The role of spike timing for thalamocortical processing

W Martin Usrey

Although the response properties of sensory neurons in the thalamus and cerebral cortex have been studied for decades, relatively few studies have examined how sensory information is processed at thalamocortical synapses. Recent studies now show that the strength of thalamocortical connections is very dynamic and spike timing plays an important role in determining whether action potentials will be transferred from thalamus to cortex.

Addresses
Center for Neuroscience, University of California at Davis, 1544 Newton Court, Davis, California 95616, USA;
e-mail: wmusrey@ucdavis.edu

Current Opinion in Neurobiology 2002, 12:411–417

0959-4388/02/$ – see front matter

Published online 27 June 2002

Abbreviations
LGN lateral geniculate nucleus
MGN medial geniculate nucleus

Introduction

For all sensory systems except olfaction, sensory information is relayed to the cerebral cortex via neurons in the thalamus. Like all projection neurons, thalamic neurons use action potentials as the basic unit for encoding information. Over the past 40 years, researchers have been documenting the patterns of thalamic activity that occur in response to sensory stimuli [1–3]. Early on, it was recognized that appropriate stimuli increase the firing rate of thalamic neurons. Later, it was recognized that different populations of thalamic neurons respond in either a transient or a sustained fashion to the presentation of a stimulus. More recently, thalamic neurons have been shown to fire in one of two modes — burst mode or tonic mode — with both modes able to encode sensory information [4–7]. Finally, recordings from small ensembles of thalamic neurons have shown that responses between neurons can be highly synchronized [8–10]. Given the range of neural responses that occur in the thalamus, the question arises: how does the cortex process these inputs? This question has been actively debated over the years with some arguing that the mean firing rate of presynaptic inputs (rate code) dictates the transmission of sensory information [11–13], whereas others assert that the timing of presynaptic inputs (temporal code) plays a significant role in sensory processing [14–19].

With recent advances in multielectrode recording technology, researchers have begun to examine, *in vivo*, how the cortex responds to different patterns of thalamic input. By recording simultaneously from monosynaptically connected neurons in the thalamus and cortex, the interval over which thalamic inputs interact to drive cortical responses can now be measured (Figure 1). It is also possible to determine the effective strength of thalamic bursts and to compare this strength to that of isolated spikes in terms of their probability to drive cortical responses. In this review, I discuss recent results from multielectrode experiments that address how information is transferred at the thalamocortical synapse in several sensory systems; I also outline some of the limitations imposed by these approaches.

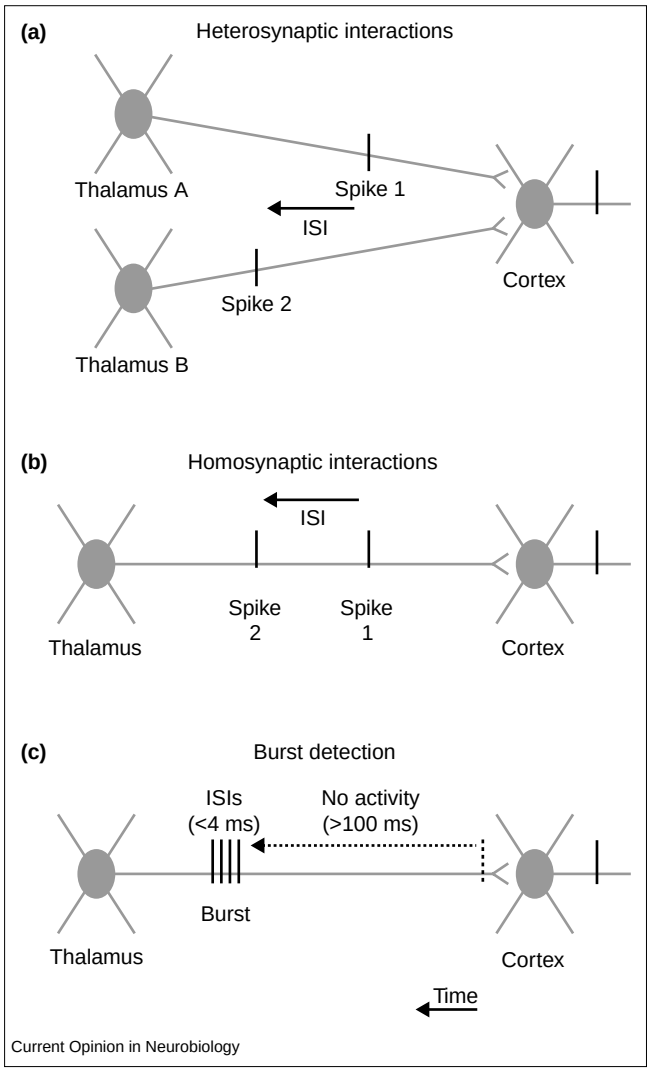
Thalamocortical connections

From the outset, it is important to note the existence of significant differences between thalamocortical synapses and corticocortical synapses. Results from studies examining thalamocortical processing, therefore, may not always translate to corticocortical processing. For instance, synaptic currents and release probability are likely to be greater for thalamic inputs than for cortical inputs [20,21]. In addition, the amount of anatomical convergence also differs significantly between these two types of cortical synapse. Only 10–100 thalamic axons synapse onto a given cortical neuron, whereas thousands of cortical inputs may converge onto individual cortical neurons [22–24]. Finally, the nature of short-term synaptic plasticity (i.e. paired-pulse depression and facilitation) has been reported to differ for thalamocortical and corticocortical synapses [20,21,25••].

