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Putaminal Activity for Simple Reactions or Self-Timed Movements

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Lee, Irwin H. and John A. Assad. Putaminal activity for simple reactions or self-timed movement. *J Neurophysiol* 89: 2528–2537, 2003. First published January 15, 2003; 10.1152/jn.01055.2002. To examine the role of basal ganglia-cortical circuits in movement initiation, we trained monkeys to make the same arm movements in two ways—in immediate reaction to a randomly timed external cue (cued movements) and also following a variable delay without an explicit initiation signal (self-timed movements). The two movement types were interleaved and balanced in overall timing to allow a direct comparison of activity before and during the movement. Posterior putaminal neurons generally had phasic, movement-related discharges that were comparable for cued and self-timed movements. On cued movements, neuronal activity increased sharply following cue onset. However, for self-timed movements, there was a slow build-up in activity that preceded the phasic discharge. This slow build-up was time-locked to movement and restricted to a narrow time window hundreds of milliseconds before movement. The difference in premovement activity between cued and self-timed trials was present before the earliest cue-onset times and was not related to any differences in the overall time-to-move between the two types of trials. These features suggest that activity evolving in the basal ganglia-cortical circuitry may drive the initiation of movements by increasing until an activity threshold is exceeded. The activity may increase abruptly in response to an external cue or gradually when the timing of movements is determined by the animals themselves rather than an external cue. In this view, small changes in activity that occur in advance of the much larger perimovement neuronal activity may be an important determinant of when movement occurs. In support of this hypothesis, we found that even for cued movements, faster reaction times were associated with slightly higher levels of activity hundreds of milliseconds before movement.

INTRODUCTION

A central question in motor control is how neural circuits determine the particular moment to initiate voluntary movements. Evidence from human movement disorders such as Parkinson's and Huntington's diseases suggests that basal ganglia-cortical circuits may be involved, but the exact role of these circuits is unclear. One possibility is that the organization of the basal ganglia-cortical circuitry could act to amplify small increases in neuronal activity, leading to movement. The basal ganglia form a series of parallel loops with cortex (Albin et al. 1989; Alexander et al. 1986; DeLong 1990; Hoover and Strick 1999), which could provide positive feedback to evolve wide-scale increases in neuronal activity. It may thus be possible to look back in time before movements to identify neuronal activity that eventually drives movement.

However, assuming there exists a neurophysiologic distinction between the initiation and generation of movement, activity that precedes movement may be related to either process. One approach to making this distinction is to compare neuronal activity preceding the same movement when that movement is initiated in different ways. For example, movements can be made in immediate reaction to an external sensory cue (simple reactions) or can be "internally triggered" in that they do not immediately follow any external cue (Gilden et al. 1995). Evidence from event-related potentials (Deecke 1996), brain imaging (Jahanshahi et al. 1995; Jenkins et al. 2000), and single-unit studies in monkeys (Kimura et al. 1992; Okano and Tanji 1987; Schultz and Romo 1992) suggests that, while there are intriguing differences in the patterns of brain activity between externally and internally triggered movements, the two types of movement generally involve common areas in the basal ganglia and cortex. This could reflect common circuits and mechanisms for movement initiation. The goal of this study is to examine mechanisms for movement initiation by making a closer comparison of neuronal activity during externally and internally triggered movements.

While it is straightforward to train monkeys to make externally cued movements, it is trickier to control self-initiated movements. For example, one could allow monkeys to make unrestricted spontaneous movements, but this would be unlikely to yield sufficiently reproducible movements. Another approach is to train monkeys to make only one type of movement to receive rewards but allow the animals freedom to choose when to move. Neuronal activity could be compared with when the same movements are made in immediate reaction to an external sensory cue. However, granting monkeys complete temporal freedom is impractical since the animals would be motivated to move without delay to receive rewards, and each reward might thus provide a cue for the subsequent movement. A more feasible approach is to provide the animals a "start-of-trial" cue and then to require them to wait for a fixed interval of at least several seconds before moving, so the animals do not react immediately to the start-of-trial cue. The expiration of the wait period is not signaled. We refer to such a movement as *self-timed*. Self-timed movements differ fundamentally from simple reactions in that the time from an external cue until movement is self-chosen, whereas simple reaction times are not self-chosen (Gallistel and Gibbon 2000;

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Gilden et al. 1995). Variations of self-timed movements have been examined in several previous studies (Okano and Tanji 1987; Schultz and Romo 1992).

Here we used a novel task to compare self-timed and externally triggered movements. We designed the task with two goals in mind. First, we wanted to interleave self-timed and externally cued movements to avoid the animals' adopting a different preparatory state as they might if they could predict whether an upcoming trial would be self-timed or externally cued. For instance, we did not want the animals to suppress movement before cue onset as they would likely do if the cued trials had been presented in a block. One way to interleave trials might be to train animals that they may move on their own if a "go" cue does not appear within a set amount of time. However, in that case, every self-timed trial would take longer than every externally cued trial, and it would be difficult to guarantee that any differences in neuronal activity were not due simply to differences in elapsed time. Our second goal was thus to ensure that overall elapsed time from the start of a trial until movement was similar between self-timed and externally cued movements.

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. For each cell, the preferred direction of movement, determined previously using a direction-tuning task (see *Electrophysiological recording*), was used on every trial. 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.

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 without reward. 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 following 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 without any further change of the visual stimulus. Such trials were designated "self-timed." On other trials, the fixation spot changed color at a random time 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." To prevent the animals from ignoring the cue (and simply moving after the 2,000-ms delay), the fixation spot turned red on other trials, indicating that the animal had to withhold movement for an additional 2,000 ms to receive reward. These trials were designated "nogo." For both cued and nogo 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.

Since 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 were too skewed toward early cue-appearance times, 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. Following each self-timed trial, the decay constant was decreased by 50 ms. Following any combination of two cued or nogo 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, go or nogo, was selected at random with an even chance of either outcome. For both animals, the decay constant settled around 600 ms. This procedure was very effective in eliciting similar frequency and similar overall timing of the various trial types (see RESULTS).

