Systems/Circuits

Suppression of Spontaneous Activity before Visual Response in the Primate V1 Neurons during a Visually Guided Saccade Task

Jungah Lee,[1] Kayeon Kim,[1] Sooyoung Chung,[2] and Choongkil Lee[1]

[1]Department of Psychology, Seoul National University, Kwanak, Seoul 151-742, Republic of Korea, and [2]Institute of Brain Sciences, Korea Institute of Science and Technology, Seoul 136-791, Republic of Korea

Visually guided saccadic eye movements are thought to involve multiple stages of processing in diverse brain structures including the primary visual cortex (V1). The variability of neural activity in each of these structures may present ambiguities for downstream stages in identifying sensory and motor signals among spontaneous discharges. The response time of saccadic eye movements made toward a visual target is correlated with the time of the first spikes in V1 that are evoked by the target (Lee et al., 2010). This suggests that downstream neurons receiving the output of V1 are faced with a challenging task of discriminating first spikes of visual response against spontaneous discharge. Here we report a novel response property of the macaque V1 neurons. Immediately before neurons discharge a burst of activity to a visual saccade target, spontaneous discharges were transiently suppressed. This suppression was maximal ~18 ms after target onset. Based on simulations of artificial spike trains, we propose that the transient suppression enhances temporal contrast for identifying the onset of visual response by increasing the reliability of detection of response onset by downstream neurons, thereby facilitating visually guided behavioral responses.

Introduction

Cortical cells are embedded in networks of excitation and inhibition (Douglas and Martin, 1991), and discharge spontaneous spikes at a variable rate (Shadlen and Newsome, 1998). Extraction of perceptual or behavioral information from event-related spikes that are added onto spontaneous spikes is a challenging task for downstream neurons. This is especially so when correlation between perceptual or behavioral events and spikes is low or the correlation is established by the timing of spikes in the midst of spontaneous discharges, such as the correlation between the timing of the onset of a spike train evoked by a visual target in the primate primary visual cortex (V1) and the latency of saccadic response made to the target (Lee et al., 2010). Thus, downstream neurons are faced with a task to identify the onset of event-related signals, and, in doing so, the task is susceptible to ongoing spontaneous discharges.

In the current report, we describe a novel finding that may help resolution of this common problem of identifying the signal onset: in a rapid visual detection task performed by trained monkeys, a large number of V1 cells rapidly reduced the level of their spontaneous firing immediately before they gave off a burst of activity to a brief visual stimulus used as a saccade target. Previous studies have examined the spike activity of the awake monkey V1 during visually guided saccade tasks (Supèr et al., 2001; Palmer et al., 2007). However, to our knowledge, no one has described in V1 the suppression of spontaneous discharge followed by excitation in response to a visual saccade target. This work was previously published in the form of a conference abstract (Lee et al., 2012).

Materials and Methods

Animal preparation and data collection. The data for visually guided saccades in the current study are based on the V1 spike data from two male monkeys (IR and CR) that were also used in a previous report (Lee et al., 2010). The data for fixation trials were additionally obtained from the same animals. All experimental procedures were approved by the Seoul National University Animal Care and Use Committee and were identical to a previous description (Lee et al., 2010), unless stated otherwise.

Briefly, extracellular single-unit activity was recorded from the V1 of two monkeys while they performed a visual detection task with their heads restrained. In each trial, a small dot was presented for fixation at the center of the monitor. After a variable duration of fixation, the fixation target went off, and at the same time, a Gabor stimulus was presented at randomly chosen one of two or four locations, one of which coincided with the receptive field (RF) location of the cell under study. The orientation and size of the Gabor stimulus, when presented at the RF location, were optimal for the cell. The contrast of the Gabor stimulus was randomly chosen from 4, 16, and 64%. The contrast and position of stimulus were shuffled in a given block, and the animal's task during saccade trials was to detect the stimulus and to make a saccadic eye movement toward

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Correspondence should be addressed to Dr. Choongkil Lee, Department of Psychology, Seoul National University, Kwanak, Seoul 151–742, Republic of Korea. E-mail: cklee@snu.ac.kr.

