# Cortical Feedback Controls the Frequency and Synchrony of Oscillations in the Visual Thalamus

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Thalamic circuits have an intrinsic capacity to generate state-dependent oscillations of different frequency and degrees of synchrony, but little is known of how synchronized oscillation is controlled in the intact brain or what function it may serve. The influence of cortical feedback was examined using slice preparations of the visual thalamus and computational models. Cortical feedback was mimicked by stimulating corticothalamic axons, triggered by the activity of relay neurons. This artificially coupled network had the capacity to self-organize and to generate qualitatively different rhythmical activities according to the strength of corticothalamic feedback stimuli. Weak feedback (one to three shocks at 100–150 Hz) phase-locked the spontaneous spindle oscillations (6–10 Hz) in geniculate and perigeniculate nuclei. However, strong feedback (four to eight shocks at 100–150 Hz) led to a more synchronized oscillation, slower in frequency (2–4 Hz) and dependent on $GABA_B$ receptors. This increase in synchrony was essentially attributable to a redistribution of the timing of action potential generation in lateral geniculate nucleus cells, resulting in an increased output of relay cells toward the cortex. Corticothalamic feedback is thus capable of inducing highly synchronous slow oscillations in physiologically intact thalamic circuits. This modulation may have implications for a better understanding of the descending control of thalamic nuclei by the cortex, and the genesis of pathological rhythmical activity, such as absence seizures.

*Key words: corticothalamic; spike and wave; absence seizure; $GABA_B$; spindle waves; thalamus; thalamic reticular nucleus; closed loop system*

Thalamic circuits can display different types of oscillation characterized by their frequencies and levels of synchrony. The most common rhythmical activity seen in intact thalamic circuits is the 7–14 Hz spindle rhythm, which consists of periodically recurring waxing and waning oscillations (Andersen and Andersson, 1968; Steriade and Deschênes, 1984; von Krosigk et al., 1993; Contreras et al., 1996). In slice preparations from the ferret, 6–10 Hz spindle oscillation can be self-generated provided that the circuitry linking the dorsal lateral geniculate nucleus (LGNd) and the perigeniculate nucleus (PGN) is conserved intact. Blockade of $GABA_A$ receptors by application of bicuculline transforms the spontaneous spindling pattern to a slower and more synchronized oscillation at 2–4 Hz (von Krosigk et al., 1993; Bal et al., 1995a,b). This slower rhythm is strikingly similar to the typical 3 Hz frequency of absence seizures in humans, in which the thalamus is thought to be a key player (Gloor and Fariello, 1988).

The genesis of these autonomous rhythms is now well understood in terms of the thalamic recurrent circuits and intrinsic cellular properties involved (Steriade et al., 1993). However, our understanding of thalamic rhythmic generation remains limited concerning its control by external sources, such as the feedforward retinal projection or the feedback projection from cortex. We know that cortical feedback provides an extremely dense projection to the thalamus (Guillery, 1969; Liu et al., 1995; Erisir et al., 1997a,b; Liu and Jones, 1999), which may serve to control faster rhythms of thalamic oscillation, in the gamma frequency range (20–60 Hz) reported *in vivo* during sensory processing (Ghose and Freeman, 1992; Sillito et al., 1994; Neuenschwander and Singer, 1996). Corticothalamic feedback is also essential in coordinating widespread, coherent, sleep-related synchronized oscillation of different thalamic nuclei (Contreras et al., 1996). More recently, computational models have predicted that corticothalamic feedback could control the transitions between different ranges of thalamic oscillation, defined by their frequency and synchrony (Destexhe, 1998).

Here we test this hypothesis using a new ferret slice preparation preserving the optic tract and the optic radiation bundle in which corticofugal fibers can be stimulated, while maintaining intact the endogenous genesis of spindles (see Fig. 2*A*). The sequence of synaptic and voltage-gated cellular events following activation of cortical feedback was studied with intracellular current-clamp recordings of perigeniculate and LGN relay neurons. Computational models and multiple extracellular recordings were used to assess the level of local recruitment and synchronized activity in the network. From the experimental results and computational models we propose principles of functional network organization able to explain the cortical control of thalamic oscillations.

## MATERIALS AND METHODS

*Slice preparation.* Adult ferrets, 3- to 15-months-old ($n = 24$) (Marshall Europe, Lyon, France; Dostes, St. Creac, France), were anesthetized with sodium pentobarbital (45 mg/kg). LGNd slices (350 $\mu$m) were prepared in a solution (see below) in which NaCl was replaced with sucrose while maintaining an osmolarity of 307 mOsm (adapted from Aghajanian and Rasmussen, 1989). After preparation, slices were placed in an interface-style recording chamber (Fine Science Tools, Heidelberg, Germany). The bathing medium contained (in mM): NaCl, 124; KCl, 2.5; $MgSO_4$, 1.2; $NaH_2PO_4$, 1.25; $CaCl_2$, 2; $NaHCO_3$, 26; dextrose, 10, and was aerated with 95% $O_2$ and 5% $CO_2$ to a final pH of 7.4. Bath temperature was maintained at 34.5–35.5°C. LGNd slices were cut in a plane parallel to the most proximal extent of the optic tract (see Fig. 2*A*). This new procedure preserved a portion of the optic radiation containing corticothalamic axons and their synaptic connections to thalamic cells, as well as several millimeters of the optic tract. Extracellular multiunit recordings from LGN laminae revealed periodic spontaneous spindle waves that were indistinguishable from those obtained from sagittal slices used previously (von Krosigk et al., 1993; Bal et al., 1995a). The presence of this network activity indicates that synaptic connections between perigeniculate and thalamocortical cells were functionally intact.

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*Electrophysiology.* Extracellular recordings were obtained with low-resistance (<5 MΩ) tungsten microelectrodes (Frederick Haer, Bowdoinham, ME). Intracellular recording electrodes were made on a Sutter Instruments P-87 micropipette puller from medium-walled glass (WPI, 1B100F) and beveled on a Sutter Instruments beveler (BV-10M). Micropipettes were filled with 1.2 M K acetate and had resistances of 90–120 MΩ after beveling. Cells were included in the present study if they exhibited a stable resting membrane potential for at least 10 min (typically 30–180 min), were able to generate bursts of overshooting action potentials, and exhibited apparent input resistances of at least 30 MΩ (on average 80.4 ± 32.8 MΩ; $n = 15$). LGN cells had an average resting membrane potential of 62.2 ± 3.8 mV ($n = 16$).

Cells were identified in extracellular recordings according to their location, the duration of their action potentials, and the temporal structure of their action potential bursts: in PGN cells, but not in thalamocortical cells, the frequency of action potential generation within each burst increased, then decreased in frequency in an "accelerando-decelerando" pattern (Domich et al., 1986; Hu et al., 1989; Bal et al., 1995b).

The optic radiation (OR) was stimulated at a distance of 400–800 μm from the PGN, using bipolar tungsten electrodes similar to those used for extracellular recordings, spaced 200–450 μm apart, and oriented perpendicular to the corticothalamic fiber bundles (see Fig. 2*A*). Tips were electroplated with gold in a 2% $HAuCL_4$ solution. Stimulations ranged from 10 to 40 μA (0.1 msec duration). Feedback stimuli of corticothalamic fibers were triggered by the activity of thalamic relay cells using a custom data acquisition software (Acquis1; developed by G. Sadoc, Unité de Neurosciences Intégratives et Computationnelles, Centre National de la Recherche Scientifique Gif-sur-Yvette, Agence Nationale pour la Valorisation des Applications de la Recherche Biological). The software detected the LGN discharges in intracellular (Axoclamp-2B amplifier; Digidata 1200 analog-to-digital converter; Axon Instruments, Foster City, CA) and multiunit recordings by a voltage threshold, and set the latency at which a command was sent to an OR-stimulating unit (A360; WPI). In some intracellular recordings, the voltage threshold was set below the peak of the low-threshold calcium spike. A minimum interstimulus interval of 100 msec was set after first spike detection to avoid overstimulation triggered by the recurrence of spikes within the burst itself. The results presented here, using the feedback paradigm, were obtained in 21 slices taken from 17 animals.

Electrical stimulation of the optic radiation resulted in orthodromic activation of corticofugal axons and generated mixed IPSPs and EPSPs, recorded intracellularly in thalamocortical relay cells. Antidromic invasion was observed only exceptionally (2 of 40 LGN cells), and those cases were discarded from the present analysis. Antidromic spikes were recognized by their short and stable latency (0.67 ± 0.1 msec from artifact to peak; $n = 50$ events) and the lack of underlying EPSP, whereas monosynaptic corticothalamic EPSPs, recorded in the same cell, had a longer and more variable latency (2.74 ± 0.29 msec; $n = 50$ events) consistent with the latency of EPSPs mediated monosynaptically in LGN principal cells by slowly conducting corticogeniculate fibers described previously *in vivo* (Tsumoto et al., 1978; Ahlsen et al., 1982). The effect of antidromic activation was also tested using the model (data not shown), which indicated that the antidromic activation of a minority of LGN or PGN cells had no detectable effect on network behavior. Thus, whereas the contribution of antidromic activation of LGN relay cells to the response of LGN and PGN cells cannot be completely ruled out, it certainly remains small compared to the contribution of the orthodromic activation of corticothalamic axons.

To block $GABA_B$ responses, the antagonist CGP 35348 (gift of Ciba-Geigy) was delivered locally with the pressure-pulse technique in which an air puff (3 psi extruded volume of 2–20 pl) (Picospritzer; General Valve, Fairfield, NJ; 10–100 msec). The drug was applied either to the surface or in the depth of the slice within 50–100 μm of the entry point of the recording electrode.

*Data analysis and statistics.* Analysis was performed using Acquis1, a custom software. The level of cell recruitment and synchronized activity in the network was best visualized by half rectifying the multiunit signal, and then smoothing it by a moving average technique to enhance the detection of cells coactive within a given window. Smoothed integration was performed with a 10 msec time constant, except for the responses illustrated in Figure 6*A* (20 msec). Autocorrelation functions were applied to the reconstructed local field potential and to the intracellular current-clamp recordings, after removal of action potentials and stimulation artifacts by a software routine (Bringuier et al., 1997). Measurements of the period of oscillatory activity were derived from the abscissa of the first peak in the normalized autocorrelation functions calculated on at least 80, and up to 500 cycles of oscillation. Nonparametric Wilcoxon matched paired tests were applied to the oscillation period values observed in the control case and in the presence of a cortical feedback (with a significance level of 0.05).

