Stimulus-Dependent Modulation of Spike Burst Length in Cat Striate Cortical Cells

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DeBusk, B. C., E. J. DeBruyn, R. K. Snider, J. F. Kabara, and A. B. Bonds. Stimulus-dependent modulation of spike burst length in cat striate cortical cells. J. Neurophysiol. 78: 199–213, 1997. Burst activity, defined by groups of two or more spikes with intervals of \( \leq 8 \text{ ms} \), was analyzed in responses to drifting sinewave gratings elicited from striate cortical neurons in anesthetized cats. Bursting varied broadly across a population of 507 simple and complex cells. Half of this population had \( \approx 42\% \) of their spikes contained in bursts. The fraction of spikes in bursts did not vary as a function of average firing rate and was stationary over time. Peaks in the interspike interval histograms were found at both 3–5 ms and 10–30 ms. In many cells the locations of these peaks were independent of firing rate, indicating a quantized control of firing behavior at two different time scales. The activity at the shorter time scale most likely results from intrinsic properties of the cell membrane, and that at the longer scale from recurrent network excitation. Burst frequency (bursts per s) and burst length (spikes per burst) both depended on firing rate. Burst frequency was essentially linear with firing rate, whereas burst length was a nonlinear function of firing rate and was also governed by stimulus orientation. At a given firing rate, burst length was greater for optimal orientations than for nonoptimal orientations. No organized orientation dependence was seen in bursts from lateral geniculate nucleus cells. Activation of cortical contrast gain control at low response amplitudes resulted in no burst length modulation, but burst shortening at optimal orientations was found in responses characterized by supersaturation. At a given firing rate, cortical burst length was shortened by microinjection of \( \gamma \)-aminobutyric acid (GABA), and bursts became longer in the presence of \( N \)-methyl-bicuculline, a GABA \(_A\) receptor blocker. These results are consistent with a model in which responses are reduced at nonoptimal orientations, at least in part, by burst shortening that is mediated by GABA. A similar mechanism contributes to response supersaturation at high contrasts via recruitment of inhibitory responses that are tuned to adjacent orientations. Burst length modulation can serve as a form of coding by supporting dynamic, stimulus-dependent reorganization of the effectiveness of individual network connections.

INTRODUCTION

Because of the all-or-nothing nature of nerve action potentials, the information carried by neurons can only be represented indirectly, in some form of a code. The most obvious code is a roughly proportional mapping of signal amplitude to action potential frequency (Adrian and Zotterman 1926). Considerable effort has been directed toward detecting more subtle relationships between causal signals and temporal firing patterns in single units (e.g., Bridgeman 1980; Lestienne and Strehler 1987; Optican and Richmond 1987; Perkel and Bullock 1968; Perkel et al. 1967; Tsukada et al. 1982). These studies have demonstrated the existence of interesting relationships between detailed structure of the spike train and particular stimuli. The patterns that emerged have, however, not proven sufficiently clearcut to have much influence on the general approach to the interpretation of neural responses.

Most quantitative analysis of responses from the visual cortex continues to be based on averaged poststimulus time histograms (Henry et al. 1973), which invoke the implicit presumption that the cells perform nothing more than simple frequency integration. Response amplitude, the sine qua non of such experiments, is usually represented by the DC firing rate (number of spikes averaged over the stimulus duration) for complex cells or the response power at the frequency of stimulation (calculated from a Fourier transformation of the poststimulus time histogram) for simple cells (Movshon et al. 1978; Skottun et al. 1991). Use of these tools has revealed an enormous amount about the behavior and characteristics of cortical cells, but these methods neglect any information that might be present in the sequences of individual action potentials. Not only might this obscure insights into the physiological mechanisms underlying the complexity of cortical receptive field organization, use of average firing rate as a response indicator could also be misleading in terms of its application to the excitation of postsynaptic cells. Some recent efforts have sought coding schemes in the specific temporal order and value of intervals of spike sequences (e.g., Lestienne and Strehler 1987; Richmond and Optican 1990). The impact of those results is weakened by the absence of evidence supporting biologically plausible decoding schemes that permit the brain to take advantage of information that is present in the spike train as revealed by computer analysis. The work presented here was motivated by a search for information contained in the temporal sequences of spikes that could easily and naturally be used in the decision-making processes of postsynaptic neurons.

In one of the earliest descriptions of recording from cat visual cortex, Hubel (1959) remarked on the irregularity of the single-unit discharges, with the firing often occurring in bursts separated by silent intervals. Cattaneo et al. (1981a,b) subsequently documented a dependence between “clustered spikes” (bursts) and stimulus orientation in complex cells. They found that responses to stimuli presented at or near the optimal orientation tended to contain a higher percentage of spikes in bursts compared with responses to nonoptimally oriented stimuli. Our results are basically extensions of these observations. We have applied a simple metric for burstiness.
to cat striate cortical cell responses. Burst activity was found to be a stationary property of most cortical cells, both simple and complex. Although the frequency of occurrence of burst events was proportional to the firing rate, the behavior of burst length was more complicated, because it depended on both the firing rate and stimulus characteristics. Burst length was clearly modulated by stimulus orientation, with bursts growing shorter when nonoptimal orientations were presented. Acknowledging the involvement of GABAergic mechanisms in orientation selectivity (Sillito 1975, 1979, 1984), we found that microiontophoretic injection of γ-aminobutyric acid (GABA) near the recording site reduced burst length even when the stimulus was optimally oriented. Conversely, injection of bicuculline, a GABA\_A receptor blocking agent, increased burst length. In both cases these results are independent of firing rate. Even though adaptation to contrast reduces response frequency in cortical cells, we found no changes in burst length when this mechanism was activated, at least when cells did not show response supersaturation at higher contrasts. Collectively, these experiments suggest that the activity of the GABAergic mechanisms involved in defining the spatial structure of the cortical receptive field is indirectly visible through analysis of the burst structure in the spike train. At the same time, mechanisms associated with the cortical contrast gain control (Bonds 1991; Ohzawa et al. 1985) are found to be independent of the processes responsible for burst length modulation.

