

Dynamic Interactions Determine Partial Thalamic Quiescence in a Computer Network Model of Spike-and-Wave Seizures

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Lytton, William W., Diego Contreras, Alain Destexhe, and Mircea Steriade. Dynamic interactions determine partial thalamic quiescence in a computer network model of spike-and-wave seizures. *J. Neurophysiol.* 77: 1679–1696, 1997. In vivo intracellular re-recording from cat thalamus and cortex was performed during spontaneous spike-wave seizures characterized by synchronously firing cortical neurons correlated with the electroencephalogram. During these seizures, thalamic reticular (RE) neurons discharged with long spike bursts riding on a depolarization, whereas thalamocortical (TC) neurons were either entrained into the seizures (40%) or were quiescent (60%). During quiescence, TC neurons showed phasic inhibitory postsynaptic potentials (IPSPs) that coincided with paroxysmal depolarizing shifts in the simultaneously recorded cortical neuron. Computer simulations of a reciprocally connected TC-RE pair showed two major modes of TC-RE interaction. In one mode, a mutual oscillation involved direct TC neuron excitation of the RE neuron leading to a burst that fed back an IPSP into the TC neuron, producing a low-threshold spike. In the other, quiescent mode, the TC neuron was subject to stronger coalescing IPSPs. Simulated cortical stimulation could trigger a transition between the two modes. This transition could go in either direction and was dependent on the precise timing of the input. The transition did not always follow the stimulation immediately. A larger, multicolumnar simulation was set up to assess the role of the TC-RE pair in the context of extensive divergence and convergence. The amount of TC neuron spiking generally correlated with the strength of total inhibitory input, but large variations in the amount of spiking could be seen. Evidence for mutual oscillation could be demonstrated by comparing TC neuron firing with that in reciprocally connected RE neurons. An additional mechanism for TC neuron quiescence was assessed with the use of a cooperative model of γ -aminobutyric acid-B (GABA_B)-mediated responses. With this model, RE neurons receiving repeated strong excitatory input produced TC neuron quiescence due to burst-duration-associated augmentation of GABA_B current. We predict the existence of spatial inhomogeneity in apparently generalized spike-wave seizures, involving a center-surround pattern. In the center, intense cortical and RE neuron activity would be associated with TC neuron quiescence. In the surround, less intense hyperpolarization of TC neurons would allow low-threshold spikes to occur. This surround, an “epileptic penumbra,” would be the forefront of the expanding epileptic wave during the process of initial seizure generalization. Therapeutically, we would then predict that agents that reduce TC neuron activity would have a greater effect on seizure onset than on ongoing spike-wave seizures or other thalamic oscillations.

INTRODUCTION

The computer simulations presented here are used to explore possible basic mechanisms underlying an unexpected

finding from intracellular recordings in vivo, namely, that an important proportion of thalamocortical (TC) neurons is quiescent during cortically initiated seizures. These seizures consisted of spike-wave (SW) complexes at 2–4 Hz, sometimes associated with faster activities at 10–15 Hz (Steriade and Contreras 1995). In that previous study, simultaneous impalements of TC and cortical cells performed during paroxysms developing from sleep patterns showed that a large number (60%) of TC neurons displayed a sustained hyperpolarization during the cortical seizure. These hyperpolarizations were associated with repetitive inhibitory postsynaptic potentials (IPSPs) coincident with paroxysmal depolarizations and spike bursts in cortical cells, and with long (200–300 ms) spike bursts in thalamic reticular (RE) cells (Steriade and Contreras 1995). After seizure cessation, TC neurons returned to resting membrane potential.

A major feature in the dynamics of thalamic neurons is the low-threshold Ca²⁺ spike (LTS) that follows a relatively prolonged hyperpolarization (Jahnsen and Llinas 1984a,b). This phenomenon has been shown to be due to the T-type Ca²⁺ channel (Coulter et al. 1989; Crunelli et al. 1989; Hernandez-Cruz and Pape 1989; Suzuki and Rogawski 1989). The T channel can produce intrinsic repetitive bursting in TC neurons (Leresche et al. 1991; McCormick and Pape 1990). Intrinsic bursting also occurs in RE neurons, but the mechanism is somewhat different (Destexhe et al. 1996b; Huguenard and Prince 1992). One minimal circuit that can give rise to coordinated oscillations is a circuit of isolated RE neurons that is effective in producing sleep spindles (Steriade et al. 1987) and whose synchronizing properties have been modeled (Destexhe et al. 1994a,b; Golomb et al. 1994). Corticothalamic projections and connections between TC and RE cells tend to reinforce spindle oscillations (Contreras and Steriade 1996; Destexhe et al. 1993b; Steriade et al. 1972, 1993; von Krosigk et al. 1993; Wang et al. 1995).

The neural activity in epilepsy suggests a high degree of synchrony among populations involved. The extreme activity and adverse outcome seen in status epilepticus may well be manifestations of such high neuronal involvement. Other types of epilepsy are less detrimental. In absence epilepsy, a type of epilepsy that produces SW activity in the thalamus, it is remarkable how rapidly a patient can go from normal cognitive activity to generalized SW complexes and back to cognition, seemingly without skipping a thought. This suggests that many neurons participate in the seizure through

inhibition rather than extreme excitation, leaving them in a better position to resume normal function after ictal cessation. Computer simulation studies have demonstrated that apparent widespread population activity may in some cases be surprisingly sparse. In hippocampal simulations, Traub et al. (1987a,b) have demonstrated that population activity can emerge through the intermittent activation of single neurons whose individual activity was not rhythmic. This resulted from the fact that an individual neuron would be involved in one cycle of an ongoing oscillation and then not involved again for many cycles. Subsequently the same neuron would fire together with a group of neurons that differed from those firing together previously. Therefore this population phenomenon consisted of different populations on different cycles.

In studying a complex system, the appropriate level for meaningful investigation is not known in advance (Lyttton and Sejnowski 1992). To some, the very goal of reductionism in complex systems may seem misguided. Experimentally, however, the reductionistic approach to corticothalamic networks has proven extremely successful, pinpointing essential elements determining oscillatory activity (Steriade et al. 1993). In the present paper we isolate a rather simple circuit, namely the TC-RE reciprocal interaction, and also describe the influence of corticothalamic volleys. The two-neuron TC-RE model has limitations because it omits the intra-RE connections that have been described morphologically (Deschenes et al. 1985; Yen et al. 1985), electrophysiologically (Bal and McCormick 1993; Huguenard and Prince 1994; Ulrich and Huguenard 1996), and in computer network models (Destexhe et al. 1994a; Golomb et al. 1994). Therefore we reassessed the TC-RE interaction in the context of a larger model that includes these and other connections. Because RE neurons are GABAergic, reciprocally connected to TC neurons, and highly active during both wake and sleep states as well as in various experimental models of thalamic oscillations (Steriade et al. 1986), it seems likely that they are a major source of hyperpolarizing postsynaptic potentials in TC neurons. Indeed, after disconnection from RE inputs, prolonged, rhythmic, spindle-related TC neuron IPSPs show dramatically reduced duration and rhythmicity (Steriade et al. 1985). We therefore posit that, at intermediate strengths, these hyperpolarizing potentials could serve to prime LTSs in TC neurons, whereas at higher strengths these hyperpolarizations would render TC neurons inactive. Thus the RE neuron input would be required for TC activity in one setting while precluding activity in another setting.

In this study we have deliberately avoided the exhaustive reproduction of detailed biophysical data, concentrating instead on exploring dynamics in networks that are capable of generating quiescence in TC neurons. The advantage of this approach is that we were able to explore dynamics in detail to identify critical parameters that suggest general predictions to be tested experimentally. The disadvantage of this simplifying approach is the need to cross-check results among several models. We start with a simple model that proposes a dual role for RE neuron input with the possibility of transitions between two functional modes: the mutual mode, in which the TC neuron fires spike bursts in phase with the RE neuron, and the quiescent mode, in which the TC neuron is prevented from firing by steady hyperpolariza-

tion. We cross-check with three other computer models: one emphasizing the generality of the results in a different parameter regime, another demonstrating a different aspect of synaptic dynamics that we believe to be important, and the third showing comparable behavior in a much larger 54-neuron network. No one model has precisely the "right" parameters to make it the Rosetta stone of thalamic physiology. Instead, each simulation is in itself a complex system with emergent behavior that requires "virtual experimentation" and analysis to explain (Wolfram 1984).

METHODS

Simulations were run on a Sun Sparcstation 10s and Intel Pentium PCs with the use of the NEURON simulator (Hines 1993). Each neuron was represented by a single compartment with a $1,000\text{-}\mu\text{m}^2$ area.

Voltage-sensitive channels included were similar to those used in previous papers (Destexhe et al. 1993). The TC neuron had the following voltage-sensitive channels and typical maximal conductances \bar{g} (in mS/cm^2): fast sodium conductance, 0.03; delayed rectifier conductance, 0.002; T channel conductance, 0.001; H conductance, 1.2×10^{-4} . In the RE neuron the values were (in mS/cm^2): fast sodium conductance, 0.1; delayed rectifier conductance, 0.01; T channel conductance, 1.75×10^{-3} ; slow calcium-dependent potassium channel, 0.005; nonspecific calcium-sensitive cation channel, 3.5×10^{-4} . Calcium removal in both neuron types was effected by a previously described calcium pump (Destexhe et al. 1993). The parameter adjustments required to go to the second parameter set used for Figs. 8 and 9 were as follows (in mS/cm^2): 10% increase in \bar{g}_T in the TC neuron (0.0011), 43% increase in \bar{g}_T in the RE neuron (0.0025), and 50% decrease in the Michaelis-Menten rate of the calcium pump (from 1×10^4 to 5×10^{-5}).

The synaptic projection from TC to RE neuron involved α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) components. The connection from RE to TC utilized γ -aminobutyric acid-A (GABA_A) and GABA_B components. All synapses were parameterized with the use of the two-state model previously described (Destexhe et al. 1994c; Lyttton 1996). Parameters were as follows. AMPA: $\alpha = 1.1/\text{ms} \cdot \text{mM}$, $\beta = 0.19/\text{ms}$, $C_{\text{dur}} = 1.1$ ms, reversal potential ($E_{\text{rev}} = 0$ mV), $\bar{g} = 0.002$ μS . NMDA: $\alpha = 0.072/\text{ms} \cdot \text{mM}$, $\beta = 0.0066/\text{ms}$, $C_{\text{dur}} = 5.0$ ms, $E_{\text{rev}} = 0$ mV, $\bar{g} = 0.0$ μS (used for stimulation only). GABA_A : $\alpha = 0.53/\text{ms} \cdot \text{mM}$, $\beta = 0.18/\text{ms}$, $C_{\text{dur}} = 1.0$ ms, $E_{\text{rev}} = -90$ mV, $\bar{g} = 0.002$ μS . GABA_B : $\alpha = 0.01/\text{ms} \cdot \text{mM}$, $\beta = 0.005/\text{ms}$, $C_{\text{dur}} = 150$ ms, $E_{\text{rev}} = -95$ mV, $\bar{g} = 0.0055$ μS .