*Models.* Computational models of thalamic neurons were designed based on previous studies (Destexhe et al., 1996; Destexhe, 1998). LGN and PGN neurons were modeled by single compartment representations including various intrinsic voltage- and calcium-dependent currents, such as $I_T$, $I_h$, $I_{Na}$, and $I_K$ in LGN cells and $I_T$, $I_{Na}$, and $I_K$ in PGN. These intrinsic currents were represented by Hodgkin–Huxley-type models. In addition, $I_h$ contained an upregulation by intracellular calcium as described previously (Destexhe et al., 1996). LGN and PGN neurons generated bursts of action potentials with a strength and voltage dependence similar to that observed experimentally.

Postsynaptic currents mediated by glutamate (AMPA and NMDA receptors) and GABA ($GABA_A$ and $GABA_B$ receptors) were simulated using kinetic models of postsynaptic receptors (Destexhe et al., 1998b). The synaptic interactions modeled were LGN → PGN (AMPA receptors), PGN → PGN ($GABA_A$ receptors), and PGN → LGN ($GABA_A$ and $GABA_B$ receptors; Fig. 1*A,B*), as found experimentally (von Krosigk et al., 1993). Each cell type established connections within a local area of 10% of the size of the network, in a topographically organized manner (Destexhe et al., 1996). Corticothalamic feedback was mediated by AMPA receptors on both LGN and PGN cells. NMDA receptors were also incorporated in some simulations (conductance of 25% of that of AMPA receptors), but they did not affect the present results (data not shown). mGluR receptors have been described in LGN and reticularis neurons (von Krosigk and McCormick, 1993; Cox and Sherman, 1999), but were not incorporated here.

Feedback simulations were designed similarly to the experiments reported here. In a network consisting of two one-dimensional rows of 100 LGN and 100 PGN cells, the suprathreshold activation of a single LGN cell was chosen as trigger (Fig. 1*A*). When this LGN cell fired, the first spike was used to trigger a burst of presynaptic stimulation of corticothalamic synapses, after a delay of 10–50 msec. As in experiments, the number and strength of stimuli were varied.

## RESULTS

We first describe with the model the paradigm and the hypothesis tested here, namely that corticothalamic feedback can control the type of oscillation displayed by the thalamus. We then investigate this theoretical prediction experimentally, and establish the characteristics of the control of thalamic oscillations by cortical feedback. Finally, based on these experimental data, we return to the model to analyze the network mechanisms underlying the cortical control of thalamic oscillations.

### Models predict that corticothalamic feedback can control thalamic oscillations

A thalamocortical network model was introduced previously to model ~3 Hz spike-and-wave seizures based on the biophysical properties of neurons and synapses in thalamocortical circuits (Destexhe, 1998). This model formulated one main prediction, that corticothalamic feedback can force the intact thalamus from control spindles (8–12 Hz) to a different oscillatory mode, slower (~3 Hz) and more synchronized. To test this prediction in thalamic slices, one must reconstitute the thalamus-cortex-thalamus loop. We have thus elaborated a paradigm that consists of forming an artificial feedback loop between the activity of the LGN neurons and the stimulation of corticothalamic fibers (Fig. 1*A*). This can later be tested experimentally.

We first simulated this paradigm using a model network of 100 PGN and 100 LGN cells interconnected via AMPA, $GABA_A$, and $GABA_B$ receptors (Fig. 1*A*). Cells were modeled by a single-compartment incorporating calcium- and voltage-dependent currents (Fig. 1*B*) as in previous models (Destexhe et al., 1996). The spike activity of one LGN cell was used to trigger the stimulation of corticothalamic EPSPs across the entire network. A burst of action potential in the trigger LGN cell started a high-frequency (100 Hz) burst of AMPA-mediated corticothalamic EPSPs in LGN and PGN neurons (see Materials and Methods). The strength of the feedback stimulation was adjusted by controlling the number of corticothalamic EPSPs (number of shocks).

In the case of mild feedback (one to four shocks at 100 Hz for the conductance settings given in Materials and Methods), the pattern of LGN and PGN discharge was typical of spindle oscillations (Fig. 1*C*; one shock): individual LGN cells showed subharmonic bursting activity, and were not tightly synchronized. In this case, the presence of the feedback did not disrupt the pattern of spindle oscillations, but only slightly increased the synchrony of LGN cells (see below). This is consistent with previous models showing that mild corticothalamic feedback can control the onset and distribution of spindling activity, but does not change its cellular features (Destexhe et al., 1998a).

A radically different picture was obtained for stronger feedback stimulation. When the number of stimuli was increased to five shocks or more, the pattern of bursting changed qualitatively, and the

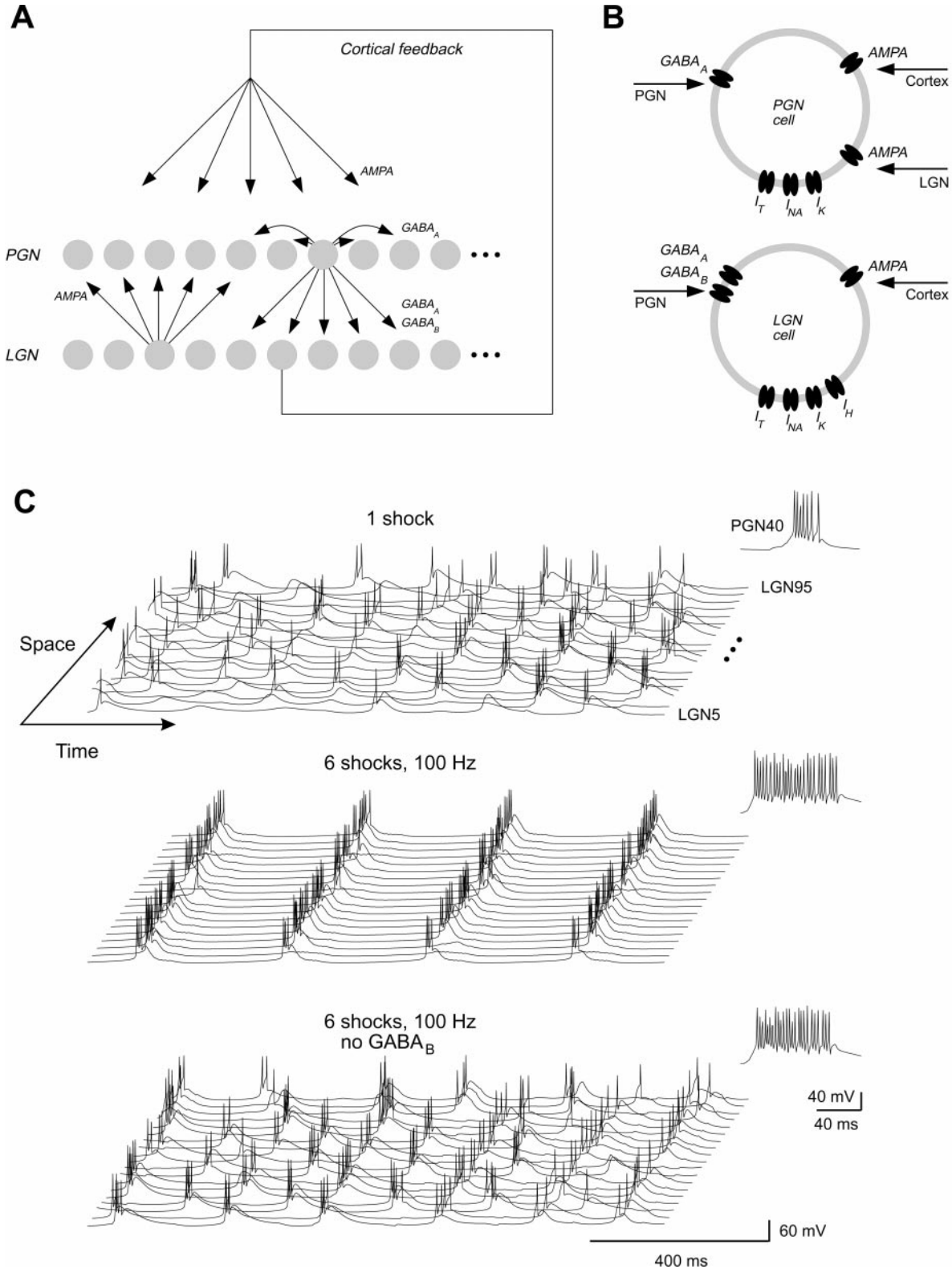


*Figure 1.* Computational model prediction of the control of thalamic oscillations by corticothalamic feedback. *A,* Scheme of the thalamic circuit. A network consisting of two one-dimensional layers of LGN and PGN neurons (100 cells each) was simulated with topographic connections mediated by glutamate (AMPA) receptors and GABAergic ($GABA_A$ and $GABA_B$) receptors as indicated. One cell (LGN cell 10) was the trigger of the cortical feedback, which was simulated through AMPA conductances in all cell types. The connectivity and conductances used were identical to a previous study (Destexhe et al., 1996) with additional corticothalamic feedback conductances of 1–4 $\mu$S in PGN and 0.05–0.5 $\mu$S in LGN cells. *B,* Scheme of the different ionic mechanisms present in each cell type. The voltage-dependent currents $I_T$, $I_h$, $I_{Na}$, and $I_K$ were needed to simulate the intrinsic bursting patterns of thalamic neurons. *C,* Spatiotemporal network activity raster plots, detailing the results of the simulation of the feedback experiment. *Top,* Feedback stimuli consisting of a single shock produced bursting patterns typical of spindle oscillations. *Middle,* Strong feedback (6 shocks at 100 Hz) synchronized the burst discharges of LGN cells and switched the oscillation frequency to 3 Hz in the entire network, although only one cell served as the trigger. *Bottom,* Suppressing $GABA_B$ receptors led to the reverse transformation from 3 to 10 Hz spindle oscillations, and the feedback was ineffective in inducing the 3 Hz rhythm. Each graph represents 19 equally spaced LGN cells in the network, and an example of PGN burst is shown in *inset*. A delay of 25 msec was used in all simulations.

