Dual function of thalamic low-vigilance state oscillations: rhythm-regulation and plasticity

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ABSTRACT

During inattentive wakefulness and non-REM sleep, neocortex and thalamus co-operatively engage in rhythmic activities that are exquisitely reflected in the EEG as distinctive rhythms spanning a range of frequencies, from <1 Hz slow waves to 13 Hz alpha waves. In 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 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 on-going oscillations during inattention and non-REM 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-REM sleep, the human 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 waves[1] (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 brain stem and hypothalamus[2,3]. Although in the thalamus these low-vigilance state-dependent activities are generated by diverse cellular, synaptic and network mechanisms, intracellular recordings from thalamocortical (TC) **[G]** and nucleus reticularis thalami (NRT) **[G]** neurons highlight a critical common feature: the rhythmic occurrence of action potential bursts driven by voltage-dependent Ca^{2+} spikes[4–10] (Figs. 1, middle and right columns, & 2). During sleep spindles **[G]**, delta and slow waves of non-REM sleep, these action potential bursts have high intra-burst frequencies (100-500 Hz) in both TC and NRT neurons and are driven, following relatively 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] (Fig. 2 & Box 1). During alpha waves of relaxed, inattentive wakefulness and theta waves of light non-REM 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] (Figs. 1, middle column, & 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 firing[14] 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 on-going 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 EEG[15], significant 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 generator(s) 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 and 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 re-instate the modulatory neurotransmitter tone found *in vivo* during deep non-REM sleep can produce oscillations at delta frequency in slices of primary and association cortices, which are mainly driven by powerful reciprocal excitation of layer 5 intrinsically bursting neurons[21,22].

TC neurons of first-order **[G]** , higher-order **[G]** and intralaminar thalamic nuclei **[G]**, 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 animals[23,24]. In contrast to the neocortex, delta oscillations in thalamic neurons occur via cell-intrinsic mechanisms **[G]**. Specifically, the dynamic interaction of T-VGCCs with hyperpolarization-activated cyclic-nucleotide gated (HCN) channels in TC neurons[4,20,25] and Ca^{2+}-activated K^+ currents in NRT neurons[26] forms the pacemaker mechanism that enables individual thalamic neurons to elicit LTS-bursts at delta frequency (Figs. 1, middle and right column, & 2). Consequently, although no study has, as yet, directly investigated the relative contribution of neocortex and thalamus to EEG delta waves of natural sleep, the presence of delta frequency-generators in both brain regions suggests that neocortex and thalamus might both have a role in producing this EEG rhythm (Fig. 2).

Slow (< 1 Hz) Waves. Together with delta waves, EEG slow waves of stage N3 of non-REM sleep also contain slow (< 1 Hz) waves[27] that reflect the synchronous, rhythmically alternating

depolarized "Up" **[G]** and hyperpolarized "Down" states **[G]** 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) oscillations[5] (Fig. 1, middle and right columns). Despite the long-standing view that these oscillations are generated by intracortical mechanisms and 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 participation[30,37]. Thus, whereas both neocortex and thalamus in isolation have different generators of slow oscillations (see below) (Fig. 2), the co-operation between these brain regions is essential to generate slow (<1 Hz) waves in the EEG during stage N3 of natural non-REM 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 inhibition[22,32]. In 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 ($I_{Twindow}$) **[G]**, the Ca^{2+} activated non-selective cation current (I_{CAN}) and the HCN current[9,11,17,39]. A similar mechanism drives slow (< 1 Hz) oscillations in NRT neurons except for the additional requirement of Na^+- and Ca^{2+}-activated K^+ currents[34]. Importantly, due 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] (cf. Figs. 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 Down-to-Up state are always marked *in vitro*, and very often *in vivo*, by the occurrence of an LTS-burst[5,6,9,30,33,34] (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 neurons[5,6,9,34] (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

neurons[6,28,34] (Fig. 1, right column), reflecting the presence of spindles in the corresponding states of sleep slow waves in the EEG[40,41].

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/late '80[43,44]. 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 spindles[7,8] (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 (Figs. 1, middle and right column, & 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 sleep[43,44,46]. However, the neocortical feedback to TC and NRT neurons provides essential contributions to some sleep spindle properties[47,45,48].

Alpha (8-13 Hz) and Theta (4-7 Hz) Waves. Alpha waves are present in the EEG during relaxed inattentive wakefulness, i.e. in the behavioural state that falls between fully attentive wakefulness and stage N1 of non-REM sleep[1,27] (Fig. 1, left column), and also during attentive perception[49,50]. 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 non-REM sleep[1,27] (Fig. 1, left column) and not those generated during fully awake conditions[51], which have different underlying mechanisms.

Although occurring during very different behavioural states, alpha waves of inattentive wakefulness and theta waves of N1 non-REM sleep share a similar mechanism in thalamus. As shown *in vitro* and *in vivo*[10], both waves are driven by a subset of gap junction-linked TC neurons[10,52] that generate HTSs phase-locked to each cycle of the corresponding EEG rhythm (Figs.1, middle column, & 2) (Box 1). 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 state[53]. Significantly, 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%,

respectively[53]. NRT neurons do not exhibit HTSs and HT-bursts and the firing of the vast majority (90%) of these neurons is not correlated to the EEG alpha rhythm in freely behaving cats[53].

