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Activity of Tonically Active Neurons in the Monkey Putamen During Initiation and Withholding of Movement

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Lee, Irwin H., Aaron R. Seitz, and John A. Assad. Activity of tonically active neurons in the monkey putamen during initiation and withholding of movement. *J Neurophysiol* 95: 2391–2403, 2006. First published January 11, 2006; doi:10.1152/jn.01053.2005. Tonically active neurons (TANs) of the primate striatum are putative interneurons that respond to events of motivational significance, such as primary rewards, and to sensory stimuli that predict such events. Because TANs influence striatal projection neurons, TANs may play a role in the initiation and control of movement. To examine this issue, we recorded from putaminal TANs in macaque monkeys trained to make the same arm movement in two ways—in reaction to an external cue and also after a variable delay without an explicit instruction to move (self-timed movements). On other trials, the animals had to withhold movement following an external cue. The task design ensured that the three types of trials were effectively randomly interleaved, equally frequent, and similar in overall timing. Separately, we presented "playback" trials in which the same sequence of visual stimulation and reward was presented while the animals fixated without making the arm movement. We found that TAN responses were strongly affected by behavioral context. In particular, TAN responses were strikingly stronger when the animals actively withheld movements than on the corresponding playback trials, even though the stimulus sequence and reward timing were identical and no movement was made in either case. Many TANs also became active in the absence of a proximate sensory cue on self-timed movements, suggesting that TANs may reflect internal processes that are specific to self-timed movements. These results suggest that TANs may directly participate in, or monitor the motivational significance of, an animal's actions as well as external events.

INTRODUCTION

The primate striatum, a part of the basal ganglia that is a major recipient of cortical and limbic input, is believed to be involved in a broad range of functions, including the control of voluntary movement and the integration of reward-related information (Houk et al. 1995). Two types of striatal neurons can be identified using extracellular recording techniques, phasically active neurons (PANs) and tonically active neurons (TANs). PANs, which likely correspond to the medium spiny projection neurons of the striatum (Kimura et al. 1996), show diverse task-related activations, including set- and movement-related activity (Crutcher and Alexander 1990; Crutcher and DeLong 1984; Lee and Assad 2003) and activity related to anticipating reward (Apicella et al. 1991a; Hassani et al. 2001; Hikosaka et al. 1989; Shidara et al. 1998). TANs, which are believed to correspond to cholinergic interneurons (Kimura et al. 1996; Wilson et al. 1990), show activations related to external events of motivational significance, such as primary rewards or adverse stimulation (Apicella et al. 1991b, 1997; Kimura et al. 1984; Ravel et al. 1999, 2001; Yamada et al. 2004), sensory stimuli that predict upcoming reward or adverse stimulation (Aosaki et al. 1994; Kimura et al. 1984; Ravel et al. 2003), and conditioned stimuli that reliably elicit reward-seeking or aversive behavioral reactions from animals (Blazquez et al. 2002). These findings have led to the hypothesis that TANs play an important role in striatal-based reinforcement learning, helping to build flexible stimulus-response associations, and/or encoding temporal relationship between motivationally relevant external events (Apicella 2002; Graybiel 1995; Kimura et al. 2003).

Although previous work on TANs has emphasized their potential role in associative learning, the properties of TANs suggest they may also influence striatal output—and thus the control of movement—in real time. Cholinergic interneurons constitute only 1–2% of striatal neurons but synapse directly on medium spiny neurons and have broad axonal arbors that suggest a widespread modulatory influence (Wilson 1998). Moreover, TANs exhibit synchrony, so a network of TANs could act to coordinate output from areas greater than the axonal span of a single TAN (Aosaki et al. 1995; Raz et al. 1996). TANs typically respond with a transient decrease in their tonic firing (often followed by a brief rebound), which may modulate cortical inputs that actually drive PAN activity (Aosaki et al. 1995). For example, if TANs are cholinergic and exert a tonic inhibitory effect through muscarinic receptors (Calabresi et al. 2000; Kawaguchi et al. 1995), a pause in TAN firing might lead to a disinhibition of PANs. By modulating PANs that are involved in the control of movement, the activity of TANs could thus influence movement generation. By the same logic, activation of TANs might play a role in withholding or suppressing movements. These hypotheses suggest that it would be useful to examine the activity of TANs under a variety of conditions of movement initiation. These might include movements that are initiated as simple reactions to sensory cues or movements that are more "self-timed" in that they are not abruptly cued by external stimuli.

In a previous study, we developed a behavioral paradigm in monkeys to compare arm movements that are identical except for how they are initiated—either in abrupt reaction to an external sensory cue (*cued* movements) or in a *self-timed* fashion, without a preceding sensory trigger (Lee and Assad 2003). Self-timed movements differ fundamentally from simple reactions in that the time from an external cue until

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movement is self-chosen, whereas simple reaction times are not self-chosen (Gallistel and Gibbon 2000; Gilden et al. 1995; Lee and Assad 2003). We focused on the activity of PANs in the posterior putamen. The vast majority of PANs were active during both cued and self-timed arm movements. However, we found a consistent slow build-up of neuronal activity hundreds of milliseconds before the first detectable electromyographic evidence for arm movement. This build-up was specific to self-timed movements; for cued movements, there was a more abrupt increase of firing to the high level of phasic movement-related activity. We proposed that these data could reflect a threshold mechanism in the corticostriatal circuitry for movement initiation. We also recorded the activity of TANs in the same experiment.

Here we report on the patterns of activity observed in TANs during visually cued movements and self-timed movements and also during the active suppression or withholding of planned movements. We found that the modulation of TAN activity by visual cues can be highly dependent on the context of the associated movement or nonmovement and that TANs can even show movement-related activations in the absence of sensory cues. These findings are relevant both to models of how TANs signal motivationally significant events and how TANs may contribute to the on-line control of movement.

METHODS

Behavioral paradigm

Two male rhesus monkeys (13.6 and 7.2 kg) were trained to guide a spot of light to a target using a vertically mounted joystick, which allowed full two-dimensional control of the displacement of the spot. The spring-loaded joystick returned to the center before each trial, so that the movements were always made relative to the starting center joystick position. Animals were required to confine the spot's movement to a 5°-wide (visual angle) invisible "corridor", although after training, the movements were very accurate and rarely strayed from the corridor boundaries. For every neuron, we first determined the preferred direction of movement using a direction-tuning task (see following text). In the main task, the preferred direction of movement was used on every trial.

On all trials, the animal first fixated gaze on a yellow spot of light at the center of the stimulus monitor (Fig. 1). The animals had to maintain gaze within 1° of the fixation spot throughout all trials or the trial would abort immediately without reward (in fact, fixation breaks were rare: <5% of trials). A central target (1.6° wide) and a peripheral spot (0.5° wide) then appeared, separated by 8°. To prevent the animals from immediately moving in response to the spot/target onset, we required the animals to wait ≥2,000 ms after the spot/target onset or the trial would abort without reward. After the expiration of the 2,000-ms delay (which was not signaled), the animal was free to move the spot to the target. On some trials, the animal did in fact move at some time after the 2,000-ms delay without any explicit external cue to move. Such trials were designated "self-timed" because the animals chose when to move themselves without external prompting. On other trials, the fixation spot changed color at a random time (see following text) after the 2,000-ms delay (cue onset) but before the animal moved. If the fixation spot turned green (go cue), the animal had to start moving within 500 ms of the color change or the trial would abort. These trials were designated "cued. " If the fixation spot instead turned red, the animal had to withhold movement for an additional 2000 ms to receive reward. These trials were designated "no-go". No-go trials allowed us to assess the effects of withholding movement and also prevented the animals from ignoring the cue and simply moving after the 2,000-ms delay. For both cued and no-go trials, the cue onset time was randomly chosen from an exponential distribution so that the animal could not use elapsed time to predict the cue onset. (The cue did *not* change, however, if we detected a movement of the joystick before the randomly chosen cue onset time, i.e., on self-timed trials). Thus rather than our dictating the outcome of individual trials, the identity of a given trial was determined by whether the animal decided to start moving before a randomly chosen cue onset time, much like a race process. On both cued and self-timed trials, the animals were rewarded for successfully guiding the spot to the target.

