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# GROUPING OF BRAIN RHYTHMS IN CORTICOTHALAMIC SYSTEMS

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**Abstract—Different brain rhythms, with both low-frequency and fast-frequency, are grouped within complex wave-sequences. Instead of dissecting various frequency bands of the major oscillations that characterize the brain electrical activity during states of vigilance, it is conceptually more rewarding to analyze their coalescence, which is due to neuronal interactions in corticothalamic systems. This concept of unified brain rhythms does not only include low-frequency sleep oscillations but also fast (beta and gamma) activities that are not exclusively confined to brain-activated states, since they also occur during slow-wave sleep. The major factor behind this coalescence is the cortically generated slow oscillation that, through corticocortical and corticothalamic drives, is effective in grouping other brain rhythms. The experimental evidence for unified oscillations derived from simultaneous intracellular recordings of cortical and thalamic neurons *in vivo*, while recent studies in humans using global methods provided congruent results of grouping different types of slow and fast oscillatory activities. Far from being epiphenomena, spontaneous brain rhythms have an important role in synaptic plasticity. The role of slow-wave sleep oscillation in consolidating memory traces acquired during wakefulness is being explored in both experimental animals and human subjects. Highly synchronized sleep oscillations may develop into seizures that are generated intracortically and lead to inhibition of thalamocortical neurons, via activation of thalamic reticular neurons, which may explain the obliteration of signals from the external world and unconsciousness during some paroxysmal states. © 2005 Published by Elsevier Ltd on behalf of IBRO.**

**Key words: neocortex, thalamus, grouped rhythms, states of vigilance, seizures.**

Contents



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*Abbreviations:* ACh, acetylcholine; EEG, electroencephalogram; EPSP, excitatory postsynaptic potential; FRB, fast-rhythmic-bursting; IPSP, inhibitory postsynaptic potential; LG, lateral geniculate; LTS, low-threshold spike; MEG, magnetoencephalogram; PET, positron emission tomography; PGO, ponto-geniculo-occipital; PPT, pedunculopontine tegmental; PSW, polyspike wave; rCBF, regional cerebral blood flow; RE, thalamic reticular; SW, spike-wave; TC, thalamocortical.

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I shall elaborate the concept that, instead of strictly defining the frequency bands that characterize various rhythms of the electroencephalogram (EEG) and even splitting them into sub-types, it is more rewarding and closer to the reality to analyze the major EEG oscillations as grouped within complex wave-sequences. The progress in analytical methods used in studies on experimental animals, such as simultaneous intracellular recordings of cortical and thalamic neurons, as well as the advance in more global methods used in human investigations, i.e. EEG and magnetoencephalogram (MEG), led to the description of a multitude of oscillations generated in the cerebral cortex and/or thalamus. This great variety in wave frequencies and patterns is due to different electrophysiological and connectivity features of cortical, thalamic reticular (RE), and thalamocortical (TC) neurons, which generate most brain rhythms.

Francis Crick once asked me: "why so many oscillations?" At least for slow-wave sleep, the question was justified because the three cardinal rhythms defining this state (spindles, delta, and slow oscillation) are all associated with prolonged hyperpolarizations of TC and cortical neurons, which are effective in inhibiting the transmission of afferent signals and, thus, each one of these oscillations predisposes to brain disconnection and falling asleep. In more recent years, the above question received a definite answer from analyses of the neuronal circuitry and transmitters in the corticothalamic system, which fully explained how different brain rhythms coalesce into complex wave-sequences. The idea of grouping brain rhythms originally stemmed from analysis of sleep rhythms, with frequencies less than 15 Hz (Fig. 1). However, further studies showed that waking-like oscillations (beta, 20–30 Hz; and gamma, 30–60 Hz) are coalesced with the depolarizing phase of the slow sleep oscillation (Fig. 2). This might be thought as the substratum of peculiar forms of mental activity occurring episodically during slow-wave sleep. Moreover, while most investigators consider beta and gamma rhythms as distinct oscillatory types, our intracellular recordings have

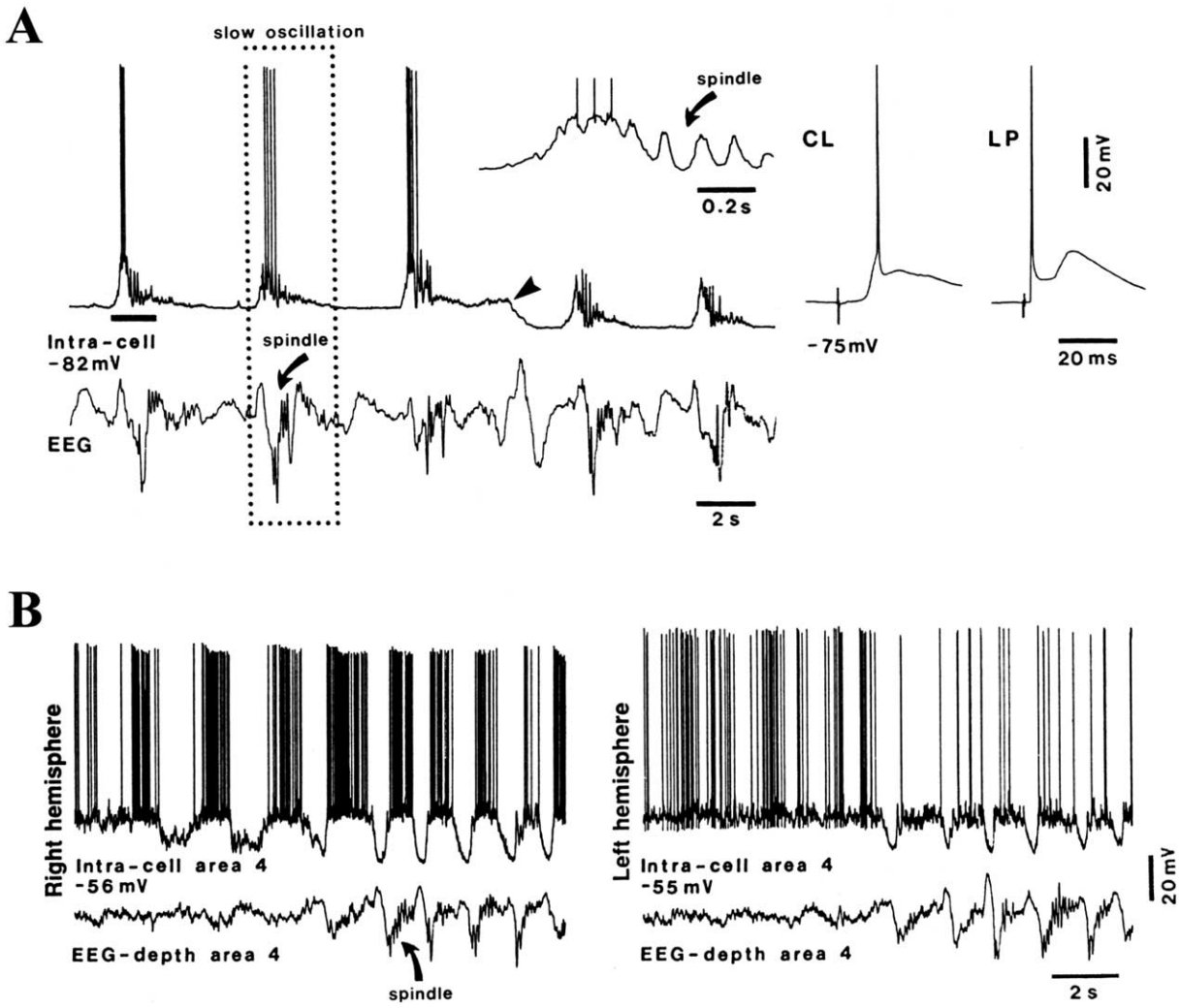


**Fig. 1.** The cortical slow oscillation groups thalamically generated spindles. (A) Intracellular recording in cat from cortical association area 7 (1.5 mm depth). Electrophysiological identification (at right) shows orthodromic response to stimulation of thalamic centrolateral (CL) intralaminar nucleus and antidromic response to stimulation of lateroposterior (LP) nucleus. Note slow oscillation of neuron and related EEG waves. One cycle of the slow oscillation is framed in dots. Part marked by horizontal bar below the intracellular trace (at left) is expanded above (right) to show spindles following the depolarizing envelope of the slow oscillation. (B) Dual simultaneous intracellular recordings from right and left cortical area 4 in cat. Note spindle associated with the slow oscillation and synchronization of EEG when both neurons synchronously displayed prolonged hyperpolarizations. Modified from Steriade et al. (1993d, 1994)

shown that beta activity transforms into gamma oscillation under slight membrane depolarization, and global EEG studies in humans support the idea that these two rhythms should be considered as grouped into one single entity since they occur in conjunction and fluctuate simultaneously during different mental activities (see *Slow oscillation and fast (beta/gamma) and ultra-fast rhythms*).

Thus, the variations in distinct oscillation frequencies are less important than the unified picture of brain oscillations, which was first revealed by performing *in vivo* intracellular recordings from formally identified long-axon and local-circuit neurons in the cortex or cortex and thalamus (Steriade et al., 1993b,e; Contreras and Steriade, 1995).

In this article, I will successively analyze (i) some aspects of the neuronal circuitry that are relevant to the generation and synchronization of low-frequency and fast rhythms; (ii) the coalescence of these rhythms investigated by intracellular recordings in animals, as well as congruent results from studies in humans on grouped brain oscillations; (iii) the role of spontaneously occurring rhythms in synaptic plasticity and memory consolidation, as resulting from animal and human studies; and (iv) the transformation of sleep oscillations into electrical seizures of the spike-wave (SW) type, suggesting possible neuronal substrates of unconsciousness during absence epilepsy.

