Thalamus controls recurrent cortical dynamics

Jose Manuel Alonso & Harvey A Swadlow

Previous work has suggested that cortical recurrent circuits can self-sustain their activity without thalamic input. A study now demonstrates that this is not the case in the awake brain, which tightly locks cortical timing to thalamic activity.

Children often enter a brain state in which sensory stimulation becomes irrelevant and they repeatedly fail to respond to parents calling their name. We could attribute this behavior to cortical recurrent networks that engage in self-sustained activity and disengage from their thalamic inputs, which convey changes in the outside world. For more than a decade, self-sustained recurrent activity was thought to be a prominent feature of cortical networks in the brain. Not anymore. A study by Reinhold *et al.*[1] in this issue of *Nature Neuroscience* demonstrates that the primary visual cortex cannot self-sustain activity for more than a few tens of milliseconds without the support of thalamic input.

In an impressive series of experiments, the authors recorded intracellularly from neurons receiving the bulk of the thalamic input in layer 4 of primary visual cortex in mice. They then measured changes in their responses to a visual stimulus as they manipulated cortical and thalamic inputs with optogenetic methods. By silencing the cortex (**Fig. 1a**), they found that the thalamic input contributed 80% of the total excitation to layer 4 neurons during the first 10 ms of the response, and it was not until 40 ms that cortical recurrent circuits started to contribute more than the thalamus. By 250 ms, cortical recurrent circuits were amplifying the thalamic input by more than a factor of 3, confirming measurements of cortical amplification previously obtained in rodents and carnivores[2–4].

The authors made another important discovery when they silenced the thalamus with 1-ms precision after the visual cortical response had started (**Fig. 1b**). If the thalamic input were just a weak spark that ignites a self-sustained cortical amplifier, cortical activity would be expected to last for several hundreds of milliseconds after the thalamus stopped responding. Surprisingly, after silencing the thalamus, the cortical response returned to baseline with a time constant of 10 ms, which is approximately the integration time window of a single cortical neuron and two orders of magnitude faster than the response decay observed when the thalamus was active. The authors were able to replicate this extremely rapid decay in different cortical layers, including those that do not receive thalamic input, and it was observed in different brain states, including anesthesia, awake and awake-running. The response decay was just a few milliseconds slower in higher order visual cortex, which led the authors to conclude that the cortical response timing may be tightly locked to the thalamic inputs at further stages of cortical processing beyond the primary visual cortex.

Silencing the thalamus not only reduced visual cortical responses, but also reduced the spontaneous cortical activity of the awake primary visual cortex by 70%, which led the authors to conclude that the thalamus not only time-locks visual cortical responses, but also drives cortical spontaneous activity. Silencing the thalamus did not inactivate the spontaneous bouts of activity that are commonly observed in anesthetized cortex, just as epileptic seizures cannot be stopped by removing sensory stimulation. Thus, the results from Reinhold *et al.*[1] confirm that cortical recurrent circuits can generate and sustain activity without the thalamus for several hundreds of milliseconds[5–7], but only under anesthesia and in the absence of sensory stimulation.

It is well known that thalamic firing rates are high in alert subjects and are reduced considerably under general anesthesia, during slow-wave sleep and during drowsiness. Because thalamocortical synapses exhibit depression[8], the high firing rates in alert subjects result in chronic depression at the thalamocortical synapse[9,10]. Notably, the authors found that the changes in thalamocortical responses associated with such activity-dependent synaptic depression may be sufficient to explain the failure of the cortex to respond to high temporal frequencies in the anesthetized brain (**Fig. 1c**). Previous work demonstrated that changes in alertness in the awake state also affect the spontaneous activity and temporal frequency tuning of thalamic neurons[11], together with thalamocortical depression[10]. Taken together, these results suggest that changes in alertness and attention may continuously adjust the cortical tuning to differing temporal frequencies by simply affecting response amplitude as modulated by thalamocortical depression.

How is it possible that the thalamic inputs have such a strong effect if they make up only a small proportion of the total excitatory synapses in layer 4 neurons[12]? Several features of the thalamic inputs could increase their synaptic effect, including the large size and proximal location of their synaptic boutons to the cortical soma, their high firing rates and their precise synchrony. In addition, Reinhold *et al.*[1] found that cortical inhibition time-locks the cortical response to the thalamic inputs. The authors show that the decay of the cortical response slows by 10 ms when cortical inhibition is silenced. Thus, intracortical inhibition enforces the fast decay time of cortical recurrent networks and allows them to follow the fast temporal frequencies of thalamic inputs during the awake state.

