Using Biophysical Computational Neural Models to Investigate Neuropsychiatric Disorders

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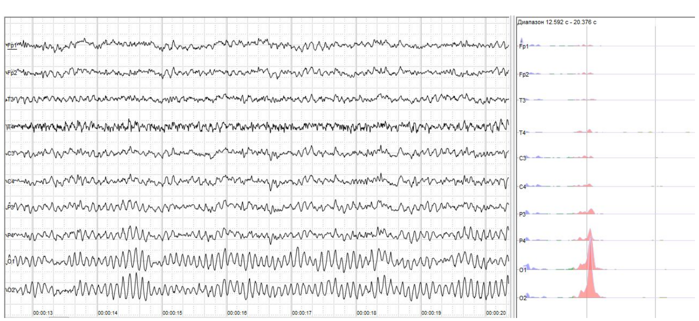
From computational neuroscience → computational psychiatry . . .

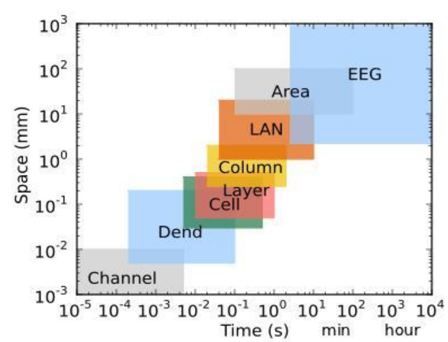
Psychiatry has fundamental problems in defining and diagnosing mental disorders/illness, partly due to obvious difficulties in measuring origins of symptoms (brain is largely inaccessible).

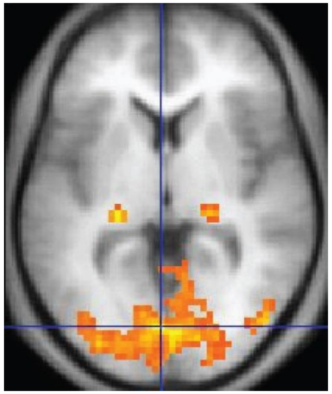
In order to better understand, diagnose, and treat mental disorders, clinicians/scientists should leverage insights gained from the integrative methodologies used in computational and experimental neuroscience.

However, computational neuroscience is a complex field, taking years of training. . .

To allow computational neuroscience and psychiatry to make the largest impact, new computational/algorithmic tools are needed that integrate multiscale brain dynamics and behavior, and allow scientists to rapidly test their hypotheses on the neural origins of mental disorders.



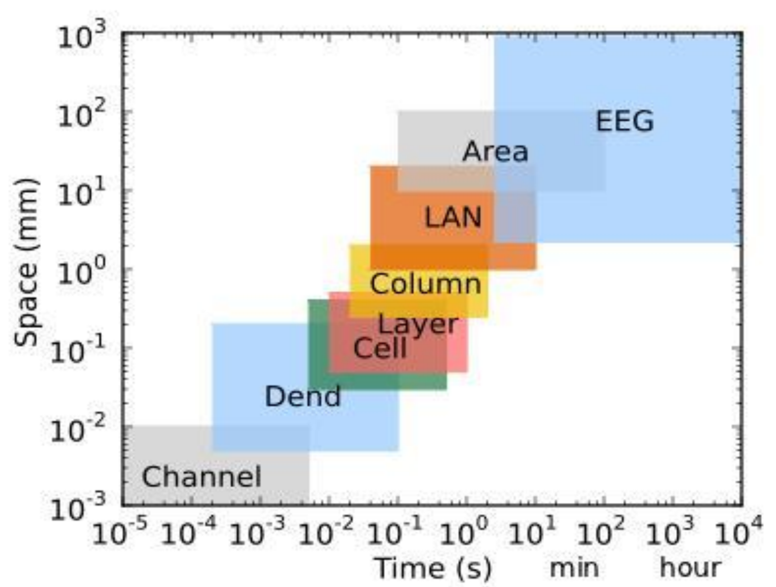




(Images from Wikipedia)

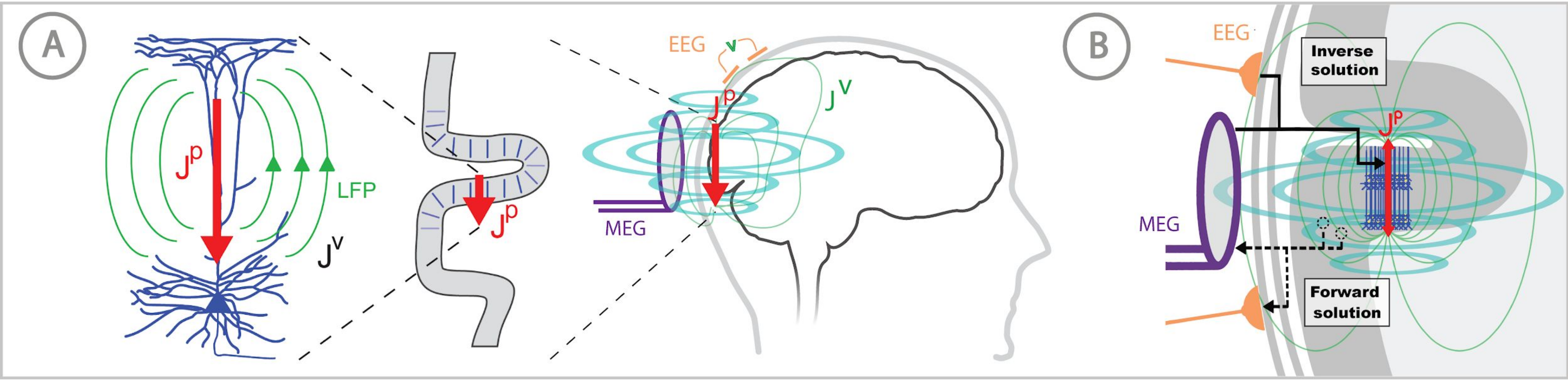
Outline: modeling tools (solutions) & modeling case studies

1. Build open-source modeling tools (Human Neocortical Neurosolver: HNN) to help researchers understand circuit level origins of human brain dynamics (EEG/MEG)
2. Use auditory thalamocortical models to link functionally relevant brain rhythms in non-human primate to human electrophysiological data
3. Use hippocampal network models to study schizophrenia
4. Use multi-scale models of primary motor cortex to study neocortical hyperexcitability and its pharmacological treatments
5. Use models of sensory/motor cortex to understand learning/behavior → beyond deep learning?



1. Problem in human neuroscience

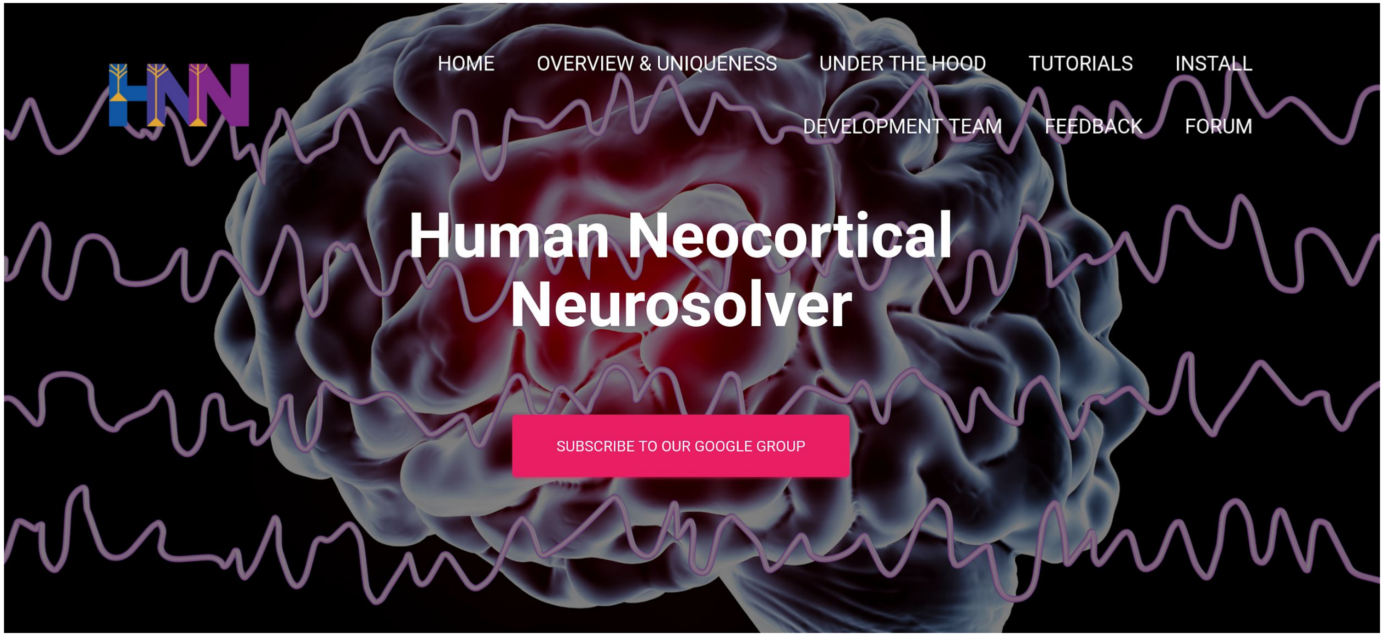
- **Question:** How do we link human macroscopic, noninvasively measured MEG/EEG signals to their underlying cell/circuit-level generators?
- **Data:** Source localized human MEG/EEG current dipole signals
- **Model:** Biophysical circuit models of the thalamocortical system that generate current dipole signals directly comparable to experimental data
- **Result:** New open-source modeling tool allowing clinicians/researchers to import their data and use the model to simulate commonly observed patterns (event-related potentials, low frequency rhythms), enabling hypothesis testing of circuit-level generators of the observed patterns



Neymotin *et al.*, eLife 2020

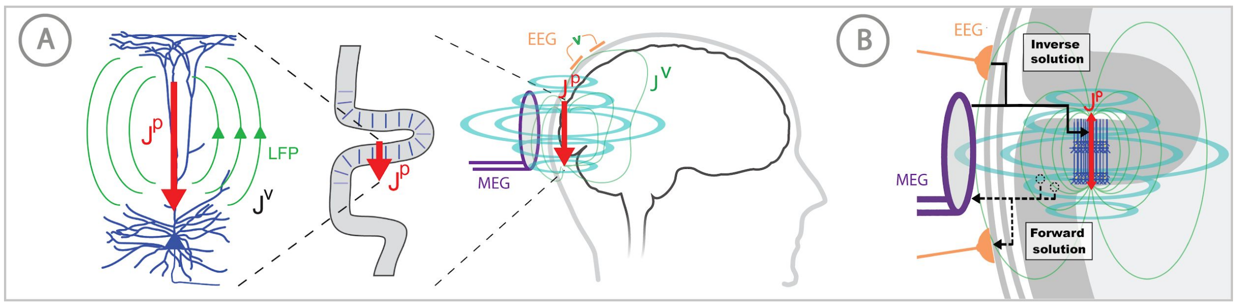
New open-source modeling tool: Human Neocortical Neurosolver (HNN)

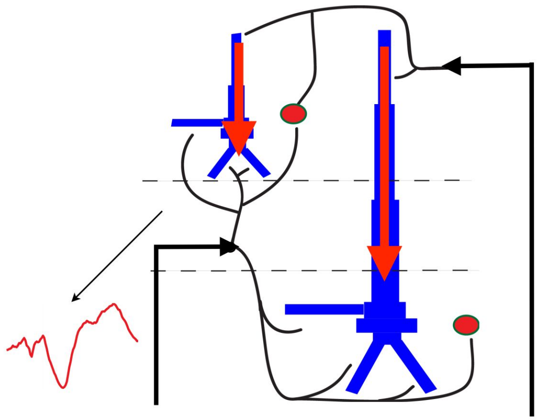
- Use biophysical thalamocortical models to test hypotheses on cell/circuit-level origins of human neural dynamics in health & disease
- Imports Human MEG/EEG data for model comparison/fitting

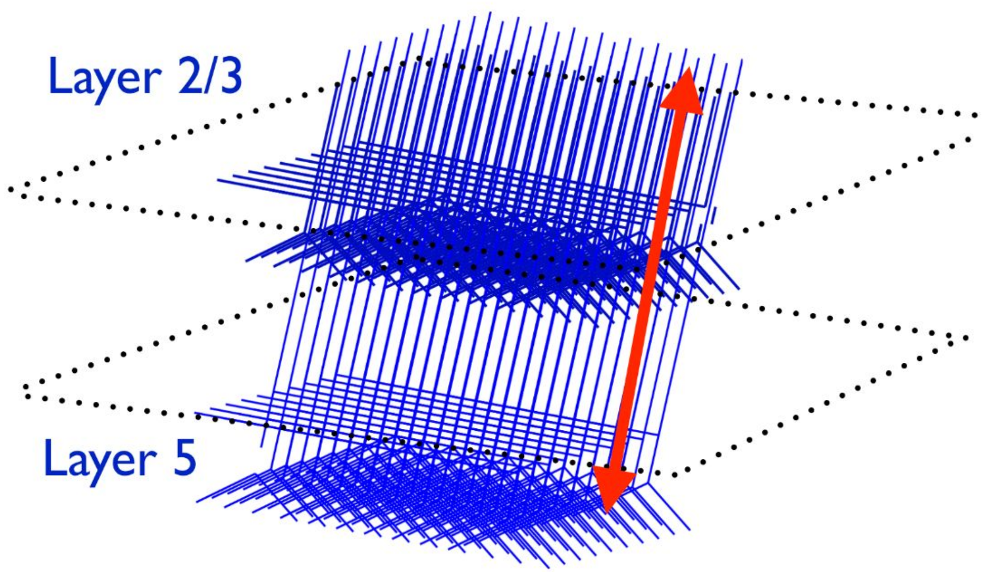


- https://hnn.brown.edu includes background, tutorials, documentation, publications (eLife)
- HNN workshops/presentations at Computational Psychiatry (http://computationalpsychiatry.org/cp18/), Cutting EEG, and SFN meetings, ...

The HNN model simulates the primary currents contributing to MEG/EEG





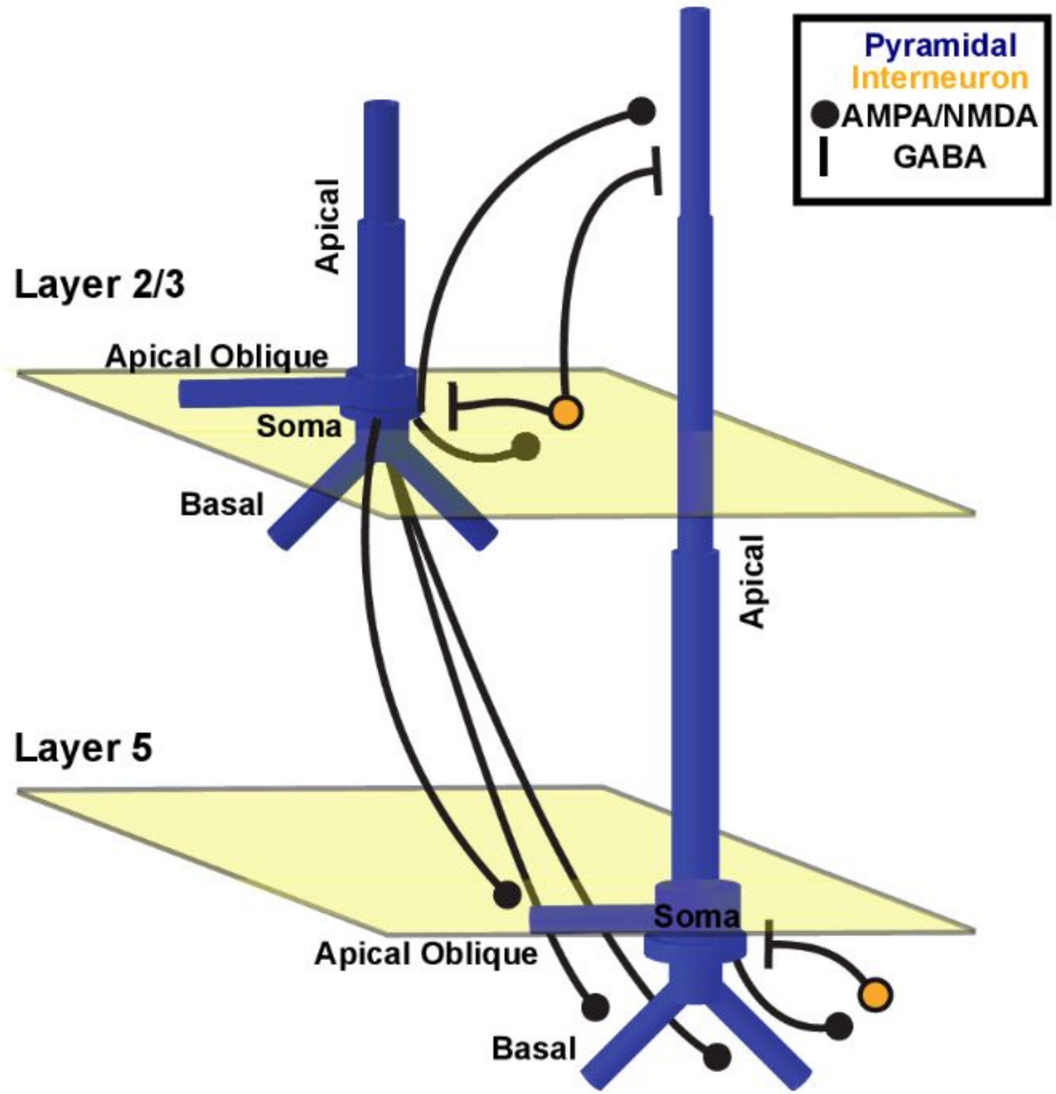


HNN's laminar neocortical microcircuit model

Layered cortical network of pyramidal neurons and interneurons

Individual neurons are compartmental models using parallel conductance equations with standard Hodgkin-Huxley ion channels

Pyramidal neurons generate current dipole signal directly comparable to source-localized signals obtained from MEG/EEG experiments

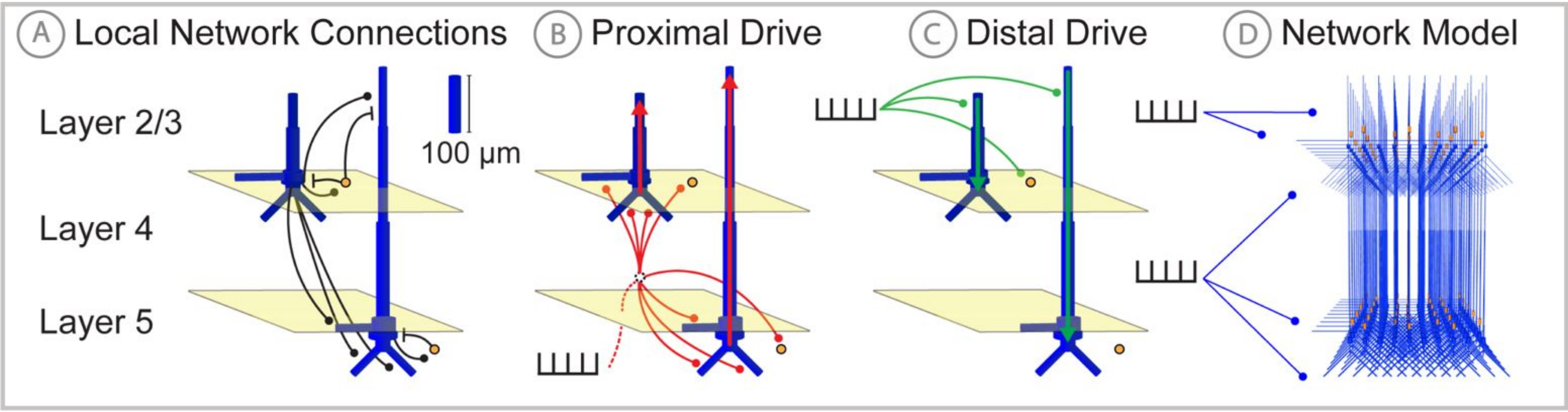


Activating HNN's microcircuit model

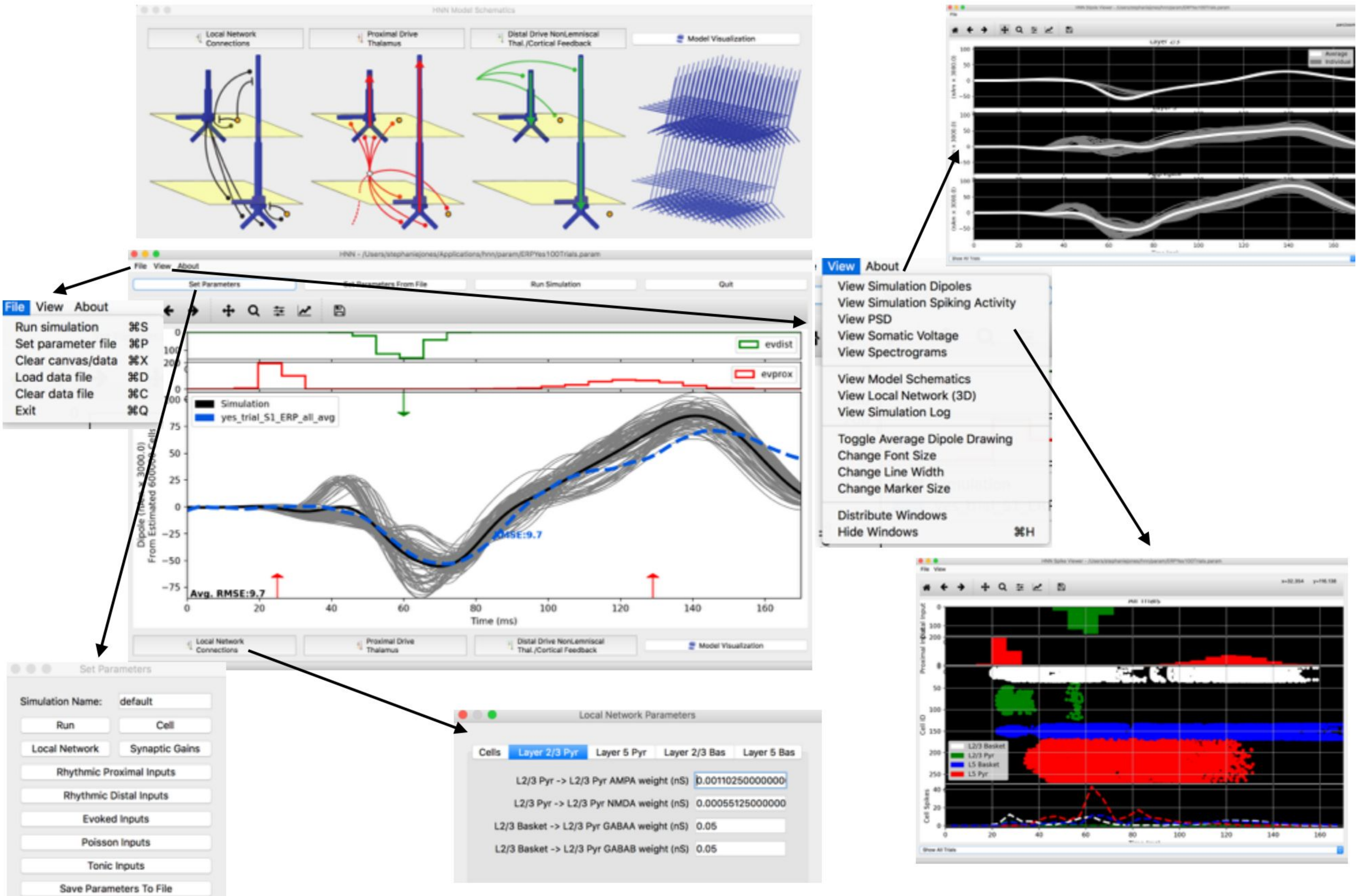
Proximal drive represents synaptic inputs from **thalamic core**

