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BRAIN ACTIVATION, THEN (1949) AND NOW: COHERENT FAST RHYTHMS IN CORTICOTHALAMIC NETWORKS

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INTRODUCTION

It is natural to commemorate 10 years since Giuseppe Moruzzi died by writing about changing concepts in a field that he promoted almost a half century ago (33), the more as I spent a part of my scientific life on the track of ascending activating systems. The two messages of this paper are as follows: *a*) the notion of EEG activation, used in the original description of the effects induced by brainstem reticular stimulation (33), despite no evidence at that time that cellular responsiveness is enhanced upon brain arousal, was fully substantiated by subsequent investigations of thalamic and cortical neurons; and *b*) the term EEG desynchronization, that many of us have used to designate the two brain-active states of waking and REM sleep, is partially wrong because, although the synchronizing devices underlying sleep oscillations are decoupled during brain arousal, fast activities at 20-80 Hz (mainly 30-40 Hz) are coherent within intracortical, intrathalamic and corticothalamic networks.

I. *Increased excitability and short inhibitory processes upon arousal.*

Moruzzi and Magoun (33) inferred brain "activation" processes from changes in spontaneous EEG waves. A decade later, this was demonstrated by the enhancement of cortical evoked potentials following stimulation of the brainstem reticular core (3, 12) and increased thalamic responses upon reticular-elicited arousal, in spite of unchanged amplitudes of responses simultaneously recorded from prethalamic axons (56). The initial concept of a globally energizing system was refined to include sculpturing inhibition in the activated response (17), as required during adaptive behavioral states. These data are now confirmed at the intracellular level, the chemical codes of most brainstem ascending activating systems are elucidated, and the ionic currents implicated in the enhanced thalamocortical responsiveness are disclosed (58, 61).

The activated EEG patterns induced by stimulation of the brainstem reticular core or occurring naturally during waking and REM sleep are associated with a prolonged (20 sec) depolarization and tonic firing in thalamocortical neurons, accompanied by an increase in their apparent input resistance (10), thus explaining

the enhanced probability of thalamic responses to incoming volleys during arousal. These effects, produced by pulse-trains to mesopontine cholinergic nuclei, are sensitive to blockers of muscarinic receptors (10). Similar actions may be exerted by setting into action locus coeruleus, though monoamine-containing neurons innervate the thalamus much less than cholinergic cell-aggregates (60). In fact, acetylcholine (ACh) and noradrenaline (NA) similarly produce the replacement of rhythmic burst firing of thalamic neurons, characteristic for the state of resting sleep (58, 59), by tonic firing, largely due through a suppression of a "leak" K^+ current, termed I_{KL} (29).

Although the reticular formation, initially viewed as a monolith, was dissected experimentally and some claimed the specificity of different components building up this structure, the number of identified cholinergic and monoaminergic neurons is by far smaller than that of neurons located within the classical fields of the brainstem core. What about those cells, located in territories where there is virtually no cholinergic or monoaminergic cell body, that are also implicated in ascending activating processes as their increased firing rates precede by 10-20 sec the most precocious EEG and behavioral signs of brain activation (65, 68)? It is generally thought and preliminary evidence is accumulating to indicate that those neurons, from the rostral mesencephalic tegmentum to the magnocellular and giant reticular fields in the pons and medulla, use glutamate as neurotransmitter. However, the long-lasting depolarizing effects exerted by brainstem core stimulation on thalamocortical neurons do not fit with the conventional notion of brief actions elicited by glutamate. Nonetheless, when considering the postsynaptic activation of glutamate metabotropic receptors, resulting in a long-lasting (up to 1 min) depolarization due to a reduction in I_{KL} (31), we must conclude that the actions of ACh and glutamate are quite similar. Like brainstem reticular neurons outside the cholinergic nuclei, neurons recorded from mesopontine cholinergic nuclei increase their discharge frequencies and excitability, in advance of the transition from resting sleep to either wakefulness or REM sleep (Fig. 1; 55). These data are supported by studies using microdyalisis in behaving animals, showing an equally increased release of ACh in the thalamus during waking and REM sleep (69). The next step would be to formally identify the glutamatergic nature of brainstem-thalamic neurons that display a firing profile during behavioral states of vigilance (65, 68) similar to that of cholinergic cells (55). This congruent behavior of brainstem neurons using two different neurotransmitters, ACh and glutamate, that are released in a similar way during brain-active states of waking and REM sleep, is quite different from that of monoaminergic neurons that become virtually silent in REM sleep (60).

The ascending activating brainstem glutamatergic system, acting in parallel with the descending activating corticothalamic glutamatergic system (31), is also decisive in driving nucleus basalis (NB) cholinergic neurons that innervate the cerebral cortex. Indeed, both serotonergic and cholinergic brainstem neurons that project to NB (6, 18) inhibit cholinergic NB cells (20). Thus, the origin of NB activation from the brainstem should be searched in the glutamatergic actions of brainstem-NB cells. This hypothesis (49) was confirmed experimentally (38).