The authors should be commended for these impressive experiments that advance our understanding of thalamocortical function. However, as is true for all scientific discoveries, the experiments did not answer all questions, and they have raised new ones. The authors show that inhibition helps to enforce the fast decay of the cortical response, but they did not investigate the contributions of different inhibitory networks. It is possible that only a subset of inhibitory neurons limits the cortical self-sustained activity and that the cortex uses these inhibitory networks to modulate the response decay. In addition, the cortical inactivation was not restricted to layer 4, but affected other cortical layers that receive feedback inputs from higher order cortex. Thus, it is still possible that feedback from other cortical areas could provide a source of cortical self-sustained activity that was not monitored in these experiments. More importantly, cortical silencing affected the feedback from layer 6 cortical neurons to the thalamus. Thus, the strong thalamic contribution that the authors observe

Jose Manuel Alonso & Harvey A. Swadlow are in the Department of Biological and Visual Sciences, State University of New York, College of Optometry, New York, New York, USA, and the Department of Psychology, University of Connecticut, Storrs, Connecticut, USA.
e-mail: jalonso@sunyopt.edu or harvey.swadlow@uconn.edu

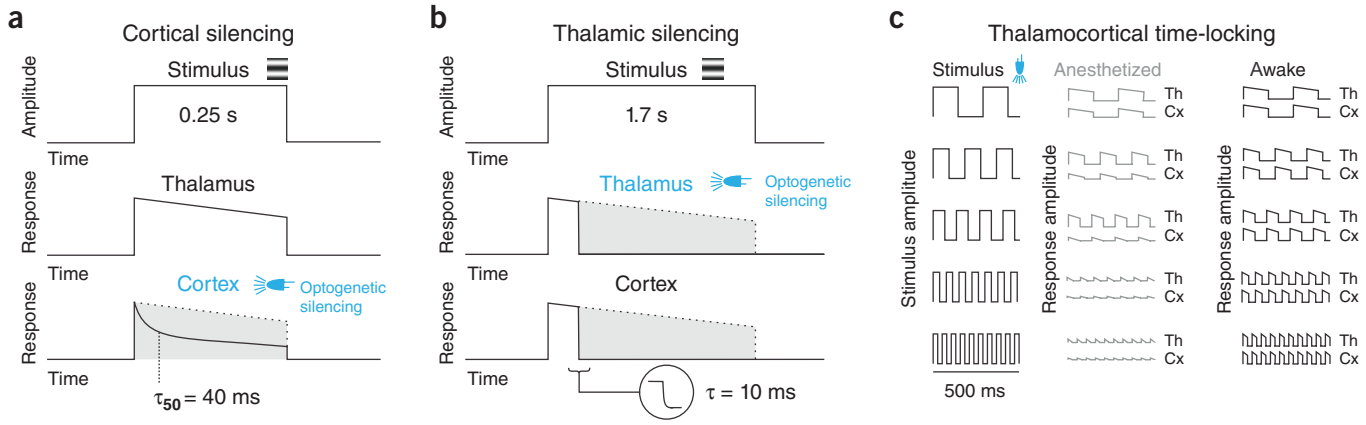

Figure 1 The influence of thalamic inputs in visual cortical responses. (**a**) Reinhold *et al.*[1] optogenetically silenced the visual cortex in mice while measuring the response of layer 4 cortical neurons to a visual stimulus (a static grating that lasted 1.7 or 0.25 s). These experiments demonstrate that the thalamus provides more than 50% of the total excitatory responses in the cortical neuron during the first 40 ms (τ_{50}). (**b**) Optogenetically silencing the thalamus made the cortical response fall very rapidly, with a decay time of 10 ms, which is the integration time of a single cortical neuron. (**c**) The short decay time of 10 ms made it possible for the cortex to follow stimulation at high temporal frequencies (reliably transmitted by the thalamus when the animal is awake). Under anesthesia, the cortical responses to high temporal frequencies were strongly reduced as a result of weaker thalamic responses and changes in thalamocortical synaptic depression. Th, thalamus; Cx, cortex.

