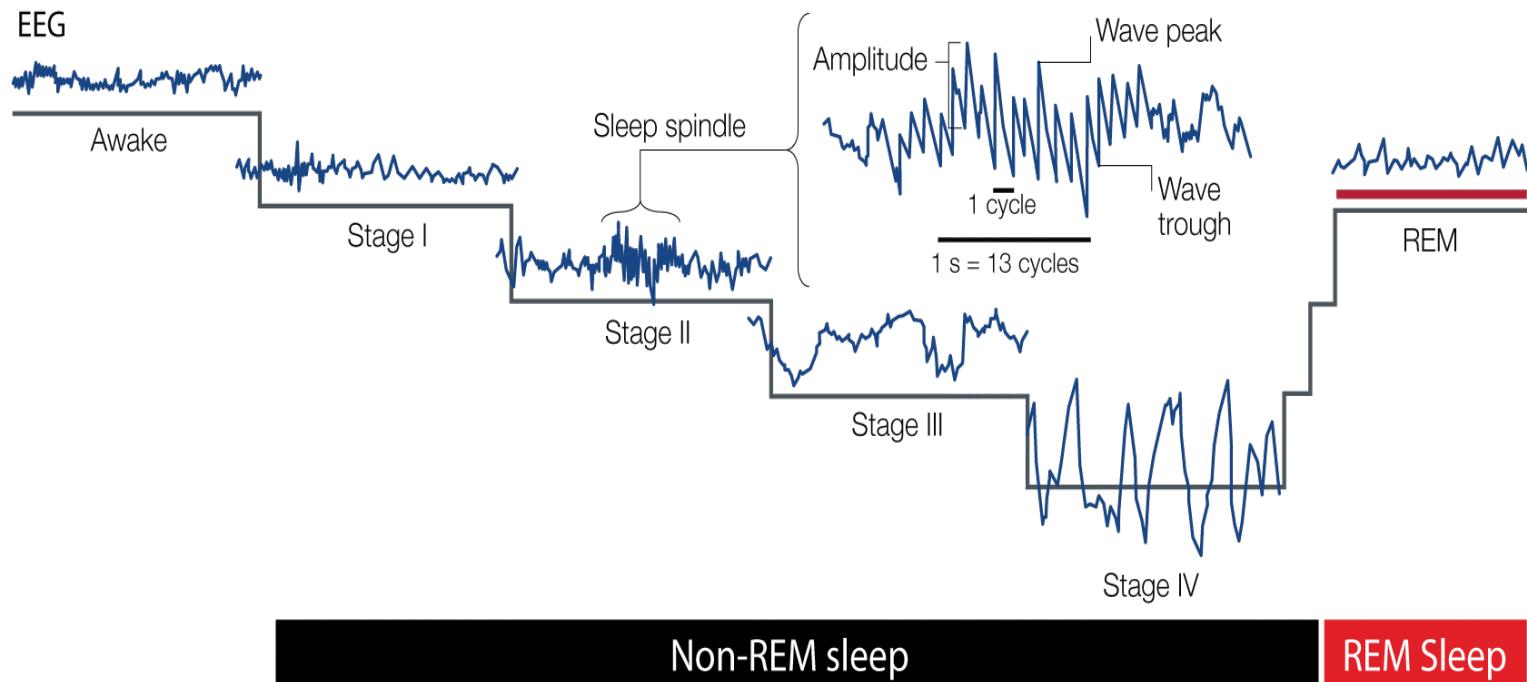


Sleep spindles – new insights on an old topic

Maxim Bazhenov
University of California, Riverside

Different sleep states are characterized by specific patterns of EEG activity



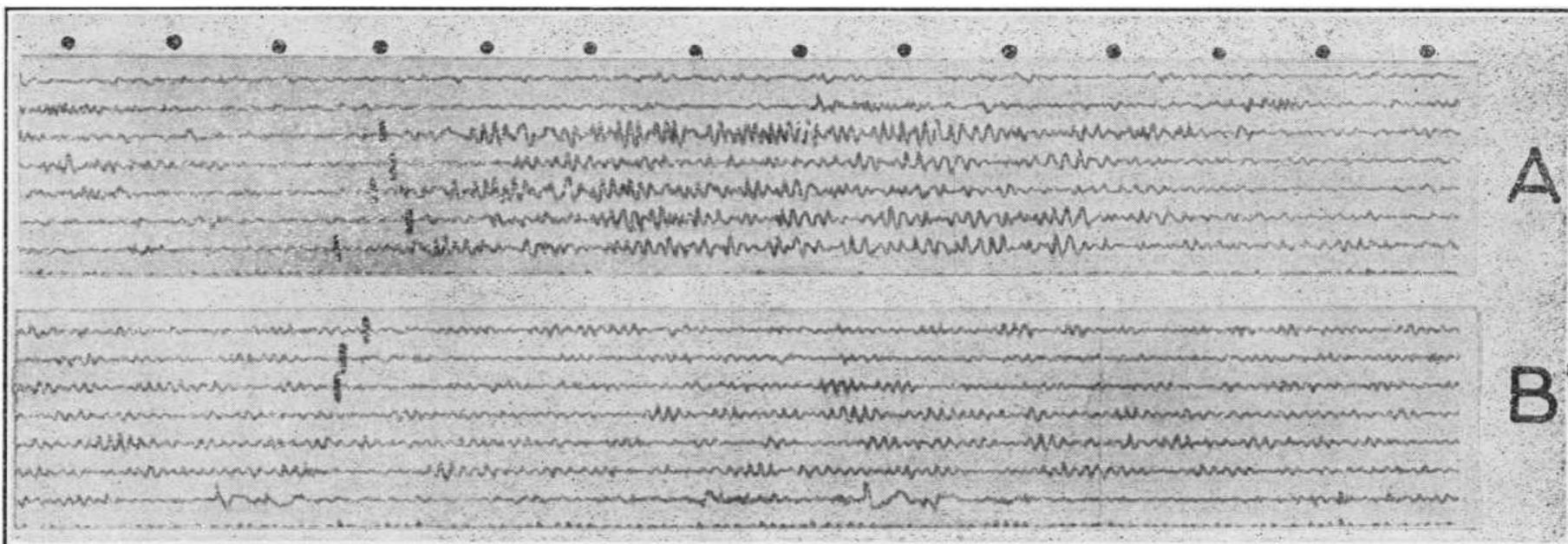
Bonjean et al., Sleep Medicine, Springer (2009)

Sleep Spindles

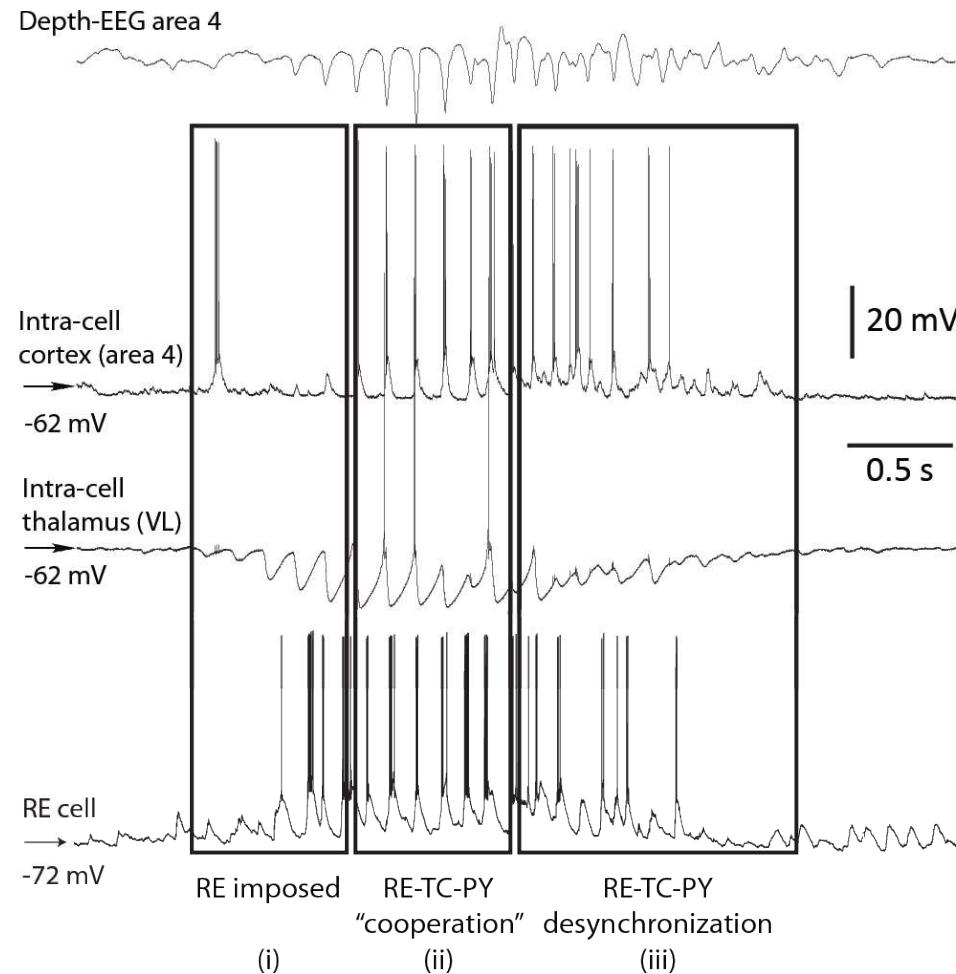
Alfred L. Loomis, E. N. Harvey, G. Hobart, Potential rhythms of the cerebral cortex during sleep. Science 81:597-598. 1935.

Our investigation of the brain potential rhythms during night sleep (brain electrodes on high forehead and crown of head) has led us to the following conclusions:

- (1) They are undoubtedly of cortical origin and distinct from muscle potentials and movement artifacts. Different persons show quite different potential records.
- (2) In a night record certain hours of sleep show many "spontaneous" bursts of waves, while other hours show relatively few.
- (3) They often appear in trains lasting 5 to 12 seconds, at intervals of $\frac{1}{2}$ to 2 minutes.
- (4) The frequency is on the average an irregular 10 per second, but frequently very regular bursts lasting 1 to $1\frac{1}{2}$ seconds of 14 per second frequency appear. The amplitude builds regularly to a maximum and then falls regularly so that we have designated these "spindles," because of their appearance in the record.



Sleep spindle oscillations *in vivo*

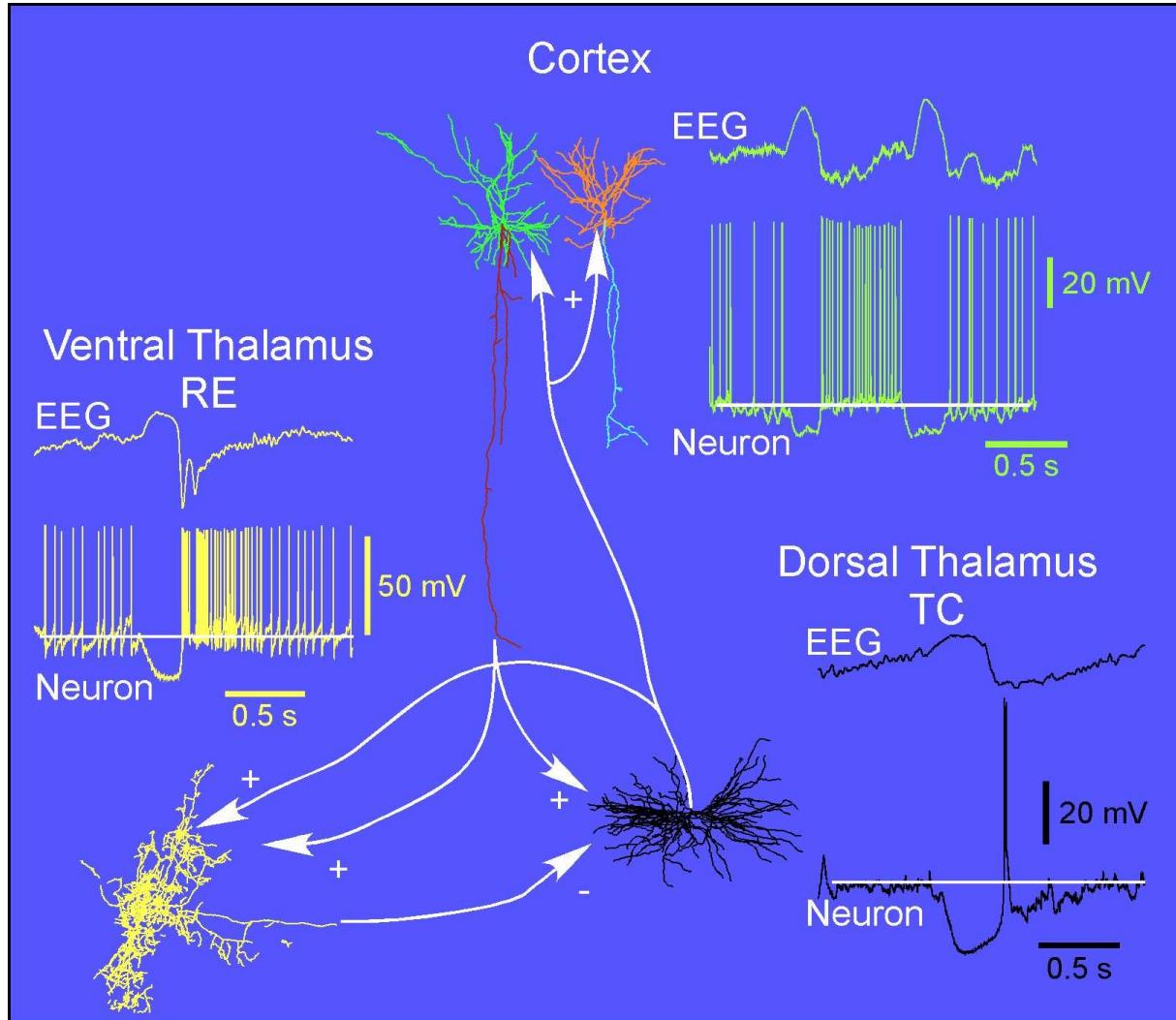


Timofeev and
Bazhenov, 2005

Sleep spindle oscillations consist of waxing-and-waning field potentials at 7-14 Hz, which last 1-3 seconds and recur every 5-15 seconds.