Cortical stimulation was simulated with the use of a mixed AMPA/NMDA excitation to the RE (\bar{g} 0.2 and 2 nS, respectively) and AMPA excitation of the TC (\bar{g} 2 nS). In Fig. 12, cortical stimulation was simulated with repetitive AMPAergic activation of the RE neuron alone. In this model, a different GABA_B model was used, with inclusion of cooperativity in the activation kinetics (Destexhe and Sejnowski 1995). Details of the simulation method in this figure are given in Destexhe et al. (1996). Most oscillations were initiated with a brief hyperpolarizing pulse in the TC neuron (Fig. 4A).

For the large network simulations (Figs. 10 and 11), intrinsic parameters were identical to the original parameter set. Each of nine columns was headed by a single RE neuron that controlled 5 TC neurons for a total of 54 cells. Within a column, reciprocal connectivity was complete. Between columns, connectivity probability from TC neuron to RE neuron and from RE neuron to TC neuron were equal. Different densities were assayed. The simulations shown used densities of 0.67 for the immediate neighboring column and 0.34 for the following column in either direction with wraparound. REs were always connected to neighboring RE neu-

rons and were connected with a probability of 0.5 to RE neurons two columns distant. Synaptic strengths of inputs to the TC neuron were randomized uniformly ($GABA_A$: 0.3 ± 0.2 nS, $GABA_B$: 0.3 ± 0.2 nS). Inputs to the RE neuron were not randomized ($GABA_A$: 0.3 nS, AMPA: 0.5 nS). All synaptic delays were taken to be 0.5 ms.

For the two-neuron network, 6 s of simulated time took 3 min to run on a 100-MHz Pentium or a Sparcstation 10 running Solaris 2.4.

RESULTS

More than 500 neurons were recorded intra- and extracellularly in various cortical areas, the rostromedial district of the RE nucleus, and various dorsal thalamic nuclei (see Steriade and Contreras 1995). Of these, 124 neurons were entrained in spontaneous seizures. In computer simulation, ~600 models were evaluated. Four parameter sets were explored in detail out of many that were assayed.

Physiology: quiescent TC neurons in vivo

The spontaneous seizures that were recorded were complex mixtures of electrographic patterns including typical SW and polyspike-wave patterns at 2–4 Hz. Seizures were recognized by their abrupt start and termination, by the large increase in the amplitude of the waves, and by a high degree of neuronal synchronization (Fig. 1). During seizures, cortical neurons showed strong depolarizations constituting paroxysmal depolarizing shifts, occurring in close time relation with the spike components of the electroencephalogram (EEG).

RE neurons discharged relatively long bursts (150–300 ms) in relation to the EEG spikes (Figs. 2*B1* and 3). Many of these prolonged bursts were modulated at 10 Hz or were made up of multiple smaller bursts at 10 Hz (3rd burst in Fig. 3*B*). RE neuron bursts appeared to be riding a depolarization, presumably due primarily to cortical driving (Fig. 3). Active TC neurons presumably also contributed to these compound excitatory postsynaptic potentials.

TC neurons showed two types of behavior: 1) 40% of TC neurons were entrained into the seizures and discharged high-frequency spike bursts concomitant with the EEG spikes (see Steriade and Contreras 1995); 2) 60% of TC neurons were quiescent during the seizure and exhibited an almost continuous synaptic bombardment. These synaptic potentials mainly consisted of IPSPs (Fig. 1, details 1 and 2, ●). Excitatory postsynaptic potentials of cortical origin were also seen. Occasionally the TC neuron could “escape” from the prolonged synaptic bombardment and generate a low-threshold spike without superimposed fast sodium action potentials (Rush and Rinzel 1994). Hyperpolarization of TC neurons was a mixture of sustained, tonic hyperpolarization of 10–15 mV (Fig. 2*A*, after the right angle arrow) and phasic hyperpolarizations recurring at ~10 Hz (● in Figs. 1 and 2). These phasic IPSPs coincided with paroxysmal depolarizing shifts in the cortical neuron (Fig. 1).

Computer model: two modes of oscillation

Thalamic activity in vivo generally features sparse TC activity with relatively greater RE activity. Therefore we explored

in detail a computer model that demonstrated the two modes that feature RE activity: the mutual oscillation mode, in which both neuron types fire, and the quiescent mode, in which only the RE fires. These two modes depended primarily on the strength of inhibition from RE to TC.

With weaker inhibition, a mutual oscillation was produced in which a burst in each modeled neuron was matched by one in the other (Fig. 4*A*). This resulted because the TC-RE excitatory drive was sufficient to produce a nearly immediate burst in the RE neuron. The RE burst produced a mixed $GABA_A$ and $GABA_B$ IPSP in the TC, sufficient to deactivate the T channel and produce a subsequent low-threshold spike, completing the cycle (Fig. 4, *middle inset*). The frequency of oscillation was primarily determined by the duration of the complex IPSP. The intrinsic oscillatory frequency of the TC neuron also played a role with IPSPs of brief duration (Lyttton et al. 1996).

Close inspection of the RE neuron oscillation showed the oscillation to be of a “period 2” or higher type, meaning that two or more distinct periods took place before the pattern repeated. These two periods were seen readily in the RE neuron trace: a burst (1st period) and a subsequent subthreshold depolarizing hump (2nd period) that can be seen between each burst (Fig. 4, ↓). This brief depolarization represented T channel current that fell short of the threshold needed to trigger sodium spikes. The failure to form a burst could be traced back to residual inactivation from the preceding large, partially TC-driven burst. The subthreshold depolarization, although not large enough to produce a full burst, was sufficient to further inactivate the T channel. Therefore another delay, comparable with that occurring between the burst and this subthreshold depolarization, occurred before the neuron would burst again. During this delay, T channel deactivation increased to the point where a full burst could be generated on the following cycle. This gave a frequency that was half of what it would be had these subthreshold depolarizations resulted in bursts, and approximately half of that seen with the oscillation shown in Fig. 4*B*.

In the other mode, which we will call the quiescent mode, drive from RE to TC continuously hyperpolarized the TC neuron (Fig. 4*B*). This mode was favored by increasing the conductance of $GABA_B$. The RE neuron showed repetitive single-spike LTS-based bursting at a higher frequency determined by interactions between the depolarizing nonspecific calcium-sensitive cation channel and T calcium channel and the hyperpolarizing slow calcium-dependent potassium channel, as demonstrated previously (Avanzini et al. 1989; Bal and McCormick 1993; Destexhe et al. 1994c). TC neuron silence was due both to the frequency and the size of the RE neuron bursts. The smaller bursts were associated with smaller IPSPs, albeit still of sufficient size to generate an LTS. The higher interburst frequency did not leave sufficient time for this LTS to develop however. In vivo, still faster bursting appears to be caused by cortical driving rather than by intrinsic mechanisms (Steriade and Contreras 1995).

The fact that RE neuron bursting was relatively rapid was more important than the strength of the inhibition in preventing activity in the TC neuron. If this frequency were slower, the TC neuron would have time for I_T to deactivate and generate a low-threshold spike. In fact, the higher bursting frequency of the RE neuron in the quiescent mode was

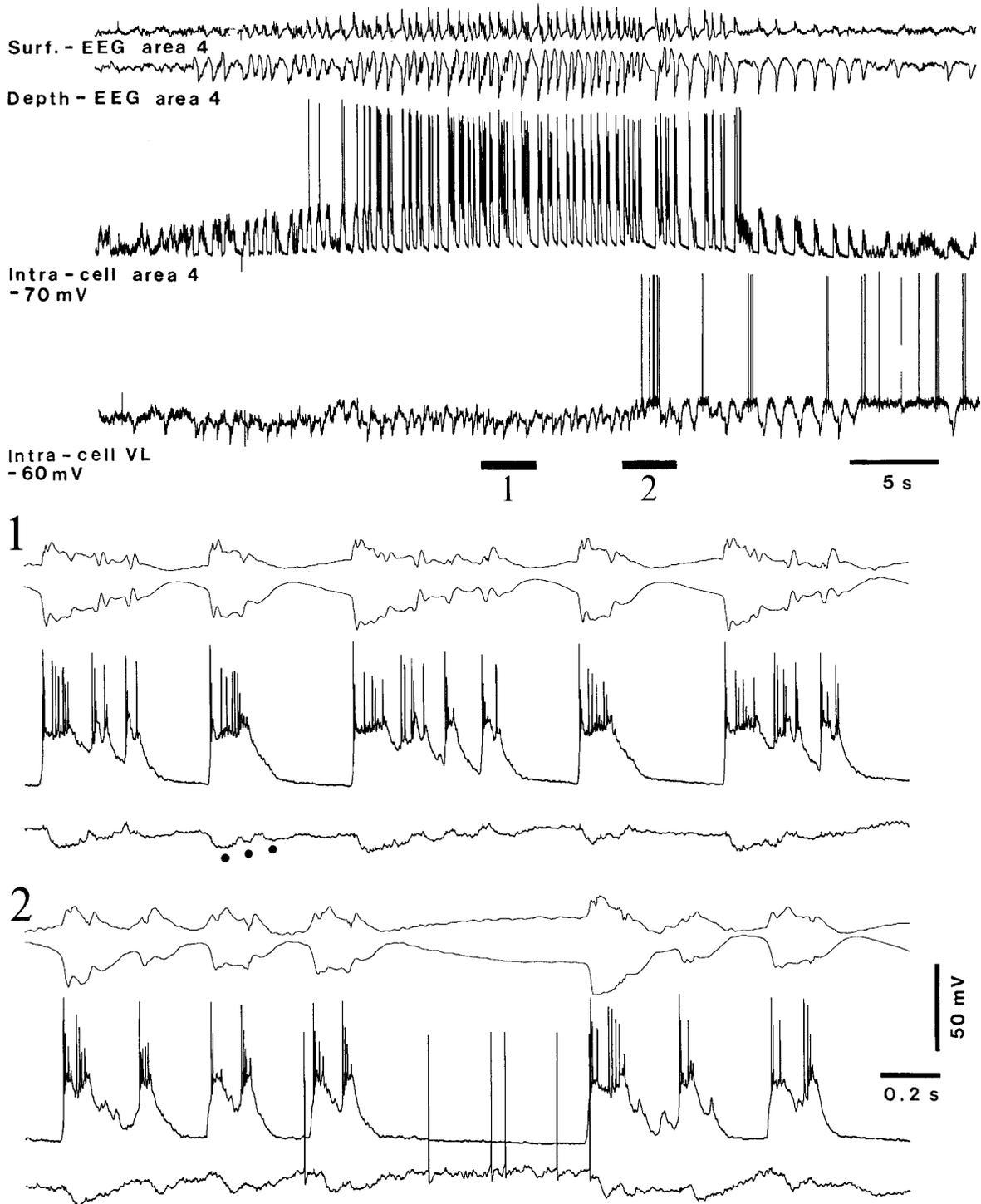


FIG. 1. Spontaneous seizure in intracellularly recorded cortical and thalamocortical (TC) neurons under ketamine-xylazine anesthesia. Cortical cell from motor cortex, together with the surface and depth electroencephalogram (EEG) from the vicinity, was recorded simultaneously with a TC neuron from the ventrolateral (VL) nucleus. The spontaneous development from the slow sleep oscillation into a polyspike-wave epilepsy pattern was reflected as high-amplitude negative polyspikes in the depth EEG that reversed polarity at the surface. Cortical cell showed paroxysmal depolarizing shifts of up to 30 mV related to the depth EEG negative deflections and TC neuron showed repetitive inhibitory postsynaptic potentials (IPSPs) at 10 Hz. Polyspikes recurred at 2–3 Hz. During the seizure the TC neuron remained quiescent with the exception of a brief (0.65 s) period of silent EEG that was accompanied by TC neuron depolarization and firing of single spikes (see detail 2).