J. Lee's present address: Department of Psychology, University of Canterbury, Christchurch 8140, New Zealand.

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it within 600 ms of target onset. Successful saccades were rewarded with drops of fruit juice.

All timing information including stimuli and spike data were derived from signals digitized at a rate of 25 kHz by a single computer. A voltage signal from a photometer that was facing the monitor was downsampled later to 1 kHz and used to determine stimulus onset time, which was defined as the first time point above the baseline voltage. The error associated with this procedure for determining the stimulus onset time was at most 1 ms. Spike timing sampled by the same computer was referenced to this time.

Data analysis. To determine whether the level of spike activity decreased during the latent period (i.e., the period from target onset to response onset), we derived suppression index (SI), for each stimulus contrast condition for each cell as follows:

$$\mathrm{SI} = \frac{\sum_{1}^{n} N_{\mathrm{latent}}}{\sum_{1}^{n} < N_{\mathrm{baseline}} >} - 1,$$

where n is the number of trials, N_{latent} is the number of spikes during the latent period, defined as one of three durations, 20, 30, and 40 ms after target onset, and N_{baseline} is the mean baseline spike count of a given trial. To obtain a reliable baseline, we averaged spike counts obtained from 100 baseline periods, each of which started at a randomly chosen time between −200 and −100 ms of target onset and lasted for the same duration as the latent period. We avoided 100 ms of period immediately before target onset, due to a potential decrease in spike activity in this period. We derived SI from the spike sequence summed over all trials, because in individual trials, it was difficult to estimate suppression due to the low level of spontaneous activity of most cortical cells. The statistical significance of SI was appraised with a bootstrap method; SI was compared against a distribution of SI values derived from the condition in which the firing rate during analysis window was randomly chosen from baseline activity.

Simulation. A potential advantage of signals with suppression before response onset is thought to be the enhancement of signal-to-noise ratio (SNR) through suppression of spontaneous discharge, which thereby enhances the temporal contrast of response onset to make the detection of response onset more reliable. We attempted to evaluate functional consequences of suppression before first spikes by comparing temporal contrast of artificial spike trains generated with and without suppression.

We generated spike trains following a Poisson process into time bins of 1 ms at a spontaneous firing rate of 10 spikes/s for a period up to the first stimulus-evoked spike, which was made to occur at a variable time with a mean of 60 ms, SD of 20 ms, and minimum of 35 ms from target onset. After the first spike, spike trains were generated with a firing rate of 100 spikes/s. These values were taken from single-neuron data for the stimulus contrast of 64% (Lee et al., 2010). Spike occurrence was suppressed within 2 ms of neighboring spikes, mimicking an absolute refractory period. Suppression before the first spike was mimicked by simply suppressing spike occurrence before the first spike of visual response for 20 ms. Since the timing of the first spike shows a variability, this procedure is, in essence, the same as introducing a suppression after target onset.

The spontaneous discharge is not necessarily a noise, but is seen analogous for the sake of quantifying the contrast between response spikes (signal) above spontaneous spikes (noise). From the definition of SNR, we derived a definition of temporal contrast, $C(t)_{\mathrm{dB}}$, as a change in the logarithm of the root mean square of spike density, $r(t)$:

$$C(t)_{\mathrm{dB}} = 20 \times \left(\log_{10} \sqrt{\frac{1}{\tau} \int_{t-\tau}^{t} [r(t)]^2 dt} - \log_{10} \sqrt{\frac{1}{\tau} \int_{t-2\tau}^{t-\tau} [r(t)]^2 dt} \right),$$

where τ is the width of the analysis window and $C(t)_{\mathrm{dB}}$ is a quantity representing a change in spike activity in dB units. We also examined temporal contrast defined in another way, $c(t)$:

$$c(t) = \left[\int_{t-\tau}^{t} r(t)dt - \int_{t-2\tau}^{t-\tau} r(t)dt \right] \Big/ \tau,$$

where τ is a precision of temporal contrast. This is based on a linear sum of $r(t)$, which may be more physiologically appropriate than $C(t)_{\mathrm{dB}}$, given the assumption that downstream neurons detect the onset of response based on the difference of input signals integrated over a fixed duration. Simulated detection occurred when the temporal contrast $c(t)$ reached a threshold change that was set at 3 SDs above mean temporal contrast during a baseline fixation period of 300 ms before target onset. The reliability of detection was estimated with the SD of detection (threshold-crossing) time across repeated tests.

