ELSEVIER

Neurocomputing 26–27 (1999) 525–531

NEUROCOMPUTING

www.elsevier.com/locate/neucom

Long-range connections synchronize rather than spread intrathalamic oscillatory activity: Computational modeling and in vitro electrophysiology

Vikaas S. Sohal, John R. Huguenard*

Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford CA 94305-5122, USA

Accepted 18 December 1998

Abstract

We developed thalamic network models based on known heterogeneity of thalamic reticular cell axonal arborizations, with short- and long-range projection patterns. To study how long-range connections influence thalamic oscillations, we compared a model containing only short-range connections with another containing both short- and long-range connections. In both networks, 3 Hz oscillations propagated at physiologically realistic speeds. However, the network without long-range connections produced phase differences that were much larger than those that we measured in vitro. This suggests that long-range projections do not increase the speed at which intrathalamic oscillations propagate. Instead, they may synchronize activity across thalamic subnetworks.

1. Introduction

Thalamic slices generate oscillations resembling 7–14 Hz sleep spindles [12,14,15], and these can be transformed into synchronized ≈ 3 Hz oscillations related to pathological oscillations observed in vivo [14,15]. Both types of oscillations propagate along thalamic slices [9]. Computational models have used the speed at which oscillations propagate in vitro to infer that connections between thalamic reticular (RE) and thalamocortical (TC) cells extend over a region approximately 100 μm in radius [4,6].

* Corresponding author. Tel.: + 1-650-723-5522; fax: + 1-650-723-1080.
E-mail address: john.huguenard@stanford.edu (J.R. Huguenard)

0925-2312/99/$ – see front matter
PII: S0925-2312(99)00030-2

We recently found that axonal arborizations of some RE cells extend over a radius of approximately 100 μm [1], consistent with the aforementioned predictions about connectivity [4,6]. However, we also found that an equal number of RE cells have diffuse projections extending over radii of several hundred μm [1]. The relatively large distances over which diffuse projections extend are not in accord with estimates based on propagation speeds observed in vitro, nor are their functional implications known. We used a combination of computational modeling and in vitro electrophysiology to study the possible influence of such long-range connections on thalamic oscillations.

2. Slow, synchronized intrathalamic oscillations in vitro

In vitro recordings from thalamic slices were performed as previously described [8]. Fig. 1A and B show contour plots of extracellularly recorded activity from RE and TC cells, respectively, as functions of time (running horizontally) and distance (running vertically). These figures show that as in previous experiments [8], excitation of RE cells elicits ≈ 3 Hz oscillations. They also show that these oscillations remain highly synchronized across widely separated RE and TC cells.

3. Interactions between RE and TC cells produce synchronized network oscillations

Earlier in vitro studies [8,15] and models [4,6], demonstrated that interactions between RE and TC cells produce synchronized oscillations at ≈ 3 Hz. Fig. 2A and B show contour plots of activity in a model of 64 RE and 64 TC cells. TC neurons, based on earlier single-compartment models [7,10], included a leak, a low-threshold calcium current, voltage-dependent potassium and sodium currents underlying action potential generation, and a hyperpolarization-activated mixed cation current. RE neurons, based on a previous model [5], included a leak, voltage-dependent potassium and sodium currents underlying action potential generation, and low-threshold calcium current. We included AMPA synapses from TC to RE cells and $GABA_B$ synapses from RE to TC cells ($GABA_A$ receptors were blocked). $GABA_B$ synapses from RE to TC cells were included in both short- and long-range connections. We did not model $GABA_B$ synapses between RE cells, which are extremely weak [13].

4. Effects of pharmacological manipulations on intrathalamic oscillations

To validate the model, we simulated pharmacological manipulations whose effects on intrathalamic oscillations have been studied in vitro. The model reproduced the following effects, which have also been observed experimentally: T-channel blockade shortens the duration but increases the period of oscillations [8,11]; suppression of synaptic transmission reduces both the duration and period of oscillations (Yue and Huguenard, unpublished data); at low concentrations cholecystokinin (CCK) may extend the duration of oscillations, whereas at higher doses CCK always shortens the duration of oscillations [2].

