Published in final edited form as:

J Neural Eng. 2019 February ; 16(1): 016013. doi:10.1088/1741-2552/aaeb03.

Rhythmic Modulation of Thalamic Oscillations Depends on Intrinsic Cellular Dynamics

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Abstract

Rhythmic brain stimulation has emerged as a powerful tool to modulate cognition and to target pathological oscillations related to neurological and psychiatric disorders. However, we lack a systematic understanding of how periodic stimulation interacts with endogenous neural activity as a function of the brain state and target. To address this critical issue, we applied periodic stimulation to a unified biophysical thalamic network model that generates multiple distinct oscillations, and examined thoroughly the impact of rhythmic stimulation on different oscillatory states. We found that rhythmic perturbation induces four basic response mechanisms: entrainment, acceleration, resonance and suppression. Importantly, the appearance and expression of these mechanisms depend highly on the intrinsic cellular dynamics in each state. Specifically, the low-threshold bursting of thalamocortical cells (TCs) in delta (δ) oscillation renders the network relatively insensitive to entrainment; the high-threshold bursting of TCs in alpha (α) oscillation leads to widespread oscillation suppression while the tonic spiking of TC cells in gamma (γ) oscillation results in prominent entrainment and resonance. In addition, we observed entrainment discontinuity during α oscillation that is mediated by firing pattern switching of high-threshold bursting TC cells. Furthermore, we demonstrate that direct excitatory stimulation of the lateral geniculate nucleus (LGN) entrains thalamic oscillations via an asymmetric Arnold tongue that favors higher frequency entrainment and resonance, while stimulation of the inhibitory circuit, the reticular nucleus, induces much weaker and more symmetric entrainment and resonance. These

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Declarations of interest: none

results support the notion that rhythmic stimulation engages brain oscillations in a state- and target-dependent manner.

Keywords

Thalamus; Oscillation; Stimulation; Entrainment; Resonance; Biophysical Model; Neuronal Network

Introduction

The thalamus plays a critical role in thalamocortical oscillations (Steriade et al., 1993; McCormick and Bal, 1997; Hughes et al., 2004; Huguenard and McCormick, 2007) and may be capable of independently generating multiple distinct oscillations (Li et al., 2017). Thalamic disturbances result in aberrant thalamocortical rhythms that have been associated with a number of neurological and psychiatric disorders such as Parkinson's disease, depression, and schizophrenia (Niedermeyer, 1997; Llinás et al., 1999; Hughes and Crunelli, 2005). Targeting abnormal thalamocortical oscillations with both invasive stimulation such as deep brain stimulation (DBS) and non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) have emerged as new and effective therapeutic techniques that aim to restore physiological brain dynamics (George et al., 1995; Benabid et al., 1996; McConnell et al., 2012; Leuchter et al., 2013). However, a mechanistic understanding of how these stimulation paradigms interact with endogenous neural activity and, in particular, neural oscillatory patterns in the thalamus is currently lacking. It is also not clear how the stimulation effects depend on the physiological state of the thalamus and the stimulation dose such as frequency and amplitude. Addressing these questions requires a mechanistic understanding of the mechanisms underlying thalamic oscillations and a systematic examination of the stimulation effects on thalamic network dynamics.

To understand the cellular and circuit mechanisms of thalamic oscillations, we have developed a unified biophysical thalamic network model containing both the lateral geniculate nucleus (LGN) and the reticular nucleus (TRN) of the thalamus (Fig. 1A; Li et al., 2017). The model is able to generate multiple distinct oscillations (δ , spindle, α and γ oscillations) as a function of neuromodulation and synaptic excitation (Fig. 1B). The successful manifestation of multiple distinct oscillations in one unified computational construct enabled us to study the impact of stimulation on thalamic network dynamics in different oscillatory states. As a proof of concept, we applied periodic stimulation to the thalamic network under three oscillatory states (δ , α and γ oscillations) and showed that entrainment of thalamic oscillations was state-dependent (Li et al., 2017). Nevertheless, as we focused on the cellular and circuit mechanisms of thalamic oscillations in the previous study (Li et al., 2017), the examination of stimulation on thalamic oscillations was limited. Notably, we used only one fixed stimulation amplitude (0.2 nA) and applied stimulation to the LGN only. In addition, a detailed analysis of how the emergence of response mechanisms related to intrinsic cellular dynamics was lacking. Thus, a more systematic investigation of the state-dependent stimulation effects on thalamic oscillations is needed.

In this study, we sought to provide a full account of how rhythmic stimulation modulates thalamic oscillatory dynamics by systematically varying the stimulation amplitude from weak to strong perturbation. In addition to ascending frequency stimulation, descending frequency stimulation was also explored to determine any possible stimulation history-dependent modulation effect. Moreover, we stimulated the TRN, the nucleus that inhibits the LGN and compared the effects with direct LGN stimulation. By employing the stimulation protocol consisting of periodic pulses (Li et al., 2017) that conceptually resemble DBS or rTMS, we examined thoroughly the effects of LGN or TRN stimulation on three major oscillatory states (δ , α , and γ oscillations). We found that entrainment of thalamic network oscillations critically depends on the endogenous frequency and that direct target engagement of thalamic oscillations is guided by an asymmetric Arnold tongue that favors higher frequency entrainment and resonance. The stimulation effects are state-dependent in that stimulation of fast frequency γ oscillation induces stronger entrainment and resonance while stimulation of lower frequency oscillations (δ and α) produces more prominent suppression. In addition, whether suppression occurs during stimulation of δ and α oscillations depends on the direction of stimulation. Moreover, stimulation is able to induce state transition by modulating the cellular dynamics. Overall, this biophysical modeling study offers mechanistic insights on the application of brain stimulation as a perturbation technique to target pathologically altered thalamic network dynamics associated with neurological and psychiatric disorders.

Methods

Network Structure

The thalamic network model was described in detail in our previous study (Li et al., 2017). Here we recapitulate the important features of the model. The network consists of four different types of neurons: high-threshold bursting thalamocortical cells (HTCs), relay-mode thalamocortical cells (RTCs), LGN local interneurons (INs) and thalamic reticular (RE) nucleus cells (Hughes et al., 2004; Lorincz et al., 2008, 2009). Specifically, the thalamic network contains 49 (7×7) HTC cells, 144 (12×12) RTC cells, 64 (8×8) IN cells and 100 (10×10) RE cells, all placed in a two-dimensional grid. The network connectivity among the four types of neurons is illustrated in Figure 1A. HTC cells are connected with gap junctions and provide feedforward excitation to INs, which in turn deliver feedforward inhibition to RTC cells (Lorincz et al., 2008, 2009). a small percentage (20%) of RTC cells are also connected with HTC cells via gap junctions (Lorincz et al., 2008). Both HTC and RTC cells send glutamatergic synapses to RE neurons, while receiving GABAergic feedback inhibition from the RE population (Pinault, 2004; Fuentealba and Steriade, 2005). RE neurons are connected with both gap junctions (Landisman et al., 2002; Landisman and Connors, 2005) and GABAergic synapses (Huntsman et al., 1999). Lastly, about 10% of RE neurons project GABAergic synapses to local interneurons (Liu et al., 1995). The gap junction connections are local (less than 2 unit distance) while the chemical synapses are global, both of which are random and relatively spare. Detailed network connectivity is given in Li et al. (2017).

Single-cell Models

All single cell models in the thalamic network contain one single compartment and multiple ionic currents described by the Hodgkin-Huxley formalism (Hodgkin and Huxley, 1952). The current balance equation is given by:

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{KL}(V - E_{KL}) - \sum I^{int} - 10^{-3} \sum \frac{I^{syn}}{A} + 10^{-3} \frac{I_{app}}{A} \quad (1)$$

where $C_m = 1 \mu\text{F}/\text{cm}^2$ is the membrane capacitance for all four types of neurons, g_L is the leakage conductance (nominal value: $g_L = 0.01 \text{ mS}/\text{cm}^2$ for all four types of cells) and g_{KL} is the potassium leak conductance modulated by both acetylcholine (ACh) and noradrenaline (NE). E_L is the leakage reversal potential ($E_L = -70 \text{ mV}$ for both HTC and RTC cells; $E_L = -60 \text{ mV}$ for both IN and RE neurons), and E_{KL} is the reversal potential for the potassium leak current ($E_{KL} = -90 \text{ mV}$ for all neurons), I^{int} and I^{syn} are the intrinsic ionic currents (in $\mu\text{A}/\text{cm}^2$) and synaptic currents (in nA) respectively and I_{app} is the externally applied current injection (in nA). The following total membrane area was used to normalize the synaptic and externally applied currents in Eqn (1): HTC and RTC cells: $2.9/10^{-4} \text{ cm}^2$ (McCormick and Huguenard, 1992); INs: $1.7 \times 10^{-4} \text{ cm}^2$ (Zhu et al., 1999); RE cell: $1.43 \times 10^{-4} \text{ cm}^2$ (Destexhe et al., 1996; Bazhenov et al., 2002). The modeled ionic currents with detailed kinetics information for each cell type can be found in Li et al. (2017).

Synaptic currents and short-term synaptic depression

The gap junctional current was computed as $I_{gap} = (V_{post} - V_{pre})/R_g$, where V_{pre} and V_{post} are the membrane potentials of the presynaptic and postsynaptic neurons respectively. In the model, glutaminergic synaptic current was mediated by both AMPA and NMDA receptors, while GABAergic synaptic current was mediated by GABA_A receptors. The synaptic current was calculated by the following equation (Wang and Buzsáki, 1996; Li and Cleland, 2013):

$$I_{syn} = g_{syn} s B(V) (V - E_{syn}) \quad (2)$$

where g_{syn} is the maximal synaptic conductance and E_{syn} is the synaptic reversal potential. The function $B(V)$, which implements the Mg^{2+} block for NMDA currents, is defined as $B(V) = 1/(1 + \exp(-(V + 25)/12.5))$ (Traub et al., 2001; Bazhenov et al., 2002). For AMPA and GABA_A currents, $B(V) = 1$. The gating variable s represents the fraction of open synaptic ion channels and obeys a first-order kinetics (Destexhe et al., 1993, 1994):

$$\frac{ds}{dt} = \alpha [T] (1 - s) - \beta s \quad (3)$$

where $[T]$ is the concentration of neurotransmitter in the synapse and α and β are forward and backward binding rates. The neurotransmitter is assumed to be a brief pulse that has duration of 0.3 ms and amplitude of 0.5 mM following an action potential in the presynaptic neuron (Destexhe et al., 1996). All synaptic parameters including the maximal synaptic

conductance, synaptic reversal potentials and channel rate constants are given in Li et al. (2017).