Distal drive represents synaptic inputs from **thalamic matrix and corticocortical feedback**

Each type of drive pushes pyramidal neuron dendrite current flow in opposing directions

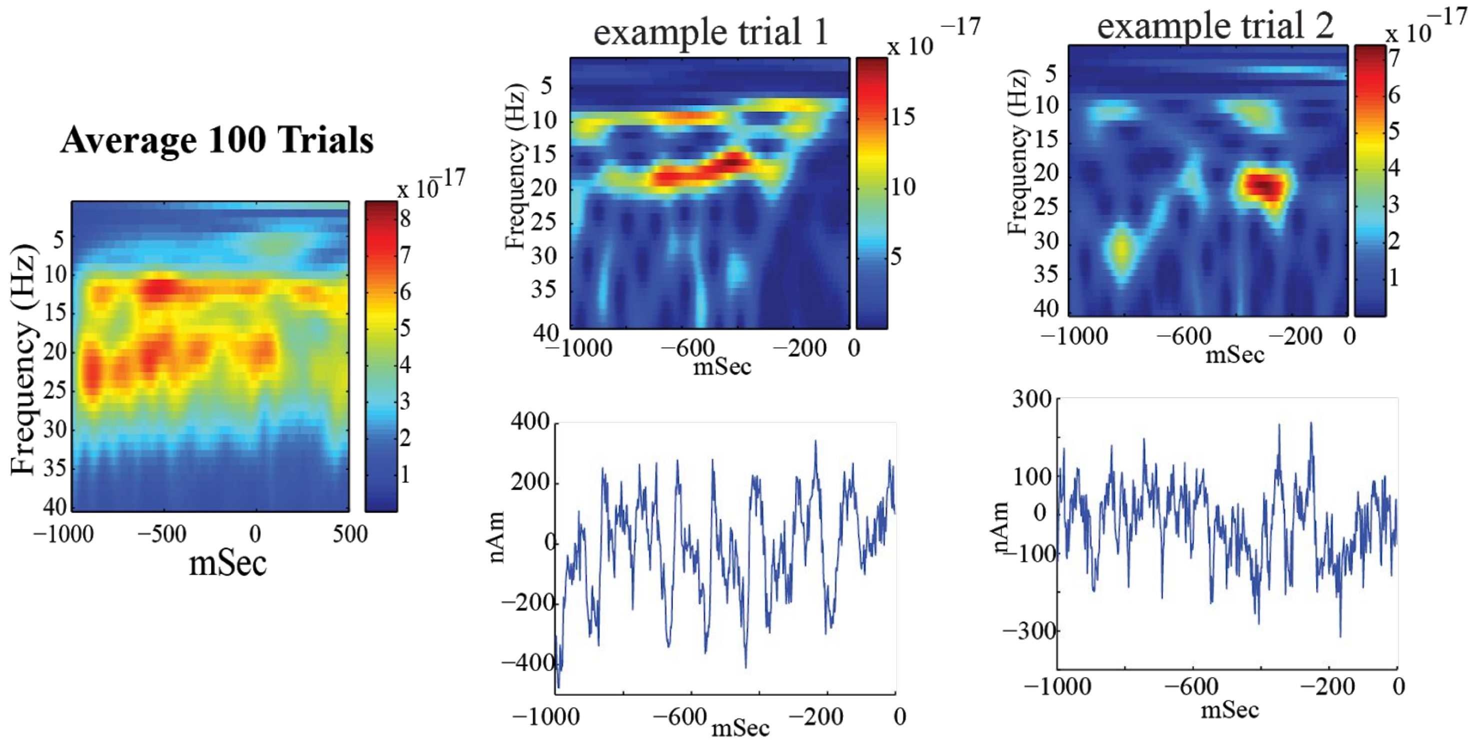


HNN’s graphical user interface



Low-frequency alpha/beta rhythms widely observed in human MEG/EEG signals, altered in disease

Source-localized MEG signals from somatosensory cortex have transient alpha/beta events inversely correlated with attention/detection of tactile stimuli; alpha/beta events detectable in auditory/visual cortex, with similar function (i.e. inhibition of unattended modality: Lakatos *et al.*, Nature Neurosci 2016)



Low frequency oscillations (delta, theta, alpha, low gamma) are altered in schizophrenia (Lisman JAMA Psychiatry 2016; Lakatos *et al.*, J Neurosci 2013; Kopell *et al.*)

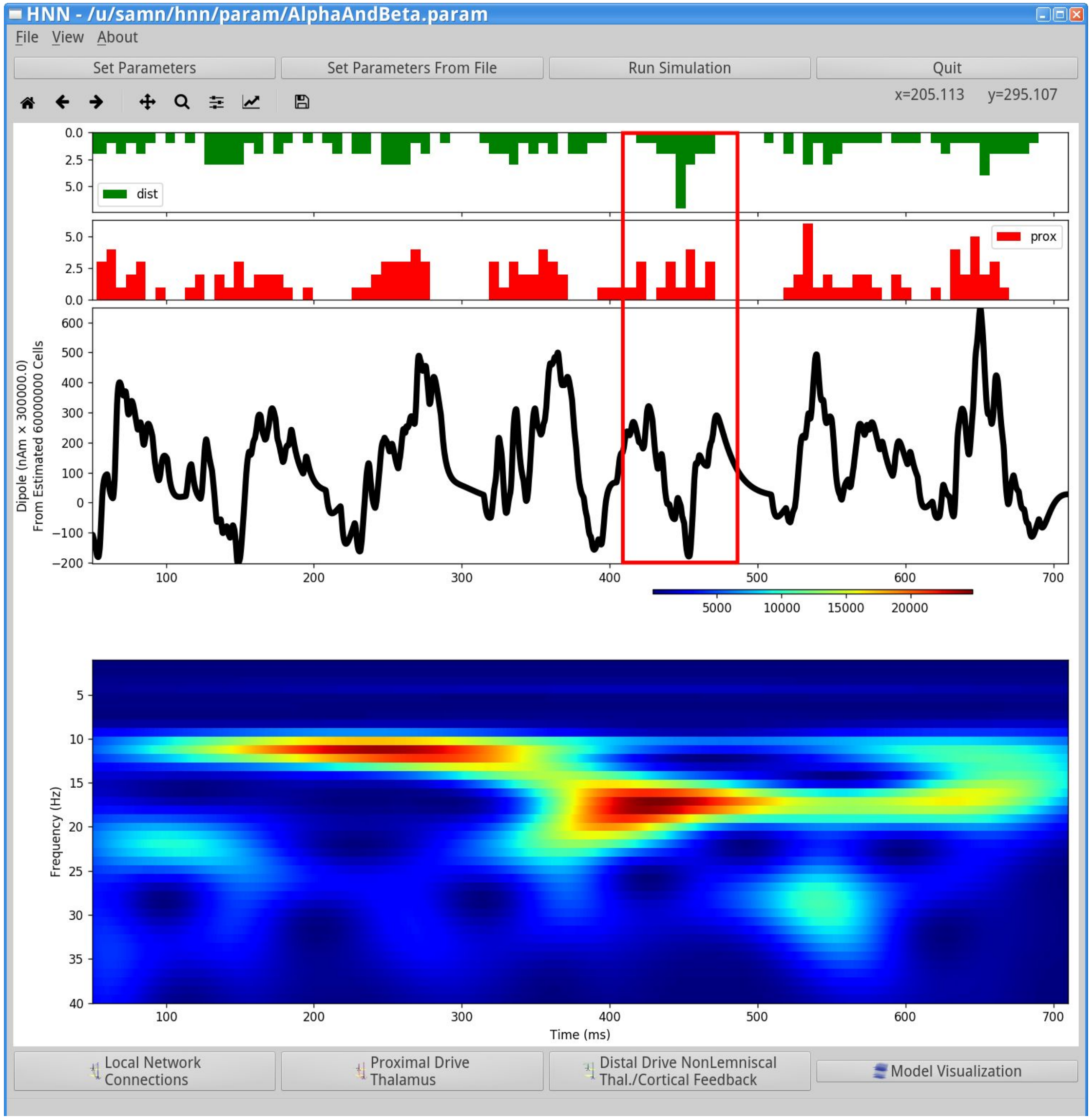
Using HNN to model alpha/beta rhythms

Stochastic 10 Hz rhythmic inputs to proximal/distal dendrites in phase (antiphase) produce beta (alpha) rhythms/events

Model beta mechanism validated with invasive laminar electrode array recordings (Sherman *et al*., PNAS 2016)

Use the software to investigate origins of rhythms, how circuit alterations lead to reduced/enhanced ability to respond to stimuli in health and in disease

<u>**Next:**</u> use invasive laminar electrode array (LFP/CSD/MUA) data from nonhuman primates to optimize/validate models and investigate auditory/speech processing



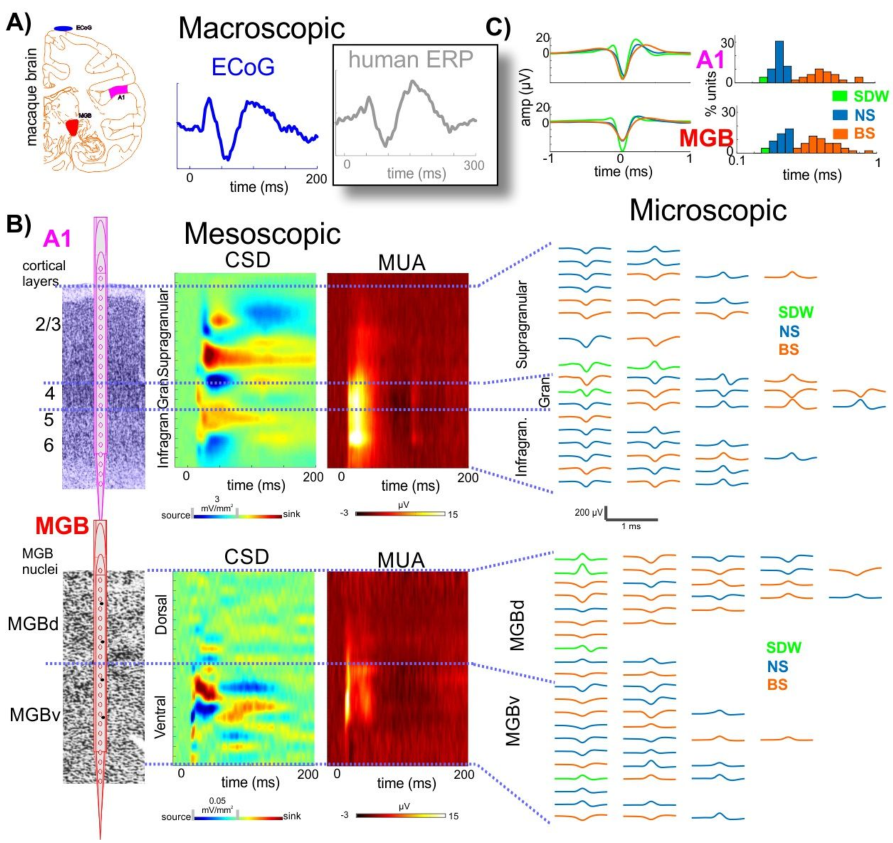
2. Integrating electrophysiology in nonhuman primates (NHP) during auditory stimulus/speech processing with computer modeling

Question: How does thalamocortical circuitry generate and potentially use oscillations to support auditory & speech processing? Why does the circuitry fail to properly entrain to stimuli in neuropsychiatric disorders?

Data: Multi-area/multilaminar ephys data (thalamus, A1, V1) at multiple scales (single-unit, multi-unit, LFP, CSD, ECoG) from Lakatos lab @ NKI; human iEEG data from S. Bickel (Northwell)

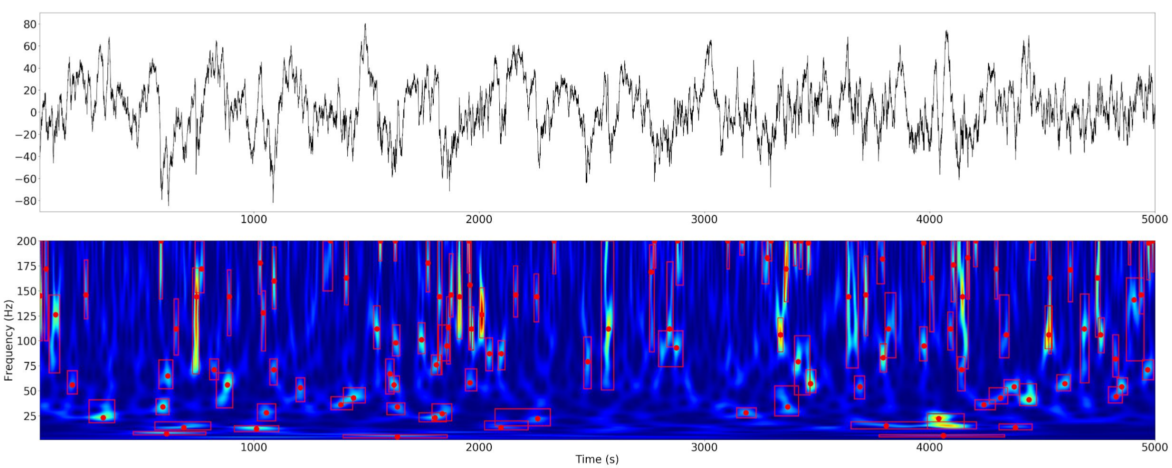
Model: Detailed biophysical thalamocortical system circuits

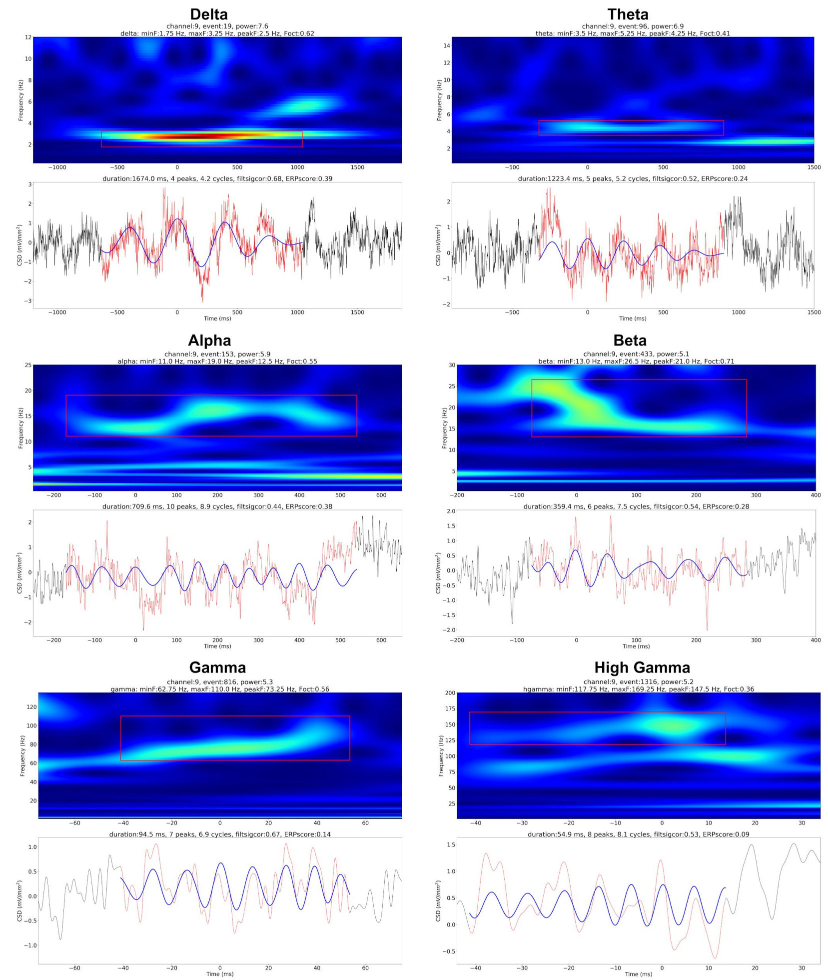
Result: Model generates LFP/CSD comparable to experiment, allowing prediction on circuit generators, mechanisms, and neuromodulation targets



At rest: complex temporal pattern of oscillations

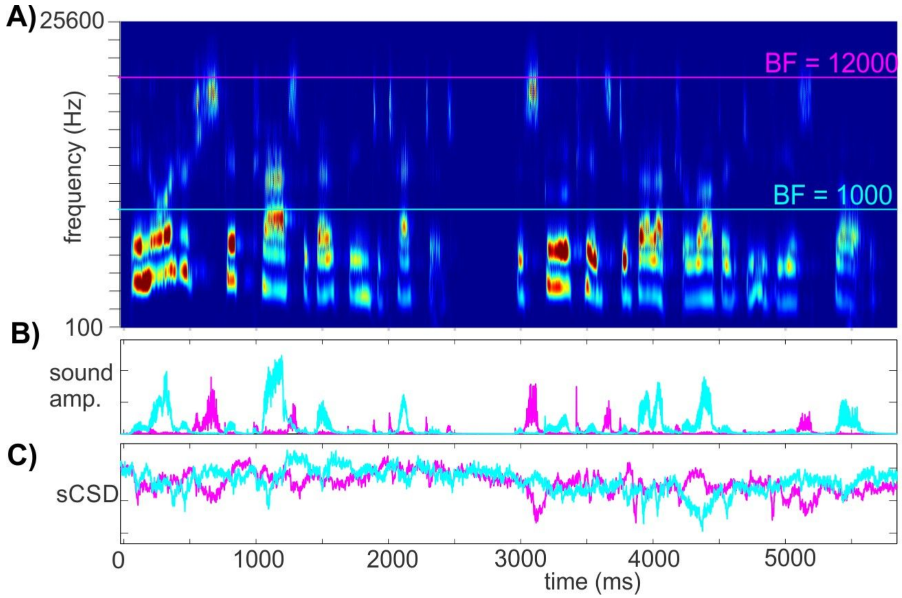
Using the data (Lakatos lab) to optimize the model





Integrating NHP electrophysiology during auditory processing with modeling

1. Determine mechanisms supporting flexible oscillations needed to track rhythmic auditory stimuli (speech). **Model** determines strengths of connectivity between cortex and thalamus, suggests ways to increase oscillation flexibility.
2. Determine thalamocortical mechanisms of oscillatory phase reset for aligning brain rhythms to stimuli, could be used to parse auditory objects. **Model** predicts in vivo neuromodulation strategies to improve this process.
3. Determine mechanisms supporting auditory object formation, hypothesized to occur through periodic inhibition. **Model** tests how different interneuron populations contribute to this process, providing additional in vivo neuromodulation strategies.



