

NODE

#7

WORKSHOP

AUGUST 7-8, 2018 | MONTREAL, CANADA

Precision Medicine: Uncovering Cellular Mechanisms of Alzheimer's Disease with TheVirtualBrain

ANA SOLODKIN, UC IRVINE HEALTH/NEUROLOGY



SEARCHING FOR CURES

THE WALL STREET JOURNAL.

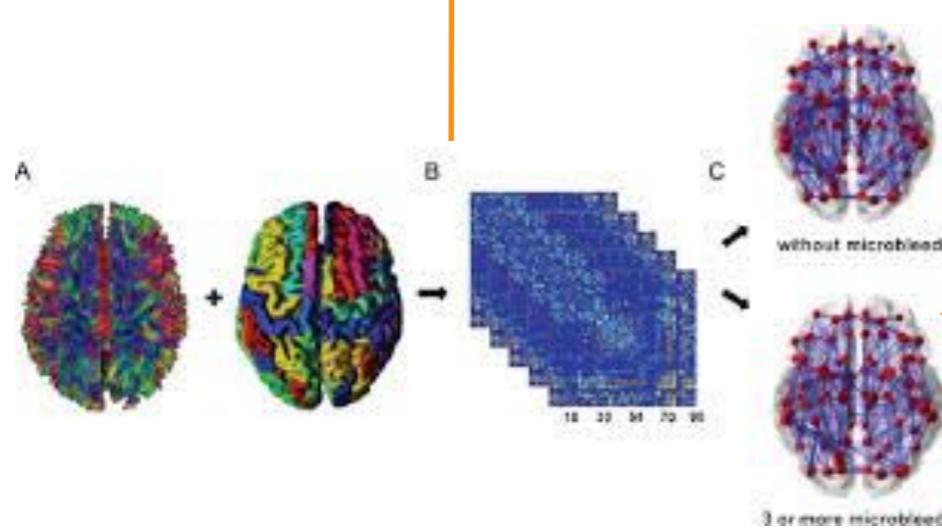
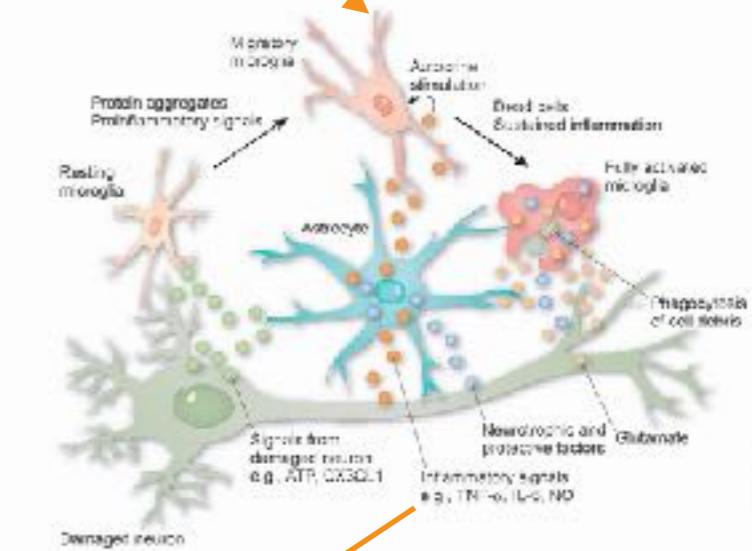
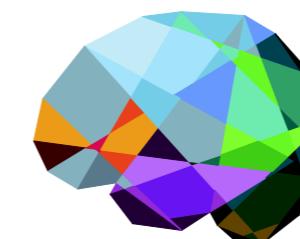
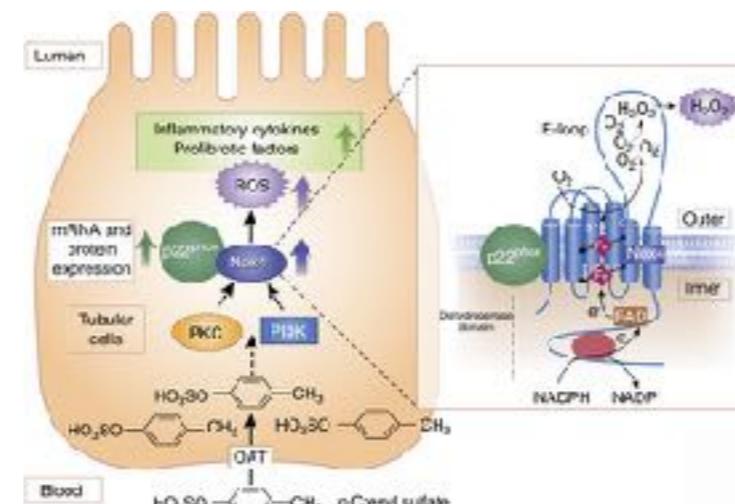
Eli Lilly, AstraZeneca Drop Two Late-Stage Alzheimer's Drug Trials

The move is the latest setback toward finding a cure for the degenerative illness



June 12th, 2018

SEARCHING FOR CURES



THE VIRTUAL BRAIN.

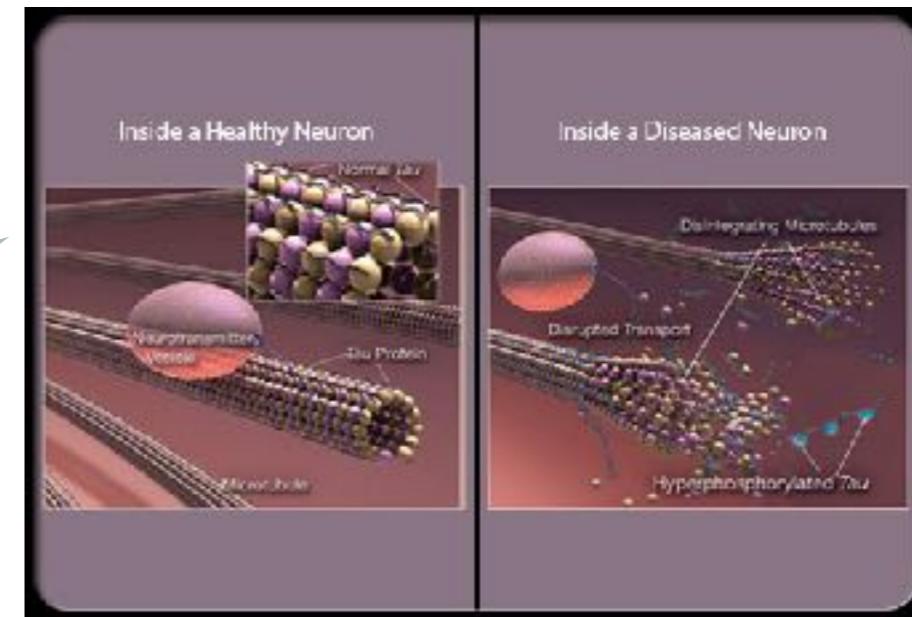
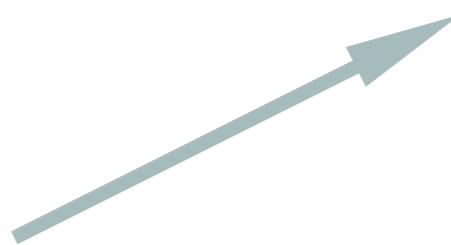
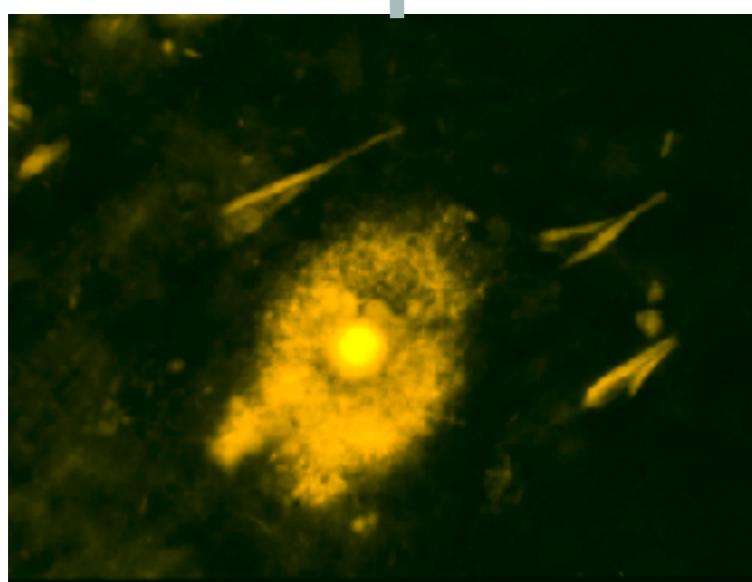
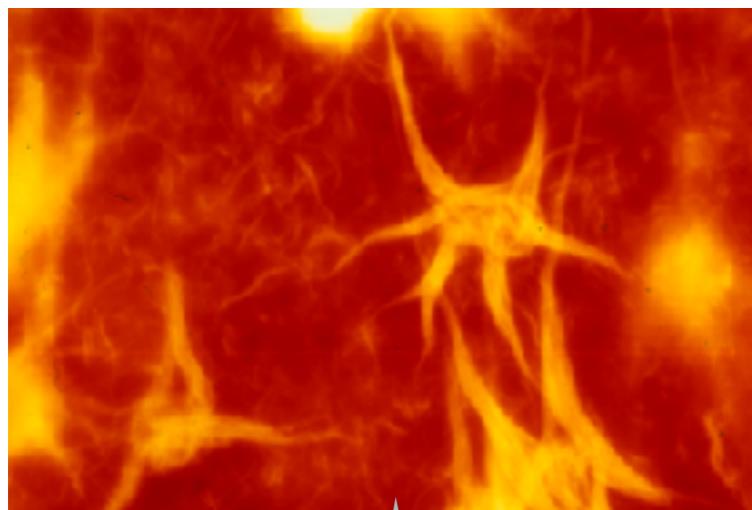
Affected aspect	Affecting chandelier cells	Affected cell type not identified	Affecting PV basket cells
Input	<i>FoxJ1</i>	<i>Nrgf</i> <i>Fmr1</i> <i>Cdk5</i> <i>Mgat2</i> <i>Mgat1</i>	<i>FoxJ1</i>
Intrinsic		<i>Mgat2</i> <i>Cystathione</i> <i>Serata</i> <i>Savant</i>	
Output	<i>FoxJ1</i> <i>Nrgf</i>	<i>Fact1</i> <i>Lhx2a</i> <i>Shank3</i> <i>Cdk5</i> <i>Gdnf10</i> <i>Mgat2</i> <i>Cdk5</i>	<i>Mgn2</i> <i>Mgn3</i> <i>R451Q</i>

