Neuronal Plasticity in Thalamocortical Networks during Sleep and Waking Oscillations

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Spontaneous brain oscillations during states of vigilance are associated with neuronal plasticity due to rhythmic spike bursts and spike trains fired by thalamic and neocortical neurons during low-frequency rhythms that characterize slow-wave sleep and fast rhythms occurring during waking and REM sleep. Intracellular recordings from thalamic and related cortical neurons in vivo demonstrate that, during natural slow-wave sleep oscillations or their experimental models, both thalamic and cortical neurons progressively enhance their responsiveness. This potentiation lasts for several minutes after the end of oscillatory periods. Cortical neurons display self-sustained activity, similar to responses evoked during previous epochs of stimulation, despite the fact that thalamic neurons remain under a powerful hyperpolarizing pressure. These data suggest that, far from being a quiescent state during which the cortex and subcortical structures are globally inhibited, slow-wave sleep may consolidate memory traces acquired during wakefulness in corticothalamic networks. Similar phenomena occur as a consequence of fast oscillations during brain-activated states.

Are spontaneously occurring brain oscillations, which characterize various states of vigilance, epiphenomena with little functional significance? This question may apply especially to low-frequency rhythms (0.5–15 Hz), which define slow-wave sleep (SWS or non-REM), because this behavioral state was previously regarded as associated with global inhibition of the cerebral cortex and of subcortical structures, which underlies the annihilation of consciousness. However, recent studies using intracellular recordings of electrophysiologically characterized cortical cell types in naturally sleeping animals showed unexpectedly high levels of spontaneous neuronal activity during SWS (Steriade et al., 2001) (Figure 1). And, although the thalamic gates are closed for signals from the outside world during SWS, because of obliteration of synaptic transmission in thalamocortical neurons, the intracortical dialog and responsiveness of cortical neurons to callosal volleys are maintained and even increased during SWS (Steriade et al., 1974; Timofeev et al., 1996). These data suggest that SWS, which is commonly regarded as reflecting complete brain quiescence, may serve important cerebral functions, among them the consolidation of memory traces acquired during wakefulness. The fast rhythms, within the β/γ frequency bands (generally 20–60 Hz), which are present in the background electrical activity during the brain-activated states of waking and REM sleep, are also thought to enhance temporal coherence of responses and firing probability of cortical neurons. All in all, it appears that 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.

The general meaning of plasticity is an alteration in neuronal properties resulting from experience, which may evolve from transient changes to permanent formation of new connections. Neuronal responses vary as a function of network activities, which depend on behavioral states. Different mechanisms underlying plasticity include pre- and postsynaptic alterations, such as modifications in the release of neurotransmitters and postsynaptic sensitivity (Buonomano and Merzenich, 1998), as well as nonsynaptic mechanisms, such as conductance changes of intrinsic currents that modify neuronal responsiveness (Marder, 1998; Turrigiano et al., 1998).

Perhaps the first clear hypothesis relating states of vigilance and, in particular, sleep with plastic activity in the cerebrum belongs to Moruzzi (1966). He postulated that sleep does not concern the fast recovery processes in routine synapses underlying stereotyped activities, but the slow recovery of learned synapses. By routine synapses, Moruzzi meant those which are concerned with transmission of signals along inborn pathways (such as sensory and motor projections, which transmit impulses in the timescale of milliseconds), while he applied the term “learned synapses” to new contacts between neurons, extremely labile, “as can be inferred from the study of memory and conditioned reflexes” (p. 353). Since then, the topics of synaptic plasticity and memory storage have evolved toward analyses of neuronal networks and properties of single neurons in corticothalamic systems and in the hippocampus and related structures, down to the molecular level (see Kandel and Squire, 2000). During the past decade, the possibility that SWS-related and other types of spontaneous brain oscillations may lead to neuronal plasticity was investigated in intact brains of animals during sleep-waking patterns, and in vitro studies identified the intrinsic properties of neurons and types of neurotransmitters implicated in these processes. The modulation of voltage- and transmitter-gated conductances of single thalamic and neocortical neurons by network synaptic activities, and the transformation of firing patterns produced by intrinsic cellular properties during shifts in natural states of vigilance, are discussed elsewhere (Steriade, 2001a, 2001b; Timofeev et al., 2001b).

