Synchronized Activities of Coupled Oscillators in the Cerebral Cortex and Thalamus at Different Levels of Vigilance

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The cerebral cortex and thalamus constitute a unified oscillatory machine displaying different spontaneous rhythms that are dependent on the behavioral state of vigilance. *In vivo* multi-site recordings from a variety of neocortical areas and related thalamic nuclei in cat, including dual simultaneous intracellular recordings, demonstrate that corticofugal volleys are effective in synchronizing fast (20–50 Hz) and low-frequency (<15 Hz) oscillations in thalamocortical networks, characterizing activated and de-afferented states. (i) Fast spontaneous oscillations depend on the depolarization of thalamic and cortical cells and appear in a sustained manner during waking and REM sleep. Corticothalamic neurons, discharging high-frequency (400 Hz) spike-bursts at 30–40 Hz, are good candidates to synchronize fast oscillations in reentrant thalamocortical loops. Weakly synchronized, fast spontaneous oscillations may be reset and become robustly coherent after relevant sensory stimuli in waking or internal signals during the dreaming state. (ii) During quiescent sleep, the long-range synchronization of brain electrical activity results from synchronous hyperpolarizations in forebrain neurons. The corticothalamic inputs during the depolarizing component of the slow oscillation (<1 Hz) are effective in grouping the thalamic-generated sleep rhythms (spindles at 7–14 Hz and delta at 1–4 Hz) into complex wave-sequences. These inputs also control the shape of spindles, and favor the long-range synchronization and nearly simultaneous appearance of spindles. (iii) The cortical control of thalamic activity is also demonstrated in spike-wave seizures developing from sleep patterns. More than half of thalamocortical neurons are silent during spike-wave seizures, being tonically hyperpolarized, and display IPSPs (closely related to the paroxysmal depolarizing shifts of cortical cells) that are determined by the pattern of activities in thalamic reticular cells. All these data congruently show the power of cortical control upon thalamic oscillators.

Introduction

Changes in the spontaneous oscillatory behavior of neurons related to shifts in behavioral states of vigilance reflect the properties of reciprocally connected thalamic and cortical networks under the influence of modulatory systems. The coherent rhythmicity of low- and high-frequency field potentials results from synaptic interactions among large numbers of neurons, distributed in a variety of cortical and thalamic territories (Bremer, 1958; Creutzfeldt *et al.*, 1966; Andersen and Andersson, 1968; Steriade *et al.*, 1996a,b). With the advent of modern studies revealing intrinsic cellular properties and ionic conductances in brain slices, it became evident that the neuron is capable of displaying unexpectedly complex behaviors, even in isolation (Llinás, 1988). Although state-dependent oscillatory properties of given networks are partially engraved in the intrinsic properties of neurons, neurons with similar voltage-gated conductances can generate various functional states because they are embedded in different networks, while neurons with dissimilar intrinsic properties may exhibit nearly identical patterns of rhythmic activity because they are linked within the same oscillatory system (Steriade *et al.*, 1990, 1993d).

In this paper I expose data, from *in vivo* intracellular studies on cats, to show the conjunction between intrinsic cell properties and synaptic operations in local circuits and large-scale networks in the generation and synchronization of spontaneous activity in the living brain. Intact brain preparations display combined oscillations within wave-sequences which include, over a period of only 1 s, different types of low-frequency oscillations, as in resting sleep, followed by fast oscillations which are commonly attributed to behaviorally active states. These complex patterns are due to the fact that, at each synchronized cortical volley, the oscillatory machinery of the thalamus is set into action, with the consequence of grouping thalamic oscillations by cortical ones, while the ensuing period of depolarization provides the necessary background for the development of fast rhythms. Here, then, the theme is the potency of corticothalamic volleys in synchronizing spontaneously occurring high-frequency and low-frequency (sleep and paroxysmal) oscillations.

Fast Rhythms: Cellular Properties and Synchronization in Corticothalamic Networks

Fast rhythms, between 20 and 80 Hz (mainly 30–40 Hz), may be involved in the mechanisms of synchronization among neurons responding to different features of the same perceptual object (reviewed in Singer and Gray, 1995). This view led to a series of hypotheses implicating these oscillations in high cognitive processes and conscious states. If we remain on more solid ground, the fast rhythms are part of the background electrical activity of the brain and their appearance, in the absence of relevant stimuli and even during states of deep unconsciousness, depends on the depolarization of cortical and thalamic neurons, which may be tonic and long-lasting, as in waking and rapid-eye movement (REM) sleep, or episodic, as in resting sleep.

The fast rhythms are usually termed gamma. Some distinguish gamma from beta rhythms (<30 Hz), which might further be divided into two components. Such an analytical effort with terminology is worthy of a better cause as, at both field potential and intracellular levels, the frequency may shift by a factor of two (from 20 to 40 Hz) within epochs as short as 1 s, without any visible alteration in the behavioral state of alertness in behaving animals. This explains why I simply call *fast rhythms* the oscillations whose frequencies are generally >20 Hz. What really matters and accounts for the doubling of the oscillation frequency during microepochs, which can hardly be related to changes in behavioral performances, is the increased depolarization in cortical and thalamic cells (Steriade *et al.*, 1996a,b; see also Fig. 1). This emphasizes the role of ascending activating modulatory systems not only in changing the brain

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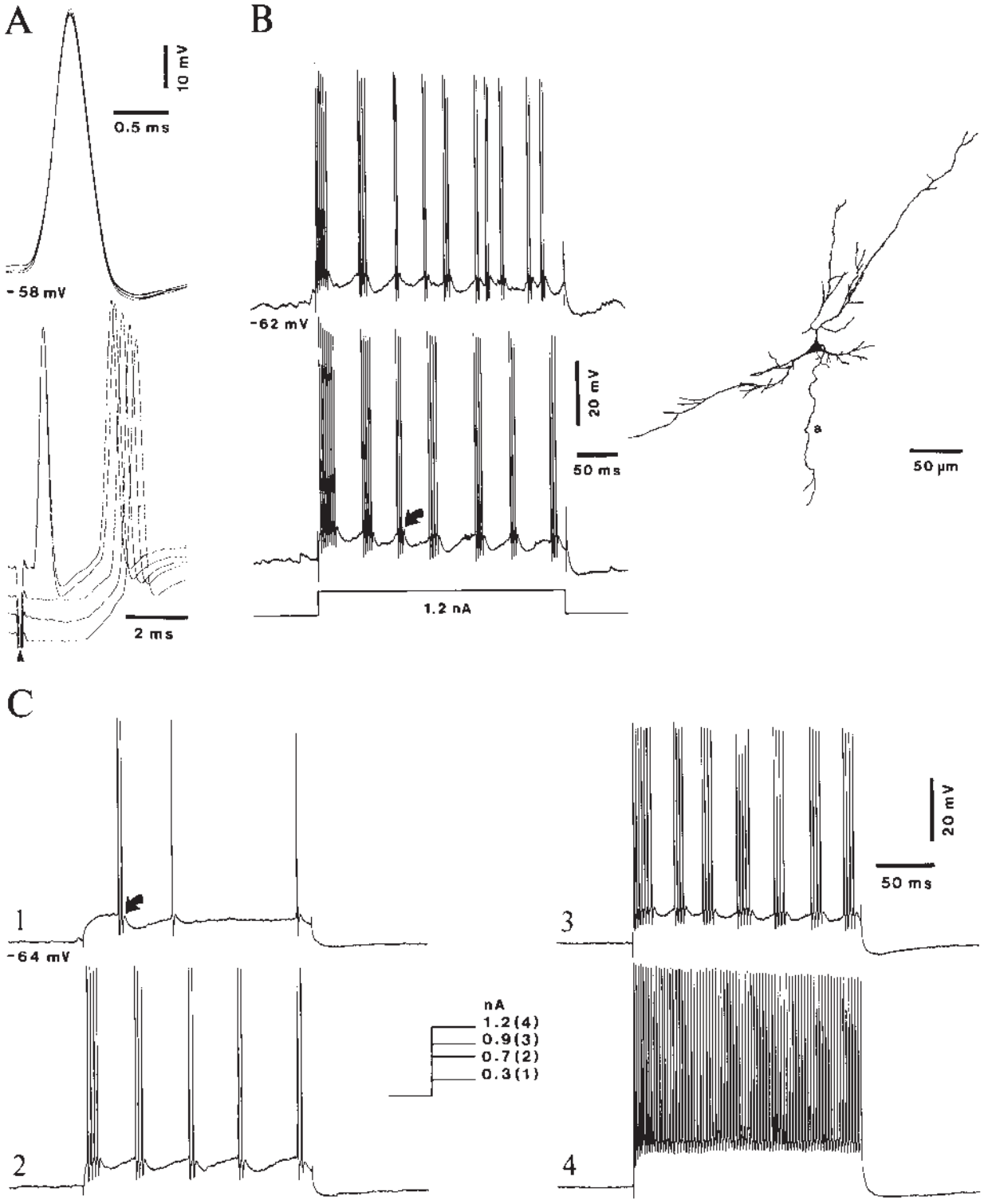


Figure 1. Corticothalamic cells display a continuum of discharge patterns, from single spikes to rhythmic (20–40 Hz) high-frequency (300–500 Hz) spike-bursts and eventually to fast tonic firing without adaptation (~400 Hz), elicited by depolarizing current pulses with different intensities. Intracellular recordings (cats under ketamine–xylazine anesthesia) of corticothalamic neuron located in layers V–VI of cat suprasylvian areas 5–7. (*A*) Spontaneous action potentials of a corticothalamic cell had duration of 0.35 ms at half amplitude. Below, electrophysiological identification of thalamic projection and input of the same neuron. Stimulus to thalamic lateral posterior (LP) nucleus (arrowhead) elicited antidromic activation (0.5 ms latency) and orthodromic spikes (2 ms latency). Five superimposed traces; the two top traces (at a V_m of –58 mV) depict both antidromic and synaptic responses, whereas antidromic spikes failed at more hyperpolarized levels. (*B*) Another corticothalamic neuron, antidromically invaded from central lateral (CL) rostral intralaminar nucleus. Intracellular staining (at right) showed its location in lower layer V (*a*, axon). Depolarizing current pulses elicited spike-bursts recurring rhythmically at ~25 Hz. (*C*) Another corticothalamic cell, antidromically activated from the LP nucleus. Depolarizing current pulses with different intensitites (0.3, 0.7, 0.9 and 1.2 nA in *1–4* respectively) elicited changing discharge patterns, from single spikes to spike-bursts (~35 Hz) and, eventually, fast firing (~400 Hz) without frequency adaptation. In this and following figures from intracellular recordings, membrane potential is indicated. Data from experiments by M. Steriade, I. Timofeev, N. Dürmüller and F. Grenier.

state from sleep to arousal, but also in producing variable frequencies of fast rhythms during a given state.

Cellular Properties Generating Fast Rhythms

Direct depolarization of cortical and thalamic neurons generate narrow-frequency fast oscillations or, more usually, fast rhythms whose frequencies rise in parallel with the increasing strength of the depolarizing current pulse. This was described in sparsely spiny interneurons of frontal cortical layer IV studied in guinea-pig slices, and the rhythm was ascribed to a voltage-dependent persistent Na^+ current, with the involvement of a delayed rectifier (Llinás *et al.*, 1991; see also Amitai, 1994; Gutfreund *et al.*, 1995). Fast intrinsic oscillations have also been observed *in vivo*, in regular-spiking, antidromically identified callosal and corticothalamic neurons recorded from layers III–VI in motor and association cortical areas (Nuñez *et al.*, 1992), as well as in neurons firing high-frequency spike-bursts recurring at a frequency of 30–40 Hz, recorded from the visual (McCormick *et al.*, 1993; Gray and McCormick, 1996) and association (Steriade *et al.*, 1996a) cortical areas. In the thalamus, depolarization-dependent fast oscillations can be triggered in neurons from relay nuclei (Steriade *et al.*, 1991b), where they are preferentially generated at dendritic sites by activation of P/Q-type Ca^{2+} channels (Pedroarena and Llinás, 1997), in reticular neurons (Pinault and Deschênes, 1992a) and in a cellular class recorded from the rostral intralaminar nuclei, projecting to association cortex with very high conduction velocities (40–50 m/s) and discharging upon depolarizing current pulses (or during natural states of waking and REM sleep) exceedingly high-frequency (900–1000 Hz) spike-bursts at a frequency of 30–40 Hz (Steriade *et al.*, 1993c). Different investigators have reported that, in both neocortex and thalamus, the proportions of neurons displaying voltage-dependent fast oscillations represent 10–30% of the total number of tested neurons.

Such a diversity of cortical and thalamic neuronal types defies the idea that special cellular types would exclusively be implicated in the generation of fast rhythms. Superficial (layers II–III) pyramidal neurons from visual cortex intrinsically generate high-frequency spike-bursts, recurring rhythmically at a frequency of 20–70 Hz (Gray and McCormick, 1996). These neurons, if properly connected, may contribute to the generation of synchronous cortical fast rhythms, in concert with many other neuronal types. Similar electrophysiological characteristics belong to some neurons recorded throughout layers II–VI in cortical somatosensory area 3b, motor area 4, and association areas 5 and 7 of cat suprasylvian gyrus (Steriade *et al.*, 1996a).

In our recent experiments, a group of neurons recorded intracellularly from suprasylvian areas 5, 7 and 21 displayed fast oscillations consisting of spike-bursts without showing a preferential location for certain cortical layers. Intracellular staining showed that most of these cells had pyramidal-shaped somata, while a minority were aspiny or spiny stellate cells. Figure 1*A* depicts the identification of a corticothalamic cell from layer VI in area 7 that was activated antidromically and synaptically from the lateral posterior nucleus. Corticothalamic cells are able to discharge rhythmic (20–40 Hz), high-frequency spike-bursts (~400 Hz) in response to depolarizing pulses (Fig. 1B). Being parts of corticothalamocortical loops, such cells are ideal candidates for transferring the fast rhythmic activity to the thalamus and, after intrathalamic synchronization processes of fast rhythms (Steriade *et al.*, 1996b), to receive back the reflection of these integrated oscillations.