Because we did not dictate the outcome of the trials, we needed to ensure that the occurrence and overall timing of cued and self-timed trials would be similar. For example, if the random distribution of cue-appearance times was too skewed toward early cue-appearance

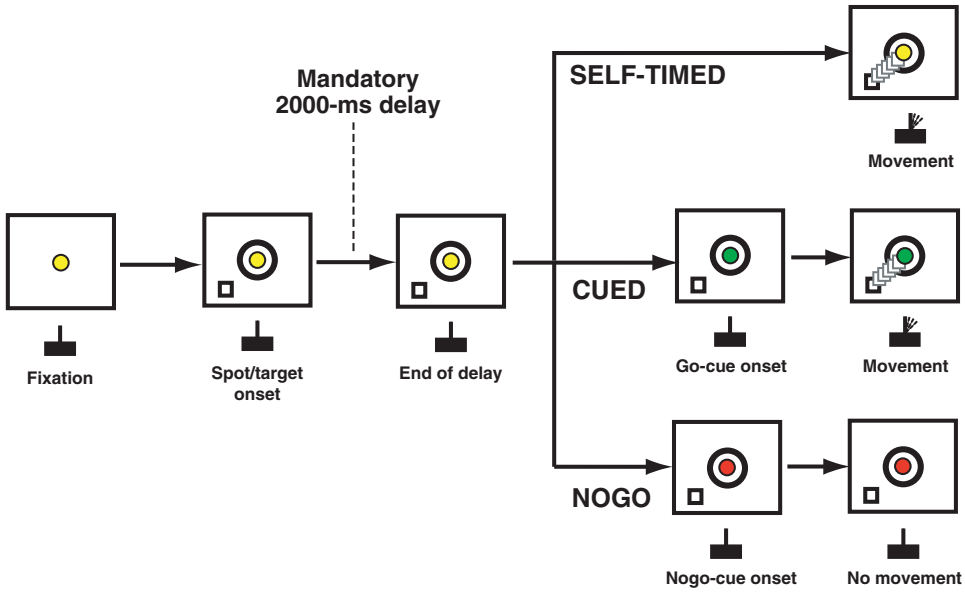


FIG. 1. Design of experiment (not drawn to scale). Each panel depicts the stimulus monitor at one phase of a trial. The joystick position is shown below each panel to indicate whether movement has begun. The smaller, central, round spot is the gaze-fixation spot, which also served as an indicator to move on cued trials or withhold movement on no-go trials. The circle surrounding the fixation spot is the target of the movement and the peripheral square is the spot of light that the animal moved to the central target.

times, then the animals would mostly make cued movements and would tend to move earlier on cued than self-timed trials. To balance the proportion and timing of cued and self-timed trials, we used a staircase procedure that modified the decay constant of the exponential distribution of cue-onset times to equalize the probability of a trial resulting in a cued or self-timed movement. After each self-timed trial, the decay constant was decreased by 50 ms. After any combination of two cued or no-go trials, the decay constant was increased by 50 ms. Before each trial, the cue-onset time was randomly chosen from the updated distribution, and the type of cue change, green or red, was selected at random with an even chance of either outcome. We previously presented detailed behavioral evidence that showed that this procedure resulted in the three trial types being effectively randomly interleaved, equally frequent, and similar in overall timing, and that also solidified the distinction between self-timed and cued trials (Fig. 3 of Lee and Assad 2003). Some of that evidence is reviewed in RESULTS.

To control for the effect of the visual stimulation alone (cue-color change and/or the visible moving spot) without associated arm movement, we also included short blocks of trials in which the cue changes and spot trajectories were replayed to the animal as it fixated and passively viewed (*playback* trials). Playback trials were aborted without reward if the animals moved the joystick. Playback trials were exact visual replays of all three trial types. That is, the spot moved with no change in the color of the fixation spot (corresponding to self-timed) or the spot moved after a change in the fixation-spot color to green (corresponding to cued) or the fixation spot changed to red with no movement of the spot (corresponding to no-go). The timing of all visual events (and reward delivery) was exactly as in the corresponding cued, self-timed, and no-go trials. Playback trials were employed to compare activity elicited by visual stimulation alone to that involved in visual stimulation plus task performance. We will use the nomenclature "active" and "playback" to describe trials from the main task and trials from the playback conditions, respectively. For example, a cued-active trial is one in which the fixation point turned green and the animal actually made the hand movement, whereas a cued-playback trial is a visual replica of the same trial but with no hand movement. Blocks of playback trials were interleaved with active trials at least twice for each neuron.

Electrophysiological recording

Once the animals were trained, they were surgically implanted with head post, scleral search coil, and recording chambers following National Institutes of Health and Harvard Medical School guidelines. The chambers were placed in the left hemisphere because both animals exclusively used their right hands to move the joystick. One chamber was centered at A13, L15, aligned vertically to allow a dorsal approach to the putamen. The other chamber was centered at A11 with an approach of ~40° relative to vertical (roughly normal to the skull). Electrophysiological recordings were made from single neurons in the putamen using tungsten microelectrodes and a guide-tube/grid system. Spike times were recorded with 1-ms resolution. An MRI image (MPRAGE; TR 11.1; TE 4.3/1; TA 13:37) was obtained after the recording chamber had been implanted, using mineral-oil filled capillary tubes placed at known grid positions as fiducial markers. (Lee and Assad 2003). Electrode penetrations were targeted to the posterior putamen (A10–A17). For the angled chamber, penetrations were continued through the width of the putamen until the globus pallidus (GP) was encountered. For the vertical chamber, separate penetrations were made medial to the putaminal sites to positively identify the GP. GP units were clearly identified from putaminal units by their much higher spontaneous firing rates (DeLong 1971).

When we isolated a putaminal neuron, we first ran a direction-tuning task to assess whether the cell was activated by the hand/arm movements used to move the joystick and, if so, to determine the preferred direction of movement for the neuron. In the direction-tuning task, the animal first fixated on a yellow fixation spot at the center of the screen. After the animals had fixated for a random delay of 400–700 ms, the spot and target appeared at one of eight locations about the target, evenly spaced at 45° intervals, corresponding to eight different directions of movement. The direction was chosen pseudo-randomly from trial to trial. After another random delay of 500–2,000 ms, the fixation spot turned green to signal the animal to begin moving within 500 ms. The direction that elicited the largest neuronal activity was tested in the main task. We also had the animals continually run the direction-tuning task to activate arm-related putaminal units while we were advancing the microdrive. This was particularly useful for identifying PANs, which otherwise have very low spontaneous firing rates.

Horizontal and vertical components of the eye position and joystick displacement were recorded at 200 Hz. Electromyographic (EMG) activity was also recorded in separate sessions using tin-disk surface electrodes to measure as broad a signal as possible. By video inspection, the animals did not bend the wrist to move the joystick (as a human would) but rather moved the entire arm about the elbow and shoulder. EMG recordings were thus made from the deltoid, biceps, and triceps muscles. Between trials the monkeys sometimes appeared to loosen their grip and then re-grip the joystick by flexing their fingers at the start of a new movement. To get some gauge of the hand flexion, we also recorded EMG activity from forearm flexors. The amplified signal was band-pass filtered at 100–5,000 Hz and digitally rectified. Eight different directions of movement were tested in separate blocks of trials.

Identification of putaminal cell types

Within the putamen, both PANs and TANs were encountered. Subjectively, PANs and TANs were readily distinguishable based on the higher spontaneous firing rates of TANs and the presence of arm-movement related activity in many PANs but not TANs (Crutcher and DeLong 1984). However, to classify units in an unbiased fashion, we subjected each unit to several quantitative classification tests. First, all units were tested with the direction-tuning task. We calculated a movement index equal to (peak firing rate − baseline firing rate)/(peak firing rate + baseline activity) and also calculated a direction-tuning index equal to the normalized amplitude of the resultant of eight vectors formed by multiplying the peak firing rate for each direction by the unit vector in that direction. Baseline firing for all units was also determined for a "free reward" task in which the monkey sat quietly while receiving juice rewards at random intervals. From this task, we also determined whether there were reward- or sensory-related responses to the click of the solenoid valve used to deliver the reward, as has been reported in free-reward tasks for TANs but not PANs (Aosaki et al. 1995). As an additional measure of each cell's activity pattern, we computed the median inter-spike interval for each cell. Finally, we measured the width of the averaged extracellular action-potential waveform for each unit (analog signals sampled at 32 kHz), as TANs have been reported to have wider action potentials than PANs (Crutcher and DeLong 1984).

Data analysis

For each neuron, the mean response for each trial type was determined by aligning all trials of a given type to the relevant behavioral event (cue onset, movement onset, reward, etc.) and computing the trial-average activity in nonoverlapping 50-ms bins. Population responses were computed by averaging together the mean responses of all the cells.

