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1
2 **Dual function of thalamic low-vigilance state oscillations:**
3 **rhythm-regulation and plasticity**
4

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36 **ABSTRACT**

37 **During inattentive wakefulness and non-REM sleep, neocortex and thalamus co-**
38 **operatively engage in rhythmic activities that are exquisitely reflected in the EEG as**
39 **distinctive rhythms spanning a range of frequencies, from <1 Hz slow waves to 13 Hz**
40 **alpha waves. In thalamus, these diverse activities emerge through the interaction of cell-**
41 **intrinsic mechanisms and local and long-range synaptic inputs. One crucial feature,**
42 **however, unifies thalamic oscillations of different frequencies: repetitive burst firing**
43 **driven by voltage-dependent Ca²⁺ spikes. Recent evidence reveals that thalamic Ca²⁺**
44 **spikes are inextricably linked to global somatodendritic Ca²⁺ transients and are essential**
45 **for several forms of thalamic plasticity. Thus, we here propose that alongside their**
46 **“rhythm-regulation function”, thalamic oscillations of low-vigilance states have a**
47 **“plasticity function” that, through modifications of synaptic strength and cellular**
48 **excitability in local neuronal assemblies, can shape on-going oscillations during**
49 **inattention and non-REM sleep and may potentially reconfigure thalamic networks for**
50 **faithful information processing during attentive wakefulness.**

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55 From the moment we enter a state of relaxed inattentive wakefulness through to the
56 deepest stages of non-REM sleep, the human EEG expresses a range of distinctive waves,
57 progressively increasing in amplitude and decreasing in frequency, the most prominent of
58 which are the alpha rhythm, sleep spindles, delta waves and slow waves¹ (Fig. 1, left column).
59 The emergence of these EEG rhythms is reliant upon finely-tuned interactions between
60 neocortical and thalamic neuronal assemblies, with strong modulation from many subcortical
61 regions including brain stem and hypothalamus^{2,3}. Although in the thalamus these low-
62 vigilance state-dependent activities are generated by diverse cellular, synaptic and network
63 mechanisms, intracellular recordings from **thalamocortical (TC) [G]** and **nucleus reticularis**
64 **thalami (NRT) [G]** neurons highlight a critical common feature: the rhythmic occurrence of
65 action potential bursts driven by voltage-dependent Ca²⁺ spikes⁴⁻¹⁰ (Figs. 1, middle and right
66 columns, & 2). During **sleep spindles [G]**, delta and slow waves of non-REM sleep, these action
67 potential bursts have high intra-burst frequencies (100-500 Hz) in both TC and NRT neurons
68 and are driven, following relatively short periods of membrane hyperpolarization, by a Ca²⁺
69 spike reliant on the opening of low voltage-gated T-type Ca²⁺ channels (T-VGCCs)¹¹. This
70 Ca²⁺-spike is commonly known as the low-threshold spike (LTS)^{12,13} (Fig. 2 & Box 1). During
71 alpha waves of relaxed, inattentive wakefulness and theta waves of light non-REM sleep, action
72 potential bursts in TC neurons have a notably lower frequency (50-70 Hz) and are driven by
73 high-threshold Ca²⁺ spikes (HTSs) (Box 1) that likely involve both T-VGCCs and high voltage-
74 gated L-type Ca²⁺ channels (L-VGCCs)¹⁰ (Figs. 1, middle column, & 2). The near ubiquitous
75 presence of LTSs and HTSs in TC and NRT neurons during low-vigilance states raises the
76 question of why individual thalamic neurons are paradoxically engaged in the energetically
77 expensive generation of rhythmic burst firing¹⁴ during periods of attentional and behavioural
78 inactivity that are classically associated with energy preservation.

79 Here, we provide an up-to-date synopsis of the roles of LTSs and HTSs in thalamic
80 oscillations of low-vigilance states and then appraise recent evidence regarding the cellular
81 mechanism of thalamic LTS generation and the inextricable link between LTSs, T-VGCCs and
82 global somatodendritic Ca²⁺ signalling in TC and NRT neurons. Finally, we review the crucial
83 involvement of rhythmic LTSs at frequencies relevant to low-vigilance state oscillations in
84 several forms of thalamic cellular and synaptic plasticity. These recent insights lead us to
85 propose that, alongside their role in providing an essential contribution to the full expression
86 of the corresponding EEG rhythm (which hereafter we refer to as the ‘rhythm-regulation
87 function’), thalamic oscillations of low-vigilance states, through their dependence on global
88 Ca²⁺ spikes, have a ‘plasticity function’ that can modify synaptic strength and intrinsic cellular

89 excitability in thalamic networks to stabilize and control on-going oscillations and potentially
90 contribute to optimal information processing during attentive wakefulness.

91

92 **LTS and HTS role in EEG rhythms**

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

102 *Delta Waves (0.5-4Hz)*. Under standard conditions, neocortical slices do not express delta
103 oscillations. However, pharmacological modifications that re-instate the modulatory
104 neurotransmitter tone found *in vivo* during deep non-REM sleep can produce oscillations at
105 delta frequency in slices of primary and association cortices, which are mainly driven by
106 powerful reciprocal excitation of layer 5 intrinsically bursting neurons^{21,22}.

107 TC neurons of **first-order [G]**, **higher-order [G]** and **intralaminar thalamic nuclei [G]**,
108 as well as NRT neurons, can all exhibit relatively short periods of delta oscillations *in vivo*
109 (usually a few cycles), whereas sustained delta oscillations are consistently observed in
110 decorticated animals^{23,24}. In contrast to the neocortex, delta oscillations in thalamic neurons
111 occur via **cell-intrinsic mechanisms [G]**. Specifically, the dynamic interaction of T-VGCCs
112 with hyperpolarization-activated cyclic-nucleotide gated (HCN) channels in TC neurons^{4,20,25}
113 and Ca²⁺-activated K⁺ currents in NRT neurons²⁶ forms the pacemaker mechanism that enables
114 individual thalamic neurons to elicit LTS-bursts at delta frequency (Figs. 1, middle and right
115 column, & 2). Consequently, although no study has, as yet, directly investigated the relative
116 contribution of neocortex and thalamus to EEG delta waves of natural sleep, the presence of
117 delta frequency-generators in both brain regions suggests that neocortex and thalamus might
118 both have a role in producing this EEG rhythm (Fig. 2).

119 *Slow (< 1 Hz) Waves*. Together with delta waves, EEG slow waves of stage N3 of non-REM
120 sleep also contain slow (< 1 Hz) waves²⁷ that reflect the synchronous, rhythmically alternating

121 depolarized “Up” [G] and hyperpolarized “Down” states [G] observed in almost all neocortical
122 and thalamic neurons so far investigated *in vivo*^{5,6,28-31} and *in vitro*^{9,22,32-35}, termed slow (< 1
123 Hz) oscillations⁵ (Fig. 1, middle and right columns). Despite the long-standing view that these
124 oscillations are generated by intracortical mechanisms and imposed upon a passive thalamus
125 (reviewed in Ref. 36), it has now been conclusively demonstrated both in naturally sleeping
126 and anesthetized animals that the full expression of sleep slow waves in the EEG requires active
127 thalamic participation^{30,37}. Thus, whereas both neocortex and thalamus in isolation have
128 different generators of slow oscillations (see below) (Fig. 2), the co-operation between these
129 brain regions is essential to generate slow (<1 Hz) waves in the EEG during stage N3 of natural
130 non-REM sleep.

131 When synaptic transmission is blocked, only a small number of neocortical neurons
132 exhibit slow (< 1 Hz) oscillations *in vitro*^{21,22,38}. Consequently, this activity in neocortical
133 networks is primarily generated by the interaction between synaptic excitation and
134 inhibition^{22,32}. In contrast, in the TC neurons of sensory, motor and intralaminar thalamic nuclei
135 slow (<1 Hz) oscillations are generated by a cell-intrinsic mechanism that requires the finely
136 tuned interplay between the leak K⁺ current, the T-VGCC window current (I_{Twindow}) [G], the
137 Ca²⁺ activated non-selective cation current (I_{CAN}) and the HCN current^{9,11,17,39}. A similar
138 mechanism drives slow (< 1 Hz) oscillations in NRT neurons except for the additional
139 requirement of Na⁺- and Ca²⁺-activated K⁺ currents³⁴. Importantly, due to the critical voltage-
140 dependence of I_{Twindow}^{11,17,39}, slow (< 1 Hz) oscillations in individual TC and NRT neurons can
141 be easily transformed into delta oscillations (and vice-versa) by altering the membrane
142 potential and hence the magnitude of I_{Twindow}^{9,33,34} (cf. Figs. 1,2,6-8 in Ref. 34). Notably,
143 periods of delta oscillations can be observed during the Down states of slow (< 1 Hz)
144 oscillations in TC and NRT neurons both *in vivo* and *in vitro*^{5,6,9,34} (referred to as delta waves
145 nested within slow waves) (Fig. 1, middle and right column), thus contributing to the
146 concurrent expression of these two waves in the EEG during stage N3 of natural sleep.

147 Thalamic LTS-bursts have numerous important involvements in slow (< 1 Hz)
148 oscillations. First, in both TC and NRT neurons the transitions from Down-to-Up state are
149 always marked *in vitro*, and very often *in vivo*, by the occurrence of an LTS-burst^{5,6,9,30,33,34}
150 (Figs. 1 & 2). Second, as indicated earlier, LTS-bursts at delta frequency can be present during
151 the Down state of slow (< 1 Hz) oscillations in both TC and NRT neurons^{5,6,9,34} (Fig. 1, middle
152 and right column). Third, LTS-bursts at spindle frequency are observed both during the Up
153 states and the Up-to-Down state transitions of slow (< 1 Hz) oscillations in single NRT

154 neurons^{6,28,34} (Fig. 1, right column), reflecting the presence of spindles in the corresponding
155 states of sleep slow waves in the EEG^{40,41}.

156 *Sleep Spindles (7-14 Hz)*. Originally suggested by Morison and Bassett (1945)⁴², a thalamic
157 generator for sleep spindles was conclusively demonstrated by studies in the mid/late '80^{43,44}.
158 In subsequent years, *in vitro* experiments showed that the LTS-driven, mutual synaptic
159 interaction between excitatory TC and inhibitory NRT neurons is the generator of sleep
160 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
161 spindle wave in TC neurons, whereas individual NRT neurons can fire an LTS at each cycle
162 (Figs. 1, middle and right column, & 2). The neocortex is not equipped with spindle wave-
163 generating networks, thus elimination of the thalamic input to the neocortex abolishes spindles
164 in the EEG during natural sleep^{43,44,46}. However, the neocortical feedback to TC and NRT
165 neurons provides essential contributions to some sleep spindle properties^{47,45,48}.

166 *Alpha (8-13 Hz) and Theta (4-7 Hz) Waves*. Alpha waves are present in the EEG during relaxed
167 inattentive wakefulness, i.e. in the behavioural state that falls between fully attentive
168 wakefulness and stage N1 of non-REM sleep^{1,27} (Fig. 1, left column), and also during attentive
169 perception^{49,50}. The mechanisms underlying the alpha waves of these two behavioural states
170 might be different, and here we will restrict the discussion to those occurring during inattentive
171 wakefulness. Similarly, we will discuss the theta waves that are present in the EEG of humans
172 and higher mammals during stage N1 of non-REM sleep^{1,27} (Fig. 1, left column) and not those
173 generated during fully awake conditions⁵¹, which have different underlying mechanisms.