The cell in Figure 1*C* demonstrates that neurons generating depolarization-dependent spike-bursts within the frequency range of fast rhythms do not display a single, peculiar firing mode. In fact, there was a continuum of discharge patterns upon injection of depolarizing pulses with increasing intensities, from 0.3 to 1.2 nA. After a passive response to a subthreshold pulse and single spikes or, occasionally, a spike-doublet in response to a depolarizing current pulse of 0.3 nA (*1*), the neuron discharged rhythmic (25–30 Hz) spike-bursts, spike-doublets or triplets (interspike intervals 2.5–3 ms) to a pulse of 0.7 nA (*2*); well-developed spike-bursts (400 Hz) were fired at 35 Hz by slightly increasing (0.9 nA) the intensity of the depolarizing pulse (*3*); and, finally (*4*), tonic firing (400 Hz), without frequency adaptation, was elicited by increasing the strength of direct depolarization to 1.2 nA. This variety of discharges in the same neuron includes patterns that might be ascribed to intrinsically bursting cells, but also to fast-spiking cells displaying tonic firing at high rates (more than 400 Hz) without spike frequency adaptation. Chagnac-Amitai and Connors (1989) documented different firing properties in type 3 regular-spiking neurons and in intrinsically bursting neurons; it resulted that, despite some differences, both these cellular classes have a depolarizing afterpotential, DAP (see their fig. 1). This can also be detected in the present Figure 1, and the DAPs generate double, triple or more spiking. A similar event, critical for the generation of spike-bursts, was reported in fast oscillating cells from visual cortex (Gray and McCormick, 1996). Chagnac-Amitai and Connors (1989) have concluded (p. 1153) that, in most ways, especially due to the presence of DAPs, intrinsically bursting cells are similar to a certain class (type 3) of regular-spiking cells. Moreover, intrinsically bursting neurons may develop, when adequately depolarized, into typical regular-spiking cells. This was observed during a single depolarizing current pulse when rhythmic bursting developed into single-spiking in a layer V neuron (see fig. 3D in Connors and Gutnick, 1990); during arousal elicited by pedunculo-pontine tegmental stimulation, when the slow oscillation of the intrinsically bursting cell was transformed into a period of single-spike, tonic firing (see fig. 5A in Steriade *et al.*, 1993a); and as an effect of muscarinic, adrenergic or glutamate metabotropic receptor activation (Wang and McCormick, 1993). Thus, under the influence of brainstem cholinergic/adrenergic and thalamocortical systems, cortical neurons may change their discharge patterns, otherwise supposed to be invariant. If we now turn to the present Figure 1, two other patterns of discharges (spike-bursts recurring rhythmically at 20–40 Hz and tonic discharges as in fast-spiking neurons) are observed in the same element.

Although the fast oscillations triggered by depolarizing current pulses are intrinsic, similar fast rhythmic activities in thalamic neurons may be due to inputs arising in the cerebral cortex or ascending pathways. The configuration of fast depolarizing potentials in thalamocortical cells recorded from the ventral lateral nucleus is similar to that of responses evoked in the same cells by stimulation of deep cerebellar nuclei (Steriade *et al.*, 1991b; Pinault and Deschênes, 1992b; Sawyer *et al.*, 1994; LeBel *et al.*, 1996; I. Timofeev and M. Steriade, unpublished data) and deep cerebellar nuclear cells belong to the family of single-cell oscillators, at frequencies from 20 to 40 Hz (Jahnsen, 1986; Llinás and Mühlethaler, 1988; Mouginot and Gähwiler, 1995). Similar relations probably exist in the visual system (Ghose and Feeman, 1992), as photically evoked fast oscillations (40–80 Hz) are recorded from the optic tract

(Steriade, 1968) and retinal and lateral geniculate neurons are synchronized within the frequency of fast rhythms (Neunschwander and Singer, 1996).

Synaptic activities may boost the intrinsic properties of cortical neurons discharging rhythmic spike-bursts at fast frequencies. The fast rhythms that extend over the depolarizing phase of the slow cortical oscillation are best expressed in those instances in which presumably dendritic recordings are performed (see fig. 9 in Steriade *et al.*, 1996a). In the same study, we also observed that depolarizing current pulses elicit single spikes, spike doublets or spike-bursts grouped within rhythmic sequences at 30–40 Hz that are potentiated by background synaptic activities. These data indicate that fast rhythms occur as a result of combined intrinsic properties and synaptic activities. Interestingly, the intrinsic propensity of some neocortical neurons to display high-frequency spike-bursts, recurring within the frequency range of fast rhythms, may be used in synaptic operations that do not characterize alert states but spindles, an oscillation during early sleep that is associated with blockade of information transfer in thalamocortical systems and unconsciousness. The neuron in Figure 2 discharged high -frequency spike-bursts at ~40 Hz in response to direct depolarization. Bursts or spike-doublets with similar interspike intervals were fired in response to thalamic inputs during spontaneous spindles. And compound depolarizations building up cortical spindles consisted of subthreshold rhythmic depolarizing events at ~40 Hz.

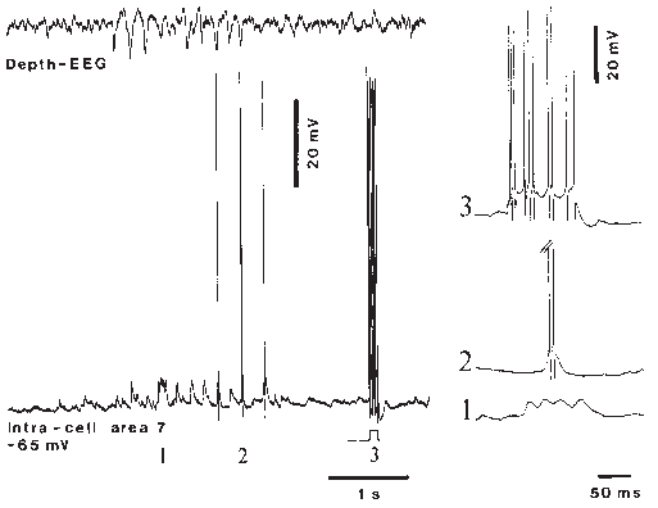


Figure 2. Cortical neurons generating intrinsically spike-bursts at ~40 Hz also display subthreshold EPSPs at ~40 Hz during sleep spindles. Cat under barbiturate anesthesia. Suprasylvian area 21 cell at a depth of 1.2 mm, intracellularly recorded simultaneously with focal EEG waves from the depth of area 5 (12 mm apart). During an EEG spindle sequence, the neuron displayed rhythmic depolarizations at ~6 Hz and, occasionally, spike-bursts that were similar to those elicited by direct depolarization. One of the subthreshold depolarizing wavelets at ~40 Hz during spindles (*a*), a spike-burst during spindles (*b*) and the bursting response at ~40 Hz to a depolarizing current pulse (*c*) are expanded on the right. Data from experiments by M. Steriade, I. Timofeev and N. Dürmüller.

Synchronization of Fast Oscillations in Corticothalamic Networks

Multi-site extracellular recordings of unit discharges and field potentials, together with single or dual intracellular recordings from cortical and thalamic neurons, have demonstrated that fast oscillations are synchronized in reciprocally connected neocortical and thalamic foci, as ascertained by monosynaptic responses in both, descending and ascending, directions (Steriade *et al.*, 1996b). By contrast to the long-range synchronization of low-frequency oscillations (<15 Hz) that characterize the state of resting sleep and extend over the whole hemisphere (Amzica and Steriade, 1995a,b; Contreras *et al.*, 1996a), to also include relay and reticular neurons in the thalamus (Contreras and Steriade, 1995; Contreras *et al.*, 1997b), the coherence of fast rhythms becomes weak beyond 5 mm in cat's cortex (Steriade *et al.*, 1996a) and also decreases with distance in other species (Bullock and McClune, 1989; Murthy and Fetz, 1992). Provided that care is taken to identify direct connections among recorded sites in cortical areas and appropriate thalamic nuclei, strong correlations are observed between the fast rhythms generated at different sites. Data similar to those in the present Figures 3 and 4, in which fast (30–40 Hz) recurring depolarizations in thalamic relay ventrolateral neurons are correlated with focal waves from cortical area 4, have been obtained by recording activities from ventroposterior nucleus and area 3b, lateral geniculate nucleus and visual association area 21, and rostral intralaminar nucleus and association area 5 (Steriade *et al.*, 1996b).

The intracortical, intrathalamic and corticothalamic synchronization of fast rhythms challenges the term 'desynchronization'. Despite the fact that the protocols of experiments by Moruzzi and Magoun (1949) noted that they may have stumbled over a puzzling form of inhibition because brainstem reticular stimulation most often induced a flattened or depressed EEG, they went beyond the observed facts and inferred an ascending activating system. Actual activation of thalamocortical responsiveness was demonstrated only a decade later by increase, as an effect of brainstem reticular stimulation, of centrally evoked cortical field potentials (Bremer and Stoupel, 1959; Dumont and Dell, 1960) and photically evoked responses in the lateral geniculate nucleus, without changes in simultaneously recorded responses from optic tract axons (Steriade and Demetrescu, 1960). Figure 5 shows the cortical EEG activation response to stimulation of mesopontine cholinergic nuclei and supports our claim that desynchronization should only refer to the suppression of slow-wave sleep rhythms, because the fast (~40 Hz) activity is increased in amplitude and synchronized among various cortical foci. Fast waves also appear during the period preceding brainstem stimulation, when slow waves characterize brain electrical activity (Fig. 5). However, fast rhythms are uninterrupted during waking and REM sleep, whereas they are suppressed during the prolonged hyperpolarizations that are associated with the long-lasting depth-positive waves of the slow sleep oscillation (Steriade *et al.*, 1996a,b). The disturbing appearance of fast rhythms during slow-wave patterns (disturbing, because these rhythms are commonly associated with information processing and cognitive events) is not due to the anesthetic agent because similar patterns are observed during natural slow-wave sleep (Fig. 6, SWS).

What are the Synchronizing Mechanisms of Fast Rhythms?

(i) Intracortical projections are particularly abundant within the association suprasylvian gyrus (Grüner *et al.*. 1974; Avendaño *et al.*, 1988), where a large part of our experiments have been conducted. The intracortical horizontal projections may span up to 8 mm in the visual cortex (Gilbert, 1992) and they have also been described in other sensory cortices (Jones *et al.*, 1978; Imig and Reale, 1981; Cauller and Connors, 1994), as well as among sensory and motor cortical fields (Avendaño *et al.*, 1992).

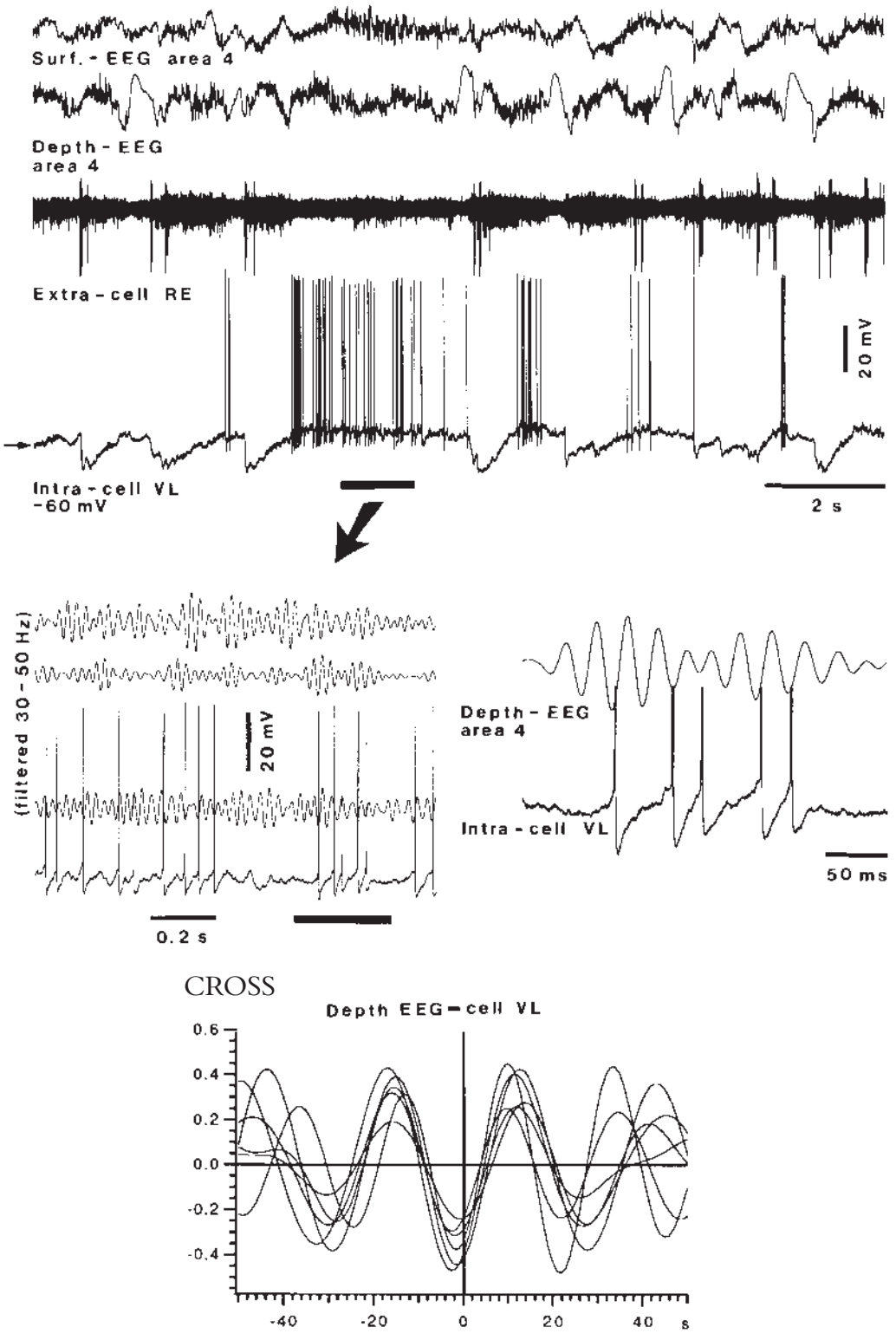


Figure 3. Episodes of tonic activation are associated with coherent fast rhythms (40 Hz) in cortical EEG and intracellularly recorded thalamocortical neuron. Cat under ketamine–xylazine anesthesia. *Top*, four traces represent simultaneous recordings of surface- and depth-EEG from motor cortical area 4, extracellular discharges of neuron from the rostrolateral part of the thalamic reticular (RE) nucleus and intracellular activity of thalamocortical neuron from ventral lateral (VL) nucleus. EEG, RE and VL cells displayed a slow oscillation (0.7–0.8 Hz) during which the sharp depth-negative (excitatory) EEG waves led to IPSPs in VL cell, presumably generated by spike-bursts in cortically driven GABAergic RE neuron. The part marked by the horizontal bar, taken from a short-lasting period of spontaneous EEG activation, is expanded below (arrow), with EEG waves and field potentials from the RE nucleus filtered from 30 to 50 Hz; the part marked by the horizontal bar in this panel is further expanded on the right to illustrate relations between action potentials of VL cell and depth-negative waves in cortical EEG at a frequency of 40 Hz. Cross-correlations (CROSS) between action potentials and depth-EEG show a clear-cut relation, with opposition of phase, between intracellularly recorded VL neuron and EEG waves. Modified from Steriade *et al.* (1996a).

