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Thalamic Bursts and Single Spikes Evoke Distinct Inhibitory States in the Primary Sensory Cortex

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Review of Hu and Agmon

Brain circuits must faithfully transform sensation into the precise firing of neurons in the cortex, several synapses downstream from the periphery. To ensure accurate perception, these circuits exploit the unique firing properties of each component neuronal population. Most sensory information is relayed to the thalamus, whose neurons respond to sensation with single action potentials but can also fire in high-frequency bursts. These thalamic bursts are enigmatic: they are more effective than single action potentials at evoking cortical spiking (Swadlow and Gusev, 2001) but do not occur during typical active sensation (Fanselow et al., 2001). Bursts and single spikes represent distinct functional states (Sherman, 2001), but we do not know whether they activate distinct downstream ensembles. This is important because it may determine how sensations are encoded and cortical plasticity is evoked across behavioral states.

If thalamic bursts and single spikes activate cortical circuits differently, they might do so by differentially activating cortical inhibitory neurons, which strongly control the recruitment of broader cortical circuits (Swadlow, 2003; Gabernet et al., 2005). In addition to targeting excitatory cortical neurons, the thalamus provides monosynaptic inputs to fast-spiking (FS) and somatostatin-positive (SOM) inhibitory cortical neurons. These inhibitory subclasses have distinct synaptic and intrinsic properties, and participate in distinct microcircuits. In juveniles, single thalamic action potentials reliably evoke short-latency spikes in cortical FS neurons (Cruikshank et al., 2007), but rarely evoke spikes in SOM neurons (Gibson et al., 1999; Cruikshank et al., 2010). FS and SOM neurons exhibit depressing and facilitating postsynaptic responses, respectively, to repetitive input from local excitatory neurons (Reyes et al., 1998). It is thus reasonable that these neurons would exhibit distinct responses to thalamic bursts and single spikes, a subject not yet explored on the single-cell level.

Recently, Hu and Agmon (2016) examined the responses of different cortical neuronal subtypes to single thalamic spikes and bursts with high resolution by simultaneous whole-cell recording of a ventrobasal thalamic neuron with a downstream, monosynaptically connected somatosensory barrel cortex neuron in a slice. Their experiments were conducted in juvenile mouse brains, the age at which thalamic input strongly activates cortical FS, but not SOM, neurons. Cellular targeting was achieved by channelrhodopsin expression exclusively in the ventrobasal thalamus, fluorescently tagged SOM neurons, and waveform characterization of excitatory and FS cells. Strengthening earlier data from Gibson et al. (1999), single presynaptic thalamic action potentials evoked the highest amplitude and shortest latency EPSP in FS cells. The only SOM neuron successfully recorded had the least reliable unitary EPSPs.

How do the postsynaptic responses of these thalamorecipient classes compare when the presynaptic thalamic neuron is bursting rather than firing single spikes? Hu and Agmon (2016) induced bursting with current injection in single thalamic neurons and recorded the resulting EPSPs, which temporally summated to produce a burst EPSP (bEPSP), in each cortical neuron. FS neurons displayed a depressing bEPSP, mirroring their responses to high-frequency local excitation (Reyes et al., 1998). Excitatory cells exhibited a smooth, summating bEPSP without clear peaks corresponding to each presynaptic action potential. The SOM neuron responded with a facilitating bEPSP whose highest amplitude peak was typically the last. Thus, cortical SOM neurons can indeed respond reliably to thalamic input, but only during thalamic bursts.

Hu and Agmon (2016) corroborated these findings by whole-cell recording in barrel cortex while eliciting bursts in single presynaptic cells through minimal photostimulation of the thalamus. All FS neurons exhibited depressing bEPSPs, while SOM neurons had facilitating responses. They also observed that while the timing of initial spikes within a thalamic burst was consistent across trials, the timing of later spikes in a thalamic burst was more variable. This implied that SOM neurons should spike more for thalamic bursts than for single spikes, but the burst-induced spikes should have high temporal jitter. To test this, the authors depolarized the postsynaptic cells to just under spike threshold and assessed spikes elicited by thalamic bursts. They found that FS neurons primarily fired a single action potential during the initial bEPSP peak and that SOM neurons fired with variable latency during later peaks.

