Sharp, Local Synchrony Among Putative Feed-Forward Inhibitory Interneurons of Rabbit Somatosensory Cortex

HARVEY A. SWADLOW, IRINA N. BELOOZEROVA, AND MIKHAIL G. SIROTA
Department of Psychology, The University of Connecticut, Storrs, Connecticut 06269

Swadlow, Harvey A., Irina N. Beloozerova, and Mikhail G. Sirota. Sharp, local synchrony among putative feed-forward inhibitory interneurons of rabbit somatosensory cortex. *J. Neurophysiol.* 79: 567–582, 1998. Many suspected inhibitory interneurons (SINs) of primary somatosensory cortex (S1) receive a potent monosynaptic thalamic input (thalamocortical SINs, SINstc). It has been proposed that nearly all such SINstc of a S1 barrel column (BC) receive excitatory synaptic input from each member of a subpopulation of neurons within the topographically aligned ventrobasal (VB) thalamic barreloid. Such a divergent and convergent network leads to several testable predictions: sharply synchronous activity should occur between SINstc of a BC, sharp synchrony should not occur between SINstc of neighboring BCs, and sharp synchrony should not occur between SINs or other neurons of the same BC that do not receive potent monosynaptic thalamic input. These predictions were tested by cross-correlating the activity of SINstc of the same and neighboring BCs. Correlations among descending corticofugal neurons of layer 5 (CF-5 neurons, identified by antidromic activation) and other neurons that receive little or no monosynaptic VB input also were examined. SINs were identified by a high-frequency (>600 Hz) burst of three or more spikes elicited by VB stimulation and had action potentials of short duration. SINstc were further differentiated by short synaptic latencies to electrical stimulation of VB thalamus (<1.7 ms) and to peripheral stimulation (<7.5 ms). The above predictions were confirmed fully. *1*) Sharp synchrony (±1 ms) was seen between all SINstc recorded within the same BC (a mean of 4.26% of the spikes of each SINtc were synchronized sharply with the spikes of the paired SINtc). Sharp synchrony was not dependent on peripheral stimulation, was not oscillatory, and survived general anesthesia. Sharp synchrony was superimposed on a broader synchrony, with a time course of tens of milliseconds. *2*) Little or no sharp synchrony was seen when CF-5 neurons were paired with SINstc or other neurons of the same BC. *3*) Little or no sharp synchrony was seen when SINstc were paired with other SINstc located in neighboring BCs. Intracellular recordings obtained from three SINs in the fully awake state supported the assertion that SINs are GABAergic interneurons. Each of these cells met our extracellular criteria for identification as a SIN, each had a spike of short duration (0.4–0.5 ms), and each responded to a depolarizing current pulse with a nonadapting train of action potentials. These results support the proposed network linking VB barreloid neurons with SINstc within the topographically aligned BC. We suggest that sharp synchrony among SINstc results in highly synchronous inhibitory postsynpatic potentials (IPSPs)in the target neurons of these cells and that these summated IPSPs may be especially effective when excitatory drive to target cells is weak and asynchronous.

INTRODUCTION

A recent proposal (Swadlow 1995) maintains that a richly divergent and convergent axonal network links ventrobasal (VB) thalamocortical ''barreloid'' neurons (Land et al. 1995; Van der Loos 1976) with a special class of cortical neuron in the topographically aligned barrel column[1] of primary somatosensory cortex (S1). These cortical neurons are believed to be inhibitory interneurons (suspected inhibitory interneurons, SINs). They are identified by a high-frequency (>600 Hz) burst of three or more spikes to electrical stimulation of afferent pathways, and they have action potentials of short duration (Swadlow 1989, 1990, 1995). It was found that most of the SINs within and near layer 4, and some of those found in layer 5, received a potent monosynaptic input from VB thalamus (thalamocortical SINs, SINstc). Experiments examining functional synaptic connectivity between individual VB barreloid neurons and topographically aligned SINstc lead to the proposal that a subclass of barreloid neurons have axons that diverge to provide synaptic input to nearly all of the SINstc of the aligned S1 barrel column (Swadlow 1995).

Such a highly interconnected thalamocortical network is suggestive of the ''complete transmission line'' between successive nodes of a network described by Griffith (1963, also see Abeles 1991). These networks are characterized by a very reliable transmission between input and output nodes, but at a cost of sacrificing ''complexity of task'' (Griffith 1963). In fact, the properties of S1 SINs match this description quite closely. They have lower thresholds to both electrical stimulation of VB thalamus and to peripheral stimulation than any other class of cortical neuron studied. SINs also respond to a broader range of stimulus frequencies than do antidromically identified efferent neurons (Swadlow 1989, 1990). These cells have sacrificed complexity of task, however, in that they lack the directional selectivity seen in many of the VB thalamocortical afferent fibers that provide their input (Simons 1978; Simons and Carvell 1989; Swadlow 1989).

Another predictable consequence of the proposed divergent and convergent presynaptic network is sharply synchronous activity among the postsynaptic elements. Sharp synchrony would result because of the near-simultaneous excitatory postsynaptic potentials (EPSPs) generated in recipient neurons by common inputs (cf. Moore et al. 1970). Along this line, Sears and Stagg (1976) predicted that a ''short-term'' synchrony should be observable among homonymous motoneurons and that the duration of this synchrony should be comparable with the rise time of an EPSP. This prediction was based on work by Mendell and Henneman (1971) show-

[1] We have adopted the term ''barrel column'' from Van der Loos and colleagues (e.g., Welker et al. 1988) to refer to a layer 4 barrel (Woolsey and Van der Loos 1970) plus the cortical tissue above and below it.

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ing that each muscle spindle 1a afferent fiber branches profusely before contacting nearly all homonymous motoneurons. A brief synchrony indeed was found between intercostal motoneurons and was subject to considerable subsequent analysis (Kirkwood and Sears 1978; Kirkwood et al. 1982a,b; Sears and Stagg 1976).

The proposed network linking VB barreloid neurons with SINstc of the corresponding S1 barrel column leads to several testable predictions: *1*) sharply synchronous activity should occur between SINstc of the same barrel column, *2*) sharp synchrony should not occur between SINstc of neighboring barrel columns because VB thalamic afferents generally are limited to a single S1 barrel column (Jensen and Killackey 1987), and *3*) sharp synchrony should not occur between neurons of a barrel column that receive little or no monosynaptic thalamic input.

The present work has confirmed these predictions using closely spaced independent microelectrodes to record the extracellular activity of SINstc. Control procedures ensured that closely spaced electrodes were not recording from the same neurons or detecting common artifacts. We found sharply synchronous activity between SINstc of the same barrel column but not between SINstc of neighboring barrel columns or between other neuronal classes of the same barrel column that receive minimal monosynaptic thalamic input. In addition, we provide confirming intracellular evidence that SINstc are indeed GABAergic interneurons. Together, these results suggest that cooperative activity among SINstc of a barrel column may mediate sharply synchronous waves of feed-forward inhibition[2] onto their postsynaptic targets.

METHODS

Recordings were obtained from the S1 representation of the vibrissae of adult, fully awake Dutch-belted rabbits. Some of the methods have been described recently (Swadlow 1989, 1990, 1995) and are reported briefly here. The great majority (>90%) of recordings were obtained from barrel columns representing the medium-large central vibrissae (25–40 mm in length) or the very large (40->60 mm) posterior-ventral vibrissae. A few recordings were obtained from barrel columns representing smaller vibrissae (15–25 mm in length).

General surgical methods

Initial surgery was performed under pentobarbital sodium anesthesia (initial dose, 25–35 mg/kg) using aseptic procedures. After removal of skin and fascia above the skull, the bones of the dorsal surface of the skull were fused together using stainless steel screws and acrylic cement. A stainless steel rod was oriented in a rostrocaudal direction, was positioned over the midsagittal suture, and was cemented to the acrylic mass. This rod had an initial diameter of 6 mm, but was ground to a width of 2 mm at its midpoint (medial of S1) to make additional space available on the skull. The rabbit was held rigidly by this bar during later surgery and recording sessions. Three stimulating electrodes were implanted within and above the vibrissae representation of VB thalamus after physiological mapping of this structure with a finely tapered microelectrode. Stimulating electrodes were separated by 0.5–1.0 mm and were constructed of platinum-iridium wire (125 μm diam) that was insulated with Teflon to within 0.5 mm of the tips. These electrodes were secured to the acrylic mass on the skull, and additional cement was used to cover all of the skull except a central opening above the region of S1 to be studied. A layer of silicone rubber cement always covered the exposed skull between recording sessions and also was used to buffer the wound margins from the acrylic cement on the skull. A small entrance (~1 mm diam) was drilled into the skull above the estimated position of the S1 vibrissae representation and the cortical representation of individual vibrissae was located using extracellular mapping procedures (Gould 1986; Swadlow 1989). The entrance in the skull was extended if necessary. This entrance then was filled with gelfoam soaked in an antibiotic ointment and capped with acrylic cement. The remaining exposed skull then was treated with antibiotic ointment and covered with a thick layer of the silicone rubber cement.

Extracellular recording procedures

Methods ensuring the humane treatment of our subjects during immobilization of the head and single-unit recording have been described recently (Swadlow 1989, 1990, 1995). After the initial surgery, described in the preceding text, all subsequent recordings were obtained from fully awake rabbits. Rabbits were held snugly within a body stocking from which the head protruded and were placed on a foam rubber pad. The steel bar on the head then was fastened to a restraining devise in a manner that minimized stress on the neck when the head was immobilized. Although electroencephalography (EEG) was not monitored in these experiments, previous work using the identical restrained rabbit preparation (Swadlow and Weyand 1987) has shown that gentle tactile stimulation is an effective means of eliciting EEG arousal (as manifested by hippocampal theta activity). Facial stimulation, such as that used during receptive field testing in the present experiment, is especially effective in this regard. Rabbits sat awake, with eyes open throughout these experiments and appeared very alert throughout receptive field testing and subsequent analyses. After immobilization of the head, the only procedures required before recording were the removal of the acrylic-covered plug of gelfoam (usually ~1 × 1 mm) overlying the cortex to be studied, cleaning of an even smaller region of dura that lay beneath this plug, and insertion of the microelectrodes. After each recording session, this small entrance was resealed with moist gelfoam that was impregnated with antibiotic ointment and covered with acrylic cement. It is noteworthy that although rabbits may respond to gentle tactile stimulation of the facial region with movements of the nose or vibrissae, no such responses are observed during the above procedures. Rabbits did not appear disturbed by these manipulations.

Three to seven simultaneous microelectrode penetrations were made each recording session using seven motor-controlled microdrives (Eckhorn and Thomas 1993). ''Fiber'' microelectrodes (Reitboeck 1983) were fabricated from platinum-tungsten wire (90%:10%), insulated with quartz glass (60–80 μm OD). After pulling these fibers to fine tips in a helium filled chamber, they were sharpened using a diamond-coated grinding wheel. Impedance (at 1,000 Hz) were usually 2–4 MΩ. These electrodes were further tapered to ensure maximum diameters of <60 μm throughout the depth of the cortex by immersing the shanks (but not the tips) in hydrofluoric acid.

