Coherent neuronal dynamics driven by optogenetic stimulation in the primate brain

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Summary

Coherent neuronal dynamics play an important role in complex cognitive functions, but the causal role of neuronal coherence is unclear. Optogenetic stimulation allows causal tests of the functional significance of coherent neuronal activity. While non-human primates are important for studying the neural mechanisms of complex cognitive functions, optogenetic perturbation of neuronal dynamics has had limited application in this animal model. Here, we develop a computational framework and perform experiments to test how optogenetic stimulation perturbs coherent neuronal dynamics. We show that stimulation-evoked neural responses arise from temporal windows of excitatory and inhibitory activity that vary parametrically with optogenetic stimulation parameters. We experimentally identify the effective temporal window of excitation and inhibition and use the window in a computational model to design model-based stimulation sequences. These results demonstrate optogenetic perturbations of coherent neuronal dynamics and advance the use of optogenetic tools to study complex cognitive functions in the primate brain.

Introduction

Coherent neuronal dynamics are patterns of neural activity due to correlations in the spiking activity of individual neurons and neural population activity, typically measured using local field potential (LFP) activity (Pesaran et al., 2018). The importance of coherent neuronal dynamics has been emphasized across a range of complex cognitive functions including working memory (Pesaran et al., 2002; Salazar et al., 2012; Siegel et al., 2009), decision making (Hawellek et al., 2016; Pesaran et al., 2008; Wong et al., 2016), coordination (Dean et al., 2012; Hagan et al., 2012), attention (Buschman and Miller, 2007; Gregoriou et al., 2009), and perception (Gray et al., 1989; Womelsdorf et al., 2006). While their precise function remains controversial (Uhlhaas et al., 2009), coherent neuronal dynamics at different frequencies in the beta (12-30 Hz) and gamma (30-100 Hz) bands are thought to play different functional roles (Buschman and Miller, 2007). To more decisively test the role of coherent neuronal dynamics in complex cognitive functions, we need to be able to selectively manipulate temporally-patterned neuronal activity.

Optogenetic stimulation can perturb behavioral processes (Dai et al., 2014; Jazayeri et al., 2012; Stauffer et al., 2016) and neuronal dynamics (Adesnik and Scanziani, 2010; Cardin et al., 2009). Early work tested computational models that predict cell-type-specific manipulations underlie the impact of optogenetic stimulation on coherent neuronal dynamics. In some studies, driving interneurons using pulse trains of optogenetic stimulation perturbed coherent neuronal activity (Cardin et al., 2009; Sohal et al., 2009). In other studies, driving pyramidal neurons using continuous optogenetic stimulation generated coherent dynamics, specifically gamma activity (Lu et al., 2015; Ni et al., 2016). In each case, consistent with the cell-type specific models, the effect of optogenetic stimulation on coherent neuronal dynamics depends on which neurons have been transduced. Importantly, this work indicates that expression of different cell-

type-specific optogenetic constructs is needed to perturb neuronal dynamics at different frequencies (Cardin et al., 2009). However, how to use optogenetic stimulation to identify and compare specific functional roles for coherent neuronal dynamics at different frequency ranges remains unclear. If co-expression of multiple cell-type-specific optogenetic tools in specific layers is required, identifying functional roles for different temporal patterns of activity will be particularly challenging. The challenge is especially acute when studying complex cognitive functions in non-human primates because of the relative lack of cell-type specific tools.

In general, coherent neuronal dynamics are not simply due to laminar, cell-type specific mechanisms. Coherent neuronal dynamics also depend on the temporal precision and synchrony of spike timing, and the relative timing of post-synaptic excitatory (E) and inhibitory (I) responses (Chariker et al., 2018; Gabernet et al., 2005). Stimulating specific cell-types drives synaptically-mediated responses in a variety of cell-types present in the neuronal network (Buzsáki and Wang, 2012; Gloveli et al., 2005; Phillips and Hasenstaub, 2016; Pike et al., 2000; Tukker et al., 2007). As a result, how stimulation drives coherent neuronal dynamics depends on the relative timing of E-I responses. If so, this suggests that parameters for optogenetic stimulation pulse trains to generate a particular pattern of coherent neuronal dynamics can be selected in two complementary ways: 1 - how each stimulation pulse drives an effective temporal integration window of excitation and inhibition; and 2 – how sequences of stimulation pulses recruit relative timing of E-I responses appropriate to generating particular coherent neuronal dynamics.

Motivated by this reasoning, we tested the hypothesis that optogenetic stimulation can drive coherent neuronal dynamics at different frequencies by varying E-I responses and their relative timing through the choice of particular stimulation parameters. We first developed a computational model of coherent neuronal dynamics in response to optogenetic stimulation in terms of a temporal window of excitation and inhibition—the E-I window. We experimentally

tested the model predictions by expressing ChR2(H134R) in macaque cortex delivered by an AAV2/5 viral injection, and measuring spiking and local field potential (LFP) responses to optogenetic stimulation. We first examined the impact of altering the shape of the E-I window by varying the stimulation pulse duration. We then considered the complementary manipulation of altering stimulation pulse sequences and present an experimental protocol for designing stimulation sequences that manipulate coherent neuronal dynamics. The results demonstrate how to generate coherent dynamics across frequencies in the beta and gamma frequency bands according to model predictions. This study provides an approach to testing and comparing the causal role of different naturalistic coherent neuronal dynamics in computation and behavior.

Results

Modeling optogenetic-stimulation-evoked coherent neuronal dynamics.

Spike-field coherence (SFC) measures coherent neuronal dynamics by estimating the strength of correlations between spiking activity of individual neurons and neural population activity in the form of simultaneously-recorded LFP activity. When the spike times of a neuron can be predicted from fluctuations in LFP activity at a particular frequency, the spiking is said to be coherent with LFP activity at that frequency. Neurons that fire consistently at a particular phase of LFP activity are coherent with LFP activity. In short, neuronal coherence is defined by coherent spiking and LFP activity and can be measured by estimating SFC between spiking and nearby LFP activity (Pesaran et al., 2018, 2002).

Figure 1 presents a model of optogenetic-stimulation-evoked coherent neuronal dynamics with the corresponding idealized neural responses. We model neuronal spiking according to a conditional intensity function, $\lambda(t)$, which represents the instantaneous firing rate, such that probability of a spike occurring at time t is given by $\lambda(t)\Delta t$ (Brown et al., 2003).

In the absence of optogenetic stimulation, we model background spiking activity as a Poisson process with a constant rate, λ_0 (**Figure 1A**). We model background LFP activity as a process with increased power at low frequencies–"brown noise". For simplicity, we further assume that background LFP activity is uncorrelated with spiking activity and does not affect the value of $\lambda(t)$.

Direct activation of transduced neurons leads to excitatory and inhibitory synaptic currents within the local network of neurons. The resulting currents generate excitatory (E) and inhibitory (I) currents with different temporal structure in post-synaptic neurons (Cruikshank et al., 2010; Haider et al., 2013; Higley and Contreras, 2003; Wehr and Zador, 2003). Excitatory currents lead neurons to fire spikes more frequently. Inhibitory currents lead neurons to fire spikes less frequently. The relative timing of the E and I currents determines when neurons fire spikes. Therefore, we model the impact of optogenetic stimulation on spiking as an excitatory- and inhibitory-dependent temporal change—an excitation-inhibition (E-I) window—in the conditional intensity function, $\lambda(t)$ (**Figure 1B**, Spike generation).

