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Response latencies of cells in the cat's lateral geniculate nucleus are less variable during burst than tonic firing

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Abstract

We measured the variability in latency of the first spike seen in cells of the cat's lateral geniculate nucleus following the onset of a visual stimulus. We found that, in each of the 11 cells tested, this variability was significantly lower during burst than during tonic firing. We suggest that this difference confers an advantage in signal detection during burst compared to tonic firing. This complements other reported advantages of burst firing for signal detection seen in signal-to-noise ratios and in the ability to efficiently drive postsynaptic cells.

Keywords: T current, Low-threshold spike, Thalamus, Vision

Introduction

The transfer of retinal information through the lateral geniculate nucleus to visual cortex does not occur passively but rather involves dynamic processes that are regulated by behavioral state (for reviews, see Sherman, 1995; Sherman & Guillery, 1996; Sherman & Koch, 1998). Underlying cellular mechanisms depend in part on intrinsic membrane properties of relay cells that affect their response to retinal inputs and the control of these properties by nonretinal inputs. Perhaps the most important of these membrane properties is the voltage-gated, low-threshold Ca^{2+} conductance. This conductance is inactive at depolarized membrane levels but can be activated from a hyperpolarized level by depolarizing events, such as EPSPs (Jahnsen & Llinás, 1984*a*,*b*). When this Ca^{2+} conductance is inactive, relay cells respond in *tonic mode*, which is characterized by a steady stream of unitary action potentials, and this linearly reflects the activating stimulus (Jahnsen & Llinás, 1984*a*,*b*; Guido et al., 1995; Sherman, 1995). When this Ca^{2+} conductance is activated, a Ca^{2+} spike is produced, leading to a brief, high-frequency burst of conventional action potentials, and this represents the *burst mode*. Burst firing is a highly nonlinear response to the activating stimulus (Guido et al., 1995; Sherman, 1995).

Since visual stimuli evoke responses in geniculate cells during both response modes (Lo et al., 1991; Guido et al., 1992, 1995; Guido & Weyand, 1995; Sherman, 1995; Mukherjee & Kaplan, 1995), the obvious question regards the significance for visual processing of these two modes. It has been suggested that, because relay cells firing in burst mode respond to visual stimuli with higher signal-to-noise ratios, this mode is more useful for detecting novel targets, as might be required by "scanning attention" (Posner & Petersen, 1990; Guido & Weyand, 1995). Receiver Operating Characteristic (ROC) analysis confirms that cells in burst mode more reliably detect visual stimuli than when they are in tonic mode (Guido et al., 1995; Sherman, 1995; Sherman & Guillery, 1996). However, while better for detection, burst firing is nonlinear, so that shifting to tonic mode once a target is detected would enhance the ability of cortex to extract accurate features of the stimulus, as required for "focal" attention (Posner & Petersen, 1990; Guido et al., 1995; Sherman, 1995; Guido & Weyand, 1995; Sherman & Guillery, 1996).

Rapid signal detection would also require reliable timing in the neuronal responses to visual stimuli, and this is another feature of burst firing that, if present, could also enhance the reliability of signal detection. That is, from the perspective of cortex, rapid signal detection is based on recognizing that the first spike after a stimulus is not a spontaneous event but is in fact related to that stimulus. The less variable this poststimulus latency of the first spike, the easier and quicker signal detection is likely to be. We thus investigated this feature for a population of geniculate relay cells that exhibited both tonic and burst responses to visual stimuli.

Methods

We performed experiments on adult cats using methods described in detail elsewhere (Lo et al., 1991; Lu et al., 1992, 1993; Guido et al., 1995) and which are outlined below.

Animal preparation and recording

For initial surgery, we anesthetized the cats with 2–3% halothane in a 1:1 mixture of N_2O/O_2. During subsequent recording, we