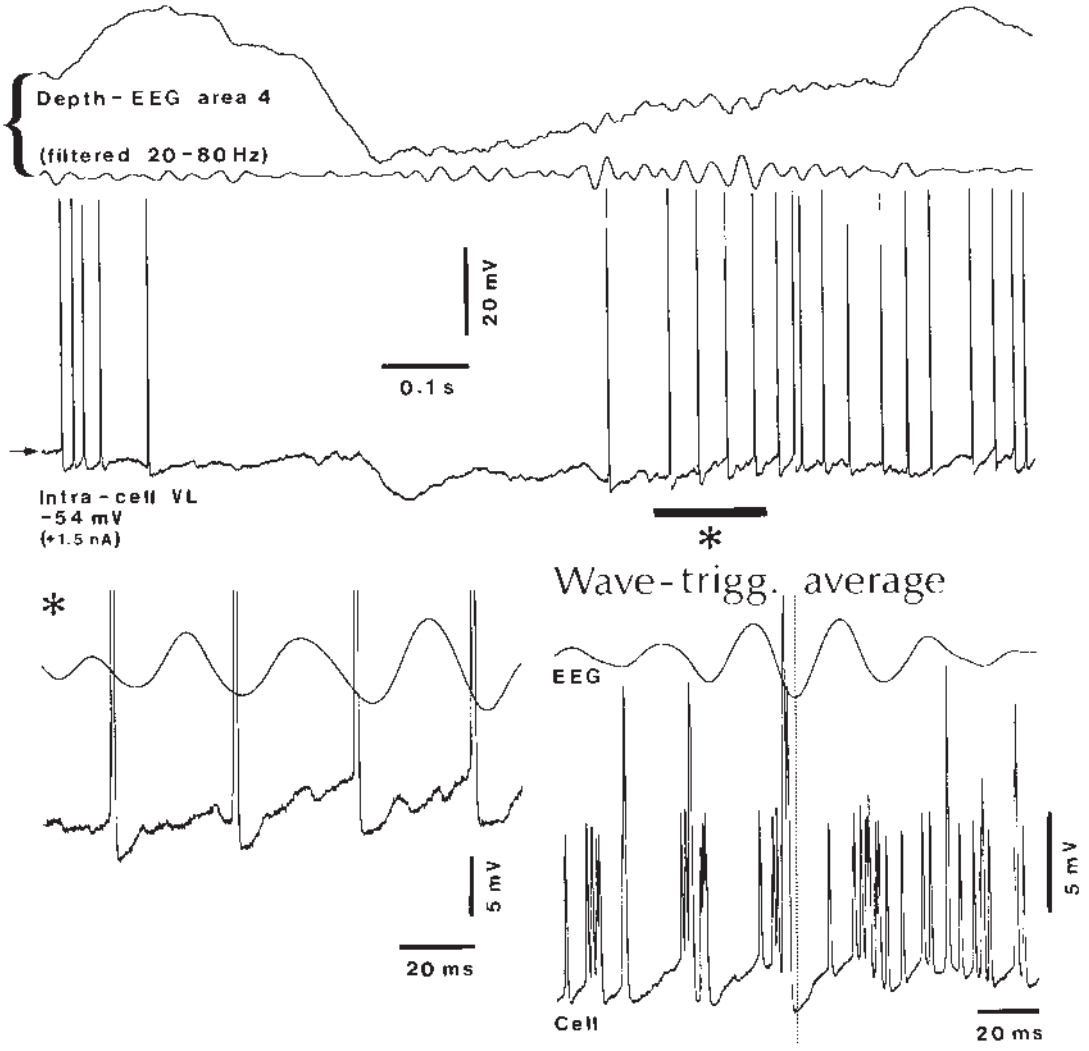


Figure 4. Coherent fast (30 Hz) rhythms in intracellularly recorded thalamic ventral lateral neuron and cortical field potentials recorded from the depth of area 4. Cat under ketamine–xylazine anesthesia. *Top*, three traces depict depth-EEG activity from area 4, filtered EEG waves (20–80 Hz) and intracellular activity of thalamocortical neuron. The episode includes one cycle of the slow oscillation (recurring at ~1 Hz), consisting of a long-lasting depth-positive EEG wave, partially associated with the cell's silenced firing, and followed by fast (~30 Hz) activity in both cortex and thalamus, eventually leading to another cycle of slow oscillation (initiated by another depth-positive EEG wave). The part marked by the horizontal bar and asterisk is expanded below, on the left. Note the correspondence between action potentials of thalamic cell and depth-negative field potentials in cortex. On the right is shown the wave-triggered average; negative components of depth-cortical EEG waves were used to trigger action potential in a thalamic neuron (see dotted line). Note, from the left to the dotted line are shown groups of action potentials recurring within the frequency range of the fast rhythm (~30 Hz). Data from experiments by M. Steriade and I. Timofeev.

The reciprocal, anterior-to-posterior and return excitatory connections within the cat suprasylvian gyrus have been disclosed through dual simultaneous intracellular recordings from areas 5 and 7 (Amzica and Steriade, 1995b). Note that fast oscillations are in-phase throughout the cortical depth, but the possibility of volume conduction is precluded because action potentials are present over the negative components of field potentials throughout the cortical depth, short time-lags are detected between the superficial and deep layers, and a dramatic reduction of fast activity is observed in the white matter (Steriade *et al.*, 1996a). Current-source-density analyses of the unexpected in-phase fast oscillations revealed that microsinks and microsources are alternatively distributed; thus, the smaller currents along the vertically oriented apical dendrites may account for the absence of depth reversal of fast rhythms across the cortical depth (Steriade and Amzica, 1996). In addition to excitatory projections through recurrent axonal collaterals of pyramidal neurons, a substantial amount of excitation results from disinhibition, through contacts between GABAergic basket cells (Kisvárday *et al.*, 1993). Experimental and modeling studies in neocortex and hippocampus have emphasized the role of inhibitory interneurons in short- and long-range synchronization of fast activities (Lytton and Sejnowski, 1991; Buzsáki and Chrobak, 1995; Whittington *et al.*, 1995; Traub *et al.*, 1996; Plenz and Kitai, 1997). As to the interhemispheric spread of fast rhythms (Engel *et al.*, 1991; Murthy *et al.*, 1992), it is secured by neurons with identified callosal projections that support voltage-dependent fast oscillations (Nuñez *et al.*, 1992).

(ii) Intrathalamic synchronization can be achieved through the reticular nucleus as there is no, or only negligible, cross-talk between thalamocortical cells (Jones, 1985). Although some data have emphasized the intrinsic nature of fast oscillations in reticular neurons exclusively and have denied their involvement in network operations as such rhythms have not been found to

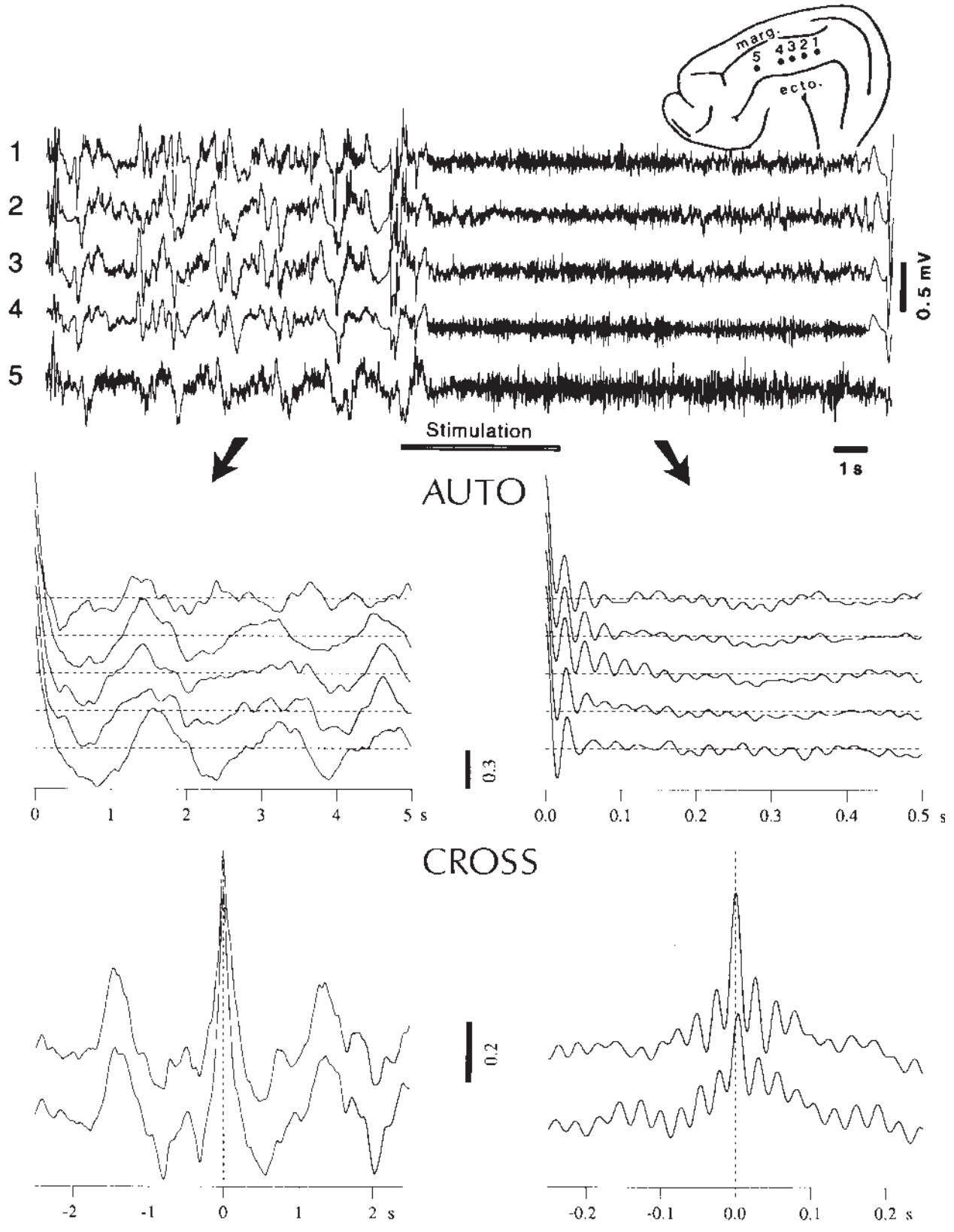


Figure 5. Synchronization of fast (30–40 Hz) spontaneous cortical rhythms elicited by stimulation of mesopontine cholinergic nuclei. Cat under ketamine–xylazine anesthesia. *Top*, slow oscillation and its disruption by brainstem stimulation (300 Hz, horizontal bar), associated with appearance of fast activity whose amplitude exceeds that of fast waves during sleep-like patterns. Numbers of recorded neocortical foci correspond to those indicated on the suprasylvian gyrus (areas 5 and 7). Other abbreviations: marg. and ecto., marginal and ectosylvian gyri. *Middle*, autocorrelation (AUTO) of activities from the five cortical foci, showing slow oscillation at ~0.7 Hz before stimulation (left) and fast rhythms (35–40 Hz) after stimulation (right). *Bottom*, cross-correlation (CROSS) between sites 2 and 3 (upper trace) and 2 and 4 (lower trace). Data from experiments by M. Steriade and F. Amzica.

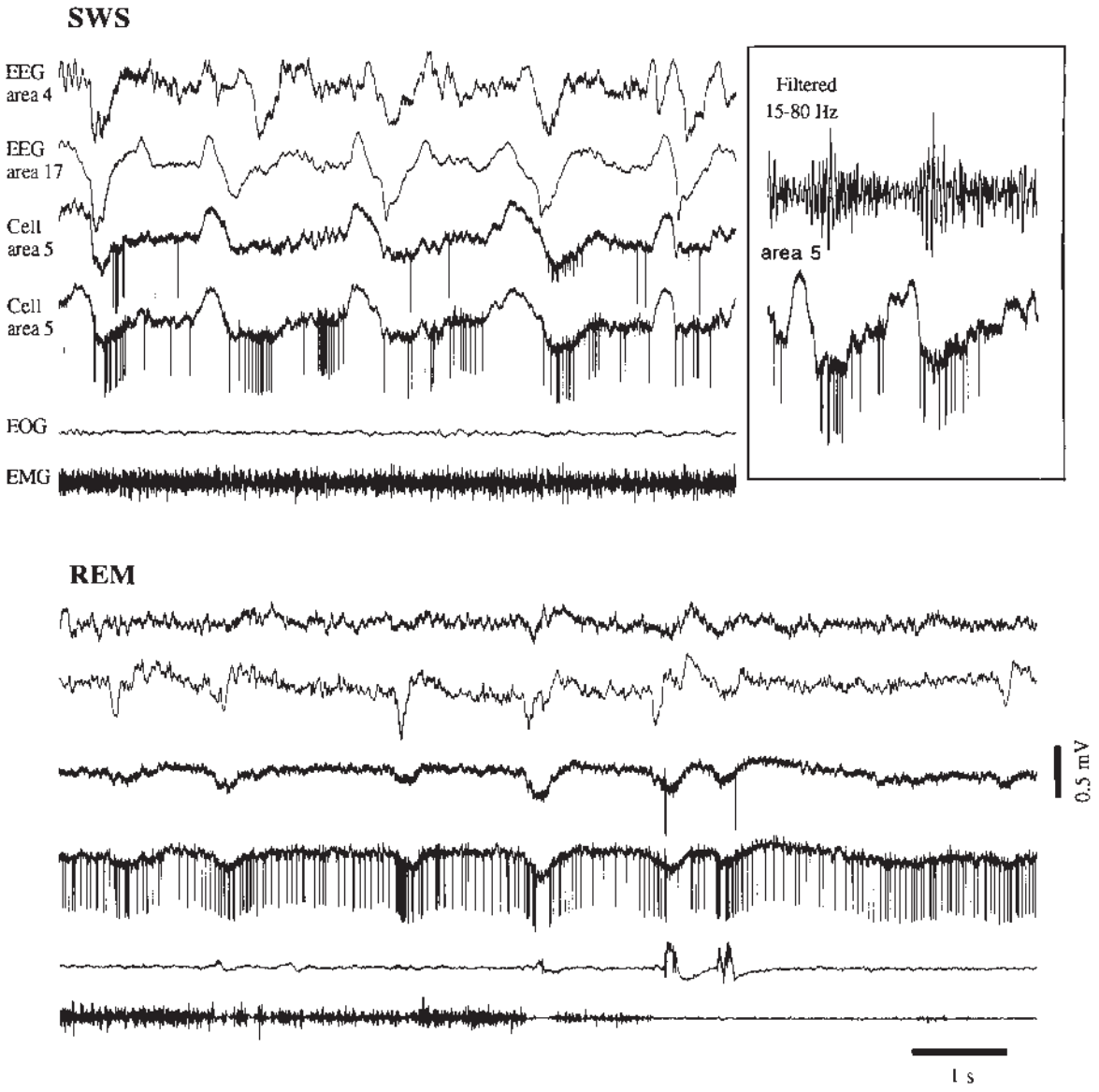


Figure 6. Patterns of slow oscillation during natural sleep are similar to those under ketamine–xylazine anesthesia. Selective reduction of fast rhythms during the inhibitory periods of the slow oscillation during natural sleep. Chronically implanted, naturally sleeping cat. SWS, slow wave sleep. REM, rapid-eye-movement sleep. SWS is separated from REM by a non-depicted period of 34 s. Six traces represent: depth-EEG from motor (precruciate) area 4; depth-EEG from visual area 17; unit discharges and slow focal potentials from association area 5 in the anterior suprasylvian gyrus; a similar recording from an adjacent focus (2 mm apart) in area 5; electrooculogram (EOG); and electromyogram (EMG). The right part in SWS panel shows reduction, up to disappearance, of fast rhythms (filtered 15–80 Hz) during the prolonged depth-positive wave of the slow oscillation that, in intracellular recordings, is associated with hyperpolarization of cortical and thalamic neurons. Data from experiments by M. Steriade and F. Amzica; inset in SWS is adapted from Steriade *et al.* (1996a).