Visual, auditory, and somatosensory inputs to the cortex come primarily from neurons located in the lateral geniculate nucleus (LGN), medial geniculate nucleus (MGN) and ventrobasal complex of the thalamus, respectively. Axons from these nuclei terminate primarily in cortical layer 4, but all primary sensory cortical areas also receive thalamic input to the more superficial cortical layers.

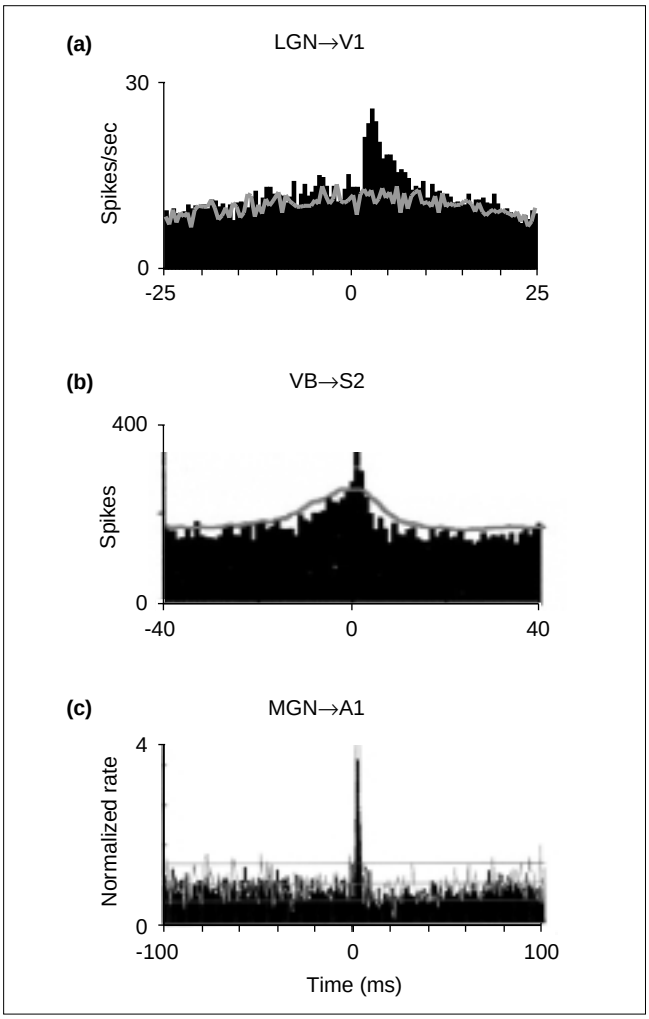
It is technically difficult to identify and record simultaneously from pairs of monosynaptically connected neurons in the thalamus and cortex. This difficulty arises, in part, from the number of neurons in each structure. For instance, it has been argued that an individual layer 4 neuron in cat primary visual cortex receives input from only about 30 of the possible 360,000 LGN neurons that project to the cortex [23,24]. Fortunately, primary sensory areas of the cortex and the thalamic nuclei that supply them are organized according to topographic maps. The sensory surface of the specific pathway and the connections between the two structures obey this organization. Therefore, to identify a pair of connected neurons in the visual pathway, the placement of recording electrodes follows the retinotopic organization of the LGN and visual cortex, such that the neurons that are isolated and recorded from have overlapping receptive fields. However, receptive field overlap between two neurons does not necessarily mean that they are monosynaptically connected. Connectivity is typically assessed by cross-correlating the spike trains of

Figure 1



Thalamocortical interactions can be broadly divided into three categories. (a) and (b) Cortical neurons integrate thalamic spikes that arrive via converging axons (heterosynaptic interactions), as well as multiple spikes that arrive via single axons (homosynaptic interactions). By measuring the efficacy of spikes that occur at different interspike intervals (ISIs), one can determine the time course and dynamics of interaction for these two categories of input. (c) Thalamic bursts represent a special category of thalamic activity. By recording from pairs of connected neurons in the thalamus and cortex, one can measure the efficacy of burst spikes (the percentage that evoke a cortical spike) and non-burst spikes.