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The results of the study by Hu and Agmon (2016) revealed unique responses of excitatory, FS, and SOM cortical neurons to thalamic input. Compared with single presynaptic spikes, thalamocortical bursts did not greatly increase the spiking of FS neurons. Swadlow and Gusev (2001), however, found that bursts *in vivo* do increase spiking in FS neurons, but as a consequence of presynaptic quiescence preceding the bursts, a condition not analyzed by Hu and Agmon (2016). Excitingly, Hu and Agmon (2016) also revealed that bursts allow single thalamic neurons to drive cortical SOM neurons to spike. This suggests that bursting is the primary thalamic firing mode that recruits the cortical SOM network.

These findings have interesting implications for how short-term synaptic dynamics are specified. Short-term synaptic depression and facilitation are generally attributed to specializations that decrease or increase presynaptic release probability, respectively (Zucker and Regehr, 2002). The observation by Hu and Agmon (2016) that thalamic bursts elicited depression in FS cells and facilitation in SOM cells is identical to FS and SOM synaptic dynamics for unitary inputs from local excitatory neurons (Reyes et al., 1998; Beierlein et al., 2003). This argues that postsynaptic neuronal identity may instruct presynaptic dynamics in a similar way at both thalamic and cortical synapses, perhaps through retrograde signaling mechanisms unique to each postsynaptic cell type. Interestingly, a single thalamic axon branches to synapse onto both excitatory and FS cortical neurons (Gabernet et al., 2005), but these synapses exhibit distinct short-term dynamics (Hu and Agmon, 2016). This indicates that different presynaptic terminals of the same axon can function with distinct release properties. It further suggests that each thalamorecipient neuronal subtype communicates distinctly with the presynaptic axon terminals that provide its thalamic input without affecting terminals of the same axon that synapse onto other cell types. Further work should uncover whether a single thalamic axon can target both FS and SOM cortical neurons and whether these inhibitory neuronal subtypes instruct presynaptic release dynamics at their thalamic inputs.

The results of the study by Hu and Agmon (2016) provide important information about thalamocortical communication, but there are some limitations. While layer 4 is the primary recipient of sensory information from the thalamus, nearly all of the cells that Hu and Agmon (2016) recorded were in layer 5B. The extent to which data can be extrapolated to thalamorecipient layer 4 cells is unclear. Additionally, spiking in excitatory neurons was not evaluated. Their gradually sloping bEPSP combined with short-term depression in strong, FS-mediated feedforward inhibition, however, suggest that burst-induced firing of excitatory neurons is temporally variable like that of SOM cells. In this case, burst-induced spiking in excitatory neurons may not encode sensory input with temporal precision.

If bursting reduces temporal precision, how could it enhance sensory encoding? Nicolelis and Fanselow (2002) proposed that thalamic neurons are primed to encode sensory input 100 ms after bursts because deinactivation of low-threshold calcium currents during afterhyperpolarization increases postsynaptic excitability. Hu and Agmon (2016) speculate that thalamic bursting may also prime excitatory cortical neurons to encode upcoming sensory input, via the following two mechanisms: (1) depression of FS-mediated feedforward proximal inhibition, which increases the integration window of excitatory neurons; and (2) isolation of thalamic inputs by facilitated SOM-mediated distal inhibition. These short-term dynamics are specific to burst-activated synapses and would exclusively affect transmission arriving from the thalamus, and only after its neurons recover from afterhyperpolarization.

The experiments of Hu and Agmon (2016) also suggest a novel way that thalamocortical bursts might contribute to cortical plasticity. Disinhibition of excitatory cells, such as during burst-induced FS depression, is widely thought to promote the induction of long-term synaptic plasticity. Sensory deprivation increases the probability of thalamic bursts (Linden et al., 2009), which may contribute to deprivation-induced cortical plasticity by decreasing FS-mediated inhibition. Interestingly, major structural plasticity is evident in the neonatal cortex and the neonatal thalamus strongly activates cortical SOM neurons (Tuncdemir et al., 2016) and weakly recruits cortical FS neurons (Daw et al., 2007). Considering the postsynaptic dynamics in FS and SOM neurons observed by Hu and Agmon (2016) in juveniles, this suggests that the cortical population recruited by thalamic bursts in juveniles is similar to that recruited by single thalamic spikes in the highly plastic neonatal circuit.