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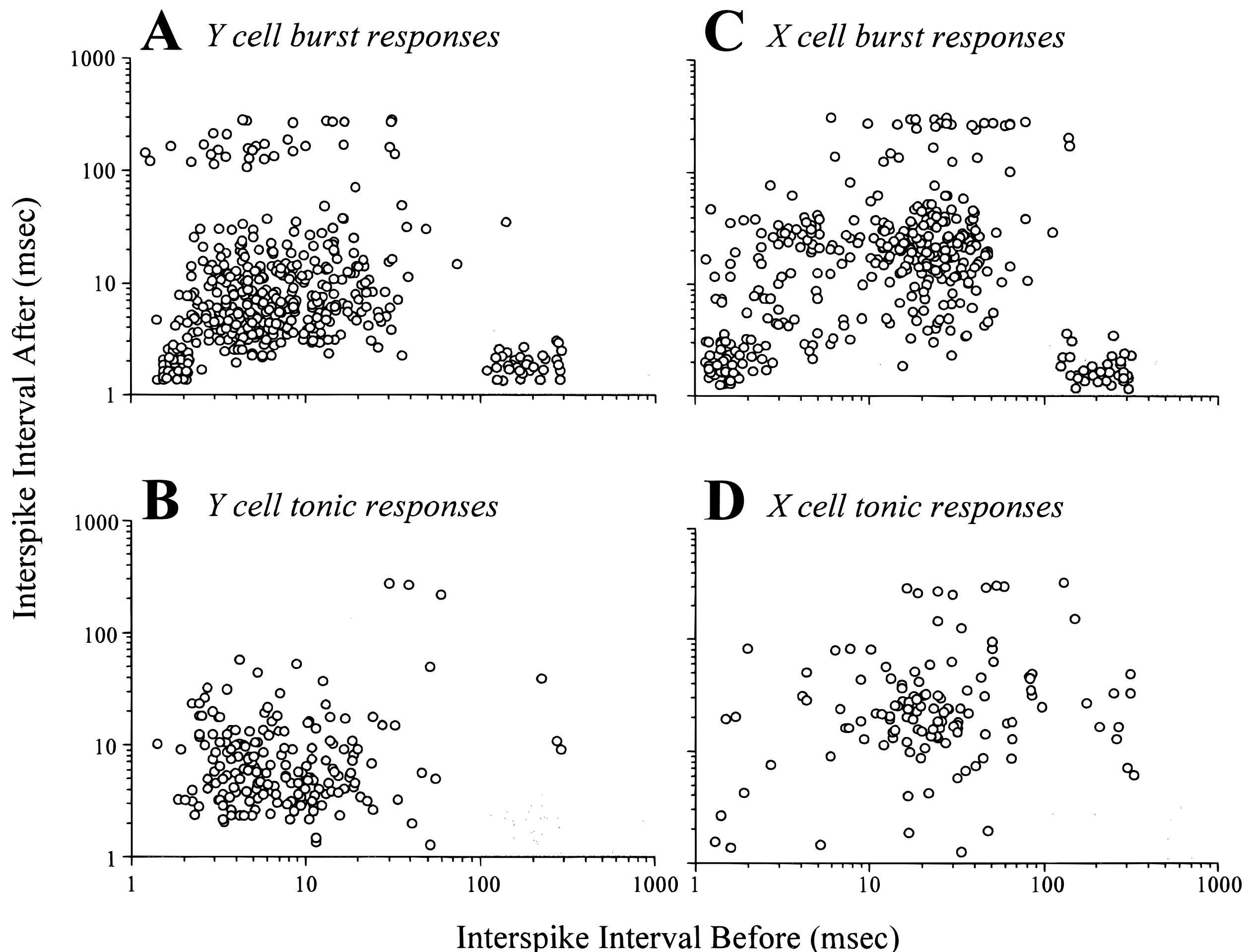

Fig. 1. Scatterplots showing pattern of interspike intervals for representative geniculate neurons: A and B are from an on center Y cell, and C and D are from an on center X cell. Responses include those to the flashed spot as well as the period before spot onset. For each spike is plotted the interspike interval preceding it on the abscissa versus the interspike interval following it on the ordinate. A,C: Interspike intervals for responses to 30 cycles of a bright spot flashed at 2 Hz for which the stimulus evoked a burst response. As noted previously (Guido et al., 1992) the initial response during such trials is a burst, and this is often followed by tonic firing. This scatterplot thus includes both burst and tonic spikes. The shaded region in the lower right of the scatterplot indicates our criteria for the first spike of a burst (i.e. a preceding interspike interval of ≥100 ms followed by one of ≤4 ms). B,D: Interspike intervals for responses to 10 cycles of a bright spot flashed at 2 Hz for which the stimulus evoked only tonic firing. No burst firing was seen among these responses.