be correlated with activities in dorsal thalamic nuclei and EEG (Pinault and Deschênes, 1992a), other studies have shown that fast (20–60 Hz) oscillations in the thalamic reticular nucleus appear in grouped sequences that are coherent with similar oscillations in cortically projecting thalamic nuclei and EEG (Steriade *et al.*, 1996b). The resetting and transiently increased amplitude of fast intrinsic oscillations in thalamic relay cells by short-lasting outward pulses suggests that short IPSPs originating in GABAergic neurons may reinforce fast oscillations in thalamocortical systems (Pedroarena and Llinás, 1997). Such inhibitory impulses probably arise in thalamic reticular cells as they display tonic, single-spike firing and high (30–40 Hz) discharge rates during the wake state (Steriade *et al.*, 1986).

(iii) Corticothalamic synchronization is achieved through both specific thalamocortical loops and connections through intralaminar and reticular nuclei. Cortical stimuli at 30–50 Hz lead to a dramatic increase in EPSP amplitudes in related thalamic cells (Deschênes and Hu, 1990; Lindström and Wróbel, 1990). The rostral intralaminar nuclei, mainly the central lateral one, are reciprocally related to widespread neocortical areas (Jones, 1985). Thus, the high-frequency (900–1000 Hz) spike-bursts recurring rhythmically at 40 Hz in cortically projecting intralaminar neurons (Steriade *et al.*, 1993c) may influence similar patterns of electrical activity in association (Steriade *et al.*, 1996a) and visual (Gray and McCormick, 1996) cortices where intralaminar neurons project toward superficial layers (Cunningham and LeVay, 1986). These data are congruent with the role of intralaminar nuclei in thalamocortical

synchronization of fast oscillations, postulated on the basis of magnetoencephalographic recordings in humans (Llinás and Ribary, 1993; Llinás *et al.*, 1994). It is also possible that some regions in the posterior parts of the intralaminar nuclear complex are required to coordinate the sensory-elicited fast oscillations between the primary and secondary cortical auditory fields (Barth and MacDonald, 1996). Coherent activity in the frequency range of fast oscillations (20–50 Hz) between rostral intralaminar and lateral geniculate nuclei has recently been described during instrumental conditioning of cats trained to generate groups of fast oscillations (Amzica *et al.*, 1997). This unexpected synchronization between two thalamic nuclei that are not directly interconnected may be explained by an intermediate link in the cerebral cortex as intralaminar central lateral neurons project to visual cortex and coherent fast oscillations were demonstrated between visual cortex and lateral geniculate nucleus (see above). Large-scale corticothalamic synchronization is also provided by corticothalamocortical loops returning not only to the same area, but also to distant fields (Kato, 1990).

Brain Activation, Feature Binding and Consciousness

The present interest in fast oscillations was aroused by hypotheses about their possible role in focused attention and in binding different features of the external world into global percepts (see Singer and Gray, 1995; Llinás and Churchland, 1996). Fast oscillations can be recorded during states of expectancy, when animals and humans pay intense attention to different stimuli (Lopes da Silva *et al.*, 1970; Bouyer *et al.*, 1981; Murthy and Fetz, 1992; Desmedt and Tomerg, 1994). It was hypothesized that, in addition to the spatial dimension of topographical maps, a temporal component may generate an indefinitely large number of representations that would extract the relevant characteristics of a given configuration (Abeles, 1982). The current postulate is that the firing patterns of neurons responding to different parts of the same object should be temporally coherent (von der Malsburg and Schneider, 1986; Crick and Koch, 1990; Llinás, 1990; Singer and Gray, 1995).

Alternatively, the fast oscillations are considered as part of the background electrical activity of the brain, simply reflecting a condition of neuronal depolarization which is potentiated by central core activating systems (Steriade, 1993). Stimulation of mesopontine cholinergic nuclei induces fast rhythms and tonic depolarization in thalamocortical systems (Steriade *et al.*, 1996a,b), an effect that survives extensive lesions of nucleus basalis (Steriade *et al.*, 1991b); and stimulation of nucleus basalis or endogenous acetylcholine potentiates the fast oscillations (Metherate *et al.*, 1992; see reviews of cellular mechanisms by McCormick, 1990, 1992). Thus, the synchronization of responses evoked by optimal sensory stimuli may just be the tip of the iceberg, as multi-site, extra- and intracellular recordings demonstrate spontaneously occurring fast rhythms during brain-active states associated with tonic depolarization of thalamic and cortical neurons (wake and REM sleep) but also, more episodically because of the suppression of fast rhythms during the prolonged hyperpolarizing phase of the slow oscillation, in natural resting sleep and deep anesthesia (Steriade *et al.*, 1996a,b).

The fact that fast rhythms appear during states characterized by obliteration of consciousness, when thalamocortical gates are closed to the external world, does not preclude that the same intrinsic properties and network operations underlie feature binding, necessary for cognitive experiences during adaptive behavioral states. Depolarization is a prerequisite for the development of fast oscillations. It was proposed that activation of thalamocortical circuits at ~40 Hz upon arousal (Steriade *et al.*, 1991b, 1996a) sets the stage for the phase-locked 40 Hz oscillation between parietal and prefrontal areas when cognitive electrogenesis is initiated (Desmedt and Tomberg, 1994). Similarly, a generalized activation process is developing underneath and simultaneously with the instrumental conditioning of 20–50 Hz rhythms, although the spatial selectivity of the conditioned response, together with its extinction and simultaneous drop in the corticothalamic synchrony of fast rhythms, suggests that 'learning' involves more than a diffuse increase in activation (Amzica *et al.*, 1997). The view that fast oscillations are implicated in brain attentive processes, either focused or associated with more diffuse arousal, rather than playing a role in sensorimotor binding, is supported by experiments on awake monkeys (Murthy and Fetz, 1997a,b). Then, the issue is the development of behaviorally relevant oscillations on the basis of spontaneously occurring, depolarization-dependent fast rhythms. Indeed, weakly synchronized, fast spontaneous oscillations can be reset and become robustly coherent over a time window of ~600 ms after a synchronous afferent volley (Steriade and Amzica, 1996; Steriade *et al.*, 1996a), suggesting that a similar phenomenon may occur after sensory stimuli during wakefulness or ponto-geniculo-occipital (PGO) potentials during the dreaming state.

If some elementary processes of cognitive events and their relations with fast oscillations can be investigated at the cellular level, this author is uncomfortable in venturing beyond observable facts when ill-defined terms (such as 'consciousness') are used, because our armamentarium is not, and (arguably) never will be, sophisticated enough to understand these general notions by using isolated pieces of correlative evidence from more or less circumscribed brain structures.

Low-Frequency Rhythms in Thalamocortical Loops during Normal and Paroxysmal States

Corticofugal volleys exert decisive effects on thalamic operations. It has been a common belief that, in contrast to the considerable number of corticothalamic axons, the function of this projection is not known. However, recent work indicates that the patterns and synchronization of thalamic rhythms are decisively influenced by activities in corticothalamic projections. These effects relate to the grouping of thalamic rhythms by cortical ones (Steriade *et al.*, 1993b, 1994; Contreras and Steriade, 1995), the cortical control of spatiotemporal coherence of thalamic spindle oscillations (Contreras *et al.*, 1996a, 1997b) and other aspects characterizing resting sleep, but also concern the information processing during the wake state as the feature-linked synchronization of lateral geniculate neurons is disrupted by removal of the visual cortex (Sillito *et al.*, 1994). Since data demonstrate that various sleep rhythms are grouped together by corticothalamic volleys and appear under the umbrella of the slow cortical oscillation, the neocortex and thalamus should be explored as a unified oscillatory machine, in addition to the investigation of local circuits. In what follows I substantiate this statement by results from experiments investigating sleep oscillations and their development to seizures, particularly those with spike-wave or polyspike-wave complexes intermingled with runs of fast spikes.

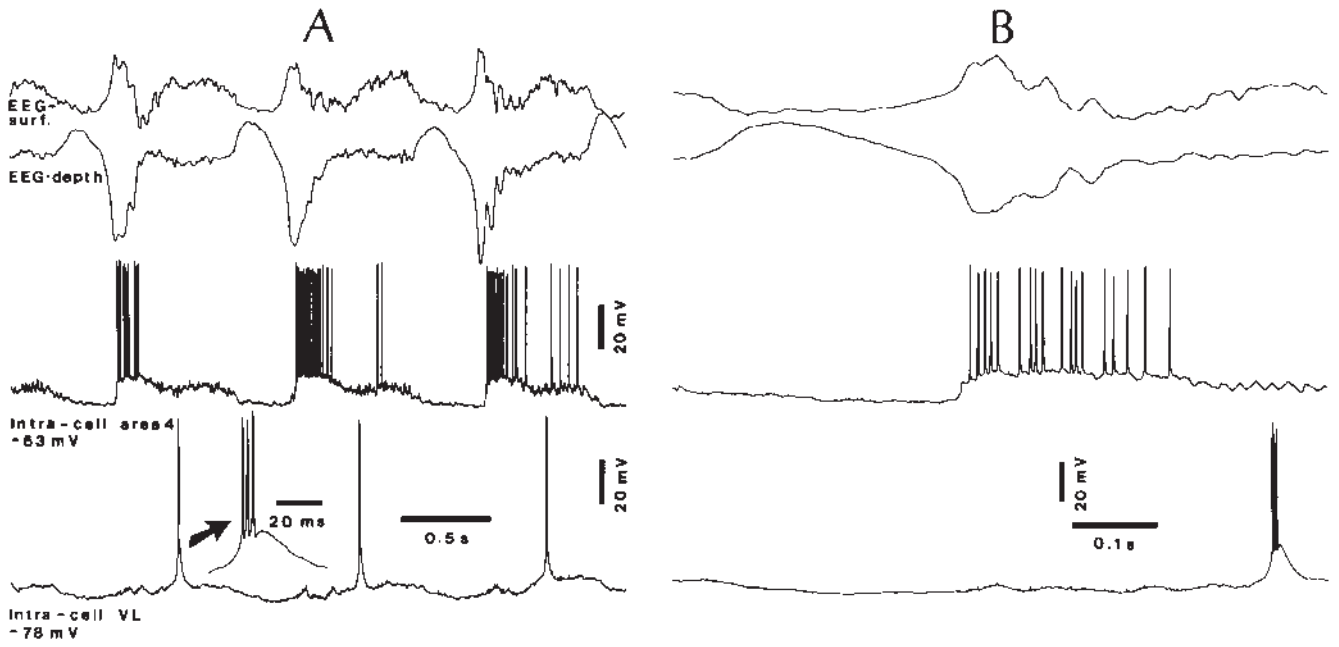


Figure 7. The slow oscillation (~0.9 Hz) in dual simultaneous intracellular recordings from regular-spiking cell in cortical area 4 and thalamocortical cell in the ventrolateral nucleus. Cat under ketamine–xylazine anesthesia. Arrow in *A* points to a low-threshold spike-burst. An expanded cycle is shown in *B*. Note: (*a*) depth-positive (upward) EEG waves are associated with hyperpolarization of cortical and thalamic cells, whereas the sharp depth-negativies are associated with depolarization and action potentials in cortical cell, while the thalamic neuron displays a rebound spike-burst with a delay of 150–200 ms; (*b*) brief sequence of EEG spindles after the depth-negative (surface-positive) sharp deflection; and (*c*) fast depolarizing waves (40–50 Hz) in cortical neuron during the sustained depolarization. Data from experiments by M. Steriade and D. Contreras.

Complex Wave-Sequences, Comprising Various Sleep Rhythms, Are Produced by the Slow Cortical Oscillation

Cortical volleys synchronize thalamic neurons and activate spindle oscillations (7–14 Hz), even by stimulating the contralateral cortex to avoid backfiring of thalamocortical cells (Steriade *et al.*, 1972; Contreras and Steriade, 1996, 1997). This demonstrates the role of corticothalamic projections in the synchronization of spindles. The cortical effect is observed not only by using electrical stimuli, but is also elicited by the synchronous depolarization of neocortical neurons during a spontaneously occurring slow oscillation (<1 Hz), first described in intracellular recordings from anesthetized cats (Steriade *et al.*, 1993e) and also found during the state of resting sleep in cats (Steriade *et al.*, 1996a) and humans (Achermann and Borbély, 1997; Amzica and Steriade, 1997a,b). The slow oscillation is generated intracortically as it survives extensive thalamectomy (Steriade *et al.*, 1993f), is absent in the thalamus of decorticated animals (Timofeev and Steriade, 1996) and its synchronization is disrupted by disconnection of intracortical synaptic linkages (Amzica and Steriade, 1995b).