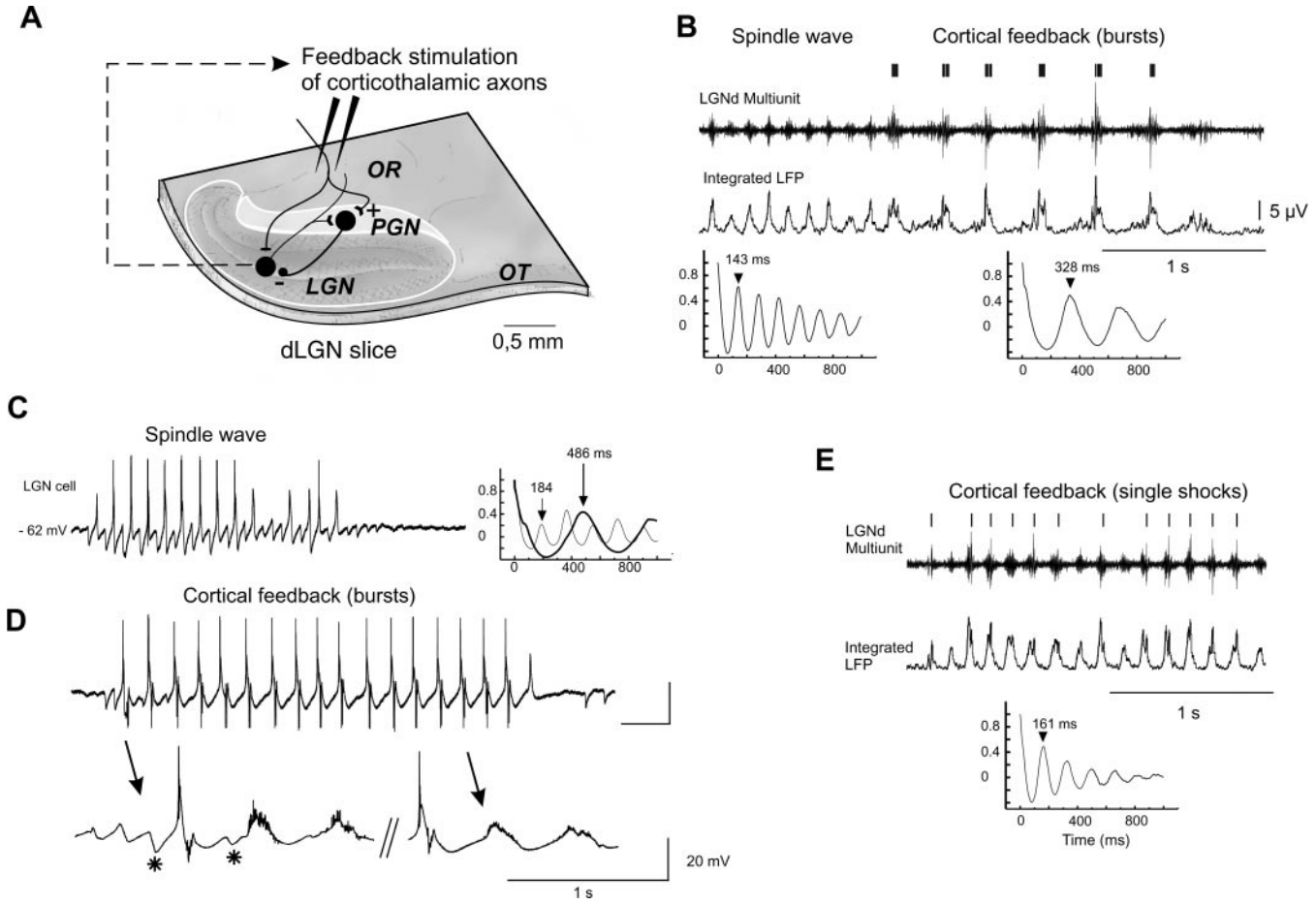


*Figure 2.* Control of thalamic oscillations by corticothalamic feedback in ferret thalamic slices. *A,* In the self-generating spindling thalamic slice, lateral geniculate (*LGN*) relay neuron axons projecting to the cortex via the optic radiation (*OR*) give off a collateral branch to the perigeniculate nucleus (*PGN*). The GABAergic PGN neurons generate direct inhibitory feedback to the relay neurons of the LGN. Corticothalamic axons run in the OR and synapse on LGN and PGN cells. Bipolar stimulating electrodes were placed in the OR. *OT,* Optic tract. *B,* A 7 Hz control spindle is slowed down to a 3 Hz oscillation by the feedback stimulation of OR at a latency of 20 msec after the detection of multiunit bursts activity (5 shocks; 100 Hz). *Middle trace,* Smooth integration of the multiunit signal (integrated local field potential). *Bottom traces,* Autocorrelation functions applied on the integrated LFP before and after the transition. *C,* Intracellular recording of a thalamocortical cell during spontaneous spindle oscillation. The first peak (184 msec) of the autocorrelation function indicates the period of network oscillation (i.e., the inverse of its beating frequency). *D,* Cortical feedback stimulations (4 shocks; 100 Hz; 50 msec delay) triggered by the burst firing of the cell slows the network oscillation to ~2 Hz. Downward deflections in the cell are stimulation artifacts. Action potentials were truncated for clarity. The spike-triggering average below was made from before and after the first 2 sec of 12 and 64 oscillatory sequences, respectively; it indicates the persistence of fast compound IPSPs at the beginning of the oscillation (*asterisk*). An autocorrelation function of this slow oscillation is superimposed in *C* as the *thick trace* (486 msec). *E,* Weak (single shock) feedback stimulation delivered to OR.

network switched to slow (2–4 Hz) oscillations (Fig. 1*C*; six shocks). In this case the degree of synchrony was higher than spindles because all cells fired within the same phase of the oscillation. This activity is consistent with a previous model, in which the entire system switched to synchronized 3 Hz oscillations in the presence of an abnormally strong corticothalamic feedback (Destexhe, 1998).

The biophysical mechanisms underlying the change of rhythmic activity in this model were the following. In control conditions (one to four shocks), the corticothalamic EPSPs evoked burst firing patterns in PGN cells consisting of a small number of spikes (from 1 to 10 spikes; Fig. 1*C, inset, top trace*). This low number of spikes was maintained because of the presence of lateral $GABA_A$-mediated inhibition between PGN cells, as shown experimentally (Sanchez-Vives et al., 1997; Huntsman et al., 1999). With strong feedback (five shocks or more), the corticothalamic stimuli were able to overcome the limiting effect of this lateral inhibition and forced PGN cells to produce prolonged burst discharges (10–30 spikes; Fig. 1*C, inset, middle trace*). These longer spike trains are ideal for the activation of $GABA_B$ receptors in LGN cells (Destexhe and Sejnowski, 1995; Kim et al., 1997). Thus, $GABA_B$-mediated IPSPs were evoked in LGN cells only with strong feedback stimulation, leading to the 3 Hz rhythm. With suppression of $GABA_B$ receptors, the model reverted to patterns similar to spindling activity (Fig. 1*C, no* $GABA_B$).

The model thus indicates that strong corticothalamic feedback can force the thalamic circuit to generate a slow and highly synchronized oscillation. This feedback paradigm is investigated experimentally below.

## Corticothalamic control of oscillations in thalamic slices

We implemented the feedback paradigm using a ferret slice preparation that preserved the optic tract and the optic radiation bundle, allowing corticofugal fibers to be stimulated, while maintaining intact the endogenous genesis of spindles (Fig. 2*A*). The activity of corticothalamic fibers was triggered by the output signals of thalamocortical relay cells, recorded either intracellularly, or extracellularly as a multiunit signal. Stimulations of corticothalamic fibers ranged from a single shock to a train of shocks, with a preset frequency (100–150 Hz) and delay of onset (5–140 msec), after the discharges of relay cells. However the triggering and timing of this corticothalamic feedback were determined entirely by the endogenous firing rhythm of the LGN itself. Thus, we studied a functionally structured closed loop circuit, which maintained the ability to self-organize its activity. Autocorrelation functions were used to study the oscillatory frequency of the spike activity in identified neurons and multiunits, relative to the average beating frequency of the network.