maintained anesthesia throughout the recording session with 0.3–1.0% halothane in a 7:3 mixture of N_2O/O_2, and we treated all wound edges and pressure points with a long-lasting topical anesthetic. The cats were paralyzed, artificially respired, and their temperature, heart rate, and end-tidal CO_2 were monitored and kept within normal physiological limits. We also monitored EEG and blood pressure as an aid to ensure that anesthesia was maintained at appropriate levels. After placing the cat in a stereotaxic apparatus, we performed hydraulically sealed craniotomies for the recording electrode (centered on A 5.0, L 9.0) and for stimulating electrodes to straddle the optic chiasm (centered on A 13.0 and extending 2.0 mm to each side of the midline). For the latter, we applied single pulses (0.1-ms duration, 100–500 μA, <1 Hz) to activate geniculate neurons orthodromically from the optic tract. We dilated the pupils and blocked accommodation pharmacologically, we protected the corneas with zero-power contact lenses containing an artificial pupil with a diameter of 3 mm, and we applied spectacle lenses as deemed necessary by streak retinoscopy to focus the eyes onto a tangent screen 57 cm distant or onto an electronic display monitor 28.5 cm distant. We plotted and projected retinal landmarks, including the optic disk and *area centralis*, onto the tangent screen.

Single neurons in the geniculate A-laminae were recorded extracellularly or intracellularly using fine tipped micropipettes filled with 2–4 M KAc or 2 M NaCl (extracellular only). The electrode impedances ranged from 20 to 40 MΩ. Neuronal activity was amplified through a high-impedance amplifier, displayed on an oscilloscope, fed through an audio monitor, and stored on an 8-channel FM tape recorder interfaced with a computer for off-line analysis. We fed action potentials through a window discriminator for off-line computer analysis. We stored the spike arrival times of the responses to visual stimuli with a resolution of 0.1 ms.

Visual stimulation and cell classification

We first analyzed receptive-field properties by flashing small spots of light on the tangent screen, thereby determining ocular dominance, receptive-field location, receptive-field size, and center type.

We then replaced the tangent screen with a display monitor to present either vertically oriented, counterphase modulated, sine-wave or square-wave modulated, bright and dark spots on a moderate background. The gratings were used in the "null test" to aid cell identity as X or Y, and the flashed spots were used to evaluate the first response seen after stimulus onset (see Results). These spots were either dark (for off center cells) or bright (for on center cells); they were the diameter of, and centered on, the receptive-field center and were modulated at 0.5–1.0 Hz between background (30 cd/m^2) and dark (10–22 cd/m^2) or bright (45–90 cd/m^2) for 80–100 cycles.

We classified all geniculate neurons as X or Y using a standard battery of tests. This included linearity of spatial summation in response to grating stimuli, receptive-field center size, response latency to electrical stimulation of optic chiasm, and response to a large, fast moving stimulus of high contrast to activate the surround (i.e. dark for an on center cell and *vice versa*).

We used our previously described criteria to distinguish between tonic and burst response modes (Guido et al., 1992, 1995; Lu et al., 1992, 1993). Briefly, burst responses were distinguished from tonic activity as clusters of action potentials with interspike intervals $\leq$4 ms ($\geq$250 Hz) preceded by a silent period of $\geq$100 ms (Fig. 1). This short interspike interval reflects the high-frequency discharge of spikes that ride the crest of the low threshold Ca^{2+} spike, and the preceding silent period reflects the requisite duration of hyperpolarization needed to deinactivate the underlying Ca^{2+} conductance. Response mode typically varies from trial to trial and this allowed us to sort visual responses into trials representing burst and tonic firing (Guido et al., 1995; Godwin et al., 1996). Trials were sorted into respective categories on the basis of their initial response to stimulus onset (see Guido et al., 1995; Godwin et al., 1996).

Results

Fig. 1 illustrates our criteria graphically for typical geniculate X and Y neurons. During burst firing (Figs. 1A and 1C), the first spikes in the bursts form a distinct cluster of interspike intervals, having preceding intervals that are $\geq$100 ms succeeded by ones that are $\leq$4 ms (see Methods). There is another cluster at the lower left of each of these scatterplots for which interspike intervals before and after are $\leq$4 ms. These represent the second to penultimate spikes in the burst. The last spike in the burst is represented by most of those with prior interspike intervals $\leq$4 ms followed by interspike intervals $\geq$4 ms. Another cluster can be seen for spikes followed by interspike intervals $\geq$100 ms. Most of these are the last spike (mostly tonic) before a burst is initiated. The remaining spikes in this scatterplot are tonic spikes. Figs. 1B and 1D show analogous data from the same cells during tonic firing. The clustering of spike intervals during burst firing (Figs. 1A and 1C) is not apparent during tonic firing (Figs. 1B and 1D). This indicates that burst and tonic firing are quite distinct and that our criteria for distinguishing between firing modes are effective.