Alpha wave-generating intrinsic and network mechanisms, mostly involving layer 5 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 waves[57,58]. 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 non-REM 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 neocortex and thalamus which are capable of locally eliciting oscillations at alpha and theta, spindle, slow and delta frequency. However, simply on the basis of the structurally widespread and functionally powerful reciprocal connections between 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 neocortex and/or thalamus. Thus, as neocortical dynamics affects thalamically-generated oscillations so does thalamic activity influence neocortically-generated waves, with these interactions facilitating/reinforcing the overall synchrony in large thalamic and cortical neuronal populations[59]. 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 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 LTSs[60], aligning them with fast Na^+-action potentials that originate in the axon initial segment before spreading to the soma and dendrites[61]. In contrast, subsequent *in vitro* studies indicated that the majority of T-VGCCs underlying thalamic neuron LTSs are in the dendrites[62-66], 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 dendrites[67,68]. 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 (i.e. initiation in a specific subcellular region) that underlie other all-or-none neuronal signals (e.g. Na^+-action potentials, dendritic Ca^{2+} or NMDA spikes[69,70]), LTSs are generated by a unique global mechanism that requires depolarization of the whole cell and simultaneous widespread recruitment of spatially distributed T-VGCCs[68] (Fig. 3a,b). This is made possible by the specific electrotonic **[G]** 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 neurons[69,70].

This mechanism inextricably links LTSs in thalamic neurons to synchronous, transient increases in intracellular Ca^{2+} concentration throughout the entire somatodendritic tree[64,68]. 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 neurons[71] and voltage-gated R-type Ca^{2+}

channels in NRT neurons[72], but does not rely on dendritic backpropagating action potentials **[G]** (bAPs), as demonstrated by its insensitivity to tetrodotoxin[62,64,71]. In fact, when TC and NRT neurons are depolarized (and thus T-VGCCs are mostly inactivated), action potentials backpropagate very inefficiently into the dendritic tree[62,64,72,73] (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 dendrites[62,64,71,74] (Fig. 4b). Significantly, $\Delta[Ca^{2+}]_{LTS}$ have now been demonstrated in TC neurons of the rat LGN, ventrobasal (VB) and posterior medial (PoM) nuclei[64,67], cat medial geniculate body (MGB)[74] and in mouse and rat NRT neurons[62,75,76], highlighting their conservation in both glutamatergic and GABAergic neurons as well as in functionally different thalamic nuclei and across species. Due to the known similarities in morphological and electrophysiological properties of TC neurons in limbic and intralaminar thalamic nuclei, it would seem unlikely that global $\Delta[Ca^{2+}]_{LTS}$ will 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/buffering and as a consequence Ca^{2+} can accumulate progressively during spike trains[64,70]. In 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 sarco/endoplasmic reticulum Ca^{2+} ATPases[64,74]) 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 oscillations[74] (Fig. 4c). Significantly, $\Delta[Ca^{2+}]_{LTS}$ during slow (< 1 Hz) oscillations have longer decay times than during delta oscillations[74] (Fig. 4c), probably as a result of the activation of I_{CAN} and $I_{Twindow}$ during the former, lower frequency activity[9,17,39]. It is tempting, therefore, to speculate

that $\Delta[Ca^{2+}]_{LTS}$ transients associated with oscillations of different frequencies may serve diverse roles in thalamic neurons, as we previously suggested[36].

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. Since 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/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(s) underlying the generation of the HTSs that underlie alpha waves of inattentive wakefulness and theta waves of stage N1 sleep in TC neurons[10,53] still remain somewhat elusive. Nevertheless, the partial contribution of T-VGCCs to HTSs[10] (Fig. 2) (Box 1) indicates that they may share a mechanism similar to LTSs and require involvement of dendritic Ca^{2+} channels. Indeed, individual HTSs are associated with significant dendritic Ca^{2+} transients (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 (i.e. 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 potentials[14] during behavioural states which are commonly associated with energy preservation. One answer might be that, compared to tonic action potentials, bursts provide a higher reliability of signal transmission[79–82] since they are less sensitive to noise[83], and more effectively trigger responses in some classes of neocortical neurons[84–86], probably by selectively engaging the resonance properties of the postsynaptic cells[87]. 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 are exclusively discussing

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 wakefulness[79,88,89]. Whether LTS-dependent plasticity may also occur in thalamus during the latter behavioural state remains to be demonstrated.

