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Invited Review

Bursting of Thalamic Neurons and States of Vigilance

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Llinás, Rodolfo R. and Mircea Steriade. Bursting of thalamic neurons and states of vigilance. *J Neurophysiol* 95: 3297–3308, 2006; doi:10.1152/jn.00166.2006. This article addresses the functional significance of the electrophysiological properties of thalamic neurons. We propose that thalamocortical activity, is the product of the intrinsic electrical properties of the thalamocortical (TC) neurons and the connectivity their axons weave. We begin with an overview of the electrophysiological properties of single neurons in different functional states, followed by a review of the phylogeny of the electrical properties of thalamic neurons, in several vertebrate species. The similarity in electrophysiological properties unambiguously indicates that the thalamocortical system must be as ancient as the vertebrate branch itself. We address the view that rather than simply relays, thalamic neurons have sui generis intrinsic electrical properties that govern their specific functional dynamics and regulate natural functional states such as sleep and vigilance. In addition, thalamocortical activity has been shown to be involved in the genesis of several neuropsychiatric conditions collectively described as thalamocortical dysrhythmia syndrome.

INTRODUCTION

This article addresses the functional significance of the electrophysiological properties of thalamic neurons with the aim of setting such properties into the context of global brain function.

This context may be addressed by contrasting the functional role of the thalamocortical (TC) system with that of the tectal plate (the colliculi) that, prima facie, may be considered as having an equivalent function. One may wonder what advantage is realized by having two integrative CNS regions that transform sensory input into purposeful motor output. Indeed, as both systems evolved in parallel, their roles may be considered as mutually essential to vertebrate survival. Thus the tectal system, with its rapid multi-sensory organization, sets the instantaneous orienting responses crucial to the maintenance of life. By contrast the TC system, with its extensive corticothalamic recurrence and temporal binding properties, may be viewed as creating the complex combinatorial sensory-motor landscape (Kersten and Yuille 2003; Llinás 2001; Mountcastle 1998, 2005; Steriade 2001a) required for the elaboration of the intentionality that characterizes vertebrate behavior.

We propose that the latter TC activity, omnipresent in both the waking and sleeping states, is the product of the intrinsic electrical properties of the TC neurons and the connectivity their axons weave. We will begin with an overview of the electrophysiological properties of single neurons in different functional states. This will be followed by a review of the phylogeny of the electrical properties of thalamic neurons. The similarity of such properties unambiguously indicates that the TC system must be as ancient as the vertebrate branch itself.

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Firing properties and ionic conductances of thalamocortical neurons

The study of the electrophysiological properties of thalamic neurons began in earnest in the early and middle 1960s with in vivo intracellular recordings using feline preparations (reviewed in Andersen and Andersson 1968; Purpura 1970). For the most part, in these studies, thalamic neurons were considered simple relay elements between sensory inputs and the cerebral cortex. Subsequent electrophysiological studies of thalamic relay functions, after electrical or physiological stimulation, supported this basic assumption. However, with the development of in vitro recording, it became evident that central neurons are endowed, given the richness of theirs ionic conductances, with intrinsic electrophysiological properties beyond a simple relay function (Llinás 1988; Traub et al. 2005; Trimmer and Rhodes 2004).

Starting in the early 1980s, two sets of studies carried out independently, but nearly simultaneously, were the first to address thalamic electrophysiology with the goal of understanding the electrical character of these neurons without any specific input bias. These studies, one carried out in vivo (Deschênes et al. 1982, 1984; Steriade and Deschênes 1984) and the other in vitro (Jahnsen and Llinás 1984a,b; Llinás and Jahnsen 1982), soon reached a convergent view of thalamic function that differed fundamentally from the accepted dogma at the time (Steriade and Llinás 1988).

Rather than simply relays, thalamic neurons were viewed as having sui generis intrinsic electrical properties that gave them specific functional dynamics. These studies came to one of us (Steriade) as an extension of investigations on neuronal network operations during states of vigilance, to the other (Llinás), as an extension of the characterization of the intrinsic properties of brain stem neurons, in particular, the inferior olive group, where similar ionic currents were initially described (Llinás and Yarom 1981a,b).

These studies converged and their results agreed. One provided in vivo context, whereas the other contributed the advantage of ionic and biophysical characterization in vitro. Both sets of studies demonstrated that thalamic neurons were not simple links in a connectivity chain but were rather the fundamental arbiters for global brain states.

Thalamic neurons, on being depolarized from resting potential levels positive to −55 mV, fire tonically both under in vivo and in vitro conditions. Such tonic firing was shown to be protracted according to the duration of the membrane depolarization. Under in vitro conditions, tonic spike generation is supported by a tetrodotoxin (TTX)-sensitive Na^+ conductance

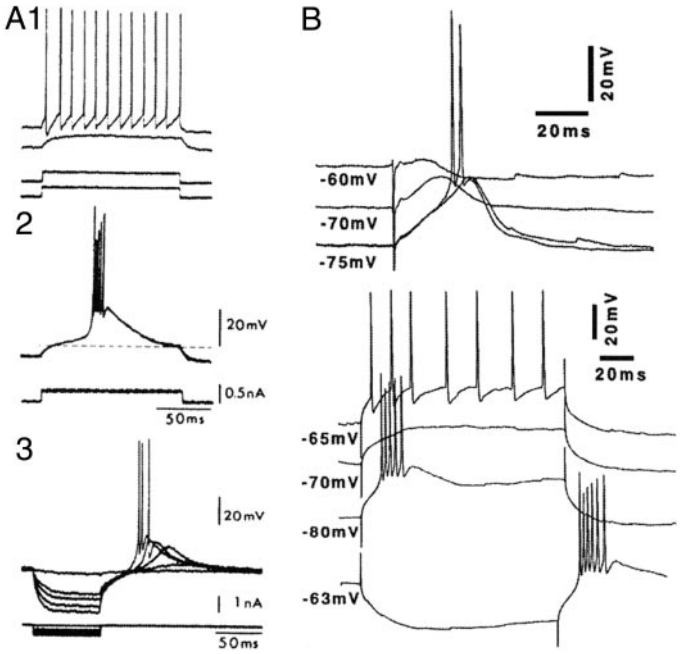

FIG. 1. Similarities between the low-threshold spike (LTS) of thalamocortical (TC) neurons in vitro and in vivo. *A*: thalamic neuron recorded from dorsal thalamic slice of guinea pig maintained in vitro. *1*) Subthreshold current pulse (bottom trace) from rest membrane potential produced a subthreshold depolarization of the cell; the same stimulus, delivered after an imposed DC depolarization of the cell, produced repetitive, single-spike (tonic) firing. *2*) Following hyperpolarization of the cell, current pulse similar to that in *1* produced an LTS crowned by a high-frequency burst of action potentials. *3*) Rebound LTS also occurred after hyperpolarizing pulses of different amplitudes. *B*: TC neuron from the ventrolateral (VL) nucleus, recorded in vivo (cat under ketamine-xylazine anesthesia). Top 3 traces depict the neuronal responses to stimulation of the internal capsule at 3 different membrane potential (note excitatory postsynaptic potential triggering LTS, eventually reaching the threshold for action potentials, at −75 mV). Bottom 4 traces (depolarizing and hyperpolarizing current pulses) show tonic firing at −65 mV; passive response at −70 mV; spike-burst at −80 mV; and spike-burst at the break of a hyperpolarizing pulse, at −63 mV [modified from Llinás and Jahnsen (1982), *A,* and Contreras and Steriade (1995), *B*].

