

Tonic and burst firing: dual modes of thalamocortical relay

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All thalamic relay cells exhibit two distinct response modes – tonic and burst – that reflect the status of a voltage-dependent, intrinsic membrane conductance. Both response modes efficiently relay information to the cortex in behaving animals, but have markedly different consequences for information processing. The lateral geniculate nucleus, which is the thalamic relay of retinal information to cortex, provides a reasonable model for all of thalamus. Compared with burst mode, geniculate relay cells that are firing in tonic mode exhibit better linear summation, but have poorer detectability for visual stimuli. The switch between the response modes can be controlled by nonretinal, modulatory afferents to these cells, such as the feedback pathway from cortex. This allows the thalamus to provide a dynamic relay that affects the nature and format of information that reaches the cortex.

All thalamic relay cells respond to excitatory inputs in one of two different modes, which are known as burst and tonic. The response mode depends on the state of a voltage- (and time-) dependent inward Ca^{2+} current that is known as I_T , because it involves T type Ca^{2+} channels located in the membranes of the soma and dendrites¹⁻⁵. In burst mode, I_T is activated and an inflow of Ca^{2+} produces a depolarizing waveform, known as the low threshold spike (LTS) that, in turn, usually activates a burst of conventional action potentials. When a relay cell has been relatively depolarized for ~100 ms or more, I_T becomes inactivated and the cell fires in tonic mode. However, after ~100 ms or more of relative hyperpolarization, inactivation of I_T is alleviated and the cell fires in burst mode. Some important cellular properties that underlie the control of the Ca^{2+} channels are summarized in Box 1.

The two firing modes strongly affect the manner by which thalamic relay cells respond to incoming inputs. It had been thought that only tonic firing occurs during normal, waking behavior and that bursting is limited to drowsiness, slow-wave sleep or certain pathological conditions. However, new data, which are reviewed below, suggest that burst firing is an important relay mode during waking behavior. Crick⁶ first suggested that burst firing of thalamic relay cells could play an important role in attention (see below) and recent evidence supports the notion that this might, in fact, occur. Here the evidence is reviewed regarding the control of response mode by the thalamic circuitry, and some possible implications of having both modes of firing available to relay cells are speculated.

Tonic and burst modes are both relay modes
Burst mode was first described for slow-wave sleep, drowsiness and certain pathological conditions⁷⁻⁹. This is reflected in long bouts of rhythmic bursting

that are synchronized across large populations of relay cells. This process dominates relay cell responses to such an extent that this mode of firing prevents normal relay functions. According to this view, as an animal awakes (or is released from a pathological state), relay cells depolarize, thereby inactivating I_T and promoting tonic firing, which is seen as the only useful relay mode.

However, recent data, mostly arising from studies on the lateral geniculate nucleus in rodents, cats and monkeys¹⁰⁻¹⁶, indicate that burst firing serves as an effective relay mode in the awake state¹⁷. Geniculate cells occasionally fire in burst mode, but fire arrhythmically and respond vigorously to visual stimuli when doing so^{13,15,16,18,19}. Examples of such burst mode firing in an awake, behaving monkey are illustrated in Fig. 1. Switching between tonic and burst firing occurs irregularly every several 100 ms to every several seconds, presumably reflecting slow changes in membrane potential that switch I_T between inactivated and de-inactivated (Box 1). The extent of bursting in geniculate neurons of cats and monkeys during wakefulness is relatively low, but is more common during visual stimulation (~10% of the time in monkeys)^{11,18}. It is plausible that bursting levels might depend on untested behavioral factors and vary considerably from estimates made to date. For example, whereas bursting in the awake, behaving cat occurs with an overall probability of only 0.09 in any 1 s period, there is a '...high incidence of bursting during the initial phase of fixation (i.e., 1st cycle of visual stimulation)...'¹⁸. Bursting is also evident in somatosensory thalamus in awake monkeys¹¹.