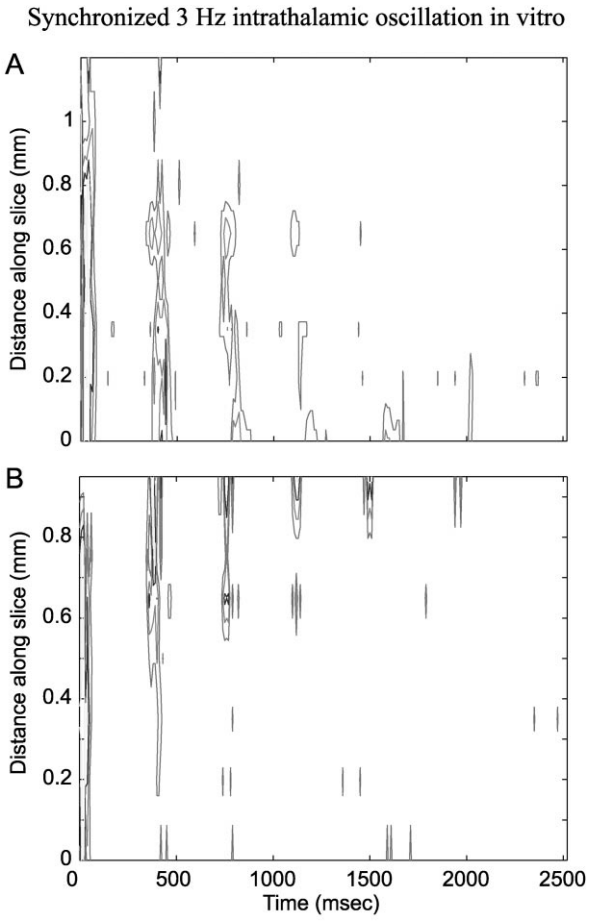

Fig. 1. Synchronous, slow ($\approx$ 3 Hz) intrathalamic oscillations in vitro, evoked by stimulation of internal capsule. Long-lasting slow oscillations are promoted by blocking $GABA_A$ synaptic responses with BMI [2,8,14]. A. Contour plot of extracellular multi-unit activity at several locations in nRT. B. Contour plot of extracellularly activity from TC cells at several locations in VB. Oscillatory activity persisted for approximately 2 s. Activity is expressed as the firing frequency per unit time (ratemeter-type output) normalized by the maximum firing frequency at that location. Each contour corresponds to an incrementally higher firing frequency. These recordings were not simultaneous, but in all cases time = 0 is the time at which the internal capsule was stimulated.

5. Propagation of synchronous oscillations

To study possible functions of long-range connections from RE to TC cells we compared the behavior of the model containing both short- and long-range connections to that of a network containing only short-range connections. We used anatomical [1] and physiological [3] data to determine the ratio between $GABA_B$ conductance associated with short- and long-range connections onto a single TC cell. We chose the remaining free parameter, the total $GABA_B$ conductance onto a TC cell,