During most recording sessions, the electrodes were configured in a concentric arrangement, with an interelectrode spacing of 200 μm (total diameter of the 7-electrode array was ~400 μm). In some experiments, a triangular arrangement of three electrodes was used, spaced at distances of 80–100 μm. For experiments that were aimed at simultaneous recordings from different barrel columns, two parallel linear arrays were used (3–4 electrodes each) with a spacing of 350–500 μm.

[2] The action of SINstc may be considered to be ''feed-forward'' because they receive excitatory thalamic input and form presumptive inhibitory synapses with other cortical neurons that also receive excitatory thalamic input (White 1989).

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After preamplification and filtering (low- and high-frequency 1/2 band-pass = 300 and 10,000 Hz, respectively), spike data were led to a digital oscilloscopes for display and analysis of synaptic or antidromic latencies. Spike data also were digitized at 25–33 kHz, and action potentials were discriminated on-line, using a commercially available software package (DataWave Technologies). This package allows spikes to be sorted based on a number of parameters derived from voltage amplitude and time measures. Spike waveforms were saved, along with stimulus information, and were subsequently reexamined and discriminated off-line. Only well-discriminated neurons were selected for analysis in this study.

Identification of S1 SINs and efferent neurons

In previous studies of S1 (Swadlow 1989, 1995), SINs were defined as those neurons that responded synaptically to electrical stimulation of VB (at 3–5 times threshold intensities, 0.1–0.2 ms rectangular pulses) with a burst of three or more spikes occurring at peak frequencies in excess of 600 Hz. Although not required for identification as a SIN, cells meeting the above criteria also were shown to have spikes of short duration. In the present work, the above criteria were modified slightly for those cells that responded to the VB stimulus in the following two ways: two spikes (rather than 3+) at a frequency of 600 Hz+ or three or more spikes at frequencies of 500–599 Hz. These cells were classified as SINs if they exhibited an action potential duration of <0.7 ms. SINs were considered to be monosynaptically activated via thalamocortical input if they met the following two criteria: they responded synaptically to electrical stimulation of VB (3–5 times threshold intensity) at a latency of < 1.7 ms and they responded to air-puff stimulation of the vibrissae at a latency of < 7.5 ms (Swadlow 1995, Figs. 3–5).

Descending corticofugal neurons were identified by their antidromic activation after electrical stimulation of VB thalamus. The principal criterion for the identification of antidromic activation was the test for collision of impulses (Bishop et al. 1962; Fuller and Schlag 1976). This method allows antidromic responses (elicited by electrical stimulation of the axon) to be identified by their extinction after collision with an appropriately timed spontaneous or orthodromically evoked impulse.

Estimating cortical depth and the differentiation of descending corticofugal efferent neurons of layers 5 and 6

Histological reconstruction of microelectrode tracts was not usually possible because very closely spaced penetrations were made in individual rabbits during periods of several weeks or months. To accommodate this problem, a normalization procedure was used in which two physiological reference points (1 located in the upper portion of layer 2, the other located near the border of layers 5 and 6) were used to create a ''relative depth'' scale, and the depth of all neurons within each penetration were located according to this scale. The superficial reference point, assigned a relative depth value of 0, consisted of the reversal point of a surface-negative evoked potential and was located ~200 μm below the border of layer 1 with layer 2. For each subject and location, the time of the peak of this surface-negative potential was determined at the surface of the cortex (4.5–6 ms after VB stimulation), and the reversal depth was determined at this interval. In two rabbits, 30 microlesions (10 μA cathodal, 5- to 10-s duration) were made at the site of this reversal, and 22 of these were recovered. The mean depth of these microlesions was ~200 μm beneath the border between layers 1 and 2.

As in previous studies of rabbit S1 (Swadlow 1989–1995) the border of layer 5 and 6 was used as a reference point for depth comparisons among neurons in different penetrations. This is possible because this border is marked by an abrupt change in the characteristics of descending corticofugal efferent axons (Swadlow 1989, 1990). Whereas virtually all descending corticofugal neurons of layer-5 (CF-5 neurons) have rapidly conducting axons, those of layer-6 (CF-6 neurons) have axons that conduct much more slowly and exhibit a ''supernormal'' period of reduced antidromic latency at appropriate intervals after a prior action potential. Thus when the microelectrode reaches a certain depth, the characteristics of those neurons activated antidromically via VB thalamic stimulation changes dramatically. In each penetration, the most superficial CF-6 neuron was identified by an antidromic latency (from the thalamic stimulation site) of >3 ms and by an antidromic latency decrease of >4% to a stimulus that followed a prior impulse (spontaneous or electrically elicited) at an interval of 6–12 ms. This most superficial CF-6 neuron was assigned a relative depth of 100, and all descending corticofugal neurons located deeper in the penetration were classified as CF-6 neurons. The position of all other neurons within the penetration were assigned a depth value according to this relative scale. Because some layer-6 corticofugal neurons have antidromic latencies of <3 ms, it was inevitable that some such cells would be located superficial to the first corticofugal neuron studied that met both of the criteria for having reached layer-6. For this reason, corticofugal neurons found at relative depths of 85–99 were considered to be of uncertain laminar origin and were excluded from further analysis. Corticofugal neurons projecting to and/or beyond the thalamus have been found to originate exclusively in layers 5 and 6 (e.g., Jones 1984). In the present study, therefore, these neurons found at relative depths of <85 were classified as descending corticofugal neurons of layer-5 (CF-5 neurons).[3]

Air-puff stimulation and measurements of latencies to peripheral stimulation

Brief air puffs of graded intensity were delivered via a high-speed solenoid valve connected to a compressed air supply. The output of the valve was led to the preparation via a 40-cm-long stiff, thick-walled Teflon tubing (3 mm OD, 1.2 mm ID). The output of the tubing was positioned from 5 to 20 mm from the vibrissa (or vibrissae) to be stimulated. This was accomplished by means of a micromanipulator, which could be rotated around an axis of 360° so that directionally selective vibrissae could be stimulated along their optimal axis. Pressures were calibrated periodically with a Bruel and Kjaer condenser microphone (cartridge type 4136) and preamplifier. The rise time of the pulse (from 5 to 60% of total amplitude) was 0.5–0.6 ms, and total pulse duration was 3.5–4 ms. Maximum pressures of 3×10^4 dynes/cm^2 were attained. The latency of the device (3.1 ms at a distance of 5 mm from the receptor surface) was subtracted from all neuronal latency measures.

Latency measurements were derived from poststimulus histograms compiled from >100 stimulus presentations, delivered at a rate of 1/s and time stamped at a resolution of 100 μs. Latency was taken at the first bin after 5 ms that had a value exceeding the value of each of the 50 bins between 0 and 5 ms and was followed immediately by a bin which also exceeded this same value.[4]

[3] The laminar origins of corticofugal neurons of rabbit S1 have not yet been determined. In rabbit visual cortex, although the great majority of corticotectal neurons originate in layer 5, some such neurons are found among the pyramidal cells of layer 4 (Swadlow and Weyand 1981). Thus it is possible that some of the neurons here classified as CF-5 neurons are actually in layer 4.

[4] For any given bin, the probability that these two conditions will be met by chance = 0.0004 (0.02 × 02). SINstc were of primary interest here, and these cells had, by definition, latencies of <7.5 ms. Thus there were 24 possible opportunities (5.1–7.4 ms) to obtain a SINtc-like latency. The probability of obtaining such a value by chance in at least one of the 24 bins was <0.01.

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Identifying the cortical representation (barrels) of individual vibrissae

Before placement of the seven-electrode recording array, a single microelectrode was used to roughly map a small (<1 mm diam) region of cortex representing medium-large vibrissae. The estimated center of a barrel column was located by observing strong responses dominated by a single vibrissa, and the position of the seven-electrode array was centered at this location. Once the array of recording electrodes was in place, each electrode was lowered slowly to the vicinity of layer 4, where short-latency responses to peripheral stimulation are most prevalent. The depths of each of the electrodes were adjusted so that latencies of <7.5 ms were seen in the multiple-unit responses to an intense air-puff stimulus, which maximally activated several vibrissae. At this point, we estimated which of the vibrissae provided the main input to each of the microelectrodes by observing the responses evoked to manual stimulation of individual vibrissae. This estimation then was verified by measuring the latencies of responses to controlled stimulation of individual vibrissae. This was accomplished by means of a chamber that was attached to the end of the air-delivery system. This chamber enclosed a single vibrissa and shunted the expelled air away from other vibrissae. Using this selective stimulation, the ''principle whisker'' (PW) for each microelectrode was defined as that whisker that yielded responses at latencies of <7.5 ms. These latencies are considered to be mediated by monosynaptic VB input (Swadlow 1995) (preceding text). All electrodes that generated such responses from the same PW were considered to be in the same barrel column. In most cases, stimulation of only a single whisker elicited these responses, but in a few cases, two neighboring whiskers elicited short-latency responses. These electrode sites were believed to be at the border of two barrel columns. The PW for each electrode was tested at several sites as the electrode was lowered to be sure that the electrode had not entered a new barrel column.

Cross-correlation analyses

Cross-correlograms (CCGs) were implemented on an off-line analysis program (DataWave Technologies). Correlations were compiled from both spontaneous and stimulus-induced activity. Stimulus induced correlations (the shift predictor) (Aertsen et al. 1989; Gerstein and Perkel 1972; Perkel et al. 1967) were subtracted from the raw CCG using a linear shift procedure. The shift predictor was an average of two CCGs obtained by pairing data records from one of the neurons under study with records from the second neuron that had been shifted by one and two trials. This average was subtracted from the raw CCG to obtain the residual record not attributable to the stimulus. One cortical neuron was arbitrarily assigned as reference neuron, and spikes of this neuron (occurrence at *time 0*) were related to spikes of the second neuron. In most cases, air-puff stimuli were delivered at 1/s, and >4,000 spikes were collected from each of the neurons under study. When time permitted, second independent data set was collected and repeat reliability of CCGs was ascertained.

Shift-corrected CCGs initially were constructed using a binwidth of 1 ms. CCGs showing sharp peaks were analyzed further using a binwidth of 0.2 ms. Such high-resolution CCGs were used to determine the time of the peak in the CCG and determine the duration of the peak.

Measures of the amplitude and time course of sharply synchronous and broadly synchronous activity

The topography of many of the shift-corrected CCGs considered here is suggestive of a sharp peak (sharp synchrony, centered at 0 delay) that is superimposed on a much broader peak (broad synchrony). An index of the amplitude of these two types of synchronous response was obtained for each neuron pair using shift-corrected CCGs with a binwidth of 1 ms.