LTS-dependent thalamic plasticity

Hebbian plasticity requires temporal association between pre- and postsynaptic activity to modify synaptic strength, and several Hebbian cellular learning processes that require bAPs have been identified that can enhance or reduce synaptic efficacy based on the timing between bAPs and postsynaptic potentials[90]. Similarly, a number of non-Hebbian learning rules that do not rely on temporal association of pre- and postsynaptic activity have also been described[91]. The weak bAPs of TC and NRT neurons[62,73] (Fig. 3a,b) cannot alone strongly depolarize the dendritic tree and are thus unlikely to be a reliable mechanism for induction of Hebbian synaptic plasticity in these neurons. In 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 (since 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 (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 tree[92], alongside the global mechanism of LTS generation[68] and strong attenuation of bAPs in thalamic neurons[62,73], the picture becomes clear. As such, whereas L-VGCCs are crucial for this form of iLTP at GABAergic synapses on TC neurons, they can only be recruited by the robust global membrane potential depolarization provided by T-VGCC-dependent LTSs (ΔV in Fig. 5, panel a) 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 VB nucleus[93] (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, i.e. 7 trains of LTSs, with each train containing 4 LTSs at delta frequency (1.6 Hz) and being delivered at 0.1 Hz (cf. 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, since iLTP is preferentially elicited by rhythmic LTSs at 0.1 Hz whereas iLTD 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 VB TC neurons onto NRT neurons, pairing presynaptic input with postsynaptic LTS-bursts results in LTP[94] (Fig. 5c). This plasticity requires GluN2B NMDA 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 non-REM sleep.

At the cortico-thalamic synapses on VB 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 VB TC neurons[96]. Interestingly, both forms of plasticity require postsynaptic depolarization which, under physiological conditions, can only be provided in thalamic neurons by LTSs, and possibly HTSs, but not by bAPs[68].

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 strength[97] (Fig. 5d). This gap-junction coupling LTD requires Ca^{2+} entry through voltage-gated channels[98] but is insensitive to tetrodotoxin[97], 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 dendrites[99], i.e. LTSs might modulate electrical synapses throughout the dendritic tree, whereas bAPs can only affect 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/spindle frequency (2 - 8 Hz for 5 sec) stimulates the release of cAMP which in turn causes increased activation of HCN channels[100,101] (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 function[102–104], suggesting downscaling of strength at particular synapses during sleep, whilst preserving enhanced strength at synapses that had been strongly activated by novel features during the preceding period of wakefulness. Indeed, evidence in support of these views are starting to accumulate for neocortical synapses[105–107]. 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 re-scaling 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 on-going oscillations. For example, GABAergic NRT-TC synapses may be either potentiated or depressed depending upon whether the postsynaptic cell is preferentially expressing LTSs at slow (<1 Hz) oscillations[71] or nested delta waves[93] frequency, respectively (Fig. 5a,b). This bidirectional plasticity may allow TC neuron slow oscillations to strengthen NRT-TC synapses, leading in turn to larger IPSPs, more robust post-inhibitory rebound LTS-bursts and enhanced 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 **[G]** 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 plasticity[108].

Concluding remarks

In summary, currently available evidence indicates that together with the well-accepted "rhythm-regulation function", thalamic oscillations of relaxed wakefulness and non-REM 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 only been tested at slow and delta but not spindle frequency[71], iLTD was studied at delta but not at other oscillation frequencies[93], and the LTP at TC-NRT synapses[94] and the LTD at the NRT-NRT electrical synapses[97] 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 cognition[109], 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 nuclei[71] whereas iLTD has been demonstrated in the first-order VB nucleus but not in higher-order nuclei[93]. Moreover, is 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, hypothalamus[2,110]). Furthermore, it may be possible that the parvalbumin- and somatostatin-containing subsets of NRT neurons[111,112], which have different spatial distribution, physiological properties and targets[112,113], experience different forms of plasticity. Fourth, plasticity should be tested using induction protocols that more faithfully reproduce the complex dynamics of natural low-vigilance state oscillations, i.e. spindle waves nested within slow (< 1 Hz) oscillations, alpha waves occurring during slow oscillation Up states, etc. Importantly, would the longer somatodendritic Ca^{2+} signals of the slow (< 1 Hz) oscillation produce different synaptic or cell-intrinsic plasticity compared to the more rapid $\Delta[Ca^{2+}]_{LTS}$ of delta oscillations (cf. Fig. 4c)? Undoubtedly, the most necessary, though technically demanding, challenge, however, will be to move beyond *in vitro* approaches and investigate these forms of thalamic plasticity induced by low-vigilance state oscillations under natural waking-sleeping conditions and thus identify their behavioural consequences.

Box 1. The high-threshold spike.

High-threshold spikes (HTSs) of TC neurons are small, brief depolarizations that occur at membrane potentials slightly more depolarized than tonic firing (a,b). They were originally identified with extracellular and intracellular recordings *in vitro* and extracellular recordings in freely moving cats during relaxed wakefulness[10]. HTSs are present in about 30% of TC neurons in visual, somatosensory and motor thalamic nuclei of mice, rats and cats (other thalamic nuclei have not yet been investigated)[10,16,52,53] (a,b,d) and their presence has now been conclusively confirmed by *in vivo* intracellular recordings in awake mice (e). Though the voltage waveform of HTSs is entirely contained within membrane potentials > -55 mV (a,b,d,e), they are generated by the opening of probably both T- and L-type voltage-gated Ca^{2+} channels[10]. The HTSs of TC neurons in the dorsal lateral geniculate nucleus are phase-locked to the thalamic local field potential (LFP) *in vitro* (d) and to the alpha-frequency LFP recorded simultaneously in the primary visual cortex *in vivo* during relaxed wakefulness (e). The burst of action potentials generated by an HTS, i.e. the HTS-burst, is markedly different from the burst elicited by a low-threshold spike, i.e. the LTS-burst, in that it has i) an intra-burst frequency between 50 and 70 Hz (b,c), and ii) a constant inter-spike interval (ISI) (b,c)[10,16], i.e. it lacks the characteristic decelerando pattern of LTS-bursts in TC neurons. Notably, extracellularly recorded bursts of action potentials with identical features to those of HTS-bursts have been reported in motor thalamic nuclei of awake monkey[114] and humans[115].