## Neuronal circuitry in the corticothalamic system

I use the term corticothalamic, instead of TC, because axons in the descending pathway are much more numerous than in the ascending projection (Jones, 1985; White, 1989). Besides, the slow sleep oscillation, which is the

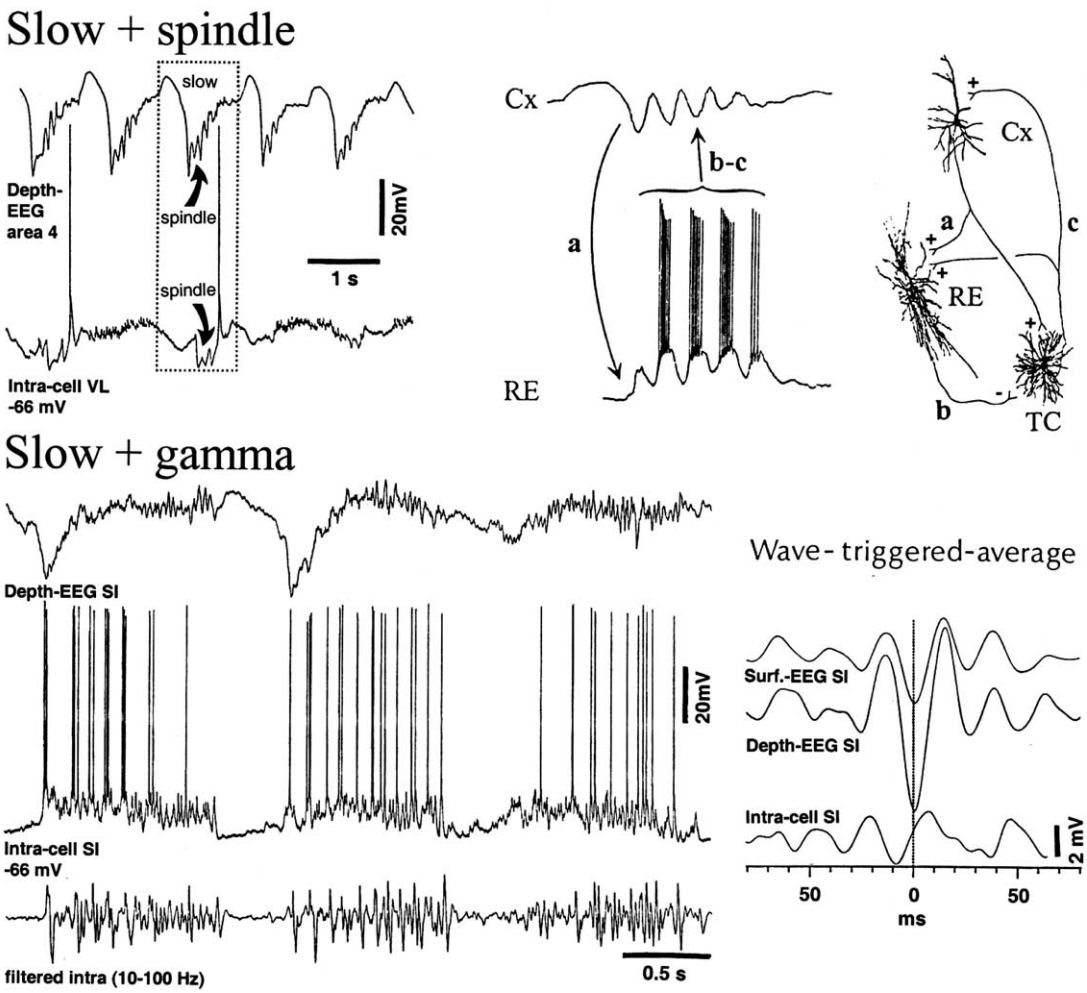


**Fig. 2.** Coalescence of slow oscillation with spindle and gamma rhythms. Intracellular recordings from cortical and thalamic neurons in cats. *Slow+spindle*, combined slow oscillation and spindle. Left: depth-EEG from cortical area 4 and intracellular recording of TC neuron from ventrolateral (VL) nucleus. The excitatory component (negative depth-EEG wave, downward deflection) of the slow cortical oscillation (0.9 Hz) is followed by a sequence of spindle waves at 10 Hz (arrows). One typical cycle of these two combined rhythms is indicated by dotted box; note IPSPs in VL neuron leading to a postinhibitory rebound. Right: top and bottom traces represent field potential from the depth of association cortical area 5 and intracellular recording from RE neuron. In neuronal circuits (far right), synaptic projections are indicated with small letters, corresponding to the arrows at left, which indicate the time sequence of the events. The depolarizing phase of the field slow oscillation (depth-negative, downward deflection) in the cortex (*Cx*) travels through the corticothalamic pathway (*a*) and triggers in the RE nucleus a spindle sequence that is transferred to TC cells of the dorsal thalamus (*b*) and thereafter back to the cortex (*c*), where it shapes the tail of the slow oscillatory cycle (see middle panel). *Slow+gamma*, fast activity (40 Hz) crowns the depolarizing phase of the slow oscillation. Three traces depict: depth-EEG waves from primary somatosensory cortex (S1), intracellular recording from S1 neuron, and filtered intracellular trace (between 10 and 100 Hz). Note fast waves (40 Hz) during the depolarizing phase of the slow sleep-like oscillation and absence of such fast waves during hyperpolarization. Modified from Steriade et al. (1993c, 1996b); Contreras and Steriade (1995); Timofeev and Steriade (1997).

main factor in the coalescence of brain rhythms, is generated intracortically, even in the absence of the thalamus (Steriade et al., 1993e; Sanchez-Vives and McCormick, 2000). Moreover, even though sleep spindles are generated within the thalamus, their near-simultaneous occurrence over widespread territories is produced by corticothalamic projections (Contreras et al., 1996a, 1997). Finally, fast-rhythmic-bursting (FRB) cortical cells are particularly well suited to generate coherent gamma rhythms in the corticothalamic system because some of them, located in deep cortical layers and projecting to the thalamus (Steriade et al., 1998a; Cardin et al., 2005), may synchronize cortical and thalamic generators of this oscillation. Thus, the cerebral cortex has a prevalent role in the generation and synchronization of different brain rhythms.

Some of the main neuronal types and networks implicated in brain oscillations are (i) corticothalamic neurons, (ii) the recurrent inhibitory circuit between RE and TC neurons, and (iii) thalamically projecting brainstem cholinergic (and other neuromodulatory) projections.

Although all corticothalamic neurons are glutamatergic and thus excitatory, the effect of a synchronous cortical drive (an electrical volley or a spike-burst during natural states of vigilance) on RE neurons is excitatory and followed by rhythmic spike-bursts in the frequency range of spindles, whereas TC neurons simultaneously display bi-

phasic inhibitory postsynaptic potentials (IPSPs) leading to low-threshold spikes (LTSs) in isolation or crowned by fast action potentials (see Fig. 1 in Steriade, 2000). This contrasting effect on RE and TC neurons is due to the fact that excitatory postsynaptic currents (EPSCs) elicited in RE neurons by minimal stimulation of corticothalamic axons are 2.5 times larger than in TC neurons, and GluR4 receptor subunits in RE neurons outnumber those in TC neurons by 3.7 times (Golshani et al., 2001; Jones, 2002). These data are important in that they explain how, during the bursting mode of thalamic neurons (as is the case during slow-wave sleep and some seizures), the cortically elicited direct excitation of TC neurons is overwhelmed by the bisynaptic inhibition of these neurons, mediated by GABAergic RE neurons.

Another point in this complex circuitry, which can only be studied in intact-brain preparations (see Steriade, 2001), relates to the effects exerted on thalamic neurons by brainstem cholinergic cellular aggregates that are among the most important neuromodulatory systems in shifting the state of vigilance from the disconnected to the activated brain (Steriade and McCarley, 2005). The same neuron from the brainstem cholinergic pedunculopontine tegmental nucleus (PPT) may branch its axon to innervate both RE and TC neurons (Spreafico et al., 1993). At the TC level, PPT neurons produce direct depolarization with increase in input resistance, which explains the increased excitability in this gateway to the cerebral cortex (Curró Dossi et al., 1991). This effect is combined with, and strengthened by, the simultaneous inhibition produced by brainstem cholinergic neurons on GABAergic RE neurons (Hu et al., 1989), which leads to disinhibition of their targets, TC cells. These effects account for the suppression of thalamically generated slow-wave sleep rhythms (spindles and the clock-like component of delta waves; see below), which consist of long-lasting periods of hyperpolarizations, and account for the shift from the disconnected state of sleep to brain-active states.

### Grouping of brain rhythms: evidence from intracellular recordings in animals and EEG studies in humans

Three rhythms (spindles, 7–15 Hz; delta, 1–4 Hz; slow oscillation, 0.5–1 Hz) define slow-wave sleep, and two rhythms (beta, 20–30 Hz; gamma, 30–60 Hz) occur in a sustained manner during the brain-active states of waking and REM sleep, though these fast oscillations are also episodically present during slow-wave sleep when they possibly underlie dreaming mentation during this disconnected behavioral state (see below).

The importance of the slow oscillation resides in the fact that it groups other brain rhythms, with both low- and fast-frequencies, within complex wave-sequences (Figs. 1 and 2). The slow oscillation was first described using intracellular recordings from different neuronal types in anesthetized cats and, in the same article (Steriade et al., 1993d), was also detected in EEG recordings during natural slow-wave sleep in humans in which cyclic groups of delta waves at 1–4 Hz recurred with a slow periodicity, 0.4–0.5 Hz. The grouping of these two oscillatory types is one of the arguments supporting the distinctness between delta and slow oscillations. Another argument came from human studies (Achermann and Borbély, 1997) showing that the typical decline in delta activity (1–4 Hz) from the first to the second sleep episode was not present at frequencies characteristic for the slow oscillation (range 0.55–0.95 Hz).

The cortical nature of the slow oscillation was demonstrated by its survival in the cerebral cortex after thalamectomy (Steriade et al., 1993e), its absence in the thalamus of decorticated animals (Timofeev and Steriade, 1996), and its presence in cortical slices maintained *in vitro* (Sanchez-Vives and McCormick, 2000). This rhythm was recorded in all major types of neocortical neurons, including pyramidal-shaped and local-circuit inhibitory neurons (Contreras and Steriade, 1995), and is made up by a prolonged depolarizing ("up") phase, followed by a long-lasting hyperpolarizing ("down") phase (Fig. 1). In intracellular recordings from cortical neurons of chronically-implanted, naturally sleeping animals, the slow oscillation with clear-cut hyperpolarizing phases appears from the very onset of slow-wave sleep and disappears in wakefulness and REM sleep when hyperpolarizations are erased and the activity of cortical neurons is tonically depolarized (Steriade et al., 2001; see also acute experiments, Steriade et al., 1993a). The depolarizing phase consists of non-*N*-methyl-D-aspartate-mediated excitatory postsynaptic potentials (EPSPs), fast prepotentials, a voltage-dependent persistent $Na^+$ current ($I_{Na(p)}$), and fast IPSPs reflecting the action of synaptically coupled GABAergic local-circuit cortical cells (Steriade et al., 1993d). The hyperpolarizing (silent) phase is *not* produced by GABAergic inhibitory interneurons but is due to disfacilitation (removal of synaptic, mainly excitatory, inputs) in intracortical and TC networks, and also to some $K^+$ currents (Contreras et al., 1996b; Timofeev et al., 2001). The disfacilitation factor may be explained by a progressive depletion of extracellular $Ca^{2+}$ ($[Ca^{2+}]_{out}$) during the depolarizing phase of the slow oscillation (Massimini and Amzica, 2001), which would produce a decrease in synaptic efficacy and an avalanche reaction that would eventually lead to the functional disconnection of cortical networks.

Unlike "pure" rhythms within distinct frequency bands, generated in restricted neuronal circuits of extremely simplified experimental preparations, the living brain does not generally display separate oscillations during slow-wave sleep, but a coalescence of the slow oscillation with other sleep rhythms (spindles and delta) as well as with faster (beta and gamma) rhythms that are superimposed on the depolarizing phase of the slow oscillation (Fig. 2). Thus, such fast oscillations also appear, with lower incidence, during natural slow-wave sleep or anesthesia. Here, I briefly discuss the circuitry and neuronal mechanisms that account for the grouping of low-frequency and fast-frequency rhythms by the slow oscillation.