**METHODS**

**Preparation**

Adult cats (2.5–4.2 kg) were prepared for recording as detailed elsewhere (Bonds 1989). All procedures were performed under the guidelines of the American Physiological Society and the Vanderbilt Institutional Animal Care and Use Committee. In brief, after anesthetic induction with flurothane (Halothane), surgical anesthesia was maintained with thiamyyl sodium (Surital) ad libitum. The cats were mounted in a stereotaxic apparatus and a small craniotomy (1 × 3 mm) was performed overlying the representation of the area centralis (H-C coordinates P4-L2). After insertion of a tracheal cannula, animals were paralyzed with gallamine triethiodide (Flaxedil, 10 mg\_kg\^\_1) and was used for current compensation during injection from the other barrels. A second barrel contained carrier solution (0.9% saline with pH adjusted to 7.4) and was used for current compensation during injection into the injection electrode. Action potentials from the recording microelectrode were reduced to standard pulses and stored by the computer with a resolution of either 1.0 or 0.122 ms.

**RESULTS**

**Burst identification**

Casual examination of a raster plot of spikes resulting from stimulation of most striate cortical cells (see Fig. 2 of Hubel 1959) reveals that many of the spikes are gathered in clusters, or bursts, rather than having intervals distributed in a more continuous (Poisson-like) manner. This tendency is quantitatively apparent from interspike interval (ISI) histograms, where the short intervals within a burst form a clear peak near the origin. Figure 1 shows representative ISI histograms of driven responses from four different cells, each with a different fraction of its spikes contained in bursts (as defined below). Three features are common to these histograms. 1) A prominent peak is evident around 3–5 ms. The minimum interval observed is usually quite small, on the order of 1–2 ms. We have occasionally observed intervals as brief as 0.73 ms. Minimum intervals thus correspond to instantaneous firing rates of ~500–1,400 imp/s, which can be found even with time-averaged firing rates as low as 10–15 imp/s. 2) The falling edge of the burst peak is very steep and usually found between 7 and 12 ms, suggesting that most spikes within bursts have intervals less than or equal to those values. 3) The end of the burst peak is delineated by either a flat area or noticeable inflection in the region of 10–12 ms, which is then followed by a gradual decay of intervals out to ~100 ms. This latter feature is not evident in Fig. 1D because there are so few spikes found outside of the bursts. The presence of two regions (the sharp peak and the broader plateau) defined at different time scales implies the existence of at least two separate processes responsible...
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FIG. 1. Examples of interspike interval (ISI) histograms from 4 cells, with (A) 20.4%, (B) 43.8%, (C) 63.1%, and (D) 80.8% of spikes in bursts. These represent responses to spatially optimal drifting gratings at contrasts of 40% (C and D) or 56% (A and B). Prominent typical features include a burst peak at 3–5 ms, a dip at 8–10 ms, and a plateau or inflection at 10–30 ms. In these and all other figures, codes (e.g., lv4r10.04) are references to specific experiments.

for spike generation. Those curves with a flat area beyond 15 ms correspond to the implicitly bimodal behavior and those with a rise correspond to the explicitly bimodal behavior described in the bursting pattern of cells in the cat superior colliculus by Mandl (1993). The minimum around 10–12 ms, when present, is the result of a “burst refractory period” of several milliseconds duration during which firing probability is lower following the last spike within a burst event. The region between the sharp decay and the inflection can be thought of as a rough boundary between the short-interval (burst) and longer-interval distributions within the histograms.

The assumption of a strict delineation between burst spikes and longer-interval spikes that is based solely on intervals may initially appear simplistic. These two groups most probably form continuous distributions that have some degree of overlap; thus resolution of the two cannot be unambiguous. We have tried a variety of strategies for identification of burst events in spike trains, including adaptive filtering and a context-sensitive neural net. In terms of identification of both the number and length of the burst groups, no one method showed an advantage over any other, especially because even tedious manual identification of burst sequences was never absolutely certain. We therefore chose the simplest burst identification strategy for the following exercises. As proposed by Cattaneo et al. (1981a,b), we defined a burst as any continuous group of two or more spikes with ISIs of ≤ 8 ms. This figure was validated primarily on the basis of the location of the sharp decay of the burst peak evident in the ISI histograms, and was chosen as a compromise that appeared to balance the overlaps between the burst and longer-interval distributions. Many of the analyses presented below were repeated with burst interval limits ranging from 6 to 10 ms, with qualitatively similar results.

A burst criterion interval of 8 ms has also been used by Mandl (1993) for identification of bursts in cat superior colliculus and by Bair et al. (1994) in studies of bursting in monkey middle temporal area. The classification of as few as two spikes as bursts might seem extreme. However, even two closely spaced spikes can have functional significance. In hippocampal CA3 cells significant synaptic facilitation was found when synapses were activated twice at an interval of 5–10 ms (Miles and Wong 1986).

Prevalence of bursting in cortical cells

To assess burst behavior across a population, we took advantage of a data base of responses that has been collected over some 15 years of experimentation in our laboratory. Although many of these cells were not recorded with the specific goals of burst analysis in mind, all cells were subjected to a standard set of tests intended to characterize the cell with respect to its spatial selectivity and contrast sensitivity. The population studies presented here and elsewhere in this paper were derived from these standard tests. On the basis of the 8-ms burst criterion, we analyzed the responses of 507 striate cortical cells to determine the pattern of burst behavior across a population. Bursts were measured in responses to presentation of a randomized series of different sine-wave gratings contrasts at the optimal spatial frequency and orientation. Those responses with the highest and second-highest average firing rates generated over a 4-s stimulus presentation were extracted and analyzed. Note that these responses did not always correspond to the highest contrasts presented because of occasional response supersaturation. Histograms describing the fraction of spikes found in bursts for these two responses are shown for simple cells, complex cells, and all cells in Figs. 2, A–C, respectively. Bursting behavior varies broadly
FIG. 2. Percentage of spikes in bursts across a population of 507 cells. A and B: distribution of bursts in highest (black bars) and 2nd-highest (white bars) responses to spatially optimal drifting gratings for simple (A) and complex (B) cells. C: combined distribution across all cells. D: integral (from right to left) of distributions (highest response) for simple cells (--.--), complex (dashed curve) cells, and all cells (—). Orthogonal dashed rectangular reference shows that half of the cells have ≈42% of their spikes contained in bursts.

across the population, with bursts comprising from a few percent to >90% of total spikes in individual cells. There is a slight tendency for the complex class to have more cells with fewer spikes in bursts than the simple class. There is no apparent difference between the distributions defined by the highest and second-highest responses. When the overall distribution is integrated and normalized (Fig. 2D), we find that half of the cells have ≈42% of their spikes contained in bursts (orthogonal dashed lines).