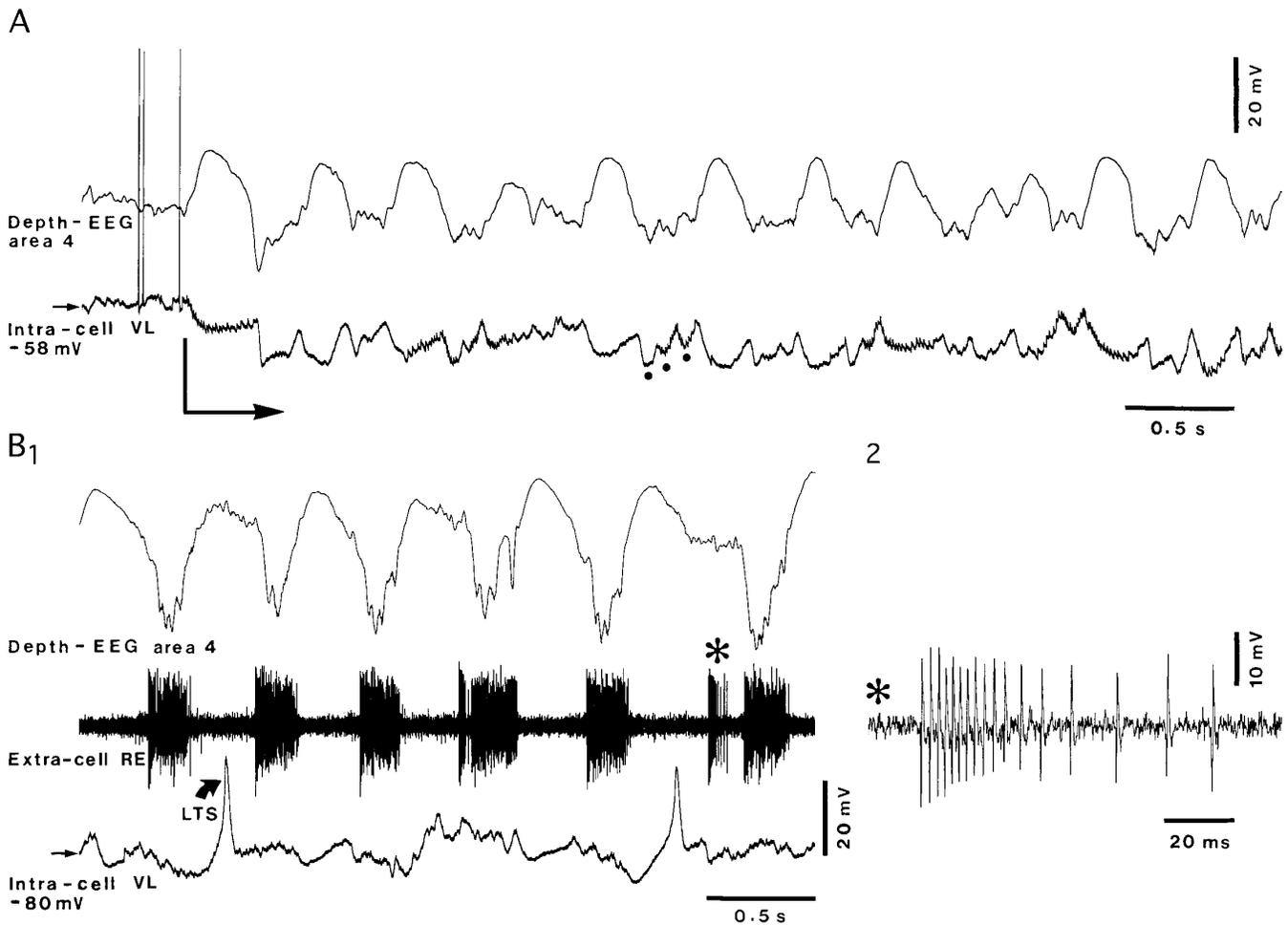


FIG. 2. Spontaneous polyspike-wave seizures are reflected by repetitive IPSPs and quiescent membrane potential in a large proportion of TC neurons. *A*: example of a VL TC neuron at rest, recorded simultaneously with the depth EEG from the precruciate motor cortex, showing no rebound bursts during the 2-Hz polyspike-wave seizure. Fast IPSPs at 10 Hz (●), related to EEG polyspikes, characterized the activity of this TC neuron during the seizure. *B*: depth EEG from the precruciate cortex was recorded together with an extracellularly recorded thalamic reticular (RE) neuron from the rostromedial sector and an intracellularly recorded VL TC neuron. Depth EEG polyspikes at 2 Hz were associated with RE neuron bursts lasting 150–300 ms, and repeated IPSPs in TC neurons that on 2 occasions led to a low-threshold spike (LTS) in isolation with no sodium spikes (∕). A burst from the RE neuron is expanded at *right* (*).

associated with a reduced burst duration, and thus a reduced IPSP. The reduction in burst length to a single spike was due to the short interburst interval available to produce RE neuron T channel deinactivation and to the absence of coincident TC neuron drive. Thus overall inhibition in the quiescent mode was no greater than that in the mutual mode. Timing altered the behavior.

Transition between modes

Given the similar overall inhibitory drive into the TC neuron in the two modes, switching between modes was relatively easy. Simulated cortical stimulation could switch between modes in either direction (Fig. 5). The drive into the RE neuron produced in TC neurons a prolonged IPSP that could be long enough to initiate or maintain the quiescent state (1st 2 stimulations), or deep enough to trigger a low-threshold spike that switched to the mutual state (3rd stimulation). In the latter case, the failure of the RE neuron to develop a full burst in the cycle following the stimulation

(Fig. 5, ↓) permitted the development of a TC neuron burst, leading to the mutual mode.

The phase of the stimulation was important in determining its ability to alter the oscillation pattern (Fig. 6). Stimulation did not always effect the change immediately, but could instead effect the transition several cycles later.

Transitions between modes also occurred spontaneously in the absence of stimulation (Fig. 7). Phase plane representations helped us further analyze these transitions. Studying trajectories of all possible pairs of state variables revealed that this spontaneous transition was primarily associated with shifts in the intrinsic state variables of the RE neuron, without substantial alteration in the entrained activity of the TC neuron. Here again, RE neuron activity determined the oscillation mode. RE neuron T channel activation and inactivation showed the clearest evidence of systematic alteration leading up to the transition. Figure 7A shows an initial mutual oscillation mode that spontaneously gave way to the quiescent mode. Eight bursts preceding the transition are shown. Individual cycles are labeled as a key to the phase

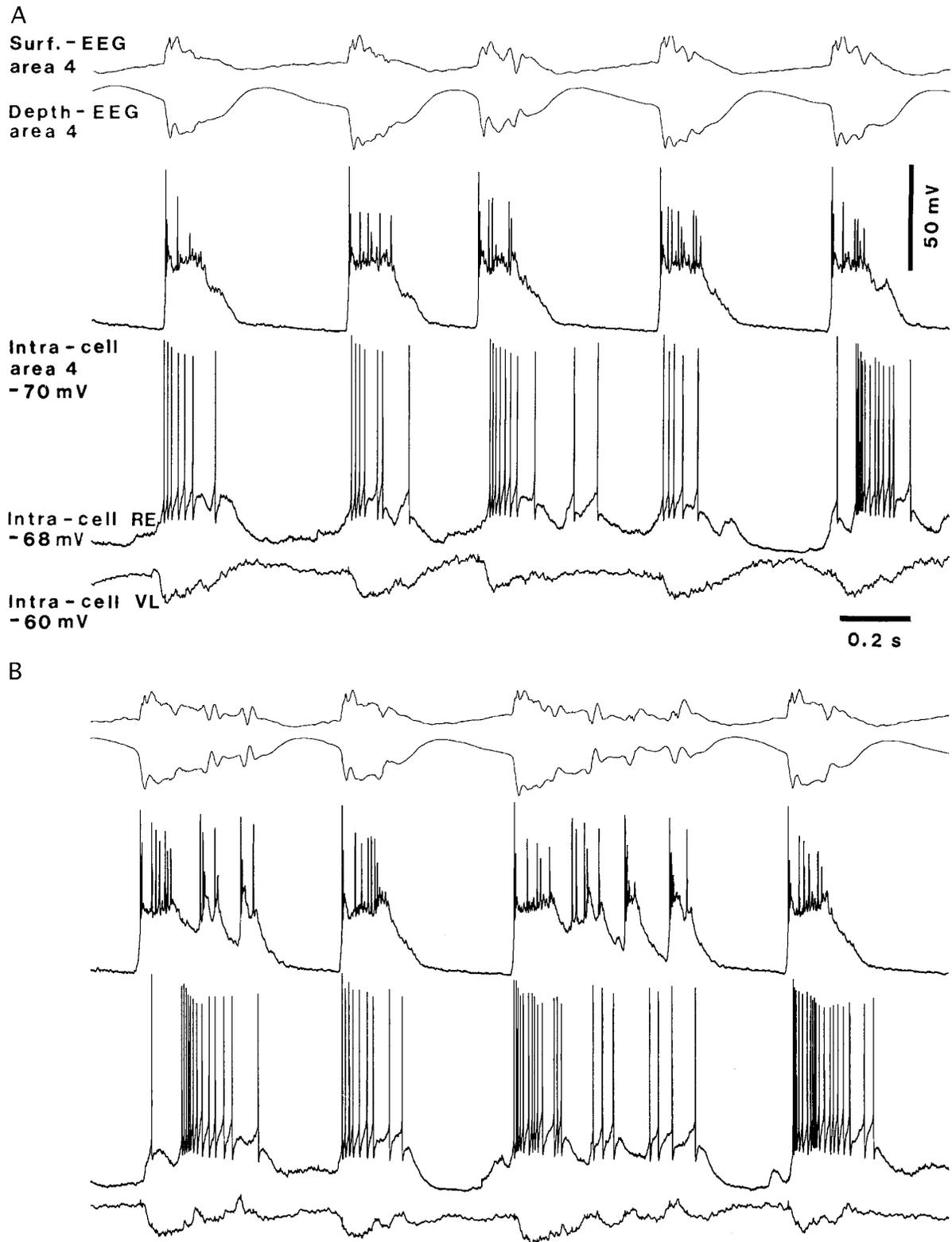


FIG. 3. Seizures in a single animal showed marked similarities between events (*A* and *B*). Motor cortical and VL TC neuron were recorded simultaneously, together with the depth and surface EEG from motor cortex, during spontaneous 2-Hz polyspike-wave seizures. Although RE neurons were recorded later rather than simultaneously, seizure stereotypy was so pronounced that the bursts aligned perfectly. Prolonged bursting in RE neurons was due to strong, rhythmic excitatory postsynaptic potentials from cortex or from active TC neurons. This was related to repetitive IPSPs in TC neurons that generated TC neuron quiescence during the seizures.