174 Although occurring during very different behavioural states, alpha waves of inattentive
175 wakefulness and theta waves of N1 non-REM sleep share a similar mechanism in thalamus. As
176 shown *in vitro* and *in vivo*¹⁰, both waves are driven by a subset of gap junction-linked TC
177 neurons^{10,52} that generate HTSs phase-locked to each cycle of the corresponding EEG rhythm
178 (Figs.1, middle column, & 2) (Box 1). This HTS-burst-based rhythm entrains the firing of local
179 thalamic interneurons and other non-HTS-bursting TC neurons giving rise to a thalamic output
180 at alpha or theta frequency, depending on the behavioural state⁵³. Significantly, periods of alpha
181 waves supported at the cellular level by HTS-burst firing are occasionally present during the
182 Up states of slow (< 1 Hz) oscillations in TC neurons *in vitro*^{9,10,33} and *in vivo*⁵⁴ (Fig. 1, middle
183 column). From a functional perspective, inhibition of HTSs and HTS-bursts within a small (<
184 1 mm³) area of lamina A of the dorsal lateral geniculate nucleus (LGN) in freely moving cats
185 markedly, selectively and reversibly decreases alpha waves in the surrounding thalamic
186 territory and in the EEG recorded from the primary visual cortex by 90% and 75%,

187 respectively⁵³. NRT neurons do not exhibit HTSs and HT-bursts and the firing of the vast
188 majority (90%) of these neurons is not correlated to the EEG alpha rhythm in freely behaving
189 cats⁵³.

190 Alpha wave-generating intrinsic and network mechanisms, mostly involving layer 5
191 neurons, have been described in the neocortex *in vitro*^{55,56} though no *in vivo* study has
192 conclusively shown whether these cortical generators play an essential role in the alpha rhythm
193 of relaxed wakefulness. On the other hand, many studies *in vivo* provide indirect support for a
194 cortical involvement in “classical” EEG alpha waves^{57,58}. Thus, whereas the precise nature of
195 neocortical alpha-generating networks is at present not clear, it is reasonable to suggest that the
196 alpha and theta waves that characterize the EEG of relaxed inattentive wakefulness and N1
197 non-REM sleep, respectively, are strongly, though not exclusively, driven by the thalamic
198 HTS-burst-generating mechanism described above (Fig. 2).

199

200 **“Rhythm-regulation function”**

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

219 EEG rhythms as “thalamic spindles” or “cortical slow oscillation” is misleading unless
220 appropriately qualified and has contributed to inaccurate views on their mechanisms.

221

222 **Mechanisms of LTS generation**

223 As illustrated in the previous sections, the importance of LTS-bursts of TC and NRT
224 neurons for low-vigilance-state oscillations has been known for several decades. However, the
225 precise site of generation of LTSs and the extent of their propagation through the
226 somatodendritic tree of thalamic neurons have remained unclear. Early experiments in inferior
227 olive neurons (another class of LTS-bursting neurons) proposed a somatic and/or perisomatic
228 origin for LTSs⁶⁰, aligning them with fast Na⁺-action potentials that originate in the axon initial
229 segment before spreading to the soma and dendrites⁶¹. In contrast, subsequent *in vitro* studies
230 indicated that the majority of T-VGCCs underlying thalamic neuron LTSs are in the
231 dendrites⁶²⁻⁶⁶, a finding seemingly incompatible with a perisomatic origin. Indeed,
232 computational models demonstrated that thalamic LTS-bursts can be most readily reproduced
233 with T-VGCCs located in the dendrites^{67,68}. Therefore, until recently, it has generally been
234 assumed that LTSs are locally initiated in thalamic neuron dendrites. However, *in vitro*
235 experiments combining dendritic patch clamp recordings and 2-photon Ca²⁺ imaging from TC
236 and NRT neurons with computational modelling have now invalidated this assumption. In fact,
237 unlike the focal mechanisms (i.e. initiation in a specific subcellular region) that underlie other
238 all-or-none neuronal signals (e.g. Na⁺-action potentials, dendritic Ca²⁺ or NMDA spikes^{69,70}),
239 LTSs are generated by a unique global mechanism that requires depolarization of the whole
240 cell and simultaneous widespread recruitment of spatially distributed T-VGCCs⁶⁸ (Fig. 3a,b).
241 This is made possible by the specific **electrotonic [G]** properties of TC and NRT neurons (Box
242 2). Therefore, in thalamic neurons LTSs cannot be focally generated in dendrites and are unable
243 to be spatially constrained to specific subcellular compartments, as is the case, for example, for
244 dendritic Ca²⁺ spikes in cortical neurons^{69,70}.

245 This mechanism inextricably links LTSs in thalamic neurons to synchronous, transient
246 increases in intracellular Ca²⁺ concentration throughout the entire somatodendritic tree^{64,68}. As
247 such, whenever an LTS is recorded at the soma of TC and NRT neurons it is also
248 simultaneously present along their whole somatodendritic axis (Fig. 3a) and this process is
249 accompanied by a transient and substantial increase in intracellular Ca²⁺ throughout the entire
250 dendritic tree (Fig. 4). This ‘whole cell LTS Ca²⁺ transient’ ($\Delta[\text{Ca}^{2+}]_{\text{LTS}}$) is mediated by T-
251 VGCCs, with a contribution from L-VGCCs in TC neurons⁷¹ and voltage-gated R-type Ca²⁺

252 channels in NRT neurons⁷², but does not rely on dendritic **backpropagating action potentials**
253 **[G]** (bAPs), as demonstrated by its insensitivity to tetrodotoxin^{62,64,71}. In fact, when TC and
254 NRT neurons are depolarized (and thus T-VGCCs are mostly inactivated), action potentials
255 backpropagate very inefficiently into the dendritic tree^{62,64,72,73} (Fig. 3b). As a result, bAP-
256 evoked Ca²⁺ transients in thalamic neurons, unlike $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$, are spatially restricted to the
257 soma and proximal dendrites^{62,64,71,74} (Fig. 4b). Significantly, $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ have now been
258 demonstrated in TC neurons of the rat LGN, ventrobasal (VB) and posterior medial (PoM)
259 nuclei^{64,67}, cat medial geniculate body (MGB)⁷⁴ and in mouse and rat NRT neurons^{62,75,76},
260 highlighting their conservation in both glutamatergic and GABAergic neurons as well as in
261 functionally different thalamic nuclei and across species. Due to the known similarities in
262 morphological and electrophysiological properties of TC neurons in limbic and intralaminar
263 thalamic nuclei, it would seem unlikely that global $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ will not be present in these
264 thalamic populations.

265 In summary, during low-vigilance states, where rhythmic LTSs predominate, burst
266 firing of both TC and NRT neurons is associated with global somatodendritic intracellular Ca²⁺
267 signalling, whereas during attentive wakefulness, where tonic firing is more typical, Ca²⁺
268 signalling is spatially constrained, a feature with important consequences for thalamic function
269 (see below).

270

271 $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ phase-locked to waves

272 In many neurons, when action potentials backpropagate into the dendrites, their
273 interspike intervals are often considerably shorter than the time required for subsequent Ca²⁺
274 extrusion/buffering and as a consequence Ca²⁺ can accumulate progressively during spike
275 trains^{64,70}. In contrast, the long refractory period of the LTS (determined by the inactivation
276 and recovery from inactivation of T-VGCCs)⁷⁷ relative to the decay time of individual
277 $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ (determined by Ca²⁺ uptake by sarco/endoplasmic reticulum Ca²⁺ ATPases^{64,74})
278 prevents summation of $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ and substantial Ca²⁺ accumulation. Indeed, as it has been
279 demonstrated directly in TC neurons of the cat MGB *in vitro*, rhythmic $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ are tightly
280 phase-locked to LTS-bursts of both delta and slow (< 1 Hz) membrane potential oscillations⁷⁴
281 (Fig. 4c). Significantly, $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ during slow (< 1 Hz) oscillations have longer decay times
282 than during delta oscillations⁷⁴ (Fig. 4c), probably as a result of the activation of I_{CAN} and
283 I_{Twindow} during the former, lower frequency activity^{9,17,39}. It is tempting, therefore, to speculate

284 that $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ transients associated with oscillations of different frequencies may serve
285 diverse roles in thalamic neurons, as we previously suggested³⁶.

286 Although it is yet to be demonstrated, the requirement of LTSs in TC and NRT neurons
287 for sleep spindle generation strongly suggests that rhythmic $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ should also occur
288 during these oscillations. Since NRT neurons can fire LTS-bursts at spindle frequency, it will
289 be interesting to determine whether the main T-VGCC subtype ($\text{Ca}_v3.3$)^{77,78} and Ca^{2+}
290 buffering/uptake processes of these GABAergic neurons permit Ca^{2+} oscillations during
291 spindles or whether, unlike delta and slow (< 1 Hz) oscillations, Ca^{2+} will accumulate in NRT
292 dendrites.

293 Unlike LTSs, the mechanism(s) underlying the generation of the HTSs that underlie
294 alpha waves of inattentive wakefulness and theta waves of stage N1 sleep in TC neurons^{10,53}
295 still remain somewhat elusive. Nevertheless, the partial contribution of T-VGCCs to HTSs¹⁰
296 (Fig. 2) (Box 1) indicates that they may share a mechanism similar to LTSs and require
297 involvement of dendritic Ca^{2+} channels. Indeed, individual HTSs are associated with
298 significant dendritic Ca^{2+} transients (unpublished observations), although the somatodendritic
299 membrane potential changes and Ca^{2+} signals that accompany HTSs at alpha and theta
300 frequencies remain to be determined.

301

302 **New function of thalamic oscillations**

303 So far we have outlined the essential contribution of thalamic low-vigilance state
304 oscillations to the full expression of these rhythms in the EEG (i.e. their “rhythm-regulation
305 function”) and the critical involvement of Ca^{2+} spike-dependent burst firing in these thalamic
306 oscillations. The question then arises as to why these oscillations use the energetically more
307 expensive LTSs (with accompanying $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$) and HTSs and not single (or trains of) action
308 potentials¹⁴ during behavioural states which are commonly associated with energy
309 preservation. One answer might be that, compared to tonic action potentials, bursts provide a
310 higher reliability of signal transmission^{79–82} since they are less sensitive to noise⁸³, and more
311 effectively trigger responses in some classes of neocortical neurons^{84–86}, probably by
312 selectively engaging the resonance properties of the postsynaptic cells⁸⁷. However, recent
313 studies (see next section) that have investigated the impact of rhythmic LTSs for synaptic and
314 cellular plasticity in thalamic neurons suggest a different, though complementary, answer to
315 this energy conundrum, which leads us to propose a novel ‘plasticity function’ for thalamic
316 oscillations of low-vigilance states. Note that, whereas below we are exclusively discussing

317 plasticity mechanisms elicited by rhythmic LTSs at frequencies relevant to low-vigilance state
318 oscillations, isolated LTS-bursts do occur in TC neurons of sensory thalamic nuclei during
319 attentive wakefulness^{79,88,89}. Whether LTS-dependent plasticity may also occur in thalamus
320 during the latter behavioural state remains to be demonstrated.