For individual cells, statistically significant changes in activity were identified using a bootstrap permutation test (Efron and Tibshirani 1993). For each cell, a distribution of pseudo trial averages was generated from a 1,000-ms period during the 2,000-ms delay ("baseline" period) before any cue change or movement occurred. To assess

whether a trial event (cue, movement, reward, etc.) caused a significant upward or downward modulation in the activity of a single neuron, we examined whether there was at least one significantly modulated 50-ms bin within the 600-ms period immediately after the relevant behavioral event (cue onset, movement onset, reward, etc.). The actual trial-average response for a particular 50-ms bin for each cell was defined as significantly different from baseline if it was greater than or less than a confidence interval of 95% percent of the bootstrap distribution.

To compute each pseudo trial average, 50-ms bins were permuted across actual trials (during the baseline period) to create *n*-pseudo trials (where *n* is the number of actual trials for that condition for that cell). These *n*-pseudo trials were averaged to get the pseudo trial average. This procedure was repeated 5,000 for each cell. Empirically, the neuronal firing rates were very stable during the 1,000-ms baseline interval, so this procedure was justified. However, we found that varying the part of the baseline period used for the permutation test, or permuting bins across the entire trial period, produced similar results.

To determine whether the activity of a given cell was significantly modulated (up or down) during the 600-ms postevent period, a Bonferroni correction for multiple comparisons was applied to the 5% significance value used for bootstrap tests. For each cell, each of the twelve 50-ms bins in the 600-ms postevent period were tested for significance, resulting in a corrected significance threshold of 99.6% (100% –5%/12). While the Bonferroni correction is conservative, we could still detect many cells with statistically significant modulations in activity.

When applying the permutation test to the playback trials, we could detect significant upward modulations in activity for many individual neurons, but, due to the limited number of playback trials collected (median of 12 trials per condition), we generally lacked statistical power to detect significant downward modulations. That is, the 99.6% confidence interval often included the lower bound of 0 spikes/s. By inspection, however, it was clear that many cells showed robust modulations. Thus for playback trials, the numbers of significantly modulated cells should be taken as a lower bound rather than a true indicator of the fraction of cells that were modulated by a particular event.

Although we often lacked statistical power to detect activity modulations for individual TANs, to confirm that the upward and downward modulations observed in the population-average responses were significant, we applied one-tailed paired *t*-test to the playback data across the entire population of TANs. This was done in a manner analogous to the permutation test. For each cell, the activity over the 1,000-ms baseline period was averaged. Across the population, each bin during the 600-ms period immediately following the relevant behavioral event (cue onset, movement onset, reward, etc.) was tested against the baseline averages. We tested if each bin was significantly modulated (up or down) during the 600-ms postevent period, and a Bonferroni correction was applied, yielding a significance threshold of $P = 0.0021$ (0.05/24 comparisons). In some cases, we also applied a similar postevent population analysis *between* active and playback conditions, using a two-tailed paired *t*-test.

RESULTS

Behavior

Several lines of evidence underscored that cued and self-timed movements were behaviorally distinct and also that the animals reacted appropriately to the cues to initiate or withhold movement. Although the detailed behavioral evidence was presented in a previous paper (Fig. 3 of Lee and Assad 2003), several key points are worth reviewing.

First, the animals clearly distinguished between the green go and red no-go cues and did not rely on a random or systematic guessing strategy. The animals performed at ~70% or better on both cued (8,168/11,147 correct; 95% confidence interval = [72.4%, 74.1%]) and no-go trials (6,850/9,622 correct; 95% confidence interval = [70.3%, 72.1%]), well above the chance level of 50%. In addition, on cued trials, the temporal coupling between the monkeys' behavior and cue presentation demonstrated that the monkeys were indeed *reacting* to the cues. For cued trials, the distribution of movement-latency relative to the onset of the go cue had a clear peak at ~400 ms, with a half-width of only 50 ms at half-height (Fig. 2*A*). The peak was distinct from the earlier part of the distribution, which was relatively flat but nonzero. This flat part of the distribution was not unexpected because on some trials, the animals must have committed to making a self-timed movement just before the fixation spot turned green but before the actual movement had begun. The width of the reaction-time distribution (relative to the go cue) was more than an order of magnitude narrower than the broad range of movement-onset times on self-timed trials (spread over ~5,000 ms after the spot/target onset, the last sensory event that could have served as a cue to move) (Fig. 3*A* of Lee and Assad 2003). As we pointed out previously (Lee and Assad 2003), this key temporal distinction argues strongly that cued movements were indeed immediate reactions to an external trigger, whereas self-timed movements were not.

We also examined the timing of the animals' errors (movements) on no-go trials. The distribution of times at which the animals moved relative to the onset of the no-go cue was maximal at zero latency and decreased over time until the distribution was nearly zero at ~300 ms postcue (Fig. 2*B*). Like the trials contributing to the flat portion of the cued-trial reaction-time distribution, these errors were probably trials in which the animals had committed to move before the cue changed. There was also a much smaller second peak in this distribution at ~400 ms that coincided with the peak of the distribution of reaction times on cued trials, suggesting that only rarely (73/9,622 trials = 0.76%) did the animals confuse the red no-go cue and the green go cue. These data confirmed

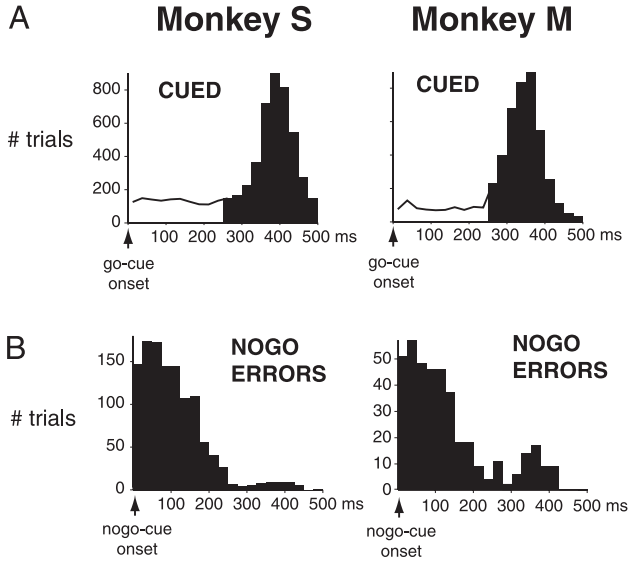


FIG. 2. Behavioral controls for each animal. *A*: distribution among cued trials of reaction times from the onset of the green go cue until start of movement. —, distribution of excluded trials with "reaction times" <250 ms. *B*: distribution of the time of movement on error trials in which the animals moved after the onset of the red no-go cue.

that the animals "reacted" to the no-go cue properly by withholding movement (rather than, for example, by deciding in advance not to move on a subset of trials, and moving–regardless of the cue—on the rest).

Figure 2 also suggests that on both cued and no-go trials, the animals needed between 200 and 300 ms to react to the cue. Therefore cued trials in which the animals initiated movement within 250 ms after the green cue (~10% of all correctly completed cued trials) were omitted from further analysis since those trials were unlikely to be truly cued.

To verify that the animals were not making covert movements on no-go trials that may have escaped detection by the joystick, we recorded surface EMGs from multiple muscle groups from the arm and shoulder of each animal. We used these EMG measurements previously to show that the timing of muscle activity was nearly identical between cued and self-timed trials with respect to the time that the joystick movement was first detected (Lee and Assad 2003). Averaged traces from the four muscle groups tested revealed no appreciable activity on no-go trials (Fig. 3). We also found no appreciable muscle activity on any type of playback trial (data not shown). On cued trials no muscle group that we examined became active earlier than ~200 ms before the joystick movement was first detected.

Putaminal neuronal activity

One hundred and sixty-two units from the arm-movement-related area in the posterior putamen were fully characterized using the main behavioral task. Based on these classification criteria, we found that putaminal units tended to cluster into two groups. The best separation among the clusters was afforded by plotting baseline-firing rate against the movement index (Fig. 4*A*), although comparing along other classification criteria also revealed distinctions between the two populations (Fig. 4*B*). PANs were defined as those units that had baseline firing rates <2 Hz and movement index >0.4. TANs were defined as those units that had baseline firing rates >1.5 Hz and movement index <0.4. The spike waveform and response to each classification task for a representative unit from each class is shown in Fig. 4*C*. Seventy-eight units were classified as PANs, 69 units were classified as TANs, and 15 units were classified as other. A more complete discussion of the activity of the PANs has been previously published (Lee and Assad 2003). However, some aspects of the PAN activity, such as responses on no-go and playback trials, were not reported previously and therefore will be addressed here. The activity of the TANs has not been previously reported and will be our main focus.