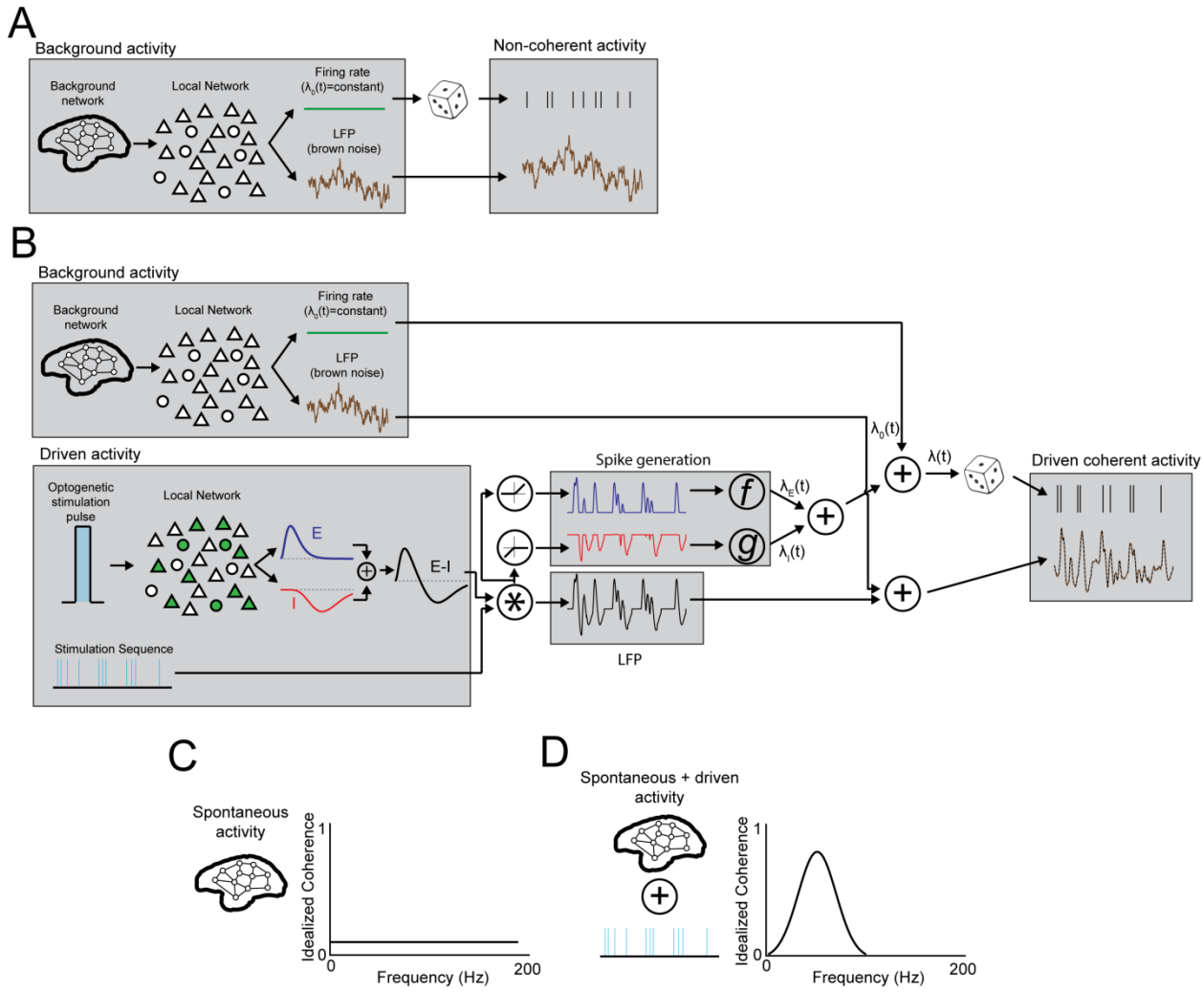

Figure 1. Excitation and inhibition drive coherent neuronal dynamics. (A) During spontaneous activity, synaptic inputs drive activity in a local network. We model spiking as being generated from a Poisson process with a constant rate and LFP as being generated from a Brown noise process. Under these assumptions, spontaneous spiking is not coherent with spontaneous LFP. **(B)** To model optogenetic stimulation of a population of transduced neurons, we simulated pulsatile responses generated by direct activation of ChR2 channels and synaptic activity. Pulsatile responses are convolved with a stimulation sequence. The summed excitatory and inhibitory (E-I, black) components comprise the simulated LFP. The individual E (blue) and I (red) activity govern the variable spiking rate in the Poisson process which generates coherent spiking. **(C)** Spontaneous activity in the model has no spike-field coherence. **(D)** Optogenetic stimulation drives correlated fields and spiking, leading to frequency selective spike-field coherence.

Since we do not have experimental access to the intracellular conductance changes in response to each stimulation pulse, we estimate the excitatory and inhibitory responses from the shape of the stimulation-evoked LFP. LFP activity predominantly reflects summed post-synaptic potentials (Buzsáki et al., 2012; Pesaran et al., 2018). Thus, the stimulation-triggered

average LFP can reveal the temporal structure of E-I windows that arise from synaptic currents in the neural population (Okun et al., 2010; Poulet and Petersen, 2008). Motivated by this, we model the stimulation-driven E-I response using the stimulation-triggered averaged LFP.

In the model, separate E and I responses to stimulation pulses are summed to create the E-I window. For illustrative purposes, we show the E response preceding the I response but this can be reversed so that I precedes E (Cruikshank et al., 2010; Haider et al., 2013). The E-I window is convolved with a pulse train to model the combined E-I response to stimulation. To simulate spiking responses, the positive- and negative-rectified responses to the pulse train are passed through a non-linear transformation and summed to generate the time varying firing rate, $\lambda(t)$. Individual action potentials are then randomly generated at each time point from a binomial random variable with $p(spike\ at\ time\ t) = \lambda(t)\Delta t$. We separately model LFP activity in response to optogenetic stimulation as a linear sum of brown noise background activity and activity due to each stimulation pulse (**Figure 1B**, LFP).

We refer to this model of neuronal coherence as the **E-I window model.** Since we model spontaneous spiking and LFP as uncorrelated, baseline activity does not contain SFC (**Figure 1C**). Since optogenetic stimulation evokes E-I windows in which action potentials are more likely to occur, changes in spike probability are coupled to LFP responses. This coupling results in spikes that are coherent with LFP activity. The coherence is due to the temporal dynamics, or shape, of the E-I windows. (**Figure 1D**).

Note that the neuronal coherence described by the E-I window model depends on predictability between spikes and LFP activity. This construction is consistent with but does not require invoking an oscillator or other phase-consistent process. This construction is also consistent with the use of SFC, as opposed to other metrics of phase consistency, to estimate coherent neuronal dynamics. This is because SFC measures predictability between spikes and

LFP activity. Note also that our approach contrasts with previous work that has used cell-type-specific optogenetic stimulation to generate neuronal coherence.

Selectively generating coherent neuronal dynamics by varying E-I windows.

According to the E-I window model, the frequency of coherent neuronal dynamics is determined by the E-I window. We first verified this prediction computationally by simulating the model. To analyze the impact of E-I windows due to each stimulation pulse, we modelled E-I windows as a weighted sum of excitatory and inhibitory components

$$EI = \beta_{exc} exc - \beta_{inh} inh$$
$$exc = Ae^{-At}\left(\frac{(At)^{\alpha_{exc}}}{\alpha_{exc}!}\right)$$
$$inh = Ae^{-At}\left(\frac{(At)^{\alpha_{inh}}}{\alpha_{inh}!}\right)$$

where α_{exc} and α_{inh} govern the temporal dynamics of the excitatory and inhibitory components, respectively (**Figure 2A**). To test how each stimulation pulse drives an effective E-I window that alters coherence, we simulated spiking and LFP activity while sweeping through values for the α_{exc} and α_{inh} parameters and used white noise Poisson stimulation pulse sequences. In our empirically measured E-I windows, excitatory responses dominated the early stage followed by inhibitory responses. This is consistent with sensory stimulation which typically generates an increase in excitation followed shortly by a corresponding inhibitory response (Higley and Contreras, 2003; Wehr and Zador, 2003). However, inhibition may be stronger and have faster rise times than excitation in certain circuits or behaviors (Cruikshank et al., 2010; Haider et al., 2013). This regime would be captured in the E-I window model by setting $\alpha_{inh} > \alpha_{exc}$. In line with the prediction, the frequency content of SFC in the simulations

varied with the E-I window duration (**Figure 2B-C**). Longer E-I windows generated SFC at lower frequencies.

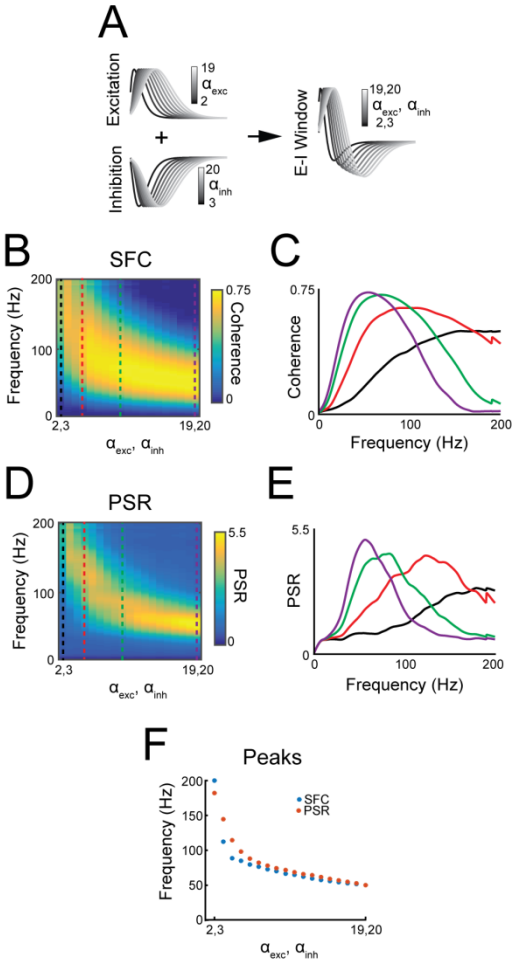

Figure 2. E-I window shape controls frequency of coherent activity. (A) Excitation, inhibition and E-I windows generated when varying α_{exc} and setting $\alpha_{inh} = \alpha_{exc} + 1$ to alter the duration of the windows. E-I is the sum of E and I windows. **(B)** Spike-field coherence that results from using the E-I windows from (A) in the model. E-I duration is measured as the time from the onset of the response and when the response returns to the stable state. **(C)** Example coherence for various E-I windows in (B). **(D)** Power spectral ratio that results from using the E-I windows from (A) in the model. (E) Example PSRs for various E-I windows in (D). **(F) F**requency of peaks in the SFC (blue) and PSR (red) for each E-I window in (A).

