Transient Pauses in Delay-Period Activity of Superior Colliculus Neurons

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Submitted 23 September 2005; accepted in final form 27 December 2005

Li, Xiaobing, Byounghoon Kim, and Michele A. Basso. Transient pauses in delay-period activity of superior colliculus neurons. J Neurophysiol 95: 2252–2264, 2006. First published January 4, 2006; doi:10.1152/jn.01000.2005. A feature of neurons in the mammalian superior colliculus (SC) is the robust discharge of action potentials preceding the onset of rapid eye movements called saccades. The burst, which commands ocular motoneurons, is often preceded by persistent, low-level activity, likely reflecting neuronal processes such as target selection, saccade selection and preparation. Here, we report on a transient pause in persistent activity of SC neurons. We trained monkeys to make or withhold saccades based on the shape of a centrally located cue. We found that after the cue changed shape, there was a measurable pause in persistent activity of SC neurons, even though the cue was located well outside the response field of the neurons. We show here that this pause is not a simple, transient inhibitory drive from neurons representing the central visual field. Rather, the occurrence of the pause depends on the occurrence of saccades made much later in the trial. The characteristics of the pause such as magnitude or duration are not predictable from the task condition, rather the occurrence of the pause across the SC neuronal population varies with whether a saccade is made much later in the trial. We developed a model that accounts for our results and makes testable predictions about the effects of signals related to inhibition in SC neuronal populations.

INTRODUCTION

The role of the mammalian superior colliculus (SC) in the generation of saccadic eye movements is well established (Moschovakis et al. 1996; Sparks and Mays 1990). In addition to the neuronal discharge preceding the onset of saccades (Munoz and Wurtz 1995; Sparks et al. 1977), neurons within the intermediate layers of the SC display a low level of discharge of action potentials while monkeys wait for a cue to make an eye movement to a peripheral location (Glimcher and Sparks 1992; Munoz and Wurtz 1995; Sparks et al. 1977). This delay-period—or persistent—activity has been associated with processes intervening between the presentation of a visual stimulus and the initiation of a saccadic eye movement such as target selection, saccade preparation, and visual attention (Basso and Wurtz 1997, 1998; Carello and Krauzlis 2004; Cavanaugh and Wurtz 2004; Dorris and Munoz 1998; Glimcher and Sparks 1992; Ignashchenkova et al. 2004; McPeek and Keller 2004; Muller et al. 2005).

Persistent activity is not unique to SC neurons. It can be found in subcortical regions (Hikosaka et al. 1989; Robinson 1989; Taube and Bassett 2003), in entorhinal cortex (Egorov et al. 2002), as well as in many cerebral cortical areas (Bisley et al. 2004; Funahashi et al. 1989; Fuster and Alexander 1971; Fuster and Jervey 1981; Gnadt and Andersen 1988). A curious observation reported in neurons of the lateral intraparietal cortical area (LIP) is that shortly after the onset of a sensory stimulus, there is a dip in the persistent activity. Importantly, the dip is present even when the sensory stimulus is located well outside the response field of the recorded LIP neuron. Because persistent activity may be viewed as a neuronal integrator accumulating sensory evidence toward a decision, the dip in LIP activity may reflect a resetting of a neuronal integrator (Mazurek et al. 2003; Roitman and Shadlen 2002). Curiously, a similar dip has been observed in a number of other cortical areas (Boch and Goldberg 1989; Richmond and Sato 1987; Richmond et al. 1983) and, most recently, preceding the saccade-related burst of neurons in the frontal eye fields (FEFs) (Sato and Schall 2001). Given that the pause or dip in persistent activity is so ubiquitous we consider here whether it exists in SC neurons and whether it plays a role in sensorimotor processing.

In the current report, we describe the characteristics of a pause in persistent activity of SC neurons and then we explore three possible explanations for the pause. First, we demonstrate that the pause in SC neuronal activity often occurs after the onset of a visual cue located in the central visual field, well outside of the response field of the recorded neuron. Second, we demonstrate that the pause is not simply a transient pulse of inhibition arising from activation of neurons representing the central visual field. Third, we demonstrate that the presence of the pause in SC neuronal activity depends both on the location of a visual stimulus and on whether a monkey makes a saccadic eye movement, well before the saccade is initiated. Fourth, we demonstrate that the number of neurons across the population expressing a pause changes with saccade occurrence. Finally, we present a mathematical model based on inhibitory influences that explains the population results we obtained. Our model makes predictions about the inhibitory influences on SC neurons and points toward a novel role for the influence of saccade decision mechanisms. Studies often emphasize how top-down mechanisms influence the activity of individual neurons, by increasing or decreasing discharge rate. Our results show that these processes also operate at the level of the population, by changing the probability that neurons will have a pause in their persistent activity.

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METHODS

Physiological procedures

For electrophysiological recording of single neurons and monitoring eye movements, cylinders and eye coils were implanted in two rhesus monkeys (Macaca mulatta) using standard procedures as described previously (Basso et al. 2005; Li and Basso 2005). Briefly, animals were anesthetized with an intramuscular injection of ketamine (5.0–15.0 mg/kg) and thereafter, intubated and maintained at a general anesthetic level with isofluorane. A subconjunctival eye coil was implanted (Judge et al. 1980). A plastic head holder for restraint and a cylinder for subsequent microelectrode recording were mounted on the exposed skull and secured with titanium screws and dental acrylic. The recording cylinder was placed stereotaxically on the midline and angled 38° back so that the electrode penetrations were directed caudorostrally, toward the SC. Antibiotics (Cefadroxil, 25 mg/kg) were provided 1 day before the operation and every day for a minimum of 4 days after the operation. Analgesia was provided by the administration of buprenorphine (0.01–0.03 mg/kg) and flunixin (1–2 mg/kg) for 48 h postsurgically as needed. Monkeys recovered for 1–2 wk before behavioral and physiological recording commenced. All experimental protocols were approved by the University of Wisconsin–Madison Institutional Animal Care and Use Committee and complied with or exceeded standards set by the Public Health Service policy on the humane care and use of laboratory animals.

