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Integration of low-frequency sleep oscillations in corticothalamic networks

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Review

Abstract. The corticothalamic system acts as a complex network in promoting the various oscillatory patterns (slow oscillation, spindles, delta) that characterize the state of quiet sleep. Local synchronizing mechanisms of any of the above-mentioned oscillations occur at the site of their genesis, thalamic or cortical. These mechanisms are assisted by the wide-range, synchronized occurrence of the cortical slow oscillation, which finally produces the coalesced picture of slow-wave sleep EEG. Multisite, simultaneous intracellular and field potential recordings in cat, as well as EEG recordings in human were performed in order to assess the state of synchrony and the propagation of various sleep rhythms in the corticothalamic network.

Key words: cortex, thalamus, sleep oscillations, intracellular, *in vivo*

INTRODUCTION

There are two major claims in this article. The cortex and thalamus form a unified oscillatory network. Therefore, instead of regarding each slow-wave sleep rhythm as generated in simple circuits, within distinct structures, we should consider that all sleep oscillatory types (spindles, 7-14 Hz; delta, 1-4 Hz; slow oscillation, 0.6-1 Hz) are grouped in complex wave-sequences by the cortically generated slow oscillation. One example is the K-complex, a major electrographic sign of resting sleep in humans and animals, which is formed by a cycle of the slow cortical oscillation followed by a brief sequence of spindles generated in the thalamus. Then, there are no pure sleep rhythms, no simple intracortical or intrathalamic circuits, but a permanent corticothalamic dialogue. Evidence will be presented to show that even oscillations which are generated in relatively simple intrathalamic circuits require corticothalamic projections for their widespread synchronization, as seen during normal sleep in both animals and humans. Dual intracellular recordings demonstrate that, at each step of the complex pathways linking various neocortical areas, corticothalamic neurons impinge on thalamic reticular neurons that, in turn, produce inhibition-rebound sequences in dorsal thalamic relay neurons projecting in the reentrant corticopetal systems, thus changing the time-course and synchronization of intracortical events.

At variance with the long-standing idea that the cerebral cortex lies in total darkness during resting sleep, neocortical neurons are quite active during this state. Recent intracellular recordings of neocortical neurons during the natural waking-sleep cycle of behaving animals indicate that, during the depolarizing phase of the slow sleep oscillation, the firing rates are equal to, and may even exceed, those observed during brain-active states (waking and REM sleep). Many possibilities are envisaged to explain why are cortical neurons active during a state in which the brain is disconnected from the external world. Among them, the rhythmic spike-bursts of thalamic and neocortical neurons during sleep oscillations may assist in specifying and reorganizing the brain circuitry, and may contribute to the strengthening of synaptic contacts that carry behaviorally relevant informations. Sleep oscillations in thalamocorticothalamic loops are followed by persistent changes in neuronal excitability, which are associated with short-term plasticity processes. Such changes may lead to self-sustained oscillations due to resonant activities in closed loops, as in memory processes. The repeated circulation of impulses in reverberating circuits may lead to synaptic modifications in target structures, favoring alterations required in memory processes. Thus, we suggest that slow-wave sleep is associated with the consolidation of memory traces acquired during the state of wakefulness.

CORTICAL SLEEP OSCILLATIONS

A slow oscillation, with sequences consisting of depolarizing-hyperpolarizing components and recurring periodically at a frequency of ~0.3 Hz to 1 Hz, was described in intracellular recordings from neocortical areas in anesthetized or undrugged brainstem-transected cats and, at the EEG level, in naturally sleeping cats and humans (Steriade et al. 1993d-e). This cellular oscillation is marked by a continuous alternation of the membrane potential between two voltage levels (Fig. 1): a depolarized and a hyperpolarized one. The membrane depolarization lasts for about 0.4-0.8 s, and is made mainly of excitatory and inhibitory postsynaptic potentials (Steriade et al. 1993d). The hyperpolarization is associated with silenced firing in the cortical network that generally lasts for 0.3 s to 0.7 s (Steriade et al. 1993d-e, Amzica and Steriade 1995b, Contreras and Steriade 1995). The hyperpolarization is due to a global disfacilitation in the corticothalamic network and is accompanied by an increase in membrane resistance (Contreras et al. 1996). This aspect is distinct from an active inhibitory mechanism that is usually associated with increased activity in inhibitory neurons and with increased membrane conductance of target neurons.

The slow oscillation has been recorded in cats under various anesthetics such as urethane, a mixture of ketamine and xylazine, nitrous oxide, as well as in unanesthetized cats with high brainstem transections (*cerveau isolé*) (Steriade et al. 1993d,e, 1994a, Amzica and Steriade 1995b), and, importantly, in naturally sleeping cats (Steriade et al. 1996, Amzica and Steriade 1998a) and humans (Steriade et al. 1993d, Achermann and Borbély 1997, Amzica and Steriade 1997). Explicit comparisons between anesthesia and natural sleep on one hand (Steriade et al. 1996, Amzica and Steriade 1998a), and between cats and humans on the other (Amzica and Steriade 1997) were made. These series of experiments preclude the possibility that the slow oscillation may be an artifact induced by anesthesia.

The slow oscillation is generated within cortical networks. It has been shown that the thalamus is not essen-