Electrophysiological recording

Once the animals were trained, they were surgically implanted with a head post, scleral search coil, and recording chambers. The cham-

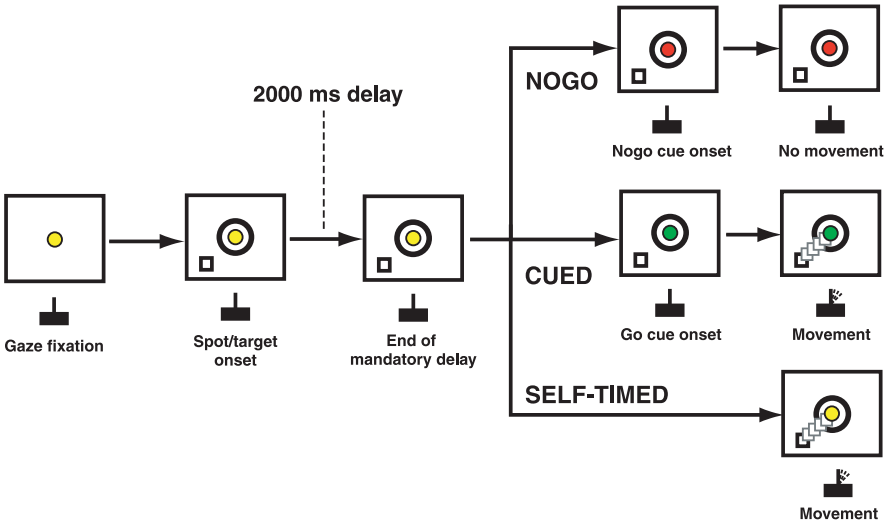

FIG. 1. Design of experiment (not drawn to scale). Each panel depicts the stimulus monitor at 1 phase of a trial. Joystick position is shown below each panel to indicate whether movement has begun. The smaller, central, round spot is the gaze-fixation spot, which also served as an indicator to move on cued trials or withhold movement on nogo trials. Circle surrounding the fixation spot is the target of movement, and peripheral square is the spot of light that the animal moved to the central target.

bers were placed in the left hemisphere, since 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 approximately 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 (Fig. 2). 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 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.

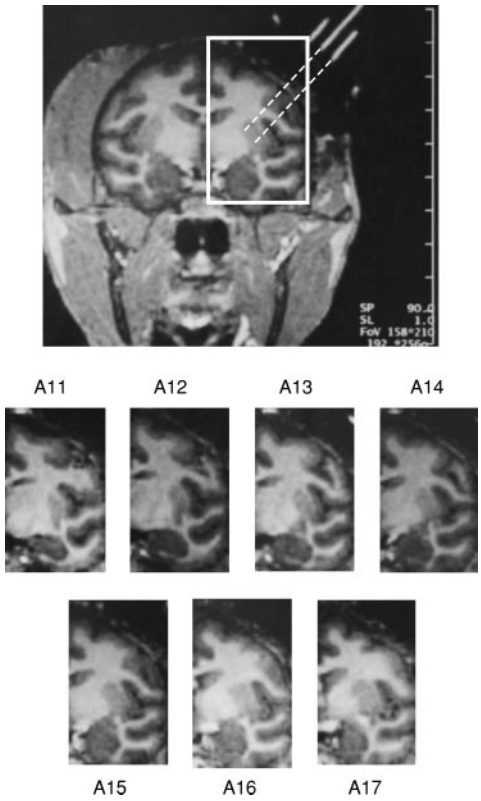

FIG. 2. MRI from monkey M. Distance between ticks of the scale bar (right edge of the large image) represents 1 cm. In the large image, capillary tubes filled with mineral oil can be seen as 3 white linear objects. All 3 tubes run parallel to the central axis of the chamber, and the longest tube corresponds to medio-lateral center of the chamber. Dashed white lines indicate approximate medio-lateral boundaries of electrode penetrations. Smaller images are taken from an area corresponding to the white rectangle on the larger image. Labels on each section indicate location along anterior-posterior axis.

Horizontal and vertical components of the eye position and joystick displacement were recorded at 200 Hz. 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 the inner forearm. 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 phasically active neurons (PANs) and tonically active neurons (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 quantitative classification tests. First, all units were tested with the direction-tuning task. We calculated a movement index equal to the (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. Second, all units were tested with a "free reward" task, in which the monkey sat quietly while receiving juice rewards at random intervals. From this task we 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). We also measured the width of the averaged extracellular action-potential waveform for each unit, because TANs have been reported to have wider action potentials than PANs (Crutcher and DeLong 1984). 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. We defined PANs as those units that had baseline firing rates below 2 Hz and movement index above 0.4.

Data analysis

The experiment was designed to detect increases in activity preceding movement that might be specific to internally initiated movements. However, since PANs have very low baseline firing rates, the statistical power for detecting statistically significant increases in premovement firing *for individual units* would be expected to be limited. For example, with mean firing rates of 6 versus 4.5 spikes/s for self-timed and cued trials, respectively (taken from RESULTS), and assuming Poisson spike trains, spike counts taken over a 250-ms interval would have a mean and variance of 1.5 (self-timed) and 1.1 (cued). Using a normal approximation, the probability of obtaining a significant difference over 24 trials (a typical number of trials collected for each trial type) would be only 32% (1-tailed *t*-test; $P < 0.05$)—and that assumes 100% of cells actually have a real difference in firing. By comparison, for a rate of 15 versus 20 spikes/s, the power for detecting the same percentage change in firing rate at a significance level of 5% would be 66%. Thus rather than concentrating on

single unit activity, most of the analyses were done across the population of all PANs.

RESULTS

Behavioral controls

To determine whether the staircase procedure successfully balanced the overall timing of self-timed and cued trials, we compiled the distributions of movement-onset times relative to the *spot/target onset* for self-timed trials (Fig. 3*A*) and cued trials (Fig. 3*B*). The distributions of self-timed and cued movements largely overlapped, to the latest movements approximately 5,000 ms after the spot/target onset. For both animals the distribution of self-timed movements rose toward the end of the 2,000-ms wait period, suggesting that the animals tried to time the wait period. These premature movements were by definition *not* cued (no go-cue or nogo-cue ever occurred before 2,000 ms). However, since we wanted to compare self-initiated and cued trials with similar overall timing, the premature movements were not included among self-timed trials in the main analysis. The mean movement times for cued trials were 2,690 ms for monkey S and 2,767 ms for monkey M, and mean movement times for self-timed trials were 2,530 ms for monkey S and 2,769 ms for monkey M (excluding premature movements). Thus differences in elapsed time per se were unlikely to account for any differences in neuronal firing between the two trial types, although this would be important to verify.