Behavioral procedures

We used a real-time experimental data acquisition and visual stimulus generation system (Tempo and VideoSync; Reflective Computing) to create the behavioral paradigms and acquire eye position and single-neuron data. Monkeys were trained to sit in a custom-designed primate chair with head fixed during the experimental session (typically 3–5 h). Visual stimuli were rear-projected onto a tangent screen at 51 cm distance using a DLP projector (LP335, Infocus) with a native resolution of 1,024 × 768 and operating at 60 Hz. The centrally located fixation spot had a luminance of 1.52 cd/m². The two possible target stimuli located within the response field (RF) of SC neurons were white and had a luminance of 2.17 cd/m². The background luminance was 0.28 cd/m². The visual stimulus presentation was controlled by VideoSync software (Reflective Computing) running on a dedicated PC with a 1,024 × 768 VGA video controller (Computer Boards). The PC was a slave device to the PC used for experimental control and data acquisition. Because there is an inherent time limitation in DLP projectors (both the vertical refresh rate and delays in the vertical sync pulse) a photocell secured to the tangent screen sent a TTL pulse to the experimental PC, providing an accurate measure of stimulus onset.

Behavioral tasks

After the onset of a centrally located fixation spot for a random time of 1,000–1,500 ms, either one or two shapes were presented within a single RF of an SC neuron (see Response field mapping). The fixation point remained illuminated along with the peripheral stimuli for a random delay of 800–1,000 ms and then the fixation spot changed shape to either a white triangle or a square (2.17 cd/m²). Monkeys were trained on two tasks at different times. In the Go/No-Go task, the triangle cue served as a signal for the monkey to make a saccade to the triangle in the RF, whereas the square cue indicated that the monkey should remain fixating. After another cue delay of 800–1,000 ms, the fixation point turned back to its original spot and this was the cue for the monkey to make a saccade to the triangle stimulus or continue fixating at the central spot for 400–600 ms to obtain a fluid reward. If the monkey acquired the saccade target and its eye position remained at that location for 400–600 ms, a liquid reward was provided. The accuracy criterion was 2° square around the target (if the target was farther than 10°, the criterion was increased to 3–4° square). The smallest distance between two stimuli was approximately 2°, whereas the largest was approximately 25°. In the Go/Go task, the trials were identical except the monkeys were required to make a saccade to either the triangle if it was cued or the square if it was cued. Saccades to the triangle or the square had to be accurate. We ensured this by making the acceptance criterion, defined by the electronic windows, nonoverlapping. Thus averaging saccades were discouraged. For both tasks we collected, on average, 30–50 trials for each condition. Single-target and two-target trials were presented in random order or in blocks. For the neuronal activity patterns described here, this did not matter, so we pooled the data collected in randomized or blocked target trials.

Response field mapping

A stimulus (generally a triangle) was moved around to assess qualitatively the boundary and the center of the visual RF of SC neurons. We then placed one stimulus in the approximate center of the RF and a second stimulus at any location around the center, but, importantly, within the boundaries of the RF. The placement of the second stimulus was determined empirically, by listening and watching the neuronal discharge on-line. We generally put the second stimulus within a region of the RF that appeared to produce suppression, although in some cases the two stimuli together resulted in enhanced responses. We maximized the stimulus positions to explore delay-period activity (see Li and Basso 2005). The separation between the two stimuli was scaled by the diameter of the visual RF. For example, if the diameter of the field was approximately 5°, the two stimuli would be located nearly 2° apart; if the diameter was approximately 10°, then the two stimuli would be located about 5° apart. We also placed the two stimuli approximately equidistant from the fixation point to keep the amplitude of the vector constant. We did not use neurons with RFs that included the fovea. For some neurons with large RFs, we were unable to determine exactly the distal boundaries of the RF.

Data acquisition

Using the magnetic search coil technique (Fuchs and Robinson 1966) (Riverbend Instruments), voltage signals proportional to horizontal and vertical components of eye position were filtered (eight-pole Bessel –3 dB, 180 Hz), digitized at 16-bit resolution and sampled at 1 kHz (Measurement Computing; CIO-DAS1602/16). The data were saved for off-line analysis using an interactive computer program designed to display and measure eye position and calculate eye velocity. We used an automated procedure to define saccadic eye movements by applying velocity and acceleration criteria of 50°/s and 5,000°/s², respectively. The adequacy of the algorithm was verified on a trial-by-trial basis by the experimenter. Single neurons were recorded with tungsten microelectrodes (FHC) with impedances between 0.3 and 1.0 MΩ measured at 1 kHz. Electrodes were aimed at the SC through stainless steel guide tubes held in place by a plastic grid secured to the cylinder (Crist et al. 1988). Action potential waveforms were identified with a window discriminator (Bak Electronics) that returned a TTL pulse for each waveform that met amplitude and voltage criteria. The TTL pulses were sent to a digital counter (National Instruments; PC-TIO-10) and were stored with a 1-ms resolution.

Neuronal classification

We classified neurons as either buildup or visual-tonic using the following statistical criteria. We computed a baseline measure of activity (average discharge rate 200 ms before the onset of the visual target), a delay-period activity (400 ms before a cue), and a saccade-period activity (100 ms before saccade onset). Using only correct
trials, we defined buildup neurons as those neurons with a significantly greater activity in the delay period compared with the baseline (t-test, \( P < 0.05 \)) and a significantly greater activity in the saccade period compared with the delay period (t-test, \( P < 0.05 \)). If a neuron had a visual response and had a significantly greater level of activity in the delay period than the baseline (t-test, \( P < 0.05 \)), but had no significant difference between the saccade period and the delay period, we classified the neuron as a visual-tonic neuron.

