The impact of 'bursting' thalamic impulses at a neocortical synapse

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Considerable effort has gone into understanding the mechanisms underlying high-frequency 'bursting' of thalamocortical impulses, their sensory information content and their involvement in perception. However, little is known about the influence of such impulses on their cortical targets. Here we follow bursting thalamic impulses to their terminus at the thalamocortical synapse of the awake rabbit, and examine their influence on a class of somatosensory cortical neurons. We show that thalamic bursts potently activate cortical circuits. Initial impulses of each burst have a greatly enhanced ability to elicit cortical action potentials, and later impulses in the burst further raise the probability of eliciting spikes. In some cases, multiple cortical spikes result from a single burst. Moreover, we show that the interval preceding each burst is crucial for generating the enhanced cortical response. The powerful activation of neocortex by thalamocortical bursts is fully consistent with an involvement of these impulses in perceptual/attentional processes.

Neurons of the mammalian thalamus provide a gateway through which all sensory information other than olfaction must pass before reaching the neocortex. Thalamic neurons operate in two distinct modes that regulate the transfer of sensory information to the neocortex[1–3]. When subjects are awake and vigilant, thalamic neurons are generally in 'relay' mode: impulses occur at high and regular rates, and synaptic transmission through the thalamus is faithful. However, when subjects are inattentive, drowsy or anesthetized, thalamic cells are generally in 'burst' mode. Here, transmission through the thalamus is less reliable, and impulses occur at low and irregular rates punctuated by high-frequency 'bursts.' The association of burst mode with sleep and anesthetic states has led to suggestions that thalamic nuclei may be functionally disconnected from neocortex during these periods. However, bursts may occur in the fully awake state[4–7], and decoupling of thalamic neurons from their sensory inputs is selective[8]. Indeed, dorsal lateral geniculate nucleus (LGND) neurons are highly sensitive to some types of visual stimulation during these periods[9], and the information content of each burst is high[10].

These and other properties of thalamic burst mode have led to suggestions that bursts could serve as 'attentional searchlights'[11] or as 'wake-up calls'[12] to sensory neocortex for novel and potentially interesting or dangerous stimuli. However, these hypotheses require thalamocortical synapses to be effective during burst mode. Although synaptic transmission between sensory afferents and dorsal thalamic relay nuclei has been extensively studied during these periods, we have no comparable information about what occurs at the thalamocortical synapse. On the one hand, thalamocortical synaptic transmission may be weakened considerably during burst mode because of the reduction in cholinergic inputs to both thalamus and cortex during periods of drowsiness and sleep[13–15]. Indeed, a reduced gain or 'transfer ratio' is precisely what occurs at the retinogeniculate synapse during states of drowsiness, sleep and light anesthesia that are associated with burst mode[3,16]. Alternatively, thalamocortical efficacy could be facilitated during burst mode because of presynaptic[17,18] (see below) or postsynaptic[19,20] mechanisms. The present work directly investigates this question in the somatosensory thalamocortical system of the awake rabbit. To do this, we exploited a potent synaptic connection between ventrobasal (VB) thalamocortical neurons and putative fast-spike GABAergic interneurons (suspected inhibitory interneurons, SINs) of the topographically aligned somatosensory cortical barrel column[21–24]. We recorded extracellular action potentials from these populations and used cross-correlation methods to examine the efficacy with which the first and subsequent impulses generated by a bursting thalamocortical neuron elicit action potentials in cortical SINs. Our strategy was to compare the efficacy values generated from bursting thalamic spikes with those generated from the entire spike train of the thalamic neuron (the control efficacy[25]). Our results show that bursting thalamic impulses powerfully activate neocortical circuits, and are consistent with an involvement of thalamocortical bursts in attentional mechanisms of sensory neocortex.

Results

Relay mode and burst mode in VB thalamus

Rabbits generally sat quietly during recording sessions. The eyes were kept open, and we observed only occasional small body movements. Under these conditions, the overall rate of 'spontaneous' VB impulses varied considerably. Some seconds or minutes would pass when the spontaneous activity of all recorded thalamic neurons was high and few bursts occurred. This would be followed by variable periods during which the spontaneous