We also needed to examine whether cued and self-timed trials were evenly interspersed. If trials were instead clustered, the animals may have determined in advance the type of trial they would perform, creating differences in their preparatory and/or motivational state before each trial. For example, the monkeys may have been more motivated to make self-timed movements near the beginning of sessions and more likely to wait for the cue onset late in sessions. Our staircase procedure should have acted to eliminate such bias, but this must be verified. To examine this, we analyzed the occurrence of se-

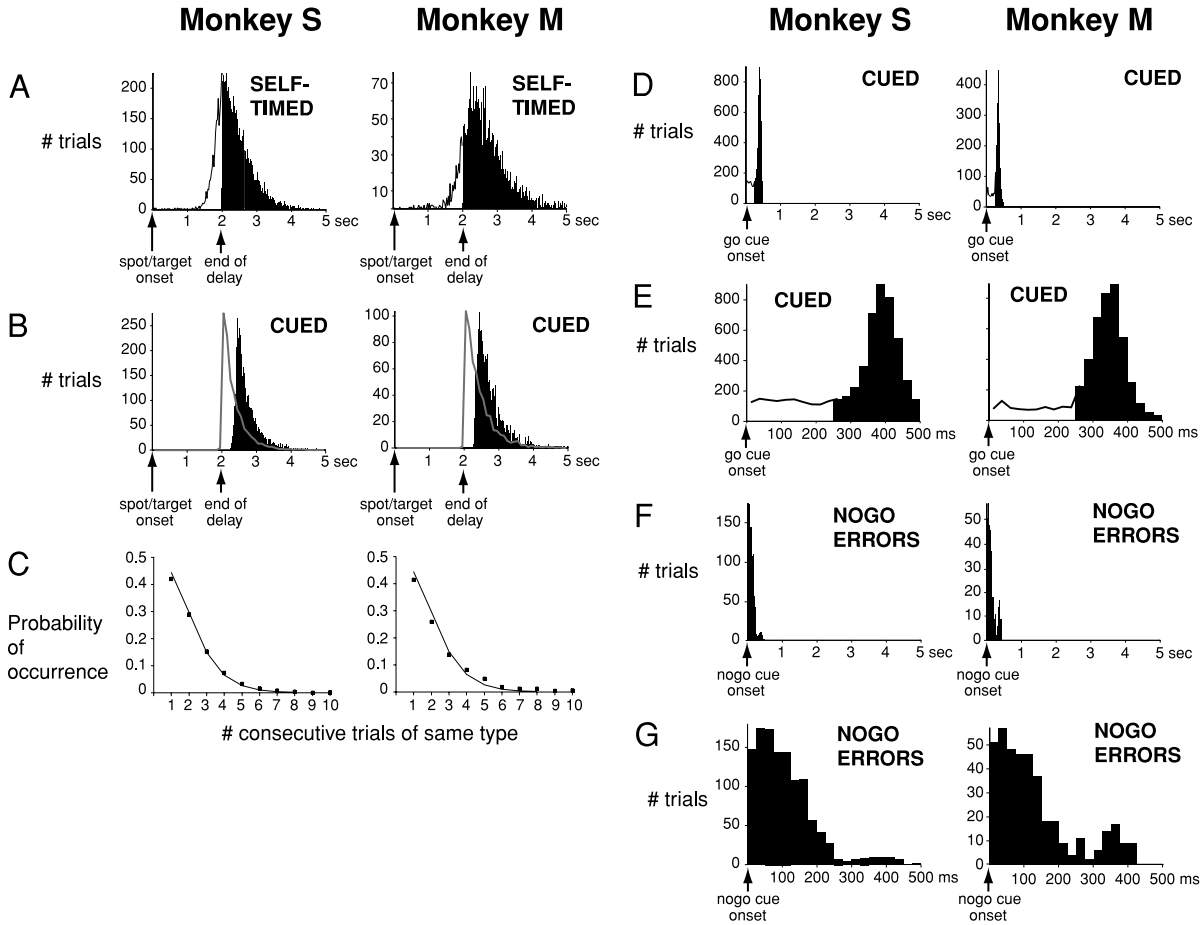

FIG. 3. Behavioral controls for each animal. *A*: distribution among self-timed trials of time from spot/target onset until start of movement. Thin line indicates the distribution of premature movements in which movement was made before the end of mandatory 2,000-ms delay. *B*: distribution among cued trials of time from spot/target onset until start of movement. Superimposed thin line indicates the distribution of cue-onset times. *C*: distribution of the number of trials occurring in sequences of 1,2, . . . ,10 consecutive trials of the same type (cued, self-timed, or nogo) from the actual data (squares) and that expected from chance given an unbiased random choice on each trial (continuous line). The chance probability of a trial occurring in a sequence of N consecutive trials of the same type is $N(1/3)^{(N-1)}/\left[\sum_{n=1}^{\infty} n(1/3)^{(n-1)}\right]$. *D*: distribution among cued trials of reaction times from the onset of the green go cue until start of movement. Thin line is for excluded trials with "reaction times" <250 ms. *E*: same as *D* but with expanded time scale. *F*: distribution of the time of movement on error trials in which the animals moved following the onset of the red nogo cue. *G*: same as *F* but with expanded time scale.

quences of consecutive trials of the same type. For both animals the resulting distributions were close to that expected from an unbiased, random choice on each trial (Fig. 3*C*). Sequences of five or more consecutive trials of the same type occurred more often than expected from chance (χ^2 analysis; $P < 0.05$), but on average, these were <7% of the total trials (compared with 4.5% expected from chance). Thus while we did not dictate the outcome of trials, the observed sequence of trial types was nonetheless similar to one expected from chance. This suggests that even if the animals' preparatory or motivational state varied over time, it did not vary systematically between the two trial types.

We also needed to verify that self-timed and cued movements were behaviorally distinct. The 2,000-ms wait ensured that no movements were made in immediate reaction to the spot/target onset. However, we had to verify that the movements on cued trials were indeed immediate reactions to the go-cue onset rather than just movements that happened to follow the cue onset. For both animals, the distribution of cued movements relative to the *go-cue* onset had a sharp peak at approximately 400 ms with a half-width of only 50 ms at half-height (Fig. 3, *D* and *E*). This distribution argues strongly that the movements on cued trials were immediate reactions to the go-cue: if the animals had moved independent of the go-cue, the distribution of apparent "reaction times" would have been maximal at 0 ms and then decreased monotonically. These data underscore the key operational distinction between self-timed and cued movements; cued movements were immediate reactions to an external sensory trigger while self-timed movements were not.