### Slow oscillation and spindles: the K-complex

The thalamic generation of sleep spindles and the crucial role of RE GABAergic neurons are discussed in detail elsewhere (Steriade, 2003). Recent experimental

(Fuentealba et al., 2004) and modeling (Traub et al., 2005) studies support the notion that RE neurons are pacemakers of spindles. During the depolarizing phase of the slow oscillation, the synchronous firing of neocortical neurons impinges upon thalamic RE pacemaking neurons, thus creating conditions for formation of spindles, which are transferred to TC neurons and up to cortex, at which level spindles shape the tail of the slowly oscillatory cycle (see middle panel in *Slow+spindle* in Fig. 2). This connectivity explains why a cycle of the slow oscillation is followed by a brief sequence of spindles in TC neurons and in the cortical EEG (left panel in *Slow+spindle* in Fig. 2), as seen with intracellular recordings (Fig. 1) as well as with EEG recordings in human slow-wave sleep (Amzica and Steriade, 1997; Mölle et al., 2002; Fig. 3). The sequence of grapho-elements consisting of an ample surface-positive transient, corresponding to the excitation in deeply lying cortical neurons, followed by a slower, surface-negative component and eventually a few spindle waves, represents the combination between the slow and spindle oscillations. It is termed the K-complex (Fig. 4) and is a reliable sign for stage 2 of human sleep, but it is apparent in all stages of slow-wave sleep (Niedermeyer, 2005). Spectral analysis shows the periodic recurrence of human K-complexes, with main peaks at 0.5–0.7 Hz (Fig. 4). The other frequency bands in this figure are between 1 and 4 Hz (delta band, with several ill-defined peaks) and between 12 and 15 Hz (the spindling range). The decomposition of the signal into three digitally filtered channels (Fig. 4) indicates that the S-lead reflects the slow oscillation, the $\Delta$ lead reflects the shape of the K-complex, and the $\sigma$ lead faithfully reflects the spindle activity of the original signal. The laminar profile and intracellular substrates of the K-complex during cat sleep or anesthesia revealed that the surface-recorded, positive K-complexes reverse at a cortical depth of about 0.3 mm, and that the sharp depth-negative (surface-positive) wave of the K-complex is associated with cells' depolarizations, eventually leading to a spindle sequence (Amzica and Steriade, 1998). These investigations indicate that the K-complexes are the expression of the spontaneously occurring, cortically generated slow oscillation, though K-complexes can also be evoked by sensory stimuli during sleep.

### Slow oscillation and delta waves

There are two components of delta waves. The cortical one survives thalamectomy (Villablanca, 1974; Steriade et al., 1993e). The thalamic component is generated through the interplay between two intrinsic currents of TC neurons, a hyperpolarization-activated cation current, $I_H$ (Leresche et al., 1990, 1991; McCormick and Pape, 1990), and a low-threshold transient $Ca^{2+}$ current, $I_T$ (Llinás, 1988; Huguenard, 1996). Although arising from intrinsic properties of single TC neurons, the thalamic clock-like delta activity can be synchronized by corticothalamic volleys, which set into action RE neurons that, in turn, hyperpolarize TC neurons at the adequate membrane potential at which delta potentials are generated (Steriade et al., 1991). Thus, the synchronous discharges of cortical neurons during the depolarizing phase of the slow oscillation excite RE neurons and the resulting hyperpolarization-activated delta potentials in TC cells are transferred back to cortex, where they shape the slowly oscillatory phase.

### Slow oscillation and fast (beta/gamma) and ultra-fast rhythms

The unexpected association between a slow sleep rhythm and fast oscillations that are conventionally regarded as defining the electrical activity of brain-active states is explained by the voltage-dependency of fast oscillations. Indeed, long-axon and local-circuit cortical neurons generate beta and gamma rhythmicity at relatively depolarized values of the membrane potential (Llinás et al., 1991; Nuñez et al., 1992; Gray and McCormick, 1996; Steriade et al., 1996a). Thus, fast rhythms are sustained during the steady depolarization of cortical neurons during waking and REM sleep, selectively appear over the depolarizing phase of the slow sleep oscillation, and are absent during the hyperpolarizing phase of the slow oscillation (see Fig. 2). FRB neurons, located throughout cortical layers 2–6 and projecting to the thalamus (Steriade et al., 1998a; Cardin et al., 2005), are among the best candidates to generate and synchronize beta and gamma rhythms because they may link cortical and thalamic generators of these fast oscillations. That the thalamus and neocortex display coherent beta and gamma rhythms is demonstrated by cross-correlations between intracellularly recorded TC neurons and field potentials in the appropriate cortical area (Fig. 5A). At variance with the long-range synchrony of the slow sleep oscillation (see below), fast rhythms are synchronized over restricted cortical territories and within specific circuits between TC and neocortical areas (Fig. 5A–B).

Beta and gamma rhythms can interchangeably be termed *fast* because neurons may pass from beta to gamma oscillation in very short periods of time, 0.5–1 s, with slight depolarization (Steriade et al., 1996a). Studies in humans also showed that there is no precise cutoff between the beta and gamma bands, since these activities may fluctuate simultaneously, as shown by increased activities within both beta and gamma frequency bands (21–34 Hz) during semantic memory recall (Slotnick et al., 2002). Also, tasks demanding working memory are associated with phase synchrony of both beta (20 Hz) and gamma (30–40 Hz) cortical activities (Palva et al., 2005). These authors discussed the origin of fast activity in the cerebral cortex and considered that FRB neurons are key elements in reciprocal corticothalamic loops that generate fast rhythms, as demonstrated in experimental studies (Steriade et al., 1998a). The association between slow oscillation and fast rhythms has also been reported in human sleep (Mölle et al., 2002).

The synchronized fast rhythmic activity led to hypotheses postulating that linkages between spatially distributed oscillatory elements in the visual cortex may be the bases for "feature binding" and pattern recognition function (Singer, 1999; see the evaluation of this theory in Shadlen and Movshon, 1999). It should be noted that fast rhythms

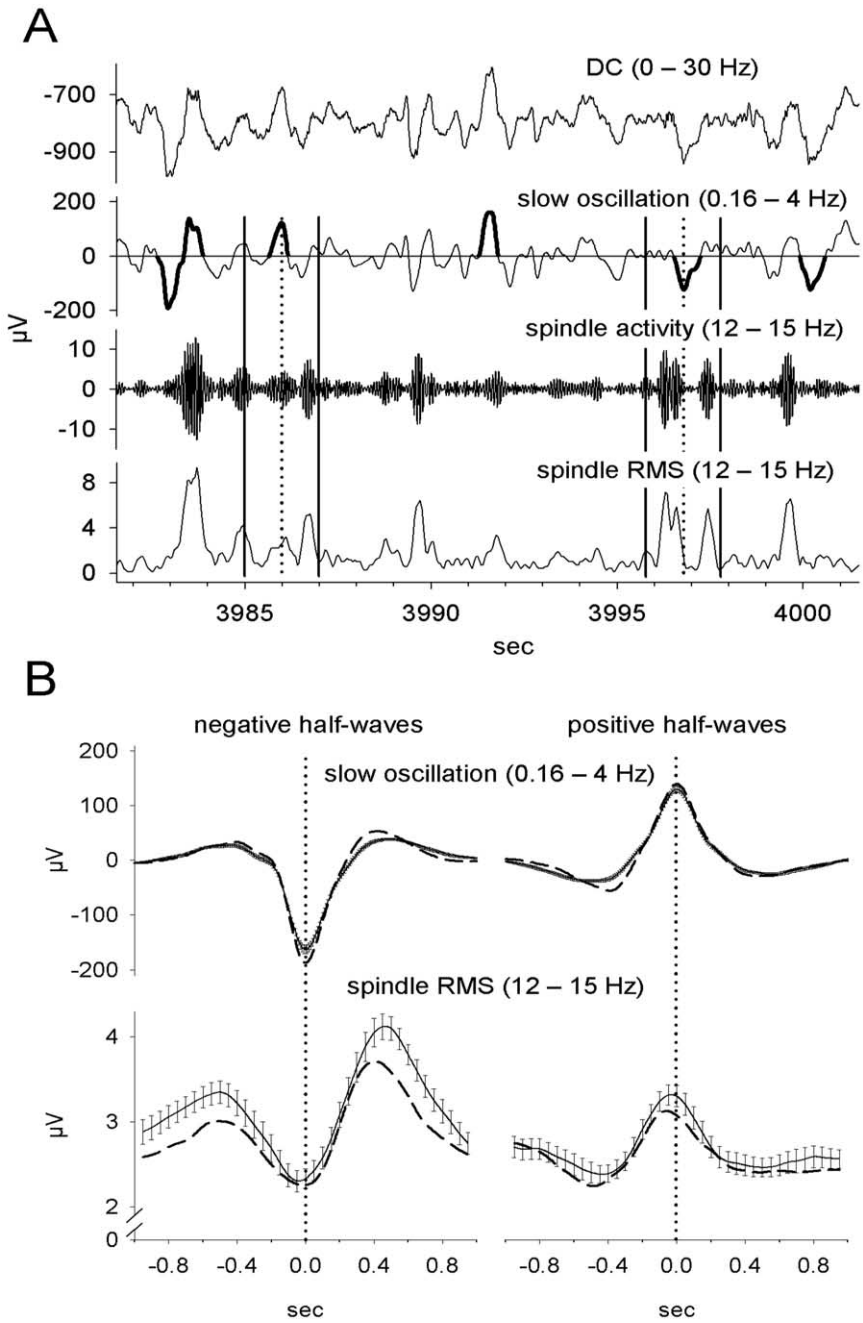


**Fig. 3.** Grouping of slow oscillation and spindle waves in human slow-wave sleep. (A) Analysis of slow oscillation-dependent changes in spindle activity. From top to bottom, DC-recorded (0–30 Hz) original EEG signal, slow oscillatory signal (0.16–4 Hz) with detected slow positive and negative half-waves indicated by a thick solid line, and spindle *rms* (root mean square) signal. For one positive and one negative half-wave each, the peak time used or for time-locked averaging and the ±1 s averaging interval are indicated by a dotted line and two sold vertical lines, respectively. (B) Grand means (across 13 subjects) of results from wave-triggered analysis of slow negative (left) and positive (right) half-waves. The mean±S.E.M. slow oscillation signal (top) and spindle *rms* signal (bottom) are shown. Dashed lines indicate mean values at Fz. Modified from and courtesy of Mölle et al. (2002).

are also present during the depolarizing phase of the slow oscillation during deep anesthesia and natural slow-wave sleep when consciousness is suspended. However, some studies have shown that fast rhythms are correlated with high cognitive and conscious processes in wakefulness and with dreaming mentation in REM sleep (Llinás and Ribary, 1993), and this aspect should be further explored.