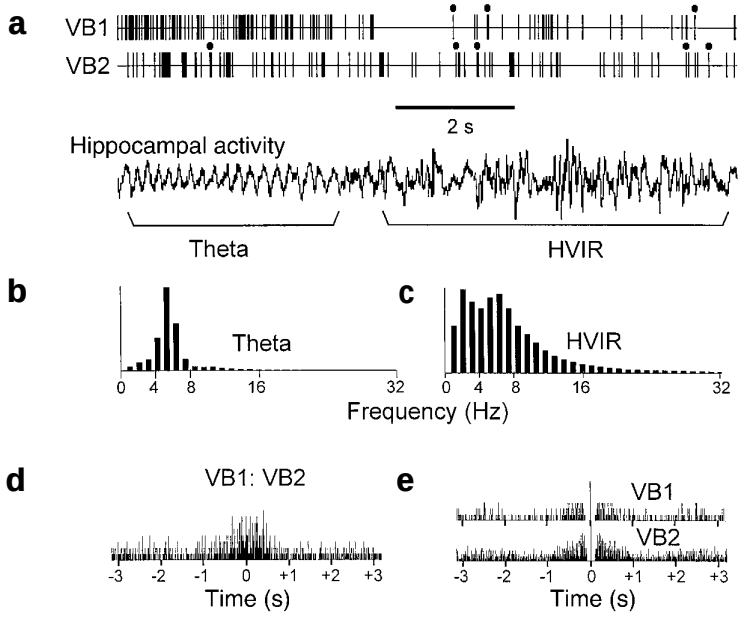

Fig. 1. Relay mode and burst mode in VB thalamus (**a**) Transition from 'relay' mode to 'burst' mode. Upper traces, ~10 s of records from the spike trains of two thalamocortical neurons (VB1 and VB2) recorded via two microelectrodes separated by ~160 microns. Vertical lines, individual action potentials; vertical line with black circle above, bursts of 2–5 action potentials. (The separate action potentials within the bursts cannot be resolved at this time scale.) Left, neurons in 'relay mode,' showing high rates of firing and only a single burst of action potentials. After about 4 s, the firing rate decreases, and the number of bursts increase. Lower trace shows that hippocampal EEG activity is correlated with these different firing patterns. During relay mode, theta activity is seen in the hippocampal EEG. This changes to high-voltage, irregular activity (HVIR) during burst mode. Summed FFT power spectra (946-ms samples) of all hippocampal EEG segments classified as being dominated by theta (**b**) and HVIR (**c**). The maximal value in each distribution was normalized to a value of 1. (**d**) Burst cross-correlogram, the correlation between the initial spike in each burst of neuron VB1 and VB2 (**a**). (**e**) Autocorrelograms of the spike trains of neurons VB1 (top) and VB2 (bottom).

impulse activity of VB neurons decreased, and burst responses were common. The irregular and bursting responses readily converted to high, regular firing either spontaneously, or after auditory or tactile stimulation. EEG recordings from the hippocampus confirmed that the periods of regular firing at high rates were associated with 'theta' activity (in the 4–8 Hz range, a sign of arousal[26]). In contrast, bursts and low spontaneous firing rates were associated with high-voltage, irregular activity (HVIR), a sign of drowsiness, inattention and sleep.

In one such recording session (Fig. 1a), two thalamocortical neurons (VB1 and VB2) were recorded simultaneously from the same VB barreloid using two microelectrodes separated by ~160 microns. Hippocampal EEG activity (Fig. 1a, lower trace) shows that the initial several seconds of this record are dominated by theta activity. During this period, spontaneous VB activity was high in both neurons, and a single burst response occurred (circles above vertical lines; individual spikes within the bursts cannot be resolved at this time scale). Within about one second, however, the EEG converted to HVIR activity, when spontaneous activity of VB neurons was much lower, and bursts were common. To quantify this relationship, we segmented data files into periods dominated by either hippocampal theta activity or by HVIR activity. Files were segmented by visual inspection (without knowledge of VB neuronal activity), aided by fast Fourier transforms (FFT) of each segment. In this manner, 20–55% of each data file was classified as 'theta,' and 30–40% was classified as 'HVIR.' The remaining portions of the files could not be classified. For each of six VB neurons studied in this manner, baseline spontaneous firing rate was approximately two times higher during the periods of theta activity (paired *t*-test, $p \leq 0.0001$; Table 1), but bursts were 8–20 times more prevalent during HVIR activity (paired *t*-test, $p = 0.001$). The summed FFT power spectra for theta and HVIR segments obtained from the entire data file that yielded the two neurons in Fig. 1a (Fig. 1b and c) had theta segments dominated by frequencies of 4–7 Hz, but HVIR segments with considerably more power in both lower and higher frequencies. A 'burst cross-correlogram' (for the initial spike in each burst) was calculated for these two VB neurons (Fig. 1d), and no sharp synchrony was seen. However, bursts showed some broad synchrony, with a half- amplitude response of somewhat less than one second. Very similar burst cross-correlograms were seen for each of 14 pairs of VB neurons. Each member of each pair of VB neurons emitted more than 100 bursts, and each pair was located within the same VB barreloid and recorded on separate electrodes that were spaced at approximately 160 microns. No clear rhythmicity, other than a preferred inter-burst interval of 150–300 ms, occurred in the 'burst autocorrelograms' (autocorrelogram

Table 1. Frequency for different classes of spike activity in each of six VB neurons that were studied during recording of hippocampal EEG activity.

