Influence of spatial information on responses of tonically active neurons in the monkey striatum

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Abstract
Previous studies have demonstrated that tonically active neurons (TANs) in the primate striatum play an important role in the detection of rewarding events. However, the influence of the spatial features of stimuli or actions required to obtain reward remains unclear. Here, we examined the activity of TANs in the striatum of monkeys trained to make spatially directed movements elicited by visual stimuli presented ipsilaterally or contralaterally to the moving arm. Among 181 neurons responding to the trigger stimulus, 127 (70%) were nonselective for stimulus location and 54 (30%) responded to only one location of the stimulus. Most of the selective responses (63%) occurred when the stimulus was presented contralaterally to the moving arm. To examine whether TAN responses are related to the location of the stimulus or to the direction of the movement, we tested a subset of the trigger-responsive neurons (n = 44) in a condition that elicited reaching toward or away from the stimulus. By comparing TAN activity between the two conditions, we found that half of the responses can be interpreted as being related to the location of the stimulus, one quarter to the direction of movement, and one quarter to the context in which stimulus-movement combination occurs. These results demonstrate that TANs are not limited to motivational processing, but may play a role in the processing of spatial attributes of stimulus and/or movement as well. These response properties suggest that TANs are involved in the flexible shifting of motor responses during spatially directed behavior.

Key words
basal ganglia, reaching movements, spatial attention, context, single unit recording
**Introduction**

Previous studies have indicated that tonically active neurons (TANs) of the monkey striatum carry information related to the motivational value of stimuli. These neurons respond to conditioned stimuli predictive of reward (Aosaki et al. 1994; Apicella et al. 1991; Kimura et al. 1984) and to primary motivating events (Apicella et al. 1997; Ravel et al. 1999, 2003). However, TANs displaying spatially selective responses to movement-triggering stimuli have been reported in monkeys performing limb-movement (Kimura 1986, 1992) and oculomotor tasks (Shimo and Hikosaka 2001). The selectivity of these neuronal responses in behavioral conditions involving rewarding stimuli for which the motor reaction is different raises the possibility that the network of the TANs might also play a role in the processing of spatial information that is essential for attentional purposes or for the initiation of specific motor acts. The influence of the spatial requirements of the task is therefore an aspect of TAN functioning which would be of particular interest with regard to the role of the striatum in the control of action. However, in the studies reporting spatial selectivity of TAN responses, the selection and guidance of movement direction were confounded with the location of the stimulus that initiated the movement. This implies that the spatially selective responses of TANs might have been related to the motor aspects of the intended movement or the spatial features of the stimulus. It remains to be established whether selectivity for stimulus location reflects the position of the stimulus calling for a movement in a particular direction or the direction of the movement itself.

Until now, there is little evidence that TANs participate in the initiation of movements. These neurons have been implicated in processes relating to stimulus detection, particularly with respect to stimulus whose detection depends on the behavioral context. In caudate nucleus, for example, TAN responses can be contingent on a particular spatial location of a visual stimulus even if no reward is associated with this stimulus (Shimo and Hikosaka 2001). On the basis of these findings it has been suggested that TANs may have a role in the detection of the context in which stimuli and actions occur. According to this view, responses of TANs act to integrate the characteristics of a given behavioral condition to the control of goal-directed behavior. In addition, it has been suggested that TAN responses may also depend on motivational (Yamada et al. 2004) and attentional aspects of task performance (Blazquez et al. 2002). Yamada et al. (2004) found that TANs in the caudate nucleus had contrasting properties in their responses to task stimuli compared with those in the putamen. In particular, the fraction of TANs responding to movement-triggering stimuli was higher in the putamen, possibly reflecting the preferential involvement of this nucleus in motor
function. This indicates that differences in the localization of TANs exhibiting distinct response properties may exist between striatal regions.

In the present study, we recorded TAN activity from the caudate nucleus and putamen in monkeys performing visually triggered reaching movements to spatially distinct targets. We also used a variant of the task that elicited reaching toward or away from the spatial location of the trigger stimulus in order to dissociate the spatial attributes of the stimulus from those of the intended movement. We report that the responsiveness of TANs can be influenced by the spatial features of the task, not just detecting stimuli linked to reward.

Materials and Methods

Animals and apparatus
Three male macaque monkeys (monkeys ENK, TIM, ART; *Macaca fascicularis*), weighing 5-6 kg, were trained to make visually guided arm-reaching movements to obtain a liquid reward. Animal housing and experimental procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the French laws on animal experimentation. The behavioral apparatus was similar to that previously described (Apicella et al. 1997; Sardo et al. 2000). Each monkey was seated in a specially designed restraining box, facing a panel 30 cm from its head (Fig. 1). The panel contained two metal knobs (10 mm x 10 mm) separated by 20 cm horizontally, as well as two light-emitting diodes (LEDs), one above each knob, at eye level of the animal. An unmovable metal bar was mounted at the center of the panel at waist level. Each trial began by keeping the hand on the bar. After a variable period of 0.5-2.0 s, a LED was illuminated with a red light that served as trigger stimulus. In response to this signal, the monkey released the bar and made a movement to contact the knob below the illuminated light in order to receive a liquid reward.