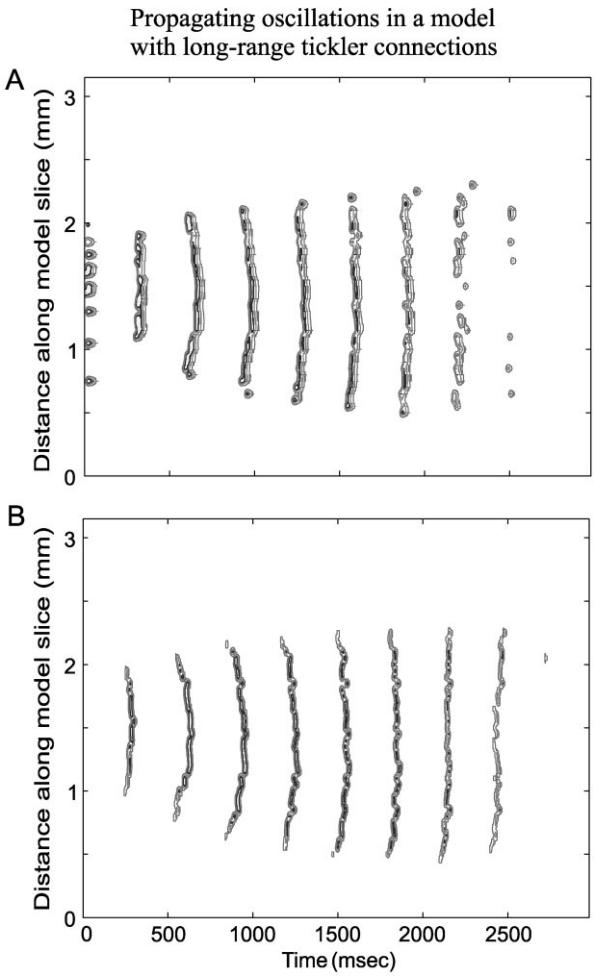

Fig. 2. Propagating oscillations in a network model with long-range tickler connections. Contour plot of concurrent RE cell (A) and TC cell (B) activity as a function of time and distance along the model slice. An oscillation is elicited by focal stimulation near the center of the slice, and subsequently propagates outward at a physiologically realistic speed of 0.28 mm/s. The radius of connections from TC cells to RE cells was 50 μm, the radius of tickler connections was 500 μm, and the radius of cluster connections was 100 μm. To initiate oscillations, RE cells near the center of the model slice were probabilistically excited above the burst threshold.

to produce $\approx$ 3 Hz oscillations that propagated at physiologically realistic speeds [9]. Whereas previous models [4,6] have used the speed at which oscillations propagate in vitro to infer the spatial extent of intrathalamic projections, we found that the $GABA_B$ synaptic conductance can be adjusted so that both networks with (Fig. 2A and B) and without (Fig. 3A and B) long-range connections reproduce experimental propagation speeds [9]. Therefore another observable, in addition to propagation speed, was needed to distinguish between these two types of networks.

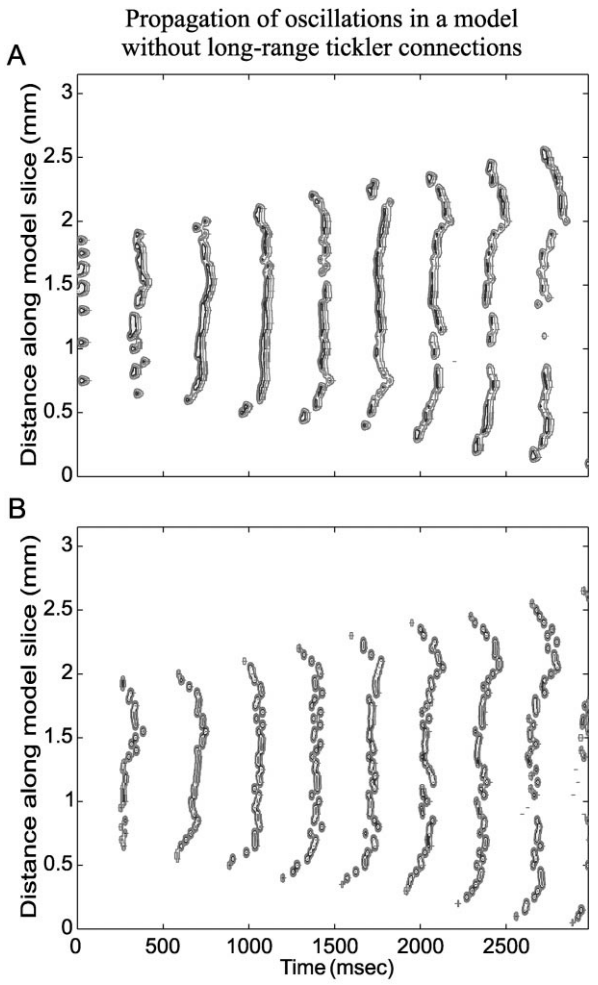

Fig. 3. Propagation of oscillations in a network model without long-range tickler connections. Contour plot of concurrent RE cell (A) and TC cell (B) activity as a function of time and distance along the model slice. An oscillation is elicited by focal stimulation near the center of the slice (equivalent to that used in Fig. 2), and subsequently propagates outward at a physiologically realistic speed of 0.24 mm/s. Note that while the speed at which oscillations propagate is similar to that in a network model with long-range tickler connections (shown in Fig. 2), in this case oscillatory activity is much less synchronized across the network. The radius of connections from TC cells to RE cells was 50 μm, and the radius of both tickler and cluster connections was 100 μm.