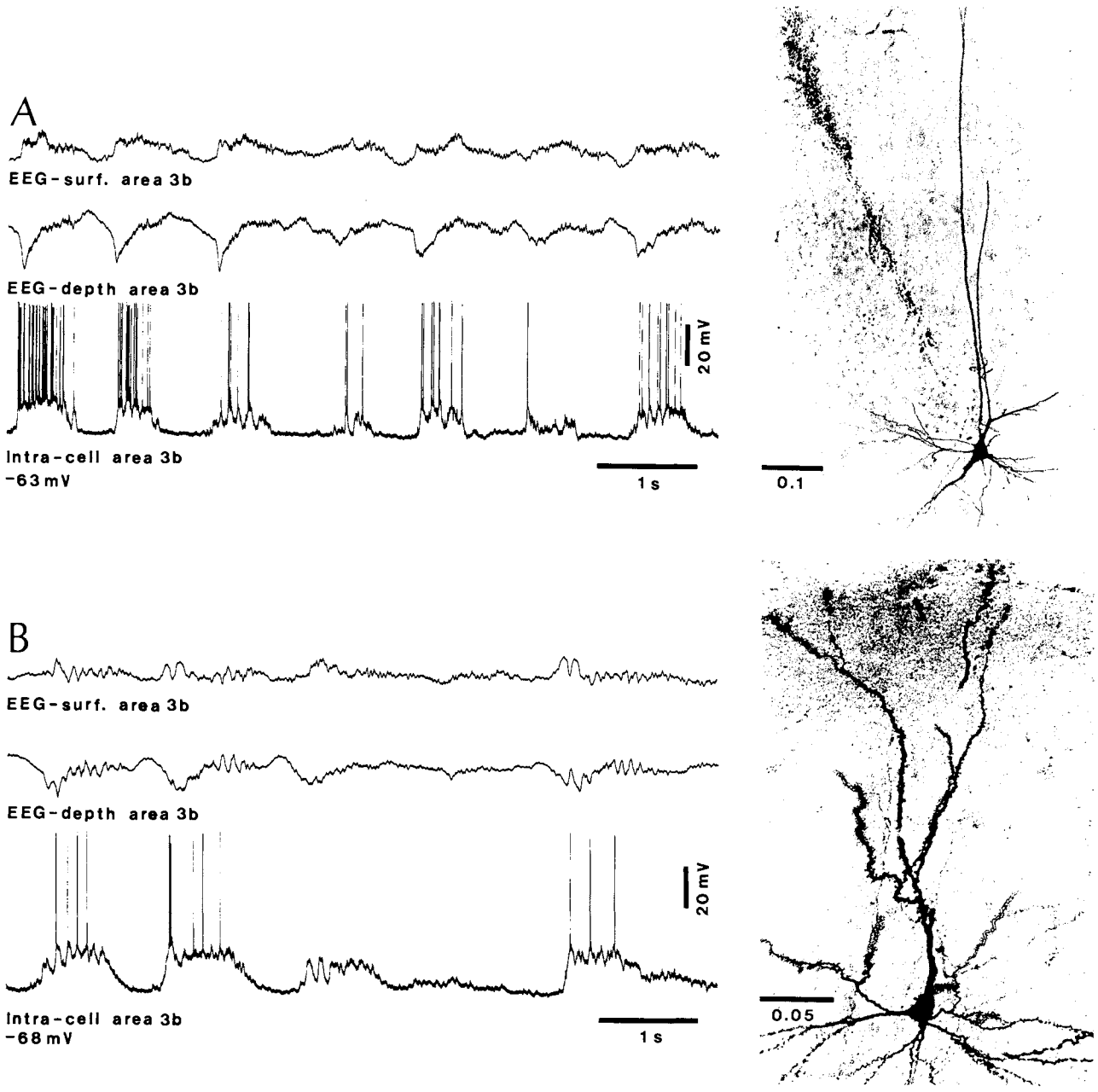

Fig. 1. Slow sleep oscillation of pyramidal neocortical cells in cat. Left panels show intracellular recordings and simultaneously recorded EEG in the vicinity of the cell. The EEG was recorded by means of coaxial electrodes located on the surface and at a depth of ~0.6 mm. Right panels are the corresponding cells stained with Neurobiotin (calibration bars in millimeters). A, pyramidal cell from the somatosensory cortex (area 3b) at 1 mm depth. Note the presence of two apical dendrites and the track left by the recording micropipette on the left side of the cell. The cell oscillated at ~0.9 Hz with sustained depolarizing potentials corresponding to the depth-EEG negative (surface-positive) potentials. B, superficial pyramidal cell (0.3 mm from the surface). It oscillated at 0.6 Hz. Note correspondence between the missing cycle (after the third depolarization) in the cellular oscillation as well as the EEG. Modified from Contreras and Steriade (1995). In this figure positivity is upwards.

tial to the expression of the slow oscillation, which survives in athalamic preparations (Steriade et al. 1993e) and is absent from the thalamus of decorticated cats (Timofeev and Steriade 1996). More recently it has been shown that the slow oscillation also develops in cortical slices of the ferret visual cortex bathed in a milieu with

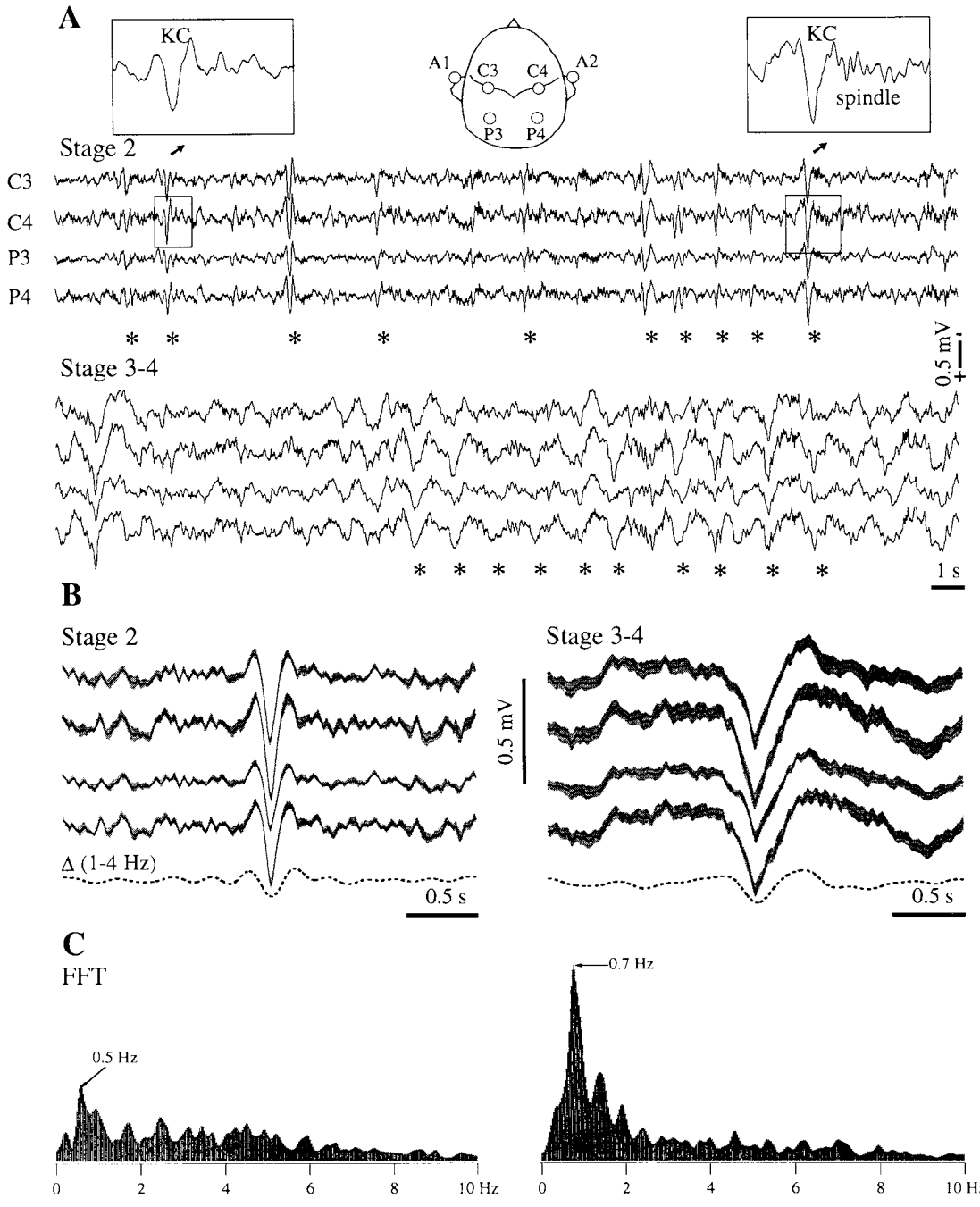

Fig. 2. Rhythmic K-complexes (KCs) in human EEG during natural slow-wave sleep. A, four leads, recorded from the two hemispheres during stage 2 sleep, show quasi-rhythmic (around 0.5 Hz) KCs. The expanded insets display a simple KC (left) and a KC followed by a spindle (right). Stage 3-4 EEG (below) is characterized by a more regular oscillation of the KCs (0.7 Hz). Asterisks mark the most obvious KCs in order to suggest their rhythmicity. B, averaged KCs ($n = 200$) from stages 2 (left) and 3-4 (right). The gray surface around the averaged KCs covers the standard deviation. The lowest trace (dotted line) results from the filtering of the average KC in the delta and (1-4 Hz). C, power spectra of 2 min epochs containing the ones displayed above. Note a principal peak at 0.5 Hz for the stage 2 episode (left), surrounded by other lower peaks as evidence for distributed rhythmicity. At variance, deep sleep shows a dominant peak at 0.7 Hz. The two FFT graphs are scaled with the same ordinate. Modified from Amzica and Steriade (1997).