Box 2. The global low-threshold spike.

Simultaneous activation of T-VGCCs at spatially distant locations relies on thalamic neuron distinctive electrotonic properties. 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 (left diagram: blue electrode to green electrode). Consequently, viewed from the soma, most neurons appear somewhat electrically compact. Although first predicted in computational models, it has only recently been revealed using dendritic patch clamp recordings that this effect is particularly strong for TC (L = 0.24λ) and NRT (L = 0.26λ) neurons[68]. 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 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 (right diagram: blue electrode), the membrane potential in the entire dendritic tree (right diagram: 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 co-incident 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.

Figure 1. Cellular thalamic counterparts of EEG rhythms of relaxed wakefulness and non-REM 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 EEG rhythms shown in the left column (N1-N3: non-REM sleep stages[27]). 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, yellow 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, yellow 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/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. 10,33,34,46,116-118.

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

Schematic drawings of 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 area highlighting the contribution of T-type voltage-gated Ca^{2+} channels in each activity. NRT neurons do not exhibit HTSs and their firing is not correlated to the EEG alpha rhythm. In most traces, action potentials have been truncated for clarity of illustration.

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 reveals 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) and 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. 73.

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-REM 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 significantly more slowly during slow (< 1 Hz) than 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 NRT-TC neuron synapses. Note the T-VGCC-elicited depolarization (ΔV) driving activation of 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 HCN channels in TC neurons lead to increased I_h ((+) in inset).

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872 **TOC Summary**

873 During inattentive wakefulness and non-REM sleep thalamic neurons exhibit diverse rhythmic
874 activities that are essential for the expression of the corresponding EEG rhythm, e.g. alpha,
875 spindle, delta and slow waves. In this perspective, Crunelli and colleagues propose that
876 together with this "rhythm-regulation function", thalamic oscillations of these low-vigilance
877 states have a "plasticity function" that, by virtue of their calcium spikes and associated global
878 somatodendritic calcium transients, modifies the strength of excitatory and inhibitory synapses
879 in local neuronal assemblies.

880

881

882 **Corresponding Authors Contributions:**

883 **Vincenzo Crunelli**

884 Substantial contribution to discussion of content

885 Writing

886 Review/Editing of manuscript before and after submission

887 **Adam (C) Errington**

888 Substantial contribution to discussion of content

889 Writing

890 Review/Editing of manuscript before submission

891

892 **Contributing Author Contributions:**

893 **Magor (L) Lorincz**

894 Researching data for article

895 Substantial contribution to discussion of content

896 Review/Editing of manuscript before submission

897 **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

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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 EEG hallmark of non-rem sleep and consists of waxing-and-waning 7-14 Hz oscillations lasting a few seconds.

- **First-order and higher-order thalamic nuclei**: This functional classification of thalamic nuclei is 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 nuclei relay information from layer 5 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 play 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 and Down states**: Based on their intrinsic properties and/or the influence of the synaptic network, some neurons present a two-state behavior, characterized by two membrane potentials, a depolarized “Up” state and a hyperpolarized “Down” state.

- **I_T window current**: The partial overlap of the T-type calcium channel activation and inactivation curves define a range of membrane potential, centered around -60 mV,

where a fraction of the channel population is not inactivated and T-channels can open generating therefore a small tonic current called the window current.

- **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**: 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 (synaptic re-scaling)**: indicates to 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.

Short Biographies

Vincenzo Crunelli received his PhD in Chemistry from the University of Catania (Italy) followed by postdoc work in Milan (Italy), Cambridge (UK) and Rehovot (Israel). His research group, currently based at both Cardiff University (UK) and Malta University (Malta) investigates the cellular and network dynamics of thalamocortical rhythms during sleep and the pathophysiological mechanisms of absence seizures.

Magor L. Lőrincz received his PhD from the Eötvös Loránd University in Budapest, Hungary. As a postdoc in the labs of Vincenzo Crunelli (UK) and Zach Mainen (Portugal) he combined electrophysiology and optogenetics to investigate brain rhythms and neuromodulation. He is now an Assistant Professor at the University of Szeged (Hungary) where his research focuses on cellular and network mechanisms of brain state-dependent neuronal activity in the thalamocortical system.

William M. Connelly completed a PhD (2010) at the University of Otago focused on the physiology and pathophysiology of GABAergic inhibition. He then moved to the lab of Vincenzo Crunelli (2011-2015) where he worked on the physiology of thalamocortical

neurons. He currently works in the lab of Greg Stuart investigating how cortical neurons integrate visual information.