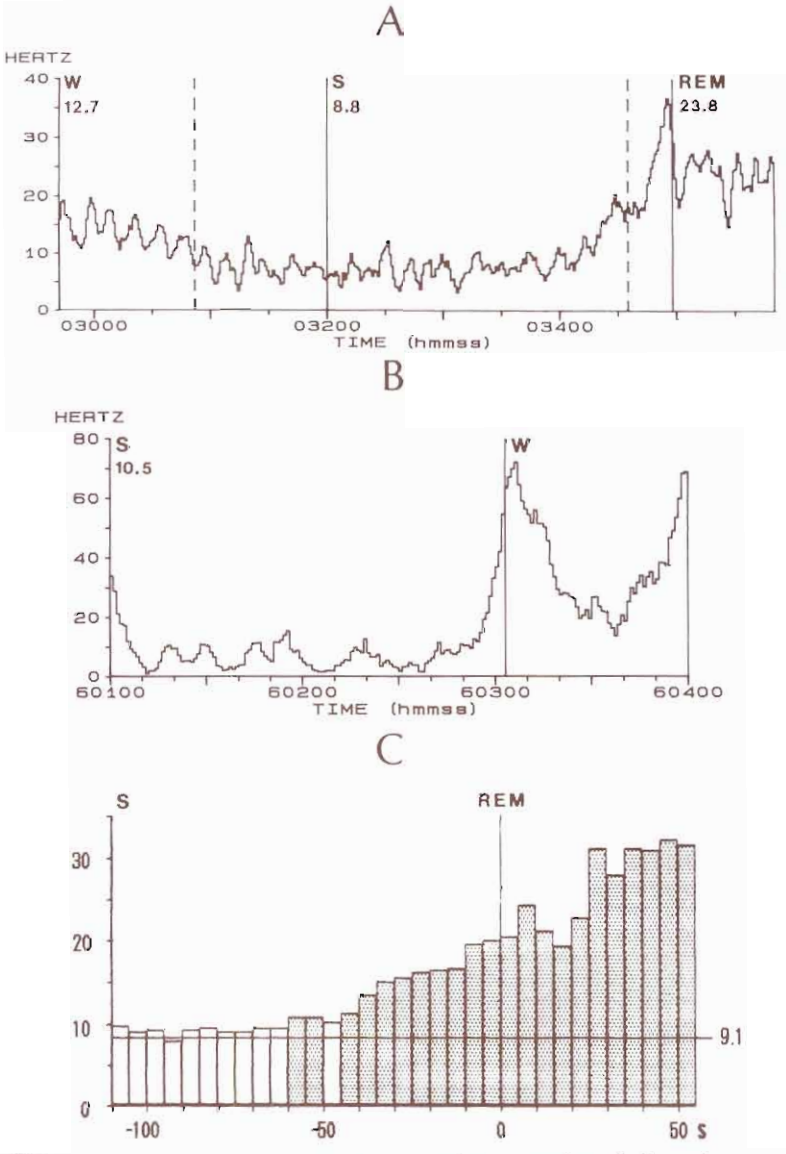

Fig. 1. - *Precursor signs of decreased firing rates of mesopontine cholinergic neurons from waking (W), to resting sleep (S), and increased firing rates from S to either W or REM sleep.*

Chronically-implanted, behaving cats. Neurons recorded from thalamic-projecting pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei. (A) Sequential firing rate of a PPT cell, antidromically activated from the rostral intralaminar thalamus, across the wake-sleep cycle. Abscissa indicates real time. Mean firing rates during W, S and REM sleep are indicated (in Hz) for each state. Transitional WS and pre-REM epochs are indicated by vertical interrupted lines (at 0:30:53 and 0:34:34, respectively). (B) Sequential firing rate of a thalamic-projecting PPT cell during transition from S to W. Same type of graph as in (A). In (C), statistical evidence in a pool of 21 thalamic-projecting PPT/LDT neurons showing increased firing rates 60 sec before EEG activation in REM sleep. Shaded 5-sec columns indicate bins with significantly ($p < 0.05$) increased firing rates from S to REM sleep. Modified from Steriade et al. (55).

It was a time, during the 1960s and early 1970s, when the increased excitability of thalamocortical cells upon arousal was believed to result from a global disinhibition, through the inhibition of both types of thalamic GABAergic neurons, reticular (RE) and local-circuit cells. Subsequently, it was observed that, however efficiently brainstem reticular stimulation blocks the prolonged inhibitory potentials appearing during sleep patterns in thalamocortical cells, this experimental condition does not suppress the early, short-lasting inhibitory phase (45, 64) during which the specificity of the response is enhanced and irrelevant information may be suppressed (16, 23, 40). After the demonstration of differential effects exerted by reticular-induced or natural arousal on the two phases of long-lasting inhibition in thalamocortical neurons, these phases were dissociated intracellularly and their differential ionic bases were revealed (9, 15, 43). As the genesis of both ($GABA_A$ and $GABA_B$) inhibitory postsynaptic potentials (IPSPs) depends on RE cells as well as on local thalamic interneurons, we took advantage of the simpler circuitry in the cat anterior thalamic nuclei that are devoid of RE inputs (67) and described three types of IPSPs that are all generated by local-circuit cells (36). The earliest IPSP (*a*-IPSP) is Cl^--dependent and is selectively evoked by prethalamic (mammillary) stimulation. The subsequent sequence of IPSPs ($GABA_{A-B}$, dependent on Cl^- and K^+, respectively) in thalamic anterior cells is similar to that previously described in lateral geniculate slices (9, 15) and they were evoked by both prethalamic and cortical volleys (36). In view of ultrastructural data showing that terminals of prethalamic axons terminate in thalamic glomeruli where they contact the presynaptic dendrites of local interneurons, whereas corticothalamic axons overwhelmingly synapse on parent dendrites (19, 37, 44), we concluded that the *a*-IPSP is generated by presynaptic dendrites, while both $GABA_{A-B}$ IPSPs are generated by the axonal firing of interneurons (36). Short pulse-trains to mesopontine cholinergic nuclei diminished or completely suppressed the $GABA_{A-B}$ IPSPs, whereas the mammillary-evoked *a*-IPSP was not reduced and, in many instances, was even enhanced (11). The effects of laterodorsal tegmental stimulation survived monoamine depletion by reserpine, thus supporting the cholinergic nature of the effect. It was proposed (66) that the ACh-evoked hyperpolarization of local-circuit thalamic cells, reported in an *in vitro* study (30), is an effect seen at the soma, while the ACh action on the intraglomerular inhibition mediated by presynaptic dendrites may be potentiating. Experimental testing supports this hypothesis (11).