Behavioral procedures
There were two task conditions, termed the « choice » and « dissociated » conditions. In each condition, the signal to move was the illumination of the red LED either on the left or on the right side of the panel, the location of the stimulus varying pseudo-randomly from trial to trial. In the choice condition, the arm movement was directed toward the target corresponding to the location of the trigger stimulus. In the dissociated condition, the monkey is required to contact the target located ipsilaterally to the moving arm whenever the trigger stimulus was presented, regardless of its location. In this latter condition, designed to dissociate the direction of movement from the location of the trigger stimulus, the ipsilateral target was continuously surrounded by a white light to indicate the constant movement direction. The
light indicating the appropriate arm-movement target was turned on at the beginning of the block of dissociated trials and turned off at the end of the block of dissociated trials. This visual signal indicated the rule which defined the dissociated condition, i.e., the mapping between the stimulus location (left or right) and the appropriate motor response (contact the illuminated target). For 50% of the trials, the movement was directed toward the spatial location of the trigger stimulus. For the remaining 50% of the trials, the movement was directed away from the spatial location of the trigger stimulus. The choice and dissociated conditions were conducted in separate blocks of 40-60 trials, the presence or absence of the continuously illuminated target providing an external cue to the monkey as to which of the two task conditions were being administered. In both conditions, monkeys had to release the bar within 1 s of the appearance of the trigger stimulus and touch the target within 1 s of releasing the bar. Trials were presented with an inter-trial interval of 3-6 s. Before the recording experiments started, all three monkeys have been trained on the choice condition until they reached a steady level of performance, performing at better than 95% correct daily, and monkeys ART and TIM have been also trained on the dissociated condition. Monkeys ENK and TIM performed the task with the right arm and monkey ART worked with the left arm.

**Electrophysiological recordings**

On completion of training, animals underwent surgery under sodium pentobarbital anesthesia (Nembutal, 35 mg/kg i.v.) and aseptic conditions. A stainless steel recording chamber (25 mm outer diameter) was implanted on the skull over the left hemisphere. The center of the chamber was aimed at the anterior commissure according to the atlas of Szabo and Cowan (1984). In the same surgery session, two pairs of periorbital silver-silver chloride electrodes were implanted into the brow ridges and temporal bones for recording eye movements, and two stainless steel cylinders were fixed to the skull with surgical screws and dental acrylic for mechanical stabilization of the head during recording sessions. Antibiotics (Ampicillin, 17 mg/kg i. m. every 12 h) were injected on the day of surgery and for 5 days after the surgery. The recording chamber was filled with an antibiotic solution (Flumequil) and sealed with a removable cap.

Single-neuron recordings were performed using tungsten microelectrodes inserted into the striatum through a stainless steel guide tube (0.6 mm outer diameter). A hydraulic microdrive (MO95, Narishige) was used to advance the microelectrode into the striatum. Single-neuron impulses were amplified, filtered with a band-pass of 0.3 to 1.5 kHz, displayed on oscilloscopes and isolated using a window discriminator. The resulting standard digital
pulses were stored on a computer, together with markers of task events. The computer also presented visual stimuli, delivered liquid reward and measured behavioral parameters. Data on spike forms were also stored for off-line analysis of spike duration. We used well-established electrophysiological criteria to identify TANs, such as spontaneous discharge rate and duration of spikes (Kimura et al. 1984; Alexander and DeLong 1985; Hikosaka et al. 1989; Aosaki et al. 1994; Apicella et al. 1997). The characteristics of the recorded neurons were analyzed using a personal computer software developed by E. Legallet. The relationships of neuronal activity were assessed on-line in the form of rasters aligned on the task events. The electrode was advanced until the spikes generated by a single neuron were well isolated. Once a neuron was isolated, we first examined its activity in the choice condition. If the isolation could be adequately maintained for a sufficient period of testing, we changed to the dissociated condition. Each neuron was recorded for a total 40-60 trials in each condition. Neuronal activity was occasionally recorded outside the context of the reaching task, when the liquid was automatically delivered alone once every 5-8 s, the interval between deliveries being randomized so that the time of reward remained unpredictable. This condition, called the « free reward condition », was designed to test the sensitivity of TANs to unexpected primary rewards (Apicella et al. 1997). Horizontal electrooculograms were recorded together with signals from neuronal activity during the behavioral testing and stored to disk as analog signals (sampling frequency : 500 Hz) for off-line analysis.

Data analysis

We calculated reaction time (RT) as the interval between the onset of the trigger stimulus and release of the bar, and movement time (MT) as the interval from the release of the bar until the hand contacted the target. Behavioral performance was assessed by calculating the mean of RT and MT of correct responses for each stimulus location and each session. Quantitative analysis of EOG data was made off-line by single-trial analysis, and involved latencies of saccadic eye movements directed towards trigger stimuli. A Wilcoxon signed rank test was used to statistically analyze any changes in the neuronal activity (Apicella et al. 1997; Sardo et al. 2000). Activity of each neuron after the onset of the trigger stimulus was compared with baseline activity determined during a control period of 500 ms just prior to the trigger presentation. A test window with a duration of 100 ms was moved in 10-ms steps starting at the onset of the trigger stimulus. A neuron was considered as responsive if its mean discharge was significantly different (P < 0.05) from the control period during at least five consecutive steps. The temporal characteristics of the responses of TANs to external stimuli typically included a short lasting depression in activity, as indicated by perivent time histograms and
the slopes of cumulative frequency distributions of neuronal impulses. We have made a number of preliminary tests to determine the most adequate number of successive steps for the detection of this pause response with our sliding window procedure based on the Wilcoxon test. In particular, the procedure allowed us to detect the period of reduced activity independently of the presence of additional response components, i.e., a rebound activation after the pause response or an initial brief increase in firing. We defined the latency of the response as the beginning of the first of the five consecutive steps showing a significant difference as against baseline firing rate calculated during the control period. Response offset was determined in the same way by searching for a loss of significant differences during five steps. The percentages of responses in relation to the total number of neurons tested were calculated for each condition and each stimulus location. Differences in proportions of responding neurons among task conditions and stimulus locations were statistically assessed with the \( \chi^2 \)-test. Response latencies, durations, and magnitudes were compared between stimulus locations with one-way analysis of variance (ANOVA).

