Reduced Thalamocortical Connectivity as a Mechanism for Abnormal Sleep Spindles

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Introduction

- **Schizophrenia**: brain disorder with symptoms such as psychosis, impaired memory, and disrupted sleep
- **Sleep spindles**: brain wave patterns that occur during stage 2 of non-rapid eye movement (NREM) sleep
  - Important for sleep maintenance, memory consolidation, and brain plasticity
- Schizophrenic patients often have abnormal spindles; however, **it is unknown what exactly causes these abnormalities**[1]
- Sleep spindles are thought to arise from interactions between inhibitory reticular (IRE) cells in the thalamic reticular nucleus (TRN) and thalamocortical (TC) cells[2]
- **Our goal** is to investigate how connectivity between IRE and TC cells affects sleep spindle activity

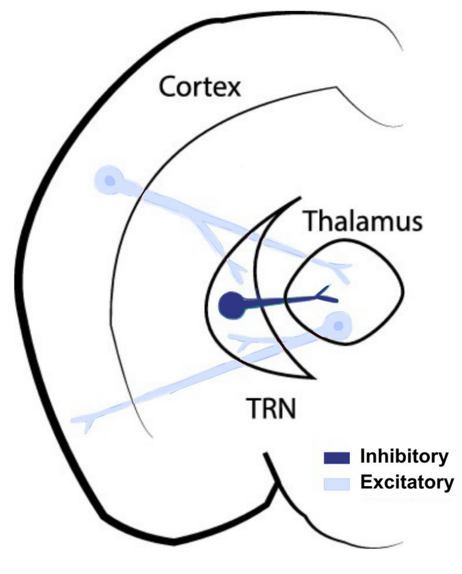
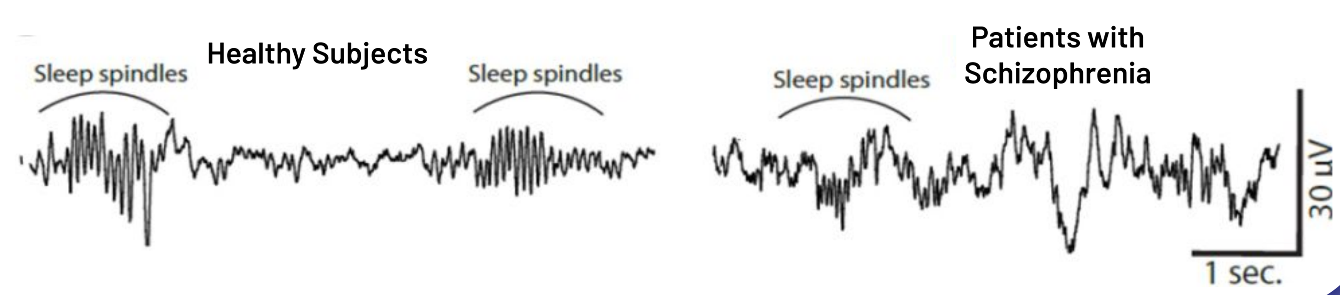


Figure 1. Diagram of thalamocortical loop[3]

Figure 2. Sleep spindles in healthy subjects vs. schizophrenic patients[4]



Methods

Model A: Adapted model of awake macaque auditory thalamocortical circuit[5]

- 721 thalamic neurons (TC, IRE, interneurons), ran at 10% cell density
  - Populations are divided into core and matrix subsets (matrix propagates activity more)
- Local field potential (LFP) recorded deep in the cortex to show pronounced effects downstream
- Stimulated all IRE cells at 8 Hz for the first second to produce clean spindles (stimulation is not necessary)
- Tuned parameters of IRE and TC interactions to produce natural spindles

Model B: Adapted model of thalamocortical dynamics during sleep[6]

- Applied stimulation at 8 Hz to IRE cells to replicate sleep spindles in stage 2 sleep
- Reduced conductance between IRE and TC cells to reflect decreased connectivity
- Recorded LFP from cortical cells
- Determined peak power of each spindle & compared average power for each trial relative to 100% connectivity using a 2-sample t-test