SHARP SYNCHRONY. The total number of spikes occurring in the central 2 ms of the CCG (±1 ms around 0 delay) was first obtained. This value was divided by the total number of spikes occurring in each of the two neurons. This procedure yielded two ratios, and the mean of these two ratios was obtained. This obtained value reflected both broadly and sharply synchronous activity. It was necessary, therefore, to subtract from this value an index of the amplitude of broad synchrony (see following text). The value that remained after this subtraction was our index for the amplitude of sharp synchrony for the 2-ms period centered at 0 delay.

BROAD SYNCHRONY. An index for the amplitude of the broad synchrony was calculated by first taking the mean number of spikes in the six bins (1 ms) occurring from −2 to −5 ms and from +2 to +5 ms. This value was divided by the total number of spikes occurring in each of the two neurons. This yielded two ratios, and the mean of these two ratios was obtained. This value was an index of broadly synchronous activity for the 1 ms periods near 0. This value then was doubled [because the index of sharp synchrony (preceding text) reflects a 2-ms period] and served as our index of the amplitude of broad synchrony.

The time course of sharp synchrony was determined by compiling CCGs at a 0.2-ms binwidth and noting the time (before and after *time 0*) when the sharply synchronous response decreased to half its maximal value (half-amplitude response). An similar index of the time course of the broad synchrony (half-amplitude response) was obtained by compiling CCGs with a 1-ms binwidth.

Intracellular analysis

Intracellular recordings were obtained from fully awake rabbits that were prepared for chronic experiments in a manner identical to that described earlier. As described in preceding text, stimulating electrodes were implanted permanently within and above VB thalamus, and a recordings were obtained through a small entrance in the skull (~1 mm diam). For the intracellular experiments, however, recordings were obtained through a small opening (~0.3 mm diam) that was teased in the dura after application of a drop of lidocaine. Most electrodes that yielded successful recordings had a DC resistance of 60–100 MΩ. Recordings were obtained using an Axoclamp 2A amplifier.

Additional experimental manipulations

One experimental strategy was to eliminate peripheral input from the principal vibrissae of SINtc pairs showing sharply synchronous responses. To do this, we first mapped the region of S1 to be studied subsequently and determined the principal vibrissae (see preceding text). Before subsequent multi-electrode experiments, we inserted a 27-gauge syringe needle into the base of this vibrissa, and it was led to a syringe filled with lidocaine (2%) via a length of polyethylene tubing. The subsequent experimental procedure was to first find a pair of SINstc that demonstrated sharply synchronous responses. Next, the base of the vibrissae was anesthetized, and the SINtc pair was again tested for synchrony. The efficacy of the anesthesia was demonstrated by the elimination of the short-latency response to stimulation of the vibrissae.

In a few recording sessions, general anesthesia was induced to see if the sharply synchronous activity was reduced or eliminated. This was accomplished by cannulating an ear vein before the experiment and infusing Brevital sodium after initial study of the SINtc pair. An initial dose of 5 mg/kg was followed by doses of 1 mg/kg every 5 min for a 15- to 20-min period. Responses to air-puff

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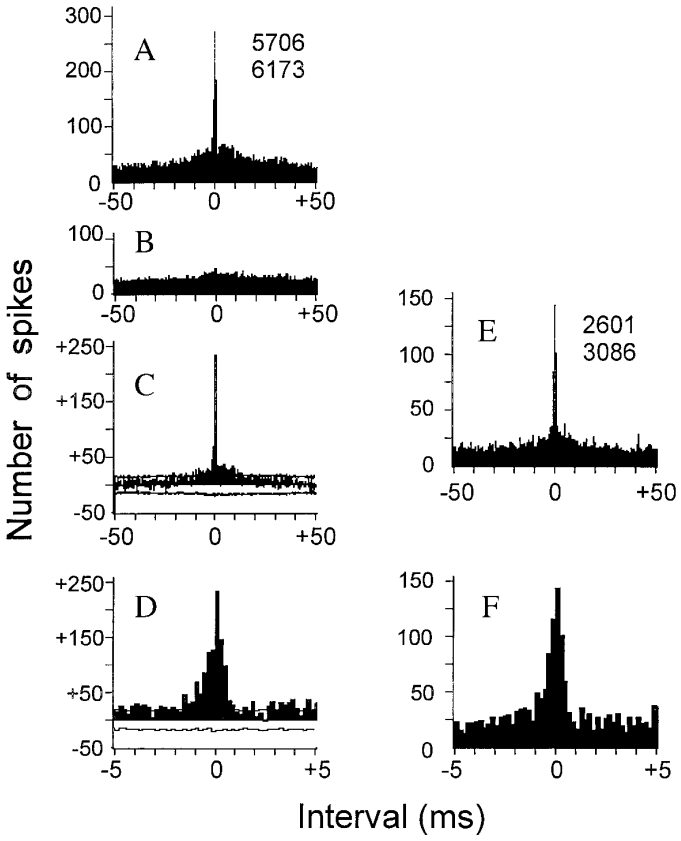

FIG. 1. Cross-correlogram (CCG) of the spike trains of two thalamocortical suspected inhibitory interneuron (SINstc) located within the same barrel column. Data presented in *A–D* were collected under stimulus conditions. *A–C* show the raw (*A*), shifted (*B*), and shift-corrected (*C*) CCGs, and *D* shows the same CCG presented in *C* but at an expanded time scale. *E*: data from the same 2 SINstc but collected in the absence of any peripheral stimulation. *F*: same CCG presented in *E* but at an expanded time scale. Note the similarity between the CCGs presented in *A* and in *E* and between *D* and *F*. All CCGs have a bin with of 0.2 ms. Numbers in *top right* of *A* and *E* indicate the number of spikes collected from the 2 SINstc. Envelope lines *above* and *below* the histograms in *C* and *D* (and in all shift-corrected CCGs presented in figure legends) represent confidence intervals ($P = 0.01$).

stimulation of the cornea were monitored to asses the effects of the anesthetic.

RESULTS

Extracellular recordings were obtained from S1 of four rabbits, and intracellular recordings were obtained from a single rabbit.

Sharp synchrony and broad synchrony between S1 SINs

Thirty-four pairs of SINstc were studied with both members of each pair located within the same S1 barrel column. Figure 1 shows the raw (Fig. 1*A*), shifted (Fig. 1*B*), and shift-corrected (Fig. 1*C*) CCG for one such pair. Sharply synchronous activity occurred at delays of near zero. This sharp synchrony appears to be superimposed on a more broadly synchronous activity (referred to as broad synchrony), lasting ~15 ms before and after each spike. Figure 1*D* shows the same CCG as in Fig. 1*C* but at an expanded time scale. Note that the sharply synchronous activity is centered near *time 0* and lasts ~1 ms (see following text).

Sharp synchrony is not dependent on peripheral stimulation. Figure 1*E* shows, for these same two SINstc, a CCG compiled from a separate data set obtained during a period of ''spontaneous'' activity. Note that the shape of the peak and time course of this CCG taken in the absence of any peripheral stimulation is nearly identical to that of the CCG compiled under stimulus conditions. Figure 1*F* shows this same CCG at an expanded time scale.

Figure 2 shows, for three additional intrabarrel column pairs of SINstc, the raw (Fig. 2, *A1–C1*), shifted (Fig. 2, *A2–C2*), and shift-corrected (Fig. 2, *A3–C3*) CCGs. The latter three CCGs are shown in Fig. 2, *A4–C4*, at an expanded time scale. Members of each pair were recorded via separate microelectrodes that were separated by 200–350 μm. For each of the neurons shown here, a sharp rise in spike probability was seen within 1 ms of an action potential in the paired neuron.

Controls for spurious sharp synchrony

Because sharply synchronous activity could be an artifact of occasional action potentials (or electrical artifacts) sampled by both microelectrode, great care was taken to eliminate these possibilities (see METHODS). Figure 3*A* illustrates two of the procedures used to control for such possibilities for the SIN pair presented in Fig. 2*A*. Figure 3, *A1a* and *A2a*, shows the interspike interval (ISI) distributions of the two neurons that generated the CCGs shown in Fig. 2, *A1–A4*. Interspike intervals as short as 1.3 ms are seen, but none are seen at values of 0.7–1.2 ms. A second method, shown to the right of these ISI histograms, compares the waveforms of synchronous versus nonsynchronous spikes (see METHODS). Synchronous spikes (those occurring at 0″ delay ± 1 ms) for these two cells are shown in Fig. 3, *A1b* and *A2b*, and nonsynchronous spikes (those occurring at delays of >10 ms) are shown in Fig. 3, *A1c* and *A2c*. Note that these two cells have somewhat different spike waveforms (compare Fig. 3, *A1b* with *A2b*). However, for each cell, synchronous and nonsynchronous spikes have identical waveforms (compare Fig. 3, *A1b* with *A1c* and *A2b* with *A2c*). Figure 3, *B* and *C*, shows the ISI distributions and spike wave-forms for the SIN pairs presented in Fig. 2, *B* and *C*, respectively.

Sharp synchrony is seen between SINstc of the same barrel column

Each of the CCGs presented in Figs. 1 and 2 were obtained from a pair of SINs, each of which received monosynaptic VB input (i.e., they were SINstc). In addition, each pair was located within the same physiologically defined S1 barrel column. Figure 4 shows a histogram of the magnitude of the sharp synchrony seen in the CCGs of 34 SINtc pairs located within the same S1 barrel column. Note that all pairs showed some sharp synchrony (mean value = 4.26%, minimum value = 1.3%).