CLINICAL CONSIDERATIONS

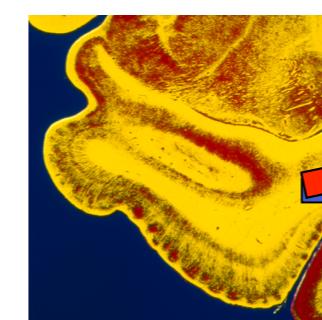
ALZHEIMER'S DISEASE

THE VIRTUAL BRAIN.

AD: A DISCONNECTION SYNDROME

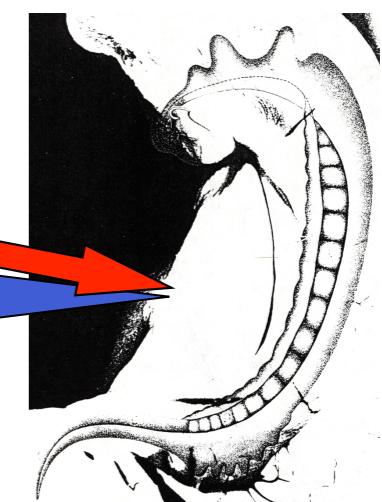


Entorhinal Cortex



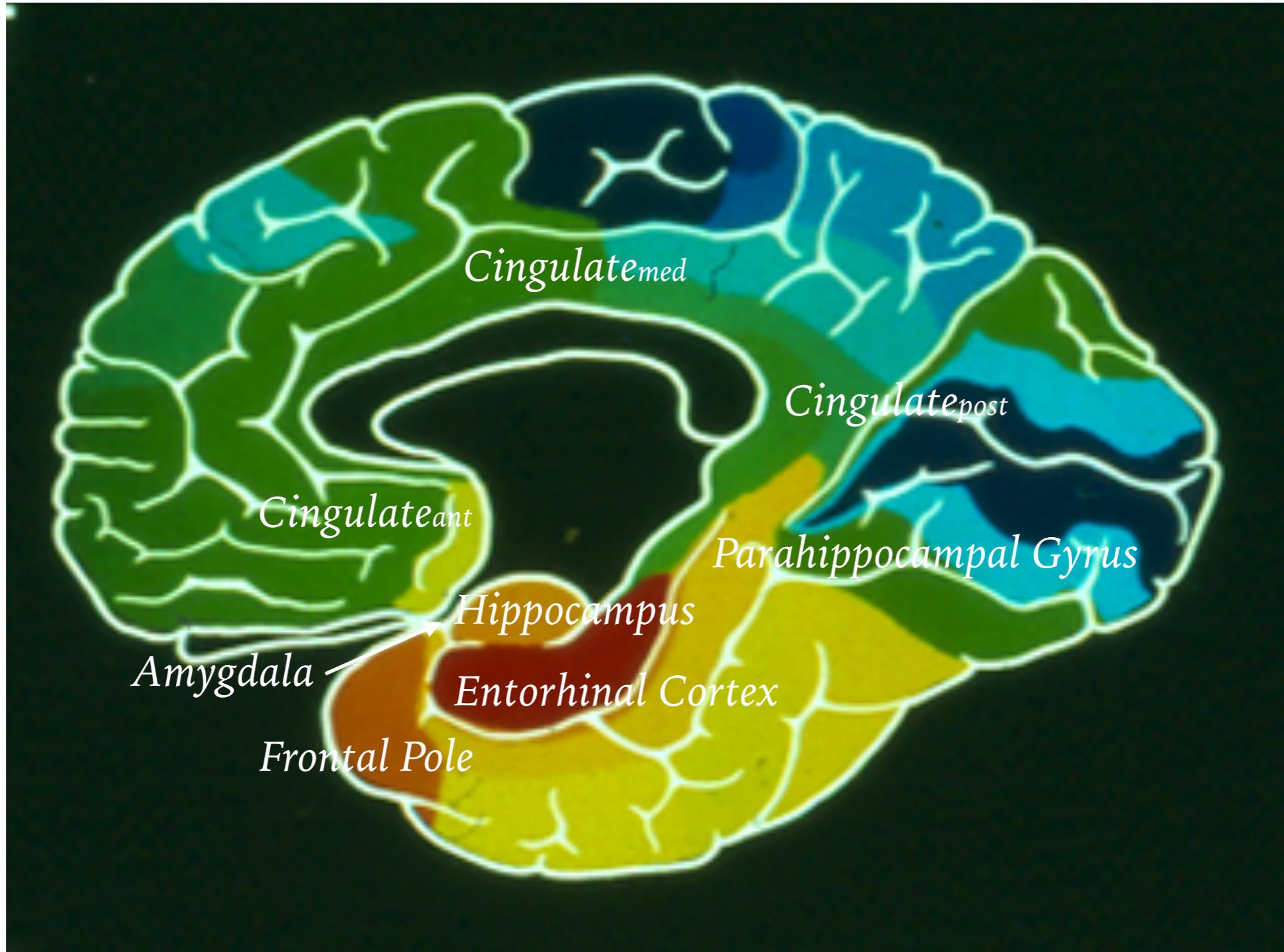
Perforant Path

Perforant Path

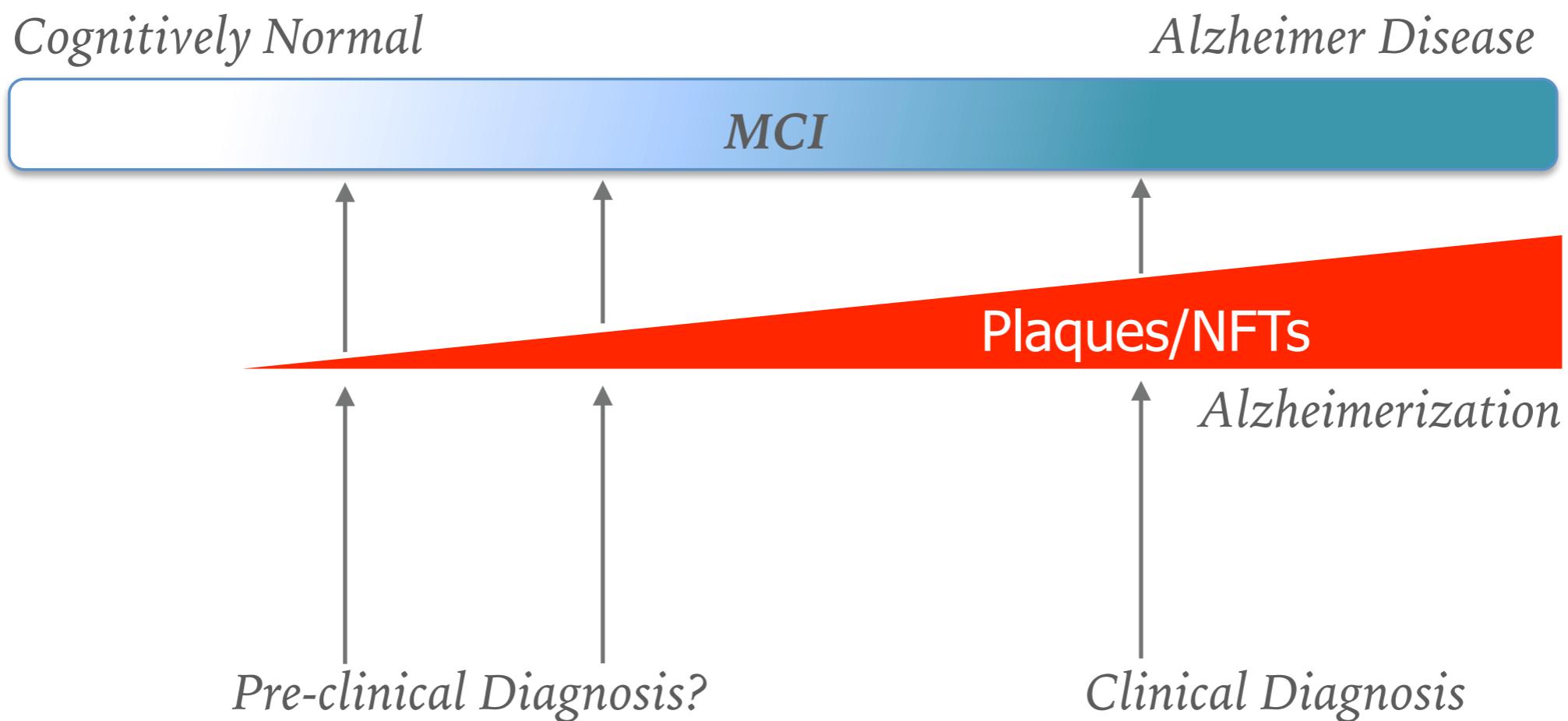


Hippocampus

DISTRIBUTION OF PATHOLOGY



AS THE REST OF THE WORLD



OUR COHORT

Our Cohort:

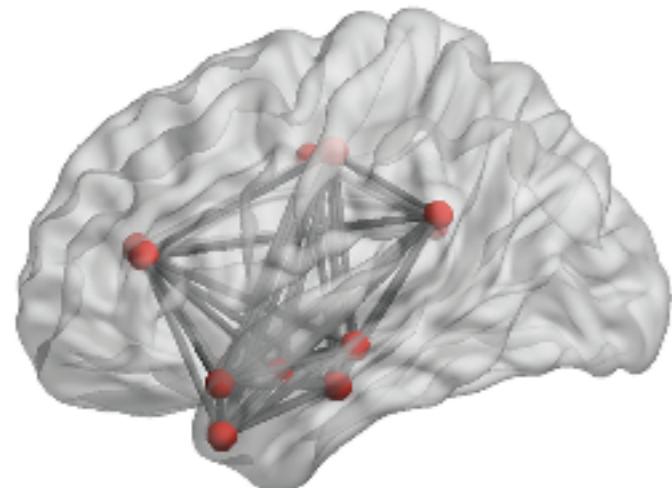
- Australian Memory and Aging Study (MAS)
 - 124 subjects
 - 27 Cognitively Normal
 - 31 Amnestic MCI
 - 16 AD



Basic Data:

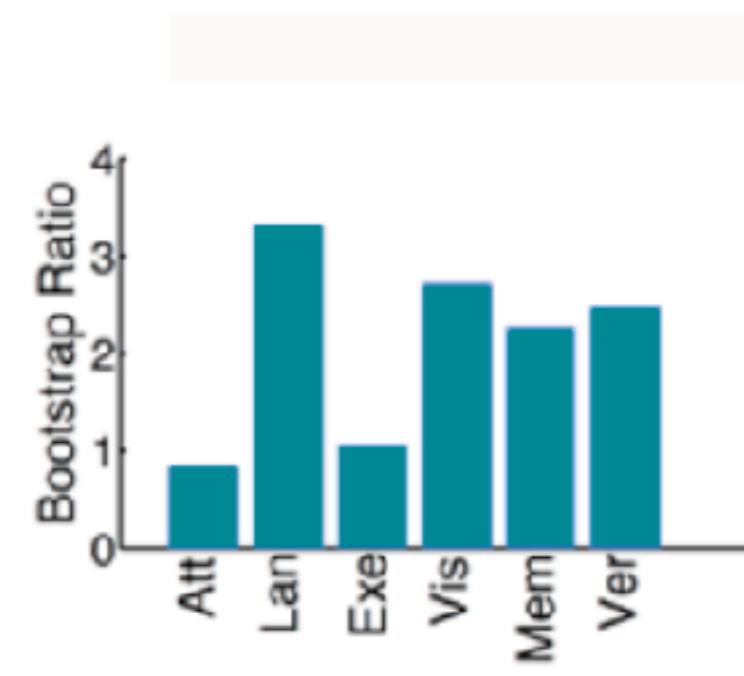
