Brain Research, 522 (1990) 147–151
Elsevier

BRES 24150

Delay, discriminatory, and modality specific neurons in striatum and pallidum during short-term memory tasks

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(Accepted 13 March 1990)

Key words: Putamen; Pallidum; Striatum; Basal ganglia; Motor; Parkinson's disease; Delayed match to sample task

The function of the striatum and its integrative capacities is addressed. The activity of single neurons in behaving *Macaca mulatta* is studied. Two new classes of neurons were found. In the striatum, but not in the pallidum, these neurons were visual modality specific. These neurons may represent a conjunction of sensory, mnemonic and motor information, and may be concerned with decisions about the emission or withholding of movements. The frontal dysfunction hypothesis of cognitive deficits in Parkinson's disease is considered.

The precise functions of the striopallidal complex are not well understood[14]. Lesion studies demonstrate that damage to the striatum, the pallidum, and structures with which they are intimately connected such as the subthalamic body, can lead to motor deficits. Studies of the activity of single cells in the striatum and pallidum have revealed a complex array of neuronal activity including responses related to movements being made or about to be made by the animal, to sensory stimuli and to environmental events of behavioural significance (e.g. refs. 7, 23). Striatal function often is closely related to the area from which it receives[22]. On one hand, the striatum has been divided into functional regions[3,23], and on the other it has been described as an integrative net in view of the extensive anatomical convergence which occurs in the striato-nigral and striato-pallidal projections[20]. Although these two views are not contrary they must be reconciled. Two questions arise. First, although the putamen usually is described as a motor structure, compared with the caudate nucleus which is ascribed cognitive-like functions, some evidence suggests otherwise[2,27]. What cognitive-like activity occurs in the putamen and does it occur within anatomically defined areas which receive from association and executive areas of the neocortex? Second, the convergence of inputs from the striatum to the pallidum suggests that further integration of information could occur beyond the striatum in the pallidum. Is there any evidence of this? A third question is: what might be the purpose of integration?

The activity of 621 neurons in *Macaca mulatta* striatum and pallidum were studied. Standard single unit recording techniques for unanaesthetised and behaving animals were used[22]. Several complex tasks were employed, the primary tasks being a visual (visual discriminanda) and an auditory (auditory discriminanda) version of the delayed match to sample (DMS) task. Visual stimuli consisted of digitised pictures and geometric shapes and were presented on a video monitor. Auditory stimuli consisted of pure tones or white noise. In the DMS task, a sample stimulus is presented which is followed by a delay after which another stimulus (the test stimulus) is presented. The animal is seated in a primate chair with a lick tube positioned near his mouth. If the test is the same as the sample (a match) then a lick will cause fruit juice (positive reinforcer) to be ejected into the animal's mouth. A lick at any other time produces aversive hypertonic saline. A number of other tasks including a serial recognition task, serial discrimination task[22,23], and a general tactile/motor task were employed and served to control for neural responses connected with attention, movement, the reward, and stimulus-reinforcement memory. The probability of reward over a series of trials was 0.5. An error rate of <5% was required on all tasks before experiments began. Neuronal activity was stored on a Microvax II as spike arrival times and analysed on- and off-line. Spike density functions (SDFs) were derived to describe neuronal activity[21]. Latency was ascertained either by inspecting the cumulative sum distribution[18,29] or on a trial by trial basis using the gamma maximum likelihood technique[28]. Individual units were localised by

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mapping X-radiographs showing electrode location in the brain onto coronal slices following the termination of the experiment.

Two main classes of cells were found in the striatum which have not previously been reported. The response to the visual DMS task is described.