Ultra-fast (or very fast) rhythms (80–200 Hz, up to 400 Hz), also called “ripples,” are superimposed over the depolarizing phase of the slow oscillation in neocortex (Grenier et al., 2001). The synchronous occurrence of ripples over many cortical sites is explained by their strict relation with the depolarizing phase of the slow oscillation, and the fact that the slow oscillation is co-

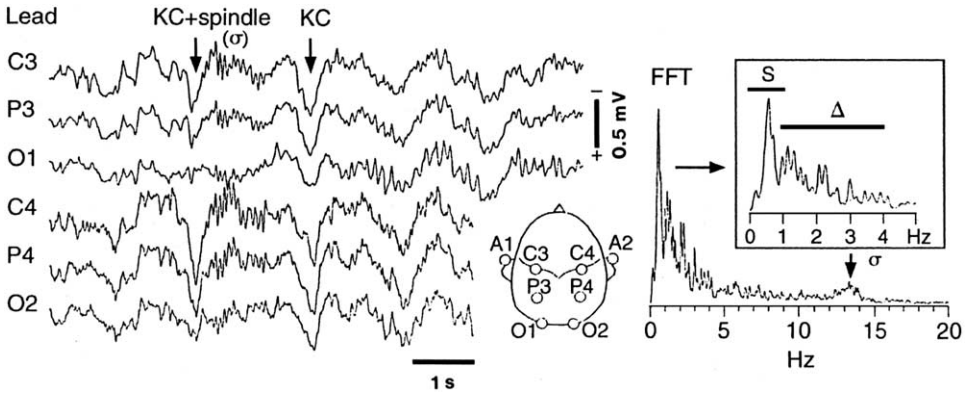


**Fig. 4.** Coalescence of slow oscillation and spindles in humans-the K-complex during natural sleep. Scalp monopolar recordings with respect to the contralateral ear are shown (see figurine). Traces show a short episode from a stage 3 slow-wave sleep. The two arrows point to two K-complexes, consisting of a surface-positive wave, followed (or not) by a sequence of spindle (sigma, σ) waves. Note the synchrony of K-complexes in all recorded sites. On the right, frequency decomposition of the electrical activity from C3 leads into three frequency bands: slow oscillation (S, 0–1 Hz), delta waves (Δ, 1–4 Hz), and spindles (σ, 12–15 Hz). Modified from Amzica and Steriade (1997).

herent in different, adjacent but also distant, cortical areas. The possible involvement of inhibition in the phase-locking of neurons during ripples was corroborated by the increased activity of fast-spiking neurons (representing local-circuit inhibitory cells) in relation with ripples. Ripples are also found in the perirhinal cortex and hippocampus, associated with bursts of sharp potentials during anesthesia, behavioral immobility and natural sleep (Chrobak and Buzsáki; 1996; Collins et al., 1999). Surgically isolated stratum oriens neurons in the CA1 region of the hippocampus can generate ripples, as predicted by a model with axonal electrical coupling (Traub et al., 1999, 2003, 2005). Such ultra-fast oscillations are also observed preceding epileptiform bursts in children with seizures caused by cortical dysplasia (Traub et al., 2001) and in initiating spontaneously occurring electrical paroxysms in cats (Grenier et al., 2003).

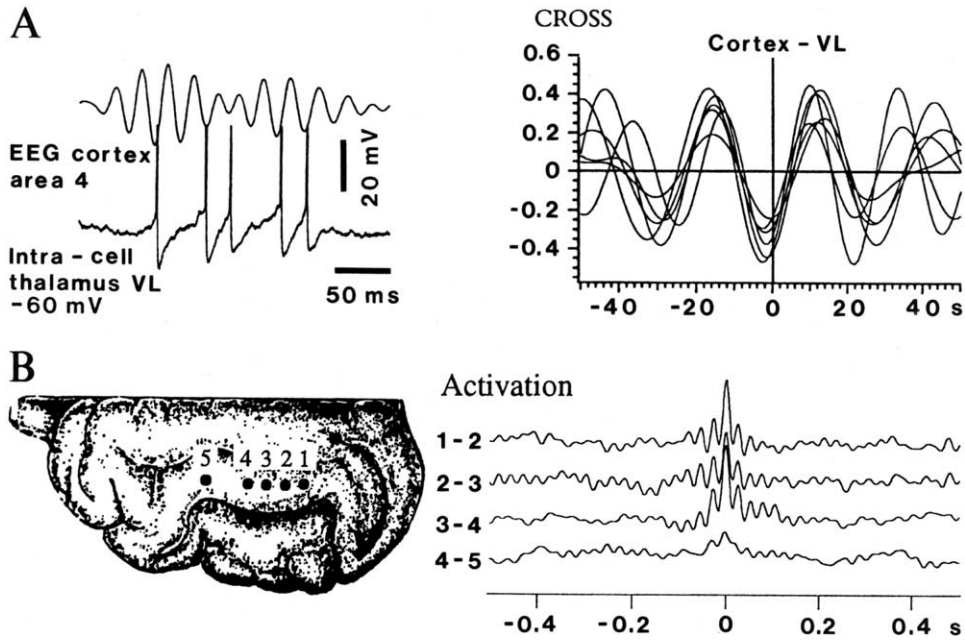


**Fig. 5.** Intracortical and corticothalamic synchronization of fast (gamma) rhythms, and their relation with the depolarizing phase of the slow sleep oscillation. (A) Short episode of activation in cat cerebral cortex, associated with coherent fast rhythms (~40 Hz) in EEG from motor cortex (area 4) and intracellularly recorded TC neuron from ventrolateral (VL) nucleus. Two traces represent simultaneous recordings of depth-EEG and intracellular activity of VL neuron (spikes truncated). Note close time-relations between action potentials of VL neuron and depth-negative waves in cortical EEG (reflecting summated excitatory events in a pool of neurons) at a frequency of about 40 Hz. Cross-correlations (CROSS) between action potentials and depth-EEG shows clear-cut relation, with opposition of phase, between intracellularly recorded VL neuron and EEG waves. (B) Synchronization of fast rhythms (35–40 Hz) among closely spaced leads in cortical areas 5 and 7 of cat. Distance between electrodes 1–2, 2–3 and 3–4: about 1.5 mm; between electrodes 4–5: about 3 mm. Cross-correlations between field potentials recorded from foci *1–2*, *2–3*, *3–4*, and *4–5* (see cortex figurine at left). Note decreased correlation with a slightly increased distance (*4–5*). Modified from Steriade et al. (1996a).

### Traveling slow oscillation in humans and actions on distant subcortical structures

The slow oscillation (generally 0.5–1 Hz) was demonstrated during natural sleep of humans using EEG (Achermann and Borbély, 1997; Amzica and Steriade, 1997; Mölle et al., 2002; Marshall et al., 2003) and MEG (Simon et al., 2000) recordings.

The intracortical propagation of the slow sleep oscillation was studied in humans, using high-density (180) EEG leads (Massimini et al., 2004). The detection of slow oscillation on the multichannel EEG is depicted in Fig. 6. The slow oscillation originates in frontal regions and propagates in an anterior–posterior direction with a speed of 1.2–7 m/s, much faster than described in cortical slices (10–100 mm/s), where only pure neighbor-to-neighbor synaptic propagation could be observed (Compte et al., 2003). The anterior frontal origin of the slow sleep oscillation in the human study (Massimini et al., 2004) suggested a stronger need for sleep of this cortical region, as also indicated by very low cerebral blood flow values in this area (Maquet et al., 1997). Marked decreased of regional cerebral blood flow (rCBF) was also found during slow-wave sleep in the medial thalamus (Hofle et al., 1997) and significant covariation between the midbrain and the thalamus was reported in a positron emission tomography (PET) study on humans (Fiset et al., 1999). This covariation is explained by direct connections between the upper brainstem core and thalamus (see Steriade, 2003).

Rather than global changes in neocortex, rCBF measured with PET in humans showed major deactivation in heteromodal association areas during slow-wave sleep, while activity in primary and secondary sensory cortices was relatively preserved (Braun et al., 1997). The anterior frontal origin of the human slow oscillation and the suggestion that this may implicate a stronger need for sleep in this cortical region (Massimini et al., 2004) is congruent with the fact that the increase in slow-wave sleep activity after sleep deprivation is highest in anterior prefrontal regions (Finelli et al., 2000).

The cortically generated slow oscillation is reflected in subcortical structures. The discharge properties of both subthalamic and globus pallidus neurons are related to neocortical activity as these neurons fire spike-bursts with a periodicity that is coincident with the cortical slow oscillation and the oscillatory activity of those basal ganglia neurons is lost during cortical inactivation through pharmacological tools (Magill et al., 2000). The close relation between the slow oscillation recorded from striatal neurons and neocortical activity that generates this oscillation was also observed (Wilson and Kawaguchi, 1996; Mahon et al., 2001).

The basolateral nucleus of the amygdala complex and the perirhinal cortex display highly synchronous slow oscillation (Collins et al., 2001) and the hippocampus also reflects slow oscillatory cortical activity, as spike-bursts in deeply lying neocortical neurons trigger population events in the hippocampus associated with ultra-fast oscillations (Sirota et al., 2003).

### Synaptic plasticity during and following brain rhythms

The question whether spontaneously occurring brain waves are epiphenomena with little or no functional significance may especially apply to the state of sleep that was considered to be associated with widespread inhibition throughout the cortex and subcortical structures (Pavlov, 1923), which would lead to abolition of cognitive and conscious events. However, the rich spontaneous firing of neocortical neurons, revealed by intracellular recordings during natural slow-wave sleep (Steriade et al., 2001), challenges the assumption that cortical neurons are inactive in this state. Although external signals are blocked at the thalamic level during slow-wave sleep, mainly because of TC neurons' inhibition during spindle waves, the intracortical dialogue is maintained (Timofeev et al., 1996) and the responsiveness of cortical neurons to callosal volleys is even increased during slow-wave sleep (Steriade et al., 1974). In humans too, this response is actually stronger in slow-wave sleep than in waking, but it abates much earlier (Massimini et al., 2005). That neocortex is active during slow-wave sleep suggests a reorganization/specification of neuronal circuits (Steriade et al., 1993b). This view is supported by studies using indicators of neuronal activities during slow-wave sleep in humans, revealing more marked changes in those neocortical areas that are implicated in memory tasks and decision-making during wakefulness (Maquet et al., 1997). In what follows, I shall discuss the role of low-frequency (spindle and slow) rhythms in synaptic plasticity. The fast rhythms, which are present in the background electrical activity during waking and REM sleep, also enhance the responsiveness of neocortical neurons (Steriade and Timofeev, 2003a). Then, spontaneous brain rhythms during different states of vigilance may lead to increased responsiveness and plastic changes in the strength of connections among neurons, a mechanism through which information is stored.