The influence of the E-I window on coherence was also present in the LFP activity alone. We defined a power spectral ratio (PSR) as the ratio of the driven LFP response to the baseline LFP response. The PSR captures the linearly-dependent influence of optogenetic stimulation on temporal structure in the neuronal activity. Consistent with SFC, the PSR also varies with E-I

duration (**Figure 2D-E**). Longer duration E-I windows drive increases in power at lower frequencies. Since driven spiking activity may not be measured at all recording sites in an experiment, the results of the PSR analysis suggest LFP activity may also measure the driven coherent dynamics.

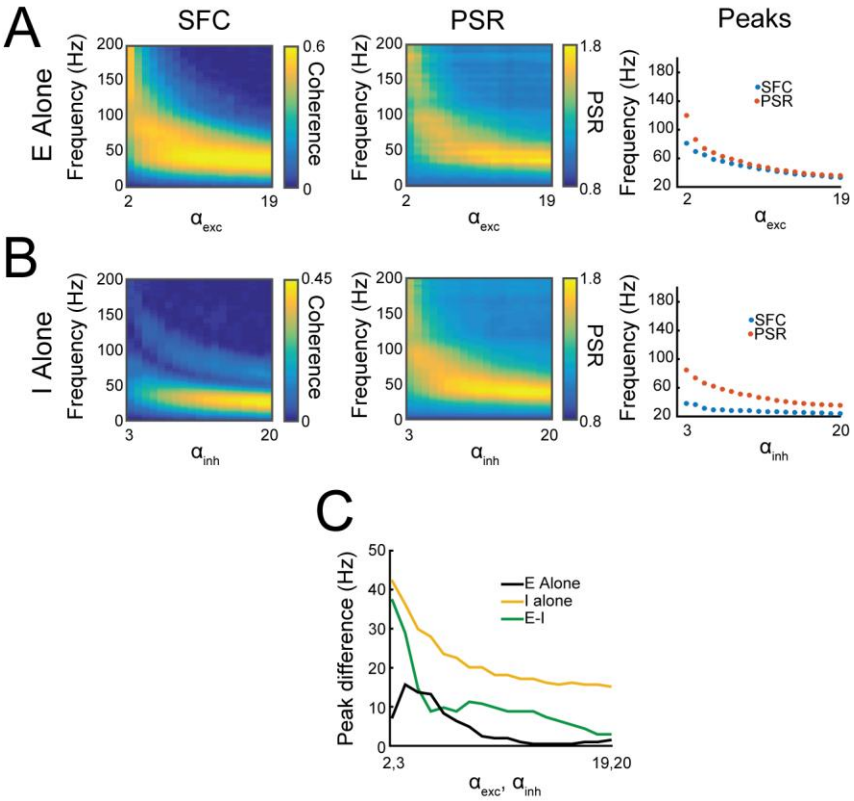

Figure 2—figure supplement 1. E-I window shape controls frequency of coherent activity. (A) Spike-field coherence (left) and power spectral ratio (right) that result from using the E windows from (Fig 2A) in the model. Right, frequency of peaks in the SFC (blue) and PSR (red) for each E window. **(B)** The same as (A) using I windows. **(C)** Differences in the peak frequencies for the each window duration for E (black), I (yellow) and E-I (green) windows.

Using both E- and I- components to simulate stimulation responses provided a wide range of driven dynamics across a wide range of frequencies (**Figure 2F**). Additional computational work suggested that the interplay of E- and I-windows was important to this result (**Figure 2—figure supplement 1**). Taken together, the simulation results suggest that coherent

neuronal dynamics can be selectively generated using optogenetic stimulation to control E-I window durations, consistent with the E-I window model.

Optogenetic stimulation robustly generates frequency-selective responses.

Next, we tested the E-I window model experimentally. The model suggested that varying the E-I window duration affects the frequency of driven coherent neuronal dynamics. This raised the question of how to experimentally vary the E-I window duration. We hypothesized that varying the duration of the stimulation pulse would drive different E-I windows, and thus alter the frequency content of the driven coherent neuronal activity.

To test this hypothesis, we injected AAV5-hSyn-ChR2(H134R)-EYFP and recorded neuronal responses in three alert macaque monkeys quietly seated in a primate chair. We recorded in the inferior and superior parietal lobules in Monkeys H and J and lateral to the post-central dimple in Monkey B (**Figure 3A**)**.** We observed strong viral expression at each injection site with robust labelling of neurons and neuropil (**Figure 3B**). We performed simultaneous *in vivo* optogenetic stimulation and recording using a fiber optic cable placed on a surgically thinned dura and adjacent to the intracortical recording electrode (**Figure 3C**). Stimulation consisted of one second long sequences of light pulses (stimulation epoch) followed by 1-3 s of no stimulation (baseline epoch) (**Figure 3D**). Optogenetic stimulation reliably generated neural responses. These responses consisted of action potentials as well as large evoked field potentials visible on an individual pulse basis in the raw data (**Figure 3E,F,G).**

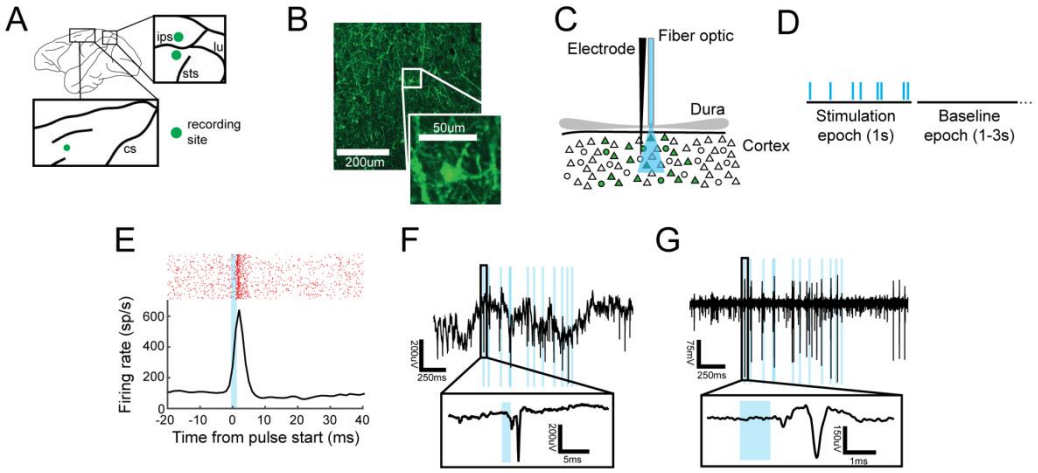

Figure 3. Optogenetic stimulation in macaque cortex. (A) Recording locations in all animals. The area of the circle corresponds to the number of sites recorded in each animal. **(B)** Example injection site with YFP labeled neurons and neuropil from horizontal section. Inset: image of a single transduced neuron. **(C)** Recordings were performed with a single, acute electrode during trans-dural light stimulation with a fiber optic place over a surgically thinned dura. **(D)** Experimental design featured a 1 s stimulation pulse sequence followed by 1-3 s without stimulation. **(E)** Example raster plot (top) and PSTH (bottom) of the spiking response triggered on each stimulation pulse for Poisson distributed trains of 1 ms pulses at 10 pulse/s rate. **(F)** Example broadband recording during a pulse train containing 1 ms pulses at 10 pulse/s rate; optogenetic stimulation (blue). *Inset*: Response to a single pulse. **(G)** Example multiunit filtered data from (E). *Inset*: Stimulation-elicited spike.

We measured neuronal responses to stimulation sequences composed of Poisson pulse trains with different pulse rates and pulse durations. **Figure 4A** presents example neuronal responses during a stimulation block with 5 ms wide pulses delivered with a 20 pulse/s Poisson pulse train. Individual stimulation pulses drove spiking activity and evoked LFP responses at the stimulation site (**Figure 4Ai,ii**). Stimulation drove spiking activity that was coherent with LFP activity at selective frequencies (**Figure 4Aiii**). To quantify the response to the pulse train, we computed the power spectrum of LFP activity during the one second long stimulation epoch and one second prior to stimulation during the baseline epoch (**Figure 4Aiv**). The peri-stimulation LFP power spectrum revealed a significant increase in power (Chi-squared test, $p<0.01$). The PSR shows that power is driven in a selective frequency range (**Figure 4Av**).