**Histology**

Near the end of neuronal data collection, we made electrolytic lesions along 4-6 tracks in each monkey by passing negative currents through the microelectrode (20 µA for 20-30 sec). After the completion of all testing, the monkeys were killed with an overdose of sodium pentobarbital and perfused transcardially with 0.9% saline followed by a fixative (4% paraformaldehyde, pH 7.4 phosphate buffer). Frozen coronal sections (50 µm thick) were cut through the region of the recordings and stained with cresyl violet. Based on the topographic organization of cortical projections, the region of the striatum explored in the present study was divided into two territories: the «sensorimotor» striatum, which predominately includes the posterior portion of the putamen, and the «associative» striatum, which includes mainly the head and body of the caudate nucleus and the anterior portion of the putamen (Parent and Hazrati 1995). Very few neurons were recorded in the so-called «limbic» striatum, which is composed of the nucleus accumbens and adjacent ventromedial caudate and ventral putamen (Haber and McFarland 1999).
Results

Behavior

The monkeys performed the task correctly on at least 95% of the trials in both the choice and dissociated conditions. Table 1 shows the mean RTs and MTs for the three animals. In the choice condition, RTs to stimuli presented contralaterally to the moving arm were longer than RTs to ipsilateral stimuli (Student t test, $P < 0.01$) in monkeys ART and ENK. Although a trend to longer RTs between contralateral and ipsilateral stimuli can be seen in monkey TIM, this difference was not significant ($P > 0.05$). In all three monkeys, movements made in response to stimuli whose location was contralateral to the moving arm were associated with longer MTs than those made in response to ipsilateral stimuli ($P < 0.01$). Monkeys ART and TIM were also tested on the dissociated condition, i.e., the condition in which the direction of the reaching movement remained the same across trials irrespective of whether the trigger stimulus was presented on the side contralateral or ipsilateral to the moving arm. Monkey ART had shorter RTs when the location of the trigger stimulus and the target of movement corresponded in space (compatible trials) than when they did not correspond (incompatible trials) ($P < 0.01$). On the other hand, in monkey TIM, RTs of the compatible trials were in the same range as of the incompatible trials ($P > 0.05$). In both monkeys, MTs of the incompatible trials were not different from MTs of the compatible trials ($P > 0.05$), suggesting that the manipulation of spatial stimulus-response correspondence did not produce a significant effect on the response execution side.

Examples of eye movement patterns recorded in the two task conditions are shown in Figure 2A. In the choice condition, monkeys usually produced saccadic eye movements toward the trigger stimulus, regardless of its location. The same oculomotor behavior was observed in the dissociated condition, but the saccade to the contralateral stimulus was followed by another saccade to the ipsilateral target in the incompatible trials, indicating a redirection of the monkey’s gaze to this target following trigger onset. Figure 2B shows the distribution of the median latencies of saccades in the direction of the trigger stimulus for the two monkeys trained in the choice and dissociated conditions. In monkey ART, saccade latencies were longer (Mann-Whitney U test, $P < 0.01$) when the stimulus was contralateral to the moving arm than when it was ipsilateral, regardless of task condition. In monkey TIM, differences in gaze behavior paralleled those seen in the RT for arm movements, the latency of saccades to the trigger stimulus being about the same, regardless of its location ($P > 0.05$). Also, the frequency of the saccades to the trigger stimulus were similar for each stimulus
location and for the two task conditions and monkeys did not show a tendency to look at a particular target at the start of the trial (data not shown).

Thus, saccade and arm movement latencies were longer when the stimulus appeared on the opposite side to the arm being used compared with when it was on the same side, with the exception of monkey TIM that did not show significant increase in latencies when the stimulus appeared contralaterally to the responding arm. The lack of spatial response bias was presumably attributable to a particular strategy in this monkey, so that RT could become independent of the spatial features of the task. As stated in the Methods, the same training schedules were employed for each monkey in the choice condition before neuronal data collection, suggesting that interindividual variations in task performance could not be attributed to differences in training levels.

Neuronal data

Based on specific electrophysiological characteristics that have been described previously (Alexander and DeLong 1985; Hikosaka et al. 1989; Sardo et al. 2000), we identified 216 neurons as TANs. Baseline firing rates of these neurons ranged from 3 to 18 spikes/s (7.3 ± 2.4, mean ± SD, n = 216). We further confirmed the identification of TANs by observing the changes in neuronal activity while monkeys performed the task. In general, TANs showed a response pattern similar to that reported previously, consisting in a brief, short-latency depression of activity after appearance of the trigger stimulus, which was often followed by a rebound facilitation in firing (Aosaki et al. 1994; Apicella et al. 1997; Kimura et al. 1984). After a first stage of recording from monkeys ENK and ART, new versions of the reaching task were introduced for the purpose of complementary analyses, thus explaining that the number of neurons tested in the choice and/or dissociated conditions in these two animals (monkey ENK, n=23; monkey ART, n=38) was smaller compared with monkey TIM (n=155).

Responses in the choice condition

Among 216 neurons tested in the choice condition, 181 responded to the visual stimulus that elicited arm movements. Of these 181 neurons, 127 (70%) responded to the trigger stimulus regardless of its location and 54 (30%) responded to only one location of the trigger stimulus. Figure 3A is an example of a neuron with a response to the trigger stimulus either when it was presented on the side contralateral or ipsilateral to the moving arm. This type of response was classified as spatially nonselective. In contrast, the neuron whose activity is shown in Figure
3B had a response occurring only for a stimulus presented contralaterally to the moving arm and not for an ipsilateral stimulus. This type of response was classified as spatially selective. Approximately two thirds of the responses that were spatially selective (11/13, 85% in monkey ART; 6/8, 75% in monkey ENK; 17/33, 52% in monkey TIM) were found to occur only when the stimulus was contralateral to the moving arm, the remaining responses (2/13, 15% in monkey ART; 2/8, 25% in monkey ENK; 16/33, 48% in monkey TIM) occurring when the stimulus was ipsilateral.