Short-term synaptic depression was implemented in all chemical synapses and was modeled by scaling the maximal conductance of a given synaptic channel by a depression variable D , which represented the amount of available “synaptic vesicles” (Bazhenov et al., 2002; Hill and Tononi, 2015). The variable D was updated according to a simple phenomenological rule (Abbott et al., 1997; Bazhenov et al., 2002):

$$D = 1 - (1 - D_i(1 - U))\exp\left(-\frac{t - t_i}{\tau}\right) \quad (4)$$

where $U = 0.07$ is the fraction of resources used per action potential, $\tau = 700$ ms is the time constant of recovery of the synaptic vesicles. D_i is the value of D immediately before the i th presynaptic spike and t_i is the timing of the i th spike event.

External inputs and neuronal heterogeneity

All neurons in the thalamic network received independent Poisson-distributed spike inputs at an average rate of 100 Hz (results maintained unchanged when higher input rates were used by scaling down the maximal synaptic input conductance). These random inputs represent both extrinsic sources of background noise and asynchronous visual inputs. Such inputs were exclusively mediated by AMPA receptors modeled as an instantaneous step followed by an exponential decay with a time constant of 5 ms (Fröhlich and McCormick, 2010). To introduce heterogeneity to model neurons, the leakage conductance (g_L) of all network neurons was drawn from a uniform distribution within $\pm 25\%$ of the default value (i.e., 0.0075 - 0.0125 mS/cm²). This leak conductance variation, random synaptic connectivity and random external inputs constituted all model noise in the thalamic network.

Model parameters for different oscillatory states

The thalamic network model is able to generate four different oscillatory states (δ , spindle, α , and γ oscillations) by varying the maximal conductance density of the potassium leak current and the random input strength (Li et al., 2017). Each of the oscillatory state corresponds to one specific behavioral condition under different cholinergic and noradrenergic modulatory level with different afferent input. Specially, δ oscillation is generated in the low ACh/NE modulation state with minimal afferent input; spindle oscillation is generated in the medium ACh/NE modulation state with slight afferent input; α and γ oscillations are generated in the high ACh/NE modulation state with weak and strong afferent inputs to TC cells, respectively (Fig. 1B; Li et al., 2017). Detailed information on model parameter selection for each oscillatory state is given in Li et al., (2017).

Stimulation protocol

During stimulation, either the LGN or TRN was stimulated. We selected a periodic pulsatile stimulus (Fig. S1A) that conceptually resembled the waveform of deep brain stimulation (DBS) or repetitive transcranial magnetic stimulation (rTMS) (Herrmann et al., 2016). The

stimulation was assumed to be global: all neurons in the LGN (TC & IN cells) or TRN (RE cells) received the same stimulus. Stimulation consisted of a train of 10 ms brief square current pulses applied at different frequency. During a typical (ascending) stimulation run, the stimulation frequency increased from 1 Hz to 50 Hz with a 1 Hz/step increment. In some other stimulation runs, the ascending frequency stimulation was followed by descending frequency stimulation where the stimulation frequency decreased from 50 Hz back to 1 Hz with a 1 Hz/step decrement. The stimulation amplitude was fixed during each stimulation run and different amplitude was tested in different run. Stimulation was performed under three major oscillatory states (δ , α and γ oscillations) and stimulation at each frequency lasted for 1 second. In addition to the monophasic stimulus, we used a biphasic charge balanced stimulus that contained both the depolarizing and hyperpolarizing phases (Fig. S1B). The pulse duration was reduced to 2 ms and there was an interphase delay of 2 ms to reduce the suppressing effect of the hyperpolarizing phase (Merrill et al., 2005). Such a stimulation waveform represents a good compromise between efficiency and safety (Merrill et al., 2005; Popovych et al., 2017). Besides, higher stimulation frequency (1-150 Hz) was tested for the biphasic pulses in order to understand possible mechanisms of DBS (Kuncel and Grill, 2005).

Simulated local field potential and spike phases

A simulated local field potential (sLFP) was constructed by filtering the mean membrane potentials across all TCs (Bathellier et al., 2006; Brea et al., 2009; Vijayan and Kopell, 2012; Li and Cleland, 2013):

$$sLFP = \frac{1}{N} \sum_{i=1}^N V_{TC}^i \quad (5)$$

where N is number of all TC cells. Filtering was carried out numerically using a band-pass filter (0.5-80 Hz for monophasic stimulus and 0.5-150 Hz for biphasic stimulus) with the MATLAB functions FIR1 and FILTFILT (Brea et al., 2009). The frequency power spectrum of the signal was obtained by a fast Fourier transform (FFT) of the filtered sLFP. The network oscillation frequency was determined from the position of the spectral peak in the frequency spectrum. During stimulation of fixed amplitude, the frequency power spectrum was calculated during each stimulation frequency step (i.e., 1 second) and the power spectrum heat map was generated using the MATLAB function IMAGESC. To assess network synchrony (see below), TC spike times were converted to phases with respect to the sLFP using the same procedures described in Li and Cleland (2013). Specifically, the positive peaks of the sLFP were assigned a phase of 0° (or 360°), and the phase of each spike (ϕ) was computed according to the equation (Lagier et al., 2004):

$$\phi = \frac{t_{spike} - t_{lastLFPpeak}}{t_{nextLFPpeak} - t_{lastLFPpeak}} \times 360 \quad (6)$$

where t_{spike} is the spike time, $t_{lastLFPpeak}$ is the time of the preceding positive sLFP peak, and $t_{nextLFPpeak}$ is the time of the following positive sLFP peak.

Synchronization and oscillation indices

The synchronization index ($\mathcal{SI}$) was calculated as follows (Bathellier et al., 2006; Li et al., 2017):

$$\kappa = 1 / N \sqrt{[\sum_{i=1}^N \sin(\varphi_i)]^2 + [\sum_{i=1}^N \cos(\varphi_i)]^2} \quad (7)$$

where φ_i was the phase of each spike relative to the sLFP peaks and N was the total number of spikes for both HTC and RTC cells. This metric reflects the length of phase distribution vector (Bathellier et al., 2006) and measures the degree of mutual synchronization between neurons: when all spikes have identical phases, the index achieves its maximal value of unity. The oscillation index ($\mathcal{OI}$) was measured by the (maximal) spectral peak in the frequency power spectrum of sLFP (Li and Cleland, 2013, 2017), which was normalized by the original spectral peak (without stimulation) under each oscillatory state to facilitate comparison among different states. This index serves as a direct measure of the oscillation power and reflects the amplitude of the sLFP oscillations (Fig. S2).

Frequency entrainment map

To obtain the frequency entrainment map and spectral peak power heat map, we stimulated the LGN or TRN with different stimulation amplitude ranging from 0.0 nA to 0.5 nA with a 0.025 nA increment per step. For each fixed stimulation amplitude, the LGN or TRN was stimulated with a continuous range of frequency ranging from 1 to 50 Hz with 1 Hz per increment. For each (stimulation) frequency step, we computed the frequency power spectrum of the sLFP and located the dominant spectral peak with corresponding dominant frequency. The spectral peak power was normalized to the original spectral peak without stimulation to generate the spectral peak power heat map (using the MATLAB function IMAGESC). The network was judged to be entrained at a particular stimulation frequency (f_s) if the dominant oscillation frequency (f_d), spectral peak power ($P_{\max}$) and the average TC firing rates (F_{HTC} and F_{RTC}) satisfied the following criteria:

$$|mf_s - nf_d| < \epsilon \quad (8)$$

$$\frac{P_{\max}}{P_0} > \sigma \quad (9)$$

$$F_{\text{HTC}} > 1 \text{ and } F_{\text{RTC}} > 1 \quad (10)$$

where P_0 was the spectral peak without stimulation; ϵ and σ were the frequency and amplitude thresholds ($\epsilon = 0.55$ Hz and $\sigma = 0.35$). For principal (1:1) entrainment, $m = n = 1$; for subharmonic entrainment, $m = 1$ and $n = 2$; for harmonic entrainment, $m = 2$ and $n = 1$.

The power criterion ensured that the network was not counted as entrained if the oscillation power was too weak (compared with the original power without stimulation) even if the dominant frequency was sufficiently close to the stimulation frequency or its harmonics/subharmonics. To obtain the average TC firing rates (F_{HTC} and F_{RTC}), the firing rates of each individual HTC and RTC cells were calculated first during each 1 second stimulation time window (for each stimulation frequency) and then averaged among the HTC and RTC population. The firing rate criterion made sure that both HTC and RTC cells had minimal spiking activity during entrainment. Using these criteria, all entrained frequency (principal, subharmonic and harmonic) for each stimulation amplitude was identified to generate the frequency entrainment map.

Numerical method

The thalamic network model was coded with C++. All simulation was performed using the fourth-order Runge-Kutta [RK(4)] method with a fixed time step of 0.02 ms. Shorter simulation step did not change the results. Simulations were run on a Dell Linux workstation under Fedora. a complete run of one full stimulation protocol (101 seconds of network activity) took about 12 hours of computing time. The model source codes are available in the ModelDB database (<http://modeldb.yale.edu/233509>; Accession number 233509).

Results

In our previous study (Li et al., 2017), we demonstrated that the thalamic network was able to generate multiple distinct oscillatory states (δ , spindle, α and γ oscillations) dependent on acetylcholine (ACh) and norepinephrine (NE) modulation and afferent excitation level (Fig. 1B). The firing patterns of two representative HTC and RTC cells each during δ , α and γ oscillations are shown in Figure 1C, D and E respectively. Notably, HTC cells fired low-threshold bursts (LTBs) during δ oscillation, high-threshold bursts (HTBs) during α oscillation and tonic spiking during γ oscillation. By comparison, RTC cells displayed LTBs during δ oscillation and tonic spiking during both α and γ oscillations. The TC cell activity during the three oscillatory states is shown in Figure 2A1, B1 and C1 respectively (reproduced from Li et al., 2017). Both HTC and RTC spikes were highly synchronized during δ and α oscillations and the neuronal bursting dynamics (i.e., number of spikes per burst) was stronger during δ oscillation than α oscillation (compare Fig. 2A1 with Fig. 2B1). In contrast, the network synchronization was substantially reduced during high-frequency γ oscillation (compare Fig. 2C1 with Fig. 2A1, B1; SI , δ oscillation: 0.93; α oscillation: 0.93; γ oscillation: 0.27). We first studied in details how stimulation of the LGN with different combinations of stimulation frequency and amplitude impacts the endogenous network dynamics for each of the three oscillatory states (δ , α and γ oscillations). Next we applied the same stimulation waveform to the TRN and compared the major stimulation effects with LGN stimulation.