Different A1 L2/3 ensembles show phase synchronization for vowels (< 8 KHz; low-frequency tuned) or consonants (> 10 KHz; high-frequency tuned), which tend to occur out-of-phase

Model: neuronal populations

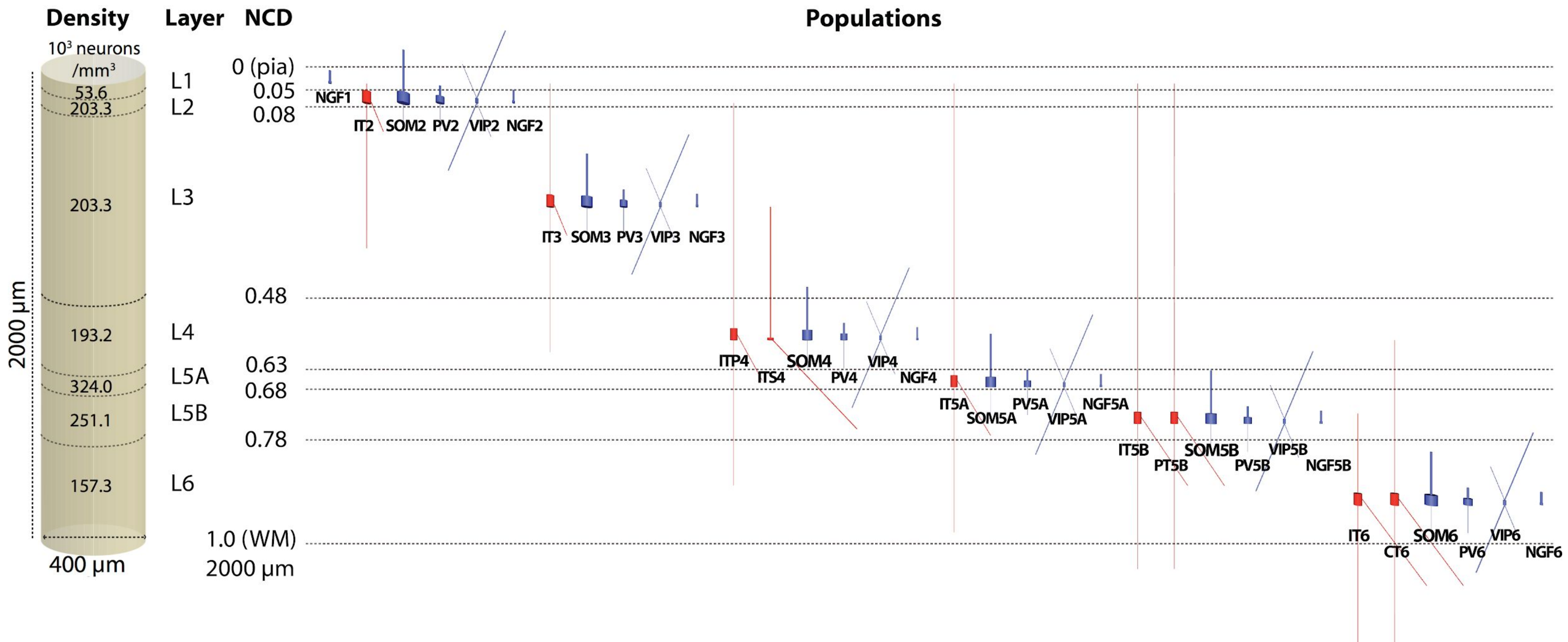
Neurons: multi-compartment, conductance-based.

Excitatory neurons: intratelencephalic (IT), pyramidal tract (PT), spiny stellate (ITS), corticothalamic (CT) and MGB thalamocortical (TC).

Inhibitory neurons: somatostatin (SOM), parvalbumin (PV), neurogliaform (NGF), vasoactive intestinal peptide (VIP), and thalamic reticular nucleus (RT).

Geometry: Simplified morphologies. Dendritic lengths sized to match the macaque cortex dimensions.

Model built with NetPyNE platform (https://netpyne.org Dura-Bernal *et al.*, eLife 2019)



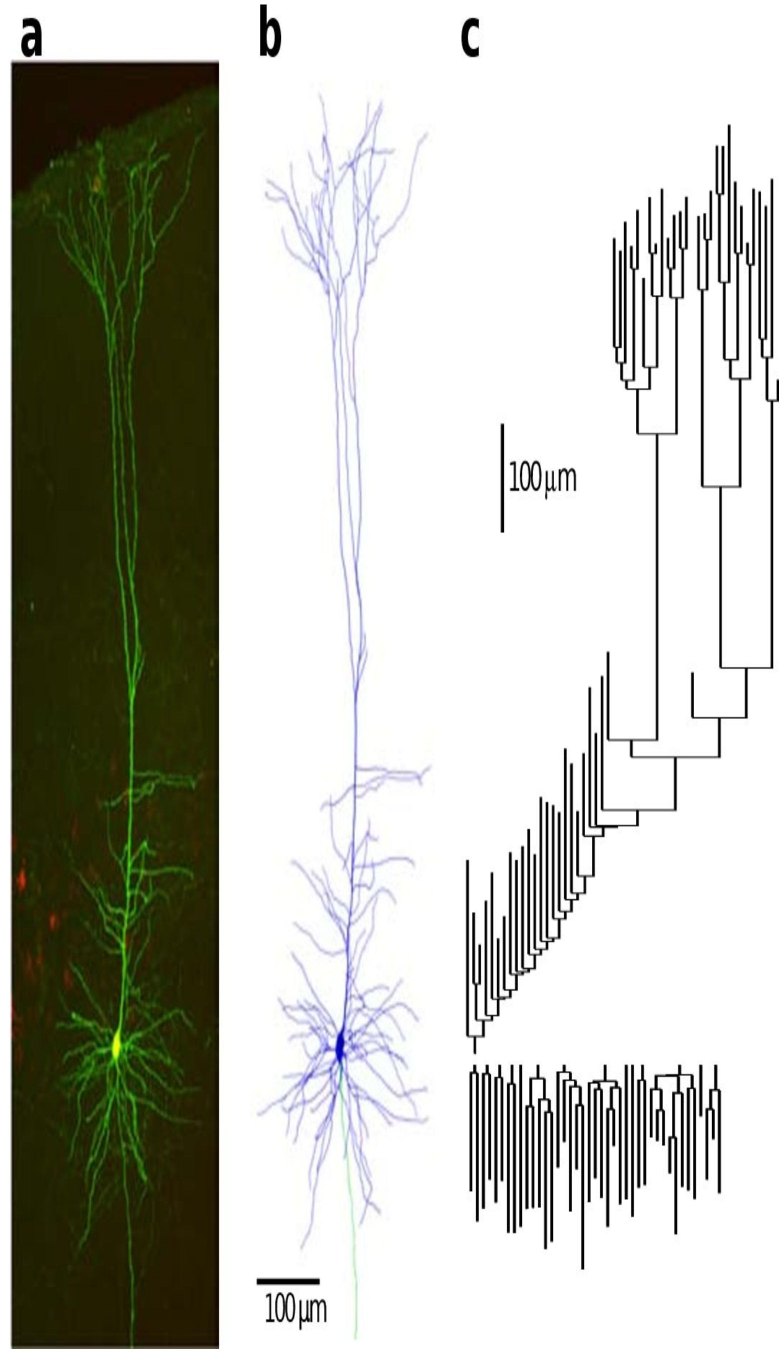
<u>Model Development Challenge:</u> pyramidal neurons have unknown spatial distribution of ion channels

- Full spatial channel distribution is unknown, but experimental literature indicates certain spatial constraints (e.g. HCN density increases distally)

- **<u>Requirement:</u>** develop detailed models with full dendrite reconstruction (~700 compartments) and simplified models (6 representative compartments) in order to produce accurate circuit dynamics

- **<u>Goal:</u>** optimize model channel densities (Na, K, Ca, HCN) in order to reproduce observed in vitro activity from current clamp recordings

- **<u>Solution:</u>** Use sequential optimization: 1. subthreshold fits; 2. firing property fits



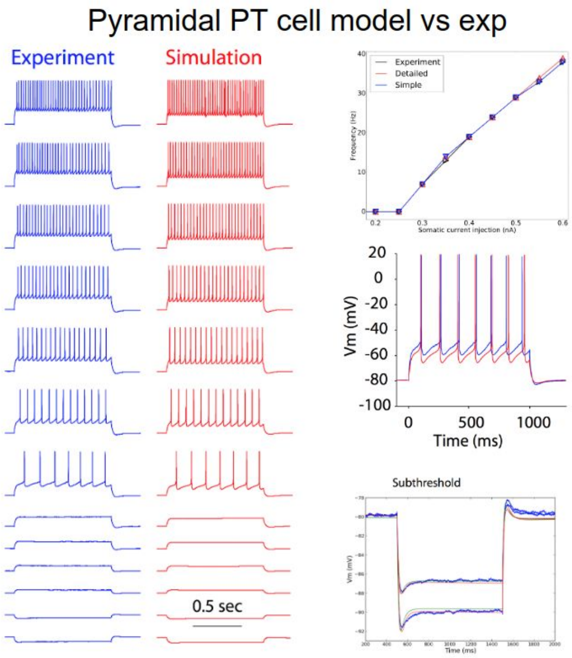
Neymotin *et al.*, J Neurophysiology 2016

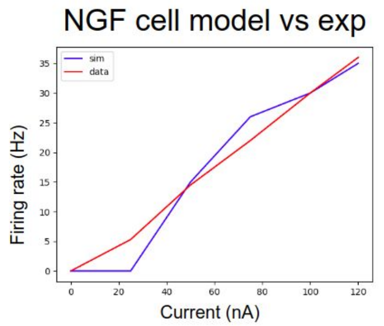
Model neuron optimization

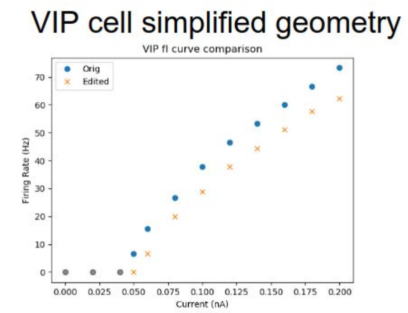
Cell types in each layer fitted to macaque or rodent electrophysiology data via multi-objective evolutionary optimization algorithm or via hand-tuning.

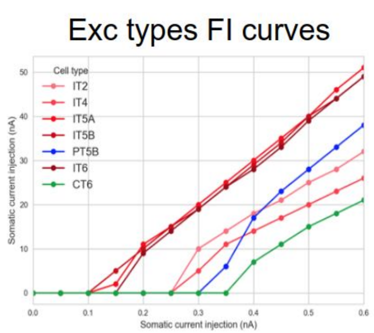
Passive parameters (e.g. leak channel, HCN channel conductance, capacitance) were tuned to fit RMP and other features of subthreshold traces, including steady state voltage and sag.

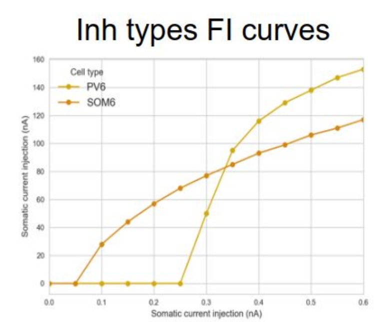
Active parameters (e.g. fast Na, K, Ca, BK channel density) were then tuned to fit features like firing rate curves, action potential shape, and adaptation.











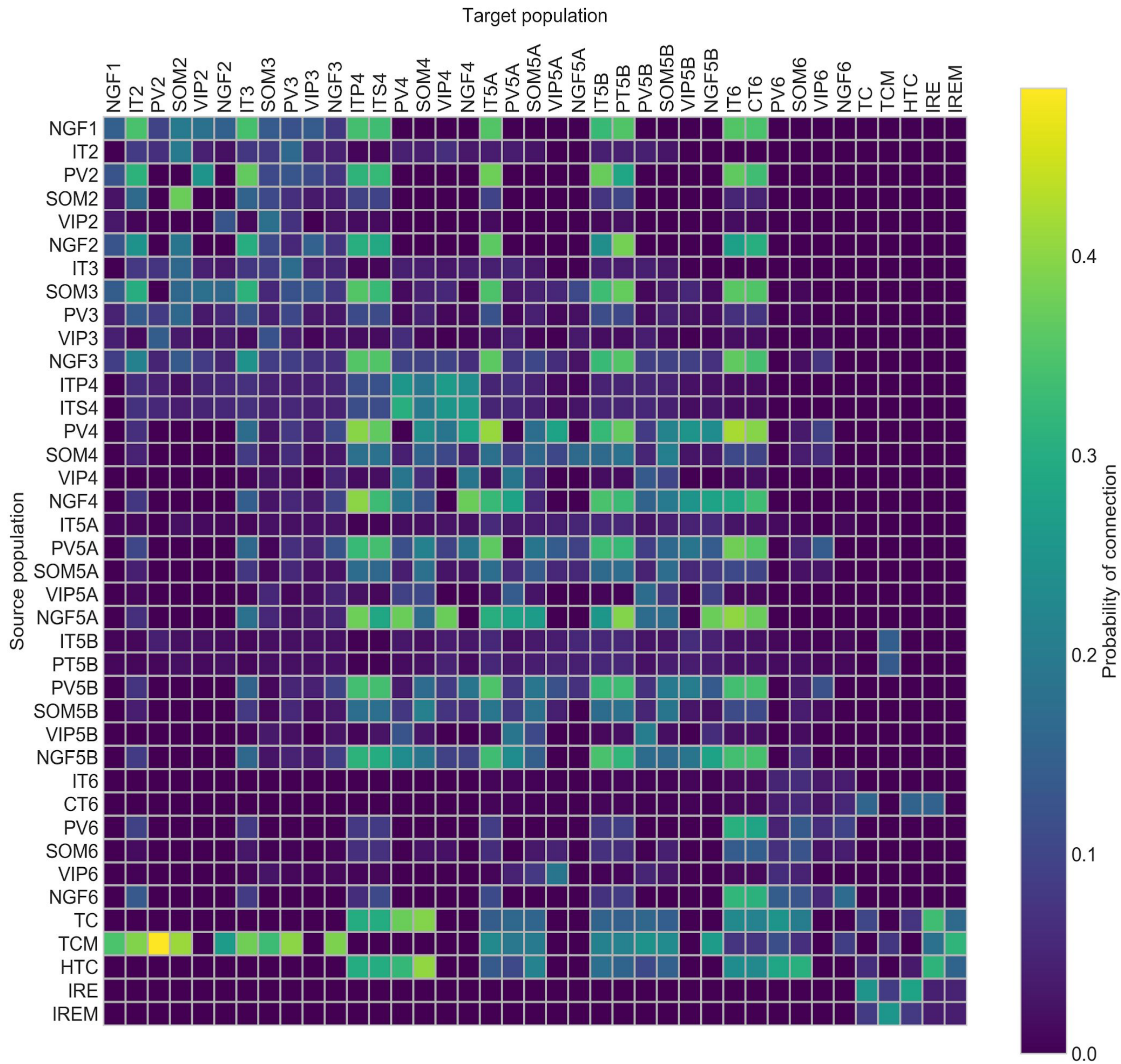
Neymotin *et al.*, J Neurophysiology 2016

Model: data-driven circuit connectivity

Experimental circuit mapping data constrains model connectivity

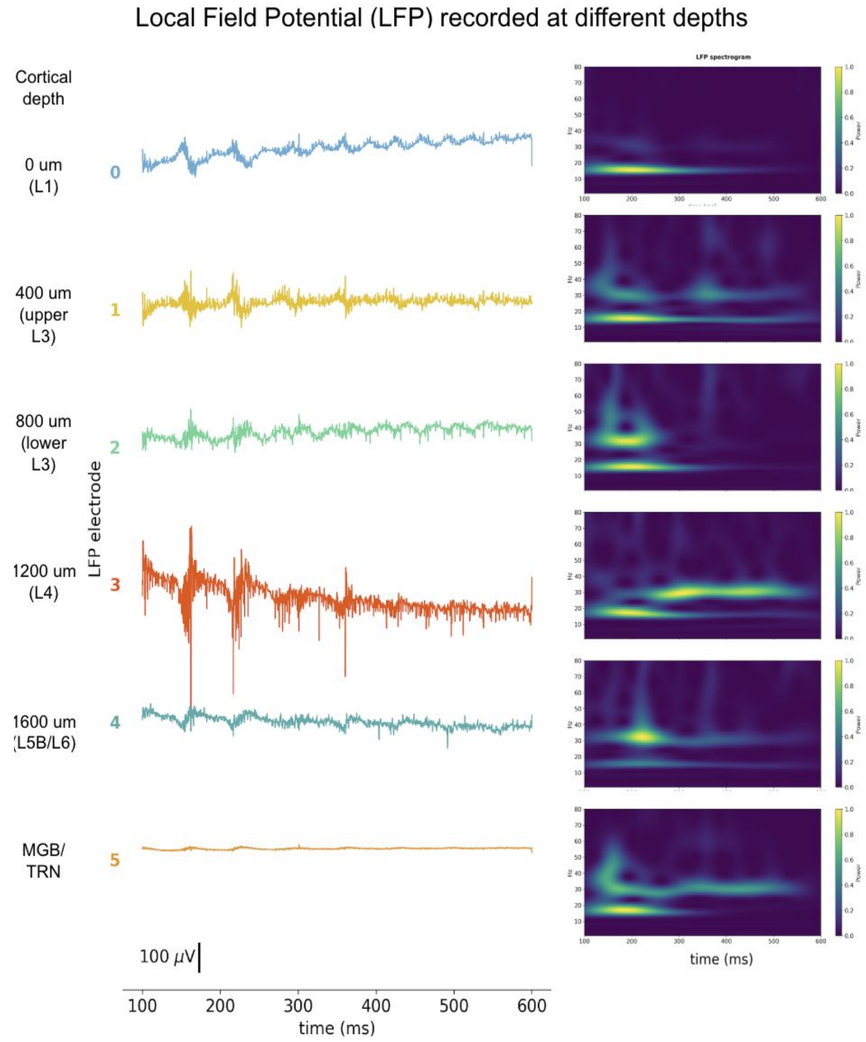
E → E/I from mouse V1,S1,A1,M1 (Levy & Reyes 2012; Yoshi et al 2015; Billeh et al 2019; Lefort et al 2009; Allen Brain Institute)

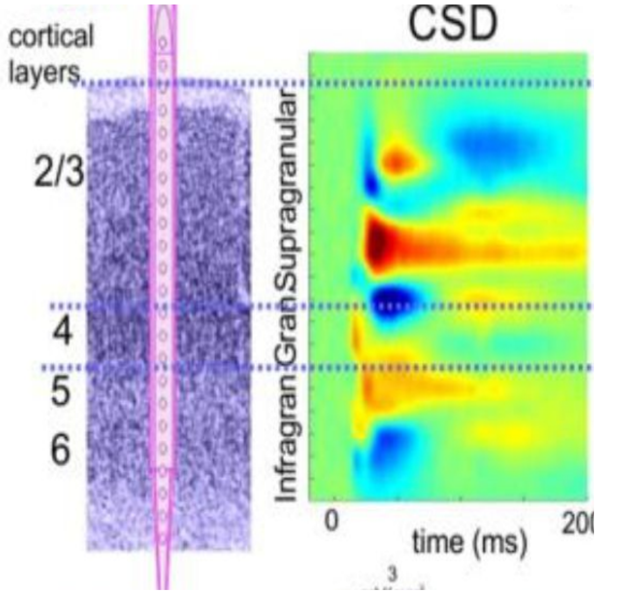
I → E/I from mouse V1,S1,A1,M1 (Sohn et al 2016; Naka et al 2016; Tremblay et al 2016; Pi et al 2013; Pi et al 2013)



Model includes biophysically-detailed LFP → comparison with *in vivo* data

The A1 model simulates laminar local field potentials, and will be used to determine the origin of different oscillation patterns observed in the data

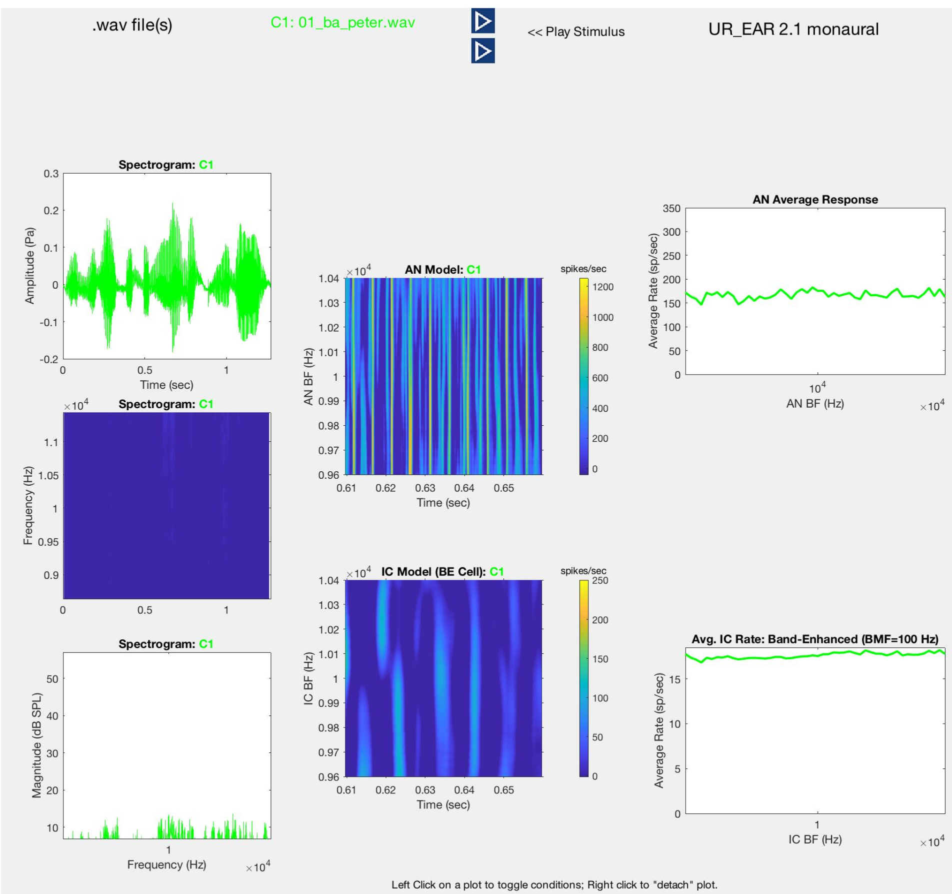


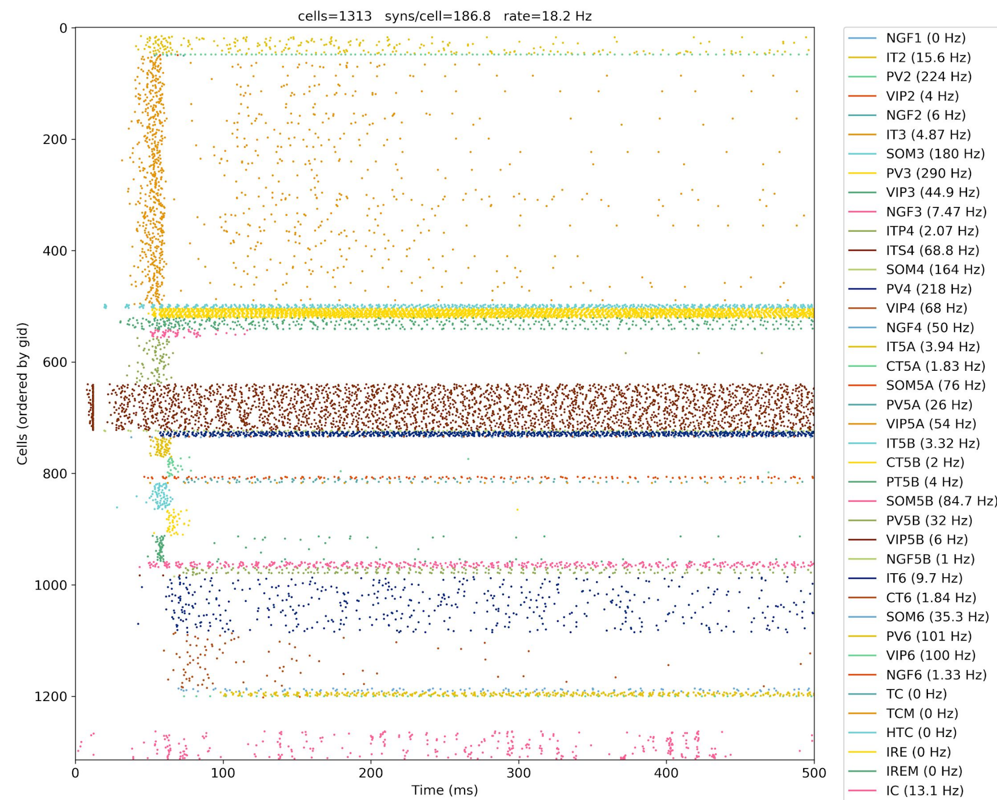


Providing auditory stimuli to the model

Pathway: sound wave → cochlea → inferior colliculus (IC) → MGB → A1

Full pathway allows comparison of NHP and model data to determine circuit mechanisms supporting sound/speech processing





