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Published in final edited form as:
Nat Rev Neurosci. 2018 February ; 19(2): 107–118. doi:10.1038/nrn.2017.151.

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Vincenzo Crunelli[#1,2,*], **Magor L. Lőrincz**[#3], **William M. Connelly**[#4], **Francois David**[5], **Stuart W. Hughes**[6], **Régis C. Lambert**[7], **Nathalie Leresche**[7], and **Adam C. Errington**[8,*]

[1]Department of Physiology and Biochemistry, University of Malta, Msida, Malta

[2]Neuroscience Division, School of Bioscience, Cardiff University, Cardiff, UK

[3]Research Group for Cellular and Network Neurophysiology of the Hungarian Academy of Sciences, Department of Physiology, Anatomy, and Neuroscience, University of Szeged, Szeged, Hungary

[4]Eccles Institute of Neuroscience, John Curtin School of Medical Research, Australian National University, Canberra, Australia

[5]Lyon Neuroscience Research Center, CNRS UMR 5292- INSERM U1028-Université Claude Bernard, Lyon, France

[*]Correspondence: vincenzo.crunelli@um.edu.mt; erringtonac@cardiff.ac.uk.

Author Contributions

Corresponding Authors Contributions:

Vincenzo Crunelli
Substantial contribution to discussion of content
Writing
Review/Editing of manuscript before and after submission

Adam (C) Errington
Substantial contribution to discussion of content
Writing
Review/Editing of manuscript before submission

Contributing Author Contributions:

Magor (L) Lorincz
Researching data for article
Substantial contribution to discussion of content
Review/Editing of manuscript before submission

William (M) Connelly
Substantial contribution to discussion of content
Review/Editing of manuscript before submission

Francois David
Substantial contribution to discussion of content
Review/Editing of manuscript before submission

Stuart (W) Hughes
Substantial contribution to discussion of content
Review/Editing of manuscript before submission

Regis (C) Lambert
Substantial contribution to discussion of content
Review/Editing of manuscript before submission

Nathalie Leresche
Substantial contribution to discussion of content
Review/Editing of manuscript before submission

Competing Interests Statement Stuart W. Hughes is an employee of and holder of stocks in Vertex Pharmaceuticals. All other authors declare no Competing Financial Interests.

Europe PMC Funders Author Manuscripts

[6]Vertex Pharmaceuticals, Oxford, UK

[7]Sorbonne Universités, UPMC Univ. Paris 06, INSERM, CNRS, Neurosciences Paris Seine - Institut de Biologie Paris Seine (NPS - IBPS), Paris, France

[8]Neuroscience and Mental Health Research Institute, School of Medicine, Cardiff University, Cardiff, UK

[#] These authors contributed equally to this work.

Abstract

During inattentive wakefulness and non-rapid eye movement (NREM) sleep, the neocortex and thalamus cooperatively engage in rhythmic activities that are exquisitely reflected in the electroencephalogram as distinctive rhythms spanning a range of frequencies from <1 Hz slow waves to 13 Hz alpha waves. In the thalamus, these diverse activities emerge through the interaction of cell-intrinsic mechanisms and local and long-range synaptic inputs. One crucial feature, however, unifies thalamic oscillations of different frequencies: repetitive burst firing driven by voltage-dependent Ca^{2+} spikes. Recent evidence reveals that thalamic Ca^{2+} spikes are inextricably linked to global somatodendritic Ca^{2+} transients and are essential for several forms of thalamic plasticity. Thus, we here propose herein that alongside their rhythm-regulation function, thalamic oscillations of low-vigilance states have a plasticity function that, through modifications of synaptic strength and cellular excitability in local neuronal assemblies, can shape ongoing oscillations during inattention and NREM sleep and may potentially reconfigure thalamic networks for faithful information processing during attentive wakefulness.

From the moment we enter a state of relaxed, inattentive wakefulness through to the deepest stages of non-rapid eye movement (NREM) sleep, the human electroencephalogram (EEG) expresses a range of distinctive waves, progressively increasing in amplitude and decreasing in frequency, the most prominent of which are the alpha rhythm, sleep spindles, delta waves and slow waves1 (Fig. 1, left column). The emergence of these EEG rhythms is reliant upon finely tuned interactions between neocortical and thalamic neuronal assemblies, with strong modulation from many subcortical regions, including the brainstem and hypothalamus2,3. Although in the thalamus these low-vigilance state-dependent activities are generated by diverse cellular, synaptic and network mechanisms, intracellular recordings from thalamocortical (TC) and nucleus reticularis thalami (NRT) neurons highlight a critical common feature: the rhythmic occurrence of action potential bursts driven by voltage-dependent Ca^{2+} spikes4–10 (FIG. 1, middle and right columns, FIG.2). During sleep spindles, delta and slow waves of NREM sleep, these action potential bursts have high intraburst frequencies (100-500 Hz) in both TC and NRT neurons and are driven, following somewhat short periods of membrane hyperpolarization, by a Ca^{2+} spike reliant on the opening of low-voltage-gated T-type Ca^{2+} channels (T-VGCCs)11. This Ca^{2+} spike is commonly known as the low-threshold spike (LTS)12,13 (BOX 1; FIG. 2). During alpha waves of relaxed, inattentive wakefulness and theta waves of light NREM sleep, action potential bursts in TC neurons have a notably lower frequency (50-70 Hz) and are driven by high-threshold Ca^{2} spikes (HTSs) (BOX 1) that likely involve both T-VGCCs and high voltage-gated L-type Ca^{2+} channels (L-VGCCs)10 (FIG. 1, middle column, FIG. 2). The

near ubiquitous presence of LTSs and HTSs in TC and NRT neurons during low-vigilance states raises the question of why individual thalamic neurons are paradoxically engaged in the energetically expensive generation of rhythmic burst firing14 during periods of attentional and behavioural inactivity that are classically associated with energy preservation.

Here, we provide an up-to-date synopsis of the roles of LTSs and HTSs in thalamic oscillations of low-vigilance states and then appraise recent evidence regarding the cellular mechanism of thalamic LTS generation and the inextricable link between LTSs, T-VGCCs and global somatodendritic Ca^{2+} signalling in TC and NRT neurons. Finally, we review the crucial involvement of rhythmic LTSs at frequencies relevant to low-vigilance state oscillations in several forms of thalamic cellular and synaptic plasticity. These recent insights lead us to propose that, alongside their role in providing an essential contribution to the full expression of the corresponding EEG rhythm (which hereafter we refer to as the rhythm-regulation function), thalamic oscillations of low-vigilance states, through their dependence on global Ca^{2+} spikes, have a plasticity function that can modify synaptic strength and intrinsic cellular excitability in thalamic networks to stabilize and control ongoing oscillations and potentially contribute to optimal information processing during attentive wakefulness.

LTS and HTS role in EEG rhythms

In the nearly 90 years since the first description of a physiologically relevant rhythm in the human EEG15, considerable effort has been directed towards gaining a deep understanding of the mechanisms and physiological significance of EEG waves. The complex picture that has emerged reveals that although the source of the EEG signals resides within neocortical supragranular layers, the rhythm generators of different EEG waves are found within both the neocortex and thalamus (FIG. 2). In this section, we briefly review the current state of knowledge regarding the neocortical and thalamic rhythm generators of delta, slow, spindle, alpha and theta waves with emphasis on the key role of rhythmic burst firing of thalamic neurons (for detailed mechanisms of low-vigilance state oscillations, see REFS. 11,16–20).

Delta waves (0.5-4Hz)

Under standard conditions, neocortical slices do not expresses delta oscillations. However, pharmacological modifications that reinstate the modulatory neurotransmitter tone found *in vivo* during deep NREM sleep can produce oscillations at delta frequency in slices of primary and association cortices, which are mainly driven by powerful reciprocal excitation of layer five intrinsically bursting neurons21,22.

TC neurons of first-order, higher-order and intralaminar thalamic nuclei, as well as NRT neurons, can all exhibit relatively short periods of delta oscillations *in vivo* (usually a few cycles), whereas sustained delta oscillations are consistently observed in decorticated animals23,24. In contrast to the neocortex, delta oscillations in thalamic neurons occur via cell-intrinsic mechanisms. Specifically, the dynamic interaction of T-VGCCs with hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in TC neurons4,20,25 and Ca^{2+}-activated K^+ currents in NRT neurons26 forms the pacemaker mechanism that

enables individual thalamic neurons to elicit LTS-bursts at delta frequency (FIG. 1). Consequently, although no study has, as yet, directly investigated the relative contribution of the neocortex and thalamus to EEG delta waves of natural sleep, the presence of delta frequency generators in both brain regions suggests that the neocortex and thalamus have a role in producing this EEG rhythm (FIG. 2).