(inactivating g_{Na}, [Nav1.2]) (Jahnsen and Llinás 1984b; Westenbrook et al. 1989) and the delayed rectifier K^+ conductance, blocked by TEA (g_K [Kv1]) (Jahnsen and Llinás 1984b; Trimmer and Rhodes 2004). Close to the firing level, high-frequency [30–60 Hz, gamma range in electroencephalographic (EEG) terminology] dendritic subthreshold oscillations (supported by P/Q-type Ca^{2+} channels [Cav2.1]) (Zhang et al. 2002) were seen (Luo and Perkel 1999; Pedroarena and Llinás 1997; Rhodes and Llinás 2005; Ströhmann et al. 1994). Such fast rhythms were also induced by depolarization of TC neurons in vivo (Steriade et al. 1991, 1996) but their ionic bases were unkonwn at that time.

The responses to membrane hyperpolarization were also fundamentally similar in the two sets of studies. At levels negative to −60 mV, de-inactivation of a Ca^{2+} conductance gave rise, on depolarization, to an inward current through T-type Ca^{2+} channels ([Cav3.1–3.3]) (Chemin et al. 2002). If sufficiently prominent, I_{Ca} becomes regenerative and activated Ca^{2+}-dependent spikes that activated high-frequency bursts of Na^+ action potentials. In the absence of Na^+ from the extracellular milieu, or in the presence of Na^+ channel blockers (TTX), the Cav3 conductance was sufficiently large to generate action potentials that were named low-threshold spikes (LTSs) (Jahnsen and Llinás 1984a) and were subsequently studied using patch-clamp technique, which allowed a direct characterization of the currents (Coulter et al. 1989; Crunelli et al. 1989). TC neurons also were shown to have a persistent Na^+ conductance ($I_{Na\ (p)}$); Jahnsen and Llinás 1984b; Pari and Crunelli 1998; Pedroarena and Llinás 1997; Tennigkeit et al. 1996) through the Nav1.6 channel (Vega-Saenz et al. 1997). Also the I_a, ([Kv4.2–4.3]) (Hugenard and McCormick 1992; Huguenard et al. 1991; Jahnsen and Llinás 1984b; Serodio et al. 1996) and I_h ([HCN2, HCN4]) (Santoro et al. 2000) currents modulate the low-frequency oscillations in these neurons (Leresche et al. 1991; McCormick and Pape 1990; Soltesz et al. 1991).

An important issue here is the role of the resting potential in the firing dynamics. Thalamic bursts arise from a hyperpolarized membrane potential level only if the membrane potential has been sustained long enough to inactivate the Cav3.1 channels and to activate the I_h current. These two conductances are a prerequisite for the generation of the LTSs responsible for rhythmic spike bursting. The significance of this finding is not always appreciated. It is not possible to generate this form of electrical activity from vigilance membrane potential level (~60 mV) unless the voltage dependence of Cav3.1 de-inactivation can be directly modified. In other words, the burst response of thalamic cells is a true intrinsic activation mode that can only be evoked by a period of sustained hyperpolarization that results in a well-defined cyclical activation pattern. These patterns will be maintained for as long as the cells remain hyperpolarized. It is no wonder then that the most invariant activities in the nervous system are those that generate slow-wave sleep. Moreover, the rhythms during this sleep state are generated not only by TC and reticular (RE) thalamic neurons but by the overlaying cortex that also generates a slow oscillation (0.5–1 Hz) (Steriade et al. 1993b). The importance of the functional coupling between cortex and thalamus, a true resonance, cannot be overemphasized. It means that as low-frequency rhythms (0.5–15 Hz) arise either at thalamic or cortical level, their activities may be maintained by the recurrence of TC and corticothalamic axons. This recurrence will be robust and will tend to maintain itself.

Short trains of spikes (generated by synaptic excitation from vigilance resting potential) cannot mimic the pattern of rapid spike-bursts (≤15 Hz in the case of spindle rhythmicity) each followed by a powerful, prolonged afterhyperpolarization that produces a pause in firing. Equally important is the fact that such bursts, given their intrinsic origin and the recurrence of the network, never occur as single events and usually hail profound change in global brain function. Also, recent modeling studies by Paul Rhodes (personal communication) indicate that the production of true bursts, by synaptic input from a "resting" potential of −60 mV in the absence of Cav3.1 calcium current activation, is fundamentally impossible. The level of current injection required for the generation of a depolarization sufficiently rapid to produce high-frequency spike burst with the required interspike interval of ≤4 ms requires that I_{Ca} generate a 35-nA inward current with a driving force of +60 mV. A similar depolarization generated by synaptic input with a driving force (E_{EPSP}) of 0 mV would require 750-nS conductance from the proximal dendrites. Even at somatic level, a minimum of 100 nS would be required to generate a potential comparative to an LTS. Assuming 1

nS/synapse, simultaneous activation of 100 synaptic inputs (close to the total input to a given TC from the retina) would be required to generate a high-frequency spike burst, but there would be no prolonged afterhyperpolarization.

In short, thalamic activity can be continuously regulated by sensory or cortical synaptic input, the latter being the more powerful. Thus when these neurons are sufficiently depolarized positive to (−50 mV), they generate subthreshold oscillations at frequencies near 40 Hz (gamma band). This activity supports TC resonance and is the functional antithesis of the rhythmicity that supports the perceptual indolence of slow wave sleep.

Dynamic plan for vertebrate brain function

Thalamic neurons can be recognized in all vertebrate forms (Jones 2006). While present day representatives of fish, amphibians, and reptiles must have changed from their ancestral roots, it is also true that their body structure demonstrates little variance from their fossil ancestry. Therefore the basic organization of the forebrain, with a recurrent thalamo-cortical organization (initially a pallium, rather than the 6-layer mammalian cortex), may have appeared (more than 400 million years ago) during the Devonian age as represented by Amblyostoma and other amphibians and fish (Romer 1966).

A set of recent comparative in vitro studies (Fig. 2) indicates that the ionic conductances and, indeed, the entire constellation of electrophysiological characteristics encountered in the mammalian thalamus, are present in "representative" forms of the different vertebrate subgroups.