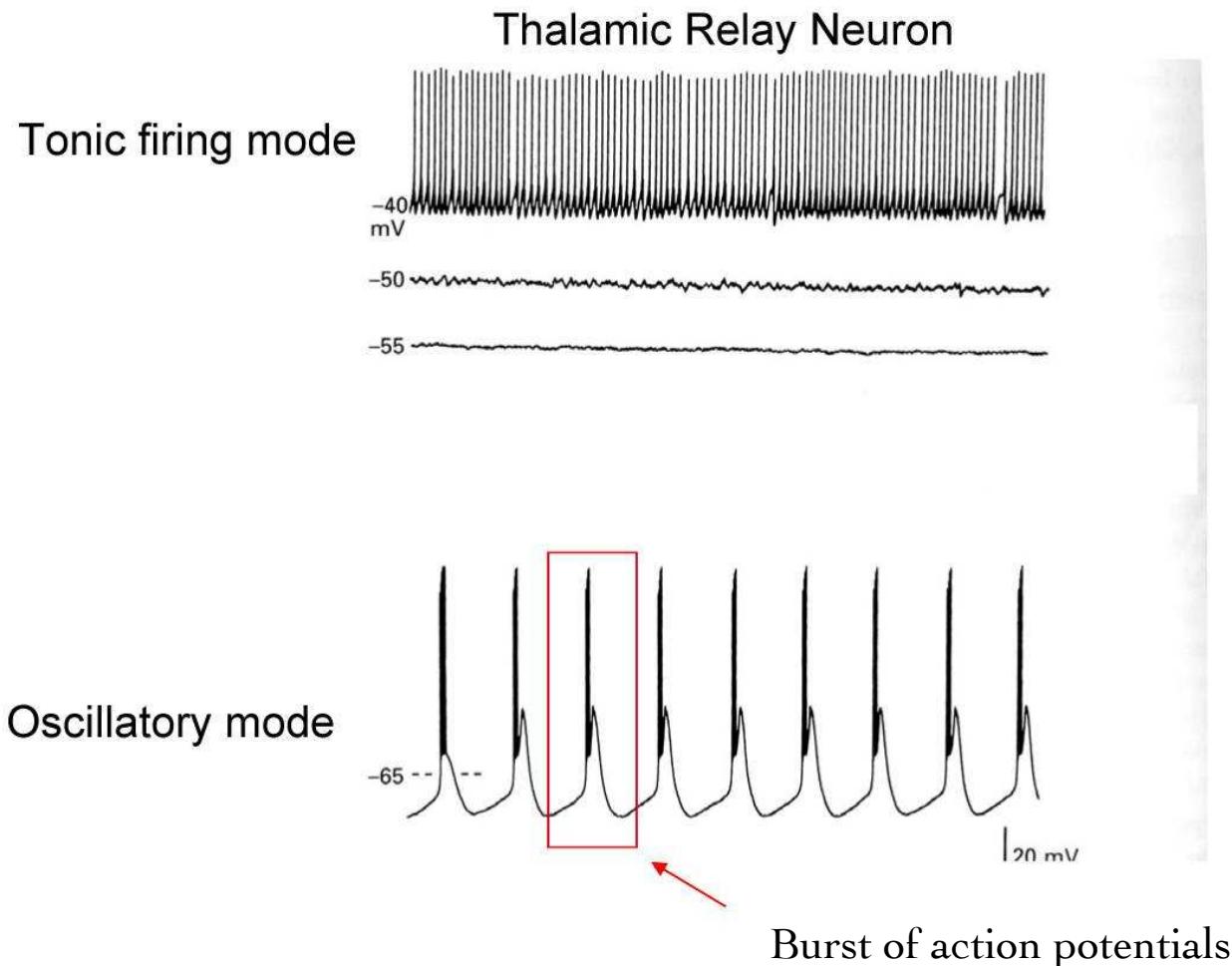
Sleep spindles have been linked to synaptic plasticity and memory consolidation

Thalamocortical circuits generating sleep oscillations

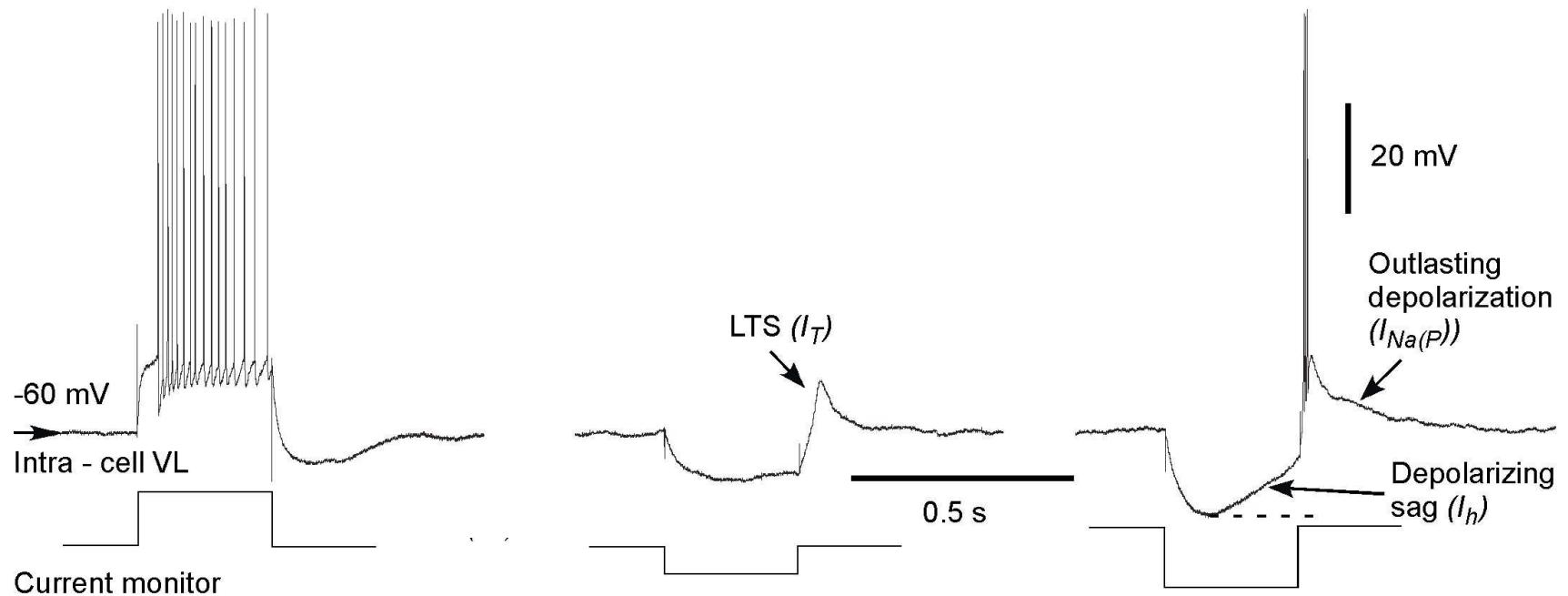


Timofeev and Bazhenov, 2005

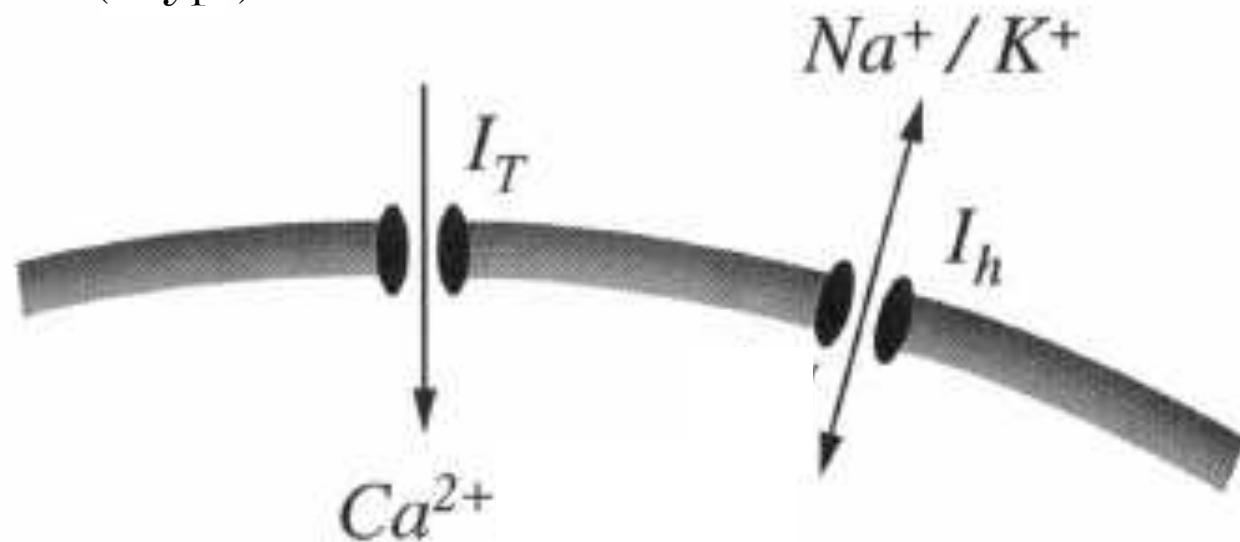
Thalamic relay cells may be in 2 different modes – tonic and bursting



Electrophysiological properties of thalamocortical neurons

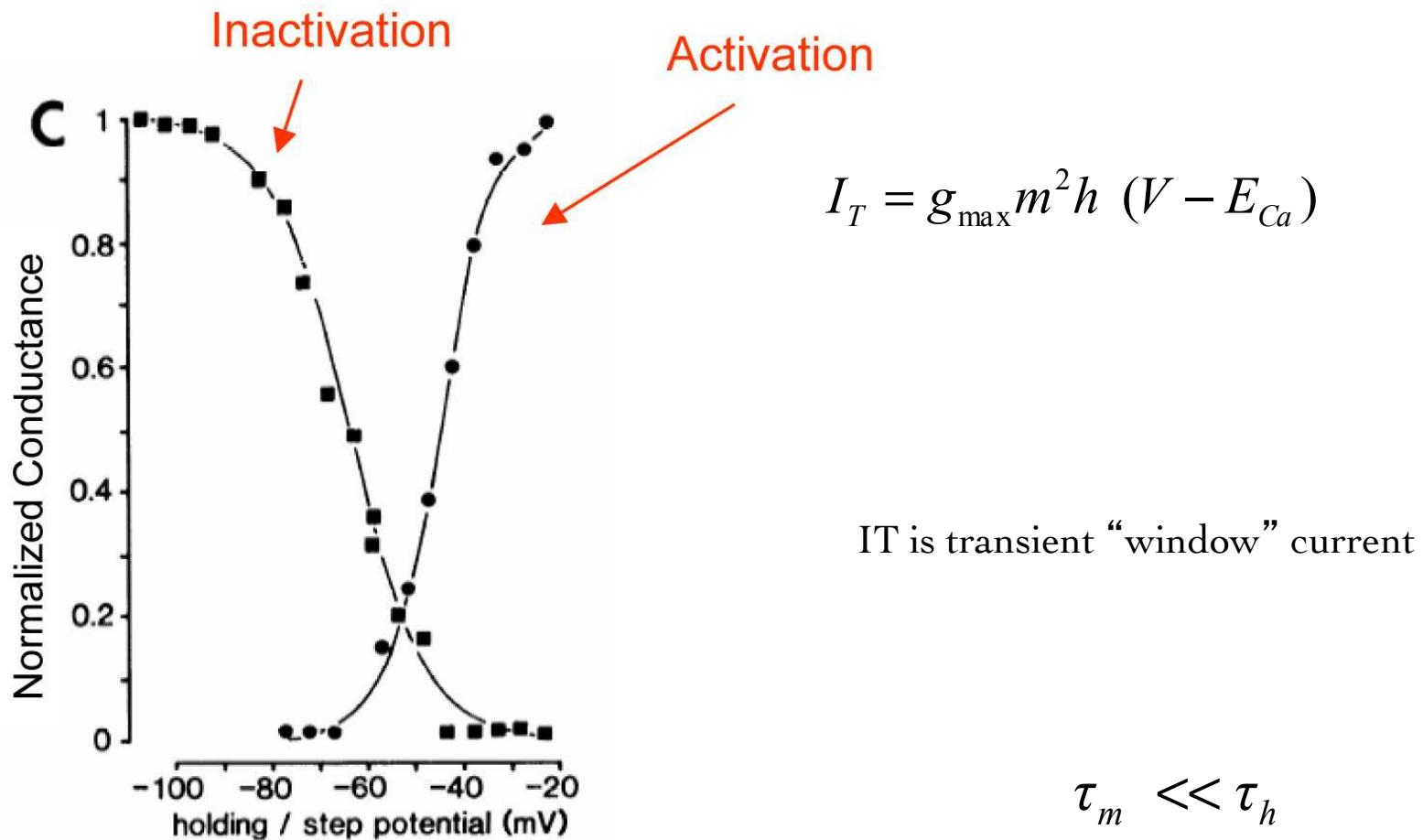


The transient (T-type) Ca⁺⁺ current IT



The channel underlying I_h in thalamic neurons is called HCN4. HCN4 is permeable to both Na^+ and K^+ ions.

The transient (T-type) Ca⁺⁺ current IT



Hernandez-Cruz & Pape 1989

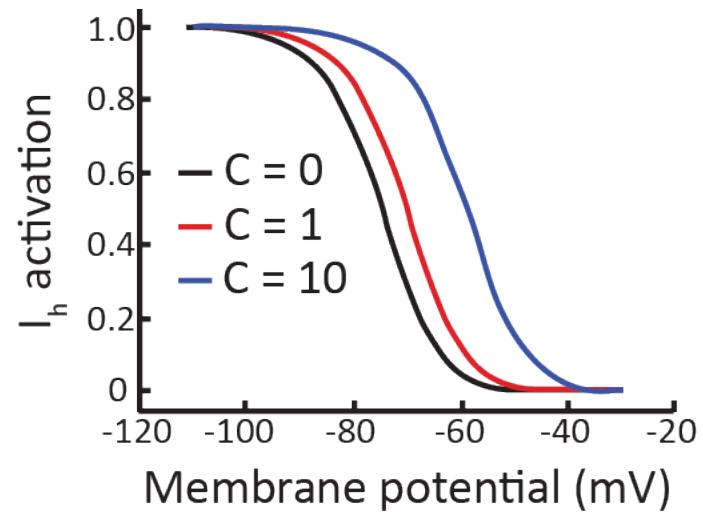
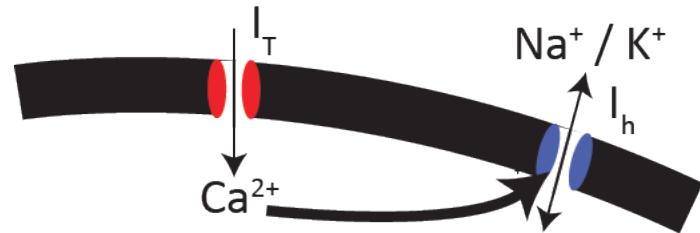
$V_m = -70\text{mV}$



(pA) -200 -400 -500 -600 -800 -1000

Kim et al 2001

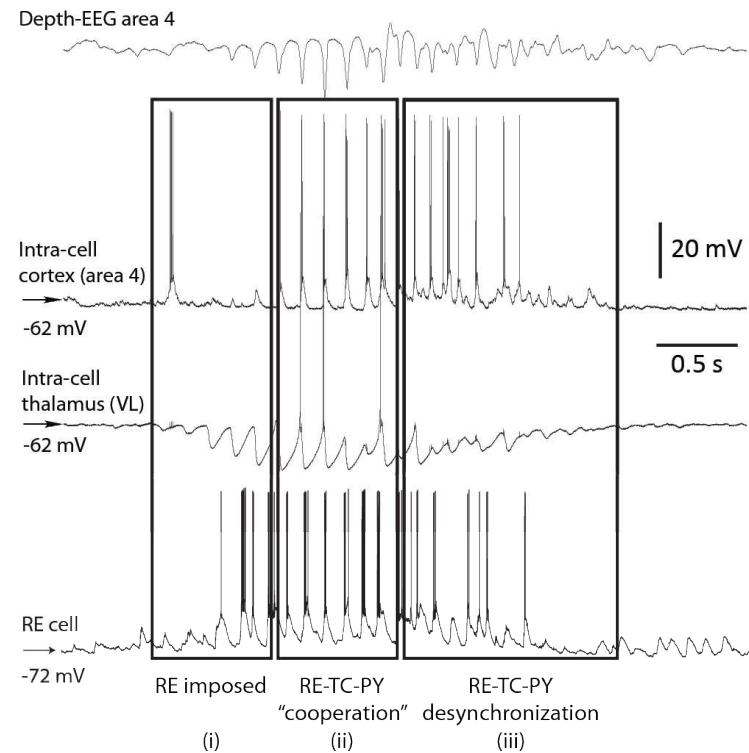
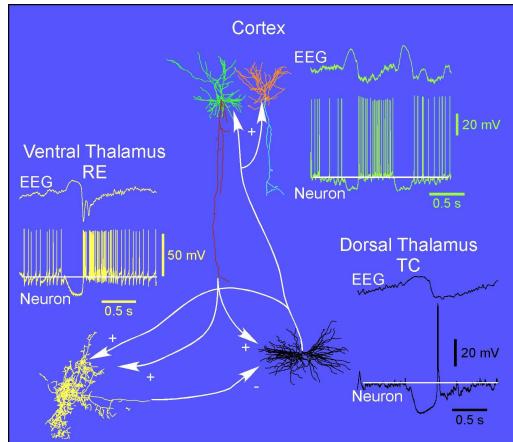
Ca^{2+} -upregulation shifts I_h activation curve