The effect of cortical feedback on autogenic reorganization of

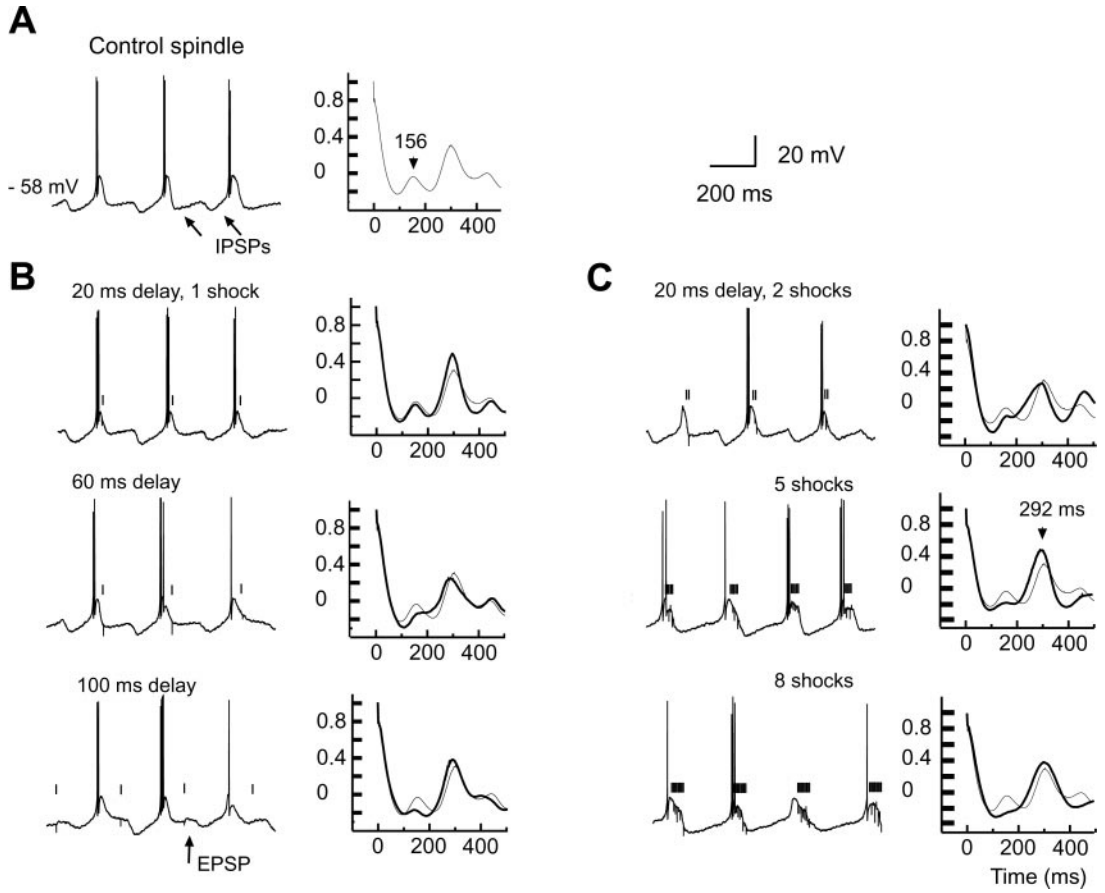


*Figure 3.* Thalamic oscillation is controlled by the intensity of the cortical feedback. *A,* Detail of a spindle wave and its control autocorrelogram displayed as the *thin trace* in *B* and *C*. *B,* Single shocks resulting in monosynaptic EPSPs (*arrow*) and performed at various delays after the bursts have little effect on the oscillation. *C,* Increasing the intensity of stimulation to a threshold of four or five shocks leads to the disappearance of fast IPSPs and slows down the network oscillation to 3–4 Hz.

thalamic rhythmic activity depended on the strength and duration of optic radiation stimulation. High-frequency burst stimuli, comprising four to six shocks at 100–140 Hz, slowed the spontaneously generated spindle oscillation frequency from the typical 6–10 Hz (6.44 ± 0.64 Hz), to 2–4 Hz (2.84 ± 0.66 Hz; $n = 17$ slices where the feedback paradigm was tested) (Fig. 2*B*). The intracellular records illustrated in Figure 2, *C* and *D*, show that this effect was attributable to a transition in the type of inhibitory feedback that developed over the first one to three cycles of oscillation: the fast repetitive IPSPs at 7–10 Hz originating from PGN cells, typical of spindle oscillation (Fig. 2*D, asterisks*), were replaced by longer, sustained IPSPs, resulting in oscillation at 2–4 Hz ($n = 7$; Fig. 2*D*).

High-frequency burst stimulation of the optic radiation was necessary to produce this transition. Short-lasting stimuli of the same intensity but comprising only 1–2 shocks at 100 Hz, delivered 0–20 msec after the relay neuron action potential, were able to entrain the oscillation but did not significantly alter the mean frequency of the spontaneous spindle rhythm (Figs. 2*E,* 3*B*) (6.17 ± 0.74 Hz for spontaneous spindles vs 6.07 ± 0.63 Hz during single shock cortical stimulation; NS; $n = 7$).

To test whether the precise timing of the stimulation affected the phase of oscillation cycle of the LGN cells, as shown in other structures (Lampl and Yarom, 1993; Volgushev et al., 1998), the delay (or phase lag) between relay neuron spikes and optic radiation stimulation was increased (60–100 msec). This produced either no significant change in the global oscillation frequency of the network, as can be seen from the unchanged frequency of IPSPs in the intracellular recording (Fig. 3*A,B, arrows*; see first peak of autocorrelograms), or a small phase lag (up to 30 msec), but did not entrain a transition to the slow oscillation frequency at 3 Hz ($n = 3$). Conversely, increasing the stimulus train to five shocks or more at the same 100–140 Hz frequency, without changing the timing relative to the relay neuron action potentials (i.e., a burst lasting 35–50 msec, triggered 20 msec after LGN firing), immediately prolonged the IPSPs, provoking a marked reduction in the global oscillation frequency, to 2–4 Hz (Fig. 3*C*; see displacement of first peak in autocorrelograms) ($n = 7$). This effect was tested and observed for relay neuron spike-optic radiation stimulation delays ranging from 0 to 80 msec.

The rhythmic inhibition of LGN relay neurons by PGN cells is essential both to the generation of spindle waves and to the production of slow oscillation in the 2–4 Hz range. This was seen in relay cells that were disconnected from the PGN layer because of the slicing procedure. In these neurons no IPSPs resulting from spindle activity could be detected; train stimulation of cortical fibers resulted in monosynaptic EPSPs but did not generate either slow oscillation or action potential bursting ($n = 3$; data not shown).

## Increased synchrony of the forced slow oscillation

Cortical-feedback-induced slow oscillation was characterized by increased synchrony of firing within the lateral geniculate relay neuron and perigeniculate neuron populations. This was measured from the integrated activity of multiunit recordings, which quantifies the relative number of units coactive within a given time window (10–20 msec) and reflects both the strength of recruitment and the degree of synchrony between the sampled cells in the network (Fig. 4). In a synchronized oscillation, the population produces burst discharges in a concerted manner, although individual neurons may not necessarily fire action potential bursts in every cycle of the global population oscillation. Thus, activity is not always simultaneous between the different neurons. For example, a

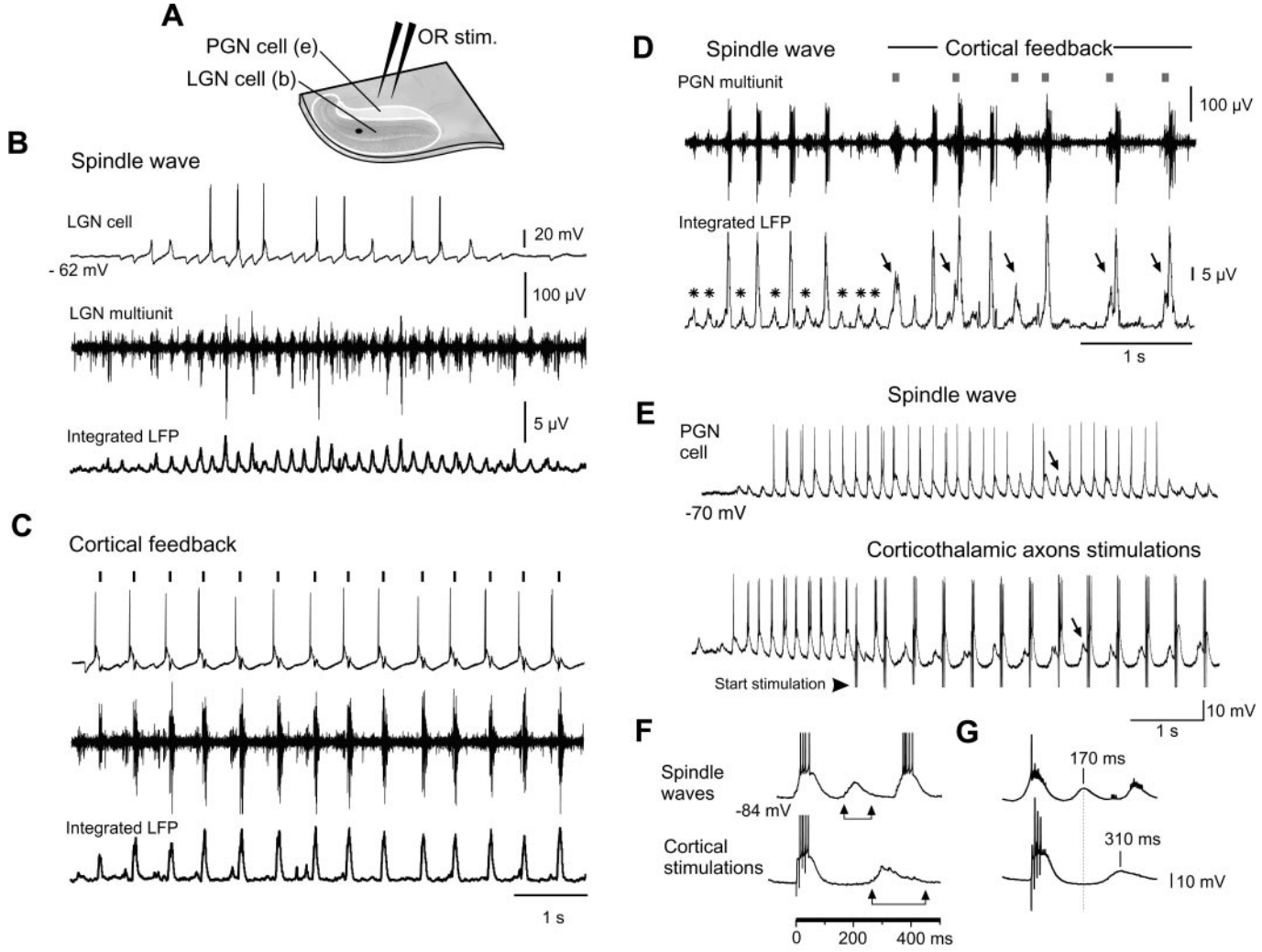


*Figure 4.* Synchronization of thalamic cells by the corticothalamic loop. *A,* Scheme showing the locations of the intracellular recordings that were done successively for the LGN cell and the PGN cell in the same slice, on an anteroposterior axis passing between the branches of the stimulating electrode (the likely orientation for the thalamocortical (TC)–PGN reciprocal connections). Multiunit recordings made at location indicated by the *filled circle*. For both cells, stimulation parameters were kept identical (27 μA intensity; 4 shocks at 100 Hz). *B,* Simultaneous intracellular and multiunit (*filled circle*) recordings in the LGN during a spindle wave. *C,* Same recordings during a slow network activity resulting from cortical feedback stimulations (50 msec delay) triggered by the action potentials in the intracellular recording. *D,* Control multiunit recording in the PGN (spindle wave) and its transformation during cortical feedback stimulation (6 shocks at 100 Hz, 30 msec delay). An extracellular single-unit thalamocortical cell, recorded with another electrode, was the trigger of the feedback (data not shown). The integrated trace shows the amplification of the population bursts (*arrows*) compared to control (*asterisk*), indicative of an enhanced synchrony of the activity of PGN cells. *E,* Intracellular recording of a PGN cell during spontaneous spindle waves and OR stimulation imposed periodically, but this time without feedback (4 shocks at 100 Hz, 400 msec interstimulus interval). *Arrows* show the EPSPs originated from the rebound firing of thalamocortical cells in adjacent layers. *F,* Detail of these compound EPSPs and their averages (*G*) during spindle (*top trace*; $n = 83$; triggered on the first spike of the burst) and OR stimulations delivered at 500 msec intervals (*bottom trace*; $n = 56$; triggered on the first EPSP). For the average, only EPSPs not leading to the generation of low-threshold calcium spike and bursting were selected.

given cell may participate in only one of two or three successive cycles apparent in the network beating (Fig. 1*C, top panel*), but each of the bursts that it does fire will be generated in phase within the global network oscillation. This explains why the period of the oscillation obtained for integrated activity and the spiking of a single unit might differ (Fig. 4*B*).