### Experimental studies on animals

The experimental model of sleep spindles is the sequence of augmenting (or incremental) responses, defined as thalamically evoked cortical potentials that grow in size during the first stimuli at a frequency of 5–15 Hz, which mimics the initially waxing pattern of spindle waves. Similar incremental responses can be evoked in the thalamus by stimulating the cortex within the frequency of spindle waves. The cellular mechanisms of augmenting responses have been studied in slices maintained *in vitro* (Castro-Alamancos and Connors, 1996) and using simultaneous intracellular recordings from TC and related cortical neurons *in vivo* (Steriade et al., 1998b). In the intact brain, augmenting responses evoked by rhythmic (10 Hz) thalamic stimulation are characterized in cortical neurons by an increase in the secondary depolarization, at the expense of the primary EPSP. The secondary depolarization in neocortical neurons follows by 3 ms the postinhibitory spike-burst in simultaneously recorded TC neurons (Steriade et al., 1998b) (Fig. 7A). Another factor that may account for the

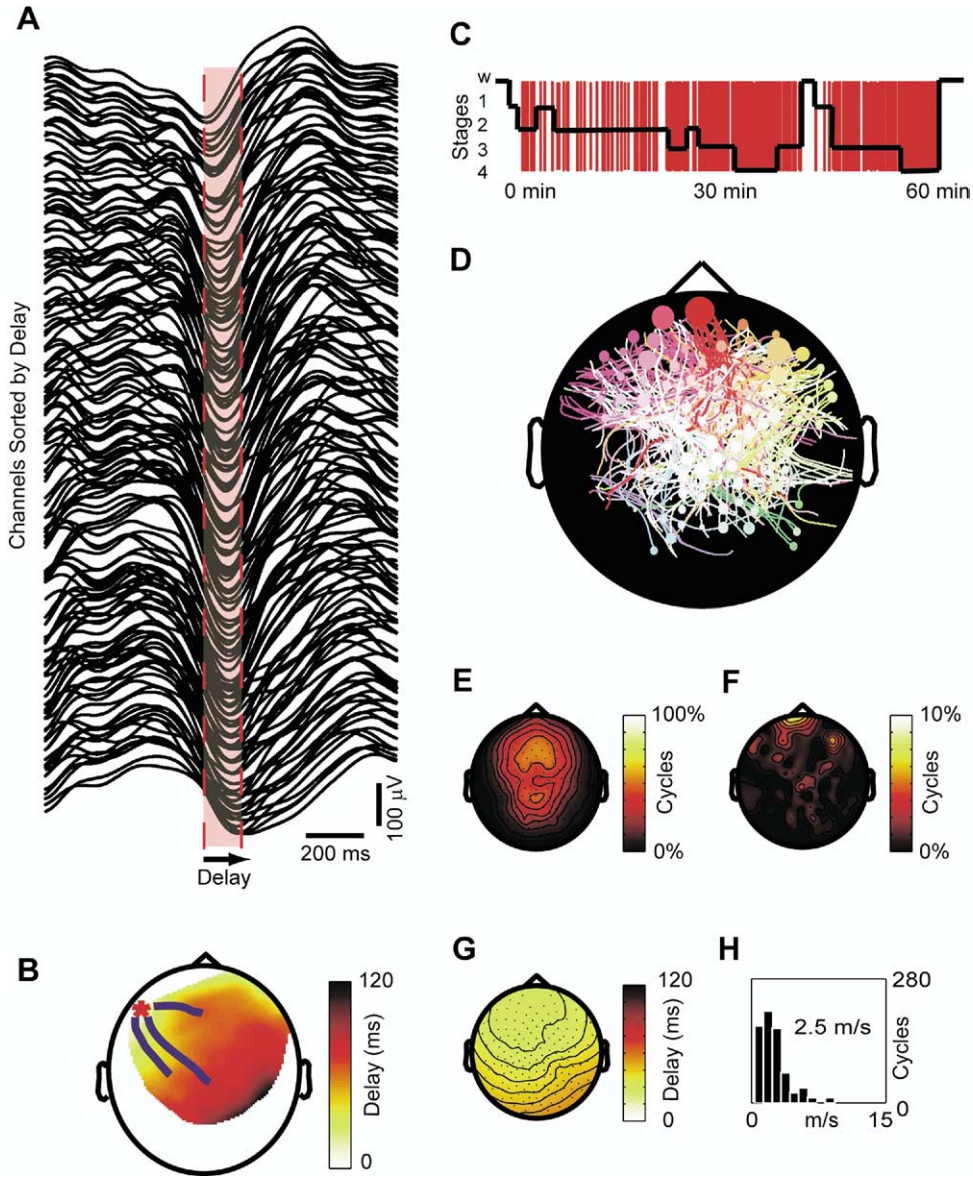


**Fig. 6.** The slow oscillation in human sleep as a traveling wave. (A) The signals recorded with 256-channel EEG during one cycle of the slow oscillation (SO) are ranked from top to bottom according to the delay of the negative peak of the SO. In this example, the delay from the negative peak at the top trace to the negative peak at the bottom trace is 120 ms. (B) Spatial distribution of the delays. The lines starting around the origin represent the streamlines calculated on the vector field of delays. The SO originates locally and propagates orderly to the rest of the scalp. Thus, each cycle of the slow oscillation behaves as a traveling wave. (C) Time of occurrence of SOs superimposed on the hypnogram. During 1 h of sleep several hundred cycles can be detected by means of an automated algorithm. (D) Coverage map. Superimposition of the streamlines describing the propagation of all the SOs detected for the first hour of sleep. The size of each dot is proportional to the number of cycles originating from each electrode. This representation shows that virtually any pattern of origin and propagation is possible although anterior electrodes tend to start more SOs and streamlines traveling in the antero-posterior direction are more numerous. (E) Probability of each EEG sensor being affected by a SO. Sensors in the fronto-central region had a 70% chance of being affected by a SO, while parietal and occipital electrodes detected few, or no, SOs. (F) Origin density map. The probability of each electrode being the origin of a SO is interpolated to obtain an origin density map. Foci with a higher origin density are detected in anterior regions of the scalp. (G) Average direction of propagation. Note the prevalent anterior–posterior direction of propagation of the SO. (H) Distribution of propagation speeds. Average speed was calculated for all the cycles traveling on the antero-posterior axis. On average, the SO sweeps over the cerebral cortex in the antero-posterior direction at a speed of 2.5 m/s. Modified from and courtesy of Massimini et al. (2004).

increased amplitude of the secondary depolarizing component during augmentation is the activation of local-circuit cortical interneurons, which would hyperpolarize pyramidal neurons and de-inactivate the $Ca^{2+}$-dependent LTS in these neurons, thus further enhancing augmented waves. The role of cortical inhibitory interneurons in augmenting responses was also shown in a modeling study (Bazhenov et al., 1998).

Synaptic plasticity evoked by augmenting potentials in the projection pathway from thalamus to cortex is not only seen by progressively enhanced amplitudes of responses during the pulse-train but also by persistence of self-sus-

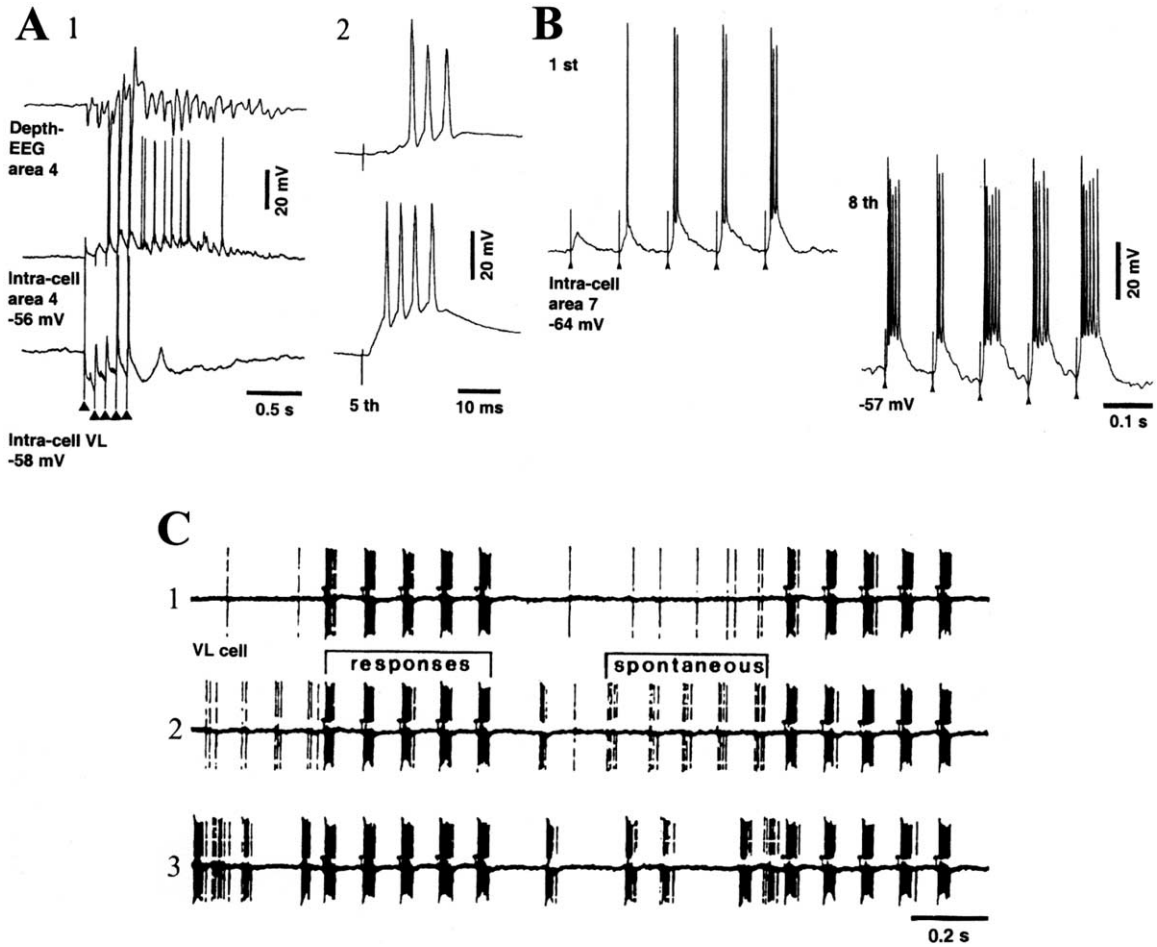


**Fig. 7.** Synaptic plasticity in TC and intracortical systems, and "memory" of electrical responses in corticothalamic system, induced by low-frequency stimuli mimicking sleep spindles. (A) Dual simultaneous intracellular recordings from cortical and TC neurons in cat (top trace is depth-EEG from area 4). *1*, Pulse-train (five stimuli at 10 Hz, arrowheads) applied to the thalamic ventrolateral (VL) nucleus produced augmenting responses in cortical neuron, whereas simultaneously recorded VL neuron displayed hyperpolarization. *2*, Expanded 5th response; the augmented response in cortical neuron followed the rebound spike-burst of VL neuron. Note self-sustained oscillatory activity at 10 Hz in cortical neuron after cessation of thalamic stimuli, despite persistent hyperpolarization in the VL neuron. (B) Intracellular responses of cat area 7 bursting cortical neuron to repetitive callosal stimulation (10 Hz). The thalamus ipsilateral to the recorded neuron was extensively lesioned using kainic acid. The intracortical augmenting responses to the 1st and 8th pulse-trains are illustrated. Note depolarization by about 7 mV and increased number of action potentials within bursts after repetitive stimulation. (C) Extracellular recording of VL neuron in brainstem-transected cat. Motor cortex stimulation with pulse-trains at 10 Hz (stimuli are marked by dots). In *1*, the pattern of responses in thalamic VL neuron in early stages of rhythmic pulse-trains. In *2–3*, responses at later stages of stimulation. Note appearance of spontaneous spike-bursts resembling the evoked ones, as a form of "memory" in the corticothalamic circuit. Modified from Steriade (1991); Steriade et al. (1993e); Steriade and Timofeev (2001).

tained potentials, with the same pattern and frequency as those of responses during the prior stimulation period (Steriade et al., 1998b). Setting in action the feedback corticothalamic projections with pulse-trains at 10 Hz results in evoked responses but also, after protracted stimulation, in "spontaneously" occurring spike-bursts whose form and rhythmicity are similar to those of evoked responses, as if the repetition of volleys were imprinted in the "memory" of the corticothalamic network (Fig. 7C). Synaptic plasticity can take place not only in corticothalamic and the ascending TC pathway but also in the cortex of athalamic animals (Fig. 7B). That short- and medium-term (5–30 min) neuronal plasticity can occur inside cortical circuitry was also shown using callosal stimulation (Cissé et al., 2004). One of the mechanisms that may explain the increased neuronal responsiveness to rhythmic and repeated pulse-trains at 10 Hz, simulating sleep spindles, is the activation of high-threshold $Ca^{2+}$ currents and enhanced $[Ca^{2+}]_{in}$ that, in association with synaptic volleys reaching the neuron, may activate protein kinase A (Abel et al., 1997) and/or Ras/mitogen-activated protein kinase (Dolmetsch et al., 2001), which are involved in memory consolidation (see also the results by Cirelli et al., 2004, based on molecular correlates). The term memory consolidation, often used in both animal experiments and human studies, may not necessarily imply that the cellular phenomena revealed in experiments are the same as those underlying memory events in humans.