Slow (< 1 Hz) waves

Together with delta waves, EEG waves of stage N3 of NREM sleep contain slow (< 1 Hz) waves27 that reflect the synchronous, rhythmically alternating depolarized UP states and hyperpolarized Down states observed in almost all neocortical and thalamic neurons so far investigated *in vivo*5,6,28–31 and *in vitro*9,22,32–35, termed slow (< 1 Hz) oscillations5 (FIG. 1, middle and right columns). Despite the long-standing view that these oscillations are generated by intracortical mechanisms and are imposed upon a passive thalamus (reviewed in REF. 36), it has now been conclusively demonstrated both in naturally sleeping and anesthetized animals that the full expression of sleep slow waves in the EEG requires active thalamic participation30,37. Thus, whereas both the neocortex and thalamus in isolation have different generators of slow oscillations (see below) (FIG. 2), the cooperation between these brain regions is essential to generate slow (<1 Hz) waves in the EEG during stage N3 of natural NREM sleep.

When synaptic transmission is blocked, only a small number of neocortical neurons exhibit slow (< 1 Hz) oscillations *in vitro*21,22,38. Consequently, this activity in neocortical networks is primarily generated by the interaction between synaptic excitation and inhibition22,32. By contrast, in the TC neurons of sensory, motor and intralaminar thalamic nuclei, slow (<1 Hz) oscillations are generated by a cell-intrinsic mechanism that requires the finely tuned interplay between the leak K^+ current, the T-VGCC window current ($I_{Twindow}$), the Ca^{2+}-activated non-selective cation current (I_{CAN}) and the HCN current9,11,17,39. A similar mechanism drives slow (< 1 Hz) oscillations in NRT neurons except for the additional requirement of Na^+- and Ca^{2+}-activated K^+ currents34. Importantly, owing to the critical voltage-dependence of $I_{Twindow}$11,17,39, slow (< 1 Hz) oscillations in individual TC and NRT neurons can be easily transformed into delta oscillations (and vice-versa) by altering the membrane potential and hence the magnitude of $I_{Twindow}$9,33,34 (figures 1,2,6-8 in REF. 34). Notably, periods of delta oscillations can be observed during the DOWN states of slow (< 1 Hz) oscillations in TC and NRT neurons both *in vivo* and *in vitro*5,6,9,34 (referred to as delta waves nested within slow waves) (FIG. 1, middle and right column), thus contributing to the concurrent expression of these two waves in the EEG during stage N3 of natural sleep.

Thalamic LTS bursts have numerous important involvements in slow (< 1 Hz) oscillations. First, in both TC and NRT neurons the transitions from the DOWN state to the UP state are always marked *in vitro*, and very often *in vivo*, by the occurrence of an LTS burst5,6,9,30,33,34 (FIGS.. 1, 2). Second, as indicated earlier, LTS bursts at delta frequency can be present during the DOWN state of slow (< 1 Hz) oscillations in both TC and NRT neurons5,6,9,34 (FIG. 1, middle and right column). Third, LTS bursts at spindle frequency are observed both during the UP states and the UP-to-DOWN state transitions of slow (< 1

Hz) oscillations in single NRT neurons6,28,34 (FIG. 1, right column), reflecting the presence of spindles in the corresponding states of sleep slow waves in the EEG40,41.

Sleep spindles (7-14 Hz)

Originally suggested by Morison and Bassett (1945)42, a thalamic generator for sleep spindles was conclusively demonstrated by studies in the mid-to-late 198043,44. In subsequent years, *in vitro* experiments showed that the LTS-driven, mutual synaptic interaction between excitatory TC and inhibitory NRT neurons is the generator of sleep spindles7,8 (FIG. 2). Both *in vivo*43–46 and *in vitro*7,8, an LTS is not present at each cycle of the spindle wave in TC neurons, whereas individual NRT neurons can fire an LTS at each cycle (FIG. 1, middle and right column, FIG. 2). The neocortex is not equipped with spindle wave-generating networks; thus, elimination of the thalamic input to the neocortex abolishes spindles in the EEG during natural sleep43,44,46. However, the neocortical feedback to TC and NRT neurons provides essential contributions to some sleep spindle properties47,45,48.

Alpha (8-13 Hz) and theta (4-7 Hz) waves

Alpha waves are present in the EEG during relaxed inattentive wakefulness, that is, in the behavioural state that falls between fully attentive wakefulness and stage N1 of NREM sleep1,27 (FIG. 1, left column) and also during attentive perception49,50. The mechanisms underlying the alpha waves of these two behavioural states might be different, and here we will restrict the discussion to those occurring during inattentive wakefulness. Similarly, we will discuss the theta waves that are present in the EEG of humans and higher mammals during stage N1 of NREM sleep1,27 (FIG. 1, left column) and not those generated during fully awake conditions51, which have different underlying mechanisms.

Although they occur during very different behavioural states, alpha waves of inattentive wakefulness and theta waves of N1 NREM sleep share a similar mechanism in the thalamus. As shown *in vitro* and *in vivo*10, both waves are driven by a subset of gap junction-linked TC neurons10,52 that generate HTSs phase-locked to each cycle of the corresponding EEG rhythm (BOX 1; FIG.1, middle column; FIG. 2). This HTS-burst-based rhythm entrains the firing of local thalamic interneurons and other non-HTS-bursting TC neurons, giving rise to a thalamic output at alpha or theta frequency, depending on the behavioural state53. Notably, periods of alpha waves supported at the cellular level by HTS burst firing are occasionally present during the UP states of slow (< 1 Hz) oscillations in TC neurons in *vitro*9,10,33 and *in vivo*54 (FIG. 1, middle column). From a functional perspective, inhibition of HTSs and HTS bursts within a small (< 1 mm^3) area of lamina A of the dorsal lateral geniculate nucleus (LGN) in freely moving cats markedly, selectively and reversibly decreases alpha waves in the surrounding thalamic territory and in the EEG recorded from the primary visual cortex by 90% and 75%, respectively53. NRT neurons do not exhibit HTSs or HT bursts and the firing of the vast majority (90%) of these neurons is not correlated to the EEG alpha rhythm in freely behaving cats53.

Alpha-wave-generating intrinsic and network mechanisms, mostly involving layer five neurons, have been described in the neocortex *in vitro*55,56 though no *in vivo* study has conclusively shown whether these cortical generators play an essential role in the alpha

rhythm of relaxed wakefulness. On the other hand, many studies *in vivo* provide indirect support for a cortical involvement in classical EEG alpha waves57,58. Thus, whereas the precise nature of neocortical alpha-generating networks is at present not clear, it is reasonable to suggest that the alpha and theta waves that characterize the EEG of relaxed inattentive wakefulness and N1 NREM sleep, respectively, are strongly, though not exclusively, driven by the thalamic HTS-burst-generating mechanism described above (FIG. 2).

Rhythm-regulation function

As summarized in the previous section and illustrated in FIG. 2, intrinsic and network generators exist in both the neocortex and the thalamus, which are capable of locally eliciting oscillations at alpha, theta, spindle, slow and delta frequency. However, simply on the basis of the structurally widespread and functionally powerful reciprocal connections between the neocortex and thalamus it would be unreasonable to argue that the alpha, theta, spindle, slow and delta rhythms recorded in the EEG during low-vigilance states solely and uniquely rely on the rhythm-generating processes of one of these brain regions without any contribution from the other. Indeed, in all studies where this question has been directly addressed under unrestrained fully behaving conditions (see earlier discussion), the EEG rhythms of low-vigilance-states have been found to be either modulated, regulated or controlled (to various degrees and in different properties) by the neocortex and/or thalamus. Thus, as neocortical dynamics affects thalamically generated oscillations so does thalamic activity influence neocortically generated waves, with these interactions facilitating and/or reinforcing the overall synchrony in large thalamic and cortical neuronal populations59. Notably, the extent of this rhythm-regulation function of thalamic low-vigilance state oscillations varies greatly among different EEG rhythms, ranging from the strong rhythm imposed on the neocortex by the thalamically generated sleep spindles to the more subtle thalamic modulation of slow oscillations recorded in the neocortex. Within this scenario, therefore, referring to some of these EEG rhythms as thalamic spindles or cortical slow oscillation is misleading unless appropriately qualified and has contributed to inaccurate views on their mechanisms.

Mechanisms of LTS generation

As illustrated in the previous sections, the importance of LTS bursts of TC and NRT neurons for low-vigilance-state oscillations has been known for several decades.