François David received his PhD in 2007 in Cognitive Science (Université Lumière, Lyon, France) focussing on computational neuroscience. He then investigated the thalamocortical rhythms in vivo and in vitro with Regis Lambert and Nathalie Leresche in Paris and Vincenzo Crunelli in Cardiff. He is now back in Lyon studying vigilance states and cognition.

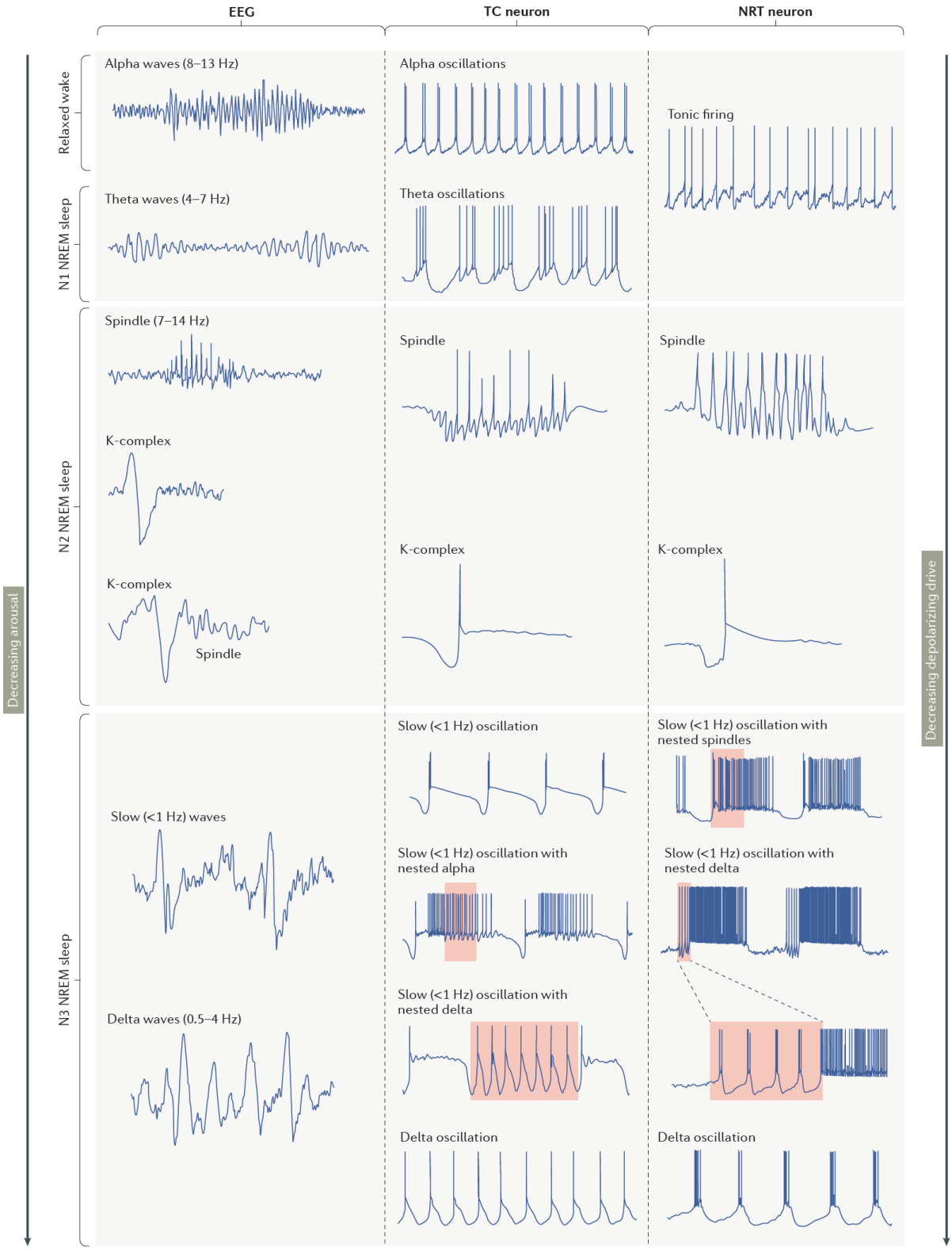
Stuart W. Hughes received his PhD from Cardiff University (UK). He is currently Director and Head of Pharmacology at Vertex Pharmaceuticals Europe Ltd (Oxford, UK) where his main areas of focus are in neuroscience and orphan diseases. He has previously held the positions of Wellcome Research Fellow and Senior Lecturer at Cardiff University and Principal Research Scientist at Eli Lilly & Co (UK) and has a longstanding interest in the mechanisms of sleep-related brain rhythms.

Régis C. Lambert received his PhD from the University of Strasbourg, France, working in neuroendocrinology. During his postdoctroral fellowship, he focused on biophysics of calcium channels. As a Professor of the University Pierre and Marie Curie, he is currently leading a group with Nathalie Leresche in the Department Neuroscience Paris Seine, which focuses on thalamic excitability with particular emphasis on T-type calcium channels.

