Spike timing-based regulation of thalamocortical signaling

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For decades, thalamic burst and tonic spiking modes have been theorized to regulate sensory signaling in the thalamocortical circuit. In this issue of Neuron, Borden et al. demonstrate a timing-based mechanism by which thalamic spiking mode controls sensory responses in the awake cortex.

The natural world presents the nervous system with a constant stream of sensory inputs that must be prioritized and triaged based on an organism’s current state and immediate goals. Most incoming sensory information passes through the thalamus to reach the cortex. This influential position in the sensory processing stream endows the thalamus with the potential to modulate or gate cortical responses to the outside world.

A prominent theory about thalamic sensory gating is articulated by the “wake-up call” hypothesis (Sherman, 2001). This proposes that the ability of thalamic relay neurons to spike in two distinct modes—tonic mode, in which normal Na+/K+-driven spikes occur in a relatively linear relationship with the stimulus, and burst mode, in which Ca2+ currents cause short, high-frequency bursts of spikes—regulates the information content of the ascending thalamocortical signal. These two spiking modes allow the thalamus to provide either an accurate relay of stimulus information or a less accurate, but stronger, signal useful for stimulus detection (Sherman and Guillery, 2002). In tonic mode, a higher spontaneous spike rate and relatively linear stimulus response help convey detailed information about stimulus features. In burst mode, neurons transmit sensory information in a more “all-or-nothing” manner, sacrificing nuance for an enhanced efficacy of transmission at the thalamocortical synapse (Swadlow and Gusev, 2001). A transition from tonic to burst mode transforms the ascending sensory signal from faithful copy to a distorted but loud wake-up call. Both signaling modes are valuable: at the airport, while standing around waiting to board a flight, one wants to hear the details of a boarding announcement; having fallen asleep at the gate, one simply wants to hear it at all.

The transition between burst and tonic thalamic firing modes must be controllable to be useful for sensory gating. A dependence on the membrane potential of the thalamic neurons confers such control via a voltage-dependent inactivation or de-inactivation of T-type calcium channels (Suzuki and Rogawski, 1989). Under hyperpolarized conditions, T-type calcium channels are de-inactivated, allowing the neuron to fire short, high-frequency bursts while tonic firing is suppressed. This bursting is in turn suppressed by sustained, more depolarized membrane potentials that cause tonic spikes but inactivate the T-type calcium channels. In this way, the response mode of a thalamic relay neuron is determined by the various hyperpolarizing and depolarizing influences on its membrane potential. Massive synaptic inputs from the cortex and brainstem provide ample sources for achieving these voltage changes and thus possible substrates for a signal to control the burst/tonic transition.

While these physiological and anatomical findings support the wake-up call hypothesis, how changes in thalamic response mode impact sensory processing in the cortex of intact and non-aneurthetized animals has remained elusive. This is due in part to the technical difficulty of acquiring both cortical and thalamic electrophysiological data during precisely controllable and rapidly reversible perturbations of the thalamus in awake animals.

In this issue of Neuron, Borden, Wright, et al. use a novel combination of optogenetic hyperpolarization of the thalamus,
Borden, Wright, et al. expected the response in primary somatosensory cortex (S1) to sensory-evoked thalamic burst spikes to follow previous findings on thalamocortical signaling: as burst spikes produce a more potent effect at the thalamocortical synapse than tonic spikes (Swadlow and Gusev, 2001), they should also produce an overall increase in the amplitude of the S1 sensory-evoked response. To test this, the authors monitored the S1 sensory response to whisker deflection using wide-field imaging of a genetically encoded voltage indicator while manipulating the thalamus. Wide-field voltage imaging offered the authors an excellent combination of spatial and temporal resolution. Under anesthesia, induction of thalamic bursting caused a general scaling up of the S1 sensory response to whisker deflection. In contrast, in awake mice there was instead a spatial and temporal sharpening of the sensory response. Spatial sharpening manifested in the voltage imaging as a decrease in the activated cortical area, with greater suppression of the surround compared with the center activation (Figure 1B). Temporal sharpening of the response was evident as a more rapid return from peak response to pre-stimulus baseline.

Silicon probe recordings in S1 allowed further dissection of the cortical response (Figure 1C). Of particular interest was the effect of thalamic bursting on inhibitory fast-spiking single units (FSUs); while their overall spike rate responses—like those of the aggregate S1 population—were invariant to the induction of thalamic bursting, synchrony between the spike times of these inhibitory units was enhanced. Stronger synchrony among S1 neurons is likely to have potent effects on local and long-range corticocortical signaling.

Borden, Wright, et al. turned to computational modeling for insights about mechanisms that could explain the invariance of cortical spike rate to thalamic spiking mode—a puzzle because burst spikes should, in principle, more potently excite their targets—as well as the synchronization of cortical responses observed among FSUs during thalamic hyperpolarization. For this, they leveraged a network model previously developed by the same group (Wright et al., 2021), in which a layer-4-like network of excitatory neurons...
and inhibitory integrate-and-fire neurons was driven by inputs simulating the observed thalamic burst or tonic spike trains. The network’s cortical responses replicated both the invariance of the overall S1 spike rate to thalamic spiking mode, as well as the burst-mode synchronization of FSU responses.

Importantly, the authors then used the model to perform an in silico test of a hypothesis to explain why overall cortical spike rate responses were largely unaffected by thalamic hyperpolarization and the transition to burst mode. The authors hypothesized that while thalamic burst spikes would more potently excite a cortical neuron, this effect could be offset by a decrease in synchrony (and therefore potency) among the different thalamic neurons that excite that same cortical neuron. In essence, there was more synchrony among spikes received from an individual thalamic neuron but less synchrony among spikes received from different thalamic neurons. After selectively scrambling the synchrony of thalamic spike trains while preserving their other features, the authors observed a decrease in the simulated cortical response. In other words, less thalamic synchrony led to a smaller cortical response, consistent with their hypothesis.

Using a powerful combination of several techniques, including single- and multi-unit recordings in VPM thalamus and S1 cortex, array recordings in cortex, imaging of a genetically encoded voltage sensor, and computational modeling, Borden, Wright, et al. have provided novel insight into how thalamic state impacts sensory processing in the thalamocortical circuit. Exciting topics for future work include relating the timing-based regulation of thalamocortical signaling and cortical synchrony uncovered in this study to processing downstream of S1 and to behavior.

DECLARATION OF INTERESTS
The authors declare no competing interests.

REFERENCES


Why study mechanisms of brain stimulation therapies? To modulate the right neurons, in the right way, at the right time

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Clinical applications of vagus nerve stimulation (VNS) are burgeoning, but mechanistic work lags behind. In this issue of Neuron, Bowles and colleagues show that VNS timed with positive reinforcement improves motor learning and cortical function by a cholinergic mechanism.

Vagus nerve stimulation (VNS) has been in clinical use for 25 years with intractable epilepsy and 17 years with treatment-refractory major depression. In epilepsy, VNS responder rates are low and range widely for reasons that are not well understood. The mechanistic “black box” of VNS has not deterred interest in potential therapies that involve nearly every organ of the body and every corner of the brain. A non-exhaustive list includes inflammatory disorders (such as rheumatoid arthritis), lung injury, cardiovascular control, obesity, diabetes, migraines, pain management, anxiety, tinnitus, Parkinson’s and Alzheimer diseases, autism spectrum disorder, traumatic brain injury, and stroke (Wang et al., 2021).

Can a single therapeutic approach really have benefits across such diverse disorders? If so, will responder rates be...