as Cajal bodies[9]. This element is important in ribosomal RNA modification and RNA splicing. Cajal bodies are most easily detected by immunostaining for the protein coilin. They have also drawn attention because they harbor the survival of motor neuron (SMN) protein, mutations in which cause spinal muscular atrophy. Cajal bodies are often closely associated with nucleoli, which are sites of ribosomal DNA transcription and pre-ribosome assembly. However, the 700 or so proteins that comprise the nucleolus suggest that these organelles have more complex functions. Indeed, nucleoli are also places where mRNA editing by the adenosine deaminase enzyme ADAR occurs, where the chromosome end-lengthening telomerase ribonucleoprotein enzyme is stored in normal but not cancerous cells, and where the biogenesis of the signal recognition particle, the molecular assemblage that mediates the transfer of certain nascent polypeptides into the endoplasmic reticulum, takes place.

What could nucleolar and Cajal body localization signify for neurons and the circuits in which they participate? At this point, it is too early to say for sure—for example, the localization of endogenous AIDA-1d in either cultured cells or in the brain has yet to be visualized. However, from the known roles of these subnuclear structures, we can speculate on a number of potentially important functions. Jordan and colleagues tested one predicted outcome: the regulation of the protein synthetic capacity of the cell. Because nucleoli and Cajal bodies are important for ribosome biogenesis, regulating their number could affect the capacity of the cell to synthesize protein. Indeed, siRNA knockdown of AIDA-1d results in a modest decline in the levels of total protein synthesis observed following prolonged blockade of inhibitory synapses. Another potential action could be to charge newly made mRNAs onto ribosome-containing ribonucleoprotein particles destined for transport to the dendrites and synapse[10]. Such mechanisms could act in concert with signals that regulate transcription or could be independent of them. One outcome of such transport could be to tune the protein synthetic capacity of the cell to particular states. Indeed, the current report shows that nucleolar number and organization is a function of neuronal maturation as well as levels of synaptic excitation.

Finally, one could imagine that synaptic signaling to nucleoli, Cajal bodies and other subnuclear structures involved in RNA metabolism could also have a more selective role in orchestrating the synaptodendritic proteome. For example, mRNA editing, which occurs in these subnuclear elements, is important in generating neuronal-specific forms of key synaptic proteins, including ion channels and components of the vesicular trafficking machinery[11]. Neuronal activity can also regulate alternative splicing of NMDA receptor–subunit mRNAs[12]. Thus, synaptic signaling to these nuclear epicenters of the RNA world could have far-reaching consequences for information processing and storage in neurons.

COMPETING INTERESTS STATEMENT
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It's about time for thalamocortical circuits

Court Hull & Massimo Scanziani

The timing of thalamocortical excitation and inhibition is critical to local microcircuits. Two new papers shed light on the development and performance of a somatosensory microcircuit that regulates the integration of thalamic inputs.

The timing of sensory stimuli is a fundamental parameter used by the neocortex to construct representations of the external world. In the somatosensory system, the timing of cortical spikes can accurately follow the pattern of stimuli generated while touching an object[1]. This temporal precision is likely to be essential for proper tactile discrimination. To enforce precise timing, the cortex uses a simple circuit that is activated by thalamic afferents[2]. These thalamocortical afferents provide the main input to the somatosensory cortex and form excitatory, glutamatergic synapses onto a subset of cortical neurons. In this issue, two papers examine the development and function of a microcircuit activated by thalamocortical afferents. Daw *et al.* show that the ontogeny of this thalamocortical microcircuit involves a set of rapid, coordinated steps that transform it into a precise coincidence detector[3]. Once the circuit is mature, Cruikshank and colleagues demonstrate that it relies on divergent kinetics and strength of excitation from thalamocortical afferents for reliable performance[4].

Upon entering the cortex, individual thalamocortical afferents contact both excitatory projection neurons (glutamatergic principal cells) and local inhibitory interneurons (GABAergic cells). Thus, somatosensory information is immediately distributed to both excitatory and inhibitory cells. Surprisingly though, thalamocortical synapses onto inhibitory interneurons are much stronger than those onto excitatory principal cells[2,5,6]. By contacting both inhibitory and excitatory cells, thalamocortical afferents lay the foundation for a simple disynaptic circuit that provides powerful, local feedforward inhibition (**Fig. 1**).