The distribution of reaction times on cued trials also had a nearly uniform "tail" between 0–250 ms (dashed lines in Fig. 3, *D* and *E*). The tail was not unexpected since on some trials the cue may have coincidentally appeared after the animal had committed to making a self-timed movement but before he actually moved the joystick. To eliminate these potentially ambiguous cases, trials with movements that occurred <250 ms after go-cue onset were considered neither cued nor self-timed and were excluded from the main analysis (these comprised approximately 10% of successfully completed movement trials). In support of this criterion, the probability of error movements following the onset of the nogo cue declined to near zero by 250 ms (Fig. 3, *F* and *G*). A second, much smaller, peak of nogo error trials occurred for both animals at approximately 400 ms, close to the peak movement time for cued trials, suggesting that only rarely did the animals confuse the red nogo cue with the green go cue (Fig. 3, *F* and *G*).

It was also essential to confirm that the arm movement per se was the same for cued and self-timed trials. We therefore measured EMG activity from arm and shoulder muscles to determine whether there were any differences in the onset of muscle activation between the two trial types, such as covert flinching on self-timed trials, that may not have been detected by the joystick. There were no systematic differences in the onset of EMG activity, which typically began 100–200 ms before joystick movement for both trial types (Fig. 4). The directions of movement that elicited the largest activity on each electrode are shown in Fig. 4, but activity was also similar between cued and self-timed movements for other nonoptimal directions. There were also no systematic differences in the peak velocities for cued versus self-timed trials; only 12/78 units showed a significant difference in peak velocity (2-tailed *t*-test; $P < 0.05$), and these were equally divided between faster for cued movements and faster for self-timed movements. Thus cued and self-timed trials differed only in the way that movement was initiated.

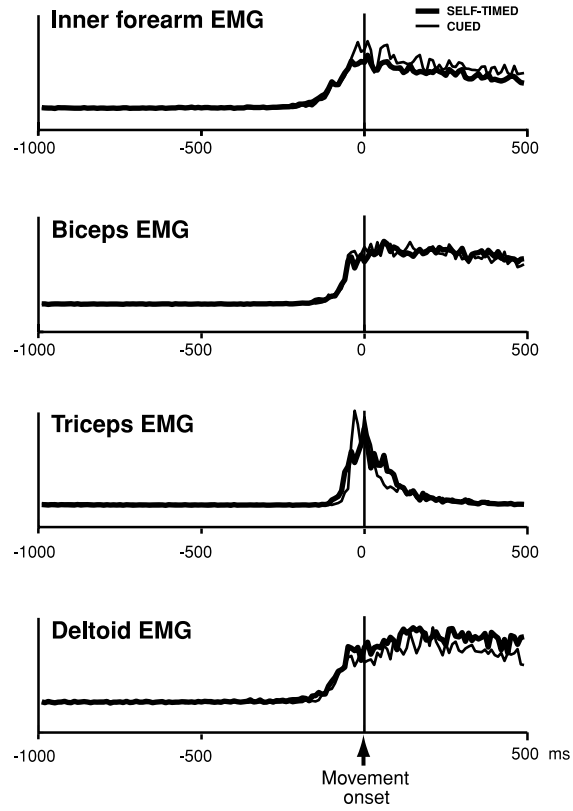

FIG. 4. Average electromyographic activity from inner forearm, biceps, triceps, and deltoid muscles for cued and self-timed trials, aligned on start of movement.

Neuronal activity

One hundred sixty-two units from the arm-movement–related area in the posterior putamen were fully characterized using the main behavioral task. Seventy-eight units were classified as PANs, 69 units were classified as TANs, and 15 units were classified as other. Only the 78 PANs are analyzed in this paper. Figure 5 shows the neuronal activity of all 78 PANs on cued and self-timed movements, aligned on the first detected movement of the joystick. Most PANs had a low baseline firing rate but brisk peri-movement activity starting a few hundred milliseconds before the start of joystick movement. A few cells had an elevated baseline activity well before the start of movement that then declined around the start of movement. These were generally rare in the posterior putamen. On first inspection, the activity of individual neurons was similar between cued and self-timed trials (Fig. 5). In fact we found very few putaminal PANs that were activated selectively by either cued or self-timed movements: 61/78 PANs were significantly modulated by both types of movements, while only 5/78 were significantly modulated just on cued trials and another 5/78 just on self-timed trials (2-tailed *t*-test of mean firing rate in the period ±200 ms of movement onset vs. firing rate measured between when the animal had established gaze fixation and