Results

Figure 1 illustrates the activity of a representative cell (Fig. 1*A–C*) and population spike activity summed over 101 neurons (Fig. 1*D–F*) during a visually guided saccade task. The suppressive modulation of spike activity was not clear in single-cell activity and was better seen in the population activity. With a stimulus contrast of 64%, for example, a transient decrease of spike activity from baseline level was apparent at ~18 ms after target onset (arrowhead), and after this point the activity started to increase and reached its peak activity at ~60 ms after target onset (Fig. 1*F*).

It was conceivable that trained monkeys could anticipate the time of target appearance, and that this modulated spike activity near the time of target onset (Lima et al., 2011). In fact, the population spike density appeared to start decreasing even before target onset (Fig. 1*D–F*). This was also visible in those trials in which the saccade target was presented in the hemifield opposite to the RF (Fig. 1*G*,*H*). The spontaneous activity was maximally reduced at the time of target onset. We estimated the time of reduction start, assuming that the activity linearly decreased starting at some point before target onset until maximal suppression. For this purpose, we used the mean spike density of all trials in which saccade targets were presented in the hemifield opposite to the RF. The sum of squared error between the density and two intersected lines (one fitting the density before reduction start at its mean level and the other fitting the successive decrease) was minimal when the two lines met at 36 ms before target onset. Thus, due to target anticipation, the spontaneous discharge decreased starting at ~36 ms before target onset until target onset, and recovered rapidly and overshot the baseline thereafter.

Figure 2*A* illustrates a quantitative summary of suppression of spike activity before excitation in response to a target in the RF. For 20 ms of the latent period, the SI was negative and decreased with the stimulus contrast; the SI differed significantly between 4 and 64% contrast conditions (Wilcoxon rank-sum test, $p < 0.01$). The SI became higher with a longer analysis window for a given stimulus contrast. This was due to the intrusion of the spikes at a short latency into the analysis window. The SI computed over the period of 40 ms for 64% contrast became positive, indicating that the spike count during this period increased over the baseline. These results indicate that the spike activity was suppressed briefly after the onset of the visual stimulus used as a saccade target and the suppression increased with stimulus contrast.

When the stimulus was presented in the hemifield opposite to the RF, the SI was near zero with an analysis window of 20 ms and

