



A wake-up call from the thalamus

S. Murray Sherman

The role of thalamic burst firing in normal behavior has been controversial, but a paper in this issue offers powerful evidence that bursting may serve as a 'wake-up call' to cortex.

Virtually all information that reaches neocortex and thus conscious awareness is relayed via the thalamus. Thalamic relay cells have intrinsic properties that enable them to respond to inputs in two distinct modes¹, known as 'burst' or 'tonic'; every relay cell of every thalamic nucleus behaves in this way. These modes are thought to importantly influence the type of information relayed to cortex, with burst mode better suited for stimulus detection, and tonic mode providing a more faithful, linear relay of information.

However, there remains some controversy about the role of thalamic cell bursting in normal behavior. Bursting was initially thought to occur only during certain phases of sleep and epilepsy and to represent responses dictated by intrinsic cell and circuit properties; as a result, the pattern of bursting would not be much influenced by incoming information and thus instead would prevent its effective transmission to cortex. Arguments are still made that burst mode is not present in thalamic neurons during the normal waking state and thus does not serve any useful relay function². However, this notion seems impossible to sustain in view of recent evidence of bursting in awake animals, including humans; such burst responses are evoked by sensory stimulation, which suggests instead that bursting is an effective relay mode (reviewed in refs. 3, 4). Specifically, certain features of bursting led to the notion that it could serve as a sort of 'wake-up call' to signal cortex that something has changed in the environment^{3,4}.

In this issue, Swadlow and Gusev⁵ offer powerful new evidence that burst mode is a normal firing mode of thalamic neurons during the waking state and represents a powerful way to get informa-

tion into the cortex. They demonstrated this via an ingenious and technically demanding set of experiments in awake rabbits from which they simultaneously recorded from somatosensory thalamic relay cells and their target cells in layer 4 of somatosensory cortex during spontaneous activity. EEG was used to monitor the behavioral state of the rabbits, and cross-correlograms (to compare spike timing in thalamic and cortical cells) were used to verify functional synaptic connectivity between cell pairs, from thalamic to cortical neurons. These correlograms showed that a spike in the thalamic cell reliably precedes one in the cortical cell by an interval consistent with spike propagation up the axon plus synaptic delay, a strong indicator of a monosynaptic connection. From these correlograms, Swadlow and Gusev could also determine the probability that an action potential in the thalamic afferent would evoke one in the postsynaptic cortical cell. They could distinguish burst from tonic firing via the distinctive interspike interval pattern that occurs during bursting. Using this approach, Swadlow and Gusev showed that the first action potential of a burst is

more than twice as likely to evoke an action potential than is an action potential during tonic firing. Figure 1 shows schematically what their data imply regarding the postsynaptic responses of cortical cells. This is the first such demonstration of a difference between the cortical postsynaptic effects of burst and tonic thalamic firing modes. The advantage the authors have documented for burst mode, they conclude, is consistent with the idea that burst firing can signal changes in the environment to the cortex³.

To begin to understand why this might occur and why the observation is interesting, it is useful to review some of the cellular properties of thalamic relay cells related to tonic and burst response modes^{3,4}. Burst-mode responsiveness is based on a voltage-gated Ca²⁺ conductance that operates via T-type Ca²⁺ channels located in the membranes of the soma and dendrites. These channels are inactivated by depolarization, and their inactivation is removed (that is, they are de-inactivated) by hyperpolarization, thus allowing them to be activated by a suitable depolarization, such as an EPSP (Fig. 2). If the thalamic cell is slightly depolarized at the time an incoming signal arrives, the result is tonic firing (Fig. 2a). If, instead, the cell is first slightly hyperpolarized, the incoming signal activates an all-or-none Ca²⁺ spike and burst firing (Fig. 2b). Importantly, the inactivation state of T channels is governed by a complex combination of membrane voltage and time. That is, the more hyperpolarized the membrane, the faster the T channels de-inactivate, and the more depolarized, the faster they inactivate. With normal physiological levels of membrane potential, it