RESULTS

Data from 81 SC neurons in two monkeys contribute to these results: 67 neurons were classified as buildup and 14 were classified as visual-tonic (see methods). Of these, 31 buildup neurons were recorded in the Go-Go task and 36 were recorded in the Go/No-Go tasks. Visual-tonic neurons were recorded in the Go/No-Go task only. Although variable, we found visual-tonic neurons in the dorsal SC (mean = 1.1 mm, SD = 0.7 mm from the surface) and buildup neurons below visual-tonic neurons (mean = 1.6 mm, SD = 0.6 mm from the surface).

Because we are interested in a population level analysis, we pooled all the neurons so that any single neuron could contribute to multiple conditions. First, we briefly describe the behavior of SC neurons in the different conditions of the task. Second, we describe the methods used to identify the pause in SC neurons. Third, we describe the characteristics of the pause across the population of SC neurons. Fourth, we show how the pause across the population of neurons was modulated by the location of a visual stimulus and by whether a saccade would be made later in the trial. Finally, we present a simple conceptual and mathematical model based on competitive, inhibitory interactions to explain our results.

Behavior of SC neurons

We recorded SC neurons in two tasks: a Go-Go task in which saccades were required on all trials and a Go/No-Go task in which saccades were made on half the trials. In both tasks, Go-Go and Go/No-Go, the trial types were presented in blocks or randomly interleaved. Because we found no difference in the pause characteristics whether the trials were blocked or interleaved, we pooled each of these trial types. Below, we briefly describe the behavior of our sample of SC neurons in these two tasks and then describe the transient pause reported herein.

In general, when a single stimulus was located in the center of the RF of a neuron, SC neurons had a robust discharge shortly after the onset of the visual stimulus and had a lower level, tonic discharge during the period while monkeys waited for a cue. The cue, located at the fovea, indicated whether or where to make a saccade (Fig. 1A) and, at this time, SC neurons often had a transient pause in discharge rate (Fig. 1A, middle). After the pause, the low-level discharge resumed until the saccade-related burst occurred coincident with the initiation of the preferred saccade (Fig. 1A, rightmost panel).

Across the sample of 36 SC neurons, we observed a modulation of the low-level discharge in the different conditions of the Go/No-Go task. For example, one target in the center of the RF resulted in maximal discharge compared with when one stimulus was located within a single RF and no saccade would later be required (Fig. 1B, cf. red and blue traces). Similarly, when two stimuli were located within a single RF and a saccade would be required the activity was higher than when no saccade would be required (Fig. 1B, cf. green and yellow traces). This indicates that there are stimulus–stimulus interactions within single RFs of SC neurons and that these interactions are modulated by top-down signals (Li and Basso 2005). Note that the examples shown here were taken from the blocked target trials in which the monkeys knew which trial type would occur over time. A similar pattern was observed in the interleaved trials except that the initial visual responses were overlapping for the two stimulus conditions (Fig. 1B, green and yellow traces). Our observations are reminiscent of work in V2 and V4 showing that visual stimulus interactions are influenced by attention (Reynolds et al. 1999) and therefore suggest that signals related to target selection and the decision to make or withhold a saccade operate in a fashion similar to that of signals related to attention (Li and Basso 2005).

In the Go-Go task, the behavior of SC neurons was similar with one notable exception. Because the centrally located cue indicated an impending saccade in both conditions, the neuronal activity increased in both conditions after the cue and during the saccade. The only difference was that when the centrally located cue indicated a saccade to the center of the RF, the neuronal activity was higher than when the cue indicated a saccade to the edge of the RF, not unexpectedly (cf. Fig. 2, A and B). We should point out that in all of these conditions there was a noticeable dip in the tonic discharge of
many SC neurons occurring shortly after the onset of the centrally located cue (Figs. 1 and 2). Herein we report on the transient pause in the delay period of SC neurons seen shortly after the onset of the centrally located cue.

Figure 2 shows an example of a single SC buildup neuron recorded in five different conditions of our task. The single stimulus “Go to the center of the RF” is shown in A and the single stimulus “Go to the edge of the RF” is shown in B. The single stimulus “no-saccade condition” is shown in C, and in D and E the two stimulus conditions are shown. In D, the two stimulus “Go to the edge” is shown, whereas in E, the two stimulus “no-saccade condition” is shown. The middle traces in each panel are aligned to the onset of the cue. Although variable, a clear decrease in neuronal activity was present in most conditions (indicated by the gray shaded region). We found that the magnitude of pauses in single neurons was variable with the different task conditions and therefore not reliably predicted within single neurons. However, across the sample of SC neurons, we found that the probability of measuring a pause varied consistently, depending on the task conditions. We explore this finding below.

Identification and characteristics of the pause in SC neurons

Adopting the method used by Schall and colleagues (Sato and Schall 2001), we used a quantitative method to determine whether a pause was present in the discharge of SC neurons (Fig. 3, B and C). We plotted a 600-ms epoch of neuronal discharge aligned to the onset of the cue that indicated the trial type (e.g., Go/No-Go), well before the cue to make a saccade. We plotted the data using a spike density function by convolving each action potential occurrence with a Gaussian (σ = 10 ms) (MacPherson and Aldridge 1979; Richmond et al. 1987). We also plotted the data after convolving the spike trains with a growth decay exponential function developed to resemble a postsynaptic potential (Sato and Schall 2001). These two spike trains are shown in Fig. 3B. We measured the mean and 2SD of the neuronal discharge rate 200 ms before the cue onset. Beginning at the time of cue onset, we determined when the neuronal discharge fell 2SD below the mean for ≥15 ms and defined this as the onset of the pause (Tpause). To identify the end of the pause we made two measurements (Fig. 3B). First, we computed the instantaneous slope of the spike density function shown in Fig. 3B and compared the time points with a 0 slope (Fig. 3C). The first time point after the onset of the cue when the slope remained above 0 for ≥15 ms, was defined as Trise. This measurement was important because it prevented the identification of artifactual pauses (those arbitrarily defined as <15 ms). After Trise, the time when the neuronal discharge rate first reached 2SD below the mean discharge rate was defined as the end of the pause (Tend). The time between Tpause and Tend was defined as the duration of the pause (Dur).