The frequency of the slow oscillation is ~0.3–0.6 Hz under urethane anesthesia; it is 0.5–0.9 Hz under ketamine–xylazine anesthesia; and increases up to ~1 Hz during natural slow-wave sleep in cats and humans. During natural sleep, the slow oscillation occurs synchronously over morphologically distant and functionally different (sensory, motor and association) cortical areas (Fig. 6) and is virtually identical to the slow oscillation under ketamine–xylazine anesthesia, the best experimental condition for performing single or dual intracellular recordings of this oscillation *in vivo* (Fig. 7). The use of this anesthetic may increase the degree of synchronization and induce a stereotyped pattern of the slow sleep oscillation which makes it favorable for intracellular analyses, similar to the use of barbiturates when revealing the cellular substrates of spindles.

The resemblance between the electrographic patterns of the slow oscillation during natural sleep and ketamine–xylazine anesthesia concerns the two major components of this oscillation in neocortical neurons: a long-lasting (0.4–0.8 s) cellular hyperpolarization (associated with a depth-positive EEG wave), followed by a prolonged depolarization initiated by a sharp event (associated with a depth-negative EEG deflection) that leads to a brief spindle sequence and, eventually, to a depolarizing plateau associated with fast oscillations (Fig. 7). The K-complex, a major grapho-element of the sleep EEG, described as an initially surface-positive transient followed in some instances by a spindle sequence (Niedermeyer, 1993), but whose cellular substrates have remained unknown, has recently been investigated intracellularly in animals and at the field potential level in humans (Amzica and Steriade, 1997a,b). The conclusions of these studies are as follows. (i) The K-complexes recur periodically, with peaks in spectral analyses at 0.5–0.7 Hz. They result from a synchronized cortical network that imposes rhythmic excitatory and inhibitory actions on cortical and thalamic neurons. (ii) The surface K-complex reverses in cat cortex at 0.3 mm. At the cortical depth, it mainly consists of a sharp negative deflection, reflecting synchronous depolarizations of cortical neurons, impinging upon thalamic neurons, and generating a brief sequence of spindle waves. Thus, the K-complex is part of the slow cortical oscillation (the depth-negative, surface-positive excitatory component) that may trigger a brief sequence of spindle waves.

The relations between cellular and EEG field potentials are similar in identified superficial and deeply lying pyramidal neurons and local-circuit basket cells (Contreras and Steriade,

1995). The prolonged hyperpolarization is associated with an increase in the input resistance of cortical and thalamic (reticular and relay) cellular types, which suggests that the dominant mechanism of this phase is a generalized disfacilitation in corticothalamic networks, whereas the input resistance is lowest during the subsequent sharp depolarization (Contreras *et al.*, 1996b). The fast rhythms, superimposed on the depolarizing plateau, are selectively reduced or abolished during the prolonged hyperpolarizing periods (see above, inset in Fig. 6, top SWS panel). which again emphasizes the depolarization-dependency of fast oscillations. With transition from SWS to REM sleep, the slow oscillation disappears and generalized activation patterns are observed, including widespread and synchronously occurring PGO waves (Fig. 6; see also Amzica and Steriade, 1996).

Dual intracellular recordings from cortical and thalamic neurons demonstrate a spectacular simultaneity of long-lasting hyperpolarizations during the slow oscillation (Fig. 8) and are at the basis of the proposal that the synchronization of the EEG results from synchronous hyperpolarizations in cortical and thalamic neurons (Fig. 9; Steriade *et al.*, 1994; Contreras and Steriade, 1995). Thus, in contrast to the short-range synchronization of fast oscillations, the slow oscillation involves large populations of heterogenous cell-types in the cortex and thalamus. Because one of the two key components of the slow oscillation is a prolonged hyperpolarization of cortical and thalamic cells, this oscillation produces a state of brain deafferentation by largely overwhelming the operations in different domains of cortical and thalamic microcircuitry which are devoted to integrative processes during the adaptive state of wakefulness. Indeed, the responses of cortical and thalamic neurons evoked by stimuli to brainstem afferent pathways are greatly diminished during the long-lasting hyperpolarizations, whereas the intracortical and corticothalamic dialog may remain operative during certain phases of the slow oscillation (Timofeev *et al.*, 1996). As known, the thalamus is the first relay station where significant decrease in synaptic responsiveness to afferent signals is observed from the onset of drowsiness, before overt manifestations of sleep (Steriade, 1991).

In line with the idea that corticothalamic drives play a crucial role in grouping different sleep rhythms, the sharp depolarizing component of the slow oscillation, associated with synchronous firing in cortical neurons, periodically excites the GABAergic thalamic reticular cells and thus produce IPSPs in their targets, the thalamocortical cells (Fig. 10). At more hyperpolarized levels, thalamocortical neurons fire rebound spike-bursts, with variable delays after the corticothalamic volleys (see above, Fig. 8). This assists in generating and synchronizing thalamic spindles (see the next section). The slow cortical oscillation also groups delta waves (1–4 Hz) in sequences recurring with a rhythm below 1 Hz (Fig. 11). This is one of the compelling arguments for dissociating the two (delta and slow) sleep rhythms. The differences in the dynamics between the slow oscillation (<1 Hz) and delta waves (>2 Hz) in human sleep (Achermann and Borbély, 1997) corroborate the cellular data from experiments on cats (Steriade *et al.*, 1993f; Fig. 11). In addition to the cortically generated delta activity, thalamocortical cells generate intrinsically a rhythm within the frequency range of delta waves (1–4 Hz), resulting from the hyperpolarization-activated interplay between two currents, I_h and I_t (McCormick and Pape, 1990; Leresche *et al.*, 1991; Soltesz *et al.*, 1991; Curró Dossi *et al.*, 1992). Corticothalamic volleys effectively synchronize thalamic neuronal pools displaying the clock-like delta rhythm at 1–4 Hz (Steriade *et al.*, 1991a) and thus create favorable conditions to reflect the intrinsic delta thalamic oscillation at the cortical cellular and EEG levels (see figs 1–2 in Steriade *et al.*, 1993f). The concept of corticothalamic potentiation upon low-frequency bursting in thalamic relay cells (Steriade *et al.*, 1991a) is supported by experiments on thalamocortical slices in which the contribution of cortex to low-frequency spike-bursts in thalamic neurons was demonstrated by the absence of such responses after removal of cortex in the slice (Kao and Coulter, 1997).

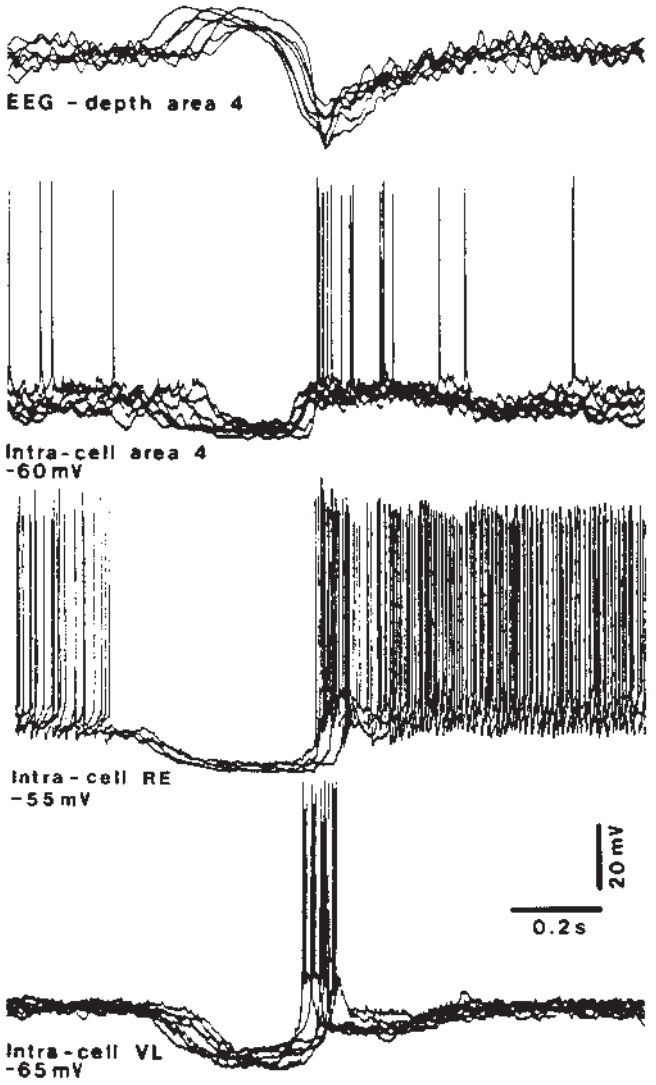


Figure 8. Synchronization of slow oscillation in cortical and thalamic neurons. Cat under ketamine–xylazzine anesthesia. Simultaneous intracellular recordings from area 4 and thalamocortical neuron in the ventrolateral (VL) nucleus. The intracellular activity of the thalamic reticular (RE) neuron was similar with respect to different components in the slow EEG oscillation. All activities are aligned on the peak of EEG depth-negativity. Note the simultaneity of long-lasting hyperpolarizations (related to the depth-positive component of the slow oscillation) in all (cortical and thalamic) cell-types. The depth-negative EEG deflection was associated with spike-trains in cortical cell and spike-bursts in thalamic cells. Adapted from Contreras and Steriade (1995).

Corticothalamic Inputs Governing Spindle Generation and Synchronization

Spindles, a hallmark oscillation that characterizes the early stages

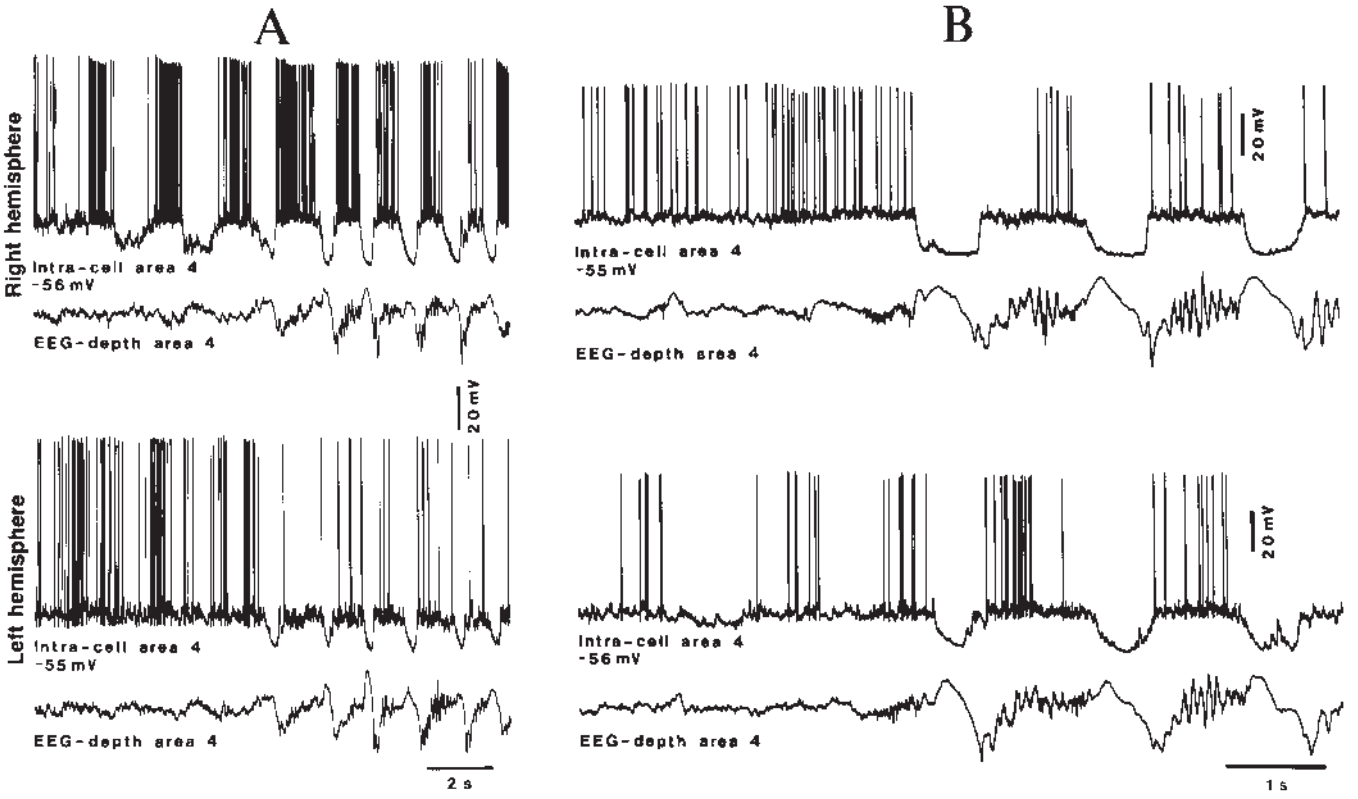


Figure 9. The synchronization of EEG is concomitant with simultaneous hyperpolarizations in neocortical neurons. Dual intracellular recordings from right and left areas 4. Two neuronal couples (*A* and *B*) are shown. Note in *A* that, while right area 4 neuron started to display low-amplitude, rhythmic hyperpolarizations, left area 4 neuron still displayed tonic firing, and the EEG showed an activated pattern; only when both cells simultaneously displayed large hyperpolarizations was the EEG fully synchronized with the patterns of slow oscillation and brief spindle sequences. In *B*, simultaneous hyperpolarizations in the two neurons occurred suddenly. Adapted from Steriade *et al.* (1994) and Contreras and Steriade (1995).

of resting sleep, consist of sequences of waves at 7–14 Hz that recur periodically with a slow rhythm of 0.2–0.5 Hz. Spindles are generated in the thalamus even after decortication and high brainstem transection (Morison and Bassett, 1945). Also, waxing-and-waning augmenting responses, mimicking spindles, can be generated in the thalamus of decorticated animals (Steriade and Timofeev, 1997). The cellular mechanisms underlying the generation and synchronization of spindles have been elucidated in experiments on cats conducted *in vivo* (Steriade and Deschênes, 1984, 1988; Steriade *et al.*, 1985, 1987; Contreras *et al.*, 1993; Contreras and Steriade, 1996; Contreras *et al.*, 1996a, 1997b; reviewed in Steriade and Llinás, 1988; Steriade *et al.*, 1990, 1993d, 1997) and in ferret lateral geniculate–perigeniculate slices maintained *in vitro* (von Krosigk *et al.*, 1993; Bal *et al.*, 1995a,b; Kim *et al.*, 1995; Bal and McCormick, 1996; reviewed in McCormick and Bal, 1997). The data obtained *in vivo* and *in vitro* are largely in agreement and complement each other.