The burstiness of a particular cell seemed to be a very consistent property when the cell was driven by spatially optimized stimuli. Bursts were not limited to higher response amplitudes. Figure 3A shows a representative plot of the percentage of spikes contained in bursts as a function of firing rate for four different cells. No indication of a consistent dependence of burstiness on firing rate is apparent, with fractions of ≈30–60% of the spikes found in bursts at even the lowest firing rates in all but one cell. We also examined the temporal stationarity of cortical bursting. Over time, cells in the lateral geniculate nucleus (LGN) have two distinct response modes, one generating bursts and a “linear” mode characterized by a more continuous spike distribution (Kaplan et al. 1993; Sherman 1996). The burst mode arises when the cell is hyperpolarized, which supports generation of a low-threshold Ca$^{2+}$ spike on which is superimposed a burst of regular action potentials (Jahnsen and Llinas 1984). The bimodal behavior of LGN cells becomes evident when observing the cell’s firing over some tens of minutes (Kaplan et al. 1993). We saw no such bimodal tendency in the cortical cells from which we recorded. In part this is reflected by the consistent tendency for burstiness across the general population, in that nearly all cells showed some degree of bursting. We also tracked the fraction of spikes in bursts across time. Figure 3B shows a burst analysis from a series of five recordings made from a single cell over a span of 90 min. Each recording, of ≈6 min in duration, tested the response to seven different stimulus orientations. For clarity, results from only three of the stimulus conditions are shown (---), as well as the mean percentage of spikes in bursts across all seven conditions (solid line). Although there are small local differences, no marked variation of overall burst behavior is seen over this time interval.

Another characteristic of bursting in LGN cells is a silent period of ≈100 ms that precedes a burst, at least for stimulation with temporal frequencies ≤8 Hz (Lu et al. 1992). We analyzed the spiking behavior before bursts in the cortex by building a histogram of intervals between the last spike preceding a burst and the burst itself. By definition, all of these intervals were >8 ms. Across a population of 1,210 cells, this histogram had a peak located at ≈15 ms and decreased smoothly for longer intervals. Of over four million intervals, 83% fell in the range of 0–100 ms, and only 17% were >100 ms. There is thus no evidence for an extended silent period preceding cortical bursts, which suggests that cortical bursting is not a phenomenon that directly reflects LGN burst generation.

Some have suggested that bursting in LGN is dependent on the animal’s state of arousal (Kaplan et al. 1993; Steriade and Llinas 1988). We cannot rule out the possibility of an influence of our anesthetic regimen on the generation of burst patterns, but any such influence appears to be consistent both across time and across our entire cell population. The clear existence of bursts in recordings from the visual cortex of awake, behaving cats (Cattaneo et al. 1981b; Hubel 1959) would indicate that cortical bursting is not uniquely associated with a sleep state.

**Spike generation as a quantized process**

ISI distributions have generally been assumed to result from spike generation processes that are continuous in na-
is a quantized process. Although the number of bursts might depend on the overall average firing rate, once a burst is started, the average firing rate within the burst is constant under all conditions.

Although shorter intervals (<8 ms) were independent of average firing rate, the dependence of the longer-interval distributions (>8 ms) on overall firing rate is not as obvious. In Fig. 4, there is no subjective impression of a rightward shift of the histogram peaks found beyond 8 ms as firing diminishes, which would be expected if the generation of these longer-interval spikes were a continuous process. A transformation that predicts a scaling of the time axis (shift) that is based solely on the average firing rate (Gestri et al. 1966) is

\[(t' - \lambda) = \frac{\mu - \lambda}{\mu' - \lambda} (t - \lambda)\]

where \(t\) represents time measured on the old scale and \(t'\) represents the new mapping of the time. \(\mu\) is the average ISI of the interval distribution to be scaled and \(\mu'\) is the average interval of the distribution that is to be referenced. \(\lambda\) represents the minimum spike interval to be expected in either distribution, i.e., the refractory period (Cattaneo et al. 1981b). Cattaneo et al. showed that in some cases, and especially with simple cells, ISI distributions with different mean intervals (i.e., different average firing rates) could be scaled such that they closely resembled each other in both shape and amplitude. This implied that in these cases spike generation followed a continuous distribution and that the process depended only on the mean ISI.

Because we found a number of exceptions to this result, we performed time scaling across a large data set to assess the tendency for the ISI histogram peak (for longer, nonburst intervals) to shift as a function of average firing rate. For each cell, we varied firing rate by presenting eight or nine different contrast levels in random order. ISI histograms were constructed for each response and the histograms were normalized and smoothed across five 1-ms bins. For each cell, the histogram that contained the largest number of spikes (greatest average response amplitude) was designated as the reference histogram. The reference histogram was then time scaled to each of the other (comparison) histograms in an experimental series, measured across different contrasts presented to the same cell, by continuous variation of the scaling coefficient \(\mu'\) without regard to the mean firing rate of the comparison histogram. The minimum spike interval expected (\(\lambda\)) was set to zero, because we had observed intervals of 1 ms in many bursts. The “best-fit” time scaling coefficient was selected by calculating the correlation between the two ISI histograms over the interval of 10–50 ms (of the unscaled histogram) for each scaling coefficient and choosing the coefficient that yielded the highest correlation. This interval was selected so as to exclude burst spikes, which do not change their average intervals with contrast, and because very few spikes were found beyond intervals of 50 ms.