VB neuron	Spikes/s		Bursts/s		Isolated spikes/s		Pseudo-bursts/s	
	Theta	HVIR	Theta	HVIR	Theta	HVIR	Theta	HVIR
1	13.90	6.11	0.040	0.452	1.2	1.19	0.929	0.132
2	22.20	11.00	0.021	0.244	0.169	0.781	0.138	0.032
3	18.00	6.99	0.014	0.265	0.291	0.911	0.077	0.021
4	17.00	7.04	0.060	0.468	0.903	1.05	0.732	0.143
5	17.7	7.13	0.012	0.256	0.269	1.17	0.073	0.024
6	21.80	11.9	0.041	0.565	0.714	1.06	0.563	0.169
Mean ± s.d.	18.43 ± 3.13	8.36 ± 2.44	0.03 ± 0.02	0.38 ± 0.14	0.59 ± 0.41	1.03 ± 0.16	0.42 ± 0.37	0.09 ± 0.07

The EEG was segmented into periods that were dominated by theta activity or by high-voltage irregular activity (HVIR).

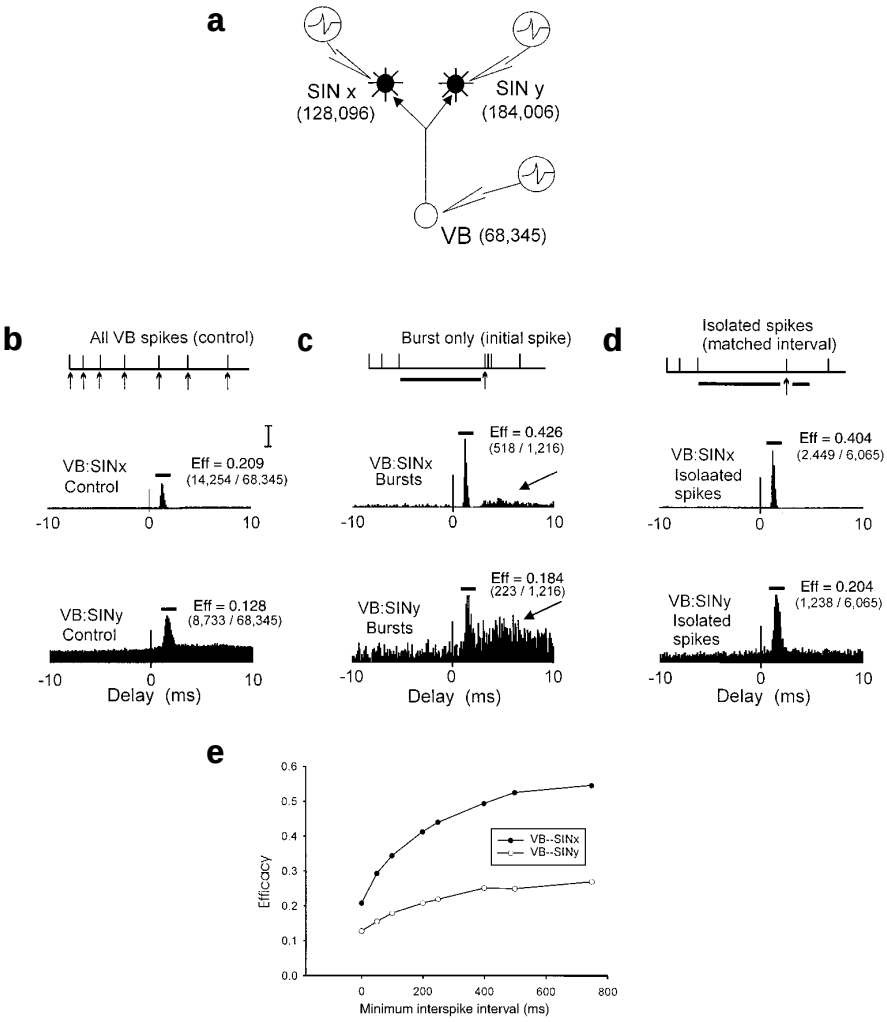

Fig. 2. Methods and results from one experiment. (**a**) An extracellular microelectrode recorded the spontaneous action potentials of a single VB thalamocortical neuron, while two electrodes recorded the spikes of two cortical SINs (SIN *x* and *y*). All correlograms were constructed using a bin width of 0.1 ms and were calculated in the absence of any stimulation. (**b**) Cross-correlograms were initially calculated using the entire spike trains of the VB neuron (vertical arrows, 68,345 spikes), SIN*x* (128,096 spikes) and SIN*y* (184,006 spikes). An index of the potency of this functional connectivity is given by the efficacy, which was computed for a period of 0.6 ms on either side of the peak in the cross-correlogram (indicted by horizontal lines above the peaks in the cross-correlograms). The computed efficacies of 0.209 and 0.128 indicate an extremely potent synaptic contact between the VB neuron and these two SINs. The ratio of the numbers of SIN spikes in the peak of each correlogram (minus the baseline) and the number of VB spikes used in the calculations is given beside each peak. (**c**) Method for selecting only initial spikes in a thalamocortical burst and computing the cross-correlograms based on these spikes. We selected only the first spike in each burst (vertical arrow) and computed the cross-correlogram with each SIN. This resulted in an enhanced efficacy for these selected VB spikes. (**d**) Method for selecting only isolated VB spikes and computed cross-correlograms based on these spikes. The duration of the interval preceding such spikes was chosen to match those seen in the burst condition (**c**, see Methods). These isolated VB spikes were highly potent in activating the cortical SINs. (**e**) For these same neurons, the duration of the required silent interval that preceded a VB spike was varied from 0 to 750 ms. Efficacy values were clearly related to the duration of this interval. All cross-correlograms were normalized for spike rate. The vertical scale bar in (**b**) applies to all correlograms, represents 500 and 100 spikes per second in the VB–SINx and VB–SINy correlograms, respectively.