The complex connections between excitatory and local inhibitory neocortical neurons in small circuits, leading to depression or facilitation, have been recently analyzed and comprehensively reviewed (Thomson et al., 2002). Both synaptic impact and balance between synaptic excitation and inhibition depend on spike frequency. The firing rates of neocortical pyramidal neurons range between 5 and 20 Hz (Evarts, 1964; Steriade,
Natural Slow-Wave Sleep Is Characterized by Prolonged Hyperpolarizations in Neocortical Neurons, but Rich Spontaneous Firing during the Depolarizing Phases of the Slow Oscillation

Figure 1. Chronic implanted cat. Five traces in the top panel depict EEG from the depth of left cortical areas 4 (motor) and 21 (visual association), intracellular recording from area 21 regular-spiking neuron (resting membrane potential is indicated), electro-oculogram (EOG), and electromyogram (EMG). Transition from waking to SWS is indicated by arrow. Part marked by horizontal bar is expanded below left (arrow). Note relation between the hyperpolarizations and depth-positive EEG field potentials. Below right, histograms of membrane potential (10 s epochs) during the period of transition from waking to SWS depicted above. Note membrane potential around $-64 \text{ mV}$ during the 20 s of waking and progressively increased tail of hyperpolarizations, from drowsiness to full-blown SWS, up to $-90 \text{ mV}$. Data from experiments by M.S., I.T., and F. Grenier (details in Steriade et al., 2001).

1978) and significantly differ in different types of electrophysiologically defined cortical cells recorded in naturally awake and sleeping animals (Steriade et al., 2001). These data suggest that, in vivo, cortical neurons are in a steady state of either synaptic depression or facilitation, which serves as a background to all additional synaptic inputs.

Here, we discuss the mechanisms of plasticity that occurs not at particular synapses, but in the acting and interacting thalamocortical neuronal networks. We shall focus on short- and medium-term neuronal plasticity that appears as a consequence of different types of spontaneous brain rhythms during natural states of sleep and waking as well as during, and outlasting, experimental models of some oscillatory types. Importantly, these results have been corroborated by studies conducted during natural human sleep.

Coalescence of Different Low-Frequency and Fast Oscillations in the Intact Brain

Three major rhythms characterize SWS: spindles (7–15 Hz), delta waves (1–4 Hz), and slow oscillation (~0.5–1
Each of these rhythms stems from distinct neuronal networks and is generated by the interplay among different synaptic mechanisms or voltage-gated currents (reviewed in Steriade et al., 1993b; and Hobson and Pace-Schott, 2002). Although these sleep rhythms may be recorded in the thalamus (such as spindles) or neocortex (the slow oscillation) after their complete disconnection, in the intact brain, they are all coalesced because of reciprocal loops between the neocortex and thalamus. This is mainly due to the virtue of the cortically generated slow oscillation that, because of coherent firing of cortical neurons during its depolarizing phase, impinges upon the thalamus and triggers complex wave sequences, which include all three types of rhythmic patterns within one oscillatory cycle (Figure 2).