However, the precise site of generation of LTSs and the extent of their propagation through the somatodendritic tree of thalamic neurons have remained unclear. Early experiments in inferior olive neurons (another class of LTS-bursting neurons) proposed a somatic and/or perisomatic origin for LTSs60, aligning them with fast Na^+ action potentials that originate in the axon initial segment before spreading to the soma and dendrites61. By contrast, subsequent *in vitro* studies indicated that the majority of T-VGCCs underlying thalamic neuron LTSs are in the dendrites62–66, a finding seemingly incompatible with a perisomatic origin. Indeed, computational models demonstrated that thalamic LTS bursts can be most readily reproduced with T-VGCCs located in the dendrites67,68. Therefore, until recently, it

has generally been assumed that LTSs are locally initiated in thalamic neuron dendrites. However, *in vitro* experiments combining dendritic patch clamp recordings and 2-photon Ca^{2+} imaging from TC and NRT neurons with computational modelling have now invalidated this assumption. In fact, unlike the focal mechanisms (that is, initiation in a specific subcellular region) that underlie other all-or-none neuronal signals (for example, Na^+ action potentials, dendritic Ca^{2+} or NMDA spikes69,70), LTSs are generated by a unique global mechanism that requires depolarization of the whole cell and simultaneous widespread recruitment of spatially distributed T-VGCCs68 (FIG. 3). This is made possible by the specific electrotonic properties of TC and NRT neurons (BOX 2). Therefore, in thalamic neurons LTSs cannot be focally generated in dendrites and are unable to be spatially constrained to specific subcellular compartments, as is the case, for example, for dendritic Ca^{2+} spikes in cortical neurons69,70.

This mechanism inextricably links LTSs in thalamic neurons to synchronous, transient increases in intracellular Ca^{2+} concentration throughout the entire somatodendritic tree64,68. As such, whenever an LTS is recorded at the soma of TC and NRT neurons, it is also simultaneously present along their whole somatodendritic axis (FIG. 3a) and this process is accompanied by a transient and substantial increase in intracellular Ca^{2+} throughout the entire dendritic tree (FIG. 4). This whole cell LTS Ca^{2+} transient ($\Delta[Ca^{2+}]_{LTS}$) is mediated by T-VGCCs, with a contribution from L-VGCCs in TC neurons71 and voltage-gated R-type Ca^{2+} channels in NRT neurons72, but does not rely on dendritic backpropagating action potentials (bAPs), as demonstrated by its insensitivity to tetrodotoxin62,64,71. In fact, when TC and NRT neurons are depolarized (and thus T-VGCCs are mostly inactivated), action potentials backpropagate very inefficiently into the dendritic tree62,64,72,73 (FIG. 3b). As a result, bAP-evoked Ca^{2+} transients in thalamic neurons, unlike $\Delta[Ca^{2+}]_{LTS}$, are spatially restricted to the soma and proximal dendrites62,64,71,74 (FIG. 4b). Notably, $\Delta[Ca^{2+}]_{LTS}$ have now been demonstrated in TC neurons of the rat LGN, ventrobasal and posterior medial (PoM) nuclei64,67, cat medial geniculate body (MGB)74 and in mouse and rat NRT neurons62,75,76, highlighting their conservation in both glutamatergic and GABAergic neurons as well as in functionally different thalamic nuclei and across species. Owing to the known similarities in morphological and electrophysiological properties of TC neurons in limbic and intralaminar thalamic nuclei, it would seem unlikely that global $\Delta[Ca^{2+}]_{LTS}$ would not be present in these thalamic populations.

In summary, during low-vigilance states, where rhythmic LTSs predominate, burst firing of both TC and NRT neurons is associated with global somatodendritic intracellular Ca^{2+} signalling, whereas during attentive wakefulness, where tonic firing is more typical, Ca^{2+} signalling is spatially constrained, a feature with important consequences for thalamic function (see below).

$\Delta[Ca^{2+}]_{LTS}$ phase-locked to waves

In many neurons, when action potentials backpropagate into the dendrites, their interspike intervals are often considerably shorter than the time required for subsequent Ca^{2+} extrusion and/or buffering and as a consequence Ca^{2+} can accumulate progressively during spike

trains64,70. By contrast, the long refractory period of the LTS (determined by the inactivation and recovery from inactivation of T-VGCCs)77 relative to the decay time of individual $\Delta[Ca^{2+}]_{LTS}$ (determined by Ca^{2+} uptake by sarcoplasmic and endoplasmic reticulum Ca^{2+} ATPases64,74) prevents summation of $\Delta[Ca^{2+}]_{LTS}$ and substantial Ca^{2+} accumulation. Indeed, as it has been demonstrated directly in TC neurons of the cat MGB *in vitro*, rhythmic $\Delta[Ca^{2+}]_{LTS}$ are tightly phase-locked to LTS bursts of both delta and slow (< 1 Hz) membrane potential oscillations74 (FIG. 4c). Significantly, $\Delta[Ca^{2+}]_{LTS}$ have longer decay times during slow (< 1 Hz) oscillations than during delta oscillations74 (FIG. 4c), probably as a result of the activation of I_{CAN} and $I_{Twindow}$ during the former, lower frequency activity9,17,39. It is tempting, therefore, to speculate that $\Delta[Ca^{2+}]_{LTS}$ associated with oscillations of different frequencies may serve diverse roles in thalamic neurons, as we previously suggested36.

Although it is yet to be demonstrated, the requirement of LTSs in TC and NRT neurons for sleep spindle generation strongly suggests that rhythmic $\Delta[Ca^{2+}]_{LTS}$ should also occur during these oscillations. Because NRT neurons can fire LTS bursts at spindle frequency, it will be interesting to determine whether the main T-VGCC subtype ($Ca_V3.3$)77,78 and Ca^{2+} buffering and uptake processes of these GABAergic neurons permit Ca^{2+} oscillations during spindles or whether, unlike delta and slow (< 1 Hz) oscillations, Ca^{2+} will accumulate in NRT dendrites.

Unlike LTSs, the mechanism generating the HTSs that underlie alpha waves of inattentive wakefulness and theta waves of stage N1 sleep in TC neurons10,53 still remain somewhat elusive. Nevertheless, the partial contribution of T-VGCCs to HTSs10 (BOX 1; FIG. 2) indicates that they may share a mechanism similar to that of LTSs and require involvement of dendritic Ca^{2+} channels. Indeed, individual HTSs are associated with significant dendritic Ca^{2+} transients (A.E. and V.C., unpublished observations), although the somatodendritic membrane potential changes and Ca^{2+} signals that accompany HTSs at alpha and theta frequencies remain to be determined.

New function of thalamic oscillations

So far we have outlined the essential contribution of thalamic low-vigilance state oscillations to the full expression of these rhythms in the EEG (that is, their rhythm-regulation function) and the critical involvement of Ca^{2+} spike-dependent burst firing in these thalamic oscillations. The question then arises as to why these oscillations use the energetically more expensive LTSs (with accompanying $\Delta[Ca^{2+}]_{LTS}$) and HTSs and not single (or trains of) action potentials14 during behavioural states which are commonly associated with energy preservation. One answer might be that, compared with tonic action potentials, bursts provide a higher reliability of signal transmission79–82 as they are less sensitive to noise83, and more effectively trigger responses in some classes of neocortical neurons84–86, probably by selectively engaging the resonance properties of the postsynaptic cells87. However, recent studies (see next section) that have investigated the impact of rhythmic LTSs for synaptic and cellular plasticity in thalamic neurons suggest a different, though complementary, answer to this energy conundrum, which leads us to propose a novel plasticity function for thalamic oscillations of low-vigilance states. Note that whereas below

we exclusively discuss plasticity mechanisms elicited by rhythmic LTSs at frequencies relevant to low-vigilance state oscillations, isolated LTS-bursts do occur in TC neurons of sensory thalamic nuclei during attentive wakefulness79,88,89. Whether LTS-dependent plasticity may also occur in the thalamus during the latter behavioural state remains to be demonstrated.

LTS-dependent thalamic plasticity

Hebbian plasticity requires temporal association between presynaptic and postsynaptic activity to modify synaptic strength, and several Hebbian cellular learning processes that require bAPs have been identified that can improve or reduce synaptic effectiveness based on the timing between bAPs and postsynaptic potentials90. Similarly, a number of non-Hebbian learning rules that do not rely on temporal association of presynaptic and postsynaptic activity have also been described91. The weak bAPs of TC and NRT neurons62,73 (FIG. 3) cannot strongly depolarize the dendritic tree alone and are thus unlikely to be a reliable mechanism for induction of Hebbian synaptic plasticity in these neurons. By contrast, the global and substantial depolarization provided by the LTS and the associated somatodendritic $\Delta[Ca^{2+}]_{LTS}$ (FIGS. 3, 4) are strong candidates for mechanisms of plasticity in thalamic neurons, as indicated by the *in vitro* studies summarized below.