In the LGN, there was stronger network synchrony during 2–4 Hz oscillations (Figs. 2*B*, 4*C*) than during spindle oscillations (Fig. 4*B*) ($n = 11$). Similarly, in the perigeniculate nucleus, the integrated activity of multiunit recordings showed that an increase in synchrony could be provoked either by LGN-triggered cortical feedback (Fig. 4*D*) ($n = 5$), or by stimulating the optic radiation at a fixed frequency (see Fig. 6*B*) ($n = 4$). This is illustrated in Figure 4*D*, which shows an example of a multiunit recording in PGN during the transition from spontaneous spindle wave to slower oscillation driven by corticothalamic feedback. In this experiment, the corticothalamic feedback was gated by the firing of a single-unit LGN cell recorded with another electrode (single-unit record not shown). In the top trace, the larger single PGN unit showed subharmonic bursting activity compared with the beating firing frequency of the local population of PGN neurons (smaller units). All units became synchronized after a few cycles when the corticothalamic feedback was activated. The slow oscillation continued for another seven cycles (data not shown) in this example. We measured the change in synchrony of the local population of PGN cells by selecting the integrated LFP of the multiunit recording corresponding to the smaller units (Fig. 4*D, stars* and *arrows*). Switching on the cortical feedback resulted in an enhanced amplitude of the integrated signal, indicating an increase in total unit action potential discharges (Fig. 4*D,* compare *stars* with *arrows*).

We previously demonstrated that the effective conduction time around the synaptic loop between LGN and PGN cells can be directly measured from the latency of compound EPSPs generated in PGN cells after the burst firing of LGN cells (Bal et al., 1995b). The latency of these EPSPs was noticeably increased when corticothalamic axons were stimulated at a fixed frequency (Fig. 4*E,F,*

*arrows*), illustrated by the shift in the latency of the averaged return EPSP from 170 to 310 msec (Fig. 4*G*). The averaged EPSP had comparable peak amplitude but increased duration (Fig. 4*G, bottom trace*), suggesting that an increased number of LGN cells participate to each cycle of slow oscillation. Increasing the period of the imposed fixed frequency stimulation from 300, 400, and 500 msec did not change the latency of the EPSPs showing that 310 msec was a preferred period for rebound activity in the network. Note that the illustrated LGN (Fig. 4*B,C*) and PGN (Fig. 4*E–G*) cells were recorded in the same slice using identical stimulation parameters, thus making it possible to compare the effect of the cortical feedback stimulation in the two types of cells. The delay between the onset of OR stimulation and the rebound burst in the LGN cell (~400 msec; Fig. 4*C*) fell within the upper timing range of the averaged return EPSPs recorded in the PGN cell (Fig. 4*G*).

We conclude that temporal summation of direct LGN excitatory feedback to PGN and increased descending corticothalamic excitatory feedback to PGN results in facilitation of burst firing by PGN neurons. This has a determinant effect on the frequency and synchrony of oscillations within the thalamus containing interconnected LGNd and PGN layers.

## Forced slow oscillation depends on $GABA_B$-mediated IPSPs

The 2–4 Hz oscillations have a frequency and synchrony similar to the bicuculline-induced slow oscillation that we reported previously in thalamic slices (von Krosigk et al., 1993; Bal et al., 1995a). Similar to the bicuculline-induced oscillation, the cortical-feedback-induced 2–4 Hz oscillation was dependent on $GABA_B$ receptors in LGN cells (Fig. 5). Intracellular recordings show that blockade of $GABA_B$ receptors using the specific antagonist CGP35348, applied locally, suppressed the ability of the cortical feedback to force the LGN into the 2–4 Hz mode ($n = 4$; Fig. 5*C*). The frequencies of the control spindle waves and of the oscillation during cortical feedback in the presence of CGP35348 were indistinguishable (Fig. 5*A,C*), whereas both rhythms were significantly different from the 2–4 Hz oscillation (Fig. 5*B,D*).

Previous theoretical and experimental studies (Destexhe and Sejnowski, 1995; Kim et al., 1997; Thomson and Destexhe, 1999) have predicted that $GABA_B$-mediated IPSPs are generated only if presynaptic neurons generate prolonged high-frequency bursts of discharges. In the present case (Fig. 1), the model predicts that PGN neurons, which are the main source of $GABA_B$-mediated IPSPs in LGN cells (von Krosigk et al., 1993; Sanchez-Vives and McCormick, 1997), should fire high-frequency bursts of prolonged duration. This is indeed the case in many cells as shown in Figure 6 ($n = 8/13$ extracellular single units and intracellular records). Whereas weak to moderate feedback stimuli (one or two shocks), did not appreciably change the characteristic bursting patterns of PGN cells, beyond a threshold of four or five shocks, strong feedback stimuli led to prolonged bursting discharges (Fig. 6*A,B*). This was because increasing the number of shocks increased the number of PGN cells firing synchronously and could increase the intensity and duration of their discharge (Fig. 6*B*).

Intracellular recordings revealed that these effects were attributable to large EPSPs generated in PGN cells by the firing of corticothalamic axons ($n = 9$; Figs. 4*E,F*, 6*C*). In some cases ($n = 4$ of 9), stimulation of more than or equal to four or five shocks induced prolonged plateau potentials underlying the burst firing of PGN cells (Fig. 6*C, arrow*). Note that Figure 6, *B* and *C,* illustrates the effect of isolated corticothalamic stimuli performed outside of oscillatory sequence to minimize the effects of feedback EPSPs from LGN cells impinging on the PGN cell. Isolated single shock stimuli induced either no spike or weak discharges consisting of single or doublet spikes (Fig. 6*C*; one shock; $n = 7$). In some cases however, isolated corticothalamic single shocks could elicit bursts of 5–10 action potentials ($n = 3$ of 10). In contrast, when single shock corticothalamic stimulations were performed during spindle oscillations, they were always associated with burst firing activity in PGN cells (data not shown), as in the model (Fig. 1*C, inset*; one shock).

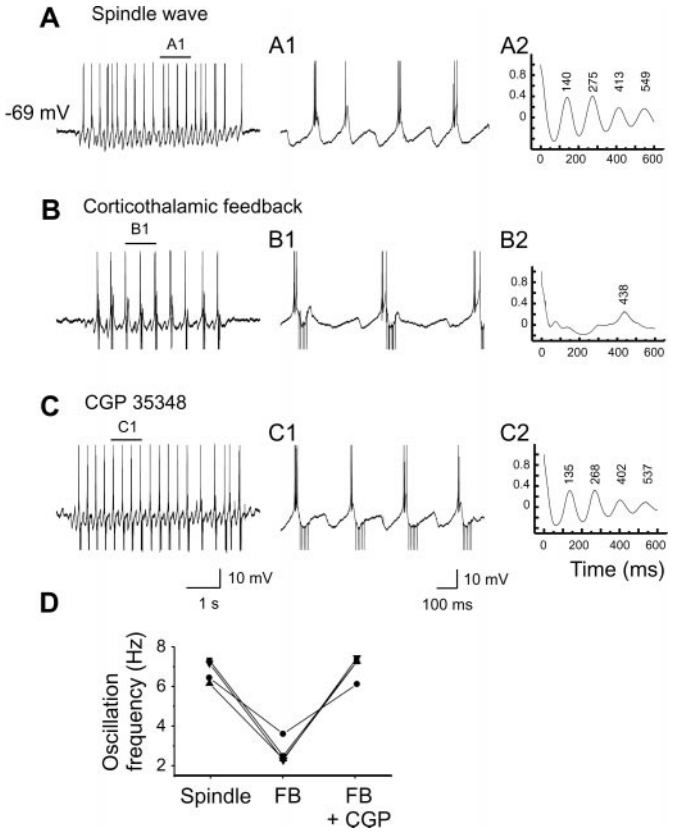


*Figure 5.* Corticothalamic-induced slow oscillation is $GABA_B$-dependent. *A,* Control 7 Hz spindle oscillation recorded in a thalamocortical cell. *B,* Corticothalamic feedback stimulation, triggered by the bursts of the same LGN cell, slows down the oscillation at 2–3 Hz. *C,* The fast 7 Hz rhythm resumes after local application of the $GABA_B$ antagonist CGP35348 (1 mM in micropipette) near the recording electrode. *D,* Graph representing the oscillation frequency of four cells recorded intracellularly versus experimental conditions: control (*spindle*); corticothalamic feedback (*FB*); and corticothalamic feedback in presence of CGP35348 (*FB + CGP*). For all cells, data points correspond to the latencies of the first peak of autocorrelation functions.

## Mechanisms underlying the corticothalamic control of oscillations

To further investigate the cellular mechanisms underlying the control of thalamic oscillations by cortical feedback, we have reexamined the model shown in Figure 1 in the light of the above experimental results. We first tested the behavior of this theoretical model as a function of the number of shocks and timing of corticothalamic feedback in the same way that had been seen for experimental data. Two conditions were necessary for the theoretical model to mimic experimental behavior faithfully: first, the AMPA-mediated cortical EPSPs had to be significantly stronger in PGN cells compared to LGN cells (~5–20 times), consistent with a previous study (Destexhe et al., 1998a). Second, the activation of $GABA_B$ receptors needed to be nonlinear: $GABA_B$ IPSPs were negligible when the number of presynaptic spikes was small, but were strong with a large number of presynaptic spikes, consistent with previous studies (Destexhe and Sejnowski, 1995; Kim et al., 1997; Thomson and Destexhe, 1999).