The slow cortical oscillation was discovered using intracellular recordings (Steriade et al., 1993c, 1993d) and was confirmed using EEG and magnetoencephalographic recordings during human sleep (Achermann and Borbély, 1997; Amzica and Steriade, 1997; Simon et al., 2000; Mölle et al., 2002). Slow sleep oscillatory cycles consist of depolarizing ("up") and hyperpolarizing ("down") phases. The up phase is formed by non-NMDA-mediated EPSPs, fast prepotentials (FPPs), a persistent Na⁺ current [INa(p)], and fast IPSPs reflecting the action of synaptically coupled GABAergic local cortical cells (Steriade et al., 1993c). NMDA components may contribute to the maintenance of up states but are not essential, because this state is generated even after systemic injection of ketamine, a powerful blocker of NMDA receptors (MacDonald et al., 1991). The synaptic depression of active synaptic connections (Tsodyks and Markram, 1997; Galarreta and Hestrin, 1998), the slow inactivation of the persistent Na⁺ current (Fleidervish and Gutnick, 1996; Fleidervish et al., 1996), as well as the activation of Ca²⁺- and Na⁺-dependent K⁺ currents (Schwindt et al., 1989, 1992) would displace the membrane potential of neurons from firing level, and the entire network would enter the hyperpolarized down state. This is a state of disfacilitation (removal of synaptic, mainly excitatory,
inputs) (Contreras et al., 1996; Timofeev et al., 2001b) and is dominated by a “leak” current and by Ca\(^{2+}\)- and Na\(^{-}\)-dependent K\(^{-}\) currents (Timofeev et al., 2000b). The synaptic depression during the up state is probably produced by progressive depletion of [Ca\(^{2+}\)], during this phase (Massimini and Amzica, 2001). The local cortical GABAergic neurons (electrophysiologically identified as conventional fast-spiking neurons and formally identified as basket cells by intracellular staining) do not fire during the hyperpolarization phase of all other neuronal types, but they display the same up and down cycles as pyramidal cells, in both anesthetized (Contreras and Steriade, 1995) and naturally sleeping, chronically implanted animals (Steriade et al., 2001; Timofeev et al., 2001b); thus they do not maintain the down state. Realistic models of the slow sleep oscillation in corticothalamic systems proposed that summation of miniature EPSPs during the down (silent) phase of the slow oscillation activates the persistent Na\(^{-}\) current \(I_{\text{Na(p)}}\) and depolarizes the membrane of pyramidal neurons sufficiently for triggering spikes and generating the next up phase (Timofeev et al., 2000a; Bazhenov et al., 2002). The transition from the slow sleep oscillation to brain-activated behavioral states is produced by the erasure of prolonged down phases in cortical neurons and their increased input resistance, as tested during the state of quiet wakefulness (Steriade et al., 2001).

The synchronization of cortical and thalamic neurons during the slow sleep oscillation, using paired intracellular recordings from these two neuronal types (Contreras and Steriade, 1995), leads to combined slow and spindle oscillations in the slow (0.5–1 Hz) or delta (1–4 Hz) bands and is played by the increased conductance of IPSPs in pyramidal cells, in both anesthetized (Contreras and Steriade, 1995) and naturally sleeping, chronically implanted animals (Steriade et al., 2001; Timofeev et al., 2001b); thus they do not maintain the down state. Realistic models of the slow sleep oscillation in corticothalamic systems proposed that summation of miniature EPSPs during the down (silent) phase of the slow oscillation activates the persistent Na\(^{-}\) current \(I_{\text{Na(p)}}\) and depolarizes the membrane of pyramidal neurons sufficiently for triggering spikes and generating the next up phase (Timofeev et al., 2000a; Bazhenov et al., 2002). The transition from the slow sleep oscillation to brain-activated behavioral states is produced by the erasure of prolonged down phases in cortical neurons and their increased input resistance, as tested during the state of quiet wakefulness (Steriade et al., 2001).

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The above data congruently demonstrate that synaptic activities in interconnected corticothalamic neuronal networks generate various low- and high-frequency oscillations that occur together during SWS, due to the synchronous firing of cortical neurons and their impact on target thalamic neurons, under the control of generalized modulatory systems. This complexity requires investigations in intact-brain preparations (Steriade, 2001b).

**Functional Role of Sleep Oscillations**

During SWS oscillations, signals from the outside world do not reliably reach the cerebral cortex, thus ensuring a safe sleep. The transfer of information is prevented throughout SWS because thalamocortical neurons are steadily hyperpolarized during this state (Hirsch et al., 1983), and afferent stimuli do not reliably produce an EPSP that reaches firing threshold. An additional role is played by the increased conductance of IPSPs in thalamocortical neurons during sleep spindles, which further diminishes the probability of faithful synaptic transmission through the thalamus (Timofeev et al., 1996). These data, from studies on experimental animals, are corroborated in humans by investigating event-related potentials and showing the role of spindles in gating information processing, to protect the sleeper from disturbing sounds (Elton et al., 1997).