Figure 2

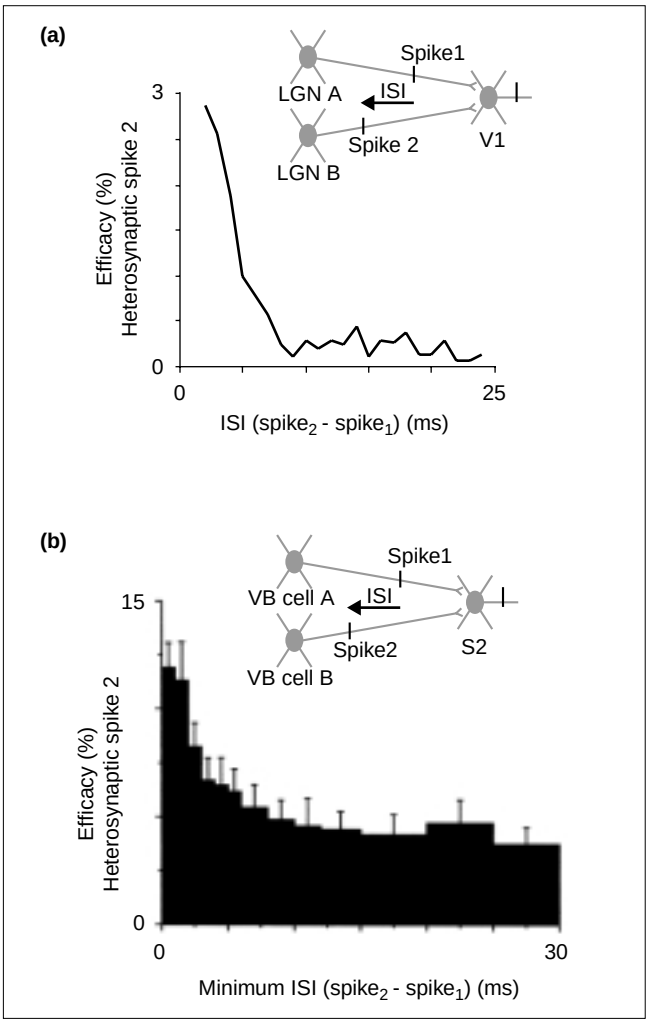


Examples of cross-correlograms made from the spike trains of simultaneously recorded neurons. (a) In the LGN and primary visual cortex (V1) of the cat, (b) in the ventrobasal (VB) complex and secondary somatosensory cortex (S2) of the cat, and (c) in the MGN and primary auditory cortex (A1) of the cat. These correlograms show the occurrence of cortical spikes relative to the occurrence of thalamic spikes (time 0 ms). A short-latency (1–4 ms) peak to the right of zero indicates that the cortical neuron often fired in response to a spike in the thalamic neuron. Gray lines indicate shuffle correlations or confidence levels for stimulus-driven correlations. Modified with permission from [29•,33•,35••].

two cells and evaluating whether a spike in one cell increases the probability of a spike in the other cell, within the time window of a monosynaptic connection (Figure 2). For the visual, auditory and somatosensory pathways, this time window is ~1–4 ms [26–28,29•]. That is, it takes approximately 1–4 ms for a spike in the thalamus to trigger a spike in the cortex.

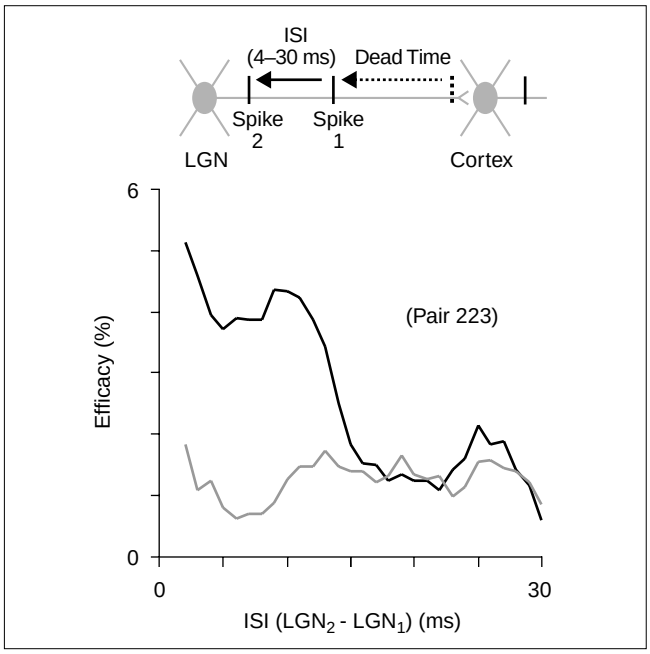
By recording simultaneously from monosynaptically connected thalamic and cortical neurons, it is possible to assess both the specificity and strength of individual connections [29•,30,31,32••,33•,34•,35••,36••]. Values typically reported to reflect the strength of a connection are: the percentage of thalamic spikes that evoke a cortical spike (termed efficacy); the percentage of cortical spikes that are triggered by the thalamic spikes (termed contribution) [37]. These values are easily computed by dividing the number of spikes in the monosynaptic peak of a cross-correlogram by either the total number of thalamic spikes (for efficacy) or by the total number of cortical spikes (for contribution). For the cat visual, auditory and somatosensory pathways, efficacy and contribution values are generally ~1–10% [29•,30,31,32••,33•,34•,35••,36••]. As a general

Figure 3



Cortical neurons detect coincident thalamic spikes. (a) Heterosynaptic interactions are strong and fast in the geniculocortical pathway of the cat. The efficacy of a geniculate spike is greatest when it arrives shortly after a spike from another geniculate neuron. Efficacy drops off rapidly (~2.5 ms time constant) as the interspike interval (ISI) increases. At ISIs >6–8 ms, thalamic spikes from two axons no longer show reinforcement. (b) Heterosynaptic interactions are also strong and fast in the pathway between the ventrobasal (VB) complex and secondary somatosensory cortex (S2) of cats. Modified with permission from [32••,35••].

Figure 4



Time course and magnitude of homosynaptic interactions in the geniculocortical pathway of the cat. The efficacy of geniculate spikes (i.e. the percentage that evoke cortical spikes) is dependent on interspike interval (ISI). For pairs of spikes with short ISIs, the efficacy of second spikes is much greater than that of the first spikes. At interspike intervals >15 ms, spikes are no longer reinforcing and the efficacy of first and second spikes is equal. Modified with permission from [32••].