Stimulation induces four major response patterns: entrainment, acceleration, resonance and suppression

Consistent with a recent computational study of an abstract cortical model (Herrmann et al., 2016), LGN stimulation induced entrainment, acceleration and resonance in the thalamic

network model under all three oscillatory states. Entrainment is a response pattern where the intrinsic oscillations are locked to the phasic stimulus (Antonsen et al. 2008; Herrmann et al. 2016; Li et al. 2017). In addition to principal entrainment (the dominant network frequency locks to the stimulation frequency in a 1:1 manner), there existed subharmonic entrainment (the dominant network frequency locks to the subharmonics of stimulation frequency) as well as harmonic entrainment (the dominant network frequency locks to the harmonics of stimulation frequency) during stimulation of thalamic oscillations (Li et al., 2017). The TC cell activity during subharmonic, principal and harmonic entrainment is illustrated in Figure 2A2, B2 and C2 respectively. During (the first) subharmonic entrainment, the dominant network oscillation frequency was locked to half of the stimulation frequency (6:12 Hz; Fig. 2A3), while during principal and (the first) harmonic entrainment, the network oscillation frequency was locked to the stimulation frequency (12:12 Hz; Fig. 2B3) and twice of the stimulation frequency (34:17 Hz; Fig. 2C3), respectively. Under certain circumstances, the dominant network frequency was not locked to the stimulation frequency, but was shifted (or increased) by stimulation, a response pattern termed oscillation acceleration (Herrmann et al., 2016). For instance, in response to 50 Hz stimulation (0.2 nA) during γ oscillation, the network response frequency increased from the endogenous 30.5 Hz to 40 Hz (Fig. 3C).

In addition to frequency modulation, stimulation also shaped the network synchronization or oscillation power (Popovych and Tass, 2011; Herrmann et al. 2016). One such prominent response pattern was resonance, an enhancement of intrinsic oscillations when the stimulation frequency was close to the endogenous frequency (principal resonance), its harmonics (harmonic resonance) and/or subharmonics (subharmonic resonance) (Herrmann, 2001; Herrmann et al. 2016; Li et al., 2017). One important feature of resonance was that the network synchrony was enhanced by stimulation. For example, when the LGN was stimulated at 5 Hz during δ oscillation (endogenous frequency: 3.7 Hz), the bursting activity of RTC cells became more synchronized than without stimulation (compare Fig. 3A1 with Fig. 2A1; *SI*, controls: 0.93; 5 Hz stimulation: 0.99). As a result, the oscillation power under resonance was significantly increased compared to controls (Fig. 3A2). Note that here the concept of resonance has been extended from regular passive systems (Pikovsky et al., 2001) to intrinsic neural oscillators (i.e., the thalamic network exhibits endogenous or self-sustained oscillations; Hutcheon and Yarom, 2000; Herrmann, 2001; Herrmann et al. 2016; Lefebvre et al., 2017). In addition, resonance is not a mere enhancement of oscillation power or synchronization, but rather a property where the oscillating network responds or synchronizes maximally when the stimulation frequency matches the intrinsic frequency of the neural network. Besides resonance, we observed an opposite response type that shaped the oscillatory dynamics of the thalamic network: oscillation suppression or desynchronization (Popovych et al., 2005; Popovych and Tass, 2011; Li et al., 2017; Popovych et al., 2017). For example, during high frequency (30 Hz) stimulation of α oscillation, the oscillation power was substantially reduced (Fig. 3B2). At the same time, TC spike synchronization significantly decreased (compare Fig. 3B1 with Fig. 2B1; *SI*, controls: 0.93; 30 Hz stimulation: 0.75).

It should be noted that different response patterns could occur simultaneously. Due to the fact that the network is more prone to be entrained around the endogenous frequency and its harmonics/subharmonics (see below), resonance and entrainment often took place

simultaneously. For example, as described above, during 12 Hz stimulation of δ oscillation (0.2 nA), subharmonic entrainment was induced as the dominant network frequency (6 Hz) was locked to the subharmonics of the stimulation frequency (Fig. 2A2, A3). At the same time, stimulation significantly enhanced the oscillation power, resulting in harmonic resonance (12 Hz was close to the harmonics of the endogenous frequency; Fig. 2A3). Besides, oscillation acceleration and suppression could also occur simultaneously. As illustrated in Figure 3B, stimulation (0.2 nA, 30 Hz) not only significantly suppressed the oscillation power, but also increased the dominant network frequency from endogenous 9.2 Hz to 17.7 Hz.

Effects of stimulation depend on intrinsic cellular dynamics in different oscillatory states

To examine how different response patterns unfolded as a function of stimulation frequency and amplitude, we generated the normalized color-coded frequency power spectrum of the sLFP (i.e., frequency spectrum heat map) in response to ascending LGN stimulation (1-50 Hz) with three different stimulation amplitudes (0.075, 0.15 and 0.225 nA) for all three oscillatory states (δ , α and γ oscillations) in Figure 4. In addition, to examine how stimulation modulated the dominant oscillation dynamics and network synchronization, we plotted the peak network oscillation frequency, oscillation index (normalized spectral peak) along with synchronization index (S_I) as a function of the stimulation frequency in response to the same three stimulation amplitudes for the three oscillatory states in Figure 5. Of note, the normalized spectral peak was found to follow closely with the standard deviation of sLFP time series (Fig. S2), thus reflecting the amplitude of sLFP oscillations.

Several common effects can be observed on the dynamical interaction between stimulation and endogenous network oscillation across the three oscillatory states. First, entrainment started from around the endogenous frequency and expanded with increased stimulation intensity. Entrainment was reflected by the highlighted spectral power along the diagonal with multiple harmonic and/or subharmonic components (above and below the diagonal) in the frequency spectrum heat map (Fig. 4). The highlighted spectral power along the diagonal was relatively low and restricted to the area close to the endogenous frequency when the stimulation amplitude was relatively small (0.075 nA; Fig. 4A1-C1), but expanded considerably with higher levels of stimulation amplitude (0.15 and 0.225 nA; Fig. 4A2-C2, A3-C3). This suggested that stimulation with frequency close to the endogenous frequency could more effectively entrain the thalamic network than stimulation with frequency relatively far from the endogenous frequency (i.e., the stimulation force required to entrain the network was smaller). This observation was consistent with previous findings that systems of coupled oscillators failed to be entrained by periodic drive if the stimulation frequency was significantly different from the average frequency of the phase oscillators (Antonsen et al., 2008). Second, resonance also increased with stimulation intensity, as indicated by warmer color around the endogenous frequency and its harmonics/subharmonics with higher stimulation amplitude (Fig. 4; also see Fig. 5). In addition, the resonance peak was associated with increase of synchronization index (Fig. 5), suggesting that resonance was mediated by stimulation-induced network synchronization. Lastly, as the stimulation intensity increased, the endogenous oscillation dynamics gradually decreased, while the stimulation-induced dynamics started to dominate. For example, during

stimulation of α oscillation, when the stimulation amplitude was 0.075 nA, the endogenous dynamics (with a peak frequency of around 9 Hz) dominated with only narrow range of suppression at high frequency (around 40 and 50 Hz; Fig. 4B1, Fig. 5B1). When the stimulation amplitude increased to 0.15 nA, the entrained frequency (around 10 Hz) increased and the frequency range for suppression substantially expanded (compare Fig. 4B2 with Fig. 4B1, and Fig. 5B2 with Fig. 5B1). Notably, during suppression, the endogenous oscillation mostly disappeared (Fig. 4B2). Entrainment and suppression further increased for larger stimulation intensity (0.225 nA) and the endogenous dynamics maintained only when the stimulation frequency was less than 8 Hz (Fig. 4B3, Fig. 5B3). Such dynamical interaction was also evident during stimulation of γ oscillation where the diagonal power enhanced with simultaneous reduction of the endogenous oscillation power (peak frequency: 30-35 Hz) as the stimulation amplitude increased (Fig. 4C1-C3).

Despite the similarities in response, stimulation also induced substantially different effects among the three oscillatory states, even for the same response pattern. First, stimulation of γ oscillation evoked much stronger entrainment and resonance than δ and α oscillations, as described briefly in an earlier study (Li et al., 2017). Such differential effect was more prominent in response to higher stimulation intensities (0.15 and 0.225 nA), where both the frequency range of entrainment and the degree of resonance (reflected by highlighted spectral power along the diagonal) were larger during stimulation of γ oscillation than δ and α oscillations (compare Fig. 4C2, C3 with Fig. 4A2, A3 and Fig. 4B2, B3). In addition, the resonance peak was much wider during stimulation of γ oscillation than δ and α oscillations (compare Fig. 5C2, C3 with Fig. 5A2, A3 and Fig. 5B2, B3, *bottom*, enclosed by red ellipses). Second, δ oscillation was most robust to stimulation modulation. During stimulation of δ oscillation, the entrained frequency range only slightly increased when the stimulation amplitude increased from 0.075 nA to 0.225 nA (from 4-8 Hz to 3-10 Hz; Fig. 5A1-A3, *top*, enclosed by red ellipses). By comparison, the entrained frequency range expanded more substantially during stimulation of α and γ oscillations (Fig. 5B1-B3, Fig. 5C1-C3, *top*, enclosed by red ellipses). Also, in response to the largest stimulation (0.225 nA), substantial endogenous dynamics (with slight increase of peak frequency) persisted for δ oscillation (between 20 and 45 Hz stimulation; Fig. 4A3, Fig. 5A3), while the endogenous dynamics was greatly suppressed for α oscillation (> 20 Hz stimulation, Fig. 4B3, Fig. 5B3) and predominantly given way to entrainment for γ oscillation (> 10 Hz stimulation, Fig. 4C3, Fig. 5C3). Lastly, stimulation induced greater suppression during α oscillation than the other two states. During stimulation of α oscillation, large suppression (< 50% of original power) started to emerge with low intensity (0.075 nA, around 40 and 50 Hz; Fig. 4B1, Fig. 5B1) and the suppression frequency range rapidly expanded for larger stimulation intensities (0.15 nA and 0.225 nA, Fig. 4B2, B3; Fig. 5B2, B3). During suppression, the synchronization index was generally decreased (Fig. 5B), indicating that suppression was mediated in part by synchronization reduction (suppression was also caused by decrease in sLFP oscillation amplitude, see below). Notably, we observed a state of desynchronization with simultaneous entrainment of the sLFP oscillation (a sharp drop of *SI* between 24-29 Hz was associated with principal entrainment, Fig. 5B3). Our results concur with a previous study reporting the coexistence of neuronal desynchronization with entrainment of population field potential by periodic forcing (Popovych and Tass, 2011). By comparison,

such strong suppression occurred only with relatively large amplitude (0.225 nA) during stimulation of δ oscillation (> 45 Hz stimulation; Fig. 4A3, Fig. 5A3), and no strong suppression existed during stimulation of γ oscillation (Fig. 4C, Fig. 5C).