The integrated area over the curve and below the mean discharge rate minus 2SD from Tpause to Tend was our measure of the magnitude of the pause (shaded gray region in Fig. 3B; Parea). We also computed a magnitude measure independent of the duration (Parea/Tdur). To ensure we would detect a pause if there was one, we used only those trials in which the activity had a mean –2SD level of activity that exceeded 0. This...
exclusion criterion resulted in the removal of only 7% of the buildup neuron cases and 0% of the visual-tonic neuron cases across all the conditions. For example purposes, shown in Figs. 1B and 3A, we used the 36 buildup neurons recorded in the Go/No-Go task. For the rest of the analysis reported here, we performed these measurements on individual neurons in different tasks and trials conditions and used an average of ≥20 trials for each condition.

To determine the distribution of the pause occurrence in our sample of SC buildup neurons, we plotted cumulative frequency distributions of the measurements. In Fig. 3D we show the percentage of buildup neurons with a pause after the onset of the cue indicating whether a saccade would be required. This was computed using the Gaussian function to convolve the spike trains (Fig. 3D) and the exponential (orange line). There are two points. First, the time course is shifted by about 15 ms using the exponential. This indicates that the Gaussian function underestimates the onset time of the pause, likely arising from the fact that the Gaussian is temporally symmetric. Second, despite being temporally asymmetric (only forward in time), nearly 20% of the neurons with spike trains convolved using the exponential function still show a pause that is faster than the visual response latency of a typical SC neuron (Fig. 3D, orange line). This provides a hint that the transient pause we report on here is not a simple visual transient arising from foveal stimulation. This is a point we will explore more fully below. Overall, the shape of the probability distribution was independent of whether the Gaussian or the exponential was used to convolve the spike train data, although the number of neurons with pauses was reduced using the exponential, likely a result of the larger SD (Fig. 3B).

In light of this latter observation, and that we are interested here in the occurrence of the pause rather than the time course, we opted to present the rest of the data using the Gaussian function.

Across the sample of SC neurons, by about 100 ms, 75% of the neurons had a measurable pause (Fig. 3D). A similar result was obtained when we plotted Tdur (Fig. 3E; note that there would be fewer neurons with a measurable Tdur compared with Tpause because neurons with Tdur = 0 and Tcend ≥ 300 ms were excluded). To determine the overall distribution of neurons showing a pause and the magnitude of the pause, we plotted a frequency histogram of Parea for the 36 buildup neurons. These data were taken from delayed-saccade trials to a single target. G: frequency histogram of Parea/Tdur which provides a measure of the magnitude of the pause across the sample of SC neurons.
The pause is modulated by stimulus location

The first explanation we considered for the existence of a pause in persistent activity was that the foveal stimulus activated a population of neurons resulting in a transient inhibition. We explored this possibility by measuring the probability of a pause in 4 different conditions of the Go/No-Go task. If the pause is determined solely by an inhibitory transient from the central visual field stimulation, the pause should be the same in all task conditions. Figure 4A shows the probability of a pause measured in the Go/No-Go task trials when a stimulus was located at the center or the edge of the RF. When a stimulus was located at the center of the RF and no saccade was required [Fig. 4A, - - - ; top, 1 square (1S)] the pause probability was maximal. By 150 ms, the probability of measuring a pause in this condition was 70.5%. When the stimulus was located at the edge of the RF and no saccade was required, the pause was 48.7% by 150 ms, even less likely (Fig. 4A, - - ; 1S edge).

To confirm these observations statistically, we performed a permutation test on the cumulative probability functions across the different conditions (Efron and Tibshirani 1998). To do this, we first grouped the two distributions arising from the two probability functions together. We then sampled n values, where n was the number of values in each of the original distributions. We computed the difference of means of this resampled distribution. This was performed 1,000 times and resulted in a distribution of differences. We compared the resampled mean difference to the original mean difference to determine the probability that the original and the resampled values were drawn from the same distribution. We performed this across different time epochs: 0–100, 100–200, and 200–300 ms. Because the differences were most likely seen during the 100- to 200-ms epoch, we report only those values here. Comparing the conditions when the square (Go trial) was located at the center and the edge of the RF revealed that the original mean difference fell at the 97.9%ile of the resampled distribution. This means that there was a 0.021 chance that the mean difference values arose from the same distribution.

When a saccade would be made to the center of the RF, the pause was more likely than when a saccade would be made to the edge of the RF (cf. Fig. 4A, top and bottom). Confirming these differences statistically, the permutation test revealed that the original mean difference between the condition in which the triangle (Go trial) was located at the center and edge of the RF, fell at the 95th percentile of the resampled distribution. We also performed the same measurements on the buildup neurons recorded in the Go/Go task when a target was in the center of the RF and when a target was located at the edge of the RF. These data were taken from the single-target trials (1T and 1S). The probability of measuring a pause was 74.0% by 150 ms when a saccade was required to the center of the RF (Fig. 4B, - - -). When a saccade to the edge of the response field was required, the probability was considerably less likely (58.5% by 150 ms; Fig. 4B, - - -). To assess these differences statistically, we performed the permutation test to compare the distributions. Comparing the conditions in which the saccade target was located at the center and edge of the RF, we found that the original mean difference fell at the 95th percentile of the resampled distribution. These results indicate that the pauses we observe are influenced by the stimulus location in the RF.

However, comparing the cumulative probability functions for the No-Go condition in which the square was located at the center, and the Go condition in which the triangle was located at the center (Figs. 1 and 2A), we also found that the original mean difference fell at the 95.2%ile of the resampled distribution, indicating significant differences and revealing that saccade signals may also influence the pause we observe.