← UR Ear (Laurel Carney Lab)

Biophysical thalamocortical system model to predict origin of different oscillations

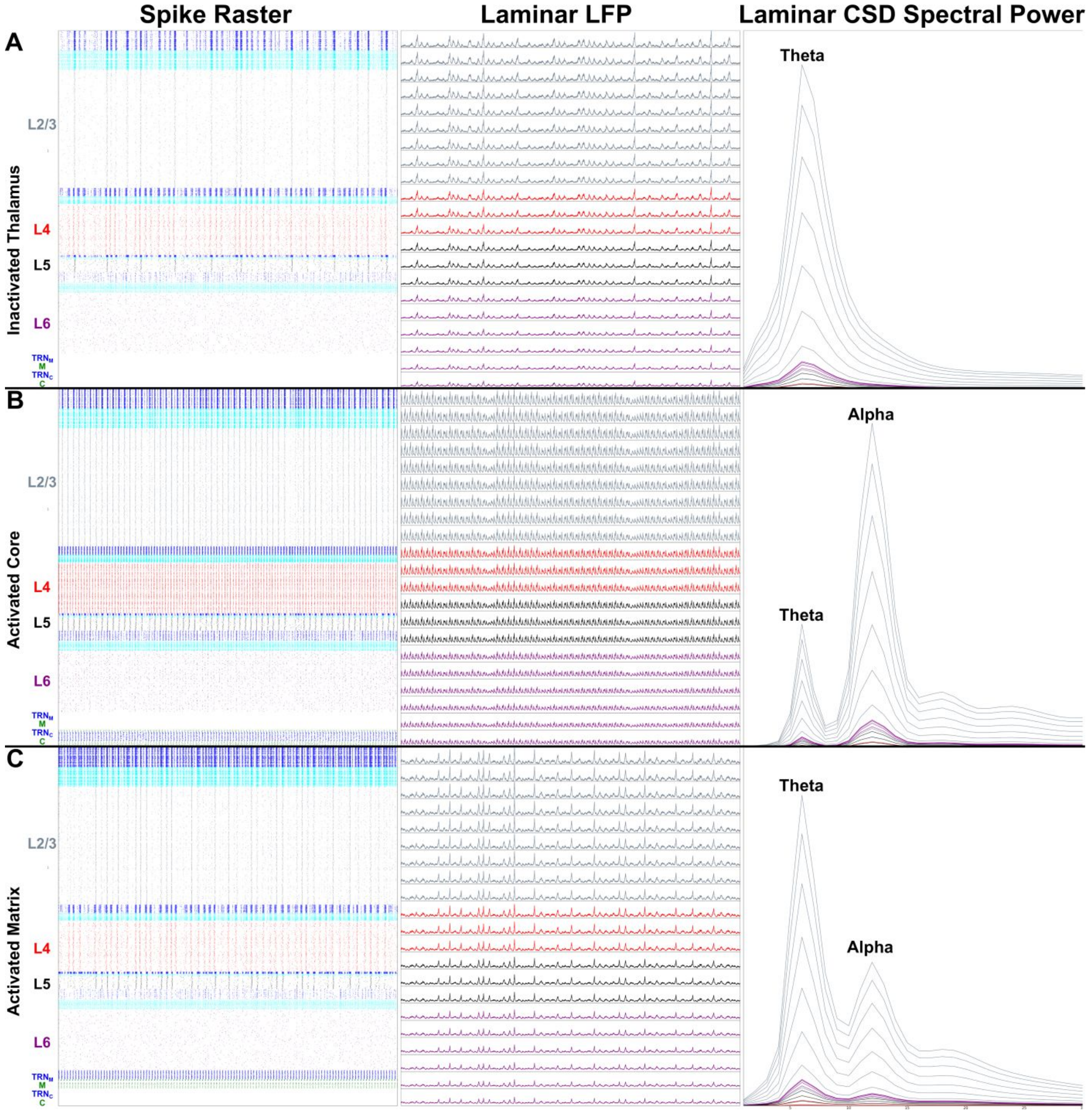
Model: thalamic core/matrix interconnected bidirectionally with neocortex → creates oscillations

Neocortical neurons (pyramidal neurons, stellate cells, PV/SOM/VIP/NGF interneurons) arranged in 6 cortical layers; thalamic neurons arranged in thalamic nuclei (reticular, relay)

Model simulates laminar LFP, CSD, MUA comparable to experimental data

Short/long inhibition produces the different oscillation frequencies observed; we will use the model to test origin of NHP data and provide neuromodulation predictions to enhance auditory processing

Next: using biophysical neural circuit models to investigate origins and treatments for neuropsychiatric disease



3. Hippocampal network model to study neuropsychiatric disorders

Background: A mutation in the HCN1 gene (5p21) is near one of 108 loci implicated in schizophrenia (Schizophrenia Working Group, Nature 2014). Another mutation is in the GRIN2A gene (glutamate ionotropic NMDAR subunit 2A on 16p13), a subunit that forms part of the ionotropic NMDA-type glutamatergic receptor (NMDAR). The psychomimetic ketamine (NMDAR antagonist) is used to model the disorder.

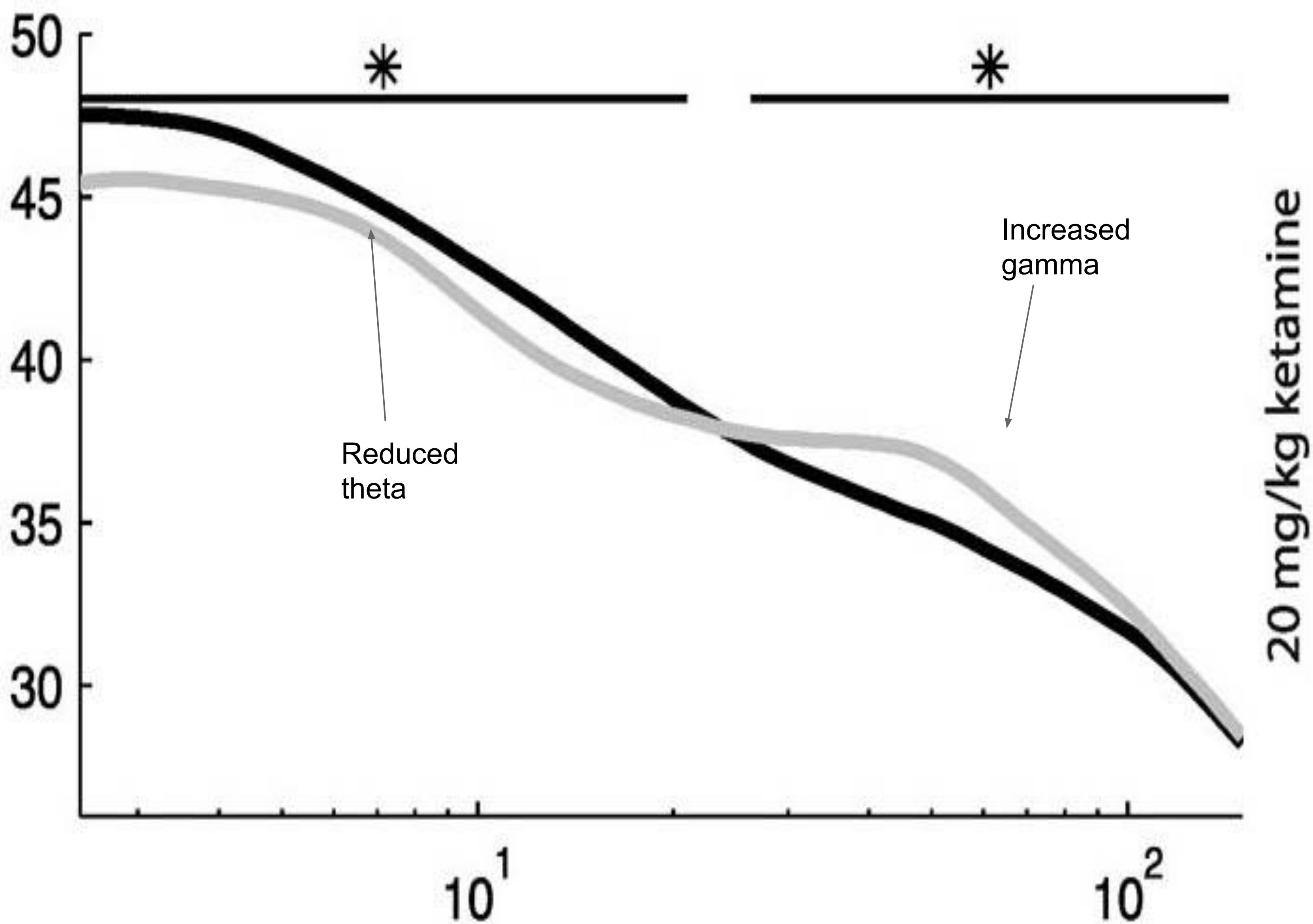
Question: NMDAR & HCN channel changes are implicated in schizophrenia. How do these alterations impact hippocampal dynamics & information processing? Can we use biophysical circuit models to predict effects of gene/circuit alterations contributing to the disorder, & match experimental observations?

Data: Hippocampal oscillations in mouse in vivo show less theta, more gamma after ketamine; human gamma/other oscillatory alterations in schizophrenia

Model: Hippocampal CA3 circuit; ketamine simulated by setting NMDA receptor conductance to zero (blockade); NMDA,HCN mutations via conductance change

Result: Model generates realistic oscillations, predicts ketamine's site of action, disease mechanisms, and novel target for therapy.

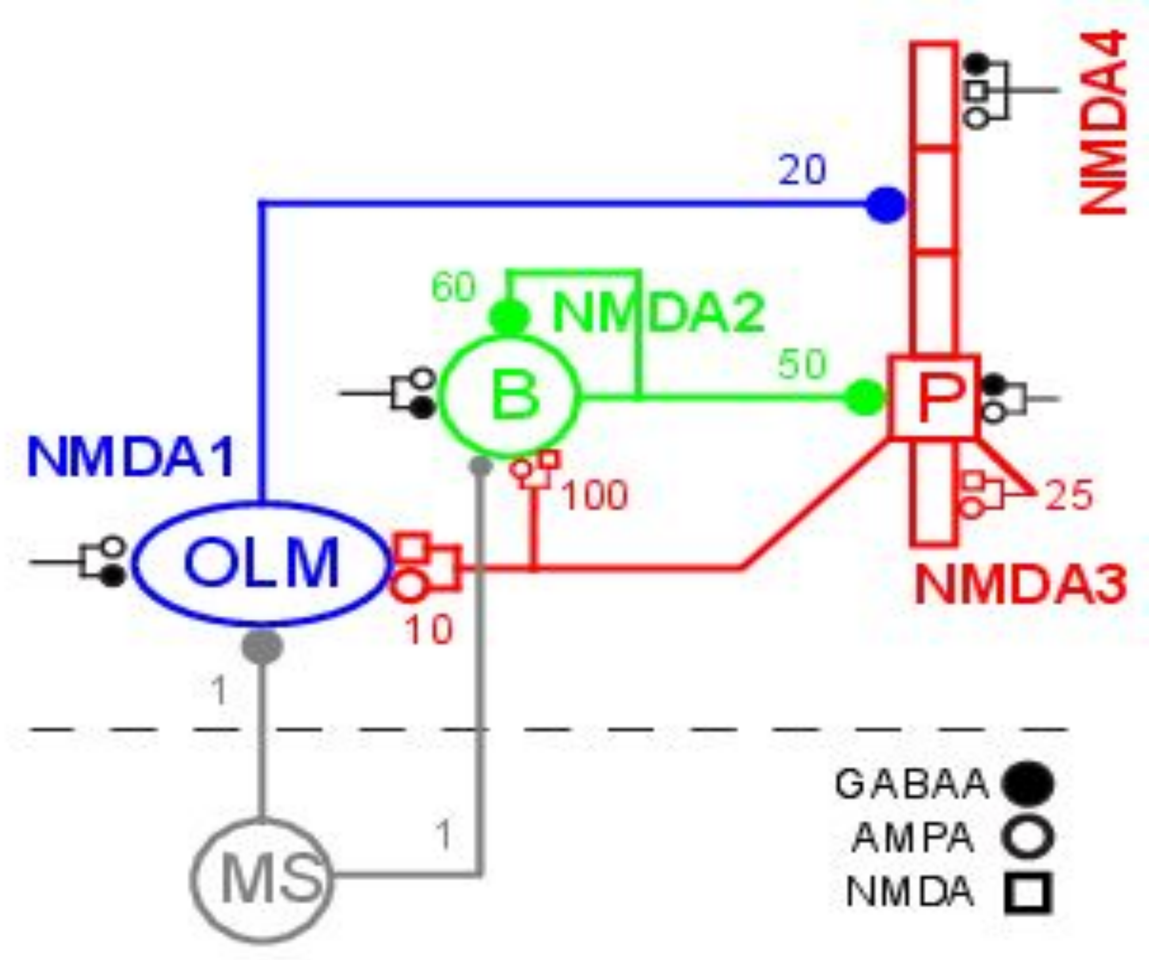
In vivo: altered hippocampal oscillations after applying psychomimetic ketamine



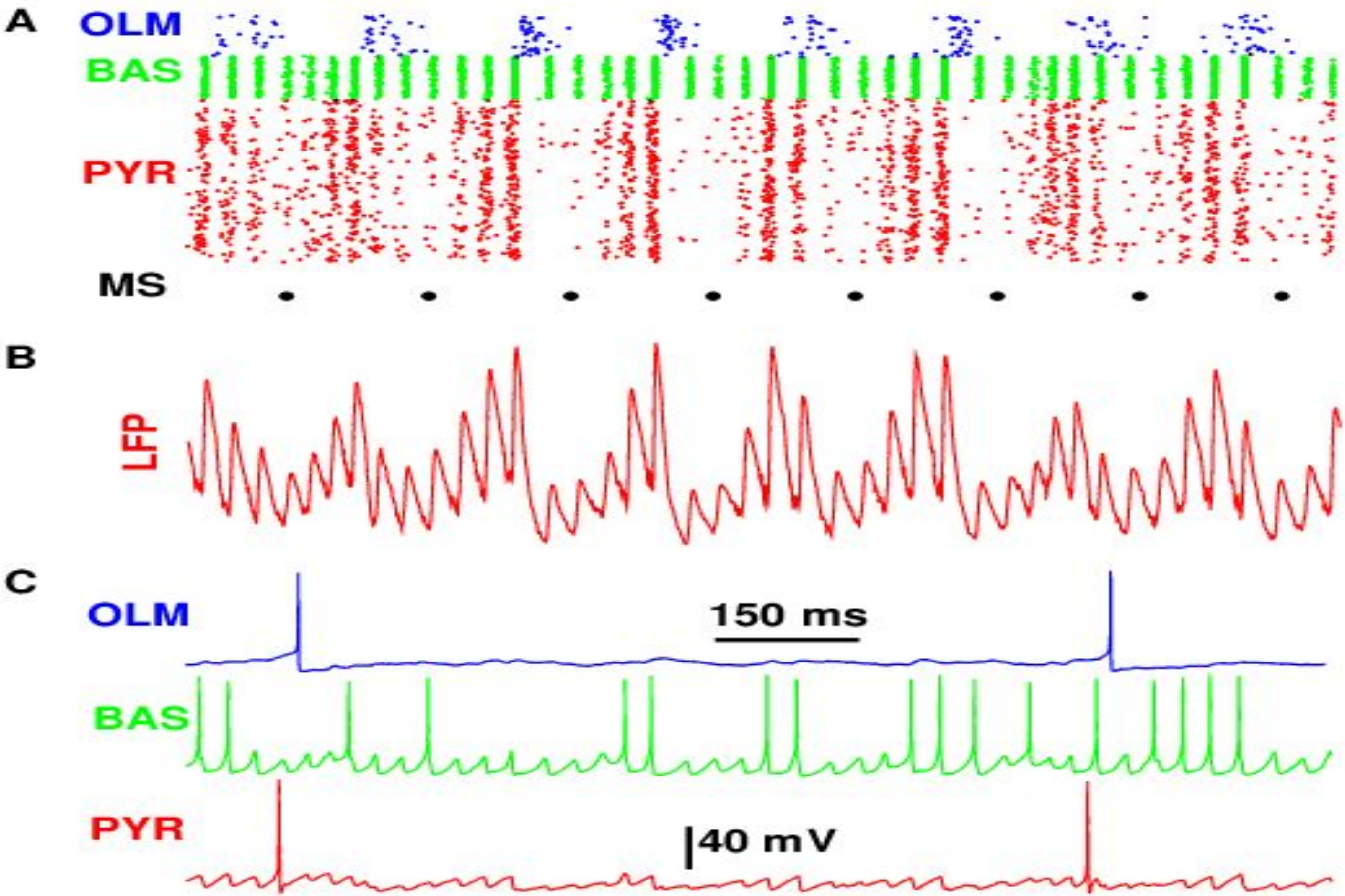
Lazarewicz *et al.*, J Cognitive Neurosci 2010

Hippocampal CA3 circuit model

Model: Circuit-level biophysical model of hippocampal CA3 containing interconnected pyramidal neurons, OLM interneurons, basket interneurons, medial septum (MS) inputs