of the initial spike in each burst) for the 2 VB neurons shown in Fig. 1a (Fig. 1e), or in 15 other such burst autocorrelograms.

The impact of the initial spike in a burst

Of more than 50 VB–SIN pairs studied, we selected a subset for detailed analysis that showed evidence of very potent synaptic connectivity (efficacy values of greater than 5%). In one case (**Fig. 2**), an extracellular microelectrode recorded the spontaneous action potentials of a single VB thalamocortical neuron, and two additional electrodes, located in the topographically aligned S1 cortical barrel, recorded the spikes of two SINs (SIN*x* and SIN*y*; Fig. 2a). Our initial cross-correlation analyses (Fig. 2b) were done using the entire spike trains of the VB neuron (more than 68,000 spikes) and the SINs (more than 120,000 spikes each). This analysis revealed a potent functional connectivity between the VB neuron and both of the SINs. In these correlograms, the VB spike occurs at '0' delay, and the cortical spike follows after a brief delay. A very brief (~1 ms) and potent increase in spike rate occurs at intervals of 1.1–2 ms following the VB action potential[23]. An index of the potency of this functional connectivity is given by the 'efficacy.' This value compares the number of SIN spikes in the peak (± 0.6 ms) of each cross correlogram with the total number of VB spikes[25] (see Methods). Computed efficacies were 0.209 and 0.128, between the VB neuron and SINs *x* and *y*, respectively, which indicates an extremely potent synaptic contact between the VB neuron and these two SINs. Next, we identified 1216 bursts of action potentials that occurred within the spike train of the VB neuron during the two hours of this recording session (Fig. 2c). We then selected the first spike in each of these bursts (vertical arrow) and computed the cross-correlogram of these selected spikes with the spike trains of each SIN. The efficacy of the initial VB spike in each burst was calculated in a manner identical to that of the control efficacy, around the peak in the cross-correlogram (± 0.6 ms). Burst efficacy increased to 0.426 and 0.184 for SIN*x* and SIN*y*, respectively. Similar increases in the efficacy for the initial spike in the thalamocortical burst were seen in each of the seven VB–SIN pairs studied, with mean efficacy values more than doubling (mean, 221% of the control value; $p = 0.005$, paired *t*-test).