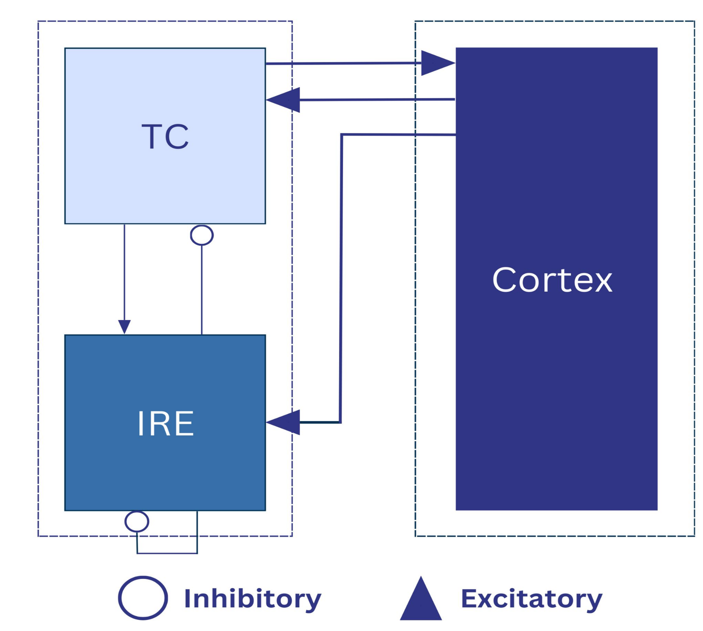


Figure 3. Schematic diagram of connections in Model A and Model B

Significant parameters:

- Maximum conductance and voltage dependence offset of T-type calcium channels in TC cells
- Synaptic strengths (specifically uPSP) between all IRE cells and core TC cells

Connectivity Level	IRE to TC GABA-A Connection Conductivity (µS)	IRE to TC GABA-B Connection Conductivity (µS)
100%	0.050	0.0020
90%	0.045	0.0018
80%	0.040	0.0016
70%	0.035	0.0014
60%	0.030	0.0012
50%	0.025	0.0010
40%	0.020	0.0008
30%	0.015	0.0006
20%	0.010	0.0004
10%	0.005	0.0002
0%	0	0

Figure 4. Connectivity values tested on Model B

Results

Model A

Spindle Parameters

Trial	Gmax	Shift	IRE-TC	IREM-TC	TC-IRE	TC-IREM
Original	0.002	3	0.83	0.83	0.2	0.23
Adjusted	0.012	-3	3.0	3.0	3.0	3.0

Figure 5. Parameter changes to create sleep spindles
Gmax: maximum conductance, shift: voltage dependence offset, cells-cells: synaptic strength between said cells

Spindle Waveform

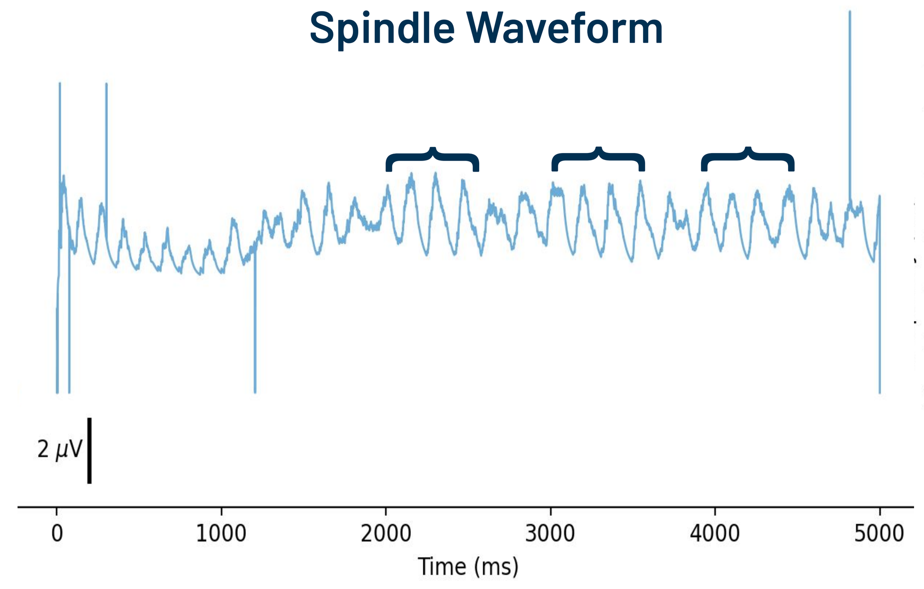


Figure 6. LFP time series with spindles bracketed, lasting close to between 0.5 and 1 s