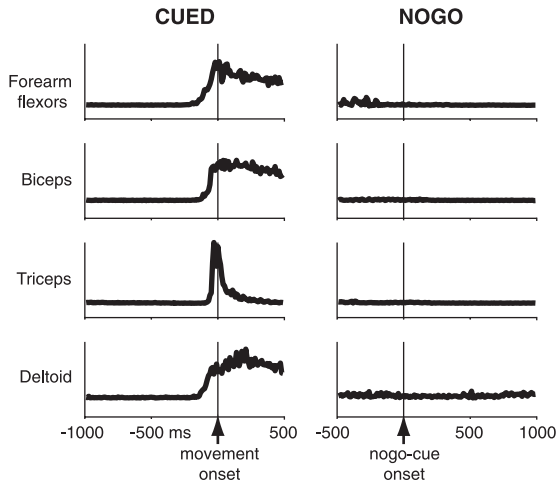


FIG. 3. Average electromyographic activity from forearm flexors, biceps, triceps, and deltoid muscles for cued trials aligned on start of joystick movement (*left*) and no-go trials aligned on no-go cue onset (*right*).

PAN activity on main task

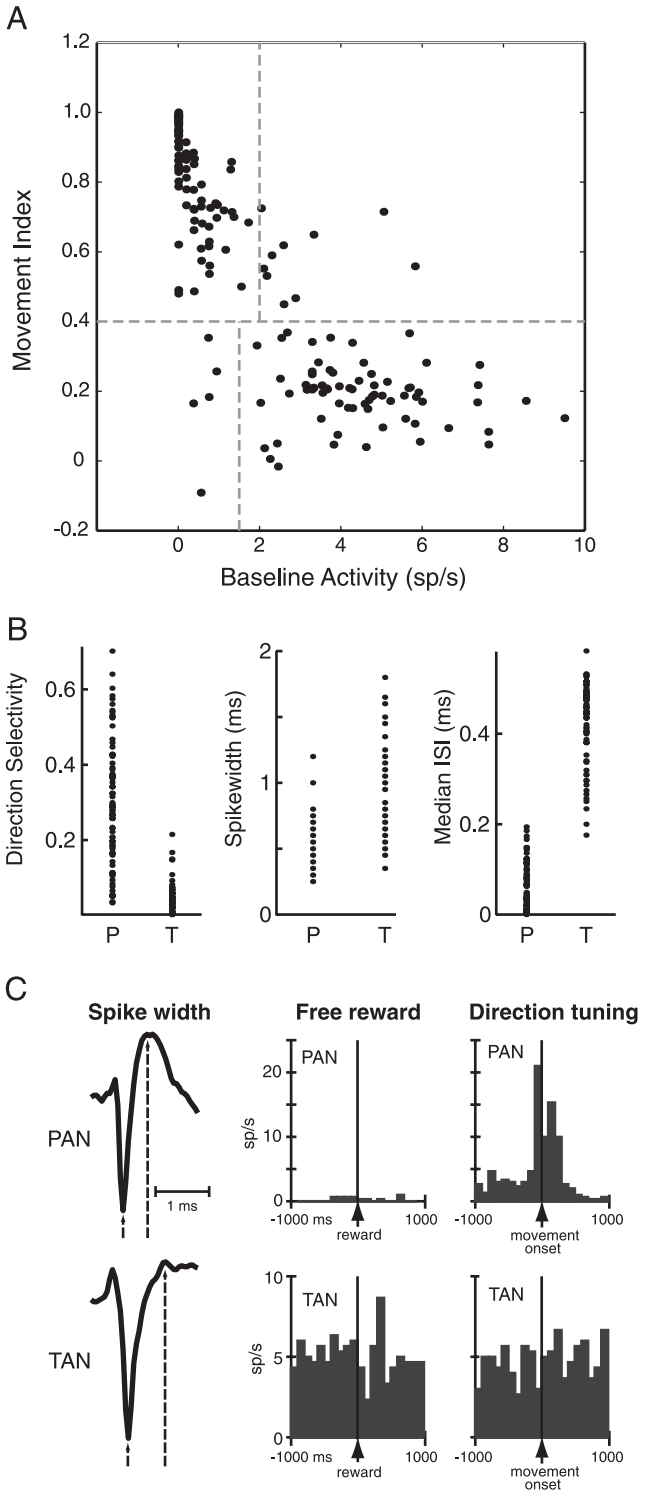
We start by examining the activity of PANs as this may be useful in interpreting the activity of the TANs. PANs responded robustly in trials requiring an arm movement (cued and self-timed trials), but responded less strongly in the no-go trials (Fig. 5*A*). In movement trials, there was a sharp rise in activity that on average peaked just before movement. A more subtle deviation from baseline was evident starting as much as 1,000 ms before the start of movement even on no-go trials. Although this increase was much smaller in amplitude than the perimovement burst of activity, it was nonetheless significant in most cells. Figure 5*B* shows a histogram of significantly activated cells for each 50-ms bin across the trial (see METHODS), and Fig. 5*C* shows a "population image" with each row representing the normalized activity of a different single PAN as a function of time (activity from all 78 PANs is thus shown).

For the no-go trials, this rise in activity began before the cue presentation and continued until ~200 ms after the cue. Activity then decreased back toward baseline except for an additional small, transient increase around 400 ms after no-go cue onset. For the 78 PANs, population-average activity was significantly higher than baseline around the time of no-go cue presentation, with 45/78 (58%) of individual PANs having significantly increased activity. This activity argues against the possibility that the animals simply waited passively for a go or no-go cue to appear; rather, the animals were likely in the process of initiating a self-timed movement (before the emergence of any EMG activity) when the no-go cue appeared and forced them to suppress the movement. As a function of time, the overall profile of the PAN activity on successfully completed no-go trials was remarkably similar to the distribution of errors due to movement on no-go trials (Fig. 2*B*). This observation is consistent with our previous analysis of PAN activity during self-timed and cued trials, which suggested that small increases in PAN activity are associated with an increasing propensity to move (Lee and Assad 2003).

TAN activity for nonmovement trials

Although most PANs responded robustly in association with movements, TANs are known to respond (typically with a decrease in activity followed by a rebound) to rewards and reward-associated sensory cues. We also found this to be the case. Figure 6*A* (*left*) shows the activity averaged over the entire population of 69 TANs for the free reward task in which rewards were delivered at unpredictable times. An upward and/or downward modulation in activity was clearly evident in nearly every one of the 69 TANs in the population image of normalized activity (Fig. 6*C*, *left*). The upward or downward modulation was statistically significant in 41/69 (60%) of the TANs.

TANs also responded robustly after the cue change on no-go trials (Fig. 6, *middle*). After cue onset, there was a decrease in activity followed by a large rebound (Fig. 6*A*). The rebound in activity peaked at ~450 ms, around the same time that movement occurred on cued trials. A robust response was apparent in most of the 69 individual TANs (Fig. 6, *B* and *C*). A significant modulation was detected in 41/69 (60%) of the TANS, similar to the free reward task.



In contrast, cue-related activity in the no-go *playback* condition was insubstantial (Fig. 6, *right*). Very few individual TANs showed significant modulation in the bootstrap-permutation test (which may be due at least in part to lower statistical power on playback trials for individual TANs; see METHODS). However, across the population of all 69 TANs, a significant downward modulation from baseline was detected at 200 ms postcue in the no-go playback trials ($P < 10^{-3}$; paired 1-tailed *t*-test; see METHODS). No significant upward modulation was detected. In comparison, the peak in spike rate at 400 ms postcue in the no-go active trials was significantly greater than the spike rate at the same time in the no-go playback trials ($P = 0.033$; paired 2-tailed *t*-test; see METHODS); likewise the dip in spike rate at 200 ms postcue in the no-go active trials trended to be lower than that in the no-go playback trials ($P = 0.066$; paired 2-tailed *t*-test). These differences are striking given that the no-go active and no-go playback conditions contained identical stimulus sequences and reward timing, and the animal did not make a movement in either case. The only difference between these trial types was that in the no-go active trials the animal had presumably been *planning* to produce a movement. Although it is difficult to establish if TAN activity on no-go active trials is related to the suppression of the planned response, it is clear that some other factor, in addition to the stimulus sequence and reward contingencies, affects whether or not a cue will elicit a response in these TANs.

