eNeuro

Research Article: New Research | Novel Tools and Methods

SIGNAL PROPAGATION VIA OPEN-LOOP INTRATHALAMIC ARCHITECTURES: A COMPUTATIONAL MODEL

https://doi.org/10.1523/ENEURO.0441-19.2020

Cite as: eNeuro 2020; 10.1523/ENEURO.0441-19.2020

Received: 25 October 2019
Revised: 13 January 2020
Accepted: 20 January 2020

SIGNAL PROPAGATION VIA OPEN-LOOP INTRATHALAMIC ARCHITECTURES: A COMPUTATIONAL MODEL

Abbreviated Title: Signaling via open-loop thalamic architectures

Jeffrey W. Brown[1], Aynaz Taheri[2], Robert V. Kenyon[2], Tanya Berger-Wolf[2], and Daniel A. Llano[1,3,4,5,*]

1. College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA
2. Department of Computer Science, University of Illinois at Chicago, Chicago, IL 60607, USA
3. Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA
4. Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA
5. Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

*Corresponding Author:
Daniel A. Llano, M.D., Ph.D.
2355 Beckman Institute
405 North Mathews Avenue
Urbana, IL 61801
d-llano@illinois.edu

Number of Figures: 4
Number of Tables: 4
Number of Words for Abstract: 223
Number of Words for Introduction: 629
Number of Words for Discussion: 2,402

Acknowledgments: We acknowledge funding through the National Science Foundation (1515587 to D.A.L., R.V.K., and T.B.-W.). We thank Profs. Thomas Anastasio, Ruoqing Zhu, and Rama Ratnam, Drs. Kush Paul and Baher Ibrahim, and Mr. Weddie Jackson for their valuable analytical, statistical, and technical insights. We also extend our gratitude to former Regional Dean M. Michele Mariscalco of the University of Illinois College of Medicine for enabling the collaboration between J.W.B. and D.A.L. This work made use of the Illinois Campus Cluster, a computing resource that is operated by the Illinois Campus Cluster Program (ICCP) in conjunction with the National Center for Supercomputing Applications (NCSA) and which is supported by funds from the University of Illinois at Urbana-Champaign. J.W.B.'s current affiliation is with the Center for Brain Function and Repair, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064, USA.

Conflict of Interest Statement: The authors declare no competing financial interests.

Funding Sources: National Science Foundation 1515587 (D.A.L., R.V.K., T.B.-W.)

Abstract:

Propagation of signals across the cerebral cortex is a core component of many cognitive processes and is generally thought to be mediated by direct intracortical connectivity. The thalamus, by contrast, is considered to be devoid of internal connections and organized as a collection of parallel inputs to the cortex. Here, we provide evidence that "open-loop" intrathalamic pathways involving the thalamic reticular nucleus (TRN) can support propagation of oscillatory activity across the cortex. Recent studies support the existence of open-loop thalamo-reticulo-thalamic (TC-TRN-TC) synaptic motifs in addition to traditional closed-loop architectures. We hypothesized that open-loop structural modules, when connected in series, might underlie thalamic and, therefore cortical, signal propagation. Using a supercomputing platform to simulate thousands of permutations of a thalamocortical network based on physiological data collected in mice, rats, ferrets, and cats and in which select synapses were allowed to vary both by class and individually, we evaluated the relative capacities of closed- and open-loop TC-TRN-TC synaptic configurations to support both propagation and oscillation. We observed that 1) signal propagation was best supported in networks possessing strong open-loop TC-TRN-TC connectivity; 2) intrareticular synapses were neither primary substrates of propagation nor oscillation; and 3) heterogeneous synaptic networks supported more robust propagation of oscillation than their homogeneous counterparts. These findings suggest that open-loop, heterogeneous intrathalamic architectures might complement direct intracortical connectivity to facilitate cortical signal propagation.

Significance Statement:

Interactions between the dorsal thalamus and thalamic reticular nucleus (TRN) are speculated to contribute to phenomena such as arousal, attention, sleep, and seizures. Despite the importance of the TRN, the synaptic microarchitectures forming the basis for dorsal thalamus-TRN interactions are not fully understood. The computational neural model we present incorporates "open-loop" thalamo-reticular-thalamic (TC-TRN-TC) synaptic motifs, which have been experimentally observed. We elucidate how open-loop motifs possess the capacity to shape the propagative properties of signals intrinsic to the

thalamus and evaluate the wave dynamics they support relative to closed-loop TC-TRN-TC pathways and intrareticular synaptic connections. Our model also generates predictions regarding how different spatial distributions of reticulothalamic and intrareticular synapses affect these signaling properties.

Introduction:

Propagation of activity across the cerebral cortex is thought to underlie multiple cognitive processes, as well as pathological processes such as epilepsy and migraine (Leao, 1944; Muller et al., 2014, 2016; Kokkinos et al., 2017). Cortical regions are highly interconnected via direct axonal projections as well as via polysynaptic pathways involving the basal ganglia and thalamus (Parent and Hazrati, 1995; Theyel et al., 2010). Cortical signal propagation is generally thought to be mediated via direct cortical connections (Felleman and Van Essen, 1991; Kötter and Sommer, 2000), but recent evidence suggests that the thalamus serves as a control point to modify cortical activity during cognitive processes such as attentional shifting (Wimmer et al., 2015). An advantage of a thalamic mode of signal propagation is the efficiency by which modulatory influences may control thalamic, and therefore cortical, propagation. The thalamus, however, is generally thought to have limited internal connectivity and therefore limited capacity to serve as a substrate for signal propagation.

A major intermediary allowing for communication between thalamocortical neurons, the thalamic reticular nucleus (TRN), is a sheet of GABAergic neurons that partially envelops the dorsal thalamus (Pinault, 2004). It has been speculated to participate in phenomena ranging from selective attention (Crick, 1984; Guillery et al., 1998; McAlonan et al., 2006) to sleep and arousal (Llinás and Paré, 1991, Steriade et al., 1993; Guillery et al., 1998; McAlonan et al., 2006) and fear responses (Dong et al., 2019), and may play a role in generating absence seizures (von Krosigk et al., 1993; Bal et al., 1995; Destexhe et al., 1996a; Huguenard, 1998; McCormick and Contreras, 2001), symptoms of neurodevelopmental disorders (Wells et al., 2016; Krol et al., 2018), and schizophrenia (Ferrarelli and Tononi, 2011). The

92 TRN projects exclusively to TC neurons, while receiving reciprocal, glutamatergic thalamoreticular (TC-
93 TRN) connections (Sherman and Guillery, 2001).
94
95 The structural microarchitecture of bidirectional pathways connecting the dorsal thalamus and TRN has
96 been the subject of ongoing debate. It was originally assumed that thalamo-reticulo-thalamic (TC-TRN-
97 TC) pathways were reciprocal, forming "closed loops" of recurrent inhibition delivered to TC neurons
98 (Figure 1A, left) (Hale et al., 1982; Steriade et al., 1993; Warren et al., 1994; Sherman and Guillery,
99 1996; Pinault, 2004). While closed disynaptic loops have indeed been confirmed, they were only
100 identified in a minority of examined TC-TRN pairs (Shosaku, 1986; Lo and Sherman, 1994; Pinault and
101 Deschênes, 1998; FitzGibbon et al., 2000; Gentet and Ulrich, 2003; Pinault, 2004). Another connectional
102 scheme between the dorsal thalamus and TRN is the so-called "open-loop" TC-TRN-TC pathway,
103 wherein a TC neuron is not reciprocally inhibited by the TRN neuron it excites (Figure 1A, right). Open-
104 loop configurations have been inferred from recordings in rodent thalamic slice preparations (Crabtree et
105 al., 1998; Crabtree and Isaac, 2002; Lam and Sherman, 2005, 2015; Lee et al., 2010) and confirmed in
106 anatomical studies (Pinault and Deschênes, 1998; Kimura et al., 2007; Kimura, 2014). Furthermore, open-
107 loop pathway variants in the form of X-TRN-TC are also known to exist, with X representing indirect
108 sources of modulation to the sensory thalamus via the TRN, including monoaminergic and cholinergic
109 brainstem nuclei, GABAergic nuclei of the basal forebrain, the amygdala, and prefrontal cortex (Morrison
110 and Foote, 1986; Hallanger et al., 1987; Asanuma and Porter, 1990; Bickford et al., 1994; Zikopoulos and
111 Barbas, 2006; Sun et al., 2013; Pita-Almenar et al., 2014; Wimmer et al., 2015).
112
113 Based on previous studies of open-loop TC-TRN-TC synaptic organization, we hypothesized that open-
114 loop synaptic modules might underlie intrathalamic and therefore intracortical signal propagation.
115 Accordingly, we systematically examined thousands of permutations of a novel network model
116 comprising thalamic, reticular, and thalamorecipient, layer-4 cortical (Co) neurons to evaluate the
117 efficacy of known thalamic synaptic motifs (open-loop pathways, closed-loop pathways, and chemical

and electrical intrareticular synapses), in isolation and in combination, in mediating signal transmission across the thalamus and cortex.

Materials and Methods:

Network architecture and simulations

We constructed a baseline model network based on Willis et al. (2015) by connecting in series three thalamocortical pathways, each consisting of a TC, TRN, and layer-4 Co neuron (for a 3-by-3 neuron network); the physiological data utilized in our model were collected in mice, rats, ferrets, and cats of both sexes. Permutations of the baseline network potentially featured both closed- and/or open-loop TC-TRN-TC motifs, with the latter constituting one mode of connectivity between parallel thalamocortical pathways. Intrareticular synapses represented the other connections between pathways, based on the identification of both GABAergic (Ahlsén and Lindström, 1982; Steriade et al., 1990; Cox et al., 1996; Sanchez-Vives et al., 1997; Shu and McCormick, 2002; Deleuze and Huguenard, 2006; Lam et al., 2006) and electrical synapses (Landisman et al., 2002; Fuentealba et al., 2004; Long et al., 2004; Deleuze and Huguenard, 2006; Lam et al., 2006) between TRN neurons. Thus, we included three different polysynaptic configurations between thalamocortical pathways in our network (Figure 1B, from left to right): 1) those with a GABAergic intrareticular synapse (TRN-TRN_{GABA}); 2) those with an electrical intrareticular synapse (TRN-TRN_{Elec}); and 3) open-loop TC-TRN-TC pathways. Thalamic, reticular, and cortical cell layers were aligned topographically, such that TC_1 projected to both TRN_1 and Co_1 (Jones, 1975; Steriade et al., 1993; Destexhe et al., 1998; Sohal et al., 2000; Sherman and Guillery, 2001). The divergence of thalamic and reticular synapses in the model was constrained to accommodate open-loop TC-TRN-TC architectures, which depend on a lack of recurrent feedback to the downstream TC neuron, in a subset of the simulated network variants: to this end, every TC neuron projected to exactly one TRN neuron, while single TRN neurons could project to either one TC neuron (whether recurrently or laterally), as in the case of entirely closed- or open-looped TC-TRN-TC motifs, or two TC neurons (one