Indeed, thalamic electrophysiology is remarkably similar among the different vertebrate phyla, as represented by fish (goldfish) (Fig. 2*A*), amphibians (frog, *B*) reptiles (turtle, *C*)

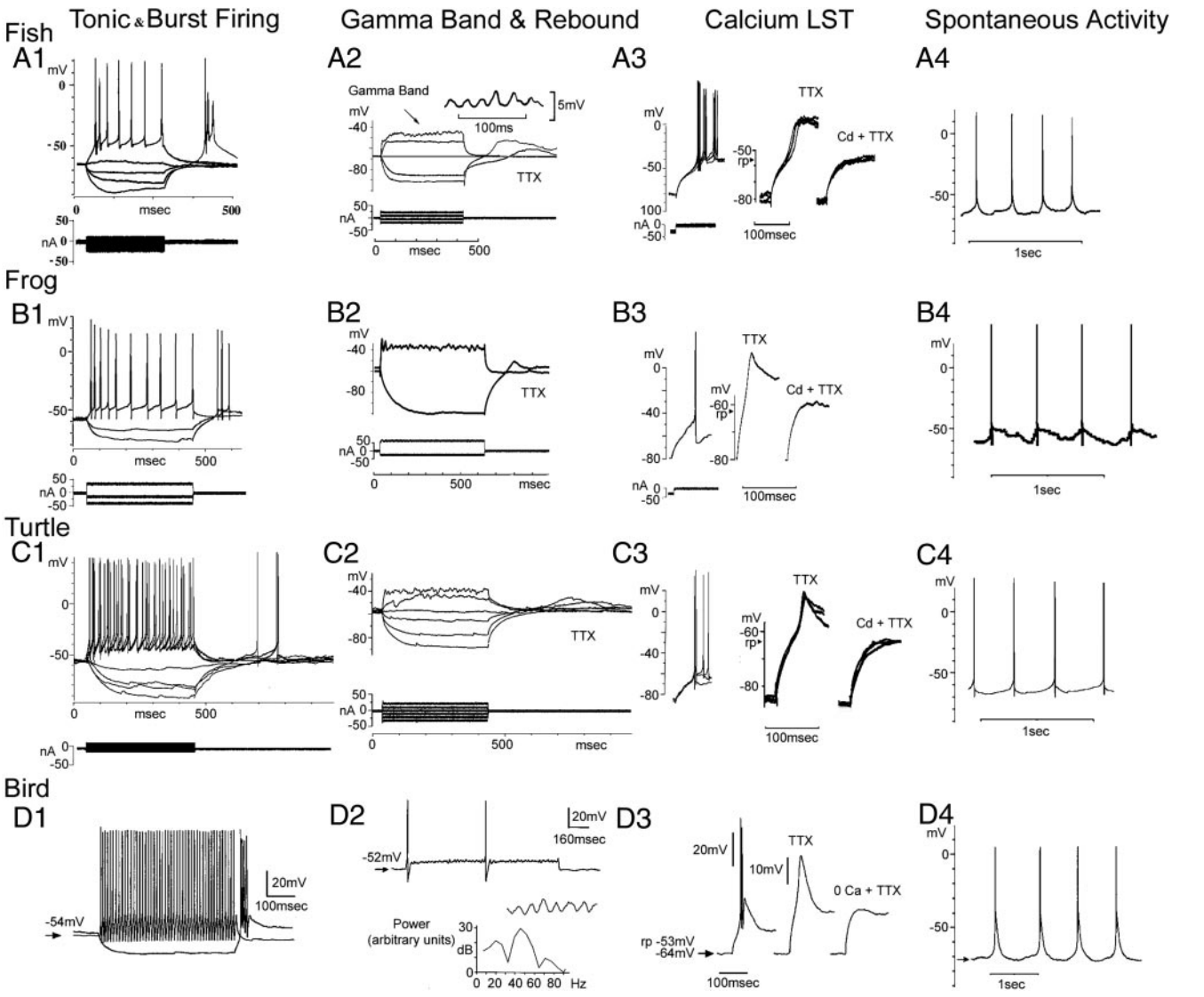

FIG. 2. In vitro thalamic electrophysiology in different vertebrates. Set of intracellular recordings from thalamic cells in fish (carp, *A*), amphibian (frog, *B*), reptile (turtle, *C*), and bird (finch, *D*). In all cases, depolarization from rest (*A1–D1*) produced tonic firing for the duration of current injection and burst firing at the brake of a inward current pulse. Following TTX superfusion (*A2–C2*) depolarization evokes subthreshold oscillation at gamma band frequency and a rebound graded potential following a hyperpolarizing pulse. In *D2* similar subthreshold gamma band activity in bird thalamic neuron. *A2* and *D2* show detail of gamma band frequency. The calcium nature of the LTS was tested by adding $CdCl_2$ to the bath (*A3–C3*) or in the absence of Ca from the perfusate (*D3*). Spontaneous low-frequency activity was observed in all neurons, with differences in frequency as illustrated (*A1–D1*). Recordings in *A–C* from G. Gamkrelidze, R. Baker, and R. Llinás (unpublished observations) and *D* from M. Luo and D. J. Perkel (1999).

(G. Gamkrelidze, R. Baker, and R. Llinás, unpublished observation), and birds (finch, *D*) (Luo and Perkel 1999; see also Person and Perkel 2005; Strohmann et al. 1994) and mammals (as reviewed in the preceding text). As in the case of mammals, thalamic neurons of the "lower" four species all fired tonically when depolarized from the resting membrane potential (Fig. 2, *column 4*). When these neurons were hyperpolarized with a short, inward current step, a rebound burst of spikes, LTS, was observed at the termination of the current step resulting in a sort of spike burst arising from a membrane voltage below the resting potential (Fig. 2, *column 1*).

After application of TTX to the bath, sodium-dependent action potentials were blocked, reviling rapid membrane potential oscillations in gamma band frequency at the crest of the depolarization step (Fig. 2, *column 2*). Low threshold all-or-none spikes followed hyperpolarizing steps (Fig. 2, *column 2*).

The rebound response is Ca^{2+}-dependent because the LTS survives in the presence of TTX but is blocked by 200 μM cadmium chloride (Fig. 2, *column 3*). This confirmed the Ca^{2+} nature of this response and the high possibility that these rebound potentials are produced as in mammalian thalamic neurons, by the de-inactivation of a T-type calcium channel after membrane hyperpolarization for a period of several hundred milliseconds. Concerning K^+ currents, these studies demonstrated the existence of both I_a and I_h currents in all species studied (not illustrated).

A significant finding was the presence of intrinsic rhythmicity when the cells were maintained at a hyperpolarized level. Spontaneous oscillatory behavior at 2–4 Hz was generated by Ca^{2+} driven depolarizations resulting in single or short bursts of spikes, followed by a hyperpolarization and a rapid repolarization before the next burst (Fig. 2 *column 4*). This is most probably generated by a combination of Cav3.1–3.3 I_h cationic current. Similar results were obtained from a diverse set of thalamic nuclei in the species mentioned. This finding emphasizes the fact that, as in mammalian forms, recordings from projection neurons in different thalamic nuclei shown similar LTS responsivity (Jahnsen and Llinás 1984a). Moreover, such uniformity in the TC electrophysiological character concerning delta oscillations was demonstrated by the work of Curró Dossi et al. (1992) in vivo (where hundreds of neurons belonging to all major thalamic nuclei were studied) and to similar findings in vitro by McCormick and Pape (1990).