(80% excitation during the first 10 ms) might have been even stronger if the cortical-thalamic loops were intact and functional. Future experiments are needed to address this question, which requires restricting the cortical silencing to layer 4 while leaving cortical-thalamic neurons active.

The contribution of the thalamic inputs to cortical responses may also change with brain state and the parameters of sensory stimulation. The authors measured the relative contributions of thalamic and cortical inputs (**Fig. 1a**) in anesthetized mice. However, given that thalamic firing decreases under anesthesia (**Fig. 1c**), it is possible that the thalamic contribution would be even stronger if the animal was awake and alert. It would not be surprising if future measurements in the awake brain find that the cortical amplification is less than threefold when animals are actively exploring their environments and are in desperate need of reliable thalamocortical transmission. The authors also used two different stimulus durations (1.7 and 0.25 s) and found that the largest thalamic contribution to cortical excitation was observed when the stimulus was short. Animals that are actively exploring their environments are more likely to be stimulated by multiple brief stimulus transients. Thus, it is possible that the relative contributions of thalamic versus cortical inputs may also change with the temporal statistics of the visual environment.

Finally, it is worth emphasizing that not all thalamocortical neurons contribute equally to visual cortical responses. For example, there are two different types of thalamocortical neurons that generate transient or sustained responses to optimal static stimuli and whose response time courses are controlled by brain state[11,13]. Thus, the decay of the cortical response will depend on the types of thalamic inputs silenced (sustained versus transient) and the brain state when they are silenced (alert versus drowsy, sleeping or anesthetized). In addition, some studies found that highly localized inactivation of thalamic inputs in carnivores silences neurons in both the middle and superficial layers of the primary visual cortex[14], whereas other studies found that most neurons in the superficial layers can remain active even if the main thalamic input to layer 4 is blocked[15]. Thus, silencing different thalamic inputs will differently affect the amplitude of the cortical response and the cortical layers transmitting sensory information. Although the authors were not able to dissect the functional contributions from different thalamocortical neurons (sustained versus transient) and different thalamic nuclei (for example, lateral geniculate nucleus versus lateral posterior nucleus), improved optogenetic tools should allow this challenge to be addressed in the future, and, by so doing, transform our understanding of how thalamocortical networks transmit sensory information. These are exciting times in which to study thalamocortical function.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Reinhold, K., Lien, T. & Scanziani, M. *Nat. Neurosci.* **18**, 1789–1797 (2015).
2. Ferster, D., Chung, S. & Wheat, H. *Nature* **380**, 249–252 (1996).
3. Li, Y.T., Ibrahim, L.A., Liu, B.H., Zhang, L.I. & Tao, H.W. *Nat. Neurosci.* **16**, 1324–1330 (2013).
4. Lien, A.D. & Scanziani, M. *Nat. Neurosci.* **16**, 1315–1323 (2013).
5. Sanchez-Vives, M.V. & McCormick, D.A. *Nat. Neurosci.* **3**, 1027–1034 (2000).
6. Timofeev, I., Grenier, F., Bazhenov, M., Sejnowski, T.J. & Steriade, M. *Cereb. Cortex* **10**, 1185–1199 (2000).
7. Constantinople, C.M. & Bruno, R.M. *Neuron* **69**, 1061–1068 (2011).
8. Gil, Z., Connors, B.W. & Amitai, Y. *Neuron* **19**, 679–686 (1997).
9. Castro-Alamancos, M.A. & Oldford, E. *J. Physiol. (Lond.)* **541**, 319–331 (2002).
10. Swadlow, H.A. & Gusev, A.G. *Nat. Neurosci.* **4**, 402–408 (2001).
11. Bezdudnaya, T. *et al. Neuron* **49**, 421–432 (2006).
12. Sherman, S.M. & Guillery, R.W. *Exploring the Thalamus* (Academic Press, New York, 2000).
13. Stoelzel, C.R., Bereshpolova, Y., Gusev, A.G. & Swadlow, H.A. *J. Neurosci.* **28**, 5018–5028 (2008).
14. Martinez, L.M. & Alonso, J.M. *Neuron* **32**, 515–525 (2001).
15. Malpeli, J.G. *J. Neurophysiol.* **49**, 595–610 (1983).