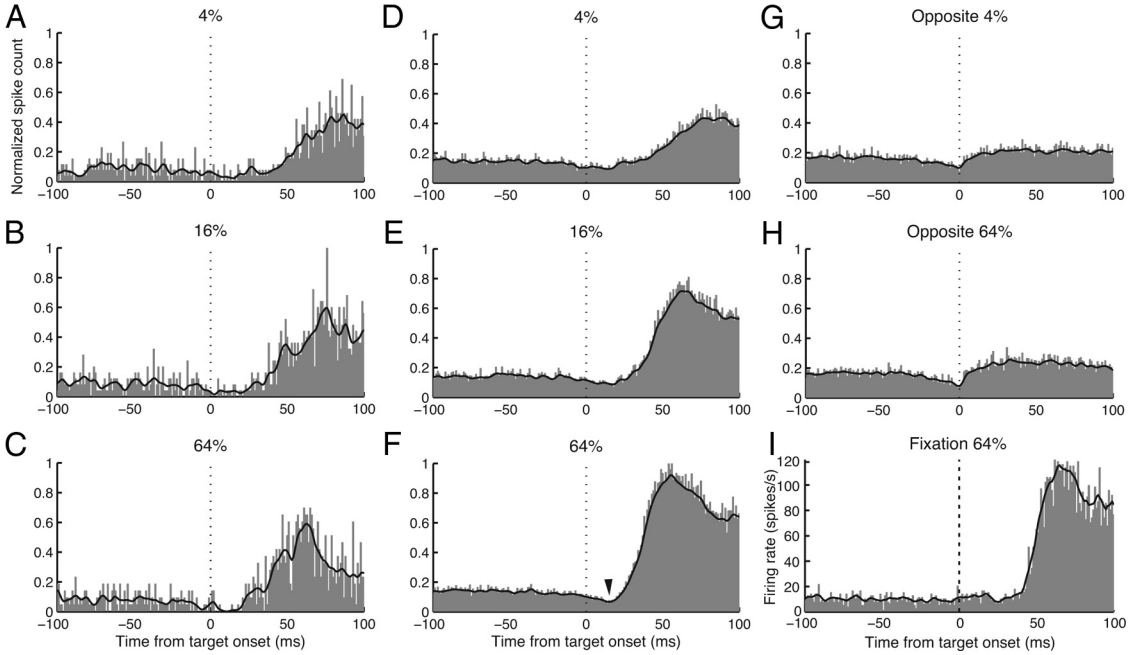

Figure 1. ***A–F***, Peristimulus time histograms (PSTHs) of a representative cell (***A–C***) and the entire sampled population (***D–F***). A Gabor stimulus of indicated contrast was presented in the RF as a saccade target. ***G***, ***H***, Population PSTHs for trials in which the saccade target was presented in the hemifield opposite to the RF. The profile was similar for 16% (data not shown). Spike activity was normalized to maximum spike count within each cell and then pooled. ***I***, Population PSTH during fixation condition compiled for 783 trials from 51 cells (32 single and 19 multiunits). The curve in each plot is spike density function.

slightly positive with longer analysis windows that covered the overshoot (Fig. 2*B*). The overall difference in SI between panels *A* and *B* in Figure 2 indicates that, unlike the activity reduction before target onset, the suppression after target onset was specific to the site of visual response and not a general phenomenon due to top-down modulation. Were the suppression caused solely by anticipation, it should occur at similar times with respect to fixation onset, regardless of the required fixation duration, which was randomized and thus unknown to the animal. However, spontaneous spikes continued until the end of fixation (i.e., target onset) (Fig. 3). Thus, suppression of spike activity was not coupled to fixation onset. We will call this transient suppression of spike activity before excitation the pre-response suppression (PRS) in the following text.

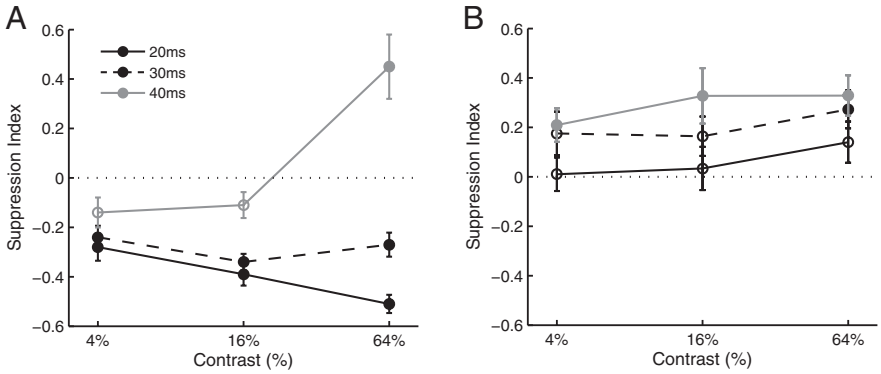

Figure 2. ***A***, ***B***, Mean SI across contrast conditions computed from 101 cells for the target in the RF (***A***) or in the hemifield opposite to the RF across fixation (***B***). Bars indicate SEMs. Negative SI values indicate suppression of spike activity after target onset. Filled symbols indicate means that are significantly different from zero. With analysis windows of 20 and 30 ms, all mean SI values in ***A*** are significantly negative ($p < 10^{-5}$, one-tailed *t* test), whereas those in ***B*** are not except one (30 ms, 64%, $p < 0.01$). With a window of 40 ms, *p* values in ***A*** were 0.02, 0.04, and 0.0007 for 4, 16, and 64% contrast conditions, respectively, whereas in ***B***, they were all significantly positive ($p < 0.01$).