$$C = ([\text{Ca}]_i / \text{Ca}_{\text{crit}})^2$$

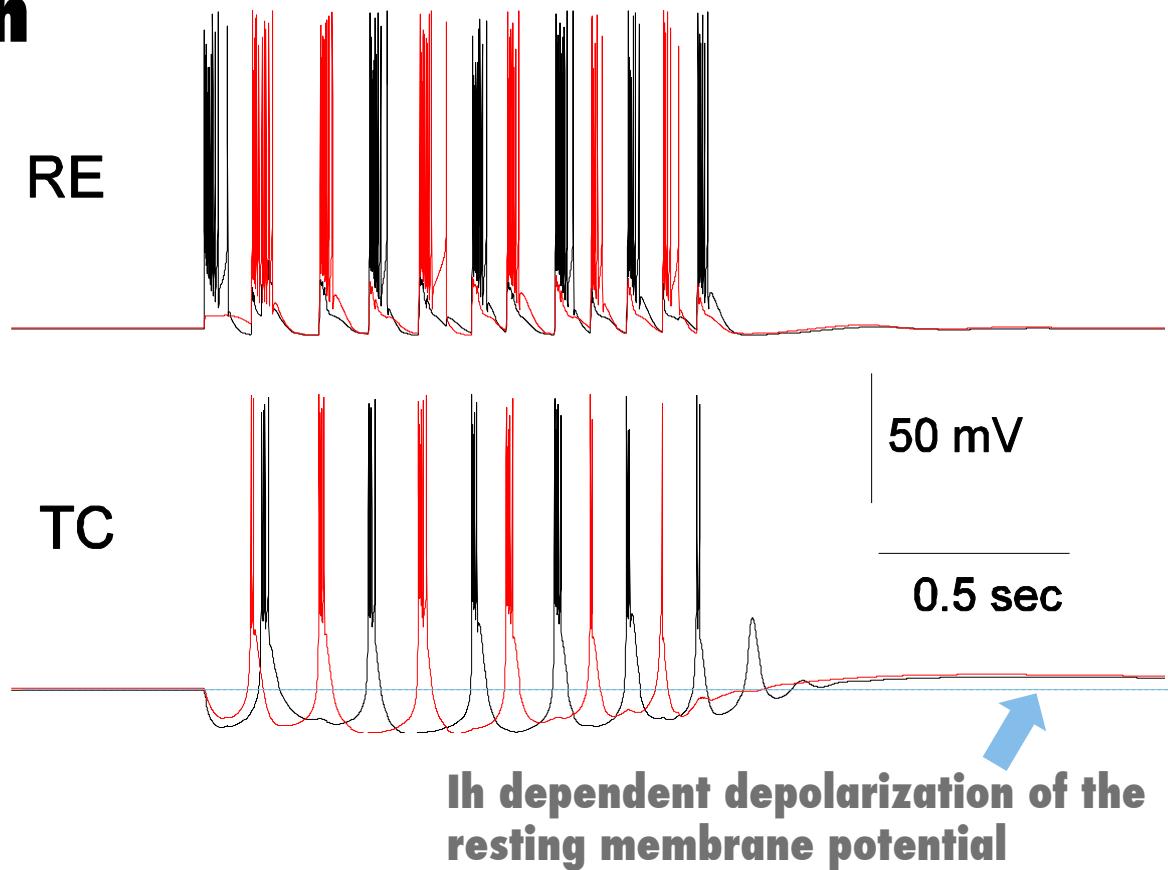
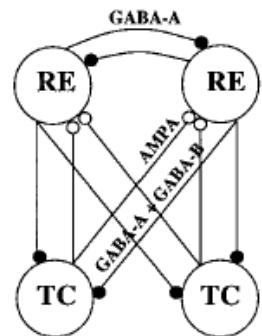
$$\text{Ca}_{\text{crit}} = 5 \cdot 10^{-4} \text{ mM}$$

There are at least three phases with different underlying mechanisms that contribute to the spindle generation:



- During the **early phase** of spindles, the reticular nucleus single-handedly drives the spindle oscillation via intrinsic mechanisms
- The **second component** of spindles, on the other hand, primarily develops as a result of interactions between reticular and relay neurons
- The **waning phase** occurs as a result of Ca^{2+} induced cAMP up-regulation of the hyperpolarization activated cation current, I_h , in relay cells (Destexhe et al)

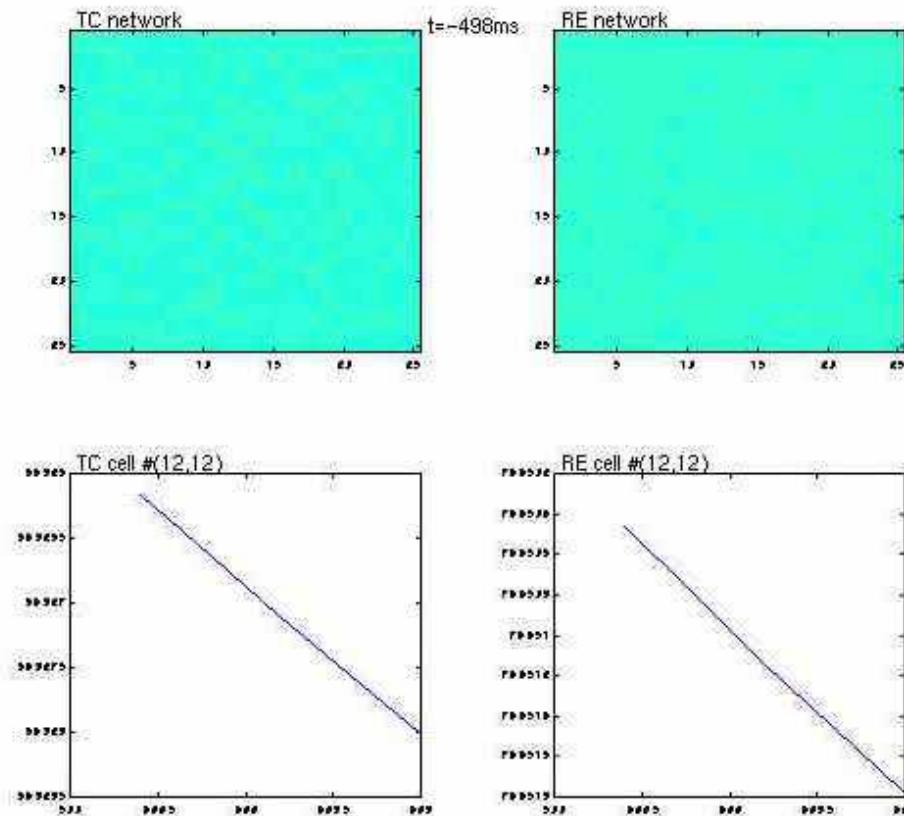
Model of spindle termination mediated by I_h up-regulation



Burst firing of reticular thalamic neurons induces inhibitory postsynaptic potentials in thalamocortical neurons. This **deinactivates low-threshold Ca^{2+} current (I_T)**, inducing burst firing in thalamocortical neurons which, in turn, excite reticular thalamic neurons allowing the cycle to start again.

Timofeev and Bazhenov, 2005

Spindle oscillations in 2D thalamic network model



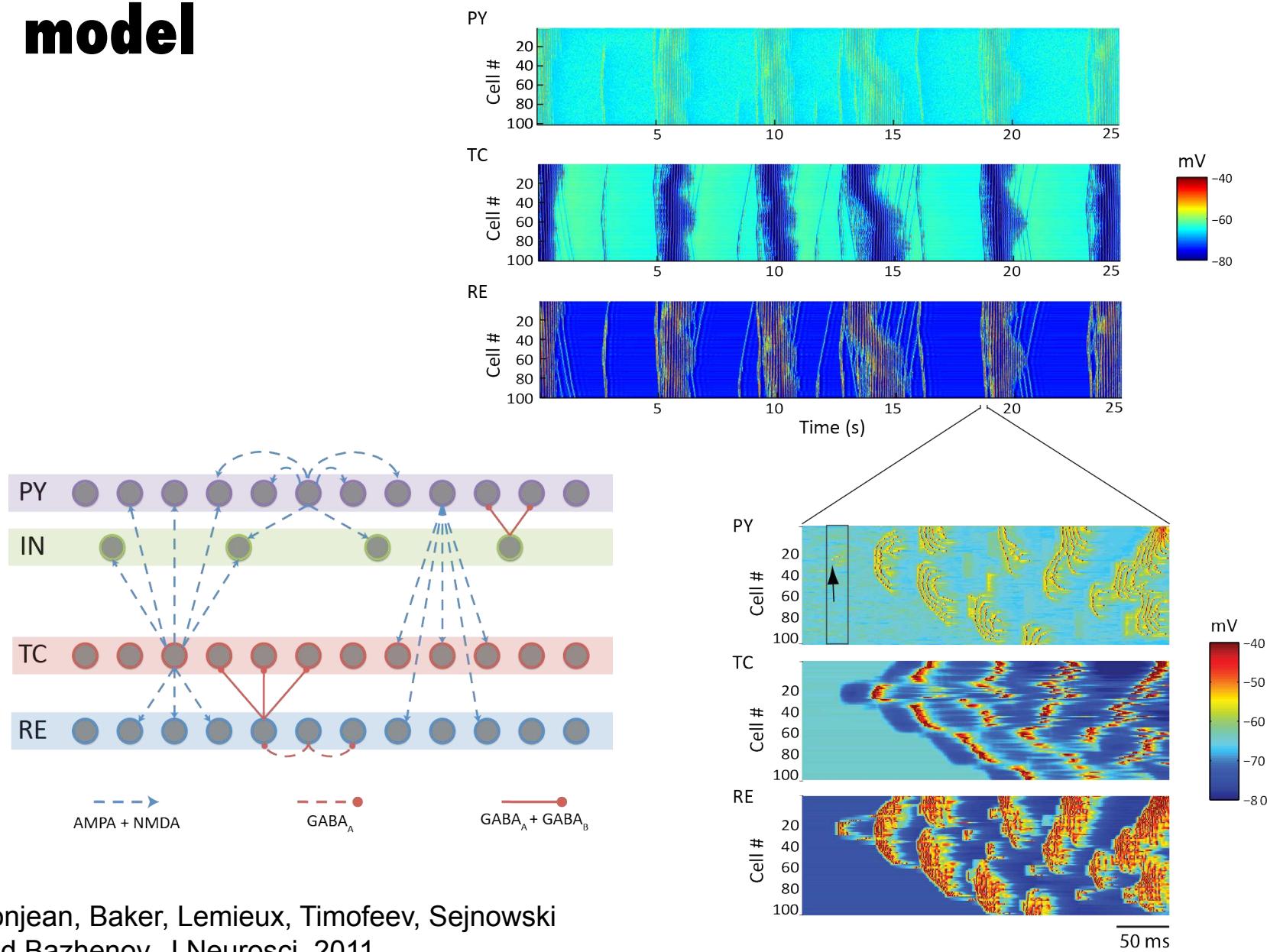
Outline

- I. Termination of sleep spindles – role of neocortex
- II. Spindle synchronization – role of neocortex

Outline

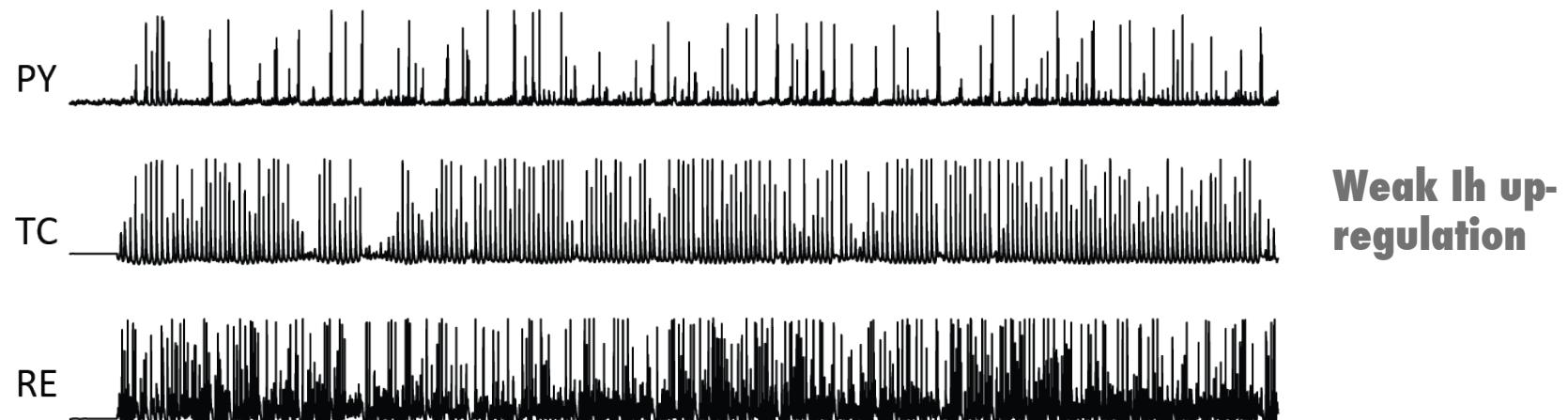
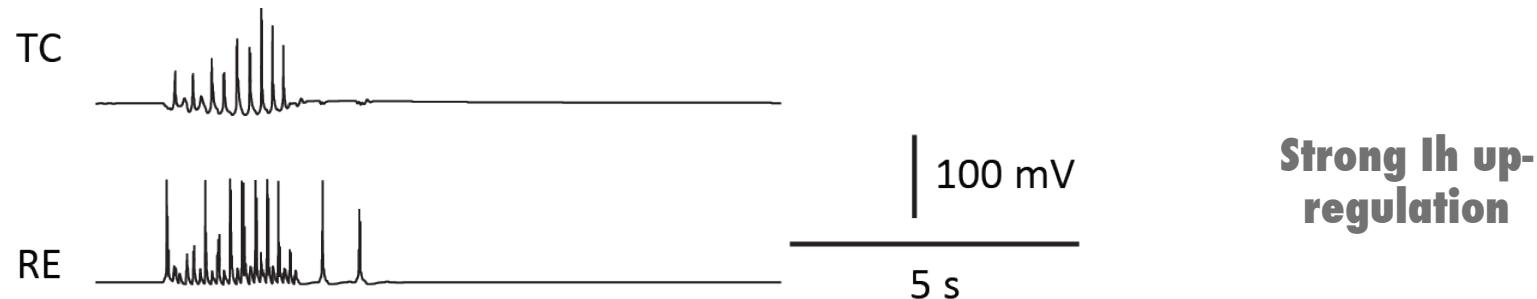
- I. Termination of sleep spindles – role of neocortex
- II. Spindle synchronization – role of neocortex

Spindle sequences in thalamocortical network model



Bonjean, Baker, Lemieux, Timofeev, Sejnowski
and Bazhenov, J Neurosci, 2011

Reducing Ih up-regulation leads to continuous spindle-like activity

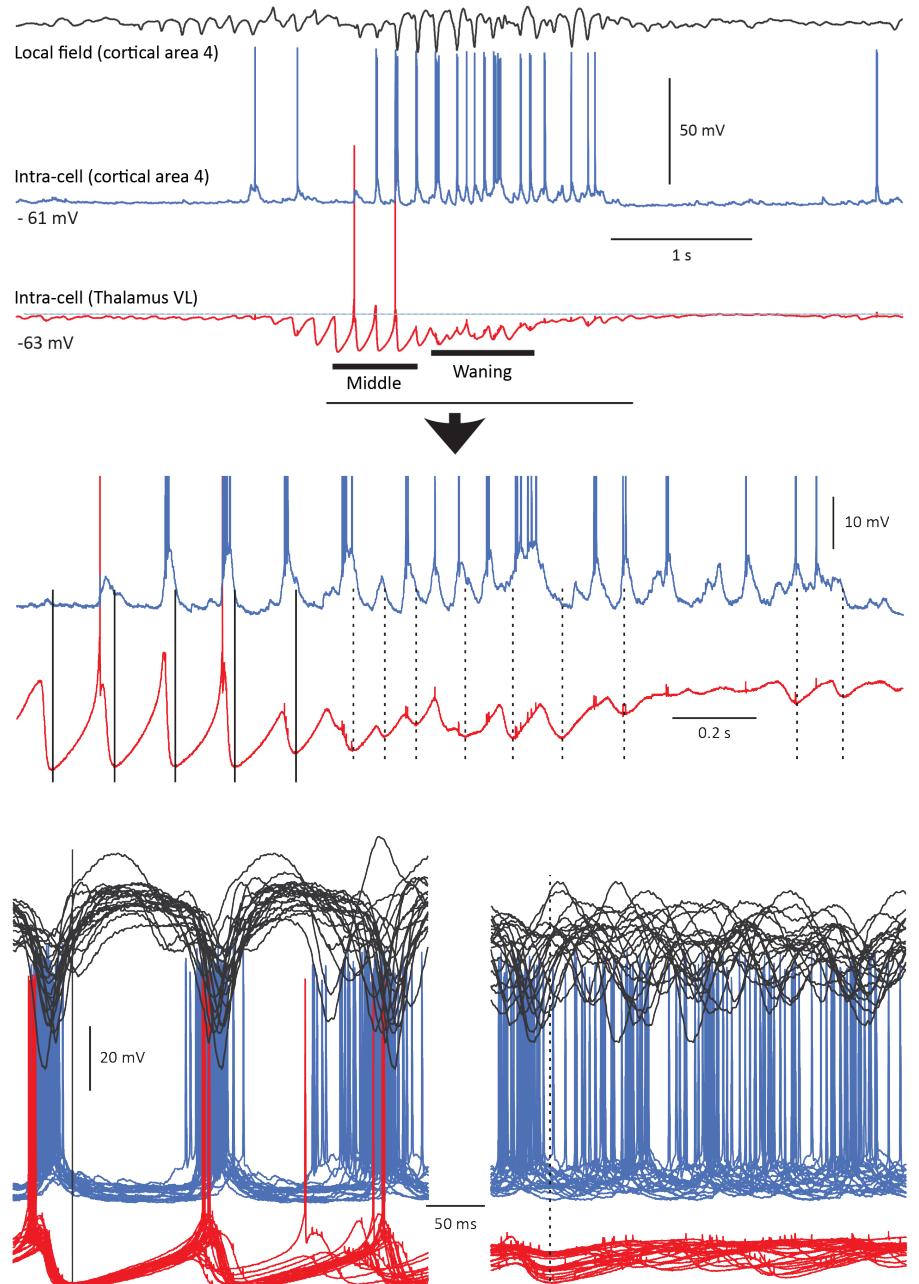


Post-spindle (induced by I_h up-regulation) depolarization of TC membrane potentials is less prominent *in vivo* than *in vitro*