We hypothesized that the differential stimulation effects on different oscillation states resulted from different intrinsic cellular dynamics. First, the existence of low-threshold bursting dynamics in both HTC and RTC cells enabled the robustness of δ oscillation to external perturbation. As shown in Figure 6A1, in response to large-amplitude and high-frequency stimulation (0.225 nA, 40 Hz), both HTC and RTC cells maintained LTBs with only slight oscillation acceleration (default: 3.7 Hz; with stimulation: 6.7 Hz; Fig. 6A3). In addition, both HTC and RTC bursts remained highly synchronized and the oscillation power with stimulation was higher than controls (Fig. 6A3). Thus, the intrinsic low-threshold bursting dynamics of TC cells during δ oscillation limited the entrained frequency range and permitted relatively stable oscillation during stimulation. Second, stimulation-induced transition from high-threshold bursting to tonic spiking in HTC cells underlay widespread suppression of α oscillation. In response to the same large-amplitude and high-frequency stimulation (0.225 nA, 40 Hz), HTC cells converted high-threshold bursting to tonic spiking (compare Fig. 6B1 with Fig. 1D, *top*), which by itself reduced the amplitude of sLFP oscillation (Fig. S2B). At the same time, RTC firing was greatly suppressed (compare Fig. 6B2 with Fig. 2B1, *bottom*) because of a combination of three factors: (1) reduced excitation from HTC cell (through the gap junctions); (2) increased random inhibition from INs; and (3) stimulation-induced inactivation of the low-threshold T-type Ca^{2+} channel. As a result, the network oscillation power was significantly reduced (Fig. 6B3). Notably, the switch from high-threshold bursting to tonic spiking in HTC cells substantially extended the entrained frequency range when subjected to large-amplitude stimulation (compare Fig. 5B3 with Fig. 5B1, B2, *top*). Lastly, the tonic spiking behavior of both HTC and RTC cells during γ oscillation allowed for wide-spread entrainment and strong resonance by stimulation. Unlike δ and α oscillations, both HTC and RTC neurons fired tonic spiking during γ oscillation (compare Fig. 1E with Fig. 1C, D). In addition, the spiking activities of HTC and especially RTC cells during γ oscillation were much less synchronized than δ and α oscillations (compare Fig. 2C1 with Fig. 2A1, B1). As a result, in response to rhythmic stimulation of a wide frequency range, the network became readily entrained and the synchronization of both HTC and RTC cells increased (compare Fig. 6C2 with Fig. 2C1). The synchronization index with the same large-amplitude and high-frequency stimulation (0.225 nA, 40 Hz) was 0.40, which was considerably higher than that without stimulation (0.27) and led to substantially larger oscillation power (Fig. 6C3). Therefore, when TC cells fired relatively unsynchronized tonic spiking during γ oscillation, the thalamic network became more responsive to phasic stimulation compared with δ and α oscillations where TC cells fired synchronized bursting.

Entrainment discontinuity during stimulation of α oscillation is mediated by firing pattern switching of HTC cells

Interestingly, we observed an “entrainment discontinuity” or “entrainment skipping” effect during stimulation of α oscillations (Fig. 5B3, *top*). The frequency range of principal entrainment (enclosed by red ellipses) and subharmonic entrainment (enclosed by blue

ellipses) was not continuous and was divided into several small patches (Fig. 5B3, *top*). They appeared either alternatively or were separated by oscillation acceleration. To understand such entrainment discontinuity effect, we plotted HTC cell activity at representative entrained (principal or subharmonic) and non-entrained stimulation frequencies in Figure 7. When the stimulation frequency (12 Hz) was close to the endogenous α frequency (9.2 Hz), HTC cells maintained HTBs which were tightly entrained by the stimulation pulses (Fig. 7A). As the stimulation frequency increased to 15 Hz, oscillation acceleration occurred and the network oscillated at 13 Hz (Fig. 5B3, *top*) where HTC cells fired a mix of bursts and single spikes (Fig. 7B). When the stimulation frequency increased further (e.g., 20 Hz), HTC bursts were completely converted into tonic spikes which became entrained by the stimulation again (Fig. 7C). Hence, the first oscillation acceleration or discontinuity was generated when HTC cells were in transition from the high-threshold bursting mode to the tonic spiking mode. During this stimulation region, the HTC intrinsic bursting dynamics was perturbed, but not completely overcome by stimulation, resulting in alternation of entrainment and unentrainment (Fig. 5B3, *top*). The principal entrainment reestablished after the transition when the HTC firing pattern completely switched from bursting to single spiking. As the stimulation frequency reached 22 Hz, slightly higher than the harmonic frequency, subharmonic entrainment (2:1) was induced where the network oscillated at half of the stimulation frequency (11 Hz, Fig. 5B3, *top*; enclosed by the left blue ellipse). Surprisingly, HTC cells switched from tonic spiking back to bursting during subharmonic entrainment (Fig. 7D). When the stimulation frequency further increased (e.g., 24 Hz), HTC bursting started to transition to single spiking again to enable 1:1 principal entrainment (Fig. 7E). Thus, the discontinuity in principal entrainment was also caused by subharmonic entrainment mediated by a switch back to burst firing pattern in HTC cells (Fig. 5B3, *top*). With higher stimulation frequency (30-35 Hz), principal entrainment gave way to oscillation acceleration again and the thalamic network oscillated at around 18 Hz (Fig. 5B3, *top*). Interestingly, when the stimulation frequency was close to the third harmonic frequency (36-44 Hz), subharmonic entrainment (2:1) reemerged (Fig. 5B3, *top*; enclosed by the right blue ellipse). The TC cell activity during 36 Hz stimulation is shown in Figure 7F where both HTC and RTC cells fired synchronized tonic spiking at 18 Hz, half of the stimulation frequency. Overall, both principal and subharmonic entrainment could be mediated by either bursting or tonic spiking of HTC cells. As the stimulation frequency increases, HTC cells switched between bursting and tonic spiking, leading to alternation of principal and subharmonic entrainment. In addition, oscillation acceleration was generated during the transition from bursting to tonic spiking or from principal entrainment to subharmonic entrainment (Fig. 5B3, *top*), adding to entrainment discontinuity. The phenomenon of entrainment discontinuity persisted when a smaller frequency step increment or longer stimulation time window was applied (see Supplemental Materials and Fig. S3).

High frequency LGN stimulation strongly suppresses δ and α oscillations and induces hysteresis

As shown in Figure 5A3 (*bottom*), strong oscillation suppression occurred during stimulation of δ oscillation in the presence of large amplitude (> 0.2 nA) and high frequency (> 45 Hz) stimulation. Interestingly, when applying the full stimulation protocol with both

ascending and descending frequency stimulation, suppression resulted in bistability or hysteresis, a phenomenon characteristic of nonlinear systems. The dominant oscillation frequency with normalized spectral peak in response to 0.3 nA stimulation is shown in Figure 8A1. As the stimulation frequency increased from 1 to 40 Hz, the spectral peak maintained mostly above the baseline (Fig. 8A1, *bottom*). However, when the stimulation frequency increased beyond 40 Hz, the spectral peak was significantly suppressed ($< 35\%$ of the control value) until the stimulation frequency decreased below 16 Hz (Fig. 8A1, *bottom*). During suppression, both HTC and RTC cells stopped bursting (Fig. 8A3, *top two panels*). Thus, there existed two stable network states between 16 Hz and 40 Hz stimulation, depending on the direction of the stimulation. During ascending stimulation, TC cells fired rhythmic (low-threshold) bursting (Fig. 8A2, *top two panels*), while during descending stimulation, TC cells stopped bursting and the network was in a quiescent state (Fig. 8A3, *top two panels*). In the case of suppression, because the membrane potentials of TC cells were modulated by the phasic stimuli, the oscillation frequency calculated from the sLFP was equal to the stimulation frequency (Fig. 8A1, *top*). However, because of complete burst suppression, such passive frequency following was not considered to be entrainment.

Strong oscillation suppression also occurred during stimulation of α oscillation and the threshold frequency for suppression decreased with stimulation amplitude (Fig. 5B). Similarly, suppression was accompanied with hysteresis effect when the full stimulation protocol was applied. Figure 8B1 shows the dominant oscillation frequency (*top*) with normalized spectral peak (*bottom*) in response to 0.1 nA stimulation. The thalamic network was strongly suppressed beginning at about 40 Hz during ascending frequency stimulation and the suppression maintained until the stimulation frequency decreased below 26 Hz (Fig. 8B1, *bottom*). During suppression, the spectral peak was reduced to about 30% of the original peak without stimulation. Hence, between 26 Hz and 40 Hz stimulation, there existed two stable network states depending on the direction of the stimulation. Either, HTC cells fired rhythmic bursting and RTC cells had robust spiking activity (Fig. 8B2, *top two panels*) or, HTC cells fired tonic spiking and RTC cells were greatly suppressed (Fig. 8B3, *top two panels*).

To investigate whether the hysteresis induced by stimulation arose from the cellular property or network interaction, we stimulated an isolated single HTC model cell in both low and high ACh/NE modulation states using the same stimulation protocol. In the low modulation state (where δ oscillation was generated), hysteresis emerged in the HTC model cell in response to 0.3 nA stimulation (Fig. S4A). Hence, hysteresis or bistability associated with suppression of δ oscillation resulted from intrinsic TC cell property, and was not primarily a network phenomenon. The reason why TC cells stopped bursting in response to high-frequency and large-amplitude stimulation was because there exists a quiescent resting state during the input-driven transition from low-threshold bursting to tonic spiking (Fig. S1 of Li et al. 2017). In contrast, in the high modulation state (where α oscillation was generated), oscillation suppression with hysteresis was not observed during stimulation of an isolated HTC model cell (Fig. S4B). Therefore, hysteresis associated with oscillation suppression evoked during stimulation of α oscillation was primary a network phenomenon (i.e., suppression of RTC activity when HTC bursting switched to tonic spiking). Nevertheless, during both δ and α oscillations, whether the network was suppressed or not (in certain

frequency range) depended on its previous state thus forming a bistable circuit. Notably, hysteresis associated with oscillation suppression was not observed during stimulation of γ oscillation (Fig. S5), mainly because stimulation did not induce strong suppression on γ oscillation (Fig. 4C).