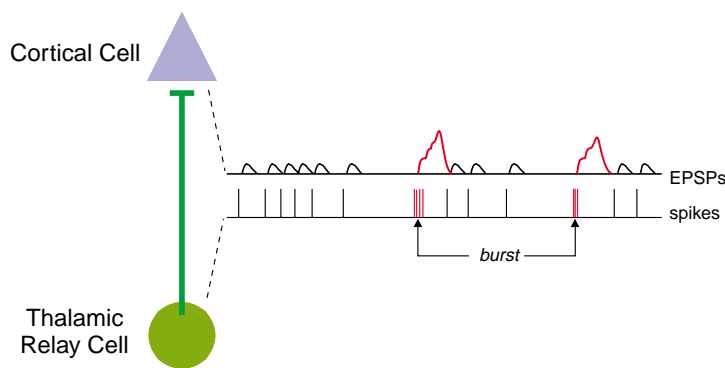


Fig. 1. Schematic interpretation of results of Swadlow and Gusev⁵. A train of action potentials for a thalamic relay cell, each shown as a short vertical line along a baseline. This can be divided into tonic (black) or burst (red) firing. The responses in the form of EPSPs are shown in the postsynaptic cortical cell. Note that the responses to bursts (red EPSPs) are larger than those to tonic firing (black EPSPs). The increased amplitude of the burst-evoked EPSPs are due to both a larger initial EPSP and temporal summation.

The author is in the Department of Neurobiology, State University of New York, Stony Brook, New York 11794-5230, USA
e-mail: s.sherman@sunysb.edu

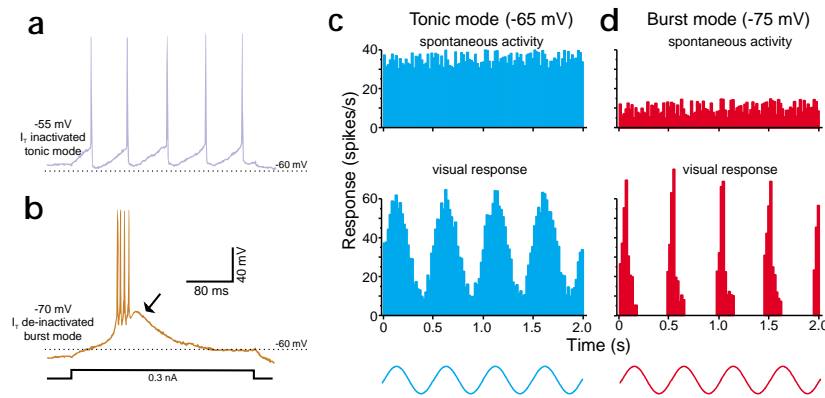


Fig. 2. Some properties of burst and tonic firing recorded intracellularly from relay cells of the lateral geniculate nucleus of cats; redrawn from ref. 3. **(a, b)** Responses of a cell recorded *in vitro* in a slice, showing the different response of the cell in burst and tonic mode to the same depolarizing current injection (bottom trace); this current injection was imposed on top of a holding current (not shown) used to change the standing membrane potential to -55 mV **(a)** or -70 mV **(b)**. When initially depolarized and in tonic mode **(a)**, the current pulse evokes a steady stream of unitary action potentials. When initially hyperpolarized and in burst mode **(b)**, the same current pulse evokes a Ca^{2+} spike (arrow), with, in this example, four action potentials riding its crest. Because these properties are common to all thalamic relay cells, they would apply as well to the thalamic cells studied by Swadlow and Gusev⁵. **(c, d)** Responses of a cell recorded *in vivo* during light anesthesia. All average response histograms are generated from one cell. Current passed through the recording electrode could keep the average membrane potential relatively depolarized and thus place the cell in tonic mode **(c)** or hyperpolarized and thus in burst mode **(d)**. Top histograms show spontaneous activity; bottom ones, responses to a sinusoidal grating drifted through the receptive field. The sine waves under each set of histograms show the contrast changes as the grating drifts through the receptive field.

takes roughly 100 ms for the T channels to inactivate or de-inactivate.