321

322 **LTS-dependent thalamic plasticity**

323 Hebbian plasticity requires temporal association between pre- and postsynaptic activity
324 to modify synaptic strength, and several Hebbian cellular learning processes that require bAPs
325 have been identified that can enhance or reduce synaptic efficacy based on the timing between
326 bAPs and postsynaptic potentials⁹⁰. Similarly, a number of non-Hebbian learning rules that do
327 not rely on temporal association of pre- and postsynaptic activity have also been described⁹¹.
328 The weak bAPs of TC and NRT neurons^{62,73} (Fig. 3a,b) cannot alone strongly depolarize the
329 dendritic tree and are thus unlikely to be a reliable mechanism for induction of Hebbian
330 synaptic plasticity in these neurons. In contrast, the global and substantial depolarization
331 provided by the LTS and the associated somatodendritic $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ (Figs. 3 & 4) are strong
332 candidates for mechanisms of plasticity in thalamic neurons, as indicated by the *in vitro* studies
333 summarized below.

334 *Inhibitory synaptic plasticity.* GABAergic synapses (of presumed NRT origin) onto TC
335 neurons of the PoM nucleus have been shown to undergo non-Hebbian long-term potentiation
336 (iLTP)⁷¹ (Fig. 5a). This plasticity occurs via retrograde signalling by nitric oxide (NO) (whose
337 production is stimulated by postsynaptic Ca^{2+} entry) to presynaptic NO-dependent guanylyl
338 cyclase. This Ca^{2+} -dependent iLTP is reliant upon postsynaptic L-VGCCs (since it is abolished
339 by the L-VGCC blocker nimodipine) and is induced by repetitive LTSs at slow oscillation
340 frequency (0.1 Hz for 10 min) but not by tonic action potential firing. Interestingly, delivering
341 LTSs at delta frequency (1 or 5 Hz) drastically reduces (by 60%) or fails to elicit iLTP,
342 respectively. At first glance, a plasticity that requires L-VGCCs and occurs during LTS-
343 bursting but not tonic firing seems counterintuitive. However, when considering the spatial
344 distribution of GABAergic synapses across the TC neuron dendritic tree⁹², alongside the global
345 mechanism of LTS generation⁶⁸ and strong attenuation of bAPs in thalamic neurons^{62,73}, the
346 picture becomes clear. As such, whereas L-VGCCs are crucial for this form of iLTP at
347 GABAergic synapses on TC neurons, they can only be recruited by the robust global membrane
348 potential depolarization provided by T-VGCC-dependent LTSs (ΔV in Fig. 5, panel a) and not
349 by weakly depolarizing bAPs.

350 An LTS-dependent inhibitory long-term depression (iLTD) has been described at the
351 NRT-to-TC neuron synapses in the VB nucleus⁹³ (Fig. 5b). Unlike iLTP, which can be induced
352 by postsynaptic LTSs without pairing to synaptic activity, iLTD requires coincident activation
353 of synaptic input with rhythmic postsynaptic LTSs and is elicited using a short (70 sec) protocol
354 that reproduces delta waves nested within slow (< 1 Hz) oscillations, i.e. 7 trains of LTSs, with
355 each train containing 4 LTSs at delta frequency (1.6 Hz) and being delivered at 0.1 Hz (cf. Fig.
356 1, middle column). Consequently, despite the LTS-dependent induction of a global $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$
357 in TC neurons and unlike iLTP where all inhibitory synapses are potentiated, only synapses
358 activated during the induction protocol undergo iLTD. Critically, iLTD, unlike iLTP, is not
359 triggered by recruitment of high voltage Ca^{2+} channels. In fact, even when evoked dendritic
360 high-voltage Ca^{2+} transients match the amplitude and spatial extent of those observed during
361 T-VGCC activation, iLTD is absent, suggesting a specific signalling pathway requiring T-
362 VGCCs. Finally, this form of iLTD requires the Ca^{2+} -phosphatase calcineurin and is of both
363 homosynaptic and heterosynaptic origin since it is gated by activation of metabotropic
364 glutamate receptors of TC neurons via glutamate released from corticothalamic afferents.

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

370 *Excitatory synaptic plasticity.* As well as plasticity at thalamic inhibitory synapses, excitatory
371 synapses onto TC and NRT neurons have also been found to undergo LTS-dependent forms of
372 LTP. At the synapses of VB TC neurons onto NRT neurons, pairing presynaptic input with
373 postsynaptic LTS-bursts results in LTP⁹⁴ (Fig. 5c). This plasticity requires GluN2B NMDA
374 receptor subunits and cannot be triggered if the postsynaptic depolarization is provided by Na^{+} -
375 dependent firing without T-VGCC activation or if LTSs are suppressed by genetic ablation of
376 Cav3.3 channels. Moreover, the TC-NRT LTP is selectively evoked by postsynaptic LTS-
377 bursts at delta frequency (1 Hz for 3 or 6 min), providing further evidence for potential T-
378 VGCC- and LTS-dependent thalamic plasticity during non-REM sleep.

379 At the cortico-thalamic synapses on VB TC neurons, Hsu et al.⁹⁵ have described LTP
380 induction by LTS-bursts (at 0.167 Hz) but not by high frequency (125 Hz) tonic action
381 potentials. The same group previously reported Hebbian NMDA-dependent LTP and non-
382 Hebbian L-VGCC-dependent LTD selectively at cortico-thalamic but not lemniscal synapses

383 on VB TC neurons⁹⁶. Interestingly, both forms of plasticity require postsynaptic depolarization
384 which, under physiological conditions, can only be provided in thalamic neurons by LTSs, and
385 possibly HTSs, but not by bAPs⁶⁸.

386 *Electrical synapse plasticity.* Rhythmic LTS-burst firing elicited at delta frequency (2 Hz for 5
387 min) in either one or both of paired-recorded, connexin-36-coupled NRT neurons can trigger
388 robust LTD of the gap-junction coupling strength⁹⁷ (Fig. 5d). This gap-junction coupling LTD
389 requires Ca²⁺ entry through voltage-gated channels⁹⁸ but is insensitive to tetrodotoxin⁹⁷,
390 demonstrating that LTSs are capable of inducing gap-junction plasticity even in the absence of
391 action potentials. On the other hand, although spike trains delivered from depolarized potentials
392 also evoke gap-junction LTD, the magnitude is smaller (by 50%) than that induced by repetitive
393 LTSs. It is possible that the difference in LTD strength associated with each firing mode relates
394 to the spatial distribution of gap-junctions on NRT neuron dendrites⁹⁹, i.e. LTSs might
395 modulate electrical synapses throughout the dendritic tree, whereas bAPs can only affect those
396 relatively close to the soma.

397 *Cell-intrinsic plasticity.* Together with a role for plasticity at chemical and electrical thalamic
398 synapses, LTSs can also induce short-lasting plasticity of intrinsic excitability in TC neurons.
399 Rhythmic Ca²⁺ entry during repetitive LTSs at delta/spindle frequency (2 - 8 Hz for 5 sec)
400 stimulates the release of cAMP which in turn causes increased activation of HCN
401 channels^{100,101} (Fig. 5e). This effect outlasts the period of LTS-dependent cellular Ca²⁺
402 elevation, thus creating a form of ‘short-term cellular plasticity’ that restrains LTS-burst
403 generation in TC neurons and should help shaping thalamic spindle and delta oscillations and
404 thus, in turn, the corresponding EEG rhythms.

405

406 **The “plasticity function”**

407 In the sections above, we have presented a framework by which thalamic oscillations
408 of low-vigilance states, by virtue of their rhythmic LTS-dependent global somatodendritic
409 depolarization and $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$, can serve a ‘plasticity function’. A likely setting where this
410 ‘plasticity function’ may be operational is the homeostatic regulation of thalamic circuits
411 during sleep. Homeostatic modification of synaptic strength is a common feature of current
412 theories of sleep function^{102–104}, suggesting downscaling of strength at particular synapses
413 during sleep, whilst preserving enhanced strength at synapses that had been strongly activated
414 by novel features during the preceding period of wakefulness. Indeed, evidence in support of
415 these views are starting to accumulate for neocortical synapses^{105–107}. Like their neocortical

416 counterparts, thalamic neurons receive continuous synaptic bombardment during wakefulness
417 from peripheral, subcortical and cortical inputs. Consequently, modifications of intrathalamic
418 synaptic strength may occur during wakefulness that could require re-scaling during
419 subsequent periods of inattention, and the previously described forms of intrathalamic
420 plasticity associated with the rhythmic occurrence of LTSs during low-vigilance state
421 oscillations offer different mechanisms for such homeostatic modifications in thalamic
422 neuronal assemblies.

423 Moreover, the diverse induction rules for synaptic and intrinsic plasticity across
424 thalamic cell types and synaptic connections that have been demonstrated for low-vigilance
425 state oscillations suggest that another context where the ‘plasticity function’ might be operating
426 is the modulation of the very same on-going oscillations. For example, GABAergic NRT-TC
427 synapses may be either potentiated or depressed depending upon whether the postsynaptic cell
428 is preferentially expressing LTSs at slow (<1 Hz) oscillations⁷¹ or nested delta waves⁹³
429 frequency, respectively (Fig. 5a,b). This bidirectional plasticity may allow TC neuron slow
430 oscillations to strengthen NRT-TC synapses, leading in turn to larger IPSPs, more robust post-
431 inhibitory rebound LTS-bursts and enhanced propagation of spindles to the neocortical-
432 hippocampal axis for active participation in memory processes. Subsequent periods of nested
433 delta oscillations, as they occur during sleep slow waves could then **rescale [G]** NRT-TC
434 synapses to ensure continuous optimal transmission. Some of these thalamic plasticity
435 mechanisms may be operative in the recently described essential and instructive role of delta
436 and spindle waves in visual cortex plasticity¹⁰⁸.

437

438 **Concluding remarks**

439 In summary, currently available evidence indicates that together with the well-accepted
440 “rhythm-regulation function”, thalamic oscillations of relaxed wakefulness and non-REM
441 sleep can have a “plasticity function” that, by virtue of their rhythmic LTSs and associated
442 global somatodendritic Ca²⁺ calcium transients, can modify the strength of excitatory and
443 inhibitory synapses in local thalamic neuronal assemblies.