Stimulation drives endogenous oscillations to cross different frequency bands by altering the neuronal or population dynamics

With sufficient amplitude, stimulation was able to drive endogenous thalamic oscillations to cross different frequency bands. For example, with an intensity of 0.3 nA, stimulation was able to entrain δ oscillation between 3 and 13 Hz (Fig. 8A1, *top*; enclosed by red ellipse), thus extending δ oscillation into both θ and α frequency bands. Similarly, simulation with the same intensity (0.3 nA) entrained γ oscillation from 20 up to 50 Hz (Fig. S5C, *top*), covering the frequency range of both β and γ bands. The crossover between different frequency bands was accompanied with or without alternation in the underlying neuronal or population dynamics of the thalamic network. For instance, in response to 6 Hz stimulation (0.3 nA) during δ oscillation, the network oscillation frequency was switched from the δ frequency band (3.7 Hz) to the θ frequency band (6 Hz), and TC neurons maintained highly synchronized LTBs (Fig. 9A1, A2). By comparison, in response to 12 Hz stimulation of 0.3 nA, though both HTC and RTC cells maintained LTBs, the population dynamics was altered by stimulation (Fig. 9B). Specifically, HTC neurons exhibited subharmonic entrainment (2:1) and burst at 6 Hz (Fig. 9B1, B2, *top*), while RTC cells were broken into two subpopulations with each population bursting at 6 Hz (Fig. 9B1, B2, *middle*). As the two RTC subpopulations burst out of phase, the overall bursting frequency was doubled to 12 Hz, the same as the stimulation frequency. The different entrainment behaviors between HTC and RTC cells resulted from the fact that HTC cells were coupled with gap junctions, while RTC cells were not (Lorincz et al., 2008, 2009). Hence, when the stimulation frequency was relatively far from the endogenous frequency, the population dynamics of the thalamic network may be changed to enable oscillation to switch from the δ frequency band (3.7 Hz) to the α frequency band (12 Hz).

We found that the crossover between different frequency bands can also be mediated by a switch in the neuronal firing dynamics. As shown in Fig. 1D and E, HTC cells fired double-spike bursts and tonic spikes during endogenous α and γ oscillations respectively. During 20 Hz stimulation (0.225 nA) of α oscillation, the thalamic network oscillation frequency was switched from α band (9.2 Hz without stimulation) to β band (20 Hz) due to entrainment (Fig. 5B3, *top*). At the same time, the firing pattern of HTC cells was completely switched from bursting to tonic spiking (Fig. 7C, *top*), a state that resembled the firing pattern of HTC cells during endogenous β (Fig. S10 of Li et al. 2017) or γ oscillation (Fig. 2C1, *top*). Thus, stimulation not only switched the oscillation frequency from α to β/γ band but also converted the neuronal firing dynamics from endogenous α oscillation to endogenous β/γ oscillation.

The stimulation-driven switch in neuronal firing pattern can also be observed during stimulation of fast β or γ oscillation. As mentioned above, HTC cells fired tonic spiking during β oscillation (Fig. S10 of Li et al. 2017). In response to 14 Hz stimulation of 0.3 nA,

the thalamic network was entrained and HTC cells switched from tonic spiking to quasi-bursting (Fig. 9C, *top*) that resembled the double-spike bursting pattern during endogenous α oscillation (Fig. 2B1, *top*). Interestingly, stimulation of γ oscillation with β band frequency (20 Hz; 0.3 nA) was also able to produce a quasi-bursting firing pattern in HTC cells in addition to entrainment (Fig. 9D, *top*). This suggests that stimulation-induced switch in neuronal dynamics was not limited to a particular stimulation frequency band within which the new (altered) firing pattern resided without stimulation. To drive α oscillation to higher frequency oscillations, stimulation converted bursting in HTC cells to tonic spiking so as to increase the oscillation frequency. On the other hand, to drive β or γ oscillation to lower frequency oscillation, stimulation acted to convert tonic spiking back to quasi-bursting in order to reduce the oscillation frequency. Thus, a switch in population or neuronal dynamics could be a strategy the neuronal network adopts to enable entrainment when the stimulation frequency was relatively far from the endogenous frequency.

LGN stimulation induces asymmetric Arnold tongue that favors higher frequency entrainment and resonance

To obtain a full map of entrainment, we stimulated the LGN with a range of amplitude from 0.025 nA up to 0.5 nA with an increment step of 0.025 nA, and for the same range of stimulation frequency (1- 50 Hz). For each stimulation amplitude and frequency, we calculated the dominant network frequency with associated peak power by computing the FFT of the sLFP (see Methods). We then generated the frequency entrainment map including principal (1:1), subharmonic (2:1) and harmonic (1:2) entrainment and the spectral peak power heat map for each of the three oscillatory states in Figure 10. Note that we imposed both a frequency and a power criteria to determine if the network was entrained at a particular stimulation condition such that during entrainment not only the peak network frequency was sufficiently close to the stimulation frequency (or its harmonics/subharmonics) but also the peak power should be greater than a minimal threshold relative to the original power without stimulation (see Methods). Across all three oscillatory states, stimulation reliably induced a characteristic entrainment pattern called Arnold tongue (Jensen et al., 1983; Tiesinga, 2002; Ali et al., 2013; Herrmann et al., 2016; Ter Wal and Tiesinga, 2017) in the thalamic network. That is, in response to stimulation of increasing amplitude, the entrained frequency range (i.e., the dominant oscillation frequency locked to the stimulation frequency) expanded from around the endogenous frequency (Fig. 10A1-C1). The principal Arnold tongue (1:1 entrainment; red circle region) dominated the entrainment map and was surrounded by much narrower subharmonic entrainment (2:1 entrainment; blue circles) and/or harmonic entrainment (1:2 entrainment; green circles). Also, as the endogenous oscillation frequency increased (i.e., from δ to γ), the region of harmonic entrainment increased (compare the green circle region among Fig. 10A1-C1). Notably, the principal Arnold tongues were asymmetric in that they extended more and faster towards higher frequency than lower frequency as the stimulation amplitude increased (Fig. 10A1-C1). In all three oscillatory states, the Arnold tongues stopped growing further into the lower frequency range after the stimulation amplitude reached a certain level, while they continued to expand towards higher frequency range (compare the left edge with the right edge of the red circle area in Fig. 10A1-C1). As a result, the region of harmonic entrainment was vertically aligned with the left edge of the principal Arnold tongue (Fig.

10A1-C1, green circle region) while the zone of subharmonic entrainment shifted substantially to higher frequency as the stimulation intensity increased (Fig. 10A1-B1, blue circle region).

Instead of the stereotypical entrainment pattern where subharmonic entrainment was sequentially presented with increasing stimulation frequency in a simplified spiking neural model of α oscillation (Herrmann et al., 2016), principal entrainment (1:1) and subharmonic entrainment (2:1) in the thalamic network appeared alternatively during stimulation of α oscillation (Fig. 10B1), as described earlier (Fig. 5B3, *top*). Consequently, the principal Arnold tongue was divided into several subregions by subharmonic entrainment (from 1:1 to 2:1 to 1:1 to 2:1 and back to 1:1, Fig. 10B1). The α entrainment map was also segregated by oscillation acceleration resulting in entrainment discontinuity as described above. Two types of entrainment discontinuity were observed in the entrainment map (Fig. 10B1). The first type existed at lower stimulation frequency (10-20 Hz) and appeared to be random in nature as the unentrained “holes” were mingled with the entrained “dots”. The second type emerged as a wider stripe at higher stimulation frequencies (20-45 Hz) and exhibited a systematic nature (Fig. 10B1). Both types of unentrained “holes” moved to higher (stimulation) frequency with larger stimulation intensity and eventually disappeared at sufficiently high stimulation amplitude (> 0.4 nA; Fig. 10B1). The Arnold tongues were more continuous during stimulation of δ and γ oscillations (compare Fig. 10B1 with Fig. 10A1, C1), suggesting that entrainment discontinuity was a unique property of α oscillation which was mediated by firing pattern switching of HTC cells.

Not only the shape of the principal Arnold tongues was asymmetric, power enhancement or resonance within the Arnold tongues was also significantly asymmetric (Fig. 10A2-C2). When the stimulation amplitude was relatively low (< 0.1 nA), there was either no change or slight suppression of the oscillation power at the tip of the Arnold tongues (e.g., Fig. 10A2). As the stimulation amplitude increased, resonance occurred where both the spectral peak power and the enhancement region near the endogenous frequency substantially increased for all three oscillatory states (Fig. 10A2-C2). However, similar to entrainment, power enhancement strongly biased higher frequency such that much wider and stronger power enhancement always took place at frequency higher than the endogenous frequency. In addition, both the region and degree of principal resonance were significantly larger than subharmonic or harmonic resonance (Fig. 10A2-C2). Our stimulation results were in contrast to the Herrmann et al. (2016) study where the Arnold tongues were more symmetric and the power enhancement region under harmonic resonance (~ 20 Hz) was wider than that under principal resonance (~ 10 Hz) (Fig. 4A of Herrmann et al. 2016).

Stimulation induces state-dependent enhancement and suppression

LGN stimulation also induced state-dependent enhancement and suppression in the thalamic network. First, stimulation evoked much more prominent power enhancement during stimulation of fast γ oscillation than slow oscillations (δ and α). As shown in the spectral peak power heat map, the region of strong power enhancement was much wider during stimulation of γ oscillation than δ or α oscillation (compare the red color area in Fig. 10C2 with Fig. 10A2, B2). Specifically, most of the peak power at the right side of the principal

Arnold tongue was greatly enhanced by stimulation during γ oscillation (Fig. 10C2), while the power enhancement occurred only relatively close to (and higher than) the endogenous frequency during stimulation of δ and α oscillations (Fig. 10A2, B2). Notably, power enhancement was the weakest during stimulation of α oscillation among the three oscillatory states (compare Fig. 10B2 with Fig. 10A2, C2). This was because the thalamic network of α oscillation was already well synchronized without stimulation (Fig. 2B1) and stimulation switched HTBs of HTC cells to tonic spiking, as discussed earlier.