Thus, the signal relayed to cortex is very different between response modes (Fig. 2a and b), including for relay cells of the lateral geniculate nucleus (Fig. 2c and d). Because this is the thalamic relay for retinal input, geniculate cells respond to visual stimuli. Responses to elemental visual stimuli, like drifting sinusoidal gratings, differ sharply between response modes. During tonic firing (Fig. 2c, bottom), the response to the grating looks sinusoidal; in other words, the response profile mimics the stimulus itself, a mark of linearity in the response. During burst firing (Fig. 2d, bottom), the response no longer looks sinusoidal: it is distorted, a mark of nonlinearity. In addition, background firing in the absence of visual stimuli is consistently lower during burst firing (Fig. 2c and d, top). Such activity can be thought of as background noise against which the response to stimulus must be detected. It thus seems from histograms that the ratio of signal (Fig. 2c and d, bottom) to noise (Fig. 2c and d, top) is greater during burst firing. Indeed, burst firing affords better signal detectability, whereas tonic firing preserves linearity, which is critical for accurate stim-

ulus reconstruction in the cortex^{3,4}. This led to the notion that thalamic bursts could serve as a 'wake-up' call for cortex.

We can speculate further regarding one scenario of how this 'wake-up' might work. If a thalamic relay cell (or a group) is in burst mode, it has necessarily been silent for a period because of the hyperpolarization needed to de-inactivate the T channels. This means that the target region of cortex has also for a time not experienced sensory input, and this might signify that the sensory region (of visual space, skin surface and so on) is not being attended. The sudden appearance of a suitable stimulus would evoke a burst in the relay cell(s), which now strongly activates target cortical cells. Interestingly, most, if not all, thalamocortical axons innervating cortical layer 4 also innervate layer 6 via branching axons, and layer 6 contains the parent cells of the feedback corticothalamic pathway⁴. Activation of corticothalamic axons produces a long, slow depolarization of the same relay cells that just responded with a burst, and this depolarization changes these relay cells to tonic mode^{3,4}. Thus, the burst not only provides a strong excitatory wake-up to cortex, it also initiates a switch in the response mode to tonic, enabling cortex subsequently to

receive a more linear and faithful representation of the changed sensory scene.

Swadlow and Gusev⁵ take this notion considerably further with their demonstration that thalamic bursting is more effective than is tonic firing at activating target cortical cells. They also offer a surprising explanation for this finding. Bursts necessarily follow a silent period of at least 100 ms or so. As noted above, this silent period is dictated by the duration of hyperpolarization needed to de-inactivate the T channels: the sustained hyperpolarization means that no action potentials can occur during this period. Swadlow and Gusev noted that single spikes that occasionally happened to follow such a sustained silent period also had an elevated probability of activating a response in the target cortical cell, a probability similar to that of the first spike in a burst. Thus, it is not the cluster of action potentials in the burst that matters, but rather that the first action potential in the burst follows a silent period. This, they reasoned, is consistent with what is known of the thalamocortical synapse, which shows depression⁶. That is, compared to an EPSP following a first action potential in an afferent, succeeding ones are depressed in amplitude for tens of milliseconds or more. The silent period requisite for bursts ensures that depression is minimized for the response to the burst, leading to an EPSP of maximum amplitude. In contrast, with tonic firing, action potentials tend to follow one another with briefer interspike intervals, leading to considerable depression in synaptic responses.

Thus Swadlow and Gusev have demonstrated how bursting in thalamic relay cells provides a powerful input to cortex via synapses showing depression. However, the beauty of burst firing is that bursts may still deliver a stronger signal to cortex than does tonic firing regardless of the specific nature of thalamocortical synapses, even via synapses that do not show depression. That is, the mirror synaptic type—one that facilitates—should also respond better to bursts. A facilitating synapse typically delivers a small EPSP to a first action potential, and for a brief period of 10 ms or so, a following action potential evokes an enhanced EPSP. As reviewed by Lisman⁷, such facilitating synapses are common in cortex, and they often require the short interspike intervals found in bursts of action potentials to achieve facilitation so that a significant postsynaptic response is registered. Lisman suggests



that bursting in cortex is often the only way to get signals across synapses, with single action potentials often failing to evoke significant postsynaptic responses. Thus two key features of bursts—the silent preceding period of 100 ms or so, and the short interspike intervals during the burst—combine to ensure that bursts produce a maximum postsynaptic signal over both depressing and facilitating synapses, which is a neat trick. This suggests, then, that thalamic bursts should always evoke maximum EPSPs in cortex, whereas tonic firing would evoke relatively weaker responses.