T-units. Figs. A_1 and A_2 show a typical example of a T-unit located in the putamen. This neuron did not respond on non-match trials; on match trials it responded with a large and brief burst of firing following the onset of the test stimulus. The unit did not respond to the sample stimulus. Thus, this unit responded differentially to the test stimulus depending on whether it was the same or different from the sample stimulus. 11.0% of the 621 neurons studied responded in some way to the test stimulus according to whether it was the same or different from the sample; these units never responded to the sample stimulus. 16% responded only on non-match trials (test different from sample), 43% only on match trials, and 41% to the test stimulus irrespective of it being the same or different from the sample. Units which differentiated matching stimuli typically had a very large and brief burst (median duration 330 ms) of activity immediately following test onset (latency 190 ms). These neuronal responses were not related to the licking since (i) the units did not respond in other tasks in which a lick response was required (e.g., auditory DMS, serial recognition task, visual discrimination task), and (ii) a peri*response* time SDF indicated that the stimulus onset better predicted neuronal activity (compare Figures A.2 and A.3).

D-units. Fig. B shows an example of a D-unit located in the putamen. Note that during the DMS task the neuron increased its activity during the delay between the sample and test stimuli. 9.5% of all units studied responded during the delay period between the successive stimuli. These units showed a distinctive ramped increase in activity following the offset of the sample stimulus. The *off*set of the response was very tightly tied to the onset of the test stimulus (median latency 190 ms) and was not related to the lick response. By examining statistically the change in the *on*set of the response under different conditions of stimulus duration and inter-stimulus interval, it was established that the *on*set of the majority of D-units (70% of those tested) also was related to the impending onset of the test stimulus rather than, for example, to the duration of the delay or the offset of the sample. Unlike T-units, which changed their response immediately following a condition change, the response of D-units typically took several trials to adapt to a new set of conditions.

Several other types of units were found, including units which responded only to the sample but never to the test stimulus (1.5%), and units which responded to both sample and test stimuli (1.0%).

Of 37 tested striatal neurons with activity of one of the types described above in the visual DMS, none responded in the auditory DMS. Thus, the activity of striatal neurons in this region was related to the processing underlying a visual but not an auditory short-term memory task. Given that the visual and auditory tasks are identical, apart from the modality of the input stimuli, this suggests that the activity of these neurons was not related to movements, or to rewards obtained in the tasks, but instead to modality-specific short-term memory-related processing. Further, neurons responsive to the visual DMS typically did not respond to any other task employed. Responses associated with licking, motivation, stimulus-reward association, memory and other factors such as attention could thus be ruled out. It is of interest that no unit responsive in the visual DMS responded in the serial recognition task despite the similarity of these two tasks: both require a stimulus to be remembered for a brief period and for a response to be emitted if a following stimulus is the same as a recently seen stimulus. However, the key differences are: (i) the presence of a warning tone prior to each stimulus in the recognition task, but only prior to each trial in the DMS task; (ii) each stimulus in the recognition task requires both remembrance and a response decision, but in the DMS task the first stimulus need only be remembered, whilst only a response decision is required of the second. In addressing the function of these units one can consider the role of the environmental input (the tone) and the relationship of memory to the response decision (vide infra).

In the recordings made from pallidal neurons it was found that some responded in both visual and auditory versions of the task. Of 37 units responsive in the visual DMS task which were also tested in the auditory version,