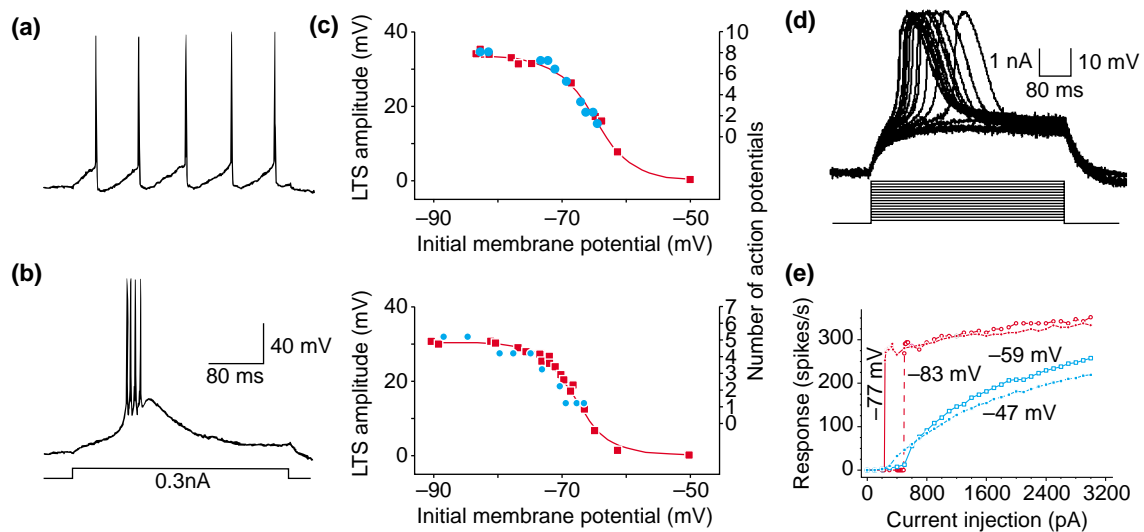
Arrhythmic bursting has also been described for thalamic neurons in awake humans²⁰⁻²². It has often been assumed that the bursting that was observed was pathological, because the human subjects suffered various pathologies that dictated thalamic recordings as part of their therapy. However, a recent study of humans²¹ showed that the same type of arrhythmic bursting occurs across a wide variety of pathological conditions. Because it was deemed improbable by these authors that such different pathological conditions could cause the same bursting, they concluded that, as in animals¹⁰⁻¹⁶, the bursting is a normal condition of thalamic functioning in awake humans.

Difference between tonic and burst firing for the relay of information

During tonic firing, action potentials in the relay cell are linked directly to an EPSP in that cell. However,

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Box 1. Cellular properties underlying tonic and burst response modes



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Fig. 1. Properties of I_T and the low threshold spike (LTS). All examples are from relay cells of lateral geniculate nucleus of the cat, recorded intracellularly from an *in vitro* slice preparation. (a), (b) Voltage dependency of the LTS. Responses to the same depolarizing current pulse delivered intracellularly are shown, but from two different initial holding potentials. When the cell is relatively depolarized (a), I_T is inactivated and the cell responds with a stream of unitary action potentials as long as the stimulus is suprathreshold for firing. This is the tonic mode of firing. When the cell is relatively hyperpolarized (b), I_T is de-inactivated and the current pulse activates an LTS with four action potentials riding its crest. This is the burst mode of firing. (c) Voltage dependency of the amplitude of LTS and burst response. Examples for two cells are shown. The more hyperpolarized the cell before being activated (initial membrane potential), the larger the LTS (red points and curve) and the more action potentials (AP) in the burst (blue points). The number of action potentials was measured first, after which TTX was applied to isolate the LTS for measurement. Redrawn, with permission, from Ref. a. (d) All-or-none nature of LTSs measured in the presence of TTX in a geniculate cell. The cell was initially hyperpolarized and current pulses were injected, starting at an amplitude of 200 pA and incremented in 10 pA steps. Smaller (subthreshold) pulses led to pure resistive-capacitative responses, but all larger (suprathreshold) pulses led to LTSs. Much like conventional action potentials, the LTSs are all of the same amplitude, regardless of how far the depolarizing pulse exceeded the activation threshold, although there is variability in the latency for smaller suprathreshold pulses. (e) Input-output relationship for a single cell. The input variable is the amplitude of the depolarizing current pulse and the output is the firing frequency of the cell. To compare burst and tonic firing, the firing frequency was determined by the first six action potentials of the response, because this cell normally exhibited six action potentials per burst in this experiment. The initial holding potentials are shown and -47 mV and -59 mV reflects tonic mode (blue points and curves), whereas -77 mV and -83 mV reflects burst mode (red points and curves). Redrawn, with permission, from Ref. b.