Besides their role in cortical disconnection, spindles are also operational in important cerebral functions. Thus, 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). It was hypothesized (Destexhe and Sejnowski, 2001) that this may provide an effective signal to efficiently activate Ca\(^{2+}\)-calmodulin-dependent protein kinase II (CaMKII) that is implicated in synaptic plasticity of excitatory synapses in cortex and other sites in the nervous system (Soderling and Derkach, 2000). Similar phenomena, with Ca\(^{2+}\) entry in dendrites and somata of cortical neurons, may occur in SWS during the rhythmic spike trains associated with oscillations in the slow (0.5–1 Hz) or delta (1–4 Hz) bands and could provide the long timescales needed to mobilize the machinery that was hypothesized as being responsible for the consolidation of memory traces acquired during the state of wakefulness (Steriade et al., 1993a). This idea was supported by human studies demonstrating that the overnight improvement of discrimination tasks requires several steps, some of them depending on the early SWS stages (Stickgold et al., 2000a, 2000b). The improvement of visual discrimination skills by early stages of sleep (with spindles and slow oscillation) led to the conclusion that procedural memory formation may be associated with these SWS oscillations (Gais et al., 2000). These authors have also shown that, after training on a declarative learning task, the density of human sleep spindles is significantly higher compared to the nonlearning control task (Gais et al., 2002).

In the hippocampus, it was predicted that neuronal synchrony associated with sharp potentials during SWS would consolidate the information and transfer it to neocortical fields (Buzsáki, 1989). Dendritic recordings from CA1 pyramidal neurons revealed bursts of fast spikes during sharp potentials as well as putative Ca\(^{2+}\) spikes (Kamondi et al., 1998), which suggested that sleep patterns in the limbic system are important for the preservation of experience-induced synaptic modifications (Buzsáki, 1998). If a rat is confined to a place field, the firing rate of a “place cell” is increased during subsequent SWS, and there is an increased correlation between cell pairs whose activities were correlated during waking behavior (Pavlidis and Winson, 1989; Wilson and McNaughton, 1994). Place field stability is maintained by long-term potentiation in the 5–10 Hz range (Rotenberg...
Figure 3. Two Types of Intrathalamic Augmenting Responses Leading to Neuronal Plasticity

Unilaterally decorticated cats under ketamine-xylazine anesthesia. See the extent of decortication and callosal cut in Figure 1 from Steriade and Timofeev (1997). Intracellular recordings from thalamocortical (TC) in ventrolateral (VL) nucleus and thalamic reticular (RE) neurons. Stimulation in VL nucleus (pulse trains of five stimuli at 10 Hz). (A) High-threshold augmenting responses. Pulse trains at 10 Hz were delivered each 2 s. Responses of TC neuron to two pulse trains (1 to 2) are illustrated (1 and 2 were separated by 18 s). Note that, with repetition of pulse trains, IPSPs elicited by preceding stimuli were progressively reduced until their complete obliteration. The spike bursts contained more action potentials, with spike inactivation. The graph depicts the increased area of depolarization from the first to the fifth responses in each pulse train as well as from pulse trains 1 and 2. The increase in the depolarization area was about 500% from the first to the fifth response in pulse train 1 and 150% in pulse train 2. Also, the area of depolarization in the response to the second stimulus in the last pulse train 2 increased by about 800% compared to the already augmented response elicited by the second stimulus in pulse train 1. (B1) Low-threshold augmenting responses of TC neuron developing from progressive increase in IPSP-rebound sequences and followed by a self-sustained spindle. Arrow indicates expanded spike burst (action potentials truncated). The part marked by horizontal bar and indicating augmenting responses is expanded at right. (B2) Incremental responses RE neuron, accounting for the low-threshold type of augmentation in TC neuron. Modified from Steriade and Timofeev (1997) and Timofeev and Steriade (1998).

et al., 1996). During SWS periods, after an episode of spatially extended behavior, patterns of neuronal correlation that were manifest during that behavior re-emerge in interactions between hippocampus and neocortex (Qin et al., 1997).