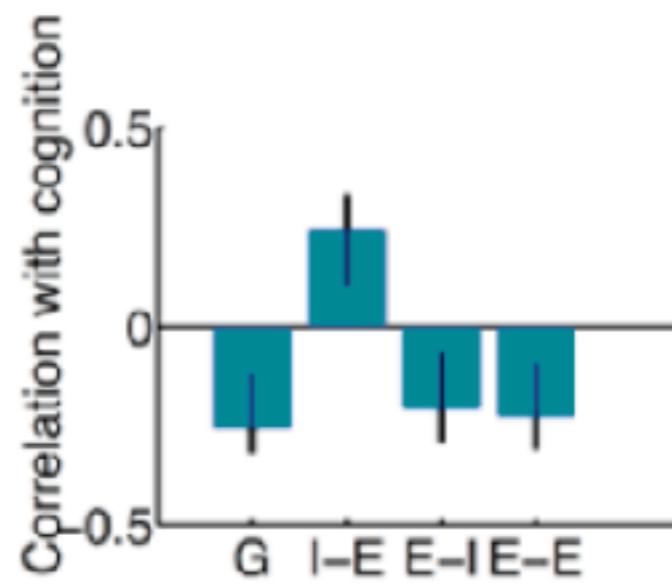
- Behavioral: cognitive + functional measures
- MR Imaging:
 - T1w
 - DWI(tensor)
 - rsfMRI (10 min)

GLOBAL AND LOCAL PARAMETERS



Better Cognitive Performance:

- *Higher local inhibition ($I-E$), lower excitability ($E-I$, $E-E$) and lower global coupling (G)*
- *Larger embeddedness*



THE VIRTUAL BRAIN



EXPLORATIONS AT THE CELLULAR LEVEL

THE VIRTUAL BRAIN.

SIMULATING RAW SIGNALS

Hypothesis

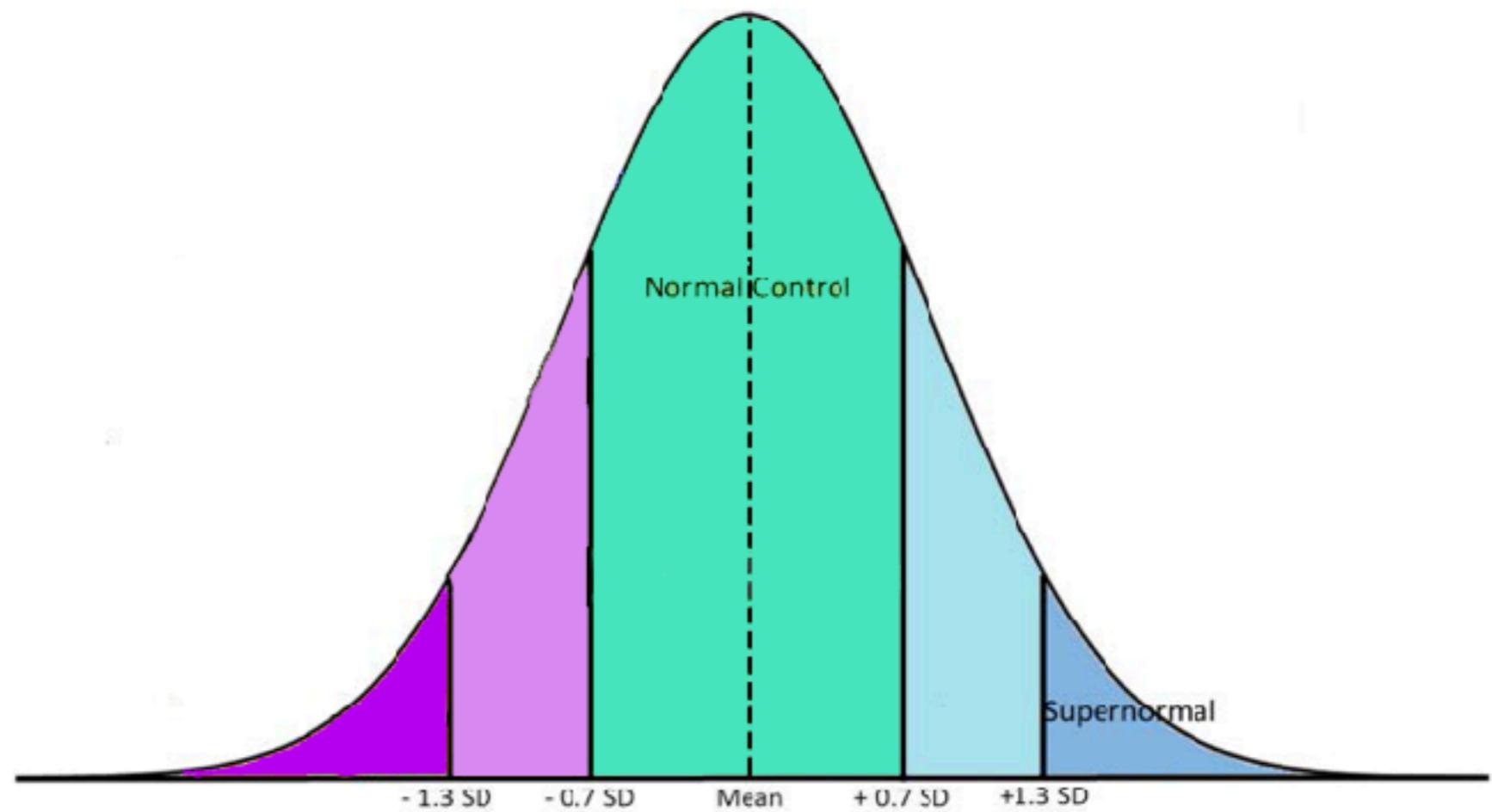
The assessment of brain dynamics at the cellular (mesoscopic) level can expand our understanding of biophysical mechanisms associated with the “disconnection” seen in AD

