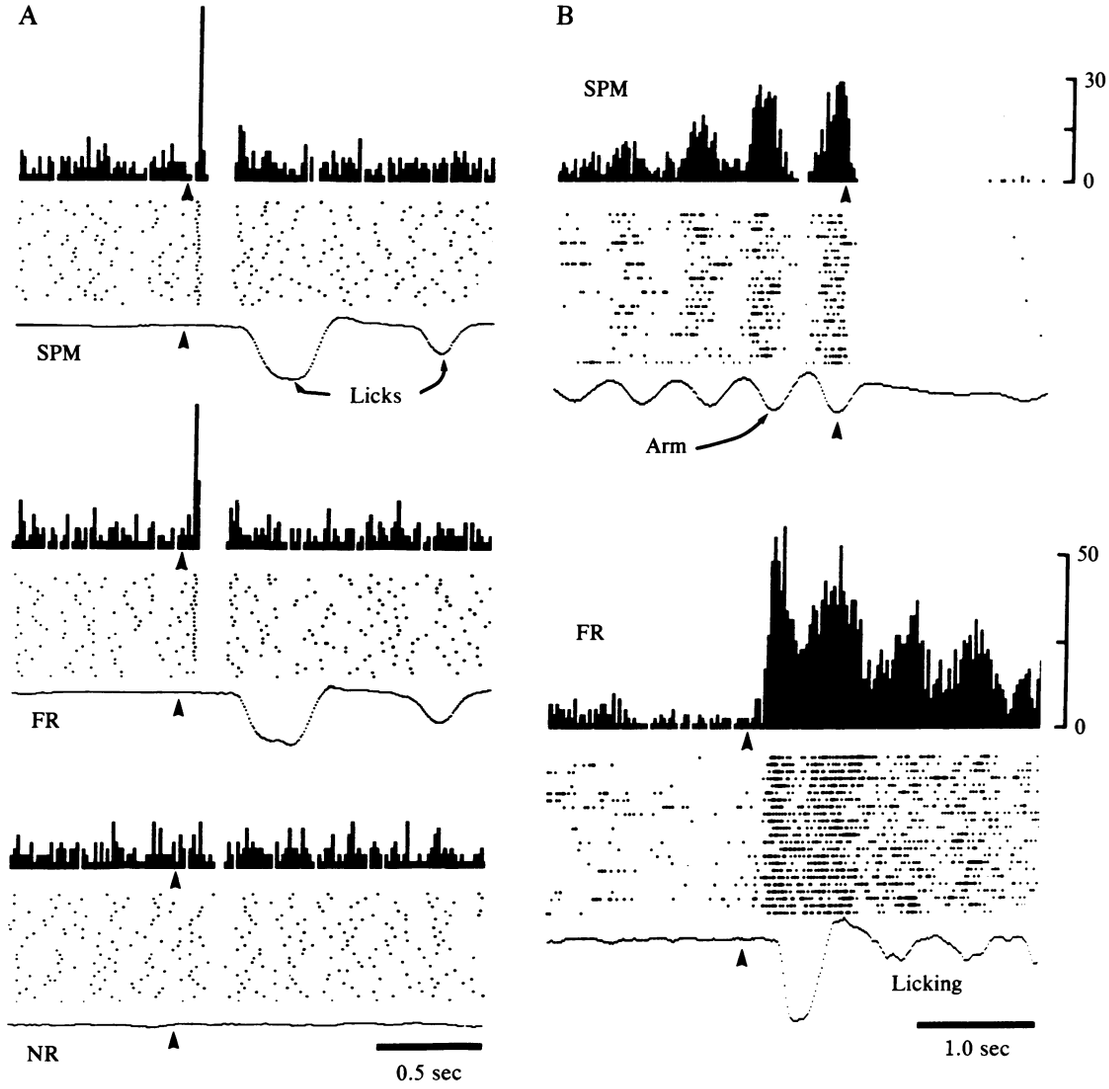

FIG. 1. Tonic and phasic putamen neurons. (*A*) Single impulses (represented by dots) were evoked in tonic neurons by each solenoid click (at arrow) when clicks triggered licks during self-paced movement (SPM) and free-reward (FR), but not during the no-reward (NR) phase of the paradigm, when motor responses failed to be elicited after solenoid clicks. (*B*) A second category of putamen neurons was for the most part silent during lack of movement but discharged with movements of a particular body part, as shown by intense activity with arm movements (*Upper*) and licking (*Lower*).

of self-paced arm movements or licking movements. In contrast, the tonic neurons responded to the solenoid clicks with single impulses well in advance of the first in the sequence of licking movements, and they showed no apparent relation to the subsequent successive licks.