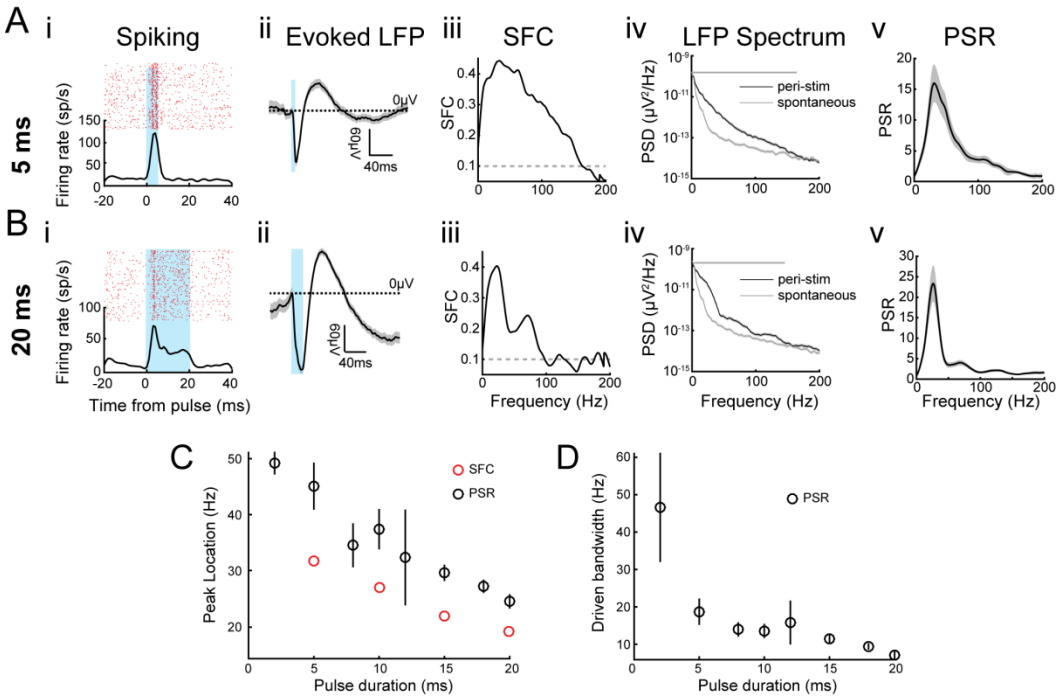

Figure 4. Neuronal dynamics driven by optogenetic stimulation. (A) Neuronal responses to 5 ms pulse duration, 20 Hz pulse rate, periodic pulse train. (i) Raster (top) and PSTH (bottom) of the response to single light pulses (blue). (ii) Mean evoked potential for all the stimulation pulses that were the last in a sequence and not preceded by a prior stimulation pulse within 50 ms, normalized by subtracting the value of the LFP at the onset of the light. Dotted line indicates 0 mV. (iii) Spike-field coherence for multi-unit activity and LFP measured on the same electrode. Dotted horizontal line shows expected coherence under the null hypothesis that coherence is zero. (iv) Power spectral density (PSD) of 1 s of data during stimulation (black line) and spontaneous activity prior to stimulation (grey line). The dotted lines are error bars determined by the Chi-squared test for p=0.01. Solid gray lines above the PSD illustrate frequency bands where the stimulus PSD was significantly different from the spontaneous PSD ($p<0.01$). (v) Power spectral ratio showing frequency specific increases in power due to stimulation. **(B)** Same as (A) for 20 ms, 20 pulses/s pulse rate, Poisson pulse train. **(C)** Population mean of peak frequency for the SFC (red) and PSR (black) for each pulse duration across all subjects. The mean SFC peak location was measured from the average SFC across the population. The PSR peak location was measured individually for each recording site then averaged across the population. Error bars show the standard error of the mean. **(D)** Population mean of the bandwidth of driven activity measured in by the width of the PSR for each pulse duration across all subjects. Error bars show the standard error of the mean.

Longer pulse durations generated longer duration changes in firing rate (**Figure 4Bi**). Interestingly, LFP activity during wider pulses showed longer periods of excitation and inhibition (**Figure 4Bii**). The longer-duration E-I window was associated with more selective changes in SFC and the LFP power spectrum (**Figure 4Biii-v**). Therefore, stimulation sequences with different pulse durations can be used to selectively generate coherent neuronal dynamics, consistent with changing the E-I window duration. Thus, the E-I window model predicted the relationship between the E-I windows and the stimulation-evoked coherent neuronal dynamics.

Optogenetic stimulation generates pulse duration-dependent responses.

We averaged SFC across a population of recording sites with driven spiking activity in response to stimulation using Poisson pulse trains with 5, 10, 15, and 20 ms duration pulses. SFC varied with pulse duration, consistent with the example site (**Figure 4C**). In addition, we analyzed LFP responses across recording sites with driven evoked potentials in the three animals for 2, 5, 8, 10, 12, 15, 18, and 20 ms duration pulses. As with the example site, the frequency content of the driven LFP varied with pulse duration across the population (**Figure 4C**).

The frequency of driven coherence decreased with pulse duration ($r^2 = 0.88$, $p = 0.062$) (**Figure 4C**, red). Consistent with the SFC, the frequency driven LFP response also depended on pulse duration ($r^2 = 0.60$, $p = 6.7\times10^{-9}$) (**Figure 4C**, black). Longer duration pulses drove more neuronal coherence at lower frequencies and did so in narrower bands ($r^2 = 0.36$, $p = 6.07\times10^{-5}$) (**Figure 4D**). Importantly the center frequency did not depend on the mean pulse rate for Poisson stimulation (**Figure 4—figure supplement 1**). The decoupling of frequency from pulse rate means that the amount of coherence can be controlled separately from the center frequency. These results show that coherent neuronal dynamics in either beta or gamma frequency bands can be generated by stimulating the same population of neurons using stimulation pulses of different durations.

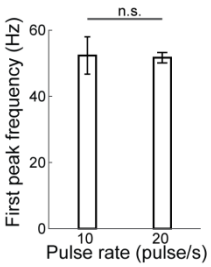

Figure 4—figure supplement 1. The response dynamics do not depend on pulse rate. Average and SEM of the standard deviation of the first fitted Gaussian for all stimulus sequences with a 10 ms pulse width across all recording sites.

E-I windows are site-specific.

E-I windows also differ across stimulation sites, potentially due to variations in expression and local network properties (**Figure 5A**). Hence at a single stimulation site, different pulse durations generate coherent neuronal activity at different frequencies, (**Figure 5B,C**). However, **Fig 5D** illustrates how responses to the same pulse duration at other sites may differ. A short pulse at Site B could drive a narrower response, similar to **Figure 5C**, but with different relative timing of excitatory and inhibitory components. The differences in E-I timing result in coherent neuronal dynamics with different frequency structure.

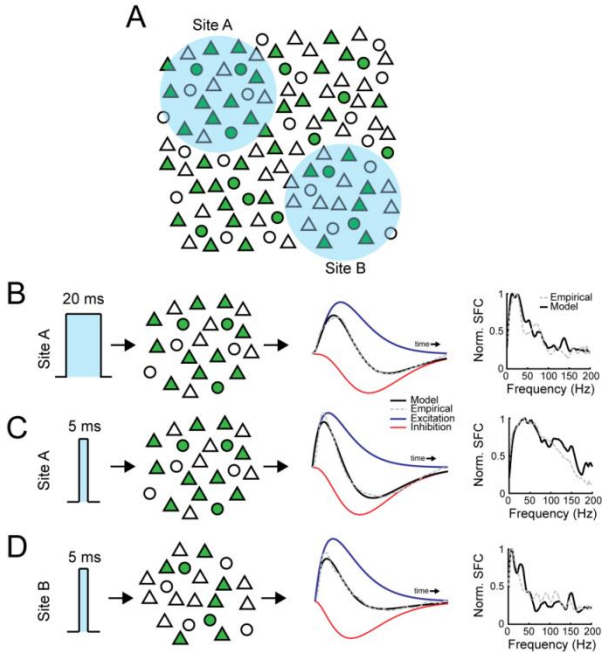

Figure 5. Site specific E-I windows generate different dynamics. (A) Transduction patterns and network connectivity can vary within a single injection site or across injection sites or subjects. **(B)** At the example site from Fig 3 (Site A) a 20 ms pulse drives a longer evoked response in the LFP (dotted gray). This can be modelled as an E-I window (black) with excitatory (blue) and inhibitory (red) components that have extended durations. This empirical E-I window generates coherent dynamics at low frequencies with a more narrow bandwidth. The E-I window parameters are A=0.097, α_{exc}=2, α_{inh}=4, β_{exc}=4.548, β_{inh}=4.730. **(C)** Same as (B) for Site A, with a 5 ms wide pulse. The E-I window parameters are A=0.097, α_{exc}=1, α_{inh}=3, β_{exc}=2.568, β_{inh}=3.654. **(D)** Same as (C) for a different site. The E-I window parameters are A=0.075, α_{exc}=1, α_{inh}=2, β_{exc}=4.312, β_{inh}=3.445.