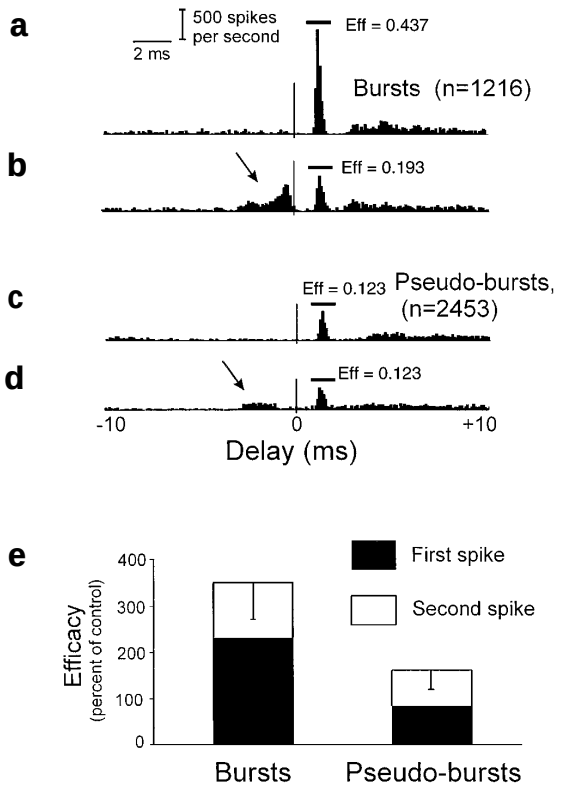

Fig. 3. Thalamocortical efficacy of first and second impulses of bursts and pseudo-bursts. (**a–d**) Analysis for one of the VB–SIN pairs shown in Fig. 2 (VB–SIN*x*) of thalamocortical efficacy of the first and second spikes in bursts (n = 1216) and pseudo-bursts (n = 2453). (**a**, **b**) Cross-correlogram generated by the first and second spike, respectively, in each burst. (**c**, **d**) Correlograms generated by the first and second spike of pseudo-bursts. For analyses generated by the second VB spike in bursts/pseudo-bursts (**b**, **d**), arrows indicate the increase in SIN spike probability that was due to the initial VB spike. Efficacy values for these analyses are calculated identically to that described in Fig. 2, with the exception that the 'chance' levels of responding are based on the interval of from –50 ms to –10 ms preceding each spike. All cross-correlograms are normalized for spike rate (vertical scale bar, 500 spikes/s; bin width, 0.1 ms). (**e**) The summed results for the six VB–SIN pairs studied in this manner. The efficacies of the first and second spike in each burst and pseudo-burst are presented, normalized with respect to the control efficacy for each VB–SIN pair (the efficacy as calculated for the entire data file). Error bars indicate the standard deviation values for the combined normalized efficacies generated by the first and second spike of each burst/pseudo-burst.

The interval preceding the initial spike in a burst

The enhanced efficacy of initial spikes in a thalamic burst could be due to a variety of postsynaptic or presynaptic mechanisms. One simple explanation is related to the long interspike interval that precedes each thalamic burst. In the slice preparation, thalamocortical synapses demonstrate a pronounced paired-pulse depression that lasts for several hundred milliseconds[17,18]. In the awake state, most thalamic neurons have spontaneous activity levels of more than 10 spikes per second (for example, see Table 1), and thalamocortical synapses, therefore, could be in a chronic state of depression. The pause in firing that necessarily precedes a thalamic burst could relieve this depression and produce a larger-amplitude EPSP on the postsynaptic membrane. If this is the case, single, isolated thalamic spikes that are preceded by silent periods comparable to those seen before thalamic bursts should also show an enhanced efficacy in eliciting spikes in cortical SINs. We found that this is indeed the case (Fig. 2d). The 1216 bursts recorded in this VB neuron followed the preceding spike at a median interval of 278 ms. Therefore, isolated VB spikes were selected that occurred at a similar interval following the preceding spike (median value, 280 ms, matched interval condition; Fig. 2d, vertical arrow; Methods). These isolated VB spikes were highly potent in activating the cortical neurons, showing efficacies of 0.404 and 0.204 in SINs *x* and *y*, respectively (Fig. 2d). These values are very similar to those seen under the burst condition (Fig. 2c).

The magnitude of the enhanced thalamocortical efficacy for these neurons was clearly related to the duration of the 'silent' period that preceded the VB spike (Fig. 2e). Similar increases in the efficacy for such isolated VB spikes (with matched preceding interval) were seen in each of the seven VB–SIN pairs studied, with mean efficacy values nearly doubling (mean, 174% of the control value; p = 0.013, paired t-test).

To further examine the involvement of the interval that precedes each burst, we compared the thalamocortical efficacy of bursts with those of 'pseudo-bursts.' Like normal bursts (see Methods), pseudo-bursts were required to consist of at least two spikes, at interspike intervals of less than 4 ms. Unlike normal bursts, however, pseudo-bursts had no lengthy preceding interval, and were required to have at least one spike in the interval of 10–80 ms preceding the initial spike in the pseudo-burst. Our analysis compared the thalamocortical efficacy of the initial two spikes of regular bursts with those of such pseudo-bursts (Fig. 3), and showed that the peaks in the cross-correlograms in response to both the first and second VB spikes are considerably stronger in bursts than in pseudo-bursts (Fig. 3a–d). In each of the VB–SIN pairs studied, the combined efficacy of the first two spikes was greater in normal bursts than in pseudo-bursts ($p < 0.001$, paired t-test). The mean efficacy values of the first and second thalamic spike in each burst and pseudo-burst were normalized with respect to the control efficacy for each pair (the efficacy as calculated for the entire data file; Fig. 3e).

The impact of later spikes in a burst

The above analysis shows that the second spike in thalamocortical bursts (and pseudo-bursts) contributed to the cortical response. Moreover, inspection of the cross-correlograms generated by the initial spike of a burst (Fig. 2c) show prolonged secondary peaks (arrows) following the sharp initial peaks, which are not seen in Fig. 2b or d. For the seven VB–SIN pairs studied, we analyzed the thalamocortical efficacy of later spikes in a burst in which the preceding spikes all failed to generate cortical action potentials (Fig. 4a). We compared the thalamocortical efficacy for initial spikes in a burst (Fig. 4a, left bar) with those of the second spike (Fig. 4a, middle bar) or third spike (Fig. 4a, right bar). Thalamocortical synaptic efficacy remains slightly above control values under these conditions for both the second and third spike in the burst.