Thus, besides their role in cortical disconnection through inhibition of incoming messages in the thalamus, spindles are

also operational in important cerebral functions. During spindles, rhythmic and synchronized spike-bursts of thalamic neurons depolarize the dendrites of neocortical neurons, which is associated with massive $Ca^{2+}$ entry (Yuste and Tank, 1996) that may provide an effective signal to efficiently activate $Ca^{2+}$ calmodulin-dependent protein kinase II (CaMKII), which is implicated in synaptic plasticity of excitatory synapses in cortex and other sites in the nervous system (Soderling and Derkach, 2000; see also Sejnowski and Destexhe, 2000).

Similar phenomena, with $Ca^{2+}$ entry in dendrites and somata of cortical neurons, may occur during the rhythmic spike-trains associated with oscillations in the slow (0.5–1 Hz) or delta (1–4 Hz) frequency bands, during later stages of slow-wave sleep. The hypothesis that the slow oscillation is responsible for the consolidation of memory traces acquired during the state of wakefulness (Steriade et al., 1993b) is supported by data showing that slow and delta (0.5–4 Hz) oscillations are implicated in cortical plasticity evoked by monocular deprivation in the developing visual cortex (Frank et al., 2001). In the latter study, microelectrode recording and optical imaging showed that the effects of monocular deprivation on cortical responses are increased by a 6 h slow-wave sleep period in the dark, and slow-wave sleep deprivation blocked this enhancement.

Synaptic plasticity has also been observed after testing with fast (20–60 Hz) pulse-trains. Stimulation of homotopic sites in the contralateral cortex with pulse-trains at 40 Hz induced prolonged facilitation of control response evoked by single callosal volleys, which lasted up to several minutes (Steriade and Timofeev, 2003a; Cissé et al., 2004). In some cases, a depolarization plateau lasted for 0.4–0.5 s after cessation of stimulation and gave rise to action potentials that closely mimicked the grouping and frequency of responses recorded during the prior period of stimulation. Spontaneous activity in the gamma frequency band (30–60 Hz) improves the coherent fluctuations in visual cortex excitability and thus may ensure more rapid and reliable transmission (Fries et al., 2001).

In the hippocampus too, neuronal synchrony associated with sharp potentials during slow-wave sleep may consolidate the information and transfer it to neocortical fields (Buzsáki, 1989). Dendritic recordings from CA1 hippocampal pyramidal neurons (Kamondi et al., 1998) suggested that sleep patterns are important for the preservation of experience-induced synaptic modifications in the limbic system (Buzsáki, 1998). Experiments on hippocampal "place cells" showed that, if a rat is confined to a place field, the firing rate of neurons is increased during subsequent slow-wave sleep, and an increased correlation is observed between cell pairs whose activities were related during waking behavior (Pavlides and Winson, 1989; Wilson and McNaughton, 1994).

### Human studies on the role of sleep in memory, learning, and dreaming mentation

The above experimental data and ideas that low-frequency oscillations (spindles and slow oscillation) are associated with synaptic plasticity are supported by human studies demonstrating that the overnight improvement of discrimination tasks requires some steps, including those in early slow-wave sleep stages (Stickgold et al., 2000a,b). Also, procedural memory formation may be associated with oscillations during early sleep stages (Gais et al., 2000). After training on a declarative learning task, the density of human sleep spindles is significantly higher, compared with the non-learning control task (Gais et al., 2002). The early part of night sleep favors retention of declarative memories (which can be brought to conscious recollection), while the late part of sleep favors retention of non-declarative (procedural, unconscious) memories (Plihal and Born, 1997). During early night (stage 2 sleep), when sleep spindles prevail, these effects are due to the rhythmic bombardment of neocortical neurons by high-frequency spike-bursts of TC neurons, while the spike-trains of cortical neurons are associated with the slow oscillation throughout slow-wave sleep. The low frequencies (0.5–15 Hz) of spike-bursts and trains of single action potentials are the main factors behind synaptic consolidation of memory traces in the neocortex.

Experimental data showing that hippocampal neurons that increase firing rates during wakefulness also display enhanced discharge rates during subsequent sleep epochs (see above) are congruent with (i) the hypothesis that the higher the amount of synaptic potentiation in cortical circuits during waking, the higher the increase in slow-wave activity during subsequent sleep (Tononi and Cirelli, 2003), (ii) human data showing that learning activity increases the density of sleep spindles (Gais et al., 2002), and (iii) results indicating that simply sensory (auditory) stimulation during wakefulness produces increased power of sleep spindles, accompanied by increased coherence between frontal and temporal cortical regions (Cantero et al., 2002).

Acetylcholine (ACh) influences memory consolidation during human sleep. The memory for a declarative wordlist task was blocked after infusion of physostigmine (a cholinesterase inhibitor that increases cholinergic activation), without interfering with a consolidation of a non-declarative task (Gais and Born, 2004). Since physostigmine did not modify memory consolidation during wakefulness when cholinergic tone is maximal, it was predicted that a *low* cholinergic tone during slow-wave sleep is essential for consolidation of declarative memory. It was suggested that high levels of ACh, known to be present during both brain-activated states of waking and REM sleep (see Steriade and McCarley, 2005), may set favorable conditions for encoding new information in the hippocampus, whereas lower ACh levels, present during slow-wave sleep, facilitate consolidation of memory traces by allowing spread of activity from hippocampus to entorhinal cortex, with consequent neocortical involvement (Hasselmo, 1999; see also Buzsáki, 1996).

At variance with the commonly used notion of global brain processes in slow-wave sleep, two major findings were reported in humans subjects, namely: slow-wave sleep activity increases 2 h after a motor learning task and the enhancement (~27%) is expressed *locally*, in parietal association areas 40 and 7 that receive converging visual

and proprioceptive inputs relevant to spatial attention and skilled actions; and, changes in local slow-wave sleep activity are strongly correlated with improved performance in the task the next day after sleep (Huber et al., 2004).

The increased cortical activity that accounts for consolidation of memory traces during slow-wave sleep also explains the presence of dreaming mentation during this state. In contrast with the assumption that dreams exclusively occur in REM sleep, a series of studies, starting during the 1960s (Foulkes, 1962), has demonstrated the presence of dreaming mentation during slow-wave sleep. In slow-wave sleep dreaming is rational and repetitive, whereas during REM sleep the internally generated perceptions are vivid, thought becomes illogical, and the intensity of emotions is higher than during slow-wave sleep (Hobson et al., 2000). Awakenings from stages 3–4 of slow-wave sleep reported a recall incidence higher (45–65%) than in stage 2 (Pivik and Foulkes, 1968; Nielsen, 2000) but lower than in REM sleep when the recall may reach 90–95% (Cicogna et al., 2000). Then, the brain is never "empty" and mental activity is present during all stages of normal sleep.

Human studies using a sleep monitoring system, which distinguishes between waking and different sleep states, described the reports of subjects who awoke during all stages of the waking–sleep cycle (Hobson and Pace-Schott, 2002; Fosse et al., 2004). The results indicate reciprocal changes of thinking and hallucinations across sleep, with directed thinking (defined as continued mental effort as well as attempts to decide and plan) more frequent during slow-wave sleep and hallucinations (endogenous sensations) more frequent during REM sleep. The intensified hallucinations with transition from slow-wave sleep to REM sleep may reflect the progressive appearance of ponto-geniculo-occipital (PGO) waves, the "stuff dreaming is made of," which occur during slow-wave sleep well in advance of muscular atonia, the cardinal sign of REM sleep, and are further synchronized throughout the cortex during REM sleep (Steriade et al., 1989; Amzica and Steriade, 1996). The transitional period between EEG-synchronized (slow-wave) and EEG-activated (REM sleep) sleep, called pre-REM period, during which PGO waves appear over the background of a fully synchronized EEG, may have importance for dreaming. Thus, TC neurons are hyperpolarized during the pre-REM period, when the sleep EEG is still fully synchronized, whereas they are tonically depolarized by 7–10 mV during REM sleep (Hirsch et al., 1983). These two states (pre-REM and fully developed REM sleep) generate different PGO-related responses of TC neurons to brainstem inputs, which influence the signal-to-noise ratio in the visual channel, i.e. the ratio between the neuronal activities related to the PGO signal and the background firing of the same neuron. During pre-REM, the activity of lateral geniculate (LG) TC neurons starts with a short, high-frequency (300–500 Hz) spike-burst coinciding with the PGO wave, but during REM sleep the rate of LG-cells' spontaneous firing is 1.5- to three-fold higher than in pre-REM and the peak-to-peak amplitudes of PGO waves are two to three times lower (Steriade et al., 1989). Thus, the greater signal-to-noise ratio in the LG-cortical channel during the pre-REM epoch than during REM sleep suggests that the vivid imagery associated with dreaming sleep may appear before fully developed REM sleep, during a period of apparent slow-wave sleep. The idea that PGO waves with greater amplitudes during the pre-REM stage may reflect more vivid imagery during that epoch than even during REM sleep (Steriade et al., 1989) corroborates earlier data showing that, after interrupting sleep immediately after the occurrence of the first PGO wave (in the pre-REM stage) and eliminating about 30 s of the slow-wave sleep stage that precedes REM sleep, the increased time of the REM sleep rebound was due to phasic events (PGO waves) rather than the loss of REM sleep per se (Dement et al., 1969). This observation fits in well with data on dream reports from the last epoch of EEG-synchronized sleep, which are indistinguishable from those obtained from REM sleep awakenings (Hobson, 1988; Hobson and Pace-Schott, 2002).

### Transition from cortical sleep rhythms to electrical seizures

The synaptic plasticity that follows rhythmic brain stimulation within the frequency range of low-frequency sleep oscillations may take paroxysmal forms. This is especially seen with cortical FRB neurons that display a peculiar enhancement of rhythmic responses, with progressively grown depolarization and dramatically increased number of action potentials, which have an epileptiform aspect (Fig. 8). The changes in responsiveness of neocortical neurons, which lead to self-sustained oscillations of the paroxysmal type, are already initiated during rhythmic stimulation with pulse-trains at 10 Hz, within the frequency range of sleep spindles. Dual intracellular recordings from TC and cortical neurons (Fig. 9) show that (i) the cortical neuron exhibited progressively enhanced responsiveness, as seen from the increased number of action potentials, whereas the TC neuron remained hyperpolarized due to the action of GABAergic RE neurons set into action by thalamic stimulation; (ii) following cessation of rhythmic stimulation, self-sustained electrical seizure occurred in the EEG and intracellular activities, consisting of spike-wave (SW) complexes at about 2 Hz that lasted for 8 s; and (iii) during the stimulation period, "spontaneous" depolarizing events appeared between pulse-trains, with the same frequency as that used during pulse-trains (see asterisk in the expanded panel at bottom right in Fig. 9). The latter aspect is reminiscent of the "memory" in the corticothalamic system, which followed protracted stimulation (see above, Fig. 7C). Then, slow-wave sleep oscillations or their experimental model (augmenting responses) may lead to self-sustained paroxysms of the SW type.