143 recurrently and one laterally), if participating in a pathway expressing some intermediate degree of
144 openness (Figure 1C).
145
146 To analyze how each variety of inter-pathway connection contributed to network dynamics, permutations
147 of the baseline network were generated by varying three synaptic properties associated with each of the
148 inter-pathway synaptic motifs; moreover, these parameters were either varied in a homogeneous or
149 heterogeneous manner. In the case of homogeneously varied synaptic network permutations, the synaptic
150 parameters associated with three inter-pathway motifs varied uniformly as a class, with all external, TC-
151 TRN, and thalamocortical (TC-Co) synaptic conductances held constant: 1) TRN-TRN_{GABA} synapses
152 ranged in conductance between 0 and 450 nS; 2) TRN-TRN_{Elec} synapses ranged in coupling coefficient
153 between 0 and 0.36; and 3) a TC-TRN-TC "openness" coefficient, defined as the weight distribution of
154 lateral vs. recurrent reticulothalamic (TRN-TC) connectivity, varied between 0 (completely closed-loop)
155 and 1.0 (completely open-loop) and with a baseline TRN-TC conductance of 80 nS. Thus, for a network
156 variant possessing an openness coefficient of 0.4 (i.e., exhibiting slightly more closed- than open-loop
157 TC-TRN-TC connectivity), the laterally inhibitory TRN-TC synapses in the network, $TRN_1 \rightarrow TC_2$ and
158 $TRN_2 \rightarrow TC_3$, would carry a conductance of 32 nS (0.4*80 nS), while the recurrent TRN-TC synapses,
159 $TRN_1 \rightarrow TC_1$, $TRN_2 \rightarrow TC_2$, and $TRN_3 \rightarrow TC_3$, would exhibit a conductance of 48 nS (0.6*80 nS). For the
160 heterogeneously varied synaptic network variants, all TRN-TRN and TRN-TC synapses were allowed to
161 vary independently. Domains for each of the synaptic variables were selected to include the range of
162 conductance or coupling strengths reported in physiological measurements and/or used in similar neural
163 models (Destexhe et al., 1996a, 1998; Sohal and Huguenard, 1998; Sohal et al., 2000; Landisman et al.,
164 2002; Long et al., 2004; Traub et al., 2005).
165
166 Ongoing afferent synaptic input was delivered to every TC neuron in the model as Poisson-modulated
167 spike trains centered at 40 Hz. An additional 200-Hz pulse train was applied to neuron TC_1 between
168 t=0.400 and t=1.500 s during every network simulation run. This high-frequency stimulus was modeled

on those used to elicit spindle-like waves in a ferret thalamoreticular slice preparation (Bal et al., 1995; Kim et al., 1995). A given network's output was compiled by assembling spike histograms (10-ms bins) averaging 1,000 simulations for every cortical neuron (Figure 1D). We quantified network dynamics as a function of variable TC-TRN-TC and intrareticular synaptic architectures by defining and measuring two properties inherent to stimulus-evoked responses in each network variant: propagation and oscillation, with the latter included in light of the fact that many characterized thalamic waveforms both oscillate and propagate through the thalamus and cortex (Sherman and Guillery, 2001). Network properties were quantified in the most downstream element of the cortical output layer, Co_3. Propagation across a network was quantified as the amplitude of the initial stimulus-evoked response in the detrended Co_3 histogram. The degree of oscillation supported by each network permutation was defined as the amplitude of the first off-center peak in the normalized autocorrelogram of post-stimulation activity (Figure 1D). Both propagation and oscillation scores are reported as normalized to the maximum scores tabulated for each property. Given the high prevalence of propagating oscillatory waves in the cerebral cortex (reviewed in Muller et al., 2018), we furthermore defined a composite "optimization" (*Op*) metric to measure the capacity of networks to simultaneously support and balance between propagation (*Pr*) and oscillation (*Os*):

$$Op = \sqrt{Pr^2 + Os^2} - |Pr - Os| \quad (1)$$

Intrinsic neuronal models

Single-compartment TC, TRN, and cortical model neurons obeyed Hodgkin-Huxley kinetics, with membrane potentials *V* varying according to the first-order differential equation

$$C\frac{dV}{dt} = -g_L(V - E_L) - \sum_i g_i(V)(V - E_i) \quad (2)$$

where *C* is the membrane capacitance, g_L and E_L are the leakage conductance and reversal potential, respectively, and $g_i(V)$ and E_i are the dynamic conductance and reversal potential, respectively, of the *i*th voltage-gated, ligand-gated (chemical synaptic), or electrical synaptic conductance (for electrical synaptic

conductances, the effective reversal potential is equal to the presynaptic membrane potential; see Equation 3a). All three varieties of model neurons expressed both the standard transient sodium (I_{Na}) and delayed-rectifier potassium (I_K) currents. TC and TRN neurons additionally included a T-type calcium conductance (T-current; I_T) and hyperpolarization-activated cation current (H-current; I_H), following the TC model of Deleuze et al. (2012). Both TRN and layer-4 Co cells expressed a slow, non-inactivating potassium conductance (I_M), following the modeling of Popischil et al. (2008), which accounts for the spike-frequency adaptation previously reported in physiological recordings from these neurons (Yamada et al., 1989; Willis et al., 2015). A list of intrinsic model cell parameters, including current conductances, reversal potentials, selected gating kinetics, and membrane capacitance, can be found in Table 1.

Synaptic models

The kinetics of chemical synapses in our model network conformed to the synaptic depression model of Tdosdyks and Markram (1997). This model presupposes a finite quantity of "resources," akin to synaptic vesicles, capable of being released by the presynaptic neuron; these resources can exist in an active, inactive, or recovered state. A parameter U_{SE} characterizes the fraction of recovered resources that can be converted to an active state (i.e., for release by the presynaptic neuron) following action potential induction in the presynaptic axon terminal(s). Following resource activation, synapses inactivate according to the time constant τ_{inact}; resources become available again for activation after a recovery period described by the time constant τ_{recov}. These parameters, along with the neurotransmitters, postsynaptic conductances, and reversal potentials characterizing all of the chemical synapses in our model, are given in Table 2.

Glutamatergic TC-TRN and TC-Co and baseline GABAergic TRN-TC synaptic parameters matched those of Willis et al. (2015), with the latter synapses allowed to vary in conductance as described above. TRN-TC signaling was mediated exclusively through $GABA_A$ receptors, mirroring other thalamic and thalamocortical models in which the slower TRN-TC $GABA_B$ conductance was omitted (Traub et al.,

2005; Rogala et al., 2013; Pham and Haas, 2018). Although evidence has been presented challenging the existence of GABAergic intrareticular synapses in certain mammalian species and age groups (Pinault et al., 1997; Landisman et al., 2002; Pinault, 2004; Cruikshank et al., 2010; Hou et al., 2016), our model avoided making assumptions regarding their presence, strength, or spatial distribution by allowing the associated synaptic conductances to vary over a range of physiological values, including zero, and in distribution. The reversal potential, conductance, and kinetics of the external synapses projecting to the TC neurons were directly based on retinogeniculate synapses (Chen and Regehr, 2003), although the generic nature of the external inputs in our model allows them to represent not only immediately upstream sensory input but also brainstem modulation (e.g., serotonergic, adrenergic) known to act on thalamic nuclei (Siegel and Sapru, 2015).

Electrical synapses between TRN neurons were based on the Cx36-dependent intrareticular gap junctions first identified by Landisman et al. (2002). For TRN neurons, the sum of electrical synaptic currents (I_{Elec}) entering any postsynaptic neuron *j* from presynaptic neuron(s) *i* was included in the rightmost term from Equation 2 and calculated as

$$I_{Elec(j)} = \sum_i g_{ij}\left(V_j - V_i\right) \quad (3a)$$

where g_{ij}, the gap junction conductance, was itself calculated as

$$g_{ij} = D(x)\frac{g_j}{1/_{CC} - 1} \quad (3b)$$

where *CC* was the electrical coupling coefficient between TRN neurons *i* and *j*, g_j was the membrane conductance of the postsynaptic neuron, and *D(x)* was a scaling factor that depended on the physical distance between the coupled TRN neurons (Dayan and Abbott, 2005; Shimizu and Stopfer, 2013). Although the individual gap junctions comprising TRN-TRN_{Elec} synapses used in the model were not explicitly coded for, differences in TRN-TRN coupling between different electrical synapses and network permutations implicitly reflected differing gap junction densities, following Traub et al. (2005). TRN-TRN_{Elec} synapses were symmetrical (non-rectifying), such that g_{ij}=g_{ji}.

We extrapolated the attenuation of intrareticular synaptic strength as a function of intracellular distance based on mappings of intrinsic connections within the TRN along a horizontal (anteroposterior) plane assembled by Deleuze and Huguenard (2006). Assuming 1) an intracellular distance of 50 µm between adjacent TRN neurons, 2) a distance *x* (in multiples of 50 µm) between non-adjacent neurons, and 3) a Gaussian falloff in synaptic strength (Sohal et al., 2000), the baseline (adjacent-neuron) conductances of TRN-TRN$_{GABA}$ and TRN-TRN$_{Elec}$ synapses were scaled for non-adjacent synapses using the function

$$D(x) = e^{-\frac{x^2}{2\lambda^2}} \quad (4)$$

where λ_{GABA}=531 µm and λ_{Elec}=130 µm.

Given the small spatial scale of our model, synaptic delays associated with finite axonal conductance times within the TRN and between the TRN and dorsal thalamus were disregarded, mirroring the simplification incorporated into previous thalamic and thalamocortical models simulating synaptic interactions on the order of 100 microns (Golomb et al., 1996; Traub et al., 2005). Although small (~1 ms) thalamocortical delays were inserted into the network model of Traub et al. (2005), these were likewise omitted on the basis of the cortex functioning solely as an output layer in our model.

Quantification and statistical analysis

Our model was coded, simulated, and analyzed in MATLAB R2018b (MathWorks, Natick, MA), utilizing both a Dell Inspiron 3847 and Hewlett-Packard Z840 running Windows 10 and nodes on the Illinois Campus Cluster (National Center for Supercomputing Applications, University of Illinois at Urbana-Champaign). Simulations, of which there were 1,000 for every network permutation, employed 0.1-ms time steps, with temporal integration based on the hybrid analytic-numeral integration method of Moore and Ramon (1974), which optimizes between accurate solutions to Hodgkin-Huxley and synaptic models and computational efficiency. All simulations commenced with a 200-ms equilibration period,

during which no external stimulation was delivered to TC neurons; this allowed all network elements to attain steady-state conditions. The number of homogeneously and heterogeneously varied synaptic network variants generated were 770 and 12,681, respectively.