TAN activity for movement trials

TANs, unlike PANs, showed little response in the population-average responses on trials that required an arm movement—the self-timed and cued trials (Fig. 7*A*), and also in the direction-tuning task (Fig. 8*A*). For the cued trials and direction-tuning trials, aligning trials on the go cue onset did not help to reveal a stronger population response. In contrast, the single-cell analysis clearly showed that the activity of many individual neurons was modulated up and/or down around the time of movement (Figs. 7*B* and 8*B*). Aligned on movement, a significant modulation was detected in 40/69 (58%) cells in self-timed trials, 25/69 (36%) cells in cued trials, and 25/69 cells (36%) in the direction-tuning task. Aligned on the go cue onset, a significant modulation was detected in 20/69 (29%) cells in cued trials and 40/69 cells (58%) in the direction-tuning task.

Whereas perimovement modulation in activity was clear and reliable for many individual TANs (Fig. 7, *B* and *C*), the

FIG. 4. Cell classification. *A*: quantitative criteria used to distinguish phasically active neurons (PANs) from tonically active neurons (TANs). Each point represents 1 cell. Spontaneous activity is plotted on the horizontal axis, and movement index is plotted on vertical axis. Classification criteria are indicated with dashed lines. PANs are in the upper left region. TANs are in the bottom right region. Cells falling into the other regions were unclassified. *B*: distributions of the values of other (unused) sorting parameters for PANs (P) vs. TANs (T). *C*: data from representative PAN (*top*) and TAN (*bottom*). Spike waveform for each unit is shown on the far left with points used to compute spike width indicated by dashed arrows (positive voltage deflection is in the upward direction). Left histogram shows the average activity during the free-reward task aligned on reward (the time of opening of the solenoid valve on the juice line). Right histogram shows the average activity during the direction-tuning task aligned on movement onset. Bins for histograms are 100-ms wide.

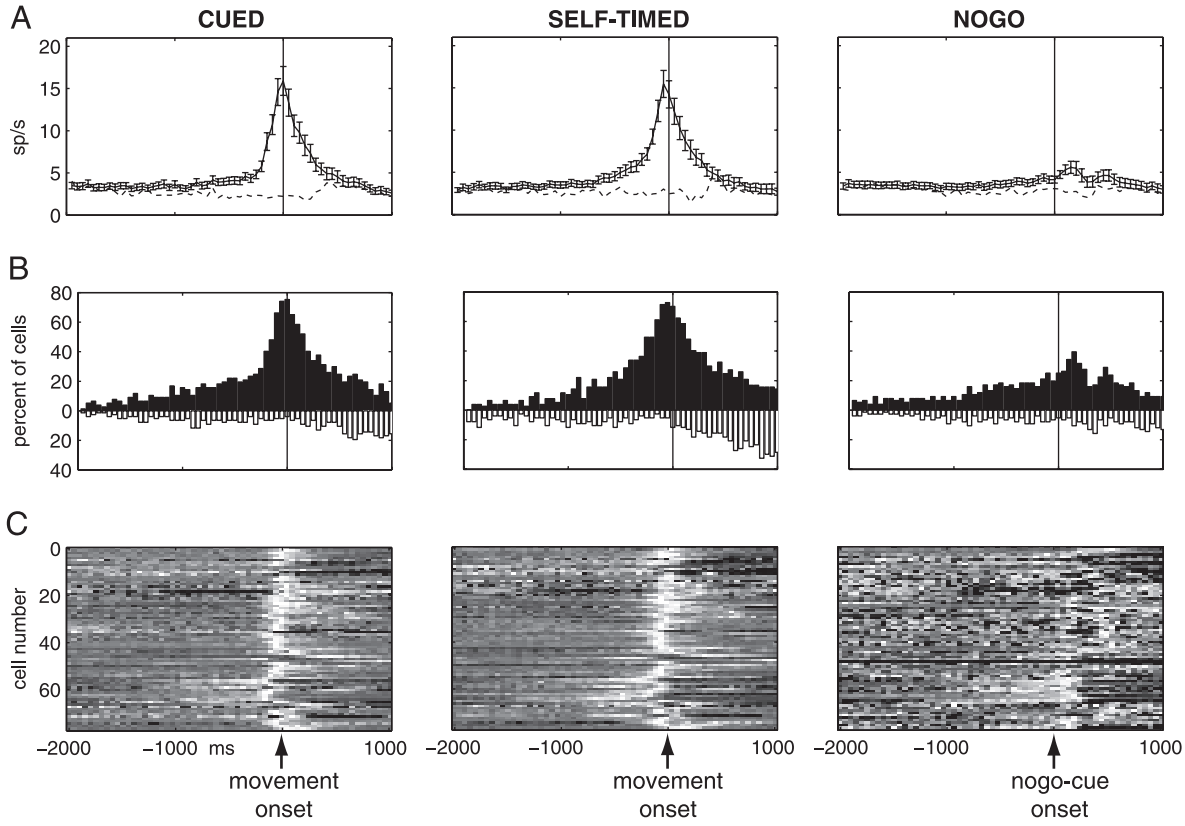


FIG. 5. PAN data. *A*: population average for cued (*left*) and self-timed (*middle*) trials aligned on movement onset and no-go (*right*) trials aligned on no-go cue onset (error bars are ±1 SE). Dotted line shows average activity for playback conditions. *B*: histograms of significantly up-modulated (*black*) and down-modulated (*white*) cells for each 50-ms bin during the trial period. The statistical significance of the activity modulation in each 50-ms bin was assessed using a bootstrap permutation test, which compared the mean firing rate in that bin to a distribution of mean firing rates constructed from a 1,000-ms baseline period (see METHODS). Population image for each condition, with each row reflecting normalized average activity for a different cell (entire population of 78 PANs is shown).

modulation was subtler in the population-average response (Fig. 7*A*)—certainly as compared with the free reward and no-go trials (Fig. 6*A*). This apparent discrepancy can be reconciled by examining only the bins for each cell that showed a statistically significant deviation from baseline (Fig. 9). Significantly modulated units were prevalent for no-go, self-timed, and cued trials, but that modulation was not well aligned among units for the self-timed and cued trials. Given that cells showed upward and downward modulations, a lack of alignment would tend to nullify the average population response. It is possible that the lack of alignment could be due to imprecision in determining the onset of the arm movement. For example, the timing of activation of arm muscles could vary with respect to the time that the actual joystick movement is detected. If so, then the onset of arm-muscle EMG activity should be similarly variable with respect to the onset of joystick movement on movement trials – but in fact we found sharp onsets to EMG activity on cued trials (Fig. 3) and also on self-timed trials (Fig. 4 of Lee and Assad 2003). Thus the lack of alignment on cued and self-timed trials appears to reflect a genuine variability in the activation of TANs relative to the start of movement.

It is also possible that this lack of alignment tended to reduce the responses of *individual* TANs averaged across multiple trials. For example, for self-timed and cued trials (Fig. 9, *A* and *B*) many individual TANs showed a profile of significant modulation that was more stretched out in time than for no-go trials (Fig. 9*C*). Although it is possible that this "smear" is a different activation profile when an arm movement is made, it may also reflect lack of trial-by-trial alignment relative to the start of movement for individual neurons. Consistent with the latter possibility, we found that the amplitude of the modulation, measured as the difference between the peak and trough of the response, was slightly larger for no-go trials than cued or self-timed trials (no-go: 9.1 spike/s; cued: 7.4 spike/s; self-timed: 7.5 spike/s). If TAN activity is not cleanly aligned to measurable events such as the cue onset or movement onset, there may exist some other "internal" alignment event that was not measured in our experiment. Regardless, it is notable that many TANs showed a clear modulation of activity on self-timed trials in which we did not provide an external cue that could have triggered the response.