In summary, we found that in a foveal stimulus alone was insufficient to explain the transient pause in buildup neurons because its presence across the sample of SC neurons was modulated by the location of a stimulus in the RF. When no saccade was required, a pause was most likely to be measured. Moreover, in the Go/No-Go task, the occurrence of a pause was less likely when the foveal cue change was combined with a stimulus at the edge of a neuron’s response field. Similarly, in the Go-Go task, if a saccade was required to the edge of a receptive field, the pause was least likely to be observed. These results suggest that both the stimulus location and the cue to make a saccade are important for the occurrence of the pause. We explore this latter observation more fully next.

Pause modulation depends on making a saccade

There are two possible explanations for the observation that the pause depends on saccades and stimulus locations.
One is that the pause is related to choosing a particular saccade target. The second possibility is that the pause reflects whether a saccade occurs, independent of the target location. To distinguish between these two possibilities, we assessed the occurrence of a pause when two visual stimuli were closely apposed within single RFs of SC neurons. In this condition, the shape of the foveal cue was used by the monkeys to decide whether to make a saccade and, if so, where. Here, we could determine whether the pause occurrence was modulated by whether a saccade would occur. The occurrence of the pause was more likely across the population of buildup neurons when the square, indicating that no saccade was necessary, was cued (Fig. 5A, - - -). A pause was 80.8% probable by 150 ms in this condition. When a triangle stimulus was presented at the center of the visual field indicating that a saccade must occur, the pause was less likely to be observed (Fig. 5A). By 150 ms the pause was only 45.5%. This difference was confirmed by the permutation test in which we found that the original mean difference fell at the 100th percentile of the resampled distribution. Interestingly, in the Go-Go task, the percentage of buildup neurons showing a pause was reduced compared with those found in the Go/No-Go task (cf. Fig. 5, A and B; permutation test = 98.2%ile). In the Go-Go task, the pause was 62% probable by 150 ms. Also, there were no differences in the probability of a pause when the cue at the fovea was a square or a triangle (Fig. 5B, cf. - - - and; permutation test = 53.5%ile). We also explored the duration of the pause by plotting the cumulative distribution of Tdur across the sample of neurons. We found that Tdur did not differ in either condition (Fig. 5, C and D). Combined, these results indicate that the occurrence of the pause is related to whether a saccade is made or withheld later in the trial and that the occurrence of a pause across the population is modulated. We should point out that to test this hypothesis we purposefully used the trial conditions in which two stimuli were located in a single RF. As such, in none of the cases used did the neuronal activity drop to zero. In other words, there was always activity present in which to measure a pause. Moreover, the number of cases in which the activity did not return to the mean minus 2SD of the baseline (there was no Tend within 300 ms) was very small. Of 57 cases, six showed this behavior in the No-Go condition, whereas nine showed this behavior in the Go condition. Indeed, this is opposite of what would be predicted if the occurrence of a sustained pause after a No-Go cue biased our results. Our observations are also consistent with those of others in SC (e.g., Wurtz et al. 2001).

Up to this point, we have described the characteristics of the pause observed in buildup neurons. The pause occurred at the time when a shape cue appeared in the central visual field—well outside the RF of the recorded neurons—and indicated whether or where to make a saccade. We demonstrated that the occurrence of a pause across neurons was modulated by whether a saccade would be made or withheld. If a saccade was cued, the pause was least likely. If a cue to remain fixating was presented, the pause was most evident. Importantly, we could not predict the properties of pauses seen in individual neurons as evidenced by a lack of modulation of Tdur. Rather the modulation resulted in a larger or smaller population of neurons having a pause. We confirmed this hypothesis by plotting the number of neurons against (Fig. 6). We found that the mean values of Parea/Tdur in these four conditions were slightly different, but none of them showed any significant difference with other conditions (Fig. 6, A–D; t-test, P > 0.05).

To explore further the hypothesis that the occurrence of a pause was related to whether a saccade was made later in the trial, we next measured the probability of measuring a pause when monkeys made mistakes and either made saccades when they should have remained fixating or remained fixating when they should have made saccades (Fig. 6E). Our monkeys were well trained so the number of neurons with errors trials was 20. The small numbers of error trials (generally <10 trials per condition) also contributed to high variability. Nevertheless, a pattern emerged. If the monkeys remained fixating and should have made a saccade, the pause was more likely than if monkeys made saccades but should have remained fixating (Fig. 6E, 20% by 150 ms; and - - - , 15% by 150 ms). The differences were small and variable (permutation test = 67.8%ile), but considering that in correct trials the 2S (No-Go) condition is more likely to show pauses than the 2T (Go) condition (Fig. 5A, permutation test = 100th percentile), the observed trend in error trials is consistent with the hypothesis that the pause is related to whether a saccade will be made later in the trial.

The pause in visual-tonic neurons is independent of saccade occurrence

We were also interested in neurons without any explicit saccade-related activity. These neurons were classified as visual-tonic and were found slightly more dorsal to buildup

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**FIG. 5.** Pause in buildup neurons is modulated by task demands. A: probability of the pause is plotted against Tpause (ms) for buildup neurons recorded in the Go/No-Go task - - - are from 2S (no-saccade required) condition and are from the 2T (saccade required) condition. B: same as in A except for the Go-Go task where saccades were required in both conditions. C: probability of measuring Tdur of a particular time is plotted for the Go/No-Go task trials and in D for the Go-Go trials. Inset boxes: visual stimulus configuration. Note in the Go-Go trials, monkeys had to make saccades to the square and the triangle stimuli, whereas in the Go/No-Go trials, monkeys remained fixating for the square cue.
neurons. Interestingly, the probability of measuring pauses in visual-tonic neurons was different from buildup neurons (Fig. 7). Visual-tonic neurons showed very little modulation in either the single-stimulus configuration (Fig. 7A) or the two-stimulus configuration (Fig. 7B). The only difference we found in the pause of visual-tonic neurons was when a saccade target was located at the edge of the response field (Fig. 7A, bottom). In this case, the probability of measuring a pause reached levels measured in the other conditions, but it took much longer (cf. Fig. 7, and —). That the number of neurons with pauses was similar in all conditions was confirmed by the results of the permutation test (1T vs. 1S at the center/1005 53.4%ile; 1S at the center vs. 1S at the edge/1005 60.7%ile; 1T at the center vs. 1T at the edge/1005 73.7%ile; 1S at the edge vs. 1T at the edge/1005 88.1%ile; 2T vs. 2S/1005 50.6%ile).