In contrast to the above finding, little or no sharp synchrony was seen between pairs of CF-5 neurons or between

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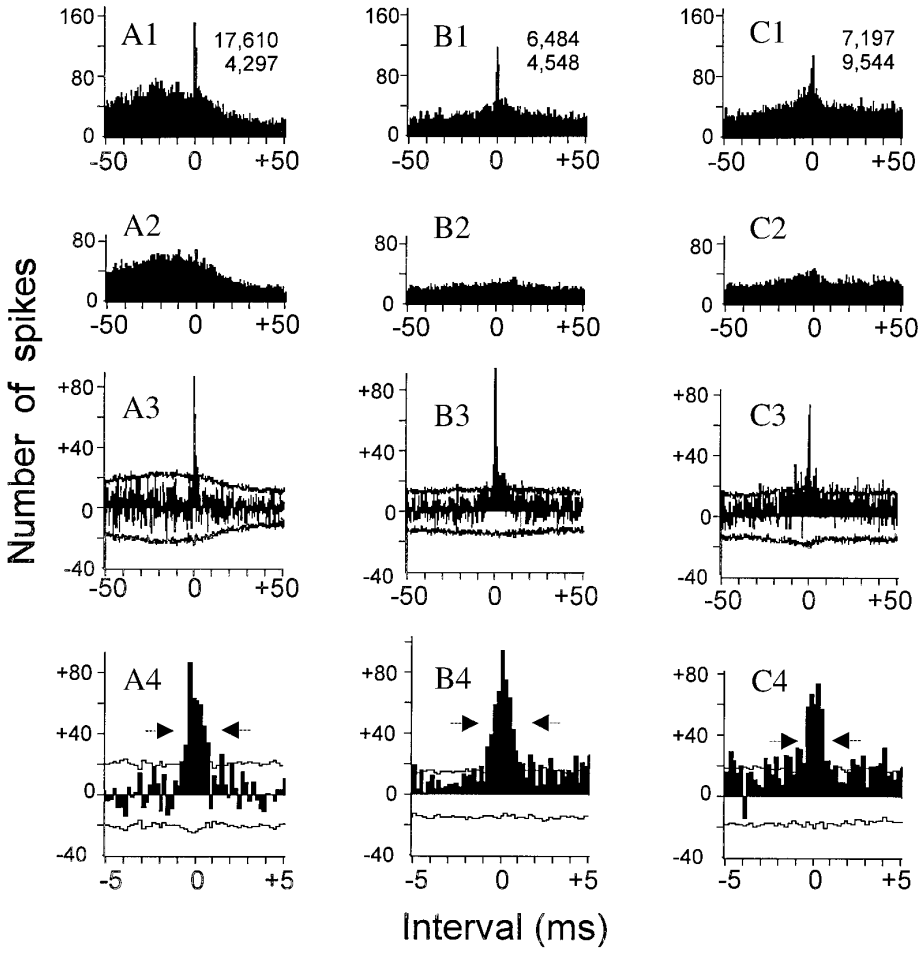

FIG. 2. CCGs of the spike trains of 3 pairs of SINstc located within the same barrel column and collected under stimulus conditions. Raw CCGs (*A1–C1*), shifted CCGs (*A2–C2*) and shift-corrected CCGs (*A3–C3*) are shown. *A4–C4* show the same CCGs shown in *A3–C3* but at an expanded time base. All CCGs have a bin with of 0.2 ms. →, in *A4–C4* indicate half-amplitude response. Calculated values for ''sharp'' synchrony for the 3 pairs shown in *A–C* were 5.7, 7.4, and 3.8%, respectively. Calculated values for ''broad'' synchrony in these 3 cells was 0.1, 2.2, and 2.0%, respectively.

CF-5 neurons and any other class of neuron (including SINs) of the same or different barrel columns. Figure 5*A* shows a shift-corrected CCG obtained from a SIN and a CF-5 neuron located within the same barrel column. Here, one of the SINstc shown in the CCG of Fig. 2*A* is now paired with a CF-5 neuron located within the same barrel column. No sharp synchrony is seen. Similarly, no sharp synchrony is seen when CF-5 neurons are paired with other CF-5 neurons within the same barrel column (Fig. 5, *B* and *C*) or when CF-5 neurons are paired with unidentified neurons which do not respond synaptically to VB stimulation (nonactivated units, NAUs, Fig. 5*D*). Figure 6 shows mean values of sharp synchrony (filled histogram) and broad synchrony (open histogram) found for SINs, CF-5 neurons, and for NAUs tested against other cell types. Note that sharp synchrony is nearly exclusively seen between SINstc.

Temporal characteristics of synchrony among SINs

Figure 7*A* shows a histogram of half-amplitude responses of the sharp synchrony seen in the 24 SIN-SIN pairs where the amplitude of sharp synchrony exceeded 3% (Fig. 4). The mean half-amplitude response for these pairs is 1.07 ms. Figure 7*B* shows the half-amplitude response duration for broadly synchronous responses that exceeded a amplitude of 1%. The mean half-amplitude response for these pairs is 37 ms.

Although most peaks in CCGs were seen at near-zero delay, variations in the delays were seen. The displacement of the peaks in the CCGs seen in the SINtc pairs was related loosely but significantly to different minimal latencies of these cells to synaptic activation after electrical stimulation of VB thalamus (at 5 times threshold intensities). Figure 7*C* shows the relationship for each SINtc pair that showed a sharp synchrony of $>3\%$ ($P = 0.0006$).

Spatial characteristics of synchrony among SINs

Sharp synchrony was observed nearly exclusively in pairs of SINtc located within the same physiologically defined barrel column. Figure 8, *top*, shows for pairs of SINstc the mean amplitude values for sharp (filled histogram) and broad (open histogram) synchrony when the pairs were found in the same barrel column *(left)* in adjacent barrel columns *(center)* or at a distance of two to four barrel columns *(right)*. Note that whereas sharp synchrony shows a precipitous decrease in amplitude when pairs are compared from the same versus neighboring barrel columns, broad synchrony is less influenced by this variable.

Figure 8*B* shows, for pairs of SINstc located in the same barrel column (solid circles) or adjacent barrel columns (open squares), the relationship between the estimated hori-

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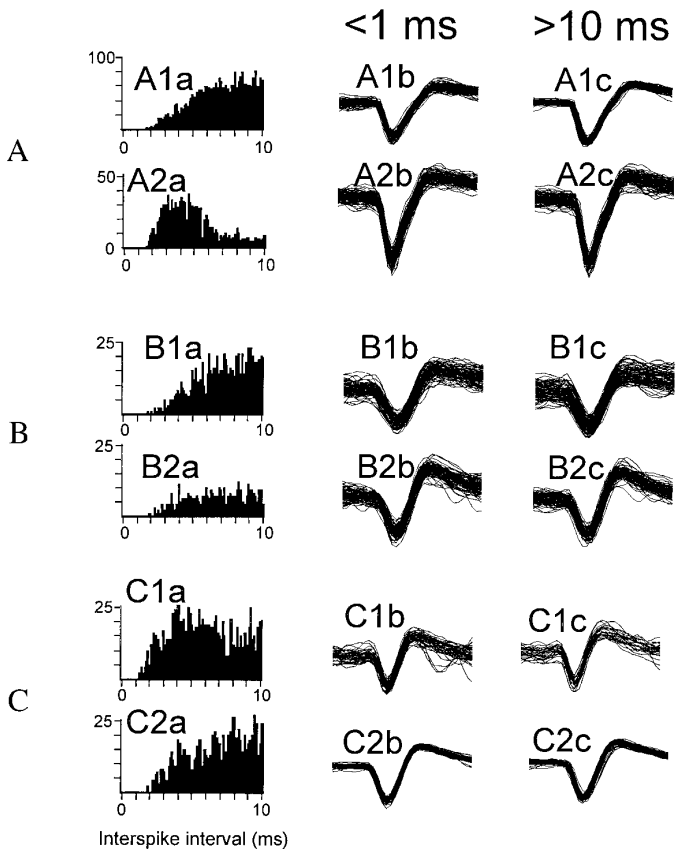

FIG. 3. Controls for spurious synchrony. Data presented in *A–C* are from the same SINtc pairs presented in Fig. 2, *A–C*, respectively. *A1a* and *A2a*: interspike interval distributions from the SINtc pair shown in Fig. 2*A*. *A1b* and *A2b*: 100 superimposed action potentials from each member of this pair that were sharply synchronous (±1 ms). *A1c* and *A2c*: 100 nonsynchronous action potentials (delay >10 ms) from this same pair. Entire sweep duration for each sweep = 1 ms. *B* and *C*: same data presented from the 2 SINtc pairs presented in Fig. 2, *B* and *C*, respectively.

zontal distance between the microelectrode tips[5] and the magnitude of the sharp synchrony. Note that for SINstc located within the same barrel column, there is a loose but significant relationship between electrode distance and the amplitude of sharp synchrony (linear regression, $P = 0.008$). In addition, it is clear that although many pairs of SINstc located in *neighboring* barrel columns were found at electrode separations of <400 μm (distances similar to those seen in some SINstc recorded from the same barrel column), this proximity had little effect on the amplitude of sharp synchrony when SINs were located in different barrel columns.

Sharp synchrony between SINstc is not dependent upon activation of the receptor periphery

SINstc of a single barrel that exhibit sharply synchronous activity receive a potent monosynaptic VB input and are

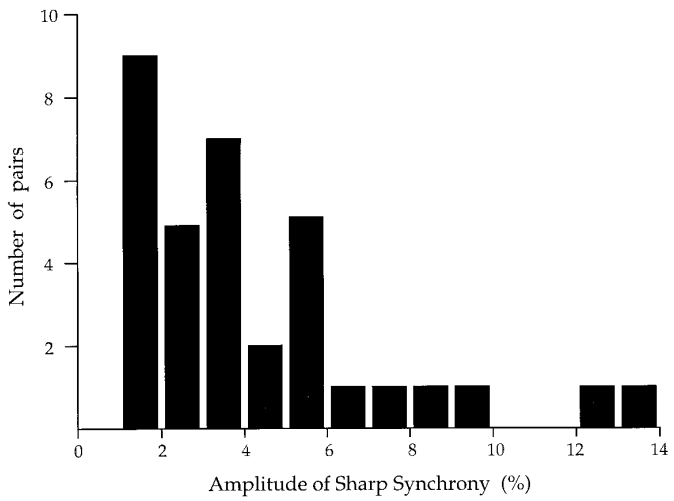

FIG. 4. Amplitude of sharp synchrony for pairs of SINstc located within the same barrel column.

dominated by the same vibrissa (see preceding text). Stimulation of this vibrissa, therefore, would be expected to generate highly synchronous activity among these cells. This stimulation may be delivered by the experimenter or it could be uncontrolled, resulting from respiration, heart beat, self-generated movements, or even a gentle breeze in the laboratory (see e.g., Hamm et al. 1985; Kirkwood 1979). Although the shift-corrected CCGs used here eliminate the effects of controlled stimulation (Perkel et al. 1967), this procedures is of no help if stimulation is uncontrolled. Similarly, CCGs compiled during spontaneous impulse activity also are subject to such effects. We therefore examined this question directly by anesthetizing the receptor periphery of four pairs of SINstc. The members of each pair were located physiologically within the same barrel column, and each pair demonstrated sharp synchrony. After recording a data set under control conditions, lidocaine was injected into the base of the whisker follicle that provided the dominant input to each

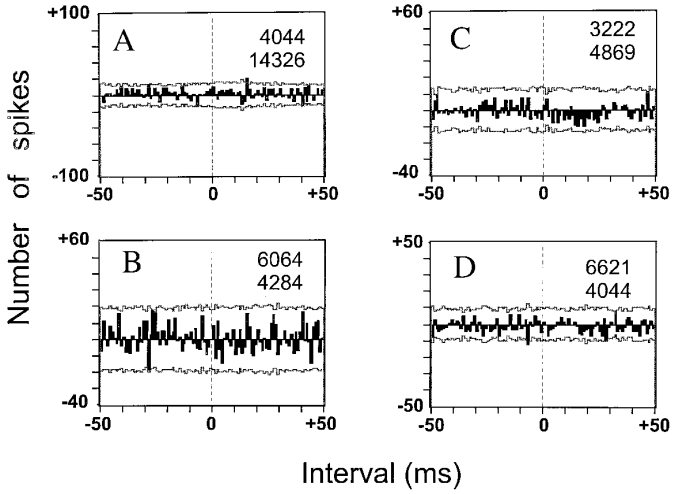

FIG. 5. Shift-corrected CCGs obtained from 4 neuron pairs composed of a SINtc and a CF-5 neuron *(A)*, 2 CF-5 neurons (*B* and *C*), and a CF-5 neuron paired with an unidentified neuron that does not respond synaptically to ventrobasal (VB) stimulation. Both neurons in each pair were located within the same barrel column.