Model-based generalization of local response dynamics.

The presence of site-specific E-I windows suggests that, in order to generate coherence in a frequency band of interest, the stimulation pulse train needs to be tailored to the E-I window at that site. However, if empirically searching through the space of stimulation parameters at each site is required, selectively manipulating coherence would be time-consuming. A model-based procedure is needed to compute the site-specific stimulation parameters without an empirical-search.

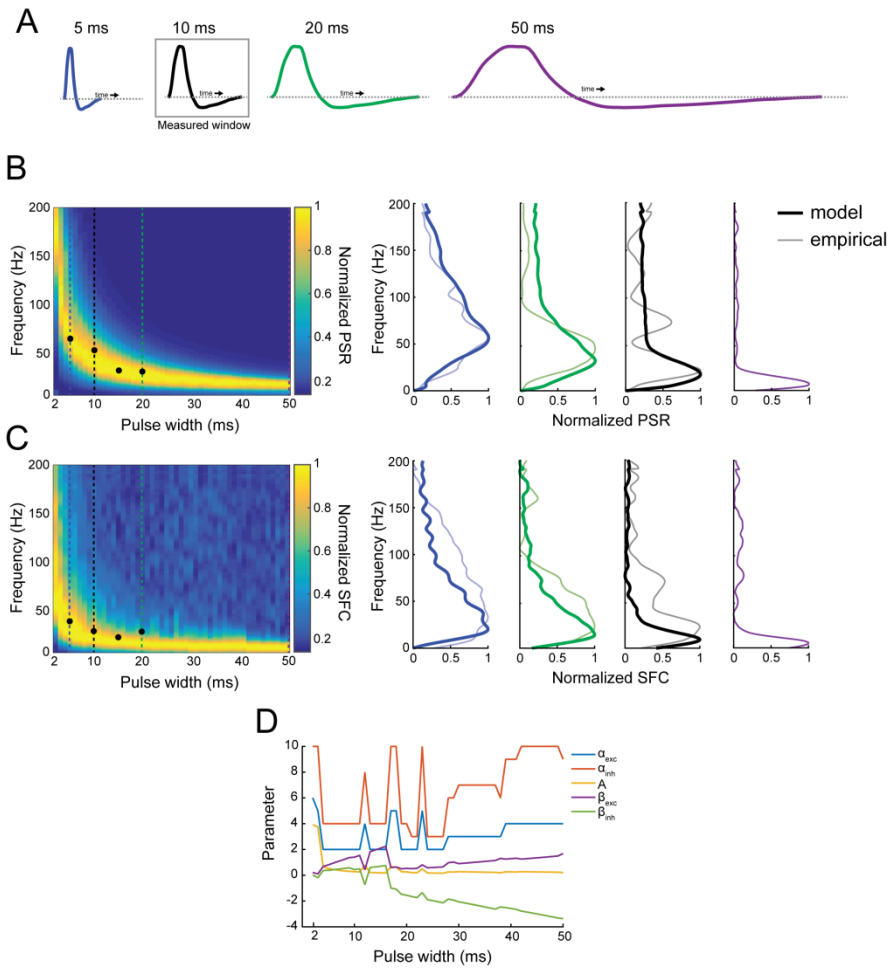

Figure 6. Using the E-I window model for model-based generalization. (A) Example E-I window for empirical data using a 10 ms pulse duration temporally scaled to simulate E-I windows for 5 ms (blue), 20 ms (green), and 50 ms (purple) pulses. **(B**) Right, Simulated PSRs for 2-50ms pulses using an example excitation window from the 10 ms condition. Black dots show the actual PSR peak location from the experimental data. Right, PSRs for simulated responses for 5 ms, 10

ms, 20 ms, and 50 ms pulse widths conditions. Lighter, thinner lines show PSRs for experimental data. **(C)** Same as B for simulated SFC. (D) E-I window model parameter for all pulse widths in (B,C).

To test whether a model-based procedure can select site-specific pulsatile stimulation parameters, we examined how stimulation parameters could be generalized across response sites. Using empirically-derived responses from one set of parameters in the E-I window model to estimate responses to other parameters allows for model-based, site-specific selection of pulsatile stimulation parameters. To do this, we temporally scaled the E-I response for a 10 ms pulse to provide an estimate of the temporal window of excitation to any arbitrary pulse duration (**Figure 6A**). Scaling longer pulse durations, which have excitation windows that capture high frequency suppression, provides a better fit to experimental data than scaling shorter pulses (**Figure 6—figure supplement 1**). Performing simulations using the E-I window model with E-I windows that are temporally scaled versions of the experimental test condition produces a map that shows which frequencies can be generated using pulsatile Poisson stimulation (**Figure 6B,** left). The E-I window model generates dynamics that match empirical results (**Figure 6B**, left; black dots). Importantly, different pulse durations can be used to generate selective responses in bands typically associated with beta and gamma frequencies (**Figure 6B,** right). The E-I window model also generates spiking that is coherent with LFP activity at beta and gamma frequencies and varies with pulse width (**Figure 6C**). The frequency content of the response is driven by parameter choice for the E-I window (**Figure 6D**). This offers a way to separately test the contribution of each of these frequency bands to behavior.

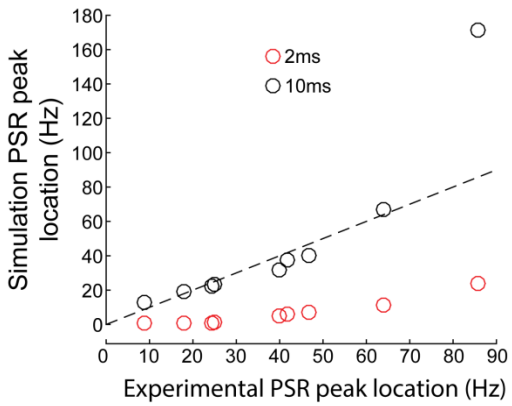

Figure 6—figure supplement 1. Simulations from short and long pulse widths. The peak of the PSR for simulations using 2 ms (red) and 10 ms (black) experimentally determined excitation windows compared to peak locations for experimentally determined PSRs for the same site. Simulations for scaled pulse widths of 2 ms, 5 ms, 8 ms, 10 ms, 12 ms, 15 ms, 18 ms, 20 ms, and 50 ms using each base pulse width (2 ms and 10 ms) are shown.

Model-based prediction of responses when varying stimulation pulse sequences.

The frequency of driven coherent neuronal dynamics can also be altered in a complementary manner by changing the temporal properties of the stimulation sequences. To generate narrow-band responses, we use a quasi-periodic stimulation pulse train where the probability of generating a stimulation pulse is given by $P(stim) = \beta(1+\alpha\sin(2\pi Ft))\Delta t$ (**Figure 7A**). Periodic stimulation can also be used to generate narrow responses. However, periodic stimulation trains have power at the fundamental frequency and its harmonics, which can drive responses outside of the desired frequency (**Figure 7B**). Quasi-periodic stimulation can reduce the stimulation harmonic content, while preserving the response at the frequency of interest leading to selective drive (**Figure 7C**). Quasi-periodic stimulation robustly generates that frequency specificity on a trial-by-trial basis (**Figure 7D**). Therefore, a quasi-periodic algorithm can generate frequency selective drive over short, behaviorally relevant periods of time.