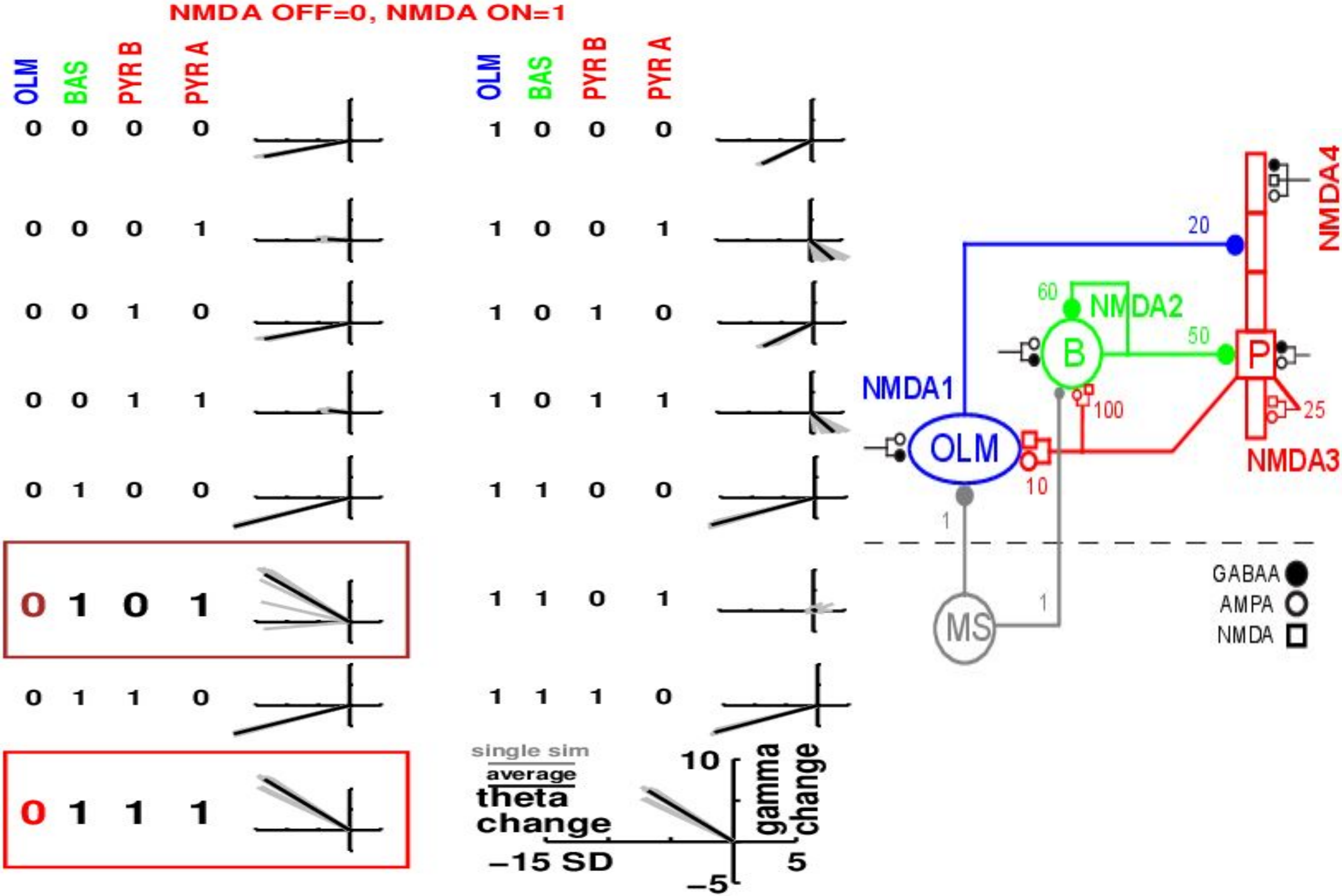


CA3 model generates theta/gamma



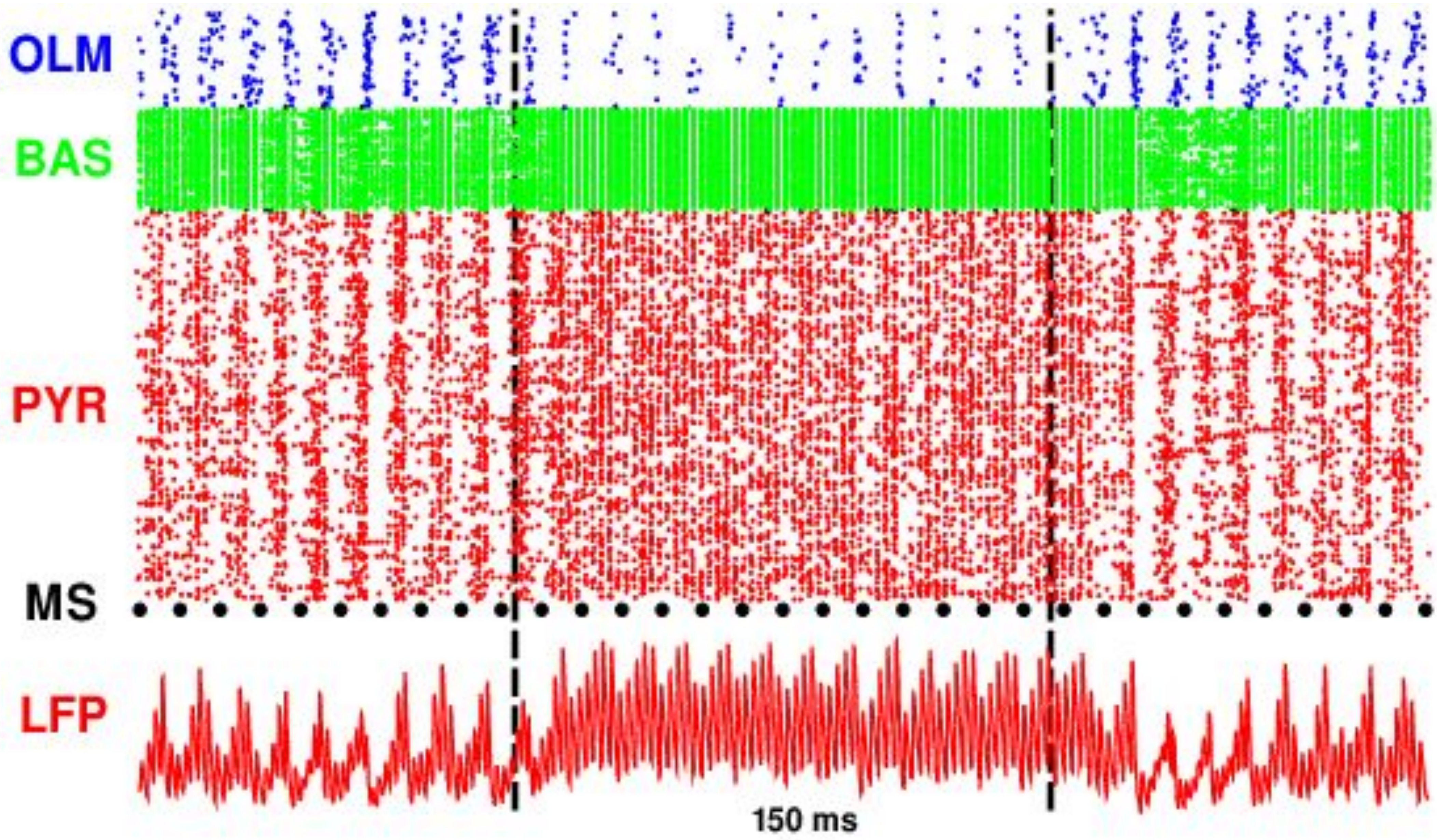
Neymotin *et al.*, J Neurosci 2011

CA3: looking for ketamine's site of action

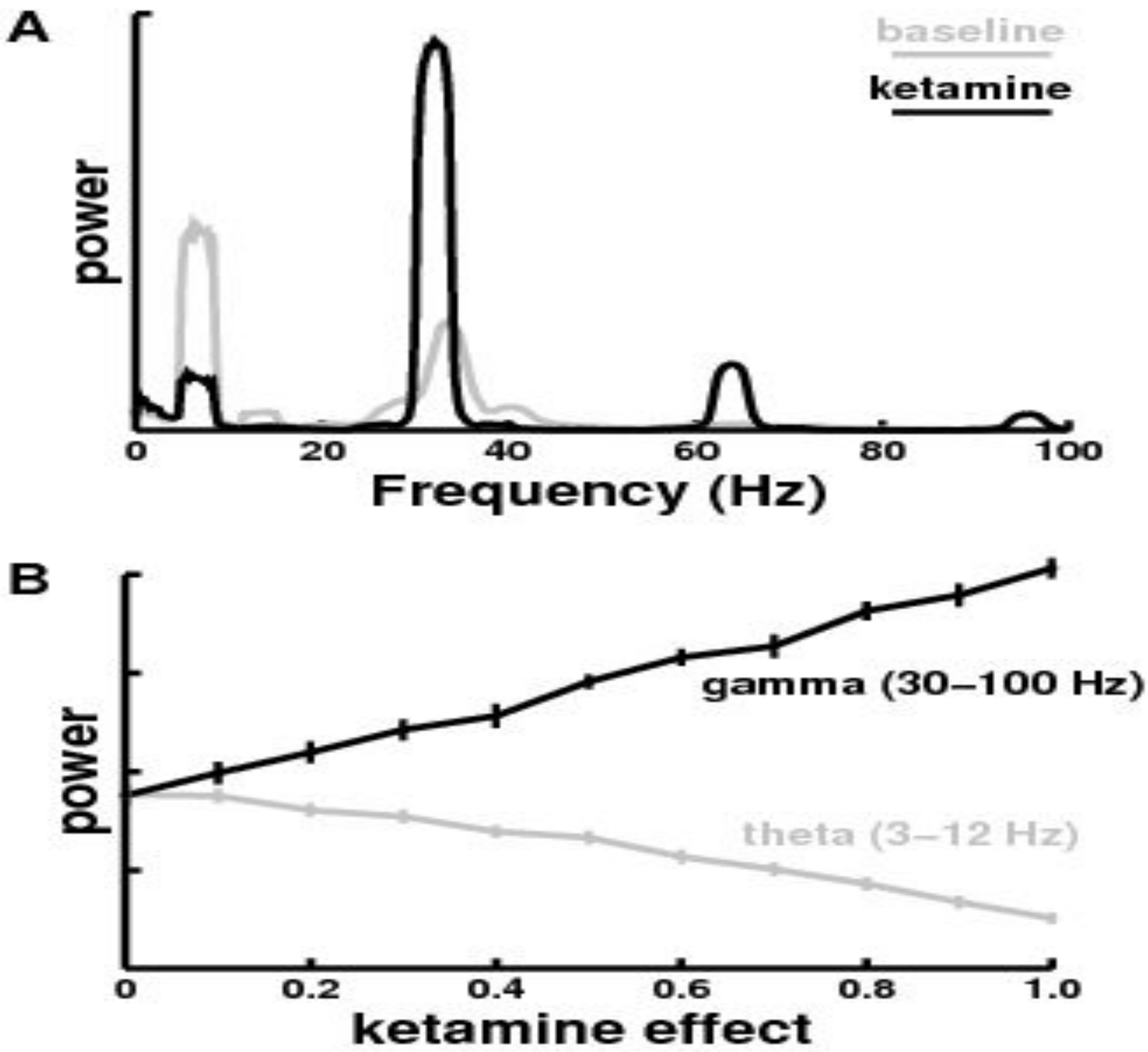


Neymotin *et al.*, J Neurosci 2011

Simulated ketamine: reduced theta, increased gamma

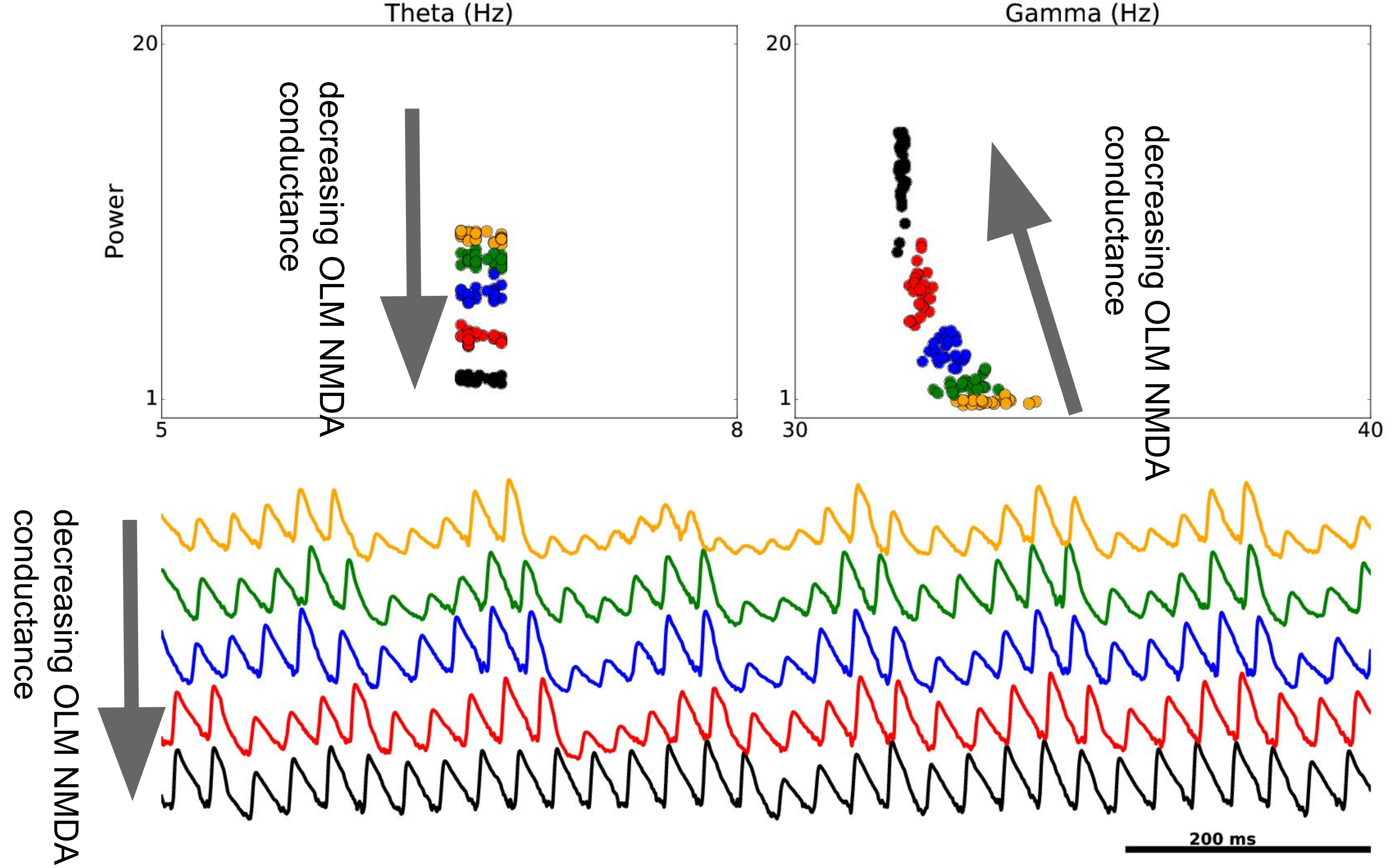


Simulated ketamine: reduced theta, increased gamma



Neymotin *et al.*, J Neurosci 2011

Simulated ketamine: OLM NMDA receptor conductance regulates theta/gamma



OLM cell NMDA receptor conductance changes can account for lower theta & higher gamma amplitudes seen in schizophrenia (e.g. in ketamine models)

Neymotin *et al.*, Hippocampal Microcircuits, Springer 2018

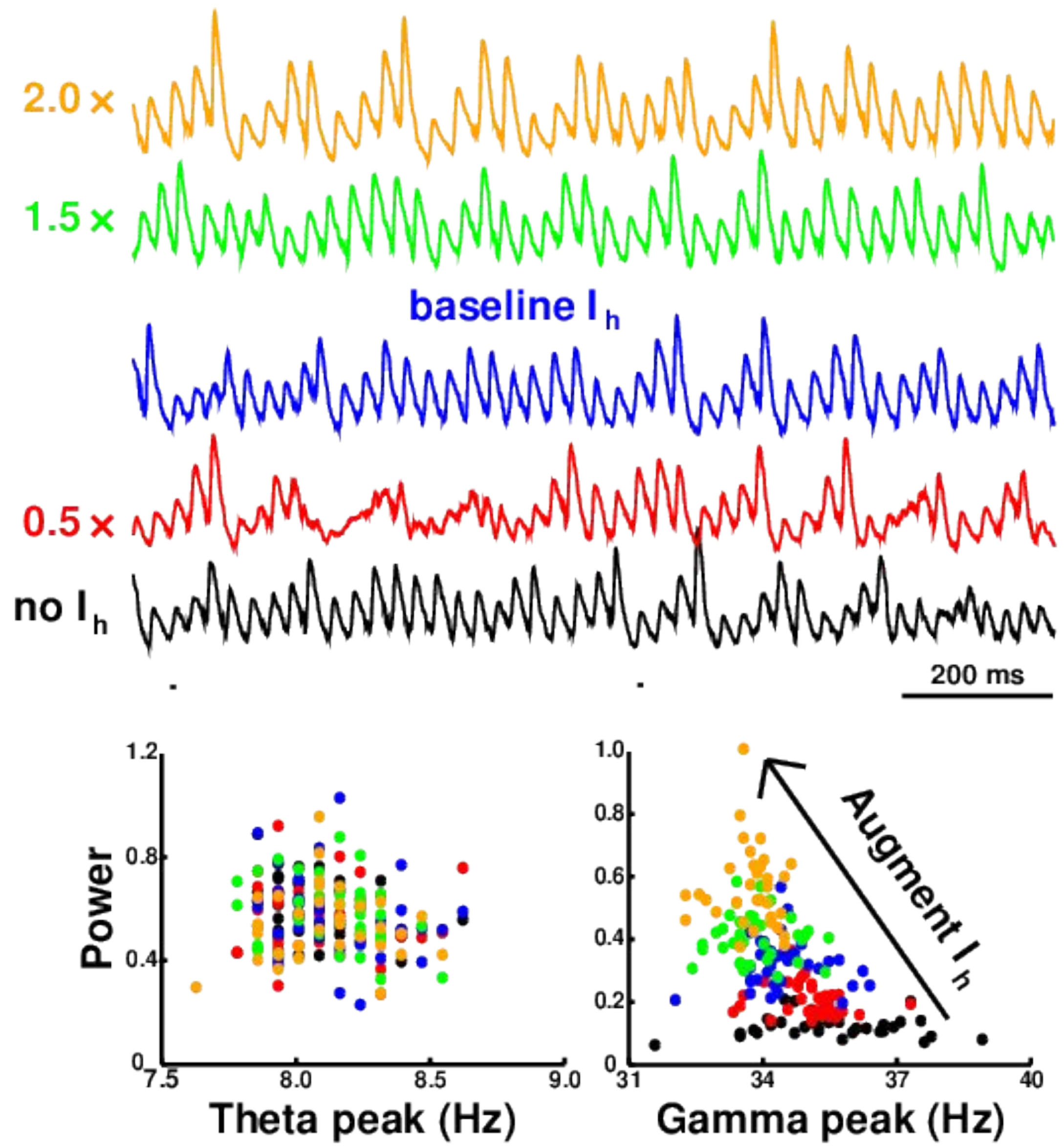
Simulation predicts that higher HCN density in basket cells could also produce higher gamma power observed in schizophrenia models

Model HCN mutations by changing HCN conductance

Basket interneurons contribute to gamma rhythms through periodic inhibition of pyramidal neurons and other basket cells

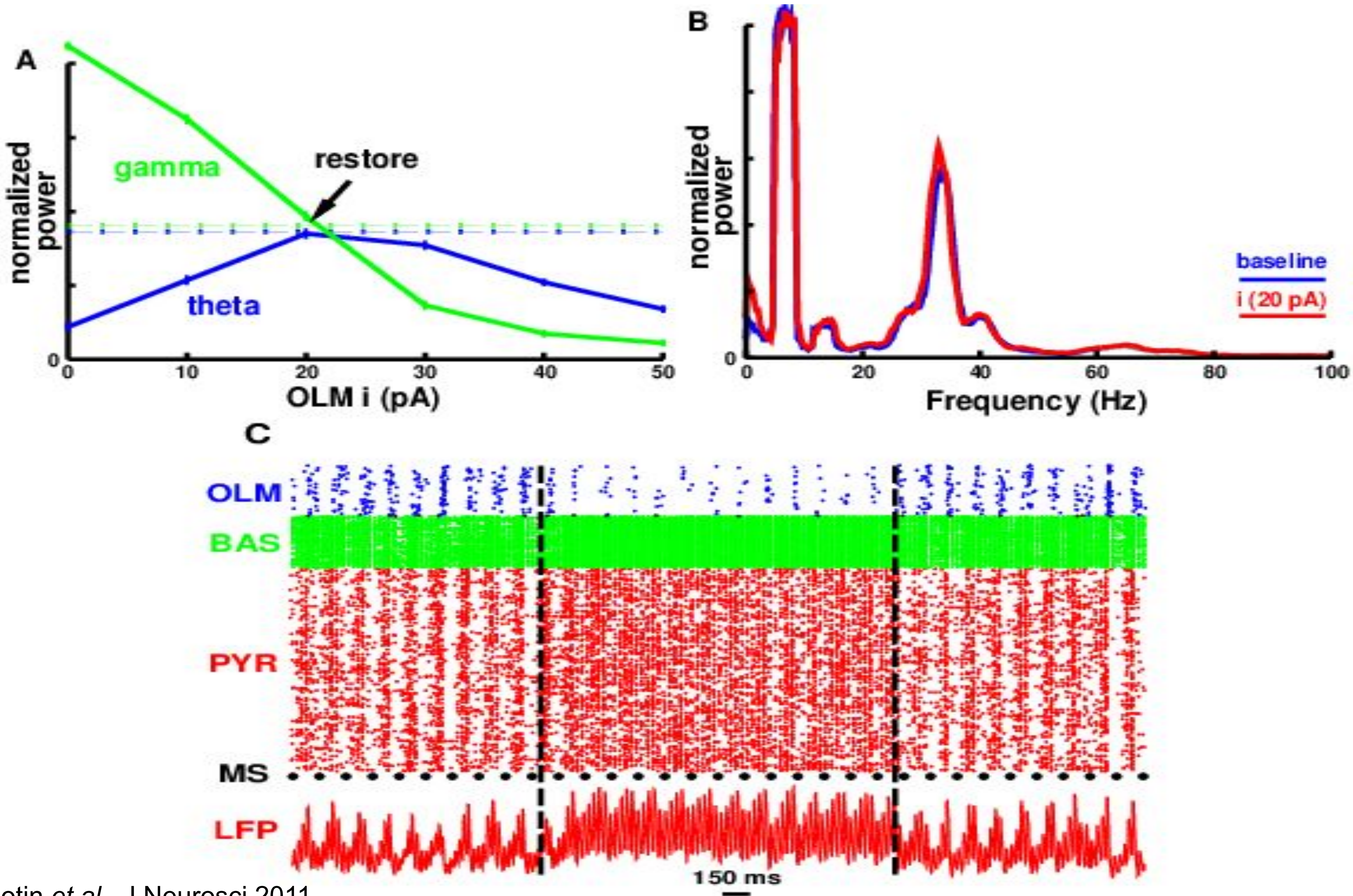
Providing extra depolarization to the basket cells through higher HCN density, causes heightened basket activity and more prominent gamma activation

Basket HCN density does not impact theta rhythms



Neymotin *et al.*, Hippocampal Microcircuits, Springer 2018

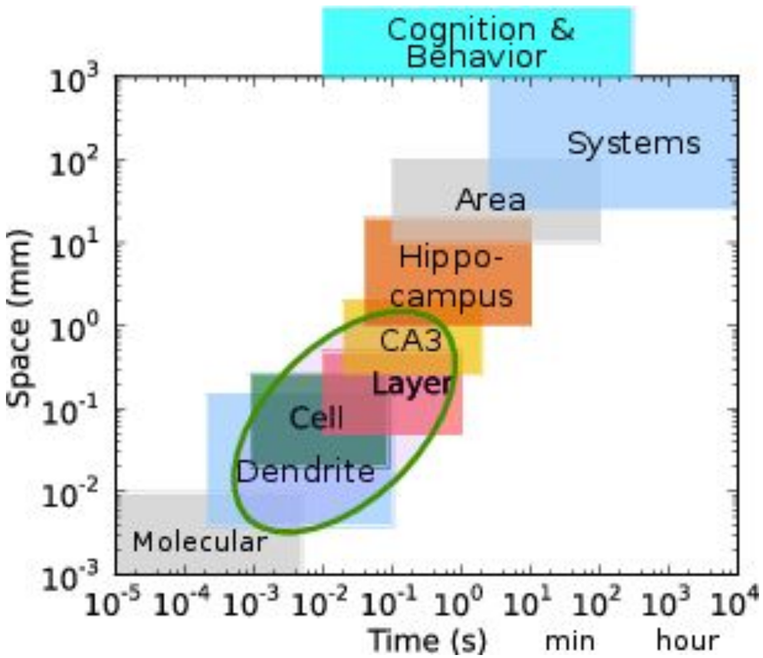
Treatment: restoring oscillations via current injection to OLM cells

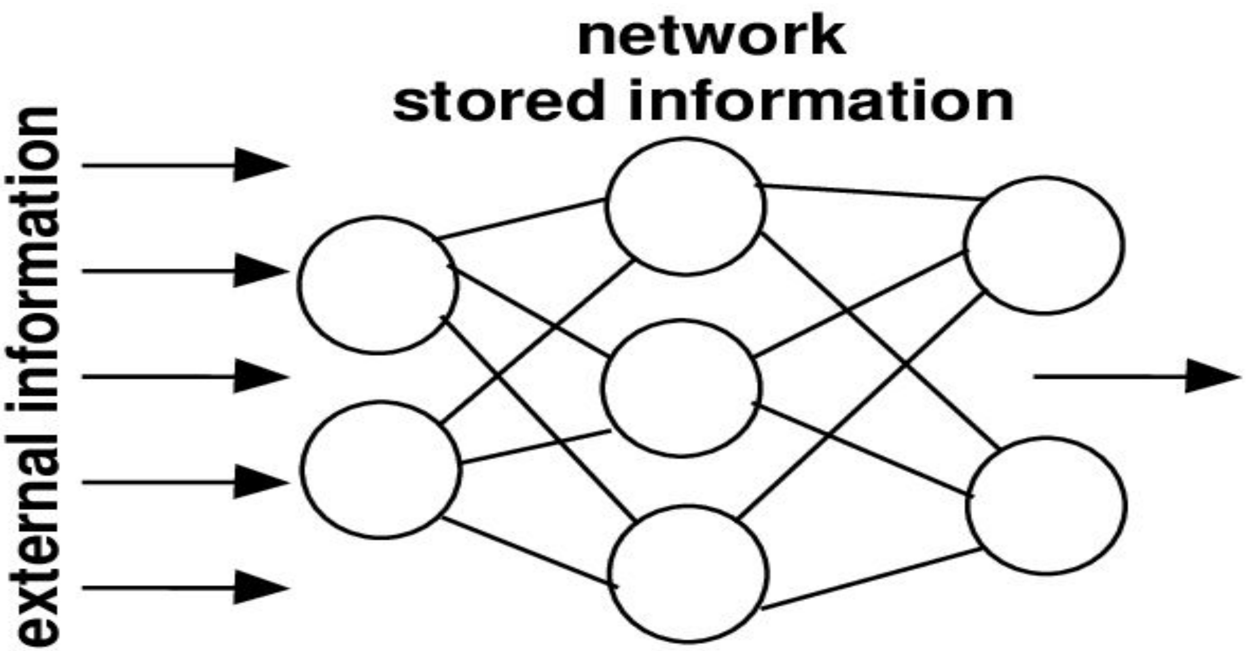


Neymotin *et al.*, J Neurosci 2011

Aberrant oscillations → altered function?