[5] It is not possible to precisely measure the distance between the cells under study. Although the quartz glass-platinum fibers used here are quite stiff, some displacement is inevitable. In addition, action potentials may be recorded at considerable distances from an electrode tip (e.g., Hentall et al. 1984; Stoney et al. 1968).

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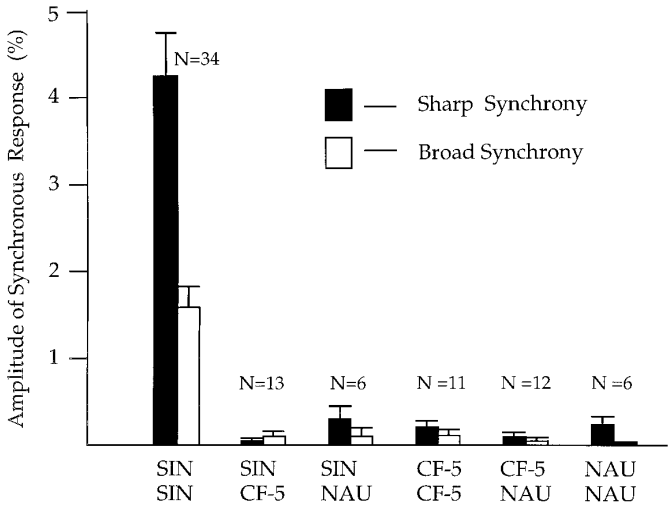

FIG. 6. Amplitude of sharp synchrony and broad synchrony for neuron pairs of different types located within the same barrel column. Number of pairs for each type studied is given *above* the bars. Error bars indicate the standard error of the mean.

SINtc pair. Figure 9*A1* shows a CCG indicating sharply synchronous activity between two SINstc of the same barrel column. Figure 9*A*, *2* and *3*, shows poststimulus histograms of the responses of these SINstc to peripheral stimulation. Each cell responded at a latency of <7 ms to this stimulus. Figure 9*B1* shows the CCGs after local anesthetic (lidocaine) delivered to the base of the principle vibrissae. This manipulation has little effect on the sharply synchronous

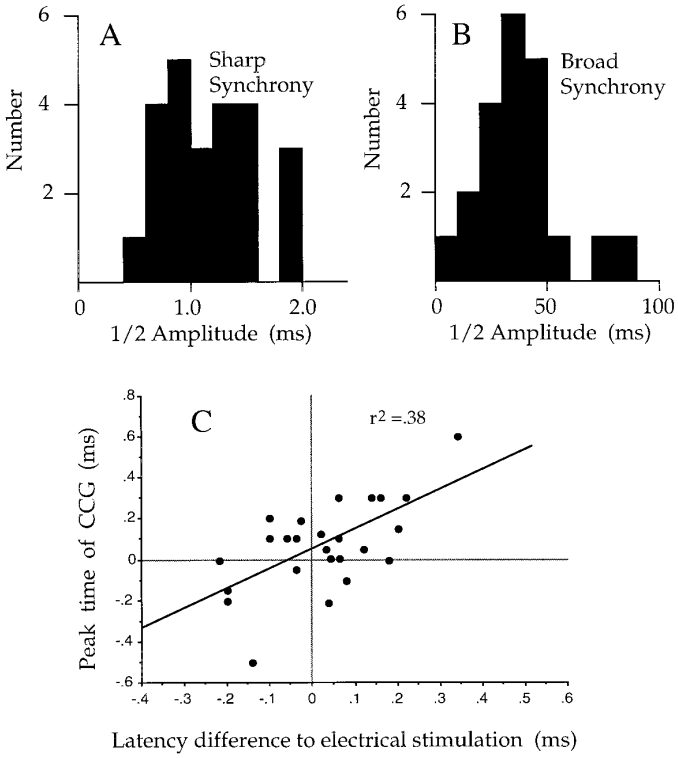

FIG. 7. Duration of sharp synchrony *(A)* and broad synchrony *(B)* at half-amplitude. *C*: relationship, for pairs of SINtc located in the same barrel column, between the time of the peak in the CCG and the difference in the latency of the 2 SINstc to electrical stimulation of VB thalamus.

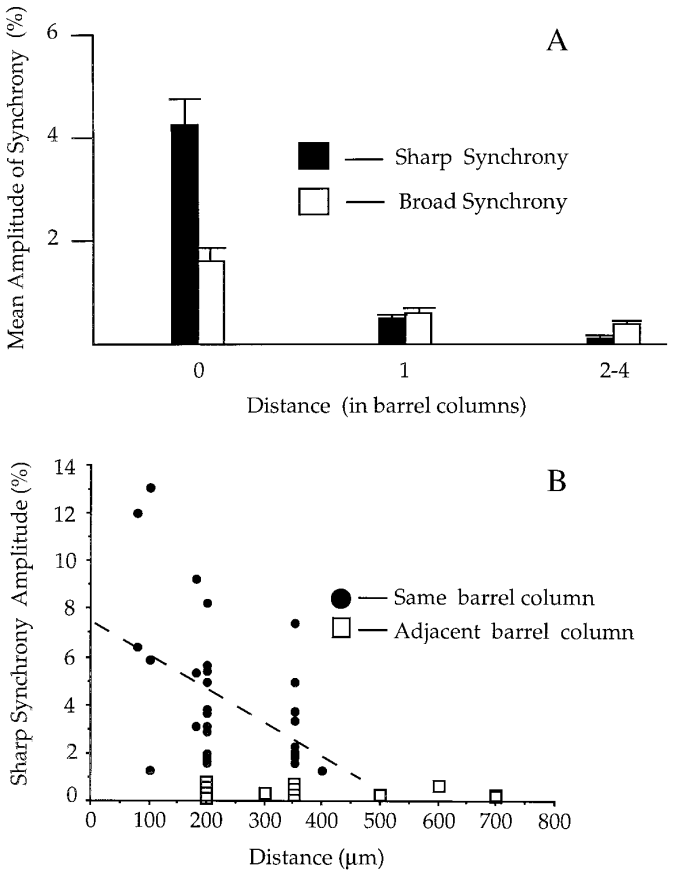

FIG. 8. *A*: amplitude of sharp synchrony and broad synchrony for SINstc when pair members are located in the same physiologically defined barrel column (*left*, $n = 34$), in adjacent barrel columns (*center*, $n = 12$), or at a separation of 2–4 barrel columns (*right*, $n = 9$). Error bars represent standard error of the mean. *B*: for pairs of SINstc located within the same or adjacent barrel columns, the relationship between the estimated horizontal distance between the microelectrode tips and the magnitude of the sharp synchrony. Dashed line, simple linear regression of amplitude of sharp synchrony vs. distance for SINtc pairs located within the same barrel column ($r^2 = 0.2$, $P = 0.008$).

activity (the peak of the CCG), although it did eliminate the short-latency response (<10 ms) to peripheral stimulation (Fig. 9*B*, *2* and *3*). Similar results were obtained from three additional SINtc pairs tested in this manner.

Sharp synchrony between SINstc is not oscillatory

Intrabarrel oscillations in cortical excitability could account for the observed sharp synchrony among S1 SINstc. Because sharp synchrony is restricted to single barrel columns, the effects of such oscillations also would be limited necessarily to a single barrel column. However, examination of two types of autocorrelograms indicate that sharp synchrony is not oscillatory.

AUTOCORRELOGRAMS OF SPIKE TRAINS OF INDIVIDUAL SINSTC ARE NOT OSCILLATORY. Figure 10, *A1–C1* presents three high-resolution (0.2-ms binwidth) CCGs of intrabarrel SINtc pairs that each showed a high degree of sharp synchrony. Note the short time scale and that no stimuli were delivered during collection of these data. Below each of these CCGs are autocorrelograms obtained from the two

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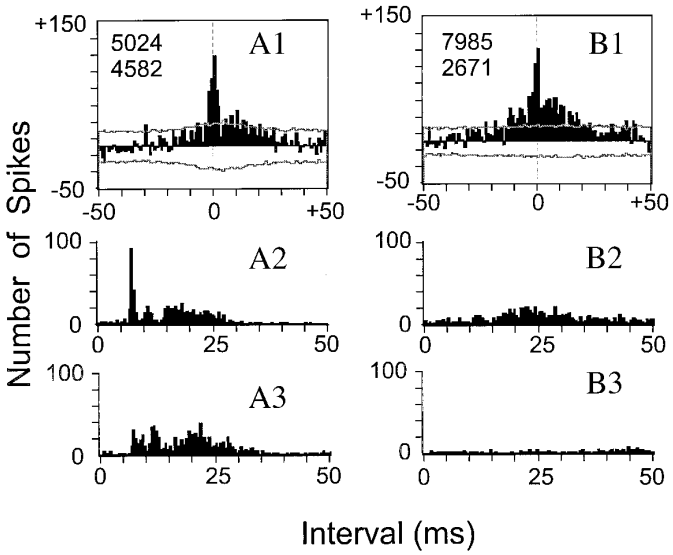

FIG. 9. Experiment showing that sharp synchrony between intrabarrel SINstc is not eliminated by anesthetizing the receptor periphery. *A1*: control shift-corrected CCG showing sharp synchrony between 2 intra-barrel SINstc. *A2* and *A3*: poststimulus time histograms of response of the 2 SINstc to peripheral stimulation. *B1*: a 2nd shift-corrected CCG between the same 2 SINstc as in *A1* but after injection of lidocaine into the base of the principal vibrissa. Note that the sharply synchronous response remains intact. *B2* and *B3*: poststimulus time histogram of the response of these 2 SINstc to the same stimulus delivered in *A2* and *A3* but after the delivery of the anesthetic. Short-latency responses are totally absent. Stimuli were presented at a rate of 1/s, binwidth = 1 ms.

SINstc in each pair (Fig. 10, *A2* and *A3*, *B2* and *B3*, and *C2* and *C3* for the CCGs in *A1–C1*, respectively). Oscillatory activity would be indicated by repeating periodic side bands (on each side of *time 0*), at a period consistent with the frequency of oscillation (cf. Eckhorn 1994). There is little sign of oscillatory activity in any of these autocorrelograms. Similar data were obtained from 20 additional SINstc that were studied under conditions of periodic stimulation. No oscillatory behavior was observed in the autocorrelograms of 15 of these cells, but the remaining 5 showed a single secondary peak, indicating a period of 80–100 ms. This component, however, was attributed to the secondary discharge (postinhibitory ''rebound'') resulting from the air-puff stimulation. This secondary peak in the autocorrelogram was eliminated by the use of the shift predictor (Perkel et al. 1967).