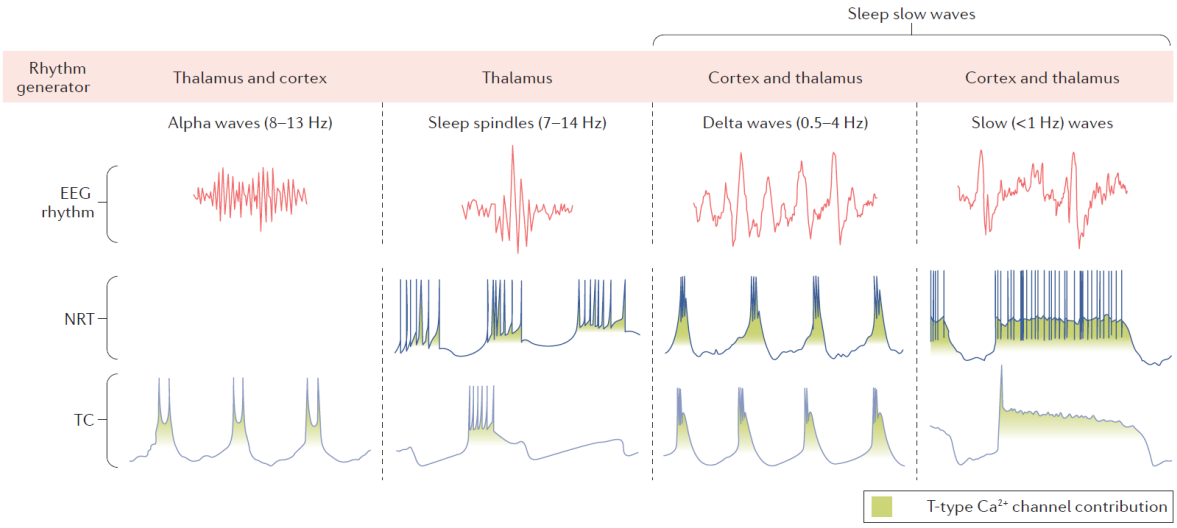
Nathalie Leresche received her PhD from the University Pierre and Marie Curie in Paris, France, working on visual processing. After postdoctoral fellowship with V. Crunelli at St. Georges' Hospital Medical School (London), she came back to France as a CNRS researcher. She is currently leading a group with Régis C. Lambert at the Department Neuroscience Paris Seine. Her research focuses on thalamocortical mechanisms in sleep and absence epilepsy.

Adam C. Errington is a Senior Research Fellow at the Neuroscience and Mental Health Research Institute, Cardiff University (UK). His laboratory investigates the structure and function of dendrites in the thalamus and their roles in physiology and neurological diseases and the role of extrasynaptic GABA signalling in the brain.

Figure 1


EEG
TC neuron
NRT neuron
Relaxed wake
N1 NREM sleep
N2 NREM sleep
N3 NREM sleep
Decreasing arousal
Decreasing depolarizing drive
Alpha waves (8–13 Hz)
Alpha oscillations
Tonic firing
Theta waves (4–7 Hz)
Theta oscillations
Spindle (7–14 Hz)
Spindle
Spindle
K-complex
K-complex
K-complex
Spindle
K-complex
Slow (<1 Hz) waves
Slow (<1 Hz) oscillation
Slow (<1 Hz) oscillation with nested spindles
Slow (<1 Hz) oscillation with nested alpha
Slow (<1 Hz) oscillation with nested delta
Slow (<1 Hz) oscillation with nested delta
Delta waves (0.5–4 Hz)
Delta oscillation
Delta oscillation

1015 **Figure 2**



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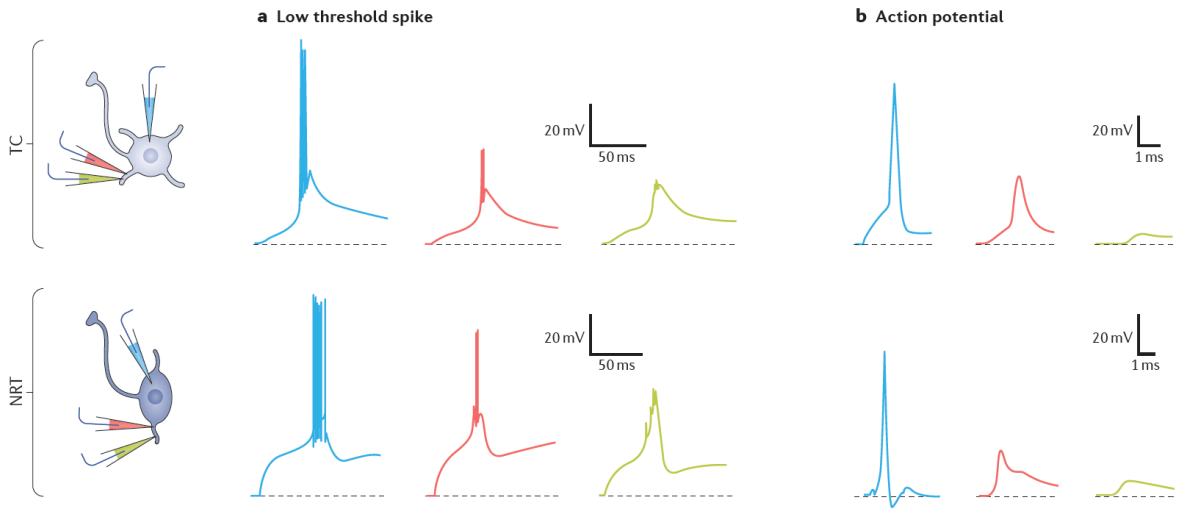
1017 **Figure 3**