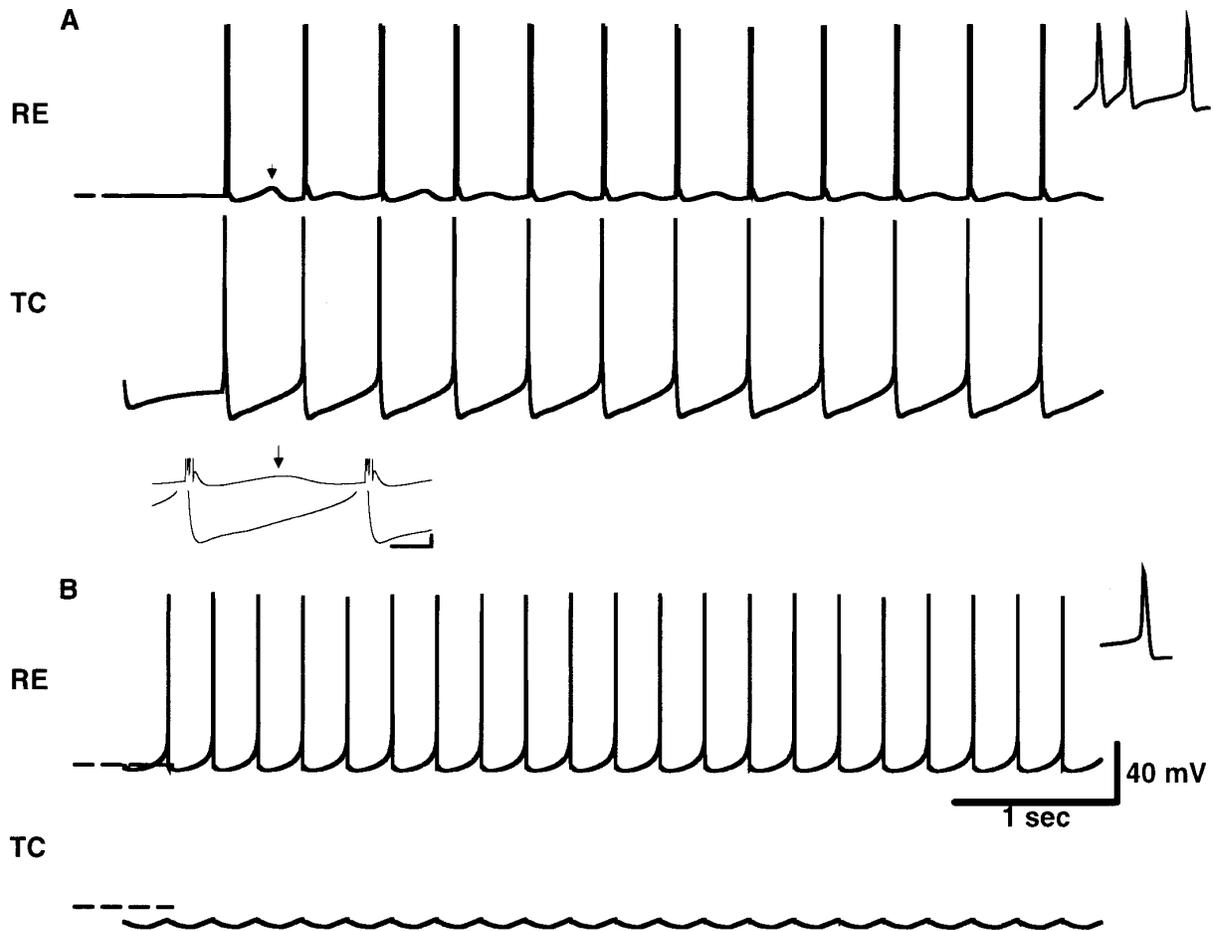


FIG. 4. Mutual and quiescent oscillations in the 2-neuron network. Dashed lines: resting membrane potential. *A*: mutual oscillation between RE neuron and TC neuron. Bursting occurs nearly in phase because the excitatory input from the TC neuron is sufficient to cause an almost immediate burst in the RE neuron. Note the subthreshold depolarizing hump (\downarrow) between each burst. *Middle inset* shows that the TC neuron burst produced immediate excitation of the RE neuron, causing it to fire (scale: 100 ms, 5 mV). The RE neuron hyperpolarizes the TC neuron, facilitating a subsequent low-threshold spike. *Right inset* shows the 3-spike RE burst in this mode. *B*: quiescent oscillation involves tonic inhibition of the TC neurons by the intrinsically bursting RE neurons. *Right inset* shows the single spike RE burst.

planes in Fig. 7*B*. Inspection of the voltage trace alone suggested that the initial mutual mode in the RE neuron would be an approximately period 2 oscillation, because the voltage appeared to go through two dissimilar cycles, burst and subthreshold excitation, before repeating. (This would not be precisely period 2 because the individual bursts and interbursts were not identical.) However, inspection of the T channel activation/inactivation (m_T/h_T) phase plane of Fig. 7*Ba* revealed that the subcycles labeled 1 and 2 were quite distinct. Therefore what appeared to be an approximate period 2 oscillation was in fact closer to an approximate period 4 oscillation.

The alternating bursts illustrated in Fig. 7, *Bb* and *Bc*, were similar, although burst *b* showed a slight progressive increase in T channel inactivation on subsequent cycles. Burst *c* showed no systematic shift. These shifts were slight, with all individual bursts being similar to one another. The alternating interbursts, labeled 1 and 2 in Fig. 7*Ba*, showed a voltage amplitude difference most clearly seen in Fig. 7*C*. The interburst labeled 1 had a sequence comparable with

that of the burst in *Bc*, showing no clear progression with time. The interburst labeled 2, by contrast, gradually shrank on subsequent cycles before disappearing entirely at the onset of the quiescent mode. The quiescent mode lacked interburst depolarizations and was therefore represented as open loops rather than full orbits in the phase plane (3). Nonetheless, the amplitude and location classes them with the orbit labeled 1. The duration of transit labeled 3 is substantially less than that labeled 1 because it does not go through the full loop, the depolarizing hump having become a full burst. In summary, the quiescent transition represents an elimination through collapse of one interburst orbit with a continuation in abbreviated form of the alternating interburst orbit.

The above phase plane diagrams are based on m and h variables that are not observable experimentally. Figure 7*C* illustrates the same interburst orbits (1 and 2 in Fig. 7*Ba*) in a phase plane of intracellular calcium and voltage, which are experimentally measurable. The inner and outer loops could still be distinguished, although they were not as clearly

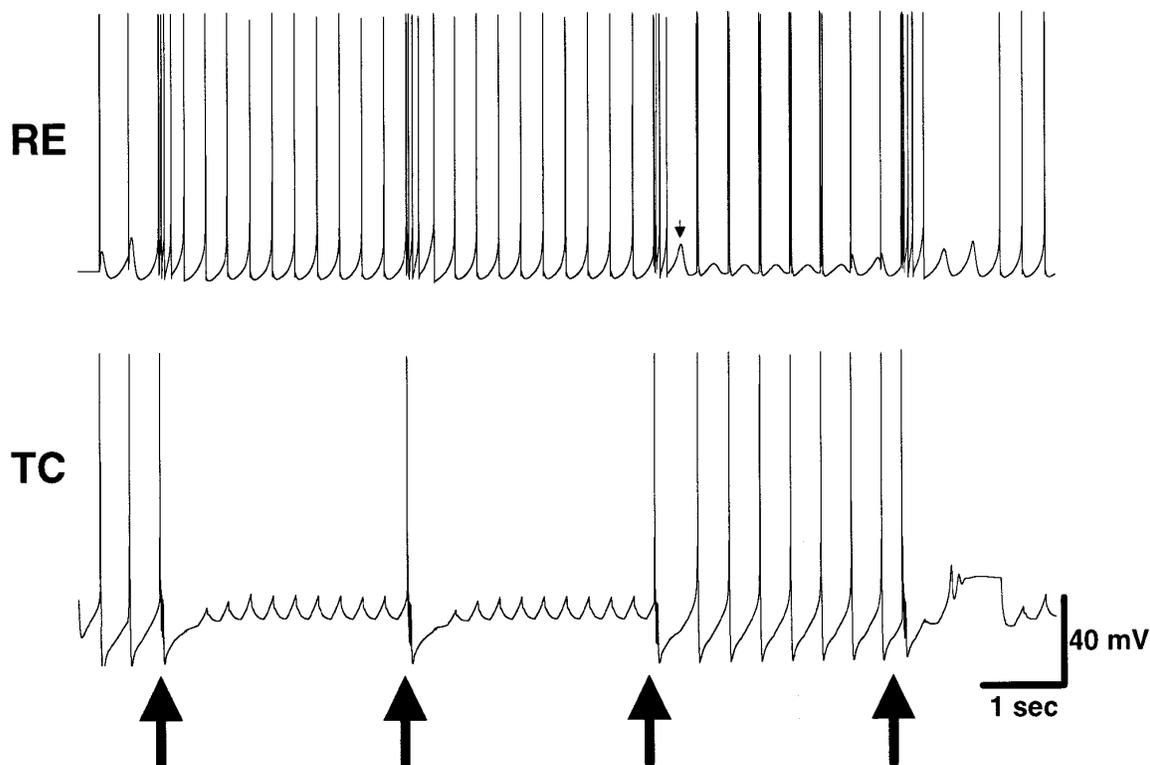


FIG. 5. Repeated cortical stimulation (\uparrow) can repeatedly switch oscillation mode. The 1st stimulation switches from mutual to quiescent mode; the 2nd is ineffectual; the 3rd switches back to mutual, and the 4th yet again to quiescent. The failure of the RE neuron to reach threshold after the 3rd stimulation (\downarrow) permits the shift to the mutual mode.

separated as they were in the m_T/h_T plane. Additionally, the gradual collapse of the inner orbit, although also visible, was difficult to see in this cross section.

Degree of quiescence is associated with inhibitory strength

To investigate the generality of the mutual and quiescent modes, we examined other parameter sets. All parameter sets that produced intrinsically oscillatory neurons of both types could produce mutual oscillation. From there, increasing $GABA_B$ strength invariably produced TC neuron quiescence. Although $GABA_B$ strength was the prime determinant of the degree of quiescence in most parameter sets, $GABA_A$ strength could also play a role in cases in which the RE neuron showed prolonged periods of high-frequency regular firing that permitted temporal summation of the relatively brief $GABA_A$ IPSPs. We performed further investigations on a parameter set that showed a complex repertoire of intrinsic activity that included multiple burst sizes and variable interburst intervals.

Figure 8 illustrates the range of activity obtained by increasing the strength of inhibitory input into the TC neuron. Each pair shows the activity in the RE neuron (*top traces*) and TC neuron (*bottom traces*). A complex mutual mode oscillation was seen, with regular TC neuron bursting coexisting with irregular RE neuron bursting interspersed with runs of rapid spiking (Fig. 8A). The regularity of TC neuron bursting suggested that the TC neuron was leading the oscillation in this case, with the RE neuron showing either a burst or brief spike

train in response to each TC neuron burst. Increased inhibition produced a more complex mutual oscillation (Fig. 8B) in which TC neuron bursting occurred at a subharmonic of that seen above. Although the TC neuron regularity demonstrated an important role of TC neuron intrinsic properties in this oscillation, the RE neuron was playing a larger role here in determining the TC neuron interburst interval. In particular, a three-burst RE neuron motif (Fig. 8B, arrows), associated here with a longer TC neuron interburst interval, was identical in form to the burst groups seen in quiescent mode (Fig. 8D). A further increase in inhibition (Fig. 8C) demonstrated that the mutual mode could spontaneously make the transition into a quiescent mode, as seen with the previous parameter set (Fig. 7A). Sufficient inhibition yielded a quiescent mode oscillation (Fig. 8D). As with other parameter sets, the RE neuron bursting pattern was less complex with TC neuron feedback absent.