The interindividual differences in latency of arm and eye movement reactions to trigger stimuli led us to examine the correspondence between response selectivity of TANs and task performance for each monkey. As shown in Figure 4, the fraction of TANs showing selective responses to the contralateral stimulus was significantly higher in monkeys ART ($\chi^2 = 9.53; \text{df} = 1; P < 0.01$) and ENK ($\chi^2 = 3.89; \text{df} = 1; P < 0.05$), as compared with monkey TIM, whereas the proportion of selective responses to the ipsilateral stimulus was similar for all three monkeys ($P > 0.05$). There was significantly more nonselective neurons in monkey TIM than in monkey ART ($\chi^2 = 3.93; \text{df} = 1; P < 0.05$). In monkeys ART and ENK, the spatial preference in terms of TAN responsiveness was obvious when the stimulus was presented contralaterally to the moving arm, the percentage of responses being higher to the contralateral stimulus than to the ipsilateral stimulus. In contrast, in monkey TIM, the proportion of spatially selective responses was not different between the two stimulus locations. It therefore appears that the spatial response bias that was observed behaviorally was paralleled by a spatial preference of TAN responses, a contralateral preference in TAN responses being associated with decreased movement speed for initiating movements in the contralateral direction.

The latencies and durations of the trigger responses are summarized in Table 2 separately for neurons showing selective and nonselective responses to the trigger stimulus. For nonselective responses, no significant differences were observed in the latency and duration of responses between the contralateral and ipsilateral stimulus locations ($P > 0.05$; one-way ANOVA followed by Fisher’s test), and so they were pooled together. The latency of the selective responses to the contralateral stimulus was significantly longer than that of the nonselective responses ($P < 0.05$), while they were similar in both selective responses to the ipsilateral stimulus and nonselective responses ($P > 0.05$). The duration of the selective responses to the contralateral or to the ipsilateral stimulus was significantly shorter than that of the nonselective responses ($P < 0.05$).
Our previous studies demonstrated that TANs are highly responsive to reward given at unpredictable times outside of a task, whereas few TANs respond to reward delivered immediately after correct reaching (Apicella et al. 1997; Ravel et al. 2001). In the present study, responses to the delivery of liquid were seen in all of the 22 neurons tested in the free reward condition, these neurons being also responsive to the trigger stimulus in the reaching task. For example, the neuron for which activity is shown in Figure 5 exhibited a response to the trigger stimulus that was specific for the contralateral location, but did not respond to reward in the reaching task. However, the same neuron gave a clear response to reward given alone outside the task. This indicates that TANs can respond to primary motivating events and to stimuli that predict reward and, in this latter case, may incorporate details concerning the spatial features of the task. It therefore appears that the spatial information was not absolutely required for producing TAN responses but demonstrates an interaction between motivational and spatial aspects. Figure 5 also illustrates eye movements recorded during neuronal data collection. As already mentioned, the direction of saccade covaried with the location of the trigger stimulus in the reaching task. On the other hand, in the free reward condition, the monkey moved his eyes spontaneously and randomly during the inter-reward interval and did not look at any particular location at the time of reward delivery. It therefore appears that TAN responses were not specifically related to eye movements.

Comparison of TAN responses in the choice and dissociated conditions

In order to examine whether responses of TANs to the trigger stimulus are related to the location of the stimulus or to the direction of the associated movement, we used, in monkeys ART and TIM, the dissociated condition which involved constant movements toward the ipsilateral target, regardless of the location of the stimulus. We tested 21 neurons displaying spatially selective responses, all occurring when the stimulus was contralateral to the moving arm (6 in monkey ART, 15 in monkey TIM), and 23 neurons with spatially nonselective responses (9 in monkey ART, 14 in monkey TIM).

When neurons showing spatially selective responses were tested in the dissociated condition, 8 neurons maintained their spatial preference, i.e., they continued to respond to the contralateral stimulus, 8 completely lost their responsiveness, i.e., they became unresponsive to both stimulus locations, 2 reversed their spatial preference, i.e. they became responsive to the ipsilateral stimulus, and 3 lost their spatial preference, i.e., they became responsive to both stimulus locations. Thus, 62% of the spatially selective responses (13 of 21 neurons) were modified when the stimulus location was dissociated from the direction of the movement. An
example of spatially selective response is illustrated in Figure 6A. In both the choice and the dissociated conditions, this neuron showed a response to the trigger stimulus presented contralaterally to the moving arm, suggesting that the neuron’s spatial preference depended on the location of the stimulus rather than the direction of the movement. Another example of a TAN with a selective response is shown in Figure 6B. However, unlike the neuron described before, the spatial selectivity was not maintained when condition was changed, suggesting that the response was specific for the spatial location of the target for reaching rather than being related to the location of the stimulus. In other neurons, changes in spatial selectivity could not be attributed simply to the location of the stimulus or to the direction of the movement. The neuron in Figure 7A, for example, showed a response to the contralateral stimulus in the choice condition and this spatial preference was reversed in the dissociated condition, the neuron becoming responsive to the ipsilateral stimulus. Figure 7B shows an example of a neuron that responded to both stimulus locations when the condition was changed. It therefore appeared that spatial selectivity in TAN response did not depend only on stimulus location or the direction of the movement but also on the particular condition in which the trigger stimulus elicited a movement.

The sensitivity to stimulus location and direction of movement was also analyzed by examining the sample of TANs with spatially nonselective responses tested in both the choice and dissociated conditions. If these responses were related to the reward-predicting significance of the trigger stimulus, irrespective of spatial features, then they should be maintained in the dissociated condition. We found that 14 neurons continued to respond to both stimulus locations in this latter condition, whereas 9 neurons changed their response properties: 5 neurons became selectively responsive to the contralateral stimulus, 3 became selectively responsive to the ipsilateral stimulus, and one became completely unresponsive. This indicates that 39% of the spatially nonselective responses (9 of 23 neurons) were altered when the spatial features of the task were changed. Figure 8A is an example of a neuron that responded to the stimulus presented at either of the two locations, although the magnitude of responses was greater for the contralateral stimulus than for the ipsilateral stimulus. Responses were maintained when condition was switched from choice to dissociated, suggesting that this neuron was concerned with stimulus detection irrespective of the direction of the movement. Another example of spatially nonselective response is illustrated in Figure 8B. In this example, the neuron displayed spatial selectivity when tested in the dissociated condition, responding to the ipsilateral stimulus but not to the contralateral stimulus. The specificity of the response indicates that it was associated with the direction of the movement.
In summary, neurons were classified as stimulus-dependent if their response properties remained unchanged under both the choice and dissociated conditions (8 neurons with spatially selective responses and 14 neurons with spatially nonselective responses), as movement-dependent if neurons with spatially selective responses became completely unresponsive (8 neurons) and neurons with spatially nonselective responses became selective of the ipsilateral stimulus (3 neurons), and as context-dependent if response properties did not simply represent stimulus location itself or movement direction itself (5 neurons with spatially selective responses and 6 neurons with spatially nonselective responses). Thus, the most prominent response type that we observed among TANs was related to the spatial location of the stimulus (22 of 44 neurons, 50%), whereas the relative frequencies of movement-dependent (11 of 44 neurons, 25%) and context-dependent responses to the trigger stimulus (11 of 44 neurons, 25%) were similar.