Spindle Frequency

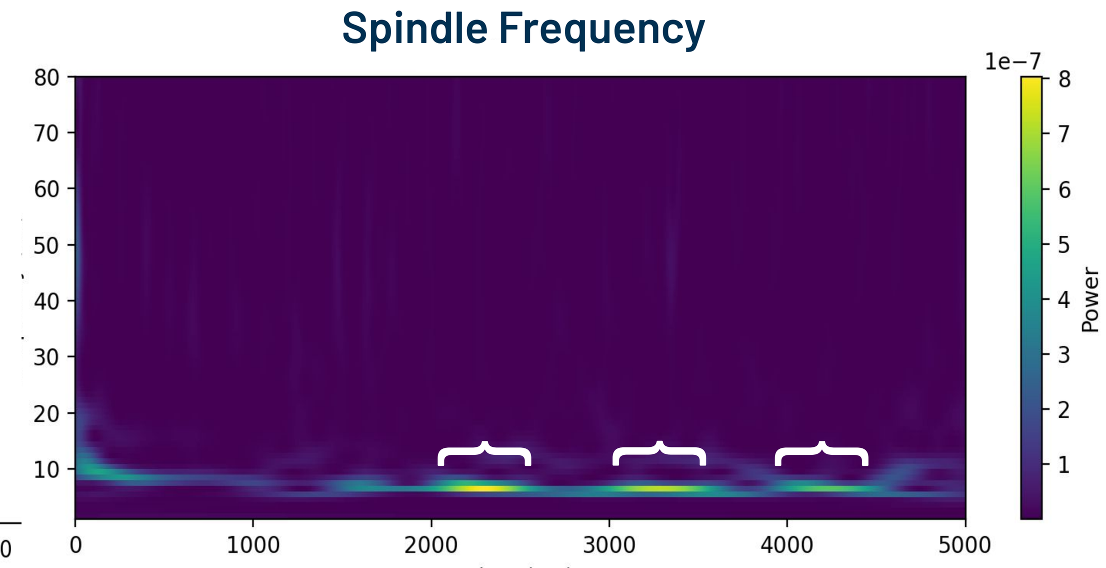


Figure 7. LFP spectrogram computed using Morlet wavelet transform. PSD graph not shown displays a peak at 6 Hz.

