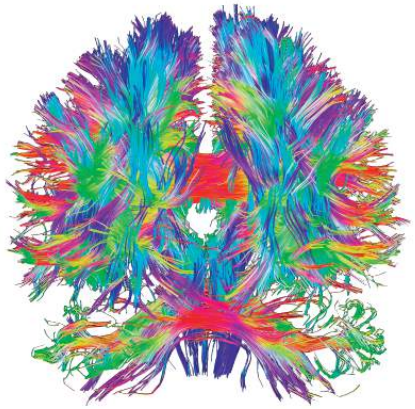
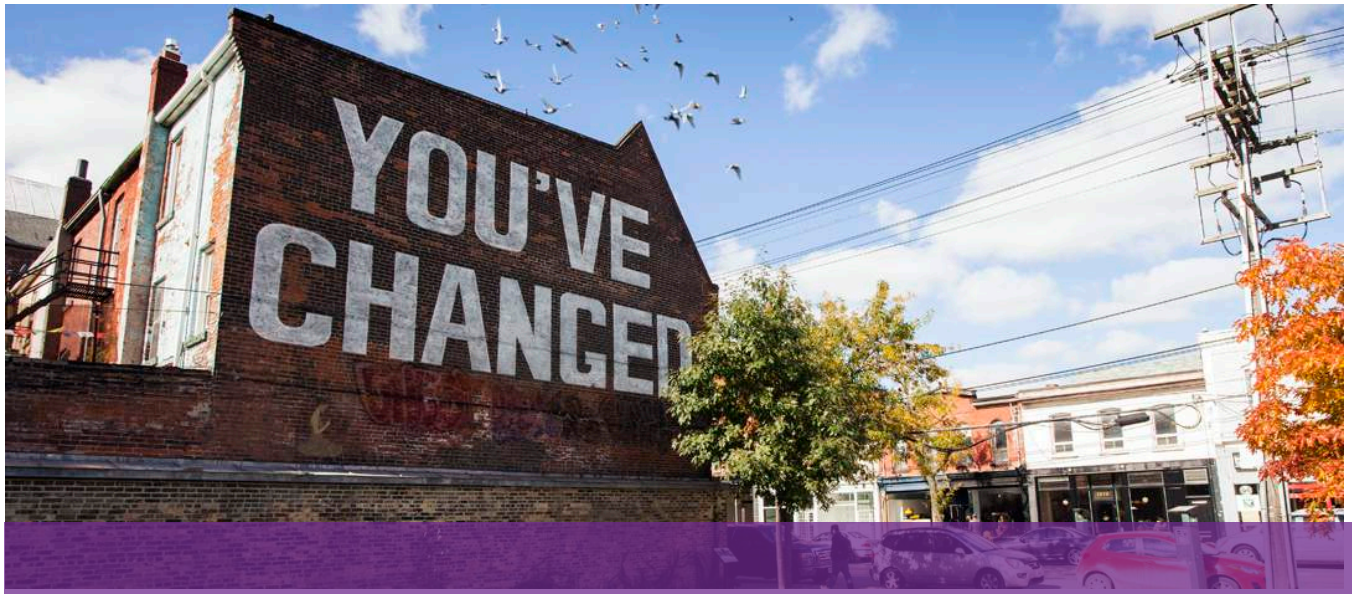
camh | Krembil Centre for Neuroinformatics



A Multiscale Approach to Brain Disorders

Sean Hill, Ph.D.
Director, Krembil Centre for Neuroinformatics
Senior Scientist, Centre for Addiction and Mental Health
Professor, Departments of Psychiatry and Physiology, University of Toronto, Canada
Titular Professor, École Polytechnique Fédérale de Lausanne, Switzerland
krembilneuroinformatics.ca

About CAMH - The Centre for Addiction & Mental Health



The Centre for Addiction and Mental Health (CAMH) is Canada's largest mental health and addiction teaching hospital.

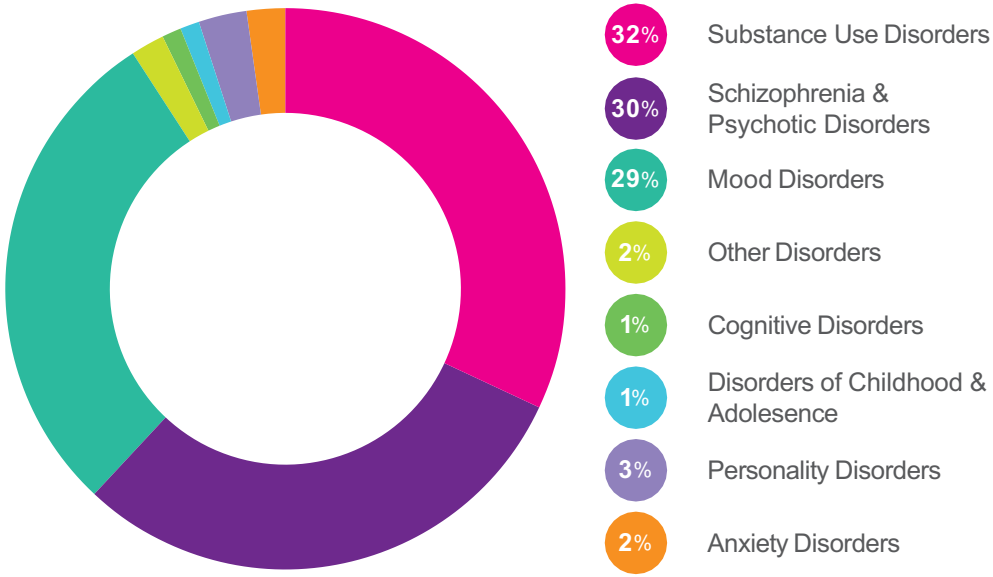
CAMH Patient Snapshot

Patients

Unique patients	31,125
Visits to emergency services	9,243
Average inpatient length of stay	24.38 days

59% had more than one diagnosis at admission

Primary Diagnosis of Inpatients on Admission



camh

Total annual visits	>	1,000,000

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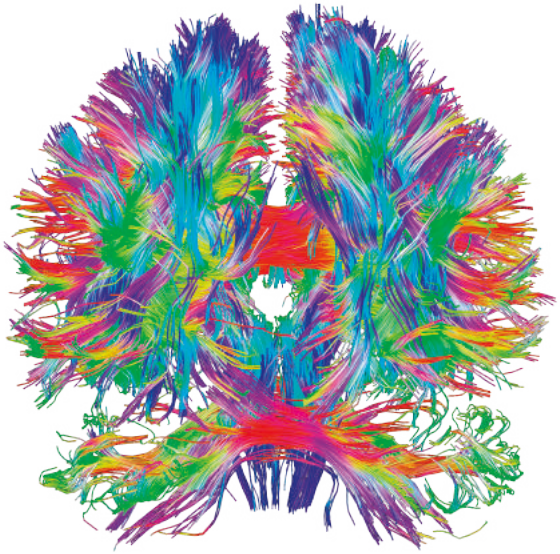
Multiscale Data
Integrating high quality clinical and behavioural data including genetics, imaging, and mobile

Artificial Intelligence
Defining, diagnosing and predicting mental illness and brain disorders

Multiscale Brain Modeling
Identifying cellular and synaptic mechanisms of brain function and dysfunction



Open Science
Open, reproducible, team science, FAIR data principles, Global collaboration

Education
Disseminating knowledge, Training the next generation of scientists

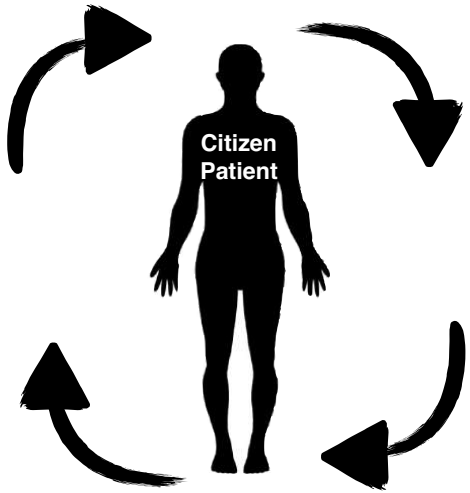
Innovation
Ethical, responsible incubator for mental health technologies

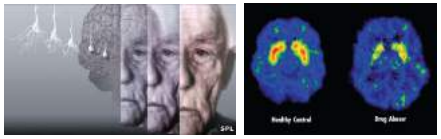
krembilneuroinformatics.ca

Krembil Centre for Neuroinformatics

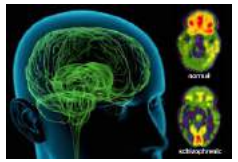
Open Science, Team Science, Data-driven Mental Health

**Clinicians,
Health Professionals**

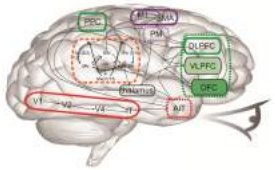


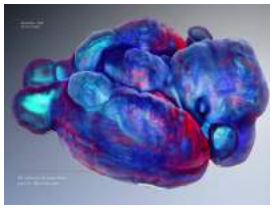


**Researchers
& Clinical
Scientists**

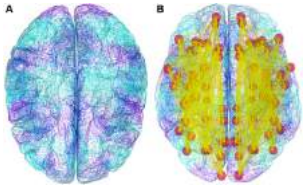


**Medical,
Information
Technology,
Wearables**

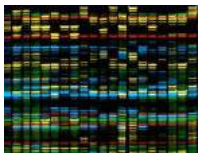


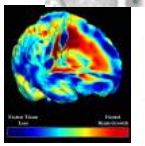


**Analysis, Brain Modeling,
Simulation, Classification,
Prediction, Machine Learning, AI**

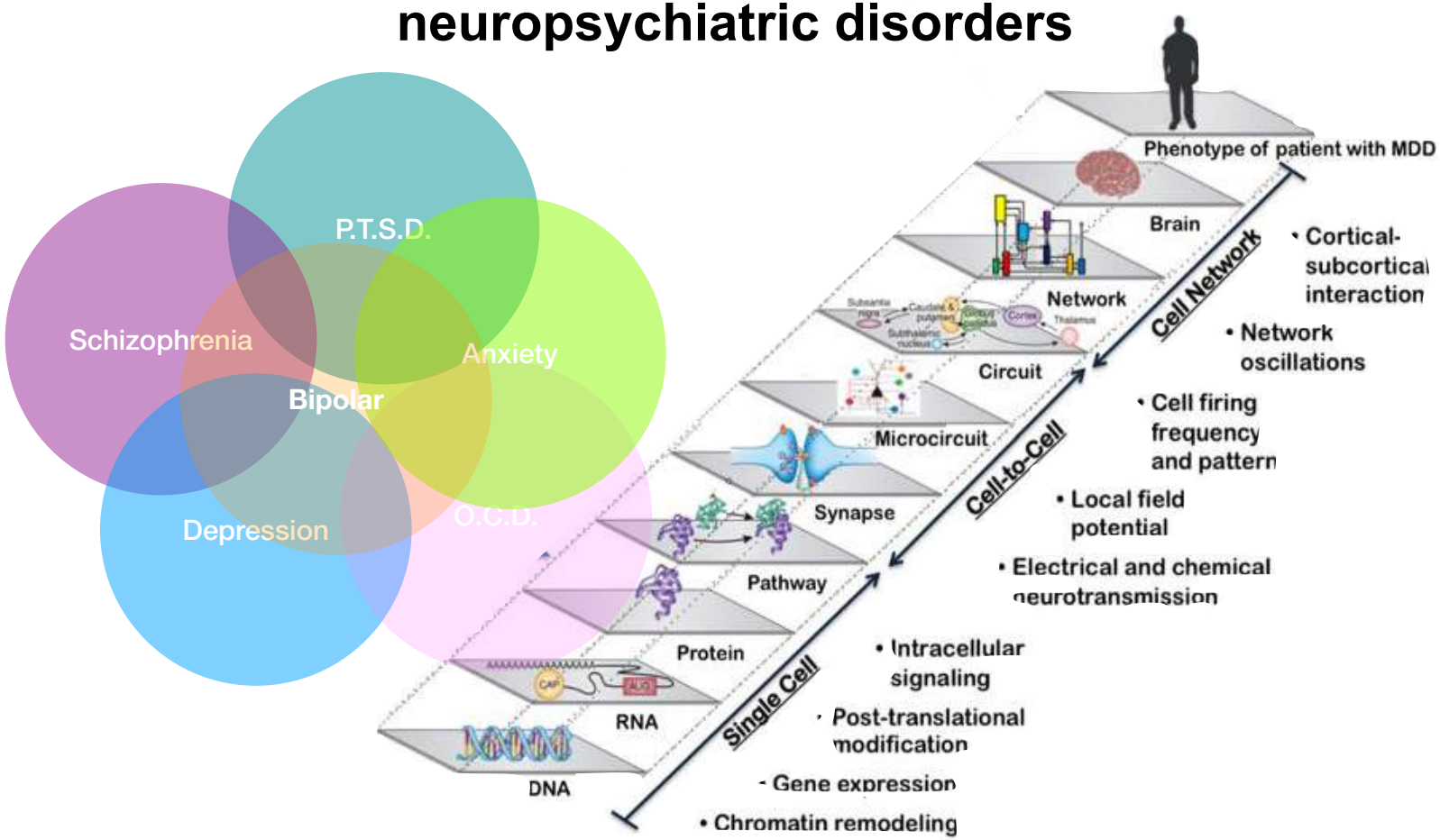


**Multiscale Data
Genomics, Brain Imaging,
Eectronic Health Records**

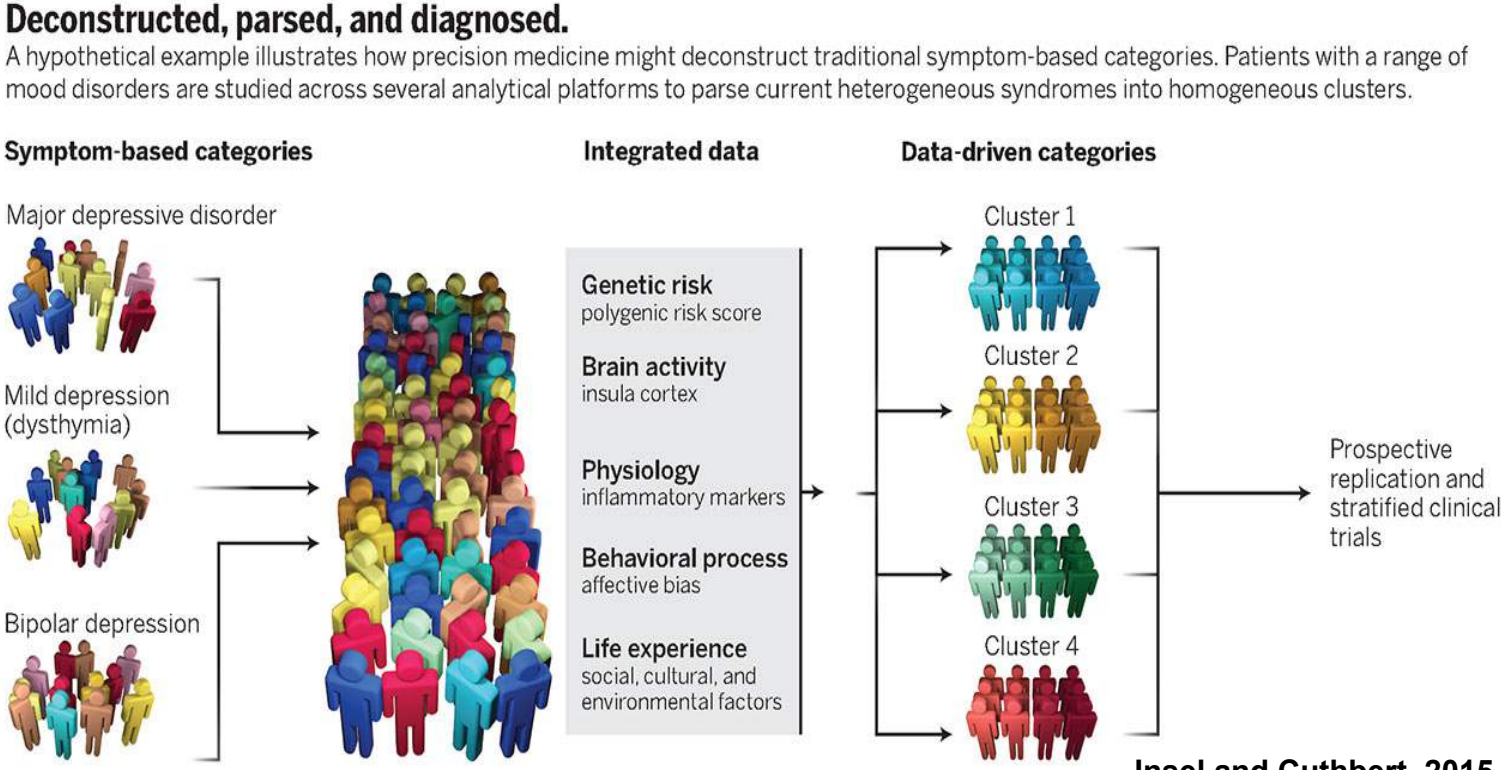




A multiscale perspective on neuropsychiatric disorders

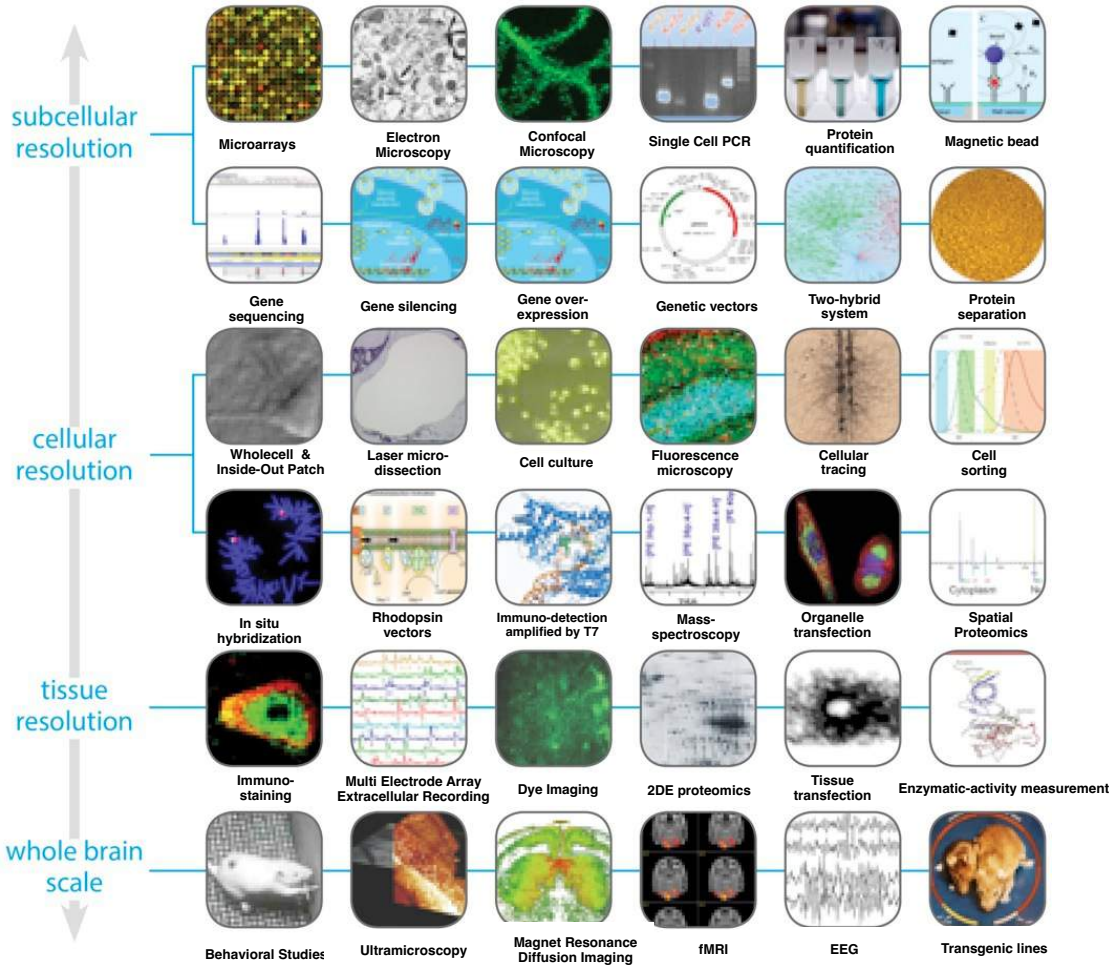


Redefine Psychiatric Nosology in Terms of Neuroscience

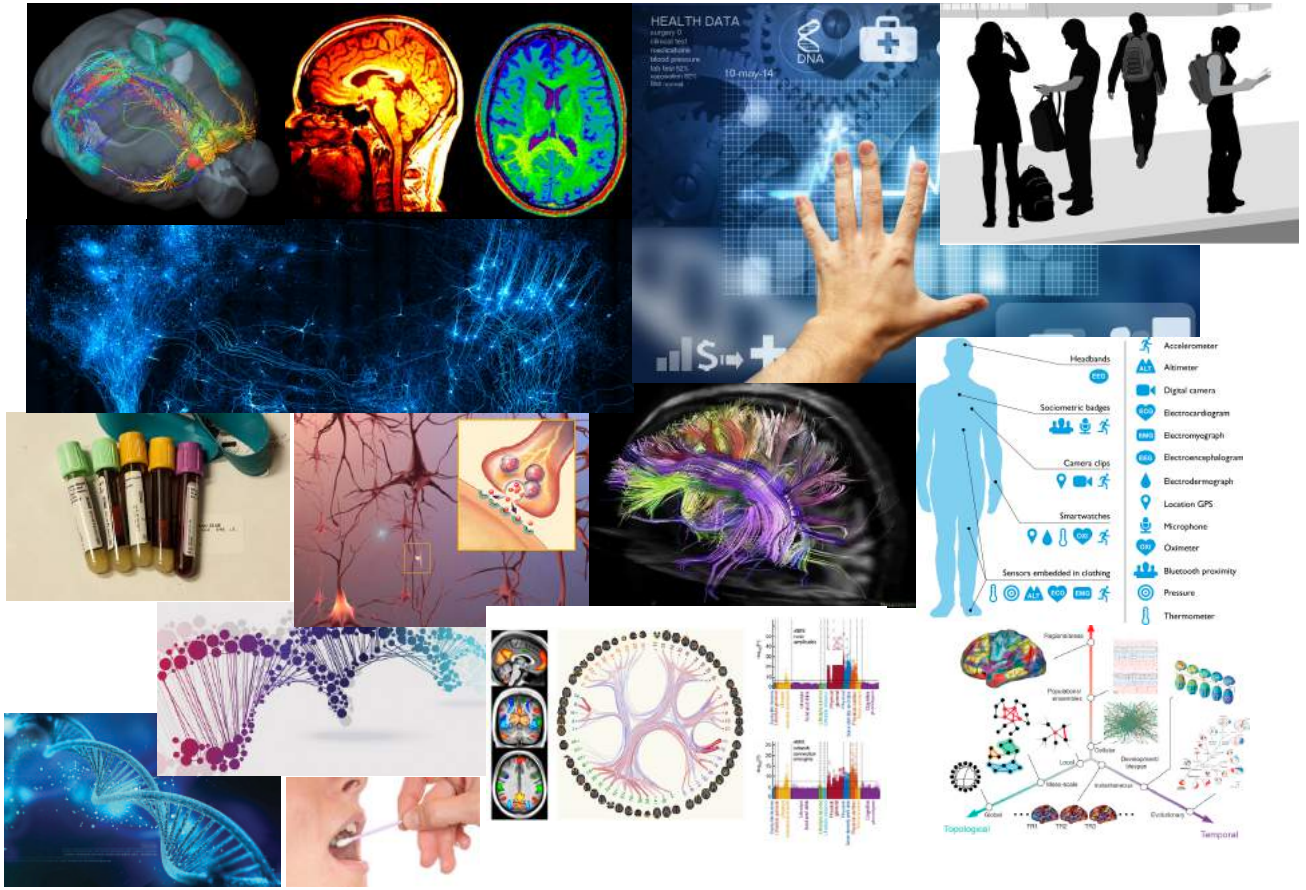


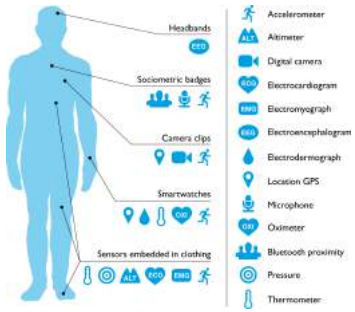
Insel and Cuthbert, 2015

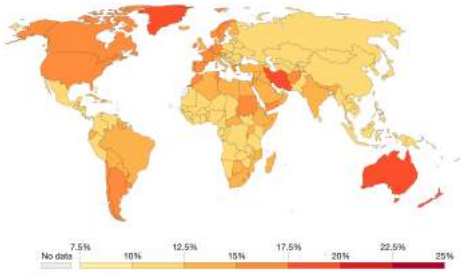
Many kinds and levels of neuroscience data



Organize, search and integrate multiple layers of brain research data from around the world to accelerate mental health research and care

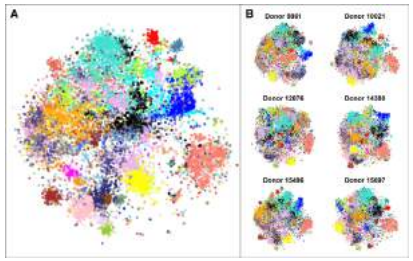


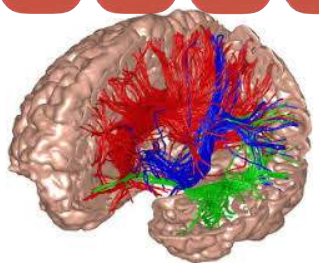


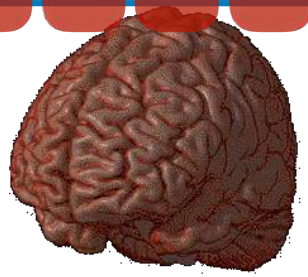


- Population
- Mobile and Wearables
- Neuroimaging
- Clinical
- Molecular
- Genomics

- Anxiety and Depression
- Mood & Personality Disorders
- Schizophrenia & Psychosis
- Trauma & Stress Disorders
- Alzheimer's & Dementia
- Addictions/Substance Use
- Developmental Disabilities
- Other disorders







CAMH BrainHealth Databank

High Quality Longitudinal Data

- CAMH patient journeys and populations
- Accumulation of rich, high quality longitudinal data

Supporting Delivery of Evidence Based Care

- Use of tablets to facilitate high quality data collection
- Visualization of patient's chart to support clinical decisions

Integrating Research Measures with Care

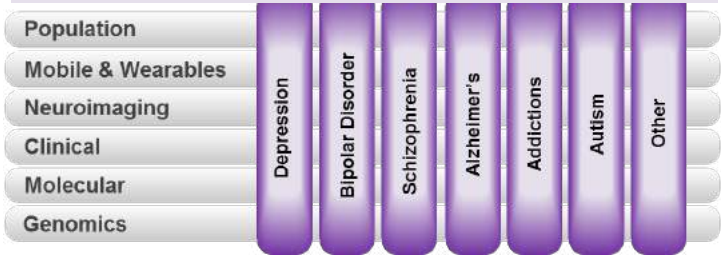
Biobank

- Genomics, proteomics

Mobile and Wearable Devices

- Sleep and activity
- Portable EEG - Brain activity

Open Data, Enabling Large Scale Analytics & Modelling



- Open, multiscale brain health atlas across the lifespan and disorders
- Robust data governance to ensure patient privacy

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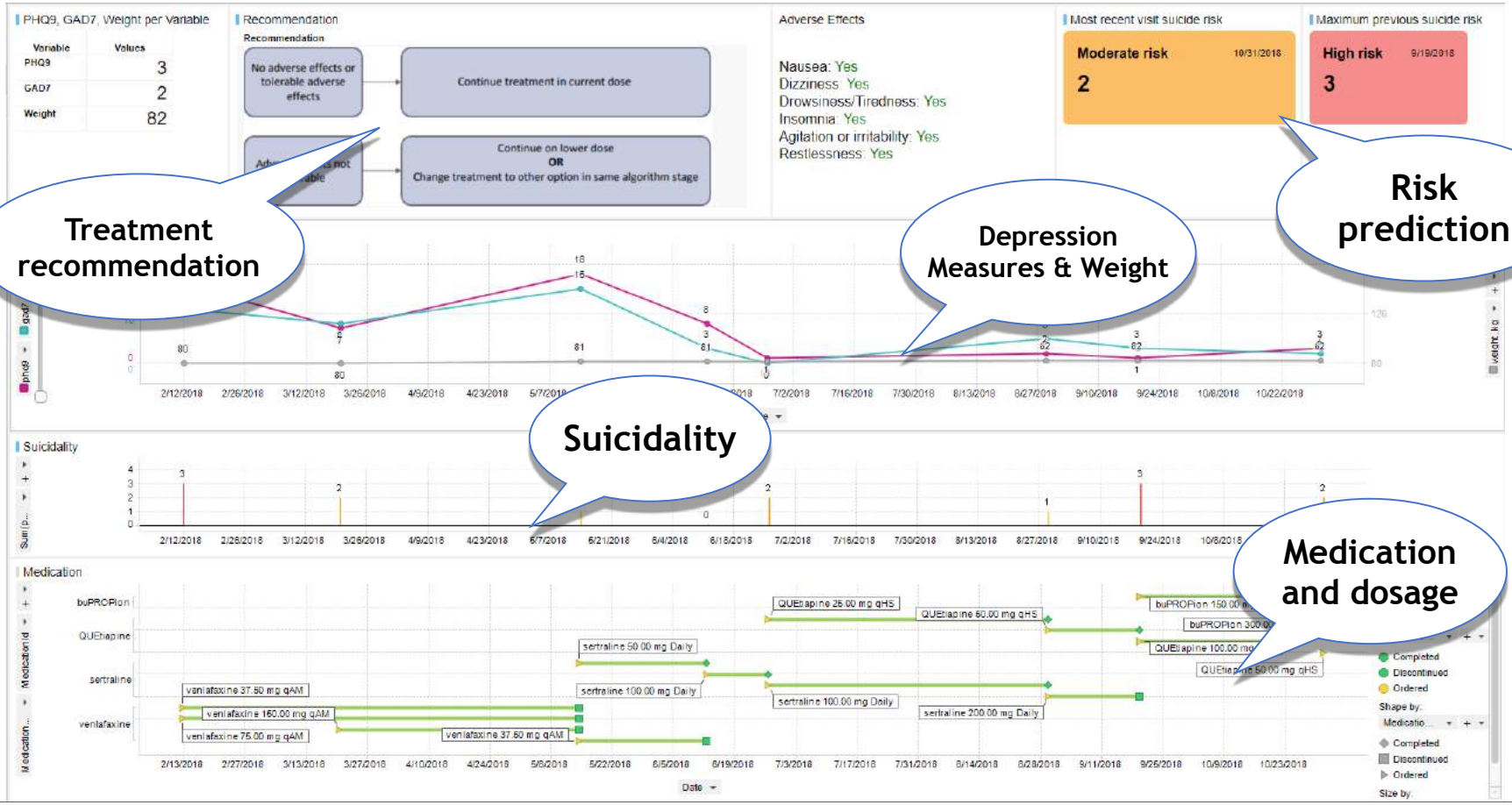
Patient trajectory and decision support



Virtually all neurologic, psychiatric and substance abuse disorders are associated with changes in **Brain Connectivity**

- **Neurological disorders**
  - Stroke
  - Epilepsy
  - Traumatic brain injury
  - Brain tumor
- **Neurodegenerative disorders**
  - Dementia
  - Alzheimers
  - Parkinson's
  - ALS
  - Multiple sclerosis
- **Developmental disorders**
  - Autism
  - Fragile X
  - Down's
- **Affective disorders**
  - Major depressive disorder
  - Disthymic disorder
  - Bipolar disorder
  - Cyclothymic
- **Anxiety disorders (including post-traumatic stress disorder)**
  - Generalized anxiety disorder
  - Panic disorder
  - Post-traumatic stress disorder
- **Psychoses**
  - Schizophrenia
- **Substance abuse disorders**
  - Alcohol abuse
  - Stimulant-dependent sleep disorder
  - Sedative-, hypnotic-, and anxiolytic-dependent sleep disorder
- **Eating disorders**
  - Anorexia nervosa
  - Bulimia nervosa
  - Nocturnal eating/drinking syndrome
- **Attention deficit/hyperactivity disorders**