To sum up, brainstem cholinergic arousal is associated with the increased excitability of thalamic and cortical neurons. The prolonged inhibitory potentials (characteristic for the state of resting sleep state when the protracted hyperpolarizations prime rhythmic inhibitory-rebound sequences in thalamocortical neurons) are blocked upon arousal, but the short-lasting *a*-IPSP of thalamic relay cells is preserved or increased. Similar results, indicating more efficient and shorter inhibitory processes upon arousal have been reported in cortical pyramidal tract neurons (57). The enhancement of the earliest IPSP provides neurons with an efficient mechanism for sculpturing incoming signals and finely tuning cellular responses, a basic requirement for discrimination purposes.

II. *Coherent fast spontaneous rhythms during brain arousal.*

The activation of brain electrical activity partly results from the suppression of prolonged inhibitory phases in thalamic and cortical neurons, but the most significant component (as it may underlie coherent firing of neurons in response to relevant stimuli) consists of oscillations within the frequency range of 20-80 Hz, mainly 30-40 Hz (hereafter termed *fast* rhythms or oscillations). The amplitudes of spontaneous fast rhythms are increased during brain arousal, as compared to the fast rhythms that are superimposed over the depolarizing envelopes of slow oscil-

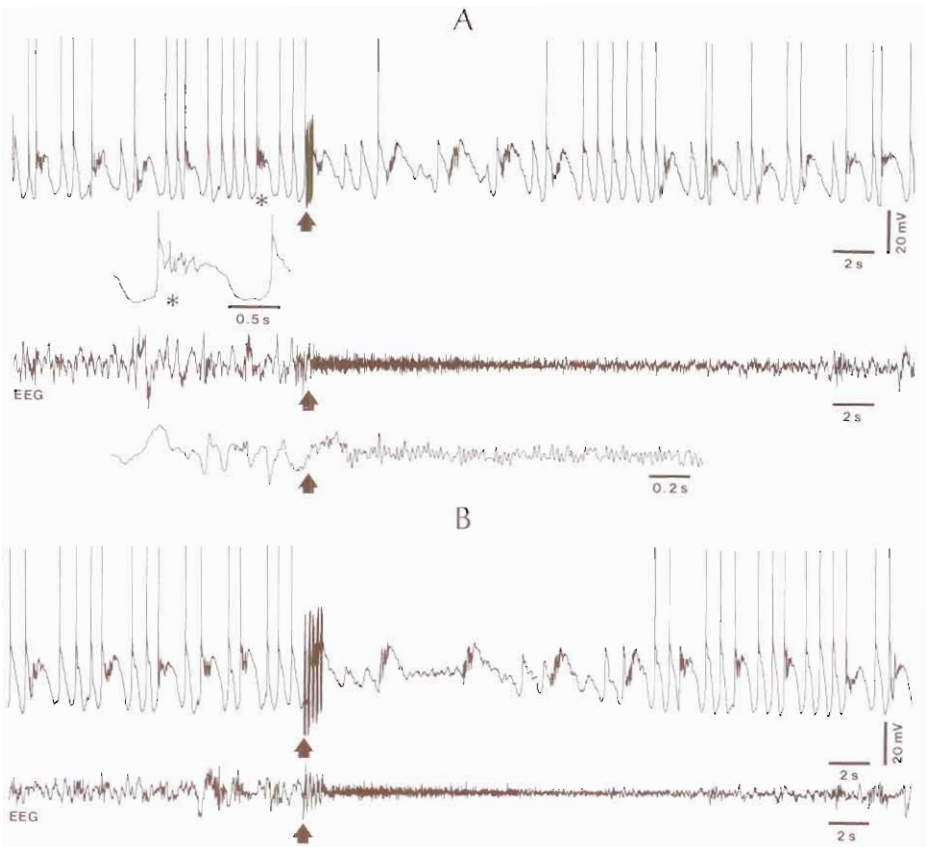

Fig. 2 - *Suppression of clock-like delta thalamic oscillation and appearance of 40-Hz rhythms by stimulation of mesopontine cholinergic nuclei.*