In clinical studies too, although absences (loss of consciousness) can only be detected in the waking state, the electrographic correlates of such seizures with SW complexes at ~3 Hz preferentially occur during the early or late stages of slow-wave sleep. The relation between SW seizures and the EEG correlates of slow-

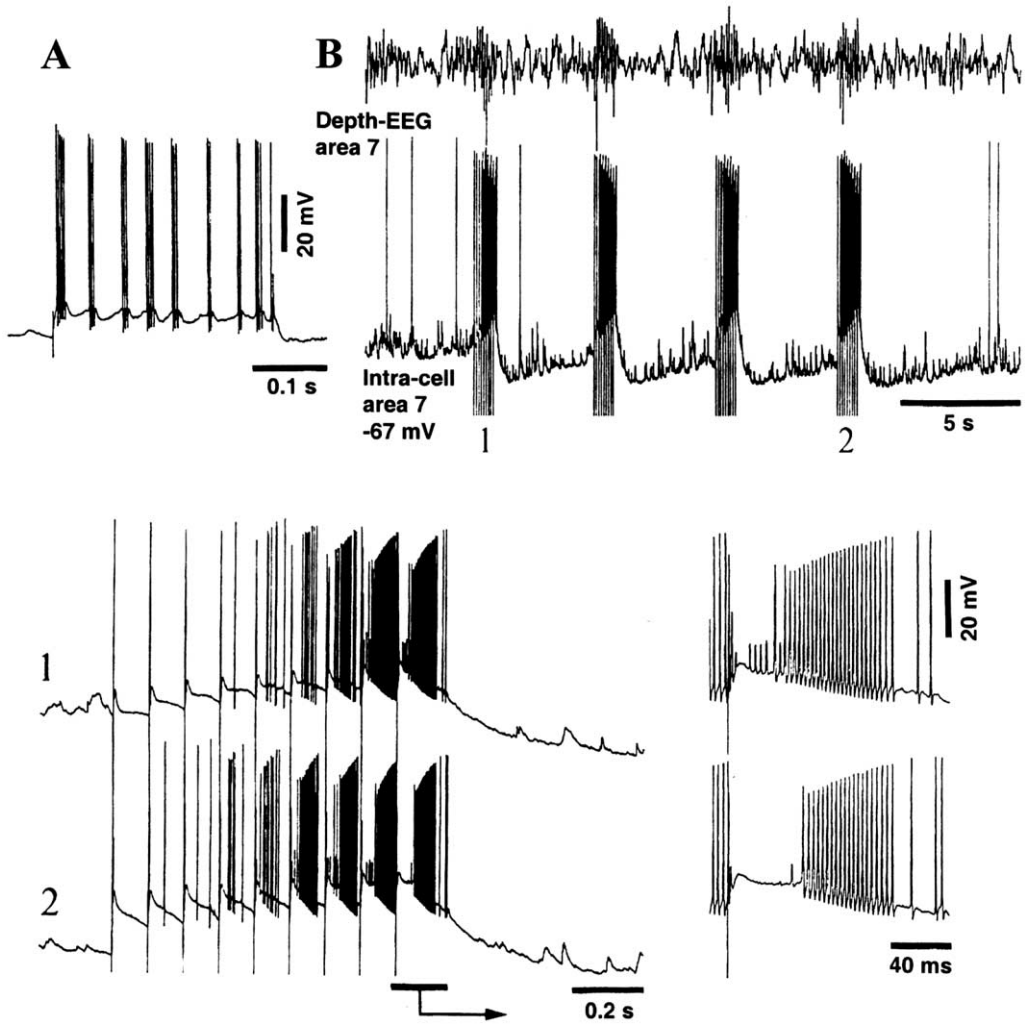


**Fig. 8.** Progressively growing, paroxysmal-like depolarization during cortically evoked augmenting responses in cortical FRB neuron from cat suprasylvian area 7. Close intracortical stimulation, in adjacent area 21. (A) Identification of FRB neuron by depolarizing current step (0.5 nA). (B) Responses of this FRB neuron to four pulse-trains, each consisting of nine pulses at 10 Hz applied to area 21. Responses to pulse-trains *1* and *2* (last) are expanded below, and responses to the last stimulus in these pulse-trains are further expanded at right (arrow). The neuron persistently depolarized during stimulation. At depolarized levels of the $V_m$, IPSPs evoked by area 21 stimuli shunted the early occurring spikes. Modified from Steriade and Timofeev (2003b).

wave sleep was repeatedly demonstrated (Kellaway and Frost, 1983; Kellaway, 1985; Shouse et al., 1996; Shouse, 2001). By contrast, SW seizures are decreased or totally absent during REM sleep (Frank, 1969). The occurrence of SW seizures is facilitated during transitional states, especially between waking and slow-wave sleep, during the state of drowsiness. This was observed in humans (Noachtar, 2001) and in behaving monkeys displaying tonic eye movements at the onset and the end of seizures, as in clinical absence seizures (Steriade, 1974; Fig. 10). SW seizures are reduced or abolished with transition from slow-wave sleep to spontaneous or sensory-elicited arousal as well as during repetitive brainstem reticular formation stimulation, and they are increased after administration of low doses of a cholinergic receptor antagonist (Danober et al., 1993, 1995).

The original assumption that SW seizures originate in the diencephalon and the conventional definition of these seizures as “suddenly generalized and bilaterally synchronous” have been challenged by recent experimental research that are also congruent with human studies. The deeply located source of SW (absence or petit-mal) seizures was ascribed to a “centrencephalic” system (Penfield and Rasmussen, 1950), based on experiments under barbiturate anesthesia reporting SW patterns evoked by stimulation of midline thalamic nuclei (Jasper and Droogleever-Fortuyn, 1949). The morphological substrate of the “centrencephalic” system was never demonstrated, since there are no bilateral projections of thalamic nuclei, and the experimental studies reported *responses* evoked by thalamic stimulation but no self-sustained activity, as it would be the case in bona fide seizures. On the other hand, SW seizures seem to be “suddenly generalized” only in EEG

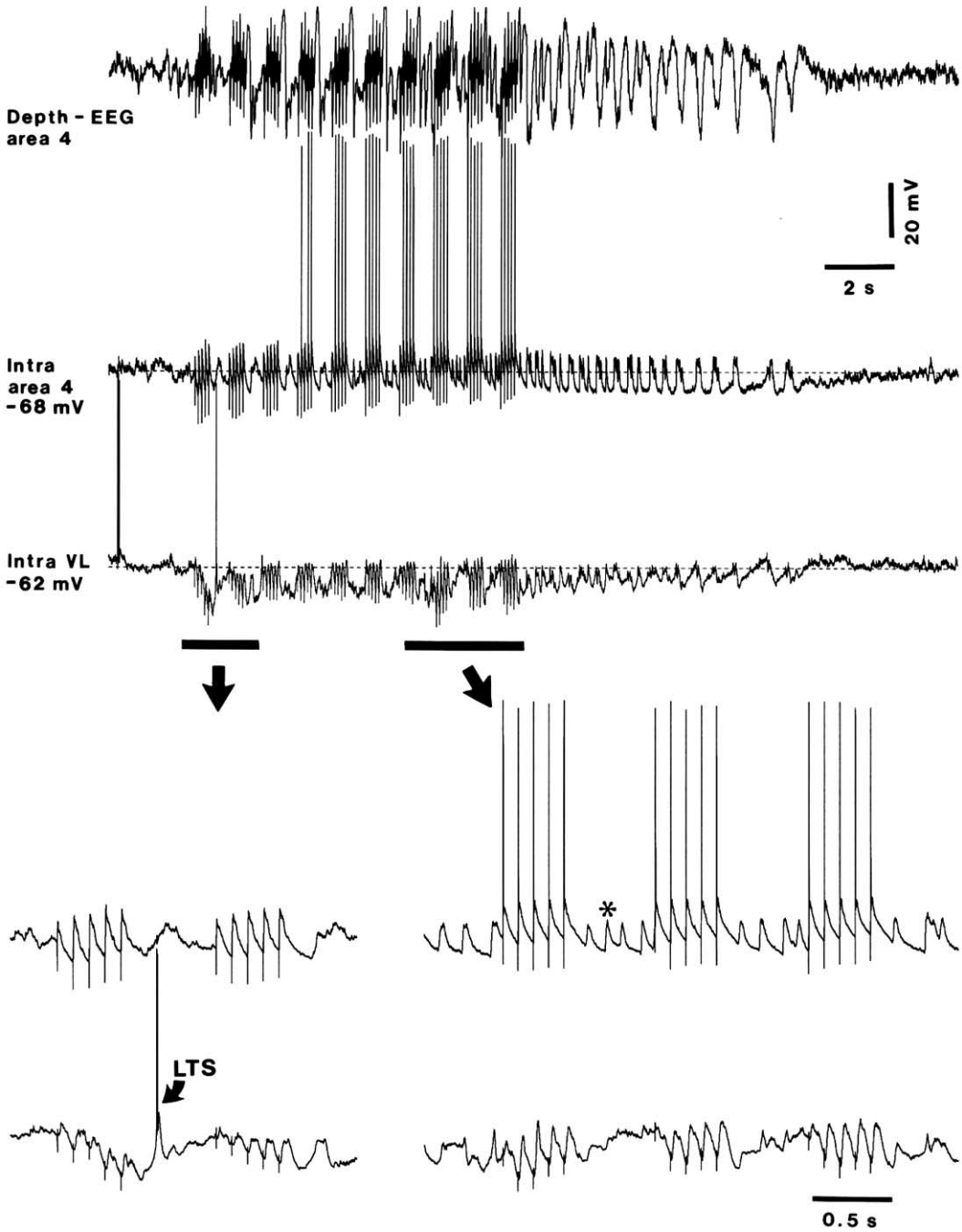


**Fig. 9.** Plastic changes in cortical responsiveness, leading to self-sustained paroxysmal oscillation, simultaneously with decreased low-threshold (LT)-type augmenting in TC neuron. Dual simultaneous intracellular recording from TC neuron in cat ventrolateral (VL) nucleus and cortical area 4 neuron, together with depth-EEG from area 4. Stimulation applied to cortex and consisting of pulse-trains at 10 Hz, repeated every second. Two parts, at the beginning and end of stimulation (marked by horizontal bars and arrows) are expanded below. Note that, although LT-type augmenting responses in TC neuron diminished from the second pulse-train, cortical augmenting responses were progressively enhanced and, after finishing the stimulation period, a self-sustained oscillation at ~2 Hz ensued, lasting for ~8 s. Also note, in cortical neuronal recording, depolarizing events with the similar frequency (10 Hz) as that used in pulse-trains, occurring between pulse-trains (asterisk in bottom right panel). Modified from Steriade and Timofeev (2003b).