In essence, three main sets of data arose from our experiments *in vivo*. (i) Spindle-related, rhythmic and prolonged IPSPs of thalamocortical cells are produced by GABAergic reticular neurons as, after disconnection from the thalamic reticular nucleus, the IPSPs are short and arrhythmic, and consequently spindles are abolished in thalamocortical systems (Steriade *et al.*, 1985). Similarly, one type of spindle-like augmenting responses of thalamocortical neurons, consisting of low-threshold responses resulting from progressively growing, chloride-dependent IPSPs followed by spike-bursts, are ascribed to incremental responses in thalamic reticular neurons (Steriade and Timofeev, 1997). (ii) Spindles are preserved in the rostral pole of the reticular nucleus deafferented from the dorsal thalamus (Steriade *et al.*, 1987). However, we emphasized in the latter study that, in the normal condition of an intact brain, excitatory inputs, such as spike-bursts in thalamocortical neurons, may be effective in triggering the oscillatory equipment of the thalamic reticular nucleus. The role of interactions between thalamocortical and thalamic reticular neurons in spindle genesis was intensively investigated in thalamic slices (von Krosigk *et al.*, 1993; Bal *et al.*, 1995a,b). And (iii) the cortex exerts a decisive role on the generation, synchronization and shape of spindles (Steriade *et al.*, 1972; Contreras and Steriade, 1996; Contreras *et al.*, 1996a, 1997b). As the main emphasis in this paper is placed on corticothalamic influences, I elaborate on the last point.

Although spindles appear in the thalamus of decorticated animals, they are under a potent control arising in the cerebral cortex. The corticofugal pathway to the thalamic reticular nucleus, that plays a crucial role in spindles, is a monosynaptic projection: during waking it elicits high-security, single-spike responses to fast stimuli, whereas during sleep patterns it triggers spike-bursts within the frequency range of spindles (Steriade and Wyzinski, 1972). Cortical inputs act on the dendrites of thalamic reticular cells and produce graded, high-frequency dendritic spike-bursts whose magnitudes are modulated by changing the intensity of the corticothalamic synaptic volley (Contreras *et al.*, 1993). At least in felines,

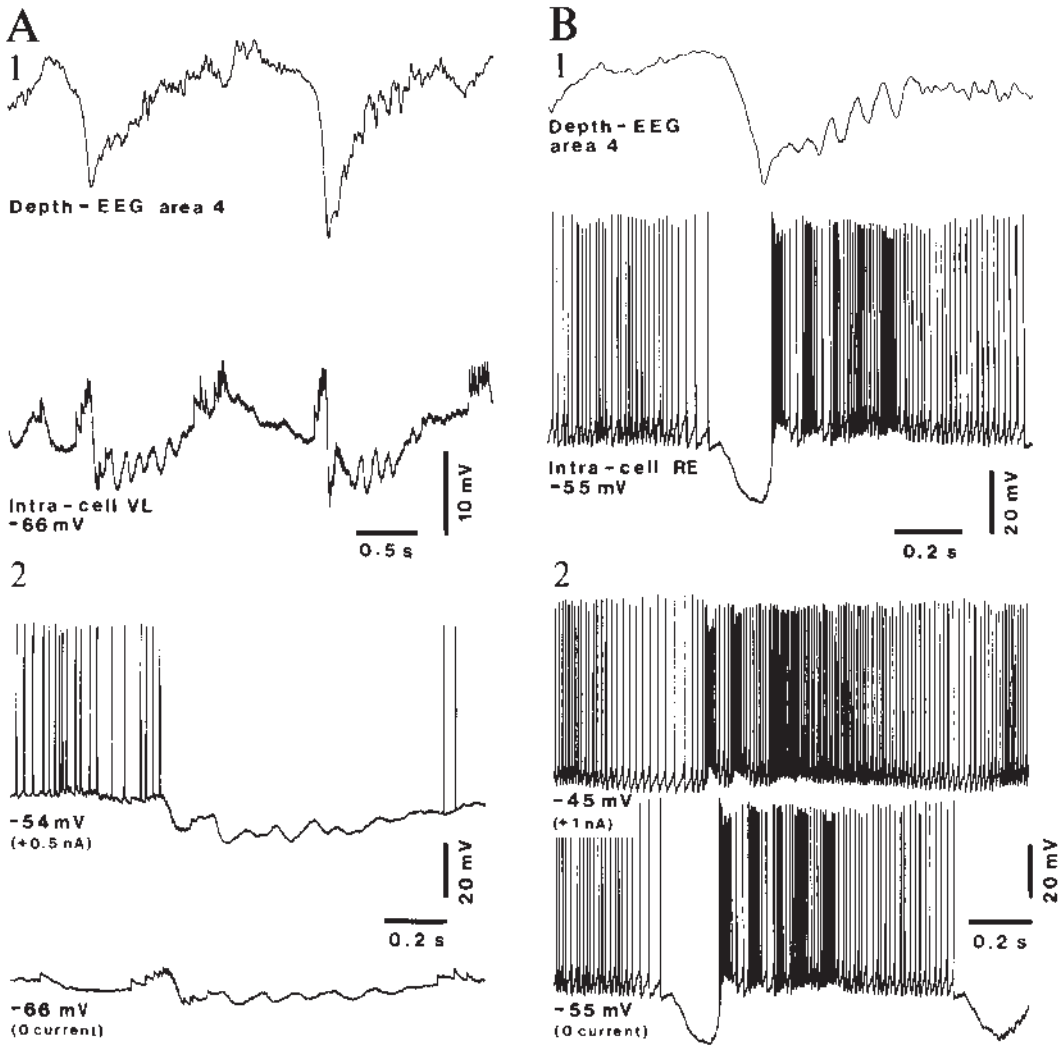


Figure 10. Effect of sharp corticothalamic volleys during the depolarizing phases of the slow sleep oscillation upon thalamocortical and thalamic reticular cells. Cat under ketamine–xylazine anesthesia. (*A*) Depth-EEG from area 4 and intracellular recording from a ventrolateral (VL) thalamocortical neuron. In *1*, two cycles of slow oscillation (0.5–0.6 Hz) at the resting membrane potential (-66 mV) of the VL cell. Note the brief sequence of spindle waves in EEG and the corresponding IPSPs in the VL cell following the sharp depth-EEG (depolarizing) component of the slow oscillation. In *2*, expanded traces to illustrate enhancement of spindle-related IPSPs with cell's depolarization. (*B*) Depth-EEG from area 4 and intracellular recording from a thalamic reticular (RE) neuron. In *1*, resting membrane potential (–55 mV). Note the spindle-related spike-bursts in association with EEG spindles that follow the hyperpolarizing phase of the slow oscillation. In *2*, expanded trace at the resting level and under depolarizing current. Data from experiments by I. Timofeev and M. Steriade.

thalamic reticular cells interact through dendrodendritic synapses (Deschênes *et al.*, 1985; Yen *et al.*, 1985). Experimental and modeling studies based on intact or dendritic-truncated reticular cells (Huguenard and Prince, 1992; Destexhe *et al.*, 1996) have shown that the typical spike-bursts of reticular cells observed during the natural state of resting sleep, with accelerando–decelerando patterns (Domich *et al.*, 1986; Steriade *et al.*, 1986), can be observed with a high density of low-threshold Ca^{2+} currents, located distally in the dendrites. These studies provide further support for the idea that corticothalamic excitatory volleys trigger spike-bursts in reticular neurons and thus, through further interactions with thalamocortical neurons, promote spindle oscillations that are visible at the macroscopic level of brain electrical activity.

Several factors have been proposed to explain the persistence of spindles in the deafferented rostral pole of reticular nucleus *in vivo*. One of them is the presence of depolarizing modulatory systems, including some corticothalamic and brainstem–thalamic projections. For example, compartmental models of thalamic reticular neurons have shown that a reticular network can be switched from the silent to the spindling oscillatory mode by activating depolarizing synapses, blocking ~20% of the leak K^+ channels (Destexhe *et al.*, 1994a). Spindles have been found in modeling studies of the isolated thalamic reticular nucleus having neurons densely interconnected with $GABA_A$ and $GABA_B$ synapses (Destexhe *et al.*, 1994b; Golomb *et al.*, 1994). However, the full synchrony of spindles within the isolated reticular nucleus can be assisted by excitatory inputs arising in corticothalamic and/or thalamocortical neurons.

The patterns of thalamic spindles differ as a function of presence or absence of cortical inputs, and they also depend on the intensity of the evoking stimulus. In intact-cortex animals, thalamic spindles occurring spontaneously under ketamine–xylazine anesthesia are short (0.4–0.5 s) and display an exclusively waning pattern, whereas in the decorticated (contralateral) hemisphere of the same animal spindles are much longer in duration (2–3 s) and have a waxing-and-waning pattern (Timofeev and Steriade, 1996). This is due to the fact that, in the

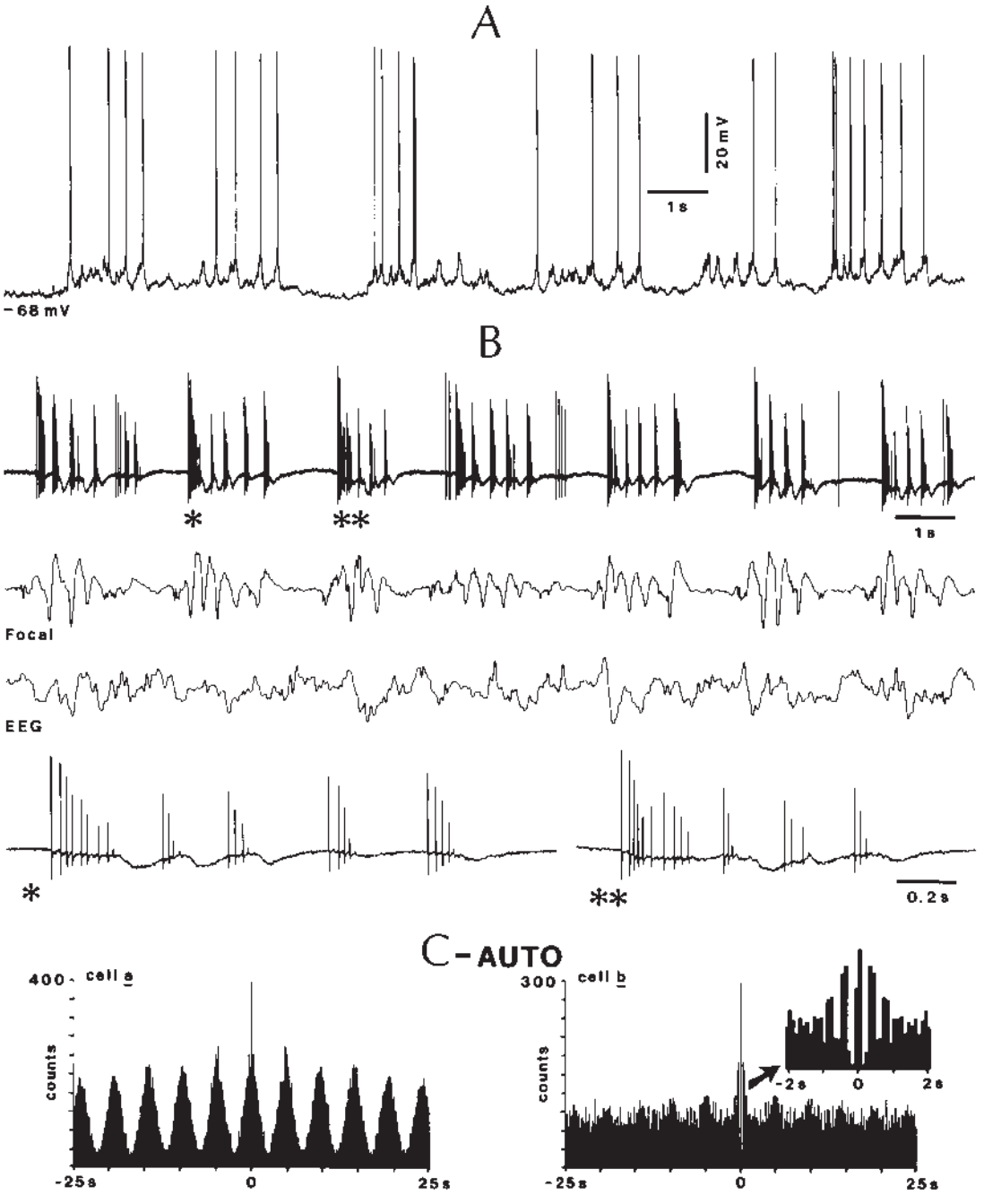


Figure 11. Grouping of delta waves by slow oscillation. Cats under urethane anesthesia. (*A*) Intracellular recording of a regular-spiking, corticothalamic cell in area 5, backfired from rostral intralaminar central lateral (CL) and driven synaptically from lateral posterior (LP) nucleus. Note the delta cellular oscillation (3–4 Hz) grouped within sequences recurring with a slow rhythm (0.3–0.4 Hz). (*B*) Extracellular recording of a bursting cell at a depth of 0.6 mm in area 7, convergently excited by LP and CL nuclei. Below the cellular trace, focal waves recorded through the same micropipette and gross EEG waves from the cortical surface are depicted. The sequence of spike-bursts marked by one and two asterisks are expanded below. Delta oscillations (3–4 Hz) are grouped by the slow oscillation (0.3–0.4 Hz). (*C*) Slow and delta rhythms in two cells, recorded simultaneously, extracellularly (*a*, single-spike discharging; and *b*, bursting cell) from motor area 4 (depth 1.3 mm). Autocorrelograms show that both cells displayed the slow oscillation (0.2 Hz) and that cell *b* also oscillated in the delta frequency (2.5 Hz) within the slowly recurring sequences (see arrow and inset). Adapted from Steriade *et al.* (1993f).