These data show that, far from being a period of com-
Figure 4. Plasticity Developing from Augmenting Responses in Thalamocortical and Intracortical Neuronal Networks

Intracellular recordings in cats under ketamine-xylazine (A), barbiturate (B), and urethane (C) anesthesia. (A) Dual intracellular recording from motor cortical (area 4) neuron and thalamocortical (TC) neuron in ventrolateral (VL) nucleus. (Right) Average of second and third responses in cortical and VL neurons. Note that the area of secondary depolarization in cortical neuron (b), which developed during augmentation (marked by dots), followed the rebound spike burst in TC neuron by ~3 ms. (B) Self-sustained, postaugmenting oscillation in area 4 cortical neuron, simultaneous with persistent hyperpolarization in simultaneously recorded TC neuron. Dual intracellular recordings from thalamic ventrolateral (VL) nucleus and cortical area 4 neurons, in conjunction with field potential from the depth of area 4. Note persistent, spindle-like oscillation at the same frequency of augmenting responses in area 4, contrasting with a single low-threshold rebound and persistent hyperpolarization in the VL neuron. (C) Changes in properties of area 7 cortical neuron after repetitive callosal stimulation (10 Hz) of the homotopic point in the contralateral hemisphere. Ipsilateral thalamic lesion using kainic acid (see such lesions in Figure 10A in Steriade et al., 1993a). Responses to pulse trains (each consisting of five stimuli at 10 Hz), repeated every 3 s, applied to contralateral area 7. The intracortical augmenting responses to the first and eighth pulse trains are illustrated. Note depolarization by about 7mV and increased number of action potentials within bursts after repetitive stimulation. Modified from Steriade et al. (1998b, A-B) and Steriade et al. (1993d, C).
complete inactivity, SWS is implicated in mental processes. Indeed, dreaming mentation is not confined to REM sleep but also appears closer to real life events during SWS (Hobson et al., 2000), and the recall rate of dream-ming mentation in SWS is quite high (Nielsen, 2000). In what follows, we will discuss the cellular data that substantiate the presence of neuronal plasticity resulting from SWS oscillations.

Neuronal Substrates of Short- and Medium-Term Plasticity during and Outlasting Slow-Wave Sleep Oscillations in Thalamocortical Networks

Neuronal plasticity during and following natural sleep spindles or their experimental model, augmenting responses (Morison and Dempsey, 1942), has recently been studied using single, dual, and triple simultaneous intracellular recordings in the in vivo thalamus of decorticated cats, intact thalamocortical networks, isolated cortical slabs in vivo, cortical slices maintained in vitro, and computational studies of realistic thalamocortical networks. First, the results show that augmenting responses are modulated by behavioral states of vigilance, displaying the highest amplitudes during SWS and being disrupted upon natural arousal or during forebrain activation elicited by brainstem reticular formation stimulation (Steriade, 1991; Castro-Alamancos and Connors, 1996a; Timofeev and Steriade, 1998). Second, thalamic and neocortical neurons increase their responsiveness during, as well as after, cessation of rhythmic responses in the frequency range of spindles, and they display self-sustained activities that strikingly resemble the patterns of responses during the prior period of stimulation, indicative of “memory” events due to resonant activities in reverberating corticothalamic loops. These data are discussed below.

In the thalamus of decorticated preparations, there are two forms of augmenting potentials (Steriade and Timofeev, 1997; Timofeev and Steriade, 1998). High-threshold responses to intrathalamic stimuli at ~10 Hz occur at a depolarized level of thalamocortical (TC) neurons, due to decremental responses in GABAergic thalamic reticular (RE) neurons, the major source of inhibitory inputs to TC neurons. Prolonged, rhythmic thalamic stimulation eliciting high-threshold potentials leads to persistent and progressive increases in depolarizing synaptic responses and decreases in inhibitory responses of TC neurons (Figure 3A). The cellular mechanism of these responses may depend on the activation of high-threshold Ca\(^{2+}\)-dependent low-threshold currents (Hernández-Cruz and Pape, 1989; Kammermeier and Jones, 1997). By contrast, low-threshold responses develop with progressively increased IPSPs and postinhibitory rebound excitations in TC neurons (Figure 3B1), produced by incremental responses of RE neurons that are evoked at higher intensity of thalamic stimulation (Figure 3B2). Computational studies showed that two essential mechanisms are needed for the generation of low-threshold augmenting responses: the transient T current deactivation and the bistabilization of the high-threshold Ca\(^{2+}\)-dependent low-threshold current (Kawaguchi, 1993; de la Peña and Geijo-Barrientos, 1996), thus enhancing augmented waves. During natural spindles too, rhythmic spike bursts of TC neurons produce inhibitory effects on cortical pyramidal neurons, as demonstrated by the transformation of reversed IPSPs, recorded with Cl\(^{-}\)-filled micropipettes, into robust bursts resembling paroxysmal depolarizations during seizures (Contreras et al., 1997). The role of cortical inhibitory interneurons in augmenting responses was also elaborated in a computational study (Bazhenov et al., 1998b).