Inhibitory synaptic plasticity

GABAergic synapses (of presumed NRT origin) onto TC neurons of the PoM nucleus have been shown to undergo non-Hebbian long-term potentiation (iLTP)71 (FIG. 5a). This plasticity occurs via retrograde signalling by nitric oxide (NO) (whose production is stimulated by postsynaptic Ca^{2+} entry) to presynaptic NO-dependent guanylyl cyclase. This Ca^{2+}-dependent iLTP is reliant upon postsynaptic L-VGCCs (because it is abolished by the L-VGCC blocker nimodipine) and is induced by repetitive LTSs at slow oscillation frequency (0.1 Hz for 10 min) but not by tonic action potential firing. Interestingly, delivering LTSs at delta frequency at 1 or 5 Hz drastically reduces (by 60%) or fails to elicit iLTP, respectively. At first glance, a plasticity that requires L-VGCCs and occurs during LTS-bursting but not tonic firing seems counterintuitive. However, when considering the spatial distribution of GABAergic synapses across the TC neuron dendritic tree92, alongside the global mechanism of LTS generation68 and strong attenuation of bAPs in thalamic neurons62,73, the picture becomes clear. As such, whereas L-VGCCs are crucial for this form of iLTP at GABAergic synapses on TC neurons, they can be recruited only by the robust global membrane potential depolarization provided by T-VGCC-dependent LTSs (ΔV in FIG. 5a) and not by weakly depolarizing bAPs.

An LTS-dependent inhibitory long-term depression (iLTD) has been described at the NRT-to-TC neuron synapses in the ventrobasal nucleus93 (FIG. 5b). Unlike iLTP, which can be induced by postsynaptic LTSs without pairing to synaptic activity, iLTD requires coincident activation of synaptic input with rhythmic postsynaptic LTSs and is elicited using a short (70 sec) protocol that reproduces delta waves nested within slow (< 1 Hz) oscillations, that is, seven trains of LTSs, with each train containing four LTSs at delta frequency (1.6 Hz) and being delivered at 0.1 Hz (FIG. 1, middle column). Consequently, despite the LTS-

dependent induction of a global $\Delta[Ca^{2+}]_{LTS}$ in TC neurons and unlike iLTP, where all inhibitory synapses are potentiated, only synapses activated during the induction protocol undergo iLTD. Critically, iLTD, unlike iLTP, is not triggered by recruitment of high-voltage Ca^{2+} channels. In fact, even when evoked dendritic high-voltage Ca^{2+} transients match the amplitude and spatial extent of those observed during T-VGCC activation, iLTD is absent, suggesting a specific signalling pathway requiring T-VGCCs. Finally, this form of iLTD requires the Ca^{2+}-phosphatase calcineurin and is of both homosynaptic and heterosynaptic origin since it is gated by activation of metabotropic glutamate receptors of TC neurons via glutamate released from corticothalamic afferents.

Thus, two forms of plasticity exist at GABAergic NRT-TC synapses that can potentiate or depress them depending on TC neuron burst-firing frequency. In particular, because iLTP is preferentially elicited by rhythmic LTSs at 0.1 Hz whereas iLTD is elicited by LTSs at 1.6 Hz, it is possible that during sleep slow waves NRT-TC synapses may be strengthened by slow (< 1 Hz) oscillations and weakened by delta (0.5-4 Hz) waves nested within slow oscillations.

Excitatory synaptic plasticity

As well as plasticity at thalamic inhibitory synapses, excitatory synapses onto TC and NRT neurons have also been found to undergo LTS-dependent forms of LTP.

At the synapses of ventrobasal TC neurons onto NRT neurons, pairing presynaptic input with postsynaptic LTS bursts results in LTP94 (FIG. 5c). This plasticity requires glutamate receptors ionotropic NMDA 2B (GluN2B) receptor subunits and cannot be triggered if the postsynaptic depolarization is provided by Na^{+}-dependent firing without T-VGCC activation or if LTSs are supressed by genetic ablation of $Ca_V3.3$ channels. Moreover, the TC-NRT LTP is selectively evoked by postsynaptic LTS bursts at delta frequency (1 Hz for 3 or 6 min), providing further evidence for potential T-VGCC- and LTS-dependent thalamic plasticity during NREM sleep.

At the cortico-thalamic synapses on ventrobasal TC neurons, Hsu et al.95 have described LTP induction by LTS-bursts (at 0.167 Hz) but not by high frequency (125 Hz) tonic action potentials. The same group previously reported Hebbian NMDA-dependent LTP and non-Hebbian L-VGCC-dependent LTD selectively at cortico-thalamic but not lemniscal synapses on ventrobasal TC neurons96. Interestingly, both forms of plasticity require postsynaptic depolarization that, under physiological conditions, can be provided in thalamic neurons only by LTSs, and possibly HTSs, but not by bAPs68.

Electrical synapse plasticity

Rhythmic LTS burst firing elicited at delta frequency (2 Hz for 5 min) in either one or both of paired-recorded, connexin-36-coupled NRT neurons can trigger robust LTD of the gap-junction coupling strength97 (FIG. 5d). This gap-junction coupling LTD requires Ca^{2+} entry through voltage-gated channels98 but is insensitive to tetrodotoxin97, demonstrating that LTSs are capable of inducing gap-junction plasticity even in the absence of action potentials. On the other hand, although spike trains delivered from depolarized potentials also evoke gap-junction LTD, the magnitude is smaller (by 50%) than that induced by repetitive LTSs.

It is possible that the difference in LTD strength associated with each firing mode relates to the spatial distribution of gap junctions on NRT neuron dendrites99, that is, LTSs might modulate electrical synapses throughout the dendritic tree, whereas bAPs can affect only those relatively close to the soma.

Cell-intrinsic plasticity

Together with a role for plasticity at chemical and electrical thalamic synapses, LTSs can also induce short-lasting plasticity of intrinsic excitability in TC neurons. Rhythmic Ca^{2+} entry during repetitive LTSs at delta and/or spindle frequency (2 - 8 Hz for 5 sec) stimulates the release of cAMP which in turn causes increased activation of HCN channels100,101 (FIG. 5e). This effect outlasts the period of LTS-dependent cellular Ca^{2+} elevation, thus creating a form of short-term cellular plasticity that restrains LTS-burst generation in TC neurons and should help shaping thalamic spindle and delta oscillations and thus, in turn, the corresponding EEG rhythms.

The plasticity function

In the sections above, we have presented a framework by which thalamic oscillations of low-vigilance states, by virtue of their rhythmic LTS-dependent global somatodendritic depolarization and $\Delta[Ca^{2+}]_{LTS}$, can serve a plasticity function. A likely setting where this plasticity function may be operational is the homeostatic regulation of thalamic circuits during sleep. Homeostatic modification of synaptic strength is a common feature of current theories of sleep function102–104, suggesting downscaling of strength at particular synapses during sleep while preserving increased strength at synapses that had been strongly activated by novel features during the preceding period of wakefulness. Indeed, evidence in support of these views is starting to accumulate for neocortical synapses105–107. Like their neocortical counterparts, thalamic neurons receive continuous synaptic bombardment during wakefulness from peripheral, subcortical and cortical inputs. Consequently, modifications of intrathalamic synaptic strength may occur during wakefulness that could require rescaling during subsequent periods of inattention, and the previously described forms of intrathalamic plasticity associated with the rhythmic occurrence of LTSs during low-vigilance state oscillations offer different mechanisms for such homeostatic modifications in thalamic neuronal assemblies.

Moreover, the diverse induction rules for synaptic and intrinsic plasticity across thalamic cell types and synaptic connections that have been demonstrated for low-vigilance state oscillations suggest that another context where the plasticity function might be operating is the modulation of the very same ongoing oscillations. For example, GABAergic NRT-TC synapses may be either potentiated or depressed, depending on whether the postsynaptic cell is preferentially expressing LTSs at slow (<1 Hz) oscillations71 or nested delta waves93 frequency, respectively (FIG. 5a,b). This bidirectional plasticity may allow TC neuron slow oscillations to strengthen NRT-TC synapses, leading in turn to larger inhibitory postsynaptic potentials, more robust rebound LTS bursts after inhibition and improved propagation of spindles to the neocortical-hippocampal axis for active participation in memory processes. Subsequent periods of nested delta oscillations, as they occur during sleep slow waves, could

then rescale NRT-TC synapses to ensure continuous optimal transmission. Some of these thalamic plasticity mechanisms may be operative in the recently described essential and instructive role of delta and spindle waves in visual cortex plasticity108.