Tonically discharging putamen cells with set-dependent responses were observed at a number of loci within the putamen, but they did not appear to be clustered in any particular somatotopic locus (e.g., orofacial, arm, or leg, as revealed by movement-related putamen cells that were silent at rest and phasically active with movement of a particular body part). Fig. 2*A* illustrates the responses evoked in eight tonic cells in a single penetration in putamen, and shows that single impulses evoked in tonic cells about 60 msec after occurrence of the solenoid click were highly synchronous along this track.

Neuronal activity in the globus pallidus was recorded in the same three click–reward contingencies, and set-dependent click responses were observed in a number of globus pallidus neurons. The globus pallidus cell illustrated in Fig. 2*B* exhibited a pause of activity in response to rewarded clicks, but this pause disappeared soon after the no-reward sequence started. Sixty globus pallidus cells showed set-dependent click responses; 39 were decreases of discharge, as shown for the cell in Fig. 2*B*, while 21 were increases of discharge.

DISCUSSION

The set-dependent responses described above have certain features in common with those seen by other investigators. Neurons in the head of the caudate nucleus respond to auditory and visual stimuli when these stimuli are used by monkeys as cues for subsequent behavior but not when these stimuli lack bahavioral significance (2). The report on caudate neurons does not specifically refer to tonic caudate neurons, but none of the raster displays in the report shows tonic discharge, and the responses depicted in these rasters involve bursts of discharge rather than single impulses. Behaviorally contingent responses have also been described in substantia nigra pars reticulata. Substantia nigra pars reticulata, like globus pallidus internal segment, is an output division of the basal ganglia, and it has been found that substantia nigra pars reticulata cells identified as projecting to the superior colliculus have memory-contingent relations to