Some aspects of the voltage dependency of I_T (Refs a–c) are illustrated in Fig. 1. Following ~ 100 ms or more of membrane depolarization relative to -60 to 65 mV, I_T becomes inactivated. The inactivation is removed (i.e. I_T is de-inactivated) by an equivalent time of relative hyperpolarization. In fact, the inactivation or de-inactivation of I_T is a complex function of voltage and time. Therefore, a stronger depolarization will

inactivate I_T more quickly. Similarly, a stronger hyperpolarization will de-inactivate I_T more quickly. Tonic firing prevails if I_T is inactivated (Fig. 1a), whereas burst firing is predominant if I_T is de-inactivated (Fig. 1b). Burst firing can be recognized in extracellular records as a result of a unique pattern of interspike intervals^{d,e}. The amplitude of I_T and the resultant low threshold spike (LTS) depends almost entirely on the level of sustained membrane hyperpolarization before I_T is activated, because the more hyperpolarized the membrane, the more T type Ca^{2+} channels are de-inactivated and consequently available to contribute to the LTS (Fig. 1c). However, from any given initial membrane potential, an all-or-none LTS is elicited (Fig. 1d) (Ref. b). Also, the size of the burst has the same relationship with the initial membrane potential as the LTS amplitude, because the number of action potentials in a burst is determined by the amplitude of the LTS (Fig. 1c). This, in turn, means that, from any given hyperpolarized holding potential, the same number of action potentials will be elicited in a burst regardless of the size of a suprathreshold activating input. Consequently, there is a highly nonlinear input-output relationship during burst firing, whereas the relationship during tonic firing is more linear (Fig. 1e).

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in burst mode, the link between the EPSP and action potentials is indirect, via the all-or-none LTS (see Fig. 1a,b in Box 1). Thus, in tonic firing, larger

EPSPs elicit higher firing rates. However, larger EPSPs in burst mode do not elicit larger LTSs and, therefore, do not elicit higher firing rates (see

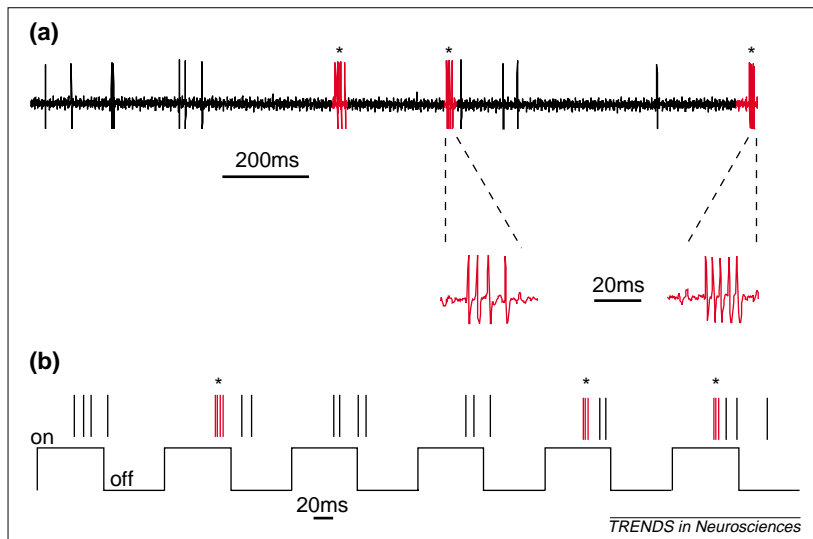


Fig. 1. Extracellular recordings from two neurons of the lateral geniculate nucleus in an awake, behaving monkey. The monkey maintained active fixation of a spot during this recording (for methodological details, see Ref. 11). (a) Responses during spontaneous activity. Asterisks indicate three bursts (red), two of which are shown with an expanded time base. All other action potentials represent tonic firing. (b) Responses of an on-center geniculate neuron during visual stimulation that consisted of whole field stimulation of light on and off. Responses to the second, fifth and sixth cycles were in burst mode (asterisks), whereas responses to other cycles were in tonic mode.