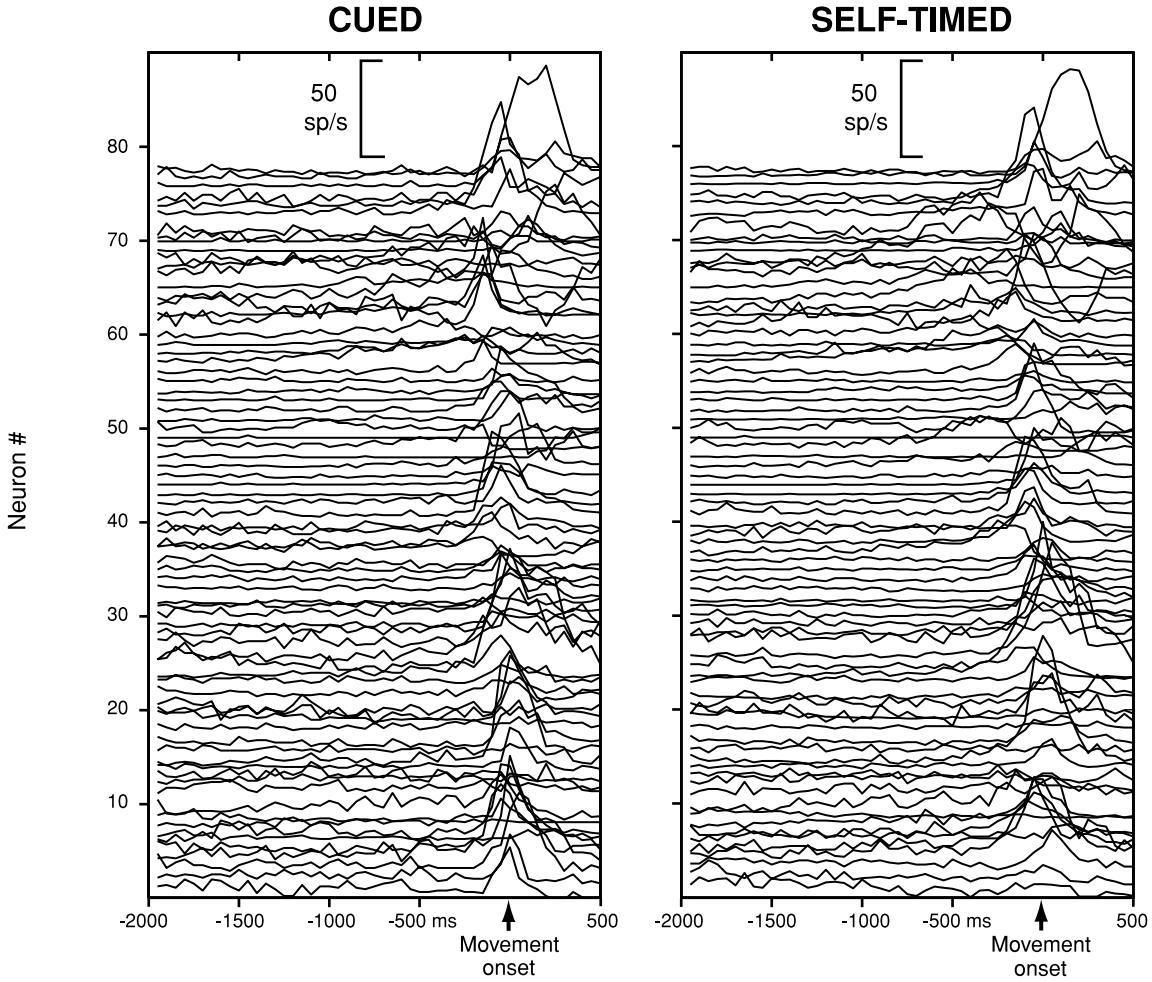

FIG. 5. Activity of all 78 phasically active neurons (PANs) to cued (*left*) and self-timed (*right*) movements. Each trace is the average activity of a single PAN, aligned on the start of movement. Responses of the same unit to cued and self-timed trials are vertically aligned between the *left* and *right columns*.

when the spot/target came on; $P < 0.05$). Nonetheless, there were specific differences in the neuronal activity between cued and self-timed trials that were consistent across the population of neurons. For example, the single PAN in Fig. 6 had similarly low levels of activity 2,000 ms before movement for both cued and self-timed trials. However, hundreds of milliseconds before movement, the activity began to increase faster for self-timed trials than cued trials. Once movement began, the activity was again very similar between the two trial types. Since the movements occurred over a broad range of times following the end of the 2,000-ms delay, the increased firing on self-timed trials was apparently time-locked to movement and was not due to elapsed time.

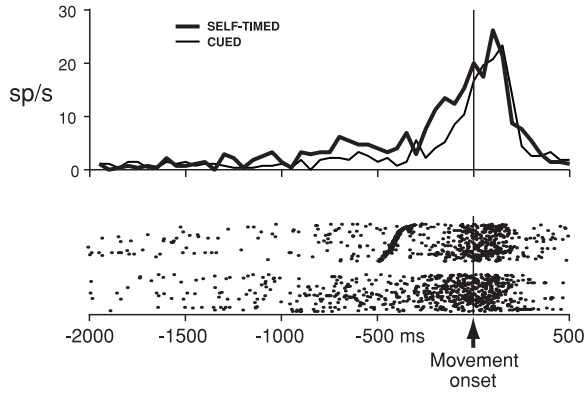

FIG. 6. Activity of single PAN on cued and self-timed trials, aligned on start of movement. Heavy dots on cued-trial raster plots indicate cue-onset time for each trial.

Population-average activity across all 78 PANs showed a similar pattern (Fig. 7*A*). There was a small, sustained elevation in firing from the start of the trial that was identical between cued and self-timed trials. Then, beginning approximately 600 ms before movement, there was a gradual build-up of population activity for self-timed trials, whereas activity was markedly flatter for cued trials over the same period. By approximately 250 ms before movement, the activity was again similar between self-timed and cued trials. This selective difference in firing was highly significant across the population of 78 PANs. For each unit, spike counts for cued and self-timed trials were computed over 250-ms bins aligned with the start of movement. For each unit, we then calculated a selectivity index for each 250-ms bin equal to $(R_t - R_c)/(R_t + R_c)$, where R_c is the mean spike count from cued trials and R_t is the mean spike count from self-timed trials. The median selectivity index was maximal for the bin 500–250 ms before movement and near 0 elsewhere (Fig. 7*B*). The distribution of selectivity indices is

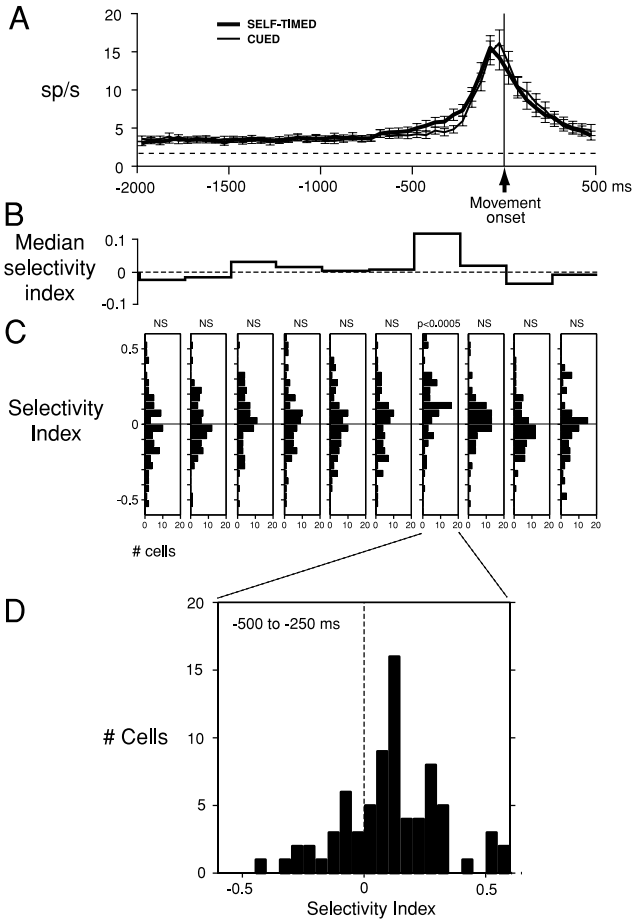

FIG. 7. Selective activity on self-timed trials across the population of PANs. *A*: population-average activity (±SE) for all 78 PANs, aligned on start of movement. Dashed line: average background-firing rate. *B*: median selectivity index $[R_t - R_c)/(R_t + R_c)$, where R_c is the mean spike count from cued trials and R_t is the mean spike count from self-timed trials] calculated for each of 10 consecutive 250-ms bins starting 2,000 ms before start of movement. Same time base as in *A*. *C*: distributions of self-timed/cued selectivity indices for all PANs, for each of the 10 250-ms bins. Same time base as in *A*. *D*: expanded view of the distribution of self-timed/cued selectivity index for the bin 500–250 ms before movement.