Simulated cortical stimulation of the mutual oscillation with this parameter set also showed the ability to change it over to the quiescent mode (Fig. 9). The first trace shows a brief period of quiescent mode starting about halfway through the period shown. Stimulation at various phases could advance the quiescent period (*2nd and 4th traces*), delay it (*5th trace*), or leave it virtually unchanged (*3rd trace*). Stimulation could also precipitate a transition in the opposite direction, from quiescence to mutual oscillation (not shown).

Network simulations

A minimal demonstration of the relevance of the TC-RE pair requires that 1) behavior similar to that seen in the two-

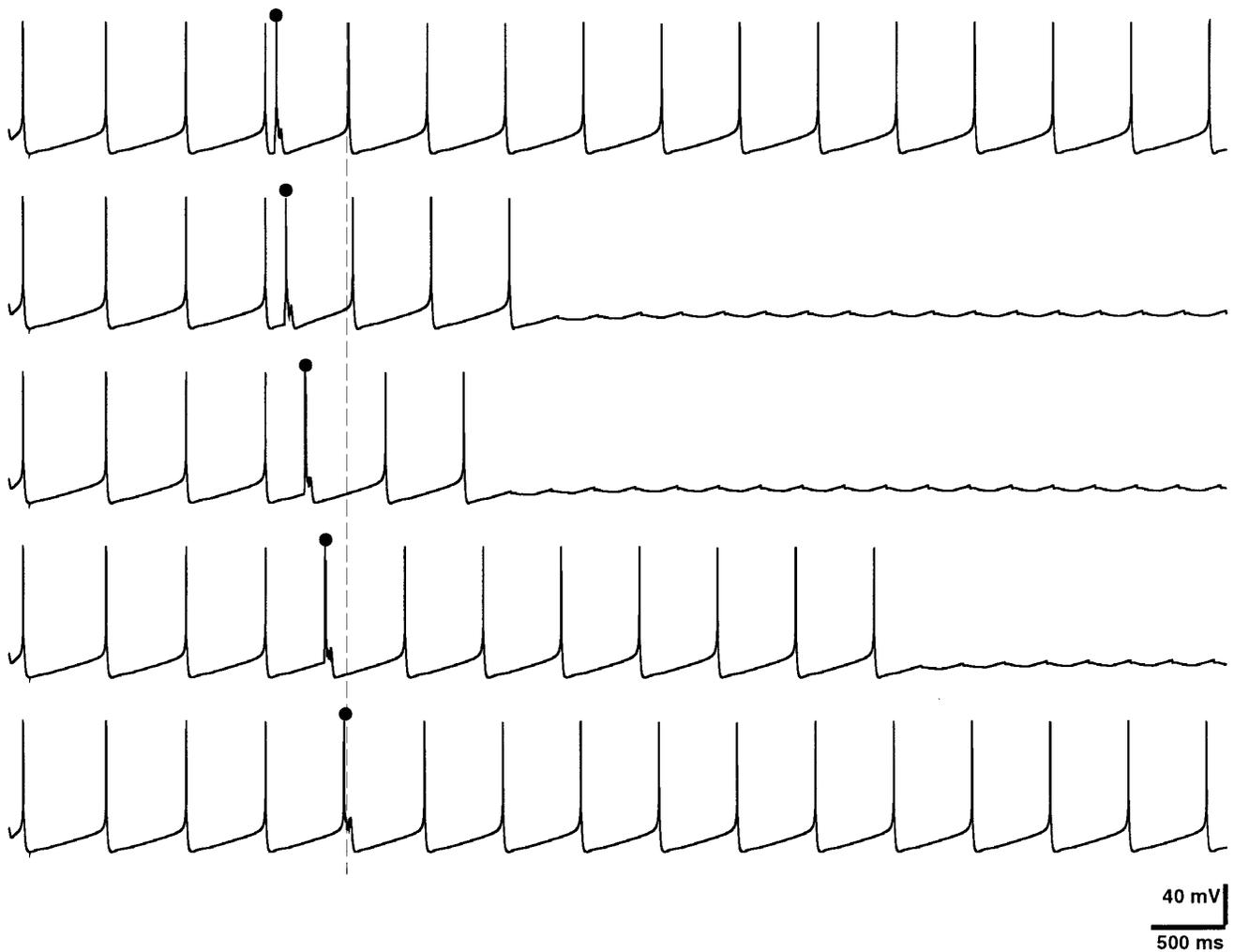


FIG. 6. TC neuron activity with cortical stimulation (●) at different phases in the cycle initiates quiescent mode at different intervals. Only the TC neuron activity is shown. *First and 5th traces*: stimulation producing no alteration in the ongoing mutual oscillation. *Second, 3rd, and 4th traces*: onset of quiescent mode after 3, 2, and 7 cycles, respectively. Dashed line: time of next cycle without stimulation.

neuron network can be seen in a larger network and 2) these similarities reflect comparable physiological relationships between the participating neurons. We simulated a multicolumnar RE neuron–TC neuron network to assess this (Fig. 10A). Activity in the TC neurons ranged from activity similar to that of the two-neuron mutual oscillation (*top trace*) to complete quiescence (*bottom trace*). Overall, the activity was similar to that seen with the second parameter set (Fig. 8) despite the much greater complexity of connections, the convergent influence on single TC neurons, and the mutual inhibition between the RE neurons. In general, the degree of activity in a TC neuron correlated with the amount of inhibitory input into that cell (Fig. 10B). However, this relationship was highly variable. This indicated that dynamic factors complemented connection strength in determining mutual oscillation and quiescent episodes.

Observations of mutually connected TC-RE pairs demonstrated that RE neuron firing usually followed TC neuron firing after a brief interval (Fig. 11). Thus the relationship between reciprocally connected neurons was comparable with that which we observed with the two-neuron network

(Fig. 4). Other RE neuron bursts were due to other converging TC neurons or to intrinsic activity of the RE neuron. Although intra-RE inhibition had significant effects on the overall oscillation, it did not eliminate the relationship between reciprocally connected cell pairs.

Synaptic factors could contribute to TC neuron quiescence

A complementary mechanism for TC neuron quiescence was investigated on the basis of a cooperative model of GABA_B response. Unlike GABA_A currents that appear even with minimal stimulation (Mody et al. 1994), GABA_B-mediated responses require high stimulation intensities to be evoked, as seen in both hippocampal (Davies et al. 1990; Dutar and Nicoll 1988) and thalamic slices (Huguenard and Prince 1994; Sánchez-Vives et al. 1995). The synaptic model used in this simulation utilized cooperativity in the activation of GABA_B-mediated current to produce this effect (Destexhe and Sejnowski 1995).

With this synaptic model, RE neuron excitatory discharges at ~10 Hz could still produce both mutual and

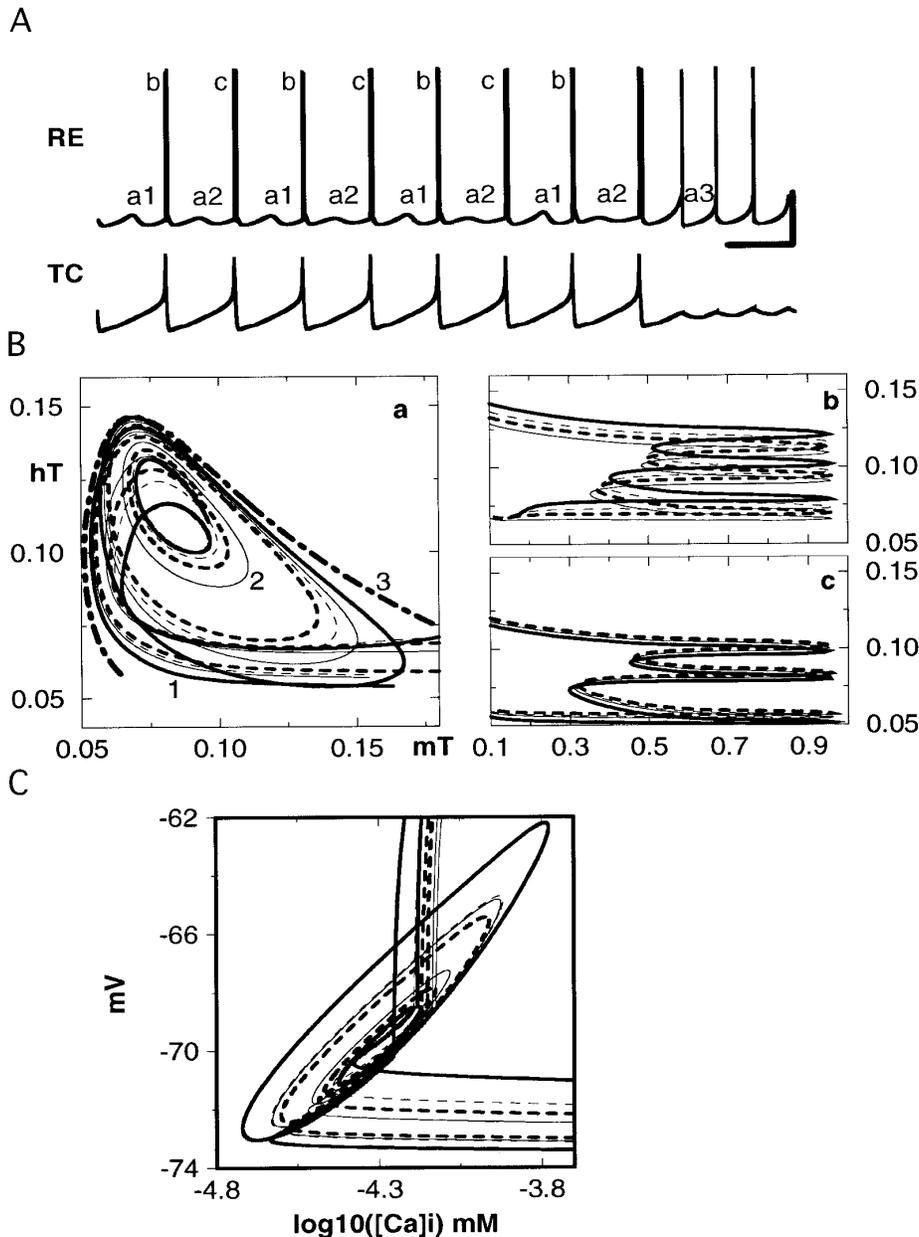


FIG. 7. Analysis of spontaneous transition from mutual to quiescent mode with bursting viewed in the RE neuron T channel m/h plane. *A*: RE neuron voltage trace (*top*) and TC neuron voltage trace (*bottom*, truncated) show 8 bursts of mutual activity followed by switch into the quiescent state. Letters next to portions of each cycle give the key for the phase planes below. Interburst intervals are labeled *a* are depicted in *Ba*; the number indicates which cycle (1, outer; 2, inner). Alternating bursts labeled *b* and *c* are shown in *Bb* and *Bc*. Initial oscillation appears to be approximately period 2 with burst alternating with an interburst depolarization. *B*: apparent approximate period 2 oscillation illustrated to be period 4: 4 cycles occur before the cycle repeats. In each phase plane, abscissa gives the value of m_T (T channel activation), ordinate the value of h_T (T channel inactivation). All trajectories run clockwise. Interbursts (1 and 2) alternated between large cycles (1) and small cycles (2). Burst in *Bb* showed a progression of gradually increasing h_T , whereas burst in *Bc* was more coherent and showed no regular shift. The inner loop labeled 2 gradually collapsed to terminate the oscillation. The subsequent interburst (3) was similar in extent to the cycle labeled 1. Sequential cycles are indicated in the following order: thin solid line, thick dashed line, thin dashed line, thick solid line. *C*: inner and outer interburst cycles seen in the voltage-calcium plane corresponded to *Ba*, 2 and 1, respectively. The collapse of the inner cycle is not as clear as in *Ba*, 2, however.