On the other hand, stimulation induced stronger and more widespread suppression during δ and α oscillations than γ oscillation (compare the dark blue area in Fig. 10A2, B2 with Fig. 10C2). During stimulation of δ oscillation, the region of strong suppression ($< 50\%$ of the original power without stimulation) appeared at the upper right corner of the spectral peak power heat map in the presence of high frequency (> 20 Hz) and large amplitude (> 0.2 nA) stimulation (Fig. 10A2). Initially suppression started at 45 Hz with stimulation amplitude of 0.225 nA. As the stimulation amplitude increased, the suppression region moved to lower frequency indicating that lower stimulation frequency could be compensated by larger stimulation intensity. Similar to δ oscillation, the strong suppression region of α oscillation started at high stimulation frequency (> 40 Hz), but with a lower stimulation amplitude (~ 0.1 nA; Fig. 10B2). With a small increase in stimulation amplitude, the suppression region expanded to much lower frequency (~ 23 Hz) where it met the band of subharmonic entrainment (Fig. 10B2). As the stimulation intensity further increased, the strong suppression region shrunk back to higher frequency along with the expansion of the principal Arnold tongue. In addition to this strong suppression region, another region with smaller degree of suppression existed between the principal resonance frequency and the subharmonic entrainment frequency when the stimulation intensity was greater than 0.15 nA (Fig. 10B2). Compared with δ and α oscillations, stimulation-induced suppression during γ oscillation was relatively moderate (compare Fig. 10C2 with Fig. 10A2, B2) and the parameter space outside the entrainment map was moderately suppressed (Fig. 10C2).

TRN stimulation induces much weaker entrainment and resonance than LGN stimulation

The stimulation effects were substantially different if the TRN, the inhibitory circuit within the thalamus (Fig. 1 A), was stimulated. The frequency entrainment map and the spectral peak power heat map for the same range of stimulation amplitude (0-0.5 nA) and frequency (1-50 Hz) as LGN stimulation during each of the three oscillatory states are shown in Figure 11. Notably, there was no Arnold Tongue in a strict sense during TRN stimulation of δ oscillation because of the irregular and sparse entrainment in the frequency entrainment map (Fig. 11A1). Also, TRN stimulation induced much narrower (principal) Arnold tongue during α oscillation (compare the red circle region in Fig. 11B1 with Fig. 10B1), suggesting that indirect TRN stimulation was much less effective to entrain TC cell activities compared with direct LGN stimulation. In addition to being much narrower, the principal Arnold tongue was more symmetric without strong bias towards higher frequency as induced by LGN stimulation (compare Fig. 11B1 with Fig. 10B1). By comparison, the principal Arnold tongue induced by TRN stimulation of γ oscillation was much wider than α oscillation (compare the red circle region in Fig. 11C1 with Fig. 11B1). Also, the Arnold tongue remained the asymmetric shape, which was comparable to that under LGN stimulation

(compare the red circle region in Fig. 11C1 with Fig. 10C1). Besides, the region of harmonic entrainment (1:2) under TRN stimulation was similar to that under LGN stimulation (compare the green circle area in Fig. 11C1 with Fig. 10C1). One major difference was that unentrainment “holes” existed in the principal Arnold tongue of γ oscillation during high frequency (> 40 Hz) and large amplitude (> 0.2 nA) TRN stimulation (Fig. 11C1), while such entrainment skipping effect was not observed under LGN stimulation (Fig. 10C1). This again suggested that indirect TRN stimulation was less effective in entraining TC cell activities.

TRN stimulation also induced much weaker resonance effect than LGN stimulation. Most notably, during δ oscillation no resonance was induced by TRN stimulation, in sharp contrast to the strong power enhancement right to the endogenous frequency under LGN stimulation (compare Fig. 11A2 with Fig. 10A2). During TRN stimulation of α oscillation, though the peak oscillation power was enhanced at the center of the Arnold tongue, the enhancement was very slight and the enhancement region was much narrower than LGN stimulation (compare Fig. 11B2 with Fig. 10B2). Despite similar shape of the principal Arnold tongue, power enhancement within the Arnold tongue of γ oscillation was much weaker and narrower under TRN stimulation than under LGN stimulation (compare Fig. 11C2 with Fig. 10C2). In particular, the strong high-frequency bias in oscillation enhancement induced by LGN stimulation (Fig. 10C2) was eliminated under TRN stimulation (Fig. 11C2). Moreover, the power enhancement region (within the principal Arnold tongue) started to shrink towards lower frequency as the stimulation amplitude increased beyond a certain intensity (> 0.25 nA; Fig. 11C2). Therefore, the high-frequency bias in oscillation enhancement under LGN stimulation was a result of direct excitatory stimulation on TC cells, which vanished when TC cells received inhibitory stimulation. Overall, similar to LGN stimulation, oscillation enhancement or resonance under TRN stimulation was state-dependent which changed from no enhancement during δ oscillation to weak enhancement during α oscillation, and to stronger enhancement during γ oscillation (compare Fig. 11C2 with Fig. 11A2, B2). Interestingly, high frequency TRN stimulation (e.g., 40 Hz) of α oscillation resulted in δ -like slower oscillations (~ 4 Hz) associated with stronger bursts in HTC cells (see Supplementary Materials and Fig. S6B). Our results were consistent with a previous report that strong stimulation of corticothalamic axons could induce synchronous slow oscillations (2-4 Hz) in the thalamic circuits (Bal et al., 2000), presumably through recruiting inhibitory reticular neurons as cortical axons recruit more strongly reticular cells than relay neurons (Golshani et al., 2001).

Biphasic charge balanced stimulation reproduces the salient effects of monophasic stimulation

In above simulation, we used monophasic pulses (Fig. S1A) to examine the effects of rhythmic stimulation on thalamic network oscillations. Although such periodic stimulus conceptually resembled the rhythmic nature of DBS or rTMS, there was some considerable difference when compared with the stimulation pulses used in practice. First, standard DBS generally use biphasic charge balanced waveform (Popovych et al., 2017) as monophasic pulses could lead to tissue damage (Merrill et al., 2005). Second, the frequency of DBS stimulation to treat abnormal conditions like Parkinson's disease, is generally greater than

100 Hz (Kuncel and Grill, 2004), while we focused on 1-50 Hz (local frequency range) in above simulation. To test whether the major results preserved in the presence of more realistic stimulation pulses, we stimulated the thalamic network (LGN) using biphasic charge balanced pulses (Fig. S1B) with a maximal frequency of 150 Hz. The simulation results are displayed in Supplementary figures S7 and S8. We observed that charge balanced biphasic pulses were able to induce similar response mechanisms as the monophasic stimulus. Specifically, the biphasic stimulus could evoke entrainment (e.g., Fig. S7A2, Fig. S8A2), resonance (e.g., Fig. S7C2, Fig. S8C2) and oscillation suppression (e.g., Fig. S7B2, Fig. S8B2). In addition, similar to monophasic stimulus, the effects of biphasic stimulation were highly state-dependent. For example, during stimulation of δ and α oscillations, the thalamic network maintained endogenous dynamics when the stimulation amplitude was 1.0 nA (Fig. S7A1, B1, Fig. S8A1, B1). In contrast, substantial entrainment started to emerge at 0.3 nA for γ oscillation (Fig. S7C1, Fig. S8C1) and both entrainment and resonance dominated when the stimulation amplitude increased to 1.0 nA (Fig. S7C3, Fig. S8C3). It should be noted that much larger stimulation intensity (and/or higher stimulation frequency) was needed to induce similar response patterns for biphasic stimulus as compared to monophasic stimulus (compare Fig. S7 with Fig. 4 and Fig. S8 with Fig. 5). This was because the second (hyperpolarizing) pulse could significantly reverse the effects induced by the first (depolarizing) pulse (Merrill et al., 2005) and we used shorter pulse duration (2 ms) for biphasic stimulus than monophasic stimulation (10 ms; Fig S1).

The use of high frequency biphasic pulses (> 50 Hz) revealed some unexpected findings that were not observed during monophasic stimulation. Across all three states, the stimulation-induced spectral power of sLFP was consistently greater at high frequency (> 50 Hz) than lower frequency (< 50 Hz; note that the color along the diagonal was warmer at high frequency range than low frequency range, Fig. S7). As a result, entrainment may first appear at high frequency for certain oscillation states. For example, during stimulation of α oscillation, substantial entrainment emerged first at high stimulation frequency (> 60 Hz) (1.5 nA; Fig. S7B2, Fig. S8B2). In addition, the endogenous dynamics was greatly suppressed in the presence of high frequency stimulation (> 90 Hz; Fig. S7B2, B3). Such phenomenon may explain why high frequency DBS (> 100 Hz) is needed in clinical applications (Kuncel and Grill, 2004).

Discussion

Modulation of brain oscillations by rhythmic stimulation protocols has become increasingly popular in recent years as a strategy to probe the causal roles of oscillations in brain functions (Thut et al., 2011; Helfrich et al., 2014) and as therapeutic control to treat neurological and psychiatric disorders (Frohlich, 2014; Krawinkel et al., 2015). However, it remains unclear how the stimulation interacts with endogenous neural dynamics and depends on the physiological state of the targeted brain area. This question becomes particularly important in light of recent experimental data indicating that the effect of stimulation is state dependent (Neuling et al., 2013; Alagapan et al., 2016). Computational modeling offers a powerful tool to examine the impact of rhythmic stimulation on oscillatory brain dynamics, but existing quantitative stimulation studies often utilized simplified neuronal models (Keener et al., 1981; Coombes and Bressloff, 1999; Tiesinga, 2002;

Popovych et al., 2005; Popovych and Tass, 2011) or focused on one particular type of oscillation pattern (Herrmann et al., 2016; Popovych et al., 2017; Ter Wal and Tiesinga, 2017), which could not fully address the state-dependent modulation effects. Of note, Tiesinga (2012) investigated how different biophysical time scales influenced LFP resonance during stimulation of a cortical network. However, the Tiesinga model focused on the interaction between gamma and slower frequency modes in the cortex rather than distinct oscillatory states. Thus, it remains unclear how rhythmic stimulation modulates thalamic network dynamics under different oscillations. To close this gap, we first developed a unified biophysical thalamic network model that was capable of generating multiple distinct oscillations (Li et al., 2007). Here, by employing a periodic stimulation protocol, we examined in detail the impact of stimulation on different thalamic oscillatory states. We observed state-dependent entrainment and resonance of thalamic oscillations along with novel response mechanisms such as entrainment discontinuity and oscillation suppression with hysteresis. Importantly, we found that these network phenomena are mediated by the distinct cellular dynamics under different oscillatory states. These simulation results offer important mechanistic insights on the modulation of thalamic oscillations in both dose- and state-dependent manner.