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1019 **Figure 4**

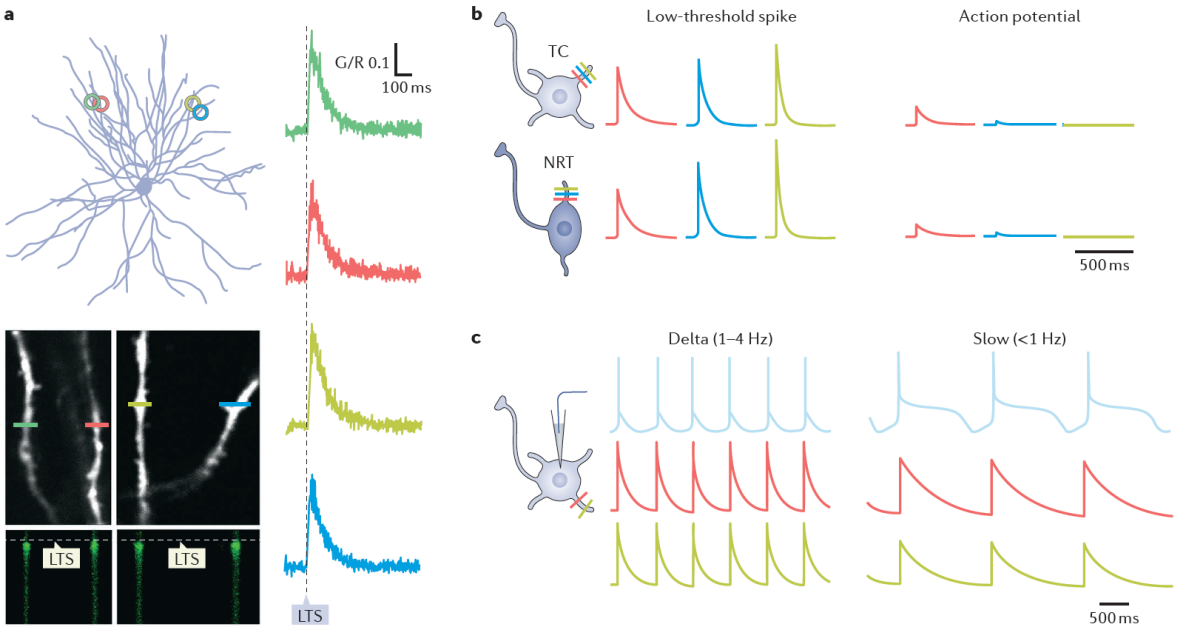

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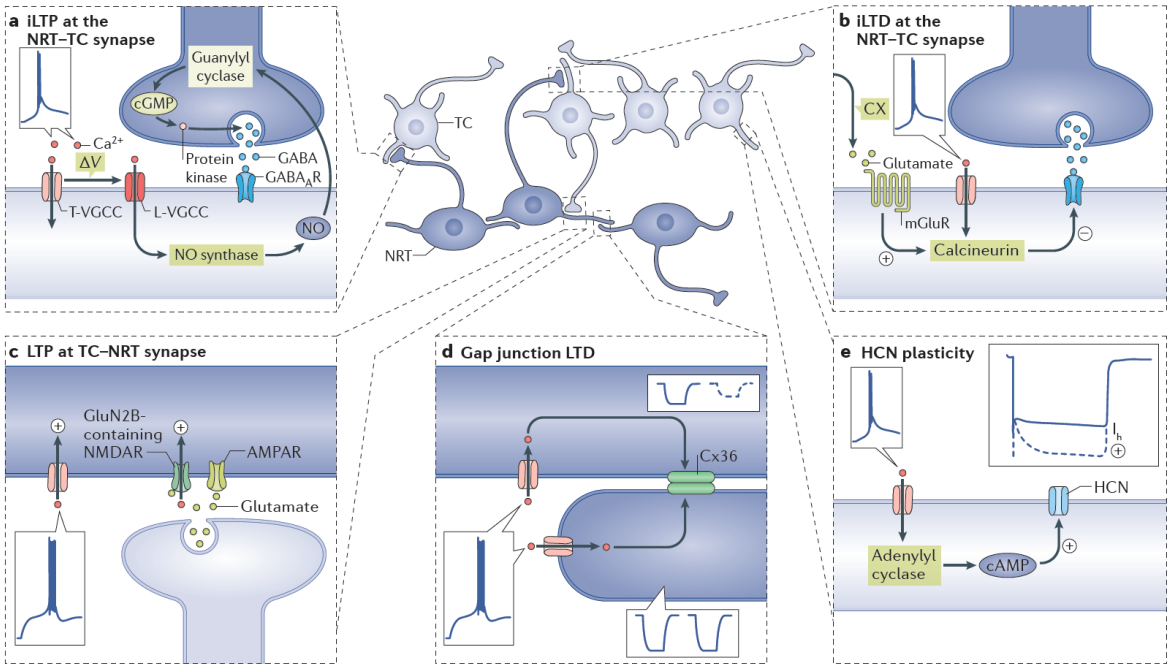
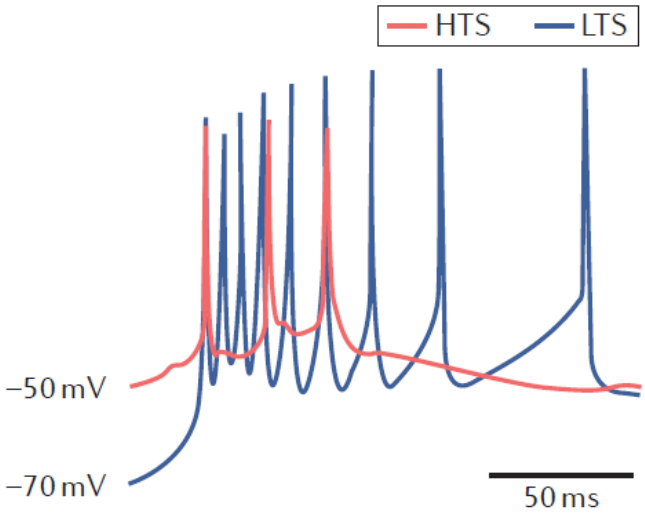
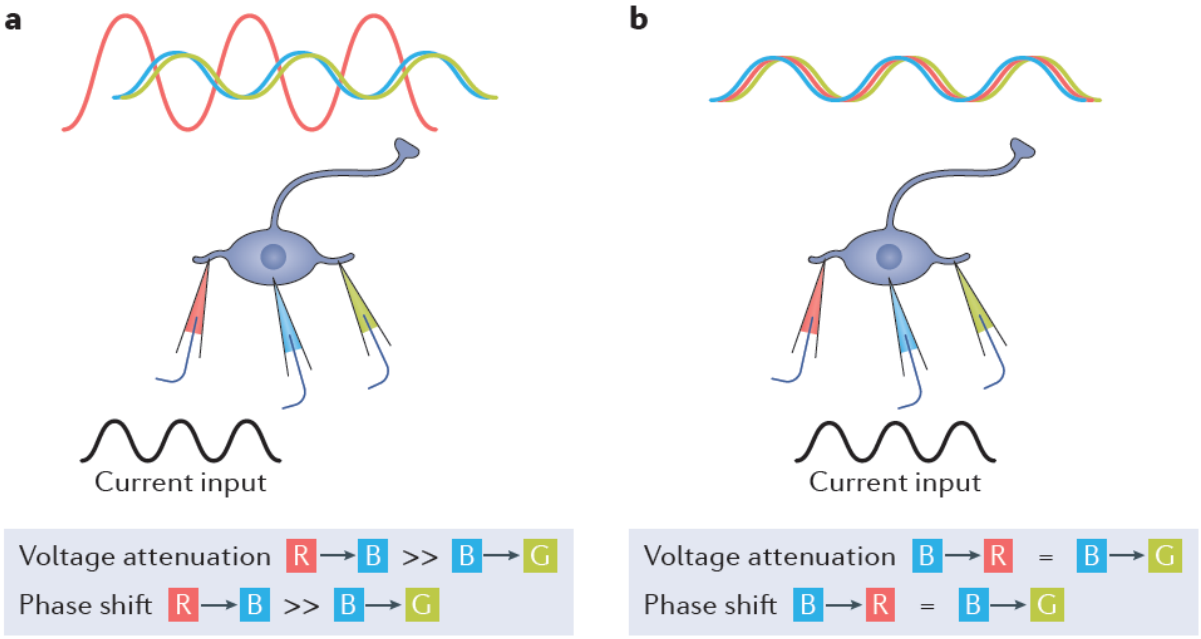
Figure 5


a iLTP at the NRT–TC synapse
Guanylyl cyclase
cGMP
Ca2+
ΔV
Protein kinase
GABA
GABAAR
T-VGCC
L-VGCC
NO
NO synthase
TC
NRT
b iLTD at the NRT–TC synapse
CX
Glutamate
mGluR
Calcineurin
c LTP at TC–NRT synapse
GluN2B-containing NMDAR
AMPAR
Glutamate
d Gap junction LTD
Cx36
e HCN plasticity
Ih
HCN
Adenylyl cyclase
cAMP

BOX 1 Figure



BOX 2 Figure


a
Current input
Voltage attenuation R → B >> B → G
Phase shift R → B >> B → G
b
Current input
Voltage attenuation B → R = B → G
Phase shift B → R = B → G