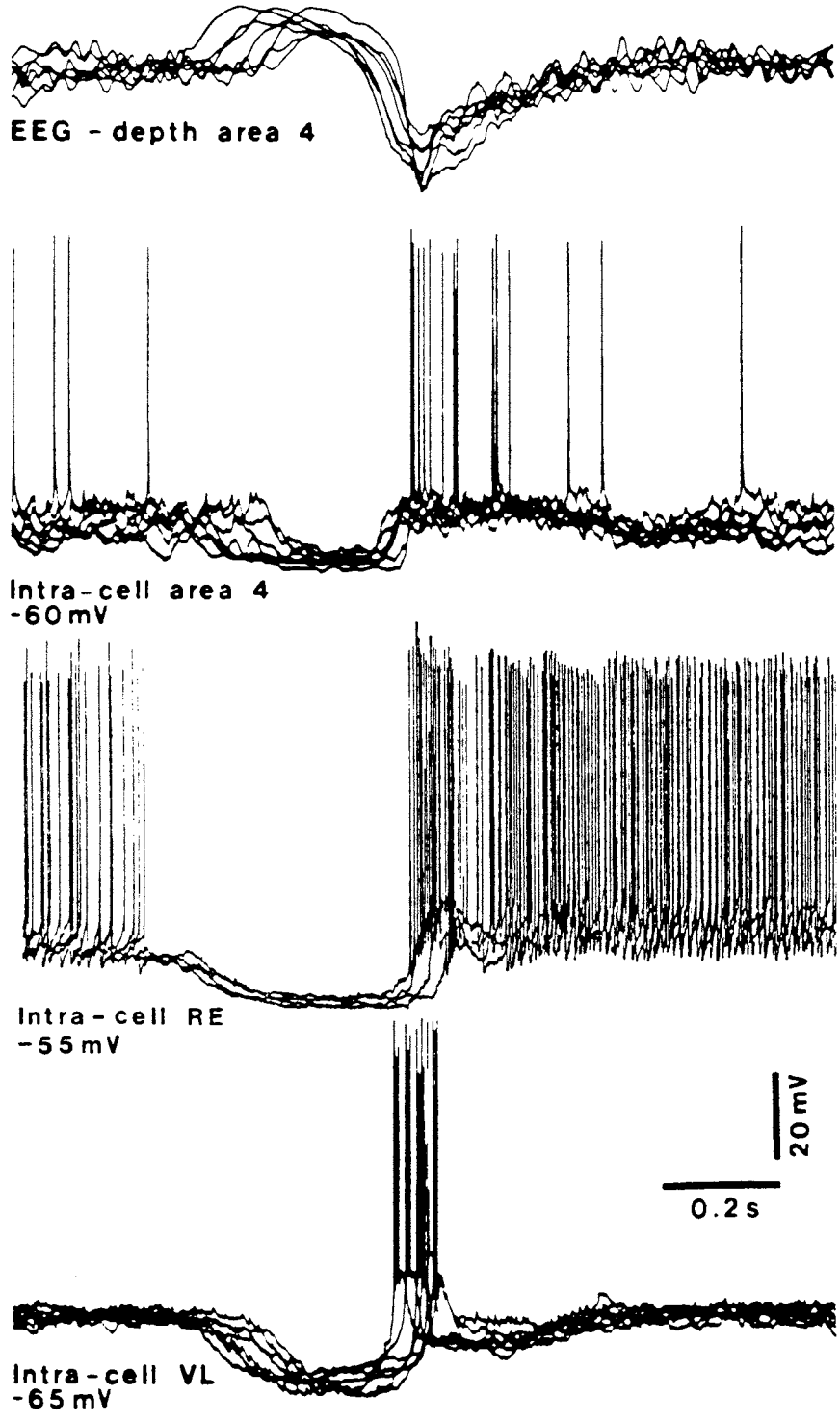

Fig. 3. Synchronization of the slow cortical oscillation in cortical and thalamic neurons. Intracellular recordings in a cat under ketamine-xylazine anesthesia. Simultaneous recordings of depth-cortical EEG and intracellular activities of an area 4 cortical neuron and a relay cell from the ventrolateral nucleus of the thalamus. The intracellular activity of a thalamic reticular neuron was similar with respect to the EEG waves. All activities are aligned with respect to the peak of the EEG depth-negativity. Note simultaneity of long-lasting hyperpolarizations in all cortical and thalamic neurons. The depth-EEG negativity was associated with spike trains in the cortical cell and with spike bursts in the thalamic neurons. Modified from Contreras and Steriade (1995). In this and all subsequent figures positivity is upwards.

ionic concentrations that match closer those found *in vivo* than the concentrations generally used *in vitro* (McCormick and Sanchez-Vives 1999). Thus, all evidence points to the cortex as the site of genesis of the slow oscillation, where it appears synchronously over large cortical areas (Amzica and Steriade 1995b). This wide range synchronization is supported by intracortical linkages. The interruption or inactivation of these intracortical connections impairs the slow oscillations synchronization (Amzica and Steriade 1995a). Such disconnection procedures dissociate activities between the anterior and the posterior hemisphere without preventing the generation of the slow oscillation (see Fig. 9 in Amzica and Steriade 1995a).

At the EEG level, each depolarizing-hyperpolarizing cycle of the cellular slow oscillation corresponds to a K-complex (Amzica and Steriade 1997, 1998a), as shown by the relationship between intracellular and field potentials in cats. The onset of the intracellular depolarization is accompanied, in depth field potentials, by a focal negativity (the peak of the K-complex), while the cellular hyperpolarization is reflected by a positive dome-like potential. These depth (intracortical) field potentials are reversed at the cortical surface (Amzica and Steriade 1995b, Contreras and Steriade 1995), and present a current distribution with a major sink in layers II-III of the neocortex (Amzica and Steriade 1998a). In humans, K-complexes are rhythmic at the pace of the slow oscillation (Fig. 2).

The duration and shape of the two components of the slow oscillation are subject to changes due to the activation or inactivation of cellular currents. Blocking of NMDA components by systemic application of ketamine induces a reduction in the duration of the depolarizing phase, and thus produces an acceleration of the rhythm (Steriade et al. 1993d). It is known that inactivation of NMDA components is also provoked by membrane hyperpolarization, naturally achieved with the progression of sleep. The shape of the intracellular depolarization may change and, at the population level, this may lead to a modified shape of the field potential, thus being a cause for the modification of the shape of K-complexes with deepening of sleep (Fig. 2).

The slow oscillation is generated only during slow wave sleep and is absent during activated states. The latter are associated with increased release of acetylcholine in the cerebral cortex (Celesia and Jasper 1966). Indeed, activation of cholinergic receptors in the cerebral cortex abolishes the slow oscillation by blocking the hyperpolarizing phase (Steriade et al. 1993a) and may neutralize the network disfacilitation that is associated with the hyperpolarizing phase of the slow oscillation (Contreras et al. 1996). Since the hyperpolarizing phase of the slow oscillation follows the discharge crowning the depolarizing phase, it has been hypothesized that it is made mainly of a slow Ca^{2+}-dependent K^+ current (Steriade et al. 1993a, 1994b). This phenomenon is similar to the slow afterhyperpolarization described in cortical neurons from the somatosensory cortical slice preparations (Schwindt et al. 1988). It has recently been proposed that glial cells, through the uptake of extracellular K^+, might influence the shape and the duration of the depolarizing phase of the slow oscillation (Amzica and Neckelmann 1999).

The basic physiological correlate of slow-wave (quiescent or resting) sleep is a profound and global alteration in brain electrical activity that distinguishes this state of unconsciousness from alert behaviors. Such a modification was thought to result from activity changes in large neuronal populations, whence the term synchronization, which was widely employed to describe the high amplitudes and relatively low frequencies of EEG, waves during resting sleep. However, the test of this assumption required simultaneous intracellular recordings of various cell-classes in the cerebral cortex and thalamus, the key structures implicated in the genesis of EEG patterns. Such evidence results from dual impalements of cortical, thalamocortical or thalamic reticular neurons *in vivo* (Fig. 3).