6. Long range, but not short range, tickler connections produce phase differences consistent with experimental measurements

We measured phase shifts between oscillatory activity at different locations in our network model and in vitro recordings. The network with long-range connections

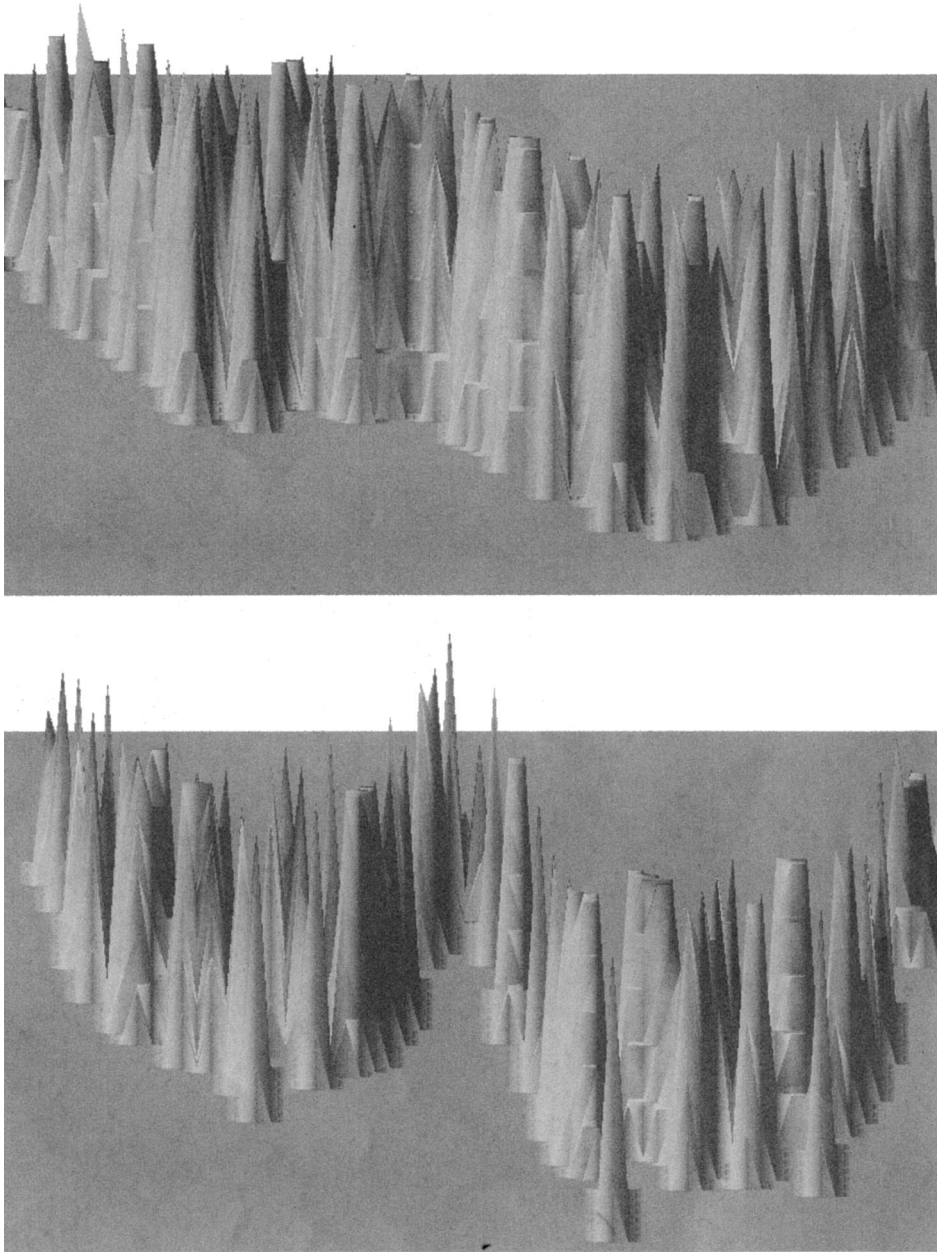

Fig. 4. Diffuse long-range connections synchronize oscillatory activity in a thalamic network model. Time runs out of the page, lateral distance along the model slice runs horizontally, and height represents thalamic relay neuron spike rate. Each panel depicts activity just after a collision between two initially out-of-phase oscillations Lower panel: In a network with long-range connections the colliding waveforms coalesce, yielding a smooth phase gradient. Upper panel: When long-range connections are absent, there is a sharp discontinuity in the phase gradient immediately following the collision.

produced relatively small phase differences, which were similar to those we measured in vitro, whereas the network without long-range connections produced much larger phase differences. These results suggest that, although they extend much further than do short-range cluster projections, long-range diffuse projections do not spread activity over greater distances or increase the speed at which intrathalamic oscillations propagate. Instead, diffuse projections may function to synchronize activity and minimize phase shifts.

One prediction of this hypothesis is that immediately after collisions between propagating oscillations, which are observed in vitro [9], phase gradients should vary smoothly across the thalamic slice. Fig. 4 compares TC cell activity in networks with and without long-range connections immediately following a collision between two initially-out-of-phase oscillations. We found that in the former (Fig. 4 upper panel), oscillations coalesce rapidly, yielding a smoothly varying phase