Statistical analysis was performed in both MATLAB and R (R Core Team, 2013), with the *glmnet* package (Friedman et al., 2010) utilized within the latter platform to perform regression analyses. Multiple linear regression was employed to establish rudimentary relationships between synaptic classes (homogeneously synaptic networks) or individual synapses (heterogeneously synaptic networks) and each of the two studied network properties, even in instances where these relationships deviated from linearity. Second-order polynomial (2°) regression models with interaction terms elucidated how synaptic interactions and nonlinearities affected these network properties. Regressions were optimized using elastic net regularization, with the specific regularization hyperparameter α selected to minimize each regression model's root-mean-square error. To convey the relative influence of different synaptic classes or individual synapses on dynamic network properties, all regression coefficients are reported here as normalized to the coefficient with the largest absolute value; the effects corresponding to NRCs with absolute values of less than 0.05 were disregarded as negligibly influential on network dynamics. Both unpaired Student *t*-tests and one-way analysis of variance (ANOVA) models were used to compare the mean property scores between different sets of networks, with Tukey's honestly significant difference tests used to ascertain pairwise difference between groups in the latter; standard errors of the mean were used a measure of variance, and null hypotheses were rejected at probability values (*p* values) below 0.05. Kolmogorov-Smirnov and Levene's tests were employed to confirm normality and homogeneity of variance, respectively, when utilizing parametric mean-comparison tests; data were transformed as needed to conform to these prerequisites.

Code accessibility

The code/software described in the paper is freely available online at https://github.com/JeffreyWBrown/Open-loop-TC-TRN-TC. The code is available as Extended Data.

Results:

Propagation and oscillation in homogeneously varied synaptic models

Stimulus-evoked responses propagated linearly across the length of homogeneous synaptic networks, occurring at average fixed intervals of 93.31 ± 0.35 ms (mean ± standard error of the mean; range, 60-110 ms) between adjacent thalamocortical pathways, across all model permutations and with a mean velocity of 0.54 mm/s, assuming a 50 μm separation between adjacent neurons in each network layer. All 770 homogeneous network variants were ranked according to their cortical propagation scores (Figure 2A, top). TC neurons exhibited both tonic firing and bursting activity, with the former mode more frequently observed (Figure 2B).

Multiple linear regression analysis (R^2=0.793, root-mean-square-error or RMSE=0.047, p<0.0001) demonstrated a strong positive correlation between the TC-TRN-TC openness coefficient and propagation score (normalized regression coefficient or NRC=1.000). By contrast, chemical and electrical TRN-TRN synaptic connectivity tended to modestly diminish propagation (NRC=-0.173 and NRC=-0.136, respectively; see Table 3). Further, other excitatory connectivity, such as cortico-cortical or corticothalamic connectivity, often postulated as being important for cortical signal propagation (Felleman and Van Essen, 1991; Kötter and Sommer, 2000; Theyel et al., 2010), was not necessary. Thus, the homogeneously varied synaptic network permutations that best accommodated signal propagation were generally ones with weak or absent synapses between TRN neurons and strong open-loop TC-TRN-TC connections. For example, Network α, which epitomizes this architecture, exhibited robust signal propagation in response to a fixed stimulus delivered to TC_1; a representative simulation of this network is shown in Figure 2B, left, and its position within the parameter space depicted in left-sided heat map of

Figure 2C is labeled. Stimulus-evoked activity in this network tended to propagate efficiently from Co_1 to Co_3: near-synchronous propagation cascades were elicited in both the TRN and cortical layers of the model, having been stimulated by propagating activity in upstream TC neurons. Smooth, linear propagation of action potentials across the network depended on the synchronous induction of inhibitory postsynaptic potentials (IPSPs) and the ensuing post-inhibitory rebound spikes in TC neurons, as mediated by T-type Ca^{2+} channels and driven by inhibition from the TRN, which occurred reliably and at fixed intervals in Network α. Relative to Network α, other network permutations exhibiting stronger intrareticular synapses did not support propagation as efficiently. We surmise that TRN-TRN_{GABA} synaptic connections reduced the incidence of IPSPs in TC neurons required for signal propagation across the network, while electrical coupling between TRN neurons destructively shunted a propagating signal away from the thalamoreticular lattice through which it predominantly traversed the network.

A 2° regression model of propagation as a function of all three synaptic class variables (R^2=0.842, RMSE=0.041, p<0.0001; Table 3) revealed modestly negative interaction term between TRN-TRN_{Elec} synapses and TC-TRN-TC openness (NRC=-0.365), indicating that in networks where both electrical synapses were strong and TC-TRN-TC openness high, the extent of supported propagation diminished nonlinearly; a smaller negative interaction between TRN-TRN_{GABA} synapses and TC-TRN-TC openness was also observed (NRC=-0.152). Together, these terms suggested that propagation was more significantly affected by connections in the TRN layer within the more open-loop networks. This relationship was evident, for example, in the right-sided heat map of Figure 2C, in which propagation scores more markedly decreased with increasing TRN-TRN electrical coupling as TC-TRN-TC openness itself increased.

Oscillatory responses recurred in Co_3 neurons at a mean frequency of 9.07 ± 0.2 Hz (range, 7.14-12.50 Hz) across all homogeneous model permutations. Propagation and oscillation scores across all 770

homogeneous networks were strongly anticorrelated (Pearson's r=-0.671, p<0.0001). Accordingly, oscillation was best accommodated in network permutations exhibiting strongly closed-loop connectivity (Figure 2A, bottom); however, the capacity to support oscillation was neither markedly linear nor monotonically decreasing as a function of increasing openness coefficient (Figure 2D). Rather, a one-way ANOVA with Tukey's tests revealed that, on average, oscillation scores peaked and remained statistically indistinguishable from one another across the subset of network permutations with openness coefficients between 0 and 0.4, with scores then decreasing in a roughly linear fashion with increasing TC-TRN-TC openness [F(10,759)=137.8, p<0.0001]; this result was consistent with a 2° regression model of oscillation (R^2=0.630, RMSE=0.128, p<0.0001; Table 3), in which the linear and quadratic terms in TC-TRN-TC openness were associated with NRCs of -1.000 and -0.052, respectively, and the effects of TRN-TRN$_{GABA}$ (NRC=0.060) and TRN-TRN$_{Elec}$ (NRC regularized to 0) on oscillation were weakly positive and negligible, respectively. Taken with the analysis of propagation, these data suggest that networks with mixed open- and closed-loop connectivity (which is likely close to physiological reality) can support the coexistence of oscillation and propagation (see *Propagation and oscillation in heterogeneously varied synaptic models*, below).

The predominant mechanism by which oscillation arose in Co_3 was through post-inhibitory rebound in TC_3, as engendered by the strong recurrent inhibition found in network permutations exhibiting primarily closed-loop TC-TRN-TC connectivity. This mode of oscillation was exemplified by Network β, a strongly closed-loop network variant. In the simulation shown of this network (Figure 2B, right), oscillatory activity was enabled by a single epoch of signal propagation. Notably, neither the presence of strong GABAergic nor electrical intrareticular synapses in Network β exerted much effect on its ability to support oscillation, as predicted by the 2° regression model.

Propagation and oscillation in heterogeneously varied synaptic models

Recent studies have highlighted heterogeneity in TRN neuronal connectivity, synaptic physiology and chemical identities (Lee et al., 2007; Halassa et al., 2014; Clemente-Perez et al., 2017). We therefore examined the impact of allowing all synaptic connections involving the TRN to be independently varied. We constructed circuit-level schematics of linear regression models for propagation (Figure 3A, top) and oscillation (Figure 3A, bottom) as functions of the 14 synaptic variables in heterogeneous networks.

Propagation in heterogeneously varied synaptic networks increased chiefly as a function of increasing the strength of the more downstream of the two laterally inhibitory TRN-TC synapses, $TRN_2 \rightarrow TC_3$: the corresponding term in a linear regression model of propagation (R^2=0.742, RMSE=0.069, p<0.0001; see Table 4) possessed an NRC of 1.000 (Figure 3A, top). Propagation scores also scaled to a lesser extent with the more upstream laterally inhibitory reticulothalamic synapse, $TRN_1 \rightarrow TC_2$ (NRC=0.608). The two inhibitory intrareticular synapses originating at the rightmost end of the model network, $TRN_3 \rightarrow TRN_1$ and $TRN_3 \rightarrow TRN_2$, both exerted a small negative effect on propagation (NRC=-0.087 and NRC=-0.084, respectively). Additionally, two TRN-TRN_{Elec} synapses, TRN_1=TRN_2 and TRN_1=TRN_3 (where the "=" denotes an electrical synapses), marginally decremented propagation in heterogeneous networks, with NRCs of -0.051 and -0.072, respectively. These findings at an individual synaptic level comported with the observation that strong TRN-TRN interactions, whether chemical or electrical, tended to impede signal propagation in homogeneous network variants.

A 2° regression model (R^2=0.857, RMSE=0.051, p<0.0001; Table 4) disclosed a large, propagation-enhancing interaction between the two laterally inhibitory synapses (NRC=0.753), underscoring the same dependence of propagation on strong open-loop TC-TRN-TC connectivity as seen in homogeneously synaptic networks, but additionally demonstrating that propagation scores increased nonlinearly as a function of simultaneously increasing the weights of $TRN_1 \rightarrow TC_2$ and $TRN_2 \rightarrow TC_3$. Interactions between TRN-TRN synapses of either variety and TRN-TC synapses tended diminish propagation, as did those between recurrent and lateral inhibitory TRN-TC synapses. Taken together, the linear and 2° regression

models indicated that heterogeneous network permutations with strong laterally inhibitory TRN-TC synapses tended to best support propagation. Consistent response propagation across the length of the network was epitomized by Network α', in which $TRN_1 \rightarrow TC_2$ and $TRN_2 \rightarrow TC_3$ were both relatively strong and those synapses impeding propagation comparatively weak (Figure 3B, left).

Heterogeneously varied synaptic architectures better supported propagation of oscillation

In contrast to the homogeneous models, there was a very small negative correlation between the propagation and oscillation scores of these networks (r=-0.0296, p=0.0008), suggesting that propagation and oscillation more easily coexist in heterogeneous than homogeneous models. This supposition was confirmed through a 2° regression analysis (R^2=0.388, RMSE=0.118, p<0.0001), which suggested that interactions between recurrently and laterally inhibitory TRN-TC synapses (NRCs ranging between 0.345 and 0.669) facilitated the propagation of oscillation, a mechanism typified by Network β' (Figure 3B, right). Two intrareticular synapses, TRN_1-TRN_3 and TRN_1=TRN_3, tended to contribute modestly to oscillation (NRCs of 0.115 and 0.117, respectively, in the linear regression model, R^2=0.253, RMSE=0.131, p<0.0001; Figure 3A, bottom), while, in their individual capacities, $TRN_1 \rightarrow TC_2$ and $TRN_2 \rightarrow TC_3$ diminished oscillation (NRCs of -1.000 and -0.892, respectively).