In Figure 3, the epochs before first spike with reduced spontaneous spikes extend to a few tens of milliseconds. Artificial spike trains with an unrealistically long refractory period of ~20–30 ms could replicate the discharge suppression before first spikes, but they also produced suppression after first spikes, hence an oscillatory discharge pattern (data not shown). The lack of spikes before first spike is also related to a low level of spontaneous activity. However, the presence of reduction in discharge rate after target onset in Figure 1*A–F* indicates that low level of spontaneous activity alone is not sufficient to produce PRS. Thus, we conclude that the duration of reduced spike activity in Figure 1*A–F*, and the lack of spikes before the first spike in Figure 3, signify suppression of spontaneous discharge in addition to a refractory period and a low level of spontaneous activity.

We attempted to determine whether PRS is also present during fixation. For this, we analyzed separately obtained data from two monkeys (24 cells from IR and 27 cells from CR). An optimal Gabor stimulus with a contrast of 64% was presented for 20 ms at the RF on a gray background with a mean luminance of 5.85 cd/m^2 while the animal maintained fixation on the central target. All recordings were done on the operculum V1 and the eccentricity of RF was ~4–5°. A saccade (point) target was presented in the hemifield opposite to the RF at least 300 ms after the Gabor stimulus offset, and a liquid reward was contingent upon a saccade made to the saccade target. Thus, the Gabor stimulus was irrelevant to the task. In this condition, no apparent PRS was observed (Fig. 1*I*), and the overall mean SI in this condition was 0.01 ± 0.58.

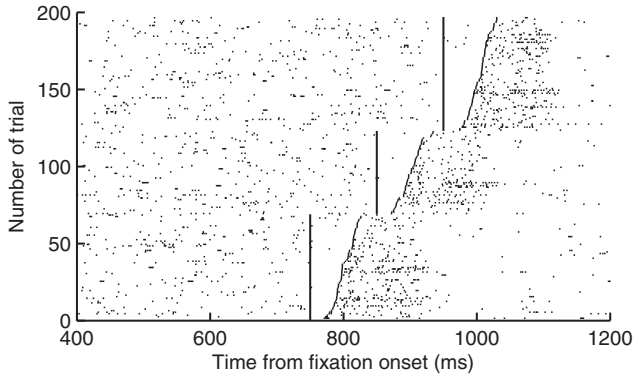

Figure 3. A raster plot of Figure 1*C*. Fixation duration was randomly chosen from 750, 850, and 950 ms. Trials were sorted by fixation duration and then by the time of first spike (Lee et al., 2010). Note a low spike activity before first spikes. Also note continued spontaneous spikes to the onset time of visual saccade target (vertical bars), indicating that the suppression before response onset was not due to the anticipation of target onset. The SI values of these trials are −0.81, −0.56, and −0.38 for 20, 30, and 40 ms of analysis window, respectively, and are significantly different from zero ($p < 10^{-5}$). The SI values of this cell for three fixation duration groups for 64% contrast and 20 ms of analysis window were −0.69, −0.94, and −0.81, and those for the entire cell population were −0.46 ± 0.41, −0.52 ± 0.48, and −0.58 ± 0.38, for 750, 850, and 950 ms, respectively. The differences among fixation groups were not statistically significant (*t* test, $p > 0.08$).