The preferential role played by various cortical cell classes, defined by their responses to depolarizing current steps, in augmentation was evaluated in different types of preparations. In vitro it was suggested that layer V intrinsically bursting (IB) neurons have the major role in the generation of augmenting responses (Castro-Alamancos and Connors, 1996b). That IB neurons are indeed implicated in augmenting responses generated by rhythmic stimulation of callosal pathway was also shown in vivo (see Figure 4C). However, when comparing the role of IB to other cortical neuronal types in vivo, augmenting responses in IB cells resembled those displayed by regular-spiking (RS) neurons recorded from the same cortical depth (Steriade and Timofeev, 2001). In that work, fast-rhythmic-bursting (FRB) neu-
neurons recorded from deep cortical layers were found to play the major role in cortical augmentation. The crucial role played by FRB neurons in widespread synchronization of augmenting responses results from thalamic projections of deeply lying cortical FRB neurons (Steriade et al., 1998a) and feedback projections to cortex, even toward areas that are remote from the site where the primary corticothalamic drive originates. This was predicted in experimental and modeling investigations (Bazhenov et al., 1998b), and the morphological substrates of return pathways to distant cortical areas in corticothalamocortical loops were revealed (Kato, 1990). The difference between the results from in vitro and in vivo investigations (preferential role attributed to IB and FRB neurons, respectively) may be ascribed to changing incidences of IB neurons in various experimental conditions, namely, IB neurons may reach very high proportions (up to 40%–50%) in slices maintained in vitro (Yang et al., 1996) or in cortical slabs prepared in vivo (Timofeev et al., 2000a), but the incidence of this neuronal type is lower in the intact cortex and, in naturally alert animals, IB neurons represent less than 5% of sampled neurons (Steriade et al., 2001).

As shown above (Figure 4A), cortical augmenting responses depend upon the low-threshold type of augmentation and related spike bursts in TC neurons. However, cortical neurons continue to exhibit self-sustained spike bursts within the same frequency range of evoked responses (10 Hz), despite the fact that TC neurons remain hyperpolarized, under the inhibitory pressure from the GABAergic RE neurons (Figure 4B). This indicates that the neocortex has the intrinsic networks that are necessary to elaborate self-sustained activities and corroborates the idea that, far from being a passive receiver of thalamically generated spindles, the cortex plays an active role in amplifying incoming thalamic inputs (Kandel and Buzsáki, 1997). That neocortical neurons display short-term plasticity even in the absence of thalamus is further demonstrated by progressive depolarization and increased number of action potentials in their rhythmic spike bursts evoked by repeated, rhythmic callosal volleys in thalamectomized animals (Figure 4C).

Neuronal plasticity induced by augmenting responses recorded in in vivo cortical slabs was compared to plasticity that develops from natural spindles in intact-brain...
Figure 6. Development from Augmenting Responses to Paroxysmal Oscillation

Plastic changes in cortical responsiveness, leading to self-sustained paroxysmal oscillation, simultaneously with decreased low-threshold (LT)-type augmenting responses in thalamocortical (TC) neuron (see Figure 3B1). Cat under ketamine-xylazine anesthesia. Dual intracellular recording from TC neuron in 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 \( \gamma \) Hz ensued, lasting for \( \gamma \) 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). M.S., I.T., and F. Grenier, unpublished data.