We analyzed the relative capacities of homogeneously and heterogeneously varied synaptic networks to support propagation, oscillation, and optimization by comparing the 20 highest scores achieved by homogeneous and heterogeneous network permutations with respect to each performance metric. No significant differences in mean propagation scores between top-performing homogeneous and heterogeneous networks were disclosed [unpaired t-test, t(38)=0.46, p=0.647; Figure 4]. We attributed this lack of differences to the fact that network permutations in which the synapses $TRN_1 \rightarrow TC_2$ and $TRN_2 \rightarrow TC_3$ were both maximally weighted would be equally capable of supporting robust signal propagation, regardless of whether these synapses were varied homogeneously or heterogeneously. By

contrast, top-scoring heterogeneous network variants better supported both oscillation [$t(38)=13.88$, $p<0.0001$] and optimization [$t(38)=18.04$, $p<0.0001$] than their homogeneous counterparts. Because networks supporting the propagation of oscillatory activity would, by definition, score high with respect to optimization, these results not only confirmed that heterogeneous networks were more likely than homogeneous networks to accommodate this oscillatory mechanism, but furthermore disclosed that propagation of oscillation across the thalamocortical network was associated with higher oscillation scores than post-inhibitory-driven oscillation in TC_3, the predominant form of oscillation observed in homogeneous networks.

Discussion:

The presented analysis suggests that open-loop TC-TRN-TC synaptic motifs (Figure 1B, right) could function as a substrate for signal propagation across the thalamus, and by extension, cortical networks without the need for direct cortico-cortical, intrareticular or corticothalamic connectivity. Post-inhibitory rebound mediated by T-type Ca^{2+} channels served as a substrate for both propagation and oscillation in the simulated networks. TRN-TRN connections, either chemical or electrical (Figure 1B, left and middle), diminished horizontal propagation by disrupting the precise timing relationships required to propagate a signal across the network. Models with heterogeneously varied TRN synapses outperformed those whose synapses varied as a class with respect to the propagation of oscillatory activity, consistent with the emerging literature documenting cellular and synaptic heterogeneity in the TRN (Lee et al., 2007; Halassa et al., 2014; Clemente-Perez et al., 2017). These data suggest that widespread propagating thalamic or thalamocortical activity, under both pathological and physiological conditions, may be mediated, at least in part, by TC-TRN-TC connections. The model makes strong predictions that can be tested physiologically.

Like most of the thalamic (Destexhe et al., 1993, 1996a; Golomb et al., 1996; Bazhenov et al., 1998; Sohal and Huguenard, 1998) and thalamocortical models (Destexhe et al., 1998; Bazehenov et al., 2002;

447 Rogala et al., 2013) that inspired our model, we utilized single-compartment, Hodgkin-Huxley neurons.
448 While these model cells contribute to the computational parsimony and practicality of network models,
449 particularly where the analysis of network dynamics is prioritized, they neglect the intrinsic cable
450 properties of real neurons and, relatedly, the spatially disparate nature of synaptic integration and
451 heterogeneous expression of intrinsic and synaptic conductances (Dayan and Abbott, 2005; Herz et al.,
452 2006). Such considerations are particularly relevant here relative to dendritic distributions of T- and H-
453 currents in TC neurons (McCormick and Pape, 1980; Destexhe et al., 1998; Williams and Stuart, 2000;
454 Traub et al., 2005) and TRN neurons (Contreras et al., 1993; Destexhe et al., 1996b; Traub et al., 2005;
455 Crandall et al., 2010). Although multicompartment neuronal models incorporating such details could
456 conceivably alter the network dynamics being studied, they were not necessary to simulate the
457 propagation of oscillatory waves seen physiologically (Bal et al., 1995; Destexhe et al., 1996a; Golomb et
458 al., 1996; Bazhenov et al., 1998; Sohal and Huguenard, 1998).
459
460 Additionally, the present model omitted explicit corticothalamic and corticoreticular synapses, both of
461 which have been identified and physiologically characterized to varying degrees (Steriade et al., 1972;
462 White and Hersch, 1982; De Curtis et al., 1989; Contreras et al., 1996; Blumenfeld and McCormick,
463 2000; Zhang and Jones, 2004; Crandall et al., 2015), though the former were effectively amalgamated
464 with both feedforward sensory and modulatory projections to the thalamus in the form of the Poisson-
465 modulated external input we delivered to individual TC neurons. Both forms of feedback have been
466 implicated in the spread of spindle waves and in the maintenance of their synchronization over large
467 distance scales (on the order of the length of the mammalian forebrain) and are furthermore known to
468 drive spindle wave formation and propagation in vivo by polysynaptically recruiting TC neurons via
469 TRN-mediated post-inhibitory rebound (Steriade et al., 1972; Roy et al., 1984; Contreras et al., 1996;
470 Contreras and Steriade, 1996; Suga and Ma, 2003; Sillito et al., 2006; Crandall et al., 2015; Sorokin et al.,
471 2017). It should be noted, however, that short-range propagation of spindle waves, which can be elicited
472 in isolated thalamic slice preparations (Bal et al., 1995; Kim et al., 1995), is preserved following

473 decortication, both in vivo and in silico (Contreras et al., 1996; Contreras and Steriade, 1996; Destexhe et
474 al., 1998).
475
476 The signaling dynamics observed in our small-scale, broadly feedforward model would undoubtedly be
477 altered by introducing corticothalamic and corticoreticular feedback, as well as cortico-cortical synapses:
478 in particular, we can predict, based on other modeling studies that have systematically explored the
479 contributions of such connections within fundamentally closed-loop thalamoreticular frameworks
480 (Destexhe et al., 1998; Rogala et al., 2013), that cortical feedback to the dorsal thalamus and TRN would
481 increase the frequency of post-inhibitory rebound in relay cells of the former, while also increasing
482 oscillatory activity through the introduction of new recurrent pathways between the thalamus and cortex.
483 While the enhancement of post-inhibitory rebound in the thalamus would a priori suggest an enhancement
484 in the extent of signal propagation mediated through open TC-TRN-TC loops, our results demonstrate
485 that the efficiency of such propagation can be attenuated by decohering activity introduced via
486 intrareticular synapses: as such, whether corticothalamic, corticoreticular, and cortico-cortical synapses
487 dynamics would ultimately enhance open-loop-mediated propagation or decrement it by interfering with
488 the temporal dynamics underlying this form of intrathalamic signaling would heavily depend on, among
489 other things, the degree to which these additional synapses spatially diverged within the dorsal thalamus
490 and TRN. Notwithstanding elaborations of cortical projections within our network model, our present
491 results suggest that open-loop TC-TRN-TC architectures may mediate a novel form of intrinsic thalamic,
492 and by extension, cortical signal propagation that exists independently of top-down modulation (for
493 example, in localized regions of the thalamus where cortical innervation is sparse) and potentially in
494 parallel to the modes of thalamocortical propagation in which both corticofugal pathways and cortico-
495 cortical synapses are known to participate. Future efforts within our modeling paradigm stand to
496 incorporate reciprocal cortical projections involving one or multiple cortical layers (see, for example,
497 Destexhe et al. 1998; Bahzenov et al., 2002; Traub et al., 2005; Izhikevich and Edelman, 2008; Rogala et
498 al., 2013).

499

500 *Comparison to related computational models and physiological data*

501 Although the production of spindle waves was not an explicit objective of our study, some of the wave
502 dynamics arising in our networks were nevertheless consistent with those inherent to spindle or spindle-
503 like waves. Despite possessing higher degrees of TC→TRN and TRN→TC synaptic divergence and
504 lacking the exclusively open-loop TC-TRN-TC architecture characterizing a subset of our network
505 variants, other isolated thalamic models allowing for longitudinal wave propagation similarly
506 accommodated this propagation along the lattice of interconnected TC and TRN neurons by way of
507 laterally inhibitory TRN-TC synapses (Destexhe et al., 1996a; Golomb et al., 1996; Bazhenov et al.,
508 1998); at short ranges, this mechanism of signal propagation also prevailed in larger-scale thalamocortical
509 models, while corticothalamic projections acted to propagate activity to more distal sites (Destexhe et al.,
510 1998; Destexhe and Sejnowski, 2003). Comparably, recurrently inhibitory TRN-TC synapses have been
511 documented to play a vital role in the generation of oscillatory behavior in the thalamus (von Krosigk et
512 al., 1993; Destexhe and Sejnowski, 2003). The temporal parameters of propagating and oscillation signals
513 in our model also matched some of those previously reported: the mean signal propagation velocity and
514 oscillation frequency measured across homogeneous networks fell within the ranges of spindle wave
515 propagation velocities and intraspindle spike frequencies reported in both physiological and
516 computational spindle wave studies (Andersen and Andersson, 1968; Steriade and Deschênes, 1984; Kim
517 et al., 1995; Destexhe et al., 1996a; Golomb et al., 1996).

518

519 The TC neurons in our model network exhibited both tonic and bursting modes of firing, consistent with
520 extensive physiological characterization (Sherman, 2001). The form of signal propagation generated in
521 our networks via open-loop TC-TRN-TC synaptic pathways, which necessarily depended on TRN-driven
522 post-inhibitory rebound in the downstream TC neuron, could, in practice, be elicited regardless of
523 whether the upstream TC neuron fired tonically or in bursts. However, bursting in thalamic neurons
524 receiving open-loop inhibition from the TRN is associated with a greater fidelity of transmission to the

cortex relative to tonic firing, as was systematically demonstrated in the computational model that directly inspired our present study (Willis et al., 2015); this finding furthermore holds relative to thalamocortical signaling efficiency more generally (Guido et al., 1995; Reinagel et al., 1999, Swadlow and Gusev, 2001; Krahe and Gabbiani, 2004).

One particularly notable point of departure relative to similar network models was the extent to which thalamoreticular, reticulothalamic, and thalamocortical synapses diverged. Although all three classes of synapses are known to diverge significantly and have been observed to target neuronal somata hundreds of microns from their origins (Jones, 1985; Cox et al., 1996, 1997; Crabtree, 1996; Pinault and Deschênes, 1998; Alonso et al., 2001; Miller et al., 2001; Sherman and Guillery, 2001), the TC-TRN, TRN-TC, and TC-Co synapses in our model were constrained to remain strictly local and minimally divergent (or non-divergent, in the case of TC-TRN and TC-Co synapses). With respect to the first two classes of synapses, this constraint was imposed to probe the impact the disynaptic TC-TRN-TC open-loop motifs characterizing a subset of network permutations, which constituted one of the foci of our study, and analyze the signal propagation they may support. This neuroanatomical scheme contrasted with previous computational models featuring parallel, interconnected thalamoreticular pathways, in which both TC and TRN synapsed bidirectionally with several neighboring TRN and TC cells, respectively, within a radius of several hundred microns (e.g., Destexhe et al., 1996a, 1998; Golomb et al., 1996; Bazhenov et al., 1998; Sohal and Huguenard, 1998; Sohal et al., 2000; Traub et al., 2005; Izhikevich and Edelman, 2008). Furthermore, the limited synaptic divergence constrained the spatial and temporal scales over which propagating and oscillating signals persisted in our model. This does not necessarily imply that thalamic and/or cortical signal propagation mediated through open-loop TC-TRN-TC architectures would be inherently limited in either distance or duration, particularly when accounting for the comparative diversity and complexity in the spatial and temporal profiles of real sensory information integrated by the thalamus relative to the highly focal, time-fixed external stimulus approximations we employed to initialize responses reliably across simulations in our model networks,