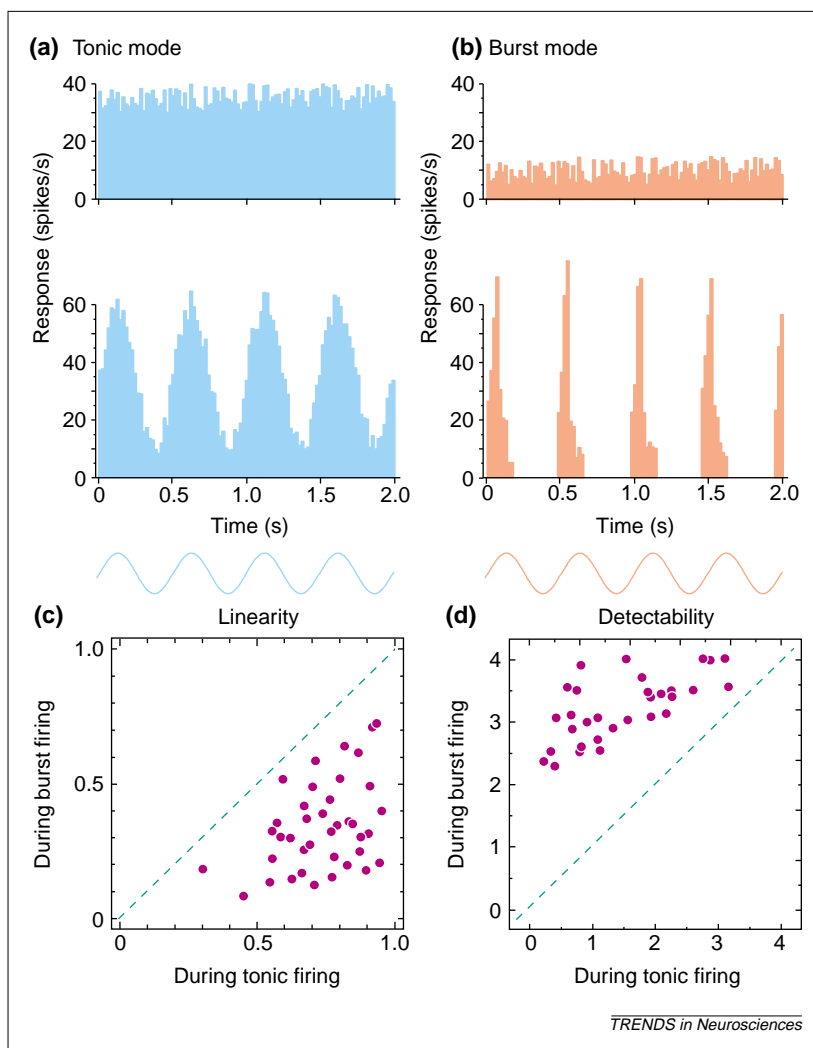


Fig. 1d,e in Box 1). Thus, the input-output relationship for tonic firing is almost linear, whereas that for burst firing is nonlinear and resembles a step function.

Studies of geniculate responses to visual stimuli *in vivo* indicate that both response modes transmit approximately equal levels of information¹². This alone shows that bursting represents a useful relay mode. Nevertheless, the quality of the information differs between modes (Fig. 2). First, during both modes, the response is brisk, but the response profile to a sinusoidal input is more sinusoidal during tonic compared with burst firing (Fig. 2a,b bottom), thus reflecting better linear summation (Fig. 2c). Second, spontaneous activity is higher during tonic firing (Fig. 2a,b top), which helps to maintain linearity by minimizing rectification of the response. More to the point, spontaneous activity represents noise against which the visual response (i.e. the signal) must be detected. The histograms in Fig. 2a,b suggest that the signal-to-noise ratio and, therefore, detectability, is higher during burst than during tonic firing. This has been confirmed by measuring detectability with techniques based on signal detection theory (Fig. 2d)^{23–25}. Thus, tonic firing affords better linearity, whereas burst firing supports better signal detection. Other differences in information relayed by each firing mode have also been reported^{15,26}.

Tonic firing minimizes nonlinear distortions in the relay, thereby supporting a more faithful reconstruction of the visual world. Burst mode maximizes initial stimulus detection, perhaps as a sort of 'wake-up call' that something has changed in the environment. It might seem odd to think of a burst as a 'wake-up call' when, during slow-wave sleep, bursting dominates the responses of thalamic relay cells. Although this notion might, therefore, be incorrect, it does seem at least equally plausible that the rhythmic, synchronized bursting