These changes should be closely associated with clinical phenotype

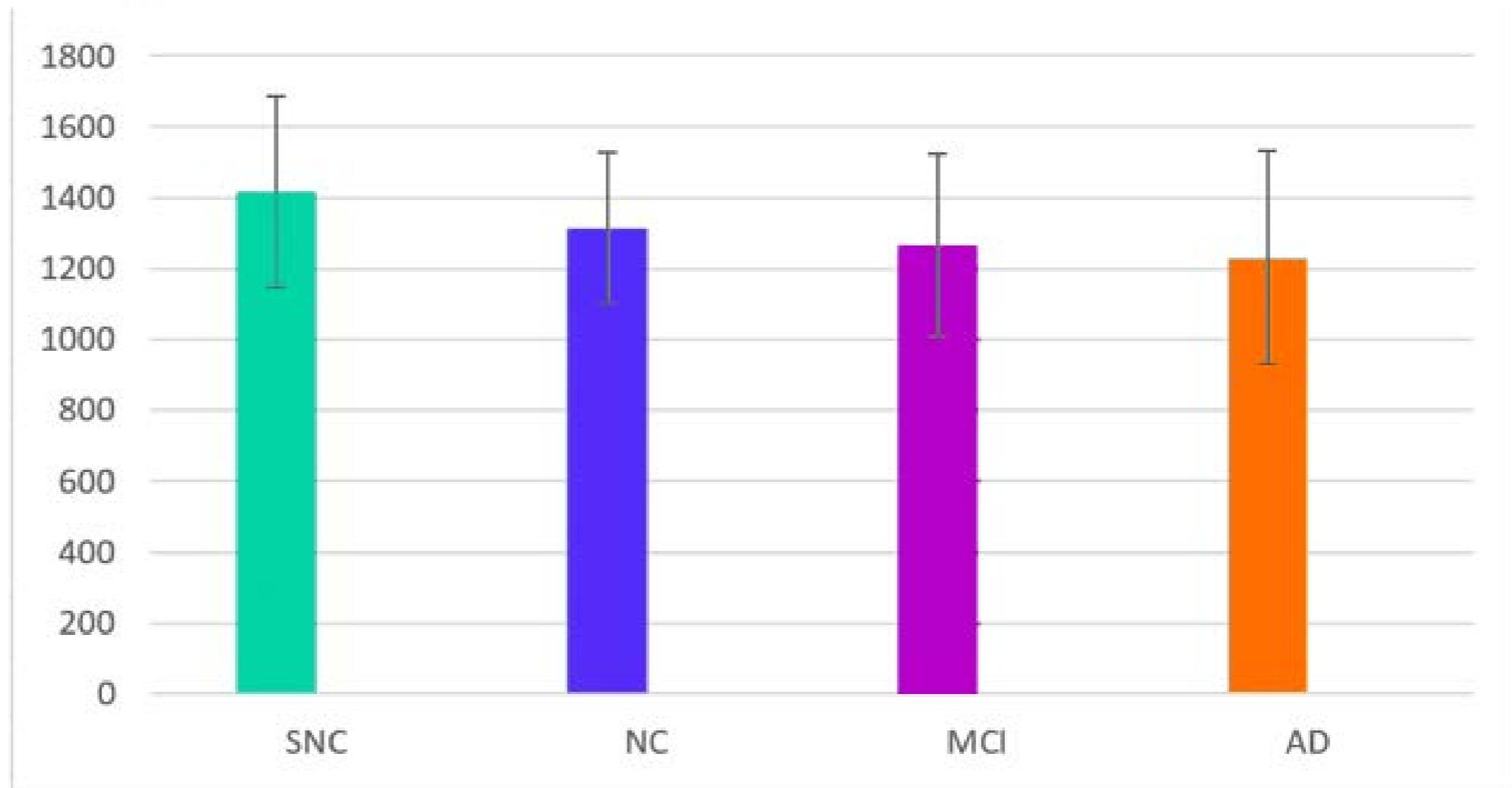
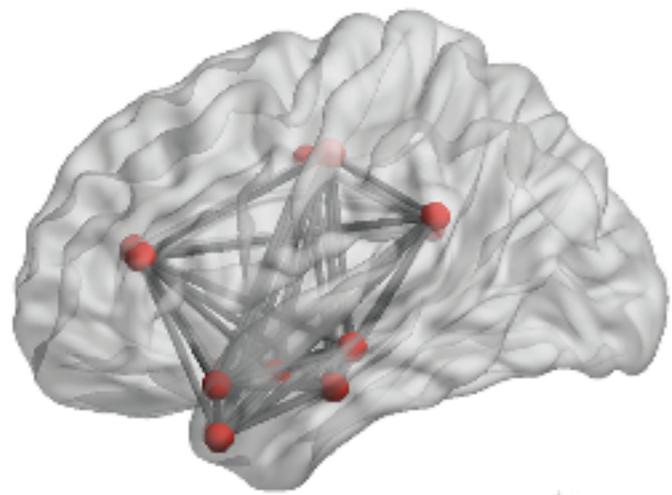
NOVEL COGNITIVE STRATIFICATION

Our cohort:

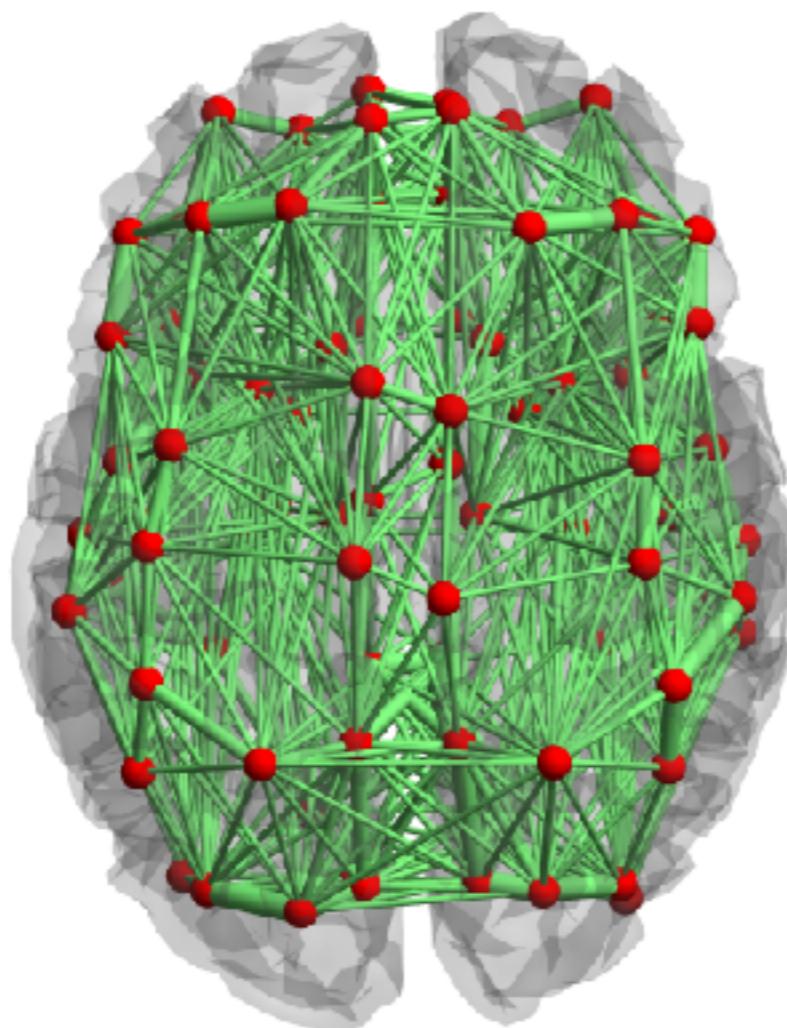
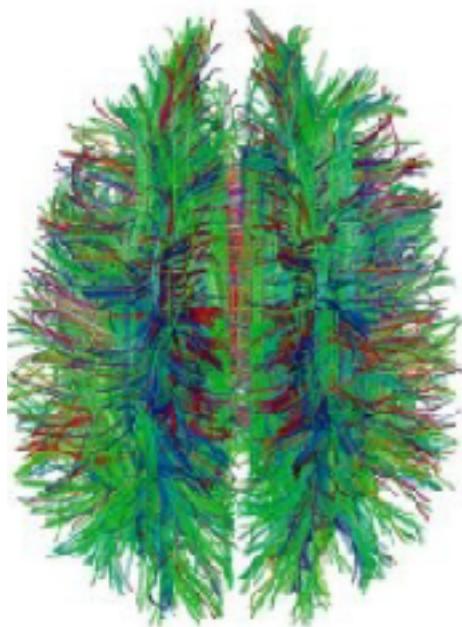
- 74 subjects
 - 11 Cognitively Super normal (> 1.5 SD)
 - 16 Cognitively Normal ($+/- 0.7$ SD)
 - 31 Amnestic MCI
 - 16 AD