Modeling population inhibition among SC neurons

An important aspect of our results is that the probability of measuring a pause varied with task conditions across the sample of neurons but we were unable to predict the magnitude of any individual pause based on the task conditions. We hypothesize that this results from dynamic inhibitory interactions. In other words, the number of neurons influenced by inhibition is not stationary across task conditions. To explore this, we developed a conceptual and mathematical model to simulate population inhibition. We imagine that the inhibition occurs across the SC map, but the model does not posit a source for the inhibition. The conceptual model is shown in Fig. 8 and does not imply known anatomical facts. It is provided to clarify the mathematical model. Because the stimuli used in our task were placed in locations that were close together—both stimuli fell within a single RF—we assumed that these stimuli activated overlapping neuronal populations (McIlwain 1975, 1986). We also assumed that the foveal stimulus activated neurons that inhibited regions of SC and that there was mutual inhibition between the activated neuronal populations. Whether this results from local, SC inhibitory mechanisms is supported by anatomical (Behan and Kime 1996; Mize 1992) and physiological (Munoz and Istvan 1998) evidence, but is controversial (Helms et al. 2004; Özgen et al. 2004) and our model is agnostic on the source of inhibition. Our final assumption is that a signal indicating the decision to make a saccade is derived external to the SC and influences SC neuronal responses dynamically, depending on task conditions.

FIG. 7. Pause in visual-tonic neurons is not modulated by saccade occurrence. A: arrangement of this panel is the same as that in Fig. 4A but for visual-tonic neurons. Inset diagram: trials condition; the arrow indicates that a saccade was required. B: arrangement of this panel is the same as that in Fig. 5A. Inset: trial type; the arrow indicates that a saccade was required. n = 26.
We computed the total level of inhibition across the SC neuronal population and simulated the number of recruited neurons over 300 ms. The number of neurons recruited at a particular point in time, \( R(n(t)) \), was described by the vector equation

\[
R(n(t)) = \frac{dR(t)}{dt} - F_i(t,d) + r(t,d) - I(t,d) \left\{ \frac{s(d)}{r(d)} + \frac{s(d)}{s(d)} \right\}
\]  

(1)

In a single-target saccade task, we supposed that two neuronal populations are activated, one representing the target location \( r(t,d) \) and one representing the fixation stimulus. \( F_i(t,d) \) represents the inhibitory drive originating from the population activated by the fixation stimulus across time and distance. We assumed that this foveal inhibition had temporal and spatial components and also that its influence was different for buildup and visual-tonic neurons. We modeled the two spatial components as Gaussians with a maximal influence at the center of the activated target population and a lesser influence at the edge of the activated target population

\[
f(d) = \frac{1}{2 \times \pi \times \sigma} e^{-|d|^2 \times \pi \times \sigma^2} \quad [-10^\circ < d < 10^\circ, \sigma = 516(\text{buildup}), \sigma = 104(\text{visual}), \mu = 0, k = 30] 
\]  

(2)

We based this on our observation that a pause was less likely to occur when the visual stimulus was located at the edge of a RF compared with when a stimulus was at the center of a RF (Fig. 4, A and B). We assumed that the influence of inhibition was broader on visual-tonic neurons than on buildup neurons (Fig. 9A, note the larger \( \sigma \) for visual-tonic neurons). For the temporal profile of foveal inhibition, we simulated a 300-ms epoch of inhibition with a peak occurring at 150 ms after the cue (Fig. 9B). This was done for both neuron types. However, we postulated that the foveal inhibition had a different temporal profile in the 1T edge condition. Specifically, the peak of inhibition for visual-tonic neurons in this condition occurred 250 ms after the cue (Fig. 9B, visual-tonic delayed). We based this on the observations we made in Fig. 7. To fully capture the data in the 1T edge condition, we also incorporated an enhancement of the inhibitory drive to visual-tonic neurons (71% greater than buildup neurons; Fig. 7B, visual-tonic delayed and enhanced). Note that these two differences in the temporal profile were implemented only for the 1T edge condition in visual-tonic neurons. The model also includes a term for the mutual inhibition between active populations of SC neurons \( I(t,d) \). This term has both a temporal \( I(t) \) and a spatial \( I(d) \) component. Whether this is mediated by intrinsic SC connectivity (Behan and Kime 1996; Mize 1992) or extrinsic sources (Appell and Behan 1990; Arai and Keller 2005; Özen et al. 2004) does not matter for the model.

**FIG. 9.** Simulated foveal inhibition and saccade functions. *A:* activation level in arbitrary units is plotted against distance in degrees. One curve is for buildup neurons and one is for visual-tonic neurons. *B:* activation level in arbitrary units is plotted against time (ms). One activation function was used for buildup neurons (thick) and two separate functions were used to simulate the inhibition influencing visual-tonic neurons. One was delayed in time, having a peak at 150 ms (bottom, −−) and a second was delayed in time and enhanced by 71% (top, −−−). This latter function was required to capture the sample results we obtained in the 1T edge condition in visual-tonic neurons. *C:* simulated decision to make or withhold a saccade signal functions used to model the sample data. −− plots activation against distance across the SC map for buildup neurons. Top thick (−−−) plots the same for buildup neurons influenced by decision signals and the middle thinner (−−) plots the same for visual-tonic neurons. Note our model predicts different effects of saccade decision signals on visual-tonic and buildup neurons.
S(d) is the decision signal indicating whether a saccade would be made. We used two functions to simulate this signal. One was for the conditions in which saccades were required [Go-Go task; S(d)_A] and the second was for conditions in which no saccades were required [Go/No-Go task; S(d)_U]. S(d) describes the influence of deciding to make or withhold a saccade on the population activity level as a function of distance across the SC map. We assumed that these signals approximated Gaussian functions. They are similar to those described for attention signals by Maunsell and colleagues (Maunsell and McAdams 2000; McAdams and Maunsell 1999). The functions are shown in Fig. 9C. Note, that in addition to having a S(d)_A and a S(d)_U function, we also used two different S(d)_A functions, one for visual-tonic neurons and one for buildup neurons.