Concluding remarks

In summary, currently available evidence indicates that together with the well-accepted rhythm-regulation function, thalamic oscillations of relaxed wakefulness and NREM sleep can have a plasticity function that, by virtue of their rhythmic LTSs and associated global somatodendritic Ca^{2+} calcium transients, can modify the strength of excitatory and inhibitory synapses in local thalamic neuronal assemblies.

Clearly, in order to build a comprehensive picture of the proposed plasticity function of thalamic low-vigilance state oscillations, further investigations are needed. First, the specific type(s) of oscillations that trigger different forms of plasticity should be systematically assessed. Specifically, iLTP has been tested only at slow and delta but not spindle frequency71, iLTD has been studied at delta but not at other oscillation frequencies93, and the LTP at TC-NRT synapses94 and the LTD at the NRT-NRT electrical synapses97 have been investigated only with a delta frequency induction protocol. Second, to help understanding thalamic sensory processing and the increasingly recognized role of the thalamus in cognition109, how generalizable are these Ca^{2+} spike-dependent plasticity mechanisms across different thalamic nuclei? For example, iLTP has been described in the higher-order PoM nucleus but has not been investigated in first-order thalamic nuclei71 whereas iLTD has been demonstrated in the first-order ventrobasal nucleus but not in higher-order nuclei93. Moreover, are any of these (or any other) plasticity mechanisms occurring in motor, limbic and intralaminar thalamic nuclei? Third, how synapse-specific is the Ca^{2+}-spike induced plasticity within particular nuclei? For instance, it remains to be seen whether the iLTP in the PoM nucleus involves NRT afferents and/or other non-thalamic GABAergic inputs (zona incerta, anterior pretectal nucleus, basal forebrain, hypothalamus2,110). Furthermore, it may be possible that the parvalbumin-containing and somatostatin-containing subsets of NRT neurons111,112, which have different spatial distribution, physiological properties and targets112,113, experience different forms of plasticity. Fourth, plasticity should be tested by use of induction protocols that more faithfully reproduce the complex dynamics of natural low-vigilance state oscillations, that is, spindle waves nested within slow (< 1 Hz) oscillations, alpha waves occurring during slow oscillation UP states and so on. Importantly, would the longer somatodendritic Ca^{2+} signals of the slow (< 1 Hz) oscillation produce different synaptic or cell-intrinsic plasticity compared with the more rapid $\Delta[Ca^{2+}]_{LTS}$ of delta oscillations (FIG. 4c)? Undoubtedly, the most necessary, though technically demanding, challenge, however, will be to move beyond *in vitro* approaches and investigate the forms of thalamic plasticity induced by low-vigilance state oscillations under natural waking-sleeping conditions, thus identifying their behavioural consequences.

Acknowledgments

We thank Drs C. McCafferty, R. Bódizs and P. Halász for critical comments. Our work is supported by the Wellcome Trust (grant 91882 to VC), the European Union (grant ITN-2016/722053 to VC), the Hungarian Scientific Research Fund (grants NF105083, NN125601 and FK123831 to MLL), the Hungarian Brain Research

Program (grant KTIA_NAP_13-2-2014-0014 to MLL), the CNRS (grant LIA528 to VC, NL, RCL), and the Agence Nationale de la Recherche (grants ANR-06-Neuro-050-01 and ANR-09-MNPS-035-01 to NL, RCL). ACE is a Jane Hodge Foundation Senior Research Fellow.

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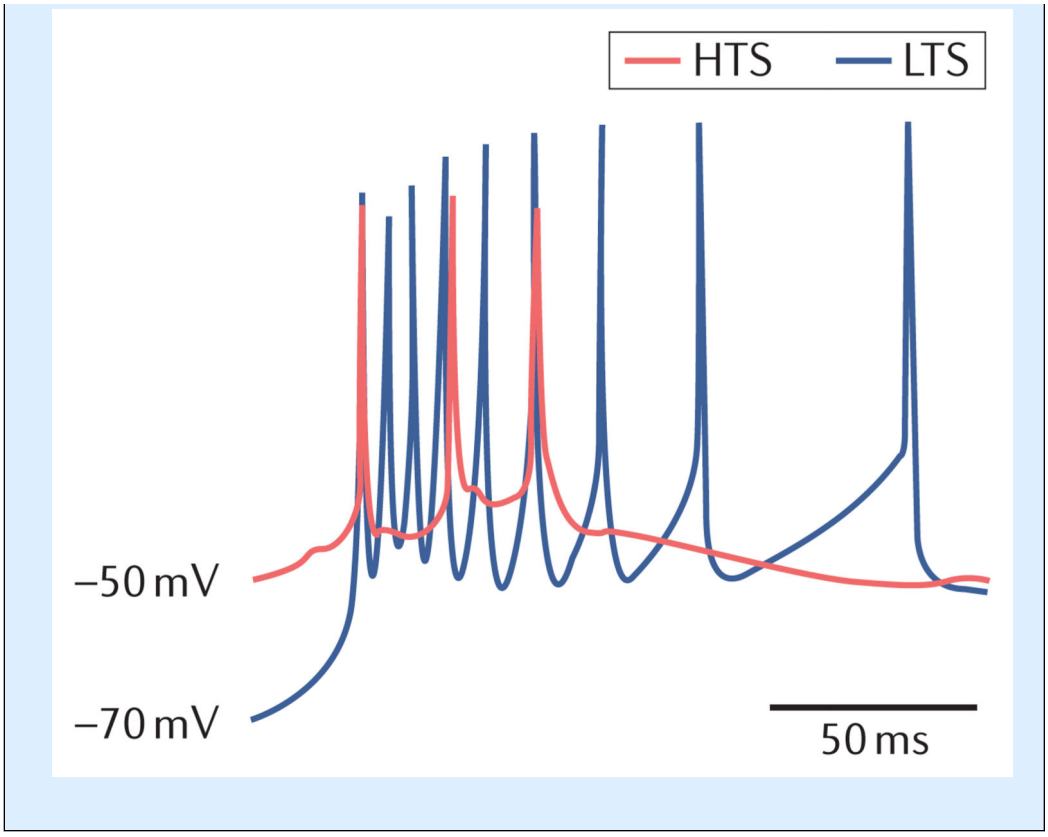
Box 1

The high-threshold spike

High-threshold spikes (HTSs) of thalamocortical (TC) neurons are small, brief depolarizations that occur at membrane potentials slightly more depolarized than tonic firing. They were originally identified with extracellular and intracellular recordings *in vitro* and extracellular recordings in freely moving cats10. HTSs are present in about 30% of TC neurons in visual, somatosensory and motor thalamic nuclei of mice, rats and cats10,16,52,53. In the dorsal lateral geniculate nucleus, HTSs are phase-locked to the thalamic local field potential (LFP) *in vitro* and to the alpha-frequency LFP recorded simultaneously in the primary visual cortex *in vivo* during relaxed wakefulness10. Although the voltage waveform of HTSs is entirely contained within membrane potentials >-55 mV, HTSs are generated by the opening of probably both T-type and L-type voltage-gated Ca^{2+} channels10. The burst of action potentials generated by an HTS, that is, the HTS-burst (figure, red), is markedly different from the burst elicited by a low-threshold spike (LTS, figure, blue), that is, the LTS burst, in that it has an intraburst frequency between 50 and 70 Hz (compared with the 100-400 Hz of an LTS burst), and a constant interspike interval10,16, that is, it lacks the characteristic *decelerando* pattern of LTS bursts in TC neurons. Notably, extracellularly recorded bursts of action potentials with features identical to those of HTS-bursts have been reported in motor thalamic nuclei of awake monkey114 and humans115.