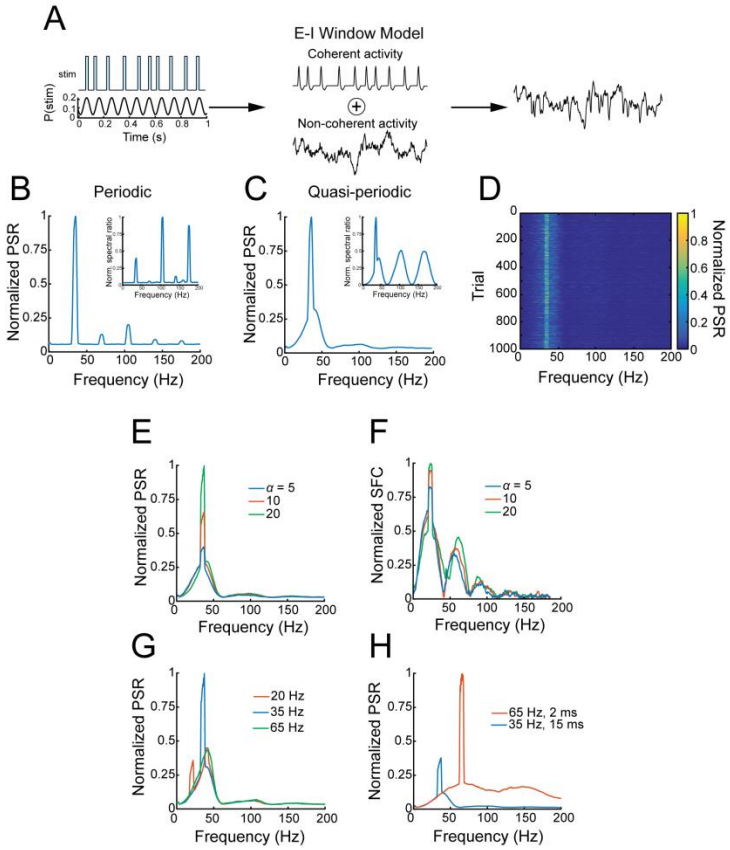

Figure 7. E-I window model predictions for quasi-periodic stimulation. (A) Quasi-periodic stimulation to generate stimulation pulses according to probability P(stim) = β(1+αsin(2πFt))Δt. β is the baseline stimulation rate and α is the modulation depth of stimulation. F is the frequency of interest. Δt is the sampling rate of the simulation pulse train. Increasing α increases stimulation intensity at frequency F. **(B)** Simulated PSR for fully periodic stimulation (F = 35 Hz) with 15 ms evoked potentials. Inset, Linear model prediction. **(C)** Simulated PSR for quasi-periodic stimulation (F = 35 pulse/s, α = 20, β = 5). **(D)** Trial-by-trial PSRs for the simulated responses from C. **(E)** Simulated PSR when varying modulation depth α. Other parameters as in C. **(F)** Simulated SFC when varying modulation depth α (F = 25 Hz). **(G)** Simulated PSR when varying frequency F. Other parameters as in C. **(H)** Simulated PSR using evoked potentials from 2 ms pulses for F = 65 Hz (red) compared with results from C (blue).

Quasi-periodic stimulation offers other benefits. With periodic stimulation, increasing stimulation intensity by stimulating more frequently can also increase the frequency of driven responses. Quasi-periodic stimulation allows frequency-selective stimulation intensity to be controlled separately from the frequency of interest itself. Increasing the modulation depth, α, results in increased driven power and coherence around the frequency of interest and not at other frequencies (**Figure 7E,F**). Changing the frequency of interest is achieved by varying F in

order to generate a range of behaviorally relevant frequencies (**Figure 7G and Figure 7—figure supplement 1**).

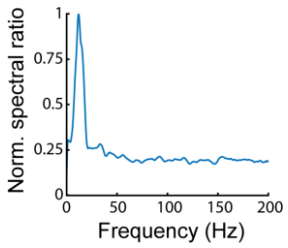

Figure 7—figure supplement 1. Stimulations for low frequency selective drive. PSR for simulations using quasi-periodic stimulation (F = 10 pulse/s) with 50 ms evoked potentials. Evoked potentials from 10 ms, 20 pulse/s conditions at an example recording site were stretched by a factor of 5 to simulate responses to a 50 ms pulse.

One concern highlighted by our results is that responses to square wave pulse trains have low power at nodes determined by the inverse of the pulse duration. These nodes occur where the stimulation sequence has no energy, at frequencies that are multiples of $\frac{1}{pulse\ width}$, as determined by the Fourier transform of a square wave. Since response linearity predicts that responses are shaped by the stimulation pulse shape, if the pulse shape has low power at a given frequency, then a periodic or quasi-periodic pulse train will not drive responses at that frequency (**Figure 7G**, green). Conversely, if the pulse shape has a peak in power at a given frequency, then the response will be greater compared to stimulation at other desired frequencies with the same pulse duration (**Figure 7G**, blue). To address this concern, we propose that the pulse duration should be chosen according to the desired response frequency (**Figure 7H**).

Discussion

Here, we investigate how optogenetic stimulation of non-human primate cortical neurons evokes coherent neuronal dynamics. We propose that optogenetically-evoked dynamics are consistent with the recruitment of a combination of excitatory and inhibitory responses leading to an effective temporal window for spiking – the E-I window. We develop the E-I window model and show the specific frequency of optogenetic stimulation-evoked coherence varies parametrically with stimulation parameters. Experimental results from optogenetically-stimulating non-human primate cortex confirmed model predictions and revealed that varying the pulse duration alters the stimulation driven E-I windows. These results show that varying optogenetic stimulation parameters alone can selectively generate coherent dynamics across a range of behaviorally relevant frequencies—beta and gamma—by varying the effective E-I window.

Cell-type specific manipulations

Our work shows that pan-neuronal optogenetic stimulation generates E-I windows that drive coherent neuronal dynamics. Previous work suggests that controlling activity in a single cell-type is necessary for driving coherence (Adesnik and Scanziani, 2010; Cardin et al., 2009; Lu et al., 2015; Sohal et al., 2009). However, direct stimulation of specific types of neurons recruits synaptically-mediated responses from other strongly connected neurons in the network (Phillips and Hasenstaub, 2016). This recruited ensemble shapes the frequency content of coherent neuronal dynamics (Kato et al., 2017). Thus, stimulation-evoked coherence measured under cell-type-specific optogenetic stimulation may also be designed according to an effective E-I window. Whether the E-I window model is as effective in predicting the impact of cell-type specific manipulations that target either E or I cells is an open question and will likely depend on the strength of recurrent connectivity in the network.

E-I window mechanisms of driven coherence

The E-I window model offers a mechanism for how E-I window affects spike timing and driven coherent neuronal dynamics. The model makes use of an LFP-based conditional intensity function in order to capture the E-I window and couple spike timing and LFP activity. We estimated the net E-I window in response to stimulation using LFP activity. LFP activity can capture the E-I window because field potentials arise from synchronous neuronal activity that occurs due to temporally structured fluctuations of local excitation and inhibition (Buzsáki and Wang, 2012; Csicsvari et al., 2003; Hasenstaub et al., 2005). Moreover, the stimulation-evoked LFPs reveal the temporal structure of stimulation-induced post-synaptic potentials (Okun et al., 2010; Poulet and Petersen, 2008),. Experimental agreement with the E-I window model predictions reinforces the idea that driven coherent neuronal dynamics depends on a mechanism involving the E-I window. The agreement also shows that stimulation-evoked LFP activity is effective in capturing the phenomenology of the stimulation-driven E-I balance without relying on precise measurements of the E and I components. Overall, our work suggests that optogenetic stimulation controls spike timing and LFP activity through the generation of E-I windows.

E-I window based stimulation compared with other stimulation pulse sequences

Continuous and periodic pulse optogenetic stimulation sequences have previously been used generate beta and gamma activity and study its effects on behavior (Adesnik and Scanziani, 2010; Cardin et al., 2009; Ni et al., 2016; Sohal et al., 2009). These forms of stimulation implicitly control the E-I window using the properties of the stimulation pulse and stimulation sequence. However, using continuous constant and pulsatile periodic stimulation drives responses at only particular frequencies (Adesnik and Scanziani, 2010; Cardin et al., 2009; Lu et al., 2015), likely related to properties of the local network (Buzsáki and Wang,

2012). The driven frequency may vary across brain regions and subjects (Lu et al., 2015; Ni et al., 2016), and some stimulation sequences may not flexibly generate activity in certain frequency bands of interest. Using the E-I window model to determine the stimulation pulse duration allows us to generate coherent activity across a broader range of behaviorally-relevant frequencies.

Another issue is that periodic pulsatile and continuous stimulation tend to generate oscillatory dynamics in narrow frequency band (Adesnik and Scanziani, 2010; Cardin et al., 2009). However, empirically observed coherent neuronal activity is not strictly oscillatory. Oscillatory activity requires the presence of consistent phase relationships over extended time period (Burns et al., 2011; Chariker et al., 2018; Pesaran et al., 2018; Xing et al., 2012). Coherent neural activity is a broader term than oscillatory neural activity, and only requires the presence of statistically significant dependencies at specific frequency bands. Empirically observed neural coherence is dynamic and episodic, with fluctuations in phase and frequency, and can be narrow-band or broad-band. By contrast, the E-I window model describes manipulations of coherent neural activity patterns which are not necessarily oscillatory or narrow-band.