Most adjacent and many distant neocortical territories are linked by means of reciprocal projections. The horizontal projections of pyramidal cells' axons, spanning from 2 mm up to 8 mm, have been emphasized in the visual cortex (Gilbert and Wiesel 1983, Mason et al. 1991, Gilbert 1992, Albowitz and Kuhnt 1993), somatosensory (Jones et al. 1978, Cauller and Connors 1994), auditory (Imig and Reale 1981), and motor (Keller 1993) cortical areas, as well as the projections between sensory and motor fields (Avendaño et al. 1992). These intragyral projections explain the strong oscillatory propensity of areas 5 and 7, the presence of coherent slow oscillations in area 5 and association visual areas, and the survival of the intracellularly recorded slow oscillation after total lesions of thalamic intralaminar and lateroposterior-pulvinar nuclei (Steriade et al. 1993e). The intracortical connections proved to be necessary links for the synchronization of the slow oscillation, since their disconnection disrupted the synchrony (Amzica and Steriade 1995a).

Recently, the slow oscillation was recorded intracellularly in behaving animals (Steriade et al. 1999). Although all types of electrophysiologically identified neocortical neurons are cyclically hyperpolarized during the natural state of slow-wave sleep, their discharges during the depolarizing phase of the slow oscillation are as high as during the tonically depolarized states of waking and REM sleep. This accounts for the only modest reduction in discharge rates of neocortical neurons during slow-wave sleep. The rich spontaneous activity and preserved synaptic excitability of neocortical neurons to internal signals suggest that the neocortex is the site of active operations during a behavioral state disconnected from the outside world.

THALAMIC OSCILLATIONS

Two types of oscillations are generated in thalamus during the state of resting sleep: spindles and one component of intrinsic, clock-like delta oscillations; the other component of delta waves is probably generated in neocortex as those waves can be recorded in the cerebral cortex after extensive thalamectomy.

Spindles

Spindles are waxing-and-waning waves at a frequency of 7-14 Hz, grouped in sequences that last 1 to 3 s and recur every 3 to 10 s (Steriade and Deschênes 1984). Spindles appear during early stages of sleep, sometimes preceding overt behavioral manifestations of sleep and are generated within the thalamus, even after decortication and high brainstem transection. The main elements implicated in the genesis of spindles are the GABAergic thalamic reticular (RE) neurons and the glutamatergic thalamocortical (TC) neurons. Spindles result from repetitive spike-bursts in RE cells that produce rhythmic inhibitory postsynaptic potentials (IPSPs) in thalamocortical (TC) neurons, leading to postinhibitory rebound spike--bursts that are transferred to cortex and produce excitatory postsynaptic potentials (EPSPs) in cortical cells, occasionally leading to action potentials (Fig. 4). The pacemaking role of the RE nucleus in the generation of sleep spindles was demonstrated by absence of spindling in target TC neurons and neocortex after disconnection from the RE nucleus (Steriade et al. 1985). Also, RE neurons can generate spindle rhythmicity after disconnection from TC neurons located in dorsal thalamic nuclei, due to the axo-dendritic and dendrodendritic connections among RE neurons (Steriade et al. 1987). Mutual inhibitory connexions between neurons of the perigeniculate nucleus (visual sector of the reticular nucleus) of the thalamus were found *in vivo* (Ahlsen et al. 1985, Deschênes et al. 1985, Yen et al. 1985). The absence of spindles in thalamic slices (von Krosigk et al. 1993) can be due to the lack of an intact collection of RE neurons as the peculiarity of RE neurons consists in their long dendrites (up to 1.5-2 mm along the curved axis of the nucleus), parallel to the surface of the underlying dorsal thalamus. Slicing the RE nucleus may cut the full extent of dendrites and the intra-nuclear axonal collaterals of neurons. A larger and more complete collection of intact RE neurons may be capable to generate spindle waves autonomously (Steriade et al. 1993c). Such an intact collection of RE neurons is present *in vivo*, but may also be present by improving the condition of thalamic slices in the future.

Indeed, a series of recent experimental data as well as modeling studies support the earlier idea (Steriade et al. 1987) that the dendritic interactions between RE neurons generate spindle waves. Concerning the synchronized spindle oscillations due to RE-to-RE inhibitory connections, as they appear naturally during the state of sleep, recent intracellular studies *in vivo* have demonstrated that the IPSPs between GABAergic RE neurons reverse and become depolarizing at the hyperpolarized membrane potentials that occur during sleep, close to the reversal potential for Cl^- ions, leading to powerful spike--bursts (Bazhenov et al. 1999). Under slight depolarization, to mimic the condition of an alert animal, RE neurons display IPSPs, whereas under slight hyperpolarization, to mimic the condition of natural sleep, RE neurons show rhythmic burst activity. These intracellular data obtained *in vivo* suggest that, at the relatively hyperpolarized membrane potentials of thalamic RE neurons that occur during the state of quiescent sleep associated with EEG synchronization, the reversed IPSPs cause burst firing in RE neurons, which may propagated within the nucleus and initiate spindle activity, as previously postulated on the basis of extracellular recordings in the deafferented RE nucleus (Steriade et al. 1987). Importantly, modeling studies based on intracellular recordings *in vivo* have shown that only transient oscillations could be obtained in a networks smaller than 25 x 25 neurons, while larger, two-dimensional networks population produced oscillations with a frequency around 10 Hz, like spindles (Bazhenov et al. 1999). Such a difference emphasizes the requirement for more numerous RE neurons in producing synchronized oscillations.