WEIGHTS OF STRUCTURAL CONNECTIONS



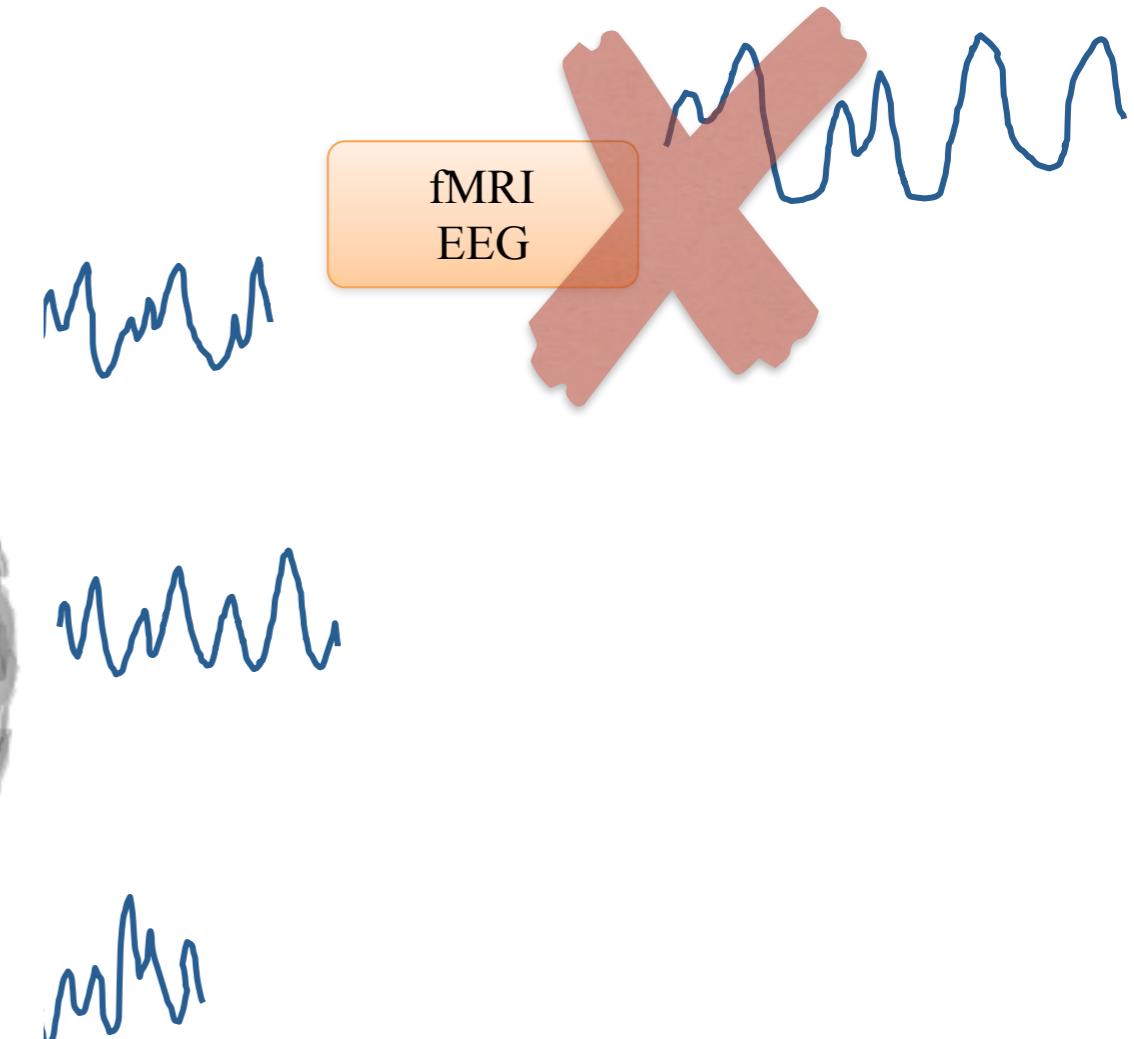
SIMULATING RAW SIGNALS (LFP)



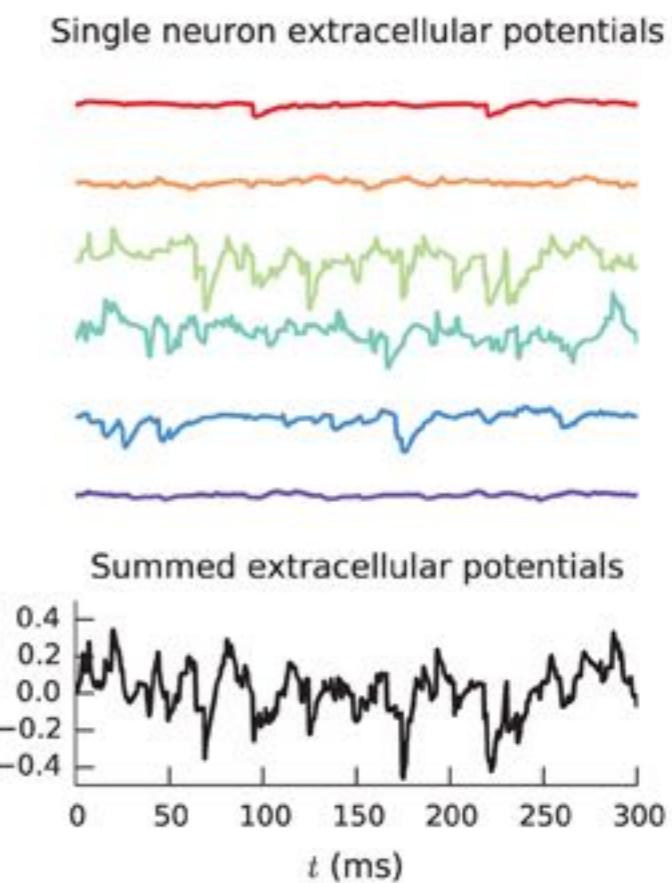
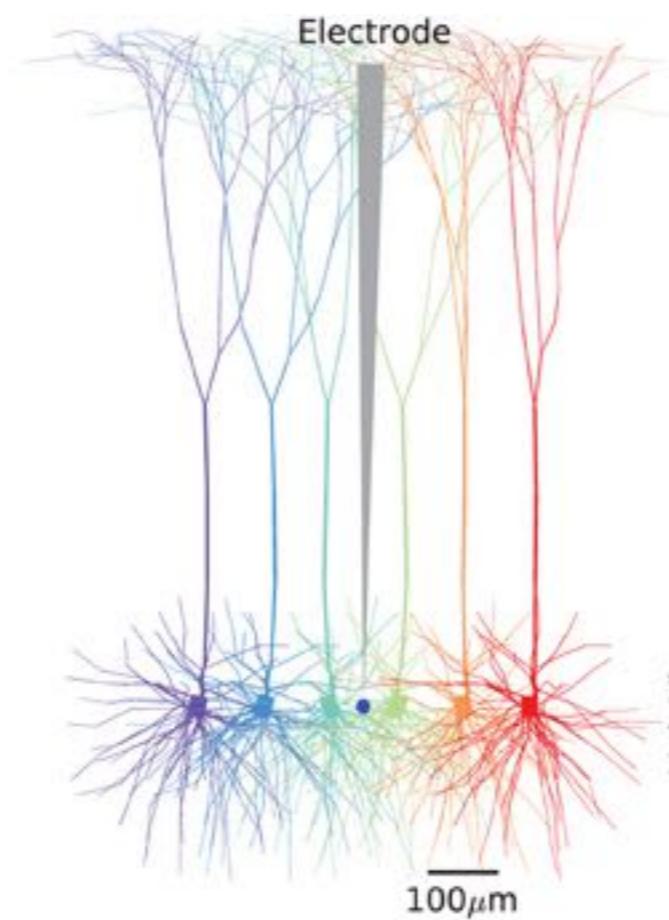
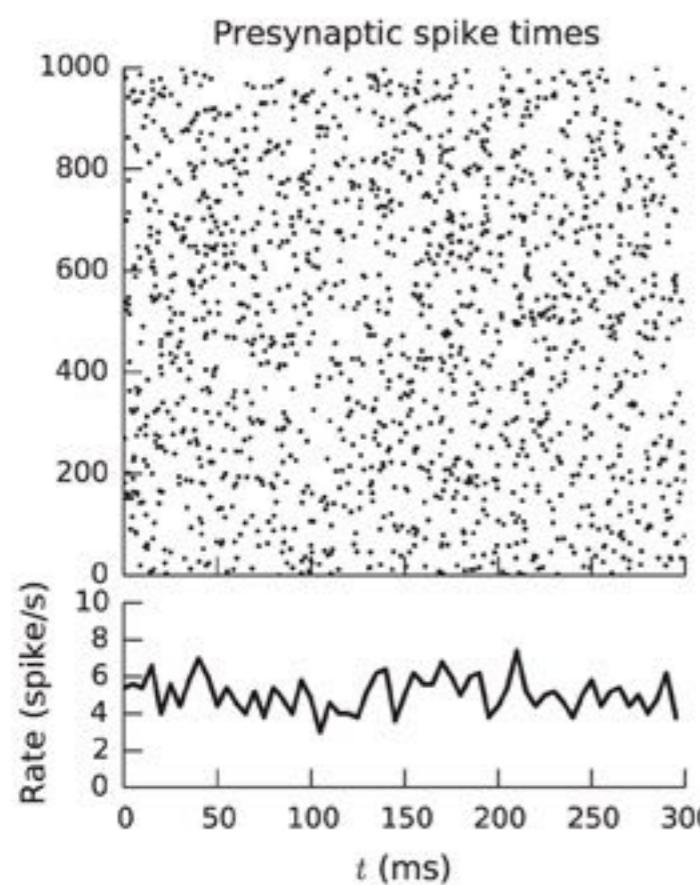
Structural
Neuroanatomical link