intact-cortex hemisphere, synchronous corticothalamic volleys during the depolarizing phase of the slow oscillation entrain, right from the start, a great cellular population or even the totality of thalamic neurons implicated in the generation of a spindle sequence, thus explaining the absence of a waxing process (Contreras and Steriade, 1996). These two different types of spindle patterns are also seen during natural sleep of behaving cats: short and exclusively waning spindles generally follow the depolarizing component of the slow oscillation, whereas longer-lasting and waxing-and-waning spindles occur in periods free of the slow oscillation (F. Amzica and M. Steriade, unpublished data). Also, spindles evoked by electrical stimuli to the cortex are relatively short and exclusively waning, compared with the much longer spindle sequences occurring spontaneously (Contreras and Steriade, 1996). When spindles are elicited by thalamic stimuli in a decorticated animal, brief

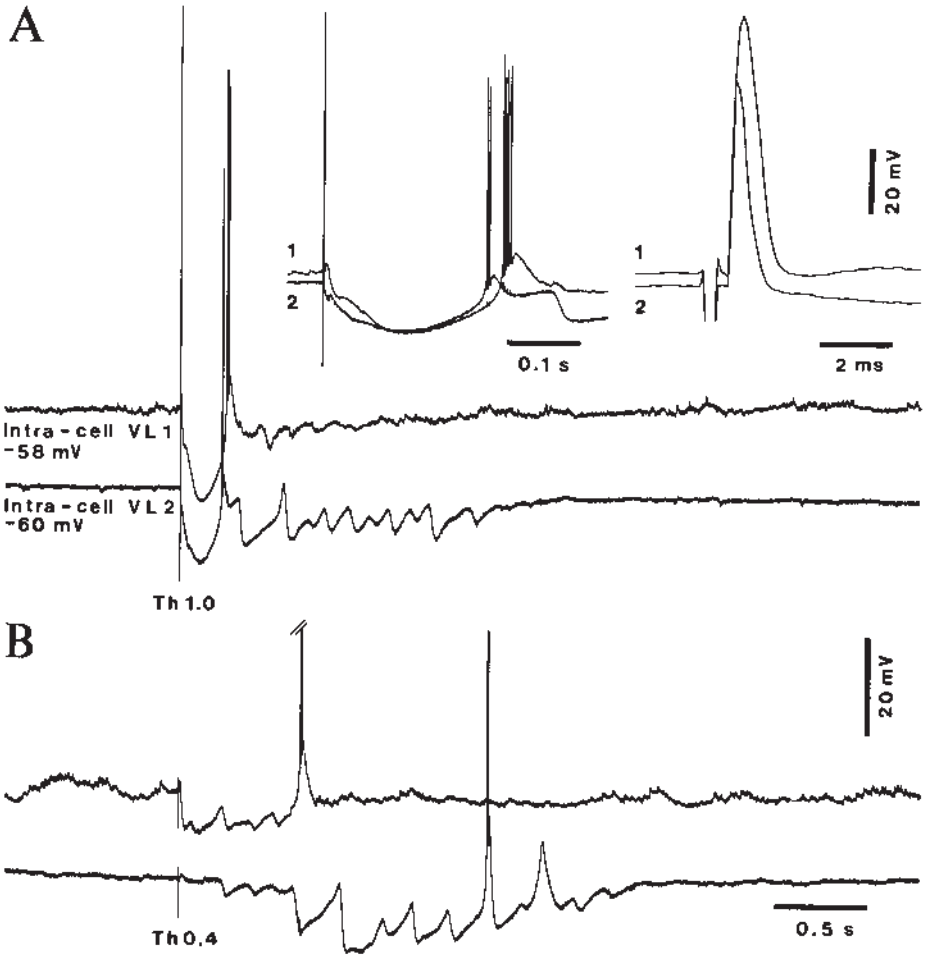
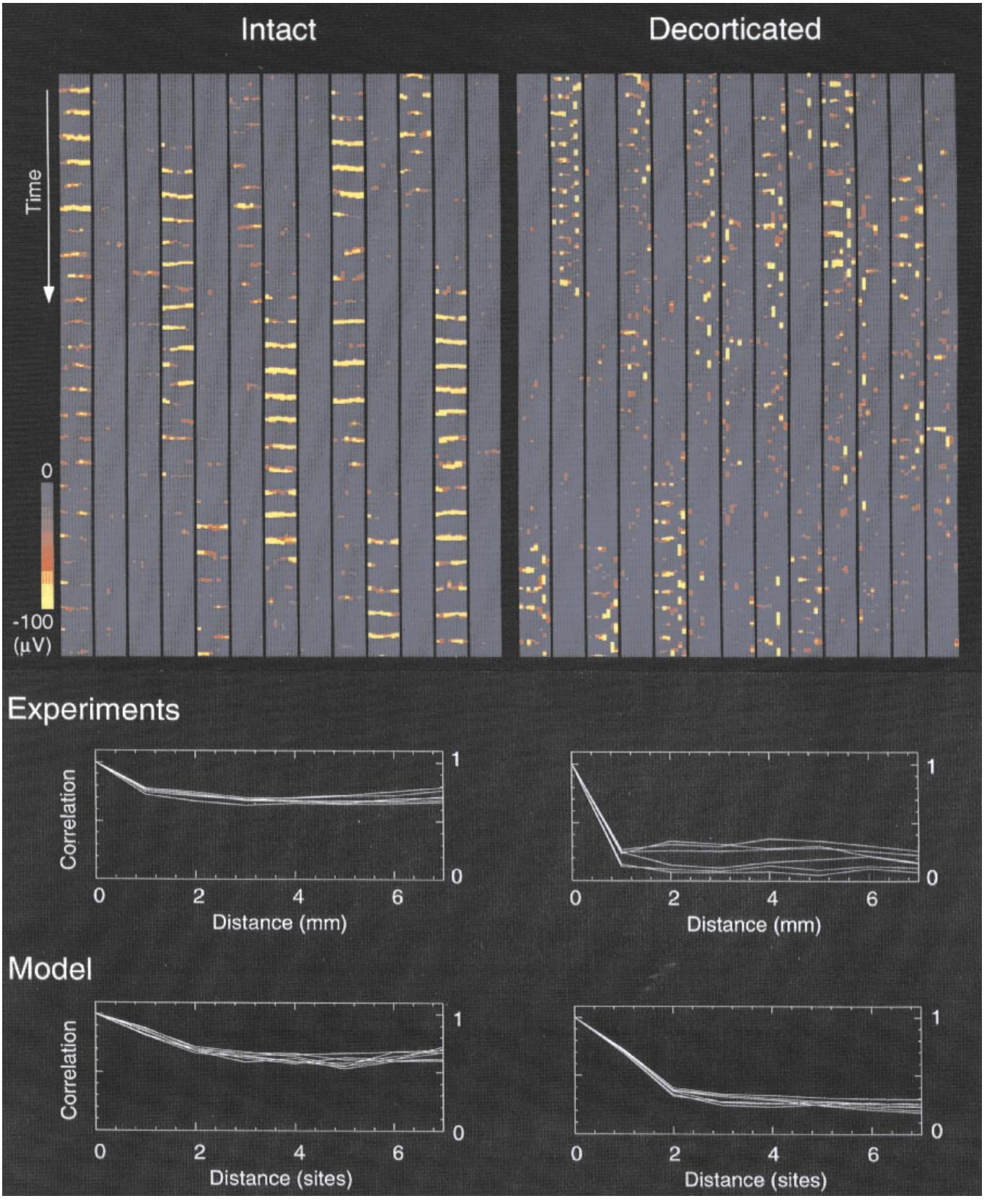


Figure 12. Waning or waxing-and-waning spindles are evoked by thalamic stimuli with different intensities. Decorticated cat under ketamine–xylazine anesthesia. Dual, simultaneous intracellular recordings of thalamocortical cells (VL1 and VL2) from the VL thalamic nucleus in the decorticated hemisphere (the two neurons were 2 mm apart). (*A*) Thalamic (Th) stimulation at maximal intensity (1.0). The initial response of VL1 and VL2 neurons are expanded at two increasing speeds. Note antidromic responses in both cells. (*B*) Thalamic stimulus at 0.4 intensity. Note short and waning spindles at maximum intensity, and longer spindles with typical waxing-and-waning pattern (especially in VL2) at lower intensity. Adapted from Timofeev and Steriade (1996).

and waning spindle sequences appear at high intensities, whereas stimuli with lower intensities evoke longer spindles, with waxing-and-waning IPSPs and postinhibitory rebound spike-bursts (Fig. 12).

In vivo, spindle sequences occur almost simultaneously throughout the thalamus and cerebral cortex during barbiturate anesthesia and natural sleep (Contreras *et al.*, 1997b). As spindle sequences recur with a slow rhythm of 0.2–0.5 Hz (Steriade and Deschênes, 1984), the interspindle lulls are 2–5 s. During natural sleep, the initiation of spindle sequences in different foci separated by 1 mm is within time-windows of ~20–80 ms, but longer periods separate spindles at different thalamic and cortical sites during barbiturate anesthesia, and even longer during spreading cortical depression (Contreras *et al.*, 1997a,b; A. Destexhe, D. Contreras and M. Steriade, submitted for publication). This emphasizes the crucial role of cortical inputs in determining the near-simultaneity of spindles in thalamocortical systems. Even when the time-lags are as long as 0.1–0.2 s, they are not predictable from a spindle sequence to the next, nor from a cortical or thalamic site to the adjacent one (Contreras *et al.*, 1997b; see also fig. 6.4B in Andersen and Andersson, 1968). At variance, experiments *in vitro* (Kim *et al.*, 1995) have shown predictable propagation of spindles in the dorso-ventral axis of sagittal visual thalamic slices, at a speed of 0.3–1.5 mm/s. We hypothesized that the difference between the near-simultaneity of spindles *in vivo* and the propagation of this oscillation *in vitro* is due to the absence of corticothalamic projections in slices, as cortical volleys synchronize thalamocortical and thalamic reticular neurons, and are therefore very effective in producing spindles (Steriade *et al.*, 1972; Contreras and Steriade, 1997). Indeed, after decortication, the spatiotemporal coherence of thalamic spindles is disrupted and the decay of correlation with distance decreases stepwise for distances >1 mm, whereas only limited decay with distance is observed in the intact-cortex hemisphere, both in experiments and in simulation studies (Fig. 13). The disorganization of spatiotemporal patterns of spindles after decortication takes place in the thalamus, as the synchrony of this oscillation is resistant to transections of horizontal intracortical connections (Contreras *et al.*, 1996a, 1997b). Only with low-intensity cortical stimulation could spindles display propagation *in vivo*, with velocities between 1 and 3 mm/s (Contreras *et al.*, 1997b), thus imitating the *in vitro* condition (Kim *et al.*, 1995).

The difference between the spatiotemporal patterns of spontaneously occurring spindles *in vivo* and *in vitro* can be ascribed to different factors. Probably the most important is that,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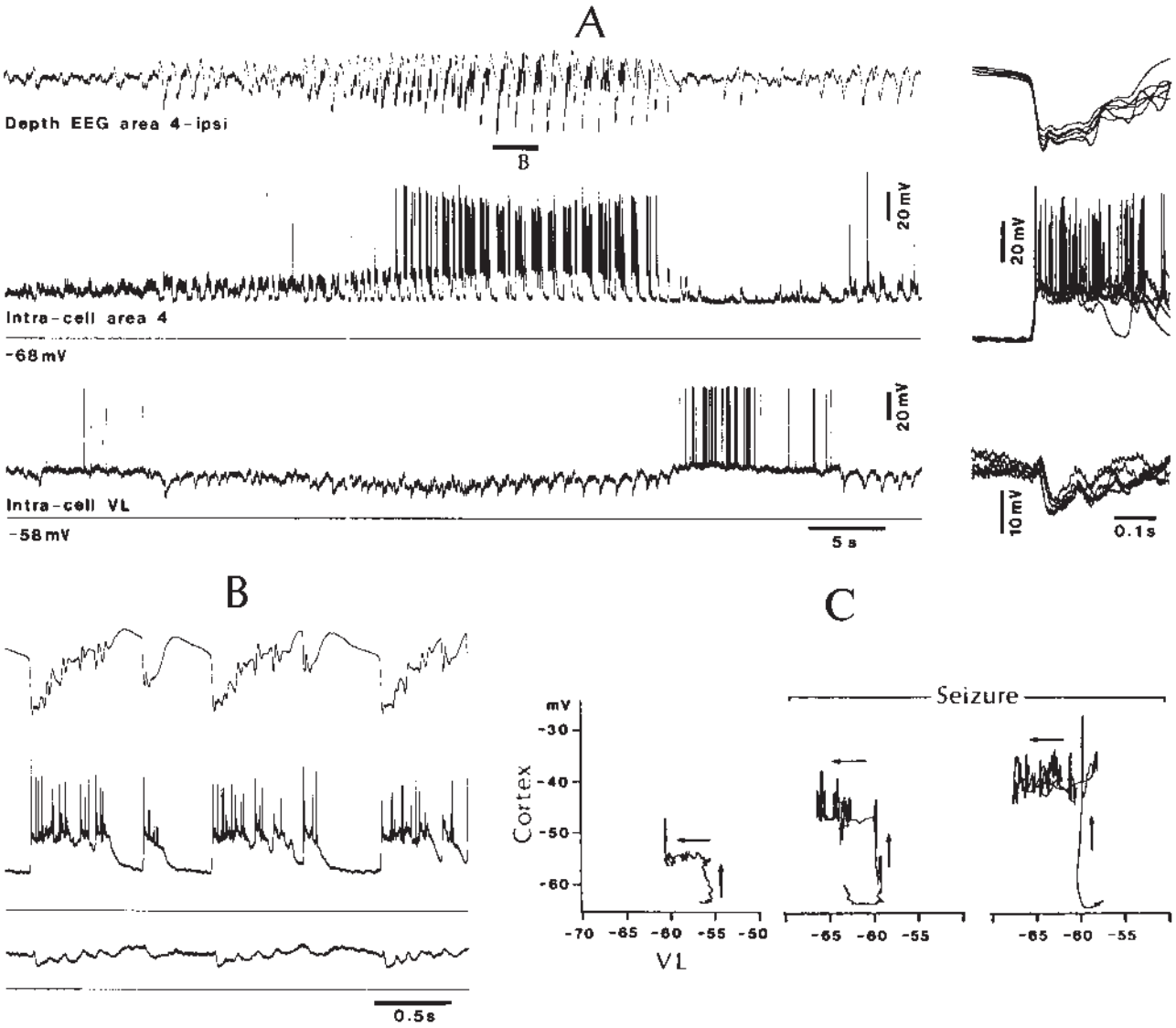

Figure 14. Dual intracellular recordings demonstrating hyperpolarization of thalamocortical (TC) cell in the ventrolateral (VL) nucleus during seizure depolarization and spike-bursts in area 4 cortical neuron. Cat under ketamine–xylazine anesthesia. (*A*) Three traces depict simultaneous recording of depth-EEG from area 4, as well as intracellular activities of area 4 cortical neuron and TC cell from the ipsilateral VL nucleus (below each intracellular trace, current monitor). The seizure was initiated by a series of EEG waves at ~0.9 Hz in the depth of area 4, continued with discharges at ~2 Hz and ended with high-amplitude, periodic (0.9 Hz) EEG sequences consisting of wavelets at 14 Hz. All these periods were faithfully reflected in the intracellular activity of cortical neuron, whereas VL thalamic neuron displayed a tonic hyperpolarization throughout the seizure, with phasic sequences of IPSPs related to the large cortical paroxysmal depolarizations and spike-bursts occurring at the end of the seizure. Note disinhibition of VL cell after cessation of cortical seizure. On the right are superimposition of six successive, expanded traces from the part indicated by the horizontal bar (*B*) and continuing with subsequent three polyspike-wave complexes. Note spiky depth-negative EEG deflection associated with depolarization of cortical cell and rhythmic IPSPs of VL thalamic neuron. The part marked by *B* is further depicted in the bottom left panel. (*C*) Phase relations between simultaneously, intracellularly recorded area 4 cortical neuron and VL thalamic neuron are preserved during sleep and development of seizure activity. The three parts represent (from left to right): one period before seizure, during EEG sleep patterns; and two periods during early and late parts of the seizure. Phase plots of averaged membrane voltage of area 4 cell (ordinate) against that of VL cell (abscissa). The development of seizure did not change the phase-relation between cells, but accentuated the amplitude of the elements constituting the normal (sleep) oscillatory behavior preceding the seizure. In essence, cortical depolarization (upward arrows) preceded the VL cell's hyperpolarization (left-directed arrows) in the three periods, although the amplitude of the membrane excursions were considerably enhanced during the seizure. Modified from Steriade and Contreras (1995) (*A*,*B*) and unpublished data (*C*).