In isolated slabs (~10 mm long, 6 mm wide, and 4–5 mm deep), the greatest increase in the amplitude of depolarization and the most dramatic increase in the number of action potentials with successive stimuli at 10 Hz was found in fast-spiking (FS), presumably local inhibitory, neurons. In the intact brain, cortical stimuli applied during the depolarizing envelope of spindle sequences accompanied by firing elicited an enhancement of the control response, which lasted from tens of seconds to several minutes (Figure 5, left column). Testing cortical excitability with repeated pulse trains giving rise to augmenting responses (Figure 5, right column) revealed that, first, the IPSP of the control response was progressively reduced in amplitude and replaced by an early depolarization, and second, single stimuli applied after the rhythmic pulse trains elicited exclusively depolarizing responses, an enhancement that remained unchanged for several minutes. This enhancement was not voltage dependent, as it remained similar at rest and after slight d.c. hyperpolarization. One mechanism that may explain this increased responsiveness is the high-frequency firing in...
Figure 7. Progressive Enhancement of Callosally Evoked Responses after Repeated Pulse Trains at 40 Hz to the Callosal Pathway

Cat under barbiturate anesthesia. Intracellular recording from area 5. Upper panel shows responses to stimuli applied to homotopic site in contralateral area 5 (superimposed traces): responses to single stimuli before rhythmic stimulation (Control), during 40 Hz stimuli, to single stimuli again after repeated pulse trains at 40 Hz, after repeated pulse train at 40 Hz, and finally to single stimuli after pulse train at 40 Hz. Bottom panel shows amplitudes (ordinate) of responses to different periods in the upper panel (see arrows); figures above horizontal bars are mean amplitudes (in mV) of callosally evoked responses during different epochs. Note facilitation of control responses after conditioning stimulation at 40 Hz. M.S., I.T., and Y. Cissé, unpublished data.

Response to rhythmic, repeated pulse trains, which would result in activation of high-threshold Ca\(^{2+}\) currents and enhanced [Ca\(^{2+}\)], 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.

In all likelihood, the cortically generated slow oscillation is also implicated in neuronal plasticity. This sleep oscillation is reflected in the thalamus by the interplay between the synaptic excitation of GABAergic RE neurons as well as TC neurons and the inhibition of TC neurons resulting from the excitation of their RE inhibitory progenitors (Steriade et al., 1993a). These in vivo data are supported by in vitro studies showing that activation of metabotropic glutamate receptor mGluR1a in thalamic slices results in a slow oscillation of TC neurons (Hughes et al., 2002). It is known that corticothalamic axons release glutamate as neurotransmitter. The recent in vitro studies have demonstrated that the mGluR1a-evoked slow oscillation in the cat lateral geniculate slices rely on the “window” component of the Ca\(^{2+}\)-dependent I\(_h\) and a Ca\(^{2+}\)-activated nonselective cation current. Another congruent result from the in vivo and in vitro experiments is the grouping of the clock-like delta oscillations, intrinsically generated in TC cells through the interplay between I\(_h\) and I\(_{\text{KCg}}\), by the cortical slow oscillation (see Figure 12 in Steriade et al., 1993a, very similar to Figure 2 in Hughes et al., 2002). These data indicate that the cortical slow oscillation influences the thalamically generated spike bursts within the frequency range of delta rhythm, which are fed back to cortex and, in turn, may shape the cortical slow oscillation (see above, Figure 2B). Sleep with oscillations within the frequency range of the slow (0.5–1 Hz) and delta (1–4 Hz) oscillations was demonstrated to be implicated in cortical plasticity evoked by monocular deprivation (MD) in the developing visual cortex (Frank et al., 2001). Microelectrode recording and optical imaging showed that the effects of MD on cortical responses are increased by a 6 hr SWS period in the dark, and SWS deprivation blocked this enhancement.