recordings and, even at this macroscopic level, clinical studies have reported that the "spike" of SW complexes propagates from one hemisphere to another with time-lags as short as 12–25 ms (Lemieux and Blume, 1986; Kobayashi et al., 1994), too short to be estimated by simple visual inspection. Indeed, experimental studies using neuronal and field potential recordings from cortex or cortex and thalamus, have shown that spontaneously occurring SW seizures are initiated in one cortical focus, are transferred to neurons in another cortical area with latencies

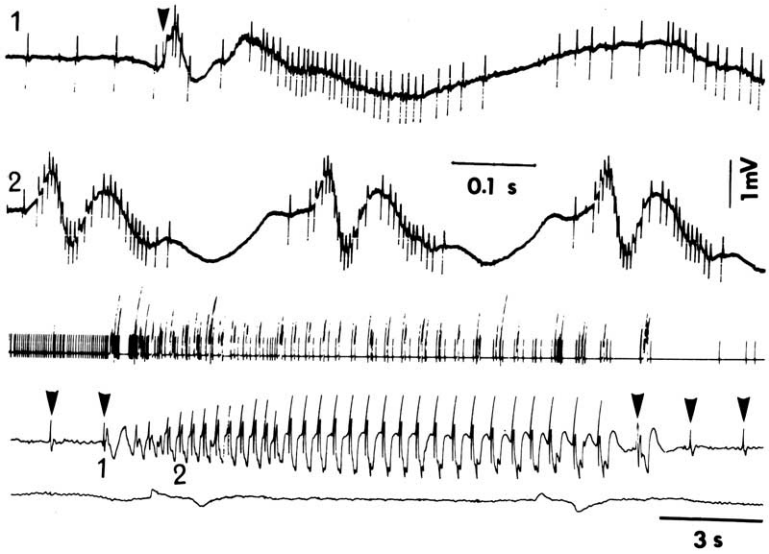


**Fig. 10.** SW seizures in chronically-implanted *Macaca mulatta*. Neuronal activity during seizure with SW complexes at 3 Hz during drowsiness in the behaving monkey. Single neuron recorded from the arm area in the precentral gyrus (area 4). The top oscilloscopic trace indicates the corresponding part (marked by horizontal bar) in the below-depicted ink-written record (the three traces represent: unit spikes used to deflect a pen of the EEG machine; each deflection exceeding the common level representing a group of high-frequency spikes; focal slow EEG waves, simultaneously recorded by the same microelectrode; and eye movements, EOG). Arrowheads indicate stimuli applied to the appropriate thalamic nucleus for neuronal identification. When the experimenter observed increased amplitude of the evoked field potential (second stimulus), stimuli were interrupted and the seizure developed in the absence of any stimulus. Note spike-bursts over the depth-negative (upward in this case) field potential of the SW complexes (the EEG "spike") and silent firing during the late part of the depth-positive "wave" component of SW complexes. Also note tonic eye movements at the onset and end of the SW seizure. Modified from Steriade (1974).

ranging from 20 to 100 ms, and finally to the thalamus after several seconds (Steriade and Amzica, 1994; Neckelmann et al., 1998; Meeren et al., 2002). That some SW seizures are locally generated and result from multiple, independent cortical foci has been reported in human studies since the late 1930s (Jasper and Hawkes, 1938).

The independence of cortically generated SW seizures, with typical SW and polyspike wave (PSW) complexes at ~3 Hz, on the thalamic circuitry was demonstrated in acutely prepared athalamic cats (Steriade and Contreras, 1998) and athalamic behaving monkeys displaying impairment of awareness during SW bursts (Marcus et al., 1968). These studies, using global methods of recordings, are corroborated by intracellular studies showing inhibition of TC neurons during cortically generated SW/PSW seizures (Fig. 11). This inhibition (Steriade and Contreras, 1995) was also found in genetic models of absence seizures (Crunelli and Leresche, 2002) and is due to the fact that, at each paroxysmal depolarizing shift in neocortical neurons, thalamic GABAergic RE neurons are excited and, consequently, they impose IPSPs on TC neurons that, because of their repetitive nature and increased membrane conductance, do not succeed in de-inactivating the transient $Ca^{2+}$ current responsible for spike-bursts. Thus, during cortically generated SW seizures, TC neurons are steadily hyperpolarized and silent (Fig. 11A). The inhibition of TC neurons during cortically generated SW seizures is further demonstrated during brief epochs when SW/PSW complexes stop and TC neurons are disinhibited, thus recovering their capacity to fire single action potentials (Fig. 11, B2).

To sum up, two major types of thalamic neurons, RE and TC, behave differently during cortically generated SW/PSW seizures. RE neurons are excited by each corticofugal drive during SW/PSW complexes (Steriade and Contreras, 1995; Slaght et al., 2002) and, then, these GABAergic thalamic neurons participate actively during cortically generated SW seizures. This conclusion is also drawn from the increase in the ionic current that underlies spike-bursts of RE cells in SW seizures (Tsakiridou et al., 1995; Avanzini et al., 1999) and the fact that the $Cd^{2+}$-induced blockage of RE-cells' spike-bursts leads to a decrease in the ipsilateral SW activity (Avanzini et al., 1992). On the contrary, the opposite occurs in TC cells that are inhibited during cortically generated SW/PSW seizures (Fig. 11). The inhibition of thalamic relay cells may explain the unconsciousness during absence seizures, due to the blockage of signals from the external world in their route to the cerebral cortex.

## CONCLUSIONS

The living brain, with intact connections between neocortex, thalamus, and various modulatory systems, displays low-frequency and fast rhythms grouped within complex wave-sequences. Some of these oscillations can be generated by interplay between intrinsic neuronal properties, but the coalescence of various rhythms and their synchronization is due to network operations in corticothalamic systems. The tendency to analyze distinct, precise frequency bands of EEG activities, in isolation from others, will hopefully be replaced by the concept of unified brain

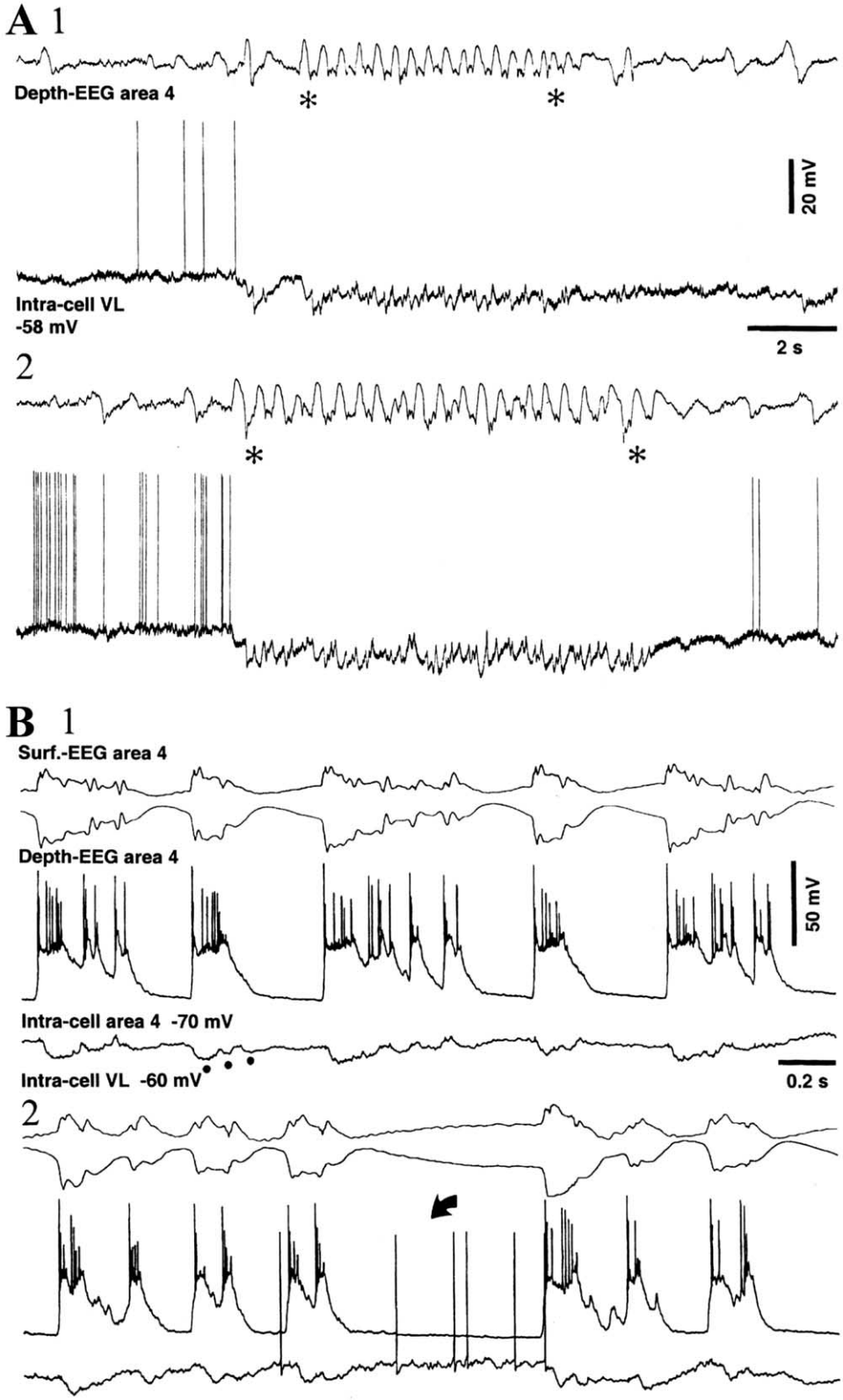


**Fig. 11.** TC neurons are inhibited during cortically generated SW seizure, and display phasic IPSPs but not spike-bursts. (A) Depth-EEG from cortical area 4 and intracellular recording of TC neuron from ventrolateral (VL) nucleus of cat. Note hyperpolarization and phasic IPSPs in VL neuron throughout cortically generated SW seizure (between asterisks); also note increased hyperpolarization and IPSPs in thalamic neuron with increased duration of the cortical seizure. (B) Dual intracellular recordings from area 4 cortical neuron and TC neuron from VL nucleus, together with surface- and depth-EEG from cortical area 4. The SW and PSW seizure developed, without discontinuity, from sleep-like EEG patterns. Note paroxysmal depolarizing shifts (PDSs) in cortical neuron, and phasic IPSPs (see three dots below the intracellular VL trace) related to cortical PDSs. Also note that, during a brief period of quiescence in cortical SW/PSW seizure (arrow in 2), the hyperpolarization of TC neuron was removed, the TC cell was disinhibited, and the neuron fired single action potentials. Modified from Steriade and Contreras (1995) and Lytton et al. (1997).

rhythms based on basic cellular mechanisms that underlie generation of brain waves. For example, the separation between "lower-frequency" and "faster" EEG spindles can be avoided by considering longer hyperpolarization-rebound sequences of some thalamic neurons in the former case, without splitting an oscillation generated by identical basic mechanisms, regardless of its wide frequency range. Similarly, fast rhythms are voltage-dependent, during either brain-active or brain-disconnected states, and the transition from beta to gamma oscillation operates in very short time periods under slight neuronal depolarization, which does not necessarily require their separate analysis. Clinical investigators have already begun to use the knowledge obtained in cellular studies on experimental animals.

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