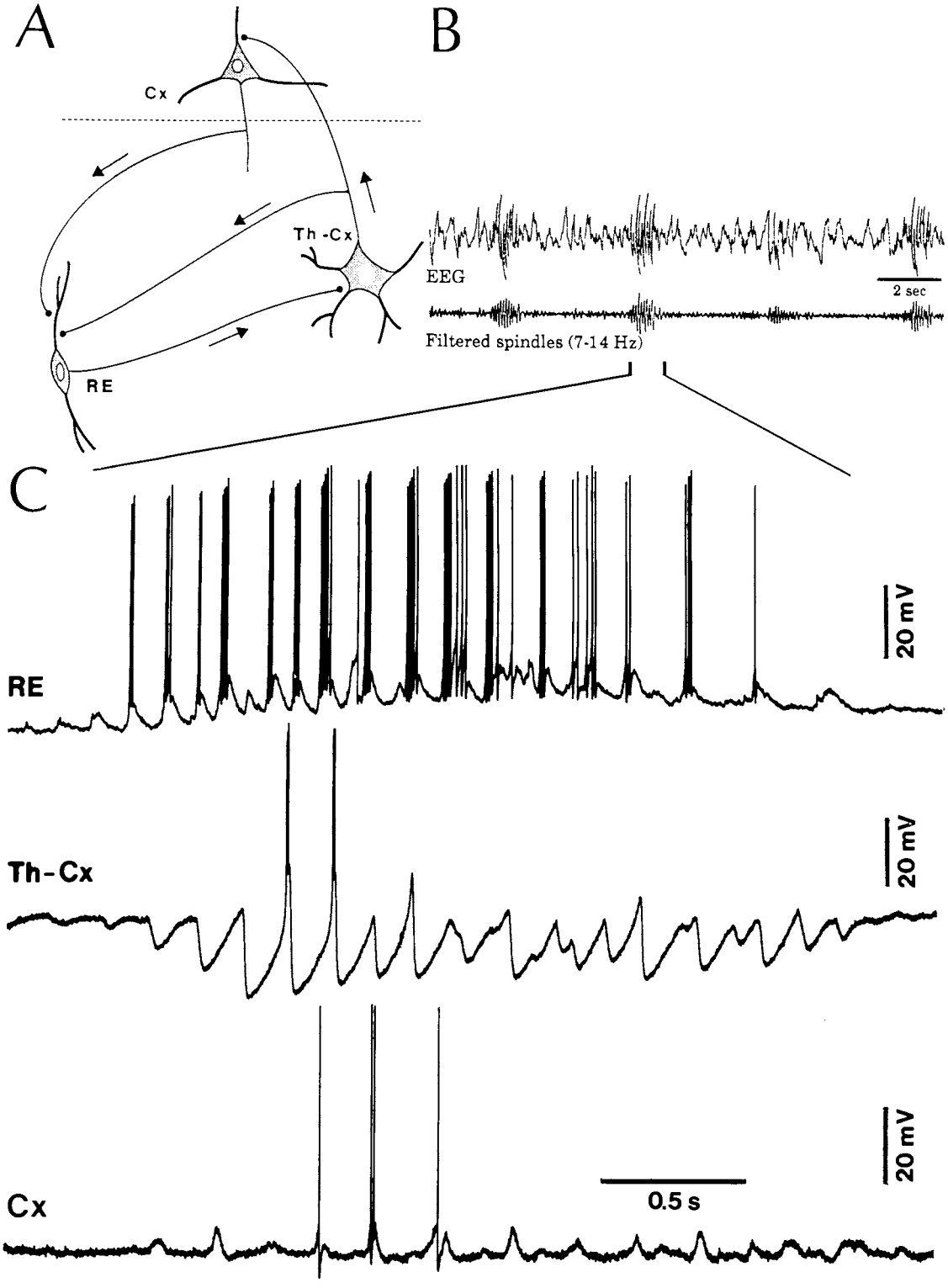

Fig. 4. Spindle oscillations in reticular thalamic (RE), thalamocortical (Th-Cx, ventrolateral nucleus), and cortical (Cx, motor area) neurons. Top, circuit of three neuronal types and two rhythms (7-14 Hz and 0.1-0.2 Hz) of spindle oscillations in cortical EEG. Bottom, intracellular recordings in cats under barbiturate anesthesia. See text. Modified from Steriade and Deschênes (1988).

All these data show that a larger and more intact collection of RE neurons, as in the intact-brain, may be able to generate spindle waves autonomously. This recent computational modeling study (Bazhenov et al. 1999) is in line with a series of previous studies using realistic ionic models of isolated networks of GABAergic RE neurons (Destexhe et al. 1994a, Golomb et al. 1994) showing that the mutual inhibition between RE neurons can synchronize them into spindle-like oscillations. Interestingly, in synchronous oscillations of cluster states, as also described in the original *in vivo* study in which spindles were only found in distinct foci of the RE nucleus supposed to contain dendritic bundles (Steriade et al. 1987), the population rhythmicity was slightly above the upper frequency range of spindles (Golomb et al. 1994), again similarly to the 15-16 Hz spindles found in the isolated RE nucleus *in vivo* (Steriade et al. 1987).

Another factor that makes difference between studies in the intact brain and in thalamic slices is that generalized modulatory systems are absent in the latter experimental condition. The depolarization of RE neurons by inputs arising in monoamine-containing systems (McCormick and Wang 1991), such as the serotonin from dorsal raphe neurons and noradrenaline from locus coeruleus neurons, promote the sensitivity of RE neurons to the IPSPs generated by intra-RE GABAergic connections, with the consequence of generating spontaneous oscillations within the frequency range of spindles (Destexhe et al. 1994b). The ventral island in the *in vivo* study in which the RE nucleus was isolated from the remaining thalamus (see Fig. 2C in Steriade et al. 1987) likely contained monoaminergic afferents that course ventrally from the brainstem in their route to the rostral pole of the RE nucleus. In network simulations, RE neurons organized with dense proximal connectivity were examined in a hyperpolarized state (-65 mV to -75 mV), similar to the *in vitro* condition when no monoaminergic synapses are activated, and in a more depolarized state (-60 mV to -70 mV) that would correspond to a weak monoaminergic activity. In the latter condition, RE neurons were brought to spindle-like oscillation, whereas in the former condition the oscillatory behavior was absent. Finally, with more depolarization, when all monoaminergic synapses were activated, RE neurons fired tonically, as during the natural state of wakefulness (Destexhe et al. 1994b). Thus, a medium level of monoaminergic-induced depolarization may change the state of isolated RE neuronal networks, from silence to oscillations within the frequency range of spindles.

As TC neurons spend much of their sleep time during spindle-related IPSPs, there is a powerful inhibition of incoming messages in their route to the cerebral cortex. Recording field potentials evoked by stimulation of prethalamic axons (a method that permits the monitoring of the presynaptic deflection reflecting the magnitude of the afferent volley, together with the synaptically relayed, thalamically generated waves) revealed that the thalamus is the first station where afferent signals are completely blocked from the very onset of sleep (Steriade 1991). This obliteration of synaptic transmission in the thalamus leads to the deafferentation of the cerebral cortex, a prerequisite for the process of falling asleep. More recently, intracellular recordings from thalamic and cortical neurons have shown that, because of their hyperpolarization during sleep, TC cells do not transfer to cortex signals from prethalamic axons, whereas the internal (corticocortical and corticothalamic) dialogue of the brain may be maintained during sleep (Timofeev et al. 1996).

Although sleep spindles are generated in the thalamus, their shape and widespread synchronization is decisively controlled by the neocortex. This conclusion resulted from the contrast between the systematic propagation of spindle sequences in ferret slices from the visual thalamus (Kim et al. 1995) and the virtual simultaneity of spindle sequences in the intact brains of cats and humans (Contreras et al. 1996, 1997a). We hypothesized that this contrast is due to the absence of cortex in thalamic slices. In fact, after decortication, the simultaneity of spindle sequences throughout the thalamus is disorganized, without however showing systematic propagation as in thalamic slices (Fig. 5). The mechanisms underlying the difference between the results obtained *in vivo* and *in vitro* were further investigated by changing the excitability state of the cat neocortex during sleep (Contreras et al. 1997b) and by studying the spatiotemporal coherence of simulated oscillations in network models (Destexhe et al. 1999). Thus, it was shown that, during natural sleep, spindle oscillatory activity began almost simultaneously over all cortical electrodes. By contrast, a diminished spatiotemporal coherence of spindle oscillations was observed during barbiturate anesthesia when corticothalamic neurons display poor spontaneous activity as well as during states of depressed cortex produced by releasing potassium over the cortex (Contreras et al. 1997b). The effect of an increased excitability of cortical pyramidal neurons is illustrated in Fig. 6 which shows that, during natural sleep, the simultaneity of oscillations