shown for each 250-ms bin in Fig. 7*C*. The bin 500–250 ms before movement was the only bin in which the mean selectivity index was significantly different from zero (Fig. 7*D*; *t*-test; $P < 0.0005$). This was also true for each animal individually (monkey S: $P < 0.0001$, $n = 50$ cells; monkey M: $P < 0.02$, $n = 28$ cells) and was still the case if we excluded the five units that were selectively activated on self-initiated trials ($P < 0.001$). The mean selectivity indices were not significantly different from zero in earlier bins or in the two 250-ms bins bracketing the start of movement (*t*-test; $P > 0.05$), consistent with the fact that the movement itself was indistinguishable between cued and self-timed trials (Fig. 4). The bin 500–250 ms before movement also contained the highest proportion of single units with higher spike counts on self-timed trials (77%; Fig. 7*D*). Of these, 30% (23% overall) had statistically significantly higher spike counts on self-timed trials (1-tailed *t*-test; $P < 0.05$). (The relatively low percentage was not unexpected given the limited statistical power due to the low firing rates in this time period; see METHODS).

The increase in activity before the start of movement on self-timed trials may be related to the internal generation of movement, but there are several other possibilities. First, although the distributions of overall movement times were similar between cued and self-timed trials (Fig. 3, *A* and *B*), they were not identical. For example, self-timed trials could occur right after the 2,000-ms delay expired, but cued trials were necessarily delayed by the earliest reaction times of the animals (approximately 250 ms). Also, there was a slightly higher proportion of later movements on self-timed trials. If the increase in premovement activity were due to elapsed time per se, the higher proportion of long self-timed trials could have produced the higher average premovement firing on self-timed trials. To examine this we separately pooled the shortest and longest third of cued and self-timed trials, based on the time of movement relative to spot/target onset. The population-average activity was virtually identical for the two pools of trials, such that the difference in activity between cued and self-timed trials was still present regardless of which pools of trials were compared (Fig. 8*A*). In particular, the shortest one-third of self-timed trials still had higher firing rates before movement than the longest one-third of cued trials. This confirmed that the increased firing on self-timed trials was specifically cou-

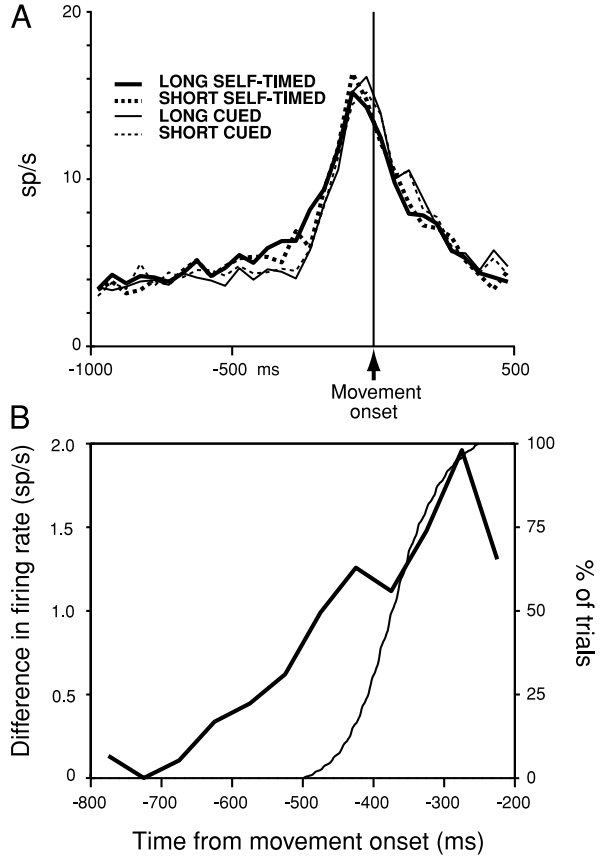

FIG. 8. *A*: population-average activity of 78 PAN units, comparing shortest and longest cued and self-timed trials, as measured by the time to move relative to spot/target onset. For cued trials, shortest one-third were <2,494 ms and longest one-third were >2,748 ms. For self-timed trials, shortest one-third were <2,297 ms and longest one-third were >2,688 ms. Activity aligned on start of movement. *B*: neuronal differences emerged before cue onset. Thick line and left scale for (premovement) difference in population-average activity (average activity on cued trials subtracted from average activity in self-timed trials), aligned on start of movement. Thin line and right scale for cumulative distribution of cue-onset times relative to the start of movement for cued trials.

pled to the start of movement and was not due to a gradual increase in firing with longer trial length.

The difference between self-timed and cued trials was also not due to transient *suppression* of activity on cued trials in response to cue onset, since the differences began to emerge before even the earliest cue presentations relative to the start of movement (Fig. 8*B*). Furthermore, sensory-related decreases in firing in the putamen have been reported only for TANs (Aosaki et al., 1995), which were rigorously excluded from this analysis (see METHODS). In particular, all individual cells with significantly higher firing rate 500–250 ms before movement on self-timed trials were unequivocally PANs, with spontaneous activity <2 Hz and excitatory, phasic, direction-selective activity during arm movements.

While we designed the task so that cued and self-timed movements would be interleaved from trial-to-trial, we recognized that this design would inevitably cause some "superposition" of cued and self-timed processes. One likely possibility is a race process in which the animals always prepared a self-timed movement, only to make a cued movement if the cue came on before the movement began. On a given cued trial we cannot know *when* the animal would have otherwise made the self-timed movement—but we can consider two scenarios. First, on some trials the cue could have appeared *after* the animal had committed to making a (self-timed) movement but *before* the actual movement began. For example, if by chance the cue came on only 10 ms before the animal started moving, the cue would have been superimposed on the self-timed process. These trials could be identified on the basis of an extremely short latency between cue-onset and movement. As explained above, the reaction-time distributions in Fig. 3, *D–G* suggest that trials in which movement occurred <250 ms after cue onset likely fell into this category. Thus those trials were considered neither cued nor self-timed and were excluded from the analysis.