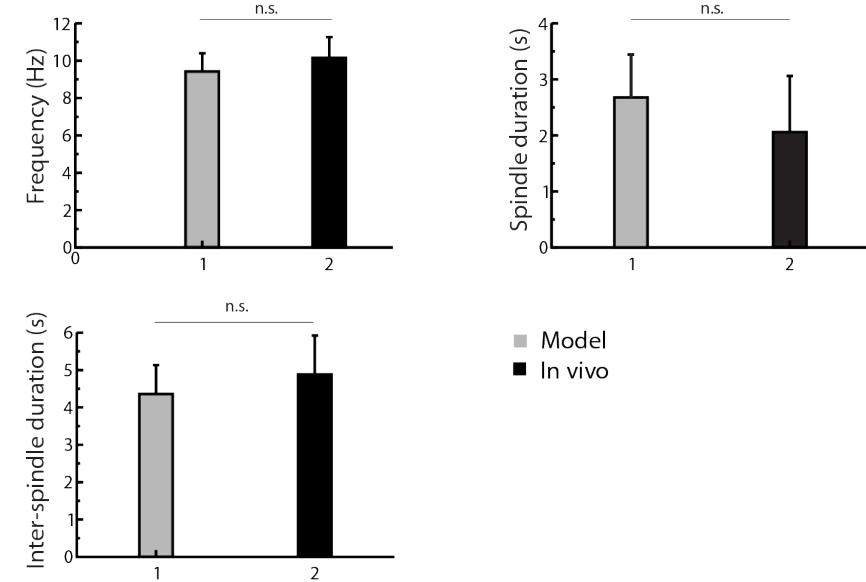
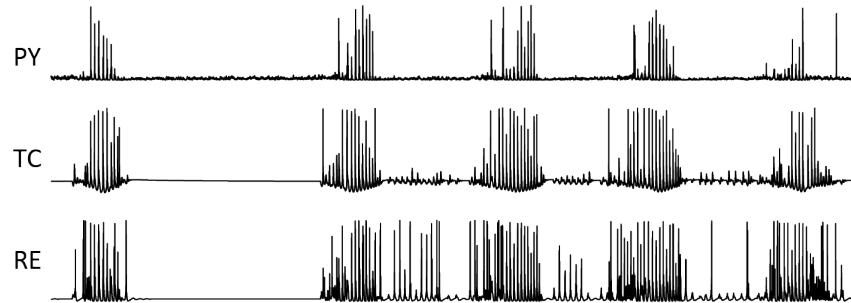
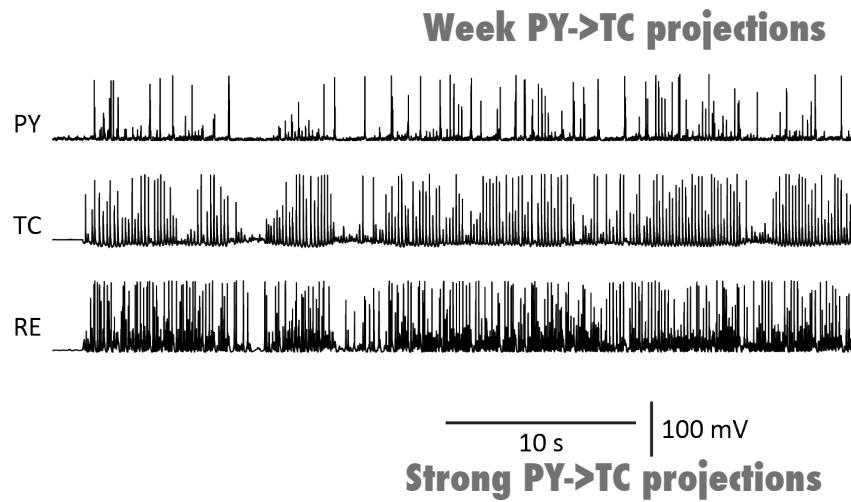
In vivo synchrony of firing between thalamus and neocortex decreases over the spindle duration

Can thalamo-cortical desynchronization contribute to termination of spindle sequence?

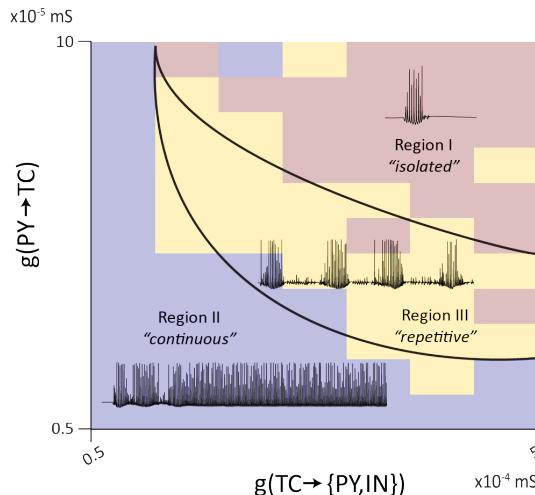
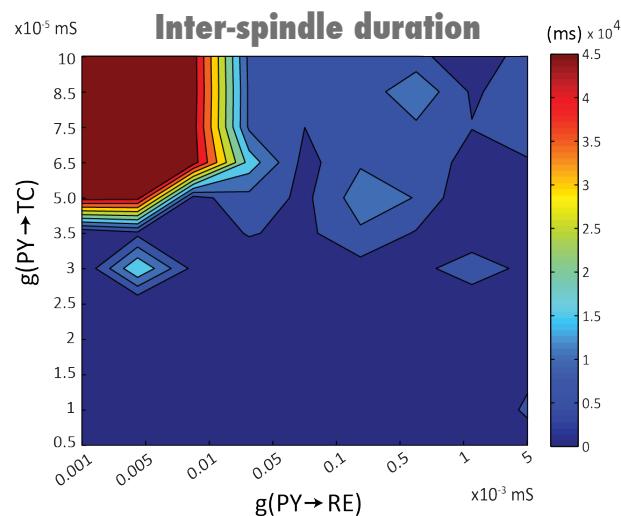
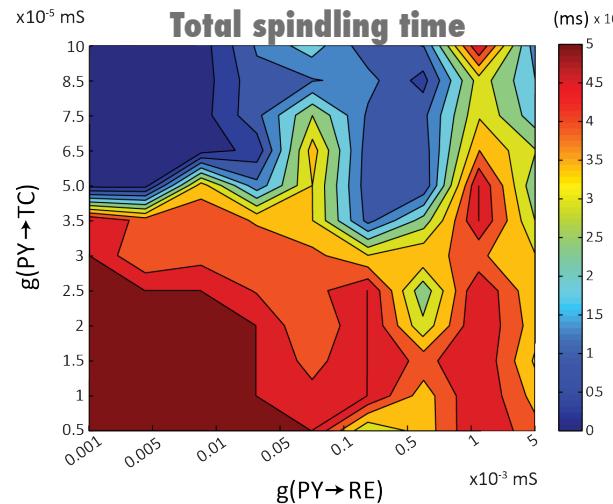
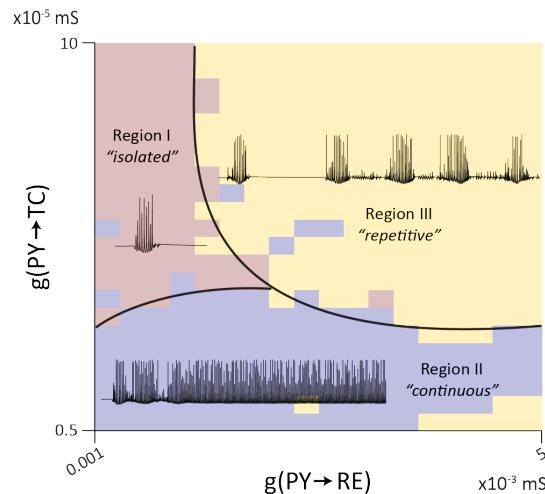
Bonjean, Baker, Lemieux, Timofeev, Sejnowski and Bazhenov, J Neurosci, 2011



Increase of thalamocortical connectivity recovers isolated spindles



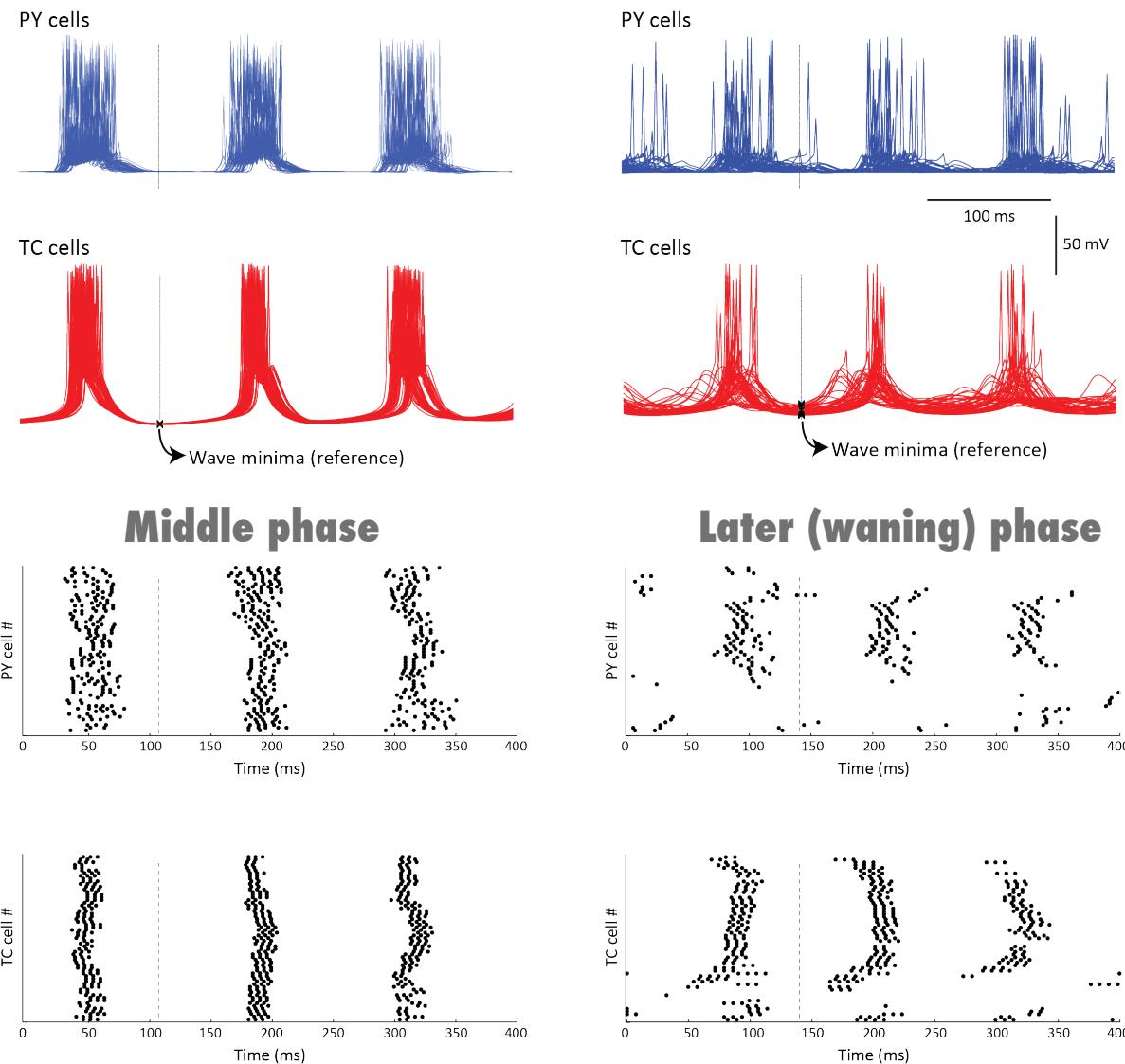
Cortical feedback on TC and RE cells modulates different spindle patterns



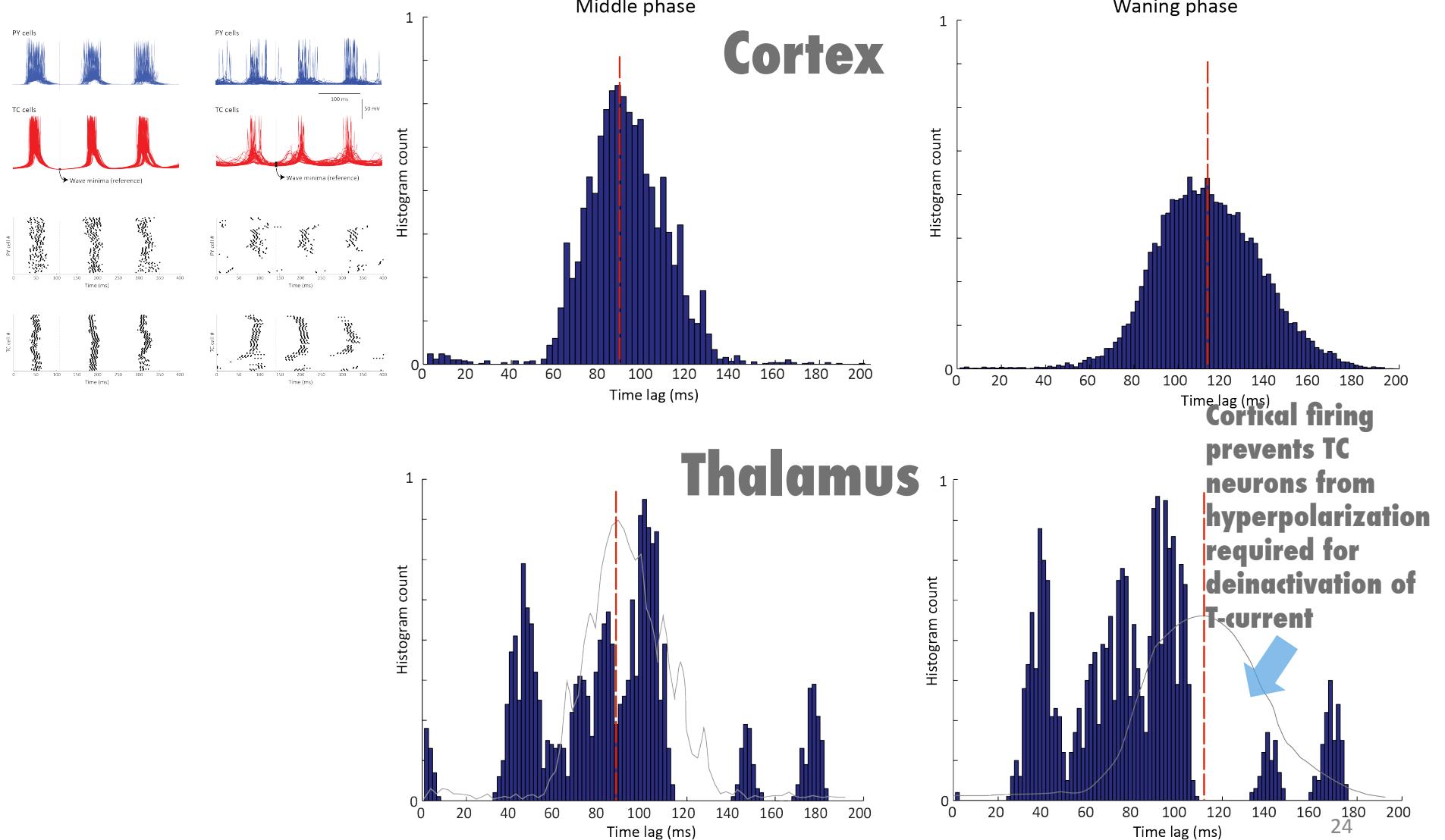
Bonjean, Baker,
Lemieux, Timofeev,
Sejnowski and
Bazhenov, J Neurosci,
2011.