Cat under urethane anesthesia. Intracellularly recorded clock-like delta oscillation in thalamic lateroposterior (LP) neuron and its suppression by pedunculopontine tegmental (PPT) stimulation (arrows). One and five pulse-trains in (A) and (B), respectively. Below the top (intracellular) trace, EEG recording from the postcruciate gyrus. In (A), an expanded epoch of EEG trace around the PPT pulse-train is also depicted to show the PPT-induced fast oscillation at 40 Hz. A sequence of fast depolarizing events (asterisk in A) is also expanded and shown below. Note PPT-induced suppression of clock-like delta oscillation, associated with membrane depolarization (see especially B), and clear-cut appearance of 40-Hz rhythms in cortical EEG. Modified from Steriade et al. (53).

lations during resting sleep or anesthesia (see Fig. 6). The blockade of sleep oscillation in a thalamic neuron and the appearance of fast EEG rhythms after mesopontine cholinergic stimulation are shown in the intracellular and field potential activities depicted in Fig. 2 (53).

The first remark on spontaneous EEG oscillations at 40-50 Hz during brainstem-induced arousal, whose amplitudes exceed those of background waves (*"accélération synchronisatrice"*), can be found in a figure legend of a paper by Bremer and coworkers on brainstem reticular potentiation of evoked potentials (4; see their Fig. 5). The erroneous description of EEG arousal reaction under the term "desynchronization", that still persists in many contemporary studies, was probably generated by the fact that, in many instances, the electrical activity of the brain was found to be flattened upon arousal.

Our recent studies (48), by means of multi-site field potential, extra- and intracellular recordings from cat neocortex, vindicate Bremer's isolated observation and demonstrate that an acceleration in the frequency of spontaneous rhythms upon brain arousal is associated with their enhanced amplitudes and short-range synchronization. In essence, we have shown that fast spontaneous oscillations outlast by 10-20 sec a pulse-train to mesopontine cholinergic nuclei in acutely prepared animals (Fig. 3) and occur in a sustained manner during natural states of waking and REM sleep. By contrast to the long-range intracortical synchronization of slow sleep oscillation, that was found not only among neighboring foci but also between areas as distant as motor and visual cortex (1, 2), the synchronization of fast rhythms during activated epochs is spatially limited to the same cortical column and, horizontally, to neighboring cortical territories (see cross-correlations in Fig. 3). Thus, fast rhythms are synchronized among closely located cortical foci, such as cat's suprasylvian association areas 5 and 7 (Fig. 3) or visual areas 17 and 18, but the coherence of fast rhythms decreases with the distance and becomes weak over 5 mm (48). Although in other experiments, conducted on monkeys performing a task requiring attention, the fast oscillations were found to be synchronous over a distance of 14 mm, some episodes occurred in only one cortical focus and the proportion of coherent oscillations decreased with the distance between recorded leads (34). The intracortical coherence is achieved through corticocortical pathways that link neuronal pools having widely separated receptive fields (5, 13, 39) and primarily involve dendrites in layers I to III, followed by vertical intracolumnar projections. Besides these excitatory projections, a substantial excitation may result from disinhibion, as GABAergic basket cells innervate other inhibitory neurons (21). Sparsely spinous, presumably inhibitory cortical cells display fast rhythms (25), with the consequence that they may phase-lock pyramidal cells at this frequency range (28).

Within the same vertical column, we found that, while the polarities of the major components of low-frequency (<15 Hz) sleep oscillation (slow rhythms and spindles) are reversed at a depth of 0.3-0.4 mm, the fast rhythms are in-phase from the surface to the deepest cortical layers (48). The possibility that this in-phase (surface-to-depth) fast oscillation reflects volume-conduction from sources extrinsic