On other cued trials, even if the animal was not fully committed to making a self-timed movement at the time of cue onset, there still might have been some neuronal activity due to the animals' preparing self-timed movements. If the cue appeared far in advance of when the self-timed movement *would have* occurred, it seems unlikely that activity related to the self-timed preparation would have developed much by the time of cue onset, and therefore any contamination from self-timed preparation would be relatively small. To address this, we computed a theoretical distribution of "lead times" based on the empirical distributions of cue-onset times for cued trials and movement-latencies for self-timed trials (Fig. 9). The medians of these distributions were approximately 600 and 700 ms for the two animals (after excluding latencies of <250 ms). In retrospect, the neuronal activity on self-timed trials had not begun to change much for times >600 ms before the start of movement. Thus for at least one-half the cued trials, the cue appeared when there was relatively little neuronal evidence of the animal's self-timed preparation. Moreover, while some element of self-timed planning must have persisted in the cued trials, that contamination would have only *reduced* the difference in neuronal activity that we observed between cued and self-timed trials from 500 to 250 ms before the start of movement. Nevertheless, that difference in activity was statistically significant, but in every other time window, the putaminal

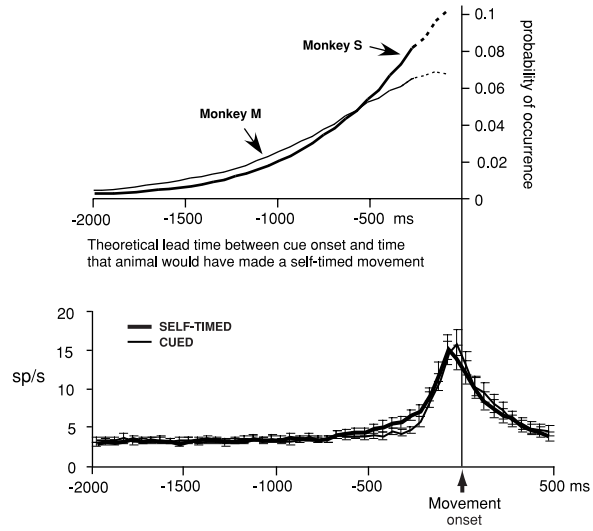

FIG. 9. Theoretical probability distributions of lead times between cue-onset time and time that the animals would have otherwise made a self-timed movement. *Top*: theoretical distributions were calculated for monkey S (thick line) and monkey M (thin line) by convolving the empirical distributions of self-timed movements relative to the spot/target onset (Fig. 3*A*) with the empirical distributions of cue-onset times (Fig. 3*B*), and normalizing the result to create a probability distribution. Dashed portions of the distributions indicate lead times <250 ms. *Bottom*: for comparison, average neuronal activity for cued and self-timed movements (from Fig. 7*A*) plotted on the same timebase as the theoretical probability distributions.

neurons from which we recorded had similar activity during both self-timed and cued trials.

If a slow increase in activity before the peri-movement discharge is related to the initiation of movement, there might also be a relationship between the level of premovement activity on cued trials and the animal's reaction time following cue onset, as has been shown for eye movements (Dorris et al. 1997; Hanes and Schall 1996). To test this, we pooled cued trials based on reaction time and compared population-average activity. In general, trials with faster reaction times had slightly elevated activity well before movement compared with trials with slower reaction times (Fig. 10*A*). The difference developed hundreds of milliseconds before cue onset (Fig. 10*B*), and similar to the cued/self-timed comparison, was minimal within 250 ms of movement (Figs. 8*A* and 10*A*). Linear regression analysis indicated that the population-average firing rate 750–250 ms before movement declined significantly with increasing reaction time ($P < 0.002$; Fig. 10*C*). These data support the notion that small variations in putaminal activity occurring long before the actual movement reflect the animal's propensity to move.

DISCUSSION

The goal of our experiment was to examine mechanisms for movement initiation by comparing neuronal activity during self-timed movements to the same movements made in immediate reaction to an external cue. In general, one could look back before any movement, however "spontaneous," and find some preceding sensory stimulus. For example, self-timed movements were always preceded by the spot/target onset. However, self-timed movements were delayed ≥2,000 ms from spot/target onset and were spread out as far as 5,000 ms

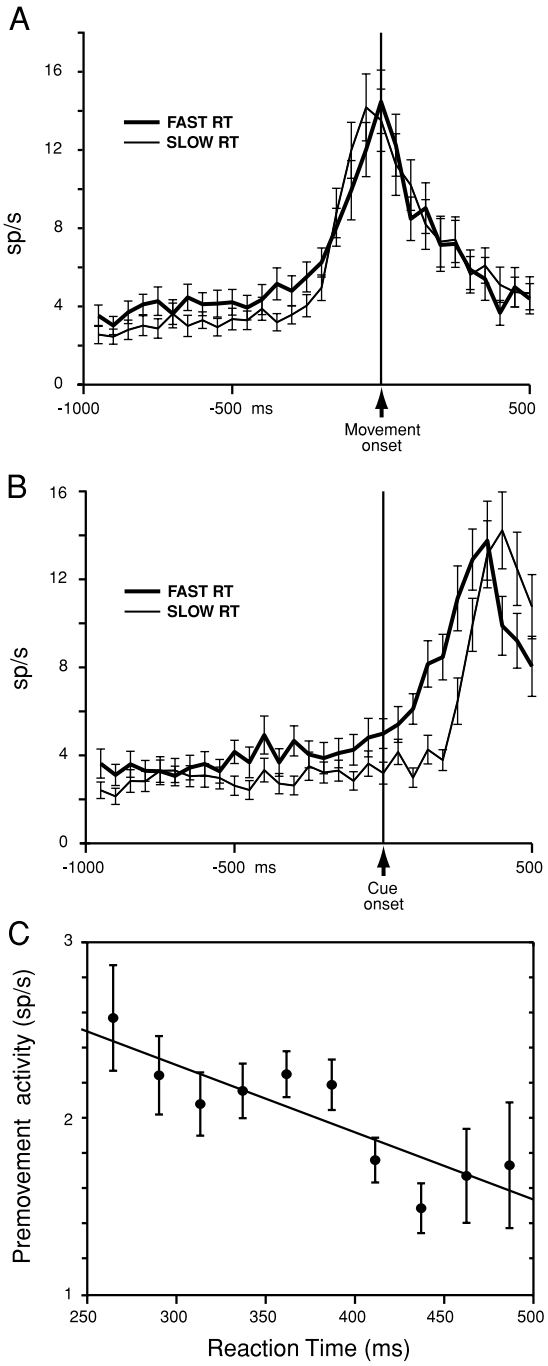

FIG. 10. Population-average activity for the one-third of cued trials with the fastest (<352 ms) or slowest (>396 ms) reaction times, aligned on (*A*) start of movement or (*B*) cue-onset time. *C*: population-average spike rates (750–250 ms before movement) among the 78 PANs vs. reaction time for cued trials. Each point is mean ± SE over a 25-ms reaction-time bin. Sloped line is linear regression ($r^2 = 0.725$). Spike rates are lower in *C* than in *A* and *B* because the averages in *C* were calculated from all individual trials, and we collected more trials from units with lower firing rates.