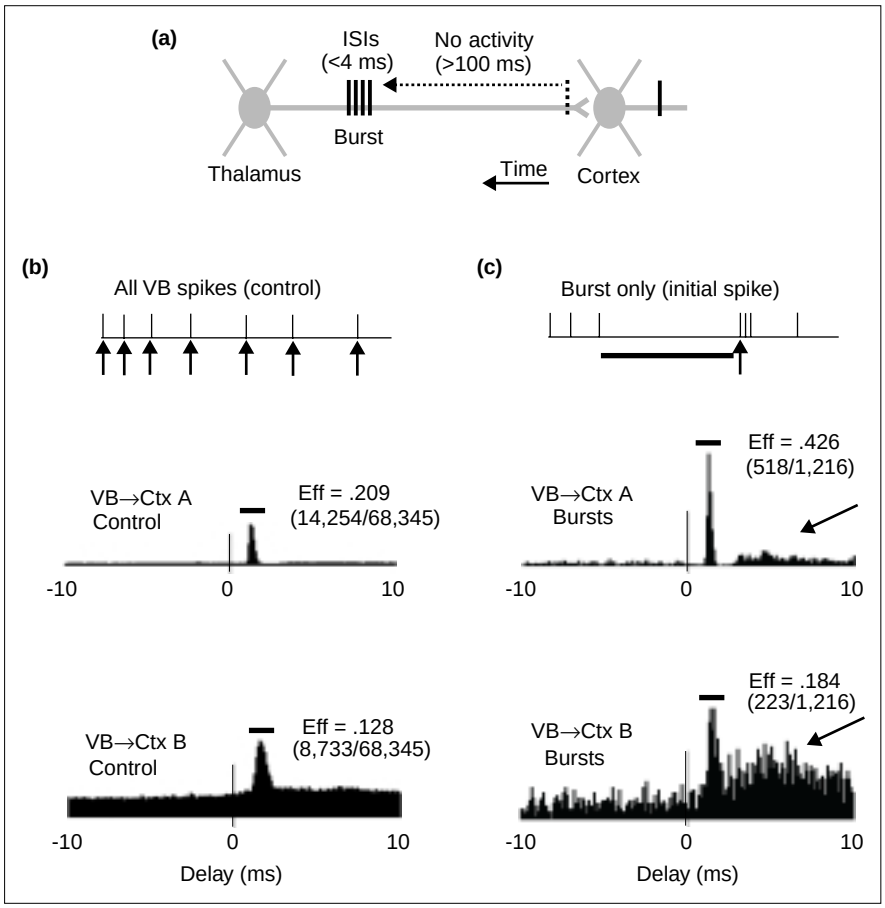
rule, efficacy and contribution values increase as the number of thalamic axons that converge onto a given cortical neuron decrease [18].

Cortical neurons and coincidence detection

As mentioned above, controversy surrounds whether or not cortical neurons detect coincident events [11–19]. Two sets of recent studies addressed this issue by using multi-electrode techniques to record from pairs of thalamic neurons that provide convergent input to a simultaneously recorded cortical neuron [8,32••,35••] (Figure 3). These experiments were performed to determine the temporal interval during which spikes from two thalamic neurons interact to increase the probability of driving a cortical spike. In the first set of studies [8,32••], pairs of LGN neurons were recorded together with their monosynaptically connected neurons in cat visual cortex. In the second study [35••], pairs of ventrobasal neurons were recorded along with their target neurons in the secondary somatosensory cortex in the cat. Both studies found remarkably similar results. The probability of driving a cortical spike was maximal when thalamic spikes occurred within <1 ms of each other. Reinforcing interactions between thalamic spikes then decreased rapidly (with a time constant of ~2.5 ms) as the time interval for spike arrival increased. At spike intervals >6–8 ms, neither study found any reinforcing interactions between two thalamic spikes. On the basis of these results, neurons in layer 4 can clearly act as coincidence detectors.

The extent to which layer 4 neurons in other cortical areas respond selectively to coincident events remains to be determined. Recent studies showed that small ensembles of neurons in the LGN and ventrobasal complex fire many of their spikes synchronously (within <1 ms) [8–10]. In the LGN, these synchronous events are known to result from the anatomical divergence of single retinal ganglion cells onto multiple LGN cells [8,9]. The existence of coincidence detection in the visual and secondary somatosensory cortices may therefore reflect the fact that both pathways contain neurons with highly synchronous discharge

Figure 5



Thalamic bursts are effective at driving cortical responses. (a) By definition, bursts are preceded by >100 ms of silence and contain more than one spike with <4 ms separating each spike in the burst. (b) and (c) Results from a recording that consisted of a single neuron in the ventrobasal complex (VB) that was monosynaptically connected to two simultaneously recorded neurons (Ctx A, Ctx B) in the primary somatosensory cortex. (b) Cross-correlograms made from the non-bursting activity of the thalamic neuron and the activity of the two cortical neurons. (c) Cross-correlograms made from the bursting activity of the thalamic neuron and the activity of the two cortical neurons. For both pairs of connections, burst spikes were more effective (Eff values) than non-burst spikes in driving cortical responses. Arrows indicate increased responses due to subsequent spikes in a burst. These recordings were performed in awake rabbits. Modified with permission from [36••].

patterns. Beyond synchrony induced by anatomical divergence, synchronous firing among thalamic neurons could also result from several different processes. For instance, as the firing rate of individual neurons increases, so will the frequency of spikes that randomly occur synchronously between the neurons. In addition, other factors including cortical feedback might serve to increase the amount of synchronous activity among thalamic neurons [38,39].