Virtually all neurologic, psychiatric and substance abuse disorders are associated with changes in **Brain Excitability**

- **Neurological disorders**
  - Stroke
  - Epilepsy
  - Traumatic brain injury
  - Brain tumor
- **Neurodegenerative disorders**
  - Dementia
  - Alzheimers
  - Parkinson's
  - ALS
  - Multiple sclerosis
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  - Sedative-, hypnotic-, and anxiolytic-dependent sleep disorder
- **Eating disorders**
  - Anorexia nervosa
  - Bulimia nervosa
  - Nocturnal eating/drinking syndrome
- **Attention deficit/hyperactivity disorders**

Virtually all neurologic, psychiatric and substance abuse disorders are associated with disruptions in **Sleep**

- **Neurological disorders**
  - Stroke
  - Epilepsy
  - Traumatic brain injury
  - Brain tumor
- **Neurodegenerative disorders**
  - Dementia
  - Alzheimers
  - Parkinson's
  - ALS
  - Multiple sclerosis
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  - Sedative-, hypnotic-, and anxiolytic-dependent sleep disorder
- **Eating disorders**
  - Anorexia nervosa
  - Bulimia nervosa
  - Nocturnal eating/drinking syndrome
- **Attention deficit/hyperactivity disorders**

Virtually all neurologic, psychiatric and substance abuse disorders are often associated with disturbances in **Brain Energy Metabolism**

- **Neurological disorders**
  - Stroke
  - Epilepsy
  - Traumatic brain injury
  - Brain tumor
- **Neurodegenerative disorders**
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  - Alzheimers
  - Parkinson's
  - ALS
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- **Eating disorders**
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  - Bulimia nervosa
  - Nocturnal eating/drinking syndrome
- **Attention deficit/hyperactivity disorders**

Virtually all neurologic, psychiatric and substance abuse disorders are often associated with increases in **Immune Response**

- **Neurological disorders**
  - Stroke
  - Epilepsy
  - Traumatic brain injury
  - Brain tumor
- **Neurodegenerative disorders**
  - Dementia
  - Alzheimers
  - Parkinson's
  - ALS
  - Multiple sclerosis
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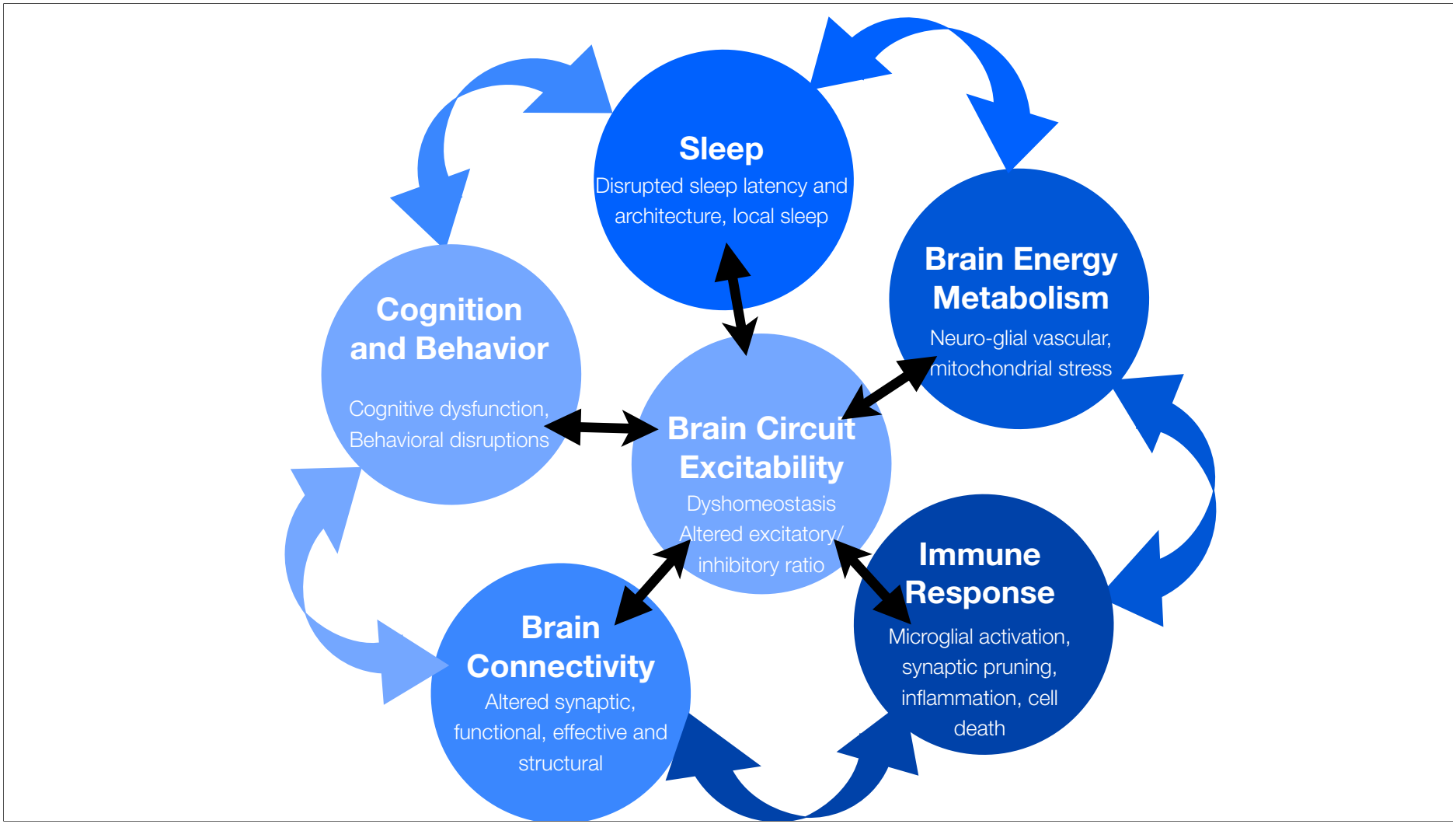
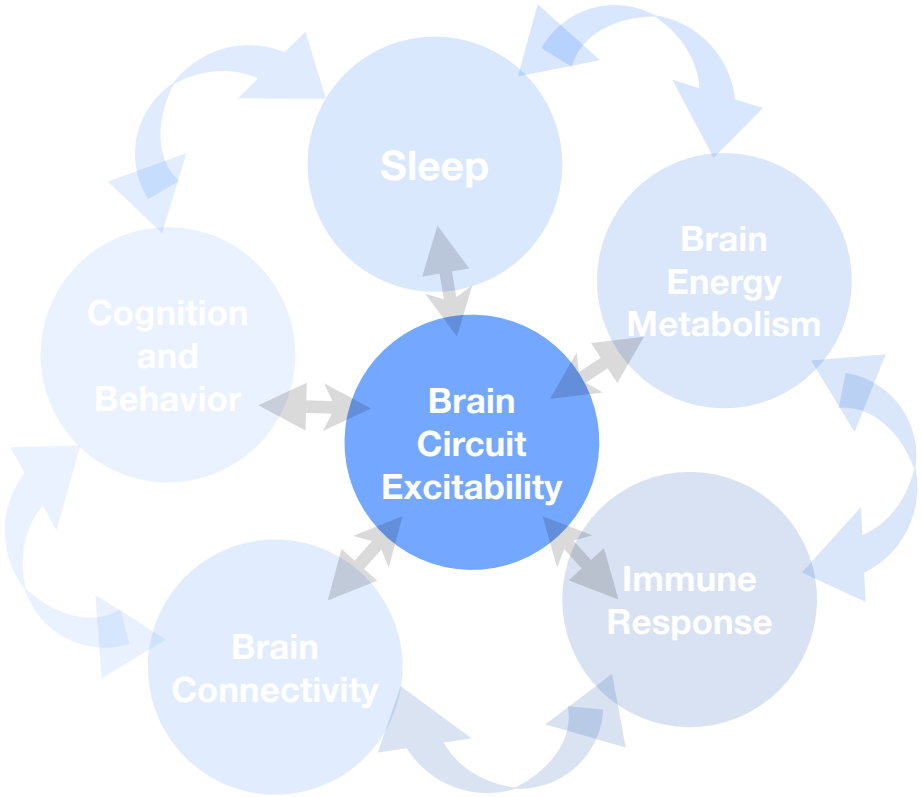
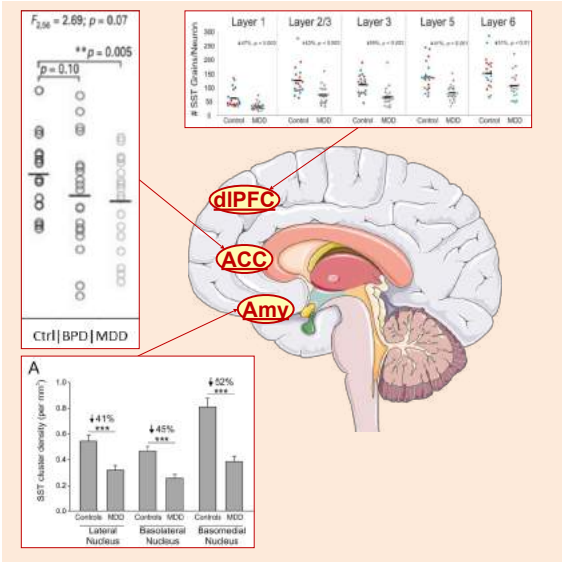
  - Sedative-, hypnotic-, and anxiolytic-dependent sleep disorder
- **Eating disorders**
  - Anorexia nervosa
  - Bulimia nervosa
  - Nocturnal eating/drinking syndrome
- **Attention deficit/hyperactivity disorders**

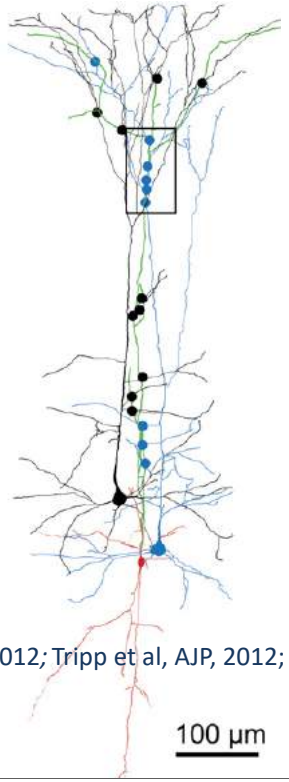

Sleep
Disrupted sleep latency and architecture, local sleep
Brain Energy Metabolism
Neuro-glial vascular, mitochondrial stress
Cognition and Behavior
Cognitive dysfunction, Behavioral disruptions
Brain Circuit Excitability
Dyshomeostasis
Altered excitatory/ inhibitory ratio
Immune Response
Microglial activation, synaptic pruning, inflammation, cell death
Brain Connectivity
Altered synaptic, functional, effective and structural

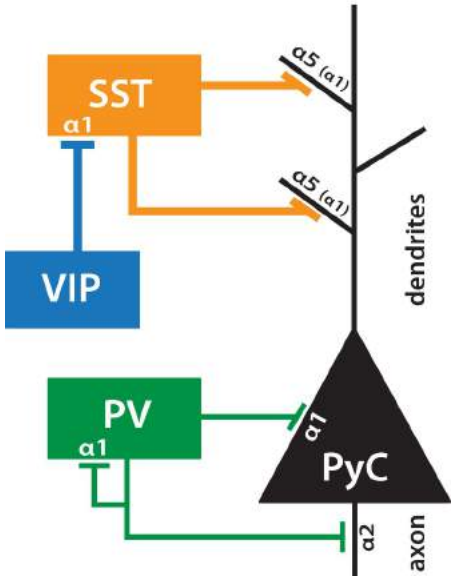
Effect of Changes in Excitability on Microcircuit Activity and Response to Stimuli



Cortical microcircuit: Somatostatin Positive Neurons in MDD







Sibille et al., IJNPP, 2008, Guilloux, Mol Psy, 2012; Tripp et al, AJP, 2012; Seney et al., *Neurobiol Dis*, 2015;

100 µm

Courtesy of Etienne Sibille

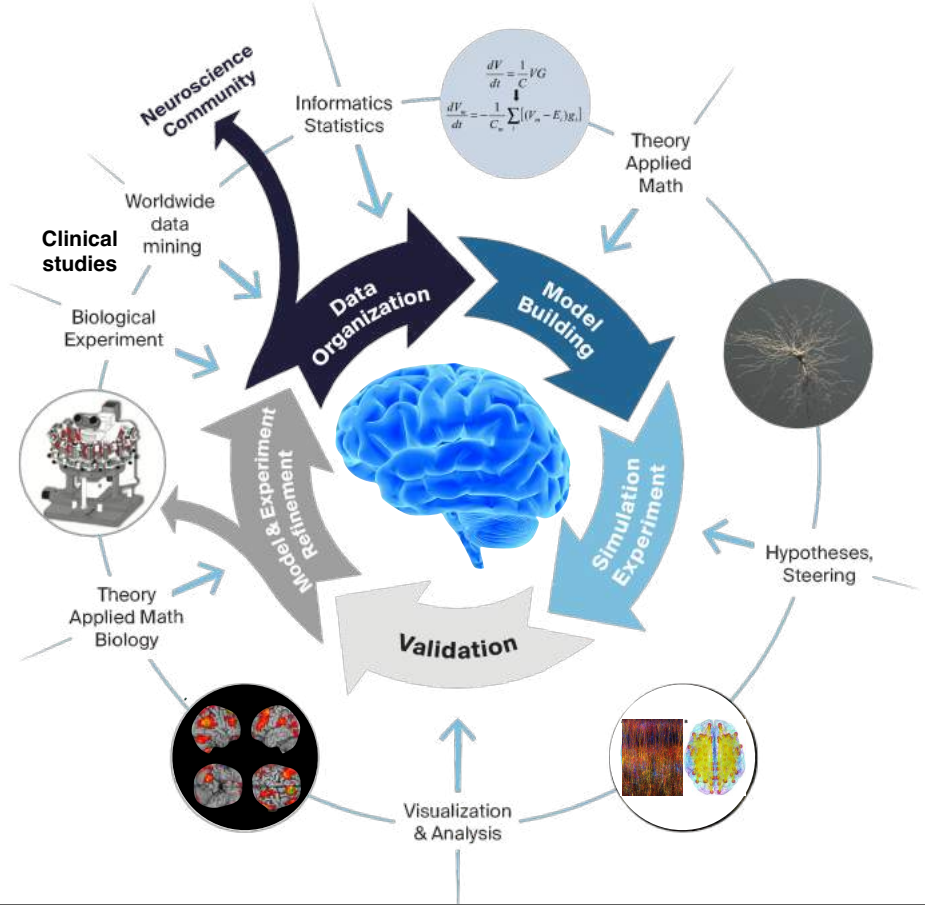
Reduced SST+ GABA neuron markers: a replicated pathology in depression and other brain disorders

Neurological disorder	Brain region	Pathological findings	References
Parkinson's disease	CSF	**Decreased**	Dupont et al, 1982
	Frontal cortex	**Decreased** (radioimmune-reactivity)	Darensbourg & Bethel, 2012; Tang et al, 2012
	Temporal cortex	**Decreased** (immune-reactivity)	Darensbourg & Bethel, 2012
Alzheimer's disease	CSF	**Decreased**	Bissette et al, 1986; Tamminga et al, 1987
	Temporal cortex	**Decreased** (immune-reactivity)	Candy et al, 1985; Rossor et al, 1980
	Frontal cortex	**Decreased** (immune-reactivity)	Candy et al, 1985; Davies & Terry, 1981
	Hippocampus	**Decreased** (gene expression per cell)	Dournaud et al, 1994
	Parahippocampal cortex	**Decreased** (neuronal density)	Klein & Al-Nawas, 2011
Major depression	CSF	**Decreased**	Agren et al, 1984; Johnstone et al, 2012; Kling et al, 1993; Molchan et al, 1993
	Dorsolateral prefrontal cortex	**Decreased** (RNA expression)	Sibille et al, 2011
	Subgenual anterior cingulate cortex	**Decreased** (RNA expression)	Tripp et al, 2011; Tripp et al, 2012
	Amygdala	**Decreased** (RNA and protein expression)	Guilloux et al, 2012
Schizophrenia	CSF	**Decreased**	Bissette et al, 1986; Reinikainen et al, 1990
	Dorsolateral prefrontal cortex	**Decreased** (RNA expression)	Guillozet-Bongaarts et al, 2013; Morris et al, 2008
	Hippocampus	**Decreased** (neuron number and density)	Konradi et al, 2011a
	Caudal entorhinal cortex	**Decreased** (neuron number and density)	Wang et al, 2011
	Parasubiculum	**Decreased** (neuron number and density)	Wang et al, 2011
Bipolar disorder	Caudal entorhinal cortex	**Decreased** (neuron density)	Wang et al, 2011
	Parasubiculum	**Decreased** (neuron density)	Wang et al, 2011
	Hippocampus	**Decreased** (neuron number and RNA expression)	Konradi et al, 2011b
	Dorsolateral prefrontal cortex	**Decreased** (RNA expression / trend level)	Sibille et al, 2011

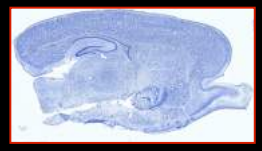
Table adapted from Lin & Sibille, *Frontiers in Pharmacology*, 2013.
Discussed in Northoff & Sibille, *Mol Psychiatry*, 2015; Sibille, *Biol Psychiatry,* 2017; Fee, Banasr & Sibille, *Biol Psychiatry,* 2017.

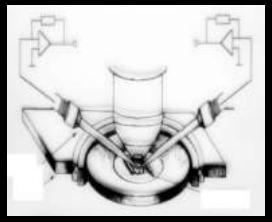
Courtesy of Etienne Sibille

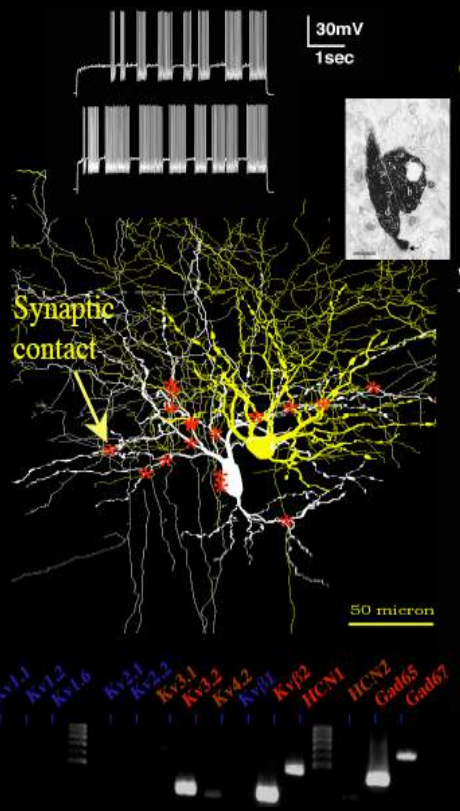
Integrative multiscale modeling



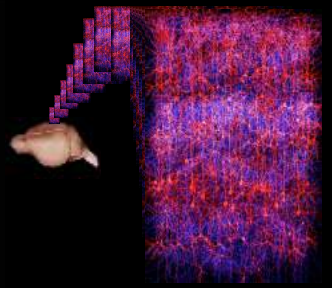
Integrating multiscale data: Neocortical microcircuitry





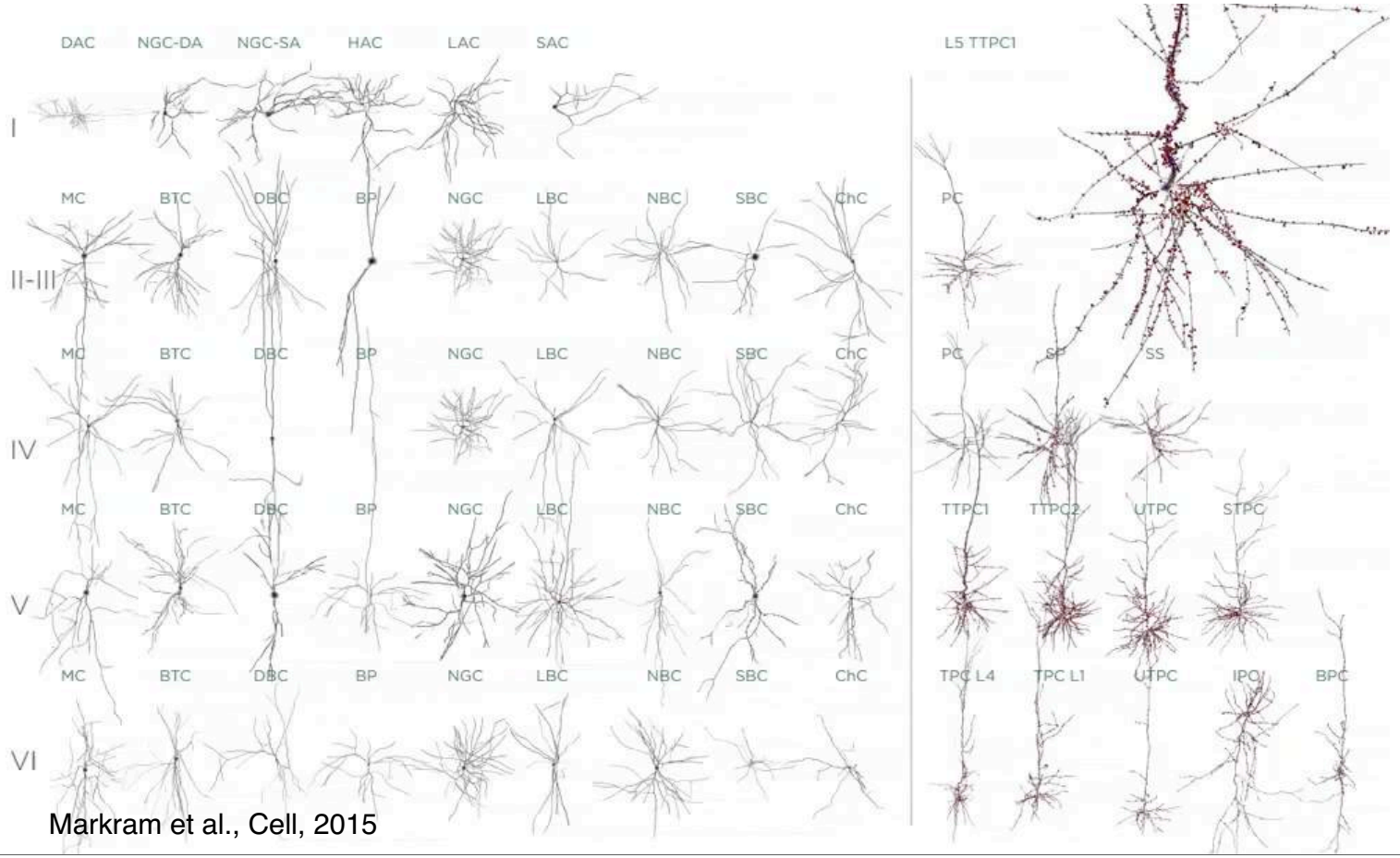


S1L1 Neocortical
Microcircuit
30'000 neurons



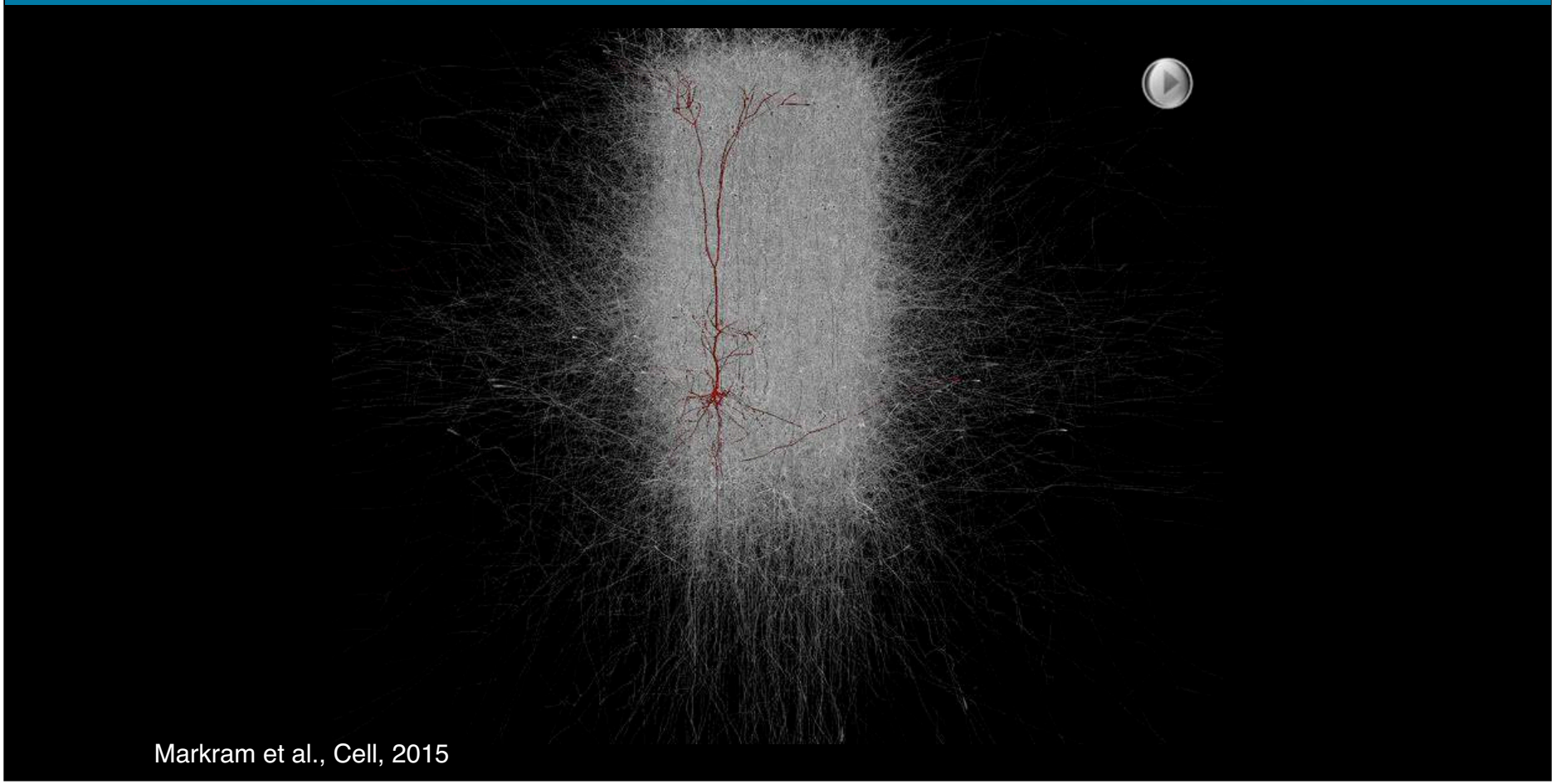
- Gene profiles
- Protein profiles
- Electrical profiles
- Morphology profiles
- Synaptic profiles
- Connectivity profiles
- Circuit profiles

Diversity of neurons in the cerebral cortex



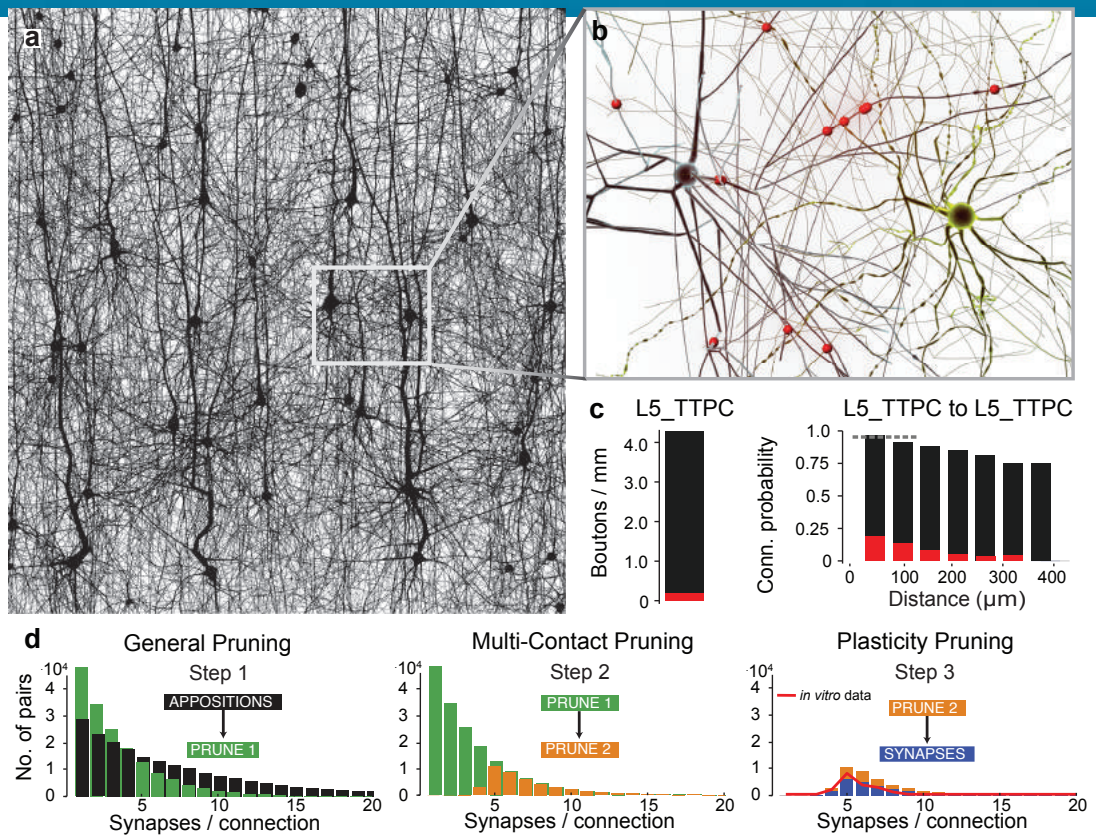
Markram et al., Cell, 2015

Building a digital reconstruction of a microcircuit



Markram et al., Cell, 2015

Establishing Realistic Synaptic Connectivity



Kozloski et al. IBM Research Journal, 2008
Hill et al., PNAS 2012

Markram et al., Cell, 2015

Reimann et al., 2015

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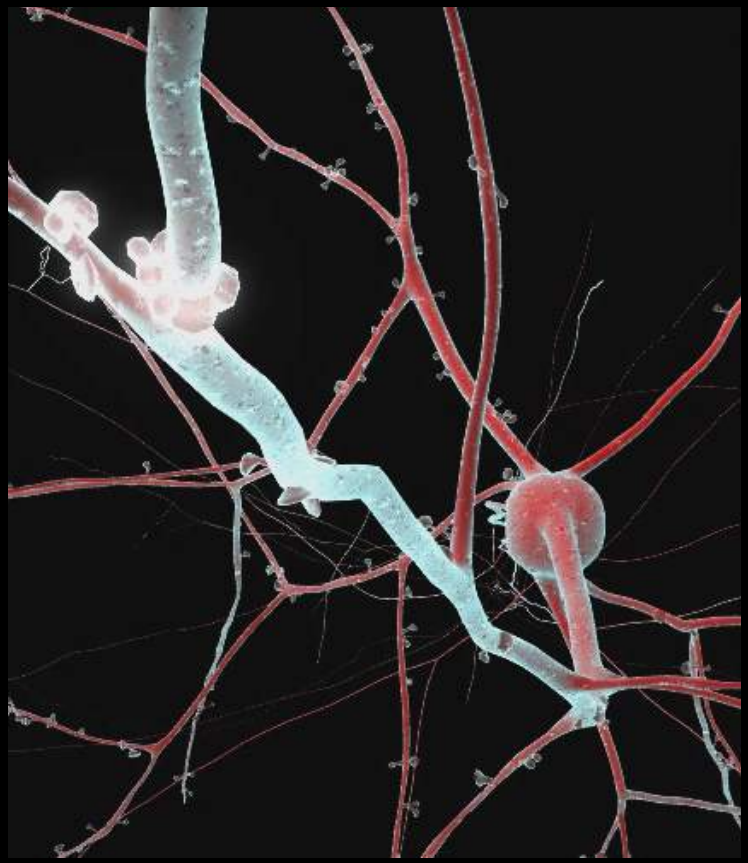
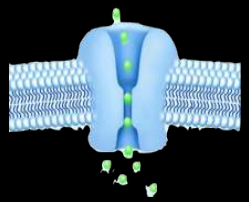
Simulating Electrical Behavior of Neurons