The findings illustrated in Fig. 2 strongly suggest that similar rhythmicity and network properties are present in all these forms. Given the ability of thalamic neurons to generate different oscillatory states, wakefulness and sleep, and possibly cognition (as reflected by subthreshold gamma band activity), may be a common denominator for all vertebrate forms.

While this view is in its inception, it is also clear that, if this is the case, what we have in the evolution of the forebrain is a tendency toward specialization of function by cytoarchitectonic differentiation and recurrent thalamocortical function (Karten and Shimuzu 1989). This differentiation may be considered as the result of evolutionary pressure for survival in a biosphere that presents an ever-increasing number of ecological niches requiring increased behavioral complexity.

These findings imply that the brain rhythms characterizing the activity of TC circuits have been enriched, but not basically changed, over the last 400 million years. Such rhythmicity and the functional states they imply are truly ancestral forms in the organization of brain function among vertebrate forms. That these neurons have the ionic channel complements required to support gamma and slow rhythm activity is strongly suggestive that similar basic electrical mechanisms correlated with wakefulness and sleep may be present across vertebrate species. Although there is no question that birds and reptiles' sleep, the evidence is less clear in amphibians and fish. It is clear, nevertheless, that the ionic mechanisms in thalamic neurons show the necessary requirements for such global functional states. Gamma band activity is present in reptiles, birds, and mammals following sensory stimuli and may be seen in rapid-eye-movement (REM) sleep in mammalians and birds.

Distinct low-threshold bursting in TC, thalamic reticular, and local-circuit neurons

The burst of fast Na^+ action potentials crowning the LTSs are generated by different mechanisms in the three main types of thalamic neurons: TC, thalamic reticular (RE), and local-circuit neurons.

In natural sleep the spike burst in TC neurons are de-inactivated by membrane hyperpolarization (see preceding text), are preceded by an interval >50 ms, and are characterized by having few (generally 3–6) spikes with progressively decreasing interspike intervals (250–400 Hz) (Domich et al. 1986). These criteria were used in subsequent animal studies, and similar spike bursts have been described in the human thalamus (Jeanmonod et al. 1996; Lenz et al. 1998; Zirh et al. 1998). Although in some cases only a single spike is evoked by LTSs, this can only be determined intracellularly. The assumption in some extracellular studies (Swadlow and Gusev 2001), that single spikes that are preceded by long intervals are generated by the same mechanism as Ca^{2+}-mediated LTS bursts, is questionable because during depolarized states associated with irregular discharges, many single spikes are preceded by intervals >0.1 s.

Because TC-cell hyperpolarization selectively occurs during slow-wave sleep (Hirsch et al. 1983) (when T-currents can be de-inactivated) and high-frequency rhythmic spike bursts only appear during this sleep stage (Glenn and Steriade 1982), the firing patterns of TC cells was generally defined as being bursting during slow-wave sleep and tonically activated (with single action potentials) during waking and REM sleep (when TC neurons are relatively depolarized). Recently, however, it was proposed that LTS-type spike bursts can also occur during wakefulness, resulting in an increased impact of afferent signals on neocortical neurons (see following text). To evaluate this hypothesis, we will examine the data claiming the presence of such bursts during waking.

Recapitulating then: LTS spike busts are preceded by a period of neuronal silence >50 ms. Because spikes within TC-cell bursts have a short interspike interval, near 3 ms (Domich et al. 1986), the second action potential is typically diminished (e.g., Fig. 2*I*), due to partial inactivation of Na^+ channels. To avoid confusion with brisk firing of single action potentials, bona fide LTS-type bursts have been illustrated with original action potentials, using extracellular recordings of thalamic neurons in human studies of various pathologies (Jeanmonod et al. 1996; Lenz et al. 1998). Generally, the presence of spike bursts during waking is claimed on the basis of data depicted at low temporal resolution, digitalized action

potentials, or scatterplots of interspike intervals (e.g., Fanselow et al. 2001; Ramcharan et al. 2000), which cannot document the progressively decreasing interspike intervals during the bursts and/or the diminished amplitude of the second spike. Recent intracellular recordings from lateral geniculate (LG) slices proposed that corticothalamic synaptic drive promotes LTS-type high-frequency bursting in LG neurons (Wolfart et al. 2005). Most of those neurons displayed "bursts" with two action potentials. Surprisingly, the amplitude of the second spike increased compared with the first spike (see Fig. 5*A* in that study), which is never the case with LTS spike bursts. Such spike-doublets are frequent during thalamic activation, but they cannot be termed high frequency (only 1 interval occurs), nor can they be ascribed to a mechanism similar to that of LTS bursts.

Moreover, thalamic modeling by P. Rhodes (personal communication) indicates that in relay cells, with dendritic excitatory/inhibitory background, plus somatic inhibitory background, no short bursts occur spontaneously. Modeling spontaneous responses with somatic background only (Wolfart et al. 2005) is not accurate because excitatory conductance is almost exclusively dendritic in TC neurons. In Rhode's model, doublets (but not high-frequency bursts) may be generated by 200 nS of coincident excitatory conductance impinging on proximal (<35 μm) dendrites but without the characteristic afterhyperpolarizing potential (AHP) that follow the LTS burst.

Distinct features of LTS bursts have been described in some intralaminar and higher-order TC neurons, compared with neurons recorded from first-order (relay) nuclei. Thus some TC cells in the central lateral (rostral intralaminar) nucleus of cat display unusually high (900–1000 Hz) intraburst frequencies (partly due to lack of the AHP) and much shorter refractory period of the LTS (60–70 ms), whereas other TC neurons have a refractory period of 170–200 ms (Steriade et al. 1993a). Also some neurons recorded from the higher-order lateral posterior nucleus, which display clustered firing to depolarizing current steps, also fire spike clusters after the LTS burst activated by depolarization from a steady hyperpolarized state; those TC neurons have an AHP much shorter (~16 ms) than that of regularly spiking neurons (~57 ms) from the same nucleus (Li et al. 2003).

As first described in naturally sleeping cats, GABAergic RE neurons fire an LTS-type burst that is essentially different from that of TC neurons as first described in naturally sleeping cats (Domich et al. 1986; Steriade et al. 1986). Distinct from the short (5–25 ms) and high-frequency (250–400 Hz) spike bursts of TC neurons, RE neurons discharge much longer spike bursts, with a peculiar pattern comprising an initial progressive decrease in interspike interval (accelerando) followed by a progressively increasing duration of intervals (decelerando) (Fig. 3*A*). This pattern characterizes not only spontaneous bursting in RE neurons but also their responses to sensory stimuli (Hartings et al. 2003).