Two critical parameters affected the transition from spindle to slow oscillations. First, the lateral $GABA_A$-mediated inhibition between PGN cells acted against the transition. This effect was tested by representing the mean frequency of the oscillation as a function of the number of shocks (Fig. 7*A*). In control conditions, a transition from 8–9 Hz spindle oscillations to 2–4 Hz slow oscillations occurred at approximately five shocks (*filled circles*).

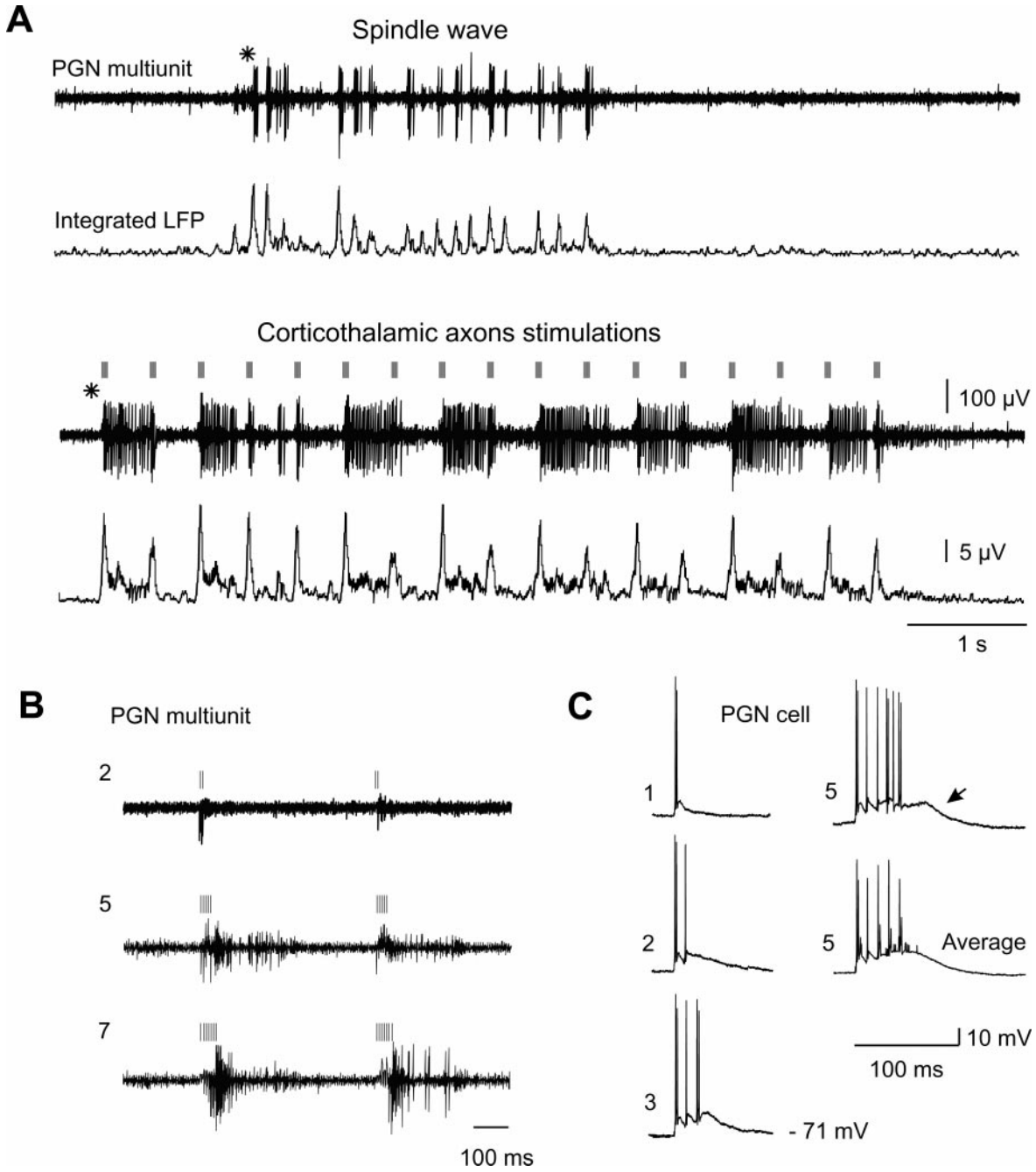


*Figure 6.* Strong corticothalamic activity enhance the burst discharge of PGN cells. *A,* Multiunit recording in the perigeniculate nucleus. Short-duration burst discharges of a PGN cell during spindle waves (*asterisk; 2 top traces*) are transformed in prolonged discharges during the rhythmic stimulations (7 shocks at 140 Hz; 400 msec interval) of corticothalamic axons (2 bottom traces). *B,* Increasing the number of shocks of stimulation (respectively 2, 5, and 7) increases the intensity of discharges recorded in the PGN. *C,* Same protocol as in *B* performed intracellularly for one, two, three, and five shocks. Average for five shocks response consists of 15 traces.

The transition could be shifted by altering $GABA_A$-mediated inhibition within the PGN nucleus (Fig. 7*A, triangles*). With 200% $GABA_A$ conductances in PGN cells, the transition occurred for eight shocks, whereas it occurred for two shocks when these conductances were reduced to 50% of the control value. Second, the conductance of corticothalamic EPSPs on PGN cells favored the transition (Fig. 7*B, squares*). A similar effect was also obtained by altering the T-current conductance in PGN cells (data not shown). These results corroborate previous experiments emphasizing the critical role of the reticular nucleus in absence seizures, and in particular, the action of the anti-absence drug clonazepam, which reinforces $GABA_A$-mediated inhibitory postsynaptic conductances in reticular neurons (Huguenard and Prince, 1994; Gibbs et al., 1996; Hosford et al., 1997). The model suggests that reinforcing these conductances augments the threshold for generating the slow oscillation. The opposite effect is predicted for the conductances mediating cortical EPSPs in reticular cells.

To test whether these two rhythms constitute distinct states in the network or if alternatively, they are part of a continuum of oscillatory states, we quantified the synchrony increase in the model by calculating the total number of spikes fired by the LGN population (Fig. 8*A*). At the onset of the feedback (*arrow;* six shocks at 100 Hz), the spindle rhythm (~10 Hz) switched to a slower frequency (~3 Hz) characterized by a marked increase of synchrony in the reconstructed local field. This synchrony increase is also evident from the spatiotemporal raster plots (Fig. 1*C*). In the

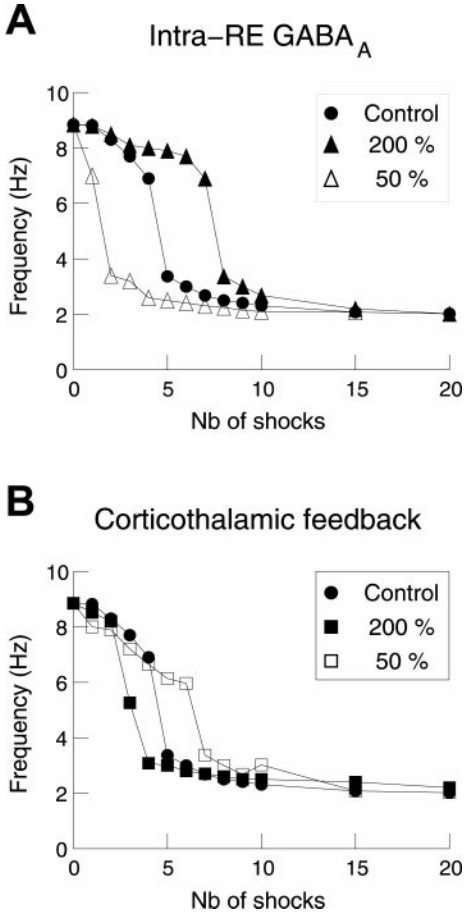


*Figure 7.* Conductances that affect the corticothalamic control of oscillations in model LGN–PGN networks. *A,* Representation of the mean network frequency as a function of the number of shocks given to corticothalamic feedback. The *filled circles* represent the control transition from 8–9 Hz to 2–4 Hz oscillations (same simulation as in Fig. 1*C*). The same transition is shown for reinforced (200%; *filled triangles*) or weakened (50%; *open triangles*) $GABA_A$ conductances within the reticular nucleus. These conductances acted against the slow oscillation. *B,* Same representation for reinforced (200%; *filled squares*) or weakened (50%; *open squares*) AMPAergic conductances underlying cortical EPSPs in thalamic reticular neurons. Reducing these AMPAergic conductances reduced the tendency of the thalamic circuit to switch to slow oscillations.

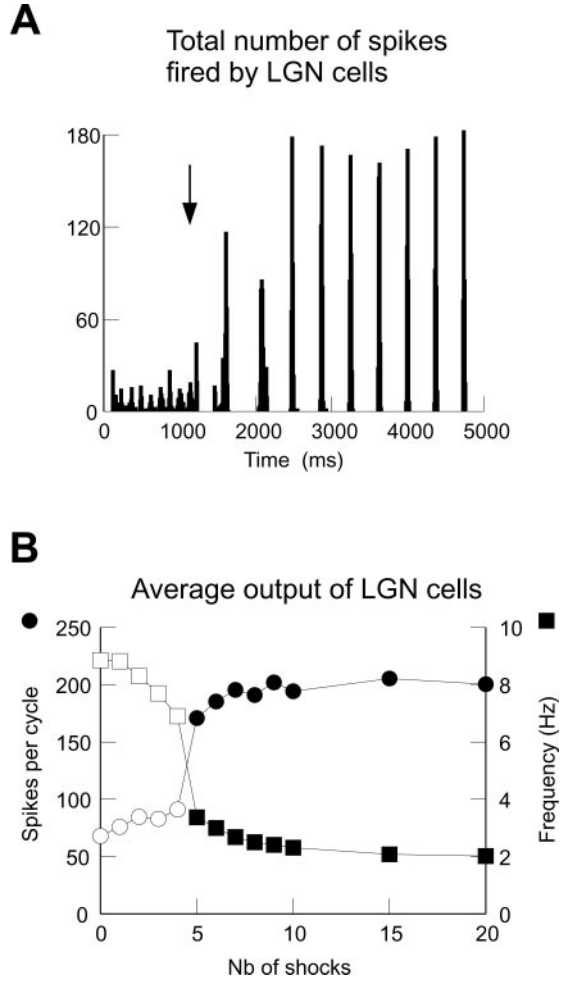


*Figure 8.* Computational evidence that the two oscillations constitute qualitatively distinct rhythmic states. *A,* Histogram of the number of spikes fired by the LGN population in a simulations of the model shown in Figure 1, *A* and *B*. The *arrow* indicates the onset of the feedback (6 shocks, 100 Hz; other parameters identical to Fig. 1*C*). *B,* Average output of the LGN population represented against the number of shocks. *Left ordinate* (*circles*), Average number of spikes fired by LGN cells per oscillation cycle. *Right ordinate* (*squares*), Frequency of the network oscillation. *Filled symbols* indicate that >25% of $GABA_B$ conductance was activated in TC cells, in which case the network switched to another type of oscillation with lower frequency and higher synchrony.

control (spindle) condition, the beating frequency of the network resulted from the coordinated activity of sparse oscillators firing at different cycles of the carrier frequency, whereas it became equal to the frequency of individual cells in the case where the strong cortical feedback forced most cells to fire together. There was a tendency for the number of spikes per burst to increase (one to three for spindles; two to four for the ~3 Hz oscillation), but the synchrony increase was principally attributable to a redistribution in the relative timing of burst initiation among LGN cells (Fig. 1*C*).