Cortical neurons not only integrate spikes from multiple thalamic axons, they also integrate multiple spikes from individual axons. Both categories of interaction — heterosynaptic and homosynaptic — occur at any given time, and the firing patterns of cortical neurons reflect both types of input. Nevertheless, an interesting question is whether or not the time course for interaction between the two categories of input is similar. As described above, the time course for interaction between spikes arriving from two separate thalamic axons is quite brief (<6–8 ms, maximal at 1 ms) [32••,35••]. By comparing the efficacy of spikes from single LGN neurons that occur at different interspike intervals, it has been possible to determine the time course for homosynaptic interactions (Figure 4). For pairs of spikes that occur at the shortest interspike intervals measured (dictated by the LGN cell's refractory period), second geniculate spikes are around four times more effective than first spikes in eliciting a cortical spike [32••]. The efficacy of second spikes then decreases as interspike interval increases until ~15 ms, where the efficacy of second spikes becomes equal to that of first spikes. Although cortical responses reflect the activity of all of their presynaptic inputs, this integration interval (~15 ms) suggests that cortical neurons should be able to increase their responses to individual LGN neurons as these LGN neurons increase their firing rate above ~66 Hz (a rate typical for LGN responses to visual stimuli).

Cortical neurons and burst detection

Thalamic neurons generate neural impulses in one of two modes — burst mode or tonic mode [4,5,40–42]. In general, burst mode dominates when animals are asleep, drowsy, or inattentive, whereas tonic mode dominates when animals are awake and alert. On the basis of this association, it was suggested that the thalamus and cortex are functionally disconnected during burst mode and that sensory processing occurs during tonic mode. Although burst mode certainly dominates during drowsiness and sleep, recent studies have shown that thalamic bursts also occur in awake animals and that bursts can encode high amounts of sensory information [6,7,43–45]. Because depolarizing currents

associated with bursts could temporally summate to drive cortical spikes, it was suggested that bursts might play an important role in sensory detection [4,5]. On the other hand, it is also possible that bursts have a decreased efficacy because cholinergic inputs to the thalamus and cortex are generally reduced during the periods (sleep and drowsiness) that accompany bursts [46,47].

A recent study by Swadlow and Gusev [36••] examined the efficacy of thalamic bursts in awake animals by recording simultaneously from neurons in the ventrobasal complex and primary somatosensory cortex (Figure 5). Their results demonstrate that thalamic bursts are extremely effective at driving cortical spikes (a mean increase of 221% over non-burst elicited spikes). One of the criteria for identifying a burst in a thalamic spike train is the requirement that the first spike in the burst follow a period of >100 ms without any spikes. Because thalamocortical connections have been shown to undergo paired-pulse depression [20,21,25••], Swadlow and Gusev [36••] speculated that the increased efficacy of a burst might simply result from a release of this depression. To test this idea, they compared the efficacy of first spikes in a burst with the efficacy of individual spikes that also followed >100 ms of silence but that were not part of a burst. The efficacy of these two groups of spikes was very similar, supporting the idea that the silent period before spike arrival is an important determinant for spike efficacy. Finally, bursts are defined not only by a period of silence preceding the burst, but also by subsequent spikes with intervals <4 ms between each spike. Analysis of the efficacy of later spikes in a burst showed that the efficacy of subsequent spikes is increased relative to control spikes. In addition, this increased efficacy of subsequent spikes is dependent on the >100 ms of silence preceding the burst. Taken together, these results show that bursts are extremely effective at driving cortical responses; any information contained in bursts is likely to be transferred to the cortex.

Limitations of multielectrode techniques

Although multielectrode techniques have significantly advanced our understanding of information processing in sensory systems, a major limitation of this approach for studying synaptic connections *in vivo* is the resulting difficulty in addressing questions of cellular mechanisms. The data collected in multielectrode experiments consist of extracellular spikes from multiple neurons; the analysis focuses on the relationship of these spikes with respect to each other. Thus, when a pair of spikes from two thalamic neurons are shown to interact with each other over a very narrow window of time (coincidence detection), it is unknown whether the temporal window for this detection is due to the membrane time constant of the cortical cell, the relative location of synapses on the cortical cell, or the recruitment of a polysynaptic circuit. Similarly, when pairs of thalamic spikes from a single thalamic axon interact in a positive, reinforcing fashion, it is unclear whether the reinforcement is due to synaptic facilitation, temporal summation, or again, the recruitment of a polysynaptic circuit. In the end, it is quite likely that many or all of these factors play a role.