AUTOCORRELOGRAMS OF SHARPLY SYNCHRONOUS EVENTS ARE NOT OSCILLATORY. Although the spike trains of individual SINtc show no signs of oscillatory behavior, the *synchronous events* still might be oscillatory. To examine this question, the moments of sharply synchronous events (±1 ms) between two SINstc were detected, and these synchronous events then were subject to autocorrelation analysis. Figure 10, *A4–C4*, shows the autocorrelograms of such synchronous events for the three pairs presented in *A1–A3*, *B1–B3*, and *C1–C3*, respectively. Note that there are no signs of oscillatory behavior. A similar lack of oscillatory behavior was seen in autocorrelograms of the moments of synchronous events between 10 additional SINtc pairs.

Sharp synchrony among SINstc is not dependent upon an awake state

Figure 11, *A* and *B*, presents CCGs compiled from the spike trains of two SINstc of a single barrel column both before (Fig. 11*A*) and after (Fig. 11*B*) intravenous injection of Brevital sodium. Although the prestimulus firing rates of these two cells each decreased to <20% of their values in the awake state (Fig. 11*C*), little effect was seen on the sharply synchronous response (however, to generate similar numbers of spikes for compilation of CCGs, a greater number of stimulus presentations were required in Fig. 11*B* than were delivered in Fig. 11*A*). Very similar results were obtained from two additional pairs of SINstc studied both in the awake and anesthetized state.

Additional characteristics of SINs showing sharp synchrony

Figure 12*A* shows a histogram comparing action potential duration of SINstc and CF-5 neurons recorded within the same microelectrode penetrations. Note that SINstc (mean = 0.54 ms) have considerably shorter action potentials than do CF-5 neurons (mean = 0.91 ms, $P = < 0.0001$, Student's *t*-test). The histograms of Fig. 12*B* compare the relative depth at which SINstc and CF-5 neurons were found. Although there is some overlap in the distributions, SINstc (mean = 48.5) were found somewhat more superficially than were CF-5 neurons (mean = 63.7, $P = < 0.0001$, Student's *t*-test).

Intracellular recording from SINstc

Intracellular recordings were obtained from three SINs, which were studied in the fully awake state for periods of

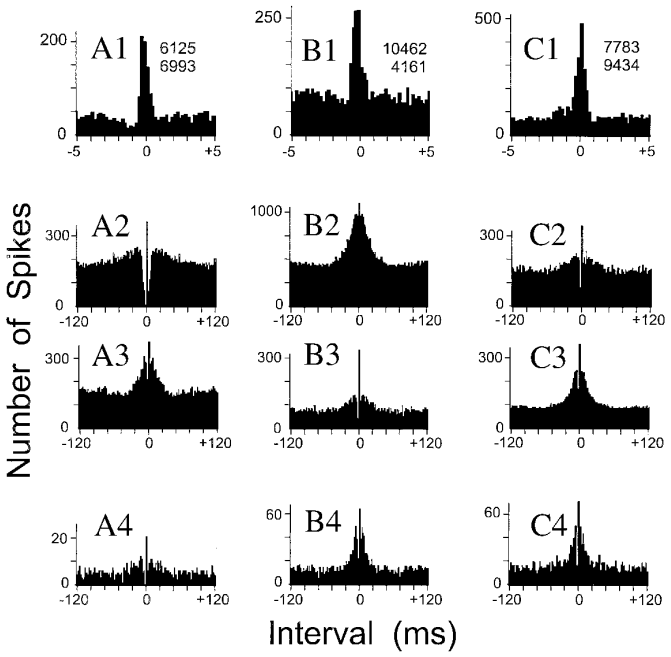

FIG. 10. *A1–C1*: CCGs of spike trains of 3 SINtc pairs, each showing a high degree of sharp synchrony. Bin width = 0.2 ms. *A2–A3*, *B2–B3*, and *C2–C3* show autocorrelograms of the spike trains of the SINstc studied in *A1*, *B1*, and *C1*, respectively. Bin width = 1 ms. *A4–C4*: autocorrelograms of the synchronous events (±1 ms) that form the peak of the CCGs shown in *A1–C1*, respectively. Bin width = 1 ms.

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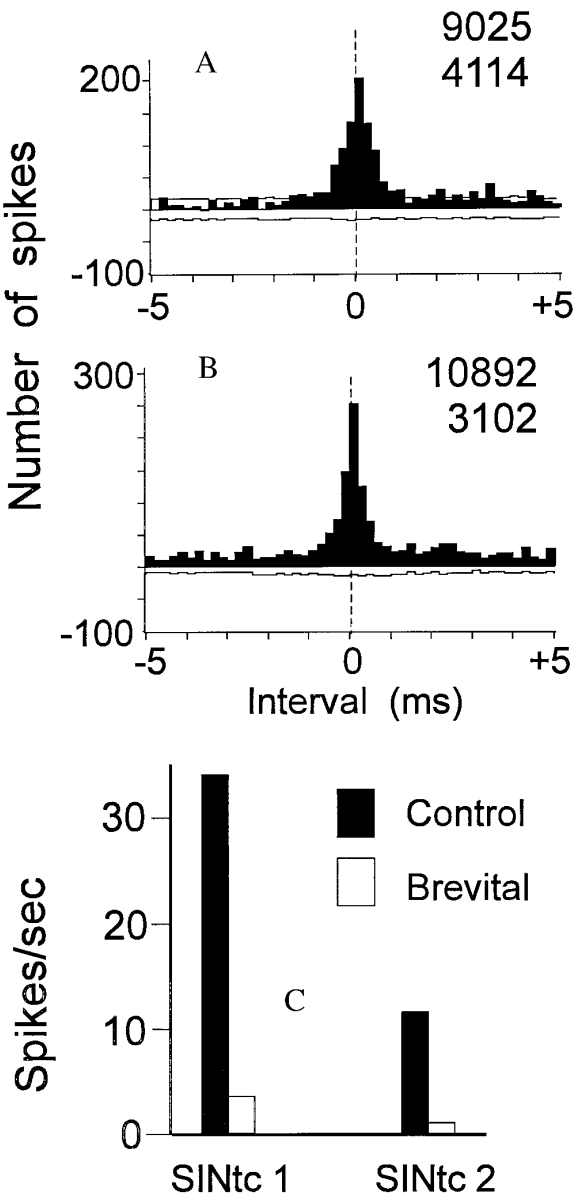

FIG. 11. General anesthesia has little effect on sharp synchrony between intrabarrel SINstc. Shift-corrected CCGs from two SINstc taken before *(A)* and after *(B)* administration of Brevital sodium anesthesia. Stimuli were presented at a rate of 1/s, binwidth = 0.2 ms. *C*: mean prestimulus firing rate (200 ms before each stimulus) of each member of these pairs both before (■) and after (□) administration of the anesthetic.

4, 10, and 12 min. Each of these three cells responded to thalamic stimulation with a burst of three or more spikes at minimal interspike intervals of <1.67 ms. Thus they each met our criteria for identification as a SIN (METHODS). Each of these cells responded to a depolarizing current pulse (0.8–1.2 nA) with a nonadapting, high-frequency (>300 Hz) response. In addition, each of these cells had a brief spike duration (<0.5 ms at half-amplitude) and showed a brief afterhyperpolarization. Figure 13*A* shows that the response of one of these cells to electrical stimulation of VB thalamus (5 times threshold intensity) consisted of three spikes, at a minimal interspike interval of 1.5 ms. Figure 13*B* shows the nonadapting response of this cell to a depolarizing current pulse (1 nA). Figure 13*C* shows a measure of the nonadapting responses seen in this SIN to a depolarizing current pulse. Here, interspike interval is plotted versus the order of the interval in the sequence elicited. It is clear that the current pulse elicits action potentials at a very high-frequency and that there is little frequency adaptation.

DISCUSSION

SINs and other cortical cell classes studied

SINs were identified by a high-frequency burst of three or more spikes to thalamic stimulation and also were shown to have action potentials of short duration. Support for the notion that these properties are characteristic of inhibitory interneurons has come from several sources (Ashwood et al. 1984; Connors and Kriegstein 1986; Eccles et al. 1954; Kawaguchi 1993; Kawaguchi and Kubota 1993; Knowles and Schwartzkroin 1981; McCormick et al. 1985; Satou et al. 1983). These neurons have been shown to have a smooth or sparsely spinous dendritic morphology that stains positively for glutamic acid decarboxylase (Kawaguchi 1993; McCormick et al. 1985) and the calcium-binding protein parvalbumin (Kawaguchi and Kubota 1993).

The hypothesis that SINs, as defined and studied here in the awake state, are GABAergic inhibitory interneurons gains considerable support from the present intracellular analysis. Thus three neurons were impaled that met our criteria for classification as a SIN [a high-frequency (>600 Hz) burst of 3+ spikes to VB stimulation] and had action poten-

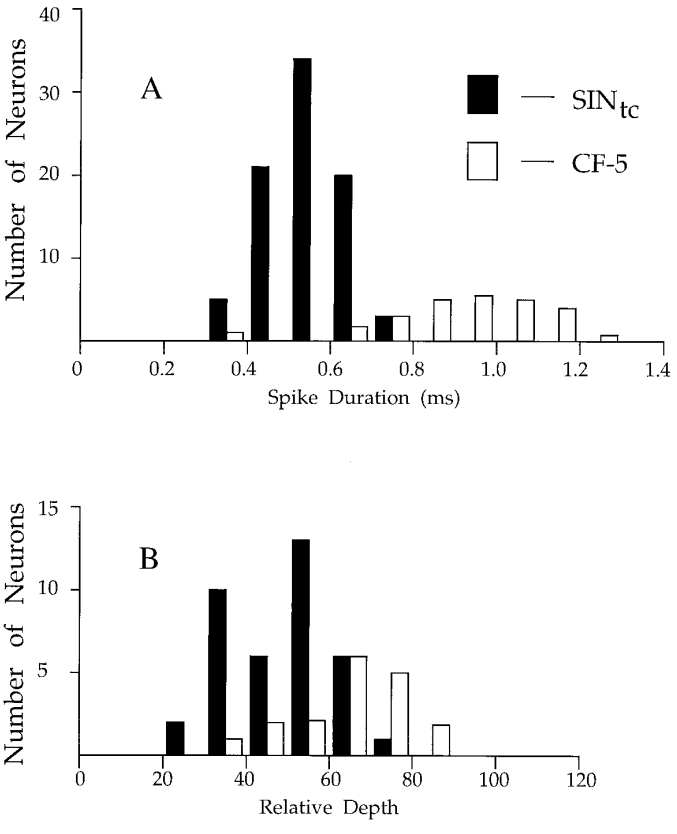

FIG. 12. Spike duration *(A)* and relative depth *(B)* of SINstc and corticofugal neurons studied here.