We conducted a trial-by-trial analysis of responses to flashing spots in 11 cells of the cat's lateral geniculate nucleus. All were recorded in the A-laminae, 10 were recorded extracellularly, and one using intracellular recording techniques. Each of the recorded cells responded to the visual stimulus in both tonic and burst response modes (Guido et al., 1992, 1995; Mukherjee & Kaplan, 1995), switching in an apparently random fashion between trials. When we sorted these responses into trials representing tonic versus burst responses (Lu et al., 1992; Guido et al., 1992, 1995), the responses during the burst firing mode were brisker and produced a sharper onset than those seen during tonic firing. Fig. 2 illustrates this for a typical example, an on center X cell that responded to the flashed bright spot 75 times in tonic mode and 25 times in burst mode.

The sharper onset of responses during the burst mode compared to tonic mode is in part due to the latency of the first spike after stimulus onset being less variable during burst than during tonic firing. Fig. 3 illustrates this point for the example shown in Fig. 2. There is less temporal scatter in the latency of the first spike during burst than during tonic firing. We do not distinguish here between a first spike that is a response to the visual stimulus and one that is spontaneous (see Discussion). Note also the irregular interleaving of burst and tonic responses to the stimulus, as if the cell shifts every few seconds between response modes (see also Guido et al., 1992, 1995; Guido & Weyand, 1995). Fig. 3A summarizes these initial spike latencies, and it is clear that there is more temporal scatter in the arrival time of these first spikes during tonic than during burst firing. This difference in variance is statistically significant ($P < 0.001$ both on an F-test and on the more conservative, nonparametric Levene Median test for unequal variance).

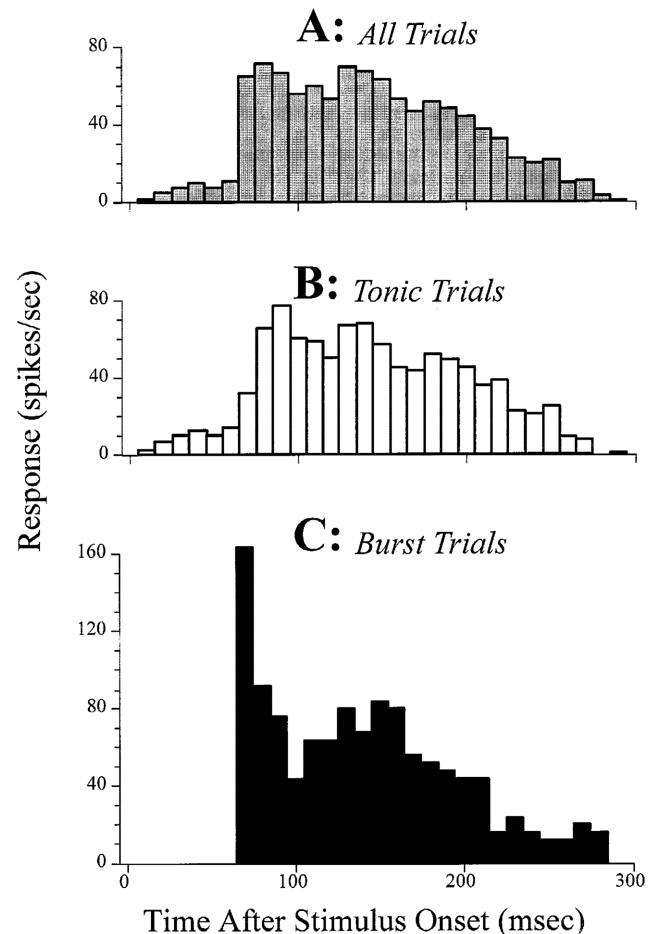

Fig. 2. Poststimulus histograms of responses of an on center X cell for 100 trials to bright spot flashed on in the receptive-field center. The onset of the visual response is plotted at time 0. It is preceded by an epoch of background illumination which is not shown. A: Overall response. B: Response for the 75 trials during which tonic responses were evoked. C: Response for the 25 trials during which burst responses were evoked.