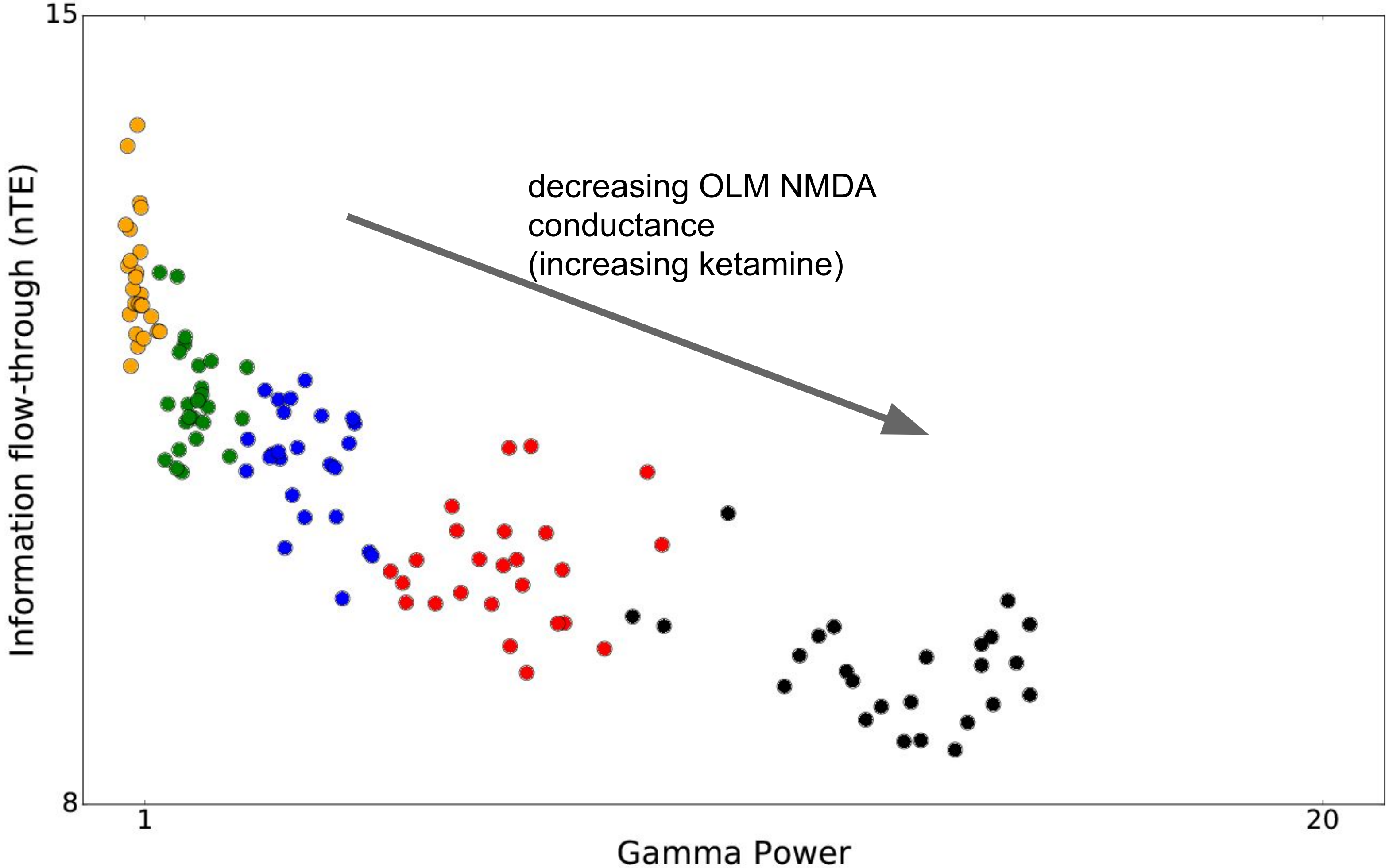
- Use transfer entropy to link dynamics/oscillations and function by measuring information transferred through the simulated hippocampal network





Neymotin *et al.*, J Comp Neurosci 2011; Neymotin *et al.*, J Neurosci 2011; Neymotin *et al.*, Hippocampal Microcircuits, Springer 2018; Sherif *et al.*, NJP Schizophrenia (under review)

Ketamine: increased gamma reduces network responsiveness to outside "world"



Oscillatory power is linked with the level of information processing in the network: overly high gamma power produces more stereotyped firing patterns and suggests mechanism for hallucinations (loss of responsiveness to external information (outside world) and over-reliance on internal information)

Neymotin *et al.*, J Comp Neurosci 2011; Neymotin *et al.*, J Neurosci 2011;
Neymotin *et al.*, Hippocampal Microcircuits, Springer 2018

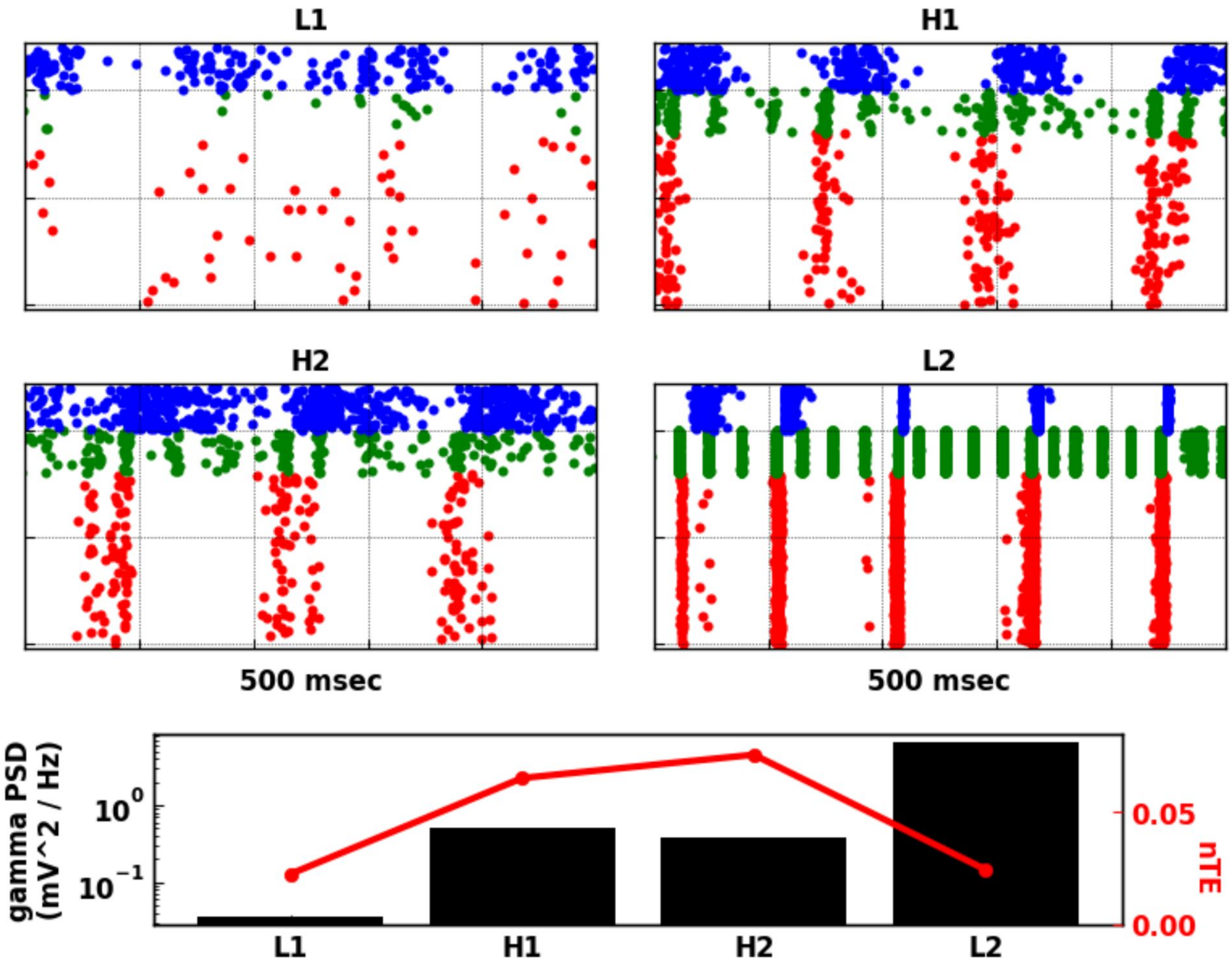
More generally: intermediate excitability and synchrony/gamma support optimal information throughput

Synchrony/gamma displays inverted-U relationship with information transfer

Overly weak synchrony/gamma associated with sparse firing and low information throughput (L1)

Overly high synchrony/gamma associated with stereotyped firing and low information throughput (L2)

Intermediate synchrony/gamma supports optimal throughput (H1,H2)



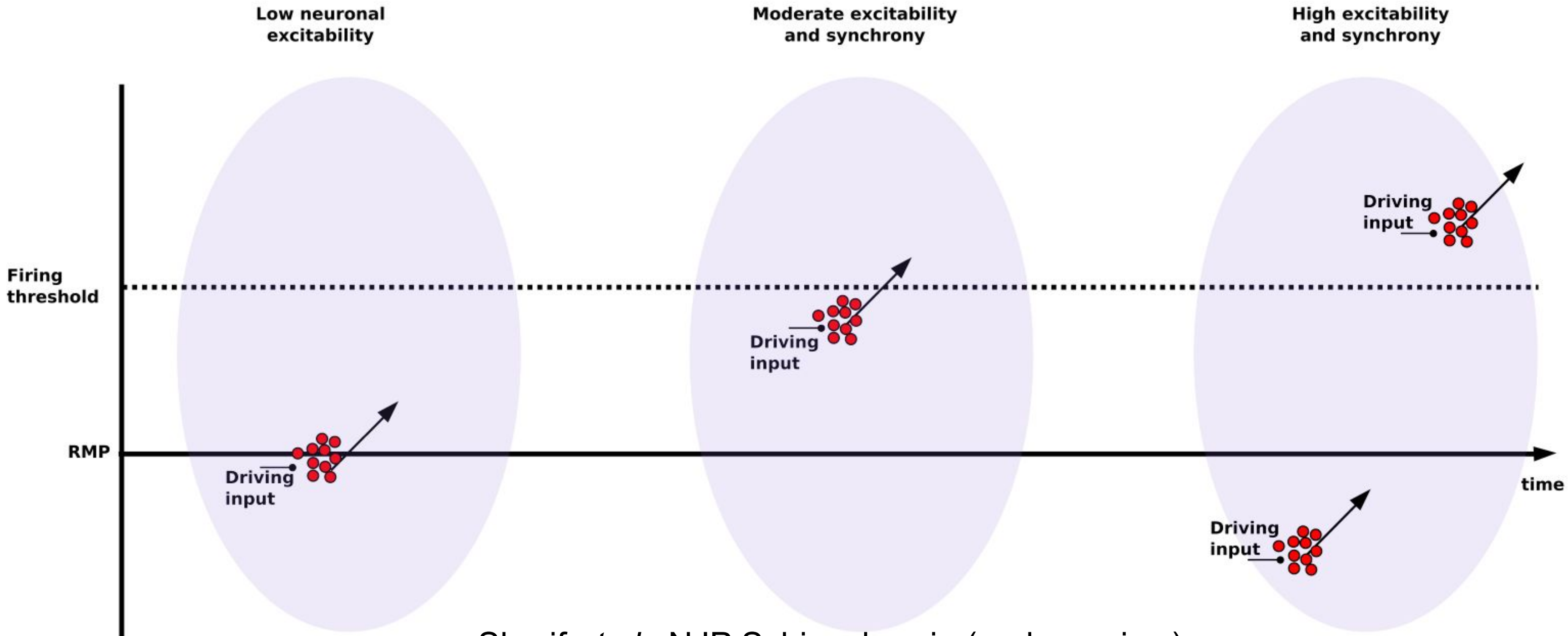
Sherif *et al.*, NJP Schizophrenia (under review)

Excitability and synchrony impact response to driving input and information flow

Low excitability: driving input insufficient to reach threshold and trigger firing, reducing information flow from driving input.

Moderate excitability: pyramidal neurons close to firing threshold → driving input is enough to push cells into firing,

High excitability: pyramidal neurons pushed back-and-forth between synchronized firing with little driving input influence relative to internal drive, and synchronized inhibition with little input influence due to distance from threshold.



Sherif *et al.*, NJP Schizophrenia (under review)

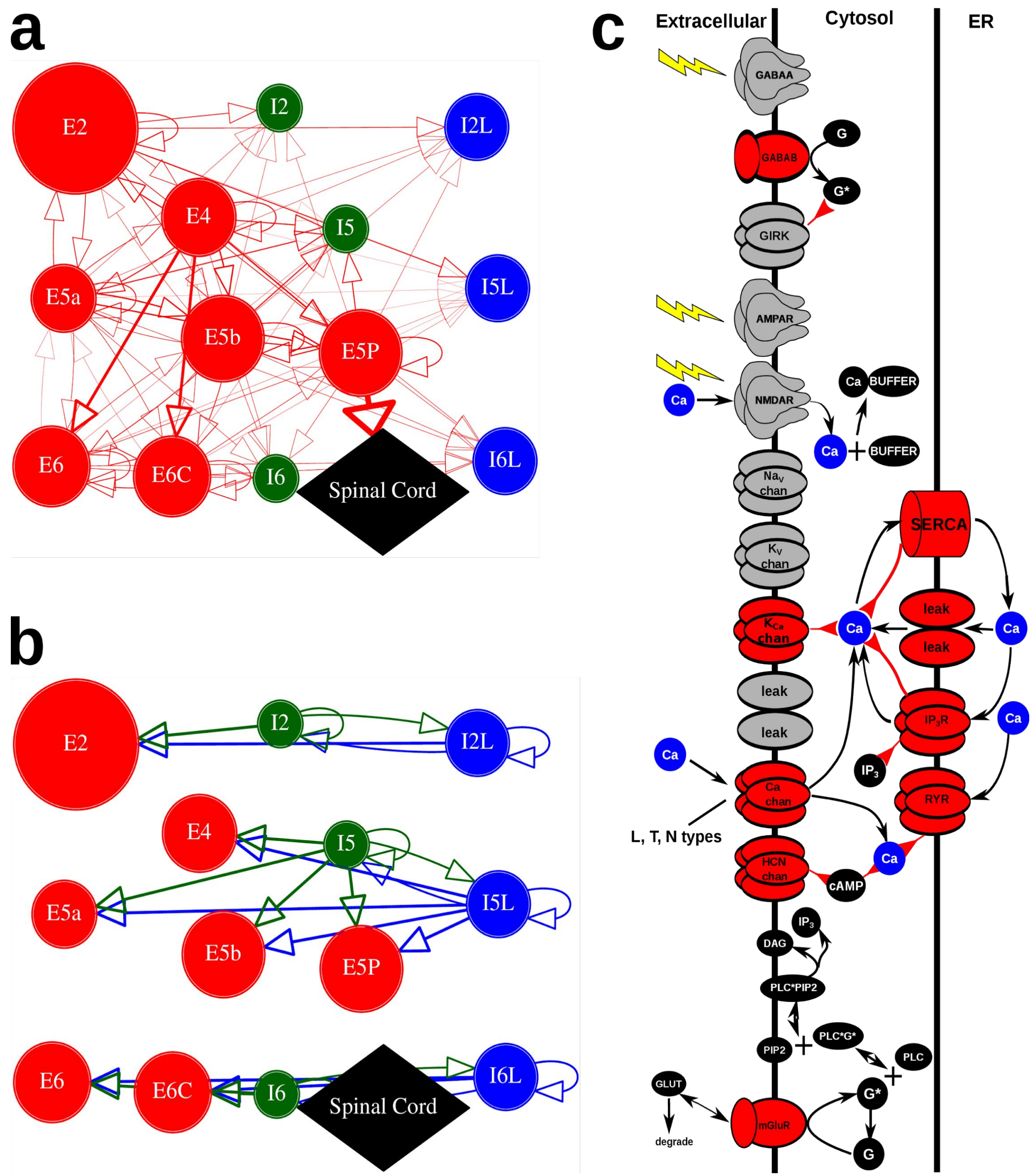
4. Multiscale simulations for pharmacological treatments of neocortical hyperexcitability

Question: Can we use multiscale models to assist development of novel multitarget therapies for complex neurological/psychiatric disorders?