ION CHANNELS



$$\begin{aligned}
\frac{d\mathrm{m}}{dt} &= \alpha_{\mathrm{m}}(V_m)(1-\mathrm{m}) - \beta_{\mathrm{m}}(V_m)\mathrm{m} \\
\frac{d\mathrm{h}}{dt} &= \alpha_{\mathrm{h}}(V_m)(1-\mathrm{h}) - \beta_{\mathrm{h}}(V_m)\mathrm{h} \\
I_{channel} &= \mathrm{m}^n \mathrm{h} g_{channel}(V_m - E_{channel})
\end{aligned}$$

Hodgkin-Huxley Equations

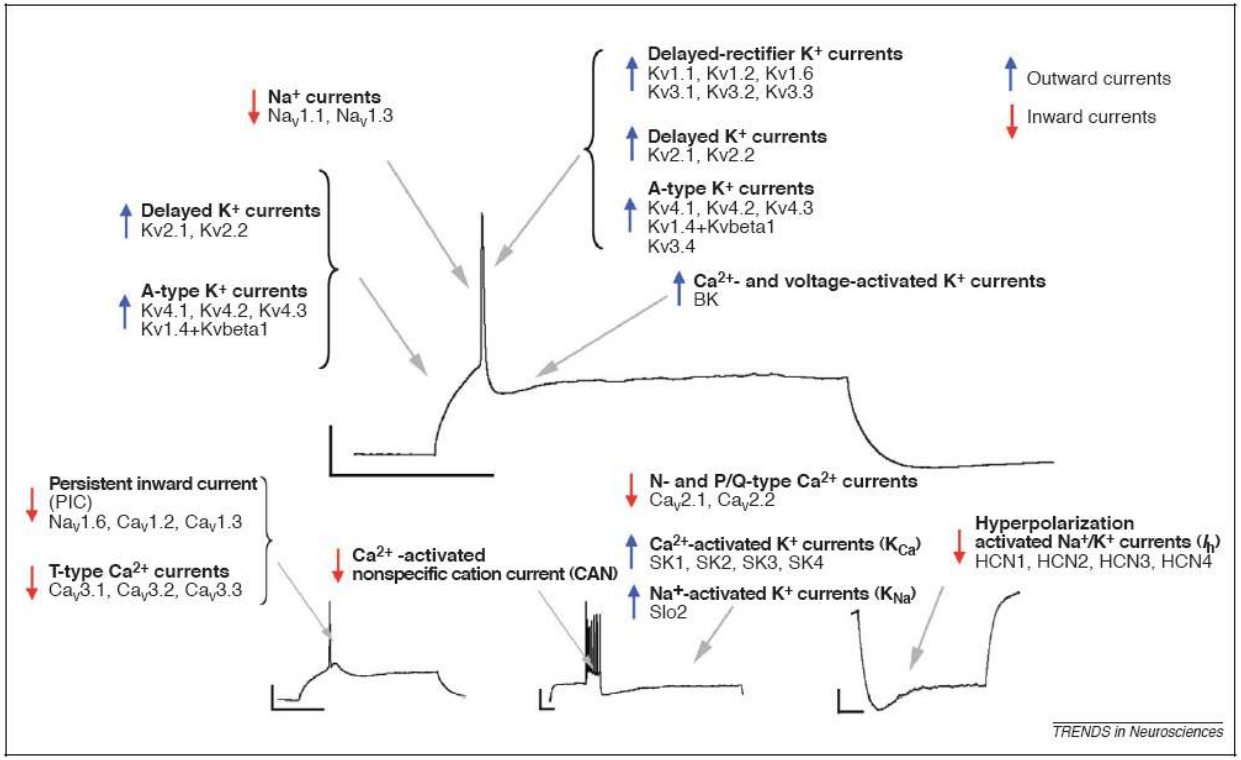
NEURONS

$$\frac{C_m dV_m}{dt} = \frac{E_m - V_m}{R_m} + I_{channels} \cdots + I_{synapses} \cdots$$
$$+ \frac{2(V_{m_{i+1}} - V_{m_i})}{R_{a_{i+1}} + R_a} + \frac{2(V_{m_{i-1}} - V_{m_i})}{R_{a_{i-1}} + R_a}$$

Rall Equations

Electrical Diversity by Combining Ion Channels

About 350 ion channel genes expressed in the brain, about 200 voltage-activated



Toledo-Rodriguez, M. Cellular signalling properties in microcircuits (2005) Trends in Neurosciences

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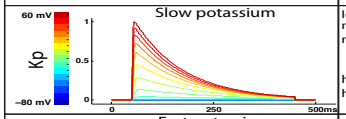
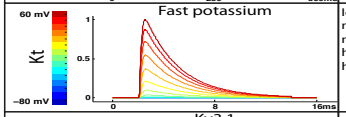
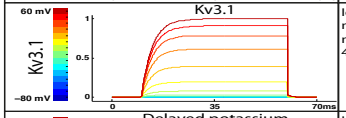
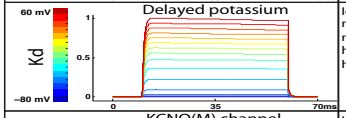
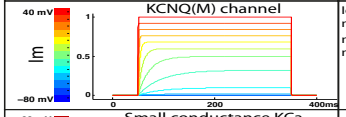
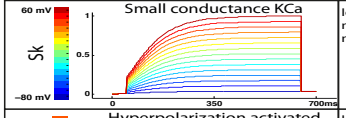
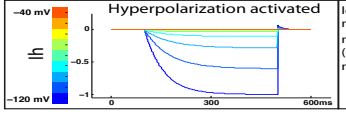
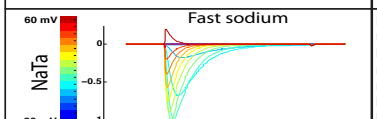
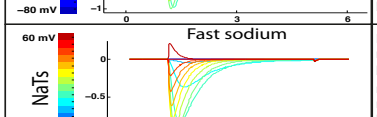
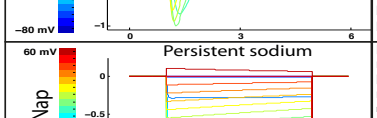
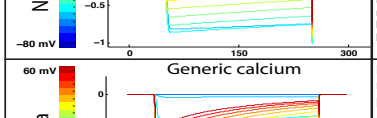
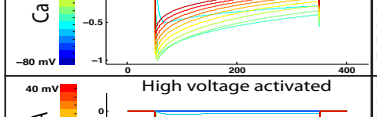
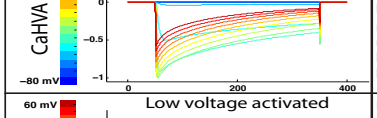
Ion channel models

Ion channels	Parameters
	Ion = K^+ Rev = -85mV g=m^3h m_∞=(1/(1 + exp(-(v+1)/12))) m_τ=if (v < -50) : (1.25+175.03*exp(-v * -0.026))/qt else : ((1.25+13*exp(-v*0.026)))/qt h_∞=1/(1 + exp(-(v+54)/-11)) h_τ = (360+(1010+24*(v+55))* exp(-((v+75)/48)^2)))/qt
	Ion = K^+ Rev = -85mV g=m^4h m_∞=1/(1 + exp(-(v+0)/19)) m_τ =(0.34+0.92*exp(-((v+71)/59)^2))/qt h_∞ =1/(1 + exp(-(v+66)/-10)) h_τ =(8+49*exp(-((v+73)/23)^2))/qt
	Ion = K^+ Rev = -85mV g=m m_∞= 1/(1+exp(((v -(18.700))/(-9.700)))) m_τ = 0.2*20.00/(1+exp(((v -(-46.560))/(-44.140))))
	Ion = K^+ Rev = -85mV g=mh m_∞= 1-1/(1+exp((v- -43)/8)) m_τ = 0.6 h_∞ = 1/(1+exp((v- -67)/7.3)) h_τ = 1500
	Ion = K^+ Rev = -85mV g=m m_∞=m_α/(m_α+m_β) m_τ=1.0/(m_α+m_β) m_α=3.3e-3*exp(2.5*0.04*(v - -35)) m_β=3.3e-3*exp(-2.5*0.04*(v - -35))
	Ion = K^+ Rev = -85mV g=m m_∞= 1.0/(1.0 + (0.00043 / ca)^4.8) m_τ = 1.0
	Ion = K^+ Rev = -85mV g=m m_∞=m_α/(m_α+m_β) m_τ=1.0/(m_α+m_β) m_α= 0.001*6.43*(v+154.9)/ (exp((v+154.9)/11.9)-1) m_β=0.001*193*exp(v/33.1)

Ion channels	Parameters
	Ion = K^+ Rev = -85mV g=m^3h m_∞=m_α/(m_α+m_β) m_τ=1.0/(m_α+m_β) h_∞ =h_α/(h_α+h_β) h_τ =1.0/(h_α+h_β) m_α=(0.182 * (v- -38))/(1-(exp(-(v- -38)/6))) m_β=(0.124 * (-v -38))/(1-(exp(-(-v -38)/6))) h_α =(-0.015 * (v- -66))/(1-(exp((v- -66)/6))) h_β =(-0.015 * (-v -66))/(1-(exp((-v -66)/6)))
	Ion = K^+ Rev = -85mV g=m^3h m_∞=m_α/(m_α+m_β) m_τ=1.0/(m_α+m_β) h_∞ =h_α/(h_α+h_β) h_τ =1.0/(h_α+h_β) m_α=(0.182 * (v- -32))/(1-(exp(-(v- -32)/6))) m_β=(0.124 * (-v -32))/(1-(exp(-(-v -32)/6))) h_α =(-0.015 * (v- -60))/(1-(exp((v- -60)/6))) h_β =(-0.015 * (-v -60))/(1-(exp((-v -60)/6)))
	Ion = K^+ Rev = -85mV g=m^3h m_∞=1.0/(1+exp((v- -52.6)/-4.6)) h_∞ =1.0/(1+exp((v- -48.8)/10)) m_τ =6.0/(m_α+m_β) h_τ =1.0/(h_α+h_β) m_α=(0.182 * (v- -38))/(1-(exp(-(v- -38)/6))) m_β=(0.124 * (-v -38))/(1-(exp(-(-v -38)/6))) h_α =-2.88e-6 * (v + 17) / (1 - exp((v + 17)/4.63)) h_β =6.94e-6 * (v + 64.4) / (1 - exp(-(v + 64.4)/2.63))
	Ion = K^+ Rev = -85mV g=m^2h m_∞=m_α/(m_α+m_β) m_τ=1.0/(m_α+m_β) h_∞ =h_α/(h_α+h_β) h_τ =1.0/(h_α+h_β) m_α=(0.055*(-27-v))/(exp((-27-v)/3.8) - 1) m_β=(0.94*exp((-75-v)/17)) h_α =(0.000457*exp((-13-v)/50)) h_β =(0.0065/(exp((-v-15)/28)+1))
	Ion = K^+ Rev = -85mV g=m^2h m_∞=m_α/(m_α+m_β) m_τ=1.0/(m_α+m_β) h_∞ =h_α/(h_α+h_β) h_τ =1.0/(h_α+h_β) m_α=(0.055*(-27-v))/(exp((-27-v)/3.8) - 1) m_β=(0.94*exp((-75-v)/17)) h_α =(0.000457*exp((-13-v)/50)) h_β =(0.0065/(exp((-v-15)/28)+1))
	Ion = K^+ Rev = -85mV g=m^4h m_∞=1.0/(1+ exp((v - -30.0)/-6)) m_τ =(5.0 + 20.0/(1+exp((v - -25.0)/5)))/qt h_∞ =1.0/(1+ exp((v - -80.0)/6.4)) h_τ =(20.0 + 50.0/(1+exp((v - -40.0)/7)))/qt

www.channelpedia.net

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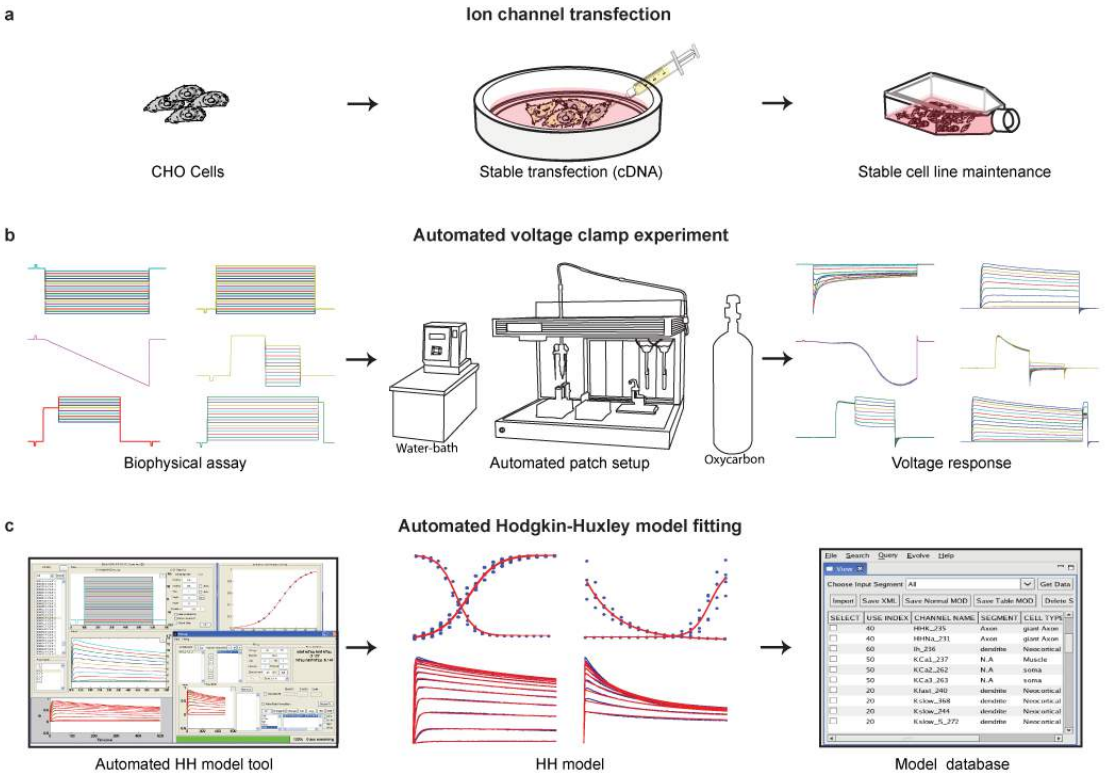
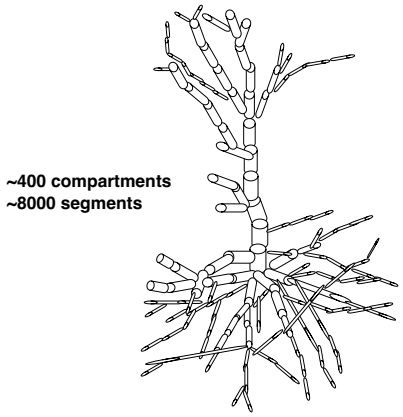
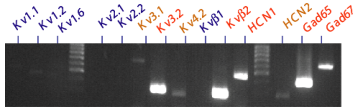
Channelpedia.epfl.ch: An integrative and interactive database for ion channels

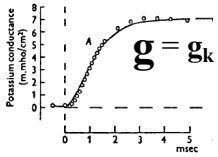


Data-driven neuronal modeling

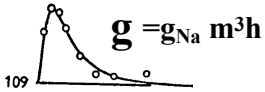




single cell rtPCR gene expression profile



Non Inactivating K Channel



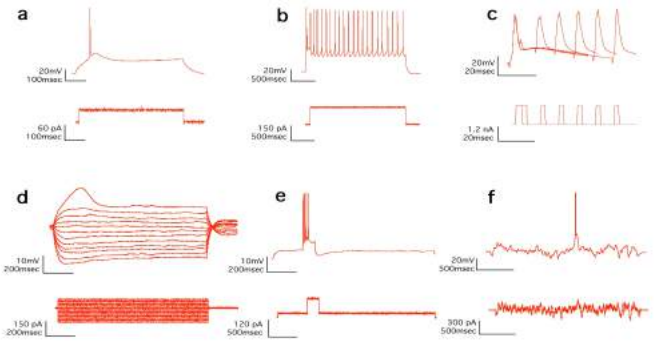
Inactivating Na Channel

Ion Channels

1. Na_p, Fast Na^+
2. Nat_t, Persistent Na^+
3. K_{fast}, Delayed Rectifier K^+
4. K_{slow}, Slow K^+
5. K_t, Transient K^+
6. LVA Ca^{2+}
7. HVA Ca^{2+}
8. I_h, H-Current
9. I_m, M-Current
10. BK, Large g, Ca^{2+} activated K^+
11. SK, Small g, Ca^{2+} activated K^+
12. Leak Current

Relative Density

- Data constrained
- Generic algorithm



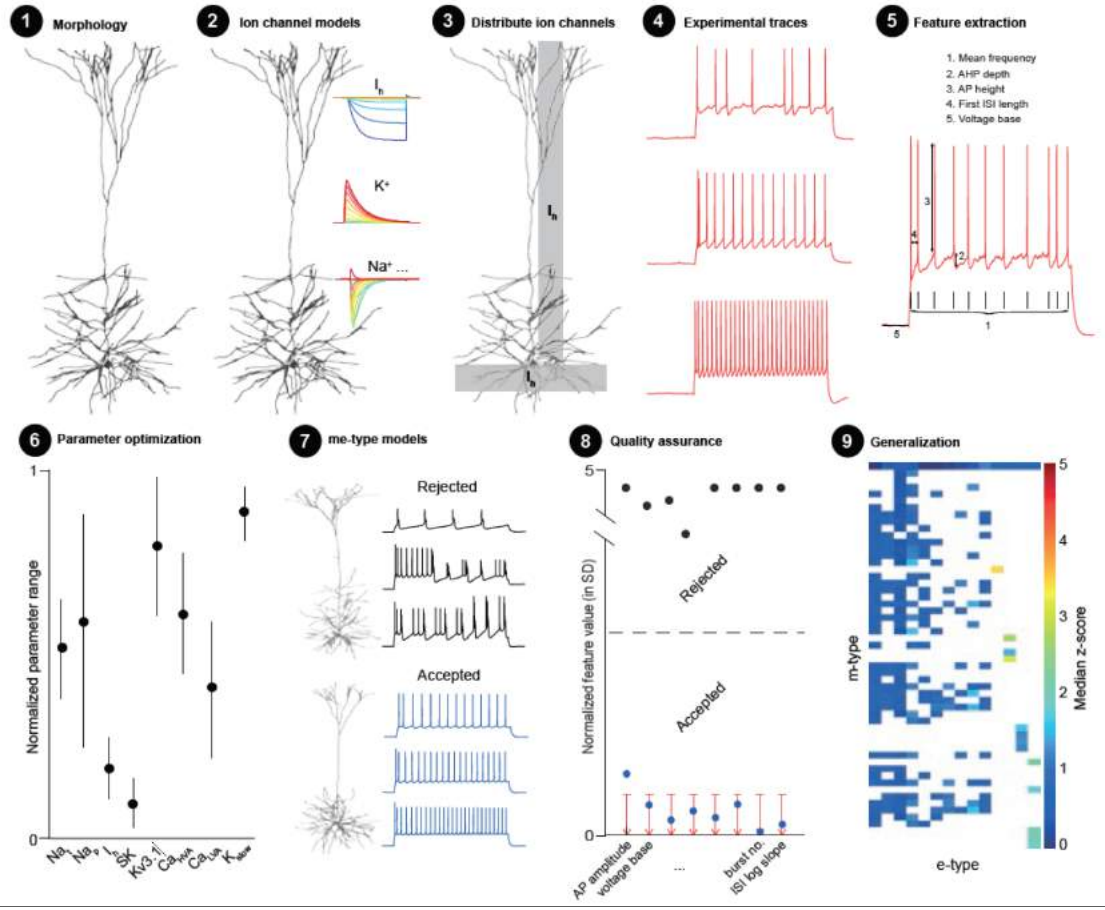
Composition

- Single cell RT-PCR
- ISH expression distribution
- literature

Distribution

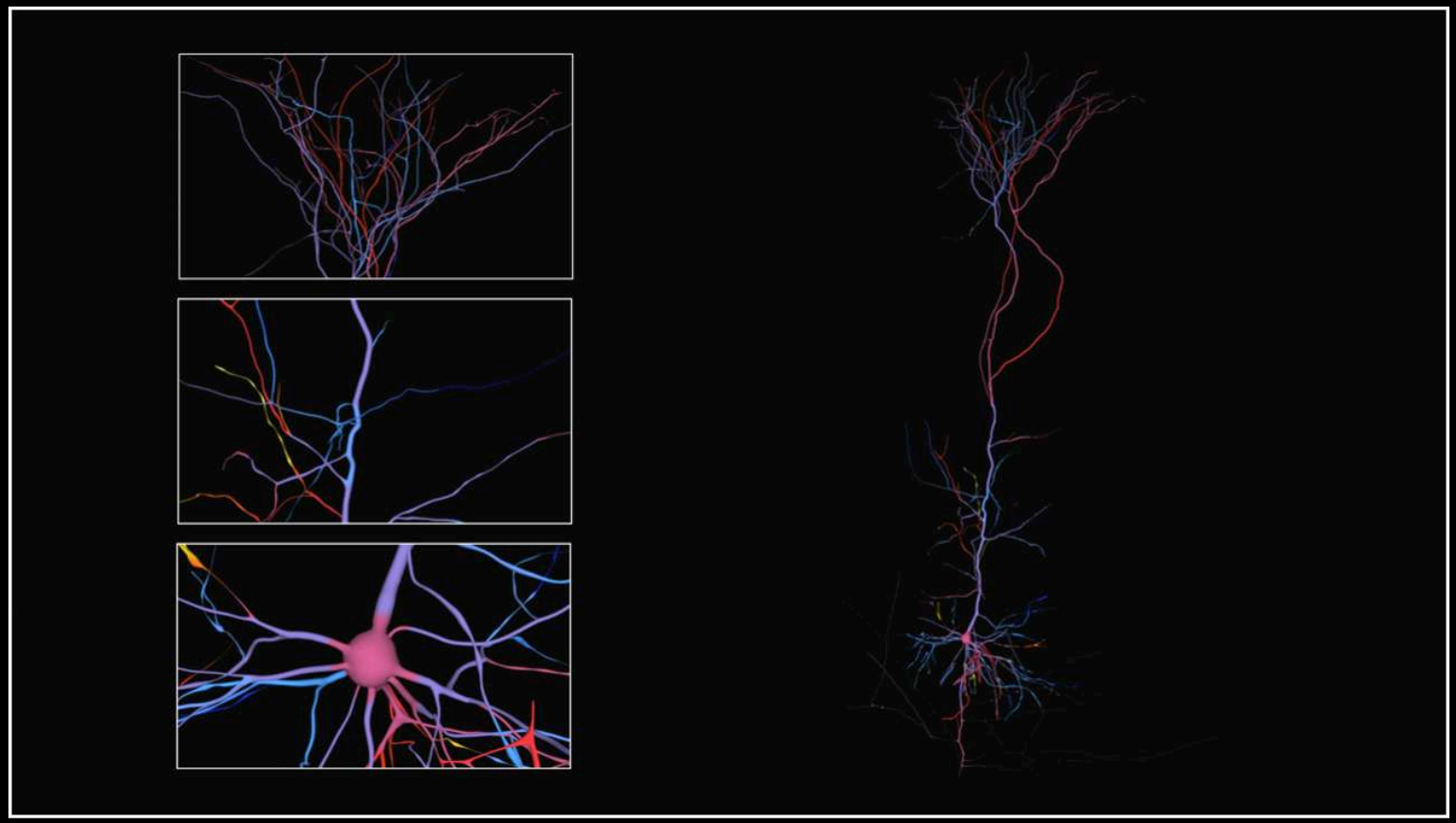
- Staining, Literature, Assumed
- Given Somatic Distance Function
- Fitted within given tolerance

Workflow to Automatically Model Electrical Behavior of Neurons



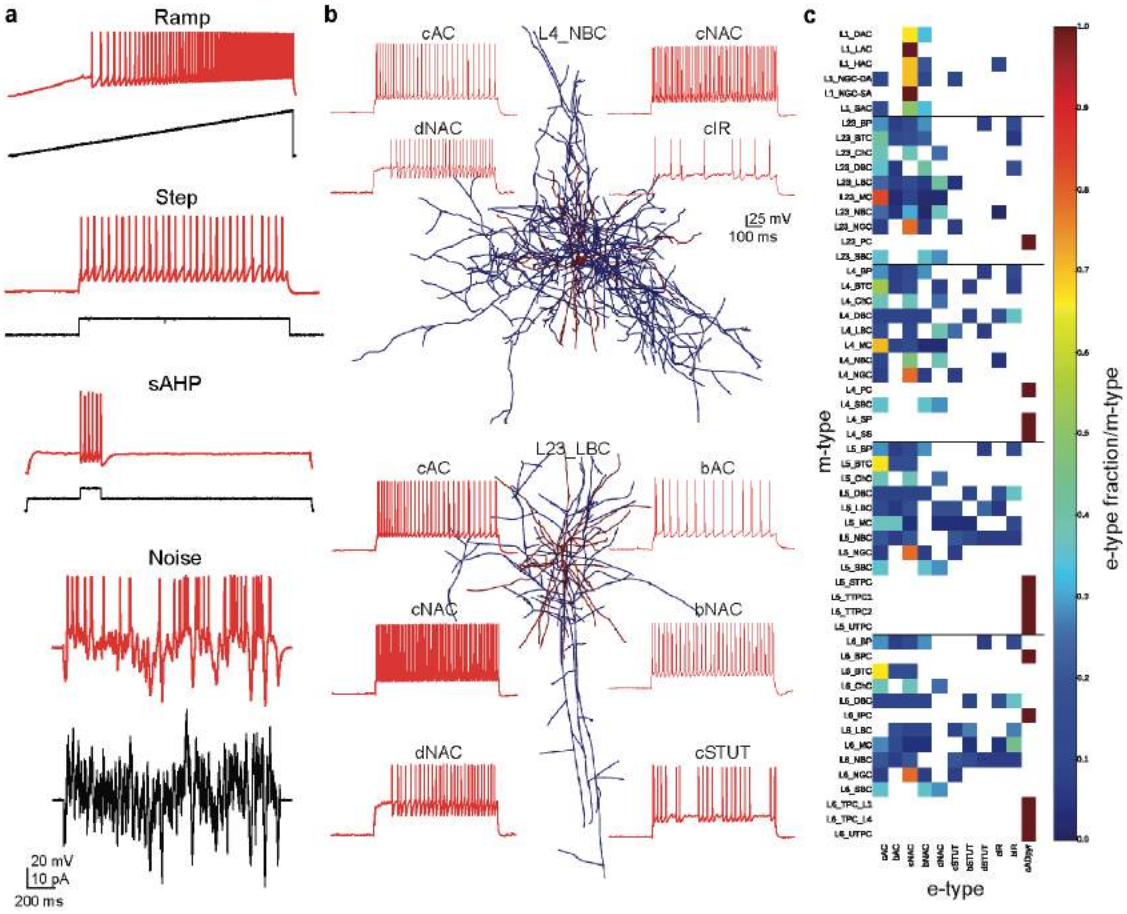
124’489 Model Neurons

Machine learning-built biophysical single cell models



Hay et al., PLOS Comp. Biology, 2012

Recreating 207 Morpho-Electric Types



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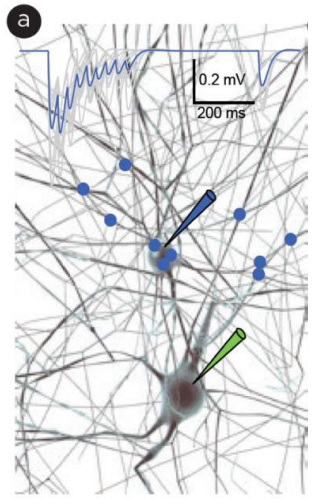
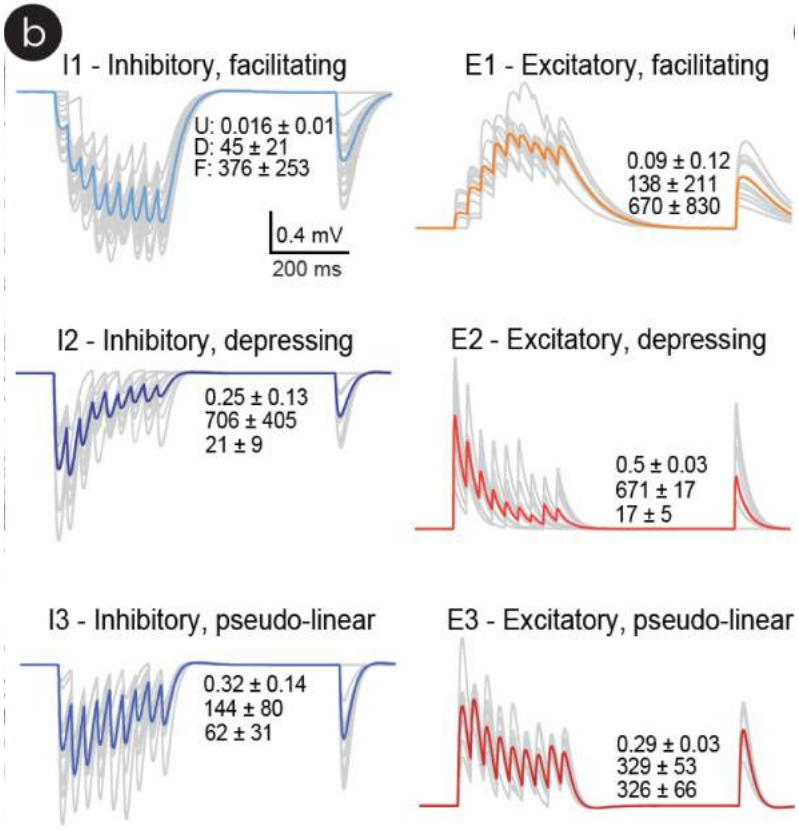
Short Term Synaptic Plasticity



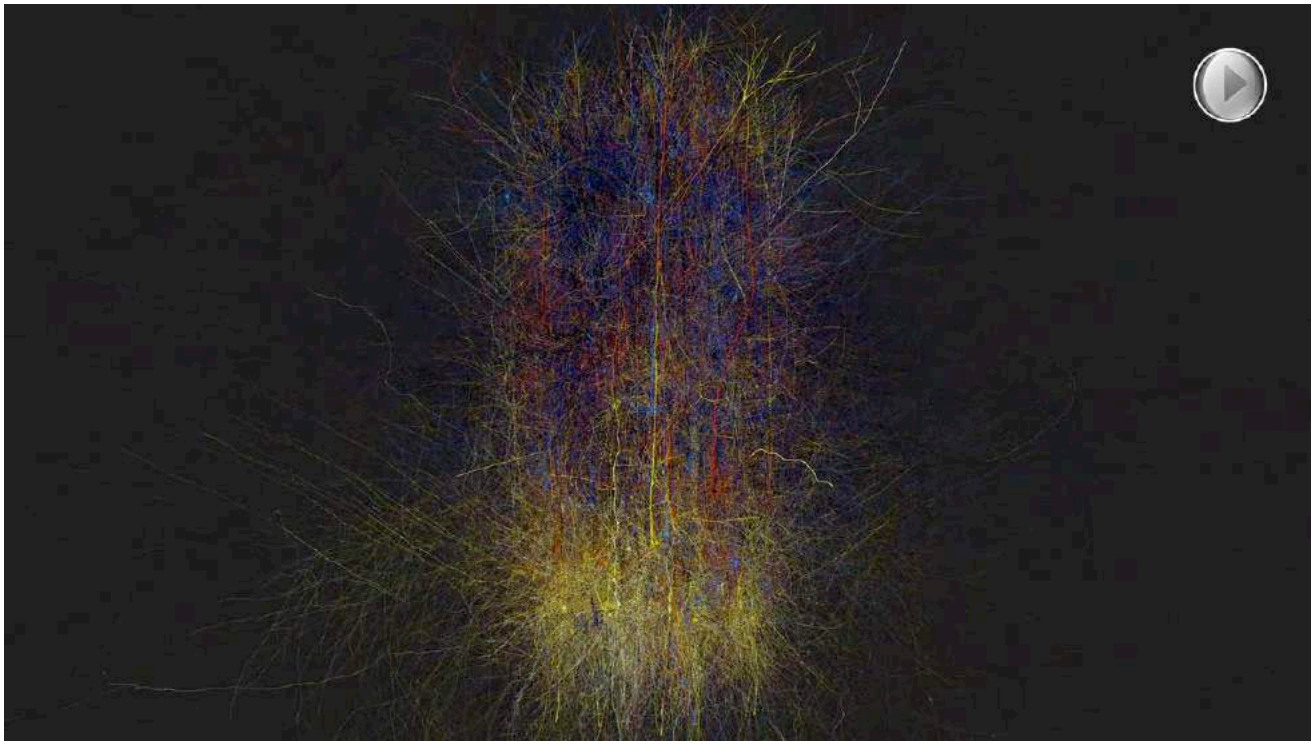
SYNAPSES: Tsodyks-Markram Equ

$$\begin{aligned}
\frac{dx}{dt} &= \frac{z}{\tau_{rec}} - ux\delta(t - t_{sp}) \\
\frac{dy}{dt} &= -\frac{y}{\tau_1} - ux\delta(t - t_{sp}) \\
\frac{dz}{dt} &= \frac{y}{\tau_1} - \frac{z}{\tau_{rec}} \\
\frac{du}{dt} &= \frac{u}{\tau_{\text{facil}}} + U(1 - u)\delta(t - t_{sp}) \\
I_{synapse}(i) &= \sum_j A_{ij} y_{ij}(t)
\end{aligned}$$