In the somatosensory cortex, thalamocortical afferents initiate feedforward inhibition by activating so-called fast-spiking interneurons, a subtype of GABAergic interneuron. Because these fast-spiking interneurons synapse onto the same excitatory principal cells that are directly contacted by thalamocortical afferents, thalamic activity results in both excitation and inhibition of cortical principal cells.

Because excitation is direct, whereas inhibition is delayed by one synapse, disynaptic feedforward inhibition lags

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monosynaptic thalamocortical excitation by 1–2 ms. The short latency between the onset of thalamocortical excitation and the onset of feedforward inhibition presents a temporal 'window of opportunity' for principal neurons to integrate excitatory inputs[2]. In other words, independent excitatory inputs onto a principal neuron summate more efficiently (toward threshold for spike generation) if they occur in the narrow time window before the onset of inhibition. Thus, this narrow window allows principal cells to acts as coincidence detectors, an operation that is critical for representing whisker velocity in rodents[7]. The standard sequence of excitation-inhibition initiated by thalamocortical afferents is also important in representing direction selectivity of whisker deflection[8] and maintaining cortical responses that are precisely time-locked to sensory input[2].

The efficiency of the thalamocortical feedforward inhibitory circuit is a result of optimizations that occur at several levels, including strong thalamocortical excitatory inputs onto fast-spiking interneurons, fast synaptic transmission from thalamocortical afferents onto fast-spiking interneurons and a strong, reliable inhibitory synapse from fast-spiking interneurons onto principal cells[2,5,6,9]. This optimized arrangement is not fixed from birth, however. As described in the new work by Daw *et al.*[3], the ontogeny of the thalamocortical microcircuit involves a set of rapid, coordinated steps that allow robust feedforward inhibition to emerge during the first week of postnatal development.

In agreement with previous work[10], Daw *et al.* show that principal cells in the somatosensory cortex of very young mice (P3–5) receive direct thalamic excitation, but lack feedforward inhibition. Here the authors investigate the cellular basis of this missing inhibition using *in vitro* electrophysiological recordings in the mouse thalamocortical slice[11]. This preparation leaves thalamocortical connections intact, and the authors perform a set of beautiful experiments that show that the neonatal thalamocortical microcircuit is incomplete in several ways. Specifically, thalamic input onto fast-spiking interneurons is very weak, connections from fast-spiking interneurons to principal cells are both weak and sparse, and GABAergic transmission is depolarizing (**Fig. 1a**). In a remarkably short time, however, this immature state of affairs changes dramatically.

Between P6 and P7, Daw *et al.* reveal a set of rapid, coordinated events that efficiently reorganize synaptic connections to engage reliable feedforward inhibition and establish a functionally mature thalamocortical microcircuit (**Fig. 1b**). During these two days, the strength of synaptic contacts from thalamocortical afferents to layer IV fast-spiking interneurons is increased several-fold, as is the strength of unitary connections from fast-spiking interneurons to principal cells. During the same period, there is a major increase in the probability of synaptic contact from fast-spiking interneurons to principal cells. Simultaneously, the reversal potential for GABAergic currents becomes more hyperpolarized with respect to the resting membrane potential of principal cells so that GABA evokes outward, inhibitory postsynaptic currents (IPSCs). The net effect of these coordinated changes is a large, synchronous feedforward GABAergic IPSC produced by layer IV fast-spiking interneurons in response to thalamocortical afferent activity. Remarkably, the authors demonstrate that even a single fast-spiking interneuron provides significant feedforward inhibition to the population of nearby principal cells in the mature thalamocortical microcircuit.

This abrupt emergence of inhibition begs the question of whether the coordinated reorganizations described by Daw *et al.* are