Experiments performed *in vitro*, using whole-cell recordings and electrical stimulation, are much better suited to address issues of underlying cellular mechanisms. This is due, in large part, to the ability to measure individual synaptic currents and to assess pharmacologically the contribution of different channels to these currents. The *in vitro* approach, however, is not without its own set of limitations. Conditions *in vitro* are not the same as those *in vivo*. Neurons *in vitro* do not receive natural patterns of input from their many synaptic sources. Likewise, individual neurons do not fire natural patterns of action potentials for sustained periods of time. Along these lines, a recent study showed that when neuromodulators are added to cortical slices and the ionic environment is changed to mimic conditions present *in vivo*, inputs that initially displayed paired-pulse depression show a reduction of this depression and, in some cases, undergo facilitation [48]. Thus, the extent to which mechanisms revealed *in vitro* relate to conditions *in vivo* is a question that deserves discussion when comparing results from different studies.

Another limitation of using multielectrode recording techniques to infer how networks of neurons interact comes from the fact that one can only record from a small subset of the neurons that provide input to a target neuron. In the experiments described in this review, the analysis for interactions between spikes was performed on no more than three neurons (two presynaptic and one postsynaptic). In the thalamocortical pathway of the cat, it has been argued that individual layer 4 neurons receive input from approximately 30 LGN neurons [23,24]. Because the firing behavior of a layer 4 neuron should reflect the activity patterns of all of these inputs as well as the activity of intracortical sources of input, a full description of the role of spike timing for thalamocortical processing would require knowledge of what these other inputs are providing, both in terms of synaptic strength and timing.

Conclusions and future directions

Spike timing plays a critical role in the processing of sensory information between thalamus and cortex. The strength of a thalamic input is dependent not only on the relative timing of spikes from other thalamic axons (heterosynaptic interactions), but also on the relative timing of spikes in individual thalamic axons (homosynaptic interactions) [8,32••,35••]. Heterosynaptic interactions are very brief with reinforcement maximal at arrival times within <1 ms and undetectable at arrival times >6–8 ms. These findings, obtained from both the visual and the somatosensory systems, indicate that cortical neurons seem well suited to detect coincident events among their pool of thalamic inputs. Homosynaptic interactions occur over longer periods of time (<15 ms) and are characterized by an increase in spike efficacy [32••]. Finally, thalamic bursts that were

once thought to occur only during states of sleep or drowsiness, have been found to be extremely effective at driving cortical responses [36••].

Although *in vivo* recording can document the patterns of thalamic activity that evoke cortical responses, it is difficult to address questions about underlying cellular mechanisms from *in vivo* work (but see [49–51]). By contrast, *in vitro* experiments are much better suited to address mechanistic issues. *In vitro* conditions are far from those that exist *in vivo*; however, it is possible to approximate more closely the *in vivo* state by stimulating neurons with more natural patterns of activity or patterns that have been recorded from animals *in vivo* [52–57,58•,59•]. Given the fact that both approaches have their own set of limitations, it is hoped that results from each approach will help guide future experiments and that answers will be found by comparing results from both approaches.

Simultaneous recordings of monosynaptically connected thalamic and cortical neurons have been performed in both anesthetized and alert animals [8,29•,30,31,32••,33•, 34•,35••,36••]. To date, however, only anesthetized studies have examined the time course for interaction between thalamic spikes [8,32••,35••] (other than bursts [36••]). It would be interesting to know, therefore, whether similar interactions (i.e. coincidence detection) occur in alert animals. Moreover, it would be interesting to know what effects attention, eye (or pinna) movements, and different stimulus properties (i.e. natural images) have on the processing of information between thalamus and cortex in alert animals. As multielectrode technology continues to improve [60], it is likely that arrays will become larger, less damaging, and more maneuverable for recording from multiple neurons. One goal for developing such arrays is to obtain larger amounts of information about how neurons within a network interact to influence, in a dynamic way, the processing of sensory information.

Acknowledgements

Thanks to A Kimberley McAllister, Jose-Manuel Alonso and Henry Alitto for comments on earlier versions of this manuscript. WM Usrey is supported by the National Institutes of Health (grants EY13588 and EY12576), the Esther A and Joseph Klingenstein Fund, and the Alfred P Sloan Foundation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Jones EG: *The Thalamus.* New York: Plenum Press; 1985.

2. Steriade M, Jones EG, McCormick DA (Eds): *Thalamus.* New York: Elsevier; 1997.

3. Sherman SM, Guillery RW: *Exploring the Thalamus.* San Diego: Academic Press; 2001.

4. Sherman SM: Dual response modes in lateral geniculate neurons: mechanisms and functions. *Vis Neurosci* 1996, 13:205-213.

5. Sherman SM: Tonic and burst firing: dual modes of thalamocortical relay. *Trends Neurosci* 2001, 24:122-126.

6. Reinagel P, Godwin D, Sherman SM, Koch C: Encoding of visual information by LGN bursts. *J Neurophysiol* 1999, 81:2558-2569.

7. Fanselow EE, Sameshima K, Baccala LA, Nicolelis MA: Thalamic bursting in rats during different awake behavioral states. *Proc Natl Acad Sci USA* 2001, 98:15330-15335.

8. Alonso JM, Usrey WM, Reid RC: Precisely correlated firing in cells of the lateral geniculate nucleus. *Nature* 1996, 383:815-819.

9. Usrey WM, Reppas JB, Reid RC: Paired-spike interactions and synaptic efficacy of retinal inputs to the thalamus. *Nature* 1998, 395:384-387.

10. Alloway KD, Johnson MJ, Aaron GB: A comparative analysis of coordinated neuronal activity in the thalamic ventrobasal complex of rats and cats. *Brain Res* 1995, 691:46-56.