444 Clearly, in order to build a comprehensive picture of the proposed ‘plasticity function’
445 of thalamic low-vigilance state oscillations further investigations are needed. First, the specific
446 type(s) of oscillations that trigger different forms of plasticity should be systematically
447 assessed. Specifically, iLTP has only been tested at slow and delta but not spindle frequency⁷¹,
448 iLTD was studied at delta but not at other oscillation frequencies⁹³, and the LTP at TC-NRT
449 synapses⁹⁴ and the LTD at the NRT-NRT electrical synapses⁹⁷ have been investigated only

450 with a delta frequency induction protocol. Second, to help understanding thalamic sensory
451 processing and the increasingly recognized role of the thalamus in cognition¹⁰⁹, how
452 generalizable are these Ca²⁺ spike-dependent plasticity mechanisms across different thalamic
453 nuclei? For example, iLTP has been described in the higher-order PoM nucleus but has not
454 been investigated in first-order thalamic nuclei⁷¹ whereas iLTD has been demonstrated in the
455 first-order VB nucleus but not in higher-order nuclei⁹³. Moreover, is any of these (or any other)
456 plasticity mechanisms occurring in motor, limbic and intralaminar thalamic nuclei? Third, how
457 synapse-specific is the Ca²⁺-spike induced plasticity within particular nuclei? For instance, it
458 remains to be seen whether the iLTP in the PoM nucleus involves NRT afferents and/or other
459 non-thalamic GABAergic inputs (zona incerta, anterior pretectal nucleus, basal forebrain,
460 hypothalamus^{2,110}). Furthermore, it may be possible that the parvalbumin- and somatostatin-
461 containing subsets of NRT neurons^{111,112}, which have different spatial distribution,
462 physiological properties and targets^{112,113}, experience different forms of plasticity. Fourth,
463 plasticity should be tested using induction protocols that more faithfully reproduce the complex
464 dynamics of natural low-vigilance state oscillations, i.e. spindle waves nested within slow (< 1
465 Hz) oscillations, alpha waves occurring during slow oscillation Up states, etc. Importantly,
466 would the longer somatodendritic Ca²⁺ signals of the slow (< 1 Hz) oscillation produce
467 different synaptic or cell-intrinsic plasticity compared to the more rapid $\Delta[\text{Ca}^{2+}]_{\text{LTS}}$ of delta
468 oscillations (cf. Fig. 4c)? Undoubtedly, the most necessary, though technically demanding,
469 challenge, however, will be to move beyond *in vitro* approaches and investigate these forms of
470 thalamic plasticity induced by low-vigilance state oscillations under natural waking-sleeping
471 conditions and thus identify their behavioural consequences.

472

473 **Box 1. The high-threshold spike.**

474 High-threshold spikes (HTSs) of TC neurons are small, brief depolarizations that occur at
475 membrane potentials slightly more depolarized than tonic firing (a,b). They were originally
476 identified with extracellular and intracellular recordings *in vitro* and extracellular recordings in
477 freely moving cats during relaxed wakefulness¹⁰. HTSs are present in about 30% of TC neurons
478 in visual, somatosensory and motor thalamic nuclei of mice, rats and cats (other thalamic nuclei
479 have not yet been investigated)^{10,16,52,53} (a,b,d) and their presence has now been conclusively
480 confirmed by *in vivo* intracellular recordings in awake mice (e). Though the voltage waveform
481 of HTSs is entirely contained within membrane potentials > -55 mV (a,b,d,e), they are
482 generated by the opening of probably both T- and L-type voltage-gated Ca^{2+} channels¹⁰. The
483 HTSs of TC neurons in the dorsal lateral geniculate nucleus are phase-locked to the thalamic
484 local field potential (LFP) *in vitro* (d) and to the alpha-frequency LFP recorded simultaneously
485 in the primary visual cortex *in vivo* during relaxed wakefulness (e). The burst of action
486 potentials generated by an HTS, i.e. the HTS-burst, is markedly different from the burst elicited
487 by a low-threshold spike, i.e. the LTS-burst, in that it has i) an intra-burst frequency between
488 50 and 70 Hz (b,c), and ii) a constant inter-spike interval (ISI) (b,c)^{10,16}, i.e. it lacks the
489 characteristic decelerando pattern of LTS-bursts in TC neurons. Notably, extracellularly
490 recorded bursts of action potentials with identical features to those of HTS-bursts have been
491 reported in motor thalamic nuclei of awake monkey¹¹⁴ and humans¹¹⁵.

492

493 **Box 2. The global low-threshold spike.**

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

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522 **Figure 1. Cellular thalamic counterparts of EEG rhythms of relaxed wakefulness and**
523 **non-REM sleep.**

524 Representative intracellular recordings from thalamocortical (TC) (middle column) and
525 nucleus reticularis thalami (NRT) (right column) neurons depicting the membrane potential
526 changes occurring in these neurons during the respective EEG rhythms shown in the left
527 column (N1-N3: non-REM sleep stages²⁷). Sleep spindles can occur in isolation or following
528 a K-complex. A K-complex in the EEG results from a single cycle of the slow (< 1 Hz)
529 oscillations. In the TC neuron column, yellow boxes highlight alpha and delta oscillations
530 nested in the Up and Down state, respectively, of slow (< 1 Hz) oscillations in N3. In the NRT
531 neuron column, yellow boxes highlight spindle waves in the Up state and delta oscillations in
532 the Down state, respectively, of slow (< 1 Hz) oscillations in N3. NRT neurons do not express
533 firing coherent with alpha/theta waves (wake state and N1). Action potentials in the traces
534 depicted in the middle and right column have been truncated for clarity of illustration. Adapted
535 with permission from Refs. 10,33,34,46,116-118.

536

537 **Figure 2. Contribution of T-type Ca²⁺ channels to low-vigilance state oscillations.**

538 Schematic drawings of EEG waves of low-vigilance states with indicated brain regions
539 of their rhythm generator(s) (top row). Schematic drawings of membrane potential oscillations
540 in thalamocortical (TC) (bottom row) and nucleus reticularis thalami (NRT) neurons (middle
541 row) during different low-vigilance states, with shadowed area highlighting the contribution
542 of T-type voltage-gated Ca²⁺ channels in each activity. NRT neurons do not exhibit HTSs and
543 their firing is not correlated to the EEG alpha rhythm. In most traces, action potentials have
544 been truncated for clarity of illustration.

545

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

547 a) In both thalamocortical (TC) and nucleus reticular thalami (NRT) neurons, paired
548 somatodendritic recordings reveals that the low- threshold spike (LTS) depolarizes the entire
549 dendritic tree to the same degree as the soma reflecting the global nature of its generation. The
550 somatic (blue) and proximal (red) and distal (green) dendritic recordings illustrate the similar
551 amplitude of the LTS throughout the dendritic tree. b) In contrast, action potentials are
552 markedly attenuated in both thalamic cell types as they propagate from the soma (blue) into
553 the proximal (red) and distal (green) dendrites. This can also be observed for the action

554 potentials in the LTS-driven bursts (a). A distance-dependent increase in the peak latency of
555 the action potential recorded in the dendritic recordings reveals that they are focally generated
556 in the perisomatic region. Adapted with permission from Ref. 73.

557

558 **Figure 4. Ca²⁺ signalling in thalamic neurons during non-REM sleep oscillations.**

559 a) Two-photon Ca²⁺-imaging of pairs of thalamocortical (TC) neuron dendrites (each
560 originating from different primary dendrites as illustrated on the reconstructed cell) reveals that
561 synchronous and remarkably similar Ca²⁺ transients occur at equivalent distances from the
562 soma during low-threshold spikes (LTSs). b) Schematic illustration of the dendritic Ca²⁺
563 transients that occur in TC and nucleus reticularis thalami (NRT) neurons during LTSs and
564 single action potentials. c) Schematic illustration of dendritic Ca²⁺ signalling in TC neurons
565 during non-REM sleep oscillations. Membrane potential oscillations at delta and slow (< 1 Hz)
566 frequencies (light blue, top traces) in TC neurons are coupled to synchronous dendritic Ca²⁺
567 oscillations in proximal (red) and distal (green) dendrites. Notably, Ca²⁺ transients throughout
568 the dendritic tree decay significantly more slowly during slow (< 1 Hz) than delta oscillations.
569 Adapted with permission from Refs. 64,74.

570

571 **Figure 5. Low-threshold Ca²⁺ spike-dependent plasticity in thalamus.**

572 Schematic drawings of the mechanisms of different forms of synaptic and cellular plasticity
573 elicited by rhythmic low-threshold spikes (LTSs) (and associated Ca²⁺ transients) at
574 frequencies relevant to oscillations of low vigilance states. a) Inhibitory long-term potentiation
575 (iLTP) at GABAergic NRT-TC neuron synapses. Note the T-VGCC-elicited depolarization
576 (ΔV) driving activation of L-VGCCs. b) Inhibitory long-term depression (iLTD) at GABAergic
577 NRT-TC neuron synapses. Note the requirement for metabotropic glutamate receptor (mGluR)
578 activation by glutamate released from cortical (CX) afferents. c) Excitatory long-term
579 potentiation (LTP) at glutamatergic TC-NRT neuron synapses. d) Long-term depression (LTD)
580 at electrical NRT-NRT neuron synapses. e) Cellular plasticity of intrinsic HCN channels in TC
581 neurons lead to increased I_h ((+) in inset).

582

583 **References**

- 584 1. Niedermeyer, E. & Lopes Da Silva, F. *Electroencephalography: Basic Principles,*
585 *Clinical Applications, and Related Fields.* Lippincott Williams and Wilkins (2004).
- 586 2. Herrera, C. G. *et al.* Hypothalamic feedforward inhibition of thalamocortical network
587 controls arousal and consciousness. *Nat. Neurosci.* **19**, 290-29 (2016).
- 588 3. Lőrincz, M. L. & Adamantidis, A. R. Monoaminergic control of brain states and
589 sensory processing: Existing knowledge and recent insights obtained with
590 optogenetics. *Prog. Neurobiol.* **151**, 237-253 (2017).
- 591 4. Leresche, N., Lightowler, S., Soltesz, I., Jassik-Gerschenfeld, D. & Crunelli, V. Low-
592 frequency oscillatory activities intrinsic to rat and cat thalamocortical cells. *J. Physiol.*
593 **441**, 155–174 (1991).
- 594 5. Steriade, M., Nunez, A. & Amzica, F. A novel slow (< 1 Hz) oscillation of neocortical
595 neurons in vivo: depolarizing and hyperpolarizing components. *J. Neurosci.* **13**, 3252-
596 3265 (1993).
- 597 6. Steriade, M., Contreras, D., Curró Dossi, R. & Nuñez, A. The slow (< 1 Hz) oscillation
598 in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation
599 in interacting thalamic and neocortical networks. *J. Neurosci.* **13**, 3284-3299 (1993).
- 600 7. Bal, T., von Krosigk, M. & McCormick, D. A. Synaptic and membrane mechanisms
601 underlying synchronized oscillations in the ferret lateral geniculate nucleus in vitro. *J.*
602 *Physiol.* **483**, 641-663 (1995).
- 603 8. Bal, T., von Krosigk, M. & McCormick, D. A. Role of the ferret perigeniculate nucleus
604 in the generation of synchronized oscillations in vitro. *J. Physiol.* **483**, 665-685 (1995).
- 605 9. Hughes, S. W., Cope, D. W., Blethyn, K. L. & Crunelli, V. Cellular mechanisms of the
606 slow (<1 Hz) oscillation in thalamocortical neurons in vitro. *Neuron* **33**, 947-58 (2002).
- 607 10. Hughes, S. W. *et al.* Synchronized oscillations at alpha and theta frequencies in the
608 lateral geniculate nucleus. *Neuron* **42**, 253-68 (2004).
- 609 11. Crunelli, V., Cope, D. W. & Hughes, S. W. Thalamic T-type Ca²⁺ channels and
610 NREM sleep. *Cell Calcium* **40**, 175-190 (2006).
- 611 12. Llinás, R. & Jahnsen, H. Electrophysiology of mammalian thalamic neurones in vitro.
612 *Nature* **297**, 406-8 (1982).
- 613 13. Deschênes, M., Paradis, M., Roy, J. P. & Steriade, M. Electrophysiology of neurons of
614 lateral thalamic nuclei in cat: resting properties and burst discharges. *J. Neurophysiol.*
615 **51**, 1196-219 (1984).
- 616 14. Attwell, D. & Gibb, A. Neuroenergetics and the kinetic design of excitatory synapses.
617 *Nat. Rev. Neurosci.* **6**, 841-849 (2005)
- 618 15. Berger, H. Uber das Elektroenkephalogramm des Menschen. *Arch.Psych.* **87**, 527-
619 570 (1929).
- 620 16. Hughes, S. W. & Crunelli, V. Thalamic mechanisms of EEG alpha rhythms and their
621 pathological implications. *The Neuroscientist* **11**, 357-372 (2005).
- 622 17. Crunelli, V., Tóth, T. I., Cope, D. W., Blethyn, K. & Hughes, S. W. The ‘window’ T-type
623 calcium current in brain dynamics of different behavioural states. *J. Physiol.* **562**, 121-
624 129 (2005).
- 625 18. Lüthi, A. Sleep Spindles. *The Neuroscientist* **20**, 243-256 (2014).