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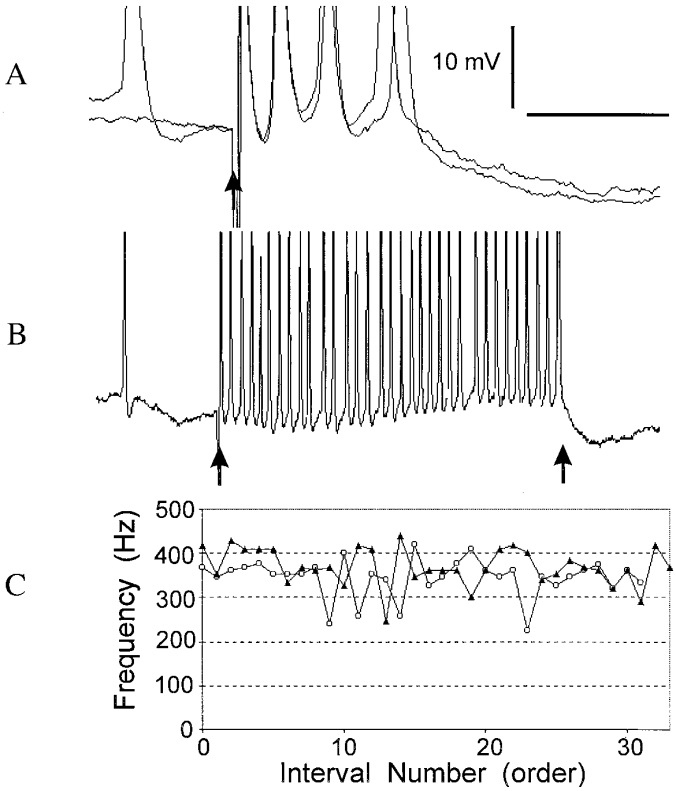

FIG. 13. *A*: intracellular record obtained from a SINtc in the awake state (2 superimpositions). This cell responds to VB stimulation (→) with a burst of 3 spikes (spikes truncated) at minimal interspike intervals of 1.6 ms (>600 Hz). *B*: nonadapting, high-frequency response of this cell to a depolarizing current pulse (→, onset and offset) of 1 nA. Horizontal cal bar = 5 ms in *A*, 40 ms in *B*. Vertical cal bar = 10 mV in *A*, 20 mV in *B*. *C*: for spikes elicited by a 100-ms depolarizing current pulse (1 nA), interspike interval is plotted vs. the order of the interval in the sequence.

tials of short duration. Each of these three cells (and *only* these cells of >30 neurons studied intracellularly) responded to a depolarizing current pulse with a nonadapting, high-frequency train of action potentials. Although we did not inject these cells with an intracellular dye, previous studies in which such cells were stained have shown them to be nonpyramidal neurons with the characteristics of GABAergic interneurons (Kawaguchi 1993; Kawaguchi and Kubota 1993; McCormick et al. 1985).[6]

CF-5 neurons represent a second class of cortical neuron studied here. These cells represent a heterogeneous population of antidromically activated descending corticofugal neurons with axons that pass near the stimulating electrodes within the thalamus. The axons of CF-5 neurons may terminate within the thalamus or descend to terminate within a host of subcortical structures (e.g., Jones 1984). CF-5 neurons were chosen for special consideration here for three reasons: they are readily identified by antidromic activation, they have levels of spontaneous and peripherally driven activity that are suitable for cross-correlation analyses (Swadlow 1989, 1990), and each of several methods employed has failed to demonstrate any monosynaptic VB thalamic input to these cells (Swadlow 1996). Thus there is no reason to expect sharply synchronous activity among CF-5 neurons, between CF-5 neurons and SINstc, or between CF-5 neurons and other neuronal classes within a barrel column.

[6] The single exception to this is the recently described ''chattering'' cells of cat visual cortex (Gray and McCormick 1996). These neurons have short spike durations and are capable of generating action potentials at very high frequencies, but they are pyramidal neurons. However, they have been reported only in superficial cortical layers and show marked oscillatory behavior. SINstc, in contrast, are found in and near to layer 4 (Swadlow 1995) and show little or no oscillatory behavior (Fig. 10).

Basis for predicted synchrony among SINstc of the same barrel column

Recent work has suggested (Swadlow 1995) that the synaptic connectivity linking VB barreloid thalamocortical afferents with SINstc of the topographically aligned S1 barrel column approximates a ''complete transmission line'' between successive nodes of a network (Abeles 1991; Griffith 1963), where each member of each node contacts each member of the successive node. The above model was based on results of physiological experiments using cross-correlation and microstimulation, which indicated that a population of individual thalamocortical neurons within a VB barreloid have axons that diverge to provide monosynaptic input to nearly all of the SINstc of the topographically aligned S1 barrel column. This model is consistent with morphological evidence showing that the terminal arbors of individual VB thalamocortical afferents of the rat virtually fill their corresponding S1 barrel (Jensen and Killackey 1987) and with studies showing that thalamocortical synapses account for a substantial proportion of all asymmetric synapses on both the dendrites (3.5–19.5%) and soma (9–67%) of GABAergic neurons within mouse barrels (Keller and White 1987). It is important to note that this model does not maintain that *all* barreloid neurons diverge in the above manner. Only a subset of barreloid neurons with well-defined receptive fields were sampled in the above study (Swadlow 1995), and it is likely that some barreloid neurons have different response properties (Sugitani et al. 1990; cf. DISCUSSION in Land et al. 1995 and Swadlow 1995).

The output of such a complete transmission line may be expected to have certain properties, many of which are demonstrated by S1 SINs. These networks are characterized by a very reliable and sensitive transmission between input and output nodes but at a cost of a decreased ability to discriminate among activity in the individual input elements (Abeles 1991; Griffith 1963). This description is fully consistent with the properties of S-1 SINs. These cells respond to both peripheral sensory stimulation and electrical stimulation of VB thalamus at thresholds that are lower than those of any efferent population, and they reliably follow higher rates of stimulus frequencies (most in excess of 30 Hz) than do efferent neurons (Swadlow 1989). However, they lack the directional selectivity seen in many VB afferents and in most cortical efferent neurons. Similar characteristics are found in ''fast-spike'' neurons (Simons 1978; Simons and Carvell 1989) in barrel cortex of the rat.

Another predictable consequence of a common, highly divergent presynaptic input to a pool of recipient neurons is a degree of sharply synchronous activity in the postsynaptic elements resulting from near-simultaneous EPSPs generated in the recipient neurons. Sears and Stagg (1976) proposed that a ''short-term'' synchrony between motoneurons should

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result from the common presynaptic (group 1a) input to motoneuronal pools serving a common muscle (Mendell and Henneman 1971). Because group 1a monosynaptic discharge of motoneurons occurs during the rise time of depolarization produced by synaptic currents (e.g., Eccles 1957), they proposed that the time course of the synchronous period should be very brief and consistent with the rise time of the EPSP (also see Kirkwood 1979; Knox 1974) A short-term synchrony among intercostal motoneurons indeed was found by cross-correlating the spikes in motoneuron axons found within nerve filaments (Sears and Stagg 1976), and subsequent experiments documented a common depolarization in spinal motoneurons that was concomitant with a spike in any of several motoneuron axons within a nerve filament (Kirkwood and Sears 1978).

The common presynaptic VB input proposed for SINstc of a barrel column (Swadlow 1995) leads to a similar prediction of sharply synchronous activity among these elements. Moreover, several characteristics of fast-spike GABAergic interneurons suggest that they might respond to common input with an even greater degree of synchrony than is seen in motor neurons. *1*) Whereas the input resistances of fast-spike GABAergic interneurons are relatively high and homogeneous (Baranyi et al. 1993; Kawaguchi 1993), motorneurons have widely varying soma sizes and resultant input resistances (Henneman et al. 1965a,b) that may impede synchronous responses to common inputs. *2*) Whereas GABAergic interneurons receive considerable excitatory synaptic input directly on their cell bodies (Keller and White 1987: White 1978, 1979, 1989), which should lead to a potent postsynaptic response, motor neurons receive their excitatory drive over a wide area of their dendritic tree. *3*) Fast-spike GABAergic cells display EPSPs with a rapid rise time (Thomson and Deuchars 1994), and this should result in a more sharply synchronous response (Kirkwood 1979; Sears and Stagg 1976).

Controls for sharp but spurious synchrony

Recordings obtained from closely spaced microelectrodes are subject to a number of errors that can lead to a spurious finding of sharp synchrony. In the present study, sharply synchronous peaks in the CCG are often composed of only 100–400 synchronous events, and relatively few false events may significantly influence these data. It is most important, therefore, to be sure that only one neuron is responsible for all of the spikes in a given record. This is essential because a second element in the record might be generated by *1*) the same neuron being studied on a second electrode; this would lead to a sharp peak in the CCG at near-zero delay, and this could be incorrectly interpreted as sharp synchrony between the two primary cells under study; *2*) a third, unidentified neuron, or an artifact seen in both records. This also would lead to a sharp peak at near-zero delay and could result in an incorrect interpretation; and *3*) a different cell type than the neuron that we have identified. This would lead to false conclusions regarding which cell types show sharp synchrony.

A number of procedures were followed routinely to control for these possibilities. *1*) Only well-isolated neurons were studied. To ensure this, digitized spike wave forms were always saved for off-line analysis. *2*) Active channels were displayed simultaneously and examined to determine if spikes under study via one electrode could be viewed via other electrodes. *3*) Interspike interval distributions always were examined to ensure that interspike intervals were appropriate for the cell type under study. Although CF-5 neurons rarely display interspike intervals of <2 ms, SINs are capable of generating interspike intervals as low as 1.1 ms. Values below this (from 0.7–1.1 ms)[7] were considered indicative of either a second neuron or an artifact in the record.[8] *4*) In control tests, we created falsely synchronous peaks by introducing an electrical artifact into the records of two neurons studied on two separate recording channels. The peaks of CCGs resulting from such artifacts were always very brief, lasting <0.5 ms. Consequently, we examined the rise and fall times of all synchronous peaks at a resolution of 0.1 or 0.2 ms. *5*) Any peaks lasting <0.6 ms were considered suspicious and subject to the following special scrutiny: when synchronous peaks were either very brief (<0.6 ms, see preceding sentence) or very strong ($>5\%$ of all spikes), we identified the synchronous spikes (0 delay $\pm$ 1 ms) and nonsynchronous spikes (delays of >10 ms) of each cell under study. We then examined the spike wave-forms under these two conditions and showed that they were indistinguishable. This test is based on the assumption that action potential wave-form should be independent of synchronous or asynchronous occurrence with action potentials of other neurons.