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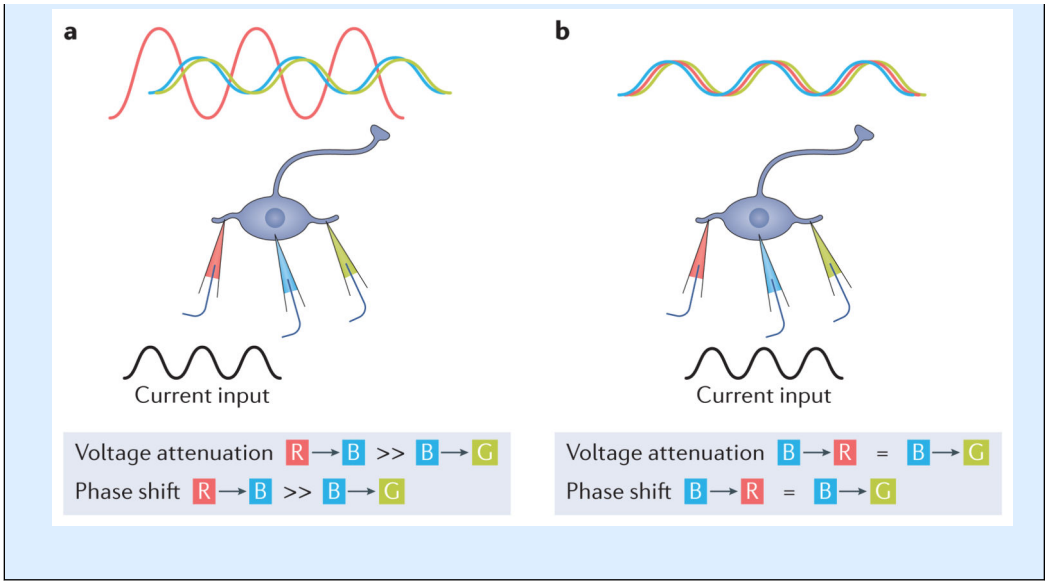
Box 2

The global low-threshold spike

Simultaneous activation of low-voltage-gated T-type Ca^{2+} channels (T-VGCCs) at spatially distant locations relies on the distinctive electrotonic properties of thalamic neurons. Dendrites are electrically distributed elements, and thus, when they receive input locally, membrane voltage gradients emerge between different points within the tree. At the opposing ends of a typical dendrite, the non-symmetric 'boundary conditions', represented by the large electrically 'leaky' soma and the thin, significantly less 'leaky' sealed dendritic tip, ensure that local membrane potential changes attenuate and shift in phase significantly more when they spread in the dendrite-to-soma direction (left diagram: red electrode to blue electrode) than in the opposite direction (a, blue electrode to green electrode). Consequently, most neurons appear somewhat electrically compact when viewed from the soma. Although first predicted in computational models, it has only recently been revealed using dendritic patch clamp recordings that this effect is particularly strong for thalamocortical (TC) ($L = 0.24\lambda$) and NRT ($L = 0.26\lambda$) neurons68. Thus, whereas their dendritic trees may be large in physical space, in electrotonic space they appear small. As a result, from the somatic viewpoint, TC and nucleus reticularis thalami (NRT) neurons behave almost as if they do not have dendrites at all and more like an isopotential sphere. Consequently, as the soma is depolarized by a synaptic input or experimentally through current injection (b, blue electrode), the membrane potential in the entire dendritic tree (b, red and green electrodes) follows with very little amplitude-attenuation or phase-shift between the somatic and dendritic voltage (at least at low frequencies). This permits coincident activation of T-VGCCs expressed throughout the dendritic tree which results in a global somatodendritic LTS and $\Delta[Ca^{2+}]_{LTS}$. Importantly, when the membrane potential is changing more rapidly than during an LTS, such as during action potentials, the membrane capacitance and axial resistance act as low-pass filters, leading to the significant attenuation of bAPs.



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Glossary

- **Thalamocortical neurons**: Glutamatergic thalamic neurons that project to the neocortex.
- **Nucleus reticularis thalami neurons**: GABAergic neurons of this thin, laterally located, thalamic nucleus that do not project to the neocortex.
- **Sleep spindles**: Oscillatory brain activity that constitutes an electroencephalogram (EEG) hallmark of non-rapid eye movement (NREM) sleep and consists of waxing-and-waning 7-14 Hz oscillations lasting a few seconds.
- **First-order.** A functional classification of thalamic nuclei based on their main driving input: subcortical or cortical. First-order nuclei relay a particular modality of peripheral or subcortical information to a primary cortical area.
- **Higher-order.** A functional classification of thalamic nuclei that relay information from layer five cortical neurons to other cortical areas and act like a hub in cortico-thalamo-cortical information pathways.
- **Intralaminar thalamic nuclei**. A collection of thalamic nuclei involved in specific cognitive and motor functions that plays a key role in the salience of stimuli of various modalities.
- **Cell-intrinsic mechanisms**: Electrical behavior of a neuron that results from its passive and voltage-dependent electrical properties without a contribution of the synaptic network.
- **UP states**: On the basis of their intrinsic properties and/or the influence of the synaptic network, some neurons transition between a depolarized potential, referred to as an UP state, and a hyperpolarized DOWN state.
- **DOWN states:** A state in which the neuronal membrane potential is hyperpolarized and transitions between this state and a depolarized UP state.
- **T-VGCC window current**: The small depolarizing tonic current that results from the fraction of T-type calcium channels that are open in a narrow membrane potential region around -60 mV.
- **Electrotonic properties**: The combined electrical properties of a neuron that alter the manner in which subthreshold voltage changes propagates throughout the axon and the dendritic tree.
- **Backpropagating action potentials (bAPs)**: The transient depolarization that occurs in the dendrites as a result of the generation of an action potential in the soma or axon initial segment.
- **Rescale:** Also known as synaptic rescaling; indicates the normalization of the strength of synaptic connections that had previously been either increased or decreased in response to (relatively long-term) changes in neuronal activity.

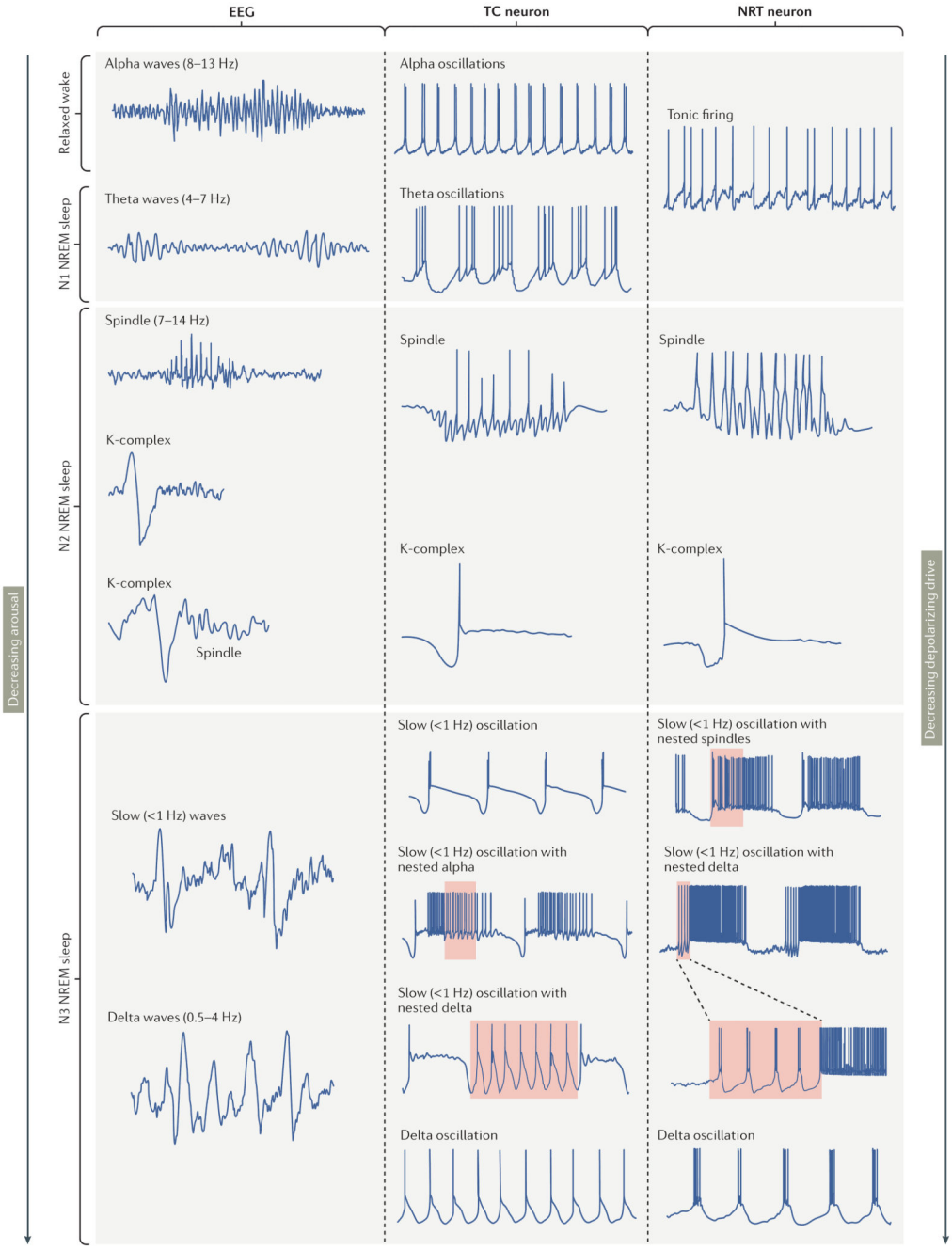

Figure 1. Cellular thalamic counterparts of electroencephalogram rhythms of relaxed wakefulness and non-rapid eye movement sleep.