Wang et al., 2006

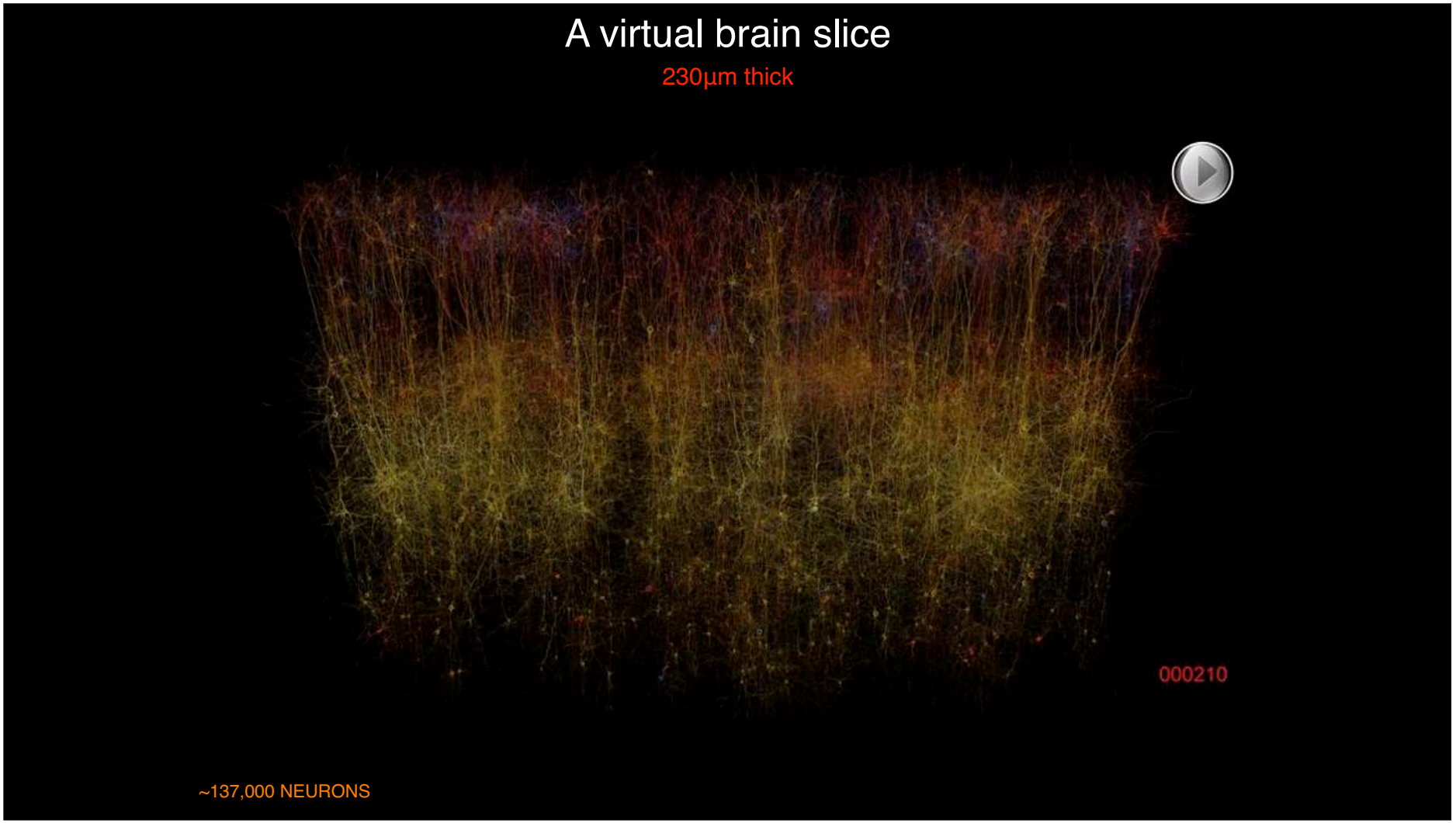
Cortical microcircuitry

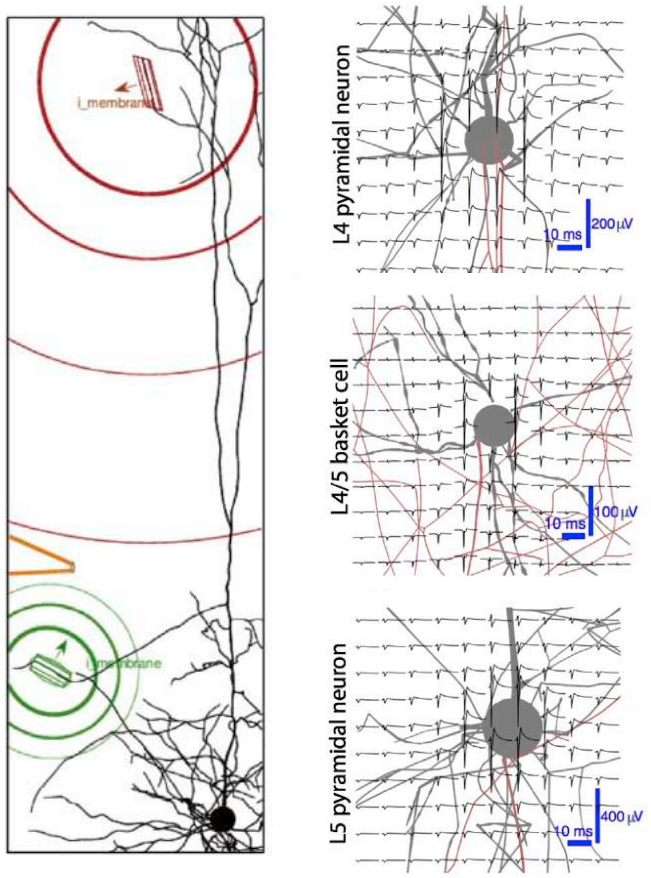


Markram et al., Cell, 2015

A virtual brain slice

230µm thick





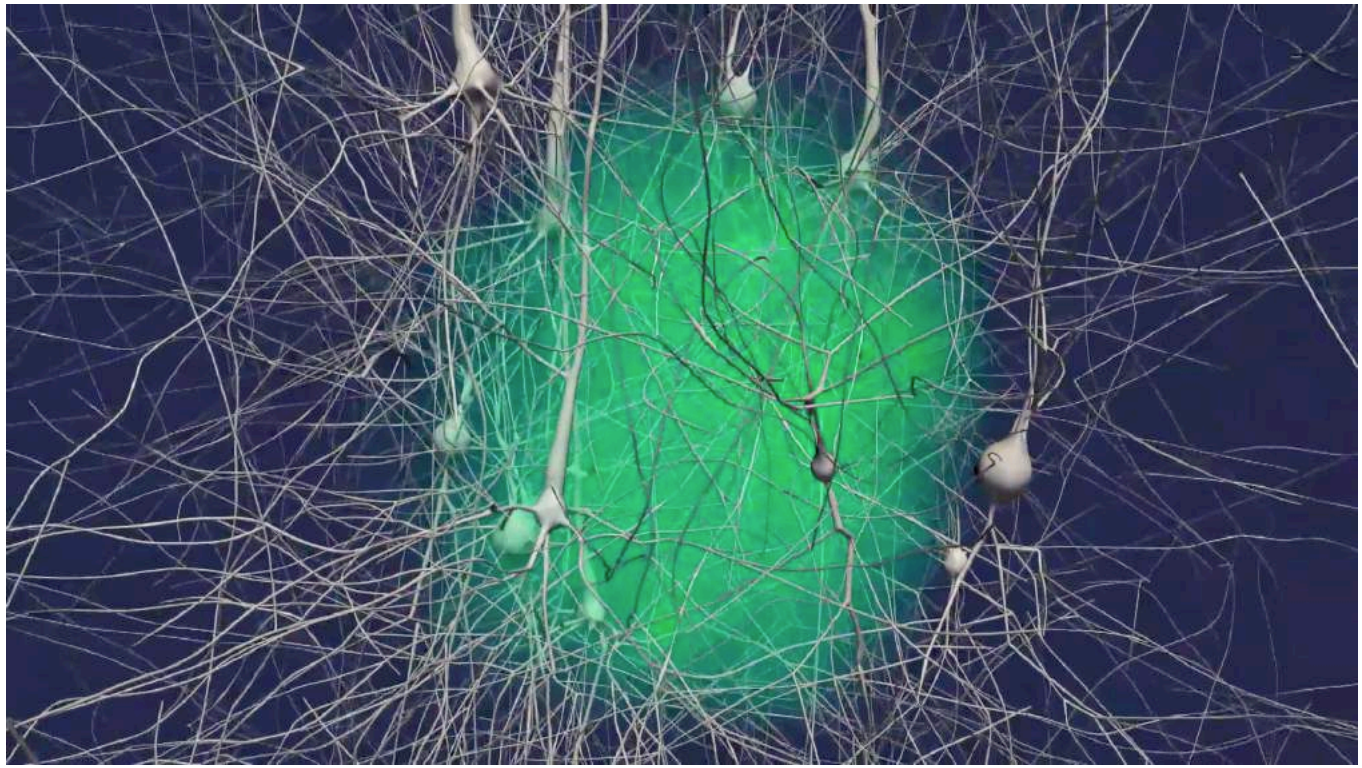
Line source approximation of the extracellular potential

$$V_e(\vec{r},t) = \sum_{j=1}^{N} \frac{\rho I_j(t)}{4\pi\Delta s_j} \log \frac{\sqrt{h_j^2 + r_j^2} - h_j}{\sqrt{l_j^2 + r_j^2} - l_j},$$

Holt and Koch, 1999

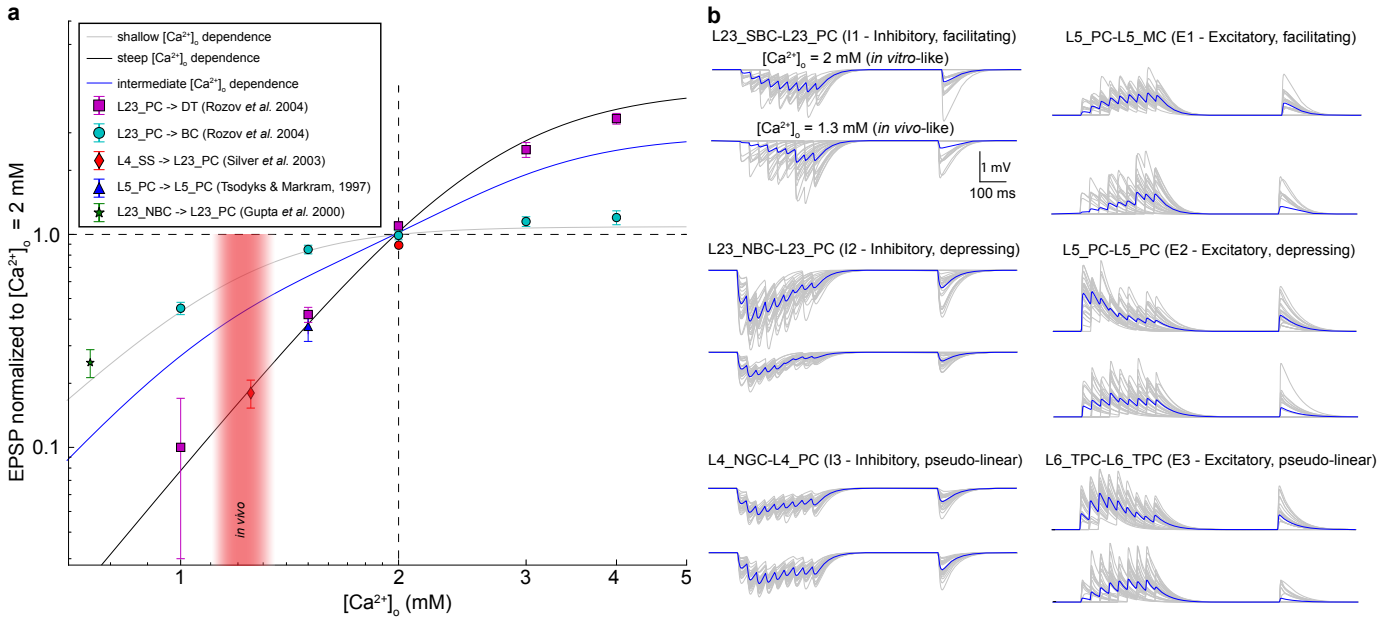
Reimann et al., Neuron, 2013 in collaboration with the Allen Institute, Seattle, WA

Bridging from the microcircuit to local field potential



Reimann et al., Neuron, 2013 in collaboration with the Allen Institute, Seattle, WA

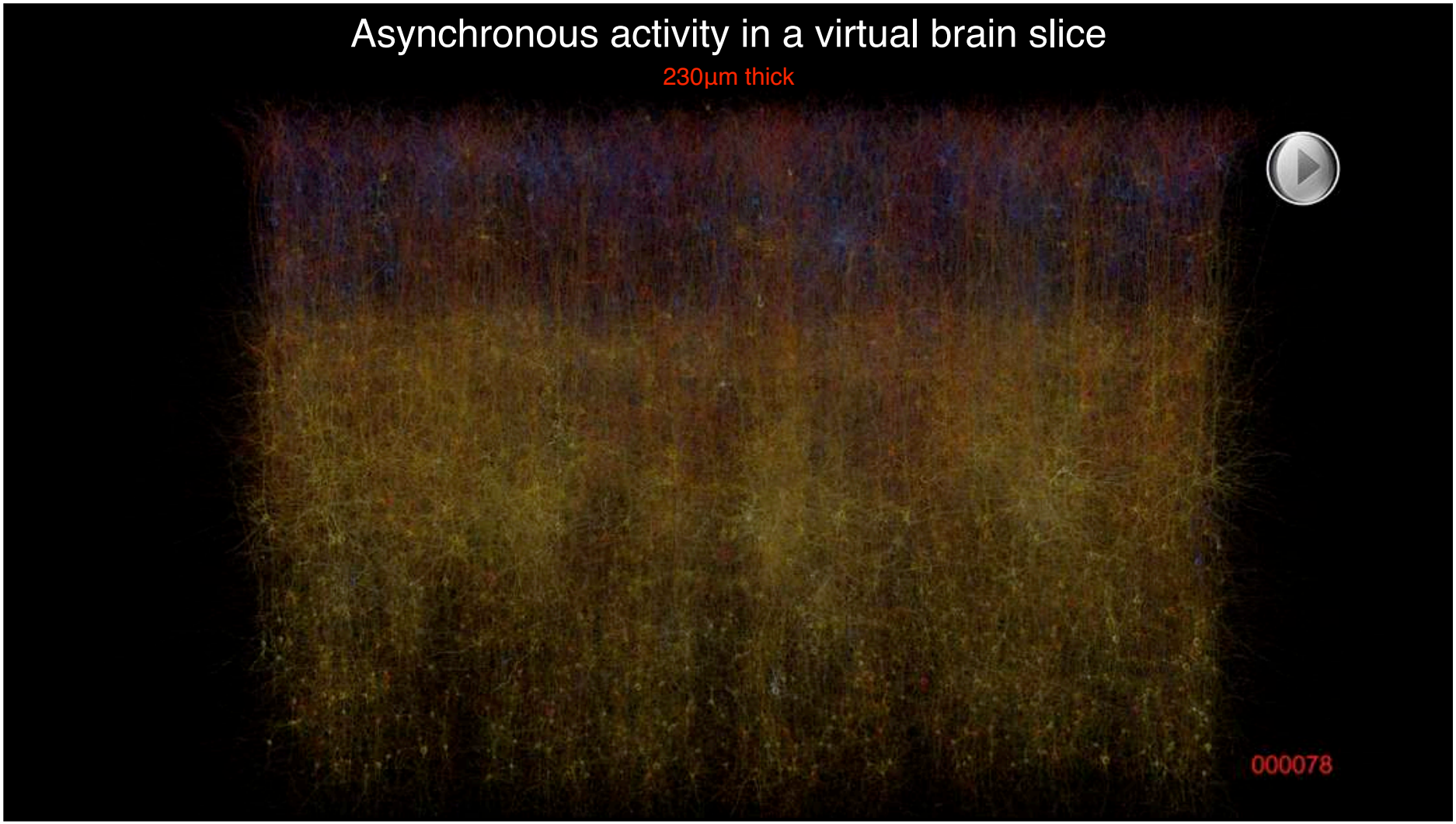
Extracellular calcium concentration affects Excitatory/Inhibitory balance



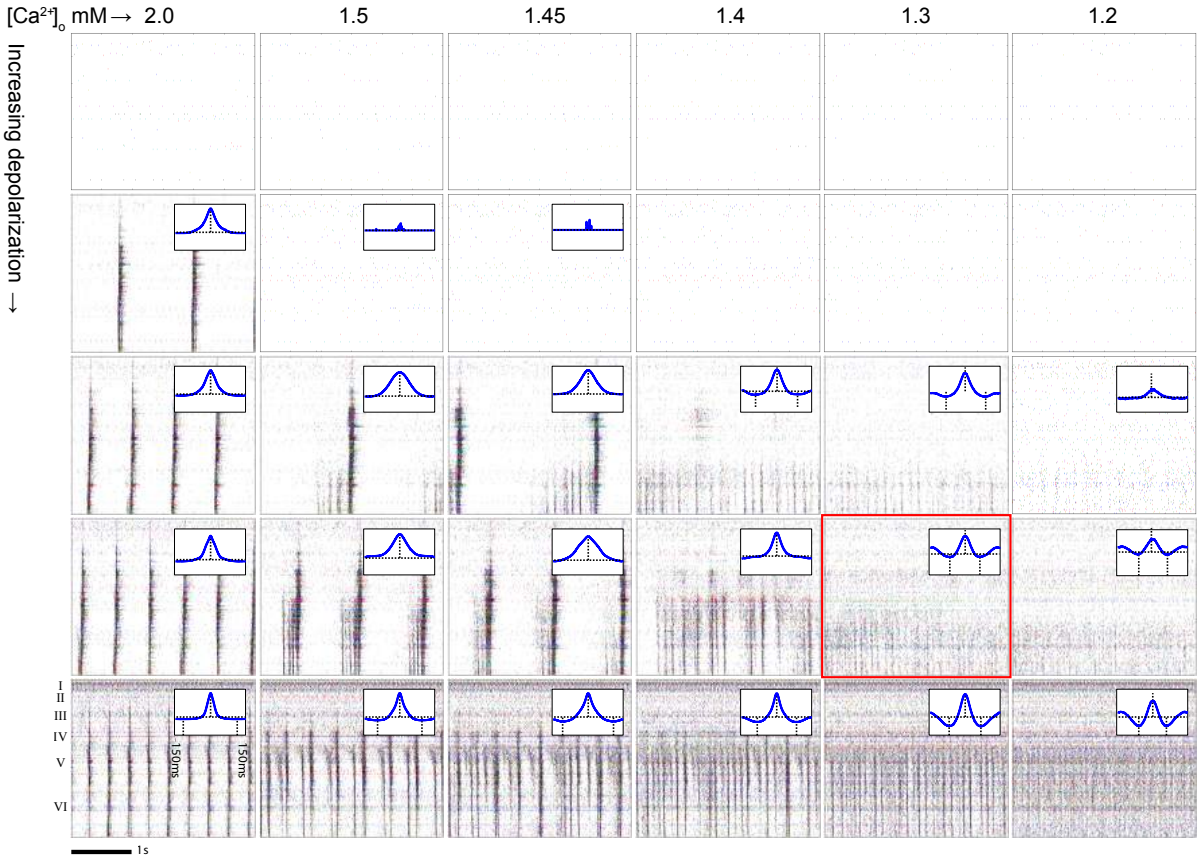
Markram et al., Cell, 2015

Asynchronous activity in a virtual brain slice

230µm thick



Changing calcium concentration creates a spectrum of cortical states



Markram et al., Cell, 2015

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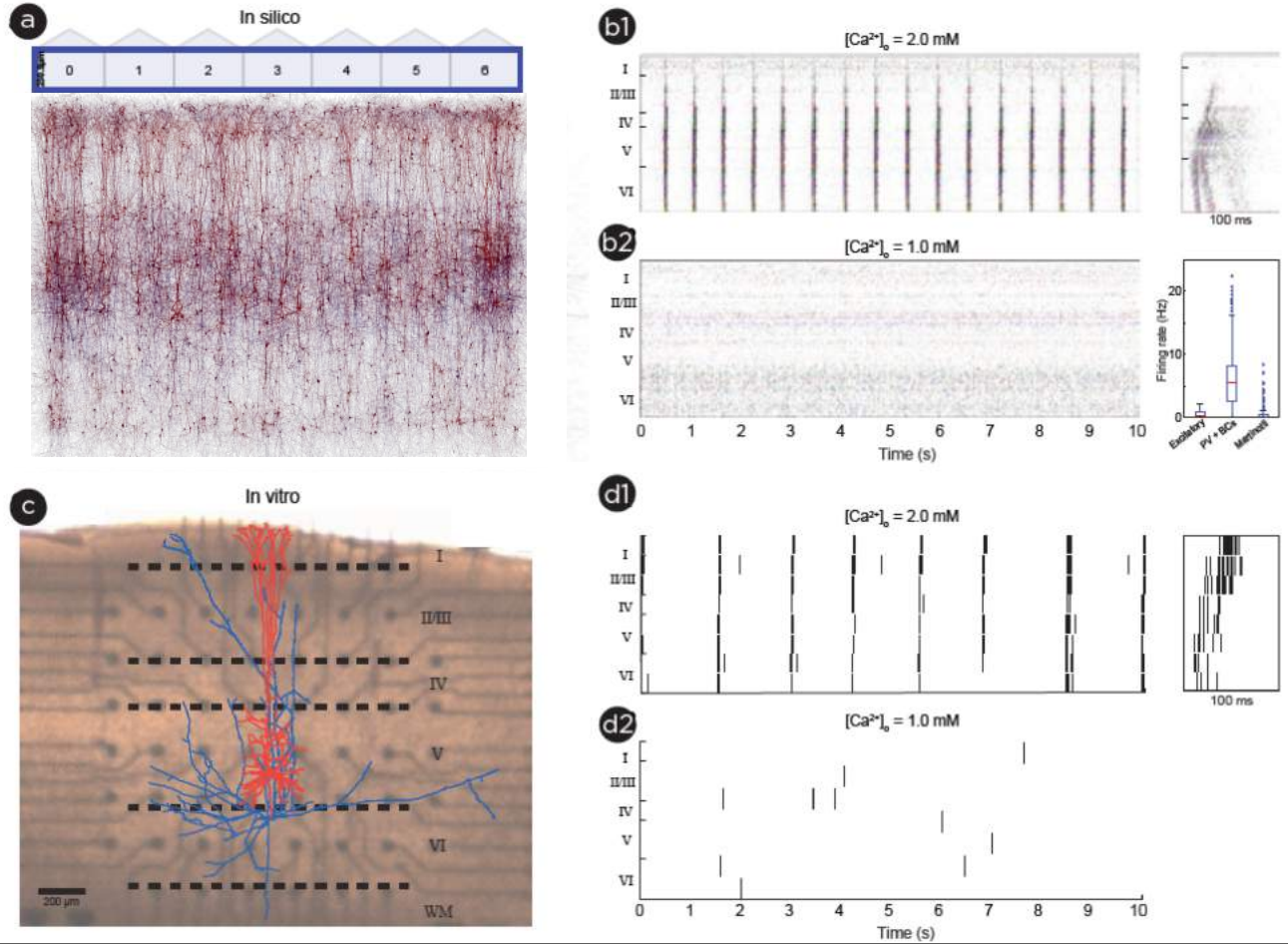
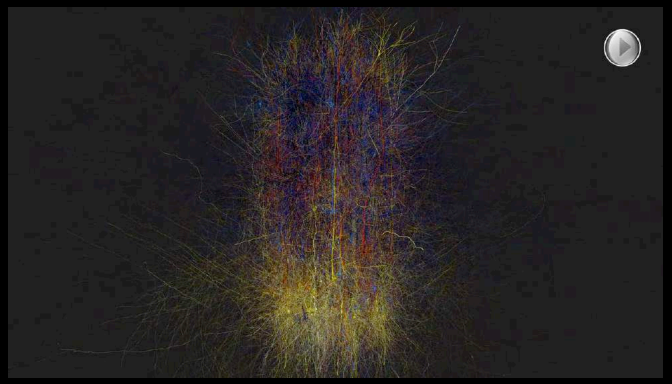
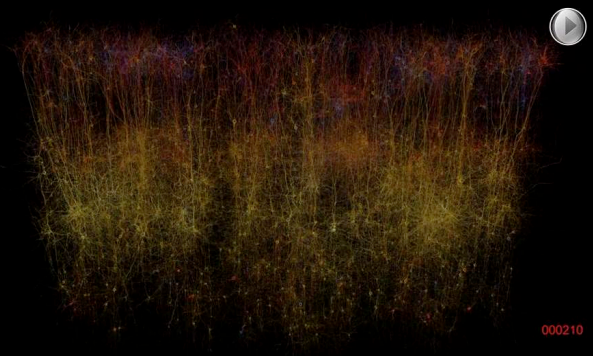
Experimental Validation

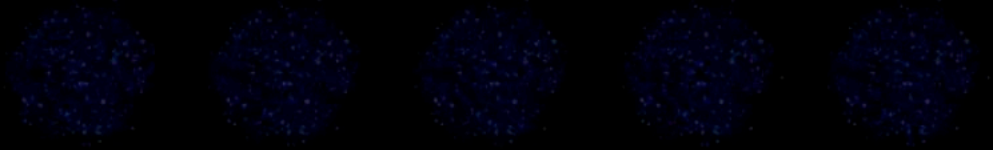


Increased Cortical Excitability Produces Sleep-like Responses

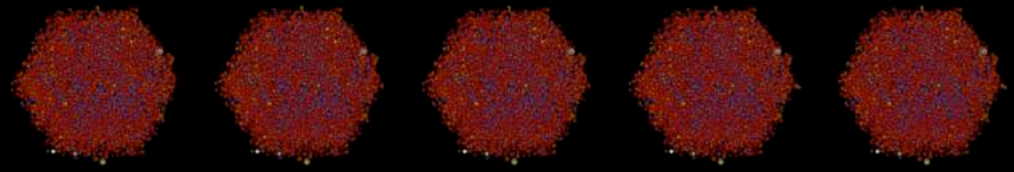




Hyper-excitable (sleep-like)



Normal excitability (awake)



Markram et al., Cell, 2015

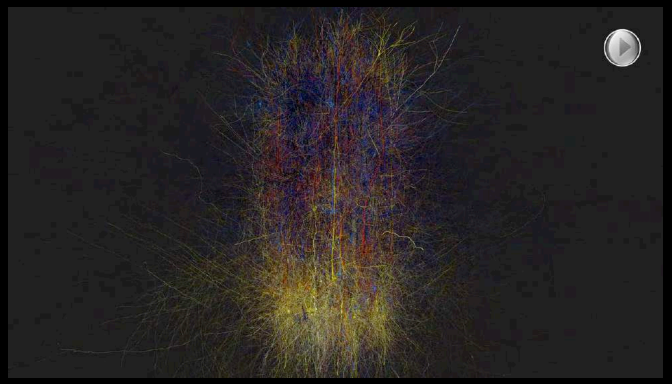
Digital Reconstruction Summary

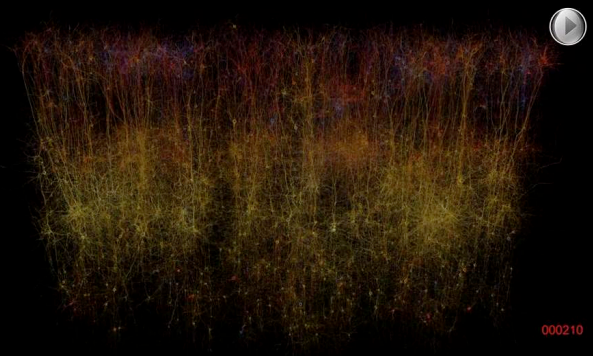
The digital reconstruction is built from laboratory data measurements and not tuned to produce specific network behaviors.

Yet it gives rise to a broad range of emergent phenomena observed in vitro and in vivo.

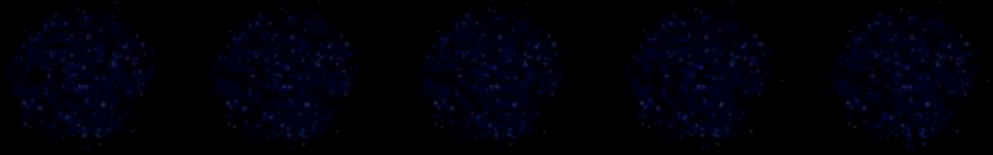
The whole is greater than the sum of the parts.