Data: Mouse primary motor cortex (M1) circuit-mapping data; current clamp recordings for L5 pyramidals

Model: Multiscale model of M1

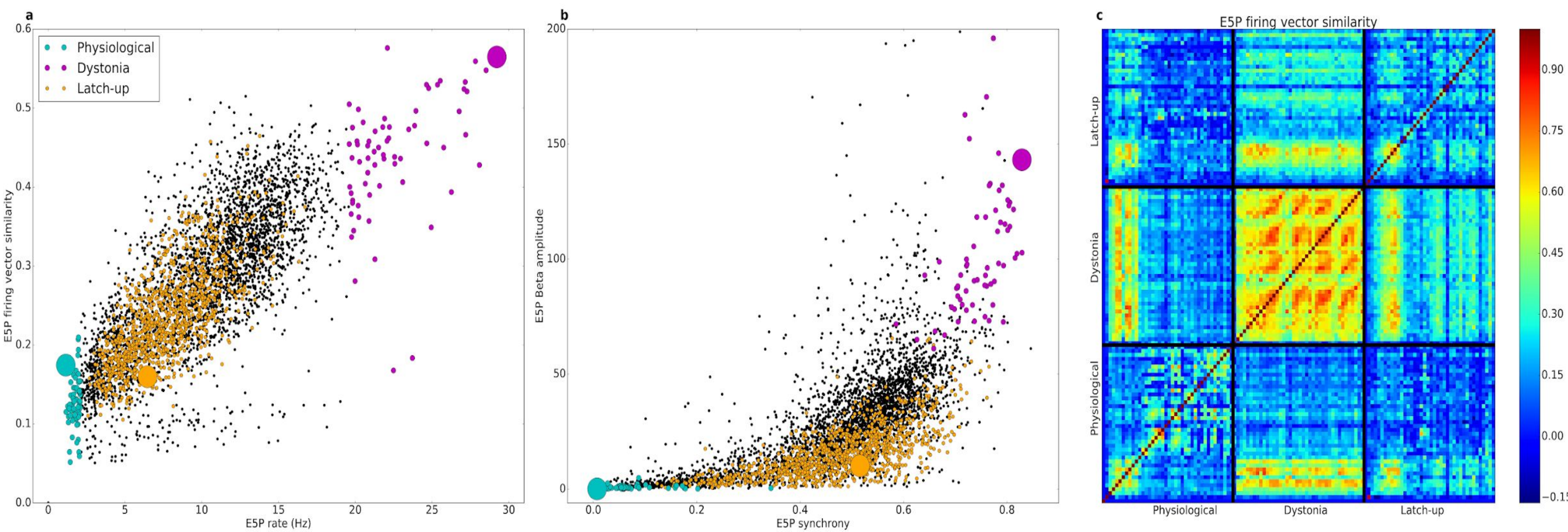
Result: Combining model with machine learning approach was successful in predicting pharmacological targets to treat hyperexcitability disorders



Neymotin *et al.*, Frontiers in Pharmacology 2016

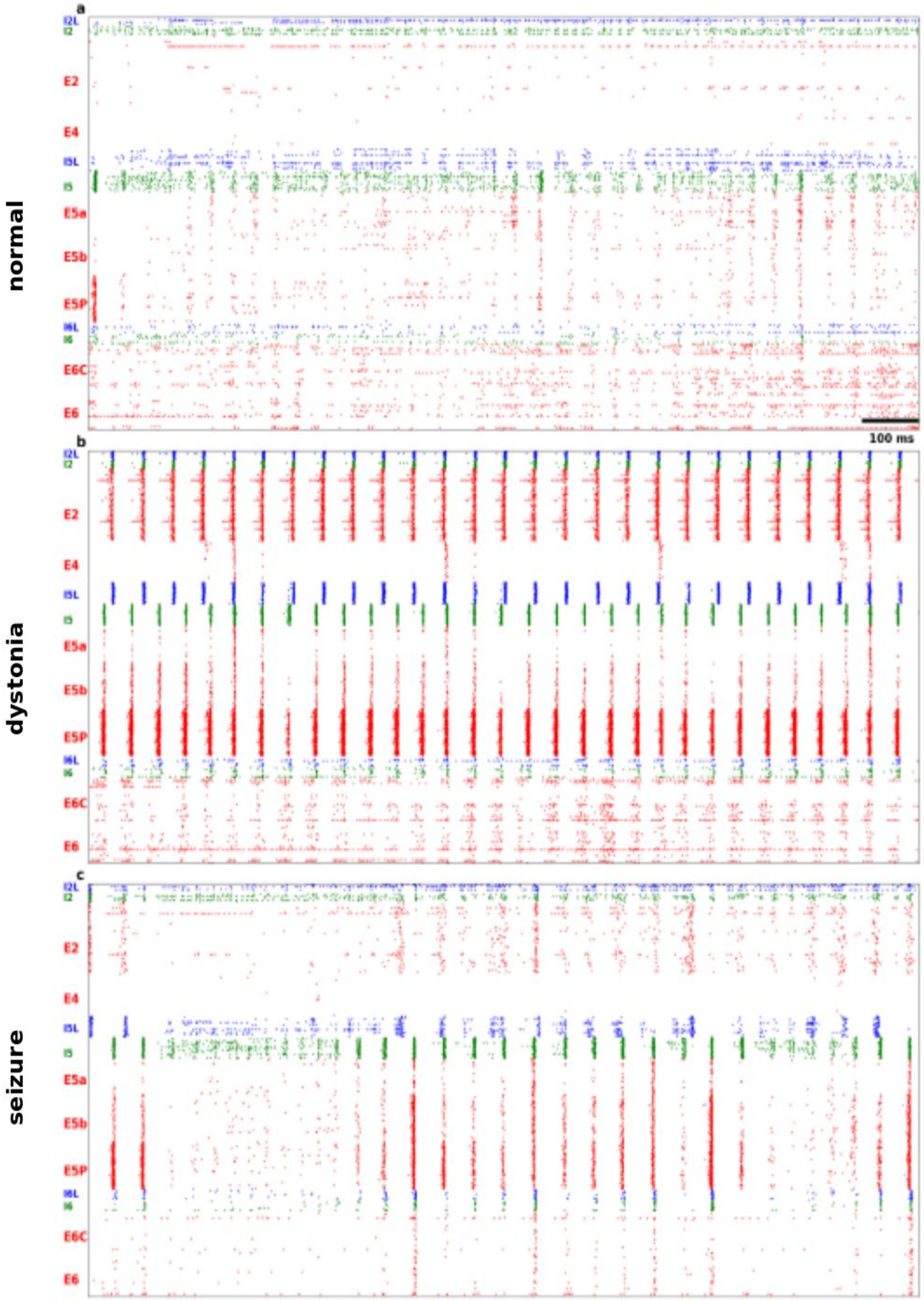
Family of motor cortex models shows three types of dynamics

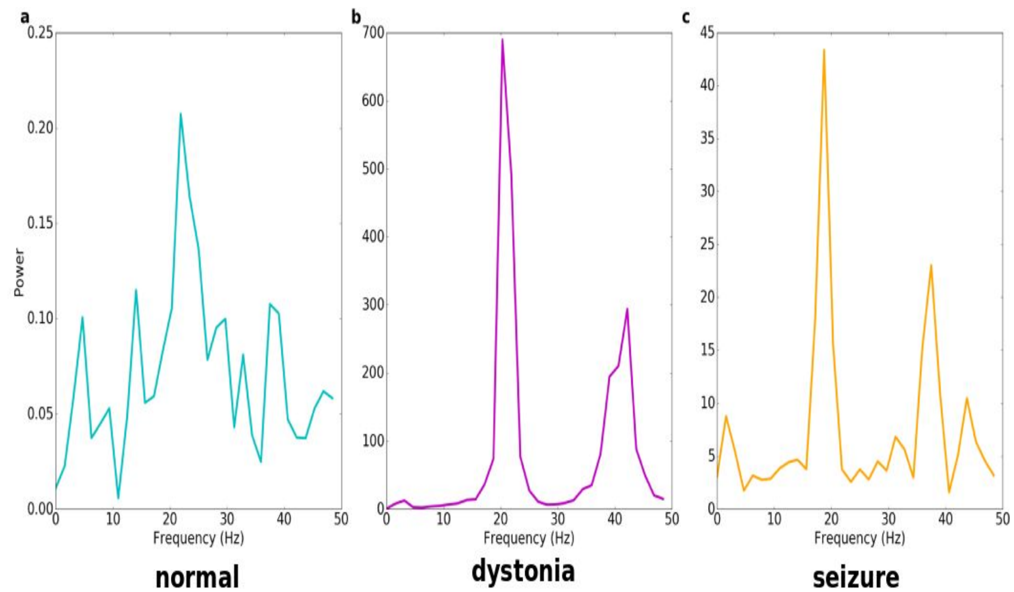
Model ion channel densities randomly perturbed, creating a family of models showing three clusters of distinct dynamics → 1. normal (low synchrony), 2. seizure/latch-up (high intermittent synchrony), 3. dystonia (high sustained synchrony)



Neymotin *et al.*, Frontiers in Pharmacology 2016

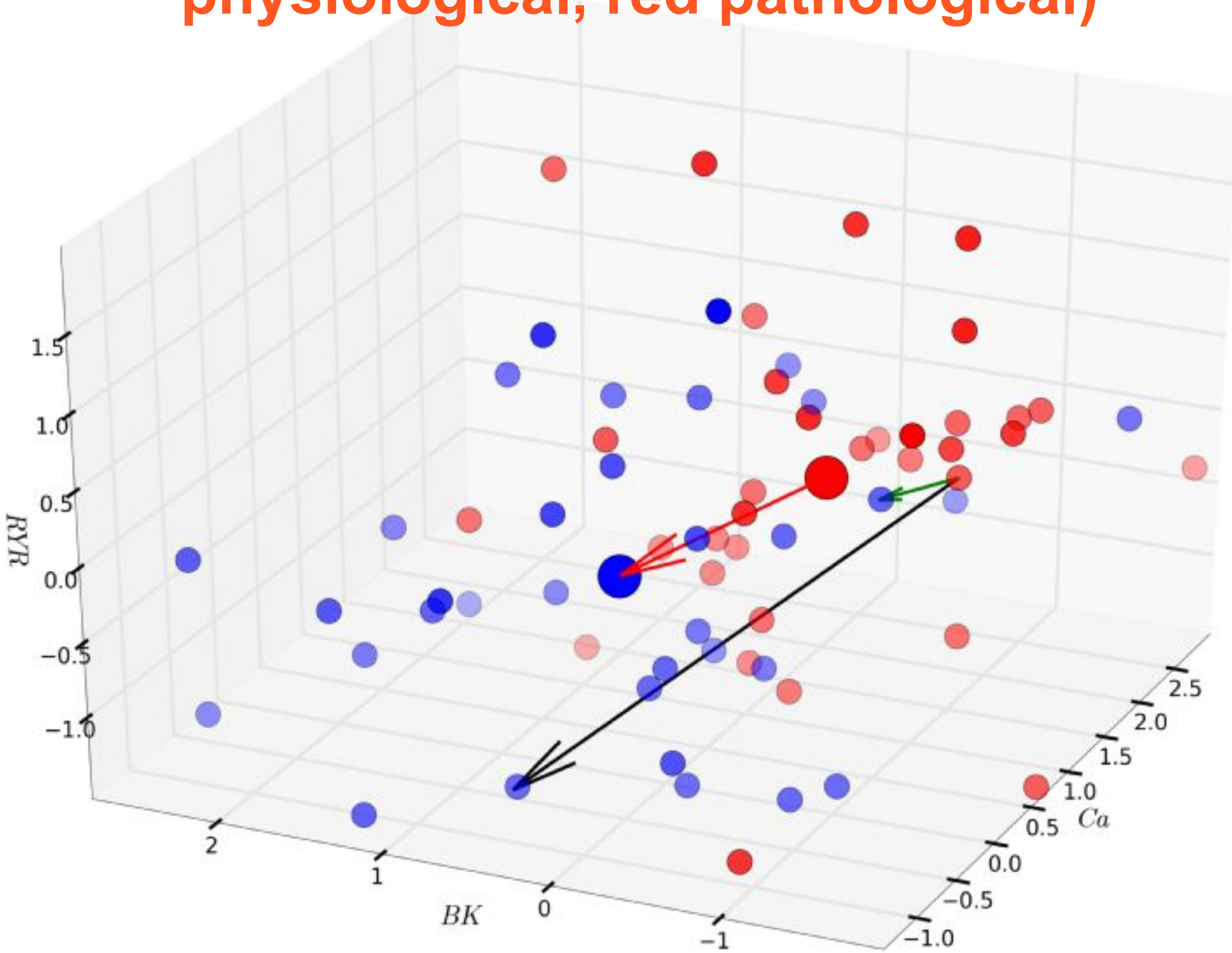
Dystonia & seizure have strong oscillations.
In seizure, many cells are in depolarization blockade.





Neymotin *et al.*, Frontiers in Pharmacology 2016

“Average” treatments won’t work (failure of averaging; blue physiological, red pathological)



Neymotin *et al.*, Drug Discovery Today: Disease Models 2016

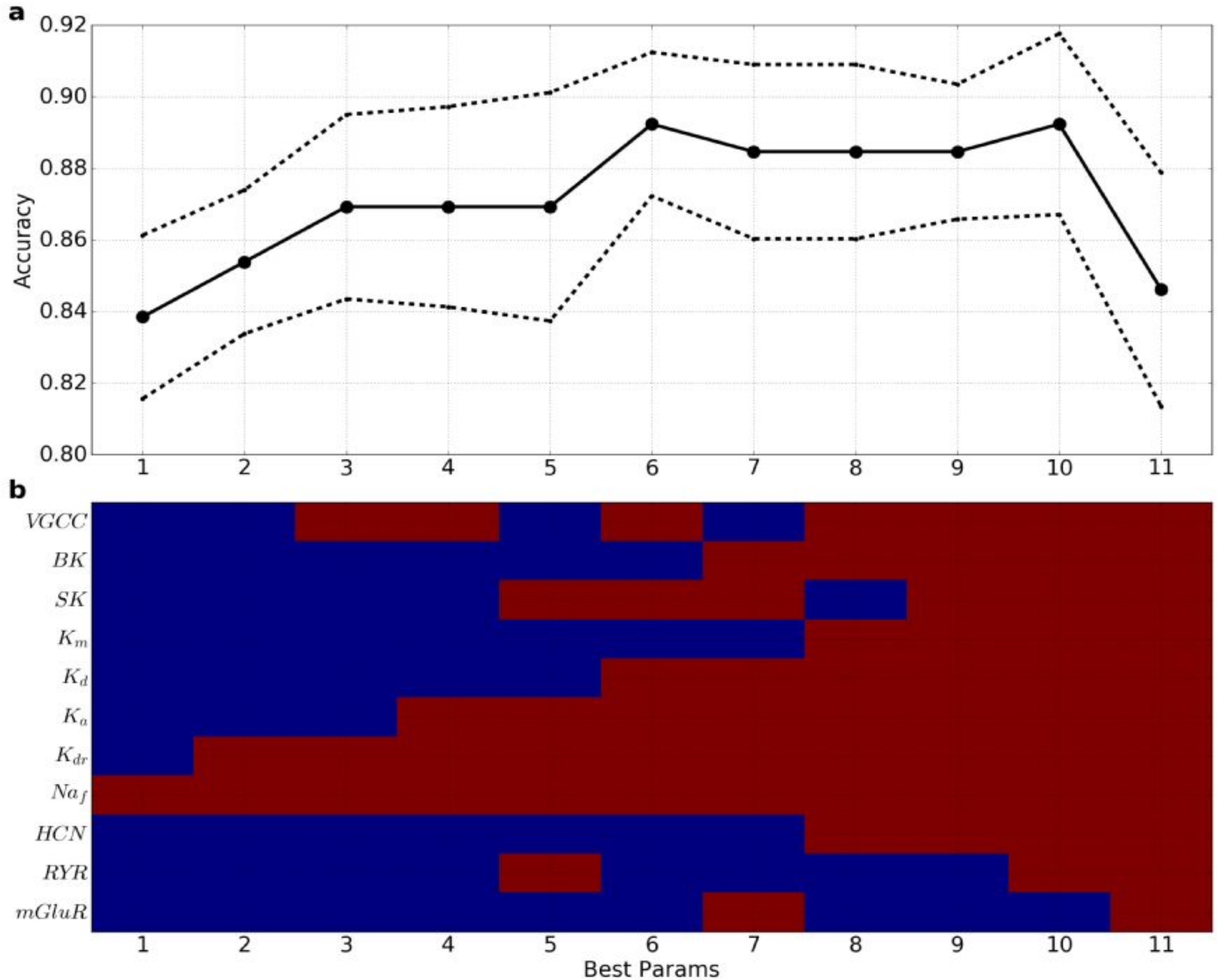
Average parameters from each class do not produce simulations representative of the class.

The multiple, distinct manifestations of pathology, demonstrate utility of personalized medicine.

Use machine learning + modeling to determine multitarget polypharmacy

Machine learning approach predicts that targeting combinations of several receptors is a more effective treatment option than a single target.

The most important determinants of hyper-excitability were Na, K, and Ca channel densities.



Neymotin *et al.*, Frontiers in Pharmacology 2016

5. Sensorimotor learning in detailed circuit models

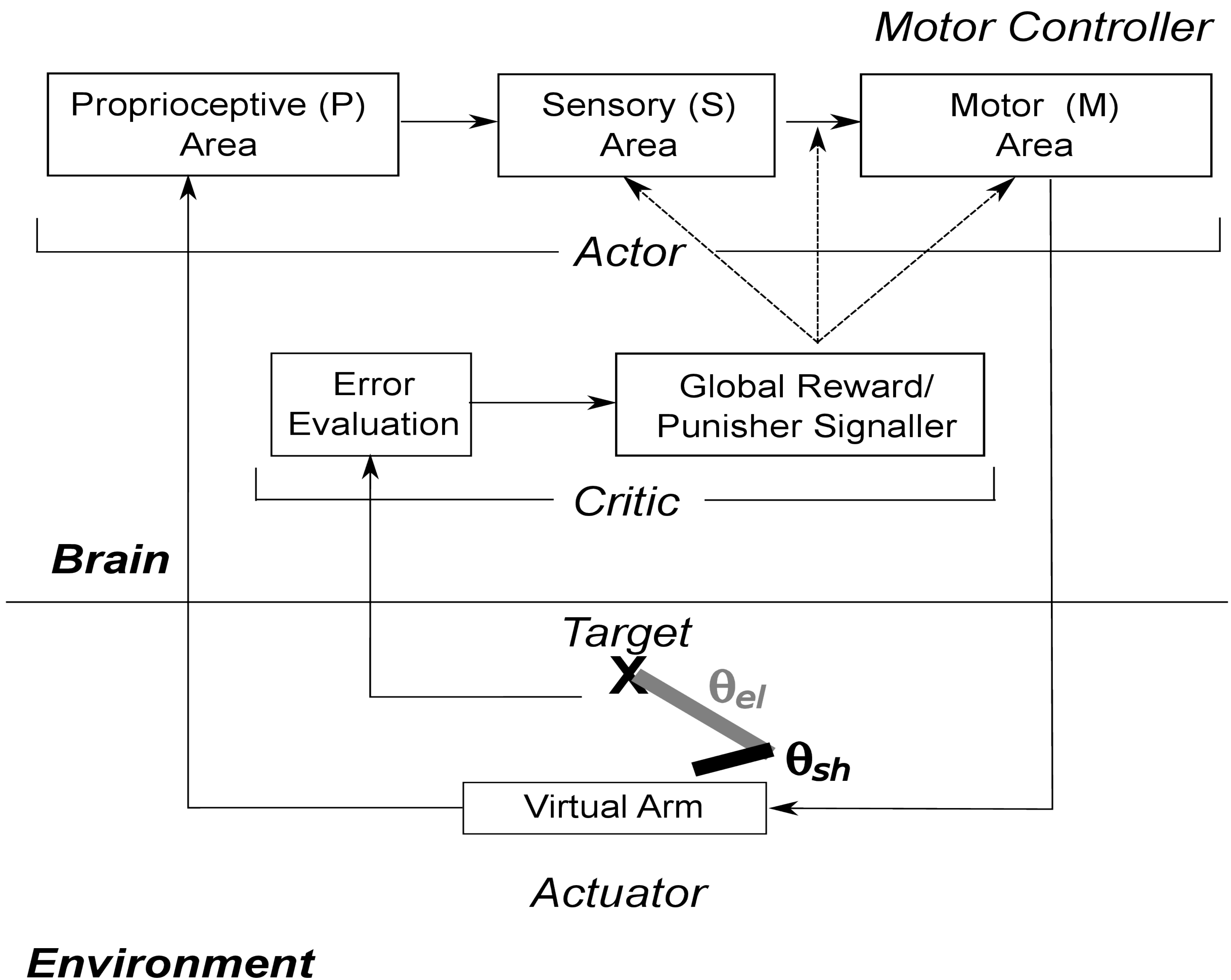
- **Questions:** Can we model the circuit mechanisms, dynamics, and learning that support sensory integration relevant for purposeful behavior? How well do realistic biophysical circuit models with biologically plausible learning rules perform against commonly used deep reinforcement learning algorithms? Can we use the more detailed circuit models to better understand in vivo learning mechanisms?

- **Data:** Electrophysiology, fMRI recorded during sensorimotor learning and decision-making experiments

- **Model:** Spiking neuronal networks of sensory, visual, and motor cortex trained using spike-timing dependent reinforcement learning

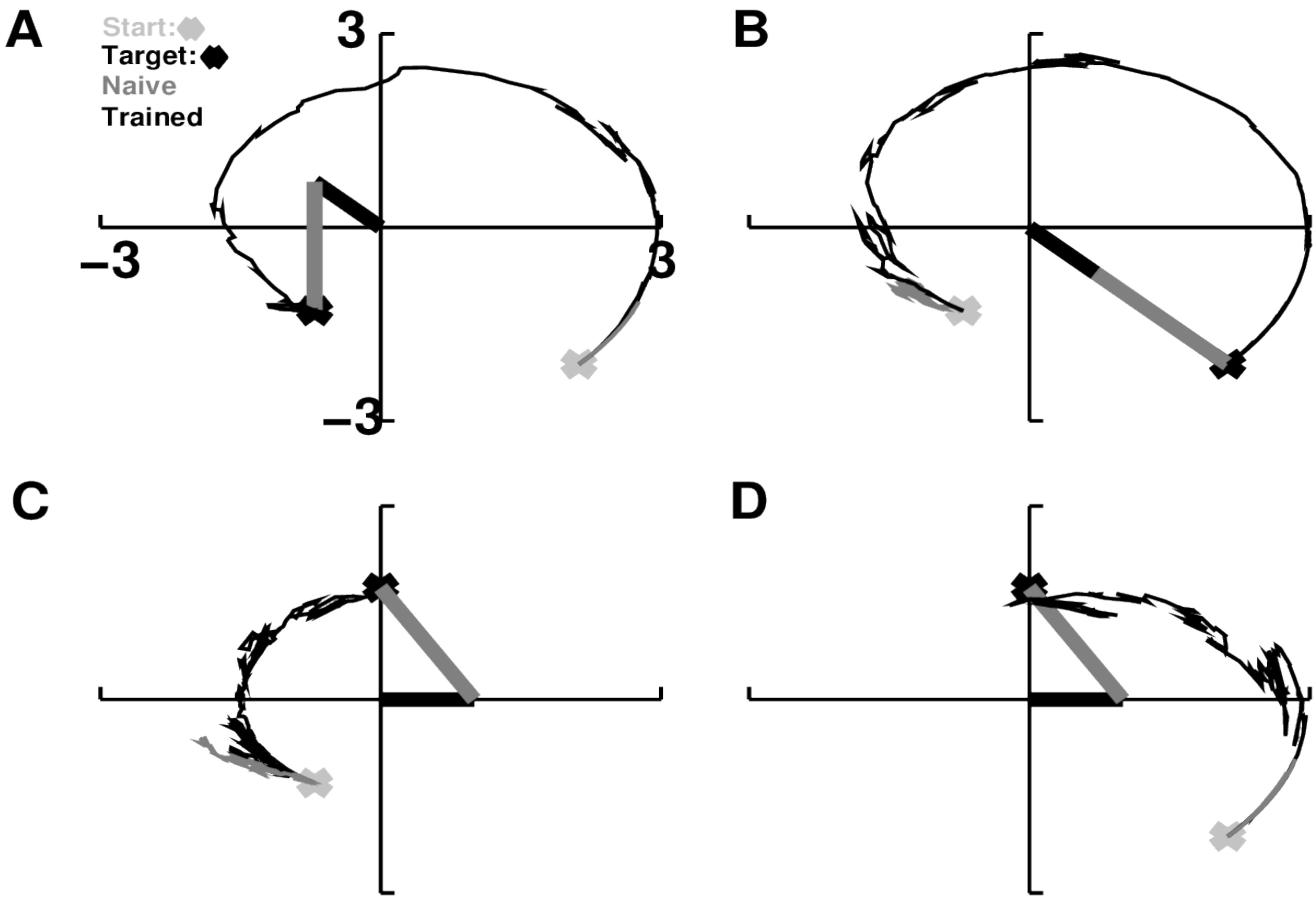
- **Result:** Models utilize sensory information to learn appropriate behavioral responses