As impressive and important as the results of Swadlow and Gusev are, there are two minor caveats that should be kept in mind. First, they limited their cortical sample to one of several cell types receiving direct thalamic input—the so-called fast-spoke GABAergic interneurons—and

only further empirical data can tell us whether this result extends to other thalamic target cell types. However, Swadlow and Gusev point out that the thalamo-cortical synapses onto spiny stellate cells of layer 4, which are the other main cell type there to receive thalamic afferents, also display suppression and therefore should respond more vigorously to burst than tonic mode. A different argument with the same conclusion was offered above, namely that bursts should always be better at activating cortex regardless of synaptic properties. Second, their data were based on spontaneous activity, and it would be interesting to see how the system behaves when the thalamic relay cells are actively excited by sensory stimulation. There is no reason based on cellular properties why sensory stimulation should cause any fundamental differences in the properties described by Swadlow

and Gusev, but there is some evidence that sensory stimulation can cause more burst firing (reviewed in ref. 3). On balance, these caveats do not change the basic message: Swadlow and Gusev have provided powerful evidence that bursting in thalamic relay cells is important in getting information into cortex in normal, behaving animals.

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MT signals: better with time

David Bradley

A new study shows the evolution of a computation in cortical area MT. Neurons that calculate visual motion go from fast approximation to a slower, more accurate solution.

Because our visual system is so effective, we do not generally think about the computational challenges it must face. Vision is simple to us; we take it for granted. This is not unlike the way we used to think of our parents. We simply failed to appreciate the complexity of things they had to deal with.

So it is with the aperture problem, a computational ‘subtlety’ that must be handled before movement in the visual field can be accurately perceived. Any seeing animal that cannot solve the aperture problem is liable to find it difficult to survive, so critical is the ability to detect and analyze visual motion. Motion represents action, and for predators and prey alike, this places its importance above color, shape and perhaps any other kind of information in a visual scene. Thus, a recent study in *Nature*¹ that shows a neural solution to the aperture problem actually unfolding is especially exciting.

The aperture problem is easy to see,

harder to understand, and very difficult to solve. To see it, cut a hole in a piece of cardboard and put a piece of paper behind it so that the paper edge is visible in the aperture (the hole) and tilted (Fig. 1a). Now slide the paper directly to the right. The edge visible through the aperture does not appear to move right. Indeed, its movement appears to be perpendicular to its orientation. This is the aperture problem: edges seen through small apertures always seem to go in a direction perpendicular to their orientation.

To understand why this is a problem, consider that in primates, motion is first calculated by neurons in primary visual cortex (V1), whose receptive fields—which are just apertures—are tiny, usually less than the size of a dime seen at arm’s length. If an object moves to the right, and a particular V1 neuron sees a vertically oriented edge, then it will correctly compute the object’s direction. But many neurons, unfortunately, will get the wrong answer; they will respond as if the object were moving perpendicular to whatever orientation appears in their receptive field (Fig. 4a).

Any vector can be decomposed into

orthogonal components. Thus, the (red) vector representing the paper’s rightward movement in Fig. 1a can be replaced with two vectors, orthogonal to each other, with one of the two new vectors parallel to the edge (Fig. 1b). Now imagine that the paper is actually moving parallel to that edge, sliding down and to the right. We would not see any movement, because there is no contrast along this edge, no texture. Therefore, returning to the situation where the paper is moving directly rightward, the component of motion parallel to the edge is invisible to us, so all we see is the component perpendicular to the edge.

This ambiguity disappears if there is a feature visible in the aperture—a line terminator, for example, or a T junction—because then the vector parallel to the edge becomes visible (because the feature creates contrast along that dimension). So the obvious solution would be to use larger apertures. But in doing this, the visual

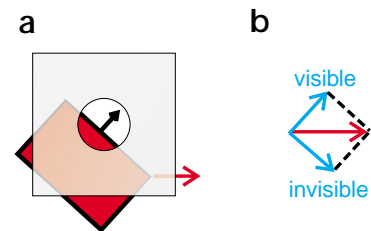


Fig. 1. The aperture problem. (a) Edges always appear to move perpendicularly to themselves when seen through an aperture. (b) The problem arises because the vector component parallel to the edge is invisible.

The author is in the Psychology Department, University of Chicago, 5848 South University Ave., G314, Chicago, Illinois 60637, USA. e-mail: dave@ccp.uchicago.edu