Locations of neurons with trigger responses

Figure 9 illustrates the locations of all TANs studied in the choice condition in all three monkeys. It can be seen that neurons were sampled from the full extent of the explored striatum, with the exception of its ventral part. Although neurons with trigger responses of the different types were distributed over the entire striatal areas from which we recorded, we found more nonselective responses ($\chi^2 = 5.19; df = 1; P < 0.05$) and selective responses to the ipsilateral stimulus ($\chi^2 = 4.55; df = 1; P < 0.05$) in the associative striatum than in the sensorimotor striatum. On the other hand, incidences of selective responses to the contralateral stimulus, although higher in the sensorimotor striatum than in the associative striatum, did not vary significantly between these two striatal territories ($\chi^2 = 3.75; df = 1; P > 0.05$). The reconstructed recording positions for the 44 neurons studied in both the choice and dissociated conditions in the two monkeys are shown in Figure 10. Incidences of the three types of neurons, with stimulus-dependent responses, movement-dependent responses, and context-dependent responses, did not vary significantly between the two striatal territories ($P > 0.05$).

Discussion

In the present study, we have investigated the sensitivity of TANs to the spatial location of a stimulus presented as a trigger signal for reaching movements in two different directions. Although most TANs were modulated in a manner that did not depend on the spatial features of the task, our findings demonstrate that about one third of the responses of TANs to the
movement-triggering stimulus were selective of one stimulus location, among which a majority preferred the location opposite to the moving arm. The nonspatially selective responses may represent a basic processing subserving behavioral reactions, such as detection of the reward-predicting value of stimuli, whereas the spatially selective responses may play a role in the processing of spatial attributes of stimulus and/or movement. Using a task condition in which the arm moved toward stimulus location or in a direction opposite to stimulus location, we were able to distinguish three types of TAN responses to the trigger stimulus, one that were dependent on the location of the stimulus, one that were dependent on the direction of movement, and one that were dependent on particular stimulus-movement combinations in a given task context. These different types of neuronal responses indicate that TANs are involved in more than the detection of rewarding events thereby providing evidence for their role in processes that are relevant for spatially oriented behavior.

Contralateral preference of the spatially selective responses

Our results show that approximately two thirds of the TANs displaying spatially selective responses preferred the contralateral stimulus location. Kimura (1986, 1992) described TANs in the putamen with selective responses to spatially distinct visual stimuli eliciting arm movements in different directions, but the relationship between the spatial selectivity of these responses and the laterality of stimulus presentation was not reported. In the caudate nucleus, the majority of TANs recorded during an oculomotor task were responsive to visual stimuli contralateral to the hemisphere from which recordings were made (Shimo and Hikosaka 2001). In our experiments, the recordings were always carried out in the striatum of the left hemisphere and TANs showed a spatial preference in their responses when the trigger stimulus was ipsilateral (monkey ENK) or contralateral (monkey ART) to the recorded striatum, indicating that there is no consistent relationship between the spatial selectivity of neuronal responses and the side of recording. These two monkeys performed the task with the left arm (monkey ART) or the right arm (monkey ENK), suggesting that the effects of stimulus laterality on TAN responses might be related to the arm to be used for the reaching movement. It is possible that the effects of stimulus laterality on TAN responses varied as a function of the requirements of the task, particularly the information type used to initiate the behavioral reaction. To perform the memory-guided saccade task that was used by Shimo and Hikosaka (2001), the monkey had to remember the spatial location of stimuli which indicated the future saccade direction and the increased responsiveness of TANs to stimuli presented contralaterally to the recorded striatum may have been related to spatial memory for the location of the stimulus. In the task that we used, stimuli triggered immediate movements
directed toward targets and the predominance of TAN responses to stimuli presented contralaterally to the moving arm was accompanied by a variation in the speed of the motor reaction elicited by the stimulus: arm movements usually were faster when target side and responding arm corresponded than when they did not correspond. This is consistent with behavioral studies in humans showing that ipsilateral reaches are initiated more quickly and were completed more rapidly than were reaches directed at contralateral targets (Fisk and Goodale 1985). These results raise the possibility that, in the context of a reaching task, the preference of TANs for contralateral stimuli reflects a degree of sensitivity to the correspondence between the effector and the side toward which the motor response was directed. Whether the requirements of the task being performed account for the apparent differences between our results and those of Shimo and Hikosaka (2001) remains an issue for further investigation.

Nature of the responses to the stimulus triggering the reaching movement

While previous studies have shown that the spatial location of the stimulus that elicited or instructed the direction of arm or eye movements may be reflected in the response of TANs (Kimura 1986, 1992; Shimo and Hikosaka 2001), none was designed to dissociate the spatial features of the stimulus from the direction of the movement associated with that stimulus. We have addressed this issue in the present study by using the dissociated version of the task in which the monkey reached toward or away from the spatial location of the trigger stimulus. We found that a substantial number of TANs changed their response properties when the task was switched from the choice to the dissociated condition, permitting identification of three different types of responses to the trigger stimulus that are predominantly influenced by the sensory, motor or contextual aspects of the reaching task. These results suggest the existence of subgroups of TANs that may play a preferential role in distinct processes related to spatial information processing. Recently, Yamada et al. (2004) reported that different subsets of TANs modulate their responsiveness according to the stimulus used for triggering actions, the motivational context of actions, or combinations of action and context. Together with this previous finding, our data provide further evidence that TANs are less homogeneous in their response properties than currently appreciated.