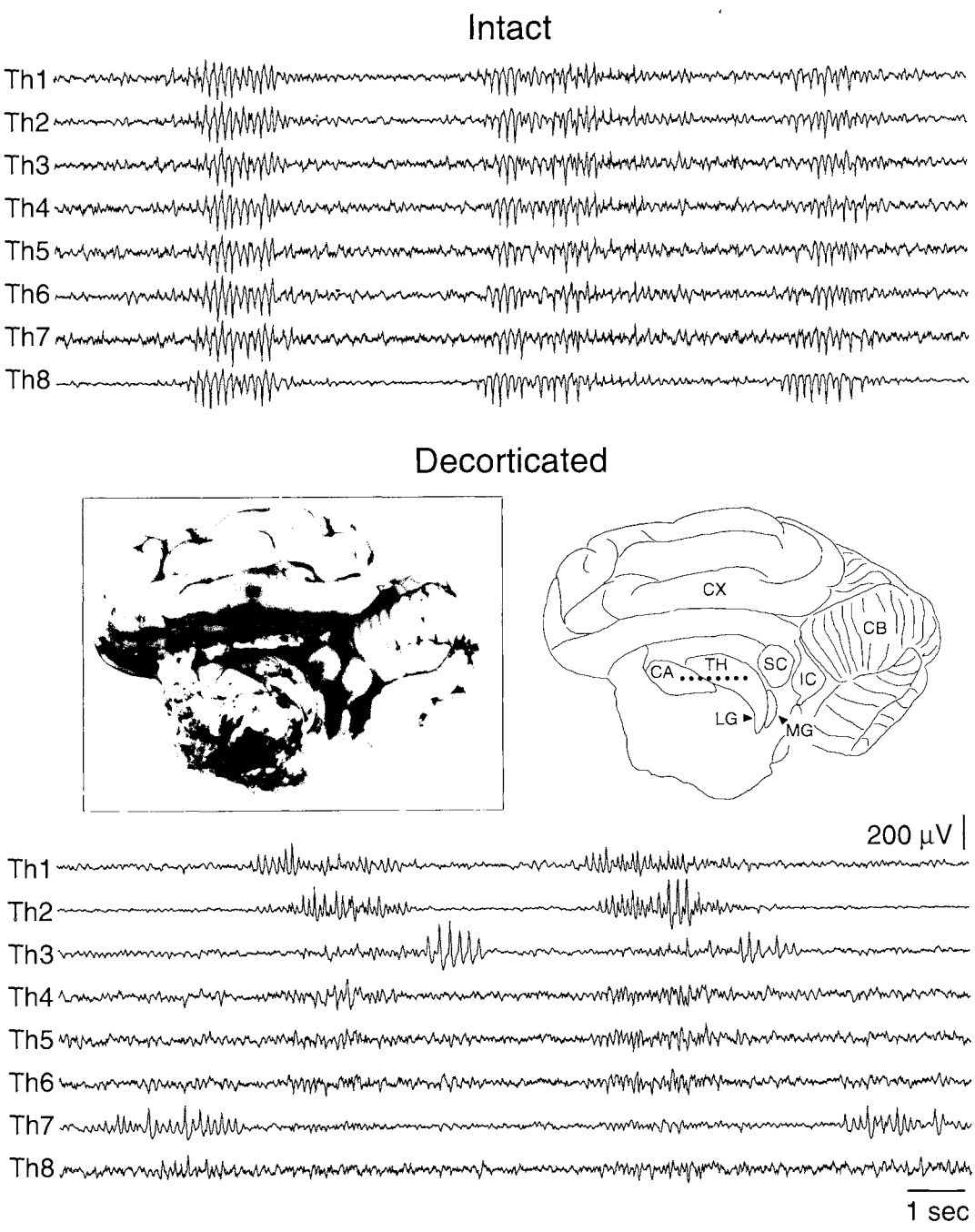

Fig. 5. Effect of removal of the cerebral cortex on the synchronization pattern of spindle oscillations in the cat thalamus. In an intact thalamocortical network under barbiturate anesthesia (upper panel), three spontaneous spindle sequences at 8-9 Hz and, lasting for 1 s to 3 s occurred almost simultaneously in the local field potentials (LFPs) recorded from eight tungsten electrodes (Th1 to Th8). Cortex of the left hemisphere was removed by suction, exposing the head of the caudate nucleus (CA), most of the dorsal thalamus (TH) including the lateral geniculate (LG) and medial geniculate (MG) bodies, and the superior and inferior colliculi (SC and IC). Also represented in the drawing are the intact contralateral (right) cerebral cortex (CX) and the cerebellum (CB). The eight thalamic electrodes are indicated by black dots in the drawing (the two or three most anterior thalamic electrodes crossed through the head of the CA to reach the thalamus). After decortication (lower panel), recordings from approximately the same thalamic locations showed that spindling continued to occur at each electrode site, but their coincidence in time was largely diminished. Modified from Contreras et al. (1996).

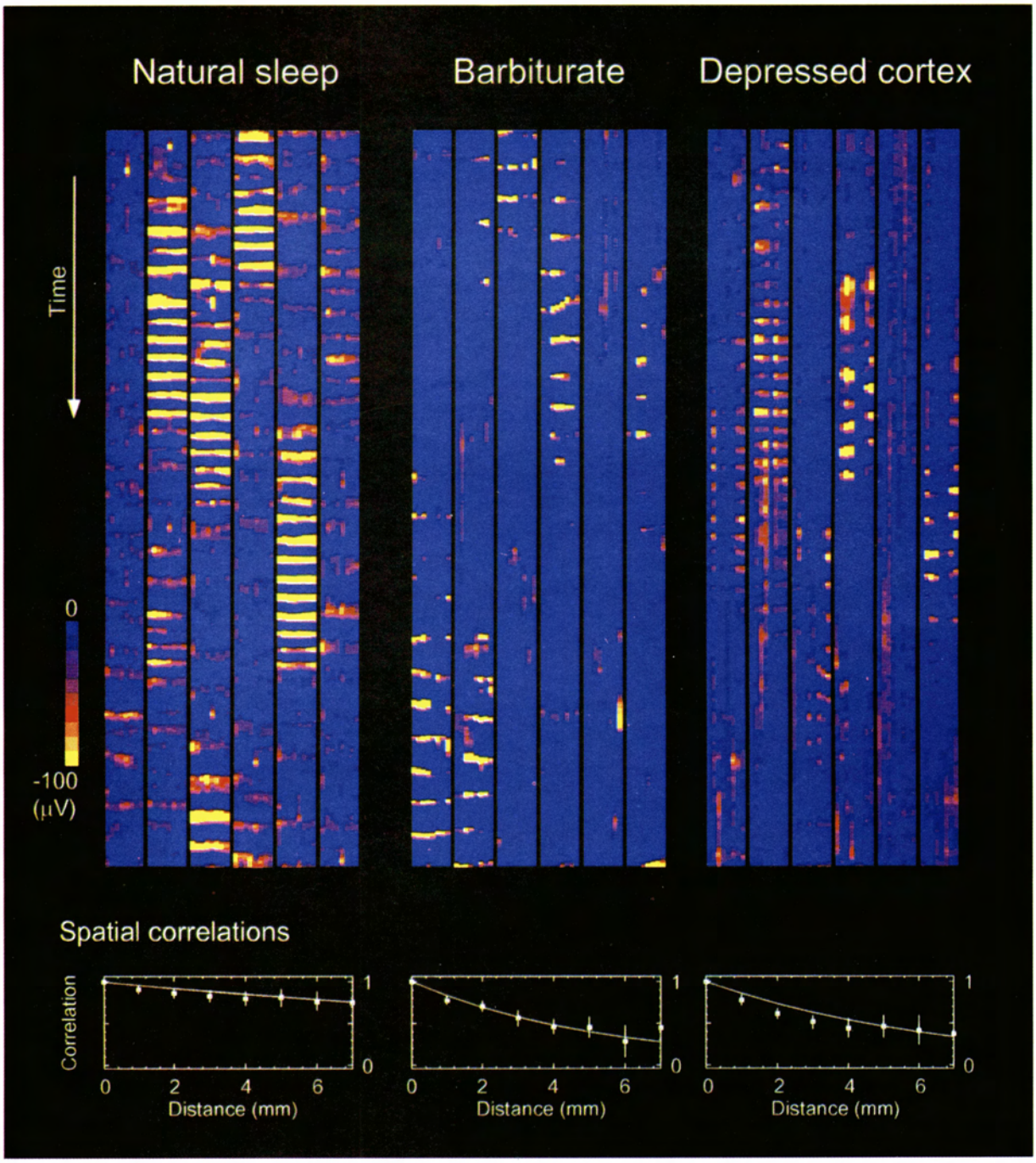

Fig. 6. The spatiotemporal coherence of spindle oscillations during natural sleep diminishes during barbiturate anesthesia and cortical depression in cat. Top panels: spatiotemporal maps of the distribution of electrical activity across the cortex were constructed by assigning a color to the value of the field potential at each electrode; the color scale ranged in 10 steps from the baseline (blue) to -100 μV (yellow). Time was divided in frames, each representing a snapshot of 4 ms of cortical activity and arranged in columns from top to bottom. Each column is about 3 s of activity (arrow is 1 s). Each frame consisted of 8 color spots, each corresponding to the local field potential of one electrode from anterior to posterior (left to right). Bottom panels: decay of correlations with distance. Cross-correlations were computed for all possible pairs of sites and the value at time zero was represented as a function of the inter-site distance in the cortex. Each point is an average over different combination of sites, and 10 different epochs of 2 s; vertical bars indicate the standard deviation. Continuous lines indicate the best fit using a decaying exponential. Modified from Destexhe et al. (1999).

is increased and the phase shifts are reduced compared to barbiturate anesthesia and the state of the depressed cortex (Destexhe et al. 1999). Therefore, these data point to the role of corticothalamic neurons in the enhancement of synchronization and appearance of nearly simultaneous spindle sequences, an oscillation generated in the thalamus and whose features are conventionally thought as being exclusively depending on intrathalamic processes. The cortical slow oscillation, associated with synchronous discharges in millions of corticothalamic neurons, has the same effect of generating synchronous spindles, as shown below (see last section).