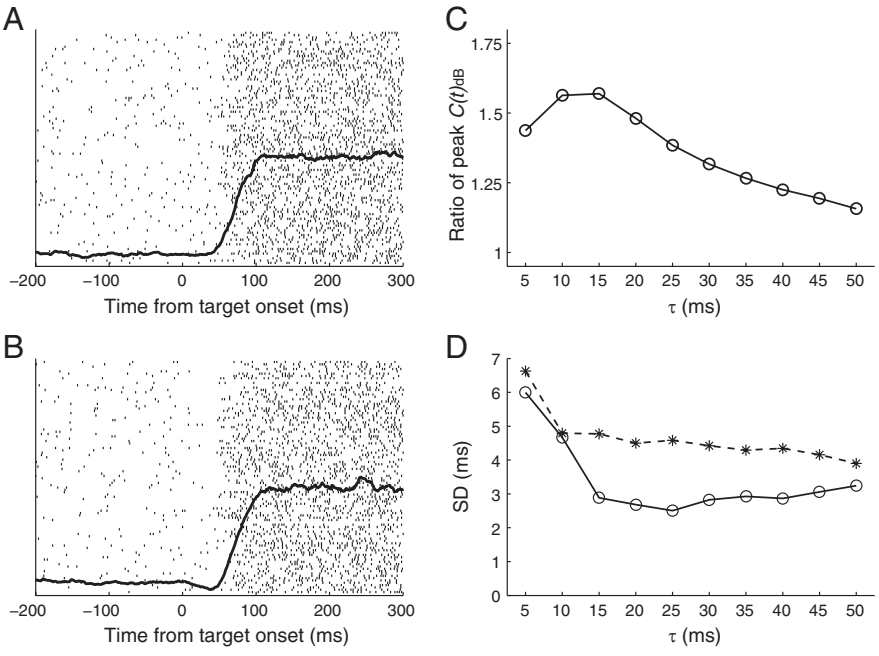

Figure 4. Simulation of PRS. ***A***, Raster and spike density of artificial spike trains. Shown are the first 100 of 500 generated spike trains and spike density based on all 500 spike trains. ***B***, Same as ***A***, but with a suppression of spike generation for 20 ms before first spike. Note a dip in spike density before response onset that mimics experimental data of Figure 1*F*. ***C***, Increase of temporal contrast, $C(t)_{dB}$, with PRS. Shown are the ratio of the peak $C(t)_{dB}$ in ***B*** (with PRS) to the peak $C(t)_{dB}$ in ***A*** (without PRS) as a function of temporal precision, τ. ***D***, SD of the time of threshold crossing of temporal contrast, $c(t)$, averaged >1000 repetitions, each computed from 500 artificial spike trains. Temporal contrast was computed with different precision for conditions with (solid) and without (dashed) PRS.

Discussion

We found that during a visually guided saccade task, ongoing spike activity of monkey V1 neurons was suppressed before excitation in response to a visual stimulus used as a saccade target. This pre-response suppression was rapid and most distinct at ~18 ms after target onset. Previous studies reported large variations in mean latency of visual response of V1, but also reported short-latency visual responses. The latency of V1 spike response was as short as 20–24 ms (Maunsell and Gibson, 1992; Romero et al., 2007), and the decrease in spike activity at changes from preferred to anti-preferred stimuli took as short as 20 ms (Bair et al., 2002). For some neurons in the anesthetized cat primary visual cortex, the initial IPSP occurred 15–20 ms after flash stimuli (Creutzfeldt et al., 1969).

The PRS appears to be driven by a combination of processes. The decrease in population spike density even before the stimulus onset (Fig. 1*D–H*) suggests temporal anticipation of target, and the lack of PRS during fixation condition (Fig. 1*I*) suggests a top-down contextual gating of the PRS. On the other hand, the effects of stimulus contrast on the magnitude of suppression (Fig. 2*A*), the space-specific effects of Figure 2, and the lack of effects of fixation duration (Fig. 3) suggest stimulus-driven processes. The stimulus-driven component of PRS is probably underestimated in Figure 1*D–F*, because a rapid increase in spike density after target onset reflecting a retreat of anticipatory suppression (Fig. 1*G*,*H*) counteracts the stimulus-driven PRS. Below, we discuss the potential mechanisms and the functional roles of the PRS.

Potential bottom-up mechanisms of PRS

Suppression by visual stimulation is, in fact, not surprising, since LGN cells (Tailby et al., 2007) already show such properties. Especially noteworthy is a property of thalamocortical relay cells (Ramcharan et al., 2000) that hyperpolarizes for ensuing deinactivation and causes low-threshold bursts of spikes. Furthermore, a similar intracortical mechanism may manifest the PRS, because the subclasses of T-type Ca^{2+} channels are expressed in the cortex (Perez-Reyes, 2003), and the temporal interval between the first and second spikes of visual response during saccade trials was often <5 ms (data not shown), indicating that initial visual responses consisted of bursting activity.