State- dependent modulation of thalamic oscillations

One major finding of this study is that we observed modulation of thalamic oscillations is state-dependent. First, LGN stimulation of δ oscillation induces the narrowest Arnold tongue compared to the two other oscillatory states (Fig. 12A1-C1). This is because during δ oscillation, TC cells fire strong intrinsic LTBs which are robust to perturbation. Second, LGN stimulation of α oscillation evokes the weakest resonance and the widest suppression among the three oscillatory states (Fig. 12A2-C2). This is due to the fact that the thalamic network is already well-synchronized during α oscillation without stimulation (Fig. 2B1) and stimulation switches HTBs of HTC cells to tonic spiking which leads to RTC suppression and reduced network synchrony, as described earlier. Our simulation results agree with the well-known earliest EEG experiment that α power is suppressed during eyes opening (Berger, 1929) suggesting that light stimulation disrupts α synchronization. In addition, an experimental study reported that high frequency DBS of subthalamic nucleus (STN) reduces pathological low-frequency oscillations (~9 Hz) and entrains neurons to fire at the stimulation frequency (McConnell et al., 2012). Our thalamic model confirms that oscillation entrainment and suppression could occur simultaneously. Third, LGN stimulation of fast thalamic oscillation (γ) evokes stronger entrainment and resonance than slow oscillations (δ and α) (Fig. 12). We hypothesize that this is because γ oscillation is mainly driven by synaptic excitation and the network synchrony or endogenous oscillation power is much lower compared with δ and α oscillations that are driven by intrinsic mechanisms (Fig. 2). Our results agree with a recent computational study showing that reduced network synchrony facilitates entrainment of cortical α oscillation (Lefebvre et al., 2017). Consistently, it has been observed experimentally that reduced α oscillation power enables entrainment (Alagapan et al., 2016) and fast γ band oscillations are instrumental to visual information processing (Elliott and Müller, 1998; Herrmann, 2001). Lastly, LGN stimulation of α oscillation produces the unique entrainment discontinuity effect (Fig. 10B1) because of firing pattern switching of HTC cells. Such entrainment skipping effect may explain why

under certain circumstances, stimulation of α oscillation fails to entrain the thalamocortical network (Bergmann et al., 2009; Johnson et al., 2010). We expect that such state-dependent effects would apply to other neuronal networks with different intrinsic properties (e.g., networks formed by regular spiking and fast-spiking neurons), which can be examined in future studies.

Stimulation induces state transition and network bistability

Another important finding from this study is that stimulation could induce state transition of the thalamus, consistent with previous findings (Kutchko and Frohlich, 2013). That is, stimulation does not merely drive the endogenous oscillation to cross different frequency bands (i.e., extension of endogenous oscillation), but also alters the neuronal dynamics to behave in a way similar to that in the new state. For example, stimulation of α oscillation with frequency in the β or γ band entrains the thalamic network to oscillate at the stimulation frequency. At the same time, stimulation switches HTBs of HTC cells to tonic spiking that is characteristic of β or γ oscillation (Fig. 7C). Interestingly, high frequency TRN stimulation of α oscillation induces δ -like oscillation by reducing the HTC bursting frequency while increasing the number of spikes per burst (Fig. S6B). Stimulation-induced thalamic oscillatory state transition may have important implication in inducing behavioral state transition, as observed experimentally (Lewis et al., 2015).

High-frequency stimulation of δ or α oscillation strongly suppresses endogenous oscillations and induces hysteresis (Fig. 8), an important phenomenon characteristic of nonlinear system. Simulation results indicate that hysteresis during stimulation of δ oscillation results from TC cell membrane property while hysteresis during stimulation of α oscillation is a combination of cellular and network phenomenon (i.e., RTC spike suppression due to conversion of HTBs to tonic spikes of HTC cells). Oscillation suppression provides an effective way to block pathological rhythm (Popovych et al., 2005, 2017) and the emergence of hysteresis suggests that the effect of stimulation is activity-dependent, which could be tested in future experimental studies.

Direct entrainment of thalamic oscillations via asymmetric Arnold tongue

By applying stimulation to the LGN across three oscillatory states (δ , α and γ), we consistently observed that modulation of thalamic oscillations critically depends on the individual endogenous frequency. Both principal frequency entrainment and resonance start from or close to the endogenous frequency (for monophasic stimulation) and the degree of entrainment and resonance increases with stimulation amplitude, giving rise to a characteristic entrainment pattern termed Arnold tongue (Fig. 10). However, the Arnold tongue is asymmetric relative to the endogenous frequency in that (1) as the stimulation amplitude increases, the network is entrained at more higher frequencies than lower frequencies; (2) when the stimulation amplitude exceeds a certain level, entrainment reaches the lowest frequency limit beyond which no lower frequency becomes entrained, while entrainment could expand to the highest stimulation frequency tested (50 Hz); (3) both the region and the magnitude of power enhancement are greater at higher frequency than lower frequency. There are two main reasons for the asymmetric nature of Arnold tongues. First, the principal Arnold tongue is surrounded by harmonic entrainment at subharmonic

frequency and subharmonic entrainment at harmonic frequency (Fig. 10). As the distance between the endogenous and harmonic frequency is greater than the distance between the endogenous and subharmonic frequency, entrainment occurs in a larger frequency range when higher than the endogenous frequency. Second, direct LGN stimulation is excitatory and increases the endogenous frequency of thalamic oscillations, thus biasing higher frequency entrainment and resonance. In support of this, stimulation of the TRN produces more symmetric Arnold Tongues (Fig. 11). Our simulation results confirm the existence of Arnold Tongue as a general property of nonlinear oscillator (Pikovsky et al., 2001) and are consistent with a previous modeling study where the coherence between two connected local cortical circuits appears along a tilted (asymmetric) Arnold tongue (Ter Wal and Tiesinga, 2017).

Relevance of the model to brain stimulation

Our model findings provide valuable insights on the application of brain stimulation to treat neurological and psychiatric disorders. For example, model simulation indicates that stimulation with a frequency slightly higher than the endogenous frequency results in optimal entrainment and enhancement. This has significant clinical implication as a slowed α frequency is a signature of a number of neurological or psychiatric disorders including major depressive disorder (MDD) and schizophrenia (Niedermeyer, 1997; Llinás et al., 1999). Notably, rTMS delivered at 10 Hz has been shown to be an effective therapeutic modality for MDD (George et al., 2010). Based on the simulation results of this study, 10 Hz stimulation would readily entrain the slowed pathological thalamic α oscillation to the same stimulation frequency (10 Hz) with maximal resonance. Combined with synaptic plasticity mechanism (Leuchter et al., 2013), 10 Hz stimulation may induce long lasting effect that restores the slowed pathological α rhythm back to the normal frequency (10 Hz). Moreover, simulation results demonstrate that high frequency stimulation strongly suppressed low frequency (δ to α band) thalamic oscillations, providing mechanistic insights into the application of high frequency DBS in suppressing pathological low frequency thalamic rhythms (McConnell et al., 2012).

Conclusions

In conclusion, we demonstrated that rhythmic modulation of thalamic oscillations is highly state-dependent. Such state-dependent modulation effects are mediated by distinct cellular dynamics under different oscillatory states. In particular, we showed that thalamic oscillations mediated by weakly synchronized tonic spiking (γ oscillations) are more prone to be entrained by stimulation than oscillations mediated by highly synchronized burst firing (δ and α oscillations). On the other hand, bursting-driven oscillations are more susceptible to suppression than oscillations mediated by tonic spiking. In addition, whether suppression occurs or not depends on the previous network state, resulting in stimulation-induced bistability. Moreover, we found that stimulation is able to induce state transition by modulating the cellular dynamics, providing the cellular basis for stimulation-induced behavioral state transition. Overall, our study provides, for the first time, insights into how the biophysics of thalamic oscillations guide the emergence of complex, state-dependent

mechanisms of target engagement, which can be leveraged for the future rational design of novel therapeutic stimulation modalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) R01 Grants MH101547 and MH111889 to F Frohlich and the National Institute on Deafness and Other Communication Disorders (NIDCD) of NIH R03 Grant DC013872 to G Li. The authors thank Stephen Schmidt, Ehsan Negahbani and Yuhui Li of the Frohlich Lab for their helpful discussions and comments on an earlier draft.

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Figure 1. The thalamic network model generates multiple distinct oscillations dependent on acetylcholine (ACh) and norepinephrine (NE) modulation and afferent input.

(A) Thalamic network structure.

(B) Location of delta (δ), spindle, alpha (α) and gamma (γ) oscillations in the 2D schematic plane as a function of ACh/NE modulation and afferent input. Arrows indicate different firing patterns of the HTC cells.

(C) Voltage traces of two representative HTC (*top*) and RTC cells (*bottom*) each during δ oscillation.

(D) Voltage traces of two representative HTC (*top*) and RTC cells (*bottom*) each during α oscillation.

(E) Voltage traces of two representative HTC (*top*) and RTC cells (*bottom*) each during γ oscillation. Figures are adapted from Li et al. (2017).

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Figure 2. LGN stimulation induces three different types of entrainment in the thalamic network.

(A) Stimulation of δ oscillation induces subharmonic entrainment. (A1) Spiking activity of HTC (*top*) and RTC (*bottom*) cells during δ oscillation without stimulation. (A2) Spiking activity of HTC (*top*) and RTC (*middle*) cells in the presence of 0.2 nA, 12 Hz stimulation. The bottom panel displays the stimulation pulses. (A3) Frequency power spectra of the simulated local field potential (sLFP) in the control case (black) and with 0.2 nA, 12 Hz stimulation (red). The blue vertical dashed line indicates the stimulation frequency (same for below).

(B) Stimulation of α oscillation induces principal entrainment. (B1) Spiking activity of HTC (*top*) and RTC (*bottom*) cells during α oscillation without stimulation. (B2) Spiking activity of HTC (*top*) and RTC (*middle*) cells in the presence of 0.2 nA, 12 Hz stimulation. The bottom panel displays the stimulation pulses. (B3) Frequency power spectra of the sLFP in the control case (black) and with 0.2 nA, 12 Hz stimulation (red).