Scaling up to behavior: sensorimotor learning



Neymotin *et al.*, Neural Comput 2013

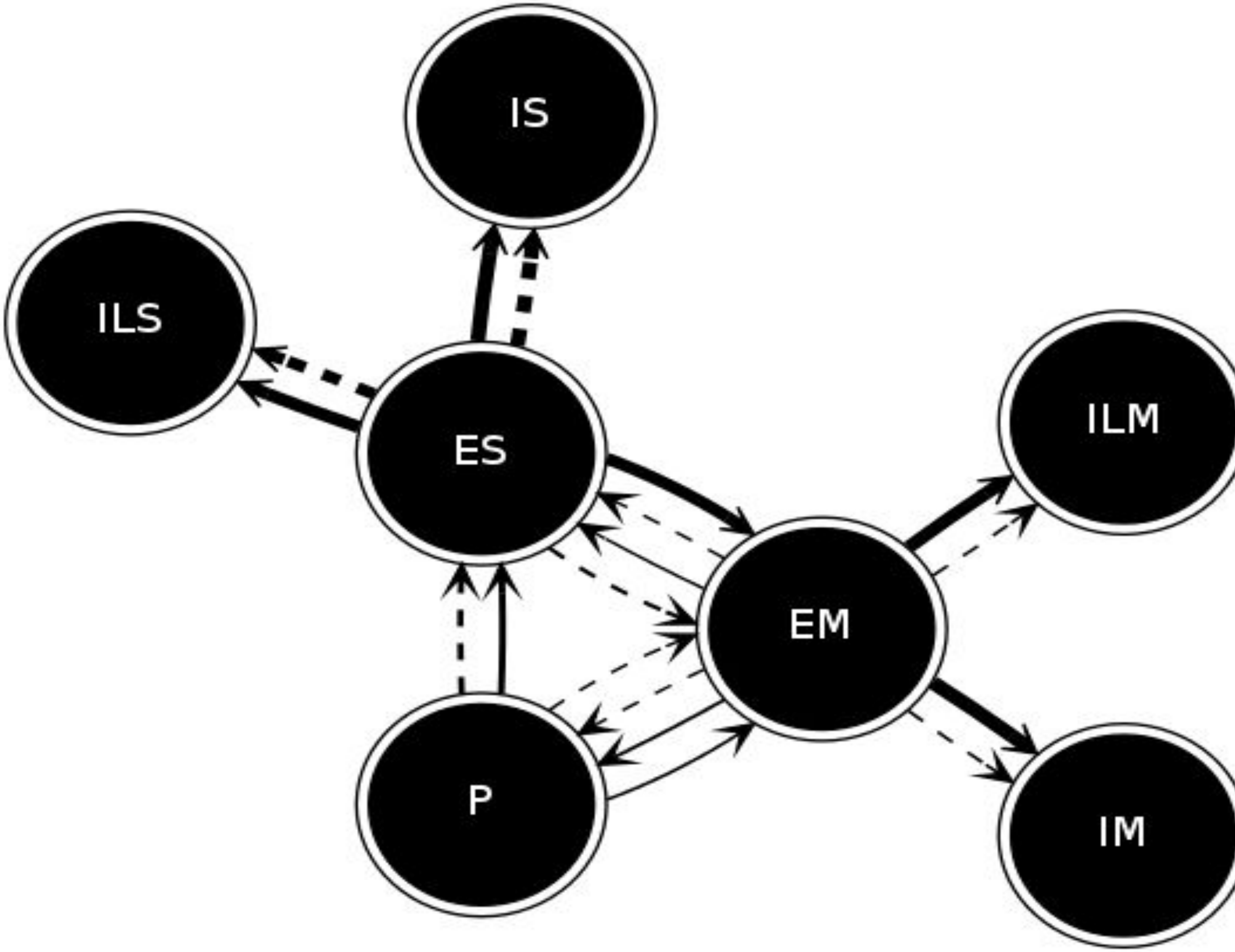
Trained network reaches target



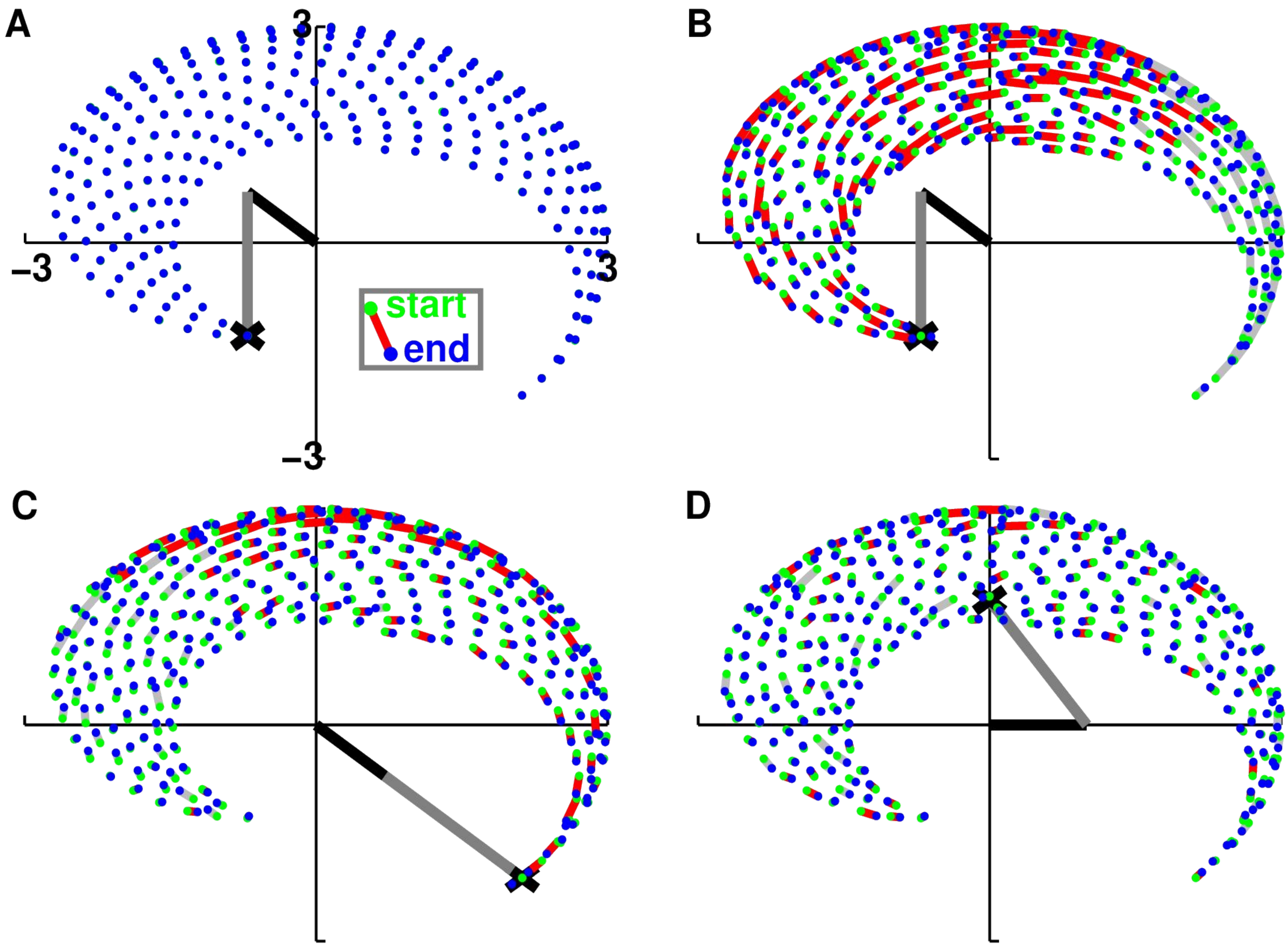
Neymotin *et al.*, Neural Comput 2013

Learning enhances information transfer

After learning, relevant sensory information is utilized more effectively.

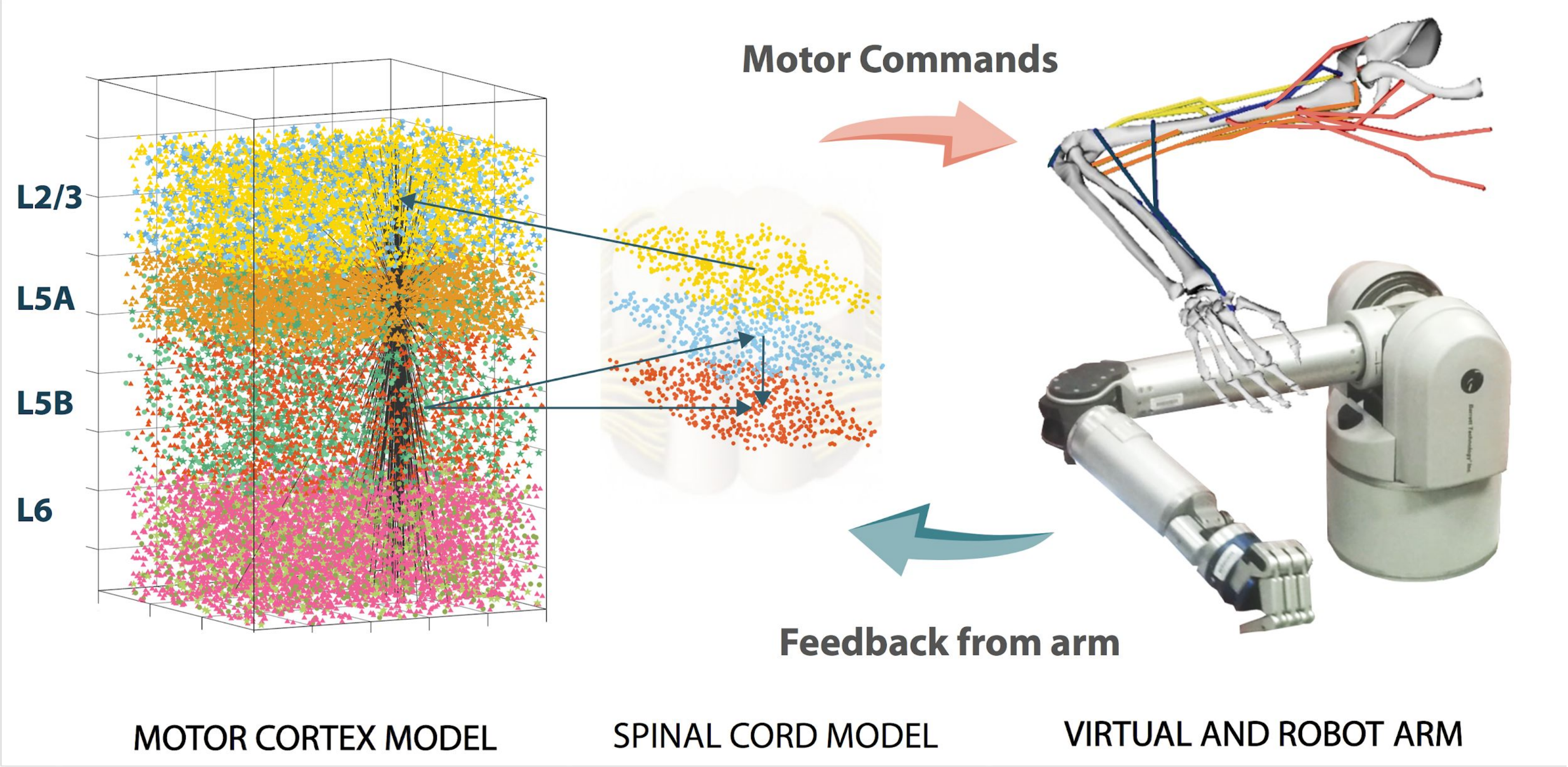


Learning produces attractors



Motor cortex/spinal cord model trained to control more realistic arm model & robot arm

6-layered neocortical architecture: each layer can perform distinct computations (gathering information in input layers, routing/selecting information to send in output layers)



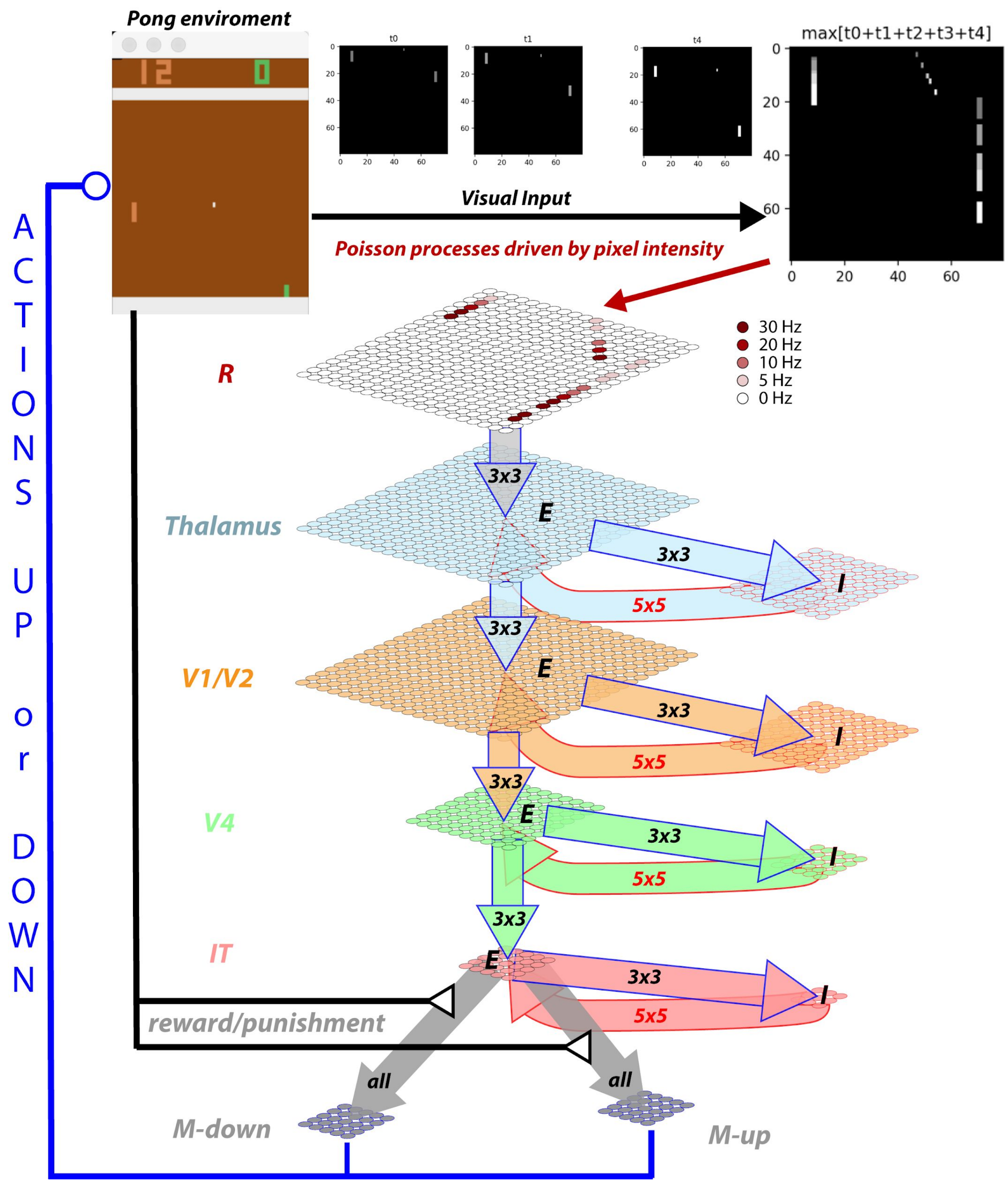
Dura-Bernal *et al.*, Front Neurorobotics 2015

Training biophysical circuit models to play games

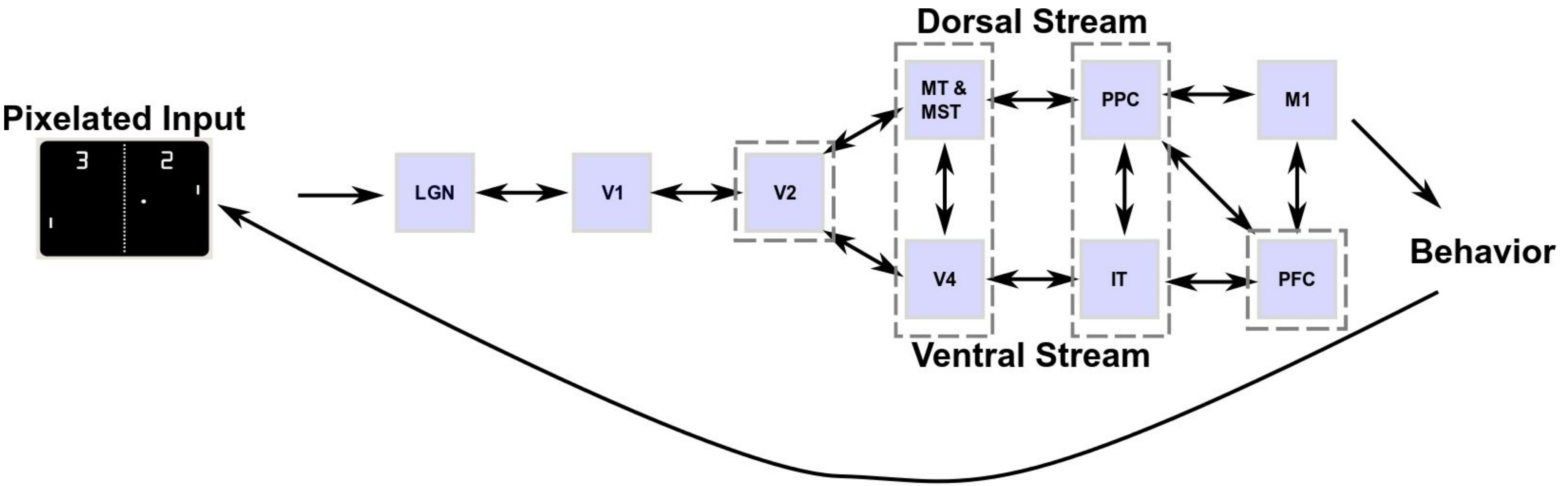
Video game frames converted to topographic inputs that drive non-homogenous Poisson process

Visual hierarchy feeds to motor population command layers which learn to process dynamic sensory information to produce behaviors maximizing reward

Only using learning rules that are considered *biologically-plausible*



Testing influence of architecture: visual hierarchy, recurrent connectivity, and top-down influence



Conclusions

- Our software/models enable researchers to predict mechanistic origins and functions of neural oscillations and activity patterns through integrating modeling with behavioral experiments while performing invasive intracranial laminar electrode array recordings in nonhuman primates and noninvasive MEG/EEG recordings in humans.

- Oscillatory power was linked with the level of information processing in networks: overly high gamma power produced more stereotyped firing patterns and may suggest a loss of responsiveness to external information (outsideworld), and potentially explains aspects of hallucinations in schizophrenia.

- We used our models standalone, and in combination with machine learning approaches, to derive novel pharmacological and electrostimulation therapies for neuropsychiatric disorders, such as schizophrenia.

- Ongoing work: training detailed circuit models of thalamocortical system to perform behaviors through streaming of dynamic signals (speech/video) and biologically-plausible learning rules

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Bibliography

SA Neymotin, DS Daniels, B Caldwell, RA McDougal, NT Carnevale, M Jas, CI Moore, ML Hines ML, M Hämäläinen, SR Jones. Human Neocortical Neurosolver (HNN), a new software tool for interpreting the cellular and network origin of human MEG/EEG data. eLife 9:e51214, 2020.

P Lakatos, A Barczak, SA Neymotin, T McGinnis, D Ross, D Javitt, M O'Connell. Global dynamics of attention and its lapses in primary auditory cortex. Nature Neuroscience 2016 19:1707-1717.

SA Neymotin, MT Lazarewicz, M Sherif, D Contreras, LH Finkel, WW Lytton. Ketamine disrupts theta modulation of gamma in a computer model of hippocampus. J Neuroscience 31(32):11733-11743, 2011.

SA Neymotin, M Hilscher, T Moulin, Y Skolnick, MT Lazarewicz, WW Lytton. Ih tunes theta/gamma oscillations and cross-frequency coupling in an in silico CA3 model. PLOS ONE 8:e76285, 2013.

SA Neymotin, BA Suter, S Dura-Bernal, GMG Shepherd, M Migliore, WW Lytton. Optimizing computer models of corticospinal neurons to replicate in vitro dynamics. J Neurophysiology 2017 117(1):148-162

SA Neymotin, S Dura-Bernal, P Lakatos, TD Sanger, WW Lytton. Multitarget multiscale simulation for pharmacological treatment of dystonia in motor cortex. Frontiers in Pharmacology 2016 7:157

SA Neymotin, GL Chadderdon, CC Kerr, JT Francis, WW Lytton. Reinforcement learning of 2-joint virtual arm reaching in a computer model of sensorimotor cortex. Neural Computation, 2013 25(12):3263-3293.

S Dura-Bernal, X Zhou, SA Neymotin, A Przekwas, JT Francis, WW Lytton. Cortical spiking network interfaced with virtual musculoskeletal arm and robotic arm. Frontiers in Neurorobotics 2015 9:13.

S Dura-Bernal, BA Suter, G Gleeson, M Cantarelli, A Quintana, F Rodriguez, DJ Kedziora, GL Chadderdon, CC Kerr, SA Neymotin, RA McDougal, ML Hines, GMG Shepherd, WW Lytton. NetPyNE,a tool for data-driven multiscale modeling of brain circuits. eLife 2019 8, e44494.

A Eguchi, SA Neymotin, SM Stringer. Color opponent receptive fields self-organize in a biophysical model of visual cortex via spike-timing dependent plasticity. Frontiers in Neural Circuits 8:16, 2014.