Thalamic delta oscillation

Delta activities are the result of a complex pattern of activities: some are made of waves, such as those built up by the K-complex (Amzica and Steriade 1997), others reflect true oscillations. The former are part of a slower oscillation (see above) and survive therefore massive thalamic lesions. This may explain the initial claim for the existence of a cortically generated delta activity, which survived complete thalamectomy (Villablanca 1974, Steriade et al. 1993e). The other component of delta activity is a true oscillation, stereotyped, clock-like, and is generated in the thalamus through the hyperpolarization-activated interplay between two intrinsic currents of TC neurons. Although this rhythm is seen in thalamic slices after blockage of synaptic transmission (McCormick and Pape 1990, Leresche et al. 1990, 1991), its appearance at the level of local field potentials and cortical EEG (Steriade et al. 1993e) is possible because corticothalamic volleys synchronize TC cells through the action of inhibitory RE neurons that fulfill two requirements: they set the membrane potential of TC cells at the required level of hyperpolarization for the generation of delta oscillation and they have distributed projections to the dorsal thalamus, thus synchronizing various TC cells (Steriade et al. 1991).

As delta oscillation appears in TC neurons at a more hyperpolarized level of membrane potential than spindles (Steriade et al. 1991, Curró Dossi et al. 1992), the two sleep oscillations are incompatible in single TC cells (Nuñez et al. 1992). These intracellular data from anesthetized preparations are supported by results obtained in naturally sleeping animals, showing that thalamic spindles are maximal at sleep onset and decrease thereafter, whereas thalamic delta waves increase gradually during resting sleep. Thus, with increasing hyperpolarization of TC cells during resting sleep, due to the progressive reduction in firing rates of cholinergic and other types of brainstem-thalamic activating neurons (Steriade and McCarley 1990), the incidence of spindles is diminished while the incidence of delta waves is largely increase during deep sleep stages. These intracellular data from anesthetized preparation found support in results obtained in naturally sleeping animals, showing that thalamic spindles are maximal at sleep onset and decrease thereafter, whereas thalamic delta waves increase gradually during resting sleep (Lancel et al. 1992). On the other hand, the reappearance of spindles toward the very end of resting sleep (Fig. 7) is attributable to a relative depolarization of TC cells, due to the increased firing rates of brainstem-thalamic reticular neurons that display precursor increased rates of spontaneous firing, 30 s to 60 s before the onset of REM sleep (Steriade et al. 1990).

COALESCENCE OF CORTICAL AND THALAMIC SLEEP OSCILLATIONS

In intact brains the slow oscillation is transmitted mainly to thalamic (RE as well as TC) neurons (see Fig. 6 in Steriade et al. 1993b), but also to other structures such as the brainstem (see Fig. 6 in Steriade et al. 1994a), the basal forebrain (Nuñez 1996) and the neostriatum (Wilson and Kawaguchi 1996). Therefore, the sleep oscillations are not seen in isolation but rather grouped. This is especially the case for thalamically generated oscillations (spindles and clock-like delta). The orderly appearance of various rhythms throughout the state of resting sleep, under the umbrella of the slow oscillation, is associated with a progressive increase in the corticothalamic coherence of sleep rhythms.

The combination of the excitatory component of the slow oscillation with spindles leads to the appearance of sleep K-complexes in both cats and humans (Amzica and Steriade 1997, 1998a). The coalescence of the slow and spindle oscillations is especially visible during light sleep. The evolution of sleep rhythms, with their progressively increased amplitudes from the end of waking state toward the end of deep resting sleep, is illustrated by means of multi-site recordings in Fig. 7 which shows that, in naturally sleeping animals, the slow oscillation dominates brain electrical activity, throughout the state of resting sleep. During light sleep, every cycle of the slow oscillation generally leads to a sequence of spindle waves, on one, another or all cortical leads. This is due