quiescent oscillation (Fig. 12). The 10-Hz frequency in this model was driven by simulated cortical stimulation to the RE neuron. Similar oscillatory patterns were obtained if both TC neuron and RE neuron were both stimulated, as long as the TC neuron IPSP was dominant. With relatively low-intensity cortical stimulation, the strength of the RE neuron burst was not sufficient to produce much GABA_B activation. The IPSP was sufficiently strong to produce a TC neuron LTS, however, leading to the mutual oscillation mode (Fig. 12A). With stronger cortical stimulation, more prolonged RE neuron burst discharges evoked a more prominent GABA_B current in the TC neuron (Fig. 12B). This current was sustained because of the high stimulation frequency compared with its slow decay. This clamped the TC neurons at a hyperpolarized membrane potential and produced the quiescent mode.

DISCUSSION

In this paper we have documented a surprisingly extensive TC quiescence associated with SW seizures *in vivo*. We have considered the implications of this finding in a variety of simple two-neuron networks that highlight the duality of the inhibitory influence from RE to TC. This duality permits the network to produce different states, either quiescent or oscillatory, despite similar patterns of input, and to produce spontaneous or delayed stimulus-associated transitions between states. Additional cooperative effects in inhibitory synapses may also contribute to these transitions.

RE neuron governs oscillatory mode

RE neurons and local thalamic interneurons are the inhibitory elements of the thalamic circuit. Although interneurons

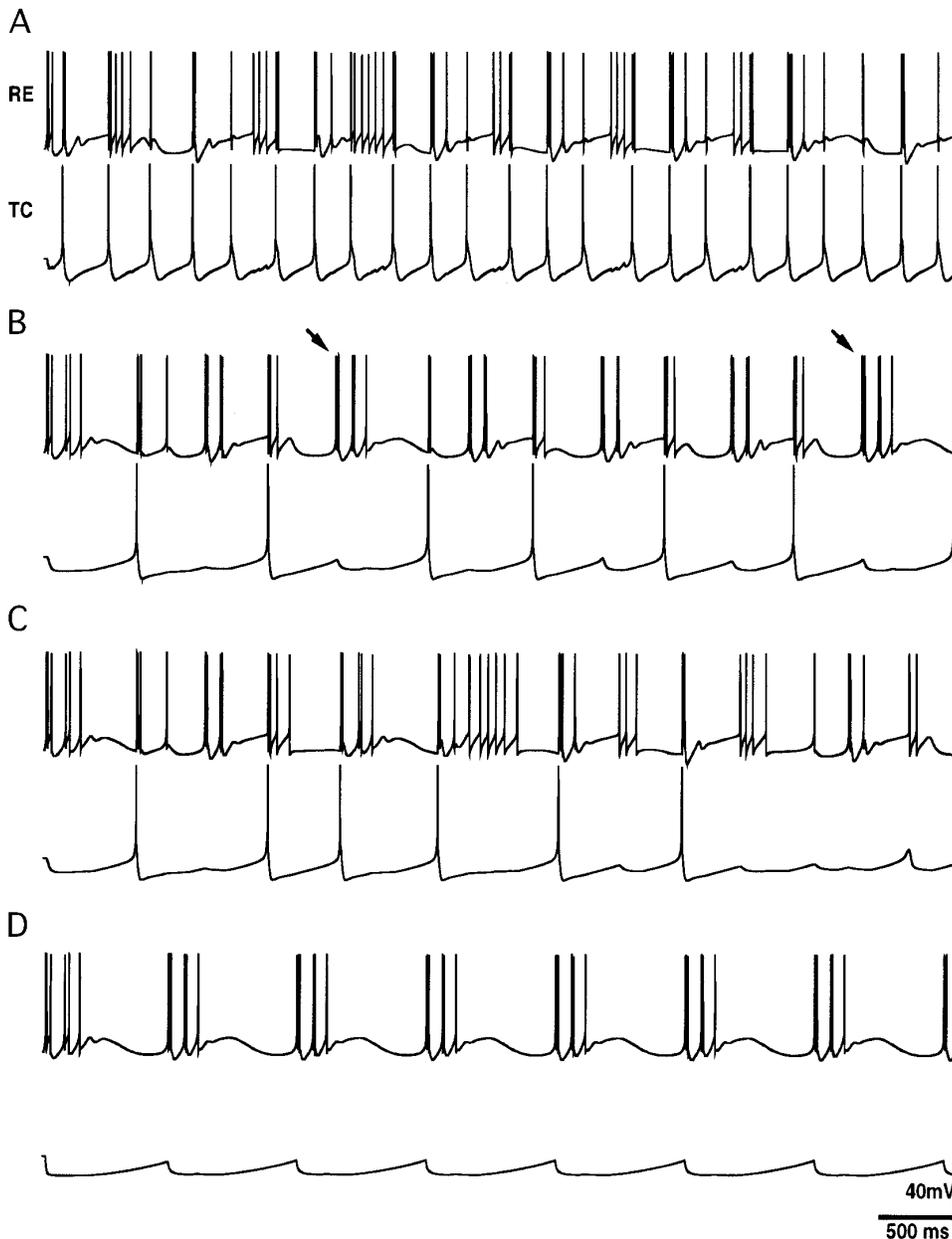


FIG. 8. Increasing inhibitory strength favors quiescent mode. Each pair of traces shows RE neuron activity at *top* and TC neuron activity at *bottom*. Total GABAergic strength increases from *A* to *D*. *A* and *B* can be classified as a mutual mode oscillation, whereas *D* is quiescent mode. *C* shows that mutual activity can give way to quiescence. Arrows in *B*: 3-burst RE motif similar to that seen in *D*.

might also be involved in thalamic oscillations (Zhu et al. 1995), the RE neuron appears to play a major role in several preparations (Steriade et al. 1985, 1987; von Krosigk et al. 1993). Therefore it is natural to consider it the primary candidate for producing an ongoing hyperpolarization leading to TC quiescence.

The relatively high rate of activity of RE neurons compared with TC neurons during SW oscillations (Steriade and Contreras 1995) suggests a concept of RE neuron dominance in these oscillations. The RE neuron control of oscillation mode shown in this paper reinforces this notion. In the first model shown, rapid RE neuron bursting produced the quiescent mode by reinforcing TC neuron hyperpolarization before the TC neuron was able to burst. Less frequent RE neuron bursting produced the mutual mode, in which TC neuron bursting fed back and helped determine the frequency of the RE neuron. In the cooperative GABA_B model, it was the number of spikes in the

RE burst that controlled TC activity by providing a prolonged activation of GABA_B currents.

In vivo, the extent and pattern of RE neuron activity may be more a reflection of cortical drive into the RE neuron than a manifestation of intrinsic activity. This drive, however irregular, would interact with the RE neuron's active conductances to produce the final spike pattern in a way that is still unknown. Quiescence would still be determined by the pattern of RE neuron activity.

Parameter variation produces large effects

Relatively minor changes to only 3 of 20 intrinsic parameters produced a vastly different firing pattern (compare Figs. 4 and 8). To get this effect, the T calcium channel density was changed in the TC neuron and RE neuron by 10 and 43%, respectively, and the rate of the RE neuron calcium

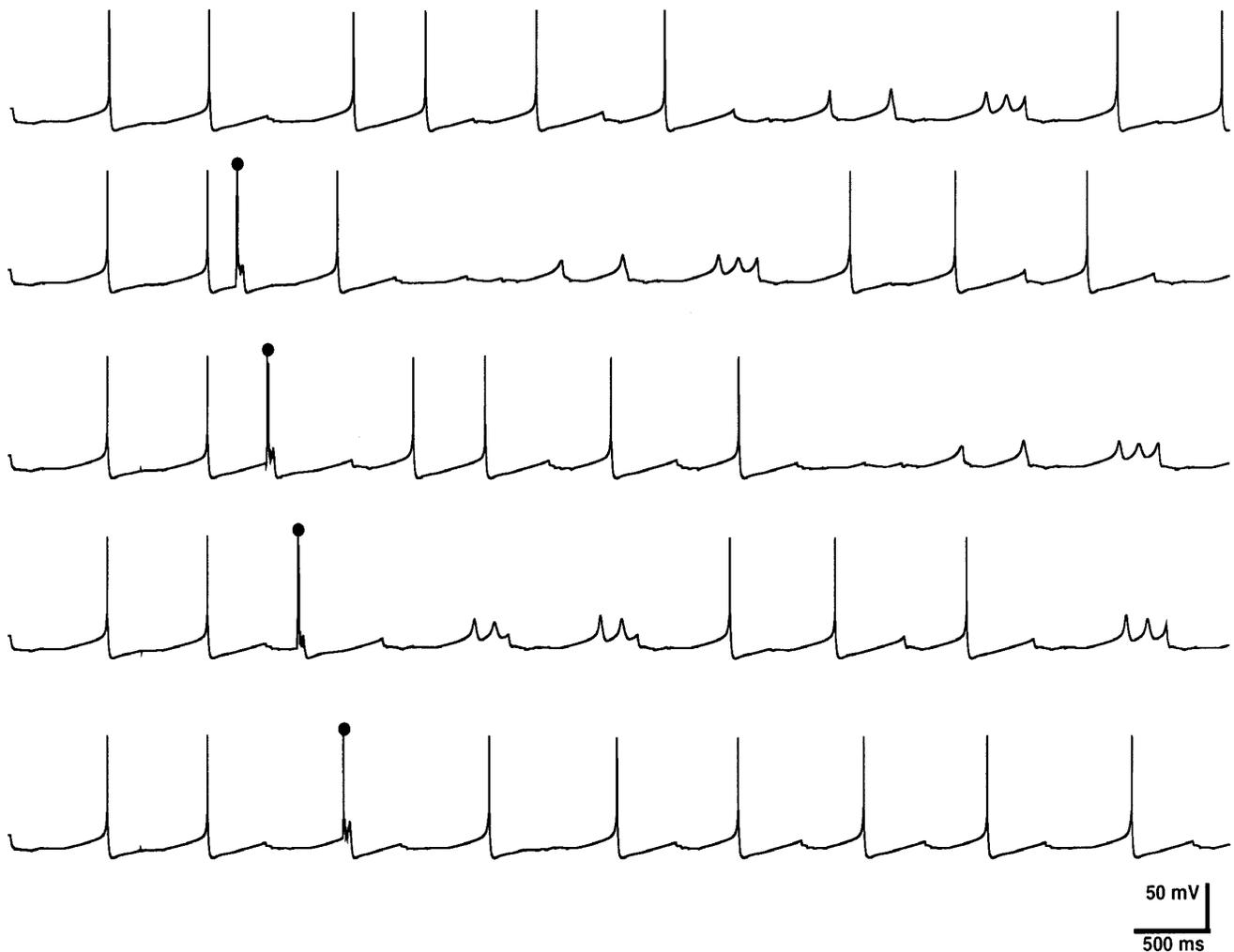


FIG. 9. Cortical resetting similar to Fig. 6 with the use of alternate parameter set. Only TC neuron activity is shown; filled circles show time of cortical stimulation. With no stimulation (*top trace*), TC neuron shows a 2-s quiescent period. *Second and 4th traces*: quiescent period moved forward with cortical stimulation. *Third trace*: quiescent period little changed. *Fifth trace*: elimination of the quiescent period with stimulation.