Thalamocortical Activity

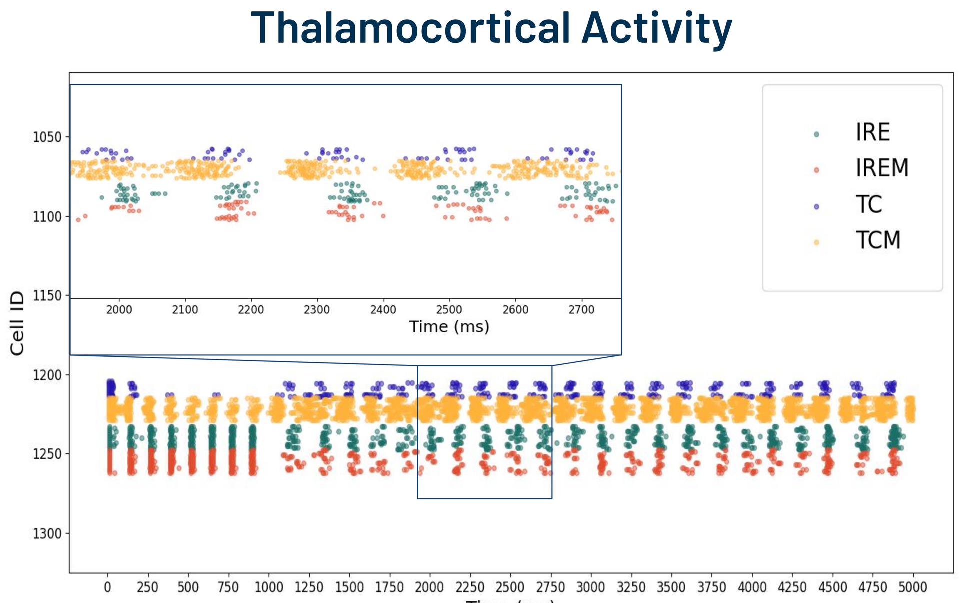


Figure 8. Raster plot depicting IRE and TC spikes across full simulation

Thalamocortical Timekeeper

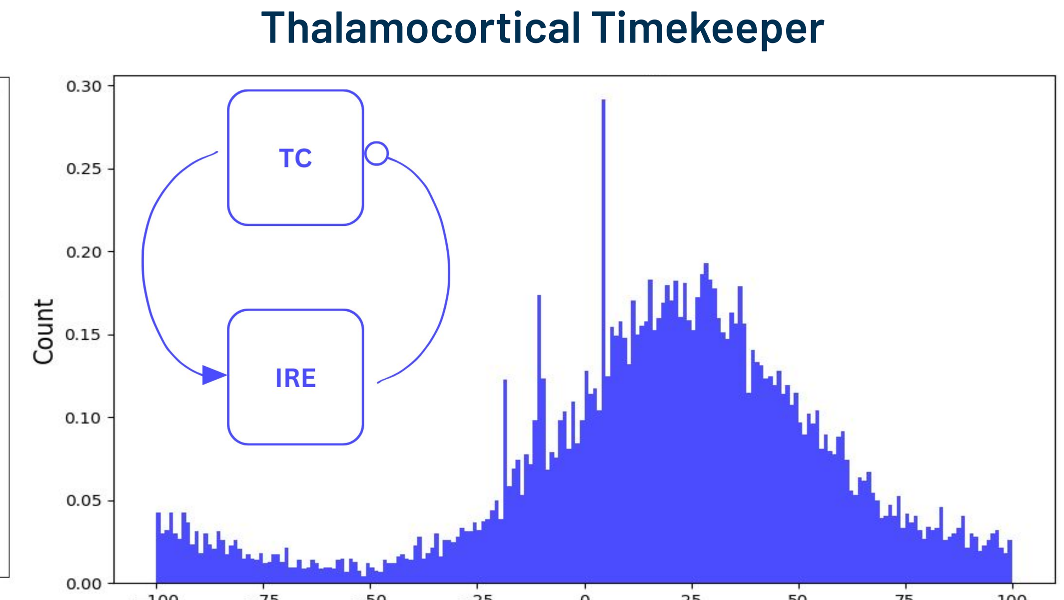


Figure 9. Cross-correlogram computed between TC and IRE cells with TC cells as the reference. Peaks occur at approximately -100 ms and 25 ms.