Dynamical Model of Local
Brain areas



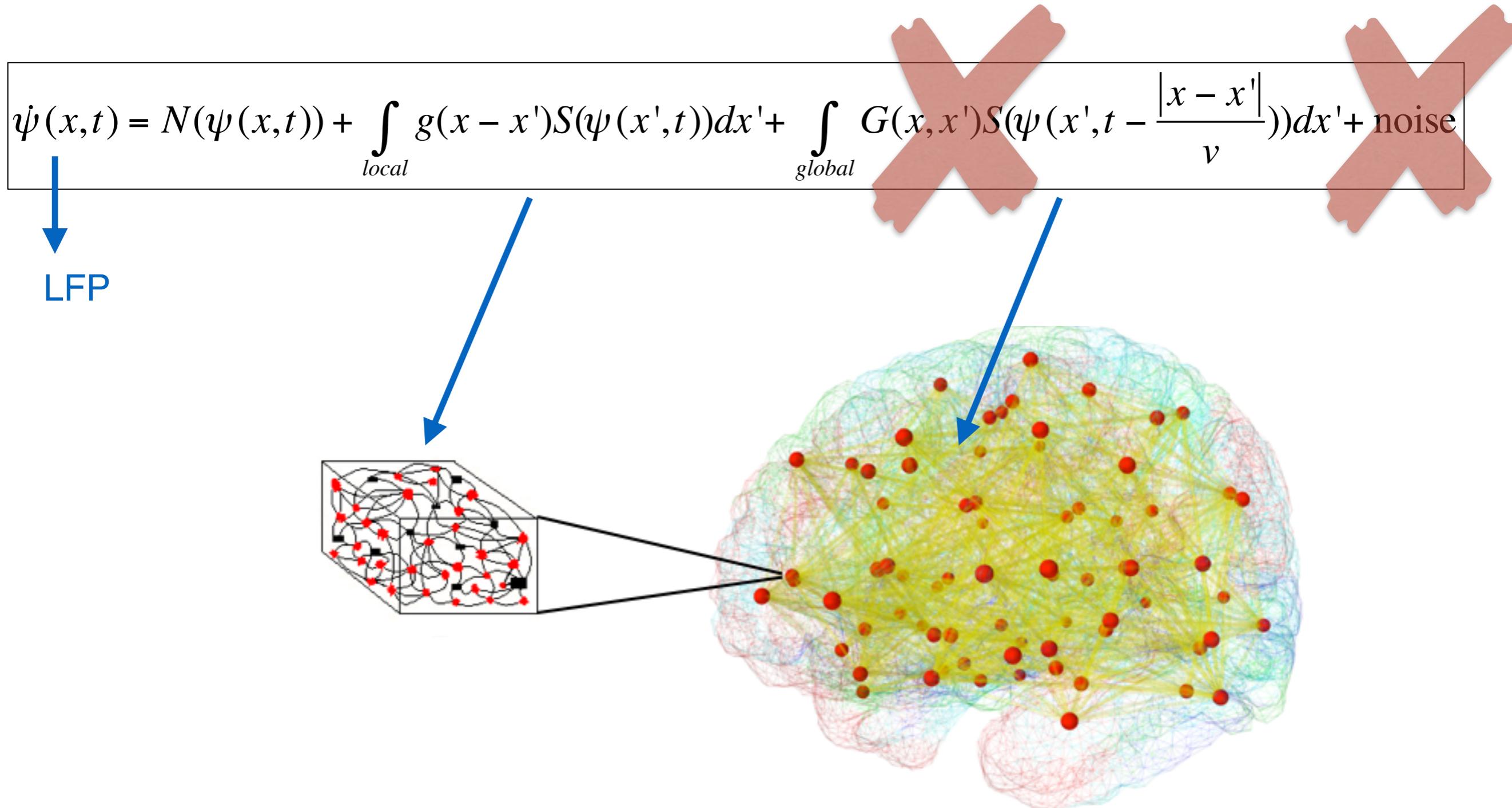
WHAT ARE LOCAL FIELD POTENTIALS?



Linden et al., 2014

LFP: Electrophysiological signal generated by the summed electric current flowing from multiple nearby neurons within a small volume of nervous tissue