We believe that the above procedures were sufficient to eliminate the vast majority of spurious spikes from our records. Support for this is derived from the consistency of our findings that sharp synchrony is found only among SINstc of a barrel column. In many cases, a SIN recorded via one electrode showed sharp synchrony with a SIN on a second electrode but not with a CF-5 neuron or other element on that same electrode. If sharp synchrony had resulted from any of the above artifactual considerations, our results would have been much less clear-cut.

Temporal characteristics of synchronous events

Sharp synchrony between pairs of SINstc within a barrel column had a mean duration (half-amplitude) of 1.07 ms and, in some SINtc pairs, was considerably less. This value is quite similar to that reported in motorneurons (Kirkwood et al. 1982b; Sears and Stagg 1976) and more recently in neurons of the lateral geniculate nucleus of the cat (Alonso et al. 1996). In each of these systems, the sharply synchronous activity was attributed to a common presynaptic input. For most SINtc pairs, the peak of the synchronous response occurred at near-0 delays. In some pairs, however, variations of ≤ 0.6 ms were seen, and the value of this delay was

[7] Values of <0.7 ms could not be recorded. Our data-acquisition system digitizes spike data before and after an amplitude threshold crossing, and such crossings that occur at intervals of <0.7 ms are forbidden. This is required to prevent obtaining more than one record from single action potentials with multiple threshold crossings.

[8] Although the interspike interval distribution is a useful tool, it provides necessary but not sufficient assurance that a single neuron is under study. The usefulness of this procedure will depend on the number of spikes contributed by the hidden neuron and the number and interspike interval distribution of spikes contributed by the primary neuron under study.

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correlated significantly with the synaptic latencies of the two SINstc to VB stimulation (Fig. 7*C*). This finding is consistent with the notion that sharp synchrony between SINstc is mediated by the thalamocortical presynaptic network.

Sharp synchrony generally was superimposed on a more broadly synchronous activity with a considerably lower amplitude and a time scale of tens of milliseconds. We do not know the origin of this response but similar broadly synchronous responses have been observed in many systems (e.g., Gochin et al. 1991; Kirkwood et al. 1982a,b; Nowak et al. 1995; Salin and Bullier 1995 for review).

Spatial distribution of synchronous events

Sharply synchronous activity was seen nearly exclusively between SINstc of the same S1 barrel column. When SINstc of neighboring barrel columns were compared, the amplitude of the synchronous response dropped precipitously (Fig. 8*A*), and synchronous responses were almost nonexistent at a distance of two to four barrel columns. Because individual thalamocortical afferents are largely restricted to a single S1 barrel column (Jensen and Killackey 1987), the restriction of sharp synchrony to single barrel columns is a predictable consequence of the presynaptic thalamocortical network proposed to mediate this effect.

A loose, but significant relationship was seen between the amplitude of the sharp synchrony between SINstc of a barrel column and the horizontal distance between the recording electrodes that were monitoring their activity (Fig. 8*B*). This could be due to at least two factors: closely neighboring SINstc may receive more common input from single VB afferents than more distant SINstc of the same barrel column and/or the inputs of single VB neurons to closely neighboring versus distant SINstc of the same barrel column may be identical, but the arrival time of these inputs may be more synchronous in the closer SINstc, and this may facilitate more synchronous responding.

Broadly synchronous responses were most prevalent between SINstc of the same barrel column, but the decrease in this response when SINstc were separated by either one or two to four barrel columns was considerably less than was seen for sharply synchronous responses. The contrasting spatial and temporal gradients of broadly and sharply synchronous responses of SINstc suggest different mechanisms underlying these phenomena (e.g., Gochin et al. 1991; Kirkwood et al. 1982b; Nowak et al. 1995).

Does sharp synchrony occur only among SINs?

Sharply synchronous activity was observed only between SINstc of a barrel column. SINstc showed no sharp synchrony when paired with CF-5 neurons or with unidentified neurons that failed to respond to thalamic stimulation. In addition, CF-5 neurons showed no sharp synchrony with other CF-5 neurons or with the unidentified cells. This lack of synchrony between CF-5 neurons and any other cells is of interest because CF-neurons appear to receive little or no synaptic input via VB thalamocortical afferents (Swadlow 1996). Thus these results are fully consistent with the notion that sharp synchrony between SINstc results from the highly divergent and convergent presynaptic network linking VB barreloids with topographically aligned S1 barrel columns.

The present results do not imply that *only* S1 SINstc show synchronous responses. This investigation was aimed primarily at the analysis of SINstc and CF-5 neurons because the connectivity of these elements with thalamocortical afferents has been studied previously (Swadlow 1995, 1996). In addition, both of these cell types can be identified reliably using electrical stimulation of VB thalamus and both have high levels of spontaneous and evoked activity suitable for the generation of CCGs. We did not examine other classes of efferent neurons in the present study, and we have no means of identifying spiny stellate cells. It is possible, therefore, that some sharp synchrony may be seen among these cells. In this regard, however, we would point out that the high degree of directional selectivity seen in many efferent populations within barrel cortex (Swadlow 1989) suggests that, unlike SINstc, they may receive input from a relatively small subset of VB barreloid neurons (most of which also show a considerable degree of directional selectivity) (Simons and Carvell 1989; Swadlow 1995). Evidence for such selectivity in thalamocortical connectivity based on receptive field properties has been demonstrated in the geniculo-striate system of the cat (Reid and Alonso 1995; Tanaka 1983). Some corticocortical efferent populations do receive a potent monosynaptic thalamic input (Swadlow and Hicks 1996), and corticocortical neurons that have similar directional preference might be expected to show some degree of sharp synchrony. However, this might be difficult to demonstrate using cross-correlation methods because these efferent populations have very low rates of spontaneous and peripherally driven activity (Swadlow 1989, 1990; Swadlow and Hicks 1996).

Is sharp synchrony among SINstc due to common presynaptic thalamocortical input?

The high degree of sharp synchrony among SINstc of the same barrel column provides considerable evidence in support of the divergent and convergent presynaptic thalamocortical network proposed to link VB barreloid neurons with SINstc of the aligned S1 barrel (Swadlow 1995). Other aspects of our results are also highly consistent with the proposed network. *1*) Little or no sharp synchrony was seen between SINstc of neighboring S1 barrel columns. This is expected because individual VB afferents synapse nearly exclusively within individual S1 barrel columns (Jensen and Killackey 1987). *2*) Little or no sharp synchrony was seen between CF-5–CF-5 pairs or SINtc-CF–5 pairs of the same barrel column. This is expected because CF-5 neurons receive little or no direct VB input (Swadlow 1996). *3*) The delay in the synchronous peak was significantly correlated with the synaptic latencies of the two cells to thalamic stimulation (Fig. 7*C*). This is expected if the synchrony is due to thalamocortical inputs.

Control experiments eliminated two potential sources of sharp synchrony other than a common thalamocortical input. *1*) Stimulation of peripheral receptors cannot account for sharp synchrony. We know this because *a*) sharp synchrony is seen when no peripheral stimulation is delivered, and the spike activity of SINstc is spontaneous, and *b*) sharp synchrony among SINstc was little affected by anesthetizing the principal vibrissa and thereby eliminating all short-la-

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tency peripheral input to the SINstc. *2*) Oscillations in cortical excitability cannot account for sharp synchrony. Oscillatory variations in neuronal excitability could generate synchronous activity among cortical neurons (Eckhorn 1994; Gray et al. 1990), and such activity among cortical interneurons has been proposed (Traub et al. 1996). However, to account for the observed sharp synchrony between SINstc, the effects of any hypothetical oscillations in excitability would necessarily be sharply limited in space (because sharp synchrony occurs within-barrel columns only), in time (because sharp synchrony is so brief), and in the neuron classes influenced (because sharp synchrony is seen between SINstc of a barrel column but not between CF-5 neurons and other cell classes that receive little or no monosynaptic VB input). In addition, because barbiturate anesthesia had no effect on sharp synchrony, any hypothetical oscillations necessarily would be insensitive to global state changes. Given these stringent requirements it is, perhaps, not surprising that neither autocorrelograms of the spike trains of SINstc nor autocorrelograms of the moments of synchrony between SINtc pairs revealed evidence of oscillatory activity.

The consistency of the obtained results with a highly divergent and convergent presynaptic network does not preclude the possibility that other mechanisms also might contribute to sharp synchrony among SINstc of the same barrel column. *1*) Although sharp synchrony among SINstc is not dependent on stimulation of the peripheral receptors, synchrony among VB thalamocortical neurons could occur in the absence of peripheral input (Alonso et al. 1997), and this could result in synchrony among cortical neurons. This question can only be answered by obtaining simultaneous recordings from thalamocortical neurons of the same VB thalamic barreloid. *2*) Although spike activity of SINstc and the moments of synchrony between SINstc are not oscillatory, we have not ruled out the possibility that sharp synchrony is dependent on *nonoscillatory* variations in cortical excitability that synchronize all SINstc of a barrel column. This possibility only can be ruled out by recording from three or more SINstc of a barrel column and determining the extent to which moments of synchrony among all pairs within the triad occur together. *3*) These experiments have not eliminated the possibility of a synchrony among SINstc induced by dendritic coupling. However, there is no morphological evidence to suggest dendritic coupling among GABAergic interneurons of barrel cortex (E. L. White, personal communication), and observed synchrony mediated by dendritic coupling occurs over a considerably longer time scale than the sharp synchrony observed here (Ishimatsu and Williams 1996). Nevertheless, we cannot altogether eliminate this possibility.

Sharp synchrony and feed-forward GABAergic inhibition

Potent peripheral stimulation serves to momentarily synchronize large numbers of neurons within a barrel column as a result of synchronous drive from thalamic afferents. However, in the absence of peripheral stimulation, our results show that only SINstc (of the cell classes studied) show sharply synchronous activity and that ~4% of the spikes of each SINtc are sharply synchronous with the spikes of all other SINstc within the same barrel column (Fig. 6*A*). Stimulation of the receptor periphery will, of course, increase the frequency of synchronous events, but these events will not fall below the minimal values described above, even in the absence of peripheral stimulation. Because the axons of GABAergic interneurons of S1 barrels are very short and remain within the barrel (Harris and Woolsey 1983), axonal conduction time will be brief, and synchronous activity among SINstc will result in a corresponding synchronous, feed-forward release of GABA onto postsynaptic targets. It recently has been suggested that precisely correlated activity among thalamic cells may strengthen the excitatory effects of thalamic input to cortical neurons (Alonso et al. 1996). In a similar vein, we suggest that the sharply synchronous release of GABA by SINstc will strengthen, through mechanisms of temporal summation, the inhibitory impact of these neurons on their postsynaptic targets. The summation of inhibitory postsynaptic potentials may be especially effective in suppressing the synaptic targets of SINstc when peripheral stimulation is weak or nonoptimal (cf. Kyriazi and Simons 1993) and provides only asynchronous excitatory inputs to these cortical target neurons.

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Address for reprint requests: H. A. Swadlow, Dept. of Physchology (U-20), The University of Connecticut, Storrs, CT 06269.

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