(C) Stimulation of γ oscillation induces harmonic entrainment. (C1) Spiking activity of HTC (*top*) and RTC (*bottom*) cells during γ oscillation without stimulation. (C2) Spiking

activity of HTC (*top*) and RTC (*middle*) cells in the presence of 0.2 nA, 17 Hz stimulation. The bottom panel displays the stimulation pulses. (C3) Frequency power spectra of the sLFP in the control case (black) and with 0.2 nA, 17 Hz stimulation (red).

Figure 3. LGN stimulation induces resonance, suppression and acceleration in the thalamic network.

(A) Stimulation of δ oscillation induces resonance. (A1) Spiking activity of HTC (*top*) and RTC (*middle*) cells in the presence of 0.2 nA, 5 Hz stimulation. The bottom panel displays the stimulation pulses. (A2) Frequency power spectra of the sLFP in the control case (black) and with 0.2 nA, 5 Hz stimulation (red).

(B) Stimulation of α oscillation induces suppression. (B1) Spiking activity of HTC (*top*) and RTC (*middle*) cells in the presence of 0.2 nA, 30 Hz stimulation. The bottom panel displays the stimulation pulses. (B2) Frequency power spectra of the sLFP in the control case (black) and with 0.2 nA, 30 Hz stimulation (red).

(C) Stimulation of γ oscillation induces oscillation acceleration. (C1) Spiking activity of HTC (*top*) and RTC (*middle*) cells in the presence of 0.2 nA, 50 Hz stimulation. The bottom panel displays the stimulation pulses. (C2) Frequency power spectra of the sLFP in the control case (black) and with 0.2 nA, 50 Hz stimulation (red).

Figure 4. LGN stimulation induces both similar and differential effects on the three oscillatory states in the thalamic network.

(A) Effect of stimulation on δ oscillation. (A1-A3) Normalized color-coded frequency power spectrum of the simulated local field potential (sLFP) when the stimulation frequency varies from 1 to 50 Hz with three different levels of stimulation amplitude (A1: 0.075 nA; A2: 0.15 nA; A3: 0.225 nA).

(B) Effect of stimulation on α oscillation. (B1-B3) Normalized color-coded frequency power spectrum of the sLFP when the stimulation frequency varies from 1 to 50 Hz with three different levels of stimulation amplitude (B1: 0.075 nA; B2: 0.15 nA; B3: 0.225 nA).

(C) Effect of stimulation on γ oscillation. (C1-C3) Normalized color-coded frequency power spectrum of the sLFP when the stimulation frequency varies from 1 to 50 Hz with three different levels of stimulation amplitude (C1: 0.075 nA; C2: 0.15 nA; C3: 0.225 nA).

Figure 5. LGN stimulation shapes the dominant oscillatory dynamics of the thalamic network in a state- dependent manner.

(A) Effect of stimulation on the dominant dynamics of δ oscillation. **(A1-A3)** *Top*: Dominant network oscillation frequency; *Bottom*: Normalized spectral peak (black) along with synchronization index (SI ; orange) as a function of stimulation frequency (1-50 Hz) in the presence of three different levels of stimulation amplitude (**A1**: 0.075 nA; **A2**: 0.15 nA; **A3**: 0.225 nA).

(B) Effect of stimulation on the dominant dynamics of α oscillation. **(B1-B3)** *Top*: Dominant network oscillation frequency; *Bottom*: Normalized spectral peak (black) along with synchronization index (SI ; orange) as a function of stimulation frequency (1-50 Hz) in the presence of three different levels of stimulation amplitude (**B1**: 0.075 nA; **B2**: 0.15 nA; **B3**: 0.225 nA).

(C) Effect of stimulation on the dominant dynamics of γ oscillation. **(C1-C3)** *Top*: Dominant network oscillation frequency; *Bottom*: Normalized spectral peak (black) along with synchronization index (SI ; orange) as a function of stimulation frequency (1-50 Hz) in the presence of three different levels of stimulation amplitude (**C1**: 0.075 nA; **C2**: 0.15 nA; **C3**: 0.225 nA). Red ellipses indicate principal entrainment (1:1) and resonance, blue ellipses

indicate the first subharmonic entrainment (2:1) and first harmonic resonance, green ellipses indicate the first harmonic entrainment (1:2) and first subharmonic resonance. The dash horizontal lines in bottom panels denote the normalized spectral peak without stimulation.

Figure 6. LGN stimulation effects depend on intrinsic cellular dynamics.

(A) During high-frequency stimulation of δ oscillation, TC cells mostly maintain the original cellular dynamics. (A1) Voltage traces of two representative HTC (*top*) and RTC cells (*bottom*) each in the presence of 0.225 nA, 40 Hz stimulation. (A2) Spiking activity of HTC (*top*) and RTC (*bottom*) cells in the presence of 0.225 nA, 40 Hz stimulation. (A3) Simulated local potential (sLFP; *top*) and frequency power spectrum of the sLFP (*bottom*) under the control (black) and stimulation (red) conditions. The blue vertical dashed line indicates the stimulation frequency.

(B) During high-frequency stimulation of α oscillation, HTC cells switch from high threshold bursting to tonic spiking and the activity of RTC cells is suppressed. (B1-B3) Same as (A1-A3), but during stimulation of α oscillation.

(C) During high-frequency stimulation of γ oscillation, TC cells become more synchronized (than controls) and were readily entrained. (C1-C3) Same as (A1-A3), but during stimulation of γ oscillation.

Figure 7. Entrainment discontinuity during LGN stimulation of α oscillation is mediated by firing pattern switching of HTC cells between bursting and tonic spiking.

(A) Spiking activity of HTC cells during 12 Hz stimulation. The stimulation amplitude is 0.225 nA and the bottom panel displays the stimulation pulses.

(B) Spiking activity of HTC cells during 15 Hz stimulation.

(C) Spiking activity of HTC cells during 20 Hz stimulation.

(D) Spiking activity of HTC cells during 22 Hz stimulation.

(E) Spiking activity of HTC cells during 24 Hz stimulation.

(F) Spiking activity of HTC cells during 36 Hz stimulation.

Figure 8. High frequency LGN stimulation suppresses δ and α oscillations and induces hysteresis.

(A) Stimulation induces hysteresis during δ oscillation. (A1) Top: Dominant network oscillation frequency; Bottom: Normalized spectral peak (black) along with synchronization index (SI; orange) as a function of the stimulation frequency. The red ellipse in the top panel indicates principal entrainment (1:1) and the horizontal dash line in the bottom panel indicates the normalized spectral peak without stimulation. (A2) Spiking activity of HTC (top) and RTC (middle) cells during ascending 20 Hz stimulation. Red text indicates the average firing rates of HTC and RTC cells. (A3) Spiking activity of HTC (top) and RTC (middle) cells during descending 20 Hz stimulation. Note that the network is in a quiescent state and the firing rate of both HTC and RTC cells is zero as indicated. The stimulation amplitude is 0.3 nA and the bottom panels in (A2, A3) display the stimulation pulses. (B) Stimulation induces hysteresis during α oscillation. (B1) Top: Dominant network oscillation frequency; Bottom: Normalized spectral peak (black) along with synchronization index (SI; orange) as a function of the stimulation frequency. The horizontal dash line in the bottom panel indicates the normalized spectral peak without stimulation. (B2) Spiking

activity of HTC (*top*) and RTC (*middle*) cells during ascending 35 Hz stimulation. **(B3)**
Spiking activity of HTC (*top*) and RTC (*middle*) cells during descending 35 Hz stimulation.
The stimulation amplitude is 0.1 nA and the bottom panels in **(B2, B3)** display the
stimulation pulses.

Figure 9. Stimulation drives endogenous thalamic oscillations to cross different frequency bands by altering the neuronal or population dynamics.

(A) During stimulation of δ oscillation, TC cells maintain highly synchronized LTBs when the stimulation frequency (6 Hz) is close to the endogenous frequency (3.7 Hz). (A1) Spiking activity of HTC (top) and RTC (middle) cells. (A2) Voltage traces of two representative HTC (top) and RTC (middle) cells each. The stimulation amplitude is 0.3 nA and the bottom panels display the stimulation pulses.

(B) During stimulation of δ oscillation, RTC cells are divided into two subpopulations when the stimulation frequency (12 Hz) is relatively far from the endogenous frequency (3.7 Hz). (B1) Spiking activity of HTC (top) and RTC (middle) cells. (B2) Voltage traces of two representative HTC (top) and RTC (middle) cells each. The stimulation amplitude is 0.3 nA and the bottom panels display the stimulation pulses.

(C) During stimulation of β oscillation (0.3 nA, 14 Hz), a quasi-bursting firing pattern in HTC cells is activated, which is tonic spiking without stimulation. The top two panels display spiking activity of HTC and RTC cells respectively, and the bottom panel displays the stimulation pulses.

(D) During stimulation of γ oscillation (0.3 nA, 20 Hz), a quasi-bursting firing pattern in HTC cells is activated, which is tonic spiking without stimulation. The top two panels

display spiking activity of HTC and RTC cells respectively, and the bottom panel displays the stimulation pulses.

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Figure 10. LGN stimulation induces asymmetric Arnold Tongues and state-dependent enhancement and suppression.

(A) Entrainment and power modulation effects during stimulation of δ oscillation. **(A1)** Map of principal (1:1; red circles), subharmonic (2:1; blue circles) and harmonic (1:2; green circles) entrainment. **(A2)** Normalized spectral peak power heat map. The stimulation frequency ranges from 1 to 50 Hz with 1 Hz/step and the stimulation amplitude increases from 0 to 0.5 nA with 0.025 nA/step.

(B) Entrainment and power modulation effects during stimulation of α oscillation. **(B1-B2)** As **(A1-A2)**, but during stimulation of α oscillation.

(C) Entrainment and power modulation effects during stimulation of γ oscillation. **(C1-C2)** As **(A1-A2)**, but during stimulation of γ oscillation.

Figure 11. TRN stimulation induces much weaker entrainment and resonance than LGN stimulation.

(A) Entrainment and power modulation effects during stimulation of δ oscillation. (A1) Map of principal (1:1; red circles), subharmonic (2:1; blue circles) and harmonic (1:2; green circles) entrainment. (A2) Normalized spectral peak power heat map. The stimulation frequency ranges from 1 to 50 Hz with 1 Hz/step and the stimulation amplitude increases from 0 to 0.5 nA with 0.025 nA/step.

(B) Entrainment and power modulation effects during stimulation of α oscillation. (B1-B2) As (A1-A2), but during stimulation of α oscillation.

(C) Entrainment and power modulation effects during stimulation of γ oscillation. (C1-C2) As (A1-A2), but during stimulation of γ oscillation.