- 626 19. Neske, G. T. The Slow Oscillation in Cortical and Thalamic Networks: Mechanisms
627 and Functions. *Front. Neural Circ.* **9**, 88 (2016).
- 628 20. McCormick, D.A. & Bal, T. Sleep and arousal: thalamocortical mechanisms. *Ann.*
629 *Rev. Neurosci.* **20**, 185-215 (1997).
- 630 21. Carracedo, L. M. *et al.* A neocortical delta rhythm facilitates reciprocal interlaminar
631 interactions via nested theta rhythms. *J. Neurosci.* **33**, 10750-10761 (2013).
- 632 22. Lőrincz, M. L. *et al.* A distinct class of slow (~0.2-2 Hz) intrinsically bursting layer 5
633 pyramidal neurons determines UP/DOWN state dynamics in the neocortex. *J.*
634 *Neurosci.* **35**, 5442-5458 (2015).
- 635 23. Dossi, R. C., Nuñez, A. & Steriade, M. Electrophysiology of a slow (0.5-4 Hz) intrinsic
636 oscillation of cat thalamocortical neurones in vivo. *J. Physiol.* **447**, 215-234 (1992).
- 637 24. Timofeev, I. & Steriade, M. Low-frequency rhythms in the thalamus of intact-cortex
638 and decorticated cats. *J. Neurophysiol.* **76**, 4152-168 (1996).
- 639 25. McCormick, D. A. & Pape, H. C. Properties of a hyperpolarization-activated cation
640 current and its role in rhythmic oscillation in thalamic relay neurones. *J. Physiol.* **431**,
641 291-318 (1990).
- 642 26. Bal, T. & McCormick, D. A. Mechanisms of oscillatory activity in guinea-pig nucleus
643 reticularis thalami in vitro: a mammalian pacemaker. *J. Physiol.* **468**, 669-91 (1993).
- 644 27. Iber, C., Ancoli-Israel, S., Chesson, A. & S, Q. The new sleep scoring manual - The
645 evidence behind the rules. *J. Clin. Sleep Med.* **3**, 107 (2007).
- 646 28. Steriade, M., Nunez, A. & Amzica, F. Intracellular Analysis Neocortical Oscillation
647 Electroencephalogram of Relations between the Slow (< 1 Hz) and Other Sleep
648 Rhythms. *J. Neurosci.* **13**, 3266-3283 (1993).
- 649 29. Amzica, F. & Steriade, M. Short- and long-range neuronal synchronization of the slow
650 (< 1 Hz) cortical oscillation. *J. Neurophysiol.* **73**, 20-38 (1995).
- 651 30. Lemieux, M., Chen, J.-Y., Lonjers, P., Bazhenov, M. & Timofeev, I. The impact of
652 cortical deafferentation on the neocortical slow oscillation. *J. Neurosci.* **34**, 5689-5703
653 (2014).
- 654 31. Crunelli, V., Lorincz, M. L., Errington, A. C. & Hughes, S. W. Activity of cortical and
655 thalamic neurons during the slow (<1 Hz) rhythm in the mouse in vivo. *Pflug. Arch.*
656 *Eur. J. Physiol.* **463**, 73-88 (2012).
- 657 32. Sanchez-Vives, M. V & McCormick, D. a. Cellular and network mechanisms of
658 rhythmic recurrent activity in neocortex. *Nat. Neurosci.* **3**, 1027-1034 (2000).
- 659 33. Zhu, L. *et al.* Nucleus- and species-specific properties of the slow (<1 Hz) sleep
660 oscillation in thalamocortical neurons. *Neuroscience* **141**, 621-36 (2006).
- 661 34. Blethyn, K. L., Hughes, S. W., Tóth, T. I., Cope, D. W. & Crunelli, V. Neuronal basis of
662 the slow (<1 Hz) oscillation in neurons of the nucleus reticularis thalami in vitro. *J.*
663 *Neurosci.* **26**, 2474-2486 (2006).
- 664 35. Cunningham, M. O. *et al.* Neuronal metabolism governs cortical network response
665 state. *Proc. Natl. Acad. Sci. (USA)* **103**, 5597-5601 (2006)
- 666 36. Crunelli, V. & Hughes, S. W. The slow (< 1 Hz) rhythm of non-REM sleep: a dialogue
667 between three cardinal oscillators. *Nat. Neurosci.* **13**, 9-17 (2010).
- 668 37. David, F. *et al.* Essential thalamic contribution to slow waves of natural sleep. *J.*

- 669 *Neurosci.* **33**, 19599-19610 (2013).
- 670 38. Le Bon-Jego, M. & Yuste, R. Persistently active, pacemaker-like neurons in neocortex.
671 *Front. Neurosci.* **1**, 123-129 (2007).
- 672 39. Dreyfus, F. M. *et al.* Selective T-type calcium channel block in thalamic neurons
673 reveals channel redundancy and physiological impact of I(T)window. *J. Neurosci.* **30**,
674 99-109 (2010).
- 675 40. Klinzing, J. G. *et al.* Spindle activity phase-locked to sleep slow oscillations.
676 *NeuroImage* **134**, 607-616 (2016).
- 677 41. Latchoumane CV, Ngo HV, Born J, S. H. Thalamic Spindles Promote Memory
678 Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and
679 Hippocampal Rhythms. *Neuron* **95**, 424-435 (2017).
- 680 42. Morison, R. & Bassett, D. Electrical activity of the thalamus and basal ganglia in
681 decorticate cats. *J. Neurophysiol.* **8**, 309-314 (1945).
- 682 43. Steriade, M., Deschênes, M., Domich, L. & Mulle, C. Abolition of spindle oscillations in
683 thalamic neurons disconnected from nucleus reticularis thalami. *J. Neurophysiol.* **54**,
684 1473-1497 (1985).
- 685 44. Steriade, M., Domich, L., Oakson, G. & Deschenes, M. The deafferented reticular
686 thalamic nucleus generates spindle rhythmicity. *J. Neurophysiol.* **57**, 260-273 (1987).
- 687 45. Contreras Diego & Steriade Mircea. Spindle oscillation in cats: the role of
688 corticothalamic feedback in a thalamically generated rhythm. *J. Physiol.* **490**, 159-179
689 (1996).
- 690 46. Fuentealba, P. & Steriade, M. The reticular nucleus revisited: Intrinsic and network
691 properties of a thalamic pacemaker. *Progr. Neurobiol.* **75**, 125-141 (2005).
- 692 47. Destexhe, A., Contreras, D. & Steriade, M. Cortically-induced coherence of a
693 thalamic-generated oscillation. *Neuroscience* **92**, 427-43 (1999).
- 694 48. Contreras, D., Destexhe, A., Sejnowski, T. J. & Steriade, M. Control of spatiotemporal
695 coherence of a thalamic oscillation by corticothalamic feedback. *Science* **274**, 771-
696 774 (1996).
- 697 49. Bollimunta, A., Mo, J., Schroeder, C. E. & Ding, M. Neuronal Mechanisms and
698 Attentional Modulation of Corticothalamic Alpha Oscillations. *J. Neurosci.* **31**, 4935-
699 4943 (2011).
- 700 50. Jensen, O., Bonnefond, M., Marshall, T. R. & Tiesinga, P. Oscillatory mechanisms of
701 feedforward and feedback visual processing. *Trends Neurosci.* **38**, 192-194 (2015).
- 702 51. Schomburg, E. W. *et al.* Theta Phase Segregation of Input-Specific Gamma Patterns
703 in Entorhinal-Hippocampal Networks. *Neuron* **84**, 470-485 (2014).
- 704 52. Hughes, S. W. *et al.* Thalamic gap junctions control local neuronal synchrony and
705 influence macroscopic oscillation amplitude during EEG alpha rhythms. *Front.*
706 *Psychol.* **2**, 193 (2011).
- 707 53. Lorincz, M. L., Kékesi, K. A., Juhász, G., Crunelli, V. & Hughes, S. W. Temporal
708 framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm.
709 *Neuron* **63**, 683-696 (2009).
- 710 54. MacFarlane, J.G., Shahal, B., Mously, C. & Moldofsky, H. Periodic K-alpha sleep
711 EEG activity and periodic limb movements during sleep: comparisons of clinical
712 features and sleep parameters. *Sleep.* **19**, 200-204 (1996).