We consider fast feedforward inhibition as another candidate bottom-up mechanism of the PRS. Afferent fibers of sensory cortex can generate IPSC via inhibitory interneurons as well as monosynaptic excitatory current in a target neuron (Swadlow, 2003). Thalamic stimulation is known to generate IPSPs followed by EPSPs in layers 2/3 of the cat visual cortex (Ferster and Lindström, 1983) and mouse somatosensory cortex (Kimura et al., 2010). This inhibition lasts for only a short period of time, estimated to be a few tens of milliseconds in the visual cortex (Douglas and Martin, 1991), and thus temporarily delays the time of threshold crossing, resulting in a brief suppression of spike generation before the response and delaying neural latency. This is consistent with a report that infusion of bicuculline, a $GABA_A$ antagonist, eliminates disynaptic suppression, thereby shortening neural latency in the mouse somatosensory cortex (Kimura et al., 2010). Furthermore, the thalamocortical latency to a postsynaptic inhibitory cell is shorter than that to an excit-

atory cell (Kimura et al., 2010). It remains to be seen that some of layer 4 neurons also show the PRS.

Top-down mechanisms of PRS

There was no apparent PRS in the fixation condition. Thus, fixation offset during saccade trials may be an important condition for PRS, like the reduction of activity following the offset of fixation target in the superior colliculus (Sparks et al., 2000). Alternatively, saccadic preparation may constitute a similar condition, like an attention-dependent increase in firing rate of putative inhibitory neurons (Mitchell et al., 2007). Thus, the PRS appears to be linked with task requirements, such as contrast detection at given locations for initiating behavioral response thereto, for which the PRS enhances task performance. The reduction of activity at the time of saccade target onset (Fig. 1*G*,*H*) also supports this view.

Functional implications of PRS

The spike densities of Figure 4, *A* and *B*, can be regarded as input signals to downstream stages that are provided by V1 neurons. A potential advantage of signals with PRS is thought to be the enhancement of SNR and thus increase in temporal contrast, so that detection of response onset may be more reliable with than without such suppression. We quantitatively examined the potential advantage of PRS for enhancement of SNR and temporal contrast, with two quantities, $C(t)_{dB}$ and $c(t)$, which are based on nonlinear and linear sums, respectively, of spike density. Both these quantities were, in essence, time derivatives, and accordingly they peaked near response onset (data not shown). With PRS, the $C(t)_{dB}$ increased >50% (Fig. 4*C*), and the reliability of contrast detection based on $c(t)$ was enhanced by ~2 ms (Fig. 4*D*) with a temporal precision of ~15–20 ms, which amounts to enhancement of >40%.

The suppression itself, rather than successive excitation, may be used as a sign of target onset for downstream neurons, thereby shortening reaction time. However, when simulated spike trains were subjected to a test in which detection was made in the same test condition but at the time when the temporal contrast reached 3 SDs below the baseline level, detection failed in >30% of tests and is thus unreliable. This indicates that the ensuing burst after suppression is probably a robust signal for contrast detection, and that the PRS facilitates detection.

Lateral inhibition (Hartline et al., 1956; von Békésy, 1967) is a common mechanism used for enhancing spatial contrast in coding sensory events. The PRS may be its temporal counterpart. If a saccadic decision relies on first spikes from V1 (Lee et al., 2010), identifying the first spike of a response imposed on a noisy background discharge would be a great challenge for decoding processes downstream to V1. Transient suppression of spike activity may enhance temporal contrast of first spikes against background activity. With a low level of spontaneous activity, it would be an extremely difficult task, even with suppression, to dissociate the first spike of the visual response from spontaneous discharges at a single-cell level. We suggest that a potential advantage of pooling activities from a population of V1 output neurons is to increase the level of spontaneous activity enabling suppression to be pronounced, as shown in Figure 1. Thus, first spikes of the response may be more easily recognized because of the suppression of population activity. This predicts that pooling outputs from more V1 neurons will give a higher fidelity for identifying the onset of visual response. The fact that correlation between timing of the first spike and the saccadic response time increases with the size of the neuronal population (Lee et al., 2010) suggests that enhancement of temporal contrast of response onset by population pooling is mediated by suppression of spontaneous activity, more so than by increasing the magnitude of the initial visual response.

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