A related issue is that in order to test the role of both broad-band and narrow-band activity in behavior, we need to be able to generate both within a single experiment. Since periodic pulsatile and continuous stimulation tend to generate oscillatory dynamics in narrow frequency bands they and may not be effective for testing hypotheses about broad-band dynamics. Additionally, periodic stimulation has power at harmonic frequencies, which can drive responses outside of the desired frequency range and confound results. We show that the choice of stimulation pulse sequence can alter the bandwidth of driven coherence while minimizing power outside of desired frequencies. This leads to an important strength of the model-based approach: E-I window-based optogenetic stimulation can identify and compare

specific functional roles for coherent neuronal dynamics at different frequency ranges with needing multiple optogenetic constructs. The E-I window model predicts how stimulation parameters can be selected to shape synaptic excitation and inhibition and generate the desired coherent neuronal dynamics. Thus, the model-based approach to parameter selection also mitigates the need for time-consuming empirical searching through the space of stimulation parameters.

Potential bias in estimates of coherent neuronal dynamics from LFP activity

The choice to use extracellular recordings for LFP activity and spiking may bias our measurements towards activity in pyramidal neurons. LFP activity is most sensitive to post-synaptic potentials in neurons with separated current sources that generate an open field geometry (Pesaran et al., 2018). Thus, contributions from neurons with extended dendritic architectures, such as pyramidal neurons, are more heavily weighted by LFP activity. Additionally, pyramidal neurons typically have larger cell bodies than other cortical neurons and thus have more easily measurable action potentials. Therefore, our measurement of both spiking activity and LFP, and thus SFC, may be biased toward contributions from pyramidal neurons. In addition to LFP activity, alternative decompositions of neural data, such as projections of population activity onto lower dimensional subspaces, may be used to estimate coherence. Such estimates may be more effective at identifying spiking that is coherent with pre- and post-synaptic activity in neuronal ensembles containing both open and closed field neurons.

Limitations of non-light based stimulation

Are forms of stimulation other than optogenetic stimulation useful for studying coherent neuronal dynamics and behavior? Electrical and magnetic stimulation approaches have been used to precisely generate temporal structure in neuronal activity (Casarotto et al., 2010; Choi et

al., 2016; Radman et al., 2007; Schmidt et al., 2014) and study the impact of temporally patterned stimulation on behavior (Bari et al., 2013; Van Acker et al., 2013). However, a significant difficulty in interpreting the results of causal manipulations is that stimulating neuronal networks can lead to a variety of non-linear and dynamic response properties in addition to coherent dynamics (Millard et al., 2013; Muldoon et al., 2016; Nassi et al., 2015). Consequently, simultaneous recordings of neuronal activity during stimulation are needed to confirm the impact of stimulation sequences on coherent neuronal dynamics as opposed to other features of the neuronal responses. Sequences of electrical and magnetic stimulation pulses can generate substantial recording artifacts that are difficult to suppress, especially for field potentials, obscuring responses and introducing significant confounds (Mueller et al., 2014; Olsson et al., 2005). Our results show that, unlike electrical or magnetic stimulation, optogenetic stimulation can be used in a manner that introduces few, if any, artifacts to simultaneous electrophysiological recordings and allows us to control for non-linear and dynamic response properties.

In conclusion, we systematically modeled neuronal responses to optogenetic stimulation in non-human primate frontal cortex. We highlight the role of generating specific E-I windows by selecting stimulation parameters—pulses and pulse sequences—to selectively perturb coherent neuronal activity. Importantly, we do so in a general manner without necessarily targeting optogenetic expression to specific types of neurons. In general, our results show that combining experimental measures with model-based predictions can be used to study how optogenetic stimulation drives network dynamics across a wide range of experimental designs, including using different brain regions, model species, and stimulation protocols. These results demonstrate that the ability to selectively generate episodic dynamics in behaviorally-relevant frequency ranges in the primate brain can be useful for understanding how coherent neuronal dynamics give rise to complex, flexible behaviors.

Methods:

Animals

Recordings were taken from two male rhesus macaques (*Macaca mulatta*) (Monkey J: 12 years, 6.5 kg; Monkey H: 11 years, 10.5 kg) and one male cynomolgus macaque (*Macaca fascicularis*) (Monkey B: 4 years, 5 kg). Monkeys J and H had been part of previous studies using the contralateral intraparietal sulcus and the ipsilateral frontal cortex. Monkey B had not been part of previous experiments. All animals were in normal health and were group housed with other conspecifics at the facility. All surgical and animal care procedures were approved by the New York University Animal Care and Use Committee and were performed in accordance with the National Institute of Health guidelines for care and use of laboratory animals.

Injection surgery

We performed injections of optogenetic viral vectors 6-25 weeks prior to recording. Subjects were maintained at a constant depth of anesthesia with isofluorane (1-2%). Monkey J and H were injected in existing craniotomies. In Monkey B, after mobilizing the scalp and other soft tissue, we made craniotomies over motor cortex to provide access for injections. Injections were made through 26 s gauge stainless steel cannulas (Hamilton) that were inserted through a thinned dura. For each injection, one microliter of AAV5-hSyn-ChR2(h134R)-EYFP was injected at a rate of 0.05 μl/min. We made injections at 2-3 depths spaced 500-750 μm across 2-4 cortical sites per animal. We injected at multiple sites simultaneously to increase total number of injections sites and thus increase the probability of having successful transduction at one or more sites. We waited 20 minutes between each injection to allow for the virus to diffuse through the tissue. After injections, chambers were reclosed with the chamber cap and periodically opened for cleaning and maintenance while the viral vector was expressing.

Optical Stimulation

We illuminated the injection site with a 473 nm Laser (Shanghai Sanctity Laser) connected to a multi-mode fiber optic cable (200 μm core, BFL-200, Thor Labs). One end of the fiber optic cable was terminated with an FC/PC connecter and connected to a collimator (PAFA-X-4-A, Thor Labs) for focusing light from the laser. At the other end of the cable we removed a small amount of buffer with a microstripper (T12S21, Thor Labs) and cleaved it with a diamond knife (S90R, Thorlabs) to ensure a flat edge for minimal power-loss.

The fiber optic was placed on top of the thinned dura. The cable was held in the microdrive and placed in the same guide tube as the recording electrode. We did not insert the fiber into the brain in order to minimize damage to the neural tissue. Light power at the tip varied from 16-20.5 mW. (510-653 mW/mm^2), as measured prior to each experiment using a power meter (PM100D, Thor Labs). Evoked potentials were visually inspected to ensure that there were no signs of artifacts from the Becquerel effect, including rapid onset or offset of neural responses locked to the timing of the light(Cardin et al., 2010). Light based artifacts typically have a capacitive charging and discharging profile, which has a rapid onset and offset tightly coupled to the onset and offset of the device. We ensured that the onset of the response and the inflection point were not aligned with the times when the light was turned on and off. The neural response is slower than the duration of the light pulse and thus continues to increase for a brief period after the light has been turned off. The onset is delayed because the ChR2 channel dynamics are slower than the chemical response and thus the membrane potential does not start to change immediately. The initial response recruits network activity, which has a slow time course. This is particularly evident for short light pulses (<=5 ms). When there is no artifact, the response inflection point occurs after the light is turned off. This is less clear for longer pulse widths (>15 ms) because adaptation and other properties of channel kinetics can lead to a decrease in the response prior to the end of stimulation.

Light pulse patterns were generated by proprietary software running in LabVIEW (National Instruments) and converted to analog signals using a DAQ card (USB-6251, National Instruments). Stimulation trials consisted of 1 s long bursts of square wave pulses. For each block of trials, we controlled three stimulation parameters: pulse width, pulse rate and pulse distribution. We varied pulse widths from 1-20 ms, pulse rates from 5-80 Hz and used both Poisson and periodic pulse distributions.

In rodents, both measurement and simulation have proposed that ~1% of light power density remains after light has passed through approximately 1 mm of brain tissue (Aravanis et al., 2007; Huber et al., 2008; Yizhar et al., 2011). However, primate brain tissue may have slightly different optical properties, thus altering the light transmission. In addition, we stimulated transdurally which may have additional effects on the light. However, we were able to record purportedly directly driven spiking (low-latency, low-jitter) as far as 1.5mm below the cortical surface (not shown), suggesting that we were activating neurons into layer 3.

We tested each recording site in pseudo-randomly interleaved blocks of recordings. Each block consisted of 30-60 repetitions of 1 s long sequences of square wave pulses (bursts), with 1-3 s of no stimulation between each stimulation burst (**Fig 3C**). We held other stimulation parameters (pulse rate, duration and intensity) constant within each block.

Poisson and periodic stimulation pulse trains were generated *in silico* using the same pulse width and rate parameters. Simulations consisted of 1000 trials for each combination of parameters.

Electrophysiology

We recorded neural signals from awake, alert macaques while they were seated, head-fixed in a primate chair (Rogue Research) in a dark, quiet room. Neural signals were recorded on glass-coated tungsten electrodes (Alpha-Omega, impedance: 0.7-0.8 MΩ at 1 kHz) held in a FlexMT microdrive (Alpha Omega). Neural signals were acquired at 30 kHz on an NSpike DAQ

system and recorded using proprietary data acquisition software. Neural recordings were referenced to a metal wire placed in contact with the dura and away from the recording site. We recorded from one site in monkey B (pre-motor cortex) and three sites in each Monkeys J and H (parietal cortex). We recorded driven LFP activity at all sites and driven multi-unit activity at one site in each subject.