551 consistent with similarly simplified stimulus representations utilized in other thalamic or thalamocortical
552 models (Destexhe et al., 1996a; Golomb et al., 1996; Bazhenov et al., 1998; Sohal and Huguenard, 1998;
553 Traub et al., 2005). In light of the limits on the spatiotemporal coherence of signals intrinsic to our present
554 model, however, we would not predict any qualitative changes in propagative or oscillatory dynamics
555 were we to increase the length of our baseline network as presently constituted by adding in parallel
556 additional TC, TRN, and Co neurons.
557
558 *The functional implications of open-loop thalamo-reticulo-thalamic synaptic motifs*
559 The spread of activity from one cortical region to another is a foundational concept at the core of our
560 understanding of sensory processing, higher-order cognitive functions such as attention and language,
561 sleep-related oscillatory phenomena, and pathological findings such as propagation of ictal discharges and
562 migraine. It has long been speculated that the TRN could serve as a control point for large-scale cortical
563 signal processing given its central location, the high degree of convergence of projections involved in
564 attention, arousal, and emotion onto the TRN, and the TRN's particularly strong control over TC firing
565 properties (Yingling and Skinner, 1976; Crick, 1984; Guillery et al., 1998; Brunia and Van Boxtel, 2001;
566 McAlonan et al., 2006; John et al., 2013). Here we showed that open-loop TC-TRN-TC architectures can
567 support at least short-range thalamocortical signal propagation. Within the thalamus, these configurations
568 have thus far been observed both within and across individual thalamic nuclei and are thought to serve as
569 pathways for intra- and cross-modal modulation, respectively (Crabtree et al., 1998; Pinault and
570 Deschênes, 1998; Crabtree and Isaac, 2002; Lam and Sherman, 2005, 2015; Kimura et al., 2007; Lee et
571 al., 2010; Kimura, 2014); as has been previously surmised, these synaptic pathways could also plausibly
572 lend themselves to sensory enhancement, multisensory integration, and attentional mechanisms (Crabtree
573 and Isaac, 2002; Pinault, 2004; Willis et al., 2015; Crabtree, 2018). At a minimum, and as inferred from
574 physiological studies, open-loop pathways should be fully capable of supporting signaling propagation
575 from one thalamic relay neuron to another through a limited number of intervening synapses (with a
576 disynaptic pathway serving as the shortest such configuration).

577

578 It should be emphasized that the specific functional roles of open-loop TC-TRN-TC pathways are likely
579 to depend on their densities and distributions within the thalamus (Halassa and Acsády, 2016). If the
580 morphological, intrinsic, and synaptic heterogeneity of TRN neurons are any indication (Scheibel and
581 Scheibel, 1966; Jones, 1975; Spreafico et al., 1991; Cox et al., 1996; Lee et al., 2007; Halassa et al., 2014;
582 Clemente-Perez et al., 2017), it is reasonable to assume that both TC-TRN and TRN-TC synapses are
583 distributed in a broadly heterogeneous manner across the thalamus. As underscored by our analysis, such
584 synaptic heterogeneity is seemingly a prerequisite for the propagation of oscillatory signals, which, in the
585 case of spindling, can occur in the thalamus independently of cortical involvement (von Krosigk et al.,
586 1993; Bal et al., 1995; Kim et al., 1995) and necessarily involves both recurrently and laterally projecting
587 TRN-TC synapses, the latter of which form of the basis of open loops; outside of this particular functional
588 context, synaptic heterogeneity is broadly speculated to improve the versatility, efficiency, speed, and
589 metabolic economy associated with signal processing (Lengler et al., 2013). If open-loop TC-TRN-TC
590 architectures are indeed to be found within a larger, synaptically diverse thalamoreticular milieu,
591 characterized by variable synaptic divergence and differing densities of sensory, cortical, and other
592 extrinsic innervation, it is moreover reasonable to expect that the degree to which the mode of
593 propagation mediated by these synaptic motifs prevails would vary across thalamic and cortical regions.
594

595 To what extent might the functionality of open loops between the dorsal thalamus and TRN depend on
596 arousal state? While sleep and other depressed states of consciousness (e.g., those pharmacologically
597 induced) are associated with thalamic hyperpolarization and therefore tend to amplify both post-inhibitory
598 rebound, which underlay the signal propagation in our model, and, by extension, low-threshold bursting
599 (Steriade et al., 1993; McCormick and Bal, 1997; Weyand et al., 2001; Urbain et al., 2019), both
600 phenomena have also been documented in the thalamic relay neurons of awake animals (Guido and
601 Weyand, 1995; Fanselow et al., 2001; Ortuño et al., 2014), and then sometimes selectively in response to
602 particular stimuli (Lesica and Stanley, 2004; Wang et al., 2007). Thus, while there is no mechanistic basis

603 on which to assume that propagation through open TC-TRN-TC loops would be restricted to a particular
604 state of wakefulness, the widespread modulatory afferents received by both the thalamus and TRN from
605 brain areas including the prefrontal cortex, basal forebrain, amygdala, and brainstem leave little doubt that
606 any form of intrathalamic or cortical signaling supported by these synaptic architectures is highly state-
607 dependent (see, for example, Halassa et al., 2014). Both forthcoming physiological investigation and
608 future modeling studies will be able to evaluate such predictions and help provide a full accounting of the
609 role of the various modes of connectivity between brain regions.
610
611 **References:**

612 Ahlsén, G, Lindström, S (1982) Mutual inhibition between perigeniculate neurones. *Brain Res* 236:482-
613 486.
614
615 Alonso JM, Usrey WM, Reid RC (2001) Rules of connectivity between geniculate cells and simple cells
616 in cat primary visual cortex. *J Neurosci* 21:4002-4015.
617
618 Andersen P, Andersson SA (1968) The physiological basis of the alpha rhythm. New York: Appleton-
619 Century-Crofts.
620
621 Asanuma C, Porter LL (1990) Light and electron microscopic evidence for a GABAergic projection from
622 the caudal basal forebrain to the thalamic reticular nucleus in rats. *J Comp Neurol* 302:159-172.
623
624 Bal T, von Krosigk M, McCormick DA (1995) Role of the ferret perigeniculate nucleus in the generation
625 of synchronized oscillations in vitro. *J Physiol* 483:665-685.
626
627 Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ (1998) Computational models of thalamocortical
628 augmenting responses. *J Neurosci* 18:6444-6465.

629

630 Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ (2002) Model of thalamocortical slow-wave sleep
631 oscillations and transitions to activated states. *J Neurosci* 22:8691–8704.

632

633 Bickford ME, Günlük AE, Van Horn SC, Sherman SM (1994) GABAergic projection from the basal
634 forebrain to the visual sector of the thalamic reticular nucleus in the cat. *J Comp Neurol* 348:481-510.

635

636 Blumenfeld H, McCormick DA (2000) Corticothalamic inputs control the pattern of activity generated in
637 thalamocortical networks. *J Neurosci* 20:5153-5162.

638

639 Brunia CH, Van Boxtel GJ (2001) Wait and see. *Int J Psychophysiol* 43:59-75.

640

641 Chen C, Regehr WG (2003) Presynaptic modulation of the retinogeniculate synapse. *J Neurosci*
642 23:3130-3135.

643

644 Clemente-Perez A, Makinson SR, Higashikubo B, Brovarney S, Cho, FS, Urry A, Holden SS, Wimer, M,
645 Dávid C, Fenno LE, Acsády L, Deisseroth K, Paz JT (2017) Distinct Thalamic Reticular Cell Types
646 Differentially Modulate Normal and Pathological Cortical Rhythms. *Cell Rep* 19:2130-2142.

647

648 Contreras D, Curró Dossi R, Steriade, M (1993) Electrophysiological properties of cat reticular thalamic
649 neurones in vivo. *J Physiol* 470:273-294.

650

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

653

654 Contreras D, Steriade M (1996) Spindle oscillation in cats: the role of corticothalamic feedback in a
655 thalamically generated rhythm. J *Physiol* 490:159-179.
656
657 Cox CL, Huguenard JR, Prince DA (1996) Heterogeneous axonal arborizations of rat thalamic reticular
658 neurons in the ventrobasal nucleus. *J Comp Neuro* 366:416-430.
659
660 Cox CL, Huguenard JR, Prince DA (1997) Nucleus reticularis neurons mediate diverse inhibitory effects
661 in thalamus. *Proc Natl Acad Sci USA* 94:8854-8859.
662
663 Crabtree JW (1996) Organization in the somatosensory sector of the cat's thalamic reticular nucleus. *J*
664 *Comp Neurol* 366:207-222.
665
666 Crabtree JW (2018) Functional Diversity of Thalamic Reticular Subnetworks. *Front Syst Neurosci* 12:41.
667 doi:10.3389/fnsys.2018.00041
668
669 Crabtree JW, Collingridge GL, Isaac JT (1998) A new intrathalamic pathway linking modality-related
670 nuclei in the dorsal thalamus. *Nat Neurosci* 1:389-394.
671
672 Crabtree JW, Isaac JT (2002) New intrathalamic pathways allowing modality-related and cross-modality
673 switching in the dorsal thalamus. *J Neurosci* 22:8754-8761.
674
675 Crandall SR, Cruikshank SJ, Connors BW (2015) A corticothalamic switch: controlling the thalamus with
676 dynamic synapses. *Neuron* 86:768-782.
677
678 Crandall SR, Govindaiah G, Cox CL (2010) Low-threshold Ca^{2+} current amplifies distal dendritic
679 signaling in thalamic reticular neurons. *J Neurosci* 30:15419-15429.

Crick F (1984) Function of the thalamic reticular complex: the searchlight hypothesis. *Proc Natl Acad Sci USA* 81:4586-4590.

Cruikshank SJ, Urabe H, Nurmikko AV, Connors BW (2010) Pathway-specific feedforward circuits between thalamus and neocortex revealed by selective optical stimulation of axons. *Neuron* 65:230-245.

Dayan P, Abbott LF (2005) Theoretical Neuroscience, revised edition. Cambridge, MA: MIT Press.

De Curtis M, Spreafico R, Avanzini G (1989) Excitatory amino acids mediate responses elicited in vitro by stimulation of cortical afferents to reticularis thalami neurons of the rat. *Neuroscience* 33:275-283.

Deleuze C, Huguenard (2006) Distinct electrical and chemical connectivity maps in the thalamic reticular nucleus: potential roles in synchronization and sensation. *J Neurosci* 26:8633-8645.

Deleuze C, David F, Béhuret S, Sadoc G, Shin HS, Uebele VN, Renger JJ, Lambert RC, Leresche N, Bal T (2012) T-type calcium channels consolidate tonic action potential output of thalamic neurons to neocortex. *J Neurosci* 32:12228–12236.

Destexhe A, Bal T, McCormick DA, Sejnowski TJ (1996a) 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 (1998) Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. *J Neurophysiol* 79:999–1016.