Fig. 2. Tonic and burst responses to visual stimulation of relay cells from the lateral geniculate nucleus of a cat (recorded *in vitro*). (a,b) Average response histograms of responses, recorded intracellularly, of one cell to four cycles of drifting sinusoidal grating (lower) and during spontaneous activity (upper). The contrast changes that resulted from the drifting grating are illustrated below the histograms as blue or red sine waves. Current that was injected through the recording electrode was used to bias membrane potential to being more depolarized (-65 mV), which produced tonic firing (a), or more hyperpolarized (-75 mV), producing burst firing (b). (c,d) Response linearity (c) and signal detectability (d) during tonic and burst firing (for details of how many of the data points were derived, see Refs 13,16). Each point in the scatter plots reflects data from one relay cell of the cat's lateral geniculate nucleus recorded *in vivo* during visual stimulation. The plots can be used to compare the response during tonic firing on the abscissa versus burst firing on the ordinate. The broken line in each plot has a slope of 1. To obtain a measure of linearity, responses to sine wave gratings were Fourier-analyzed and a linearity index was computed by dividing the linear F1 component by the sum of the higher-order nonlinear components. The larger this index, the more linear the response. Note that every single cell shows more linearity during tonic firing. For detectability, d' values were determined by receiver operating characteristic (ROC) analysis (for details, see Refs. 23–25).

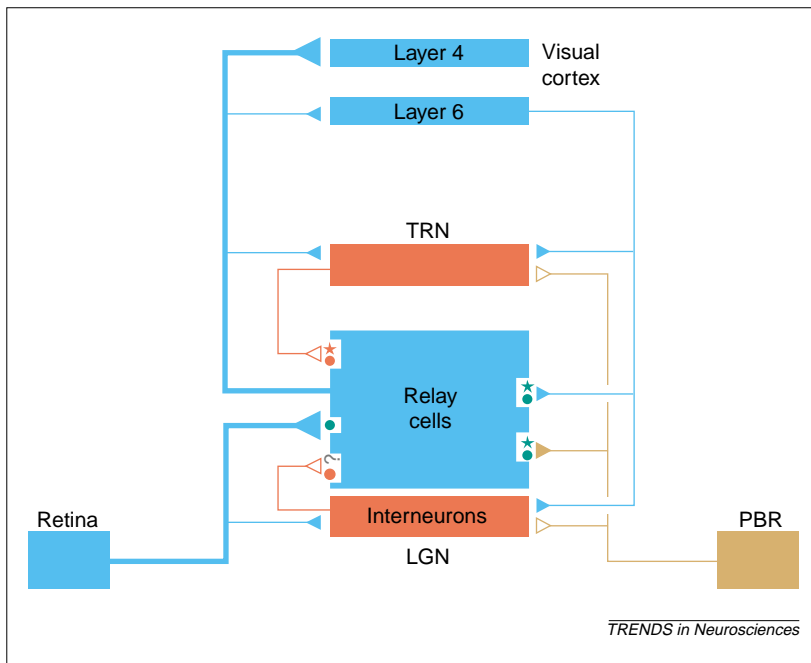


Fig. 3. Neural circuitry of the lateral geniculate nucleus with related receptors present on relay cells. Other thalamic nuclei appear to be organized according to the same pattern^{30,31}. Blue indicates cells and axons that are glutamatergic. Red indicates GABAergic cells and axons. Brown indicates cholinergic cells and axons. The cholinergic cells and axons also appear to colocalize nitric oxide. The retinal input activates only ionotropic receptors (circles), whereas all nonretinal inputs activate metabotropic receptors (stars) and often also ionotropic receptors. The question mark related to input from interneurons indicates uncertainty as to whether metabotropic receptors are involved. Thick and thin lines indicate driver and modulator inputs, respectively^{28,31}. Filled and open icons for synaptic terminals indicate excitatory and inhibitory inputs, respectively. Abbreviations: LGN, lateral geniculate nucleus; PBR, parabrachial region of the brainstem; TRN, thalamic reticular nucleus.

of relay cells during sleep reflects a different message for the cortex: one that indicates a complete lack of information being relayed from the periphery. The notion of a 'wake-up call' is similar to the previously proposed 'searchlight hypothesis' of Crick⁶. He suggested that neurons in the thalamic reticular nucleus powerfully inhibit relay cells, thereby de-inactivating I_T in these cells and causing the next excitatory input to activate a burst. This is similar to the hypothesis proposed here, although Crick includes more-specific suggestions for control of the reticular 'searchlight' and the effect of bursting on dynamic cell assemblies (see Ref. 6 for details).