- 713 55. Silva, L. R., Amitai, Y. & Connorst, B. W. Intrinsic Oscillations of Neocortex Generated
714 by Layer 5 Pyramidal Neurons. *Science* **251**, 433-435 (1991).
- 715 56. Flint, A. C. & Connors, B. W. Two types of network oscillations in neocortex mediated
716 by distinct glutamate receptor subtypes and neuronal populations. *J. Neurophysiol.*
717 **75**, 951-957 (1996).
- 718 57. Lopes Da Silva, F. H. & Storm Van Leeuwen, W. The cortical source of the alpha
719 rhythm. *Neurosci. Lett.* **6**, 237-241 (1977).
- 720 58. Lopes da Silva, F. H., Vos, J. E., Mooibroek, J. & Van Rotterdam, A. Relative
721 contributions of intracortical and thalamo-cortical processes in the generation of alpha
722 rhythms, revealed by partial coherence analysis. *Electroench. Clin. Neurophysiol.* **50**,
723 449-456 (1980).
- 724 59. Buzsáki, G. *Rhythms of the Brain* (Oxford University Press, 2006).
- 725 60. Llinás, R. & Yarom, Y. Properties and distribution of ionic conductances generating
726 electroresponsiveness of mammalian inferior olivary neurones in vitro. *J. Physiol.* **315**,
727 569-584 (1981).
- 728 61. Stuart, G., Schiller, J. & Sakmann, B. Action potential initiation and propagation in rat
729 neocortical pyramidal neurons. *J. Physiol.* **505**, 617-632 (1997).
- 730 62. Crandall, S. R., Govindaiah, G. & Cox, C. L. Low-Threshold Ca²⁺ Current Amplifies
731 Distal Dendritic Signaling in Thalamic Reticular Neurons. *J. Neurosci.* **30**, 15419-
732 15429 (2010).
- 733 63. Destexhe, a, Neubig, M., Ulrich, D. & Huguenard, J. Dendritic low-threshold calcium
734 currents in thalamic relay cells. *J. Neurosci.* **18**, 3574-3588 (1998).
- 735 64. Errington, A. C., Renger, J. J., Uebele, V. N. & Crunelli, V. State-Dependent Firing
736 Determines Intrinsic Dendritic Ca²⁺ Signaling in Thalamocortical Neurons. *J.*
737 *Neurosci.* **30**, 14843-14853 (2010).
- 738 65. Kovács, K., Sik, A., Ricketts, C. & Timofeev, I. Subcellular distribution of low-voltage
739 activated T-type Ca²⁺ channel subunits (Cav3.1 and Cav3.3) in reticular thalamic
740 neurons of the cat. *J. Neurosci. Res.* **88**, 448-460 (2010).
- 741 66. Williams, S. R. & Stuart, G. J. Action potential backpropagation and somato-dendritic
742 distribution of ion channels in thalamocortical neurons. *J. Neurosci.* **20**, 1307-1317
743 (2000).
- 744 67. Zomorodi, R., Kröger, H. & Timofeev, I. Modeling Thalamocortical Cell: Impact of
745 Ca²⁺ Channel Distribution and Cell Geometry on Firing Pattern. *Front. Comp.*
746 *Neurosci.* **2**, 5 (2008).
- 747 68. Connelly, W. M., Crunelli, V. & Errington, A. C. The Global Spike: Conserved
748 Dendritic Properties Enable Unique Ca²⁺ Spike Generation in Low-Threshold Spiking
749 Neurons. *J. Neurosci.* **35**, 15505-15522 (2015).
- 750 69. Major, G., Larkum, M. E. & Schiller, J. Active properties of neocortical pyramidal
751 neuron dendrites. *Ann. Rev. Neurosci.* **36**, 1-24 (2013).
- 752 70. Stuart, G., Spruston, N. & Häusser, M. *Dendrites* (Oxford University Press, 2016)
- 753 71. Sieber, A. R., Min, R. & Nevian, T. Non-Hebbian long-term potentiation of inhibitory
754 synapses in the thalamus. *J. Neurosci.* **33**, 15675-15685 (2013).
- 755 72. Zaman, T. *et al.* CaV2.3 Channels Are Critical for Oscillatory Burst Discharges in the
756 Reticular Thalamus and Absence Epilepsy. *Neuron* **70**, 95-108 (2011).

- 757 73. Connelly, W. M., Crunelli, V. & Errington, A. C. Variable Action Potential
758 Backpropagation during Tonic Firing and Low-Threshold Spike Bursts in
759 Thalamocortical But Not Thalamic Reticular Nucleus Neurons. *J. Neurosci.* **37**, 5319-
760 5333 (2017).
- 761 74. Errington, A. C., Hughes, S. W. & Crunelli, V. Rhythmic dendritic Ca²⁺ oscillations in
762 thalamocortical neurons during slow non-REM sleep-related activity in vitro. *J.*
763 *Physiol.* **590**, 3691-3700 (2012).
- 764 75. Cueni, L. *et al.* T-type Ca²⁺ channels, SK2 channels and SERCAs gate sleep-related
765 oscillations in thalamic dendrites. *Nat. Neurosci.* **11**, 683-692 (2008).
- 766 76. Chausson, P., Leresche, N. & Lambert, R. C. Dynamics of Intrinsic Dendritic Calcium
767 Signaling during Tonic Firing of Thalamic Reticular Neurons. *PLoS ONE* **8**, e72275
768 (2013).
- 769 77. Perez-Reyes, E. Molecular physiology of low-voltage-activated t-type calcium
770 channels. *Physiol. Rev.* **83**, 117-161 (2003).
- 771 78. Astori, S. *et al.* The Ca(V)_{3.3} calcium channel is the major sleep spindle pacemaker in
772 thalamus. *Proc. Natl. Acad. Sci. (USA)* **108**, 13823-13828 (2011).
- 773 79. Swadlow, H. A. & Gusev, A. G. The impact of 'bursting' thalamic impulses at a
774 neocortical synapse. *Nat. Neurosci.* **4**, 402-408 (2001).
- 775 80. Reinagel, P., Godwin, D., Sherman, S. M. & Koch, C. Encoding of visual information
776 by LGN bursts. *J. Neurophysiol.* **81**, 2558-2569 (1999).
- 777 81. Sherman, S. M. & Guillery, R. W. Functional organization of thalamocortical relays. *J.*
778 *Neurophysiol.* **76**, 1367-1395 (1996).
- 779 82. Balduzzi, D. & Tononi, G. What can neurons do for their brain? Communicate
780 selectivity with bursts. *Theory Biosci.* **132**, 27-39 (2013).
- 781 83. Kepecs, A. & Lisman, J. Information encoding and computation with spikes and
782 bursts. *Network* **14**, 103-118 (2003).
- 783 84. Beierlein, M., Fall, C. P., Rinzel, J. & Yuste, R. Thalamocortical bursts trigger
784 recurrent activity in neocortical networks: layer 4 as a frequency-dependent gate. *J.*
785 *Neurosci.* **22**, 9885-9894 (2002).
- 786 85. Rosanova, M. & Ulrich, D. Pattern-specific associative long-term potentiation induced
787 by a sleep spindle-related spike train. *J. Neurosci.* **25**, 9398-9405 (2005).
- 788 86. Hu, H. & Agmon, A. Differential Excitation of Distally versus Proximally Targeting
789 Cortical Interneurons by Unitary Thalamocortical Bursts. *J. Neurosci.* **36**, 6906-6916
790 (2016).
- 791 87. Izhikevich, E. M., Desai, N. S., Walcott, E. C. & Hoppensteadt, F. C. Bursts as a unit
792 of neural information: selective communication via resonance. *Trends Neurosci.* **26**,
793 161-167 (2003).
- 794 88. Guido, W. & Weyand, T. Burst responses in thalamic relay cells of the awake
795 behaving cat. *J. Neurophysiol.* **74**, 1782-1786 (1995).
- 796 89. Ortuño, T., Grieve, K. L., Cao, R., Cudeiro, J. & Rivadulla, C. Bursting thalamic
797 responses in awake monkey contribute to visual detection and are modulated by
798 corticofugal feedback. *Front. Behav. Neurosci.* **8**, 198 (2014).
- 799 90. Luscher, C. & Malenka, R. C. NMDA Receptor-Dependent Long-Term Potentiation
800 and Long-Term Depression (LTP/LTD). *Cold Spring Harb Perspect Biol.* **4**. pii:

- 801 a005710 (2012).
- 802 91. Kato, H. K., Watabe, A. M. & Manabe, T. Non-Hebbian synaptic plasticity induced by
803 repetitive postsynaptic action potentials. *J. Neurosci.* **29**, 11153-11160 (2009).
- 804 92. Jones, E. G. *The Thalamus* (Springer, 1985).
- 805 93. Pigeat, R., Chausson, P., Dreyfus, F. M., Leresche, N. & Lambert, R. C. Sleep slow
806 wave-related homo and heterosynaptic LTD of intrathalamic GABAergic synapses:
807 involvement of T-type Ca²⁺ channels and metabotropic glutamate receptors. *J.*
808 *Neurosci.* **35**, 64-73 (2015).
- 809 94. Astori, S. & Lüthi, A. Synaptic plasticity at intrathalamic connections via CaV3.3 T-
810 type Ca²⁺ channels and GluN2B-containing NMDA receptors. *J. Neurosci.* **33**, 624-
811 630 (2013).
- 812 95. Hsu, C. L., Yang, H. W., Yen, C. T. & Min, M. Y. A requirement of low-threshold
813 calcium spike for induction of spike-timing-dependent plasticity at corticothalamic
814 synapses on relay neurons in the ventrobasal nucleus of rat thalamus. *Chin. J.*
815 *Physiol.* **55**, 380-389 (2012).
- 816 96. Hsu, C.-L., Yang, H.-W., Yen, C.-T. & Min, M.-Y. Comparison of synaptic transmission
817 and plasticity between sensory and cortical synapses on relay neurons in the
818 ventrobasal nucleus of the rat thalamus. *J. Physiol.* **588**, 4347-4363 (2010).
- 819 97. Haas, J. S., Zavala, B. & Landisman, C. E. Activity-Dependent Long-Term Depression
820 of Electrical Synapses. *Science* **334**, 389-393 (2011).
- 821 98. Sevetson, J., Fittro, S., Heckman, E. & Haas, J. S. A calcium-dependent pathway
822 underlies activity-dependent plasticity of electrical synapses in the thalamic reticular
823 nucleus. *J. Physiol.* **595**, 4417-4430 (2017).
- 824 99. Lee, S., Patrick, S. L., Richardson, K. A. & Connors, B. W. Two Functionally Distinct
825 Networks of Gap Junction- Coupled Inhibitory Neurons in the Thalamic Reticular
826 Nucleus. *J. Neurosci.* **34**, 13170-13182 (2014).
- 827 100. Lüthi, A. & McCormick, D. A. H-current: properties of a neuronal and network
828 pacemaker. *Neuron* **21**, 9-12 (1998).
- 829 101. Lüthi, A. & McCormick, D. A. Modulation of a pacemaker current through Ca(2+)-
830 induced stimulation of cAMP production. *Nat. Neurosci.* **2**, 634-641 (1999).
- 831 102. Tononi, G. & Cirelli, C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res.*
832 *Bull.* **62**, 143-150 (2003).
- 833 103. Diekelmann, S. & Born, J. The memory function of sleep. *Nat. Rev. Neurosci.* **11**, 114-
834 126 (2010).
- 835 104. Watson, B. O., Levenstein, D., Greene, J. P., Gelineas, J. N. & Buzsáki, G. Network
836 Homeostasis and State Dynamics of Neocortical Sleep. *Neuron* **90**, 839-852 (2016).
- 837 105. Liu, Z.-W., Faraguna, U., Cirelli, C., Tononi, G. & Gao, X.-B. Direct evidence for wake-
838 related increases and sleep-related decreases in synaptic strength in rodent cortex. *J.*
839 *Neurosci.* **30**, 8671-8675 (2010).
- 840 106. Aton, S. J. *et al.* Mechanisms of Sleep-Dependent Consolidation of Cortical Plasticity.
841 *Neuron* **61**, 454-466 (2009).
- 842 107. Tononi, G. & Cirelli, C. Sleep and the Price of Plasticity: From Synaptic and Cellular
843 Homeostasis to Memory Consolidation and Integration. *Neuron* **81**, 12-34 (2014).