**What are the mechanisms of
termination?**

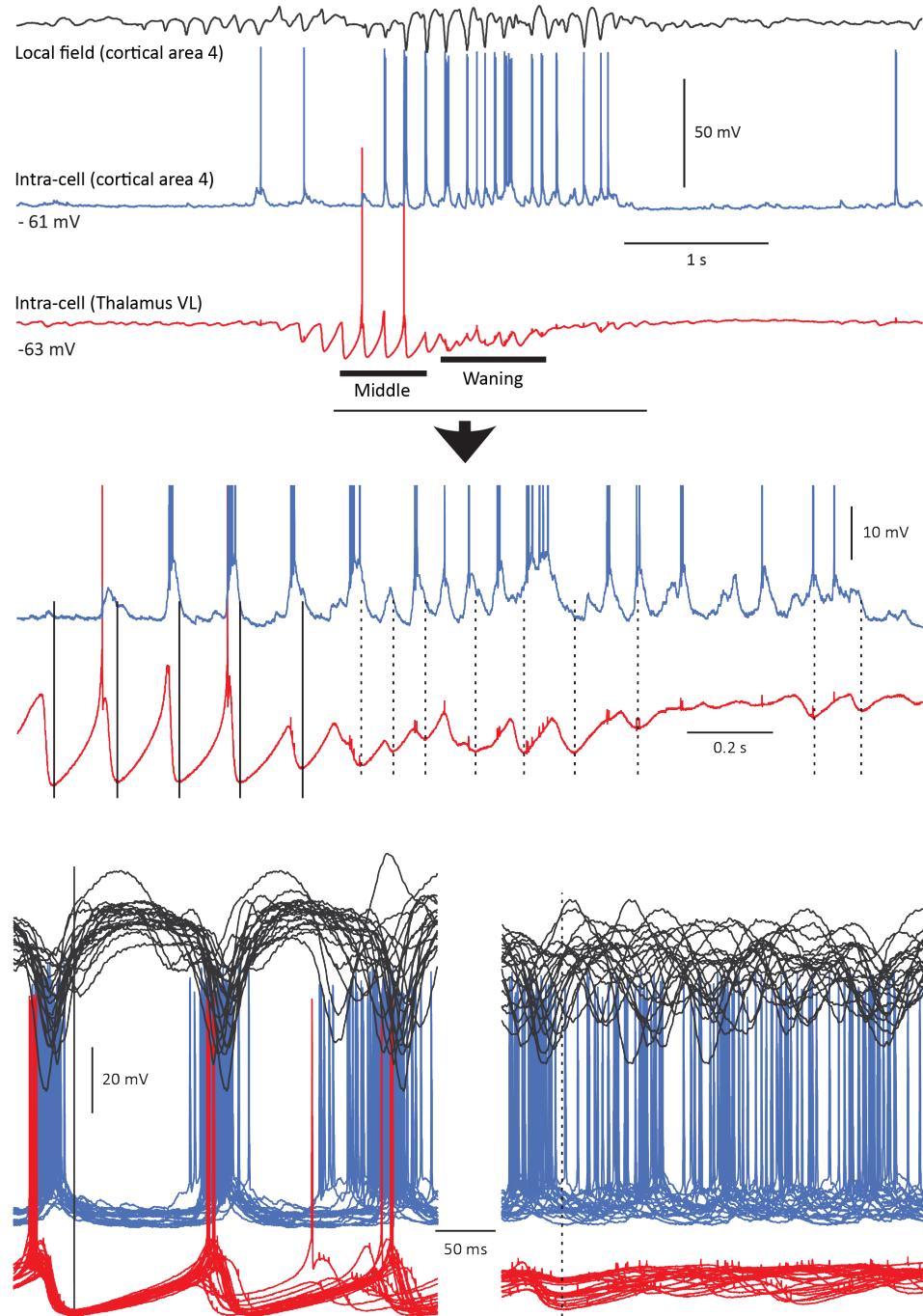
Firing in thalamic and cortical neurons is better synchronized during middle vs later phase of spindle



Distribution of the time lags between a wave minimum of TC membrane potential and the following cortical spikes



IN vivo recordings



Bonjean, Baker,
Lemieux, Timofeev,
Sejnowski and
Bazhenov, J Neurosci,
2011.

Summary

We investigated the impact of corticothalamic and thalamocortical synaptic connections on spindle modulation under conditions when the up-regulation of I_h was not sufficient to terminate spindles.

We propose that the termination of spindles *in vivo* is due to the depolarizing action of I_h in combination with the depolarizing action of corticothalamic inputs, which is caused by the lack of precise coordination of thalamic and cortical firing during the later phase of spindles.

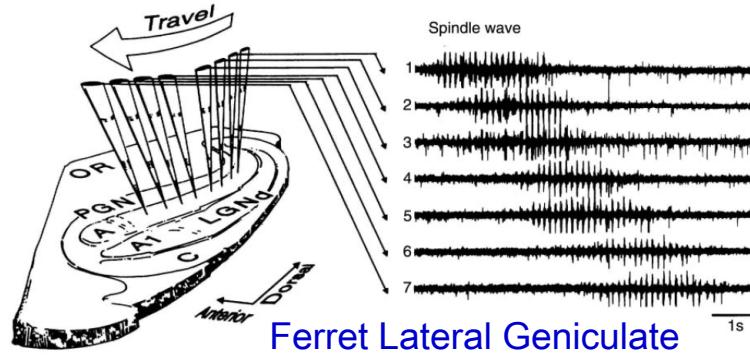
Outline

- I. Termination of sleep spindles – role of neocortex
- II. Spindle synchronization – role of neocortex

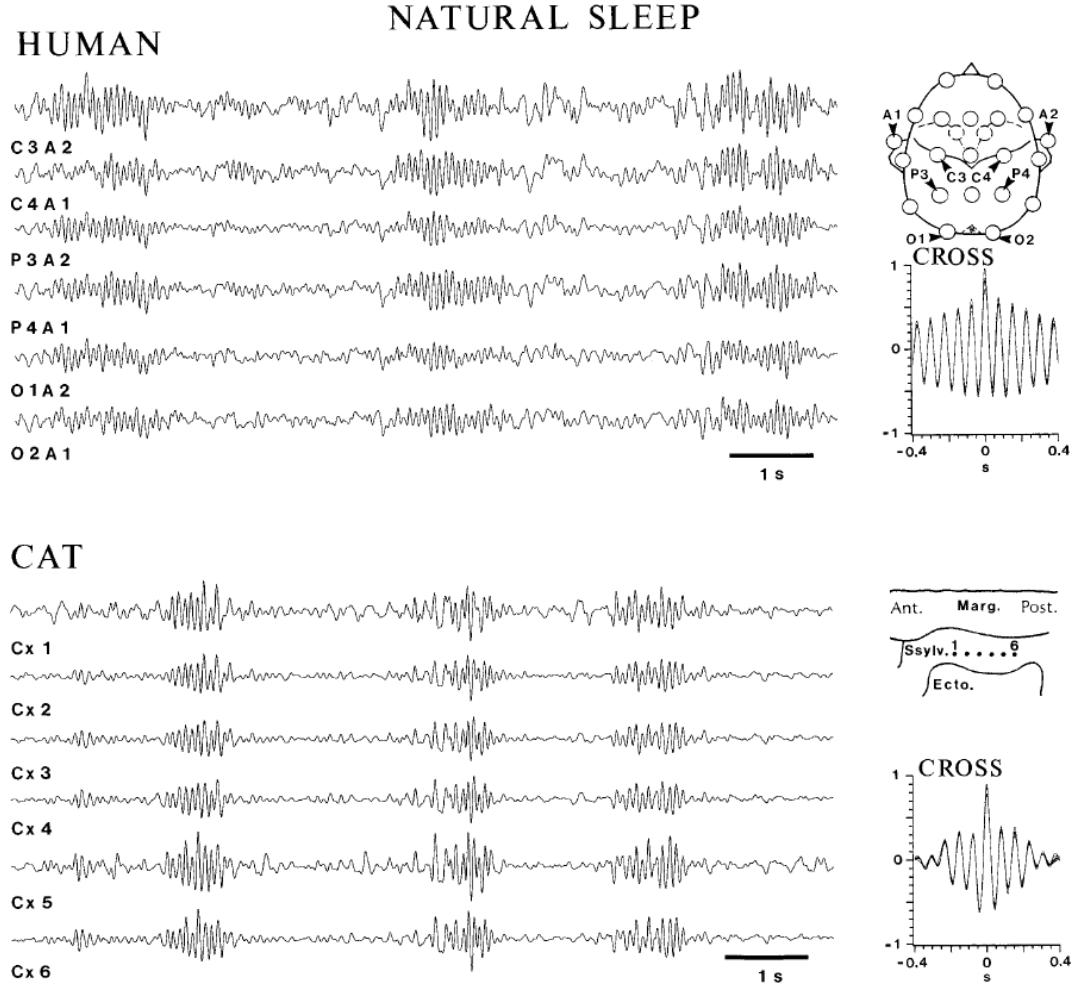
- Spindles that are generated under barbiturate anesthesia [1] or in vitro [2] can be focal.

[1] Andersen and Andersson (1968) *Physiological Basis of the Alpha Rhythm*.

[2] Kim, Bal, McCormick (1995) *J Neurophysiol* 74:1301-23.



Sleep Spindles- Animal Studies- Synchrony within and between cortex and thalamus

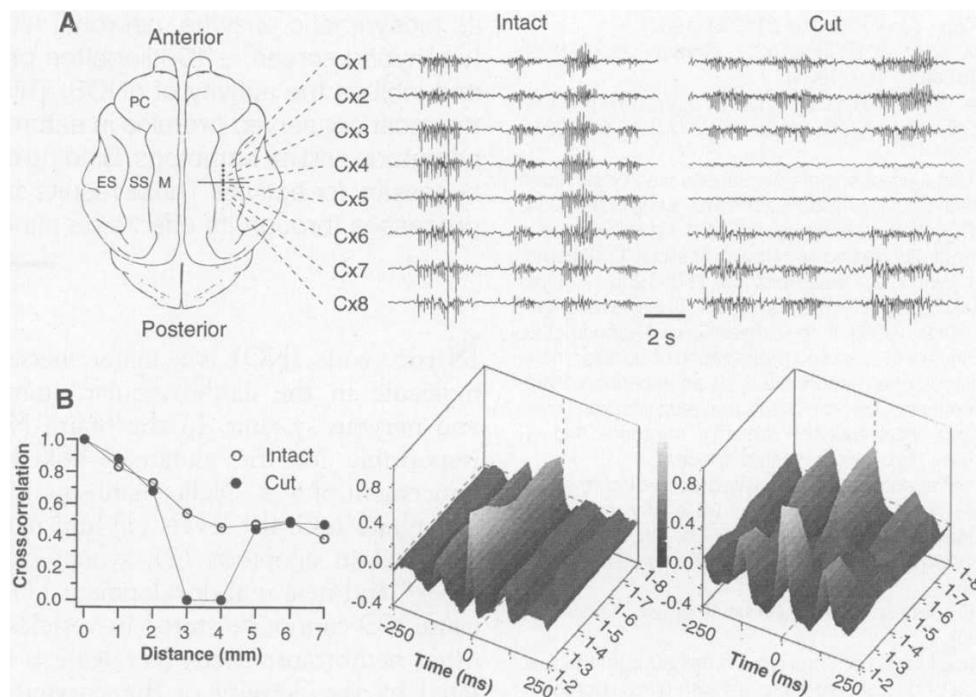


- Spindles in unanesthetized cats have been described as having remarkable synchrony across the thalamus and cortex due to corticothalamic connections [3]
- Spindles in human EEG show great synchrony across the scalp so it has been proposed that synchrony is the normal state in humans

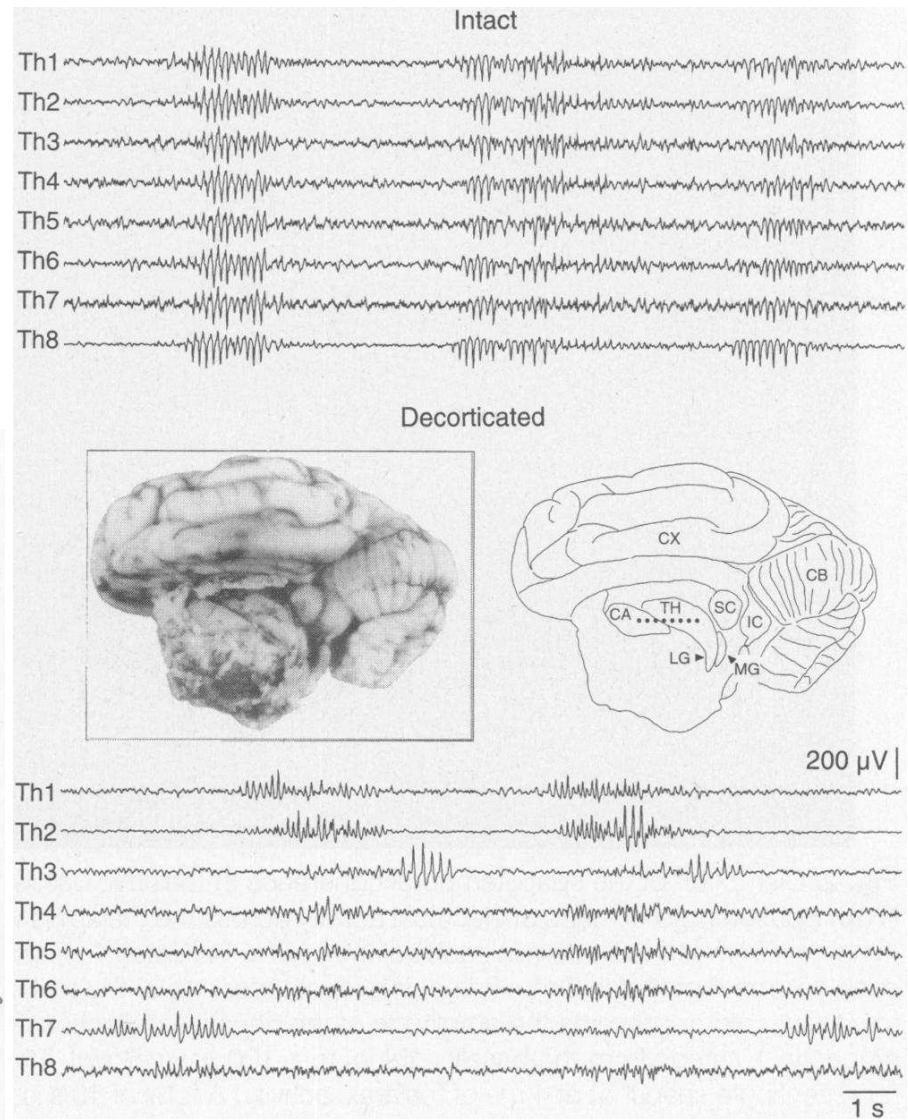
[3] Contreras, Destexhe, Sejnowski, Steriade (1997) *J Neurosci* 17:1179-1196

Sleep Spindles in barbiturate anesthetized cats: Synchrony arises from thalamocortical interaction