For the current proposal, one example to consider is the response of a geniculate cell to the sudden appearance of a novel object in a previously uninteresting or unattended region of visual space. If the cell were in burst mode, it would better signal the detection of this object and still permit a crude, initial analysis of it than if it were in tonic mode. Once the change is detected, the neuron could be switched to tonic mode so that the new object could be analyzed more faithfully. It is also plausible that bursts activate EPSPs more effectively in their target cortical cells, because recent evidence suggests that an action potential in a geniculate cell will probably activate its cortical target if it follows another action potential within ~10 ms (Ref. 27).

Control of response mode

For the aforementioned proposal to function, neuronal circuitry that efficiently controls the response mode must be present. Such neuronal circuitry does appear to exist (Fig. 3). In addition to retinal input to relay cells, which accounts for only 5–10% of synapses on geniculate relay cells (Ref. 28 for further discussion), there is innervation from local

GABAergic cells (~30%), cholinergic cells of the brainstem (~30%) and layer 6 of visual cortex (~30%). [For simplicity, minor (<5%) inputs from other sources are not described^{29–31}.] Therefore, the vast majority of inputs to geniculate relay cells are nonretinal and are concerned chiefly with modulating retinogeniculate transmission.

Synaptic inputs in the lateral geniculate nucleus operate via neurotransmitters that act on postsynaptic receptors from two classes, namely ionotropic and metabotropic receptors^{32–37}. Ionotropic receptors respond simply with a fast postsynaptic potential (PSP), typically with a latency of <1 ms and a duration of a few tens of ms. Metabotropic responses are more elaborate and require a series of complex biochemical reactions to produce a slower PSP, typically with a latency of >10 ms and a duration of hundreds of ms or more. Ionotropic receptors on relay cells include AMPA and NMDA receptors (which respond to glutamate), $GABA_A$, and nicotinic receptors (which respond to acetylcholine). Metabotropic receptors include metabotropic glutamate receptors, $GABA_B$, and muscarinic receptors (which respond to acetylcholine).

Sustained PSPs via metabotropic receptors are more suited to control the response mode. As noted earlier, inactivation or de-inactivation of I_T requires the maintenance of depolarization or hyperpolarization for ~100 ms. Ionotropic receptors are not well suited for this, whereas metabotropic receptors are ideal. It is, therefore, interesting that retinal input, which represents the 'driving' input^{28,31}, activates only ionotropic receptors, whereas all nonretinal inputs, which represent the 'modulators'^{28,31}, activate metabotropic receptors, and often also ionotropic receptors (Fig. 3). It is not clear whether individual nonretinal axons activate only metabotropic or ionotropic receptors. Nevertheless, this pattern of receptor association clearly suggests that one important role of nonretinal inputs is to control the state of I_T and, thus, the response mode. Activation of cortical and brainstem inputs to relay cells can elicit sustained EPSPs to inactivate I_T , thereby producing tonic firing^{38–40}, whereas local GABAergic inputs could elicit sustained IPSPs and cause the opposite result⁴¹. The fact that the same cortical and brainstem afferents innervate relay cells and local GABAergic cells suggests that these nonretinal, extrathalamic afferents can control the response mode effectively in a push-pull manner.

The hypothesis of a burst as a 'wake-up call' can be expanded upon as follows. Imagine a geniculate relay cell, or a small group of such cells, innervating a cortical column and in burst mode. By definition, such cells would be hyperpolarized and would have been silent for ~100 ms. Consequently, the afferent cortical column (including layer 6) would also be relatively inactive. A novel stimulus could then activate LTSs

and cause bursts of action potentials in the relay cells. This could establish a powerful synaptic input to layers 4 and 6, because most geniculate afferents branch to innervate both layers^{42,43}. If some of these activated targets in layer 6 are corticogeniculate cells then they, in turn, could depolarize the afferent geniculate cells and switch them to tonic mode. Thus, the burst would begin to activate the cortical column and prepare it to receive more linear input from the geniculate afferents.

Conclusions

The present account has undoubtedly raised more questions than it has answered about the functioning of the thalamus. Although most available data derive from studies of the lateral geniculate nucleus, the

principles that have been gleaned from these studies probably apply broadly to the thalamus. It is now clear that both tonic and burst response modes play a role in relay functions. It is important to learn how these modes are used and controlled. A plausible speculation has been presented here that could serve as a theoretical framework for future investigations. Furthermore, given evidence that bursts are particularly effective for synaptic communication in the cortex⁴⁴, the effect of firing mode on thalamocortical transmission needs to be investigated and might offer yet another distinction between response modes. The ability of thalamic relay cells to fire in the distinct tonic and burst modes, therefore, appears to underlie an important relay function of thalamus.

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