705 Destexhe A, Contreras D, Steriade M, Sejnowski TJ, Huguenard JR (1996b) In vivo, in vitro, and
706 computational analysis of dendritic calcium currents in thalamic reticular neurons. *J Neurosci* 16:169-
707 185.
708
709 Destexhe A, McCormick DA, Sejnowski TJ (1993) A model for 8–10 Hz spindling in interconnected
710 thalamic relay and reticularis neurons. *Biophys J* 65:2473–2477.
711
712 Destexhe A, Sejnowski TJ (2003) Interactions between membrane conductances underlying
713 thalamocortical slow-wave oscillations. *Physiol Rev* 83:1401-1453.
714
715 Dong P, Wang H, Shen X-F, Jiang P, Zhu X-T, Li Y, Gao J-H, Lin S, Huang Y, He X-B, Xu FQ, Duan S,
716 Lian H, Wang H, Chen J, Li XM (2019) A novel cortico-intrathalamic circuit for flight behavior. *Nat*
717 *Neurosci* 22:941-949.
718
719 Fanselow EE, Sameshima K, Baccala LA, Nicolelis MA (2001) Thalamic bursting in rats during different
720 awake behavioral states. *Proc Natl Acad Sci USA* 98:15330–15335.
721
722 Felleman DJ, Van Essen DC (1991) Distributed hierarchical processing in the primate cerebral cortex.
723 *Cereb Cortex* 1:1-47.
724
725 Ferrarelli F, Tononi G (2011) The thalamic reticular nucleus and schizophrenia. *Schizophr Bull* 37:306-
726 315.
727
728 FitzGibbon T, Solomon SG, Goodchild AK (2000) Distribution of calbindin, parvalbumin, and calretinin
729 immunoreactivity in the reticular thalamic nucleus of the marmoset: evidence for a medial leaflet of
730 incertal neurons. *Exp Neurol* 164:371-383.

731

732 Friedman J, Hastie J, Tibshirani R (2010) Regularization paths for generalized linear models via
733 coordinate descent. *J Stat Softw* 33:1-22.

734

735 Fuentealba P, Crochet S, Timofeev I, Bazhenov M, Sejnowski TJ, Steriade M (2004) Experimental
736 evidence and modeling studies support a synchronizing role for electrical coupling in the cat thalamic
737 reticular neurons in vivo. *Eur J Neurosci* 20:111-119.

738

739 Gentet LJ, Ulrich D (2003) Strong, reliable and precise synaptic connections between thalamic relay cells
740 and neurones of the nucleus reticularis in juvenile rats. *J Physiol* 546:801-811.

741

742 Golomb D, Wang XJ, Rinzel J (1996) Propagation of spindle waves in a thalamic slice model. *J*
743 *Neurophysiol* 75:750-769.

744

745 Guido W, Lu SM, Vaughan J, Godwin DW, Sherman SM (1995) Receiver operating characteristic (ROC)
746 analysis of neurons in the cat's lateral geniculate nucleus during tonic and burst response mode. *Vis*
747 *Neurosci* 12:723-741.

748

749 Guido W, Weyand T (1995) Burst responses in thalamic relay cells of the awake behaving cat. *J*
750 *Neurophysiol* 74:1782-1786.

751

752 Guillery RW, Feig SL, Lozsádi DA (1998) Paying attention to the thalamic reticular nucleus. *Trends*
753 *Neurosci* 21:28-32.

754

755 Halassa MM, Acsády L (2016) Thalamic inhibition: diverse sources, diverse scales. *Trends Neurosci*
756 39:680-693.

Halassa MM, Chen Z, Wimmer RD, Brunetti PM, Zhao S, Zikopoulos B, Wang F, Brown EN, Wilson MA (2014) State-dependent architecture of thalamic reticular subnetworks. *Cell* 158:808-821.

Hale PT, Sefton AJ, Bauer LA, Cottee LJ (1982) Interrelations of the rat's thalamic reticular and dorsal lateral geniculate nuclei. *Exp Brain Res* 45:217-229.

Hallanger AE, Levey AI, Lee HJ, Rye DB, Wainer BH (1987) The origins of cholinergic and other subcortical afferents to the thalamus in the rat. *J Comp Neurol* 262:105-124.

Herz AV, Gollisch T, Machens CK, Jaeger D (2006) Modeling single-neuron dynamics and computations: a balance of detail and abstraction. *Science* 314:80-85.

Hou G, Smith AG, Zhang ZW (2016) Lack of intrinsic GABAergic connections in the thalamic reticular nucleus of the mouse. *J Neurosci* 36:7246-7252.

Huguenard JR (1998) Neuronal circuitry of thalamocortical epilepsy and mechanisms of antiabsence drug action. *Adv Neurol* 79:991-999.

Izhikevich EM, Edelman GM (2008) Large-scale model of mammalian thalamocortical systems. *Proc Natl Acad Sci USA* 105:3593-3598.

John YJ, Bullock D, Zikopoulos B, Barbas H (2013) Anatomy and computational modeling of networks underlying cognitive-emotional interaction. *Front Hum Neurosci* 7:101.

782 Jones EG (1975) Some aspects of the organization of the thalamic reticular complex. *J Comp Neurol*
783 162:285-308.
784
785 Jones EG (1985) The Thalamus. New York: Plenum Press.
786
787 Kim U, Bal T, McCormick DA (1995) Spindle waves are propagating synchronized oscillations in the
788 ferret LGNd in vitro. *J Neurophysiol* 74:1301-1323.
789
790 Kimura A (2014) Diverse subthreshold cross-modal sensory interactions in the thalamic reticular nucleus:
791 implications for new pathways of cross-modal attentional gating function. *Eur J Neurosci* 39:1405-1418.
792
793 Kimura A, Imbe H, Donishi T, Tamai Y (2007) Axonal projections of single auditory neurons in the
794 thalamic reticular nucleus: implications for tonotopy-related gating function and cross-modal modulation.
795 *Eur J Neurosci* 26:3524-3535.
796
797 Kokkinos V, Koupparis AM, Koutroumanidis M, Kostopoulos GK (2017) Spatiotemporal propagation
798 patterns of generalized ictal spikes in childhood absence epilepsy *Clin Neurophysiol* 128:1553-1562.
799
800 Kötter R, Sommer FT (2000) Global relationship between anatomical connectivity and activity
801 propagation in the cerebral cortex. *Philos Trans R Soc Lond, B, Biol Sci* 355:127-134.
802
803 Krahe R, Gabbiani F (2004) Burst firing in sensory systems. *Nat Rev Neurosci* 5:13-23.
804
805 Krol A, Wimmer RD, Halassa MM, Feng G (2018) Thalamic reticular dysfunction as a circuit
806 endophenotype in neurodevelopmental disorders. *Neuron* 98:282-295.
807

808 Lam YW, Sherman SM (2005) Mapping by laser photostimulation of connections between the thalamic
809 reticular and ventral posterior lateral nuclei in the rat. *J Neurophysiol* 94:2472–2483.
810
811 Lam YW, Sherman SM (2015) Functional topographic organization of the motor reticulothalamic
812 pathway. *J Neurophysiol* 113:3090-3097.
813
814 Lam, YW, Nelson CS, Sherman SM (2006) Mapping of the functional interconnections between thalamic
815 reticular neurons using photostimulation. *J Neurophysiol* 96:2593–2600.
816
817 Landisman CE, Long MA, Beierlein M, Deans MR, Paul DL, Connors BW (2002) Electrical synapses in
818 the thalamic reticular nucleus. *J Neurosci* 22:1002–1009.
819
820 Leao AAP (1944) Spreading depression of activity in the cerebral cortex. *J Neurophysiol* 7:359–390.
821
822 Lee SC, Cruikshank SJ, Connors BW (2010) Electrical and chemical synapses between relay neurons in
823 developing thalamus. *J Physiol* 588:2403-2415.
824
825 Lee SH, Govindaiah G, Cox CL (2007) Heterogeneity of firing properties among rat thalamic reticular
826 nucleus neurons. *J Physiol* (Lond) 582:195-208.
827
828 Lengler J, Jug F, Steger A (2013) Reliable neuronal systems: the importance of heterogeneity. *PLoS One*
829 8:e80694.
830
831 Lesica NA, Stanley GB (2004) Encoding of natural scene movies by tonic and burst spikes in the lateral
832 geniculate nucleus. *J Neurosci* 24:10731-10740.
833

834 Llinás RR, Paré D (1991) Of dreaming and wakefulness. *Neuroscience* 44:521-535.
835
836 Lo FS, Sherman SM (1994) Feedback inhibition in the cat's lateral geniculate nucleus. *Exp Brain Res*
837 100:365-368.
838
839 Long MA, Landisman CE, Connors BW (2004) Small clusters of electrically coupled neurons generate
840 synchronous rhythms in the thalamic reticular nucleus. *J Neurosci* 24:341-349.
841
842 McAlonan K, Cavanaugh J, Wurtz RH (2006) Attentional modulation of thalamic reticular neurons. *J*
843 *Neurosci* 26:4444-4450.
844
845 McCormick DA, Bal T (1997) Sleep and arousal: thalamocortical mechanisms. *Annu Rev Neurosci*
846 20:185-215.
847
848 McCormick DA, Contreras D (2001) On the cellular and network bases of epileptic seizures. *Annu Rev*
849 *Physiol* 63:815-846.
850
851 McCormick DA, Pape HC (1980) Properties of a hyperpolarization-activated cation current and its role in
852 rhythmic oscillation in thalamic relay neurones. *J Physiol* (Lond) 431:291-318.
853
854 Miller LM, Escabí MA, Read HL, Schreiner CE (2001) Functional convergence of response properties in
855 the auditory thalamocortical system. *Neuron* 32:151-160.
856
857 Moore JW, Ramon F (1974) On numerical integration of the Hodgkin and Huxley equations for a
858 membrane action potential. *J Theor Biol* 45:249–273.
859

860 Morrison JH, Foote SL (1986) Noradrenergic and serotoninergic innervation of cortical, thalamic, and
861 tectal visual structures in Old and New World monkeys. *J Comp Neurol* 243:117-138.
862
863 Muller L, Chavane F, Reynolds J, Sejnowski TJ (2018) Cortical travelling waves: mechanisms and
864 computational principles. *Nat Rev Neurosci* 19:255-268.
865
866 Muller L, Piantoni G, Koller D, Cash SS, Halgren E, Sejnowski, TJ (2016) Rotating waves during human
867 sleep spindles organize global patterns of activity that repeat precisely through the night. *eLife* 5:e17267.
868
869 Muller L, Reynaud A, Chavane F, Destexhe A (2014) The stimulus-evoked population response in visual
870 cortex of awake monkey is a propagating wave. *Nat Commun* 5:3675.
871
872 Ortuño T, Grieve KL, Cao R, Cudeiro J, Rivadulla C (2014) Bursting thalamic responses in awake
873 monkey contribute to visual detection and are modulated by corticofugal feedback. *Front Behav Neurosci*
874 8:198.
875
876 Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-
877 thalamo-cortical loop. *Brain Res Brain Res Rev* 20:91-127.
878
879 Pham T, Haas JS (2018) Electrical synapses between inhibitory neurons shape the responses of principal
880 neurons to transient inputs in the thalamus: a modeling study. *Sci Rep* 8:7763.
881
882 Pinault D (2004) The thalamic reticular nucleus: structure, function and concept. *Brain Res Brain Res Rev*
883 46:1-31.
884