following spot/target onset. In contrast, cued movements occurred over an approximately 100-ms-wide distribution of reaction times centered at only 400 ms after the go-cue onset. Thus the timing of self-timed movements relative to the spot/target onset was completely nonoverlapping with the timing of cued movements relative to the go-cue onset. Clearly, self-timed movements were distinct from simple reactions. A number of factors likely contributed to the wide distribution of movement times on self-timed trials. First, although the animals were probably motivated to approximate the end of the 2,000-ms delay, they are limited in the precision with which they can reproduce a given time interval (Gallistel and Gibbon 2000). Furthermore, the width was undoubtedly increased by the presence of go and nogo trials, which may have led the animals to strike a balance between timing the end of the delay and waiting for the go cue or nogo cue. It is difficult to know the relative contributions of such factors. However, the essential fact is that, regardless of the animals' strategy, movements on self-timed trials were not immediately triggered by an external cue. This can be taken as a reasonable operational definition of an internally generated movement.

Our main finding was that while most PANs were activated by both cued and self-timed movements, movement-aligned neuronal activity was greater on self-timed movements between roughly 500–250 ms before the start of movement. The neuronal activity in cued and self-timed trials was similar earlier in the trials and again around the time of movement. Previous studies have shown that the same movements can elicit activity in different putaminal neurons depending on behavioral context (Alexander and Crutcher 1990; Kimura et al. 1992; Schultz and Romo 1992). For example, Schultz and Romo found that at least one-half of PANs in the anterior striatum were activated either when the animal made self-timed reaching movements throughout a block of trials or when the animal reached exclusively in response to an external cue, but not both (Romo et al. 1992; Schultz and Romo 1992). In contrast, the vast majority of posterior putaminal PANs that we examined were active for both cued and self-timed movements, with the only difference being the highly significant increase in activity on self-timed trials starting approximately 500 ms before movement. An obvious reason for our different results may be that we recorded in different parts of the putamen. Another reason may be that we did not present cued and self-timed movements in separate blocks of trial. Rather, we (and presumably the monkey) did not know in advance of a trial whether the trial would be self-timed or cued, whereas in previous studies the animals could always expect an explicit delay on every cued trial. This made it more likely that in our experiment the animal's behavioral state was similar at the beginning of each trial. This interpretation is supported by the fact that we found very little difference in firing early in the trial (Fig. 7), whereas Schultz and Romo found many neurons with large differences in preparatory activity many seconds before the start of movement (Schultz and Romo 1992). Thus we interpret the selective premovement increases in neuronal activity in our experiment as something related to the internal generation of movement. Consistent with this, Romo et al. (1992) also found an earlier build-up of activity on self-timed trials for the minority of "movement-related" units that were activated by both types of movement.

The behavioral importance of increases in firing before the perimovement burst was supported by a second observation in our study: differences in the level of premovement firing on *cued* trials were related to the animals' subsequent reaction time. As with self-timed trials, the firing differences on cued trials developed hundreds of milliseconds before the start of movement (Fig. 10*A*). These combined results suggest the intriguing possibility that the increases in premovement activ-

ity reflect an activity threshold that the basal ganglia-cortical circuitry must exceed to initiate movement. This is consistent with the fact that the increase on self-timed trials was time-locked to the start of movement, even for movements that were initiated at very different times relative to the start of a trial. A threshold model has also been suggested for saccadic eye movements, in that variability in the rate of rise of activity in the frontal eye fields and superior colliculus can account for reaction-time variability in responding to a cue (Dorris et al. 1997; Hanes and Schall 1996). For example, Dorris et al. (1997) found that the probability of a fast "express" saccade in response to a visual cue was related to the immediately preceding level of activity in build-up neurons of the superior colliculus. For cued reaching movements Jaeger et al. (1993) reported that shortened reaction times following long premovement delays were often accompanied by higher basal ganglia activity before the movement. We found that *even in the absence of a cue*, slight differences in population activity in the putamen could be related to subsequent movement. In this view, if population activity happens to exceed threshold before cue onset, a self-timed movement ensues. These increases might arise stochastically or reflect an imprecise timing process. If instead population activity is below threshold, the appearance of a go cue can abruptly increase activity to threshold and produce a cued movement. Once threshold is exceeded, the perimovement activity might unfold in an all-or-none fashion, as we found. Thus in our experiment, a similar activity threshold would be required for initiation of both cued and self-timed movements, and the two types of movement would differ only in how that threshold is exceeded. The threshold interpretation accords with the closed-loop, feedback organization of the basal ganglia-cortical circuitry. Small increases in activity at any point in the larger circuit might give rise to more substantial increases in activity that trigger movement (Romo and Schultz 1992). Activity of this sort may underlie "readiness" scalp potentials that can be recorded from human subjects up to several seconds before internally generated movements (Deecke 1996). While we only recorded from the posterior putamen, it is important to stress that similar activity would likely be found in frontal cortical areas that communicate with the posterior putamen. In this view, movement initiation does not depend on a single brain area but arises as a consequence of feedback interactions among multiple areas.

The threshold model may be related to the phenomenon of "paradoxical movements" in Parkinson's disease. Patients with Parkinson's disease tend to have reduced spontaneous movements and difficulties making self-initiated movements, yet can often overcome the inability to initiate movement if provided an external sensory trigger (Glickstein and Stein 1991). Perhaps the loss of dopaminergic input to the striatum lowers the baseline activity or excitability of putaminal projection neurons such that the population activity is less likely to exceed threshold spontaneously. However, the system might still be driven over threshold by an external sensory push—the onset of the go cue. Even with an external sensory trigger, the rate at which threshold is exceeded might still depend on the ongoing level of putaminal activity, as we found. In this regard it will be interesting to examine whether the increase in premovement activity on self-timed trials may be related to any of the modulatory neurotransmitters that influence striatal function, such as dopamine or acetylcholine (Graybiel 1990).

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