TAN activity for playback trials

Playback trials for the self-timed and cued conditions showed a very different response profile than the corresponding active trials. TANs showed a robust response when aligned to the onset of the *visual* motion (the start of motion of the spot on the display monitor; Fig. 10, *left* and *middle*). Although many cells showed clear modulation that was comparable to that of the free reward and no-go active conditions (Fig. 10*B*), we generally did not have a sufficient number of playback trials to detect a statistically significant modulation for individual

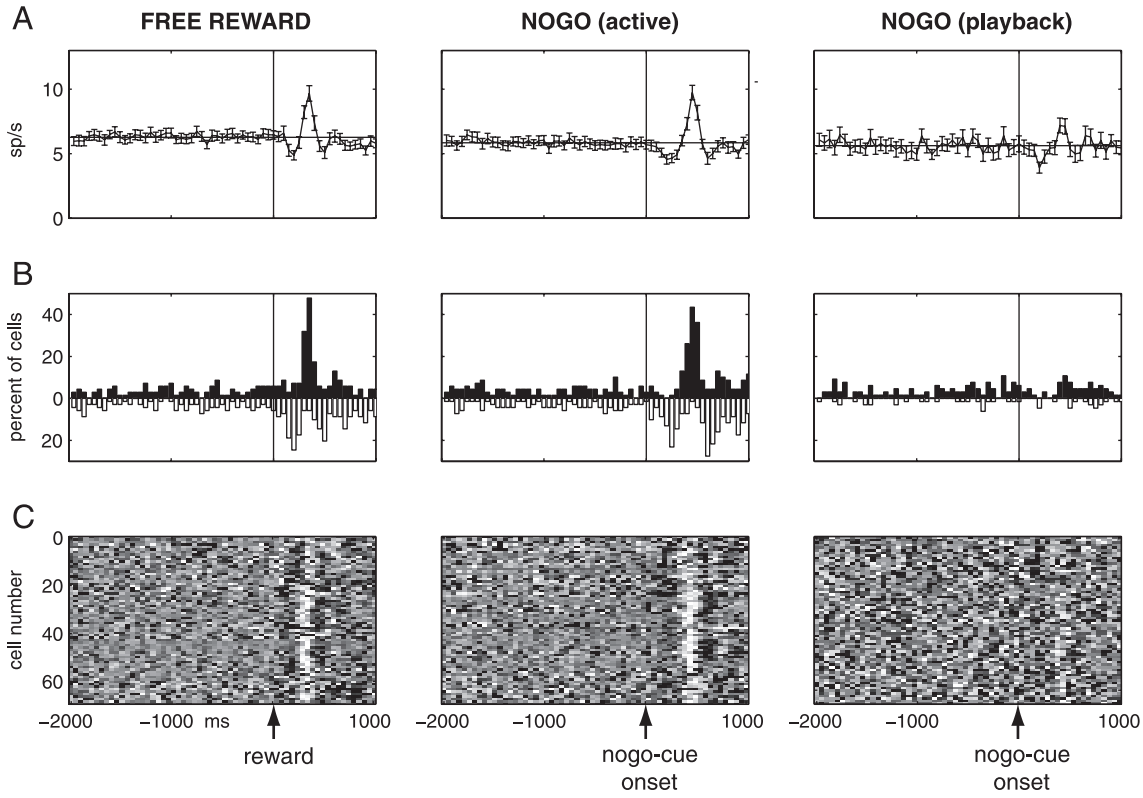


FIG. 6. TAN data for no-movement trials. Data shown are for the free-reward task (*left*), no-go active trials aligned on no-go cue onset (*middle*), and no-go playback trials aligned on no-go cue onset (*right*). Same format as in Fig. 5.

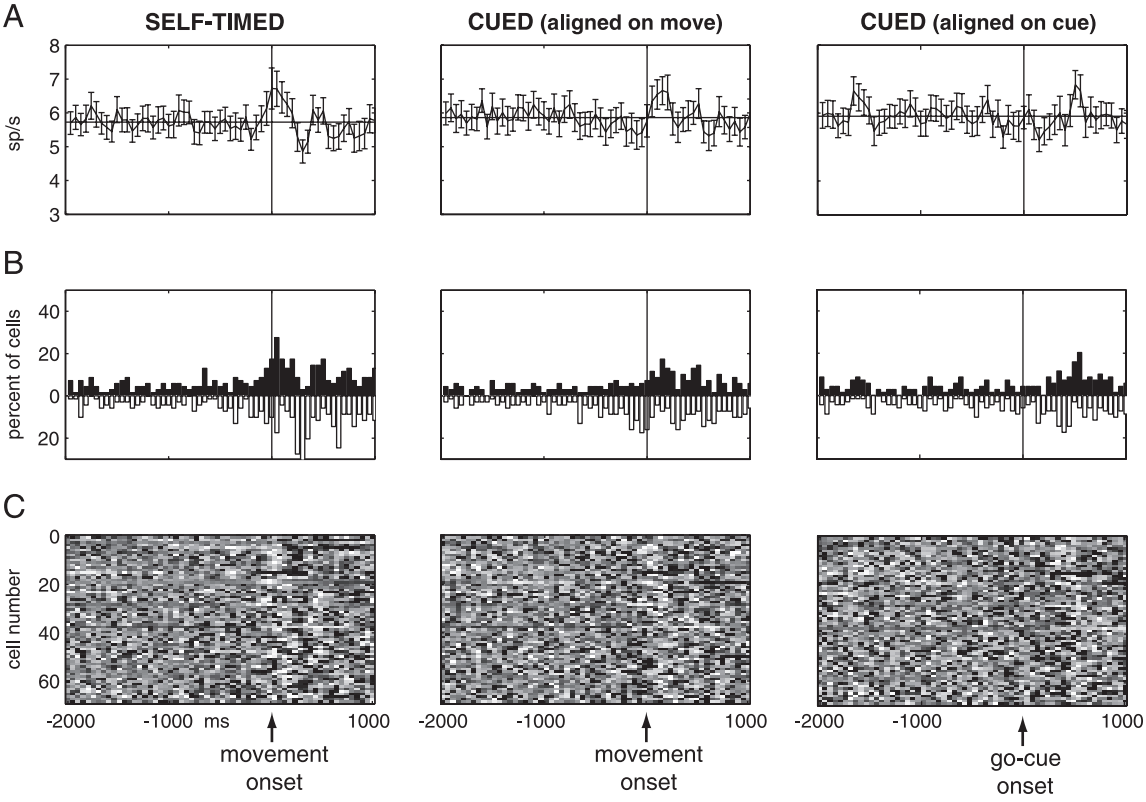


FIG. 7. TAN data for movement trials. Data shown are for self-timed trials (*left*), and cued trials aligned on movement onset (*middle*) and go cue onset (*right*). Same format as in Fig. 5.

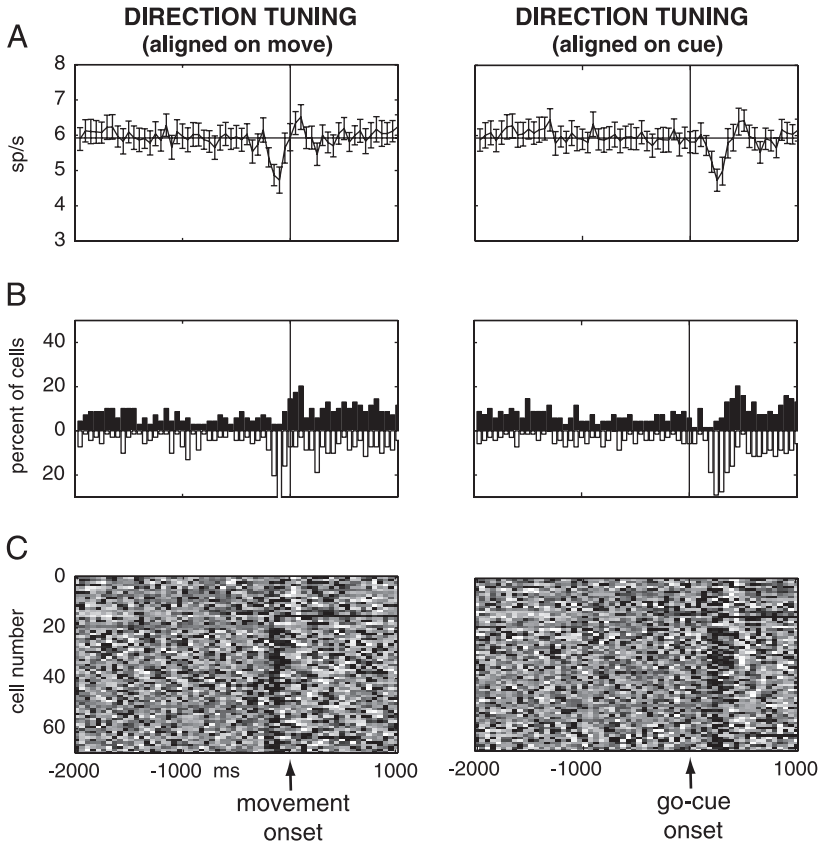


FIG. 8. TAN data for the direction-tuning task, aligned on movement onset (*left*) and go cue onset (*right*). Same format as in Fig. 7.

cells (see METHODS). However, across the population of all 69 TANs, both the peaks and dips of activity for these playback conditions were statistically significantly different from baseline (cued playback trials aligned on dot movement: dip at 250 ms, $P < 10^{-5}$; peak at 550 ms, $P < 10^{-4}$; self-timed playback trials aligned on dot movement: dip at 250 ms $P < 10^{-7}$; peak at 500 ms, $P < 10^{-8}$; 1-tailed paired *t*-test –see METHODS). Interestingly, no statistically significant peak was seen in the cued playback trials when aligned to the go cue onset (Fig. 10, *right*), although a significant dip was detected at 600 ms ($P < 10^{-3}$), which is presumably due to the dot-movement event that occurred just after the go cue onset.