pump was decreased by 50%. The latter change, largest by percentage, is relatively minor when one considers that this would occur with only a 6.3°C reduction in temperature, assuming a Q_{10} of 3. Network behavior was particularly sensitive to a change in the calcium pump, because the consequent increase in calcium levels increased the late effects of bursting via coupling to calcium-sensitive potassium channels. This remote effect of bursting promoted the greater irregularity seen with this parameter set. The increase in calcium density in the RE neuron compensated to maintain bursting in the presence of these increased hyperpolarizing forces. The slight increase in TC neuron calcium channel, needed to maintain robust bursting, underlines the interdependence of activity in the two neurons despite the dominance of the RE neuron.

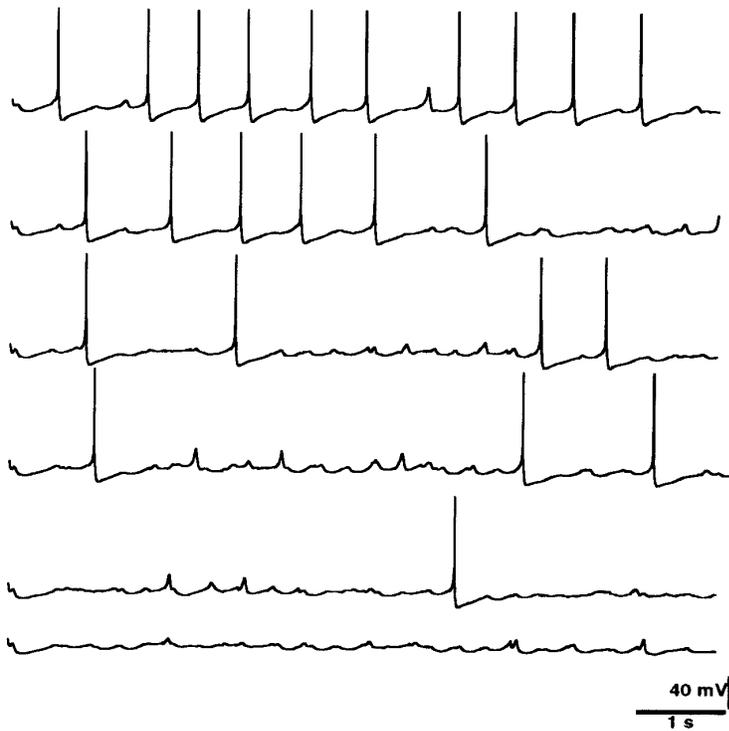
The sensitivity of behavior to relatively minor parameter alterations might lead one to despair of ever getting the right parameters. However, both sets might well be within the range of parameters that could coexist across the population of neurons, perhaps regulated by conditions related to bursting, as suggested by previous researchers (Lemasson et al. 1993).

Thalamic circuit in a larger network

The existence of circuit components that can be regarded as partially autonomous is of value in providing building blocks for developing and testing notions of large-scale corticothalamic circuitry. The concept of the cortical column has been of great value in simplifying our understanding of the cortex. Our findings suggest how a somewhat different concept of modular organization might also be of value for understanding the thalamus. Such a module would be headed up by one or a few RE neurons that would control a larger set of TC neurons.

Our exploration of a larger network served to demonstrate that the TC-RE circuit would keep the characteristics described for the two-cell model when immersed in a larger network. Convergence onto the TC neuron generally increases the chances of being in the quiescent state because of the influence of many more IPSPs coming from these many RE neurons, whereas mutual inhibition among RE neurons tends to reduce RE firing and promote TC neuron activity. These additional connections disrupted

A



B

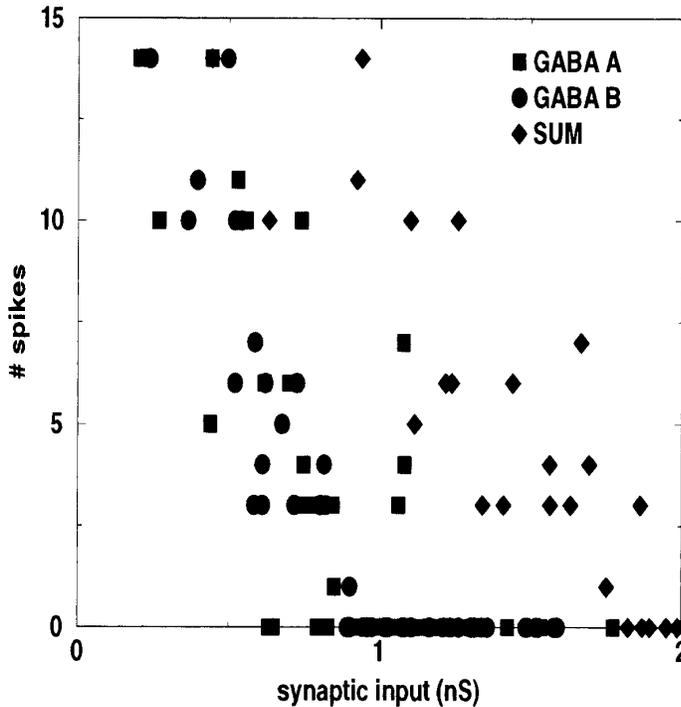


FIG. 10. Different degrees of involvement of individual TC neurons in ongoing activity in the large columnar network. *A*: some neurons appear to be involved in ongoing mutual oscillation (*top 2 traces*), whereas others burst much less frequently or are entirely silent (*bottom trace*). *B*: number of spikes during 8 s in the multicolumnar network as a function of the strength of γ -aminobutyric acid-A ($GABA_A$), $GABA_B$, or summed $GABA_A + GABA_B$ input into each TC neuron. Although the number of spikes declines with increasing inhibitory strength, very different spike numbers can be found with neurons seeing similar inhibition.

the consistency of the reciprocal relation between a single TC neuron and a single RE neuron, because IPSPs from other RE neurons could disrupt a low-threshold spike that

otherwise would have formed (Fig. 11). Convergence onto the RE neuron was less detrimental to the mutual oscillation because excitatory activation follows almost

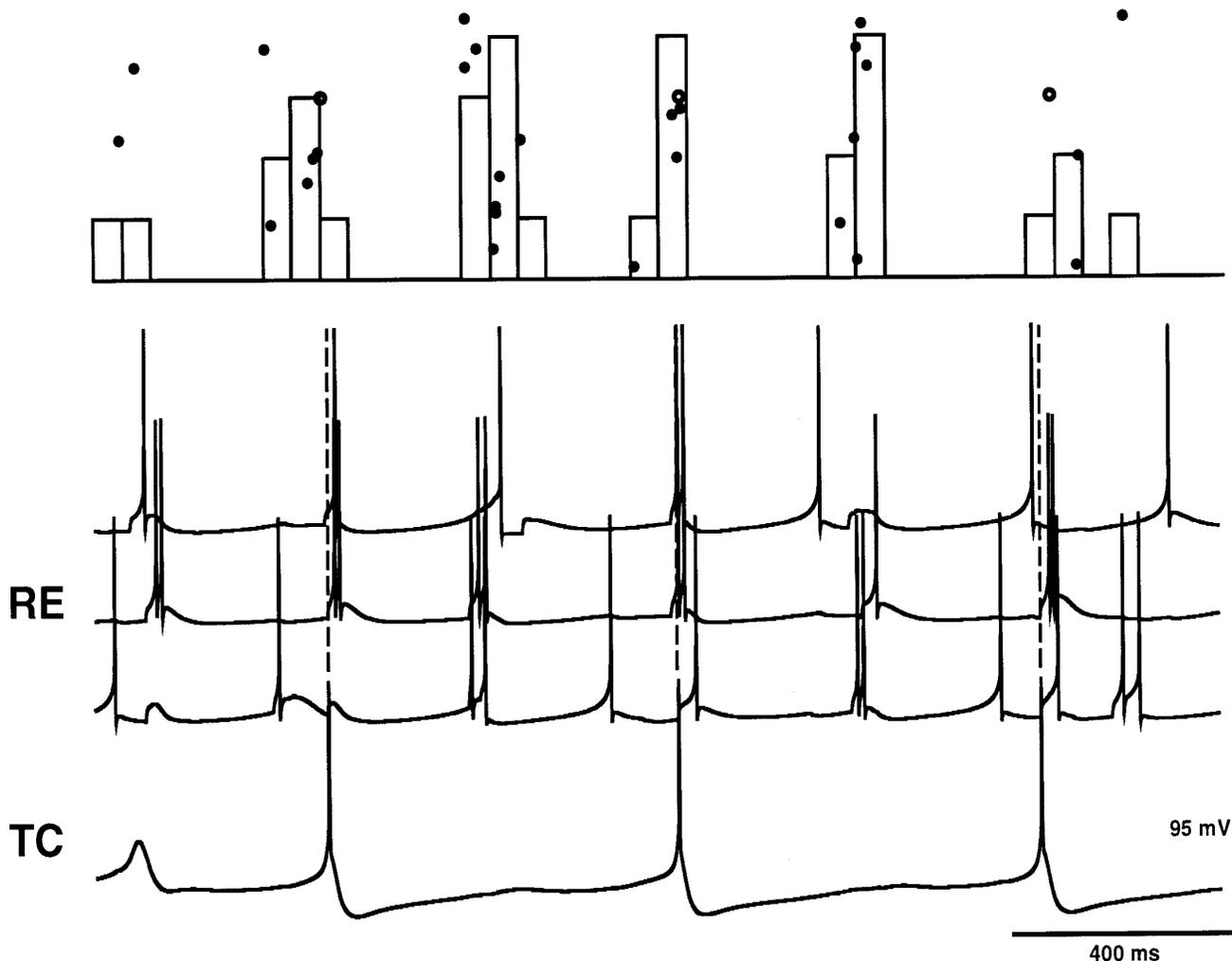


FIG. 11. Relation of TC neuron to RE neuron activity during transient synchronous activity in a large columnar network. TC neuron shown at *bottom* projects to each of the 3 RE neurons shown. Dashed extension of TC spike: TC activity generally stimulates activity in each of the RE neurons in a manner suggestive of the mutual oscillation mode. *Histogram at top*: binned activity in the TC neurons. Filled circles: precise spike time of each neuron. Open circles: spike times for the TC neuron shown in *bottom trace*.

immediately and is not subject to interference from converging TC projections.