Representative intracellular recordings from thalamocortical (TC) (middle column) and nucleus reticularis thalami (NRT) (right column) neurons depicting the membrane potential changes occurring in these neurons during the respective electroencephalogram (EEG) rhythms shown in the left column (N1-N3: non-rapid eye movement (NREM) sleep stages27). Sleep spindles can occur in isolation or following a K-complex. A K-complex in the EEG results from a single cycle of the slow (< 1 Hz) oscillations. In the TC neuron column, pink boxes highlight alpha and delta oscillations nested in the UP and DOWN state,

respectively, of slow (< 1 Hz) oscillations in N3. In the NRT neuron column, pink boxes highlight spindle waves in the UP state and delta oscillations in the DOWN state, respectively, of slow (< 1 Hz) oscillations in N3. NRT neurons do not express firing coherent with alpha and/or theta waves (wake state and N1). Action potentials in the traces depicted in the middle and right column have been truncated for clarity of illustration. Adapted with permission from Refs. 10,33,34,46,116–117.

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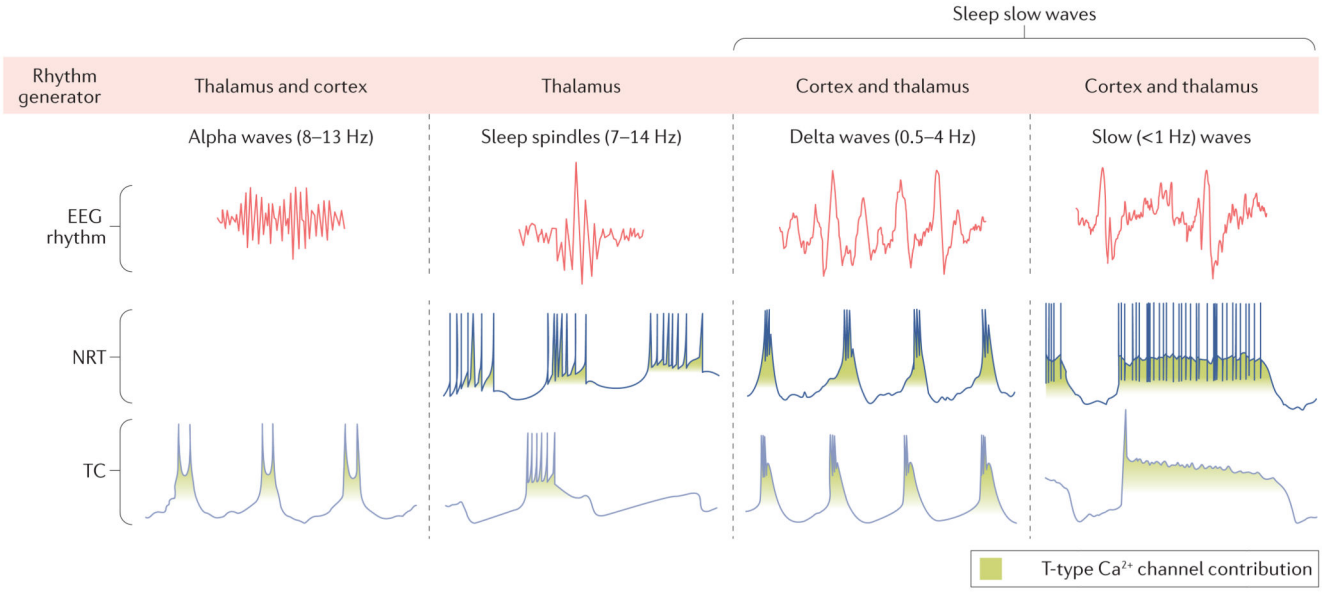

Figure 2. Contribution of T-type Ca^{2+} channels to low-vigilance state oscillations.

Schematic drawings of electroencephalogram (EEG) waves of low-vigilance states with indicated brain regions of their rhythm generator(s) (top row). Schematic drawings of membrane potential oscillations in thalamocortical (TC) (bottom row) and nucleus reticularis thalami (NRT) neurons (middle row) during different low-vigilance states, with shadowed areas highlighting the contribution of T-type voltage-gated Ca^{2+} channels in each activity. NRT neurons do not exhibit high-threshold spikes, and their firing is not correlated to the EEG alpha rhythm. In most traces, action potentials have been truncated for clarity of illustration.

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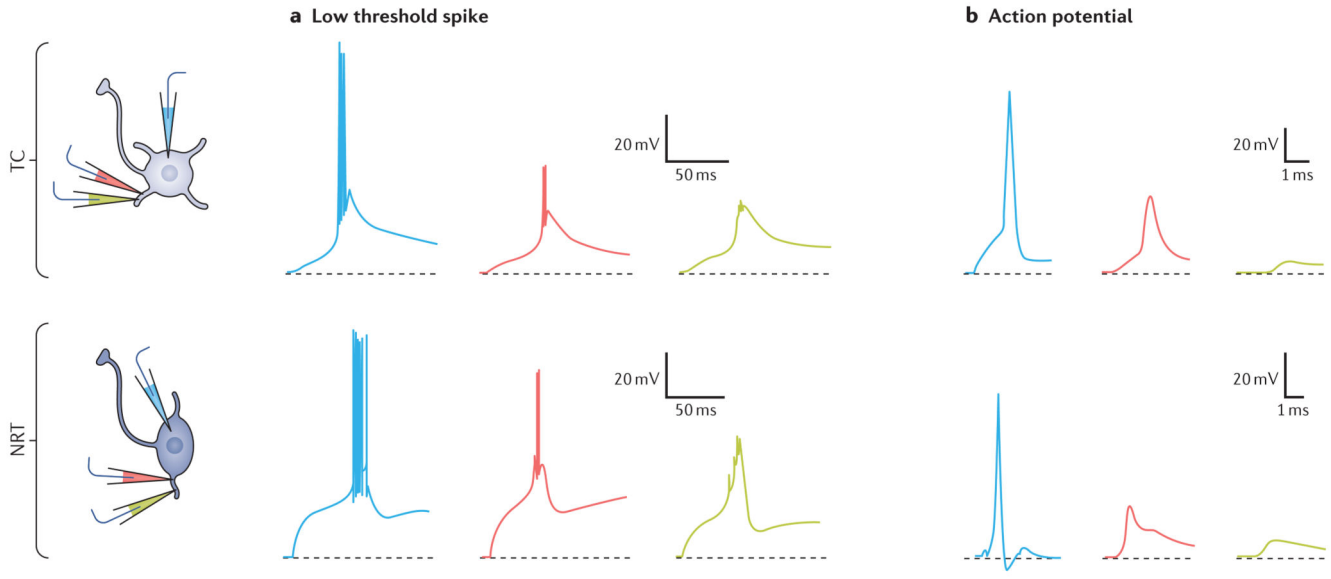

Figure 3. Low-threshold spikes and action potentials in thalamic neurons.

a) In both thalamocortical (TC) and nucleus reticular thalami (NRT) neurons, paired somatodendritic recordings reveal that the low-threshold spike (LTS) depolarizes the entire dendritic tree to the same degree as the soma, reflecting the global nature of its generation. The somatic (blue), proximal (red) and distal (green) dendritic recordings illustrate the similar amplitude of the LTS throughout the dendritic tree. b) In contrast, action potentials are markedly attenuated in both thalamic cell types as they propagate from the soma (blue) into the proximal (red) and distal (green) dendrites. This can also be observed for the action potentials in the LTS-driven bursts (a). A distance-dependent increase in the peak latency of the action potential recorded in the dendritic recordings reveals that they are focally generated in the perisomatic region. Adapted with permission from Ref. 68.