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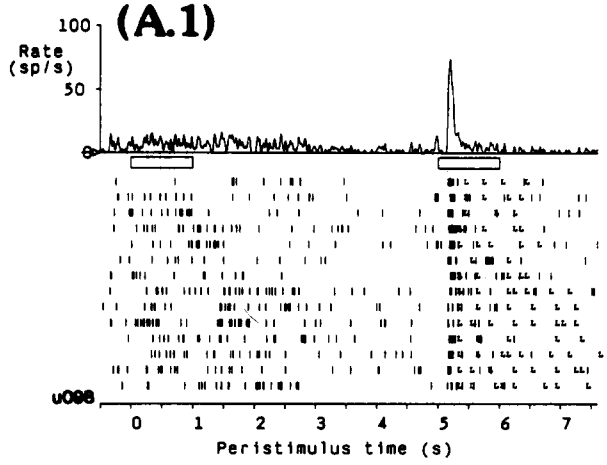
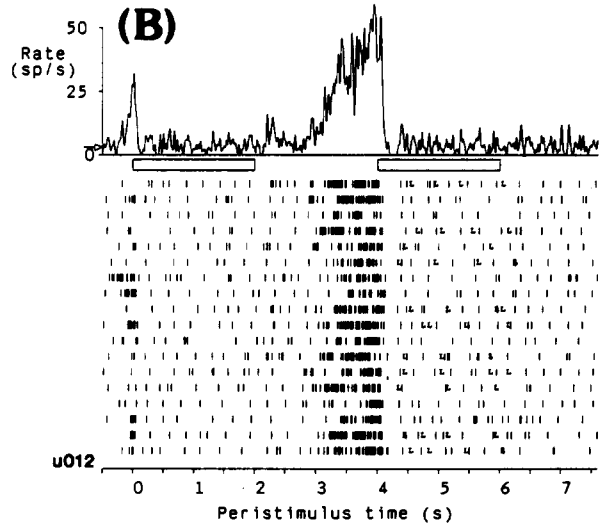
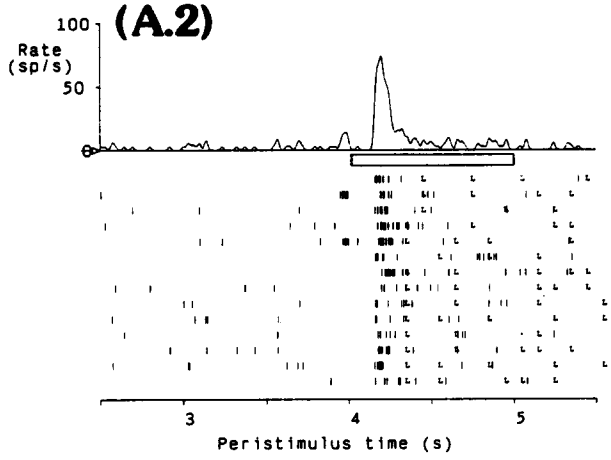
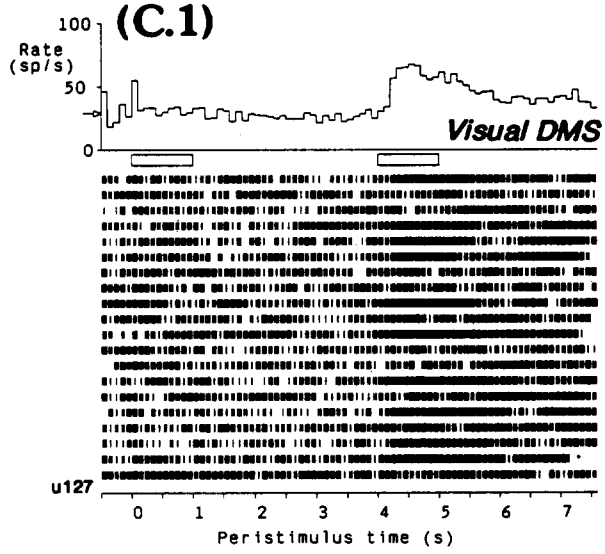
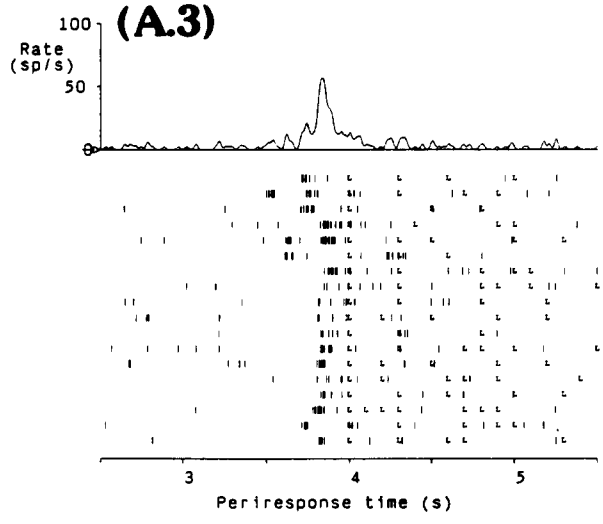
Fig. 1. Peristimulus time spike density functions (SDFs) showing neuronal activity of 3 representative neurons during the visual DMS task. Spontaneous activity is shown by an arrow on the ordinate. A standard deviation of 10 ms was used to generate the SDFs. See ref. 21 for an explanation of the SDF. The rectangles beneath each SDF indicate the timing and duration of the stimuli. L, the occurrence of a lick. A: peristimulus SDF of a T-unit (A_1) which shows a large and brief burst of activity following the onset of match trials only, shown in close up (A_2), and shown as a peri*response* SDF with the responses aligned at 4 s (A_3). B: a D-unit which fires during the delay period of the visual DMS task. C: peristimulus histogram of a neuron which responded similarly during the visual (C_1) and auditory (C_2) versions of the DMS task. Neurons shown in A and B are located in the putamen and did not respond during the auditory DMS task; the neuron in C is located in the pallidum. Note that at the end of some trials C_2 spikes are not shown because of the density of firing.