Figure 13. Control of spatiotemporal coherence of thalamic spindles by the cerebral cortex. *Top panel*, disruption of the spatiotemporal coherence of thalamic oscillation after removal of the neocortex. Spatiotemporal maps of electrical activity across the thalamus were constructed by plotting time (time runs from top to bottom in each column; arrow indicates 1 s), space (from left to right, the width of each column represents 8 mm in the anteroposterior axis of the thalamus) and local field potential (LFP) voltage [from blue to yellow, color represents the amplitude of the negative deflections of thalamic LFPs; the color scale ranged in 10 steps from the baseline (blue) to –100 μV (yellow)]. Time was divided into frames, each representing a snapshot of 4 ms of thalamic activity. A total of 40 s is represented (9880 frames). Each frame consisted of eight color spots, each corresponding to the LFP of one electrode from anterior to posterior (left to right in each column). *Middle panel* (experiments), decay of correlation with distance. Cross-correlations were computed for all possible pairs of thalamic sites, and the value at time zero from each correlation was represented as a function of the intersite distance for six different consecutive epochs of 20 s. Spatial correlation was calculated for thalamic recordings in the intact brain (left) and after removal of cortex (right). *Bottom panel* (model), decay of correlation with distance (in units of sites). Similar computation of cross-correlations as in the above panel from experiments, in the presence of cortex (left) and after decortication (right). Adapted from Contreras *et al.* (1996a) and unpublished data.

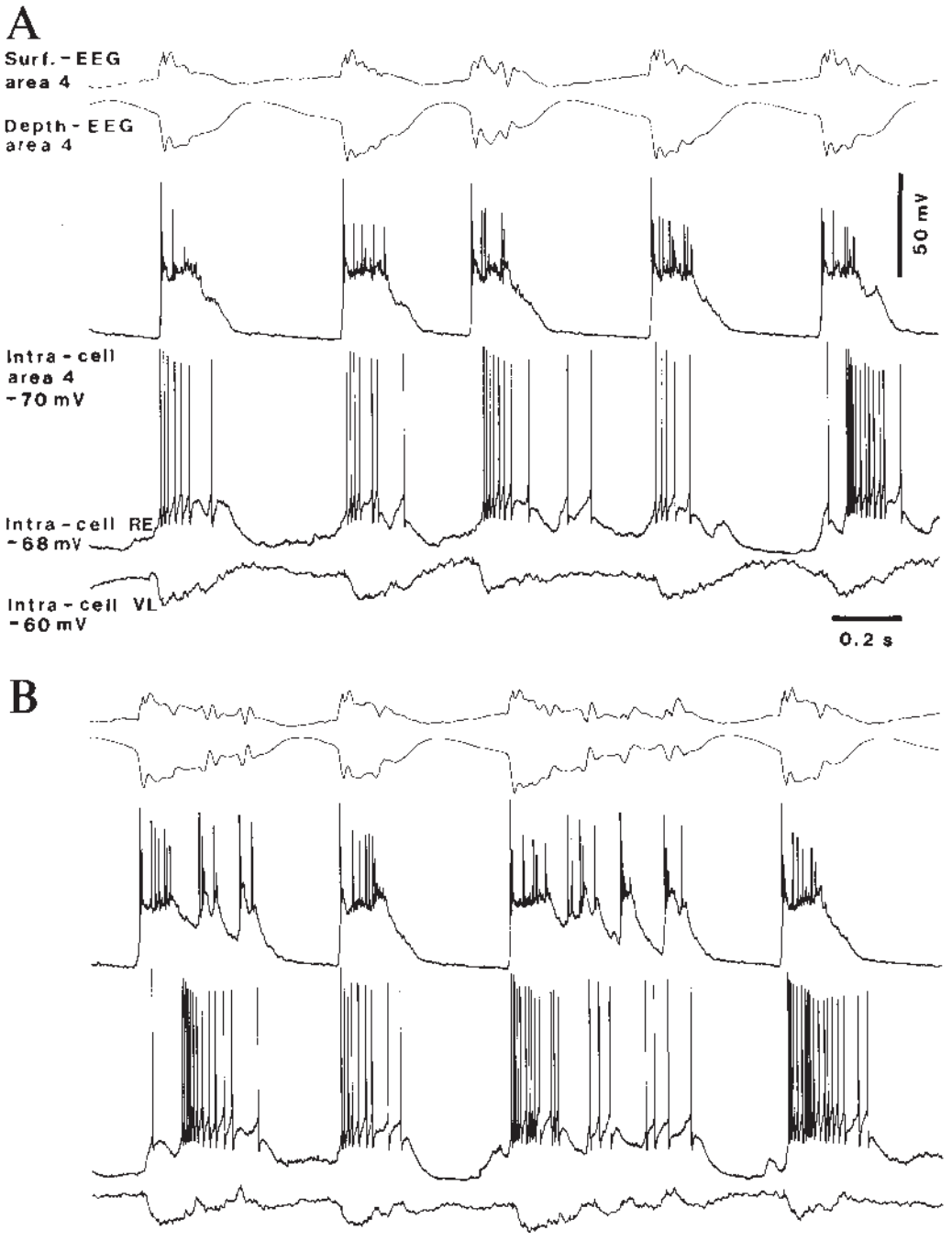

Figure 15. Inhibitory processes of thalamocortical cells during cortical seizures (polyspike-wave complexes at ~2 Hz) are due to cortically elicited excitations of GABAergic thalamic reticular neurons. Dual simultaneous intracellular recordings from cortical neuron in area 4 and thalamic ventrolateral (VL) neuron, together with surface- and depth-EEG from area 4, close to the cortical cell. A thalamic reticular (RE) neuron was intracellularly recorded in the same animal, during another spontaneous seizure that displayed EEG features virtually identical to those depicted here. The non-simultaneous RE neuron traces, shown between the cortical and VL neuron traces, demonstrate the temporal similarity of these spontaneous seizures. Note the IPSPs in the VL cell, in close time-relation with paroxysmal depolarizing shifts in cortical cell and spike-bursts in the RE cell. From Lytton *et al.* (1997).

in vivo, the slow cortical oscillation, with a frequency similar to that of spindle sequences and highly synchronized among distant cortical sites (Steriade *et al.*, 1993e,f, 1994; Amzica and Steriade, 1995a,b), provides a background corticothalamic activity that triggers burst firing in many thalamic foci during the narrow time-window of lower threshold at the end of the interspindle lull. The divergent corticothalamic projections are coupled with the divergent projections from the rostral pole of the thalamic reticular nucleus to relay and intralaminar thalamic nuclei (Steriade *et al.*, 1984). Another factor is the difference between the connectivity of perigeniculate and lateral geniculate nuclei, with rather precise topographical arrangements (Montero *et al.*, 1977), and the connectivity between rostral reticular sectors and dorsal thalamic territories, especially intralaminar and midline nuclei, that shows only rough organization and more diffuse projections (Steriade *et al.*, 1984; Kolmac and Mitrofanis, 1997). The initiating and synchronizing role played by the thalamic reticular nucleus in spindles

recorded from the decorticated hemisphere is demonstrated in those instances when spontaneous oscillations in reticular neurons precede those from thalamocortical neurons (see fig. 9 in Contreras *et al.*, 1997b).

Cortically Elicited Inhibition of Thalamocortical Neurons during Spike-Wave Seizures

Lastly, strong evidence for the potent role of corticothalamic inputs in altering thalamic activities comes from the development of sleep oscillations into paroxysms with spike-wave (SW) complexes at 2–4 Hz or polyspike-wave (PSW) complexes, often associated with runs of fast (10–20 Hz) EEG spikes (Steriade and Amzica, 1994; Steriade and Contreras, 1995). Three major features distinguish such seizures that occur spontaneously under ketamine–xylazine anesthesia and in chronically implanted animals, or are elicited by electrical stimulation of neocortex and thalamus without using epileptogenic substances.

(i) The seizures are gradually generated from the spontaneous slow oscillation and sleep spindles, or from incremental responses to repetitive stimuli (~10 Hz). At variance with the conventional definition of SW seizures, as suddenly generalized and bilaterally synchronous discharges, analyses of synchrony show that, although the above definition may seem valid at the EEG level, cellular firing from different neocortical areas and thalamic nuclei exhibit time-lags up to 50 ms or even longer as well as a gradual increase in synchronization (see figs 2–4 in Steriade and Amzica, 1994). These features and the progressive development from sleep to epileptic patterns indicate that such paroxysms are generated by a progressive synaptic build-up, sequentially distributed through direct and/or circuitous pathways within intracortical and corticothalamic networks.

(ii) The cerebral cortex plays a leading role in the generation of these seizures. This was suggested in earlier extracellular studies on naturally sleeping monkeys (Steriade, 1974) and during development from spindles to SW seizures (Gloor *et al.*, 1990) in the penicillin epilepsy model (Prince and Farrell, 1963). Recent evidence corroborates this hypothesis: whereas injection of bicuculline in the thalamus of decorticated animals produces spindles with decreased frequencies and increased spike-bursts (see also Bal *et al.*, 1995a) but no SW-type seizures, injections of bicuculline in the cortex of athalamic animals may lead to full-blown seizures characterized by SW complexes at 2–4 Hz, combined with runs of fast EEG spikes (M. Steriade and D. Contreras, in preparation; M. Steriade, F. Amzica and D. Neckelman, in preparation).

(iii) Dual intracellular recordings of thalamocortical and cortical cells show that a proportion (60%) of thalamic relay neurons display a tonic hyperpolarization during cortical seizures, with phasic IPSPs occurring in close time-relation with the paroxysmal depolarizing shifts of neocortical cells, and disinhibition at the cessation of cortical paroxysms (Steriade and Contreras, 1995; Fig. 14*A*,*B*). The depolarization of cortical neurons during seizure precedes the hyperpolarization of thalamocortical neurons, and this phase-relation is also observed during the pre-seizure epochs, with normally synchronized sleep patterns (Fig. 14*C*). The remaining 40% of thalamocortical cells discharge spike-bursts at 2–4 Hz, in phase with the depolarizing components of the cortical seizure. The unexpected inhibition in a substantial proportion (60%) of thalamocortical cells, throughout seizures that are conventionally regarded as generalized, is due to the corticofugal excitatory drives that impinge upon GABAergic thalamic reticular neurons (Fig. 15). Indeed, these neurons are consistently set into action during SW seizures and the duration of their spike-bursts increase from ~40–50 ms during the sleep period to ~200–250 ms during the SW seizures (Steriade and Contreras, 1995). Computer network models (Lytton *et al.*, 1997) undertaken to explore the mechanism(s) of the unexpected quiescence of thalamocortical neurons during SW seizures propose that the pattern of activity in thalamic reticular neurons determines prolonged inhibition in thalamo- cortical cells in the case of spike-bursts in reticular neurons that follow too closely on the previous one to permit a low-threshold spike in the target dorsal thalamic neuron. At appropriate levels of membrane hyperpolarization, some of the quiescent thalamocortical cells may develop their silent activity into powerful rebound spike-bursts at 2–4 Hz (M. Steriade and D. Contreras, unpublished data) that would contribute to the potentiation of the SW seizure.

Conclusion

Data presented here show that, during both brain-active and brain-deafferented states, intrinsic cell properties and operations in synaptic networks should be conjointly investigated to decipher the neuronal substrates of spontaneous oscillations characterizing various levels of vigilance. The emphasis on the cortical control of thalamic activities is exemplified by results from experiments on fast oscillations during activated episodes and on low-frequency oscillations during slow-wave sleep, together demonstrating the effectiveness of cortical volleys in synchronizing thalamic operations. Fast spontaneous oscillations of cortical neurons depend on their depolarization, under the control of brainstem–thalamic and basal forebrain activating systems. A group of deeply lying corticotalamic neurons, discharging high-frequency spike-bursts recurring rhythmically at 30–40 Hz, may play an important role in synchronizing corticothalamocortical networks within the frequency range of fast oscillations. The results suggest that weakly synchronized, fast spontaneous oscillations become robustly coherent over a short time-window after sensory signals during wakefulness and/or internally generated drives during dreaming sleep. During slow-wave sleep, the complexity of corticothalamic networks explains why, instead of 'pure' rhythms, coalescent oscillations are grouped in wave-sequence: at each cortical volley, the thalamic oscillatory machine is set into action and generates various types of rhythmically synchronized activities. This requires superimposed cortical networks when modeling thalamic sleep rhythms. During paroxysmal episodes resembling spike-wave seizures, corticofugal volleys lead to a tonic quiescence and phasic IPSPs in more than half of the thalamocortical neurons, due to cortically driven spike-bursts of GABAergic thalamic reticular neurons.

Notes

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