The acceleration is due to the slower rate activation of the current underlying the LTS (I_T), thus the current will peak later in RE than in TC cells, whereas the deceleration is probably due to the slow inactivation of the I_T in RE neurons (Huguenard and Prince 1992). This describes the core of the spike burst, which lasts for 50–100 ms and is often completed by a long-lasting tail of tonic firing that can last for hundreds of milliseconds (Fig. 3, *B* and *C*). This core is mediated by an LTS, whereas the tonic tail appears at a membrane potential positive to −75 mV, increases with further depolarization (Contreras and Steriade 1996), and is mediated by a persistent Na^+ current, $I_{Na(p)}$ (Kim and McCormick 1998). The most effective input for eliciting LTS bursts in RE neurons is the corticothalamic one (Golshani et al. 2001; Liu and Jones 1999), which excites dendrites of RE cells. The dendritic location of I_T in RE neurons (Destexhe et al. 1996) is consistent with the graded nature of the LTS in these cells, which depends on the distal dendritic localization of T channels coupled with the

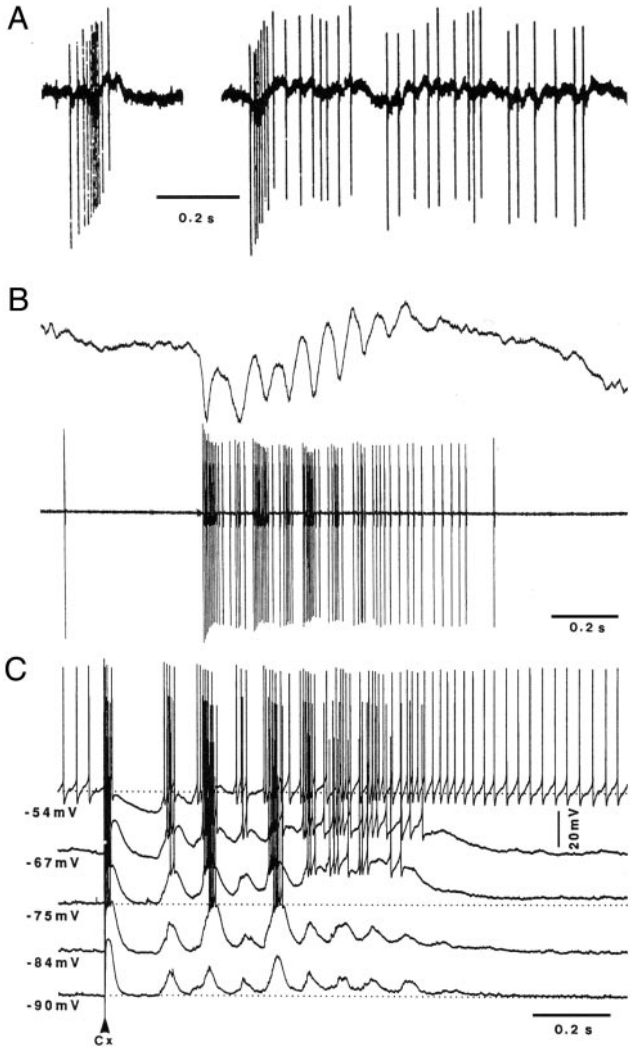

FIG. 3. Peculiar features of LTS spike bursts in thalamic reticular (RE) neurons. All 3 neurons (*A–C*) recordings from cat RE nucleus. *A*: neuron recorded from rostral RE neuron, deafferented from the remaining thalamus. Note that the core of the burst is characterized by acceleration followed by deceleration (*left*); at right, core of the burst followed by tonic firing. *B*: recording of RE neuron, simultaneous with a spindle sequence recorded from the depth of cortical motor area 4. *C*: voltage dependency of spindle oscillation in intracellularly recorded rostral RE neuron. Dotted lines in the 1st, 2nd, and 3rd sweeps tentatively indicate the different membrane potentials from which the depolarizing plateau developed. From a depolarized level (−54 mV) to a hyperpolarized one (−75 mV), there was a significant increase in the amplitude of both individual waves that constitute the spindle sequence as well as the depolarizing plateau. Further hyperpolarization progressively decreased the size of both individual waves and depolarizing envelopes. Modified from Steriade et al. (1987, *A*), unpublished data (*B*), and modified from Contreras and Steriade (1995, *C*).

constant synaptic bombardment of dendritic arbors mainly from corticothalamic network activity (Contreras et al. 1993).

In vitro (Llinás and Geijo-Barrientos 1988) and in vivo (Contreras et al. 1993) studies revealed presumably dendritic-generated Na^+ spikes that could be triggered by intracellular current injection, by activation of excitatory inputs, or by depolarizing waves of spindle oscillations. The dendritic spikes in RE neurons trigger LTSs and produce depolarization in the soma and distal dendrites. The generation of LTS reduces the apparent membrane resistance of RE neurons in a cyclical manner, by ≤80% for 20–30 ms. This is due to TC inputs during spindle oscillations and from neocortical neurons that arrive out of phase and generate a state of increased synaptic background (Fuentealba and Steriade 2005). Compared with the effects corticothalamic projections exert on TC neurons, where dendritic currents generate high-frequency rhythms (Luo and Perkel 1999; Pedroarena and Llinás 1997; Rhodes and Llinás 2005), the cortically elicited activation of RE-cell dendrites produces low-frequency sleep oscillations (Contreras and Steriade 1996).

Local-circuit GABAergic neurons represent 20–30% of the neuronal population in virtually all thalamic nuclei of cats and primates but, with the exception of the LG nucleus, are negligible in other dorsal thalamic nuclei of rodents. Initially, their bursting behavior was observed only inconsistently in slices from LG nucleus of cat and rat, leading to the conclusion that A-type K^+ current opposed I_T (McCormick and Pape 1988; Pape and McCormick 1995). Subsequent studies of morphologically identified interneurons, using shunt reducing whole cell patching (Staley et al. 1992), have demonstrated LTS bursts. LTS bursts can also be elicited by optic tract stimulation (Zhu et al. 1999a,b). The LTS bursts of interneurons differ from those of TC neurons; they have a relatively longer duration and lower intraburst frequency similar to the LTS bursts of RE neurons.

Dependence of LTS bursting activity on behavioral states of vigilance

The initial intracellular studies performed in vitro and in anesthetized animals, revealed the mechanisms underlying the spontaneous firing patterns of extracellularly recorded TC neurons during natural states of vigilance. Tonic firing was recorded during brain-activated states of waking and REM sleep, and rhythmic bursting was recorded during slow-wave sleep (Glenn and Steriade 1982).