11. Shadlen MN, Newsome WT: Noise, neural codes and cortical organization. *Curr Opin Neurobiol* 1994, 4:569-579.

12. Shadlen MN, Newsome WT: The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J Neurosci* 1998, 18:3870-3896.

13. Shadlen MN, Movshon JA: Synchrony unbound: a critical evaluation of the temporal binding hypothesis. *Neuron* 1999, 24:67-77.

14. Softky WR, Koch C: The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *J Neurosci* 1993, 13:334-350.

15. Konig P, Engel AK, Singer W: Integrator or coincidence detector? The role of the cortical neuron revisited. *Trends Neurosci* 1996, 19:130-137.

16. Stevens CF, Zador AM: Input synchrony and the irregular firing of cortical neurons. *Nat Neurosci* 1998, 1:210-217.

17. Gray CM: The temporal correlation hypothesis of visual feature integration: still alive and well. *Neuron* 1999, 24:31-47.

18. Usrey WM, Reid RC: Synchronous activity in the visual system. *Annu Rev Physiol* 1999, 61:435-456.

19. Salinas E, Sejnowski TJ: Correlated neuronal activity and the flow of neural information. *Nat Rev Neurosci* 2001, 2:539-550.

20. Stratford KJ, Tarczy-Hornoch K, Martin KA, Bannister NJ, Jack JJ: Excitatory synaptic inputs to spiny stellate cells in cat visual cortex. *Nature* 1996, 382:258-261.

21. Gil Z, Connors BW, Amitai Y: Efficacy of thalamocortical and intracortical synaptic connections: quanta, innervation, and reliability. *Neuron* 1999, 23:385-397.

22. White EL: *Cortical Circuits: Synaptic Organization of the Cerebral Cortex – Structure, Function and Theory.* Boston: Birkhauser; 1989.

23. Peters A, Payne BR: Numerical relationships between geniculocortical afferents and pyramidal cell modules in cat primary visual cortex. *Cereb Cortex* 1993, 3:69-78.

24. Reid RC, Alonso J-M, Usrey WM: Integration of thalamic inputs to cat primary visual cortex. *In The Cat Primary Visual Cortex.* Edited by Payne BR, Peters A. San Diego: Academic Press; 2002:319-342.

25. •• Chung S, Li X, Nelson SB: Short-term depression at thalamocortical synapses contributes to rapid adaptation of cortical sensory responses ***in vivo.*** *Neuron* 2002, 34:437-446.
Using whole-cell recording techniques *in vivo*, this study demonstrates that natural sensory stimulation can cause short-term depression of thalamocortical synapses in the rodent somatosensory pathway. This depression plays a major role in the adaptation of cortical neurons to repeated whisker movements.

26. Bullier J, Henry GH: Ordinal position of neurons in cat striate cortex. *J Neurophysiol* 1979, 42:1251-1263.

27. Henry GH, Harvey AR, Lund JS: The afferent connections and laminar distribution of cells in the cat striate cortex. *J Comp Neurol* 1979, 187:725-744.

28. Yen CT, Conley M, Jones EG: Morphological and functional types of neurons in cat ventral posterior thalamic nucleus. *J Neurosci* 1985, 5:1316-1338.

29. • Miller LM, Escabi MA, Read HL, Schreiner CE: Functional convergence of response properties in the auditory thalamocortical system. *Neuron* 2001, 32:151-160.
By recording from monosynaptically connected neurons in the MGN and primary auditory cortex *in vivo*, this study examines the extent to which cortical

receptive fields are directly inherited from their thalamic inputs. The authors find that some receptive field properties are faithfully propagated whereas others are significantly transformed.

30. Tanaka K: Organization of geniculate inputs to visual cortical cells in the cat. *Vision Res* 1985, 25:357-364.

31. Reid RC, Alonso JM: Specificity of monosynaptic connections from thalamus to visual cortex. *Nature* 1995, 378:281-284.

32. •• Usrey WM, Alonso J-M, Reid RC: Synaptic interactions between thalamic inputs to simple cells in cat visual cortex. *J Neurosci* 2000, 20:5461-5467.
Here, simultaneous recordings were made from monosynaptically connected neurons in the LGN and visual cortex to determine the time course for homosynaptic and heterosynaptic interactions. The results demonstrate that the temporal window for integrating spikes from different axons is very short (coincidence detection), whereas the window for integrating spikes from a single axon is longer.

33. • Alonso JM, Usrey WM, Reid RC: Rules of connectivity between geniculate cells and simple cells in cat primary visual cortex. *J Neurosci* 2001, 21:4002-4015.
This study explores the specificity of monosynaptic connections between the LGN and visual cortex in the cat. The results show that connections are extremely precise with very few mistakes.

34. • Miller LM, Escabi MA, Schreiner CE: Feature selectivity and interneuronal cooperation in the thalamocortical system. *J Neurosci* 2001, 21:8136-8144.
Using the auditory pathway as a model system, the authors of this study compare the receptive field properties of spikes that are effective at driving the cortex to those of spikes that are ineffective at driving the cortex. They show that thalamic spikes that drive the cortex are generally more selective for spectrotemporal stimulus features than spikes that don't drive the cortex.