The results can be seen in Fig. 5. The horizontal axis represents the percent reduction of average firing rates between the reference (scaled) histogram and comparison histograms. Points on the left represent comparison histograms with firing rates equal to the reference histogram, and points on the right represent comparison histograms with firing rates near zero. The vertical axis represents the percent change of the scaling coefficient yielding the highest correlation (best fit between the 2 histograms). Each point in the
FIG. 4. ISI histograms as a function of stimulus contrast for simple (left) and complex (right) cell. Vertical scale is expanded by a factor of 10 below dashed line. Time of burst peaks (at ~5 ms) does not shift over a change in mean firing rate of a factor of ~20:1. Stationarity of a 2nd peak at ~15–20 ms is suggested. Average firing rates can be derived from Fig. 3A for simple cell (●) and the complex cell (▲).

scatter plot indicates a scaling comparison between two histograms. There are 14,634 total points representing measurements from 1,210 cells (measurement sets were repeated twice for some cells). A best-fit scaling coefficient that reflects perfect time scaling, indicating a random spike generation mechanism that is wholly dependent on average firing rate, would be represented by points falling on a line with a slope of −1. Points falling at the ordinate level of zero represent best matches between the histogram waveforms with no time scaling at all.

We were surprised to find that, although there are many points that are consistent with perfect time scaling, obvious clustering is seen mainly around the zero level. We defined bands of equal area bounded by 15 and 85% of the percentage change in firing rate and by ±15% of the percentage change in time scaling along both the horizontal axis and a line of slope −1 (Fig. 5, rectangular boxes). The percentage of the total points found within these two areas was 29.6 and 9.1%, respectively, indicating that, for intervals between 10 and 50 ms, ~3 times as many experimental measurements yielded a structure within their histograms that is independent of average firing rate. Because the manipulation used to produce Fig. 5 did not acknowledge absolute firing rate, some of the points might be artifactual because of excessively low activity in the histogram that is compared with the reference. We therefore plotted the same graph with the added dimension of the average firing rate associated with the comparison histogram (Fig. 6).

Here it is apparent that the firing rates for pairs falling at the zero (nonscaled) level were substantially more robust than those falling on the line indicating ideal scaling. It is also apparent that the points falling along the right edge of Fig. 5 are from histograms representing extremely low firing rates and should probably be disregarded.

The fundamental message from Figs. 4–6 is that in most cells the intervals between impulses at both shorter (2–8 ms) and medium (10–50 ms) time scales are not governed by a generation process that is random and continuous, but rather result from quantal processes at two distinct levels. At least for experiments in which contrast alone is varied, the first-order statistics that describe the firing patterns of many cells over these intervals do not vary with spike rate. Because each of these quantized processes maintains a constant set of short term statistics, variations in overall response amplitude result from the number of times the subprocess, either slower (10- to 50-ms intervals) or faster (2- to 8-ms intervals), is initiated.
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**Fig. 5.** Time scaling of interval histograms required by changes in average firing rate. Interval histograms were prepared as described in text. Abscissa: difference between firing rate of reference histogram and comparison histogram. Ordinate: amount of time scaling required to get optimal correlation between the 2 histograms. Rectangular boxes are of equal area. 29.6% of the total data points fall within region along 0 axis, and 9.1% of the total points fall along region flanking a line of slope $-1$. Data along right margin are probably unreliable because of low firing rate in comparison histogram (see Fig. 6). Horizontal striations result from discrete binning of histograms.

**Burst pattern analysis**

Two simple statistics, based on the idea that each burst is an independent event, can be derived to describe burst activity in a spike train. Acknowledging the quantal nature of bursts, the burst frequency is defined as the average number of such events occurring per second (bursts per s). Burst length is characterized by the number of spikes per burst (SPB). Both of these attributes were experimentally found to be associated with the average firing rate, but only for burst frequency (bursts per s) was that dependence found to be simple. Because of the spatial filtering properties of cortical cells, firing rate can depend on several different stimulus parameters, including orientation, spatial and temporal frequency, and contrast. We chose to analyze the dependence of burst behavior on the variation of two parameters: contrast, which reflects only changes in stimulus amplitude, and orientation, which reflects modification of the spatial quality of the stimulus without changes in contrast (amplitude). In all cases, the burst frequency (bursts per s) was found to covary with average firing rate in a very linear fashion. The relationship between burst frequency and firing rate was constant for a given cell, regardless of the stimulus parameter that was varied to produce variation in average firing rate. In Fig. 7A, there is no apparent difference between the curve produced by variation of contrast (filled circles) and that produced by varying orientation (open squares). This behavior implies that the initiation of burst events is a straightforward reflection of the net excitation of the cell.

The dependence between burst length (SPB) and firing rate was found to be more complicated in two ways. 1) For...
any method used to change the firing rate, the relationship was decidedly nonlinear. Curves usually decelerated or even saturated at higher firing rates, implying the existence of some fixed limit on burst length regardless of excitation strength. 2) The form of the curve depended somewhat predictably on which stimulus parameter was varied to change the spike rate. In general, at a given average firing rate, burst length was shorter for stimuli that were presented at a nonoptimal orientation than for those presented at the optimal orientation. In Fig. 7B, the points resulting from variation of orientation are seen to fall below those resulting from variation of contrast, where orientation was optimal. Additional examples of this phenomenon are seen in Fig. 7, D and F. The point corresponding to the highest firing rate for orientation-parametric presentations is often seen to fall below the curve (at the same firing rate) defined by contrast-parametric presentations, even though the orientation for this datum is optimal (e.g., Fig. 7B). We attribute this shortfall to a lingering suppression resulting from interleaved presentations of nonoptimal orientations.