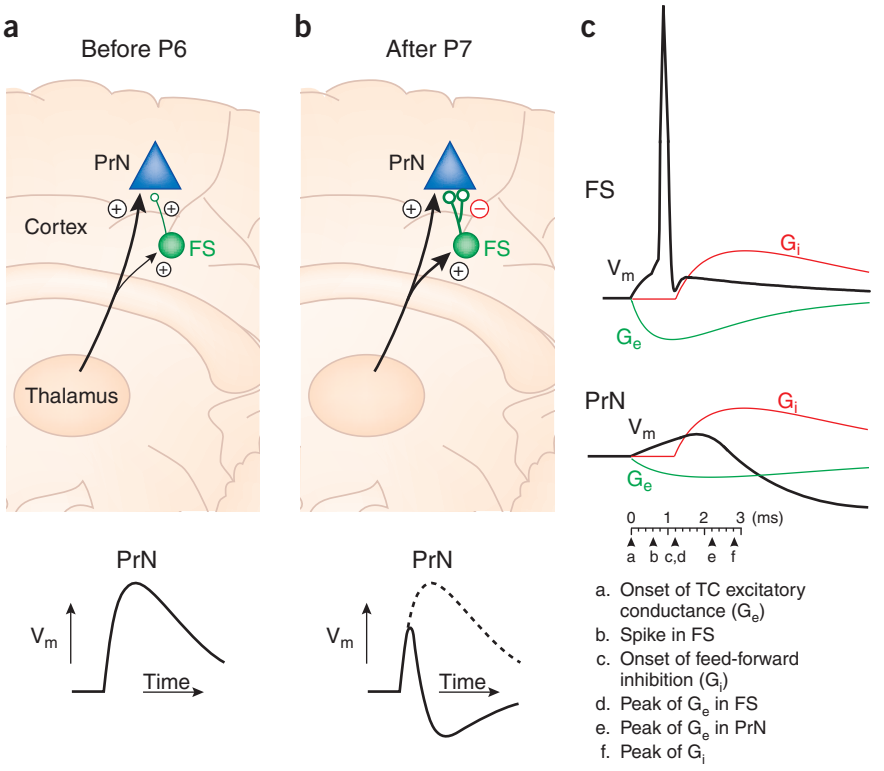

Figure 1 Development and function of the thalamocortical microcircuit. (**a**) The emergence of feedforward inhibition. In the neonatal mouse, thalamic (thalamocortical) afferents entering the somatosensory cortex excite cortical projection neurons (principal cells, PrN) in layer 4. They also provide weak excitation to GABAergic fast-spiking interneurons. In turn, fast-spiking interneurons make sparse, weak synapses onto PrNs that evoke GABAergic depolarizing postsynaptic potentials. In response to thalamic stimulation (lower), PrNs respond with a simple EPSP. (**b**) The properties of this thalamocortical microcircuit change rapidly and dramatically after P6. Now, thalamocortical afferents strongly excite fast-spiking neurons (in fact, more strongly than PrNs). Fast-spiking neurons also make powerful and abundant connections onto PrNs, and GABA release evokes inhibitory postsynaptic potentials (IPSPs). Thus, thalamocortical activity (lower) evokes a standard, mature EPSP-IPSP sequence in PrNs after P6 (compare with EPSP only, gray dashed line). (**c**) The first 3 ms of cortical sensory processing. Time 0: thalamocortical afferents excite fast-spiking cells and PrNs. The activation of a large and fast excitatory postsynaptic conductance (G_e) onto fast-spiking neurons leads to a rapid depolarization of the membrane potential (V_m). At around 0.6 ms, this generates a spike. Meanwhile, V_m rises more slowly in PrNs as a result of a slower G_e (measured at the soma) and longer membrane time constant. Time 1.2 ms: GABA released from fast-spiking interneurons initiates a $GABA_A$ receptor–mediated conductance (G_i) in PrNs. Time 2.7 ms: G_i reaches its peak. By counteracting G_e, G_i hyperpolarizes Vm to conclude the standard EPSP-IPSP sequence. If PrNs do not reach threshold for spike generation before the onset of the IPSP, they likely never will (at least in the immediate future).

regulated by sensory activity, or whether they result from a preprogrammed set of steps designed to engage feedforward inhibition at a precise developmental time point. Furthermore, it will be important to determine whether the early absence of feedforward GABAergic transmission has consequences for the maturation of thalamocortical projections.

In agreement with previous findings, Daw *et al.* show that thalamocortical afferents can activate principal cells effectively during early neonatal development. As blocking GABAergic transmission has no effect on principal cell responses to thalamocortical input before P6, this study seems to exclude any role for depolarizing GABAergic transmission in the thalamocortical microcircuit during this period.