Figure 10 illustrates the results of our simulations. The pattern was similar to that seen in the electrophysiology. Specifically, when a single target was presented and the cue indicated that no saccade would be required, the pause was most likely to occur in simulated buildup neurons (Fig. 10A, - - -). When a single target was presented at the edge of the RF and the monkey would be required to make a saccade to it, the pause was less likely to be measured (Fig. 10A). When two stimuli appeared and a saccade was required, the pause was less likely to be measured than when a saccade was not required (Fig. 10B).

We also simulated the results of our physiological experiments in visual-tonic neurons. These are shown in Fig. 10C. As described above, a different time course of inhibition from the fovea [F(t, d)] was used for visual-tonic neurons and the activation level of this inhibition was increased compared with buildup neurons. This was needed only to capture the results in the 1T edge condition. Like the results of the physiological experiments, simulated visual-tonic neurons showed the same probability of pausing for the single target condition in the Go/No-Go task, in contrast to buildup neurons (cf. Figs. 4A and 7A). Our model captured this result (Fig. 10C). The percentage of simulated visual-tonic neurons showing pauses did not differ in the Go and No-Go conditions of the task (Fig. 10C). Nor did it seem to matter that a No-Go stimulus was located at the edge of the RF (Fig. 10C). In the condition in which a saccade was required to the edge of the RF, actual visual-tonic neurons showed a reduced pause. However, as time increased to 150 ms the probability of measuring a pause was as high as in any other condition (Fig. 7, bottom). Simulated visual-tonic neurons behaved similarly (Fig. 10C). If we delayed the onset of the peak of the foveal inhibition, we found that the probability of a pause was decreased and stayed at that low level for the entire epoch (Fig. 10C, delayed; bottom). However, if we increased the inhibitory drive from the fovea by 71% (see Fig. 9C), the model fully captured the population behavior (Fig. 10B, model fully captured the population behavior (Fig. 10B, model fully captured the population behavior).

**DISCUSSION**

In this report we measured a transient suppression of persistent activity in SC neurons. The pause was associated with a cue occurring in the central visual field, well outside of the RF of the neurons we recorded. We tested three hypotheses regarding the characteristics of the pause and we provided a model of our results that both captured the observations made in the physiology and implemented assumptions that are testable predictions regarding the distribution of inhibitory influences in the SC.

First, we demonstrated that the pause was not simply a transient pulse of inhibition arising from activating neurons representing the central visual field. The pause in persistent activity occurred with a central cue change but, importantly, was modulated differently depending on the stimulus location. Second, we demonstrated that the presence of the pause in SC neurons depended on whether monkeys ultimately made saccades, well before the saccade was initiated. We found that the probability of measuring a pause was lower when monkeys were going to make saccades, particularly when two stimuli were present. In contrast, when monkeys remained fixating, the pause was more likely to be observed. Although the numbers...
of neurons were small and the result variable, a similar trend was found in error trials. Third, and importantly, we demonstrated that individual pauses were not predicted by the task conditions; rather, the number of neurons across the population expressing a pause changed. Because we measured a change in the probability that neurons will have a pause across the population of SC neurons, we interpret this finding as suggesting that there is a dynamic pattern of inhibition across the SC map as the process from vision to saccade initiation evolves. Finally, we presented a mathematical model based on inhibitory influences that explains our population results and makes predictions about these influences within the SC.

Relationship to previous reports of persistent activity

Persistent activity is found in many cortical and subcortical regions (Hikosaka et al. 1989; Robinson 1989; Taube and Bassett 2003). Persistent activity in the brain stem oculomotor system underlies the conversion of the pulselike input, indicating a desired change in eye position to the tonic level of activity required to maintain the eye at an eccentric position (Robinson 1989; Seung 1996; Seung et al. 2000). Roles for persistent activity in cerebral cortex are in the maintenance of a spatial memory (Funahashi et al. 1989, 1993; Wang 2005), visual working memory (Fuster and Jervey 1982; Miller et al. 1993, 1996), and accumulating sensory evidence to inform perceptual decisions (Mazurek et al. 2003; Roitman and Shadlen 2002). There is considerable recent interest in understanding the synaptic and network properties of persistent activity. In general, modeling efforts indicate that persistent activity relies on recurrent excitation and inhibitory interneuronal networks (Wang 2001), although biophysical properties of neuronal membranes may be an important factor (Marder et al. 2002). The basis for persistent activity in SC is unknown but it may involve similar recurrent, excitatory circuits (Helms et al. 2004; Moschovakis and Highstein 1994; Pettit et al. 1999).

Suppression of delay-period activity has also been reported previously. For example, in area 7a, the addition of a second stimulus interrupts delay-period activity during performance of a spatial memory task (Constantinidis and Steinmetz 1996). Suppression of delay-period activity of inferior temporal (IT) cortex neurons has also been reported during the performance of a delayed match to sample task. When a test stimulus appeared and matched the sample stimulus, many neurons in IT showed a suppressed level of activity (Miller et al. 1993). In a direct comparison with IT neurons, it was found that prefrontal cortex delay activity persisted after the presentation of intervening stimuli (Miller et al. 1996). Whereas delay-period activity in SC is modulated by many different task demands (Basso and Wurtz 1998; Dorris and Munoz 1998; Glimcher and Sparks 1992; Wurtz et al. 2001), the phenomenon we address here was a transient suppression of delay-period activity, which was often accompanied by a rapid increase in action potential rate (Fig. 1A). This latter phenomenon may reflect a type of postinhibitory rebound (Llinas 1988). That low-threshold $Ca^{2+}$ channels are found on SC neurons is consistent with this hypothesis (Saito and Isa 1999).