Model B

Normal Spindles

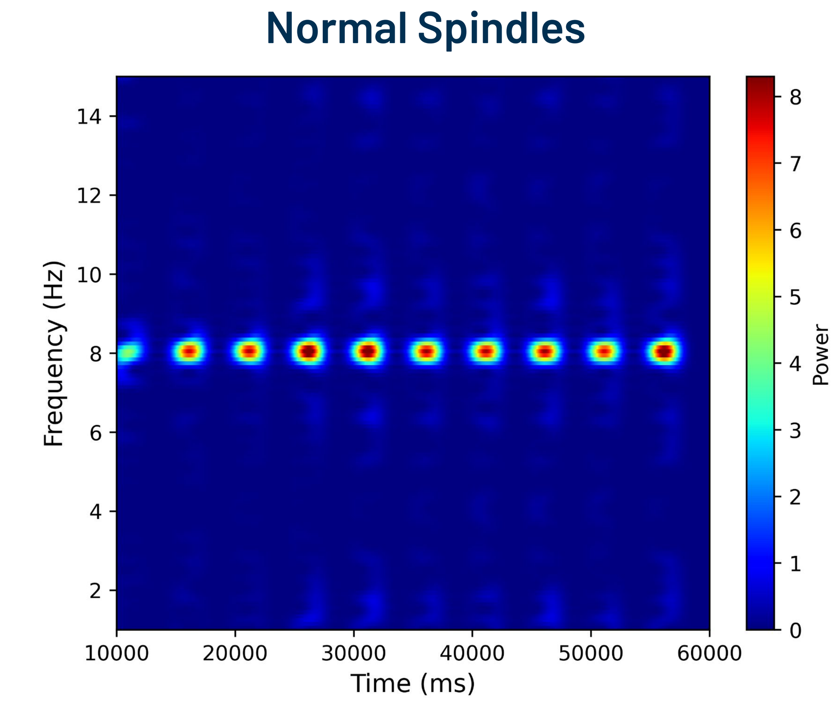


Figure 10. LFP spectrogram computed using Morlet wavelet transform. 100% connection strength between IRE and TC cells.

Abnormal Spindles

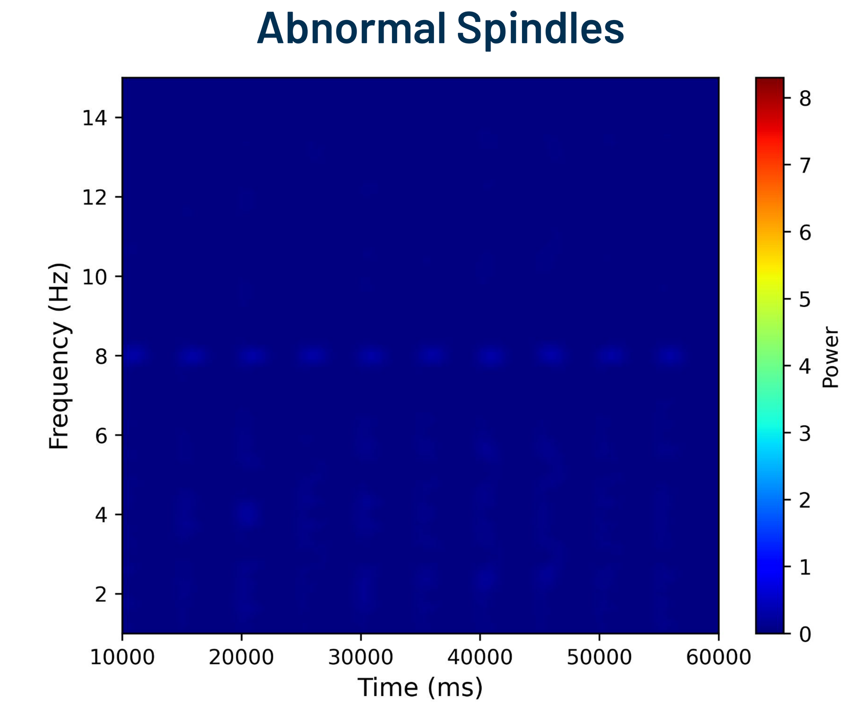


Figure 11. LFP spectrogram computed using Morlet wavelet transform. 50% connection strength between IRE and TC cells.