Although the reduction of burst length by presentation of nonoptimal orientations was qualitatively consistent across cells, it proved difficult to quantify because of the broad variation of the form of the relationship between burst length and firing rate across the cell population, evident in Fig. 7, D and F. We adopted the following strategy to demonstrate the consistency of the effect. For each presentation series, the relationship between SPB and firing rate was expressed as a best-fit third-order polynomial curve. This function was

\[
\Gamma = \frac{\int_{\alpha}^{\beta} [\text{SPB}_{\alpha}(s) - \text{SPB}_{\alpha}(s)] ds}{\int_{\alpha}^{\beta} [\text{SPB}_{\alpha}(s) + \text{SPB}_{\alpha}(s)] ds}
\]

For SPB_{\alpha}(s) \geq 0 and \text{SPB}_{\alpha}(s) \geq 0 on the range \beta \geq s \geq \alpha, \Gamma must lie in the interval [-1, 1]. For the purposes of calculating \Gamma, the SPB curves were adjusted by subtracting a constant value of 2, because each burst by definition must have at least two spikes. The elimination of this offset removes a constant

FIG. 7. Three examples of dependence of burst frequency (A, C, and E) and burst length (B, D, and F) on average firing rate. Filled circles: change of firing rate by variation of stimulus contrast. Open squares: change by variation of stimulus orientation. Solid lines: 3rd-order polynomial fits to data points. There is no apparent dependence of burst frequency on mode of stimulus variation. Burst length is shorter for presentation of nonoptimal stimulus orientations. This is quantified by integration of the area between the 2 curves bounded by the limits of the common firing rates (\alpha and \beta in B). See text for details.
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Burst analysis was also performed on 12 LGN fibers recorded in cortex. Of these, two had low firing rates and did not generate bursts. The remaining 10 showed essentially linear relationships between firing rate and both burst rate and burst length (Fig. 9, A and B). LGN cells show little orientation selectivity (e.g., Soodak et al. 1987), so the range of modulation of firing rate by changing orientation was very limited. Although we often observed some loose dependence of burst frequency on firing rate as orientation was varied (Fig. 9C), the relationship between burst length and firing rate appeared random (Fig. 9D). We conclude that organized modulation of burst length by stimulus orientation appears first at the level of the visual cortex.

Bursting and cortical contrast gain control

As shown above, modification of response amplitude by changes of stimulus contrast has a different impact on burst length than amplitude modification by changes of stimulus orientation. Lower contrasts at the optimal orientation yield longer bursts than those found at similar firing rates produced by nonoptimal orientations and higher contrasts. These measurements were made, however, with randomized presentation of different contrast and orientation values to minimize the effects of nonstationarity (Henry et al. 1973). When cortical cells are exposed to stimuli of higher contrasts in a systematic fashion, the response-versus-log contrast function undergoes a temporary rightward shift, indicating a reduction of contrast gain (Ohzawa et al. 1985). The lateral shift resulting from activation of the contrast gain control is especially apparent in the form of hysteresis curves produced by stepwise presentation of sequentially increasing, then decreasing, contrast values (Bonds 1991). This shift is equivalent to the reduction of the response at a constant contrast, and thus might potentially relate to the mechanism that reduces responsiveness for nonoptimal stimulus orientation.

FIG. 8. Difference metric ($\Gamma$) for simple (black bars) and complex (white bars) cells. A: $\Gamma$ calculated for burst frequency is centered near 0, indicating little dependence of burst frequency on mode of stimulus variation across a population of 67 cells. B: $\Gamma$ calculated for burst length shows a distinct positive displacement, indicating that in most cells bursts are shorter for nonoptimal orientations. Simple and complex cells show similar behavior in this respect.

This analysis was applied to a total of 98 cells (46 simple, 52 complex). Of these, 14 simple cells and 16 complex cells were discarded because the polynomial curves could not both be fit with a 0.1 normalized squared error criterion. One complex cell was rejected because of an inability to produce bursts. For the remaining 67 cells, histograms of the $\Gamma$ values were plotted for both burst frequency (Fig. 8A) and burst length (Fig. 8B). In the case of burst frequency, $\Gamma$, although slightly positive, is essentially centered on zero, confirming the notion that the number of bursts depends only on firing rate and not the means of firing rate modulation. For burst length, $\Gamma$ averages 0.147, demonstrating a tendency for bursts to be longer (at a given firing rate) for stimulation at the optimal orientation. In only 9 of the 59 cells (15%) was the opposite trend seen in the form of a slightly negative $\Gamma$.

area of $2(\beta - \alpha)$ from the integration of each curve. Using this definition, if the contrast-derived curve showed bursts of consistently greater length than those from the orientation-derived curve, $\Gamma$ would be positive, for the opposite $\Gamma$ would be negative, and if the curves were identical it would be zero.

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In Fig. 10A, derived from the experiments of Bonds (1991), the contrast was initially presented at 3%, then increased in 0.15-log steps every 3 s until a peak value of 14% was reached. After 3 s of exposure at that value, the contrast was similarly decreased until the lowest (3%) value was reached. Data were collected over 10 repetitions of this procedure to improve the signal-to-noise ratio. The upper and lower edges of the solid described in Fig. 10A represent the response levels from the ascending and descending contrast sequences, respectively, and the shaded region represents the response differential seen before and after exposure to higher contrasts. For example, in Fig. 10A the response at 10% contrast was 28 spikes/s when preceded by lower contrasts, but only 10 spikes/s when preceded by higher contrasts. Figure 10B shows a similar exercise on the same cell, but with a peak contrast of 56%. Some supersaturation (reduction of firing rate at high contrasts) (Li and Creutzfeldt 1984) is evident and hysteresis is greater.

If the mechanism that reduced responsiveness after exposure to high contrasts were identical to that which reduces responsiveness to nonoptimal orientations, then we would expect that, on the trajectory of descending contrasts, burst length would be reduced after adjustment for firing rate. Figure 10C shows the burst analysis of the responses from exposure to the sequence with a peak contrast of 14% (Fig.
The burst frequency (□) is proportional to firing rate in the usual manner. The relationship between burst length and firing rate shows substantial compression, but the curve follows the same path for both the rising and falling contrast trajectories. Thus, despite the changes in gain represented by the hysteresis curve, there is no evidence of a shift in the relationship between burst length and firing rate. This would argue against any linkage between the mechanisms associated with burst shortening at nonoptimal orientations and contrast gain control.