- 844 108. Durkin, J. *et al.* Cortically coordinated NREM thalamocortical oscillations play an
845 essential, instructive role in visual system plasticity. *Proc. Natl. Acad. Sci. (USA)* **114**,
846 10485-10490 (2017).
- 847 109. Acsady, L. The thalamic paradox. *Nat. Neurosci.* **20**, 901–902 (2017).
- 848 110. Halassa, M. M. & Acsády, L. Thalamic Inhibition: Diverse Sources, Diverse Scales.
849 *Trends Neurosci.* **39**, 680-693 (2016).
- 850 111. Halassa, M. M. *et al.* State-Dependent Architecture of Thalamic Reticular
851 Subnetworks. *Cell* **158**, 808-821 (2014).
- 852 112. Clemente-Perez, A. *et al.* Distinct Thalamic Reticular Cell Types Differentially
853 Modulate Normal and Pathological Cortical Rhythms. *Cell Reports* **19**, 2130-2142
854 (2017).
- 855 113. Wells, M. F., Wimmer, R. D., Schmitt, L. I., Feng, G. & Halassa, M. M. Thalamic
856 reticular impairment underlies attention deficit in *Ptchd1*(Y/-) mice. *Nature* **532**, 58-63
857 (2016).
- 858 114. Guehl, D. *et al.* Tremor-related activity of neurons in the ‘motor’ thalamus: changes in
859 firing rate and pattern in the MPTP vervet model of parkinsonism. *Eur. J. Neurosci.*
860 **17**, 2388-2400 (2003).
- 861 115. Magnin, M., Morel, A. & Jeanmonod, D. Single-unit analysis of the pallidum, thalamus
862 and subthalamic nucleus in parkinsonian patients. *Neuroscience* **96**, 549-64 (2000).
- 863 116. von Krosigk, M., Bal, T. & McCormick, D. A. Cellular mechanisms of a synchronized
864 oscillation in the thalamus. *Science* **261**, 361-4 (1993).
- 865 117. Contreras, D. & Steriade, M. Cellular basis of EEG slow rhythms: a study of dynamic
866 corticothalamic relationships. *J. Neurosci.* **15**, 604-622 (1995).
- 867 118. Amzica, F. & Steriade, M. Cellular substrates and laminar profile of sleep K-complex.
868 *Neuroscience* **82**, 671-686 (1998).
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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**

898 Substantial contribution to discussion of content

899 Review/Editing of manuscript before submission

900 **Francois David**

901 Substantial contribution to discussion of content

902 Review/Editing of manuscript before submission

903 **Stuart (W) Hughes**

904 Substantial contribution to discussion of content

905 Review/Editing of manuscript before submission

906 **Regis (C) Lambert**

907 Substantial contribution to discussion of content

908 Review/Editing of manuscript before submission

909 **Nathalie Leresche**

910 Substantial contribution to discussion of content

911 Review/Editing of manuscript before submission

912

913

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

916 .

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924

925 **Glossary**

926 • **Thalamocortical neurons:** Glutamatergic thalamic neurons that project to the
927 neocortex.

928

929 • **Nucleus reticularis thalami neurons:** GABAergic neurons of this thin, laterally
930 located, thalamic nucleus that do not project to the neocortex.

931

932 • **Sleep spindles:** Oscillatory brain activity that constitutes an EEG hallmark of non-rem
933 sleep and consists of waxing-and-waning 7-14 Hz oscillations lasting a few seconds.

934

935 • **First-order and higher-order thalamic nuclei:** This functional classification of
936 thalamic nuclei is based on their main driving input: subcortical or cortical. First order
937 nuclei relay a particular modality of peripheral or subcortical information to a primary
938 cortical area. Higher order nuclei relay information from layer 5 cortical neurons to
939 other cortical areas and act like a hub in cortico-thalamo-cortical information pathways.

940

941 • **Intralaminar thalamic nuclei.** A collection of thalamic nuclei involved in specific
942 cognitive and motor functions that play a key role in the salience of stimuli of various
943 modalities.

944

945 • **Cell-intrinsic mechanisms:** Electrical behavior of a neuron that results from its passive
946 and voltage-dependent electrical properties without a contribution of the synaptic
947 network.

948

949 • **Up and Down states:** Based on their intrinsic properties and/or the influence of the
950 synaptic network, some neurons present a two-state behavior, characterized by two
951 membrane potentials, a depolarized “Up” state and a hyperpolarized “Down” state.

952

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

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

957

958 • **Electrotonic properties:** The combined electrical properties of a neuron that alter the
959 manner in which subthreshold voltage changes propagates throughout the axon and the
960 dendritic tree.

961

962 • **Backpropagating action potentials:** The transient depolarization that occurs in the
963 dendrites as a result of the generation of an action potential in the soma or axon initial
964 segment.

965

966 • **Rescale (synaptic re-scaling):** indicates to the normalization of the strength of synaptic
967 connections that had previously been either increased or decreased in response to
968 (relatively long-term) changes in neuronal activity.

969

970

971 **Short Biographies**

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

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

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

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

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

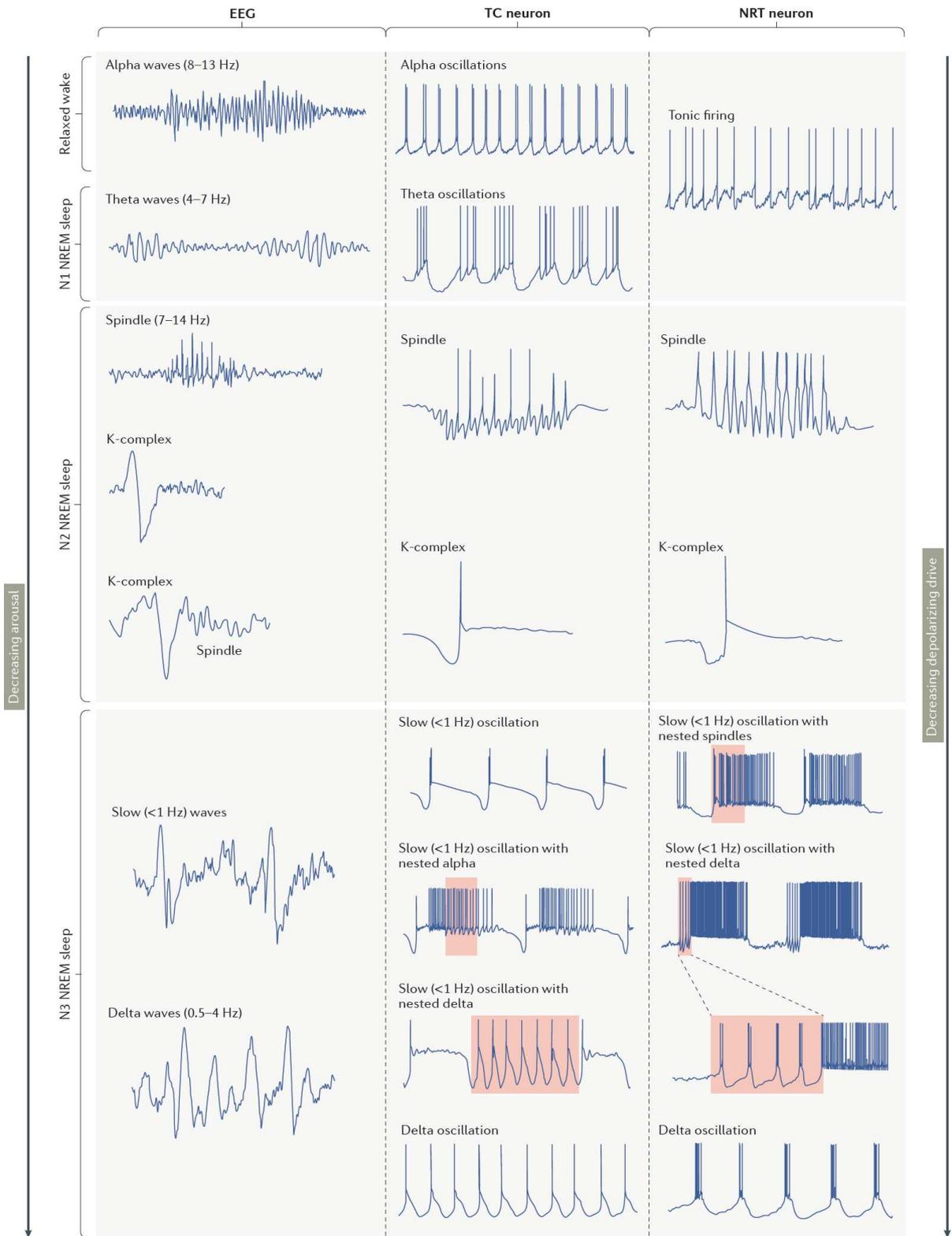
992 **Stuart W. Hughes** received his PhD from Cardiff University (UK). He is currently Director
993 and Head of Pharmacology at Vertex Pharmaceuticals Europe Ltd (Oxford, UK) where his
994 main areas of focus are in neuroscience and orphan diseases. He has previously held the
995 positions of Wellcome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

998 **Régis C. Lambert** received his PhD from the University of Strasbourg, France, working in
999 neuroendocrinology. During his postdoctoral fellowship, he focused on biophysics of calcium
1000 channels. As a Professor of the University Pierre and Marie Curie, he is currently leading a
1001 group with Nathalie Leresche in the Department Neuroscience Paris Seine, which focuses on
1002 thalamic excitability with particular emphasis on T-type calcium channels.

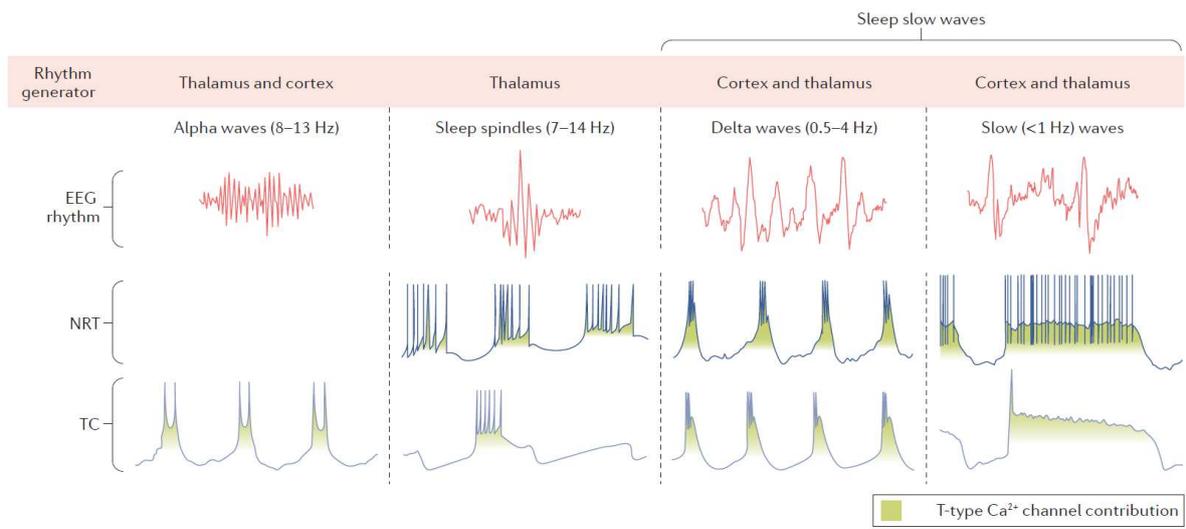
1003 **Nathalie Leresche** received her PhD from the University Pierre and Marie Curie in Paris,
1004 France, working on visual processing. After postdoctoral fellowship with V. Crunelli at St.
1005 Georges' Hospital Medical School (London), she came back to France as a CNRS researcher.
1006 She is currently leading a group with Régis C. Lambert at the Department Neuroscience Paris
1007 Seine. Her research focuses on thalamocortical mechanisms in sleep and absence epilepsy.