Fitting E-I Windows

E-I windows were fit to the form

$$EI = Ae^{-At}\left(\frac{\beta_{exc}\left(At\right)^{\alpha_{exc}}}{\alpha_{exc}!} - \frac{\beta_{inh}\left(At\right)^{\alpha_{inh}}}{\alpha_{inh}!}\right)$$

which has an excitatory component

$$E = Ae^{-At}\left(\frac{\beta_{exc}\left(At\right)^{\alpha_{exc}}}{\alpha_{exc}!}\right)$$

and an inhibitory component

$$I = Ae^{-At}\left(\frac{\beta_{inh}\left(At\right)^{\alpha_{inh}}}{\alpha_{inh}!}\right).$$

For the pure simulations, A, β_{exc} and β_{inh} were set to 1. To fit empirical E-I windows, all parameters were fit using a grid search to minimize the squared error between the modelled window and the empirical window.

E-I Window Model

To simulate LFPs using a excitation window model, we generated $\frac{T}{dt}$ samples of Brownian noise as background activity, with T =1 s and dt =1 ms. We estimated an E-I window for each recording site by fitting the stimulation pulse evoked LFP response to the following model:

$$EI = \beta_{exc} exc - \beta_{inh} inh$$
$$exc = Ae^{-At}\left(\frac{(At)^{\alpha_{exc}}}{\alpha_{exc}!}\right)$$
$$inh = Ae^{-At}\left(\frac{(At)^{\alpha_{inh}}}{\alpha_{inh}!}\right)$$

For excitatory- and an inhibitory-only simulations, β_{inh} and β_{exc} were set to zero, respectively. We simulated the driven LFP by convolving the site-specific E-I window with a sequence of delta pulses determined by the stimulation parameters. The driven LFP was and added to the background activity to generate the total simulated LFP activity.

We modelled spiking activity that was coherent with the LFP using a Poisson point process with a conditional intensity function. The conditional intensity function models stochastic spiking governed by a time-varying instantaneous firing rate modelled as

$$\lambda(t) = (\lambda_E(t) + \lambda_I(t) + \lambda_0) \cdot dt$$
$$\lambda_E(t) = f(E(t)) = e^{E(t)}$$
$$\lambda_I(t) = g(I(t)) = e^{I(t)}$$

where λ_0 is the baseline firing rate, and dt is the sampling rate. $E(t)$ and $I(t)$ are the time courses of optogenetically driven E and I response, respectively, that generate the fluctuations in the conditional intensity function, $\lambda(t)$. $E(t)$ and $I(t)$ is determined by convolving the E-I window with a Poisson process generated from the stimulus sequence parameters, then positively or negatively rectifying the E-I response to get the separate E and I responses. After a spike we used a fixed refractory period by forcing $\lambda(t) = 0$ for 3ms.

Simulations of the excitation window model were run using custom scripts in MATLAB using a 1 ms time step. For each trial, we simulated 1 s of baseline activity and 1 s of stimulation. We simulated 1000 trials for set of stimulus parameters.

Pre-processing in vivo data

Broad-band neural activity was split into multi-unit signals and local field potentials (LFP) by high-pass and low-pass filtering, respectively, at 300 Hz. LFP signals were down-sampled to 1 kHz. Multi-unit activity (MUA) was computed by applying a 3.5 standard deviation threshold to the multi-unit signals to identify putative spikes. All waveforms that exceeded this peak were labelled as multi-unit action potentials.

Data Analysis

We computed multi-unit peri-stimulus time histograms (PSTH) by aligning MUA to the onset time of light pulses. Individual spikes were collected in 1 ms bins and the corresponding histogram was smoothed by convolution with a Gaussian function with a standard deviation of 1 ms. In order to avoid corruption from nearby pulses, evoked potentials were computed by averaging LFPs aligned to the onset time of light pulses only for pulses that occurred at the end of a pulse train and did not have a pulse preceding it by less than 50 ms.

Spectral analysis was performed using multi-taper methods (Mitra and Pesaran, 1999). The accuracy of the spectral quantities we used does not depend on the center frequency of the estimate for all frequencies above the minimum resolvable frequency, given by the frequency smoothing in Hz (Jarvis and Mitra, 2001). For each recording, power spectra were computed using a 1 s analysis window and $\pm$1.5 Hz frequency smoothing. We computed power spectra for the LFP responses during entire 1 s burst (stimulation epoch) and for 1 s prior to the burst (baseline epoch). Power spectra were computed for neural signals for the baseline and stimulation epochs. Recording sites with power spectra that did not exhibit a significant difference were not included in analysis. The exclusion criteria for recording sessions did not depend on the frequency content of the driven LFP response—the desired effect—but rather only that there was any driven LFP response at all. Sites were excluded if there was no change in the LFP power between baseline and stimulation periods for the 10ms pulse width condition, which was likely due to the electrode being placed on the periphery of light cone and thus failing

to record driven neural activity. We explicitly confirm this in our experiments by moving the electrode and observing driven responses. We computed the spectrogram for each recording using a $\pm$250 ms analysis window, stepped 50 ms between windows, with $\pm$2.5 Hz frequency smoothing aligned to the start of the burst. We computed the spike-field coherence for each recording using a 1 s analysis window with $\pm$3 Hz frequency smoothing averaged across at least 30 repetitions.

Power Spectral Ratio

We also computed a spectral ratio by dividing each of these power spectra by the baseline power spectrum of the neural response. In typical linear systems analysis, the dynamical system is quiescent unless driven by input. However, spontaneous neural activity is present *in vivo*. Therefore, to understand the impact of stimulation the analysis needs to account for the presence of ongoing neural activity. We modeled the recorded neural activity during stimulation, $y(t)$, as a sum of the ongoing spontaneous activity $s(t)$, and the stimulation response $T\left[u(t)\right]$, where T is the transfer function of the neural system and $u(t)$ is the stimulus input.

$$y(t) = s(t) + T\left[u(t)\right] \tag{1}$$

Due to the linearity of the Fourier transform, we can rewrite this equation in the Fourier domain as

$$Y(f) = S(f) + H(f)U(f) \tag{2}$$

We then quantified the effects of stimulation on LFP power by computing an index given by the ratio of peri-stimulation power to baseline power. Since the ongoing activity spectrum, $S(f)$, can be estimated as the baseline LFP power spectrum, the spectral ratio is approximately proportional to the effect of stimulation without ongoing activity

$$SpectralRatio = \frac{Y(f)}{S(f)} = \frac{S(f) + H(f)U(f)}{S(f)} \tag{3}$$

$$SpectralRatio = 1 + \frac{H(f)U(f)}{S(f)} \tag{4}$$

$$SpectralRatio - 1 \propto H(f)U(f) \tag{5}$$

For the example recording, we can naively predict the neural response as a sum of spontaneous activity and a linear response to the pulse train

$$Y_p(f) = S(f) + aX(f) \tag{6}$$

where a is a scaling factor. The power ratio for the predicted response is proportional to the spectrum of the stimulus.

$$SpectralRatio = \frac{Y_p(f)}{S(f)} = \frac{aX(f)}{S(f)} + 1 \tag{7}$$

$$SpectralRatio - 1 \propto X(f) \tag{8}$$

Power spectral ratios for the neural data for each recording were fit using a sum of Gaussians model, in order to identify the peaks and widths of the power increases. This was done using the peakfit.m MATLAB function (O'Haver, 2014) with Gaussian functions used to model the peaks. Each fitted Gaussian has two parameters, the mean and standard deviation, so we collected these for the components of the model for each recording. The mean was used to measure the frequency of a peak of an increase in the power spectrum, while the standard deviation provided an estimate of the width of the power that was increased.

DATA AND SOFTWARE AVAILABILITY

Software is available in a GitHub repository linked from http://www.pesaranlab.org. Data are available upon reasonable request.

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Author Contributions:

Conceptualization: R.A.S., H.L.D., Y.T.W., M.A.H., and B.P.; Methodology: R.A.S., H.L.D., Y.T.W., M.A.H., M.M.F. and B.P.; Software: R.A.S., H.L.D., and B.P.; Formal Analysis: R.A.S. and B.P.; Investigation: R.A.S. and B.P.; Resources: R.A.S., H.L.D., and B.P.; Writing – Original Draft: R.A.S. and B.P.; Writing – Review & Editing: R.A.S., H.L.D., Y.T.W., M.A.H., M.M.F. and B.P.; Visualization: R.A.S. and B.P.; Supervision: H.L.D., Y.T.W., M.A.H., and B.P.; Funding Acquisition: B.P.

Competing Financial Interests:

The authors declare no competing financial interests.

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