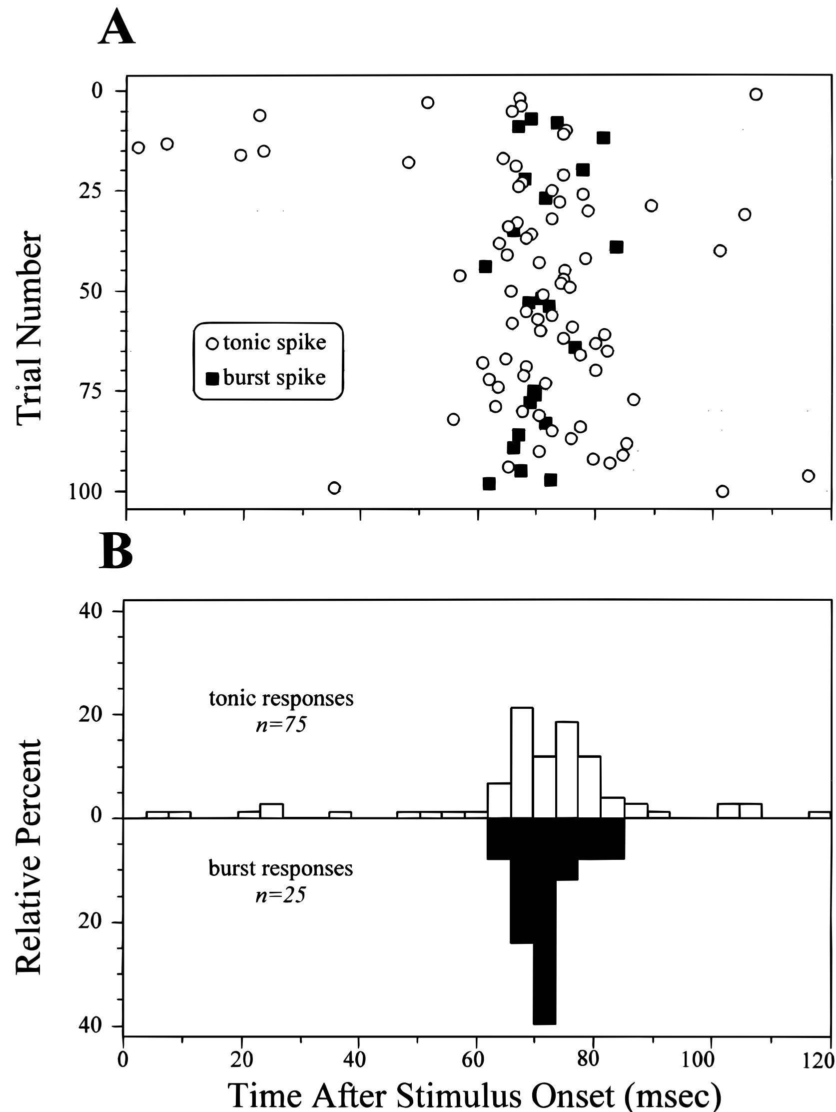

Fig. 3. Latencies of first spike shown separately for tonic and burst firing following stimulus onset on each trial for the same example as shown in Fig. 2. A: Raster diagram showing the latency after stimulus onset of the first spike for each of the 100 trials. B: Frequency histograms showing the first spike latencies from A during trials evoking tonic and burst responses.