We found that 50% of the TAN responses to the trigger stimulus were not dependent on whether the monkey moved the arm toward or away from the spatial location of the stimulus, suggesting that these responses reflect the location of the stimulus itself. This is consistent with the prominent role of TANs in detecting stimuli linked to rewards. Previous single-neuron recording studies in behaving monkeys have demonstrated that TAN responses
are time-locked to the trigger stimulus but not to the associated movement (Aosaki et al. 1994; Kimura 1992; Yamada et al. 2004). The activity changes reported here further indicate that TAN responses may also reflect the location of the stimulus in space. Because monkeys’ reaching movements were usually preceded by a saccade directed toward the stimulus presented at either of the two locations, both in the choice and dissociated conditions, there is also a possibility that TAN responses, instead of being involved in the detection process, were associated with saccadic eye movements. However, examination of eye movement data under our task conditions has shown that TAN responses were not directly linked with the direction of gaze or with the initiation of eye movements. On the other hand, it is conceivable that these responses might reflect the processes of spatial attention, as it has been suggested that TANs may be involved in some attentional functions (Blazquez et al. 2002). The absence of control over the spatial distribution of attention in our experiments does not allow us to determine to what degree TAN responses are dependent on attentional demands of the task being performed. The present study has also demonstrated that 25% of the TAN responses to the trigger stimulus were related to the direction of reach, irrespective of the side where the stimulus was presented. Thus, even if the responsiveness of TANs is traditionally considered to be more sensory than motor, our findings indicate that at least some TANs do participate in the processing of motor-dependent spatial information. This suggests that TANs may have a role in specific aspects of motor control, such as intention to move the arm in a particular direction. Finally, it was of special interest in our study to find a third type of TAN responses which did not simply reflect the location of the stimulus or the direction of the movement, but the interaction of these two aspects in a condition demanding a particular use of sensory information for the selection of an action. Thus, 25% of the TANs displayed specific response properties only under certain circumstances. For example, some neurons responded with a spatial preference for one stimulus location in the choice condition, but reversed or lost their preference when tested in the dissociated condition. Such responses, characterized as context-dependent, were interpreted to reflect the way in which sensory information is used to elicit reaching movements. In the choice condition, monkeys were required to detect the spatial information contained in the stimulus to make movements directed toward spatially distinct targets. In the dissociated condition, the stimulus provided no information other than a temporal reference for reaching toward a constant spatial target, regardless of the location of the stimulus. It is conceivable that TANs have a role in switching between conditions involving a different use of the information contained in the stimulus. Our findings are consistent with a role of TANs in signaling changes in context when stimuli are relevant as
trigger signals for action. Such an interpretation is in accordance with the report of Shimo and Hikosaka (2002) showing that TANs respond selectively to visual stimuli in a context-dependent manner, being influenced by changes in reward probability. The response of TANs, according to these authors, may be seen as signaling the act of switching between different contexts involving specific reward schedules. Other evidence has been obtained recently by Yamada et al. (2004) pointing to the fact that differences in the context in which task stimuli are presented might contribute to the differential responsiveness of TANs. In addition, these authors have reported that TANs in the caudate nucleus may participate in the process of context encoding, whereas those in the putamen may carry information about movement initiation. This suggests that TAN responses associated with the processing of contextual and motor types of information may show some differences in their localization.

Possible origins of the sensitivity of TANs to spatial features of a task

It is known that different sensory inputs converge on TANs, from the midbrain dopaminergic neurons, the thalamus and the cerebral cortex. Although the response of TANs to stimuli has been reported to be dependent on dopaminergic afferents (Aosaki et al. 1994; Raz et al. 1996; Watanabe and Kimura 1998), a differential responsiveness which is similar to the spatial selectivity of TAN responses reported here has not been observed in dopaminergic neurons (Schultz 1998). This suggests that TANs are more concerned with information processing mechanisms necessary for the organization of spatially directed behavior than dopaminergic neurons. On the other hand, many of the neurons recorded in the centromedian/parafascicular complex of the thalamus respond to movement-triggering stimuli and these responses have been associated with visuospatial processes, including spatial attention (Minamimoto and Kimura 2002). Because this thalamic area has been reported to be essential for the correct functioning of TANs (Matsumoto et al. 2001), it is possible that such thalamic neuronal responses provide spatial information to the striatum. Another possible source of afferents that underlies TAN responses related to spatial features of the task is the cerebral cortex. Recently, TANs in the putamen have been found to receive inputs from both the primary motor cortex and supplementary motor area (Nambu et al. 2002) in which neuronal responses that reflect either the stimulus location or the direction of the movement have been recorded (Alexander and Crutcher 1990b; Crutcher et al. 2004; Shen and Alexander 1997). Spatial information may also reach the striatum through projections from the dorsolateral prefrontal cortex and posterior parietal areas that contain neurons that are strongly related to visuospatial functions (Colby and Goldberg 1999; Funahashi et al. 1990; Steinmetz and Constantinidis 1995). Thus inputs from functionally distinct regions of the
frontal and parietal visuospatial processing areas could mediate the spatial information used by TANs for reaching behavior. However, cortical inputs impose upon the striatum a functional organization so that the structure can be divided into a sensorimotor territory and an associative territory (Parent and Hazrati 1995). In the present study, TANs from these two striatal territories were compared to assess regional differences in response properties and no striking differences in the anatomical distribution of TANs with spatial sensitivity appear in our data. In particular, the finding that TAN responses that were dependent on movement direction did not tend to be clustered in the posterior putamen is not consistent with the existence of a segregated population of TANs that would be predominantly «motor». As mentioned earlier, a differential distribution in the response properties of TANs has been reported by Yamada et al. (2004), neurons responding to movement-triggering stimuli being more frequent in the putamen than in the caudate nucleus. Further studies are therefore necessary to establish whether contrasting properties in TAN responses exist among striatal regions and to clarify the relationship between topographic mapping of corticostriatal projections and TAN responses associated with the processing of different types of information.