It should be emphasized that there are two prerequisites to evaluating the presence of particular firing features in TC-cells during natural states of vigilance: intracellular recordings are needed to determine the membrane potential, and recordings must be made in both naturally awake and sleeping preparations (Steriade 2001a). Only two intracellular studies of thalamic neurons have been performed in nonanesthetized animals. One focused on sleep-related changes in the membrane potential of LG neurons and described hyperpolarization of these cells during slow-wave sleep, which were associated with the appearance of "slow spikes" (Hirsch et al. 1983) The hyperpolarization that was seen during slow-wave sleep suggested that spontaneously occurring LTS bursting is confined to this stage of sleep because I_T is inactivated during brain-active states (waking and REM sleep) associated with membrane depolarization. A more recent intracellular study analyzed the firing properties of intralaminar and higher-order (pulvinar and lateral posterior) neurons in conscious, awake cats (Woody et al. 2003). They found that only 3 of 272 cells displayed LTS bursting after application of hyperpolarizing current pulses in wakeful cats. To exclude that injury reduced the incidence of LTS firing, LTS bursting was also seen in those neurons that had a membrane potential negative to −55 mV and an action potential >60 mV. Based on their findings, the authors discarded the possibility that bursting is the normal firing mode of TC neurons during waking (Woody et al. 2003).

In the absence of more information from intracellular recordings in nonanesthetized animals, data from studies using extracellular recordings during natural waking and sleep states may also be useful. With chronic extracellular recordings of cat LG neurons, it was concluded that "during wakefulness, <1% of action potentials were associated with bursting" (similarly to the values reported by Woody et al. 2003), and the authors found a "negative relationship between attention and bursting" (Weyand et al. 2001). An extracellular study on monkey LG neurons similarly reported that, during waking, the mean value of bursting was ~1.5%, whereas it was ~22% during sleep in magnocellular cells (Ramcharan et al. 2000). A study on ventroposterior neurons depicted two types of neurons, one displaying no spike burst during waking and the other firing just one spike burst throughout the entire illustrated epoch of waking (Swadlow and Gusev 2001). In most extracellular studies, spikes are digitized and depicted at low speed, which makes it difficult to assess the pattern of bona fide "LTS" spike-bursts. Some of these studies have illustrated LTS bursts in a schematic form to strengthen the hypothesis that the analyzed spike bursts were generated by a mechanism similar to that revealed intracellularly.

Thalamic RE neurons also show spontaneous tonic firing during waking, with no spike-bursts, and LTS-type bursts during early and late phases of slow-wave sleep (Steriade et al. 1986).

In summary, the available data show that LTS bursts are a rare occurrence in waking (≈1% of action potentials in background activity), whereas they appear during the hyperpolarized state of TC and RE neurons during slow-wave sleep. The case of REM sleep is complicated by the occurrence of ponto-geniculo-occipital (PGO) waves. During activated epochs without phasic events (REMs and related PGO potentials) TC neurons are tonically depolarized and fire single action potentials, whereas synchronized output of mesopontine cholinergic neurons that generate PGO waves in thalamic nuclei may induce LTS bursting as postinhibitory rebound. This has not yet been demonstrated in naturally sleeping animals, but in acute experiments the intracellular PGO response of LG cells starts with a depolarizing potential (0.2–0.3 s) that is interrupted by a short-lasting (50–60 ms) hyperpolarization accompanied by an increase in membrane conductance (Hu et al. 1989). Because GABAergic RE neurons do not fire in response to brain stem volleys, the source for the PGO-related inhibitory postsynaptic potentials (IPSPs) in TC cells is the pool of local interneurons. Similar REMs-related active inhibitory, Cl^--dependent potentials, produced by local inhibitory (fast-spiking) neurons, have been described in neocortical neurons during natural sleep (Timofeev et al. 2001).

The negligible percentage of bursting cells observed during waking is also the result of muscarinic-mediated depolarization of TC neurons during this state by brain stem-thalamic projections (Curró Dossi et al. 1991), which leads to inactivation of I_T. The increased firing rate of glutamatergic corticothalamic neurons during waking (Steriade 1978) is another factor that accounts for the virtual absence of bursting during waking. Indeed, activation of either muscarinic or metabotropic glutamate receptors, by modulatory inputs from the brain stem core or from the neocortex, strongly attenuates the Ca^{2+}-mediated LTS in LG slices (Zhan et al. 2000). The switching of firing mode from burst to tonic has also been recorded in vivo using agonists of metabotropic glutamate receptors that mimic the corticothalamic input (Godwin et al. 1996; see also Sherman and Guillery 1996).

On a priori grounds, the evoked responses of TC neurons, especially those elicited by abnormally synchronous volleys, such as electrical stimuli applied to the optic tract, may be bursting during waking because such responses include IPSPs due to feedforward activation of local-circuit GABAergic neurons (Crunelli et al. 1988) and may give rise to postinhibitory rebound spike bursts. However, during waking, external signals recur rapidly and TC neurons would not be able to follow them in the bursting mode since the refractory period of LTS is quite long (170–200 ms). Actually, intracellularly recorded TC neurons cannot faithfully follow stimuli exceeding 5–7 Hz in the bursting mode (McCormick and Feeser 1990; see the grating drifted at 5 Hz used in the extracellular study by Ramcharan et al. 2000). Much faster responses would be required during scanning attention. As yet, there is no intracellular study of evoked responses in TC neurons during natural states of vigilance.

Data from extracellular studies generally show the low probability of LTS-type bursting in response to afferent volleys. The authors who addressed this topic did not present evidence for subtle variations in the behavioral/electrographic states of the animals. This is required since short periods of inattention or drowsiness, which can easily be detected by field potential (EEG) recordings, may be associated with changes in the membrane potential of TC neurons toward hyperpolarization and thus may favor bursting (see following text). We focus here on studies conducted during natural states of vigilance because the description of extracellularly recorded burst responses under different anesthetics (Alitto et al. 2005; Grubb and Thompson 2005), when TC are steadily hyperpolarized, cannot solve the issue of bursts' dependency on distinctly different levels of vigilance.

Most extracellular studies on bursting responses have been conducted in the LG nucleus, although it "is an atypical thalamic nucleus in this regard" (Ramcharan et al. 2000). When comparison was made between LG or other first-order thalamic relay nuclei and higher-order nuclei (such as the pulvinar nucleus), the extent of bursting was greater in the latter during waking (Ramcharan et al. 2005). This result, with extracellular recordings in macaque monkeys, is at variance with the extremely low percentage (~1%) of intracellularly recorded pulvinar TC cells displaying LTSs (elicited by hyperpolarizing current pulses) during waking in conscious cats (Wood et al. 2003).

Guido and Weyand (1995) provided evidence about the behavioral state of the animal while being in the bursting versus tonic firing mode. The probability of spike bursts during any second of visual fixation was 0.09, quite low, which reflected the depolarization of TC cells during wakefulness when the LTS conductance is inactivated. Interestingly, the "burst discharges occurred primarily during the first cycle of stimulation, " probably when the animal may have been somewhat inattentive. "As subsequent cycles of the grating passed through the cell's receptive field, the response shifted from a burst to a tonic firing pattern. " The authors interpreted these data correctly by assuming that "bursting occurs because of possible lapses of behavioral quiescence and membrane hyperpolarization."