We also asked whether the multiple spikes of a thalamocortical burst can elicit multiple impulses in their cortical targets. For example, it is possible that cortical spikes in the peak of the cross-correlogram in Fig. 3b were elicited by the second spike of the VB burst only when the first VB spike failed to elicit a cortical spike. We showed for this same VB–SIN pair that this is not the case (Fig. 4b). A cross-correlogram was generated by selecting for

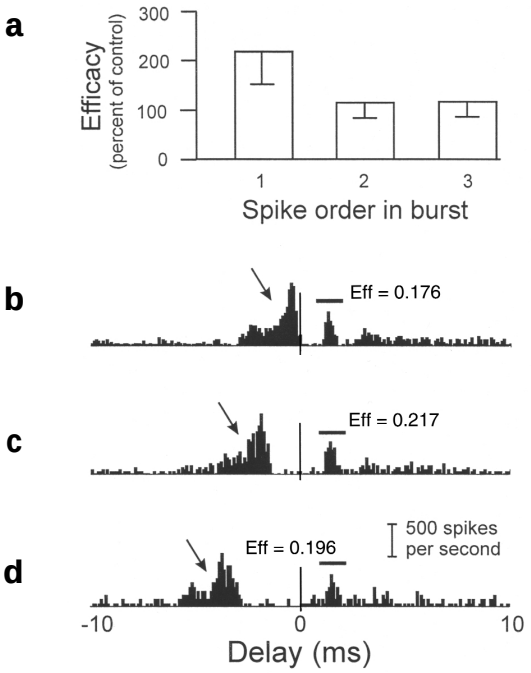

Fig. 4. The impact of later spikes in a burst. (**a**) Thalamocortical efficacy of later spikes in a burst when the initial spike(s) fail to elicit a cortical response. For the seven VB–SIN pairs under study, efficacy of the initial spike in the burst (left) is compared with the efficacy of the second (middle) and third (right) spike in the burst under these conditions. Error bars, s.d. (**b**) For the same VB–SIN pair shown in Fig. 3, we selected for analysis only the second spike in each VB burst, under conditions in which the first VB spike was successful (arrow) in eliciting a cortical spike. The resulting efficacy of the second spike remained high (0.176), showing that bursts in single VB neurons can elicit multiple spikes in their targets. (**c**) We analyzed only the third spike in each VB burst, under conditions in which the first VB spike was successful (arrow), but the second was not. (**d**) Only the fourth spike in each VB burst is selected for analysis, under conditions when the first VB spike was successful (arrow), and the second and third spike in the burst were not successful. All cross-correlograms are normalized for spike rate (vertical scale bar, 500 spikes/s; bin width, 0.1 ms).

analysis only the second spike in each VB burst, under conditions in which the first VB spike was successful in eliciting a cortical spike (Fig. 4b, arrow). Even under these conditions, the efficacy of the second spike was very high (0.176), showing that bursts in single VB neurons can elicit multiple spikes in their targets. We then selected for analysis only the third spike in each VB burst (Fig. 4c), under conditions in which the first VB spike was successful (arrow), but the second VB spike was not successful in eliciting a cortical spike. Finally, we selected for analysis only the fourth spike in each VB burst (Fig. 4d), under conditions in which the first VB spike was successful (arrow), and the second and third spikes in the burst were not successful. Efficacies remain at a very high level under all conditions for this very strongly connected VB–SIN pair. These data show that the sequential impulses of single bursts that occur in some potently connected VB neurons may elicit multiple action potentials in cortical target neurons.

Thalamocortical efficacy and EEG state

Bursts were relatively rare during hippocampal theta, and pseudo-bursts were rare during HVIR (Table 1). Because of this, we could not compare thalamocortical efficacy of these events between the two EEG states. However, we could compare, across EEG states, the thalamocortical efficacy of 'isolated' VB spikes with long preceding interspike intervals (see above). These spikes are of special interest because they may be generated by the same underlying mechanism (low-threshold calcium spike) that generates thalamic burst responses[6]. In each of the five VB–SIN pairs that were adequately studied under both states, thalamocortical efficacy of such isolated spikes was similarly enhanced over control values (mean ± s.d., 183 ± 21% of control values during theta activity; 177 ± 27% of control values during HVIR activity).