**Influence of the spatial features of a task on the activity of striatal projection neurons**

Striatal neurons that discharge spontaneously at low rates and exhibit distinct activity changes in various phases of a learned task are referred to as phasically active neurons (PANs) which correspond to GABAergic medium spiny projection neurons in the striatum (Alexander and DeLong 1985; Wilson and Groves 1981). There is evidence that certain types of task-related PANs are more represented in particular striatal territories according to the convergence of cortical inputs on segregated regions of the striatum. Especially, PANs that are involved in movement execution are largely found in the posterior putamen, whereas neurons associated with more cognitive aspects of motor control, such as preparation for movements, display an increasing gradient from the posterior to anterior regions of the putamen (Alexander and Crutcher 1990a). Previous studies have shown the spatial selectivity of PANs in that part of putamen associated with movement execution (Crutcher and DeLong 1984; Crutcher and Alexander 1990; Kimura 1990; Ueda and Kimura 2003). Only one study of PAN activity has attempted to dissociate the spatial features of the movement-triggering stimulus from those of the associated movement (Alexander and Crutcher 1990b) and it was found that spatially selective preparatory and/or movement-related activations can be related to the direction of movement, independent of stimulus location or to the spatial location of the stimulus, independent of the movement. These neurons thus share some features in common with the
response properties of TANs we observed. Although the role that PANs play with respect to TAN activity has not been clearly defined, it is possible, as suggested by Shimo and Hikosaka (2001), that the sensitivity of TANs to the spatial aspects of the task may be related to certain specificities in the relation of PAN activity to the spatial location of the stimulus or the intended movement direction. However, it is not clear to what extent the response properties of TANs depend on cortical inputs or to what extent it is elaborated by the properties of surrounding PANs.

**Functional implications**

Our study provides new information about response properties of TANs in the primate striatum. These neurons, presumed to be cholinergic interneurons, occupy a central position within the striatal circuitry, being primarily devoted to the detection of motivationally relevant stimuli (Apicella 2002). The present findings that distinct groups of TANs are sensitive to the location of the stimulus, the direction of movement, or the context in which stimulus-movement combination occurs suggest that these neurons are not limited to motivational functions, but may play a role in the processing of information about the spatial features of task performance as well. Theoretically, the motivational relevance of a stimulus appears to be the primary factor in determining the response of TANs to it. The sensitivity of these neurons to spatial features may reflect a role in integrating motivational information with specific aspects of goal-directed actions toward targets, including the detection of stimulus location, the selection of the required movement and the detection of the context of action. The response properties of TANs could be very important functionally regarding the monkey’s ability to adapt to the changed requirements of a reaching task. We suggest that the striatal network of the TANs may serve to integrate reward- and spatial-related information which in turn can affect the motor output system of the striatum to achieve appropriate spatially oriented behavior.

**Acknowledgements**

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Figure legends

Figure 1. Schematic illustration of the behavioral apparatus and the stimulus presentation in the two task conditions. The stimulus that triggered the movement (illumination of a diode) was presented either to the left or to the right of the panel in a pseudorandom fashion. Monkeys were required to respond to each stimulus by moving the hand toward the target located below the illuminated diode (choice condition) or a constant target ipsilateral to the moving arm (dissociated condition). In this latter condition, the hand moved toward stimulus location or in a direction opposite to stimulus location. Liquid reward was delivered after each correct target contact through a tube positioned in front of the monkey’s mouth. Black circles indicate illuminated diodes, and the arrows represent the direction of movement. The two task conditions were run in separate blocks of trials.

Figure 2. Eye movements recorded under the two task conditions. A. Each display shows 12-15 superimposed records of horizontal eye positions aligned on the onset of the trigger stimulus (data from monkey TIM). Upward deflections indicate saccades toward the left. B. Distributions of values of latency of saccadic eye movements toward trigger stimuli for the two locations of the stimulus in both task conditions. Total numbers of trials for each stimulus location are given by N.

Figure 3. Responses of two TANs to the trigger stimulus presented at two spatial locations. The neuronal activity was recorded while the monkey was performing the task under the choice condition. Data were collected when the location of the trigger stimulus was varied pseudorandomly during the same block of trials and were separated off-line according to the stimulus location. In this and subsequent figures that illustrate neuronal activity, data are shown as corresponding raster displays and peri-event histograms constructed for each stimulus location and aligned at the onset of the trigger stimulus which is marked by the vertical line. Each line of dots in the raster displays shows the activity during a single trial, and each dot represents a single spike. The temporal sequence of trials is preserved downward. The neuron in A responded to the trigger stimulus irrespective of the side where the stimulus was presented, while the neuron in B responded to the trigger stimulus only when it was presented on the side contralateral to the moving arm. The histogram scale is in impulses/bin and is the same for all histograms. Bin width for histograms, 10 ms.
Figure 4. Bar plots showing proportions of TANs with spatially selective or spatially nonselective responses to the trigger stimulus. Neurons from all three monkeys are included. Ordinate indicates percentage of responding neurons in each animal. Nonselective, neurons responsive to both stimulus locations; selective contralateral, neurons responsive only to the stimulus presented contralaterally to the moving arm; selective ipsilateral, neurons responsive only to the stimulus presented ipsilaterally to the moving arm.