885 Pinault D, Deschênes M (1998) Anatomical evidence for a mechanism of lateral inhibition in the rat
886 thalamus. *Eur J Neurosci* 10:3462-3469.
887
888 Pinault D, Smith Y, Deschênes M (1997) Dendrodendritic and axoaxonic synapses in the thalamic
889 reticular nucleus of the adult rat. *J Neurosci* 17:3215-3233.
890
891 Pita-Almenar JD, Yu D, Lu HC, Beierlein M (2014) Mechanisms underlying desynchronization of
892 cholinergic-evoked thalamic network activity. *J Neurosci* 34:14463–14474.
893
894 Pospischil M, Toledo-Rodriguez M, Monier C, Piwkowska Z, Bal T, Frégnac Y, Markram H, Destexhe A
895 (2008) Minimal Hodgkin-Huxley type models for different classes of cortical and thalamic neurons. *Biol*
896 *Cybern* 99:427–441.
897
898 R Core Team (2013) R: A language and environment for statistical computing (R Foundation for
899 Statistical Computing, Vienna). URL http://www.R-project.org/.
900
901 Reinagel P, Godwin D, Sherman SM, Koch C (1999) Encoding of visual information by LGN bursts. *J*
902 *Neurophysiol* 81:2558-2569.
903
904 Rogala J, Waleszczyk WJ, Lęski S, Wróbel A, Wójcik DK (2013) Reciprocal inhibition and slow calcium
905 decay in perigeniculate interneurons explain changes of spontaneous firing of thalamic cells caused by
906 cortical inactivation. *J Comput Neurosci* 34:461-476.
907
908 Roy JP, Clercq M, Steriade M, Deschênes M (1984) Electrophysiology of neurons of lateral thalamic
909 nuclei in cat: mechanisms of long-lasting hyperpolarizations. *J Neurophysiol* 51:1220-1235.
910

911 Sanchez-Vives, MV, Bal T, McCormick DA (1997) Inhibitory interactions between perigeniculate
912 GABAergic neurons. *J Neurosci* 17:8894-8908.
913
914 Scheibel ME, Scheibel AB (1966) The organization of the nucleus reticularis thalami: a Golgi study.
915 *Brain Res* 1:43-62.
916
917 Sherman SM (2001) Tonic and burst firing: dual modes of thalamocortical relay. *Trends Neurosci*
918 24:122-126.
919
920 Sherman SM, Guillery RW (1996) Functional organization of thalamocortical relays. *J Neurophysiol*
921 76:1367-1395.
922
923 Sherman SM, Guillery RW (2001) Exploring the thalamus. San Diego: Academic Press.
924
925 Shimizu K, Stopfer M (2013) Gap junctions. *Curr Biol* 23:R1026-1031.
926
927 Shosaku A (1986) Cross-correlation analysis of a recurrent inhibitory circuit in the rat thalamus. *J*
928 *Neurophysiol* 55:1030-1043.
929
930 Shu Y, McCormick DA (2002) Inhibitory interactions between ferret thalamic reticular neurons. *J*
931 *Neurophysiol* 87:2571-2576.
932
933 Siegel A, Sapru HN (2015) Essential Neuroscience, Third Edition. Baltimore: Lippincott Williams &
934 Wilkins.
935

936 Sillito AM, Cudeiro J, Jones HE (2006) Always returning: feedback and sensory processing in visual
937 cortex and thalamus. *Trends Neurosci* 29:307-316.
938
939 Sohal VS, Huguenard JR (1998) Long-range connections synchronize rather than spread intrathalamic
940 oscillations: computational modeling and in vitro electrophysiology. *J Neurophysiol* 80:1736-1751.
941
942 Sohal VS, Huntsman MM, Huguenard JR (2000) Reciprocal inhibitory connections regulate the
943 spatiotemporal properties of intrathalamic oscillations. *J Neurosci* 20:1735-1745.
944
945 Sorokin JM, Davidson TJ, Frechette E, Abramian AM, Deisseroth K, Huguenard JR, Paz JT (2017)
946 Bidirectional control of generalized epilepsy networks via rapid real-time switching of firing mode.
947 *Neuron* 93:194-210.
948
949 Spreafico R, Battaglia G, Frassoni C (1991) The reticular thalamic nucleus (RTN) of the rat:
950 cytoarchitectural, Golgi, immunocytochemical, and horseradish peroxidase study. *J Comp Neurol*
951 304:478-90.
952
953 Steriade M, Deschênes M (1984) The thalamus as a neuronal oscillator. *Brain Res* 320:1-63.
954
955 Steriade M, Jones EG, Llinás RR (1990) Thalamic Oscillations and Signaling. New York: Wiley-
956 Interscience.
957
958 Steriade M, McCormick D, Sejnowski T (1993) Thalamocortical oscillations in the sleeping and aroused
959 brain. *Science* 262:679-685.
960

961 Steriade M, Wyzinski P, Apostol V (1972) Corticofugal projections governing rhythmic thalamic
962 activity. In: Corticothalamic Projections and Sensorimotor Activities (Frigyesi TL, Rinvik E, Yahr MD,
963 eds), pp 221-272. New York: Raven.
964
965 Suga N, Ma X (2003) Multiparametric corticofugal modulation and plasticity in the auditory system. *Nat*
966 *Rev Neurosci* 4:783-794.
967
968 Sun, YG, Pita-Almenar JD, Wu CS, Renger JJ, Uebele VN, Lu HC, Beierlein M (2013) Biphasic
969 cholinergic synaptic transmission controls action potential activity in thalamic reticular nucleus neurons. *J*
970 *Neurosci* 33:2048–2059.
971
972 Swadlow H, Gusev A (2001) The impact of "bursting" thalamic impulses at a neocortical synapse. *Nat*
973 *Neurosci* 4:402-408.
974
975 Theyel BB, Llano DA, Sherman SM (2010) The corticothalamocortical circuit drives higher-order cortex
976 in the mouse. *Nat Neurosci* 13:84-88.
977
978 Traub RD, Contreras D, Cunningham MO, Murray H, LeBeau FE, Roopun A, Bibbig A, Wilent WB,
979 Higley MJ, Whittington MA (2005) Single-column thalamocortical network model exhibiting gamma
980 oscillations, sleep spindles, and epileptogenic bursts. *J Neurophysiol* 93:2194-2232.
981
982 Tsodyks MV, Markram H (1997) The neural code between neocortical pyramidal neurons depends on
983 neurotransmitter release probability. *Proc Natl Acad Sci USA* 94:719–723.
984

985 Urbain N, Fourcaud-Trocmé N, Laheux S, Salin PA, Gentet LJ (2019) Brain-state-dependent modulation
986 of neuronal firing and membrane potential dynamics in the somatosensory thalamus during natural sleep.
987 *Cell Reports* 26:1443-1457.
988
989 von Krosigk, M, Bal T, McCormick DA (1993) Cellular mechanisms of a synchronized oscillation in the
990 thalamus. *Science* 261:361-364.
991
992 Wang X, Wei Y, Vaingankar V, Wang Q, Koepsell K, Sommer FT, Hirsch JA (2007) Feedforward
993 excitation and inhibition evoke dual modes of firing in the cat's visual thalamus during naturalistic
994 viewing. *Neuron* 55:465-478.
995
996 Warren RA, Agmon A, Jones EG (1994) Oscillatory synaptic interactions between ventroposterior and
997 reticular neurons in mouse thalamus in vitro. *J Neurophysiol* 72:1993-2003.
998
999 Wells MF, Wimmer RD, Schmitt LI, Feng G, Halassa MM (2016) Thalamic reticular impairment
1000 underlies attention deficit in Ptchd1(Y/-) mice. *Nature* 532:58-63.
1001
1002 Weyand TG, Boudreaux M, Guido W (2001) Burst and tonic response modes in thalamic neurons during
1003 sleep and wakefulness. *J Neurophysiol* 85:1107-1118.
1004
1005 White EL, Hersch SM (1982) A quantitative study of thalamocortical and other synapses involving the
1006 apical dendrites of corticothalamic projection cells in mouse SmI cortex. *J Neurocytol* 11:137-157.
1007
1008 Williams SR, Stuart GJ (2000) Action potential backpropagation and somato-dendritic distribution of ion
1009 channels in thalamocortical neurons. *J Neurosci* 20:1307-1317.
1010

1011 Willis AM, Slater BJ, Gribkova ED, Llano DA (2015) Open-loop organization of thalamic reticular
1012 nucleus and dorsal thalamus: a computational model. *J Neurophysiol* 114:2353-2367.
1013
1014 Wimmer RD, Schmitt LI, Davidson TJ, Nakajima M, Deisseroth K, Halassa MM (2015) Thalamic control
1015 of sensory selection in divided attention. *Nature* 526:705-709.
1016
1017 Yamada WM, Koch C, Adams PR (1989) Multiple channels and calcium dynamics. In: Methods in
1018 Neuronal Modeling (Koch C, Segev I, eds), pp 97–133. Cambridge, MA: MIT Press.
1019
1020 Yingling CD, Skinner JE (1976) Selective regulation of thalamic sensory relay nuclei by nucleus
1021 reticularis thalami. *Electroencephalogr Clin Neurophysiol* 41:476-482.
1022
1023 Zhang L, Jones EG (2004) Corticothalamic inhibition in the thalamic reticular nucleus. *J Neurophysiol*
1024 91:759-766.
1025
1026 Zikopoulos B, Barbas H (2006) Prefrontal projections to the thalamic reticular nucleus form a unique
1027 circuit for attentional mechanisms. *J Neurosci* 26:7348-7361.

Figures:

Figure 1. Pathways and properties of thalamocortical signaling. **A:** Closed- vs. open-loop thalamo-reticulo-thalamic configurations. **B:** Three possible pathways through which a signal might propagate from one thalamocortical (TC) neuron to another via the thalamic reticular nucleus (TRN). **C:** Baseline thalamocortical model network. Broken-line synapses were allowed to vary either as a class (homogeneously) or independently of one another (heterogeneously). The black arrow corresponds to the fixed, external stimulus applied to TC_1. **D:** Sample cortical (Co) spike histograms (detrended) in a network permutation responding to a fixed, sustained stimulus delivered to TC_1 (black bar beneath the lowest trace). The propagation score assigned to any network permutation was quantified as the amplitude of the initial stimulus-evoked response in the detrended Co_3 histogram; response propagation across the cortical subnetwork (orange arrow) was consistently linear, and thus the initial response in Co_3 was observed at a fixed interval relative to the onset of stimulation. Oscillation intrinsic to any network variant was quantified as the amplitude of the first off-center peak in the normalized autocorrelogram (right) of post-stimulation activity in the detrended Co_3 histogram (within broken black box). The initial 400 ms of activity preceding the fixed stimulus (in grey) is shown here for each histogram but was not included in the calculations of either propagation or oscillation. Note that the bin heights in the Co_1 histogram shown here were truncated in order to maintain identical vertical scaling across all three cortical histograms.