1008 **Adam C. Errington** is a Senior Research Fellow at the Neuroscience and Mental Health
1009 Research Institute, Cardiff University (UK). His laboratory investigates the structure and
1010 function of dendrites in the thalamus and their roles in physiology and neurological diseases
1011 and the role of extrasynaptic GABA signalling in the brain.

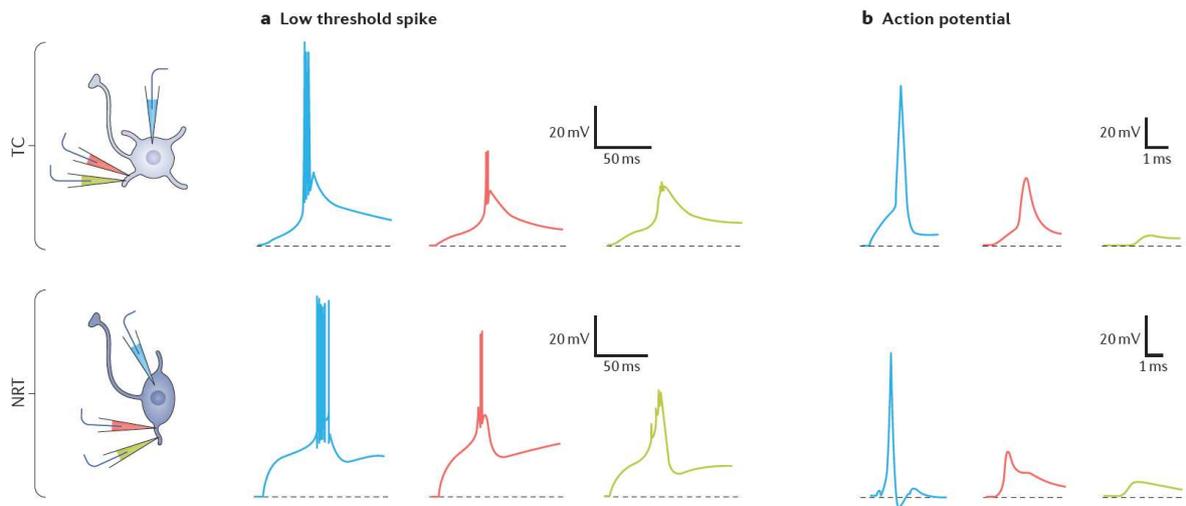
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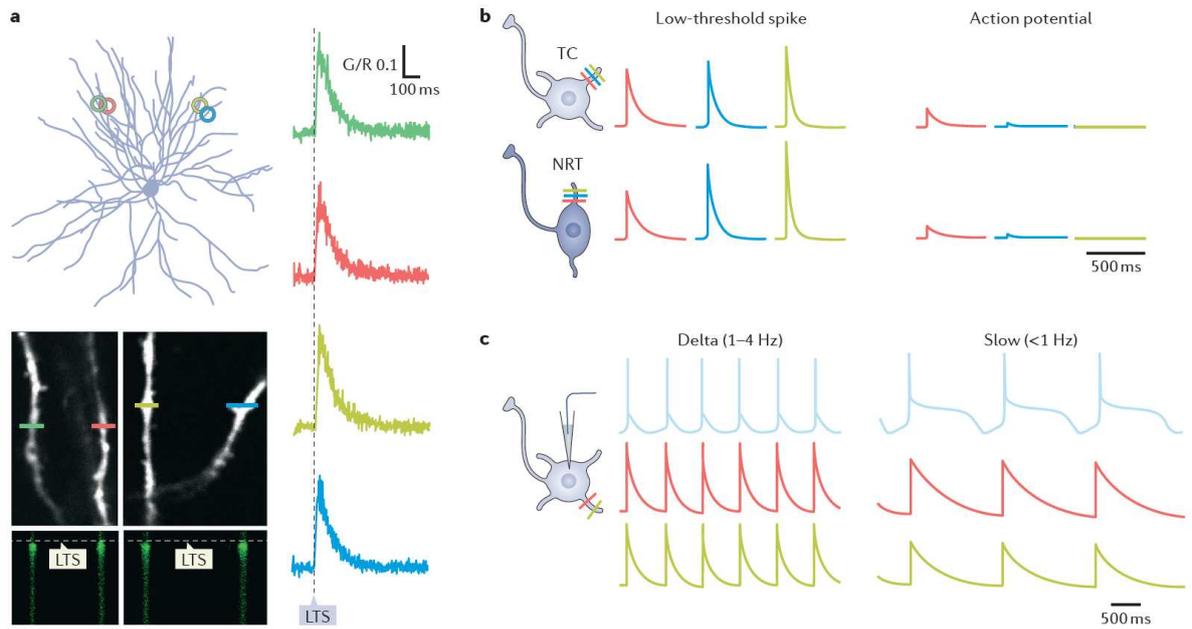


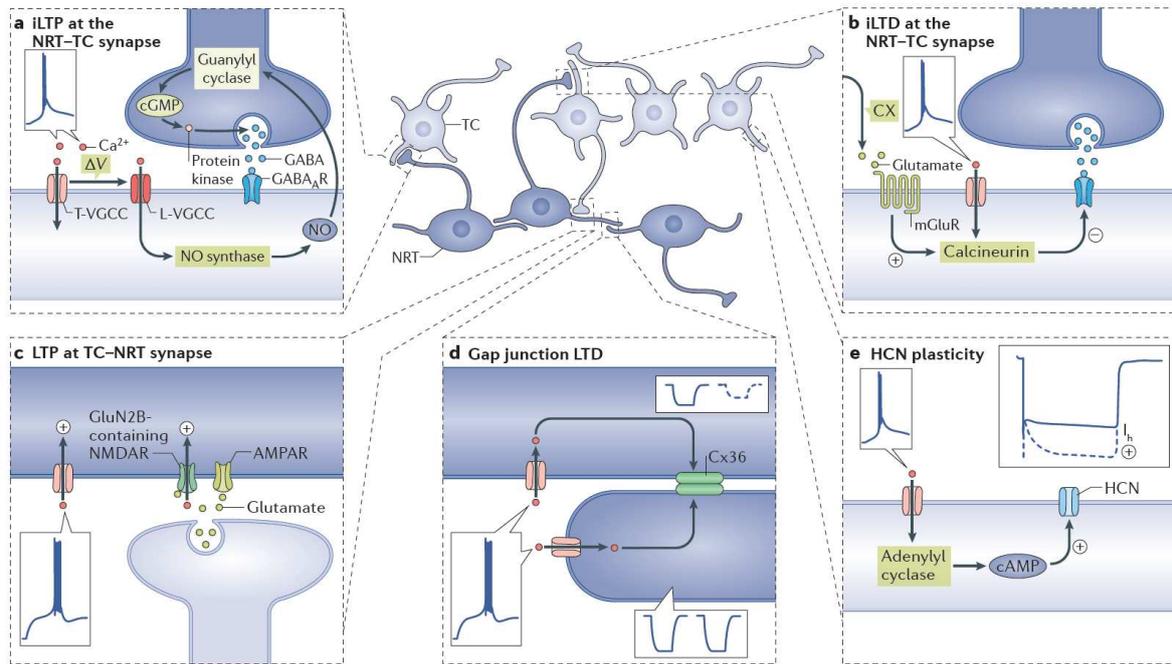
1015 **Figure 2**



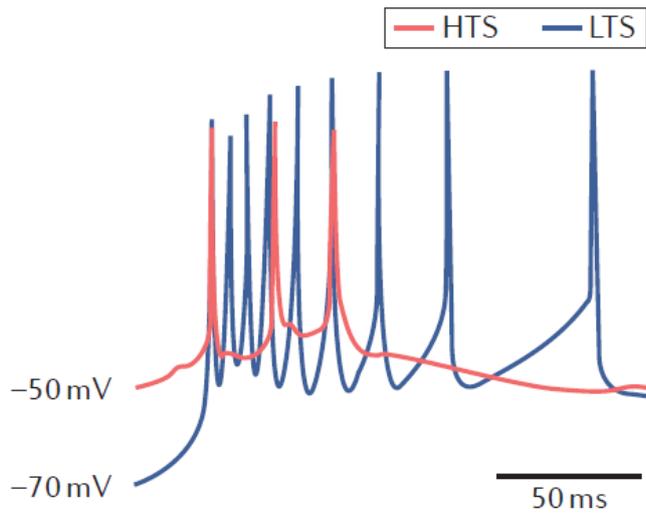
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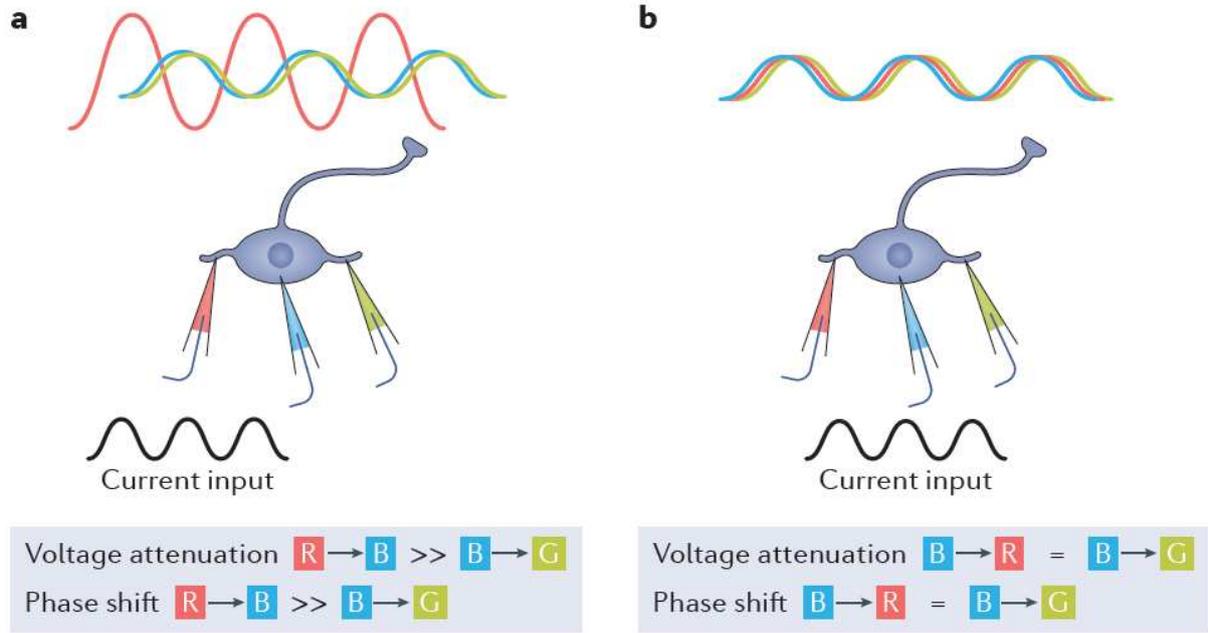


1023 **BOX 1 Figure**



1024

1025 **BOX 2 Figure**



1026