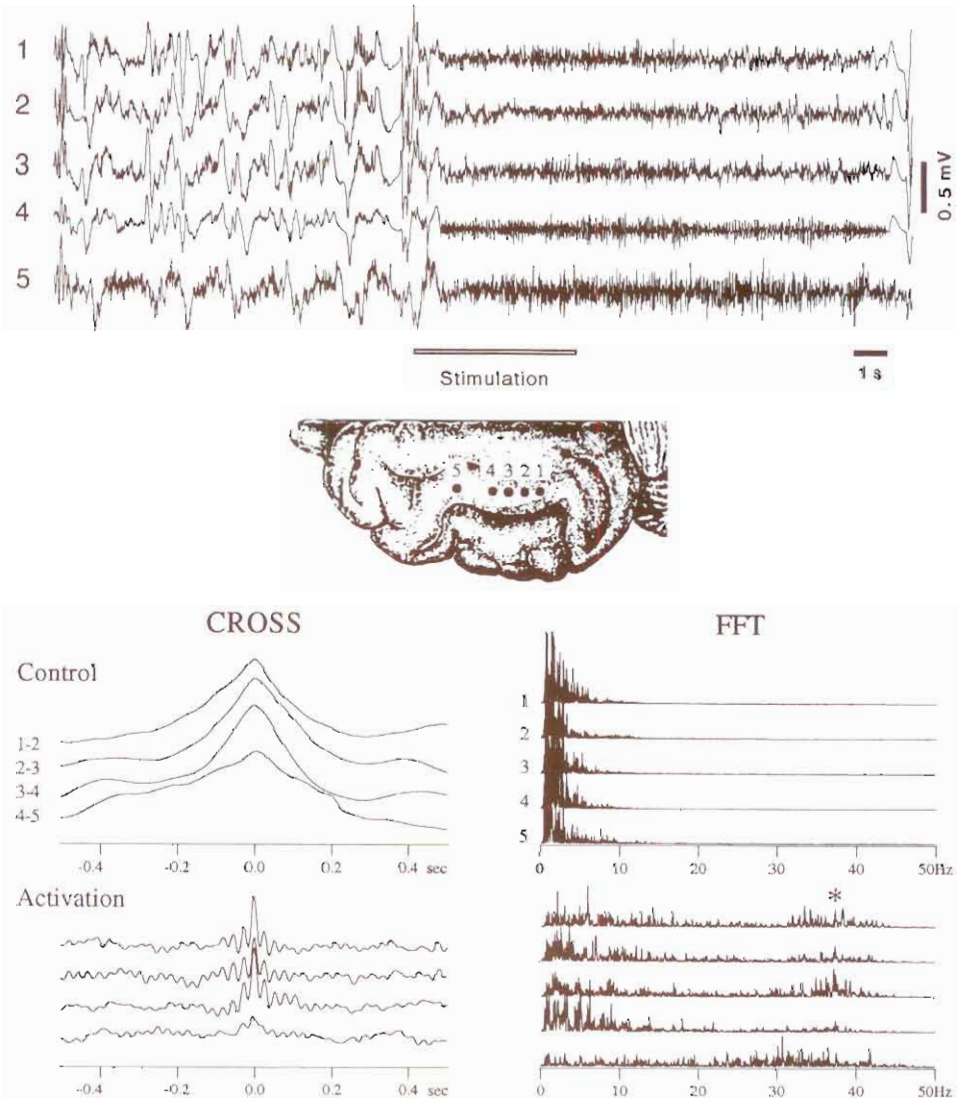

Fig. 3 - *Coherent fast (30-40 Hz) spontaneous cortical rhythms elicited by stimulation of mesopontine cholinergic pedunculopontine tegmental (PPT) nucleus.*

Cat under ketamine and xylazine anesthesia. *Top*, slow oscillation and its disruption by PPT pulse-train (300 Hz, horizontal bar), associated with appearance of fast activity whose amplitude exceeds that of fast waves during sleep patterns. Numbers of recorded cortical foci correspond to those indicated on the suprasylvian gyrus (areas 5 and 7) of the brain figurine. *Bottom*, cross-correlation (CROSS) and Fast Fourier Transform (FFT) analyses during a control period of sleep-like activities before PPT pulse-train and during the activated period elicited by PPT stimulation (in this case, PPT pulse-train lasted for 2 sec). Note: synchronized slow oscillation (0.4 Hz) during control period and synchronized fast oscillation (40 Hz) during the activated period. The coherence is greater between adjacent cortical leads (1-2, 2-3, 3-4; same electrode arrangement as in the above panel) than between leads separated by a greater distance (4-5). FFT shows the reduction in low-frequency waves (below 10 Hz) and the appearance of fast (mainly 30-40 Hz) waves. Modified from Steriade et al (48) and unpublished data in collaboration with F. Amzica.

to the explored area was discarded on the basis that the fast oscillation dropped to nearly flat records in the underlying white matter and, more importantly, the negative fast wavelets were crowned by action potentials of neurons recorded at all cortical depths. The absence of depth-reversal may be ascribed to non-spatially segregated, isochronous inputs that would generate mainly transmembrane current flow, with insignificant internal longitudinal current components. This complex pattern is probably continuously changing and moving up and down in the cortex, which would make them impossible to be detected by using a technique with a minimal spatial resolution.

The spontaneous fast oscillations are generated through a complex constellation of factors, including voltage-gated ionic currents, network properties, and potentiating effects exerted by generalized modulatory systems of thalamic and cortical neurons.

Depolarizing current pulses elicit fast oscillations (10-50 Hz) in local-circuit cells recorded from cortical slices, due to a persistent Na^+ current, with the involvement of a delayed rectifier (25). Similar fast oscillations characterize pyramidal neurons recorded *in vivo*, antidromically identified as corticothalamic and callosal cells (35). Thalamocortical cells also exhibit depolarization-dependent fast oscillations (54). It was found that a group of rostral intralaminar thalamic neurons, having peculiar electrophysiological properties, discharge fast (around 40 Hz) rhythmic spike-bursts with unusually high (900-1000 Hz) intraburst frequencies upon depolarizing current pulses (Fig. 4; 52), but also during their natural depolarization in waking and REM sleep (Fig. 5; 52). In view of the diffuse cortical projections of rostral intralaminar nuclei (19), the fast rhythms displayed by intralaminar thalamocortical neurons during brain-activated states may have a crucial role in synchronizing corticothalamocortical networks. These experimental data support the hypothesis that fast oscillations are dependent on activities in specific thalamocortical systems that provide the content of signals from the external world, while intralaminar thalamic nuclei would give rise to the context of information, depending on the general level of brain alertness (27). Thus, the intrinsic electrophysiological properties of cortical and thalamic neurons are closely linked to the network organization. Indeed, our recent experiments indicate that synaptic activities in cortical networks may boost the intrinsic properties of neurons. For example, depolarizing current pulses elicited action potentials grouped within sequences at 30-40 Hz that were potentiated by background synaptic activities, whereas pulses with the same parameters applied during cell's hyperpolarization only revealed the slowly adapting pattern of regular-spiking cortical neurons (48).