The results differ in the case of 56% peak contrast. Again, there is no modification of the linear relationship between burst frequency and firing rate (Fig. 10D, □). The path of the burst length curve (filled circles) differs markedly for firing rates generated on the rising and falling contrast trajectories, with burst lengths being shorter after exposure to higher contrasts. How is this result consistent with the absence of burst length modulation seen for the lower peak contrast? Note that in this example the highest firing rate is generated at a low contrast (14%), so that higher contrasts reduce the firing rate. Note also that the reduction in burst length is first seen when the response reaches the region of supersaturation, and it lingers until the response returns nearly to the baseline. The appearance of burst shortening at higher contrasts suggests that supersaturation could result from the recruitment of inhibitory pathways driven by cells.
tuned to an optimal orientation that differed from that of the recorded cell (Allison and Bonds 1994). At lower contrasts these cells would not be strongly driven, resulting in a "pure" contrast gain control effect (Fig. 10A), whereas at higher contrasts responses would be modified by both the contrast gain control and burst-shortening lateral inhibition arising from cells tuned to nearby orientations (Fig. 10B). Similar results were seen in the two other cells on which these kinds of measurements were made.

**Neurotransmitter substrate for burst modulation**

Microiontophoretic injection of bicuculline, a GABA_A receptor blocker, yields a broadening of orientation selectivity in many cortical cells (Pfleger and Bonds 1995; Sillito 1975, 1979, 1984). The flattening of the tuning curves suggests disinhibition that is proportionally stronger at nonoptimal orientations, in turn implying the existence of GABA_A-mediated suppression that is orientation selective. There may thus exist a causal link between activation of GABAergic suppressive mechanisms and the shortening of bursts, because both appear to be stronger with the presentation of stimuli of nonoptimal orientations. This linkage is also suggested by the observation of burst shortening in the presence of GABA and burst lengthening in the presence of bicuculline in cat somatosensory cortex (Dykes et al. 1984).

To test this hypothesis, we performed burst analysis on spike trains recorded under control conditions and in the presence of microiontophoretically injected GABA and NMB. We confirmed that burst length (after adjustment for dependence on firing rate) is reduced by GABA and increased in the presence of NMB. Experiments in which GABA was injected were problematic. We wanted a graded reduction of responsiveness, but even with a 50 mM solution (diluted to 1/10 the usual concentration), most cells became unresponsive in the presence of GABA. For this reason, control and GABA-influenced response measurements were completed in only nine cells. In each of these cases, burst length at a given firing rate was reduced by GABA (Fig. 11A). To provide a quantitative measure for the effect, the burst-length-versus-firing-rate curves were fit with linear regression. The burst length was then estimated at half the maximum firing rate of the cell (Fig. 11A, vertical dotted-dashed line) for both the control and GABA conditions. A histogram of the results (Fig. 11B) shows that in all cases burst length is reduced in the presence of GABA, with a mean reduction of 16.1%.

Injection of NMB resulted in higher firing rates, which supported a more substantial sample (n = 29 cells). In all but four cases (of 78 trials), for a constant firing rate the burst length increased from the control condition when NMB was injected (Fig. 11D). The histogram of burst lengths at 50% maximum firing rate, constructed in the same way as described above, shows an increase of the distribution mean of 38% in the presence of NMB. These observations are consistent with the hypothesis that the burst shortening observed when cells are stimulated by nonoptimal orientations is an indirect indicator of GABA-mediated inhibition.

**DISCUSSION**

**Intrinsic bursting in cortical cells**

We have shown that bursting, although not found in every striate cortical cell, constitutes a substantial portion of the firing behavior of the overall population. The significance of cortical bursting depends in part on whether the phenomenon reflects processing that is a property of the visual cortex, or whether it is simply a consequence of the bursting behavior of afferent LGN cells (Jahnsen and Llinas 1984; Sherman 1996). For three reasons, we believe that cortical bursting is not directly related to LGN burst activity. First, bursting in LGN cells is a temporally bimodal process, in that over time individual cells drift in and out of a discrete burst mode (Kaplan et al. 1993). Striate cortical bursting is stationary. The fraction of burst spikes from a given cell shows some temporal variation. But over ±1 h it is not seen to change at discrete intervals (Fig. 3B). Second, Lu et al. (1992) report that the low-threshold burst pattern of an LGN cell can be characterized by a silent period of 50–100 ms that precedes the burst. The histograms of intervals immediately preceding cortical bursts are no different from general interval distributions, except for the absence of intervals of ±8 ms. Finally, burst length in cortical cells is modulated by stimulus orientation, and no organized modulation is seen in LGN bursts (Fig. 9D). Although these arguments do not rule out some contribution from the LGN to cortical bursts, it is clear that the nature of the bursting patterns is quite different between these two structures. By similar reasoning, one can rule out the burst generation mechanism found in the thalamus (Jahnsen and Llinas 1984) as a substrate for cortical burst generation.

If the bursting reported here arises within the cortex, two alternatives for its generation present themselves. It could be an intrinsic property of the membrane of the cell itself, or it could arise from excitatory network interactions. Intrinsic bursting of a pattern consistent with that seen here has been reported in several types of neocortical cells. Bursting is prominent in layer III of the rat visual cortex (Langdon and Sur 1992), and Chagnac-Amitai and Connors (1989) describe bursting in cells of layers IV and V of isolated rat somatosensory cortex. These cells were identified as pyramidal or spiny stellate. Bursting is also seen in primary auditory cortex of the cat (Eggermont et al. 1993). Other cortical areas showing similar bursting include sensorimotor cortex in the rat (Silva-Barrat et al. 1992) and inferior olivary neurons (Llinas and Yarom 1981), cerebellar Purkinje cells (Llinas and Sugimori 1980), and hippocampal CA3 pyramidal cells (Wong and Prince 1978) of the guinea pig. In all of these cases, bursting is characterized by minimum action potential intervals ranging from ~2 to 5 ms and burst durations no longer than ~50 ms. The entry of Ca^{2+} ions appears common to all burst-generating cells (Pumain et al. 1983; Schwartzkroin and Wyler 1980), and in the neocortex burst generation is abolished after application of organic or inorganic Ca^{2+} antagonists (Pockberger et al. 1986; Witte et al. 1987).