Thus, the more often a cell fires in burst mode, the sharper the response to a flashing target and the less temporal scatter in the occurrence of the first spike after stimulus onset. In one cell, we were able to maintain good intracellular recording long enough to investigate this parameter at different membrane levels. Since the low-threshold Ca^{2+} conductance underlying burst firing is voltage dependent (Jahnsen & Llinás, 1984*a*,*b*), this enabled us to determine the effect of different degrees of tonic versus burst firing on the latency of the first poststimulus spike. Fig. 4 summarizes this experiment from an off center X cell at three different membrane potentials. At −70 mV (Figs. 4A and 4D), which is relatively close to the threshold for inactivation of the low-threshold Ca^{2+} conductance, the cell exhibited the fewest number of bursts, responding in tonic mode on 52 of 81 trials (64%). When hyperpolarized to −77 mV (Figs. 4B and 4E), which deinactivates more of the low-threshold Ca^{2+} conductance, the cell exhibited more bursts and responded in tonic mode on 36 of 93 trials (39%). Further hyperpolarization to −82 mV (Figs. 4C and 4F) further deinactivates the low-threshold Ca^{2+} conductance, resulting in even more bursts, and the cell responded in tonic mode on only 16 of 81 trials (19%). Thus, the more hyperpolarized the cell, the more bursts recorded and the sharper the onset of the response to the flashing spot (Figs. 4A–4C). As can be seen from Figs. 4D–4F, this sharper onset is because further hyperpolarization produces more responses in burst mode, and burst mode leads to initial responses with a less variable latency than does tonic firing. There is no effect of changing membrane levels on the variability of the first spike latency within the tonic or burst response modes ($P > 0.1$ on the *F*-test and Levene Median test). However, for each membrane potential, the variance in the first spike latencies was significantly greater during tonic firing ($p < 0.001$ on the *F*-test and Levene Median test).

Fig. 5 summarizes data for 10 cells recorded extracellularly (open symbols) and for the intracellular example at three membrane potentials (solid symbols). These cells were chosen because they exhibited responses to flashing spots in both response modes,