The diversity of neuronal subtypes in the sensory cortex underlies a functionally dynamic circuit that is capable of registering precise sensations and modulating synaptic connections with experience. Hu and Agmon (2016) expand our knowledge of how thalamic states differentially target these neuronal classes. An interplay between thalamic bursts and single spikes is likely necessary to optimize sensory encoding and circuit flexibility. Future work should examine whether these firing patterns have distinct impacts on circuit function downstream of the thalamorecipient neurons and whether these differences impact sensory perception.

References

Beierlein M, Gibson JR, Connors BW (2003) Two dynamically distinct inhibitory networks in layer 4 of the neocortex. J Neurophysiol 90:2987–3000. CrossRef Medline

Cruikshank SJ, Lewis TJ, Connors BW (2007) Synaptic basis for intense thalamocortical activation of feedforward inhibitory cells in neocortex. Nat Neurosci 10:462–468. CrossRef Medline

Cruikshank SJ, Urabe H, Nurmikko AV, Connors BW (2010) Pathway-specific feedforward circuits between thalamus and neocortex revealed by selective optical stimulation of axons. Neuron 65:230–245. CrossRef Medline

Daw MI, Ashby MC, Isaac JT (2007) Coordinated developmental recruitment of latent fast spiking interneurons in layer IV barrel cortex. Nat Neurosci 10:453–461. CrossRef Medline

Fanselow EE, Sameshima K, Baccala LA, Nicolelis MA (2001) Thalamic bursting in rats during different awake behavioral states. Proc Natl Acad Sci U S A 98:15330–15335. CrossRef Medline

Gabernet L, Jadhav SP, Feldman DE, Carandini M, Scanziani M (2005) Somatosensory integration controlled by dynamic thalamocortical feed-forward inhibition. Neuron 48:315–327. CrossRef Medline

Gibson JR, Beierlein M, Connors BW (1999) Two networks of electrically coupled inhibitory neurons in neocortex. Nature 402:75–79. CrossRef Medline

Hu H, Agmon A (2016) Differential excitation of distally versus proximally targeting cortical interneurons by unitary thalamocortical bursts. J Neurosci 36:6906–6916. CrossRef Medline

Linden ML, Heynen AJ, Haslinger RH, Bear MF (2009) Thalamic activity that drives visual cortical plasticity. Nat Neurosci 12:390–392. CrossRef Medline

Nicolelis MA, Fanselow EE (2002) Thalamocortical [correction of Thalamcortical] optimization of tactile processing according to behavioral state. Nat Neurosci 5:517–523. CrossRef Medline

Reyes A, Lujan R, Rozov A, Burnashev N, Somogyi P, Sakmann B (1998) Target-cell-specific facilitation and depression in neocortical circuits. Nat Neurosci 1:279–285. CrossRef Medline

Sherman SM (2001) Tonic and burst firing: dual modes of thalamocortical relay. Trends Neurosci 24:122–126. CrossRef Medline

Swadlow HA (2003) Fast-spike interneurons and feedforward inhibition in awake sensory neocortex. Cereb Cortex 13:25–32. CrossRef Medline

Swadlow HA, Gusev AG (2001) The impact of 'bursting' thalamic impulses at a neocortical synapse. Nat Neurosci 4:402–408. CrossRef Medline

Tuncdemir SN, Wamsley B, Stam FJ, Osakada F, Goulding M, Callaway EM, Rudy B, Fishell G (2016) Early somatostatin interneuron connectivity mediates the maturation of deep layer cortical circuits. Neuron 89:521–535. CrossRef Medline

Zucker RS, Regehr WG (2002) Short-term synaptic plasticity. Annu Rev Physiol 64:355–405. CrossRef Medline