Figure 5. Responses of one TAN to stimuli presented inside and outside of the reaching task. Data are shown separately for trigger stimuli and for reward delivered alone outside of the task (free reward condition). Same conventions as in Fig. 3., except that the activity of the neuron is aligned with trigger onset (left) and with the delivery of reward (right). In addition to showing a selective response to the contralateral trigger stimulus, this neuron was also responsive to reward given free outside of the task but not to reward delivered after target contact in the task. For each condition and stimulus location, superimposed traces of horizontal components of electrooculograms are shown at the top of each perievent histogram and illustrate the monkey’s ocular reaction to the trigger stimulus and reward. Eye movements and neuronal activity were recorded simultaneously in the same trials.

Figure 6. Spatially selective responses of two TANs dependent on stimulus location or direction of movement. Same conventions as in Fig. 3. Both neurons responded to the stimulus presented contralaterally to the moving arm in the choice condition. The neuron in A maintained its response when the contralateral stimulus elicited a movement in a direction opposite to stimulus location, indicating that the spatial preference is linked with the location of the stimulus rather than with the direction of movement. The response of the neuron in B was suppressed when the contralateral stimulus elicited a movement in a direction opposite to stimulus location, indicating that the spatial selectivity of this neuron is related to the target of reaching and not to the location of the stimulus.

Figure 7. Spatially selective responses of two TANs dependent on task condition rather than stimulus location or direction of movement. Same conventions as in Fig. 3. These neurons showed a spatial selectivity to the contralateral stimulus in the choice condition and they changed their response selectivity when passing from the choice to the dissociated conditions: the neuron in A became responsive only to the ipsilateral stimulus and the neuron in B became responsive to both stimulus locations.
Figure 8. Spatially nonselective responses of two TANs to the trigger stimulus. Same conventions as in Fig. 3. These neurons responded to both stimulus locations p in the choice condition. The neuron in A maintained its response with different response magnitudes for the two stimulus locations. The neuron in B became selective of the ipsilateral stimulus.

Figure 9. Anatomical locations of the neurons recorded in the choice condition. Data from all three monkeys are plotted on coronal sections of the left striatum. Anteroposterior levels are shown according to the atlas of Szabo and Cowan (1984). Grey areas represent approximate extent of the sensorimotor territory of the striatum and white areas correspond to the associative and limbic territories of the striatum. Neurons were classified as responsive to both stimulus locations (filled circles), responsive only to the contralateral stimulus (squares), responsive only to the ipsilateral stimulus (diamonds), and unresponsive (small horizontal bars).

Figure 10. Anatomical locations of the neurons tested in both the choice and dissociated conditions. Data from monkeys ART and TIM are drawn on coronal sections of the left striatum. Each drawing shows the locations of all the neurons tested in the two task conditions at a given anteroposterior level. « S » refers to stimulus-dependent responses, « M » refers to movement-dependent responses, and « C » refers to context-dependent responses.
References


Fisk JD and Goodale MA. The organization of eye and limb movements during unrestricted reaching to targets in contralateral and ipsilateral visual space. Exp Brain Res 60: 159-178, 1985.


### Table 1. Reaction and movement times for the two task conditions

<table>
<thead>
<tr>
<th>Task condition</th>
<th>Reaction time</th>
<th>Movement time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Choice</td>
<td>Dissociated</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Monkey ENK</td>
<td>280 ± 17</td>
<td>381 ± 65</td>
</tr>
<tr>
<td>Monkey TIM</td>
<td>363 ± 51</td>
<td>388 ± 63</td>
</tr>
<tr>
<td>Monkey ART</td>
<td>359 ± 25</td>
<td>429 ± 41</td>
</tr>
</tbody>
</table>

Values are means ± SD in ms. Mean reaction times (RTs) and movement times (MTs) were calculated by averaging the daily mean RTs and MTs for each animal and each stimulus location over 20-40 recording days. Ipsilateral and Contralateral refer to stimuli presented ipsilaterally and contralaterally to the moving arm, respectively. In the dissociated condition, ipsilateral and contralateral stimulus locations correspond to compatible and incompatible trials, respectively.
Table 2. *Latencies and durations of TAN responses to the trigger stimulus*

<table>
<thead>
<tr>
<th>Response type</th>
<th>N</th>
<th>Latency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective contralateral</td>
<td>34</td>
<td>119 ± 35</td>
<td>95 ± 40</td>
</tr>
<tr>
<td>Selective ipsilateral</td>
<td>20</td>
<td>106 ± 34</td>
<td>100 ± 37</td>
</tr>
<tr>
<td>Nonselective</td>
<td>127</td>
<td>97 ± 34</td>
<td>142 ± 52</td>
</tr>
</tbody>
</table>

Values are means ± SD in ms. N: number of responding neurons. *Selective contralateral*, neurons responsive only to the stimulus presented contralaterally to the moving arm; *Selective ipsilateral*, neurons responsive only to the stimulus presented ipsilaterally to the moving arm; *Nonselective*, neurons responsive to both stimulus locations.
choice condition

dissociated condition
Figure 2

A

choice condition
dissociated condition

trigger ipsilateral

trigger contralateral

trigger

250 ms

B

choice condition
dissociated condition

trigger ipsilateral

trigger contralateral

trigger ipsilateral

trigger contralateral

N

monkey ART

median 185 ms

median 208 ms

median 178 ms

median 204 ms

N

monkey TIM

median 141 ms

median 147 ms

median 184 ms

median 178 ms

latencies (ms)
Figure 3

A

B

trigger contralateral to the moving arm

trigger ipsilateral to the moving arm
Figure 5

- trigger contralateral to the moving arm
- trigger ipsilateral to the moving arm
- free reward condition
- reward
Figure 7

A

choice

dissociated

trigger contralateral to the moving arm

trigger ipsilateral to the moving arm

B

choice

dissociated

trigger contralateral to the moving arm

trigger ipsilateral to the moving arm
Figure 8

A

choice

dissociated

trigger contralateral to the moving arm

B

choice

dissociated

trigger contralateral to the moving arm

trigger ipsilateral to the moving arm
Figure 9