Synchrony within cortex is not affected by 3mm deep coronal cuts

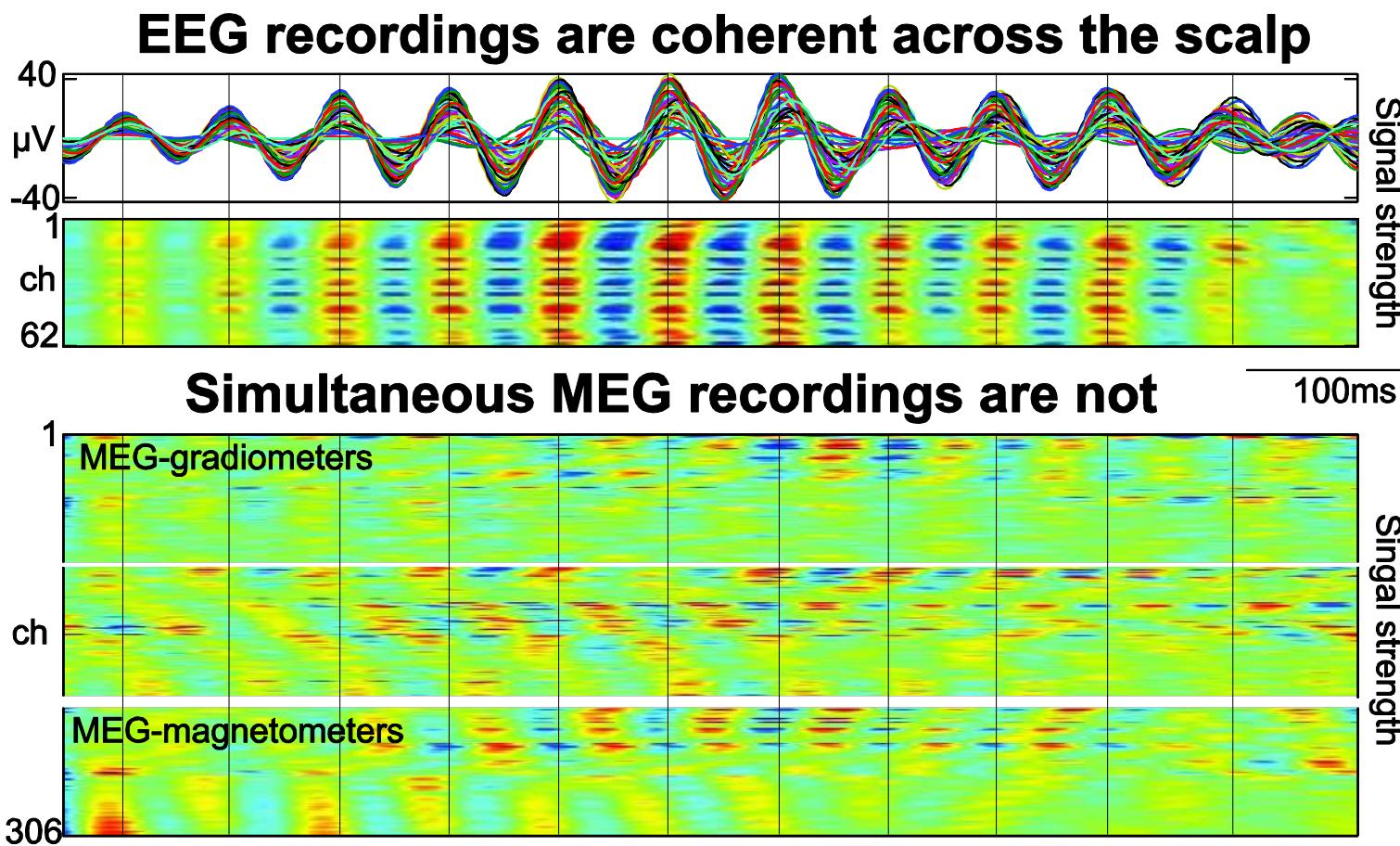


Synchrony within thalamus is abolished by decortication



Contreras, Destexhe, Sejnowski, Steriade, Science 95

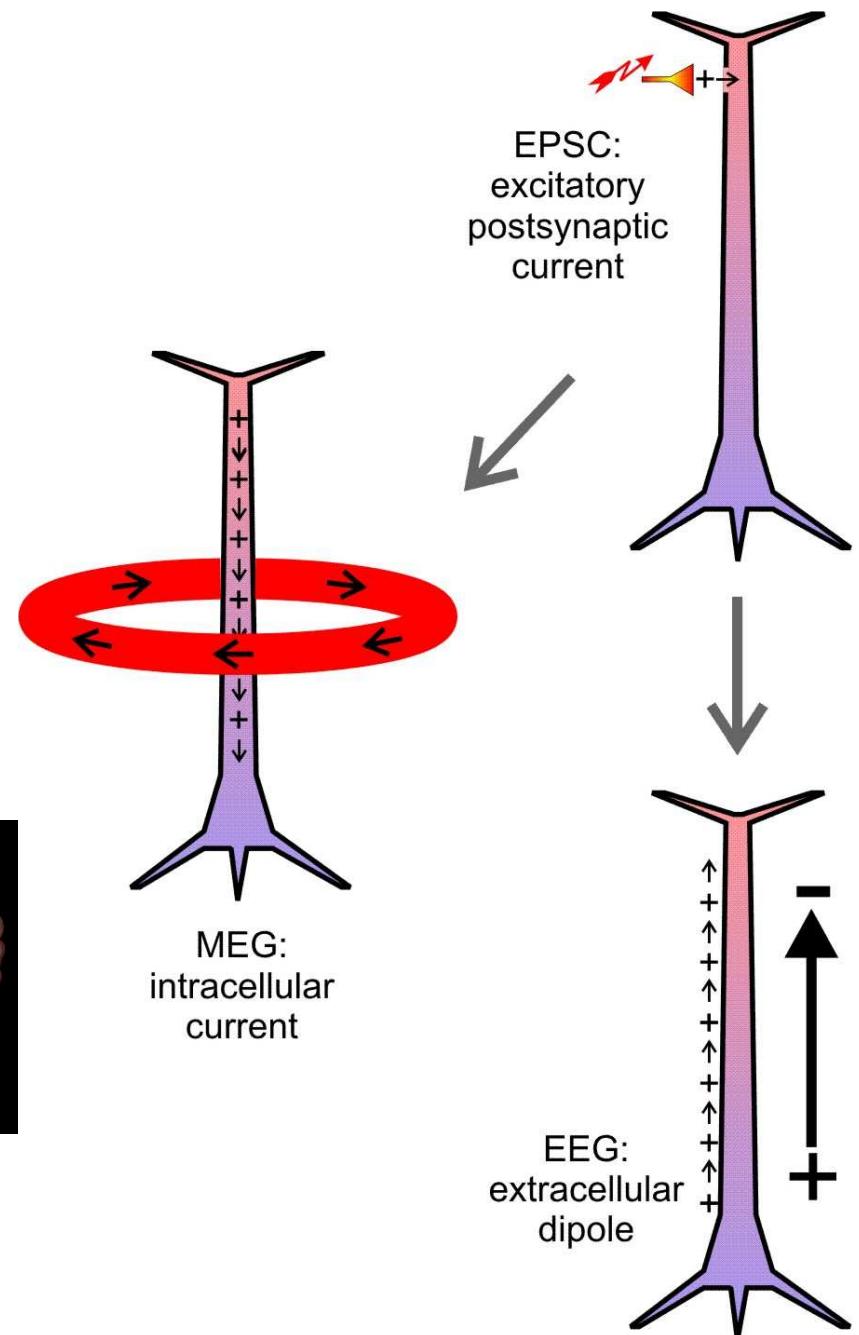
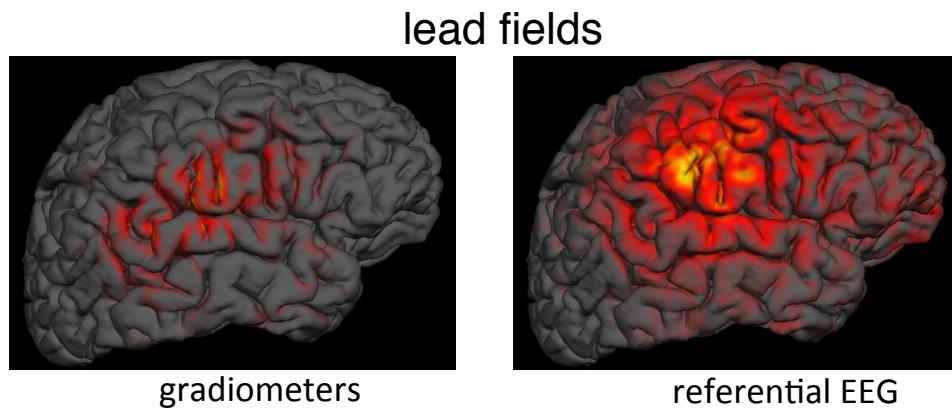
MEG and EEG give different views of Sleep Spindles



Dehghani et al., 2010

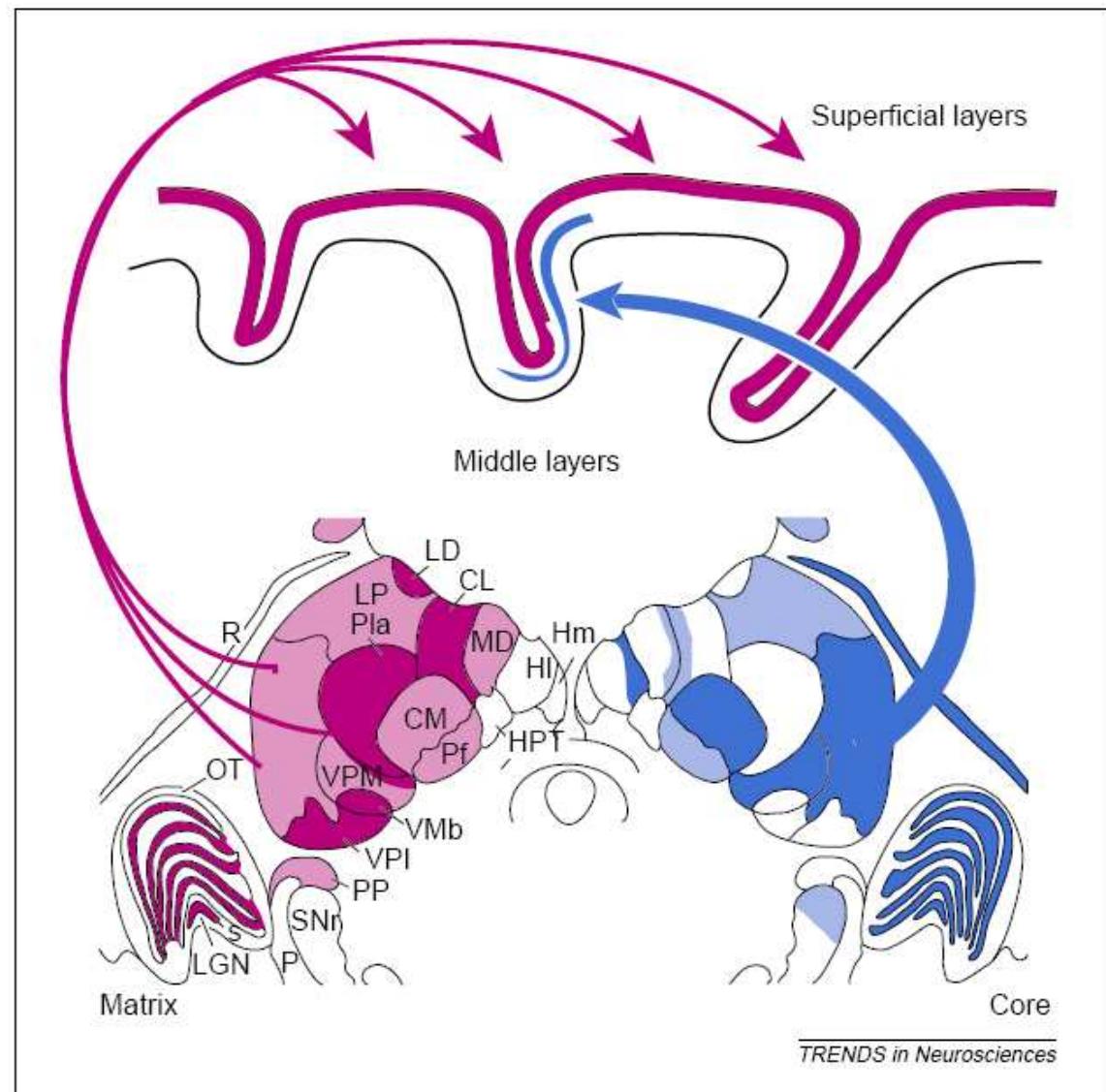
EEG vs. MEG

- EEG and MEG spindles seem to be coming from different cortical locations
- Why are MEG and EEG spindles so different?
 - Measurement
 - MEG has a more restricted field of view than EEG



The Matrix and Core Thalamocortical Systems

Anatomical studies have found 2 types of thalamo-cortical projections: Core projections are to layer IV, powerful and punctuate, carrying specific information; Matrix projections are to layer I, diffuse and modulatory.



Jones, TINS 24:595-601 2001

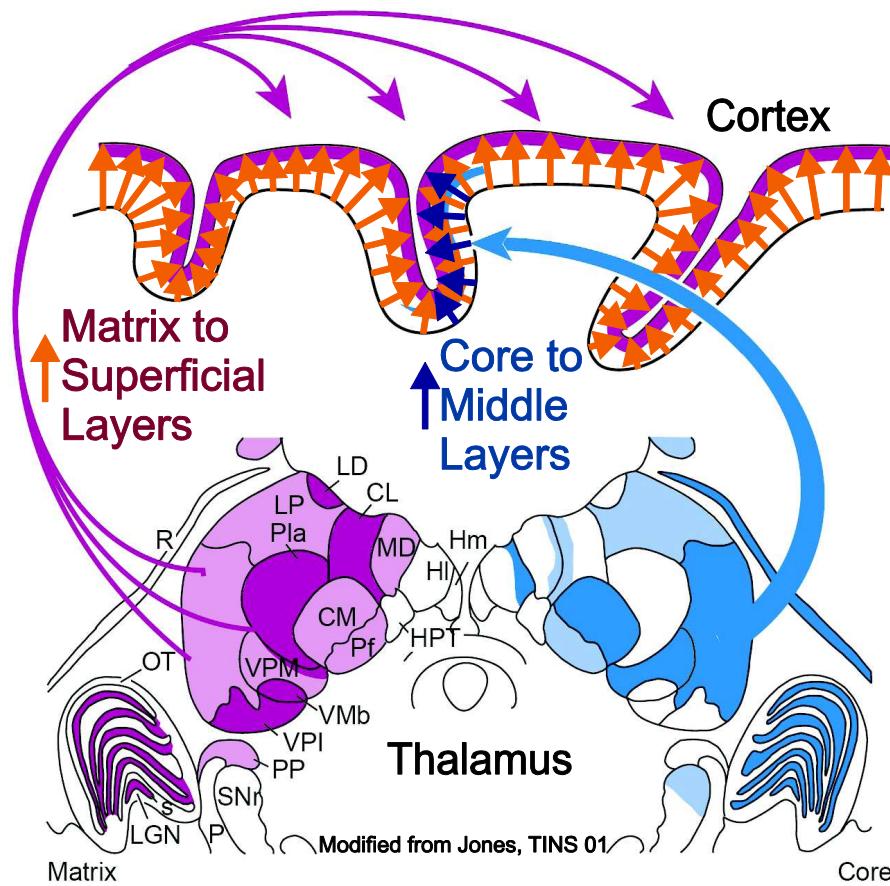
TRENDS in Neurosciences

Hypothesis:

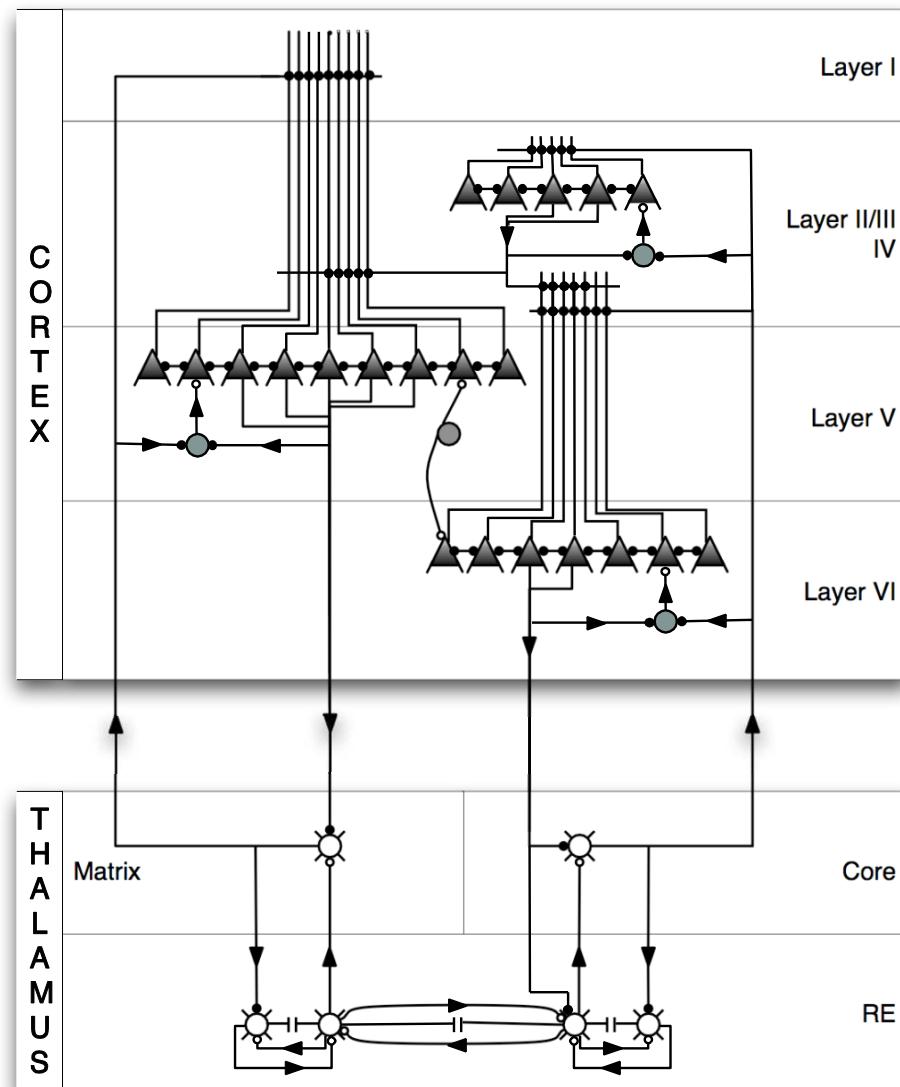
Human sleep spindles arise from the two thalamo-cortical systems.