Cortical Plasticity during Low-Frequency Oscillations Leading to Paroxysmal Events

Potentials with progressively enhanced amplitudes evoked by rhythmic stimuli may lead to self-sustained activities, similar to those seen in paroxysmal (epilepti-
form) afterdischarges (ADs). This was observed in corticothalamic networks as well as in the hippocampus and related systems. Thus, rhythmic stimulation of basolateral amygdala at 5–6 Hz evoked short-latency responses in hippocampus, which progressively increased in amplitude and developed into multiphasic patterns, evolving into paroxysmal activity with self-sustained potentials whose shapes were virtually identical to responses evoked in the final stage of stimulation (Steriade, 1964).

In those experiments, AD waves were built-up from the same circuits that mediated evoked responses but, at a critical time during stimulation, they escaped from networks giving rise to normal responses and passed over those circuits to elaborate self-sustained epileptiform activity.

Similar data have recently been reported in the neocortex, using simultaneous intracellular recordings from related cortical and thalamic neurons. The enhanced responsiveness of the cortical neuron driven by rhythmic callosal volley's in Figure 4C was followed by paroxysmal activity, which occurred within the same frequencies as the preceding slow sleep oscillation and rhythmic stimuli (see Figure 14B in Steriade et al., 1993d). The changes in responsiveness of cortical neurons, which lead to self-sustained oscillations of the paroxysmal type, are already initiated during rhythmic stimulation with pulse trains at 10 Hz. These changes consist of the appearance of “spontaneous” depolarizing events, occurring between pulse trains and having the same frequency as that used in these pulse trains (see asterisk in the expanded panel at bottom right in Figure 6). That such transformations, from normal (sleep-like) to pathological (epileptic-like) states, occur in the neocortex in the absence of the thalamus was demonstrated in animals with ipsilateral thalamectomy (Figure 4C) and in isolated cortical slabs in vivo (Timofeev et al., 2002). It is fair to state that the behavioral significance of development from neuronal plasticity, which is beneficial for normal mnemonic functions, to paroxysmal states, in those instances in which repetitive stimuli are prolonged beyond a certain limit, is not yet clearly understood.

**Neuronal Plasticity following Fast Rhythms**

Spontaneously occurring fast rhythms (~20–60 Hz) characterize the two brain-active states, wakefulness and REM sleep, during which these oscillations appear in a steady, almost uninterrupted way. Historically, the first demonstration that the EEG activated response to brainstem reticular stimulation is not only the blockage of spindles and slow waves (Moruzzi and Magoun, 1949), but also includes the appearance of fast rhythms displaying a regular acceleration and synchronization, belongs to Bremer and his colleagues (Bremer et al., 1960; see their Figure 5). This preceded by almost three decades the present excitement about these oscillations that appear during different conditions of increased alertness and accurate performance of a conditioned response, during stimulus-dependent oscillations in different cortical fields, but also spontaneously in both animals and humans cortices (references on this topic may be found in Singer, 1999, and different opinions on the temporal binding problem are exposed by Singer, 1999, and Shadlen and Movshon, 1999). The topic of this article is beyond the issue of whether or not synchronized fast rhythms in distributed neuronal pools are needed for the representation of multiple facets of the external world into single percepts. Suffice to say that fast rhythms are also synchronized during deep anesthesia or natural SWS, when consciousness is suspended (Steriade et al., 1996a, 1996b). We only present recent experiments that show the implication of fast oscillations in neuronal plasticity. Stimulation of homotopic sites in the contralateral cortex with pulse trains at 40 Hz induced prolonged facilitation of control response evoked by single callosal volley's, which lasted up to several minutes (Figure 7). 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 groupings and frequency of responses recorded during the prior period of stimulation. Spontaneous activity in the gamma frequency band improves the coherent fluctuations in visual cortex excitability and thus may ensure more rapid and reliable transmission (Fries et al., 2001). In humans challenged with performance of cognitive tasks, functional MRI showed that the power of fast rhythms (~20–35 Hz) increases in the thalamus and occipital cortex during semantic memory recall (Slotnick et al., 2002). These global data support the notion that fast rhythms are elaborated in reciprocal corticothalamic loops (Steriade et al., 1996b).

**Coda**

Future experiments should develop the above data by investigating the preferential occurrence of various forms of neuronal plasticity as a function of different brain rhythms during states of vigilance, using multisite intracellular and field potential recordings in behaving animals challenged by complex tasks.

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