Figure 2. Propagation and oscillation in homogeneously varied synaptic networks (N=770). **A:** Ordinal heat maps ranking homogeneously varied synaptic network permutations according to the extent of supported signal propagation and oscillation. Every row in a given map depicts a single network permutation, color-coded based on its synaptic makeup according to the three synaptic scales found below the maps (redder colors signify stronger or more open-loop connections). The network property ranks and synaptic makeups of two selected networks, Networks α and β, are indicated. **B:** Representative simulations and circuit diagrams depicting the normalized synaptic makeups for the two selected networks. The yellow arrow indicates when the fixed stimulus was delivered to TC_1 in each simulation. Orange highlighting indicates epochs of linear propagation, while circles are placed above spikes occurring during periods of oscillatory activity. **C:** Heat maps displaying propagation scores in TRN-TRN synaptic parameter space for the 70 fully open-loop networks (openness coefficient=1.0), with Network α highlighted (left), and propagation as a function of TC-TRN-TC openness and electrical coupling between TRN neurons for the 70 networks possessing 200-nS GABAergic TRN-TRN synapses (right). **D:** Mean oscillation scores for networks varied nonlinearly as a function of their openness coefficients, with networks possessing openness coefficients of 0 and 0.4 supporting oscillation to equal extents (one-way ANOVA with Tukey post-hoc tests, $F(10,759)=137.8$, $p<0.0001$). Individual means were computed by averaging the 70 oscillation scores associated with a given openness coefficients, and error bars indicate standard errors of the mean; N.S.=not significant.

Figure 3. Propagation and oscillation in heterogeneously varied synaptic networks (N=12,681). **A:** Network regression models illustrating how propagation (top) and oscillation (bottom) varied as a function of individual synaptic weights across simulated heterogeneously synaptic network permutations. Synapses with positive and negative normalized regressions coefficients were correlated positively and negatively with a given property and are depicted separately in the left- and right-sided circuit diagrams, respectively, for clarity. Gray synapses are either non-variable or associated with normalized regression coefficients with absolute values less than 0.05. See also Table 4. **B:** Representative simulations for two selected heterogeneous networks, whose normalized synaptic weights are depicted in the circuit diagrams. Networks α' and β' respectively illustrate propagation and propagation of oscillation across the network.

Figure 4. Heterogeneously varied synaptic architectures better supported propagation of oscillation. Propagation, as measured in those network permutations scoring highest with respect to the property, was equally supported in networks where synaptic weights varied independently of one another (heterogeneously; checkered) as in networks where synaptic strength varied homogeneously (black) by class [unpaired *t*-test, $t(38)=0.46$, $p=0.647$]. By contrast, oscillation and optimization scores were significantly higher in top-performing heterogeneous networks than their homogeneous counterparts [oscillation: $t(38)=13.88$, $p<0.0001$; optimization: $t(38)=18.04$, $p<0.0001$]. Each bar corresponds to a mean of the top 20 network propagation or oscillation scores within each synaptic architecture group; error bars indicate standard errors of the mean. ****=$p<0.0001$; N.S.=not significant.

1081 **Tables:**

Intrinsic Model Cellular Parameters			
Parameter	**TC cell**	**TRN cell**	**Co cell**
Leak conductance, g_L (nS)	3.263	3.7928	4.8128
Leak reversal potential, E_L (mV)	-60.03	-57	-60.2354
Transient sodium conductance, g_{Na} (nS)	1,500	3,000	3,000
Sodium equilibrium potential, E_{Na} (mV)	50		
Delayed-rectifier potassium conductance, g_K (nS)	520	400	140
M-type potassium conductance, g_M (nS)	-	3.5	1.5
M-type potassium time constant, τ_M (ms)	-	200	180
Potassium equilibrium potential, E_K (mV)	-100		-90
T-type calcium conductance, g_T (nS)	45	21	-
Calcium equilibrium potential, E_T (mV)	120		
H-current conductance, g_H (nS)	0.608	0.0192	-
H-current reversal potential, E_H (mV)	-33		-
Membrane capacitance, C_m (pF)	100.4	75.0	109.3865

1082 **Table 1.** Intrinsic model cellular parameters.

Model Synaptic Parameters						
Synapse	**Neurotransmitter**	**Conductance (nS)**	**τ_{recov} (ms)**	**τ_{inact} (ms)**	**Reversal Potential (mV)**	**U_{SE}**
External synapse to TC cell	(Glutamate)	32	125	2.64	0	0.76
TC-to-TRN cell synapse (TC-TRN)	Glutamate	150	500	2.64	0	0.76
TC-to-Co cell synapse (TC-Co)	Glutamate	50	160	11.52	0	0.8113
TRN-to-TC cell synapse (TRN-TC)	$GABA_A$	Variable (0-80)	167.29	16.62	-80	0.62
Chemical TRN-to-TRN cell synapse ($TRN\text{-}TRN_{GABA}$)	$GABA_A$	Variable (0-450)	225	15	-75	0.62

Table 2. Model synaptic parameters. τ_{recov}, synaptic recovery time constant; τ_{inact}, synaptic recovery time constant; U_{SE}, fraction of recovered resources (synaptic vesicles) that can be converted to an active state (Tsodyks and Markram, 1997).

Normalized Regression Coefficients for Homogeneously Varied Synaptic Networks				
Synaptic Variable	**Propagation Linear**	**Propagation 2°**	**Oscillation Linear**	**Oscillation 2°**
$TRN\text{-}TRN_{GABA}$	-0.173	-0.670	-	0.060
$TRN\text{-}TRN_{Elec}$	-0.136	-0.347	-	-
$Open_{TC\text{-}TRN\text{-}TC}$	1.000	1.000	-1.000	-0.052
$(TRN\text{-}TRN_{GABA})^2$	-	0.332	-	-
$(TRN\text{-}TRN_{Elec})^2$	-	0.164	-	-
$(Open_{TC\text{-}TRN\text{-}TC})^2$	-	0.594	-	-1.000
$TRN\text{-}TRN_{GABA}$ **x** $TRN\text{-}TRN_{Elec}$	-	0.262	-	-
$TRN\text{-}TRN_{GABA}$ **x** $Open_{TC\text{-}TRN\text{-}TC}$	-	-0.152	-	-
$TRN\text{-}TRN_{Elec}$ **x** $Open_{TC\text{-}TRN\text{-}TC}$	-	-0.365	-	-

Table 3. Normalized linear and second-order regression coefficients for propagation and oscillation in homogeneously varied synaptic networks. The regressions include 1°, 2°, and interaction terms corresponding to $TRN\text{-}TRN_{GABA}$, $TRN\text{-}TRN_{Elec}$, and TC-TRN-TC openness ($Open_{TC\text{-}TRN\text{-}TC}$). Terms associated with regression coefficients of absolute values < 0.05 are omitted. Linear regression for propagation, R^2=0.793, RMSE=0.047, p<0.0001; second-order regression for propagation, R^2=0.842, RMSE=0.041, p<0.0001; linear regression for oscillation, R^2=0.526, RMSE=0.145, p<0.0001; second-order regression for oscillation, R^2=0.630, RMSE=0.128, p<0.0001.

Normalized Regression Coefficients in Heterogeneously Varied Synaptic Networks				
Synaptic Variable	**Propagation Linear**	**Propagation 2°**	**Oscillation Linear**	**Oscillation 2°**
TRN_1-TRN_3	-	-	0.115	-
TRN_3-TRN_1	-0.088			
TRN_3-TRN_2	-0.084	-0.073	-	-
TRN_1=TRN_2	-0.051	-0.091	-	-
TRN_1=TRN_3	-0.072	-	-	-
TRN_2=TRN_3	-	-0.113	0.117	-
TRN_1-TC_1	-0.075	-	0.621	0.077
TRN_1-TC_2	0.608	0.571	-0.289	-1.000
TRN_2-TC_2	-0.128	-0.196	0.333	0.417
TRN_2-TC_3	1.000	1.000	-0.379	-0.892
TRN_3-TC_3	-0.207	-0.239	1.000	0.107
$(TRN_3\text{-}TRN_2)^2$	-	0.079	-	-
$(TRN_1\text{-}TC_2)^2$	-	-0.245	-	0.189
$(TRN_2\text{-}TC_2)^2$	-	0.174	-	-0.093
$(TRN_2\text{-}TC_3)^2$	-	-0.472	-	0.278
$(TRN_3\text{-}TC_3)^2$	-	0.187	-	-0.146
TRN_1-TRN_2 **x** TRN_1-TC_2	-	0.070	-	-
TRN_1-TRN_3 **x** TRN_3-TC_3	-	-	-	0.215
TRN_2-TRN_1 **x** TRN_1=TRN_2	-	-	-	0.111
TRN_2-TRN_1 **x** TRN_1-TC_1	-	-	-	-0.186

TRN_3-TRN_1 **x** TRN_1-TC_1	-	-	-	-0.172
TRN_3-TRN_1 **x** TRN_1-TC_2	-	-0.119	-	-
TRN_3-TRN_1 **x** TRN_2-TC_3	-	-0.096	-	-
TRN_3-TRN_2 **x** TRN_2-TC_3	-	-0.153	-	-
TRN_1=TRN_2 **x** TRN_2-TC_3	-	-	-	-0.129
TRN_1=TRN_3 **x** TRN_1-TC_1	-	-	-	-0.114
TRN_1=TRN_3 **x** TRN_3-TC_3	-	-0.079	-	-
TRN_1-TC_1 **x** TRN_1-TC_2	-	-	-	0.634
TRN_1-TC_1 **x** TRN_2-TC_3	-	-	-	0.449
TRN_1-TC_2 **x** TRN_2-TC_2	-	-0.166	-	0.361
TRN_1-TC_2 **x** TRN_2-TC_3	-	0.753	-	-0.274
TRN_1-TC_2 **x** TRN_3-TC_3	-	-0.106	-	0.669
TRN_2-TC_2 **x** TRN_2-TC_3	-	-	-	0.345
TRN_2-TC_2 **x** TRN_3-TC_3	-	-	-	-0.192
TRN_2-TC_3 **x** TRN_3-TC_3	-	-0.124	-	0.399

Table 4. Normalized linear and second-order regression coefficients for propagation and oscillation in heterogeneously varied synaptic networks. The regressions include 1°, 2°, and interaction terms corresponding to the 14 variable synapses in the networks. Equal signs denote gap junctions. Linear regression for propagation, R^2=0.742, RMSE=0.069, p<0.0001; second-order regression for propagation, R^2=0.857, RMSE=0.051, p<0.0001; linear regression for oscillation, R^2=0.253, RMSE=0.131, p<0.0001; second-order regression for oscillation, R^2=0.388, RMSE=0.118, p<0.0001.

Extended Data:

Extended Data 1. Raw and analyzed data and simulation and analysis code generated during this study.