Spindle frequency activity arises through the core thalamic projection neurons interacting with thalamic reticular neurons and focal associated cortical columns. Core spindles are largely independent across the cortical surface except that functionally related cortical columns may be synchronized even if they are not adjacent.

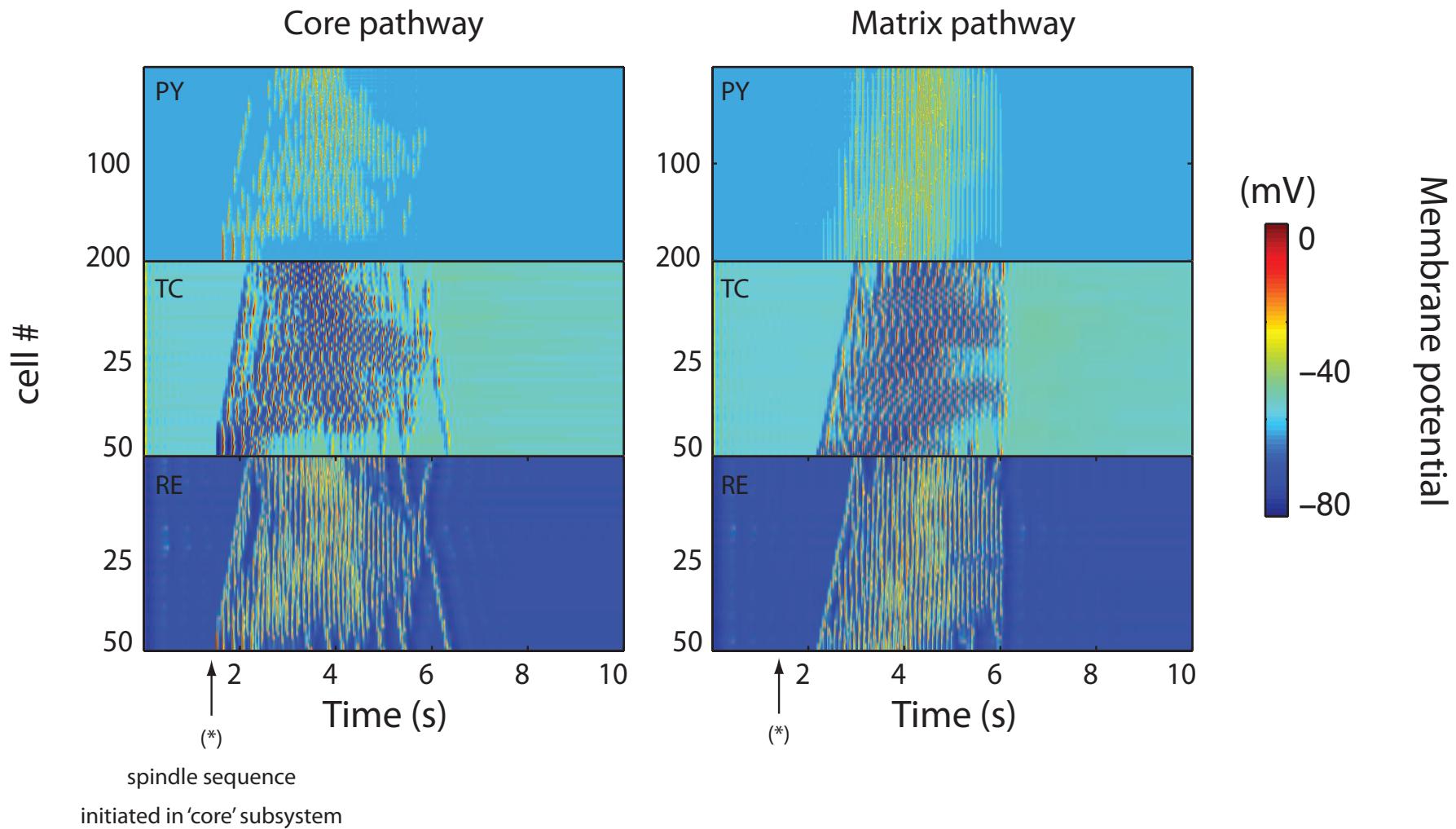
Spindles in different columns are synchronized by the matrix system. Synchronization arises because matrix thalamo-cortical and cortico-thalamic projections are widespread.



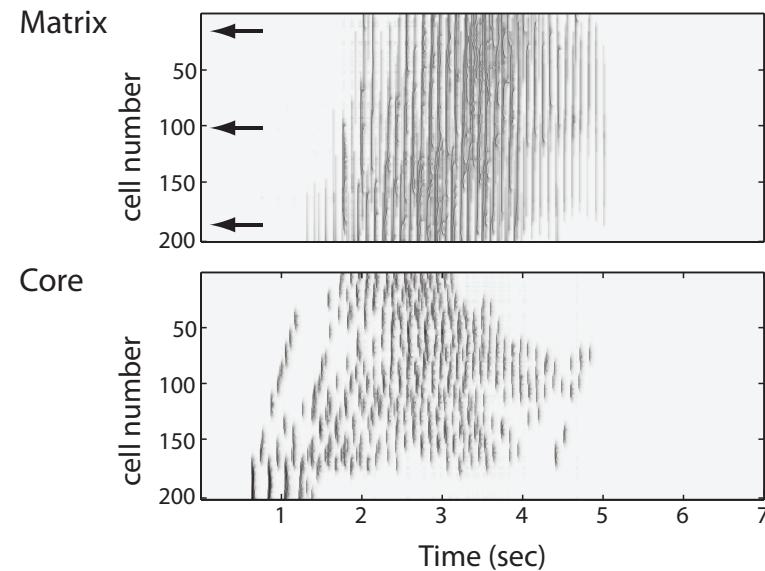
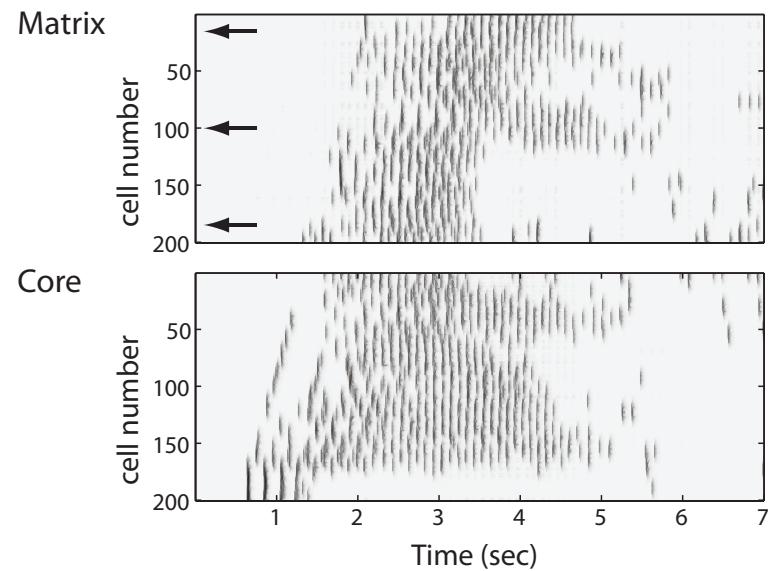
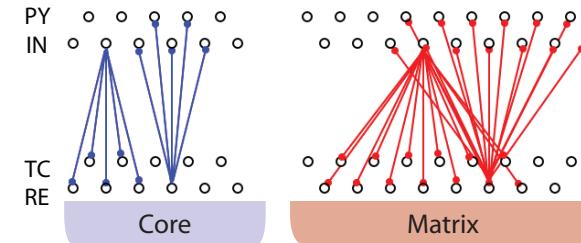
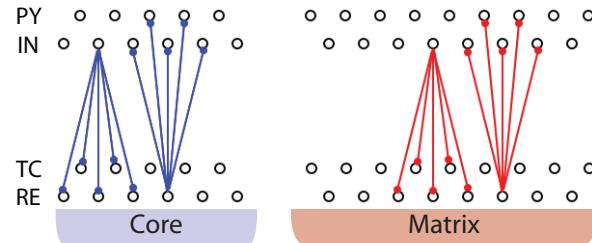
Matrix and core systems model diagram



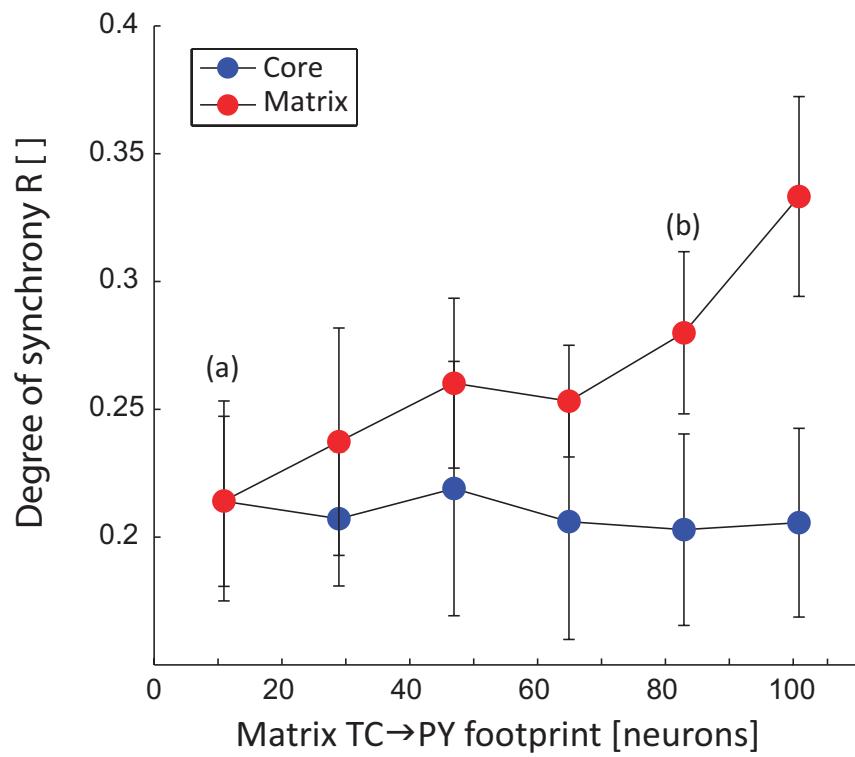
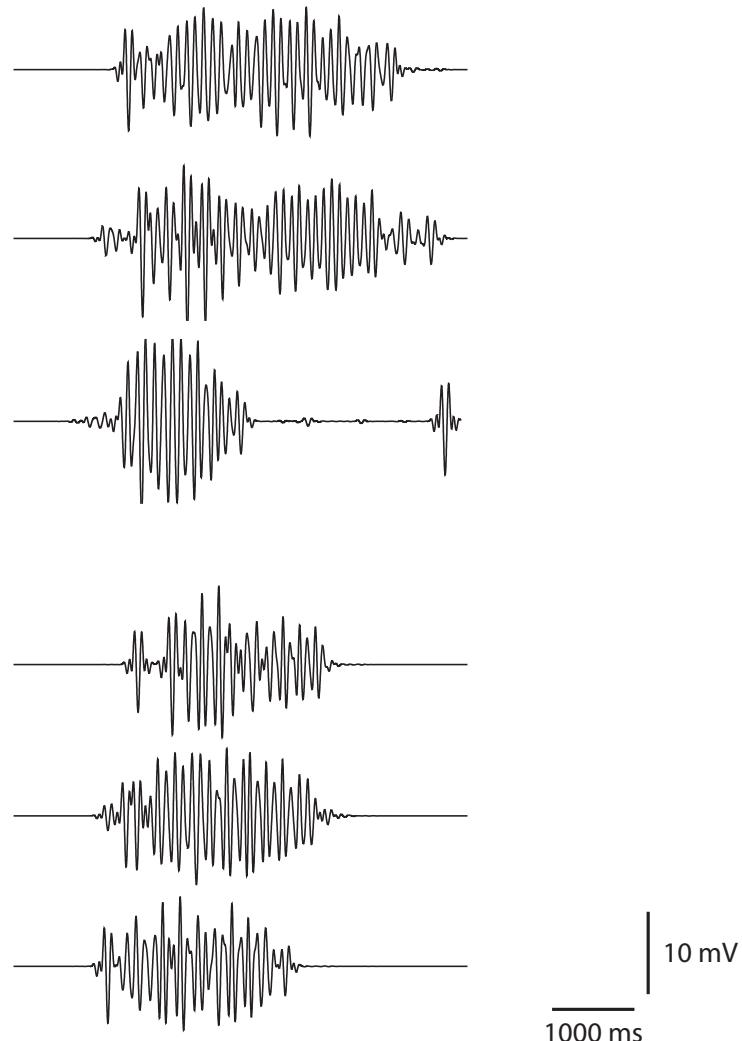
Spindles in thalamocortical system



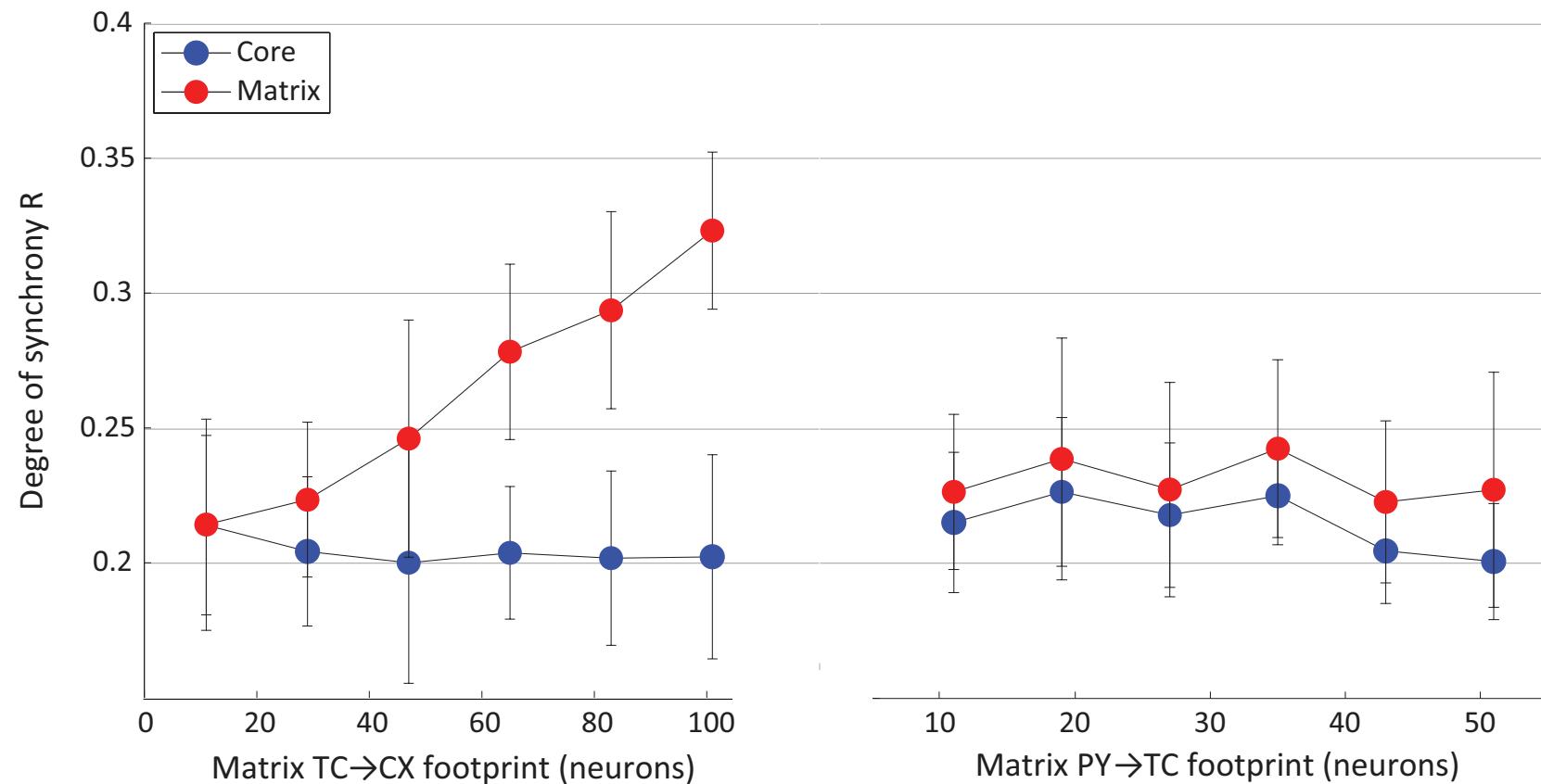
Spindle synchronization depends on widespread thalamocortical footprint