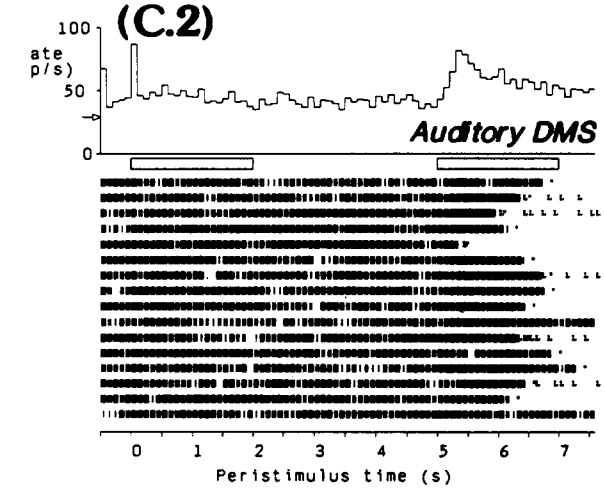

(A.1)
100
Rate
(sp/s)
50
u098
0 1 2 3 4 5 6 7
Peristimulus time (s)


(B)
50
Rate
(sp/s)
25
0
u012
0 1 2 3 4 5 6 7
Peristimulus time (s)


(A.2)
100
Rate
(sp/s)
50
3 4 5
Peristimulus time (s)


(C.1)
100
Rate
(sp/s)
50
0
Visual DMS
u127
0 1 2 3 4 5 6 7
Peristimulus time (s)


(A.3)
100
Rate
(sp/s)
50
3 4 5
Periresponse time (s)


(C.2)
100
ate
p/s)
50
0
Auditory DMS
0 1 2 3 4 5 6 7
Peristimulus time (s)

7 (19%) responded in both versions of the task. Fig. 1C shows the responses of one such pallidal neuron which were similar in the visual (C.1) and auditory (C.2) versions of the task. The finding that some of the pallidal neurons active in the DMS task were not modality-specific, whereas in the striatum only visual modality-specific DMS units were found, suggests that the pallidum may represent a further stage in information processing in which information from different parts of the striatum may be brought together.