Far from being epiphenomena of the prolonged periods of hyperpolarization during slow-wave sleep, the spontaneously occurring spike-bursts of TC neurons play an important role in synaptic plasticity at thalamic and neocortical levels. This is achieved during the rhythmic occurrence of spike bursts as during sleep spindles (7–14 Hz), and has been investigated both in vitro (Castro-Alamancos and Connors 1996a,b) and in vivo (Steriade and Timofeev 2003; Steriade et al. 1998). In essence, thalamically evoked cortical responses grow in size with successive rhythmic stimuli and self-sustained activity occurs with the same shape and frequency as that of responses during the prior period of stimulation. The augmenting responses evoked by rhythmic thalamic stimulation are characterized in cortical neurons by an increase in the secondary depolarization at the expense of the primary excitatory postsynaptic potential (EPSP). The secondary depolarization in neocortical neurons follows by 3 ms the postinhibitory spike burst in simultaneously recorded TC neurons (Steriade et al. 1998). This correlation with a very different type of global functional state further distances the LTS bursts from having a true functional role in the waking condition.

Indeed, sleep spindles may lead to consolidation of memory traces acquired during the waking state. This hypothesis is supported by human studies demonstrating that the overnight improvement of discrimination tasks requires steps in early slow-wave sleep stages when spindles prevail (Stickgold et al. 2000). After training on a declarative learning task, the density of human sleep spindles is significantly higher compared with the nonlearning control task (Gais et al. 2002). The conclusion was drawn that early part of night sleep favors retention of declarative memories, whereas the late part of sleep favors retention of procedural memories (Plihal and Born 1997).

The existence of spontaneous LTS rhythmicity during sleep has been questioned at the level of the LG nucleus, but unambiguous rhythmic bursting was found in the somatosensory thalamus (Ramcharan et al. 2000). The explanation for the presence of fewer rhythmic spike bursting in the LG is the high level of activity of retino-thalamic neurons, which maintain TC cells in a relatively depolarized state. Indeed, rhythmic activity of LG neurons is greatly enhanced when retinal neurons are silenced (Nuñez et al. 1992). Rhythmic spike bursts, within spindle frequency, occur simultaneously in multiple units of the dorsal thalamus (Steriade et al. 1977).

The possible significance of spike bursts evoked by sensory stimuli or volleys applied to prethalamic pathways can only be related to waking because during slow-wave sleep (especially during spindle oscillations) TC neurons are hyperpolarized, have an increased membrane conductance, and are not responsive to signals from the outside world. Initially it was proposed

that spike bursts evoked by photic stimulation might be beneficial for scanning attention (Guido et al. 1992), but that study was conducted under anesthesia when cognitive processes are suspended. While the tonic firing that characterizes the attentive wakeful state is better for signal analysis, it may be argued that burst firing occurring during periods of inattention or somnolence may better support signal detection and generates enhanced cortical responses (Lisman 1997; Swadlow and Gusev 2001), thus serving as a "wake-up call" (Ramcharan et al. 2000; Sherman 1996). This word usage indicates that the investigators know that the animal was not awake (drowsiness) at the time of the stimulus and that spike bursts were, by definition, not generated during the normal waking state (Steriade 2001b). Once novel stimuli generating spike bursts are detected during low levels of vigilance (drowsiness, somnolence), then TC cells switch their firing mode from bursting to tonic discharges (Guido and Weyand 1995), which permits the visual system to analyze the scene more faithfully (Sherman and Guillery 1996). The higher propensity of bursting responses in higher-order thalamic nuclei (Li et al. 2003; Ramcharan et al. 2005), as well as in nonlemniscal neurons of the medial geniculate nucleus (He and Hu 2002), may be important in that TC neurons in those nuclei project preferentially to superficial cortical layers, where they activate apical dendrites of layer 5 neurons (Thomson 2000). Thus the consequent feedback drive to the thalamus serves to maintain a high level of activity in the thalamo-cortico-thalamic loop.

Thalamocortical dysrhythmia syndrome

As stated in the preceding text, one of the most dramatic network modulations that the brain can support is that which generates the transitions from wakefulness to sleep and vice versa. This event involves a truly astronomical number of neurons and yet may take a very short time to occur as the state transitions from tonic gamma band-based cognition to the mindless burst mode. These two conditions, characterized by global slow coherence in sleep and the nimbleness of cognition with its punctate ever-changing temporal binding, exclude each other under normal conditions.

The basic question at hand is: What happens if a set of neurons in the thalamus displays low rhythmicity in an otherwise awake brain state? And, how long can this frequency mismatch last?

It has been known for a long time that the brain can engender abnormal coherent states that can last for a short or a relatively long time, such as in the case of *status epilepticus*. In addition, other forms of abnormal stable coherent grouping have been observed. In such cases, a dysrhythmic state in a portion of the thalamocortical system is "stuck" in spindle-like activity, whereas the rest of the system remains in the usual waking state. As reviewed in the following text, this dysrhythmic state actually occurs both in humans and in other animals.

The basic hypothesis is that such dysrhythmia is generated by membrane hyperpolarization or its functional equivalent (T-type Ca^{2+} channel deinactivation) in the affected thalamus. The proposed answers to the questions posed in the preceding text have been the presence of disfacilitation (Contreras et al. 1996) or deafferentation (as occurs in somatosensory or auditory input damage) or protracted inhibition (due to excessive inhibitory input from globus pallidus or the RE nucleus via abnormal slow cortical oscillations). Another possible mechanism is the genetic or pharmacological disruption of voltage gated calcium channels in thalamic neurons (Vitko et al. 2005).

In animals with contusive spinal cord injury, low-frequency thalamocortical dysrhythmia (TCD)-type oscillatory activity and phantom pain (allodinia) has been reported after thalamic deafferentation (Gerke et al. 2003). Similarly, molecular interventions that enhance low-frequency thalamic rhythmicity have been shown to produce conditions such as petit mal epilepsy in rats (Song et al. 2004; Talley et al. 2000; Tsakiridou et al. 1995; Zang et al. 2002).

As expected from these findings, reduction of T channels excitability by pharmacological means results in a reduction of such dysrhythmic phenomena (Coulter et al. 1990; Leresche et al. 1998). Furthermore, mutations that delete T-channel expression also prevent the generation of petit mal (Kim et al. 2001) and produce functional phenotypes with markedly reduced sleep behavior (Lee et al. 2004). The latter is a clear case in point that underlines the close relationship among specific ionic channel activity, associated rhythms, and different states of consciousness.

Recent studies have indicated that TCDs are encountered in disorders such as Parkinson's disease, petit mal epilepsy, and other afflictions grouped under the term "thalamocortical dysrhythmia syndrome" (Llinás et al. 1999) or TCDS.