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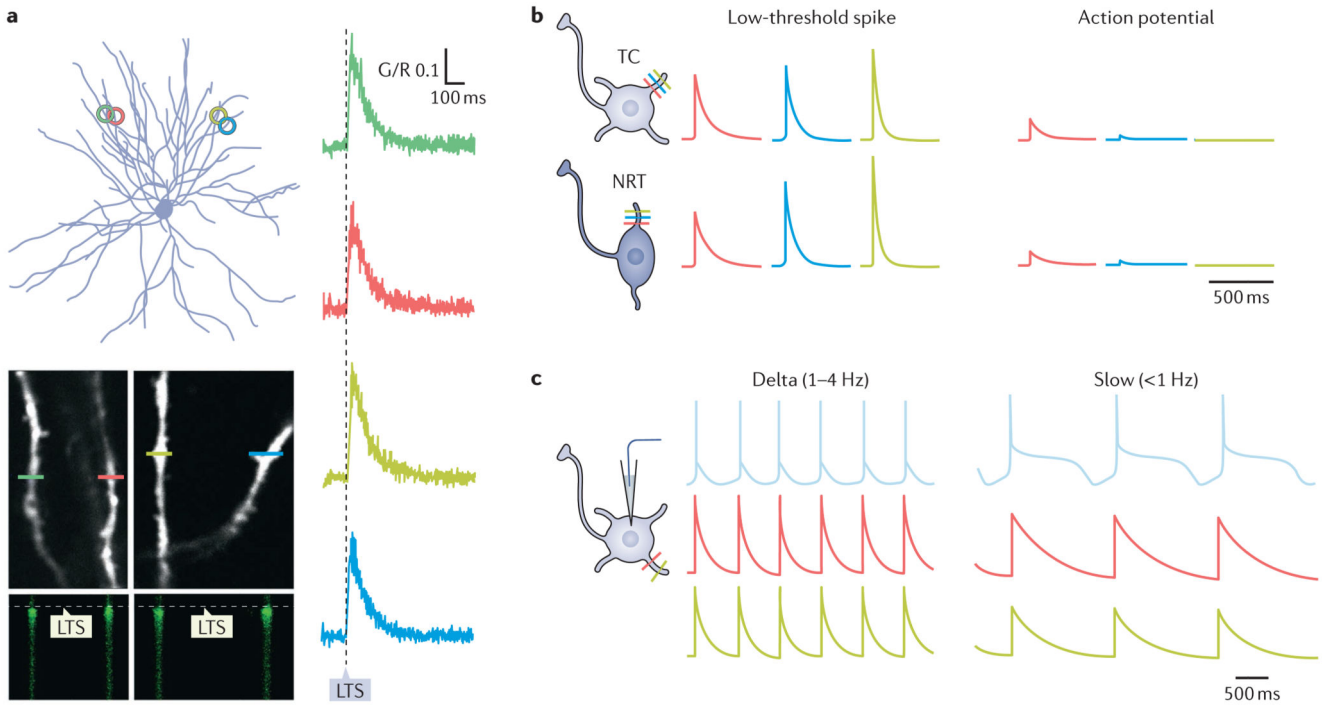

Figure 4. Ca^{2+} signalling in thalamic neurons during non-REM sleep oscillations.

a) Two-photon Ca^{2+} imaging of pairs of thalamocortical (TC) neuron dendrites (each originating from different primary dendrites as illustrated on the reconstructed cell) reveals that synchronous and remarkably similar Ca^{2+} transients occur at equivalent distances from the soma during low-threshold spikes (LTSs). b) Schematic illustration of the dendritic Ca^{2+} transients that occur in TC and nucleus reticularis thalami (NRT) neurons during LTSs and single action potentials. c) Schematic illustration of dendritic Ca^{2+} signalling in TC neurons during non-rapid eye movement sleep oscillations. Membrane potential oscillations at delta and slow (< 1 Hz) frequencies (light blue, top traces) in TC neurons are coupled to synchronous dendritic Ca^{2+} oscillations in proximal (red) and distal (green) dendrites. Notably, Ca^{2+} transients throughout the dendritic tree decay considerably more slowly during slow (< 1 Hz) versus delta oscillations. Adapted with permission from Refs. 64,74.

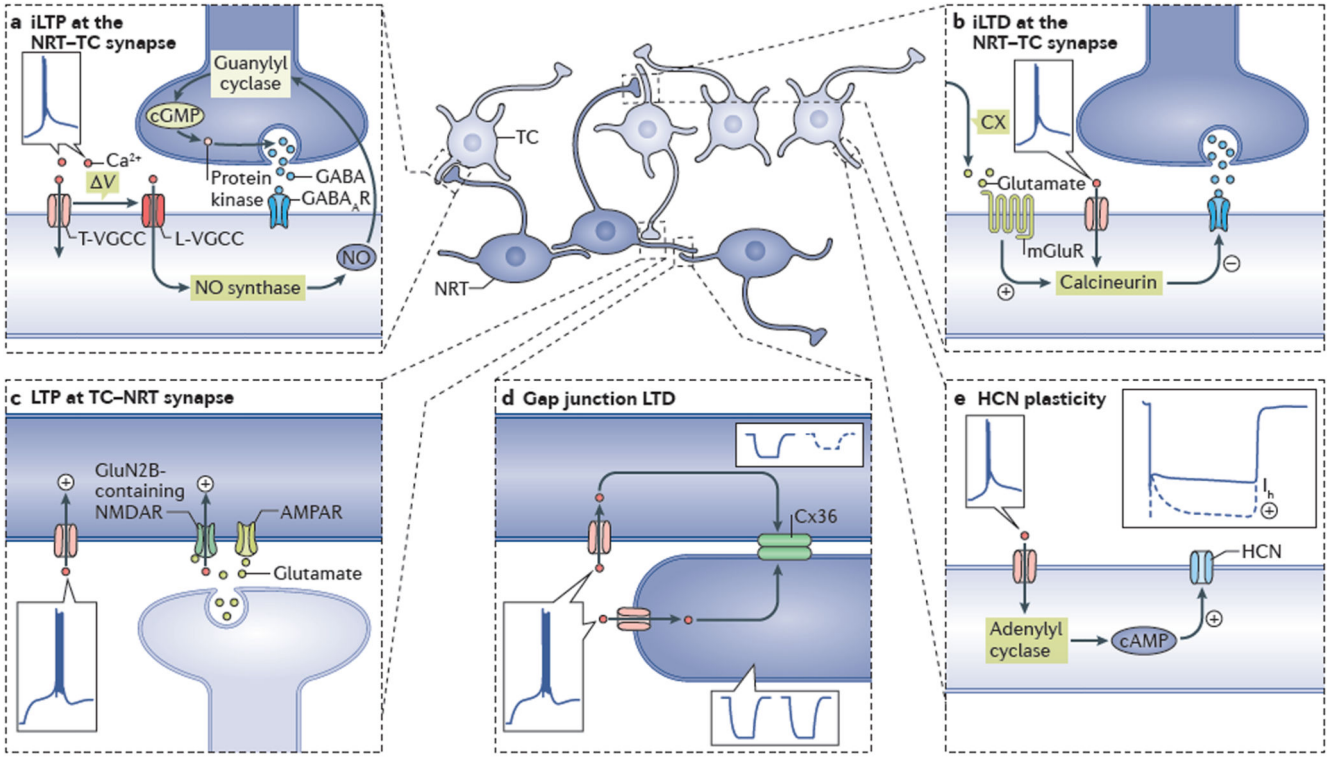

Figure 5. Low-threshold Ca^{2+} spike-dependent plasticity in thalamus.

Schematic drawings of the mechanisms of different forms of synaptic and cellular plasticity elicited by rhythmic low-threshold spikes (LTSs) (and associated Ca^{2+} transients) at frequencies relevant to oscillations of low vigilance states. a) Inhibitory long-term potentiation (iLTP) at GABAergic nucleus reticularis thalami (NRT)–thalamocortical (TC) neuron synapses. Note the low-voltage-gated T-type Ca^{2+} channels (T-VGCC)-elicited depolarization (ΔV) driving activation of high-voltage-gated L-type Ca^{2+} channels (L-VGCCs). b) Inhibitory long-term depression (iLTD) at GABAergic NRT-TC neuron synapses. Note the requirement for metabotropic glutamate receptor (mGluR) activation by glutamate released from cortical (CX) afferents. c) Excitatory long-term potentiation (LTP) at glutamatergic TC-NRT neuron synapses. d) Long-term depression (LTD) at electrical NRT-NRT neuron synapses. e) Cellular plasticity of intrinsic hyperpolarization-activated cyclic-nucleotide gated (HCN) channels in TC neurons lead to increased I_h ((+) in inset). AMPAR, glutamate receptor ionotropic AMPA; cGMP, cyclic GMP; Cx36, gap junction connexin 36; GluN2B, glutamate receptor ionotropic, NMDA 2B; NMDAR, glutamate receptor ionotropic NMDA 2A; NO, nitric oxide.

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