TAN summary data

Table 1 compiles the percentages of cells the activity of which was significantly modulated upwardly or downwardly in the three main-task conditions and also in the free reward and the direction-tuning tasks. For each condition, the analysis was performed during the 600-ms interval after the cue onset and/or joystick-movement onset (if present in that condition) and after reward. There are a number of interesting aspects to these data. First although 60% of cells were significantly modulated after reward delivery in the free reward condition, responses to reward were much less prevalent in the other tasks. In addition, although upward and downward modulations could be observed in many cells, for most conditions, the percentage of cells that showed statistically significant upward *and* downward modulations was no greater than the joint proportion of upwardly and downwardly modulated cells considered separately. Thus in our data set there was no detectable relationship between the prevalence of upward or downward modulations in single units.

DISCUSSION

Previous studies have shown that the way that TANs respond to external events can be dominated by behavioral context. TAN responses to sensory stimuli and primary rewards are highly dependent on the temporal relationships between stimuli and rewards, suggesting that TANs relay signals about the predictability of external events. This may be important for conditioning and procedural learning in the striatum (reviewed by Apicella 2002; Graybiel 1995). Our results are consistent with the general observation that TAN responses are affected by behavioral context, but we extend these observations in several novel directions.

First, we found that other factors beyond reward predictability can affect whether an external stimulus can evoke a response from TANs. On active and playback no-go trials, the same visual cue was presented (fixation spot turning red), preceding reward by the identical temporal interval (2,000 ms), yet most TANs responded much more vigorously to the cue on active than playback no-go trials (Fig. 6). Because this difference cannot be attributed to the visual stimulus sequence, task timing, physical movement, or reward contingencies, it must reflect some difference in the animal's internal state ("internal" in the strictly operational sense that response differences cannot be attributed to measurable parameters of the external world). One possibility is that the animal is generally more aroused or vigilant during active trials than during playback trials. On active trials the animals were engaged in planning a

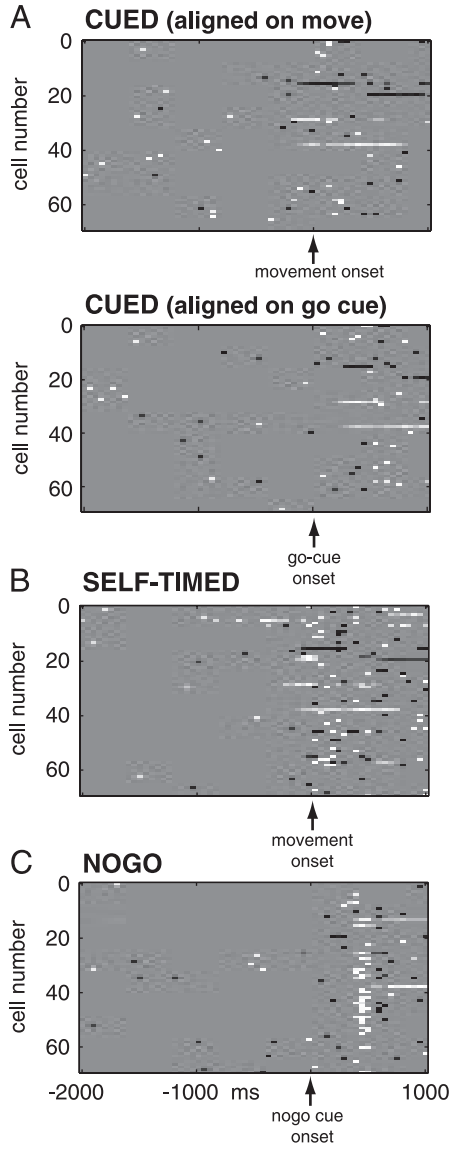


FIG. 9. Population images of the all 69 TANs indicating the timing of statistically significant modulation only. Light and dark pixels indicate bins that were significantly greater and less than baseline, respectively (see METHODS). Gray pixels represent bins that did not significantly deviate from baseline. *A*: cued trials aligned on movement onset (*top*) and go cue onset (*bottom*). *B*: self-timed trials aligned on movement onset. *C*: no-go trials aligned on no-go cue onset.

potential hand movement and in detecting and discriminating changes in the color of the fixation spot, whereas on playback trials, the animals had only to maintain gaze on the fixation spot. The reduced task load during playback trials might lead to a nonspecific reduction in the responsiveness of TANs. However, TAN responses were at least as vigorous on playback self-timed and cued trials (Fig. 10) than on the corresponding active trials (Fig. 7), suggesting that reduced arousal or vigilance were not responsible for the reduced responses on playback no-go trials.

What other differences in internal state could account for the stronger TAN responses on active than playback no-go trials? We designed the task such that during the active trial block the animals would plan to move without external prompting, presumably on every trial. This design, plus the temporal distribution of movement errors on no-go trials (Fig. 2*B*), argues strongly that the animals had to actively suppress the plan to move when the red no-go cue appeared during the active trial blocks. In contrast, during the playback block, the animals likely had no prior plan to move when the red no-go cue appeared because they never had to move on any trial. The strong TAN responses on *active* no-go trials might thus be related to the real-time suppression of movement. An intriguing hypothesis is that TAN activation could contribute to suppressing movement by directly influencing striatal projection neurons. For example, if TANs exert an inhibitory (perhaps cholinergic) influence on the projection neurons, the brisk rebound in TAN activity following the no-go cue (Fig. 6) might help to drive the PAN activity back to baseline levels (Fig. 5). However, the peak of the average rebound in TAN activity occurred later than either the decrease in PAN activity following the no-go cue or the animal's "reaction time" for suppressing a movement (inferred from the temporal distribution of no-go errors in Fig. 2*B*). Thus while TANs might contribute to the ongoing process of movement suppression, they likely do not initiate the suppression.

One important caveat to the foregoing argument is that it is not clear what the state of "suppression" is on playback trials. One might argue that total suppression is required, or rather that *no* suppression is required because movements are never required on playback trials. The bottom line is that we observed robust modulations in firing of both TANs and PANs on active no-go trials, but not playback trials, which suggests that active suppression of movement is required on active trials, but not playback trials. Interestingly, the transient increase and suppression of PAN activity that we observed on no-go trials was not observed in earlier studies of anterior striatal PANs that included no-go trials (Romo et al. 1992; Schultz and Romo 1988, 1992), possibly because in those studies the no-go trials were not interleaved with self-timed or -initiated movements.

Any direct involvement of TANs in movement suppression may have important implications for understanding movement disorders such as Parkinson's disease. For example, anti-cholinergic therapies are commonly used to treat Parkinson's disease, although the basis of their action is poorly understood (Lang and Blair 1989). If TANs are indeed cholinergic interneurons, they may provide an inhibitory signal to PANs that could contribute to suppressing movement as we have suggested in the preceding text. In the Parkinsonian condition, however, the activity of striatal projection neurons may be reduced due to loss of dopaminergic input to the striatum. Anti-cholinergic therapies might facilitate the activity of projection neurons—and thus facilitate movement—by reducing the suppressive influence of cholinergic interneurons. This disinhibition might be mediated by reducing the tonic activity of TANs, or the phasic activity, or both.

The idea that TANs may play a role in the real-time control or suppression of movement differs in some respects from the prevailing view that TANs are involved in reward/feedback signaling and associative learning (Apicella 2002; Graybiel 1995). It may simply be that different aspects of TAN activity provide separate movement-control signals and feedback signals, much like has been suggested for the activity of midbrain dopaminergic neurons (Romo and Schultz 1990).