The first example of a TCDS was recognized early in neurology and named petit mal epilepsy to differentiate it from grand mal epilepsy where tonico-clonic generalized seizures were generated. Also recognized quite early was the fact that tremor in patients with Parkinson's disease was related to the thalamus because surgical thalamectomy could alleviate this malady. More recently, both of these maladies have been associated with low-frequency thalamic oscillations that have been recorded in man (Jeanmonod et al. 1996; Schnitzler and Gross 2005).

A more general concept of TCDS was elaborated following results from MEG studies and direct thalamic recordings (Jeanmonod et al. 2001; Llinás et al. 1999) in humans (Fig. 4). This condition was characterized by having both negative and positive symptoms.

The localization of the low-frequency oscillations is thought to determine the negative symptoms. The positive symptoms are thought to be generated by a persistent abnormal gamma band frequency, an "edge effect" probably due to lateral disinhibition resulting from asymmetrical inhibitory interneuronal activity at cortical level (Llinás et al. 2005). This may be equated to the positive and negative symptoms that occur in migraine, where areas of blindness (scotoma) are often surrounded by bright halos.

This view is based on MEG and EEG studies that demonstrate a maintained abnormal coherence between high and low frequencies, an event not observed in normal individuals. This measurement provides an important clue to the pathogenesis of dysrhythmias. In normal control subjects, correlation of spectral power yields well-defined results indicating that low and high frequencies are not temporally coherent. Indeed, low and high frequencies are normally not coherent because they represent different thalamocortical functional states. It is, therefore reasonable to expect that if a portion of the thalamus is continuously hyperpolarized, i.e., "disconnected" by over-inhibition or deafferentation, ensued ongoing rhythmic LTS

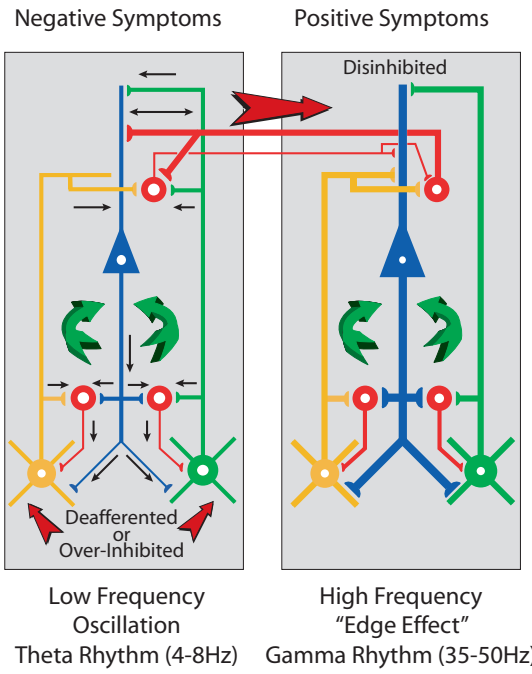

FIG. 4. Proposed thalamocortical circuits dynamics. Two thalamocortical systems are shown. The specific pathway (yellow, left of each panel) activates layer IV pyramidal cells (blue) and inhibitory interneurons (red) producing cortical oscillations by direct activation and feed-forward inhibition. Collaterals of this projection produce thalamic feedback inhibition through the reticular nucleus (red at thalamic level). The return cortico-thalamic pathway (circular arrow on the left) from layer V and VI pyramidal cells (blue) reenters this oscillatory loop to specific and reticular thalamic nuclei. The nonspecific thalamocortical pathway (green, right of each panel) projects to the most superficial layer of the cortex and gives collaterals to the reticular nucleus. Layer V and VI pyramidal cells (blue) return the oscillation to the nonspecific and reticular thalamic nuclei, establishing a second resonant loop (circular arrow on the right). The conjunction of the specific and nonspecific loops is proposed to generate temporal coherence. During thalamo-cortical dysrhythmia, protracted hyperpolarization of thalamic cells increases low-frequency neuronal oscillations. Either disfacilitation, as occurs after deafferentation or excess inhibition caused by pallidal over-activity (as in Parkinson's disease), hyperpolarizes the cells sufficiently to deinactivate T-type calcium channels and increase thalamic oscillations at theta (4–8 Hz) range. Such oscillations can entrain thalamocortical loops and generate increased coherence in affected brain regions (*left*). At the cortical level, low-frequency activation of intracortical inhibitory neurons (middle red arrow) can reduce lateral inhibitory drive and result in high-frequency, phase-locked coherent activation of neighboring cortical modules, described here as the edge effect (*right*) (modified from Llinás et al. 2005).

burst activity would be present. Such maintained activity would recruit cortical feedback firing. In consequence, an abnormal low frequency oscillatory attractor would form and a large, almost invariant, oscillatory state would exist.

Thus coherence between theta and the beta/gamma frequencies (13–40 Hz), as well as an increase in the amplitude of theta power, were found not only in Parkinson's patients but also in a wide range of neurological and psychiatric conditions (Jeanmonod et al. 2001, 2003; Llinás et al. 1999; Spencer el al 2004.). In studying these patients, it was recognized, as first described by John Hughlings Jackson, that they presented with both negative and positive symptoms (Hughlings-Jackson 1931). For example, Parkinson patients are paralyzed but show tremor, deaf patients cannot hear but may have terrible buzzing in their ears. In dysrhythmia patients, positive symptoms are thought to be generated by aberrant gamma band activity that is activated internally out of context (Llinás et al. 2005). This proposal suggests that dysrhythmia of particular cortical regions underlies the generation of corresponding symptoms. Thus neurogenic pain would reflect aberrant activation of the insular and other nociceptive cortices (secondary somatosensory and cingulate cortices) and possibly the posterior parietal and primary somatosensory cortices. Tinnitus would follow improper activation of meso-and neocortical auditory and associative temporal areas. Tremor would result from dysfunction of lateral motor and premotor cortex, whereas the anterior supplementary motor area is proposed to be dysrhythmic in Parkinsonian akinesia. Prefrontal medial, orbitofrontal, and temporopolar meso- and neocortical areas could be dysrhythmic in depression, obsessive-compulsive disorder, and psychosis (Jeanmonod et al. 2005).

While the exact extent of such dysrhythmia symptoms has to be explored in detail, one of the most promising avenues for further definition is the conjunction of molecular biology and genetics with electrophysiology and behavioral studies. Thus clear directions into future research are provided by pharmacological or surgical interventions that modify thalamocortical rhythms and ameliorate symptoms of petit mal epilepsy or central pain (allodinia) for example.

More fundamental to any specific neuro/psychiatric condition, is the fact that such abnormal states are mere modifications of the circuit dynamics that generate and support our cognitive experience. Ultimately the study of thalamocortical dynamics, we believe, is the cornerstone for a scientific definition of the category of which cognition is a member. Perhaps from such knowledge we may begin to achieve a glimmer of understanding into the nature of the human condition in all its majesty and misery.

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