Increased Excitability or Decreased Inhibition
Decreases signal/noise ratio

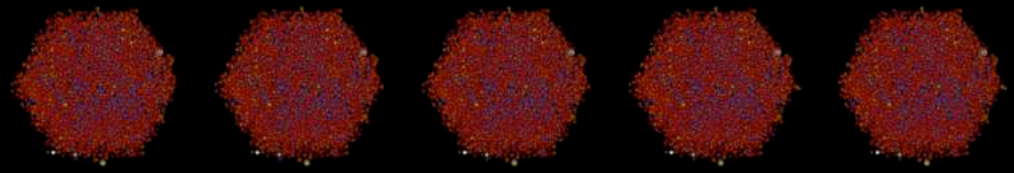




Hyper-excitable



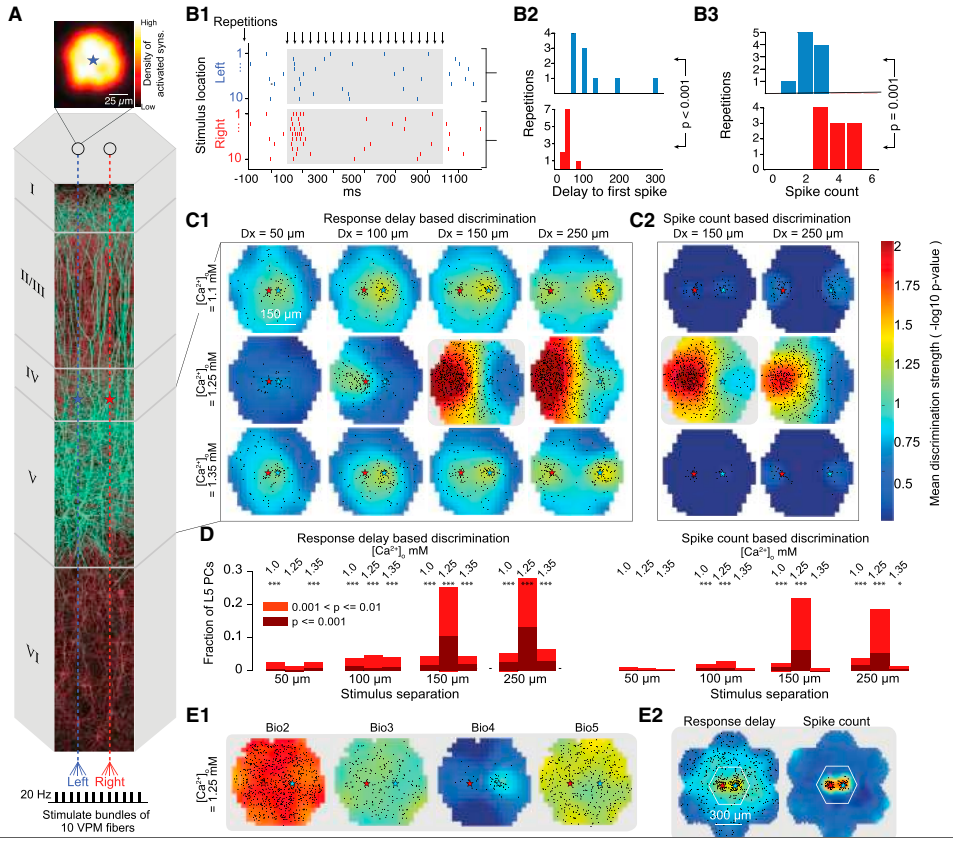
Normal excitability



2 4 8 16 32

# of stimulated VPM fibers

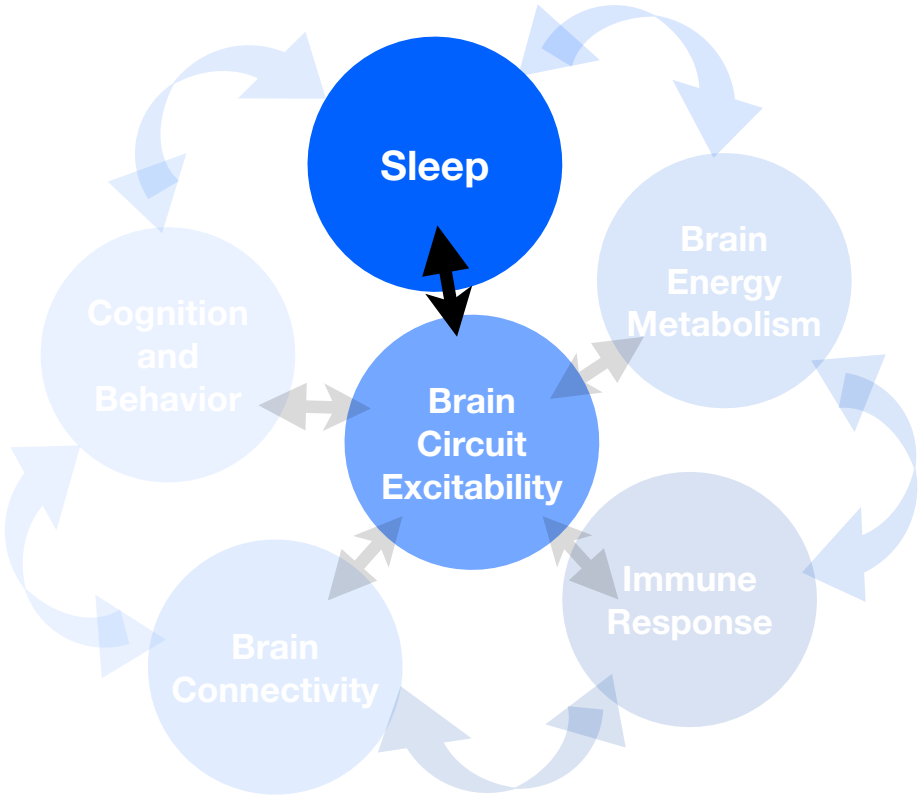
Changing Excitability Affects Stimulus Discrimination



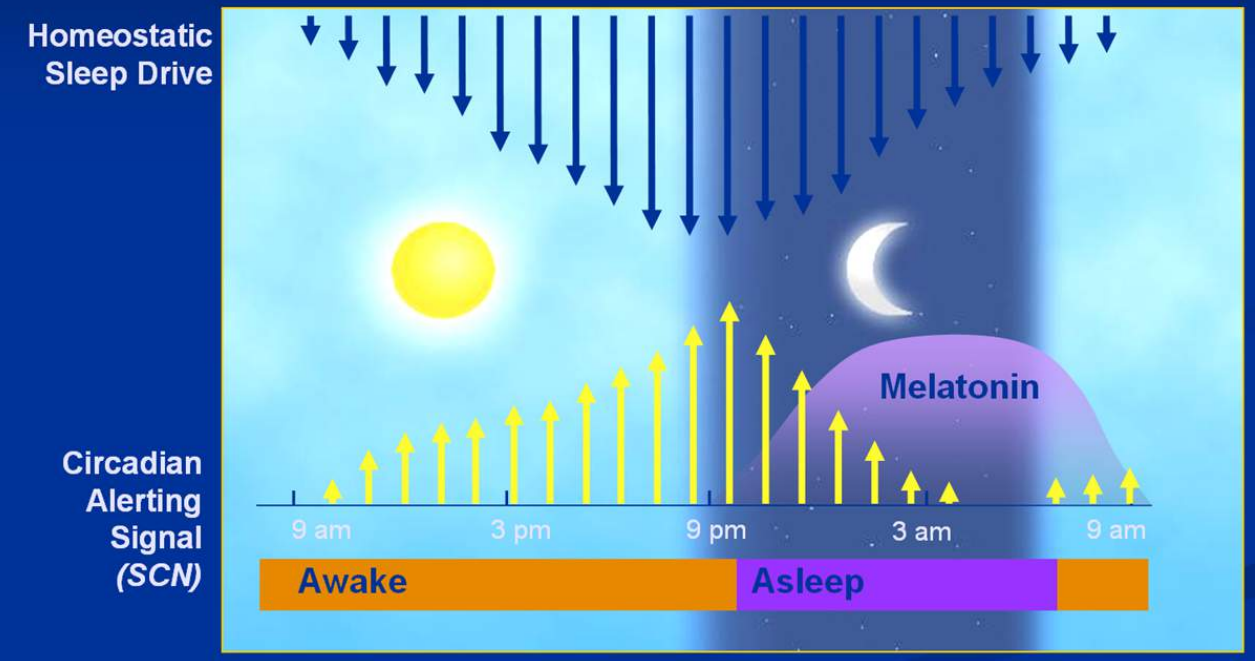
Blue Brain Credits

Henry Markram,[1,2,19,*] Eilif Muller,[1,19] Srikanth Ramaswamy,[1,19] Michael W. Reimann,[1,19] Marwan Abdellah,[1] Carlos Aguado Sanchez,[1] Anastasia Ailamaki,[16] Lidia Alonso-Nanclares,[6,7] Nicolas Antille,[1] Selim Arsever,[1] Guy Antoine Atenekeng Kahou,[1] Thomas K. Berger,[1] Ahmet Bilgili,[1] Nenad Buncic,[1] Athanassia Chalimourda,[1] Giuseppe Chindemi,[1] Jean-Denis Courcol,[1] Fabien Delalondre,[1] Vincent Delattre,[2] Shaul Druckmann,[5] Raphael Dumusc,[1] James Dynes,[1] Stefan Eilemann,[1] Eyal Gal,[4] Michael Emiel Gevaert,[1] Jean-Pierre Ghobril,[2] Albert Gidon,[3] Joe W. Graham,[1] Anirudh Gupta,[2] Valentin Haenel,[1] Etay Hay,[3,4] Thomas Heinis,[1,16,17] Juan B. Hernando,[8] Michael Hines,[12] Lida Kanari,[1] Daniel Keller,[1] John Kenyon,[1] Georges Khazen,[1] Yihwa Kim,[1] James G. King,[1] Zoltan Kisvarday,[13] Pramod Kumbhar,[1] Sébastien Lasserre,[1,15] Jean-Vincent Le Bé,[2] Bruno R.C. Magalhães,[1] Angel Merchán-Pérez,[6,7] Julie Meystre,[2] Benjamin Roy Morrice,[1] Jeffrey Muller,[1] Alberto Muñoz-Céspedes,[6,7] Shruti Muralidhar,[2] Keerthan Muthurasa,[1] Daniel Nachbaur,[1] Taylor H. Newton,[1] Max Nolte,[1] Aleksandr Ovcharenko,[1] Juan Palacios,[1] Luis Pastor,[9] Rodrigo Perin,[2] Rajnish Ranjan,[1,2] Imad Riachi,[1] José-Rodrigo Rodríguez,[6,7] Juan Luis Riquelme,[1] Christian Rössert,[1] Konstantinos Sfyrakis,[1] Ying Shi,[2] Julian C. Shillcock,[1] Gilad Silberberg,[18] Ricardo Silva,[1] Farhan Tauheed,[1,16] Martin Telefont,[1] Maria Toledo-Rodriguez,[14] Thomas Tränkler,[1] Werner Van Geit,[1] Jafet Villafranca Díaz,[1] Richard Walker,[1] Yun Wang,[10,11] Stefano M. Zaninetta,[1] Javier DeFelipe,[6,7,20] Sean L. Hill,[1,20] Idan Segev,[3,4,20] and Felix Schürmann[1,20]

Changes in Excitability Govern Changes between Wakefulness and Sleep

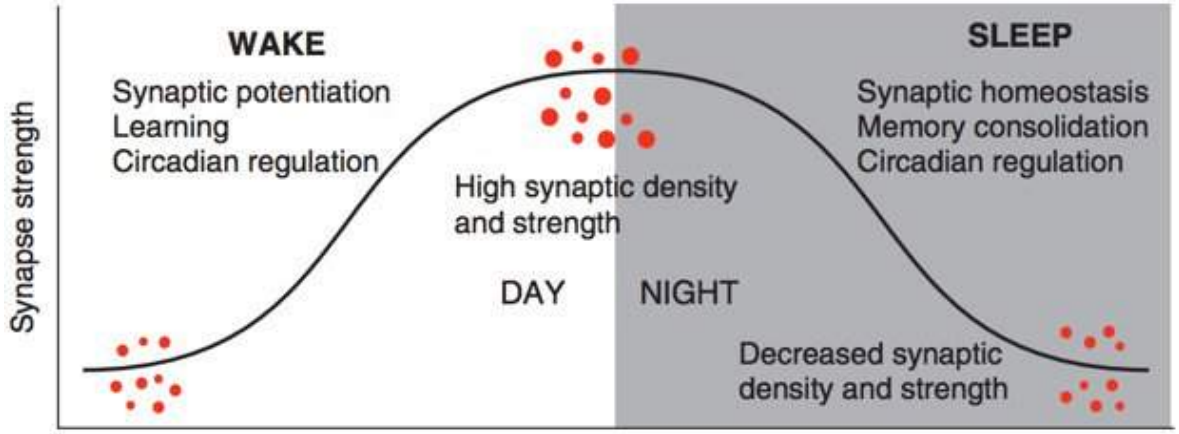


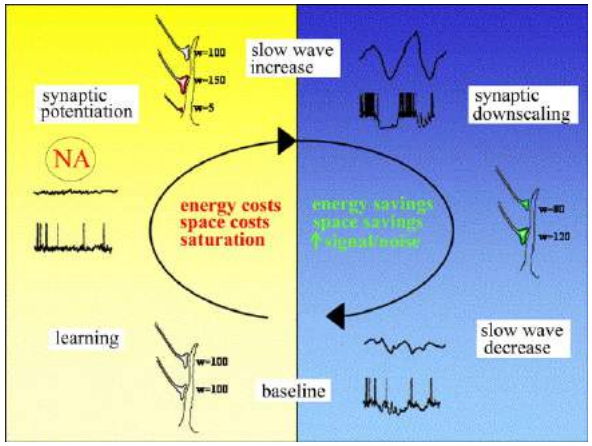
Sleep Wake Cycle: Two Process Model



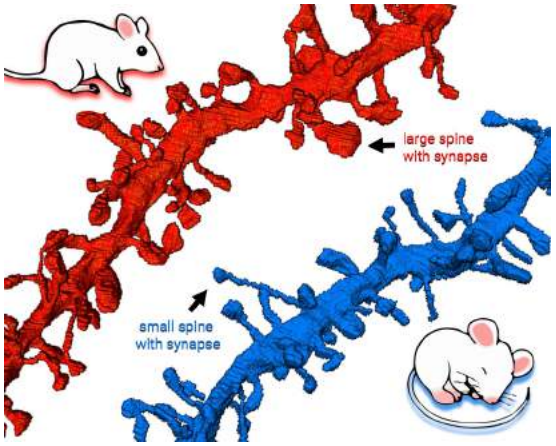
Adapted from Kilduff TS, Kushida CA. *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects.* 1999; and Kennaway DJ, Voultsios A. *J Clin Endocrinol Metab.* 1998;83:1013-1015; Edgar DM, Dement WC. And Fuller CA. The Journal of Neuroscience. 1993;13(3):1065-1079.

Synaptic homeostasis



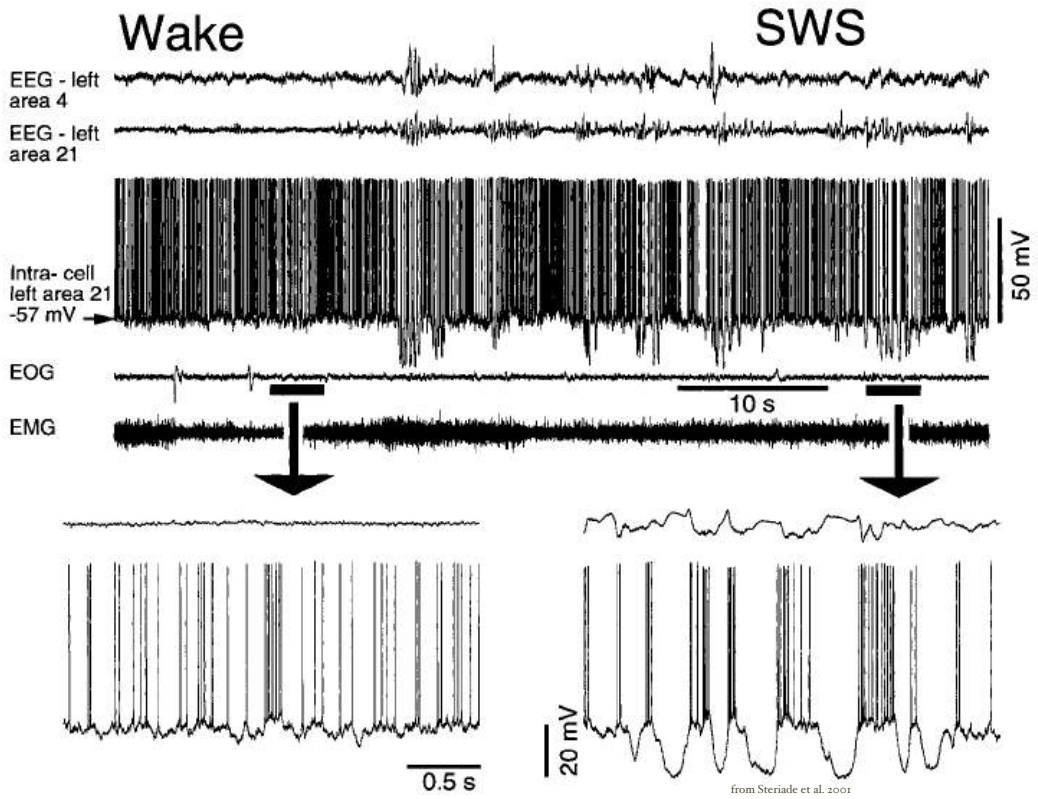


Tononi and Cirelli, 2003



De Vivo et al., Science, 2017

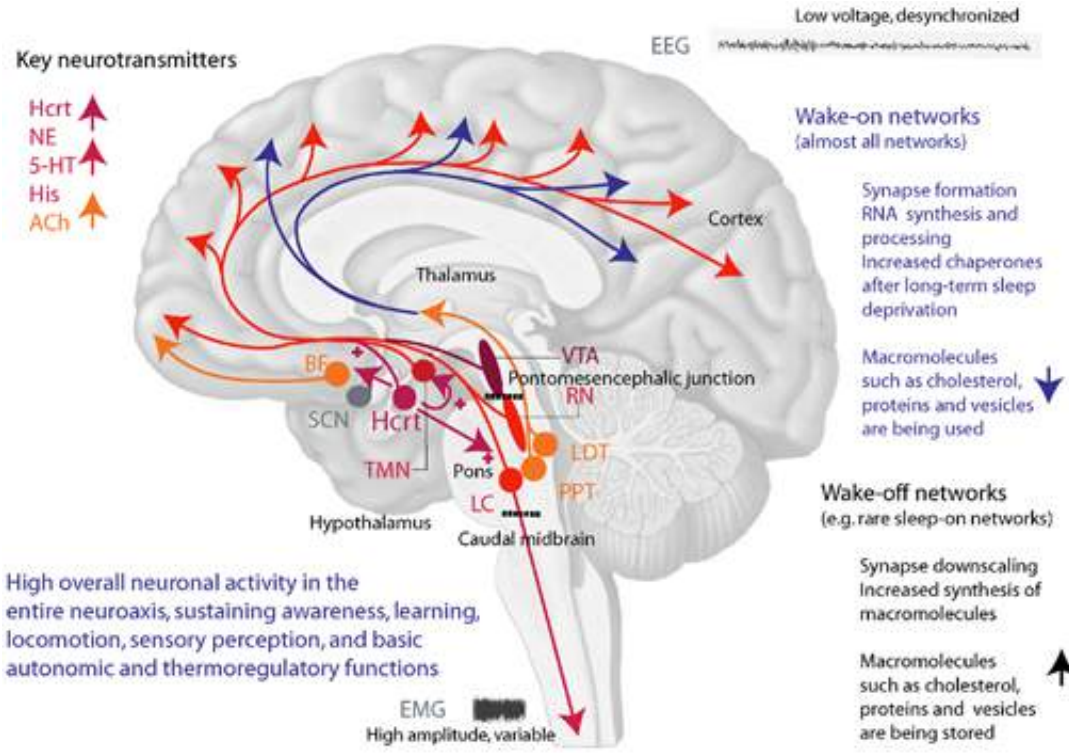
Wakefulness and Slow-Wave Sleep in the Cerebral Cortex



from Steriade et al. 2001

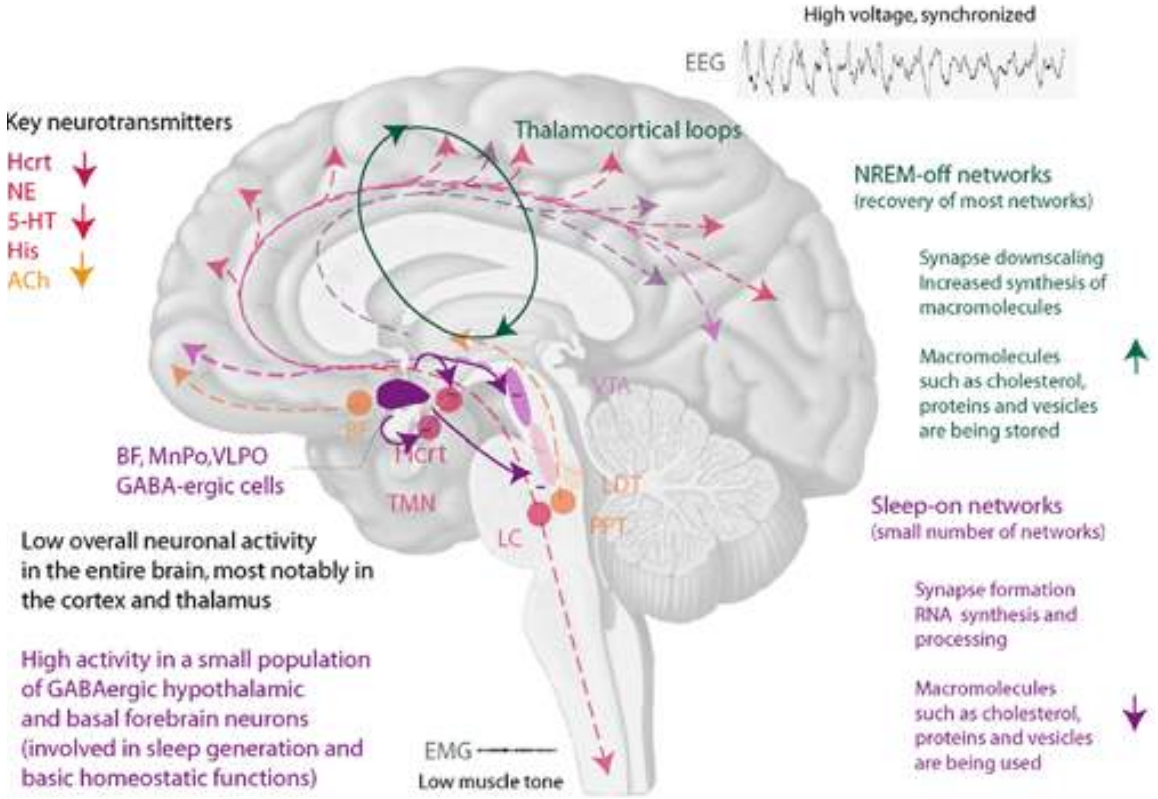
52

Neuromodulation during wakefulness



Mignot E (2008) Why we sleep: The temporal organization of recovery. PLoS Biol 6(4): e106. doi:10.1371/journal.pbio.0060106

Neuromodulation during NREM sleep

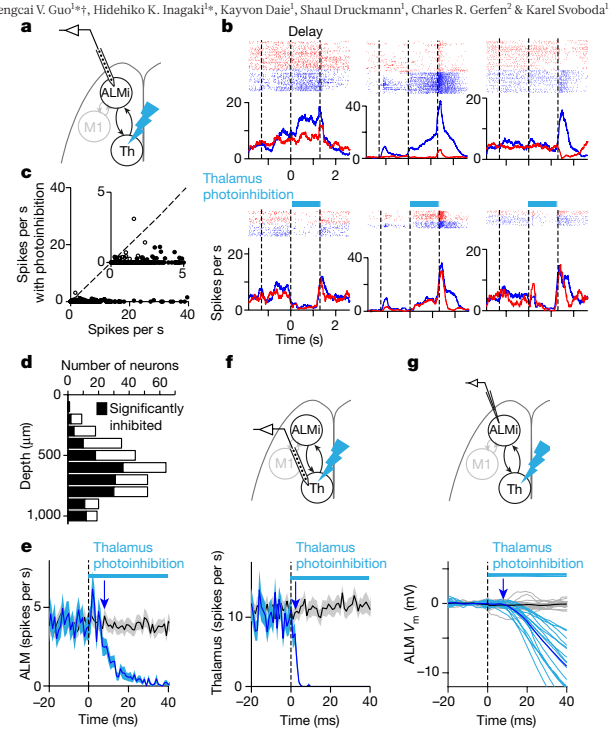


Mignot E (2008) Why we sleep: The temporal organization of recovery. PLoS Biol 6(4): e106. doi:10.1371/journal.pbio.0060106

During wakefulness, cortex is driven by thalamic input

Maintenance of persistent activity in a frontal thalamocortical loop

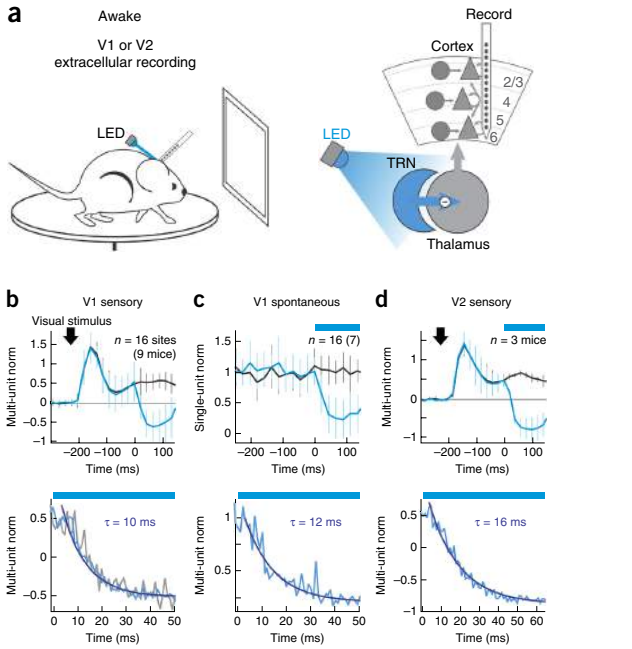
Zengcai V. Guo[1]*†, Hidehiko K. Inagaki[1]*, Kayvon Daie[1], Shaul Druckmann[1], Charles R. Gerfen[2] & Karel Svoboda[1]



11 MAY 2017 | VOL 545 | NATURE | 181

Distinct recurrent versus afferent dynamics in cortical visual processing

Kimberly Reinhold[1–4], Anthony D Lien[1–4] & Massimo Scanziani[1–4]

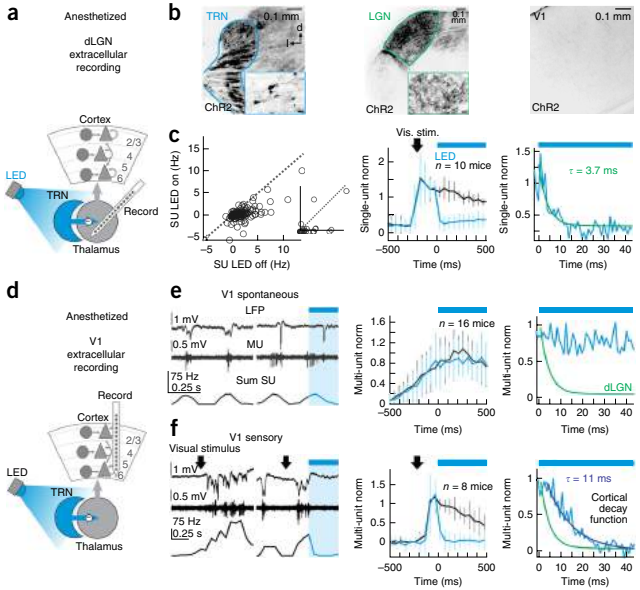


NATURE NEUROSCIENCE VOLUME 18 | NUMBER 12 | DECEMBER 2015

During sleep/anesthesia, cortex generates slow wave activity without thalamic input

Distinct recurrent versus afferent dynamics in cortical visual processing

Kimberly Reinhold[1–4], Anthony D Lien[1–4] & Massimo Scanziani[1–4]



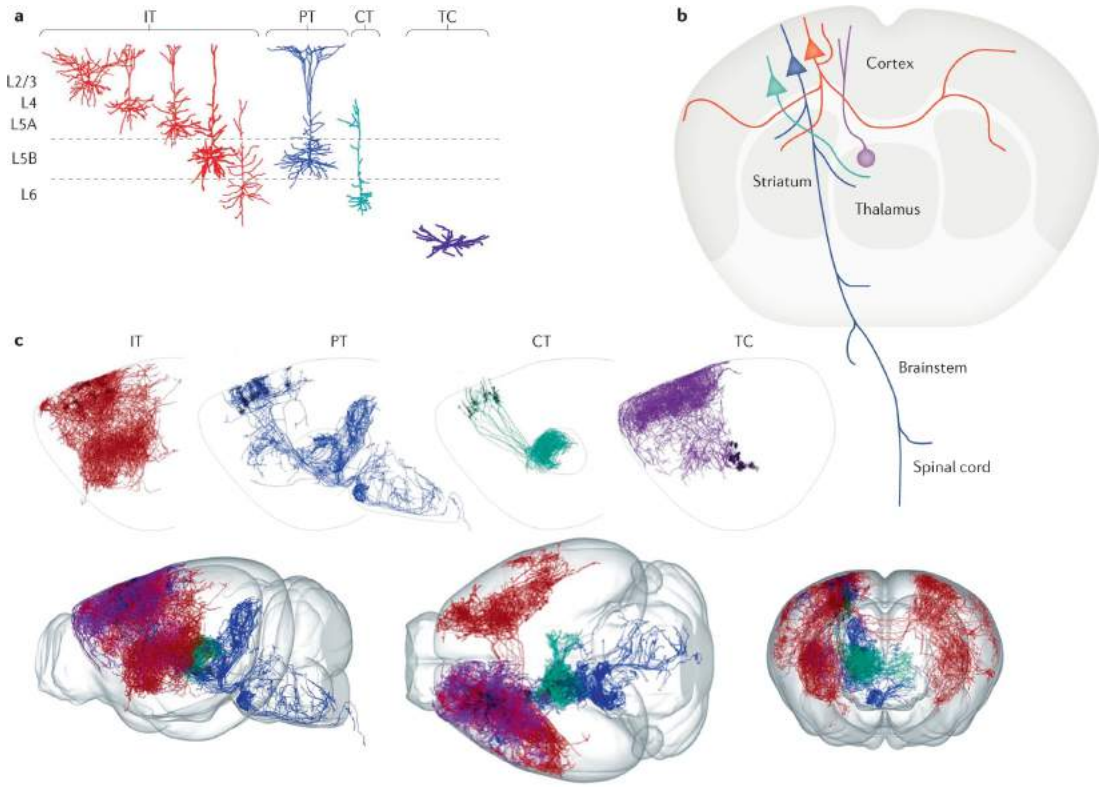
NATURE NEUROSCIENCE VOLUME 18 | NUMBER 12 | DECEMBER 2015

Also seen in

In Vitro Cortex:
Sanchez-Vives and McCormick, 2000

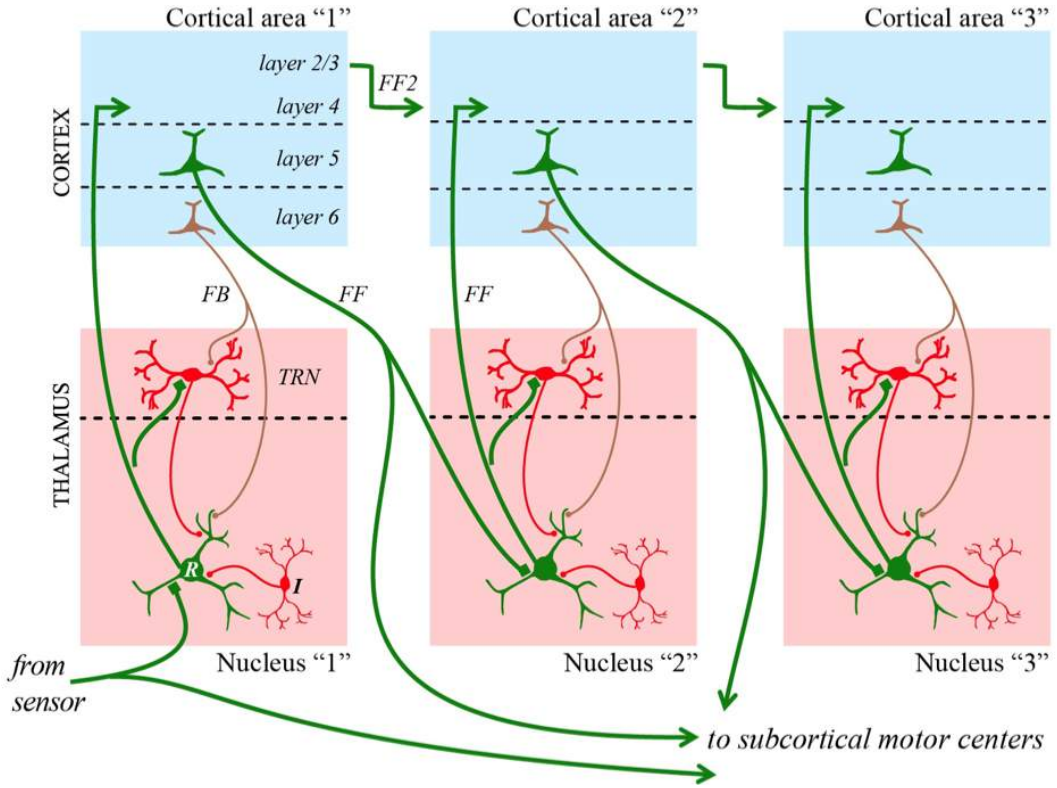
Deafferented cortical slab:
Timofeev et al., 2000