As fast oscillations are present during both brain-active states of waking and REM sleep (Fig. 5; 26, 27, 48, 52), when thalamocortical systems are similarly activated (45, 46), the modulatory systems that are mainly implicated in these fast rhythms are the ascending cholinergic and glutamatergic projections whose activity profiles across the wake-sleep cycle are similar. The potentiation of cortical fast rhythms by stimulation of mesopontine cholinergic nuclei is sensitive to muscarinic blockers (54) and therefore depends on a bisynaptic, brainstem-thalamic-cortical, cholinergic-glutamatergic projection. The direct cholinergic activation of cortex

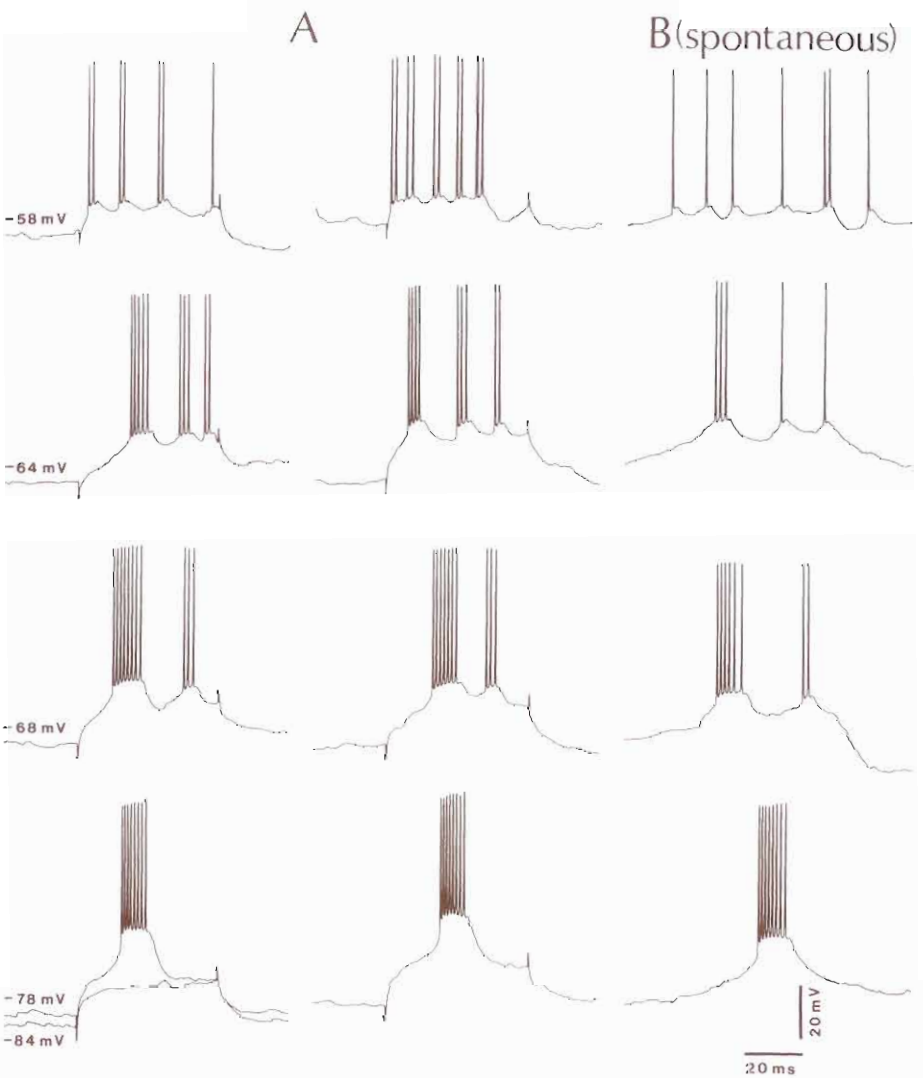

Fig. 4 - *Fast oscillatory patterns of rostral intralaminar thalamocortical neuron induced by depolarizing current pulses and occurring spontaneously.*

Cat under barbiturate anesthesia. Intracellular recording of thalamic centrolateral (CL) cell. (A) Activities triggered by depolarizing pulses (+1.2 nA, 50 msec) at different membrane potentials (V_m indicated at left). Two examples are illustrated for each V_m level. At bottom, presence of low-threshold spike, leading to high-frequency (800 Hz) spike-burst at -78 mV and its absence at -84 mV. (B) Oscillatory patterns similar to those elicited by current injection occurred spontaneously at similar V_ms (from top to bottom, -58, -64, -68 and -78 mV). From Steriade et al. (52).

depends on NB neurons and is associated with 20-40 Hz membrane potential oscillations of cortical neurons (32). Thus, both the thalamus and NB mediate the brainstem ascending activating effect on the cerebral cortex. In fact, neither extensive thalamic lesions nor NB cellular loss prevents the brainstem-induced suppres-