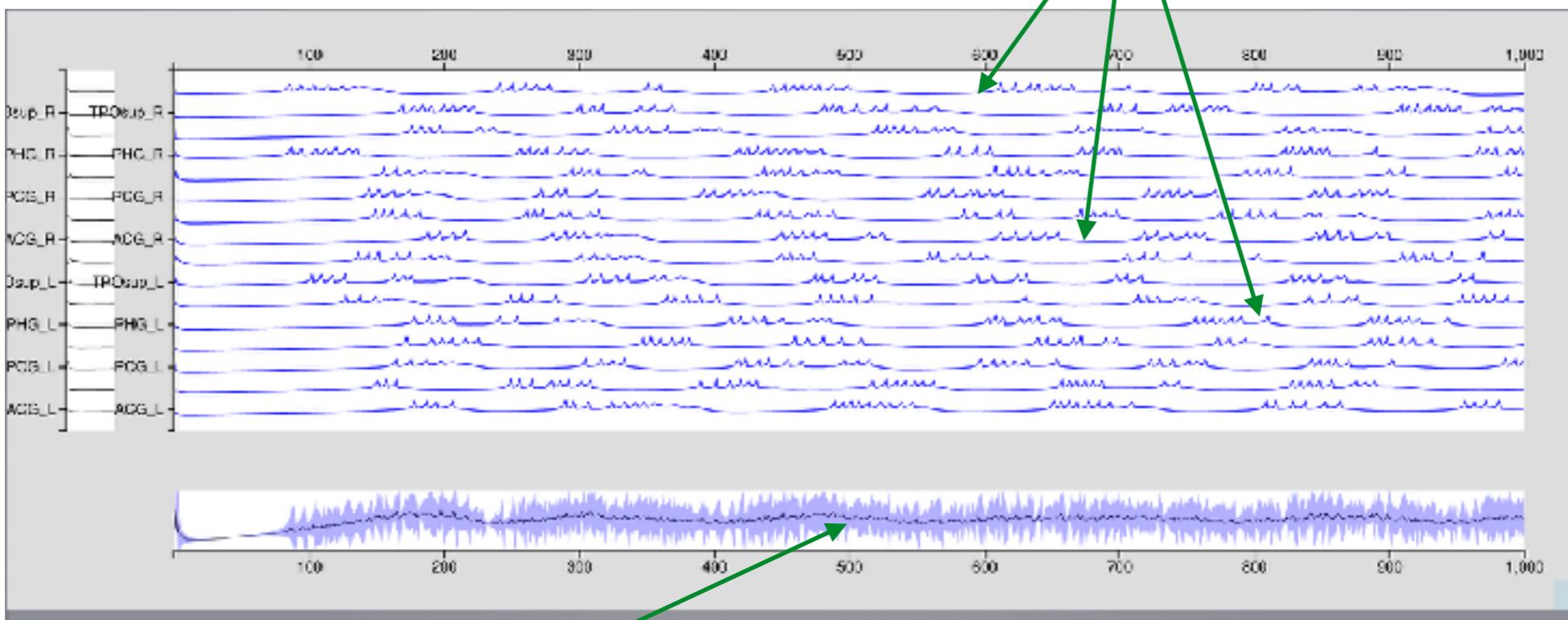
STEP 1: EFFECT OF LOCAL BRAIN DYNAMICS



TIME SERIES @ G = 0

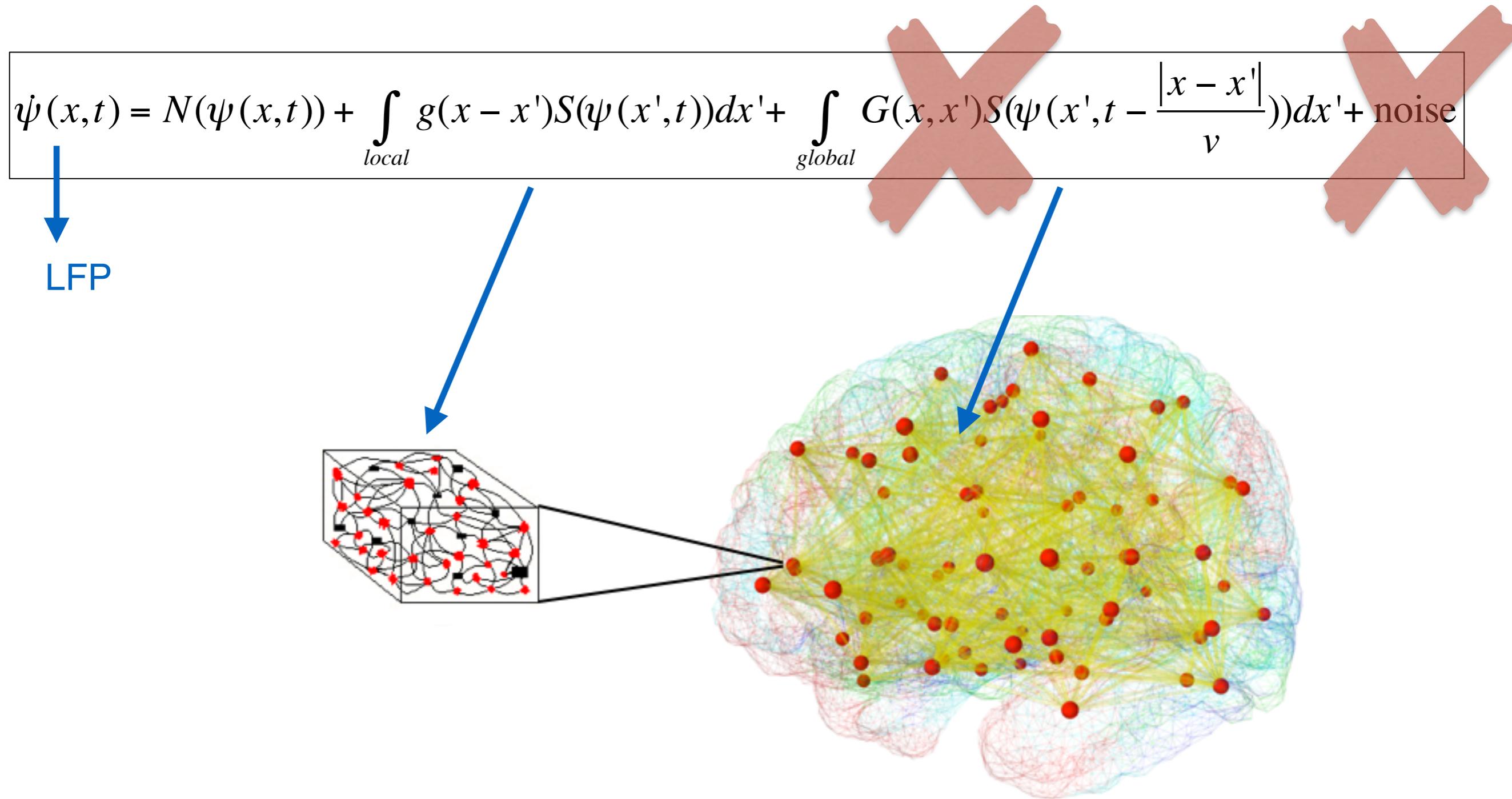
Regional Local Field Potentials

Limbic Brain Regions

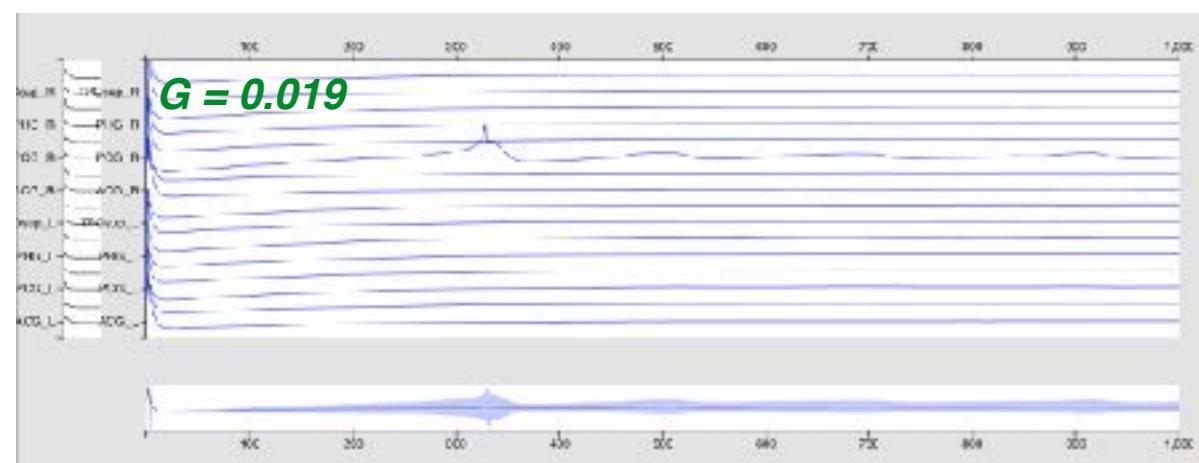
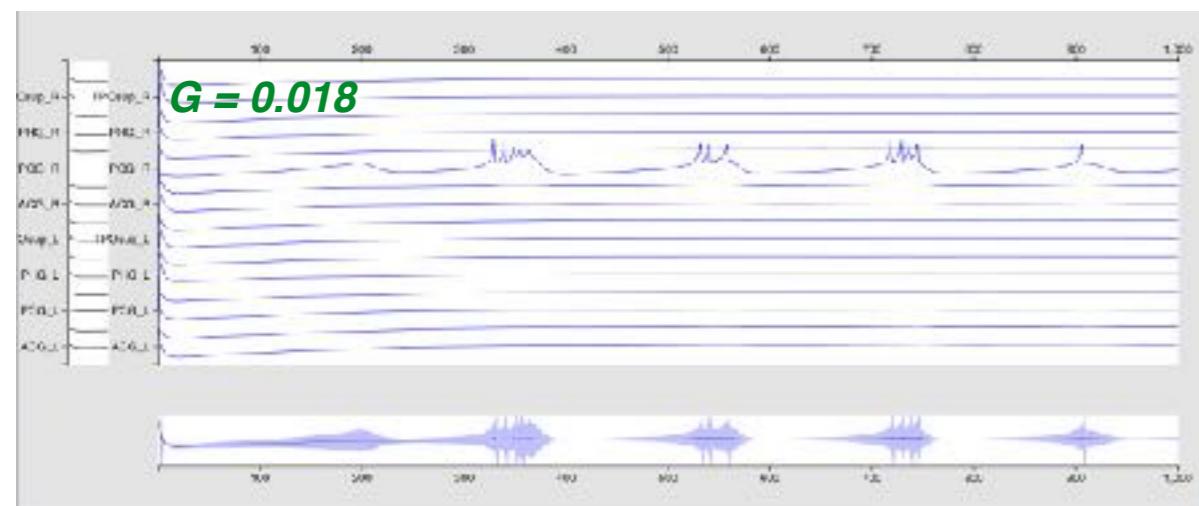
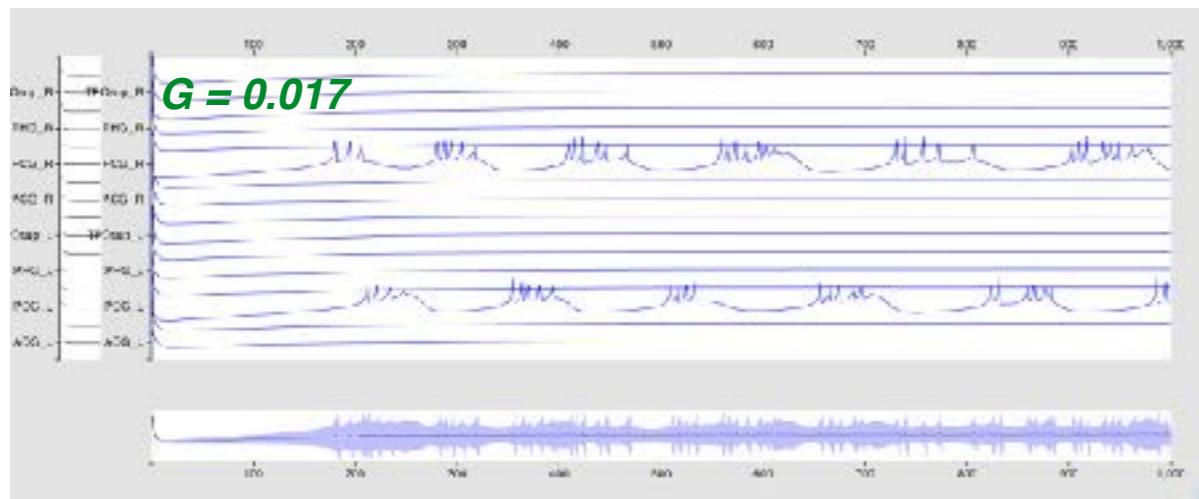