Alternatively, the TAN responses that we observed on no-go trials might not be directly involved in movement control but

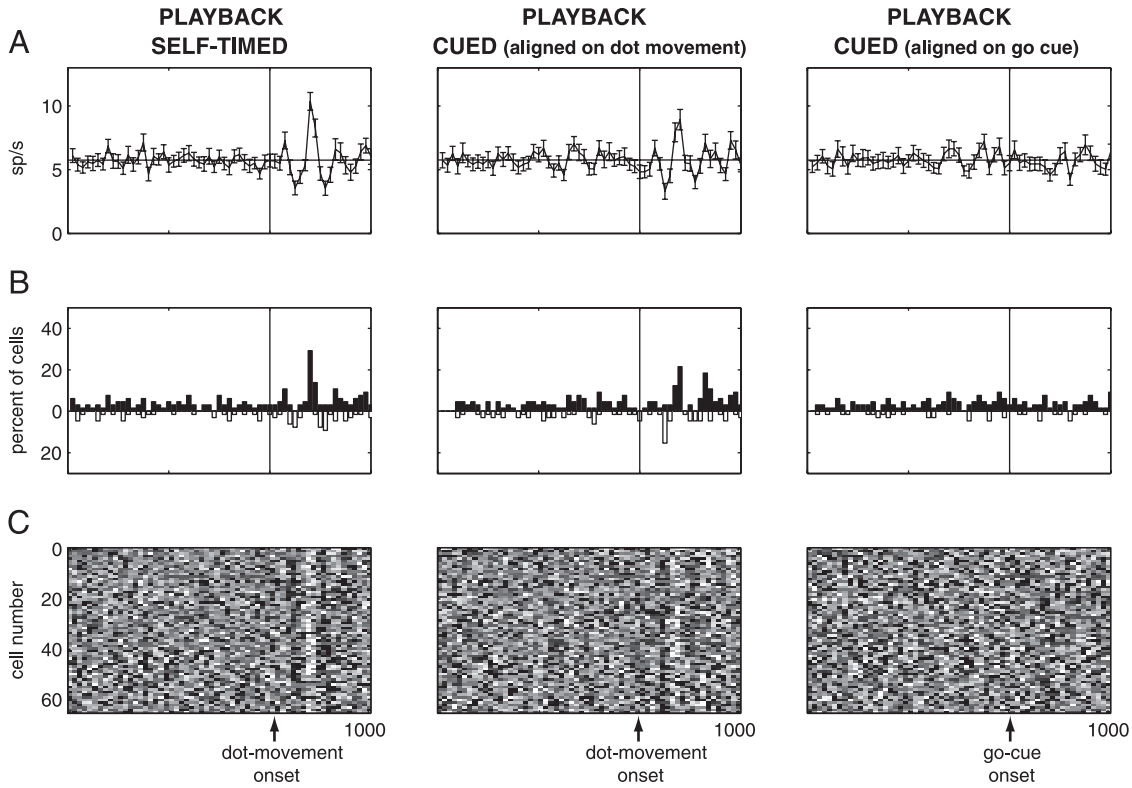


FIG. 10. TAN data for playback trials. Data shown are for self-timed-playback (*left*), cued-playback trials aligned on movement onset (*middle*), and cued-playback trials aligned on go cue onset (*right*). Same format as in Fig. 5.

rather might provide a feedback signal that the movement had been successfully suppressed. "Performance-monitoring" signals of this sort might be important for procedural learning in the striatum (Logan 1985). Neuronal signals that could subserve performance monitoring have been described for supplementary eye field and anterior cingulate neurons during a saccade-suppression task (Ito et al. 2003; Stuphorn et al. 2000). If TANs are involved in performance monitoring, it might be expected that their responses would be different on error trials in which movement was *not* successfully suppressed following the no-go cue. However, in our experiment, movement errors on no-go trials were infrequent because they presumably occurred only in fortuitous cases in which the animals happened to be on the verge of making a self-timed movement when the no-go cue occurred (Fig. 2*B*). Errors of this sort can be induced more frequently using a command/delayed-countermand sequence (Logan 1994; Schall et al. 2000), which we are also presently investigating (Eskandar and Assad 2003). Nonetheless, the idea that TANs may provide a performance-monitoring signal might provide a unifying explanation for our results and previous results from other labs: a performance-monitoring signal may provide *internal* feedback of a task well done (movement successfully suppressed, etc.) in the same way that a reward signal provides *external* feedback of a task well done. Both types of feedback signals could be important for associative learning.

A second main finding of our study was that TANs can be activated in the absence of external inputs. Previous studies emphasized that TANs respond to sensory signals that predict primary reward (or aversive stimuli) or predict other reward-predicting stimuli. By training the animals to make self-timed movements, we found that many TANs became active around the time of movement when no external sensory trigger was provided to prompt movement (Fig. 7). Because the movement times on self-timed trials were broadly distributed (over several seconds) after the last external stimulus that could have served as a cue to move (Lee and Assad 2003), the TAN activation was clearly coupled to the time of the hand movement.

Most TANs became active around the time of onset of EMG activity on self-timed trials (Figs. 7 and 3). It is thus possible that the activation of muscles elicited a somatosensory or proprioceptive signal that triggered the TAN activation. How-

TABLE 1. *Percentages of TANs showing statistically significant increases or decreases in firing rate for the various trial types*

	NG_{cue}	NG_{rew}	ST_{mov}	ST_{rew}	CU_{cue}	CU_{mov}	CU_{rew}	DT_{cue}	DT_{mov}	FR_{rew}
Increase	45%	10%	42%	7%	20%	22%	12%	29%	33%	52%
Decrease	30%	12%	32%	0%	13%	17%	10%	30%	7%	23%
Either	60%	22%	58%	7%	29%	36%	22%	58%	36%	60%
Both	16%	0%	16%	0%	4%	3%	0%	10%	4%	14%

Trial types are abbreviated as follows: NG, no-go; ST, self-timed; CU, cued; DT, direction tuning; FR, free reward. Data refer only to non-playback trials. Subscripts after trial-type labels indicate the period in which the firing rate was analyzed: cue, cue onset; rew, reward; mov, movement onset. "Either" refers to cells that showed either increases or decreases in activity, whereas "both" refers to cells that showed both increases and decreases in activity.

ever, the activation of TANs was clearly less prevalent on cued trials than self-timed trials (Fig. 7) even though the same hand movement was made in both cases. This argues that the TAN activation on self-timed trials is not exclusively due to movement but rather reflects an internal process, such as timing. This does not mean that TANs are involved in timing per se but rather that TANs may be monitoring the conjunction of primary rewards with other neuronal signals besides sensory signals. For example, if TANs can "learn" the association of sensory events that occur consistently before rewards or aversive stimuli, they may also learn the association of internal signals, such as timing signals or motor commands, that consistently precede rewards. The selective activation of TANs on self-timed trials is also reminiscent of the premovement increases in PAN activity that we previously reported for self-timed but not cued trials (Lee and Assad 2003).

A related observation was that the activation of TANs was aligned more loosely with the onset of movement on self-timed trials (Fig. 9*B*) than to the no-go cue on no-go trials or the time of reward delivery in the free-reward task (Fig. 6). This looser alignment was unlikely to have been due solely to methodological difficulties in determining the time of movement onset; rather the poorer alignment could reflect a less faithful coupling to internal events like internal timing signals. Recent work on neuronal timing mechanisms suggests that timing signals may evolve as gradual changes in neuronal activity toward a threshold level (Janssen and Shadlen 2005; Leon and Shadlen 2003). TANs might couple less well to slowly developing neuronal signals than to more abrupt signals that might occur in response to sensory stimuli or primary rewards. Regardless of the reason for the looser alignment with movement onset, it is interesting that the looser alignment seemed to result in a "distorted" population-average signal among different TANs and likely for single TANs as well. Previous studies have also reported differences in the response profiles for TANs under different circumstances (e.g., Ravel et al. 1999). Some of this variation may also be due to differences in the fidelity of coupling of TAN responses to particular external events.

A final point is that on both cued-playback self-timed-playback trials we were surprised to see that the population responses clearly followed the start of the dot's movement (Fig. 10*A*). In contrast, the pattern of TAN responses on *active* self-timed and cued trials was quite different, with many responses leading the start of the dot's movement (Fig. 7). These corresponding active and playback trials were again identical in terms of the visual stimulus sequence and task timing but differed in terms of the animals' actions and the temporal relationships of those actions to the external cues. For example, on playback self-timed and cued trials, the dot's movement consistently preceded reward and thus could come to be associated with reward. However, on active trials, signals related to initiating the hand movement would have consistently preceded the start of the dot's movement and thus could come to be associated with reward. A similar temporal interplay of associable signals was suggested by Sardo et al. (2000) to explain how an instruction signal that consistently precedes a trigger signal could come to be associated with reward. It will be important to examine in more detail the rules that govern the way that TANs associate multiple external and internal signals with reward (Apicella 2002). These mechanisms will be key to unraveling how TANs ascribe motivational significance to an animal's actions as well as events in the external environment.

GRANTS

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