Discussion

High-frequency bursts of action potentials are characteristic of many neuronal populations, and their involvement in neural information processing has generated considerable interest[19]. In some systems that demonstrate paired-pulse facilitation, the synaptic efficacy of later impulses in a burst is much higher than for earlier impulses, and bursting may serve as a kind of high-pass filter[18]. In other systems, each spike in the burst has a synaptic efficacy that is similar to that of an 'average' spike, but the overall probability of generating at least one postsynaptic spike is higher for bursts than for single spikes[27]. The present results show that bursts of thalamocortical impulses generate yet another type of enhanced postsynaptic response. Here, the enhanced activation of cortical neurons occurs in two ways: first, the initial impulse of each burst has a synaptic efficacy that is much higher than that of an average thalamocortical impulse, and second, the efficacy of subsequent impulses within the burst are very near the average value and further raise the overall probability of successfully eliciting neocortical spikes. In some strongly connected VB–SIN pairs, multiple cortical spikes are elicited by the consecutive impulses of a single burst.

Our data suggest that the interval preceding the initial spike in the burst is a key factor in generating the enhanced synaptic efficacy to this spike. Thus, we first found a clear relationship between the duration of this preceding interval and thalamocortical synaptic efficacy. Second, we found that a similar enhanced thalamocortical efficacy is generated by single isolated spikes (with matched preceding intervals) that are not part of a burst. Third, we found that the enhanced thalamocortical efficacy generated by such isolated VB spikes is independent of the EEG state (hippocampal theta or HVIR) during which they occur. Fourth, we found that the initial spike of pseudo-bursts (which have no preceding spike-free interval) does not show an enhanced thalamocortical efficacy. Nevertheless, it is possible that hidden postsynaptic factors are correlated with long interspike intervals in VB neurons, and that these contribute to the enhanced thalamocortical efficacy of VB bursts and isolated spikes.

Studies showing activity-dependent depression of thalamocortical synapses provide a plausible explanation for the potent influence of interspike interval on thalamocortical synaptic efficacy. Thalamocortical synapses onto both spiny neurons and fast-spike GABAergic interneurons show considerable paired-pulse depression[17,18] that gradually recovers over hundreds of milliseconds. If such activity-dependent depression also occurs at the thalamocortical synapse of adult, intact subjects, the high levels of spontaneous activity generated by thalamocortical neurons (for example, see Table 1) would be expected to result in a chronic state of synaptic depression. In light of this, it has been suggested[6] that the long interval that necessarily precedes the initial spike of a thalamocortical burst would allow thalamic neurons to recover from such activity-

dependent depression, and that initial spikes in a burst should evoke a maximum EPSP in postsynaptic targets. Our results are in full agreement with this suggestion.

Bursting of thalamocortical neurons has often been associated with sleep and anesthetic states[1]. The present observations in awake rabbits agree with previous work showing that thalamic bursting also occurs in the awake state[4–7]. Thalamocortical bursts were approximately 12 times more frequent during hippocampal HVIR activity than during theta activity. HVIR has been associated with relaxed immobility, grooming, inattention and slow-wave sleep in the rabbit, and theta activity has been associated with arousal and alertness, both during movement and during immobility[26,28]. We believe that our rabbits were awake but drowsy and inattentive during the HVIR seen in our experiments, for the following reasons. First, although the eyelids sometimes drooped, they were always open. Second, rabbits were responsive to sensory stimulation during these periods. An approaching visual stimulus would rapidly convert the HVIR into theta activity, and theta activity was also generated by low-intensity auditory or tactile stimulation. Third, hippocampal EEG changed spontaneously between theta activity and HVIR, sometimes within a period of less than one second (for example, Fig. 1a).

We found that spontaneous bursts were only weakly synchronous, even among VB neurons of the same barreloid. However, work in LGNd shows that bursts are generated at a very constant latency to very low intensity visual stimulation[9]. This suggests that, when in burst mode, many thalamocortical neurons with similar spatial receptive fields would generate synchronous burst responses to even weak sensory stimulation. Although the present results showing enhanced cortical responses to thalamic bursts were based on spontaneous thalamic and cortical impulses, we would expect bursts triggered by sensory events to also show enhanced efficacy at the thalamocortical synapse. If so, synchronous bursts generated in multiple thalamocortical neurons by even a weak sensory stimulus should, in turn, generate a powerful postsynaptic cortical response.

It is important to emphasize that our findings are based on thalamocortical synaptic input to a special class of cortical neuron: putative fast-spike GABAergic interneurons. These neurons have membrane properties that differ considerably from those of most cortical neurons[18,29]. It is possible, therefore, that other cortical populations may respond differently to thalamocortical bursts. Our results, however, suggest that a recovery from activity-dependent depression underlies the enhanced synaptic efficacy of the initial spike of a thalamocortical burst. If this is the case, one would expect a similar enhanced efficacy at the thalamocortical synapse onto spiny stellate neurons of layer 4. This population shows considerable activity-dependent depression at the thalamocortical synapse[17,18] and receives potent input from a subset of thalamic afferents[30]. An enhanced, burst-induced response in both cortical excitatory (spiny stellate and local pyramidal neurons) and inhibitory neurons would result in an enhanced early response in the excitatory population that is swiftly terminated (at a disynaptic delay of ~1 ms) by powerful feed-forward inhibition[21,31]. Such a potent and sharply synchronous cortical excitatory population response would be well suited to activate target neurons lying downstream and is consistent with an involvement of thalamocortical bursts in attentional mechanisms of the neocortex[4–7,9–11].