The two major classes of striatal cells reported can be described in terms of modified cortical input. The neurons described were located in the posterior 5 mm of the striatum. Within this posterior region there was a tendency for the units in the putamen to be located medially, thus overlapping the termination zones of the inferior temporal and prefrontal projections[20]. Neurons which respond during the delay of a DMS task and other neurons which discriminate recently seen visual stimuli from novel stimuli are found in the frontal[8,9] and temporal cortices[4,10]. These authors suggested that in the neocortex, these responses reflect or represent temporary stores of the information to be remembered. The D-units reported here are not so easily described: (i) it takes several trials to settle into a stable response, and if the conditions of delay are varied on a trial to trial basis, the response is erratic and weak — since the animal still performs the task, the units can play at best only a sufficient role in mnemonic processes; (ii) it is hard to reconcile a mnemonic hypothesis with the finding that the onset of the D-unit response is related to the onset of a future event (the onset of the test); (iii) it would seem natural to represent a temporary store of information in a sustained response, as others have found in the neocortex, rather than as a ramped response; (iv) the responses of these neurons were independent of stimulus quality (e.g., colour, shape) so that it is unlikely that these neurons encoded information about the visual quality of the stimulus being remembered (although they may reflect the output of an area which does encode stimulus quality). On the other hand, some units in the supplementary motor area exhibit a response similar to D-units, namely, a ramped increase in activity preceding an about to be made but currently withheld (self-timed) movement[13]. However, the D-units reported here offset sharply on trials where no response occurs, and perire-sponse time SDFs indicate that the offset is related to the onset of the stimulus rather than the response. Similarly, the T-units are not related to the movement per se. Thus, while the activity of these striatal neurons reflect the output of cortical areas involved in visual short-term memory or the generation of self-timed movements, their activity is not merely an efference copy of cortical activity. It is suggested that D- and T-units are well suited to processes associated with decision making regarding impending movements. Signals from the cortex may specify (for D-units) 'the end of the delay period is approaching', on the basis of which the striatum might become involved in preparing the behavioural response of licking; or (for T-units) 'visual match detected', on the basis of which the striatum might become involved in initiating a lick response, or, 'visual non-match detected', on the basis of which the striatum might become involved in withholding a lick response. Units such as these could be described as being neither purely motor, sensory nor mnemonic, but may represent conjunctions of these functions. Such a conjunction would be desirable since motor and sensory information must at some time be brought together for the production of coherent, successful and environmentally oriented behaviour. Sensory, mnemonic, and motor systems must be fundamentally different; for example, one can see both red and blue at the same time, but one cannot both raise and lower the right arm at the same time. Thus, both suppression and facilitation of competing sensory-mnemonic information clearly is necessary, as is the translation of sensory-mnemonic information into motor commands. The striato-pallidal complex is anatomically well placed to subserve such roles in view of its major inputs being from sensory, memory, and motor areas of cortex, in view of its position within the basal ganglia (especially within the cortico-strio-thalamo-cortical loop), and in view of the converging efferents from the striatum and the lateral inhibitory network within the striatum[12,20]. Information from different modalities may come together to bear upon motoric processes, perhaps for the first time, in the basal ganglia.

Parkinson's disease and Huntington's chorea involve damage to striatal structures and involve motor deficits. Neuropsychological studies reveal deficits also of a cognitive nature (e.g. refs. 15, 25). An estimated 10–30% of Parkinsonian patients suffer from dementia-like deficits[5,17]. It has been argued that a frontal dysfunction underlies the cognitive deficits observed in Parkinson's disease (e.g. refs. 11,19,24,25). However, (i) it is difficult neuropsychologically to disentangle a frontal dysfunction from a striatal dysfunction, and (ii) the frontal neuro-chemical depletions are much smaller than those in the striatum (e.g., 20% loss in the dopamine projection to the prefrontal cortex compared with 95% loss in the putamen and 80–85% loss in the caudate nucleus[1]), and may be overcome by mechanisms such as supersensitivity and increased turnover[11,26]. It is suggested that recourse to the frontal dysfunction hypothesis may be premature. Striatal damage may produce cognitive deficits, for example, by frustrating the access of cognitive informa-

tion to behavioural output. Thus, it may be possible to relate the unique functions of the striatum to the unique dysfunctions of Parkinsonian patients. For example, the units reported herein respond during the DMS task, but not during the serial recognition task. One relevant difference (vide supra) may be that the presence of an external marker (the warning tone) in the recognition task may obviate the need for any internal monitoring of withheld movements. If the units reported herein were related to such internal monitoring, then one could account for the well-known deficit of Parkinsonians at making movements when visual feedback is removed[6,16]. An hypothesis that some cognitive deficits observed in Parkinson's disease may be ascribed to striatal dysfunction per se deals with a clearly established functional deficit at a neural level, may be more parsimonious, and may be complementary to the frontal dysfunction hypothesis. Certainly, it emphasises the need to investigate further the complexities of basal ganglia function and the nature of the integration occurring in the basal ganglia.

The neuronal activity reported herein offers further evidence for the involvement of the striatum in complex cognitive-behavioural functions. The striatum is likely to be more than merely a relay station of cortical output.

For assistance with this work we thank Peter Cahusac and Diane Staats. This work was supported by the Medical Research Council, the British Council and the Association of Commonwealth Universities.

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