Excitatory projection neurons of the cortico-thalamo-cortical loop



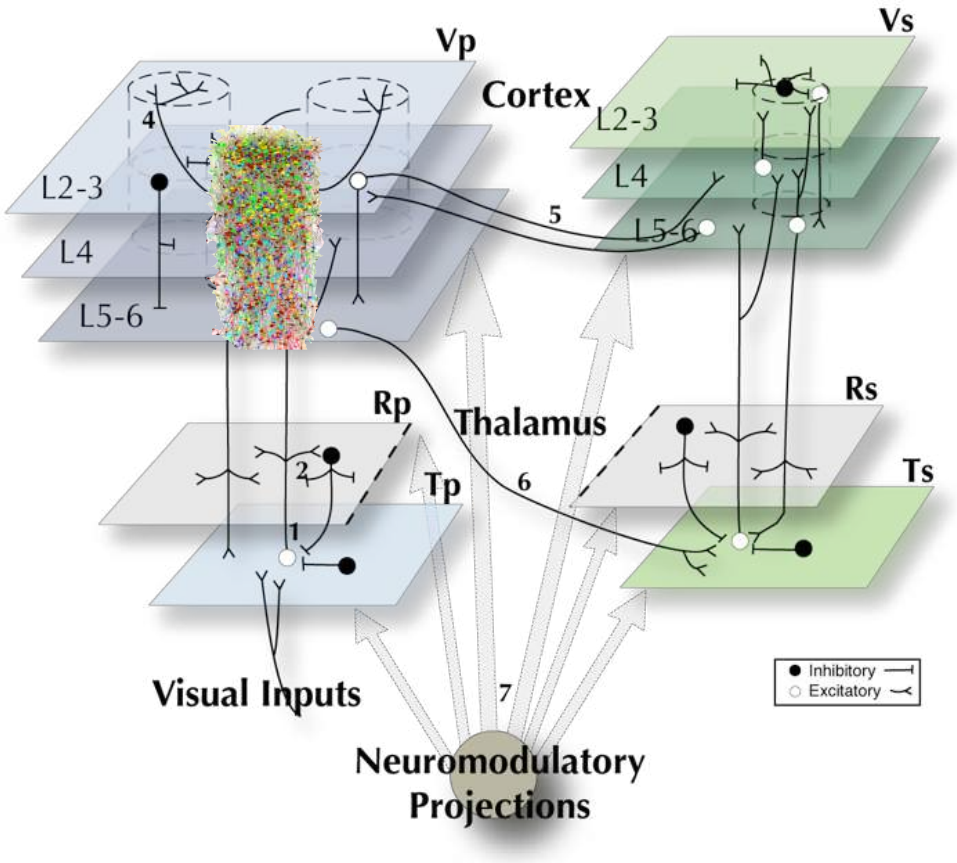
Shepherd, G.M.G., Yamawaki, N. Untangling the cortico-thalamo-cortical loop: cellular pieces of a knotty circuit puzzle. *Nat Rev Neurosci* (2021). https://doi.org/10.1038/s41583-021-00459-3

Sherman and Guillery Model of Transthalamic Cortical Communication



From Numenta ("Thalamus snubbed") based on Sherman, S.M.(2018b). Thalamocortical System II. Lecture at the Simons Institute, Berkeley. [https://www.youtube.com/watch?v=KBILhSTpzFI]

Thalamocortical Model - 65,000 neurons, ~5 million connections



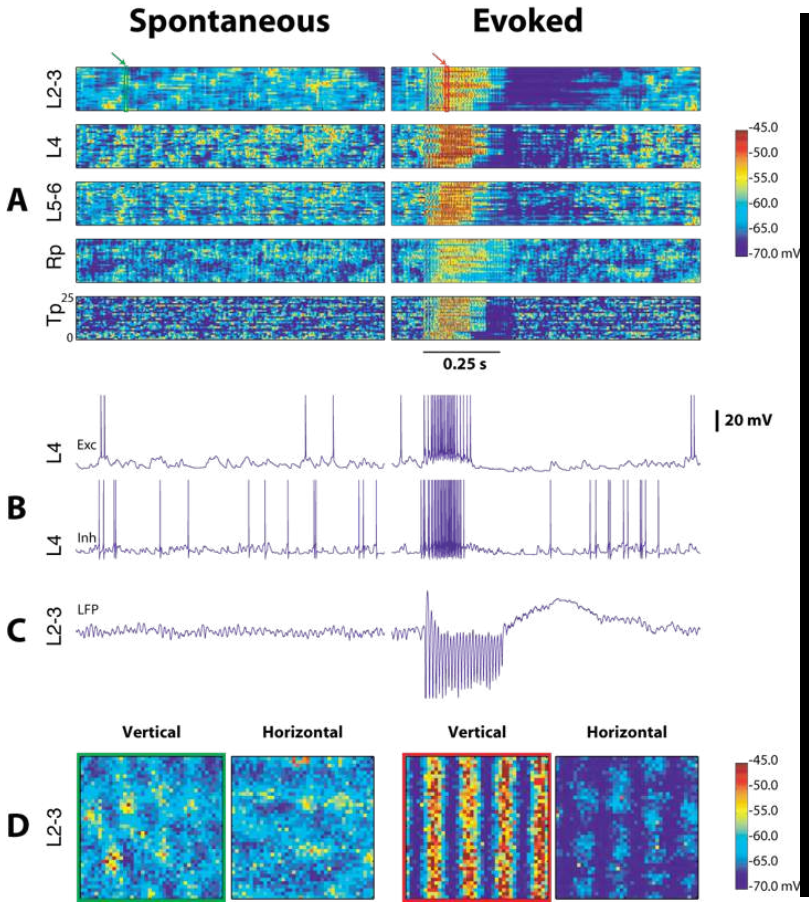
Hill and Tononi, 2005

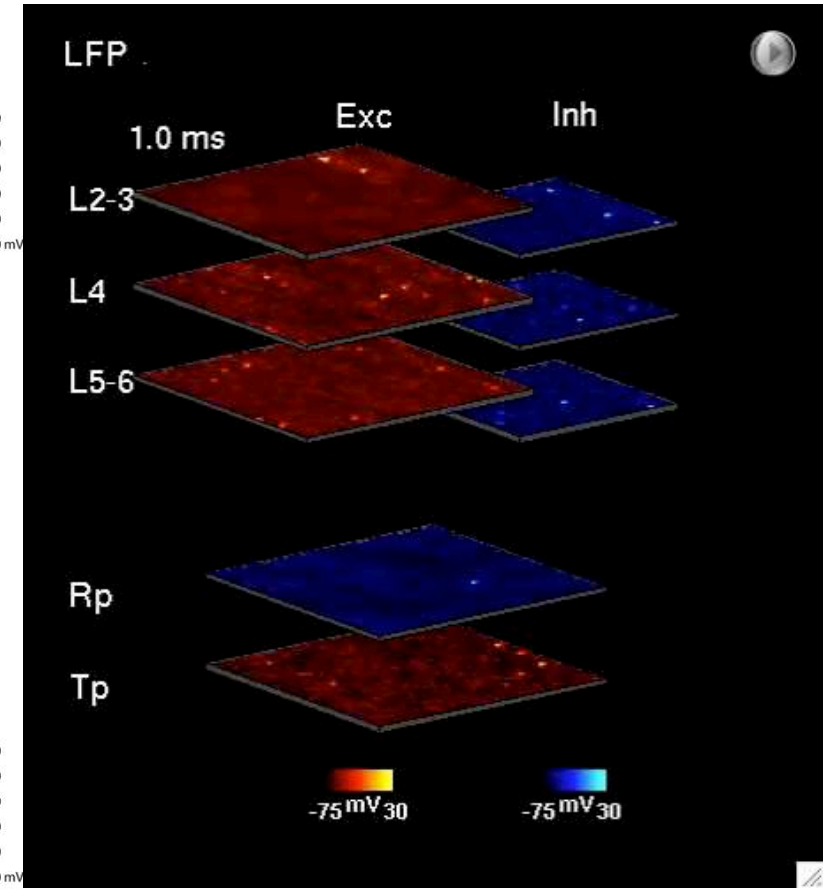
Thalamocortical model overview

- Neurons (~65,000 cells)
  - Integrate-and-fire spiking neurons
- Intrinsic currents
  - I_{KL}, I_h, I_T, $I_{Na(p)}$, I_{DK}
    Voltage-dependent and independent currents underlying intrinsic bursting properties
- Synapses (~5,000,000 connections)
  - AMPA, NMDA, $GABA_A$, $GABA_B$
  - Short-term depression
- Anatomy
  - Based on cat visual thalamocortical system
  - Patterned connections, 8 X 8 mm^2 of cortex
  - Diffuse modulatory influences affect channel conductances

60

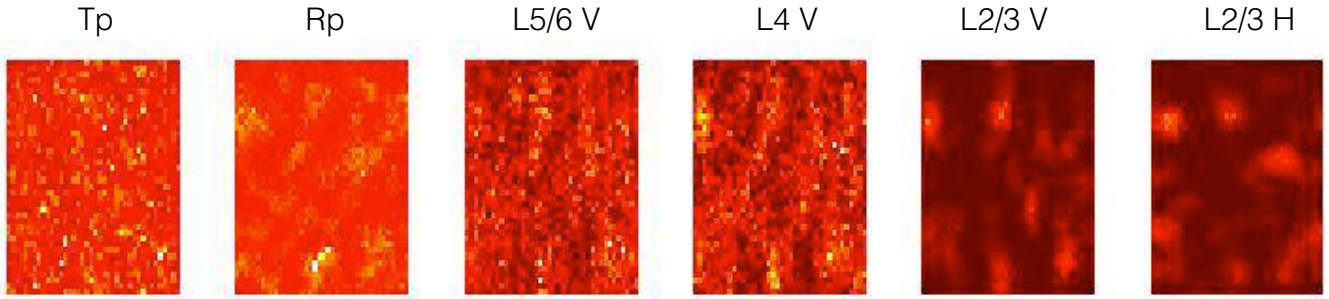
Wakefulness



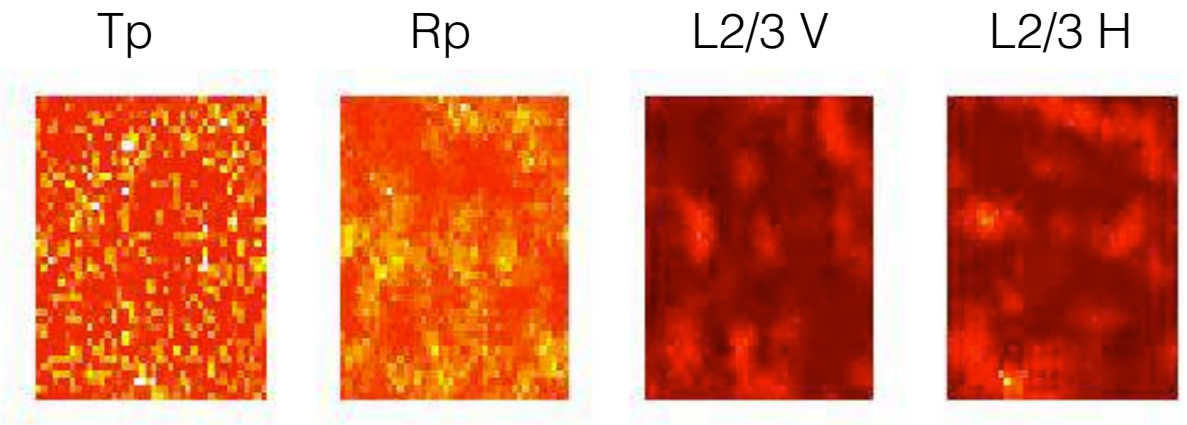


Hill and Tononi, 2005

Thalamically driven spontaneous activity during wakefulness



Orientation selectivity during wakefulness



Transition to sleep…

- **Simulate the removal of key wake-promoting neuromodulators:**
  - **Increase potassium leak conductance**

    Hyperpolarizes neurons - moving membrane potential away from firing threshold

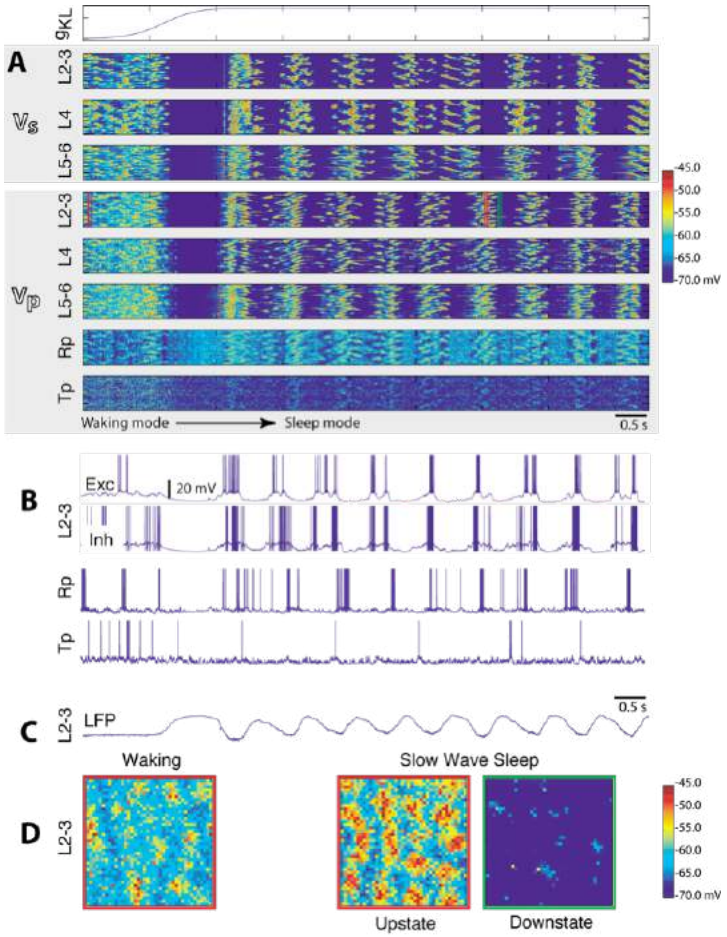
  - **Increase AMPA receptor conductance**

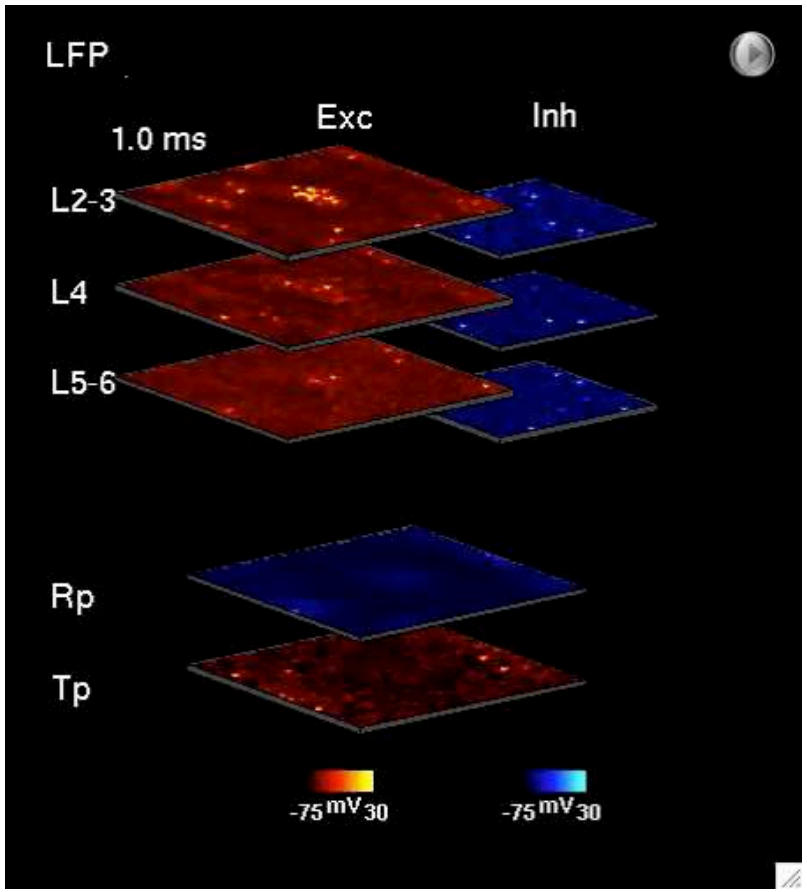
    Increases strength of excitatory connections

  - **Increase persistent sodium channel conductance**

    Increases bistable firing properties

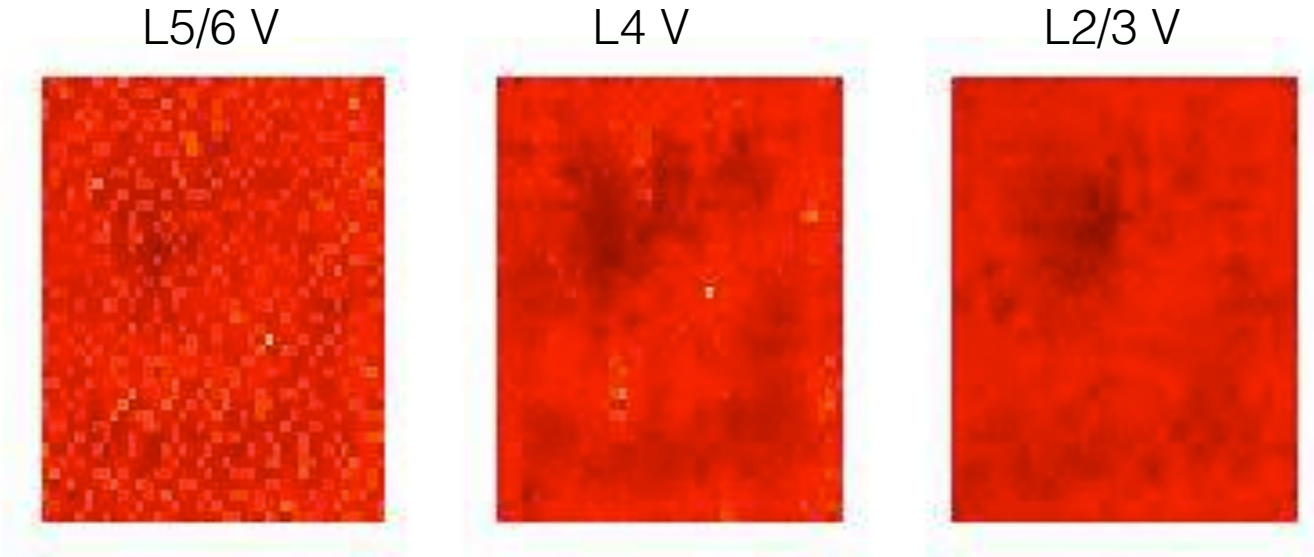
Slow Wave Sleep



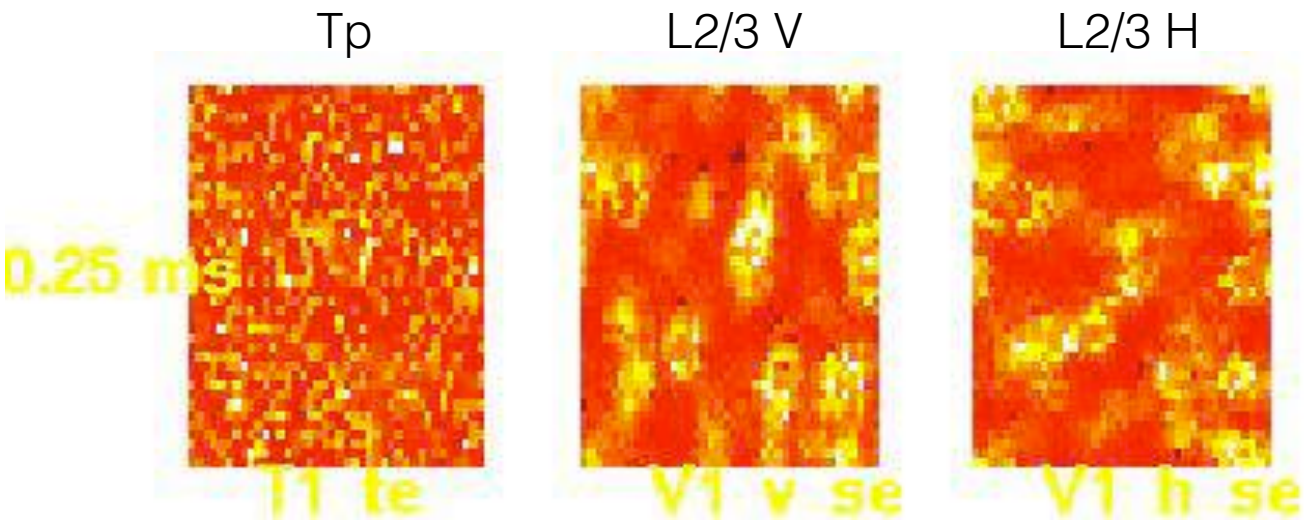


Hill and Tononi, 2005

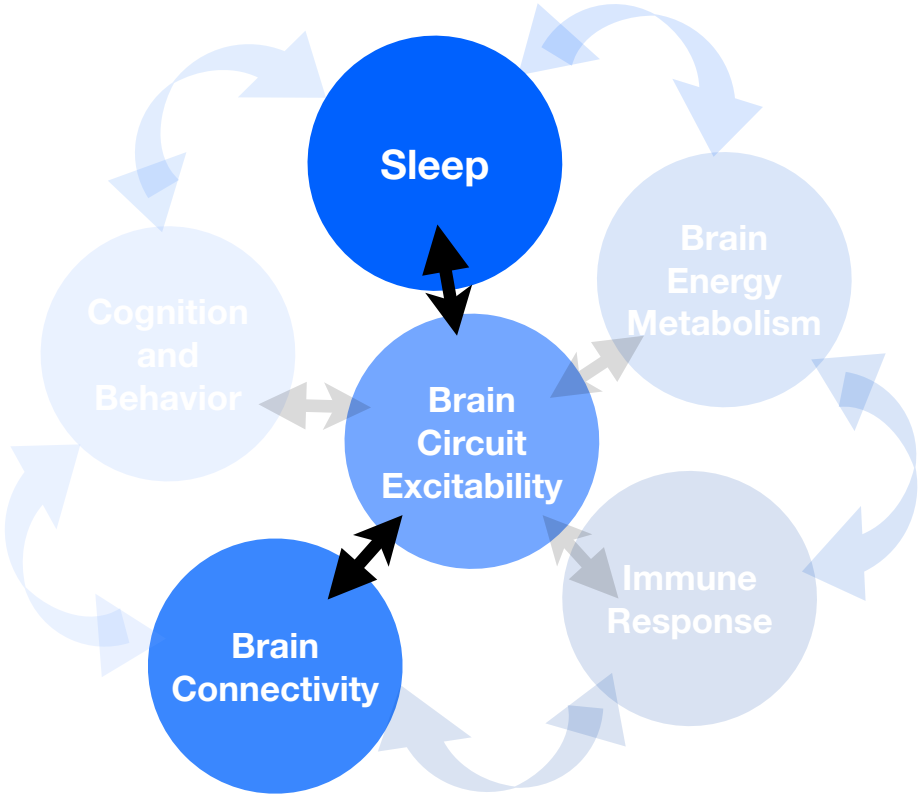
Cortically generated slow oscillation



Stimulation during slow oscillation



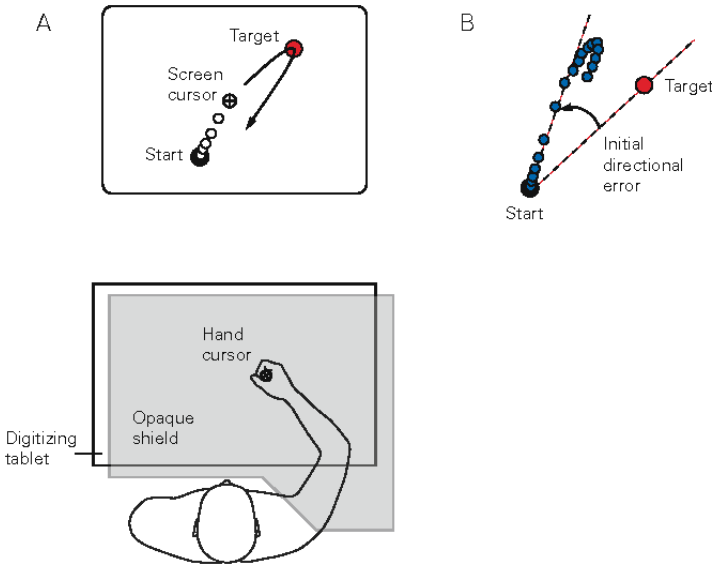
Local Sleep is Homeostatically Regulated and Associated with Synaptic Plasticity



Local sleep and learning

Reto Huber[1], M. Felice Ghilardi[2], Marcello Massimini[1] & Giulio Tononi[1]

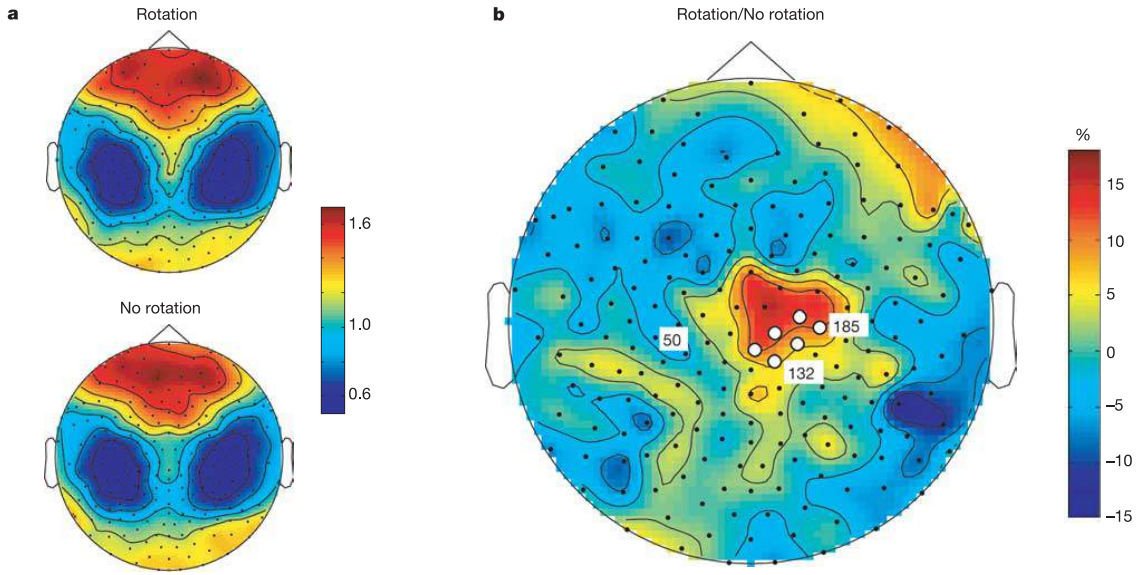
[1]*Department of Psychiatry, University of Wisconsin, Madison, Wisconsin 53719 USA*
[2]*Center for Neurobiology and Behavior, Columbia College of Physicians and Surgeons, New York, New York 10032, USA*



Local sleep and learning

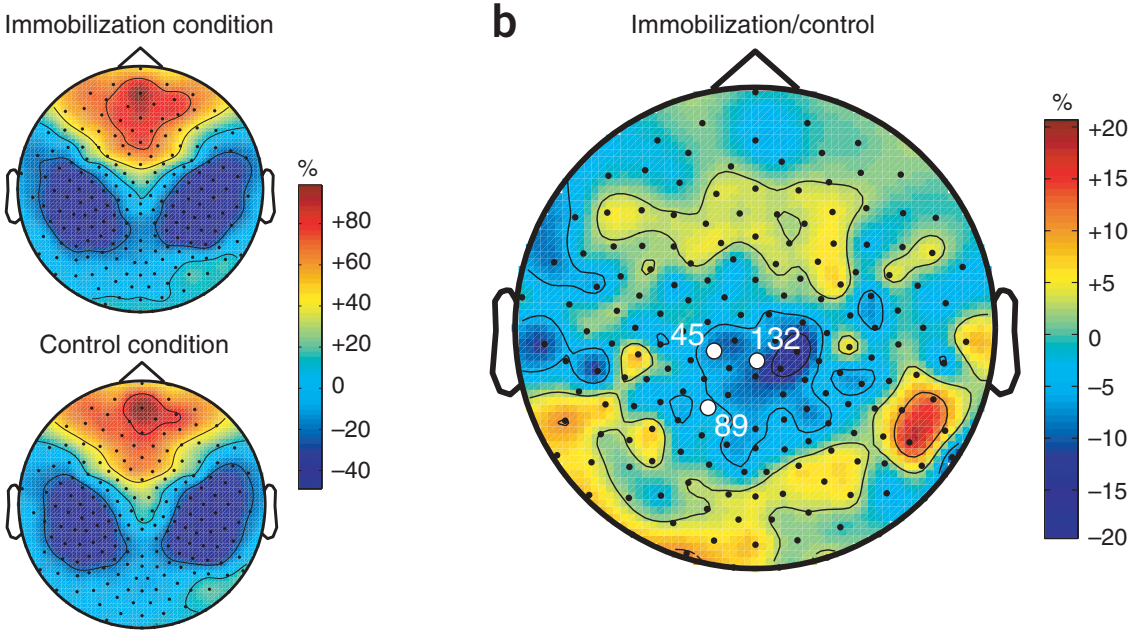
Reto Huber[1], **M. Felice Ghilardi**[2], **Marcello Massimini**[1] **& Giulio Tononi**[1]

[1]*Department of Psychiatry, University of Wisconsin, Madison, Wisconsin 53719 USA*
[2]*Center for Neurobiology and Behavior, Columbia College of Physicians and Surgeons, New York, New York 10032, USA*



Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity

Reto Huber[1], M Felice Ghilardi[2], Marcello Massimini[1], Fabio Ferrarelli[1], Brady A Riedner[3], Michael J Peterson[1] & Giulio Tononi[1]

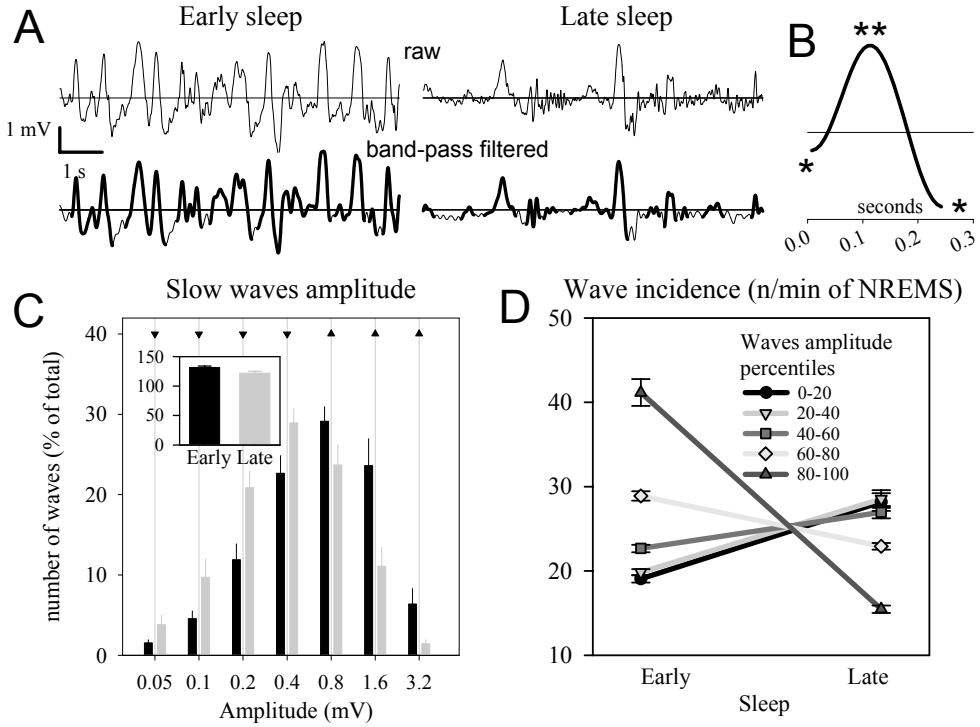


NATURE NEUROSCIENCE VOLUME 9 | NUMBER 9 | SEPTEMBER 2006

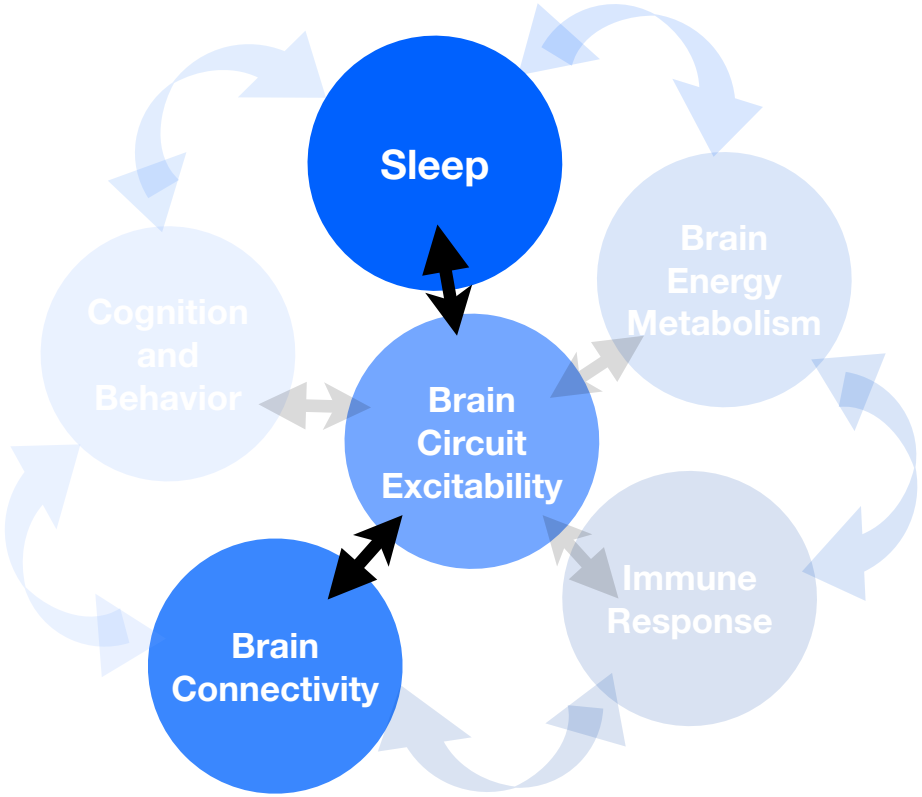
Slow waves slope and incidence decrease throughout the night