METHODS

Extracellular recordings were obtained from somatosensory (S1) cortical barrel columns and from VB thalamic barreloids of adult, Dutch-belted rabbits. Initial surgery was done under anesthesia using aseptic procedures. Subsequent recordings were obtained in the awake, unanesthetized state using procedures approved by the Institutional Animal Care and Use Committee at the University of Connecticut in accordance with NIH guidelines. Methods used to ensure the comfort of our subjects have been described in detail[23,24]. Rabbits were held snugly within a stocking and were placed on a foam rubber pad. The steel bar on the head was fastened to a restraining devise in a manner that minimized stress on the neck. Rabbits generally sat quietly for several hours of each recording session and then were returned to their home cage.

Microelectrodes were constructed of quartz-platinum filaments (40 microns, maximum diameter[32]) that were pulled under high temperature and sharpened to a fine tip. A concentric array of 7–19 such electrodes (inter-electrode spacing of 160 microns) was chronically implanted within VB thalamus, with each electrode independently controlled by a miniature microdrive. Cortical recordings were obtained from topographically aligned S1 barrels, following mapping procedures. Cortical recordings were obtained acutely, using 5–7 of the same type of electrodes described above (electrode spacing < 160 microns), but positioned using a 7-channel microdrive system[33]. VB thalamocortical neurons were identified by spike-triggered averages of field potentials elicited in the aligned S1 barrel[31]. Cortical SINs were identified by a high-frequency (> 600 Hz) burst of three or more spikes elicited by electrical stimulation of VB thalamus[23,24] and by their short-duration action potential[22,23,29].

All data were collected in the absence of peripheral stimulation, under conditions of spontaneous activity. We selected a brief window (± 0.6 ms on each side of the peak of the cross-correlogram) for calculation of efficacy values. We restricted our analysis to this brief window because peaks in the thalamocortical cross-correlogram in this system are comparably short[23] and because we wanted to limit the analysis to the effects of a single presynaptic impulse. Efficacy values were calculated by counting the number of action potentials that occurred in the SIN during this brief temporal window, subtracting a baseline number of spikes expected by chance during this period, and dividing this value by the number of triggering VB spikes. The number of SIN spikes expected by chance was based on the mean number of spikes per bin that occurred between –4 ms and +1 ms of the VB spike time. We limited our analysis to those VB–SIN pairs that showed a control efficacy greater than 0.05. In addition, we studied only those pairs in which greater than 100 burst responses of the VB neuron occurred.

Thalamocortical bursts were identified according to previously described criteria[34]. Thus, the initial impulse in a burst was required to be preceded by an interval of at least 100 ms during which no action potentials occurred and to be followed by another action potential at an interval of less than 4 ms. Subsequent impulses that occurred at intervals of less than 4 ms were identified as being part of the burst.

'Isolated spikes' (matched interval condition, Fig. 2d) were preceded by a defined period during which no action potentials occurred, and were followed by a period greater than 10 ms during which no spikes were permitted. Initially, we selected a value of 100 ms for the period preceding the isolated spikes. When using this value, however, measured interspike intervals preceding the isolated spike were considerably less than those preceding VB bursts. Therefore, for each VB cell, we lengthened the required interval preceding the isolated spike until interspike intervals matched (median values, ± 5 ms) those preceding VB bursts. This required period varied between 145 and 195 ms for the VB neurons studied in this manner.

Pseudo-bursts consisted of an initial spike that was followed by another spike at an interval of less than 4 ms and was preceded by at least one spike at intervals of 10–80 ms. Whereas most bursts consisted of three or more spikes, most pseudo-bursts consisted of two spikes. For this reason, we compared only the initial two spikes of bursts and pseudo-bursts. The procedure for calculating efficacy values to the second spike in a burst/pseudo-burst was complicated by the fact that the time period usually used for calculating 'chance' spike values (between –4 ms and +1 ms of the VB spike time, above) showed elevated spike counts due to the cortical spikes that were elicited by the first spike in the burst (arrows, Fig. 3b and d). For this analysis, therefore, we calculated the 'chance' level of responding based on the time period from 10 to 50 ms preceding the VB spike. As in the analyses presented in

Fig. 2, efficacy values were based on a brief window (± 0.6 ms on each side of the peak of the cross-correlogram).

Hippocampal EEG was obtained via two platinum-iridium microwires placed above and below (1-mm vertical separation) the CA1 layer of the hippocampus.

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