Our columnar network is similar to previous models of synchronized oscillations and propagating properties in thalamic networks (Destexhe et al. 1996; Golomb et al. 1996). However, the present model had a restricted longitudinal extent and did not include topographic axonal projections between TC and RE cells, which are prerequisites for propagating phenomena. A common conclusion emphasized by these models was the critical role for the RE nucleus in controlling the type of oscillation exhibited by the thalamic network. In the present paper we document further this critical role by showing that RE neuron activity can also determine patterns of oscillatory activity with quiescent TC neurons.

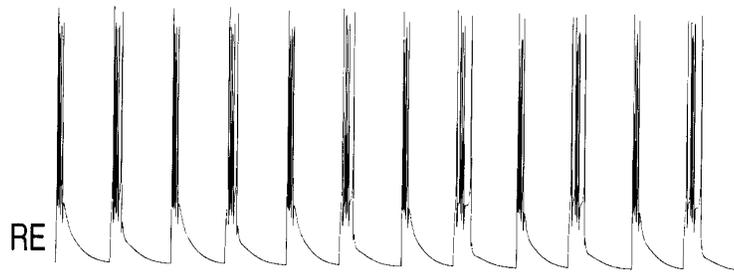
Dynamic factors help determine activity

The coexistence of two modes of TC-RE interaction is consistent with a situation in which seemingly minor influ-

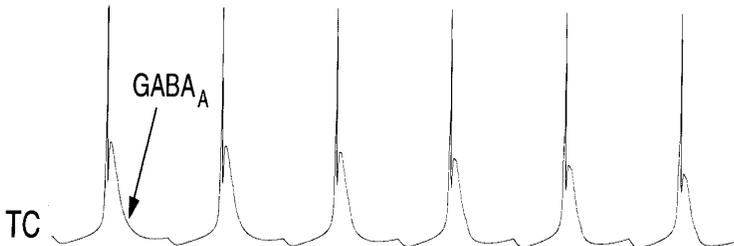
ences can produce large-scale shifts in activity. Determinants of firing pattern are generally classified as either synaptic or modulatory. Both of these mechanisms are relatively readily dealt with experimentally. A third influence on firing patterns, which we have illustrated here, involves nonlinear dynamics. Relatively simple dynamic influences involve interactions between a postsynaptic potential and the intrinsic dynamics of the postsynaptic neuron that allow postsynaptic potentials to have a paradoxical effect (Lytton 1991; Lytton and Sejnowski 1991). More complex dynamic interactions involve subtle changes in timing and cumulative shifts in hidden variables (Fig. 7). In a milieu that is inherently chaotic by virtue of its size and complexity, these may be very hard to explore in simulations and nearly impossible to explore experimentally (Hirsch and Baird 1995).

Figures 5, 6, and 9 show how changes in the timing of a simulated cortical input can either influence activity immediately, after a variable amount of time, or not at all. The means by which an input can have temporally remote effects is explored in our phase-plane analysis of Fig. 7. A single input, in

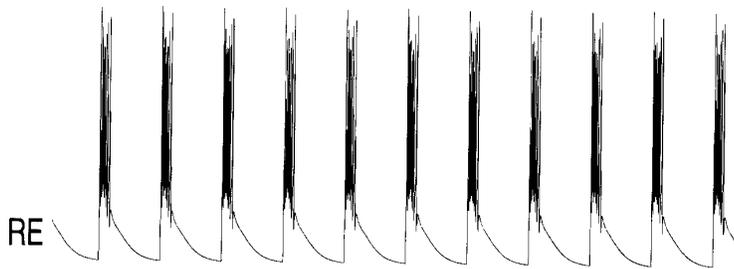
A



10 Hz,
1 spike/stim



B



10 Hz,
3 spikes/stim

40 mV
100 ms

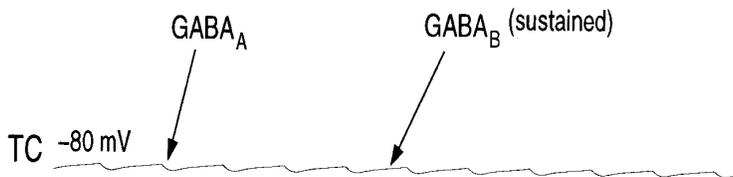


FIG. 12. Mutual oscillation and quiescent mode produced with the use of frequency-sensitive $GABA_B$ synapse model with varying strength of simulated cortical stimulation of RE neuron through α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. A: 10-Hz stimulation at low intensity (1 spike per cortical stimulation) produced the mutual oscillation. The TC neuron followed the stimulation at a subharmonic of 5 Hz. B: same frequency stimulation at stronger intensity (3 spikes per stimulus) produced the quiescent oscillation. IPSPs occurring at 10 Hz coalesced so that no TC neuron rebound was seen.

this case a simple hyperpolarization of the TC neuron, has distant effects. Our analysis demonstrated a complex progression primarily affecting the T channel. This progression took place within the context of an approximate period 4 oscillation. The phrase period 4 indicates a return to the same spot in phase space every fourth orbit. Because the progression of a dynamic system is completely determined by its position in phase space, a return would mean that the system would continue on to repeat exactly the same orbit every fourth time. In this case, the system we are analyzing is not engaged in a continuous oscillation but is instead a nonstationary system making a transition to a different type of oscillation. The system can be described as “approximately period 4” because it comes close to the same orbit every fourth time around. The specific orbit that seemed most indicative of an ongoing change was that labeled 2 in Fig. 7Ba. This orbit became gradually smaller as

a reduction in the size of the interburst depolarizing transient was associated with less initial activation and inactivation of the T channel. This alteration eventually reached a point where the net T channel activation was insufficient to generate the large RE neuron burst associated with the mutual oscillation.

True causality cannot be established in a dynamic system because state variables are linked continuously. However, this analysis did establish a critical role for the T channel in this transition. This ion channel would presumably be the most sensitive target at which a pharmacological agent could impede or augment this transition.

Synaptic mechanisms could increase inhibitory tone

A specific synaptic mechanism was also assessed to further explain TC neuron quiescence through burst strength

dependency of GABA_B responses. It has been proposed that the stronger discharges of thalamic cells following application of bicuculline could result from disinhibition of interneurons projecting to TC cells with GABA_B receptors only (Soltesz and Crunelli 1992; Wallenstein 1994). In a previous study, we proposed an alternative explanation based on burst strength dependency of GABA_B responses (Destexhe and Sejnowski 1995). The transformation of 9- to 11-Hz spindle oscillations into 3- to 4-Hz oscillations of higher synchrony in thalamic networks (Kim et al. 1995) could also be reproduced by this model (Destexhe et al. 1996).

As presented here, this model of GABA_B responses could also contribute to TC neuron quiescence. In Fig. 12, 10-Hz oscillations in RE neurons were not intrinsic but were generated by weak stimulation at 10 Hz. This in turn evoked GABA_A-dominated IPSPs in the TC neuron to entrain it as well (Fig. 12A). Stronger-intensity cortical stimulation at the same frequency could force the thalamic circuit into the quiescent mode (Fig. 12B), because the more prolonged RE neuron discharges evoked a stronger GABA_B IPSP in the TC neuron.

Experimental predictions from these studies

The studies' main results that would be experimentally testable are as follows.

1) We demonstrated that RE neuron activity was temporally associated with TC neuron activity in the mutual mode and that RE neuron activity was more regular during quiescent mode. We predict that cross-correlograms of RE neuron and TC neuron spike trains would show a peak at 2–3 ms, demonstrating the monosynaptic influence of the TC neuron. This has already been shown in part (Shosaku 1986). We additionally predict a significantly more powerful dominant frequency in the power spectrum of RE neuron activity associated with quiescent TC neurons.

2) The switch between modes by cortical shocks could be tested directly in vivo. We predict that single shocks would not only produce a single LTS in the TC neuron but also produce a significant alteration in the probability of firing for a 500-ms window following the shock. Observation of this long window would be necessary given the delayed mode switching that we observed.

3) Increasing GABA_B strength with application of agonists such as baclofen in vivo would increase the duration of TC neuron quiescent periods and the percentage of neurons that show quiescence. This prediction is consistent with the effect that presynaptic GABA_B inhibition has in decreasing intra-RE neuron inhibition, leading to enhanced inhibition in TC neurons (Ulrich and Huguenard 1996). Increasing GABA_A strength with benzodiazepines would not be efficacious in producing increased quiescence.

4) Our major prediction concerns the spatiotemporal pattern of seizure activity associated with quiescence in TC neurons. This prediction is discussed in detail below.

Generalized epilepsy and the epileptic penumbra

Our major prediction from both the experiments and modeling presented here is that SW epilepsy may be expected to show inhomogeneities in the epileptic area such that some thalamic territories are more active than others. Paradoxically,

the areas of greatest TC neuron activity are not expected to correspond to the hottest epileptic zones. On the contrary, we suggest that the areas that are subject to epileptic overdrive from cortex will be the areas with the highest percentage of thalamic quiescence. This prediction should be experimentally observable with the use of multisite recordings. Clinical correlation might also be obtained with the use of positron emission tomography or functional magnetic resonance imaging.

Additionally, we predict that SW epilepsy spreads through a process involving a focus and a neighboring epileptic penumbra (Dichter and Spencer 1969). At the focus, intense cortical and RE neuron activity would produce relative TC neuron quiescence as stated above. In the penumbra, RE neuron divergence would produce less intense hyperpolarization in TC neurons, allowing LTSs and the appearance of the mutual oscillation. This center-surround organization should be apparent with an active center in cortex and a corresponding quiescent center in thalamus. Such inhomogeneities might be transiently present on seizure initiation as one or more foci quickly coalesce and synchronize in a process of generalization. The rapidity of this process would make it hard to detect. Inhomogeneities would also occur in the established seizure either as a result of the dynamic properties that we have shown or in response to local accumulation of extracellular modulators such as adenosine or potassium. Indeed, preliminary data support the existence of such center-surround activity in thalamus (Contreras and Steriade, unpublished results).

“Spread of generalized epilepsy” would appear to be an oxymoron, because generalized epilepsy is defined electroencephalographically by its simultaneous appearance across the scalp. However, it has long been appreciated that actual synchrony of occurrence would only be possible in the presence of an external synchronizing agent such as the shock of electroconvulsive therapy or the sudden immersion of the brain in penicillin (Fisher and Prince 1977a,b; Gloor 1979). A generalized epilepsy of spontaneous occurrence must start in one or several places and subsequently spread and synchronize, as has been demonstrated in an animal model of SW epilepsy (Steriade and Amzica 1994). Our hypothesis suggests that this process of progressive synchronization might involve the rapid spread of an epileptic penumbra of bursting TC neurons, followed by a period of relative TC neuron quiescence in the established seizure. This distinction between seizure onset and the established seizure would have therapeutic implications. Agents such as ethosuximide, which depress the TC neuron T channel, would be expected to suppress seizure initiation and spread while having relatively less effect on established epileptic and nonepileptic oscillations (Kellaway et al. 1990).

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