Sleep Homeostasis and Cortical Synchronization: II. A Local Field Potential Study of Sleep Slow Waves in the Rat

Vladyslav V. Vyazovskiy, PhD[1]; Brady A. Riedner, BS[1-3]; Chiara Cirelli, MD PhD[1]; Giulio Tononi, MD PhD[1]



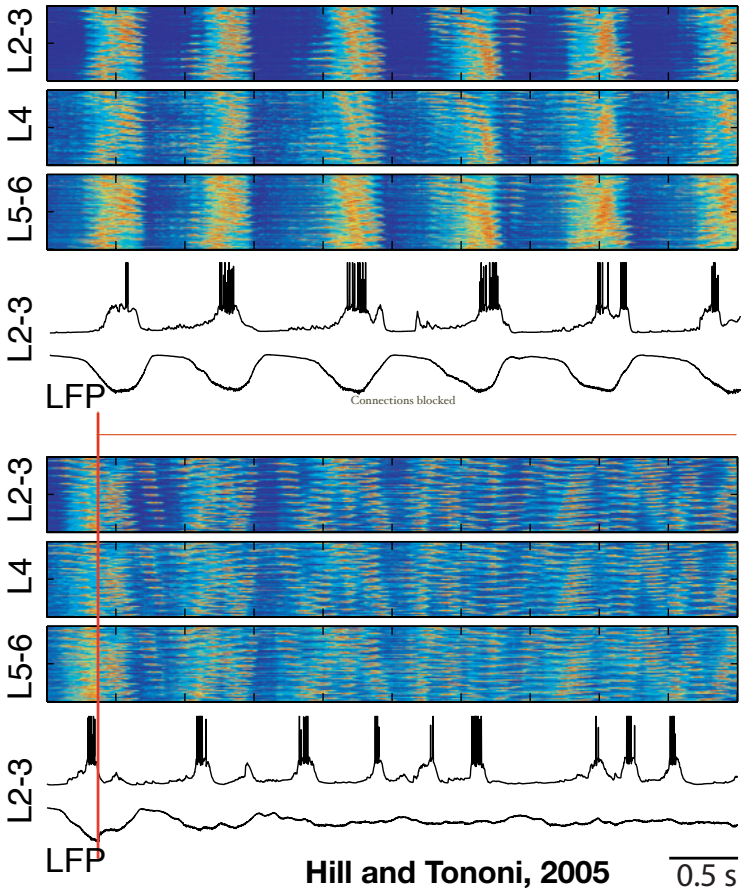
Synchronization of Slow Wave Sleep Depends on Excitatory Connectivity

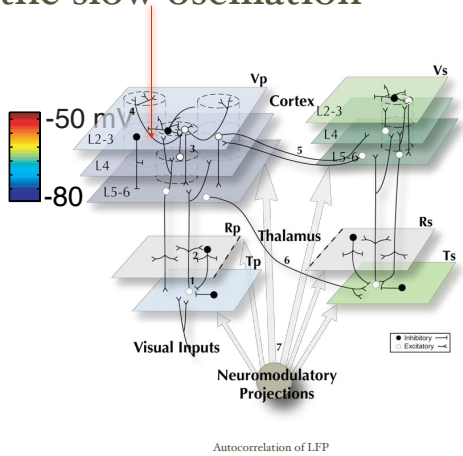


Intra-areal connections synchronize the slow oscillation

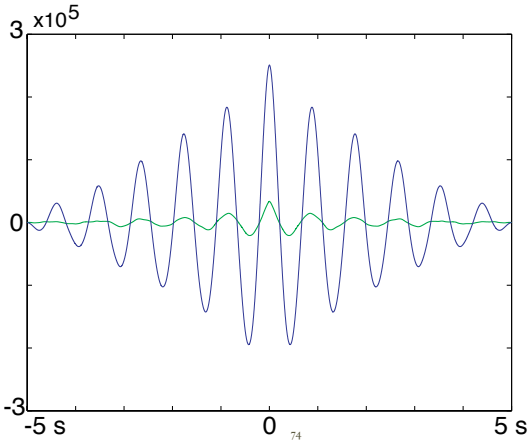
Control

Lesion





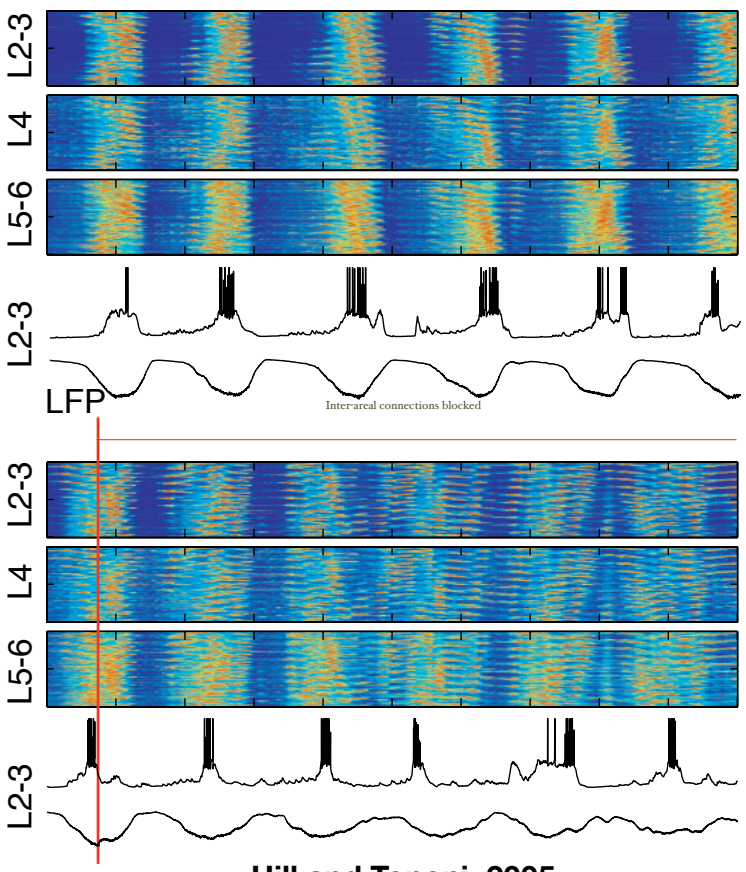
Autocorrelation of LFP



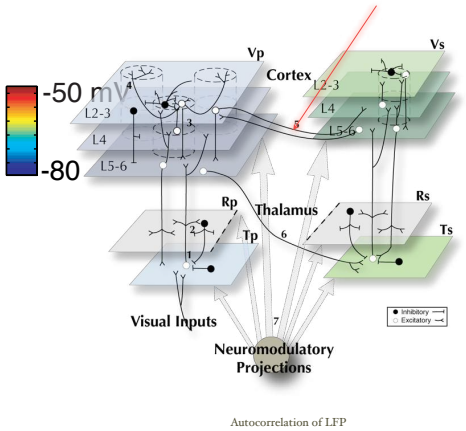
Inter-areal connections synchronize the slow oscillation

Control

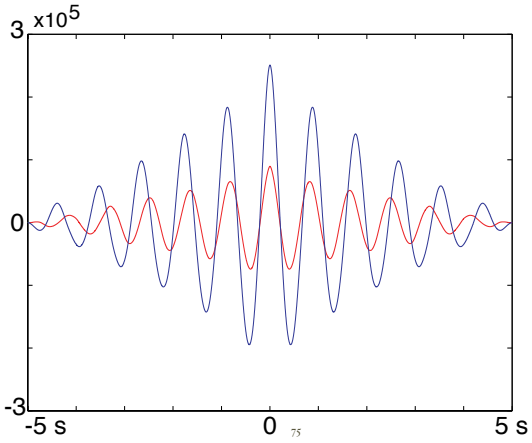
Lesion



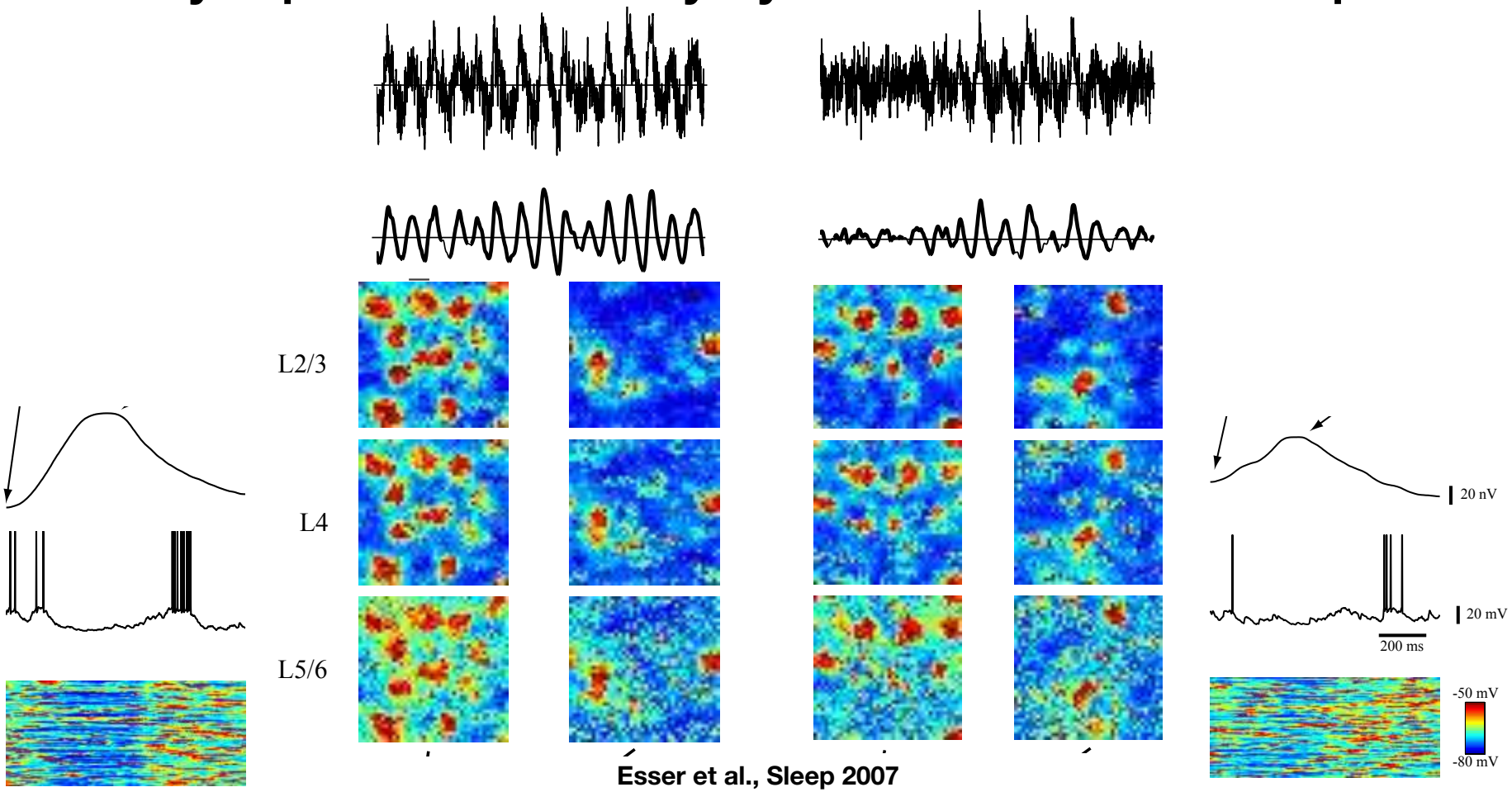
Hill and Tononi, 2005



Autocorrelation of LFP

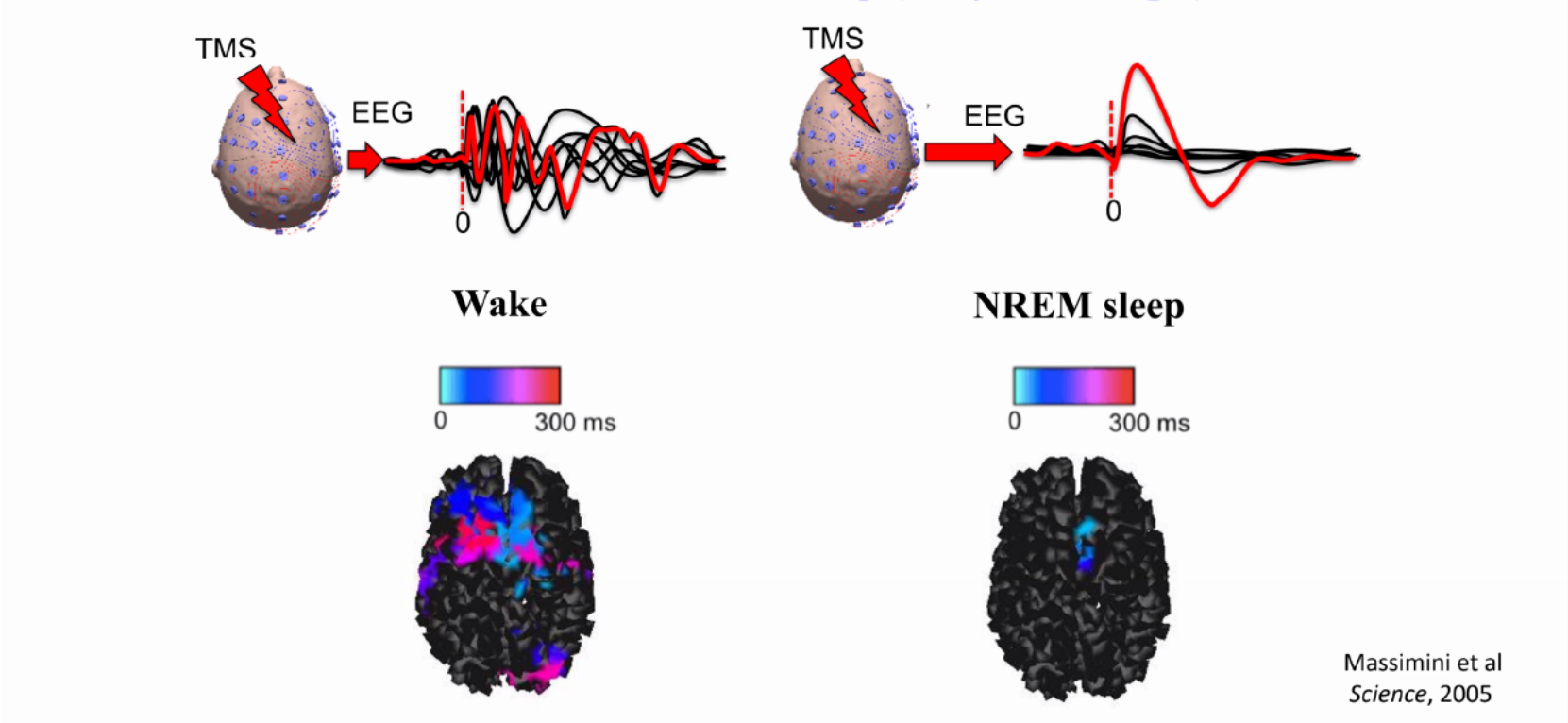


Synaptic connectivity synchronizes local sleep

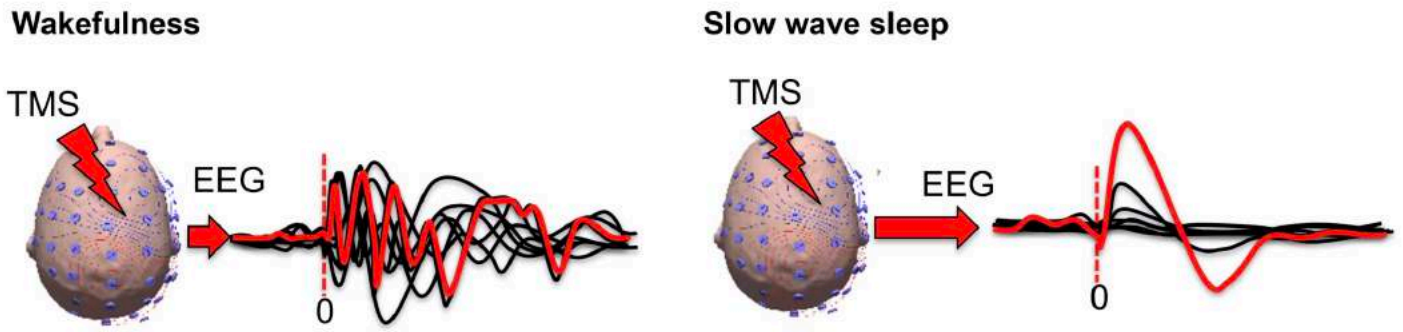


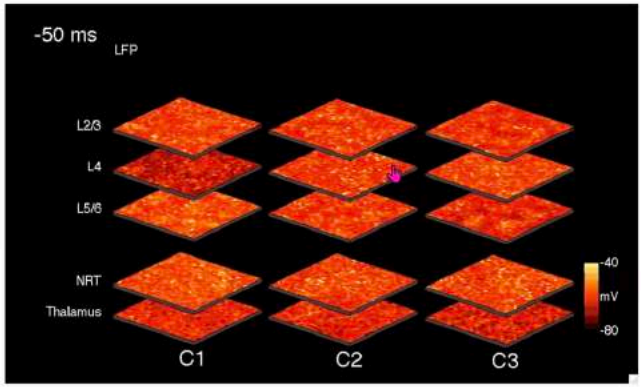
Esser et al., Sleep 2007

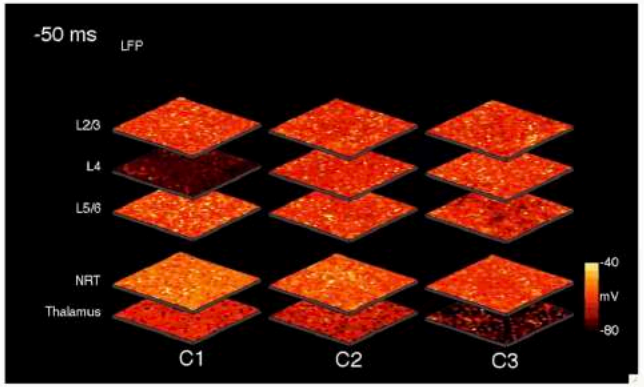
Reduced effective connectivity in sleep in humans



Reduced effective connectivity in sleep *in silico*

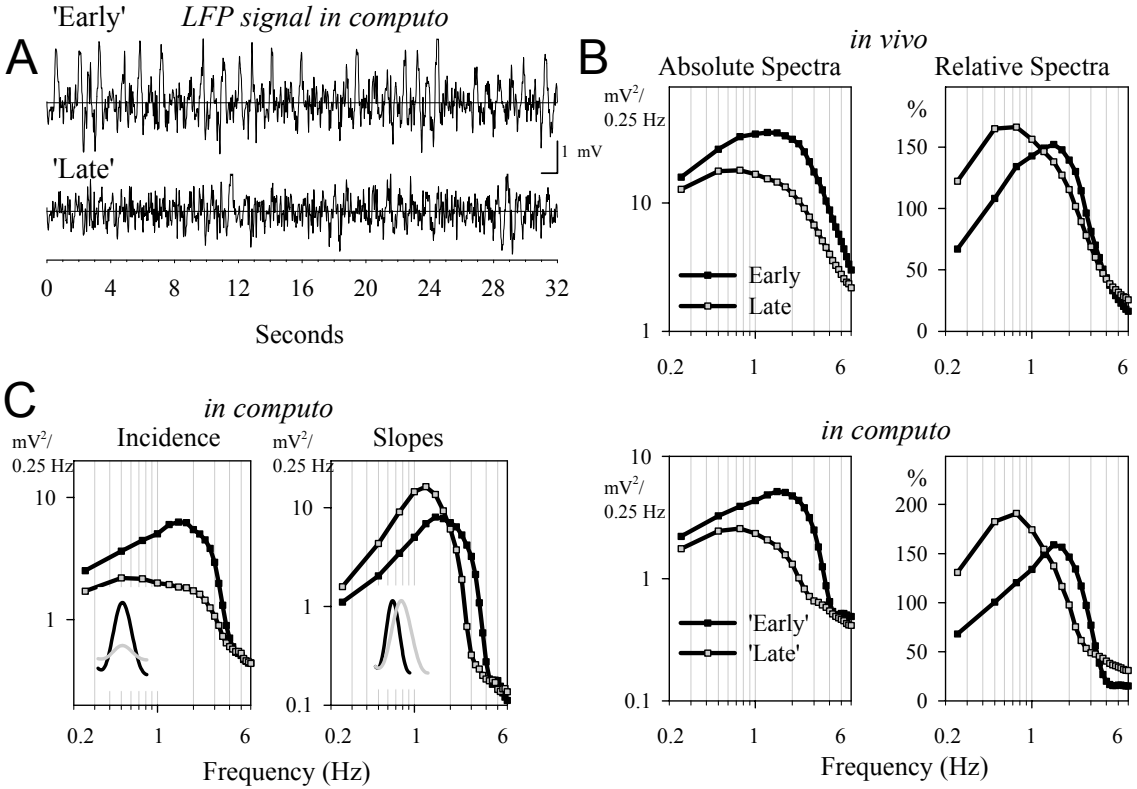






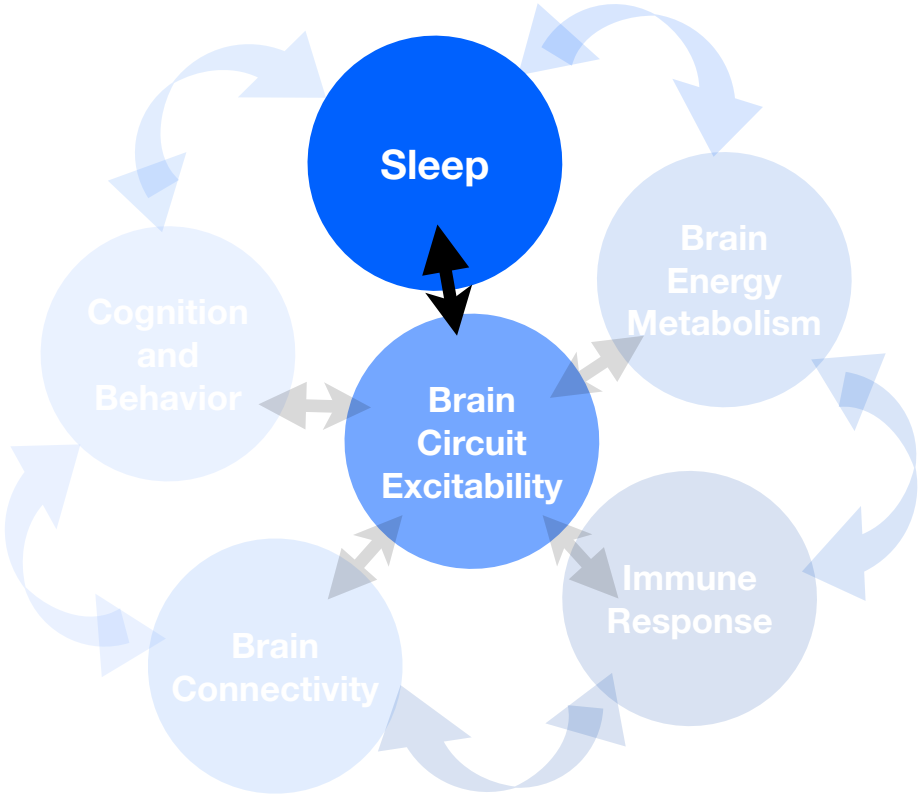
Esser, Hill, Tononi, *J. Neurophys*. 2009

Computer modeling recapitulates observed changes in LFP slope and power spectra, by changing synaptic strength

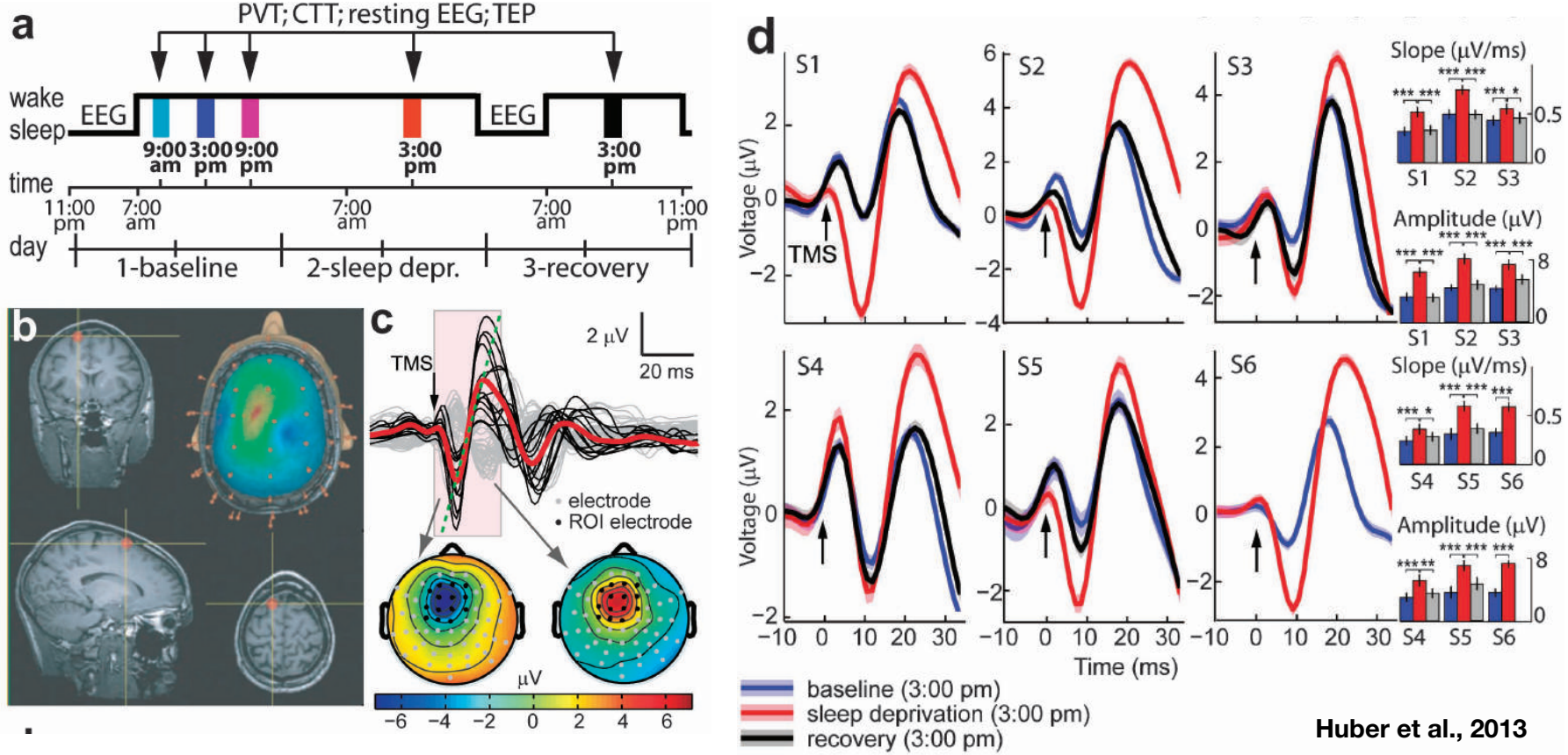


Esser et al., Sleep 2007

Sleep Homeostatically Regulates Thalamocortical Excitability

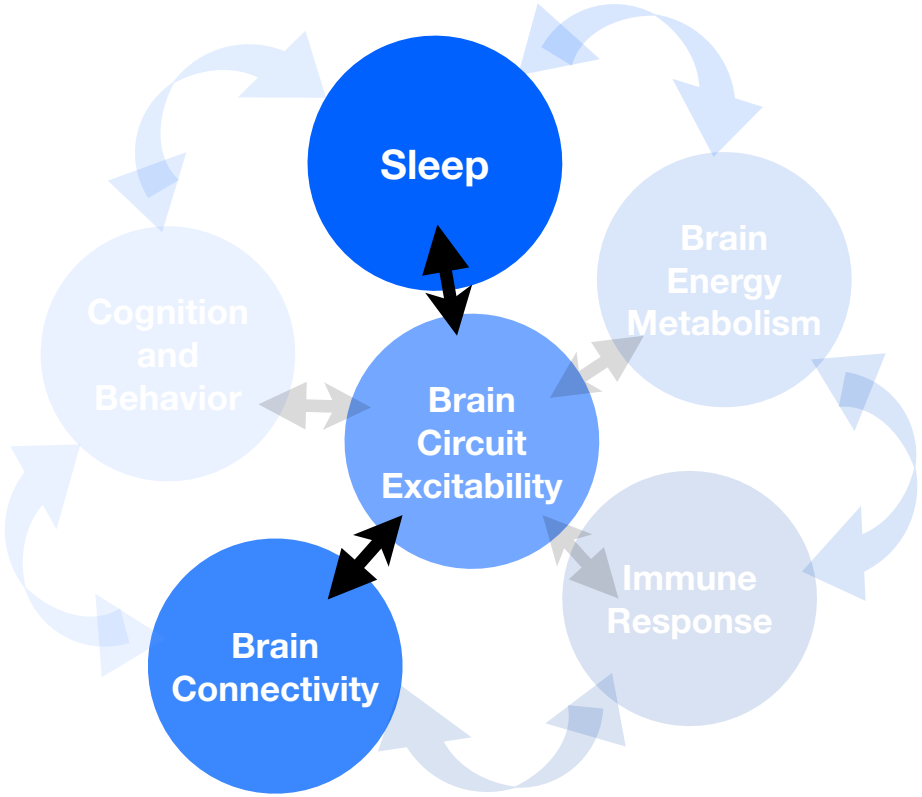


Cortical Excitability Increases with Time Awake and Decreases After Sleep



Huber et al., 2013

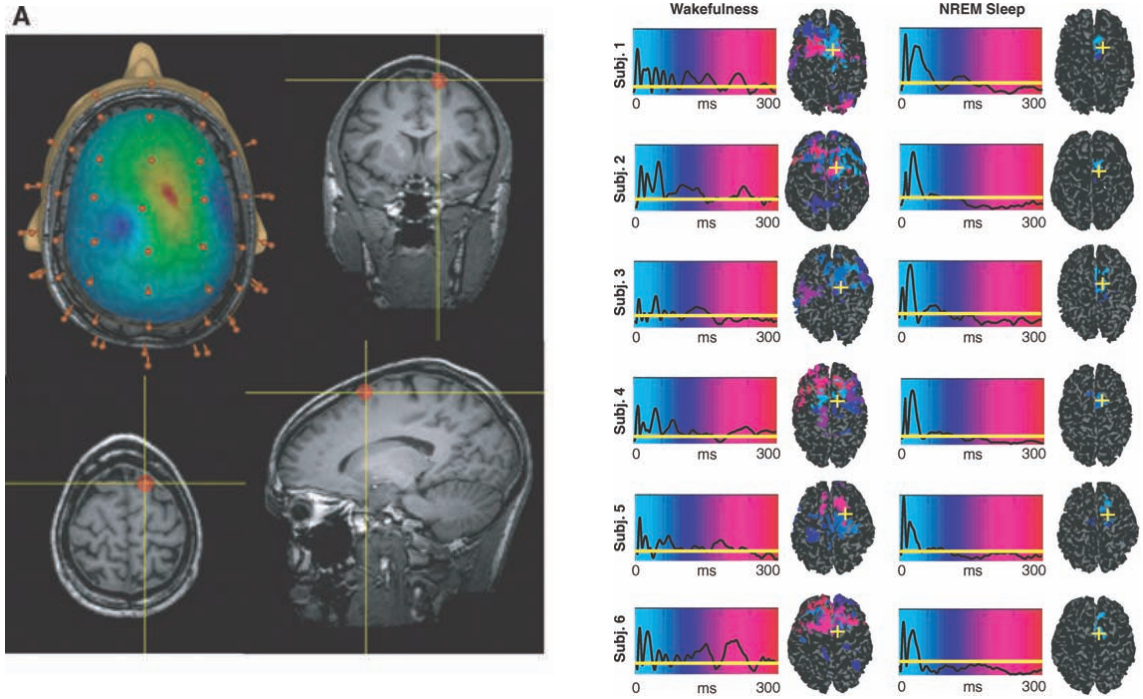
Sleep and Local Sleep-like States Alter Effective Connectivity