This suggests that the "output" signal of the LGN population, transmitted to cortex, should be more powerful during the ~3 Hz oscillation. To quantify this, the model was used to evaluate the average number of spikes per oscillation cycle evoked in LGN cells by feedback stimulation of different strengths (Fig. 8*B*). The average oscillation frequency and the ratio of $GABA_B$ conductance activated were also evaluated. When one to four shocks were evoked, there was a slight tendency to increase synchrony, but the number of LGN spikes stayed low (less than one spike on average per LGN cell). However, with five shocks or more, LGN cells shifted to a qualitatively different firing pattern with nearly all cells firing in phase (Fig. 1*C*).

Thus, the model predicts a transition between two qualitatively different rhythmic states of the thalamus, each corresponding to a different output relayed to cortex. Low corticothalamic feedback strengths evoke a rhythmic state indistinguishable from spontaneous spindle oscillations. In this case, the output of the thalamus is relatively moderate, because only a small fraction of LGN cells burst in synchrony. Above a critical value of feedback strength, thalamic circuits switch to a qualitatively different rhythmical activity, in which all LGN neurons burst in phase and at a slow (~3 Hz) frequency. In this case, the thalamus will return to the cortex a volley of action potentials of greater synchrony and therefore of a greater impact on their cortical targets.

## DISCUSSION

We have shown here that corticothalamic feedback can control the frequency and synchrony of thalamic oscillations. This property, initially predicted by computational models, was demonstrated in ferret visual thalamic slices. We discuss here how these results may help to understand the effect of corticothalamic feedback as well as the role of the thalamus in seizure generation.

### Corticothalamic feedback control of thalamic oscillations

It has been known for several decades that the thalamus plays a key role in the genesis of oscillatory behavior such as spindle waves

(Andersen and Andersson, 1968). Although an active role of the cortex was claimed >50 years ago (Morison and Dempsey, 1943; Bremer, 1949), early studies have most often considered the cortex as passively driven by a "thalamic pacemaker". It was subsequently found that corticothalamic feedback plays a role in triggering thalamic oscillations (Steriade et al., 1972) and is indispensable for the large-scale coherence of thalamic-generated oscillations (Contreras et al., 1996).

Here we have taken a step further by demonstrating that corticothalamic feedback can also control the type of oscillation displayed by thalamic circuits. Inclusion of an artificial feedback loop from LGN neurons to corticothalamic fibers shows that the oscillatory activity exhibited by this circuit can switch between two distinct oscillatory modes according to feedback strength: 6–10 Hz spindle oscillations (zero to three shocks) and 2–4 Hz highly synchronized oscillations (four or five shocks or more). Because the timing of the feedback is entirely determined by the LGN, this circuit forms a closed system without external influence. It is therefore capable of self-organizing into different oscillatory states, according to the value of a single parameter: the strength of the feedback.

The slow oscillatory mode is characterized by a marked increase in synchrony. However, more than a change in global activity, this synchrony results from a redistribution in the relative timing of spike initiation among LGN cells. The type of discharge patterns, and the dependence on $GABA_B$ receptors, are similar to the slow bicuculline-induced oscillation characterized previously in thalamic slices (von Krosigk et al., 1993; Bal et al., 1995a,b). A major difference, however, is that in the present case, the slow oscillations appear in thalamic circuits that are physiologically intact.

The mechanism underlying the feedback control of thalamic oscillations appears to involve the reticular (PGN) nucleus and its inhibitory projection to relay cells. It has been demonstrated that intrareticular inhibition plays a role in the damping of abnormally highly synchronous thalamic oscillation (Huntsman et al., 1999). Using intracellular recordings and computational models, our results indicate that cortical EPSPs evoked in PGN neurons can be powerful enough to overcome the lateral inhibition between these cells (Figs. 1*C, insets,* 4*D*). Substantiating data also comes from morphological studies showing that corticothalamic synapses are very dense on reticular thalamic neurons (Liu and Jones, 1999). Consequently, strong EPSPs from the cortex can elicit prolonged burst discharges in PGN neurons, which in turn activate a full-blown $GABA_B$-mediated component of the IPSPs in LGN cells. The rebound burst firing of LGN cells at the offset of these $GABA_B$ IPSPs re-excites the feedback, and the same cycle repeats at a frequency of 2–4 Hz. A small portion of the oscillation cycle period depends on the time course of the LGN-cortex-LGN feedback loop, and this will also be of importance in deciding the absolute frequency of network oscillation. A wide variation in the time course of this loop has been reported *in vivo* (5 to >100 msec; Schmielau and Singer, 1977; Sillito et al., 1994). This variability reflects variations of the processing time, depending on the state of the animal, and the high variability of the conduction velocity of corticogeniculate axons (propagation times ranging from 2 to ~20 msec; Tsumoto et al., 1978; Ahlsen et al., 1982).

Electrical stimulation of the optic radiation activates corticothalamic fibers orthodromically, but may also antidromically activate thalamocortical fibers. However, the contribution of such antidromic activation was surprisingly small (2 of 40 LGN cells recorded intracellularly). This small contribution could be explained by the fact that corticothalamic fibers outnumber thalamocortical axons by an order of magnitude (Sherman and Guillery, 1996). Another possibility that remains to be tested could be that the trajectory of thalamocortical axons leaving the LGN and running in the optic radiation differs from the trajectory of corticothalamic in the same visuotopic area. Antidromic activation (up to 5% of LGN cells) was also simulated by the model and had no detectable effect on the present results. In addition, it is important to note that antidromic activation of thalamocortical axons at ectopic sites occurs naturally (Pinault and Pumain, 1989) and during epileptic paroxysms *in vivo* (Gutnick and Prince, 1972; Noebels and Prince, 1978; Pinault, 1992).

Many questions are left open regarding the role of corticothalamic feedback. A large body of experimental and theoretical studies have focused on the role of corticothalamic EPSPs on information processing in the visual system. The activation of corticothalamic synapses have clear facilitatory effects on the relay of information to cerebral cortex (Widen and Ajmone-Marsan, 1960; Singer, 1977; Ahlsen et al., 1982; Sherman and Koch, 1986; Koch, 1987; McCormick and von Krosigk, 1992). In contrast, we have shown here that high-frequency corticothalamic volleys can induce a period of silence lasting ~300 msec in the LGN, mediated by $GABA_B$ receptors. This could be a way for the cortex to produce a brief deafferentation, or a "reset" signal to bring thalamic neurons into synchrony. It thus seems that the effect of corticothalamic feedback on relay cells may be radically different depending on the patterns of firing activity of thalamic-projecting cortical neurons, in addition to the state (bursting vs tonic mode) of thalamic neurons. Further experimental and theoretical work will be needed to characterize and understand these different facets of corticothalamic interactions.

## Insight on thalamic rhythmicity and role in seizure generation

Several experimental models of absence seizures have demonstrated that the cortex is indispensable to generate seizure activity (for review, see Gloor and Fariello, 1988; Danober et al., 1998). Local applications of convulsants to cerebral cortex can lead to full-blown seizures, but the integrity of the thalamus is required (Gloor et al., 1977). A possible explanation for these experimental observations was suggested by a model of spike-and-wave seizures based on a closed loop interaction between a pathological cortex and an intact thalamus (Destexhe, 1998). The main prediction of this model was that the cortex should be able to "force" the intact thalamus into a slow oscillatory mode, caused by the properties of $GABA_B$ receptors.

The present results confirm that, if the thalamus receives an abnormally strong feedback from the cortex, it tends to produce hypersynchronous 3 Hz oscillations, which are $GABA_B$ receptor-dependent. The remarkable fact is that the 3 Hz oscillations are generated by physiologically intact thalamic circuits, under the sole action of cortical feedback. It therefore predicts that an augmentation of cortical excitability, for example caused by disinhibition, may result in an abnormally strong corticothalamic feedback that can force the thalamus to oscillate at 3 Hz. These results therefore provide a possible explanation for the observation that 3 Hz spike-and-wave oscillations can be induced by cortical application of $GABA_A$ antagonists, but that a physiologically intact thalamus is required (Gloor et al., 1977).

The high-frequency shocks used to stimulate corticothalamic fibers may seem inconsistent with the relatively low rate of discharge of thalamic-projecting layer VI neurons *in vivo* (Gilbert, 1977). However, the normal conditions of discharge were represented here by corticothalamic stimuli consisting of single shocks. A similar transition could also be obtained by increasing the intensity of single-shock stimuli, instead of increasing the number of shocks (data not shown). This therefore suggests that a switch of rhythmicity should be observable *in vivo* if layer VI neurons increase their rate of discharge to produce bursts of high-frequency spikes (~100 Hz), as indeed observed *in vitro* (Golshani and Jones, 1999). Alternatively, an increase of the number of layer VI cells discharging simultaneously should also produce the conditions necessary to force the thalamus to oscillate at 3 Hz. The present study therefore predicts that during absence seizures there is an increased output of layer VI cells, either by an increase of the level of discharge of single cells, or by an increase of synchrony.