**Recurrent excitation**

Direct thalamic excitation of the input neurons of layer IV in the visual cortex is relatively sparse. In the cortical input layers, only ~10% of the synaptic connections arise from the LGN (LeVay 1986), which has led to the concept of nonlinear amplification of cortical responses by means of recurrent intracortical excitation (Douglas and Martin 1991;
Swandulla 1995). Because of synaptic delays and integration time inherent in such a regenerative system, the action potential intervals expected via this mechanism are longer than those seen in bursts. Douglas and Martin (1991) describe an excitatory response to electrical thalamocortical stimulation that could be separated into two components. The first had an excitatory postsynaptic potential (EPSP) peak latency of 3–5 ms, which was attributed to direct drive from the thalamic afferents. In most superficial, and some deep, pyramidal cells this was followed by a prominent longer depolarization that could last as long as 30 ms. Similar excitatory relationships are seen in guinea pig hippocampus, where latencies between pre- and postsynaptic firing range from 8 to 30 ms (Miles and Wong 1986). Because repetition of firing mediated by network recurrence must be at least disynaptic, intervals will be significantly longer than the 8-ms burst interval criterion used here.

In either case, whether burst timing is constrained by membrane properties or by network interactions, the intervals should be independent of the average firing rate, as found here in Figs. 5 and 6. We believe that the two stationary interval peaks, seen at time scales on the order of 3–5 ms and 10–30 ms, provide strong evidence for the existence of both intrinsic and network-mediated burst mechanisms in the striate cortex. Because we have focused on the analysis of short-interval bursts, the evidence for modulation of burst length by stimulus orientation should be assumed to address solely those bursts that are intrinsic to the membranes of the cells studied.

Inhibitory control of bursting

GABA has been reported to influence bursting patterns at a number of locations. Pontine burst neurons are strongly suppressed by GABA, and bicuculline lengthens bursts (Yabe and Furuya 1993). In dissociated rat hypothalamic cell cultures, infusion of picrotoxin, a GABA antagonist, yields spontaneously generated burst activity (Muller and Swandulla 1995). Similarly, latent excitatory linkages in rat hippocampus are revealed when picrotoxin facilitates bursting, which is suggested as a means for rapid rearrangement of functional circuitry as a result of the alteration of neurotransmitter balances (Traub and Miles 1991). In the cat somatosensory cortex, administration of bicuculline results in marked increases in burst length (Dykes et al. 1984). The functional result of these increases is an effective enlargement of the receptive field size in some neurons. In the experiments presented here, GABA administration reduces burst length and application of bicuculline increases burst length, even after the dependence on firing rate has been taken into account. The functional impact of bicuculline on striate cortical cells has been described at length (Sillito 1984), and mainly takes the form of a generalized reduction of stimulus selectivity due to increases in response amplitude for nonoptimal stimulus conditions. This conversely implies that one aspect of GABA-specific response modification is to contribute to stimulus selectivity by reducing burst length for nonoptimal stimuli. The specific activity of GABA resulting from stimulation of orientations adjacent to the optimal orientation is consistent with the finding that disinhibition via blockage of lower-layer activity can result in elevation of firing rate that is localized on one side or the other of orientation tuning curves (Allison and Bonds 1994; Allison et al. 1995). As suggested by Cattaneo et al. (1981b), we believe that burst length modulation has a disproportionate impact on orientation selectivity as reflected in the activation of the postsynaptic cell. Given integration times for pyramidal cells of 30–40 ms (Traub and Miles 1991), clustered spikes will have a marked advantage in causing the postsynaptic cell to fire, whereas shorter bursts and single spikes will be far less effective (see below). This will result in a relative enhancement of the impact of signals generated by spatially optimal stimuli, which can contribute to the refinement of tuning in successive stages.

The timing of synaptic events presents one possible objection to the idea that the restriction of burst length by GABA is a dynamic process. Whether the GABAergic signal arises from lateral or feedback connections, it must arrive within
a few milliseconds to suppress the shortest bursts. As discussed above, excitatory connections appear to have integration times significantly longer than the time required to support such a mechanism. Although data are not available for visual cortex, at least in the hippocampus inhibitory cells have a low firing threshold. CA3 pyramidal cells elicit large, fast unitary EPSPs that frequently cause inhibitory cells to fire (Miles 1990). The interval between presynaptic and postsynaptic spikes may be as short as 2–3 ms, and the probability that spikes will be transmitted as high as 0.6. This strong excitation of inhibitory cells allows single pyramidal cell spikes to initiate disynaptic inhibitory postsynaptic potentials in other pyramidal cells with latencies of 3–5 ms (Traub and Miles 1991), which is clearly adequate for suppression of bursts to lengths as short as one or two action potentials.

Are bursts a means of coding?