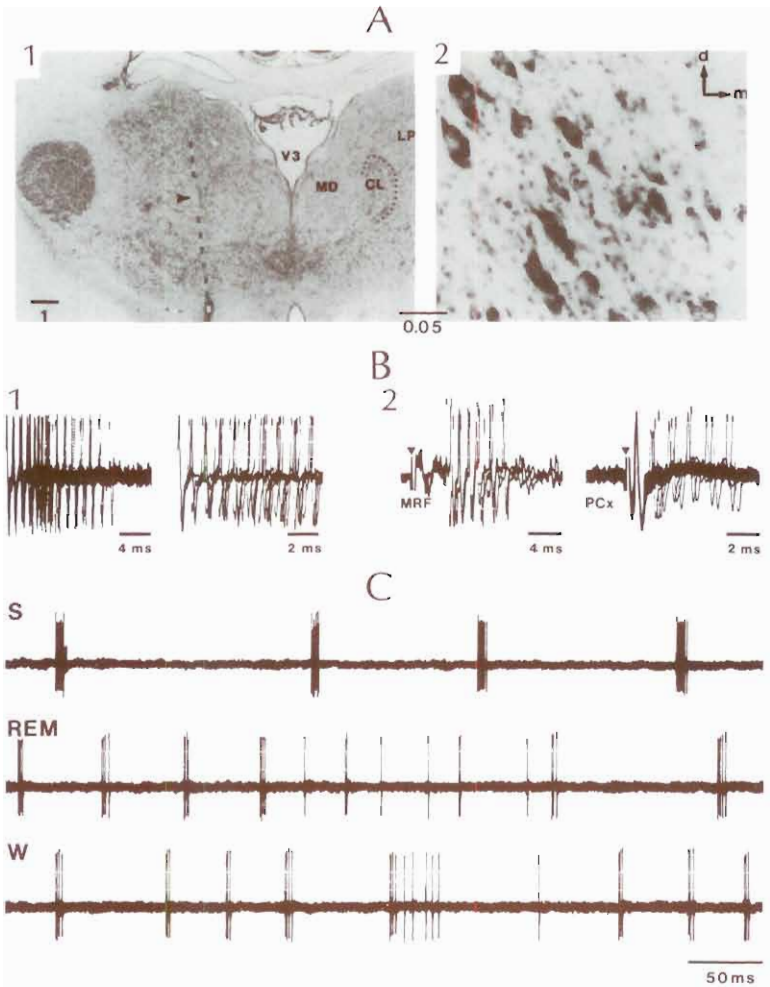

Fig. 5 - *Discharge patterns of rostral intralaminar thalamocortical neurons during waking and sleep states.*

Chronically implanted, behaving cats. (A1) Frontal section with microelectrode track (interrupted lines) through the lateral part of the centrolateral (CL) intralaminar thalamic nucleus (arrowhead). A small electrolytic lesion was made 3 mm ventral to the CL nucleus to allow localization of recorded neurons. In the contralateral thalamus, some thalamic nuclei are indicated and the dorsolateral part of the CL is marked by dots. LP, lateroposterior nucleus; MD, mediodorsal nucleus; V3, third ventricle. (A2) Neuronal population in the large-celled CL area, with large, darkly stained cells. Arrows indicate dorsal (d) and medial (m). Horizontal bars in mm. (B) Identification of input-output organization of CL neuron with peculiar burst discharge properties. In (1), spontaneously occurring spike-bursts at 1000 Hz, at two different speeds. In (2), synaptically elicited spike-burst (1000 Hz) by stimulating (arrowhead) the mesencephalic reticular formation (MRF), and antidromically elicited spike (0.4 msec latency) followed by spike-burst (1000 Hz) in response to stimulation (arrowhead) of area 5 in the parietal association cortex (PCx). (C) Discharge patterns of CL thalamocortical neuron during EEG-synchronized sleep (S), REM sleep, and wakefulness (W). The cell was recorded in this order. Note that high-frequency (900-1000 Hz) spike-bursts during S did not change into tonic, single-spike firing during W and REM sleep, as is characteristic for other thalamocortical neurons; instead, during both EEG-activated states of W and REM sleep, short (5 msec) spike-bursts with intraburst frequency of 800-1000 Hz recurred at 20 Hz. Modified from Steriade et al. (52).

sion of sleep oscillations and their replacement by depolarization in cortical neurons (54).

We should emphasize that the fast rhythms are not present only during brain-activated states of waking and REM sleep, but also during resting sleep or under deep anesthesia. The electrographic hallmark of sleep is the slow cortical oscillation (<1 Hz) that groups in periodic sequences the two other sleep rhythms, spindles and delta (7, 51, 62, 63). During the slow sleep oscillation, the fast rhythms are periodically interrupted, being selectively suppressed during the prolonged and rhythmic hyperpolarizations of cortical and thalamic neurons (Fig. 6). This supports the data indicating the depolarization-dependency of the fast rhythms and casts doubt on hypotheses relating exclusively the fast rhythms to events during states of awareness.