gradient. In contrast, without long-range connections (Fig. 4 lower panel), oscillations coalesce more slowly, so that the phase gradient exhibits large discontinuities immediately following a collision. The model also predicts that phase shifts between oscillatory activity at different points along a thalamic slice should be unaffected by T-channel blockers and decreased by suppression of synaptic transmission or application of CCK.

Acknowledgements

We thank B. Yue who assisted with the extracellular recording experiments. This work was supported by National Institutes of Health Grants NS06477 and NS34774 from the NINDS and the Pimley Research Funds.

References

[1] C.L. Cox, J.R. Huguenard, D.A. Prince, J. Comp. Neurol. 366 (1996) 416–430.
[2] C.L. Cox, J.R. Huguenard, D.A. Prince, J. Neurosci. 17 (1997a) 70–82.
[3] C.L. Cox, J.R Huguenard, D.A. Prince, Proc. Natl. Acad. Sci. (USA) 94 (1997b) 8854–8859.
[4] A. Destexhe, T. Bal, D.A. McCormick, T.J. Sejnowski, J. Neurophysiol. 76 (1996a) 2049–2070.
[5] A. Destexhe, D. Contreras, M. Steriade, T.J. Sejnowski, J.R. Huguenard, J. Neurosci. 16 (1996b) 169–185.
[6] D. Golomb, X.J. Wang, J. Rinzel, J. Neurophysiol. 75 (1996) 750–769.
[7] J.R. Huguenard, D.A. McCormick, J. Neurophysiol. 68 (1992) 1373–1383.
[8] J.R. Huguenard, D.A. Prince, J. Neurosci. 14 (1994) 5485–5502.
[9] U. Kim, T. Bal, D.A. McCormick, J. Neurophysiol. 74 (1995) 1301–1323.
[10] D.A. McCormick, J.R. Huguenard, J. Neurophysiol. 68 (1992) 1384–1400.
[11] S.D. Smith, J.R. Huguenard, The specific T-type Ca^{2+} channel blocker U92032 reduces synchronous phasic discharge in thalamus, Epilepsia (Abstract) 37 (1996) S5:116.
[12] M. Steriade, D.A. McCormick, T.J. Sejnowski, Science 262 (1993) 679–685.
[13] D. Ulrich, J.R. Huguenard, J. Physiol. (London) 493 (1996a) 845–854.
[14] D. Ulrich, J.R. Huguenard, Neurosci. Abstr. 23 (1997) 573.
[15] M. von Krosigk, T. Bal, D.A. McCormick. Science 261 (1993) 361–364.