Reducing Connectivity

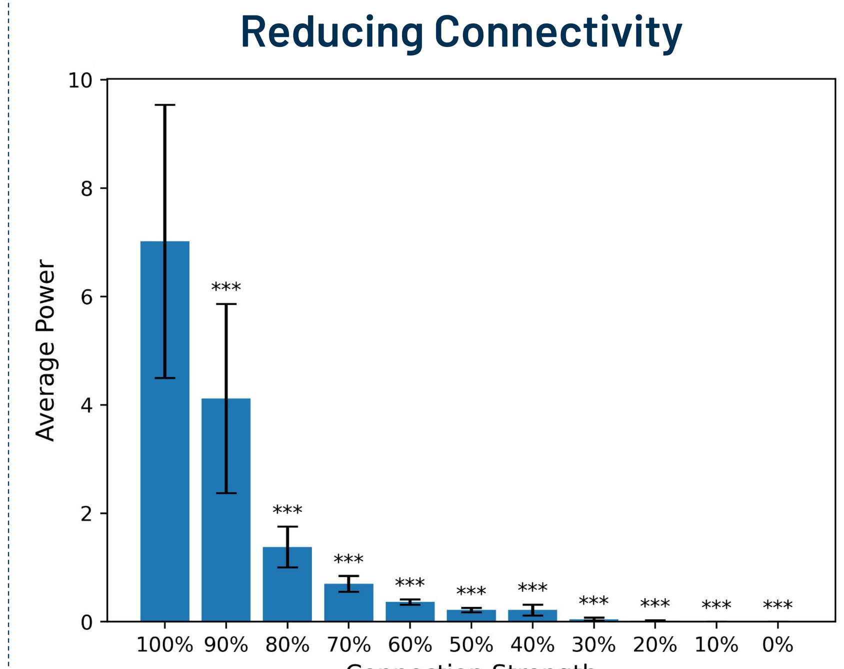


Figure 12. Average power of sleep spindles for different connection strengths between IRE and TC cells. Error bars show ± 2 SDs from mean. (***p < 0.001)

Spindle Power Isolation

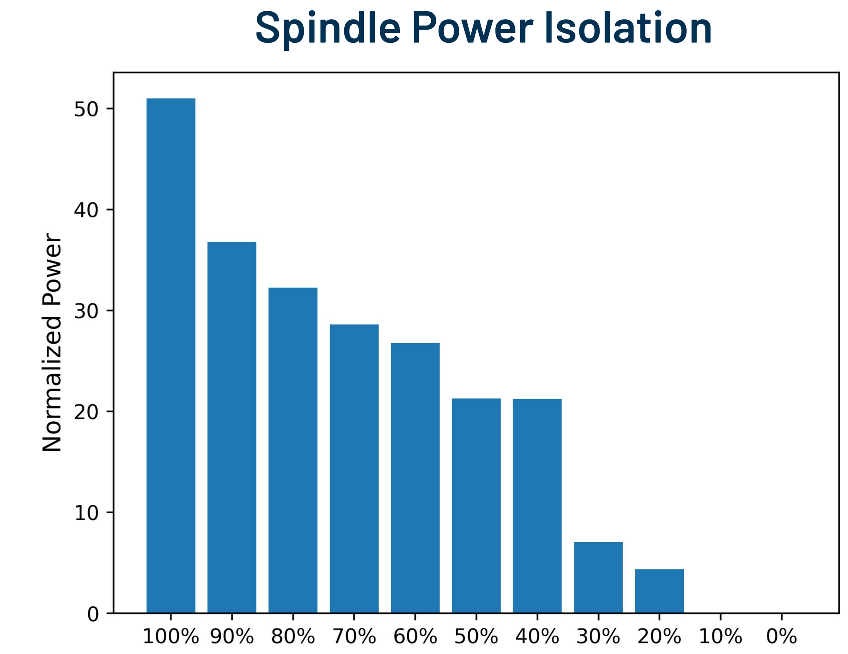


Figure 13. Normalized power of sleep spindles for different connection strengths between IRE and TC cells. Normalized power was determined by spindle power divided by total spectral power.

Discussion

Conclusions:

- **Model A** demonstrates that strong connectivity between IRE and TC cells and sensitivity of TC cells to hyperpolarizing current produces an excitatory-inhibitory loop that then generates spindles
- Interactions between IRE and TC cells form **the mechanism behind sleep spindles**
- Spindle results: duration falls within the 0.5-2 s range[7] and frequency is close to the 8-15 Hz range[7] but could be tuned further, time lag peaks deviate at most 10 ms from experimental data[8]
- **Model B** demonstrates that reduced connectivity between the TRN and thalamocortical neurons significantly reduces sleep spindle power, resulting in **abnormal sleep spindles**
  - Normalized spindle power decreased as connection strength decreased, suggesting that spindle power was more affected by reducing connectivity than other frequency bands
- Outcomes implicate abnormal sleep spindles as **biomarkers for neurological disorders** marked by reduced TRN connectivity, such as schizophrenia, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD)

Limitations:

- Model A generated sleep spindles without converting the macaque's awake state to an asleep state, which may have neglected sleep's influence on oscillations
- Maximum frequency at which Model B shows sleep spindles: 8 Hz

Future Directions:

- How do parameters other than connection strength, such as GABA concentration, affect the power of sleep spindles? What dictates the duration, frequency, and interval between sleep spindles? How do sleep spindles change as a function of state (e.g. background frequencies)?
- Further tuning of Model A to achieve more characteristics of sleep spindles

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