Breakdown of Cortical Effective Connectivity During Sleep

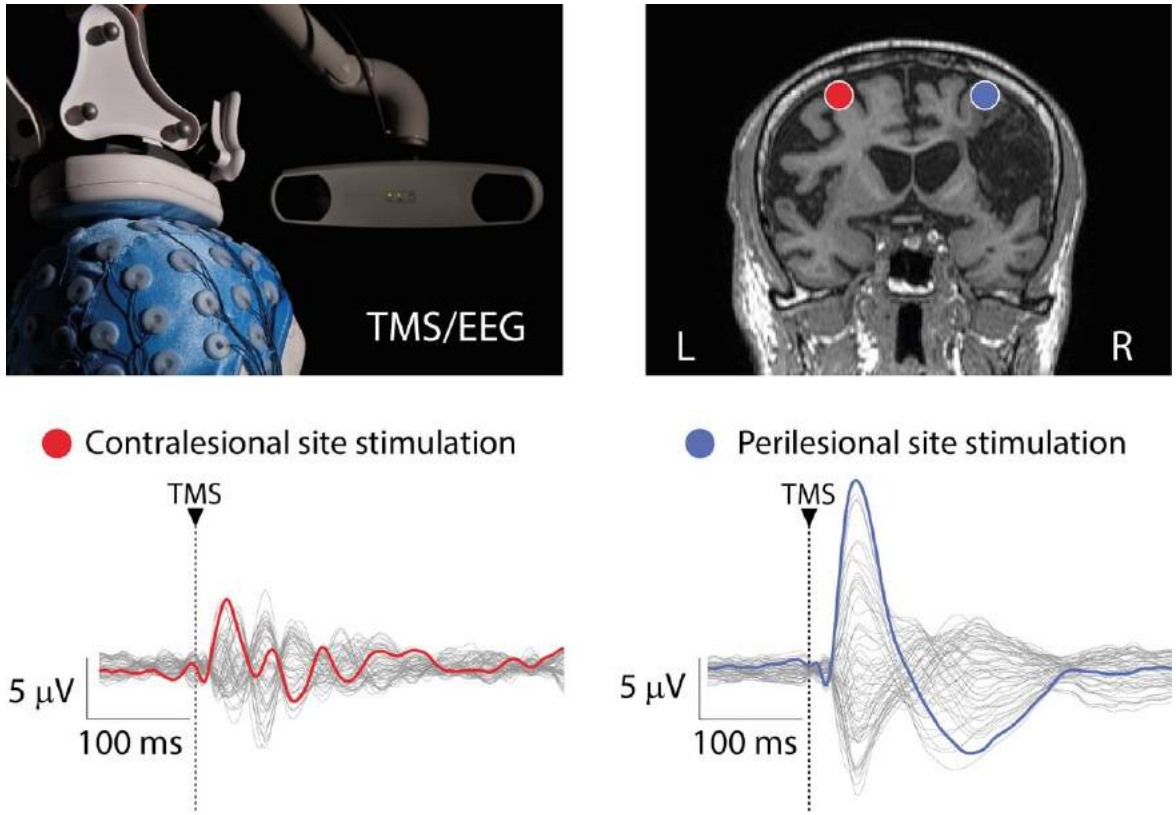
Marcello Massimini,[1,2] Fabio Ferrarelli,[1] Reto Huber,[1]
Steve K. Esser,[1] Harpreet Singh,[1] Giulio Tononi[1]*

30 SEPTEMBER 2005 VOL 309 SCIENCE www.sciencemag.org

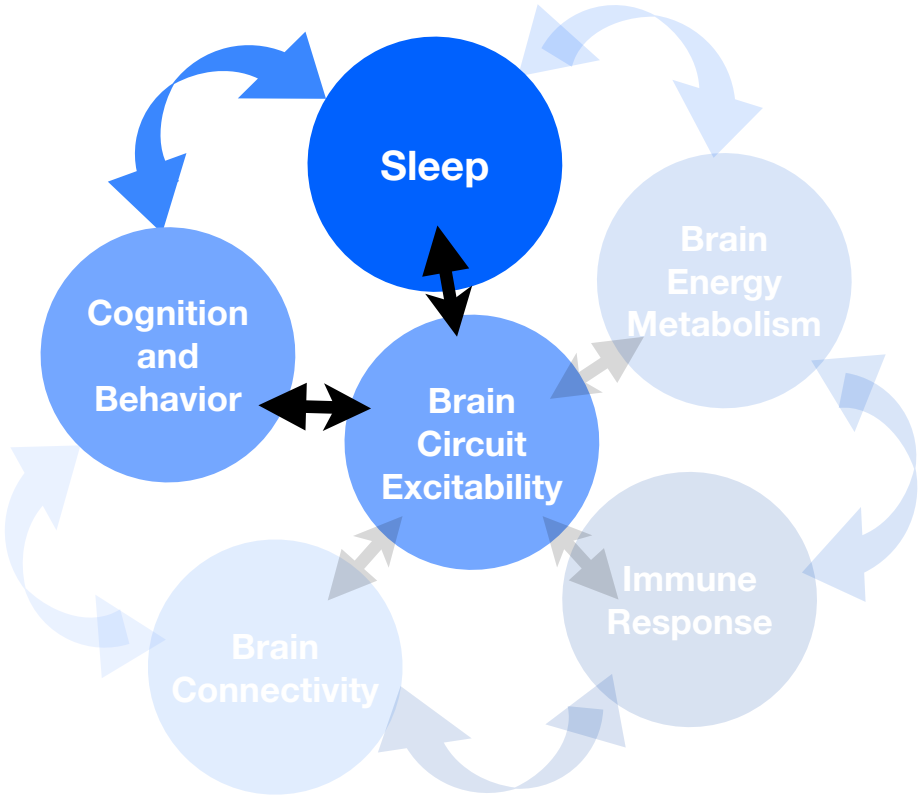


Local sleep-like cortical reactivity in the awake brain after focal injury

Simone Sarasso et al., Brain, https://doi.org/10.1093/brain/awaa338



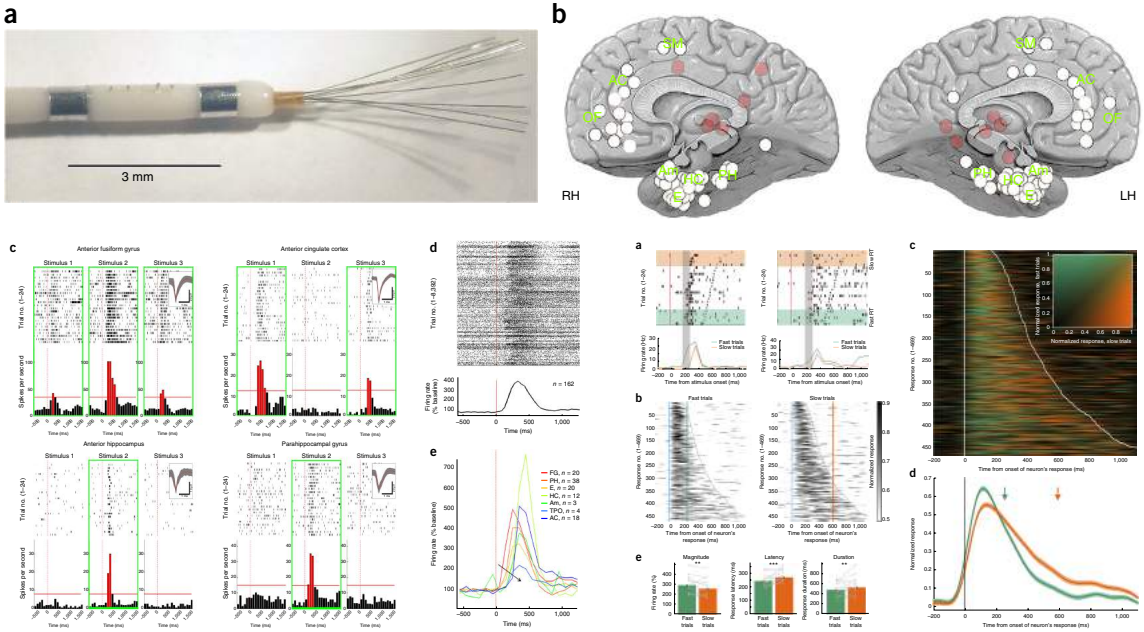
Local Sleep Interferes with Cognition



Local sleep interferes with cognition

Selective neuronal lapses precede human cognitive lapses following sleep deprivation

Yuval Nir[1], Thomas Andrillon[2–4], Amit Marmelshtein[1], Nanthia Suthana[5], Chiara Cirelli[4], Giulio Tononi[4,7] & Itzhak Fried[5–7]



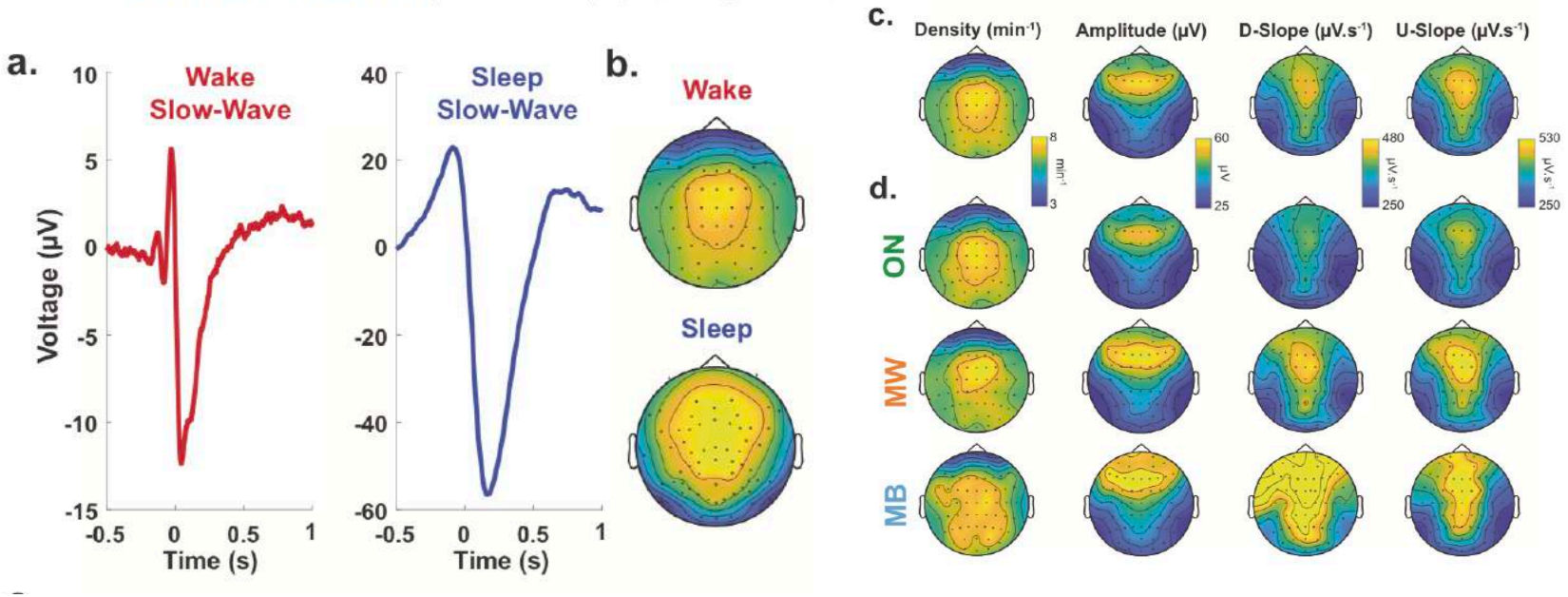
Local sleep interferes with attention

https://doi.org/10.1038/s41467-021-23890-7 OPEN

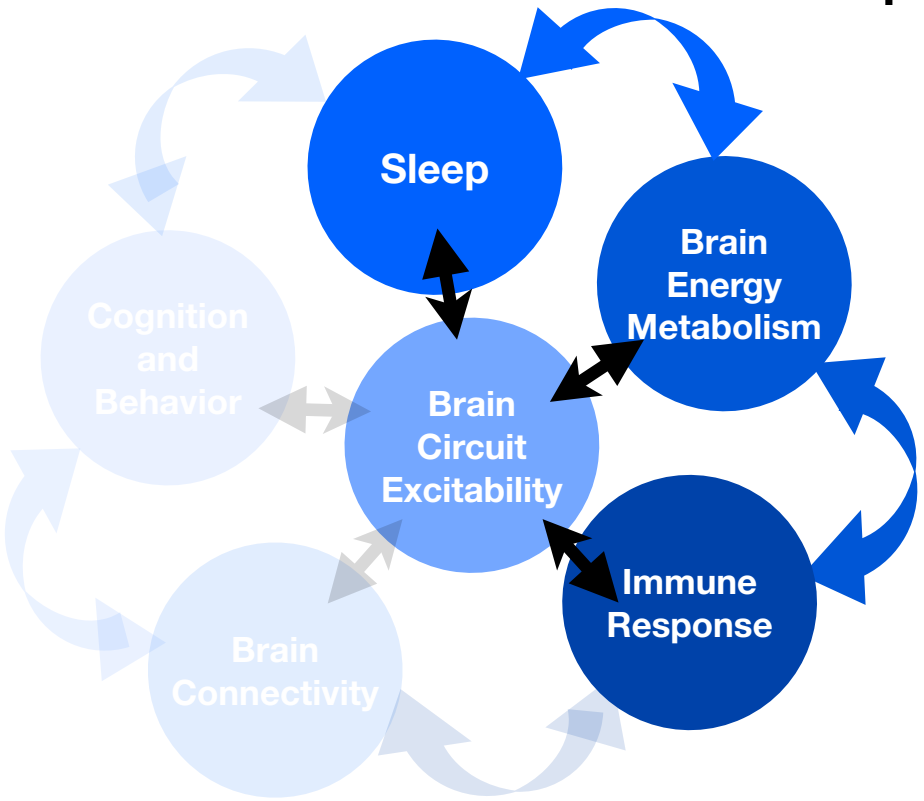
Predicting lapses of attention with sleep-like slow waves

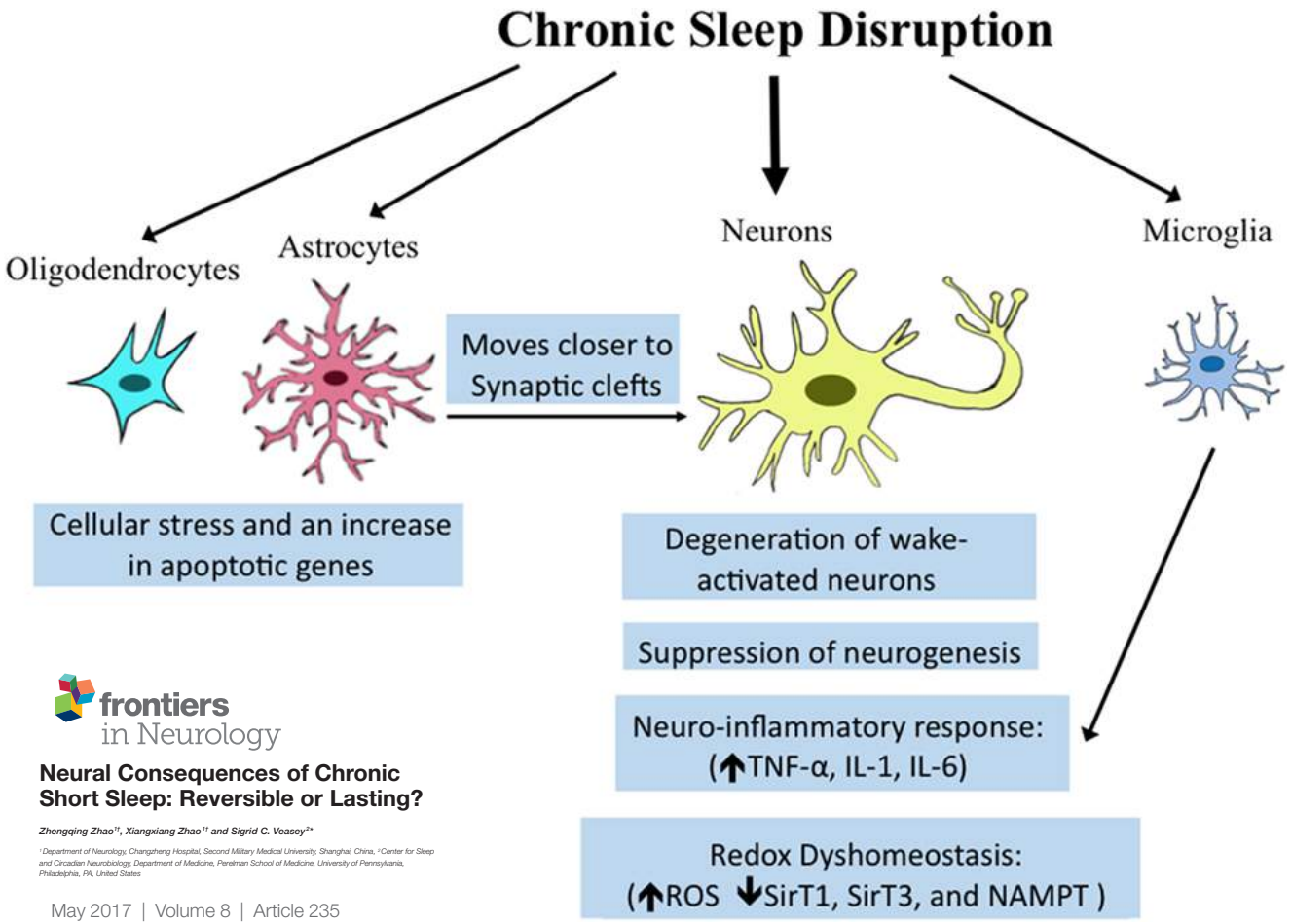
Thomas Andrillon [1,2]✉, Angus Burns [1], Teigane Mackay [1], Jennifer Windt[3] & Naotsugu Tsuchiya [1,4,5]

NATURE COMMUNICATIONS | (2021)12:3657 | https://doi.org/10.1038/s41467-021-23890-7 | www.nature.com/naturecommunications



Sleep Deprivation is associated with increased Excitability, Metabolic Stress, Microglial Activation, Dyshomeostasis and Immune Response





frontiers in Neurology

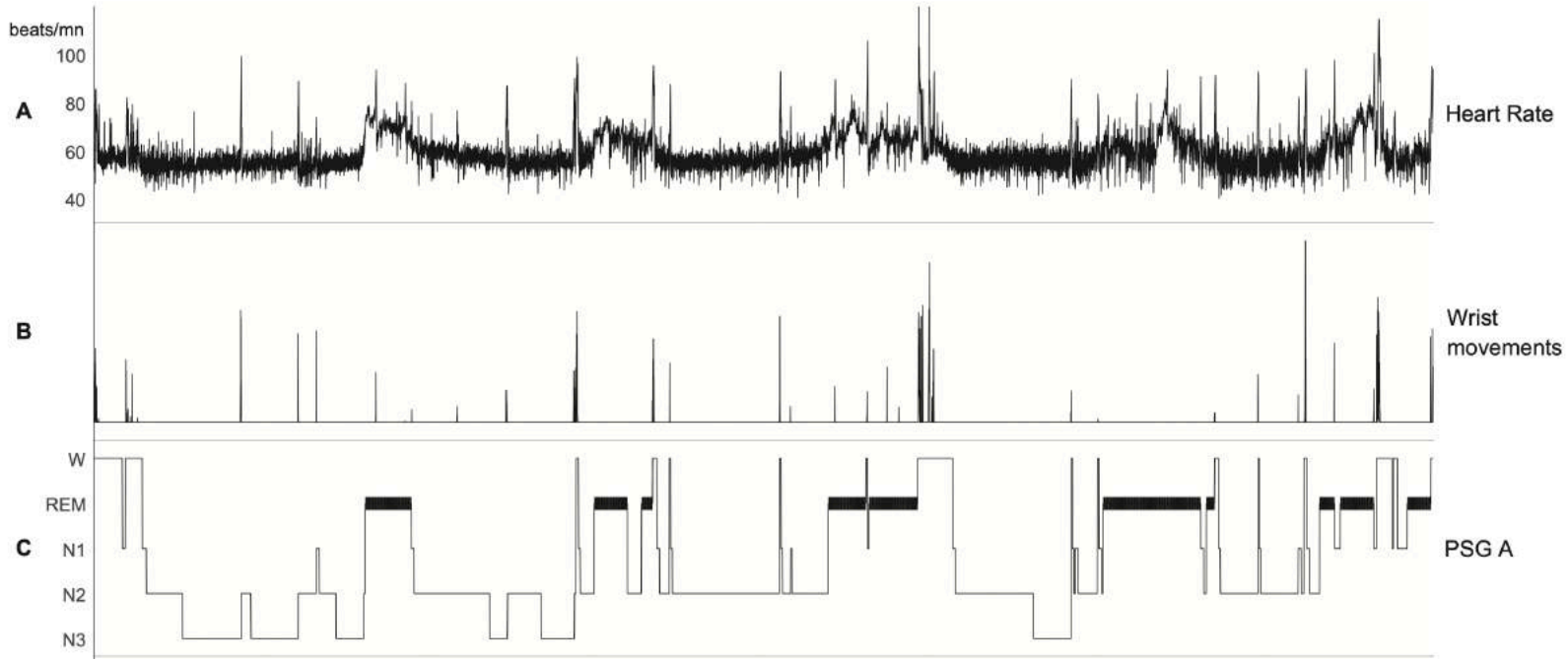
Neural Consequences of Chronic Short Sleep: Reversible or Lasting?

*Zhengqing Zhao[1†], Xiangxiang Zhao[1†] and Sigrid C. Veasey[2]**

[1] Department of Neurology, Changzheng Hospital, Second Military Medical University, Shanghai, China, [2] Center for Sleep and Circadian Neurobiology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

May 2017 | Volume 8 | Article 235

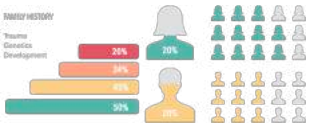
Using wearables to predict sleep architecture from actigraphy and heart rate



Muzet, Alain et al. “Assessing sleep architecture and continuity measures through the analysis of heart rate and wrist movement recordings in healthy subjects: comparison with results based on polysomnography.” Sleep medicine 21 (2016): 47-56 .

Data-Driven Digital Twins for Mental Health

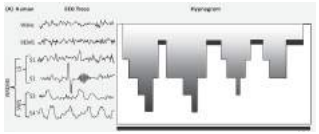
Demographics



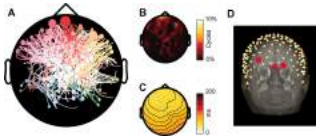
Clinical records

Social Activity

Sleep



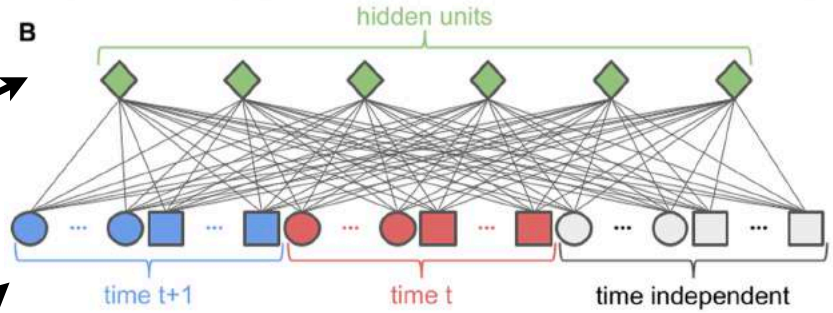
Brain Imaging



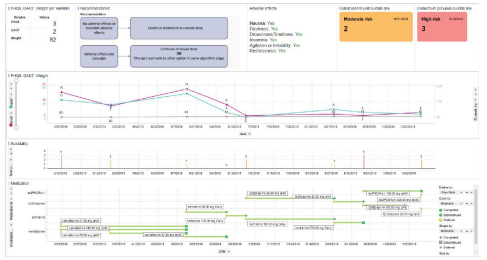
A Study population — Personalized simulation

Measurements	t=0	t=1	...	t=n
Age	71	71	...	71
PHQ9	5	4	...	5
GAD7	3	5	...	5
...	...	...	...	...
Blood marker	NA	210.1	...	202.6

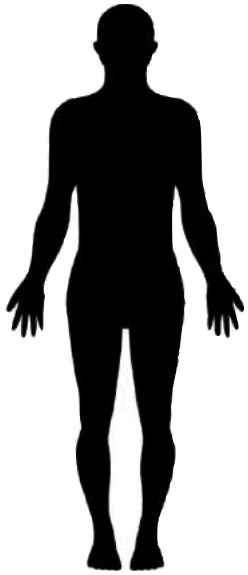
B

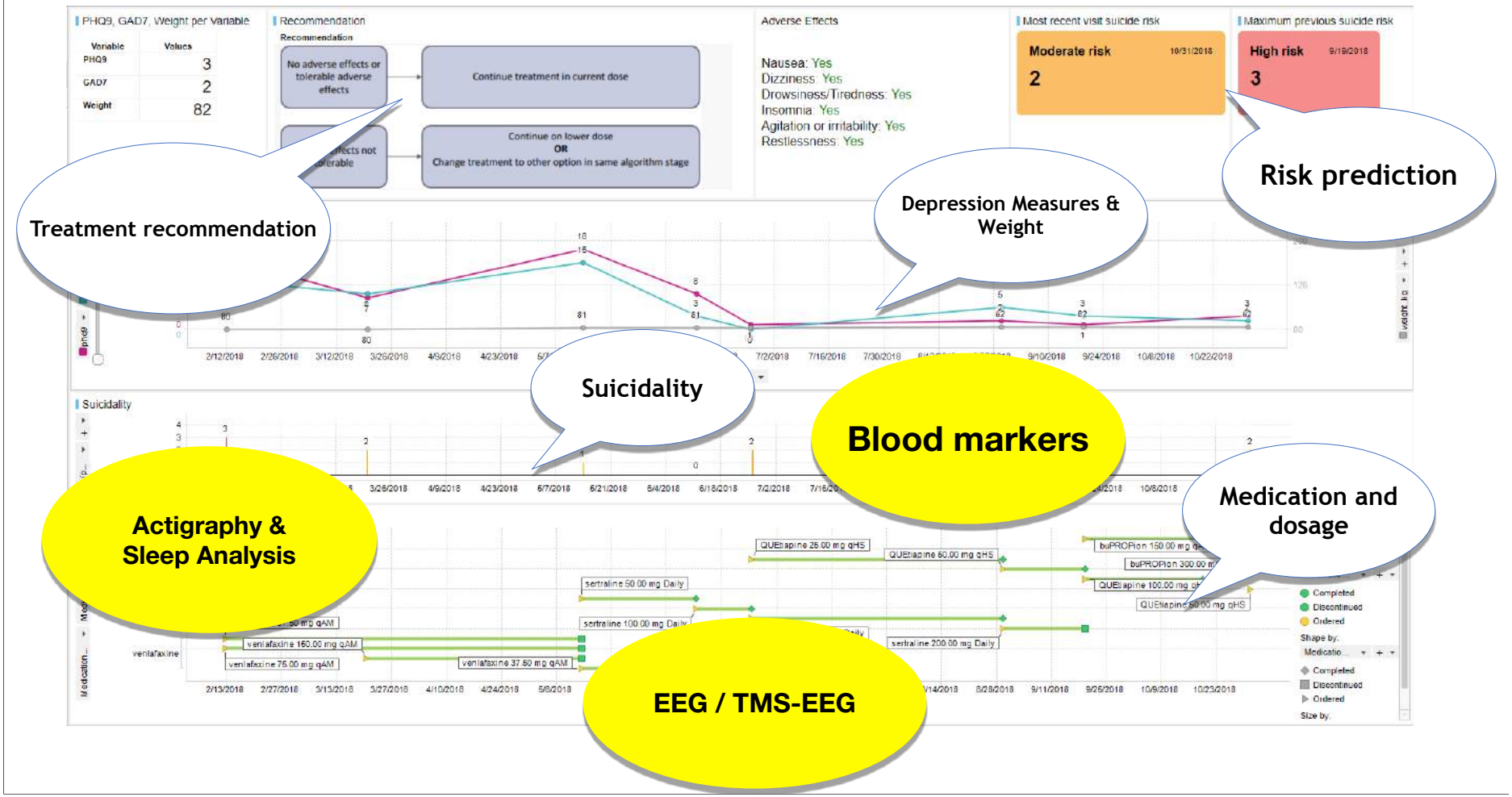


Neural Network



https://doi.org/10.1038/s41598-019-49656-2




PHQ9, GAD7, Weight per Variable
Variable
Values
PHQ9
3
GAD7
2
Weight
82
Recommendation
Recommendation
No adverse effects or tolerable adverse effects
Continue treatment in current dose
Continue on lower dose
OR
Change treatment to other option in same algorithm stage
Adverse Effects
Nausea: Yes
Dizziness: Yes
Drowsiness/Tiredness: Yes
Insomnia: Yes
Agitation or irritability: Yes
Restlessness: Yes
Most recent visit suicide risk
Moderate risk
10/31/2018
2
Maximum previous suicide risk
High risk
9/19/2018
3
Suicidality
sertraline 50.00 mg Daily
sertraline 100.00 mg Daily
sertraline 200.00 mg Daily
venlafaxine 150.00 mg qAM
venlafaxine 75.00 mg qAM
venlafaxine 37.50 mg qAM
QUEtiapine 25.00 mg qHS
QUEtiapine 50.00 mg qHS
QUEtiapine 100.00 mg qHS
buPROPion 150.00 mg q
buPROPion 300.00 m
Completed
Discontinued
Ordered
Shape by:
Size by:
Treatment recommendation
Depression Measures & Weight
Risk prediction
Suicidality
Blood markers
Actigraphy & Sleep Analysis
Medication and dosage
EEG / TMS-EEG

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Andy Wang	Research Methods Specialist – HPC Admin
Marcos Sanches	Research Methods Specialist - Biostatistics
Nikola Bogetic	IT Specialist – Dev Ops
Natalia Potapova	Research Methods Specialist – Database + EDC
Qing Chang	Research Methods Specialist – RIC/PET
Steve Hawley	Project Lead - REDCap Lead
Pierre Rochefort	IT Specialist - Research Operations
Alexander Barton	Research Methods Specialist – XNAT
Adeel Ansari	Knowledge Engineering Lead
Joanna Yu	Senior Portfolio Manager – BHDB
Rachelle Farkas	Research Methods Specialist – Labkey
Farhad Qureshi	Research Methods Specialist – Data/Visualization

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