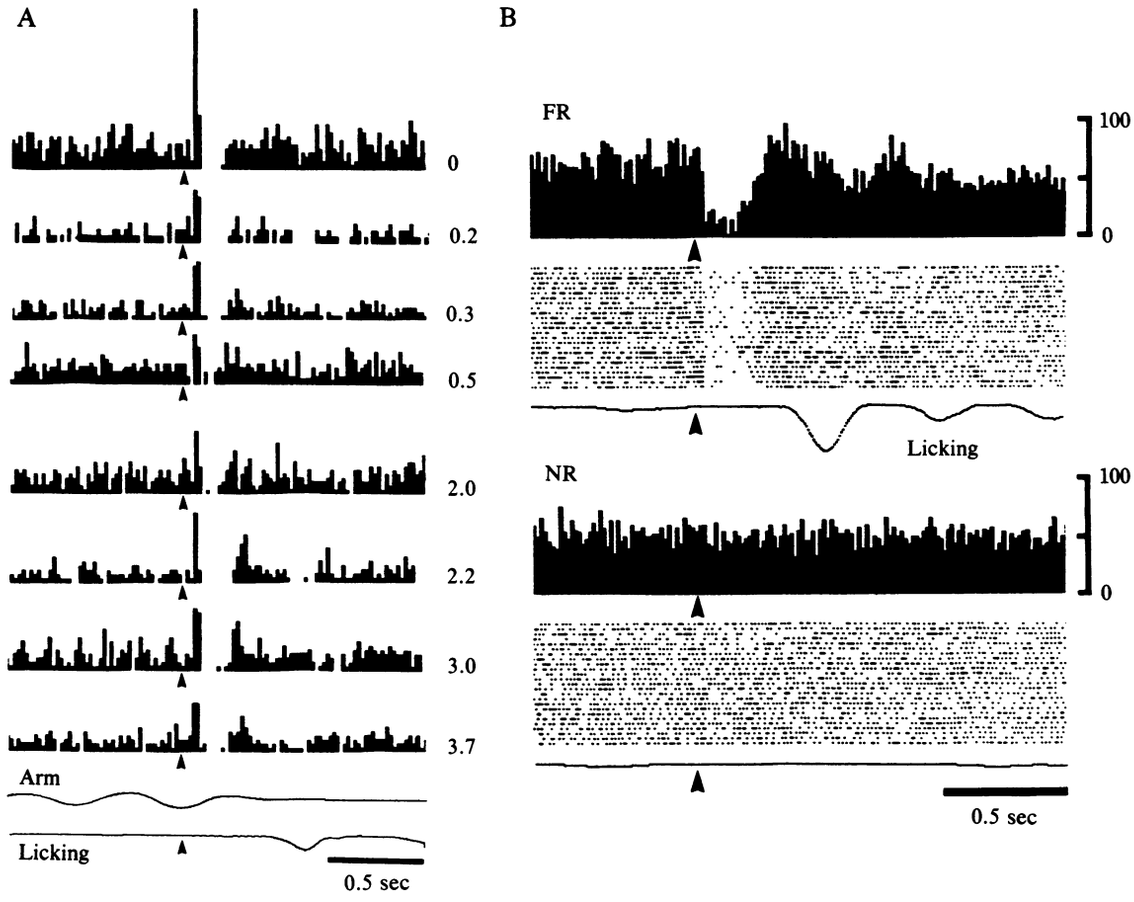

FIG. 2. Set-dependent responses in putamen and globus pallidus. (*A*) Event-related responses in eight successive tonic putamen neurons (recorded in a single microelectrode penetration) when click (at arrow) was followed by juice in free reward. Numbers at right of histograms correspond to separations (in mm) between locations of successive neurons in the penetration. (*B*) Click-evoked pause of globus pallidus discharge occurred during free reward (FR) prior to licking but was absent during no reward (NR), when licking movements failed to follow the click.

saccadic eye movements (3). This finding was obtained in a paradigm requiring the monkey to remember the location of a stimulus that was presented briefly, while the monkey was fixating a different stimulus; a later saccade was rewarded if it was made to the position of the no-longer-present stimulus. Substantia nigra pars reticulata responses revealed by the use of this paradigm were commonly undetectable when the monkey made a saccade to a stimulus that was still present. None of these cells showed a change in activity in relation to spontaneous saccades in darkness. The responses of these cells, like the responses of many of the set-dependent cells that we observed in the globus pallidus, involved a pause of discharge.

Putamen cells fall into several major histological categories (4, 5). The predominant cell (type I spiny) may account for ≈90% of the neurons, but estimates of percentages are uncertain because they are dependent on Golgi preparations in which only a small proportion of cells is visualized. Data are not available as to the discharge properties of identified type I spiny cells during behavior, but because they are so numerous and because they are the projection neurons that send axons to the globus pallidus and substantia nigra, it is commonly assumed that putamen cells that are silent during motor quiescence and that are phasically related to movement are the type I spiny cells. Given the different spontaneous activity patterns, the different relations to behavior, and the longer duration action potentials of the tonic putamen neurons, one may hypothesize that they are not type I spiny cells. Type II aspiny cells are the largest neurons in the putamen (6) and, for this reason, have a fairly good chance of being sampled in extracellular microelectrode recordings in spite of making up only ≈1% of putamen cells. Another category, the type II spiny cells, may be almost as large as the type II aspiny cells, but the number of large type II spiny cells may be only 1/10th the number of large type II aspiny cells. On the basis of their size and number, the type II aspiny cells would seem to be a possible source of the tonic putamen discharges that have been recorded, but it should be emphasized there is as yet no direct evidence on this point.

The classifications considered in the previous paragraph were based on the Golgi technique. Putamen cells may also be classified on the basis of neurotransmitters. The type I spiny cells are thought to be γ-aminobutyric acid (GABA)ergic (7–9) and the type II spiny cells contain substance P (10–12). The largest cells in the putamen (type II aspiny) stain for acetylcholinesterase, and recent studies using an antibody to choline acetyltransferase have shown that choline acetyltransferase-positive neurons are large, with few dendrites and few spines (13). Noting that the frequency of choline acetyltransferase-staining neurons in the striatum matches the frequency of acetylcholinesterase-intense neurons, Fibiger (14) has pointed out that this correspondence supports the view that the large type II aspiny neurons, accounting for ≈1% of all striatal neurons, are the cholinergic interneurons of the striatum.

Looking at the single impulses evoked in tonic cells in Fig. 1*A*, and contrasting these single inpulses with the intense

movement-related activity of the phasic cells in Fig. 1*B*, one might be inclined to minimize the functionl significance of the responses evoked in the tonic putamen cells. There is, however, a very important class of basal ganglia neurons containing small numbers of tonically active cells that lack phasic relations to movement: the dopaminergic neurons in the substantia nigra pars compacta of moving monkeys are tonically active and lack phasic relations to movement (15). By analogy, the tonic putamen cells, whose activity is described in this report, might have great significance in spite of their small numbers and infrequent impulses. It is clear that a high priority in further work on the putamen will be the definitive neurochemical and anatomical identification of the tonic putamen neurons with set-dependent event-related responses.

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