In spiking cells, all neural information is coded, in that continuously graded phenomena must be represented by discrete action potentials. Although it is theoretically possible to reconstruct a good estimate of a simple stimulus waveform by linear filtering of some spike trains (Bialek et al. 1991), total accuracy of the neural representation is neither a desirable nor practical goal. Within the broader constraint imposed by the need for discretization, coding must also alter the neural message so as to improve its utility for subsequent processing steps, even though this necessarily destroys its veridical structure. One of the biggest challenges lies in the reduction of total information. Each step in the visual processing hierarchy involves convergence. Primary cortical neurons are estimated to receive input from 10–30 afferent LGN cells (Tanaka 1985), not to mention significant recurrent excitation from other cortical cells (Ahmed et al. 1994), yet the absolute firing rate of a cortical cell is on average the same as that of an LGN cell at the same contrast level (Bonds 1993). This leads to the idea that although cortical neurons markedly reduce the total number of spikes that impinge on them, they also extract the salient components of complex visual structures and reexpress them in a condensed form by some coding scheme. The particulars of this scheme are not clearly understood. Lestienne and Strehler (1987) show that in spike trains from striate cortical cells of the rhesus monkey, sets of two to six intervals can occur in extremely well-defined temporal sequences (to a tolerance of ±0.14 ms). Lestienne and Strehler argue that the appearance of these intervals is significantly beyond chance, and that they represent a form of coding that is related to visual information. Richmond and Optican (1990) used sets of Walsh patterns (binary rectangular patterns capable of forming a 2-dimensional basis) as stimuli and extracted the principal components over intervals of 300 ms from the responses of monkey striate cortical cells. Richmond and Optican report that the coefficients of principal components (beyond the 1st, which represents simply the average firing rate) were significantly correlated to the stimuli. Using this analysis, Richmond and Optican showed that the information in the bit stream is more than twice that represented by the raw firing rate, and they suggest that this is evidence for a multidimensional temporal code that carries stimulus-related information. A subsequent study of those results concluded that the original judgment resulted from a model that was overfitted, and that a more likely figure is that about one-third of the information is carried in the temporal structure (Kjaer et al. 1994).

Both of these examples demonstrate that by some measures there is clearly more information in the spike stream than is found simply in the firing rate. However, in neither case is there evidence to suggest that the information revealed by either highly precise or complex processing is of any value to the postsynaptic neurons. Lestienne and Strehler (1987) propose a means of decoding involving precise delays and spatial integration, but given the relatively slow excitatory response of pyramidal cells, the resolution of intervals to fractions of a millisecond seems unlikely. Richmond and Optican (1990) advance several schemes for decoding temporally modulated information, including specialized geometry of the axonal-dendritic network (that could act as a spatial implementation of a filter), frequency-dependent differential release of different transmitter agents from the axonal terminal, and feedback connections from target neurons. In more recent work, the most successful detection model suggested by Richmond and Optican is a feedforward neural network. Even though its function is not unlike brain processing, the input data consist of one or more principal components (Kjaer et al. 1994), and Richmond and Optican do not describe any means by which responses in single units afferent to this network would relate to the energies of individual principal components. They do suggest that, because principal component extraction offers an advantage in resolving information, neurons could provide more information if such analysis could be performed (Heller et al. 1995).

Any method for code extraction that relies on temporal integration must take into account the limits inherent in brain function. Use of response components measured over intervals of 300 ms is not consistent with the observation that most visual responses occur with latencies of 100–150 ms (Thorpe and Imbert 1989). Integration of more than a few milliseconds at any stage of visual processing would preclude such a rapid response. Another problem stems from the use of averaged responses for the extraction of codes, because a single target neuron does not have access to this information.

The question that arises is thus not simply whether the neurons are making the code, but also whether they are capable of using it. Bialek et al. (1991) argue for a code that is “robust to errors of several milliseconds in spike timing and other corruptions of the spike train,” which seems a realistic strategy in view of the general imprecision of brain organization. They further argue that “because linear reconstruction is possible . . . analog processing of the encoded signals can be done in a simple way. It is not unusual for the postsynaptic voltage response to have the qualitative form of the optimal filter, with a relatively sharp positive peak followed by a slower negative tail. Thus, simple synapses could serve as decoders.” If one relied simply on synaptic properties and the temporal integration afforded by the dendritic arborization, together with the relatively high firing threshold of striate cortical cells (Creutzfeldt and Ito 1968), bursts of presynaptic activity would afford a dis-
tinct advantage in influencing a cell to fire. Heller et al. (1995) likewise support a low-resolution approach for information transmission. They conclude that retrieval of most of the information from a visual cortical cell requires a resolution no finer than 25 ms, and that no other method offers any advantage over simple integration over this period.

In CA3 pyramidal cells, the probability that single presynaptic spikes will result in postsynaptic firing is quite low, on the order of 0.05 (Miles and Wong 1986). Because the time constant in these cells (~30–40 ms) is significantly longer than the ISI during a burst, EPSPs that may be sub-threshold for spike triggering in isolation can summate during a burst and elicit a response in a connected neuron with a probability of 0.3–0.5 (Traub and Miles 1991). Burst firing thus seems to be an efficient, or even necessary, way of ensuring spike propagation in neural nets with low connection strength (Eggermont et al. 1993). If bursts are prerequisite to reliable transmission of information, then burst modulation would afford a readily achievable means of signal selection. The strongest bursts are the most likely to survive corticocortical transmission, and bursting may thus serve as a means for enhancing the salient response components against a background of spontaneous discharges (Phillips and Sark 1991). In the context of the results presented here, the longer bursts generated by preferred stimulus orientations act to preserve only that information for which the cell is most optimally attuned, even at low contrasts. Given the low probability of single-spike transmission and the brevity of bursts from nonoptimal stimuli, activity that is generated under these conditions may well be irrelevant. Bursting supports economical compression of visual information with an efficient and easily realizable mechanism, which we believe to be a hallmark of coding.

Dynamic reorganization

One typically views a neural network, either biological or artificial, as a network of processing elements (neurons) linked by connections that are “weighted” by some given strength at each connection site. Such a static organization is intuitively unsatisfactory, given the challenge of a rapidly changing environment (Gerstein et al. 1989). Obviously, biological weighting is a more complex process than the simple fixed coefficients found in most artificial neural nets. It is influenced by synaptic strength, electrotonic distance from the summation site, and dendritic loading, among other factors (e.g., Rall 1967). We propose that burst length modulation by different spatial forms of the stimulus provides a dynamic means of modulating connectivity coefficients, reorganizing the neural network in real time in response to different visual scenes. Such reorganization is most likely not strictly localized, because burst firing in one neuron tends to be associated with burst firing in adjacent neurons (Noda and Adey 1970). In limited circumstances the dynamics between a single pair of neurons can be shown to reflect activity of a larger group that is otherwise unobservable (Gerstein et al. 1989). Thus, despite the overwhelming possibilities for network reconfiguration as a whole, study of local interactions may provide indicators that are useful for understanding more global activities.

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