This prediction should be testable in visual cortical slices by a feedback paradigm similar to that investigated here. The discharge of intracellularly or extracellularly recorded neurons in layer VI could trigger the stimulation of ascending thalamocortical fibers. In this case, the pattern of stimulation should match the output of the LGN and could be deduced from the present model (Fig. 8*B*). This

paradigm could be used to investigate the conditions under which layer VI cerebral cortical neurons can generate the patterns of discharge necessary to generate abnormally strong corticothalamic activation, which according to the present paper, should lead to slow hypersynchronous oscillations.

*Note added in proof*. A recent study has also demonstrated that corticothalamic feedback controls thalamic oscillations [Blumenfeld H, McCormick DA (2000) Corticothalamic inputs control the pattern of activity generated in thalamocortical networks. J Neurosci 20:5153–5162.].

## REFERENCES


Aghajanian GK, Rasmussen K (1989) Intracellular studies in the facial nucleus illustrating a simple new method for obtaining viable motoneurons in adult rat brain slices. Synapse 3:331–338.

Ahlsen G, Grant K, Lindström S (1982) Monosynaptic excitation of principal cells in the lateral geniculate nucleus by corticofugal fibers. Brain Res 234:454–458.

Andersen P, Andersson SA (1968) Physiological basis of the alpha rhythm. New York: Appelton Century Crofts.

Bal T, von Krosigk M, McCormick DA (1995a) Synaptic and membrane mechanisms underlying synchronized oscillations in the ferret lateral geniculate nucleus in vitro. J Physiol (Lond) 483:641–663.

Bal T, von Krosigk M, McCormick DA (1995b) Role of the ferret perigeniculate nucleus in the generation of synchronized oscillations in vitro. J Physiol (Lond) 483:665–685.

Bremer F (1949) Considérations sur l'origine et la nature des "ondes" cérébrales. Electroencephalogr Clin Neurophysiol 1:177–193.

Bringuier V, Fregnac Y, Baranyi A, Debanne D, Shulz DE (1997) Synaptic origin and stimulus dependency of neuronal oscillatory activity in the primary visual cortex of the cat. J Physiol (Lond) 500:751–74.

Contreras D, Destexhe A, Sejnowski TJ, Steriade M (1996) Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274:771–774.

Cox CL, Sherman SM (1999) Glutamate inhibits thalamic reticular neurons. J Neurosci 19:6694–6699.

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C (1998) Pathophysiological mechanisms of genetic absence epilepsy in the rat. Prog Neurobiol 55:27–57.

Destexhe A (1998) Spike-and-wave oscillations based on the properties of $GABA_B$ receptors. J Neurosci 18:9099–9111.

Destexhe A, Sejnowski TJ (1995) G-protein activation kinetics and spillover of GABA may account for differences between inhibitory responses in the hippocampus and thalamus. Proc Natl Acad Sci USA 92:9515–9519.

Destexhe A, Bal T, McCormick DA, Sejnowski TJ (1996) Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices. J Neurophysiol 76:2049–2070.

Destexhe A, Contreras D, Steriade M (1998a) Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. J Neurophysiol 79:999–1016.

Destexhe A, Mainen M, Sejnowski TJ (1998b) Kinetic models of synaptic transmission. In: Methods in neuronal modeling (Koch C, Segev I, eds), pp 1–26. Cambridge, MA: MIT.

Domich L, Oakson G, Steriade M (1986) Thalamic burst patterns in the naturally sleeping cat: a comparison between cortically projecting and reticularis neurones. J Physiol (Lond) 379:429–449.

Erisir A, VanHorn SC, Bickford ME, Sherman SM (1997a) Immunocytochemistry and distribution of parabrachial terminals in the lateral geniculate nucleus of the cat: a comparison with corticogeniculate terminals. J Comp Neurol 377:535–549.

Erisir A, VanHorn SC, Sherman SM (1997b) Relative numbers of cortical and brainstem inputs to the lateral geniculate nucleus. Proc Natl Acad Sci USA 94:1517–1520.

Ghose GM, Freeman RD (1992) Oscillatory discharge in the visual system: does it have a functional role? J Neurophysiol 68:1558–1574.

Gibbs JW, Berkow-Schroeder, Coulter DA (1996) GABA(A) receptor function in developing rat thalamic reticular neurons: whole cell recordings of GABA-mediated currents and modulation by clonazepam. J Neurophysiol 76:2568–2579.

Gilbert CD (1977) Laminar differences in receptive field properties of cells in cat primary visual cortex. J Physiol (Lond) 268:391–421.

Gloor P, Fariello RG (1988) Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. Trends Neurosci 11:63–68.

Gloor P, Quesney LF, Zumstein H (1977) Pathophysiology of generalized penicillin epilepsy in the cat: the role of cortical and subcortical structures. II. Topical application of penicillin to the cerebral cortex and subcortical structures. Electroencephalogr Clin Neurophysiol 43:79–94.

Golshani P, Jones EG (1999) Synchronized paroxysmal activity in the developing thalamocortical network mediated by corticothalamic projections and "silent" synapses. J Neurosci 19:2865–2875.

Guillery RW (1969) A quantitative study of synaptic interconnections in the dorsal lateral geniculate nucleus of the cat. Z Zellforsh Mikrosk Anat 96:39–48.

Gutnick MJ, Prince DA (1972) Thalamocortical relay neurons: antidromic invasion of spikes from a cortical epileptogenic focus. Science 176:424–426.

Hosford DA, Wang Y, Cao Z (1997) Differential effects mediated by GABA(A) receptors in thalamic nuclei of lh/lh model of absence seizures. Epilepsy Res 27:55–65.

Hu B, Steriade M, Deschenes M (1989) The effects of brainstem peribrachial stimulation on perigeniculate neurons: the blockage of spindle waves. Neuroscience 31:1–12.

Huguenard JR, Prince DA (1994) Clonazepam suppresses GABA(B)-mediated inhibition in thalamic relay neurons through effects in nucleus reticularis. J Neurophysiol 71:2576–2581.

Huntsman MM, Porcello DM, Homanics GE, DeLorey TM, Huguenard JR (1999) Reciprocal inhibitory connections and network synchrony in the mammalian thalamus. Science 283:541–543.

Kim U, Sanchez Vives MV, McCormick DA (1997) Functional dynamics of GABAergic inhibition in the thalamus. Science 278:130–134.

Koch C (1987) The action of the corticofugal pathway on sensory thalamic nuclei: a hypothesis. Neuroscience 23:399–406.

Lampl I, Yarom Y (1993) Subthreshold oscillations of the membrane potential: a functional synchronizing and timing device. J Neurophysiol 70:2181–2186.

Liu XB, Jones EG (1999) Predominance of corticothalamic synaptic inputs to thalamic reticular nucleus neurons in the rat. J Comp Neurol 414:67–79.

Liu XB, Honda CN, Jones EG (1995) Distribution of four types of synapse on physiologically identified relay neurons in the ventral posterior thalamic nucleus of the cat. J Comp Neurol 352:69–91.

McCormick DA, von Krosigk M (1992) Corticothalamic activation modulates thalamic firing through glutamate "metabotropic" receptors. Proc Natl Acad Sci USA 89:2774–2778.

Morison RS, Dempsey EW (1943) Mechanisms of thalamocortical augmentation and repetition. Am J Physiol 138:297–308.

Neuenschwander S, Singer W (1996) Long-range synchronization of oscillatory light responses in the cat retina and lateral geniculate nucleus. Nature 379:728–732.

Noebels JL, Prince DA (1978) Development of focal seizures in cerebral cortex: role of axon terminal bursting. J Neurophysiol 41:1267–1281.

Pinault D (1992) Ectopic axonal firing in an epileptic cortical focus is not triggered by thalamocortical volleys during the interictal stage. Brain Res 576:175–180.

Pinault D, Pumain R (1989) Antidromic firing occurs spontaneously on thalamic relay neurons: triggering of somatic intrinsic burst discharges by ectopic action potentials. Neuroscience 31:625–637.

Sanchez-Vives MV, Bal T, McCormick DA (1997) Inhibitory interactions between perigeniculate GABAergic neurons. J Neurosci 17:8894–8908.

Sanchez-Vives MV, McCormick DA (1997) Functional properties of perigeniculate inhibition of dorsal lateral geniculate nucleus thalamocortical neurons in vitro. J Neurosci 17:8880–8893.

Schmielau F, Singer W (1977) The role of visual cortex for binocular interactions in the cat lateral geniculate nucleus. Brain Res 120:354–361.

Sherman SM, Guillery RW (1996) Functional organization of thalamocortical relays. J Neurophysiol 76:1367–1395.

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

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

Singer W (1977) Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. Physiol Rev 57:386–420.

Steriade M, Deschênes M (1984) The thalamus as a neuronal oscillator. Brain Res Rev 8:1–63.

Steriade M, Wyzinski P, Apostol V (1972) Corticofugal projections governing rhythmic thalamic activity. In: Corticothalamic projections and sensorimotor activities (Frigyesi TL, Rinvik E, Yahr MD, eds), pp 221–272. New York: Raven.

Steriade M, McCormick DA, Sejnowski TJ (1993) Thalamocortical oscillations in the sleeping and aroused brain. Science 262:679–685.

Thomson AM, Destexhe A (1999) Dual intracellular recordings and computational models of slow IPSPs in rat neocortical and hippocampal slices. Neuroscience 92:1193–1215.

Tsumoto T, Creutzfeldt OD, Legendy CR (1978) Functional organization of the corticofugal system from visual cortex to lateral geniculate nucleus in the cat. Exp Brain Res 32:345–364.

Volgushev M, Chistiakova M, Singer W (1998) Modification of discharge patterns of neocortical neurons by induced oscillations of the membrane potential. Neuroscience 83:15–25.

von Krosigk M, Bal T, McCormick DA (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261:361–364.

von Krosigk M, McCormick D (1993) Corticothalamic activation modulates thalamic firing through glutamate "metabotropic" receptors. Proc Natl Acad Sci USA 89:2774–2778.

Widen K, Ajmone-Marsan C (1960) Effects of corticopetal and corticofugal impulses upon single elements of the dorsolateral geniculate nucleus. Exp Neurol 2:468–502.