What is the functional significance of fast rhythms? Some postulate that fast oscillations occur in spatially distributed neuronal clusters in response to optimal sensory signals and would serve to bind different features of an object into a global percept, the so-called conjunction principle underlying conscious events (8, 14, 24,

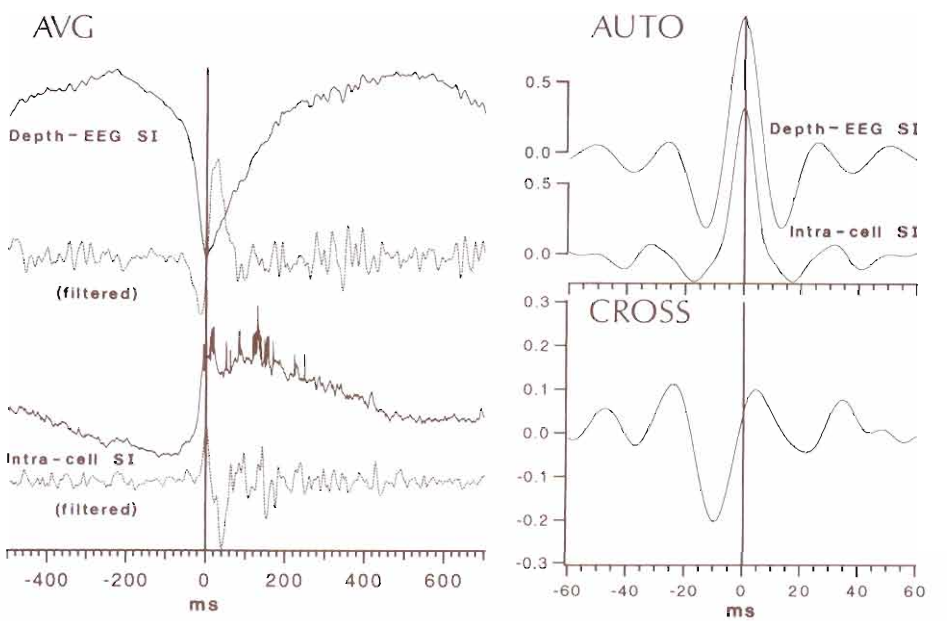

Fig. 6 - *Fast oscillations (40 Hz), occurring during sleep patterns, are dependent on cell's depolarization.*

Cat under ketamine and xylazine anesthesia. Intracellular recording at 0.8 mm depth in the primary somatosensory (SI) cortex and depth-EEG, 1 mm apart from the micropipette. Average (AVG, n=15) depicts reduction, up to suppression, of fast waves during the EEG depth-positivity and cell's hyperpolarization (dotted traces are filtered between 10 and 100 Hz). Autocorrelations (AUTO) show the oscillatory activity at 40 Hz and cross-correlations (CROSS) show the time-lag (10 msec) in the phase-opposition between depth-EEG and intracellular activity. Unpublished data in collaboration with D. Contreras.

41). The alternative view takes into consideration that fast rhythms also appear during resting sleep and deep anesthesia, states associated with mental annihilation, and proposes that such fast oscillations are part of the *background* electrical activity of the brain, reflecting the depolarization of thalamic and cortical neurons under the influence of central core modulatory systems (47, 48, 54). The fact that fast oscillations are present during behavioral states when thalamocortical gates are closed to the outside world does not exclude that, during open-brain states, the intrinsic cellular properties and network operations would underlie binding operations, significant for cognitive experiences. Indeed, fast oscillatory responses to photic stimuli are enhanced during midbrain reticular stimulation (42, 50) and such oscillations are potentiated during highly motivated behavioral states (34). When excitatory inputs coincide with the depolarizing phase of the subthreshold oscillation, they cause the neurons to fire (22). The likely possibility that non-synchronous or slightly coherent fast neuronal oscillations become robustly coherent for short periods of time after a relevant stimulus in the awake state or an internally generated drive in REM sleep should now be tested.

SUMMARY

The hypothesis of forebrain activation elicited by brainstem reticular core stimulation, formulated almost a half century ago, is now fully substantiated at the intracellular level of thalamic and neocortical neurons. Data show that stimulation of mesopontine cholinergic nuclei induces a prolonged muscarinic depolarization of thalamocortical neurons, associated with an increase in their apparent input resistance (that explains the enhanced probability of thalamic responses to incoming volleys upon arousal) and accompanied by a long-lasting activation of cortical rhythms. Activation also includes the preservation or even enhancement of short-lasting sculpturing inhibitory processes in thalamic and neocortical cells, a basic requirement for discrimination purposes. The notion of activation, that was erroneously termed as a "desynchronized" activity in thalamocortical networks, is now demonstrated to include spontaneously occurring, synchronous fast (20-40 Hz) rhythms. While the spatial coherence of sleep rhythms extends over wide territories, fast oscillations during brain arousal are synchronous within a cortical column and among closely spaced cortical areas, thalamic nuclei, and corticothalamic systems. Fast oscillations do not exclusively characterize brain-active states of waking and REM sleep, as they are also present during the depolarizing phase of the slow sleep oscillation in both cortical and thalamic cells. The subthreshold fast depolarizing spontaneous oscillations may bias thalamic and cortical cells to respond synchronously, at fast frequencies, to external stimuli in the wake state and to internal drives (such as ponto-geniculo-occipital signals) during REM sleep.

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