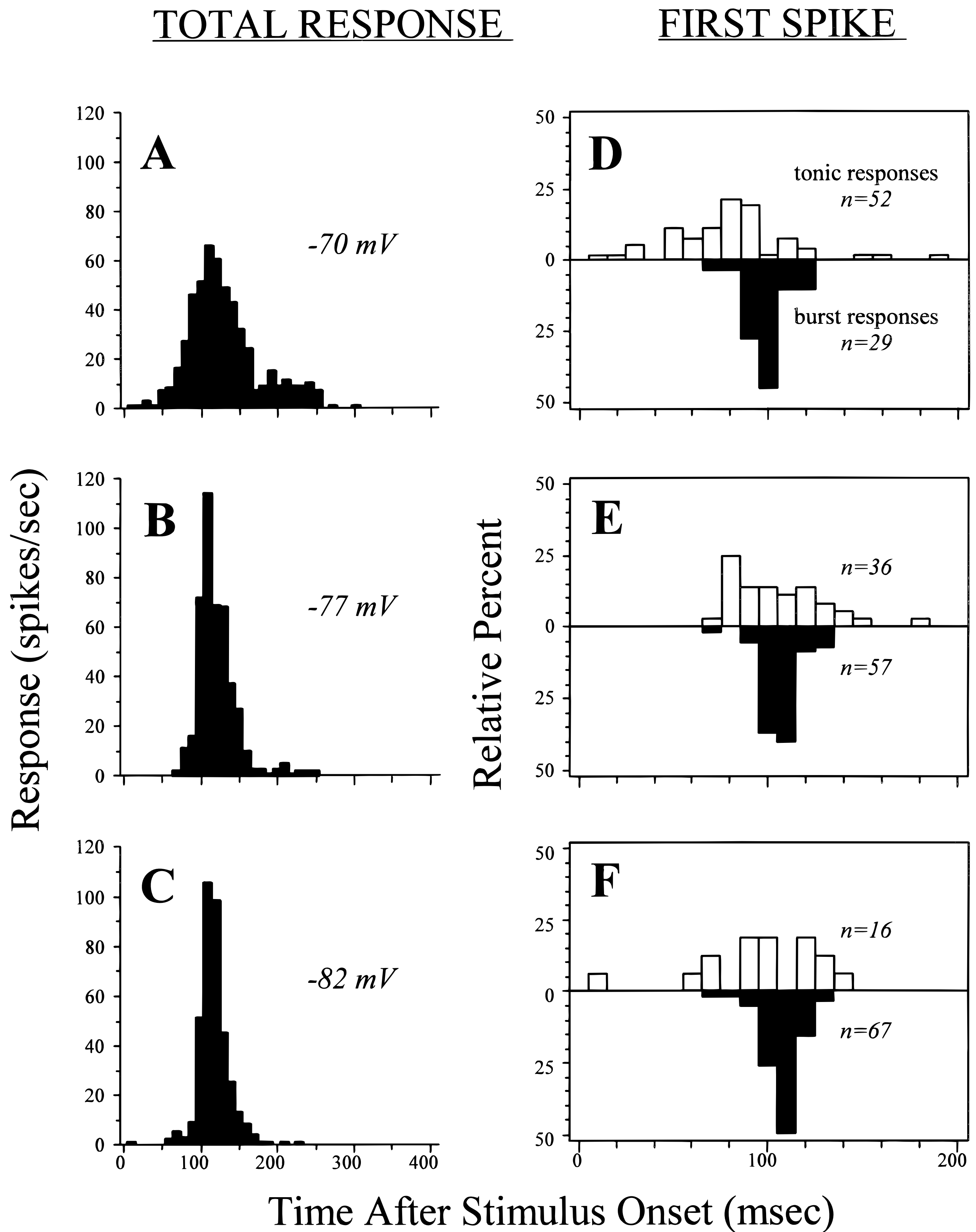

Fig. 4. Responses of an off center cell recorded intracellularly to onset of a dark spot. We recorded at different initial membrane levels achieved *via* intracellular current injection. The left column shows the poststimulus histograms of responses following onset of the spot at time 0. The right column shows the frequency histograms of the first spike latencies for each of the corresponding histograms to the left after the responses were sorted into trials evoking tonic and burst responses; this follows the convention of Fig. 3B. The number of trials evoking tonic and burst responses are shown. A,D: Initial membrane level at −70 mV. B,E: Initial membrane level at −77 mV. C,F: Initial membrane level at −82 mV.

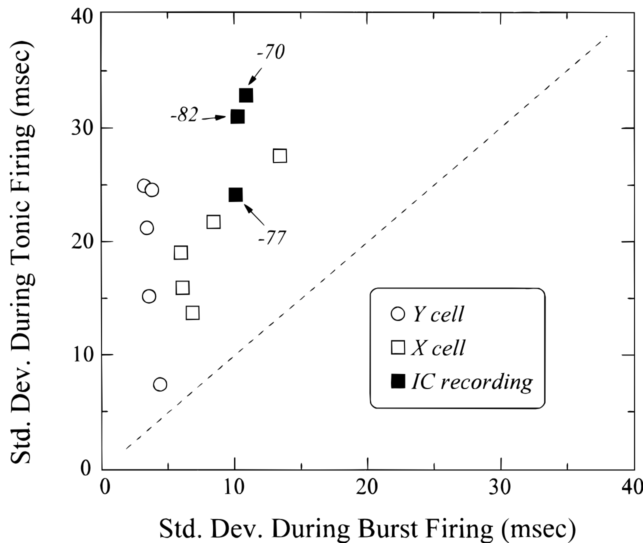

Fig. 5. Scatter plot showing for each cell the standard deviation of the first spike latencies following stimulus onset during burst firing (*abscissa*) versus that for tonic firing (*ordinate*). Three points are plotted for the cell recorded intracellularly so that data from each of the membrane levels shown in Fig. 4 could be shown. The line of slope 1 is also shown to emphasize that for every cell the standard deviation is greater during tonic firing.

and such behavior is typical for the vast majority of geniculate cells recorded in this preparation (Guido et al., 1995). As in the above examples, we sorted responses for each cell into burst and tonic responses. For *every* cell, the standard deviation in arrival times of the first spike after stimulus onset was *always* greater during tonic than burst firing ($P < 0.001$ on a binomial test). Moreover, the observation that the variance of the first spike latency was greater for tonic than burst firing for every single example ($P < 0.001$ on all comparisons on the F-test; $P < 0.001$ for most comparisons and $P < 0.01$ for a few on the Levene Median test). Thus, each cell showed significantly less latency variation to a visual stimulus when responding in burst mode compared to the responses of the same cell in tonic mode.