Thus, before the completion of this circuit, thalamocortical transmission merely activates cortical principal cells without the moderating influence of feedforward inhibition. This should allow principal cells to integrate inputs over a wider time window, and could facilitate synaptic plasticity and the development of receptive fields. It would therefore be valuable to examine whether the lack of early inhibition promotes the kind of enhanced integration of monosynaptic inputs that could favor the induction of long-term potentiation during this critical period[12,13].

Once engaged in the mature thalamocortical microcircuit, feedforward inhibition provides a powerful counterbalance to principal cell excitation. Even though thalamocortical afferents excite both fast-spiking interneurons and principal cells nearly simultaneously, fast-spiking interneurons must provide feedforward inhibition in time to restrict principal cell excitation. In other words, disynaptic inhibition must keep pace with monosynaptic excitation, or it will arrive late to the party and miss all the action.

To effectively restrict excitation, inhibition must reach principal cells before the peak of a thalamocortical excitatory postsynaptic potential (EPSP). By doing so, inhibition can set a permissive 'window of opportunity' for spike generation. In the thalamocortical microcircuit, this requires fast-spiking interneurons to spike quickly relative to principal cell excitation. Thus, the thalamocortical microcircuit faces a fundamental timing challenge. In their study, Cruikshank *et al.*[4] provide an elegant demonstration that thalamocortical synaptic transmission has been specialized to rise to the occasion (**Fig. 1c**).

One way to generate rapid feedforward inhibition would be to differentially tune synaptic transmission from thalamocortical afferents onto fast-spiking interneurons and principal cells. By using paired recordings while stimulating only a single thalamocortical afferent, Cruikshank *et al.* show us that these fibers trigger faster rising excitatory currents in fast-spiking interneurons than they do in principal cells.

Another way to ensure fast, reliable inhibition would be to tailor fast-spiking interneurons that are intrinsically more excitable than principal cells. Surprisingly, Cruikshank *et al.* show that there is no difference in the resting membrane potential or spike threshold between fast-spiking interneurons and principal cells. Furthermore, fast-spiking interneurons have a much lower input resistance than principal cells. This property actually reduces their excitability by requiring more current to drive their membrane potential to spike threshold.

In addition, the authors confirm that fast-spiking interneurons receive unitary thalamocortical inputs that are approximately fourfold stronger than those onto principal cells[2,5,6]. Moreover, they find that thalamocortical afferents contact fast-spiking interneurons with a higher probability than principal cells, as has been shown previously[6,14]. The net effect of these differences is a faster, stronger thalamocortical excitation of fast-spiking interneurons that overcomes their lower input resistance and allows them to spike quickly. In fact, once compensated by a large excitatory drive, the lower input resistance of fast-spiking cells becomes an advantage by reducing their membrane time constant and accelerating the rise-time of their EPSPs[15].

Cruikshank *et al.* clearly demonstrate that fast-spiking interneurons also provide strong feedforward inhibition within their population. Therefore, it will also be important to discover the role of this self-inhibition. The authors suggest that the fast excitatory inputs to fast-spiking cells allow them to fire action potentials before significant feedforward inhibition emerges. Because fast-spiking cells are the ones producing this inhibition, however, they must certainly reach spike threshold before inhibition can occur. One may therefore hypothesize that inhibition shortens the duration of their spike trains. Future work will thus be important to address the role of inhibition onto interneurons in the thalamocortical microcircuit.

Hence, the thalamocortical system seems to have developed synaptic specializations to ensure that feedforward inhibition is both reliable and well timed. Perhaps because of its crucial role in defining the integration time window of principal cells, feedforward inhibition has been prioritized by the thalamocortical microcircuit and is maintained by a set of fail-safe synaptic mechanisms. Because the same thalamocortical afferents activate both fast-spiking interneurons and principal cells, it will be interesting to determine the synaptic mechanisms that underlie the divergent kinetics and excitatory drive onto interneurons versus principal cells. Ultimately, it will be crucial to investigate the consequences of this powerful and precisely timed thalamocortical feedforward inhibition at the behavioral level. Manipulations that selectively slow or reduce the size of this inhibition could be used to great effect in determining its influence on tactile discrimination.

These two insightful studies show the key developmental steps and timing optimizations that allow this simple cortical circuit to function. In so doing, they also represent vital strides forward in the broader effort to deconstruct small cortical circuits and understand their role as fundamental units of processing.

COMPETING INTERESTS STATEMENT
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