35. •• Roy SA, Alloway KD: Coincidence detection or temporal integration? What the neurons in somatosensory cortex are doing. *J Neurosci* 2001, 21:2462-2473.
Here, simultaneous recordings were made from two thalamic neurons in the ventrobasal complex along with a monosynaptically connected neuron in the secondary somatosensory cortex, to determine the temporal interval during which thalamic spikes interact to drive cortical responses. The results show that cortical neurons can behave as coincidence detectors of thalamic input.

36. •• Swadlow HA, Gusev AG: The impact of 'bursting' thalamic impulses at a neocortical synapse. *Nat Neurosci* 2001, 4:402-408.
To determine whether thalamic bursts are effective at driving cortical responses, these authors performed simultaneous recordings from neurons in the ventrobasal complex and primary somatosensory cortex of unanesthetized rabbits. They show that burst spikes are extremely effective at driving cortical responses and that the increased efficacy of bursts is due to the silent period that precedes each burst.

37. Levick WR, Cleland BG, Dubin MW: Lateral geniculate neurons of cat: retinal inputs and physiology. *Inv Opthalm* 1972, 11:302-311.

38. Sillito AM, Jones HE, Gerstein GL, West DC: Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. *Nature* 1994, 369:479-482.

39. Jones EG: The thalamic matrix and thalamocortical synchrony. *Trends Neurosci* 2001, 24:595-601.

40. Steriade M, Llinas RR: The functional states of the thalamus and the associated neuronal interplay. *Physiol Rev* 1988, 68:649-742.

41. McCormick DA, Feeser HR: Functional implications of burst firing and single spike activity in lateral geniculate relay neurons. *Neuroscience* 1990, 39:103-113.

42. Sherman SM, Koch C: The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus. *Exp Brain Res* 1986, 63:1-20.

43. Guido W, Weyand T: Burst responses in thalamic relay cells of the awake behaving cat. *J Neurophysiol* 1995, 74:1782-1786.

44. Ramcharan EJ, Gnadt JW, Sherman SM: Burst and tonic firing in thalamic cells of unanesthetized, behaving monkeys. *Vis Neurosci* 2000, 17:55-62.

45. Weyand TG, Boudreaux M, Guido W: Burst and tonic response modes in thalamic neurons during sleep and wakefulness. *J Neurophysiol* 2001, 85:1107-1118.

46. Sillito AM, Kemp JA: Cholinergic modulation of the functional organization of the cat visual cortex. *Brain Res* 1983, 289:143-155.

47. Metherate R, Ashe JH: Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in the rat auditory cortex. *Synapse* 1993, 14:132-143.

48. Sanchez-Vives MV, Nowak LG, McCormick DA: Why might synaptic depression be lesser ***in vivo*** than ***in vitro?*** *Soc Neurosci Abst* 1999, 25:2191.

49. Hirsch JA, Alonso JM, Reid RC: Visually evoked calcium action potentials in cat striate cortex. *Nature* 1995, 378:612-616.

50. Ferster D, Chung S, Wheat H: Orientation selectivity of thalamic input to simple cells of cat visual cortex. *Nature* 1996, 380:249-252.

51. Azouz R, Gray CM: Dynamic spike threshold reveals a mechanism for synaptic coincidence detection in cortical neurons ***in vivo***. *Proc Natl Acad Sci USA* 2000, 97:8110-8115.

52. Markram H, Tsodyks M: Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature* 1996, 382:807-810.

53. Abbott LF, Varela JA, Sen K, Nelson SB: Synaptic depression and cortical gain control. *Science* 1997, 275:220-224.

54. Tsodyks MV, Markram H: The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. *Proc Natl Acad Sci USA* 1997, 94:719-723.

55. Varela JA, Sen K, Gibson J, Fost J, Abbott LF, Nelson SB: A quantitative description of short-term plasticity at excitatory synapses in layer 2/3 of rat primary visual cortex. *J Neurosci* 1997, 17:7926-7940.

56. Dobrunz LE, Stevens CF: Response of hippocampal synapses to natural stimulation patterns. *Neuron* 1999, 22:157-166.

57. Varela JA, Song S, Turrigiano GG, Nelson SB: Differential depression at excitatory and inhibitory synapses in visual cortex. *J Neurosci* 1999, 19:4293-4304.

58. • Chen C, Blitz DM, Regehr WG: Contributions of receptor desensitization and saturation to plasticity at the retinogeniculate synapse. *Neuron* 2002, 33:779-788.
By stimulating retinal afferents to LGN neurons with spike trains recorded *in vivo*, this *in vitro* study examines the cellular mechanisms that are responsible for paired-pulse depression at retinogeniculate synapses. Depression is primarily due to postsynaptic mechanisms and results from desensitization of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors along with saturation of *N*-methyl-D-aspartate (NMDA) receptors.

59. • Froemke RC, Dan Y: Spike-timing-dependent synaptic modification induced by natural spike trains. *Nature* 2002, 416:433-438.
This *in vitro* study explores the role of spike timing on the dynamics of synaptic plasticity in the visual cortex, by stimulating cortical axons with repeated, short segments of spike trains recorded *in vivo*. The results show that the nature and degree of plasticity (potentiation or depression) depends on the spike history of both the presynaptic and postsynaptic neurons.

60. Kralik JD, Dimitrov DF, Krupa DJ, Katz DB, Cohen D, Nicolelis MA: Techniques for chronic, multisite neuronal ensemble recordings in behaving animals. *Methods* 2001, 25:121-150.