Discussion

Relay cells of the cat's lateral geniculate nucleus respond to visual stimuli in both tonic and burst firing modes, and which of these modes is operative depends on the activation state of a voltage-gated, low-threshold Ca^{2+} conductance (Sherman & Koch, 1998; Sherman, 1995; Sherman & Guillery, 1996). Mukherjee and Kaplan (1995) have argued from modeling and theoretical considerations that, since the underlying Ca^{2+} conductance is not strictly all-or-none, these response modes may be ends of a continuum rather than distinctly different modes. This would imply that the dynamic range during burst firing (e.g. the relationship between the depolarization activating the Ca^{2+} conductance and the number of action potentials evoked by the ensuing low-threshold Ca^{2+} spike) was sufficiently large to blend smoothly with that of tonic firing. Even if this were true, the fact remains that the geniculate relay is strongly affected by these different types of response. However, the consistent observation of considerable nonlinear distortion during burst firing compared to effective linear summation during tonic firing (Guido et al., 1992; Mukherjee & Kaplan, 1995) suggests a rather abrupt switch in response properties. Furthermore, our empirical data suggest that tonic and burst responses under our conditions of visual stimulation are not ends of a smooth continuum. First, an analysis of intracellular recordings from which the firing patterns of cells could be compared to the presence or absence of low-threshold Ca^{2+} spike showed little evidence of an intermediate firing pattern (Lu et al., 1992). Second, the pattern of interspike intervals (e.g. Fig. 1) shows clear evidence of clustering in which the spikes in bursts are separated from those during tonic firing. In any case, these response modes provide a different representation of the same visual stimulus to cortex (Guido et al., 1992, 1995; Sherman, 1995; Guido & Weyand, 1995; Mukherjee & Kaplan, 1995). What the present data add to this picture is evidence that the initial response to a visual stimulus is relayed to cortex with less latency variability during burst than during tonic firing.

It could be argued that one of the reasons that tonic firing results in more variance in the latency of the first spike after stimulus onset relates to spontaneous activity. We have previously shown that the level of spontaneous activity is significantly higher during tonic than burst firing (Guido et al., 1995). It is thus more likely that a spontaneous spike will appear before the first spike that is actually stimulus evoked when the cell responds in tonic mode. While this difference in spontaneous activity undoubtedly contributes to the more variable latency measurements for tonic compared to burst firing, our data suggest that this is not the entire explanation. For example, Figs. 3 and 4 show that tonic firing produces more variance *after* the peak in the latency histograms for the first spike, and this is not easily explained by the difference in spontaneous activity. This greater variance after the peak in the histograms during tonic firing was seen for every example plotted in Fig. 5, and this suggests that the actual first stimulus-evoked response occurs with a more variable latency during tonic than burst firing.

One could argue that it does not matter if this difference in the first spike latency variability was simply explained by difference in spontaneous activity or some other variable as long as one assumes that it is the spikes transmitted by geniculate relay cells that provide the only information relayed to cortex and that cortex has no other, independent information other than the geniculate relay about the onset of a visual stimulus. If this assumption is true, and it seems quite likely, then it follows that, regardless of the explanation for the greater variance during tonic firing in the first spike latency following stimulus onset, this greater variance is a detriment to determining the actual onset of a visual stimulus.

We have shown previously that at least two differences exist in the nature of the information relayed to cortex during tonic versus burst firing (Guido et al., 1995). First, compared to tonic firing, burst firing has a much greater signal-to-noise ratio. ROC analysis has shown that a relay cell firing in burst mode is far better at signal detection than the same cell firing in tonic mode. We can now add to this advantage of burst firing in signal detection the present observation that burst firing causes the initial response to a stimulus to occur with a more regular latency. This would also enhance the ability of cortex to detect a novel stimulus more rapidly and less equivocally.

Second, burst firing produces a nonlinear distortion in the manner by which the stimulus is encoded in the spike train. This is at least partly due to the fact that the low-threshold Ca^{2+} conductance produces a Ca^{2+} spike that actually underlies burst firing. This Ca^{2+} spike may be viewed as a sort of nonlinear amplification that enables synaptic inputs to drive the hyperpolarized cell to

firing threshold. This nonlinear distortion would interfere with the ability of cortex to analyze the visual stimulus with optimal accuracy. We have suggested previously that burst firing may be preferred when signal detection is favored, and tonic firing, once a stimulus is detected and must be analyzed (Guido et al., 1995; Sherman, 1995).

Finally, the proposed advantage of burst firing for signal detection considers only the signal carried by the firing pattern of the relay cell itself. If this response is to be acted upon at cortical levels, it has to have a reliable postsynaptic effect. There is a growing body of evidence that phenomena such as paired-pulse facilitation cause bursts of action potentials with brief interspike intervals (i.e. the hallmark of burst firing) to evoke much more potent postsynaptic responses than do the same number of single presynaptic spikes (reviewed in Lisman, 1997). The conclusion from this work is that the postsynaptic effects of burst firing further enhance its ability compared to tonic firing to signal the presence of a stimulus.

Acknowledgment

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