Transient pauses in delay-period activity have also been reported before. In FEF, immediately before saccade initiation, a dip in neuronal discharge rate was measured (Sato and Schall 2001). This pause was hypothesized to be related to the resetting of a neuronal integrator or reflecting a change in state. A similar interpretation has been applied to the transient dip in discharge rate of LIP neurons (Mazurek et al. 2003). Although a conclusion would require recordings from multiple neurons simultaneously, in light of our observations, we hypothesize that the transient inhibition in SC neurons may coordinate the activity of different populations of SC neurons to generate a saccade. For example, in motor cortex, neurons discharge closely in time (5 ms, Riehle et al. 1997, 2000). The synchronization changes with different phases of a delayed movement task and, moreover, different neurons are synchronized during different portions of the task. This observation suggests that within motor cortex there is a dynamic switching of neurons participating in different populations to produce a movement. We suggest here that the transient inhibition may serve a similar switching role in SC. Support for this idea is suggested by experiments demonstrating that inhibitory mechanisms are critical for the selection of functional maps of auditory space in the external nucleus of the inferior colliculus of the barn owl (Zheng and Knudsen 1999).

Model of SC inhibitory influences

Here, we present a model, which emphasizes the role of inhibitory mechanisms, that captures the data and has assumptions regarding inhibitory mechanisms influencing SC neurons that are testable. Our model contains three basic elements. One is a powerful foveal inhibition that is tuned in space and time. The second is mutual inhibition among populations of neurons representing different locations within the SC map. The third is an external drive that differs depending on whether a saccade will be made. For the purposes of explanatory power, the two most important factors in the model are the foveal inhibition and the saccade command.

With this model architecture, there are three testable assumptions. First, inhibition resulting from activation of central visual field has the greatest influence at the center of a RF and least at the edge of a RF of neurons. We based this hypothesis on our observation that the occurrence of a pause in SC neurons across the sample was less likely when the saccade target was located at the edge of the RF. Our model also suggests that the mechanism controlling pauses in visual-tonic and buildup neurons of the SC are similar. This is so because we did not have to change the model architecture to capture the differences between visual-tonic and buildup neurons; rather, only a parameter of foveal inhibition had to change. A prediction from this assumption is that on the edge of the RF, the foveal inhibition would result in more detectable pauses in visual-tonic neurons than in buildup neurons when a stimulus is located at the edge of the RF. Indeed, this prediction was born out in the data (cf. Fig. 4A, - - - square at the edge and Fig. 7A, - - - square at the edge). By 150 ms, visual-tonic neurons had a higher pause probability (62.5%) than that of buildup neurons (48.7%).

A second assumption of our model is that mutual inhibition among populations of SC neurons exists. Therefore a prediction of the model is that when a stimulus activates a population of neurons within the SC, an inhibitory drive will also be activated and its strength will decrease with distance from the center of the active population of neurons. It is well docu-
mented that when multiple stimuli appear, SC neurons show a reduced level of activity (Basso and Wurtz 1998; McPeek and Keller 2002; McPeek et al. 2003). It is unknown whether this results from the activation of local inhibitory circuitry (Behan and Kime 1996; Mize 1992) or from external sources, or whether it scales with distance. Inhibition scaling with distance is a prediction of our model consistent with recent in vitro evidence (Özen et al. 2004). Also, our model points out that when a stimulus activates a population of SC neurons, signals related to deciding whether to make a saccade not only influence excitatory mechanisms within the SC but also act on inhibitory mechanisms. Therefore the final response of any SC neuron will be a result of a dynamic balance between excitatory and inhibitory signals.

A final assumption of our model is that there is an external excitatory drive indicating whether to make a saccade. We modeled this drive after that proposed by Maunsell and colleagues to explain attentional phenomena (Maunsell and McAdams 2000; McAdams and Maunsell 1999). A stimulus in the visual field will activate a population of neurons that can be described with a Gaussian (Sparks and Mays 1980; Sparks et al. 1977; Van Gisbergen et al. 1981, 1987; Van Opstal and Van Gisbergen 1989). When that stimulus is to be used as a saccade target, the population response will increase both at the peak and, importantly, also at the edge of the RF. The model predicts a response gain increase. Importantly, our model predicts that the effects of deciding to make a saccade will be preferential for stimuli located at the edge of the RF, similar to that suggested for motion direction detection in MT (Snowden et al. 1992). Also, our model predicts that the influence of deciding to make a saccade will be stronger in the population of buildup neurons compared with the population of visual-totic neurons. This latter prediction provides a novel insight into the SC. Our previous work demonstrated little difference in the probability of pause occurrence in visual-totic and Basso 2005). Yet, in this report, we describe a clear difference in the probability of pause occurrence in visual-totic and buildup neurons. In light of these differences we suggest that suggested for motion direction detection in MT (Snowden et al. 1992). Also, our model predicts that the influence of deciding to make a saccade will be stronger in the population of buildup neurons compared with the population of visual-totic neurons. This latter prediction provides a novel insight.

ACKNOWLEDGMENTS

We are grateful to our colleagues in the lab who provided critical comments on the manuscript and to E. Emeric and J. Schall for sharing Matlab code. We also thank J. Smith for expert technical support and the anonymous referees for critical reviews.

GRANTS

This work was supported by National Eye Institute Grant EY-13692 and a grant from the Esther A. and Joseph Klingenstein Foundation to M. A. Basso.

REFERENCES


Moschovakis AK, Scudder CA, and Hight SM. The microscopic anatomy and physiology of the mammalian saccadic system. Prog Neurobiol 50: 133–254, 1996.

Muller JR, Phillastides MG, and Newsome WT. Inaugural article: microstimulation of the superior colliculus focuses attention without moving the eyes. Proc Natl Acad Sci USA 102: 524–529, 2005.