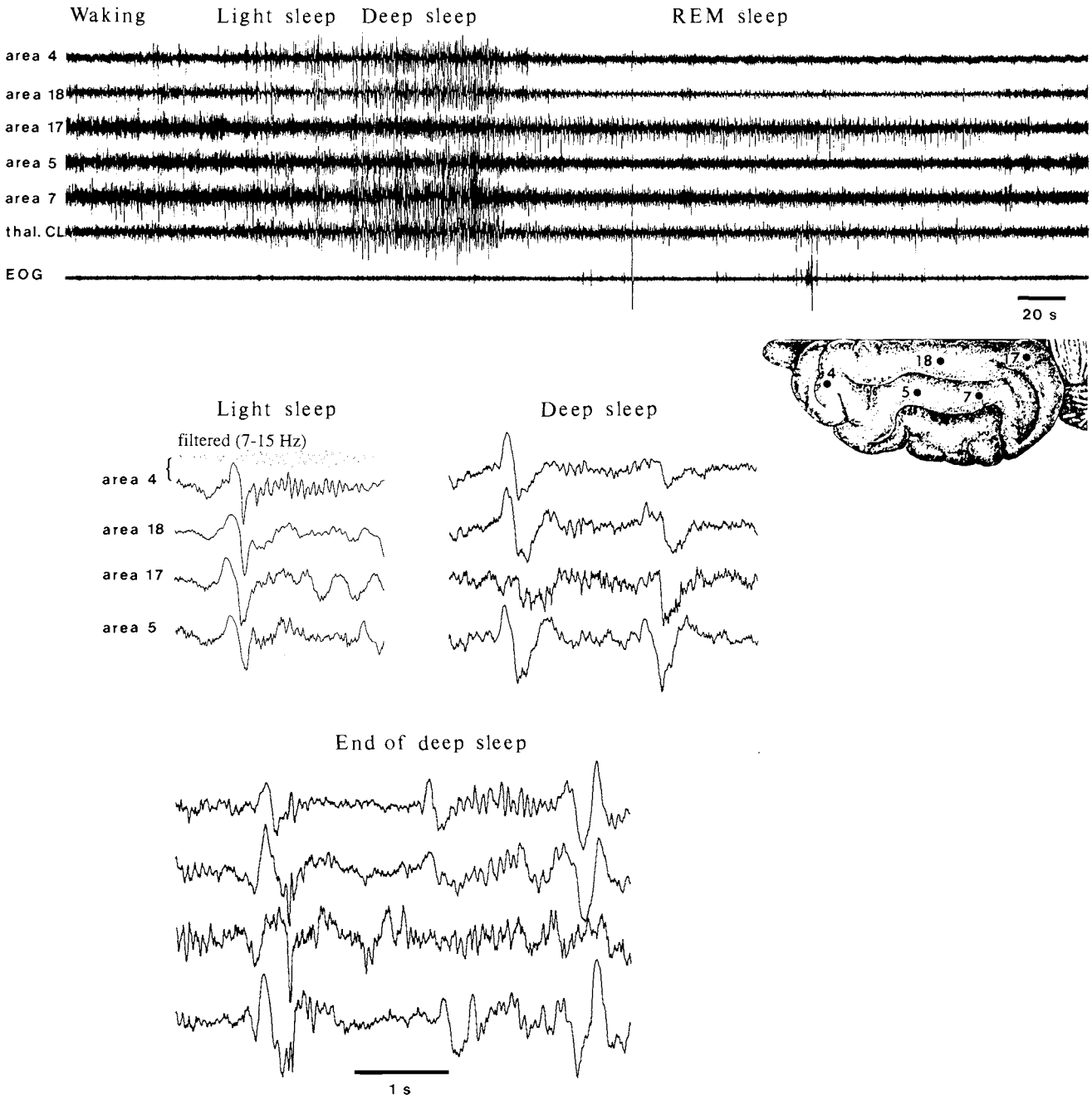

Fig. 7. Chronology of sleep rhythms in chronically implanted, behaving cat. Multi-site recordings of field potentials from the cortical depth (about 1 mm in areas 4, 18, 17, 5, 7; see brain figurine) and thalamic centrolateral (CL) rostral intralaminar nucleus. Below the long-term recording of a full wake-sleep cycle (440 s), three panels illustrate expanded recordings during light sleep, deep sleep, and the end of deep sleep before entering REM sleep. Note rhythmicity of PGO waves (at about 0.5 Hz) in area 17 during REM sleep. During light sleep, one cycle of the slow oscillation followed by a spindle sequence is depicted (top trace is a filtered trace to display spindles). Two cycles of slow oscillation (about 0.7 Hz) are depicted during deep sleep. Note, at the end of deep sleep, more pronounced spindles than during deep sleep (see text for comments). Modified from Steriade and Amzica (1998).

to the synaptic engagement of thalamic neurons implicated in spindle genesis.

The intrinsically generated delta oscillation of TC cells is influenced by the slow (<1 Hz) cortical oscillation because the rhythmic depolarizing corticothalamic drives increase the membrane conductance of TC cells and prevent the interplay between I_h and I_t, thus periodically dampening the slow oscillation (see Fig. 10A in Steriade et al. 1993b, and Box 1 in Steriade et al. 1994b). However, as corticothalamic volleys also drive GABAergic RE neurons, singly delta-oscillating TC cells may be synchronized because reticular cells set their membrane potential at the adequate level where delta rhythm is generated (Steriade et al. 1991). As to the other component of delta activity that is generated intracortically after thalamectomy (see above), it has been proposed to reflect a more complex phenomenon in which a clear distinction has to be made between oscillations and waves (Amzica and Steriade 1998b). The current confusion in the literature between delta oscillation and delta waves is probably due to the fact that the presence of a peak in power spectrum may result from an oscillation with the frequency of the peak and/or a frequent occurrence of waves with a duration and shape that would

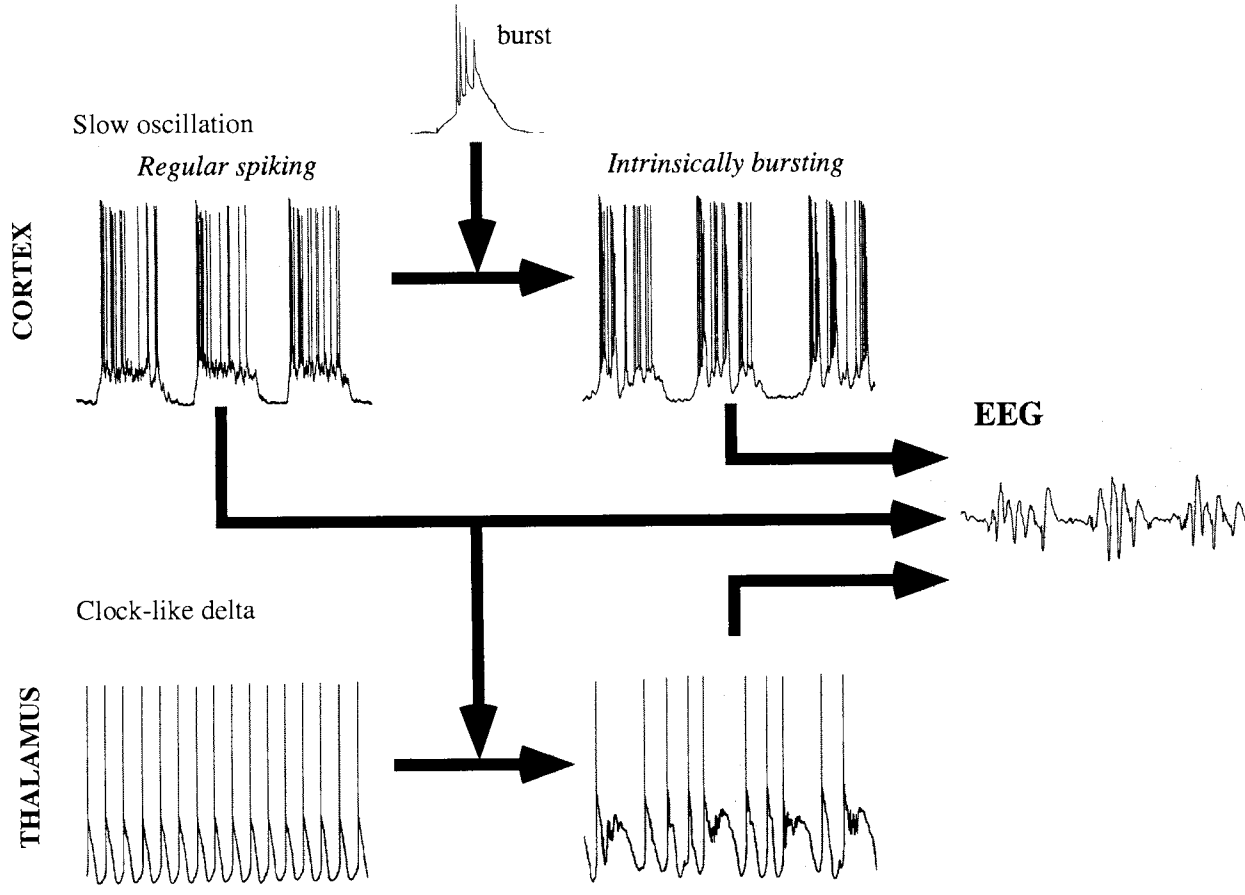

Fig. 8. Building blocks of corticothalamic networks participating at the genesis of the sleep 0.5-to-4-Hz oscillations. Upper blocks from the cortex, lower ones from the thalamus. The regular spiking cortical neuron (up, left) represents the activity of all cortical neurons involved in the genesis of the slow oscillation. The thalamocortical cell (down, left) displays the typical clock-like delta oscillation, in the absence of network impingements. The influence of the slow oscillation on thalamocortical cells is depicted in the lower, right block. The transformation of the slow oscillation by intrinsically bursting cortical neurons (burst in inset) and the generation of cortical intrinsic delta sequences is suggested in the upper right block. All three, i.e. pure slow oscillation, cortical delta and thalamic delta converge at the cortical level to generate the polymorphic slow-delta pattern of the EEG. Modified from Amzica and Steriade (1998b).

contribute to that particular peak. One possibility is that the frequency band of 1-4 Hz in the power spectrum during late stages of resting sleep results, at least partially, from the shape of the depth-negative (depolarizing) component of the slow oscillation (0.3-0.4 s), which represents the K-complex (Amzica and Steriade 1997, 1998a).

The emergence of delta activities in the EEG might be due to a complex interaction occurring in corticothalamic networks (Fig. 8). That delta and slow oscillation represent two distinct phenomena was recently demonstrated by Achermann and Borbély (1997) who showed differences in the dynamics between the slow and the delta oscillations, as the latter declines in activity from the first to the second non-REM sleep episode, whereas the former does not. Depending on the weight of synaptic linkages, on local circuit configurations and on the general behavioral state of the network, the slow oscillation, the thalamically generated clock-like delta oscillation and cortical delta waves may coalesce to produce the intricate electrographic pattern of deep sleep slow--wave pattern. The use of a more specific language (slow oscillation, thalamic clock-like delta, cortical delta) taking into account the different underlying mechanisms is necessary in order to adjust to the growing complexity of corticothalamic activities. As such, one should rely the interpretation of various EEG activities on the electrophysiological mechanisms underlying the genesis of local field potentials.

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