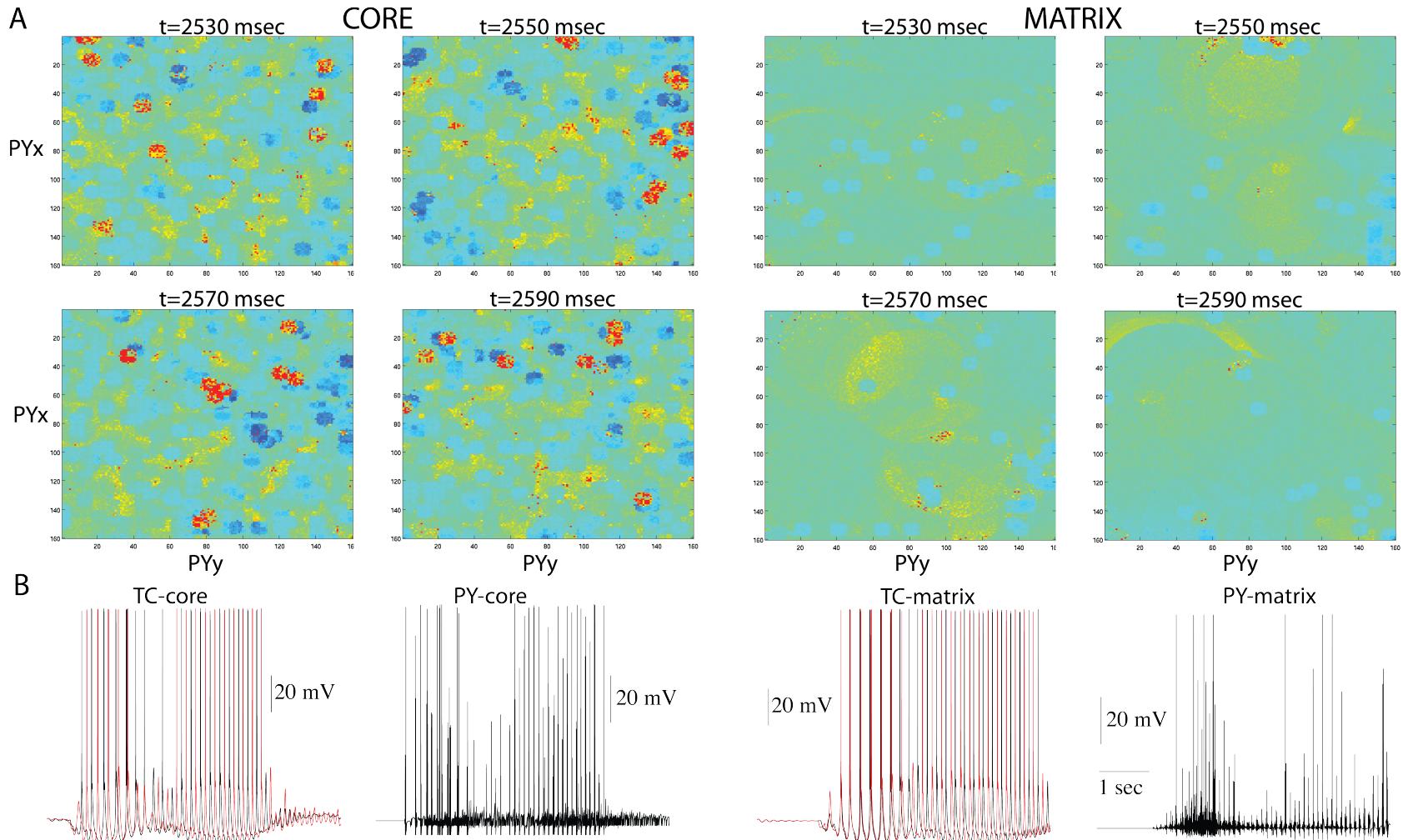
Broaden TC \rightarrow CX footprint in matrix system



Quantify synchrony: average weighted deviation of peak correlation from zero time lag

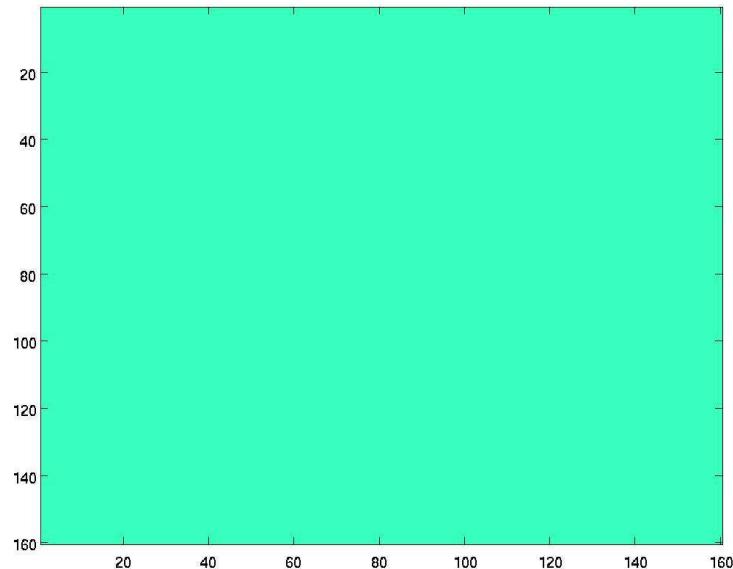


Simultaneous activity in the Core and Matrix elements of a 160x160 array of cortical 'columns.'

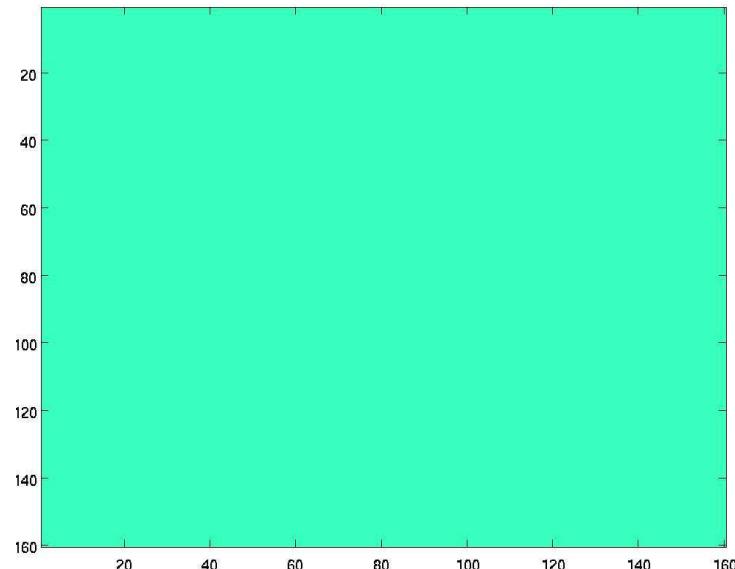


Large-scale spindle activity

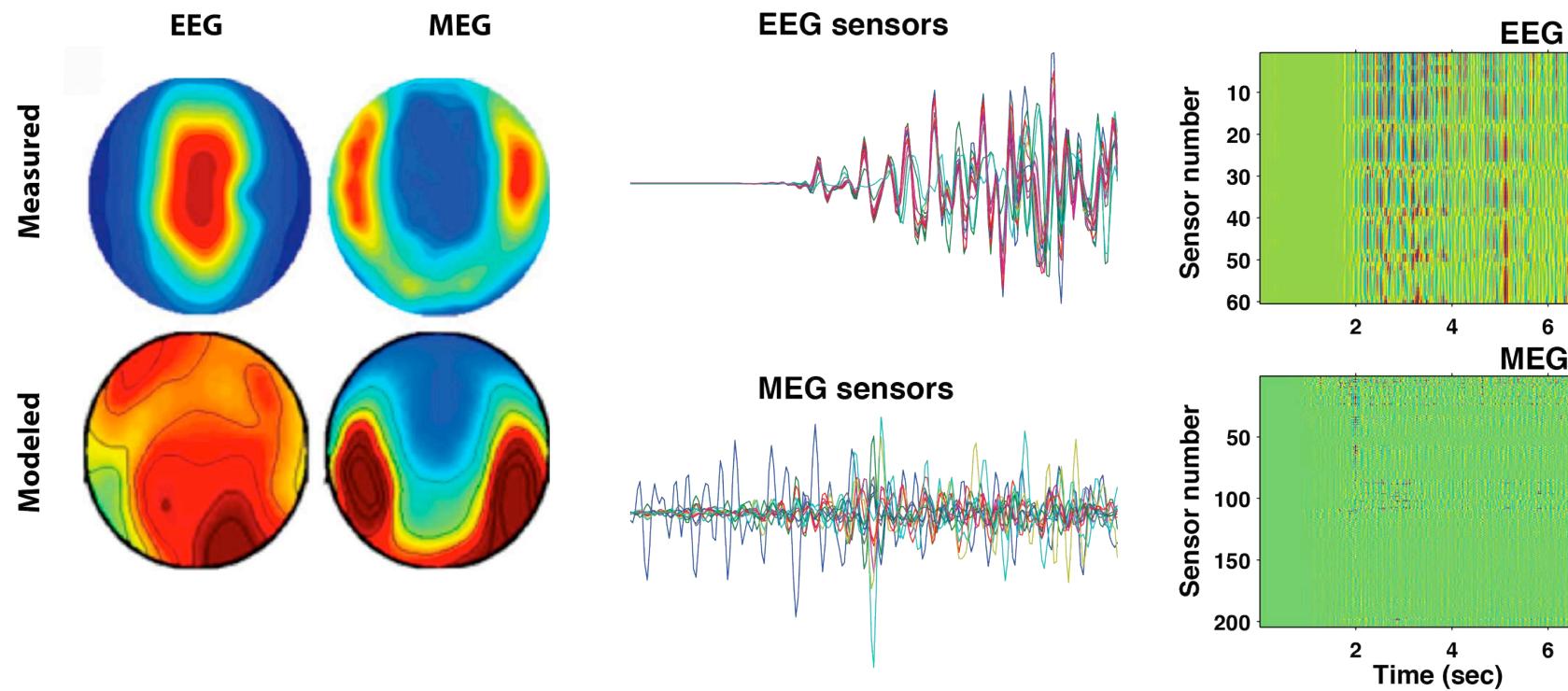
CORE



MATRIX

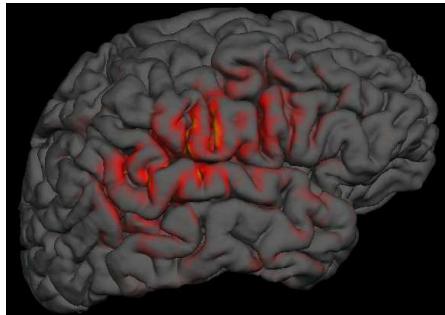


Simulated MEG and EEG from spindles generated by the large-scale thalamocortical model

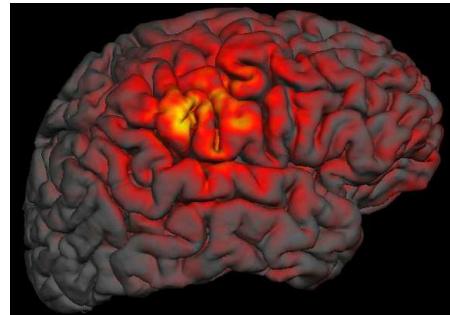


Concluding Speculations

lead fields



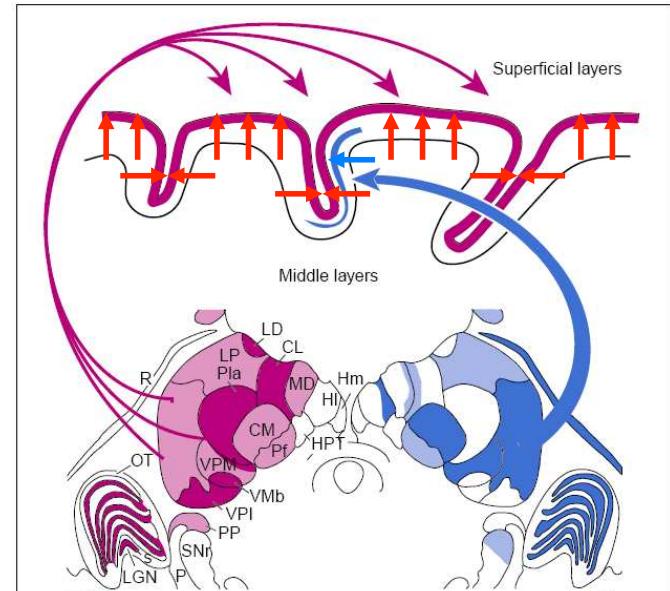
gradiometers



referential EEG

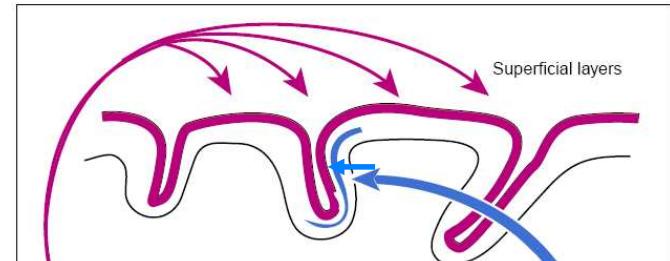
- Brain anatomy and the biophysics of the forward solution result in EEG being biased to record spindle components generated by the matrix thalamocortical system, and MEG to record spindle components generated by the core thalamocortical system
- Asynchronous activation of various core thalamocortical domains may be visible in the varying location, frequency and synchrony of the MEG spindles
- Recruitment of thalamocortical domains into synchronized discharge may be visible in EEG spindles

Dipoles of core and matrix

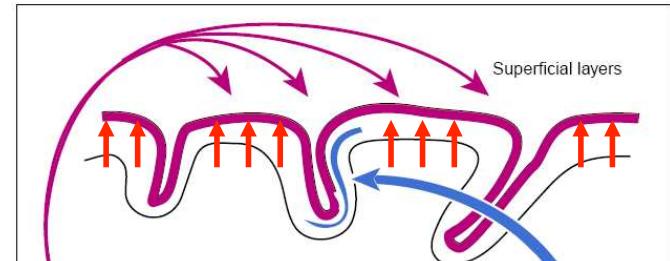


Jones, TINS 24:595-601 2001

What MEG will see



What EEG will see



Acknowledgments

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- Gregory Filatov
- Steven Skorheim
- Giri Prashanth
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- Martina Mikail

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- Terry Sejnowski (Salk Institute)
- Alain Destexhe (UNIC, CNRS)
- Sydney Cash (Harvard)
- Eric Halgren (UCSD)

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- Samat Moldakarimov
- Maxime Bonjean
- Tanya Baker

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