Average Local Field Potentials

STEP 2: INCREASING G



OSCILLATIONS @ $G > 0$

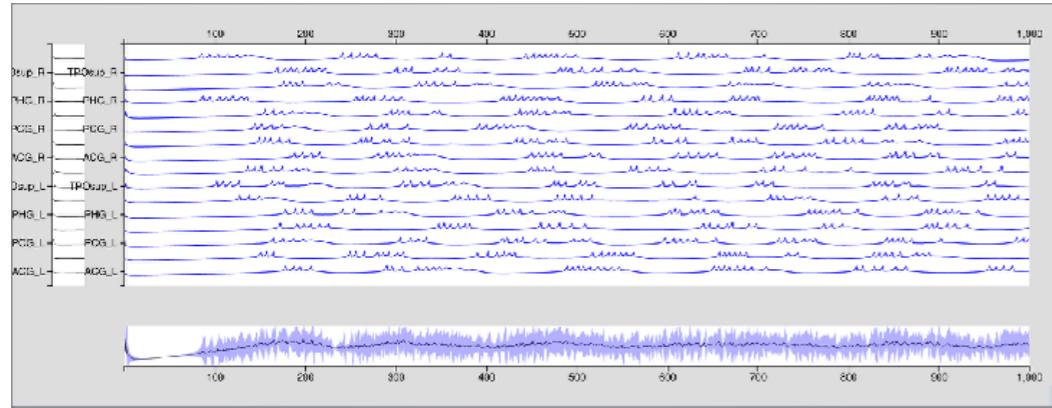


SNC
(- G)

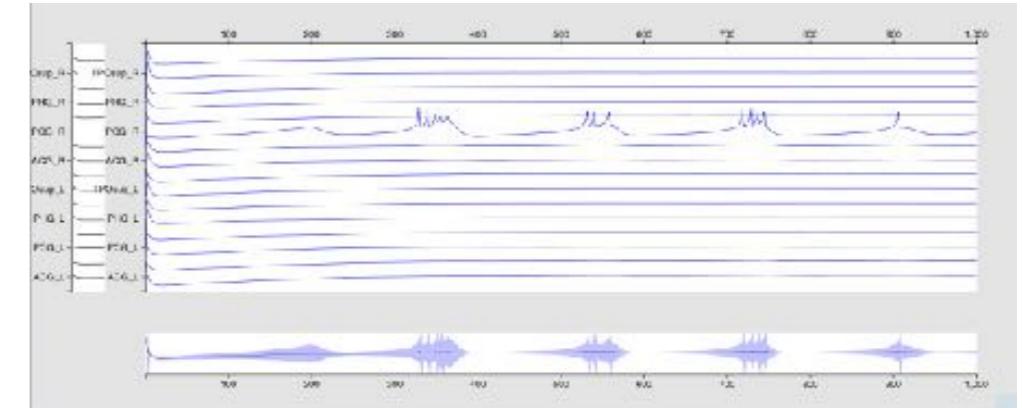
- Were present in one or two brain regions
- Location always in posterior cingulate
- Frequencies varied
- Can be spiking or not
- Stronger and more numerous in SNC
- G values were lower in SNC increasing along the cognitive continuum

AD
(+ G)

G CRITICAL AND BIFURCATIONS



Gc



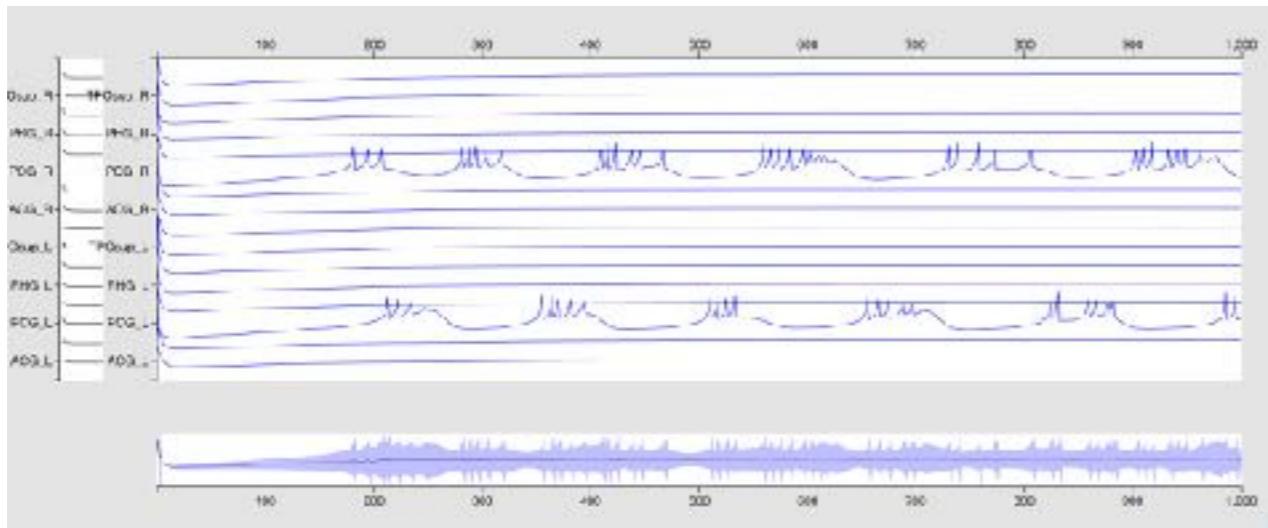
The behavior of a dynamic system converge onto an *attractor* (a point, limit cycle).

An attractor is stable when a small change in the system parameters lead to a small change in its morphology; otherwise it is said to undergo a *bifurcation*.

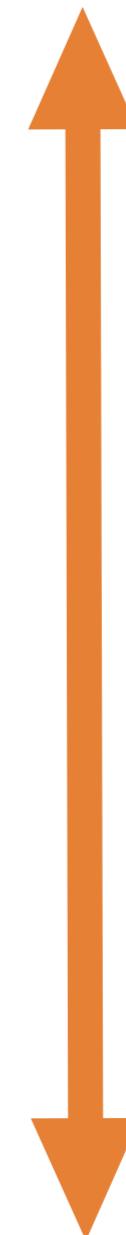
The idea is that for each neuron, the dynamics are near a bifurcation where the system can switch “modes”: Ex., from random firing to *oscillations*.

G critical (Gc) represent the bifurcation point for the system.

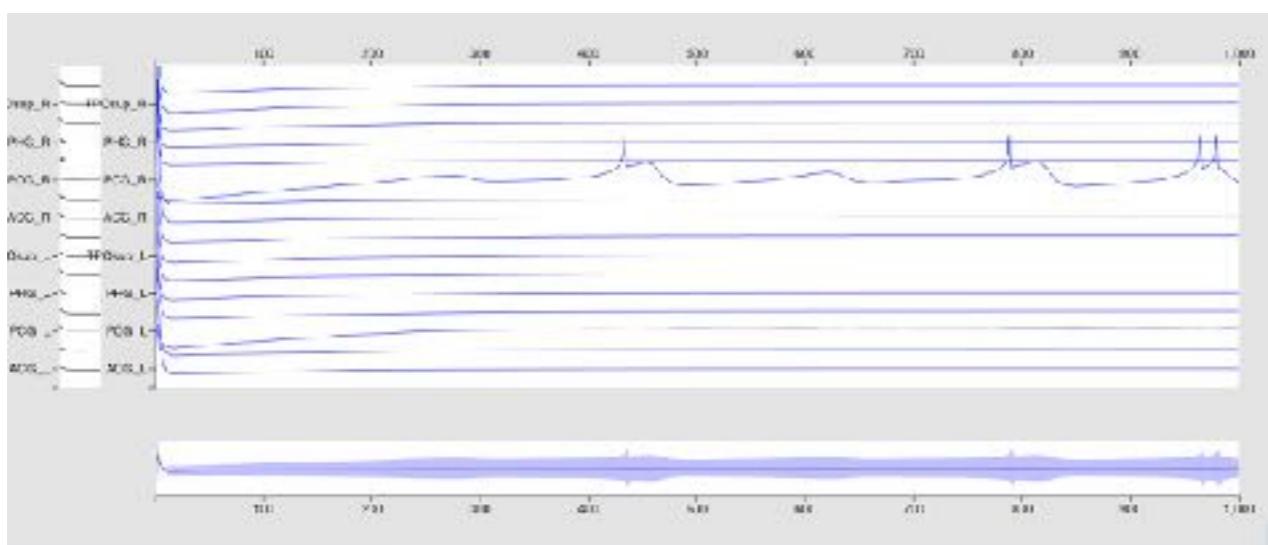
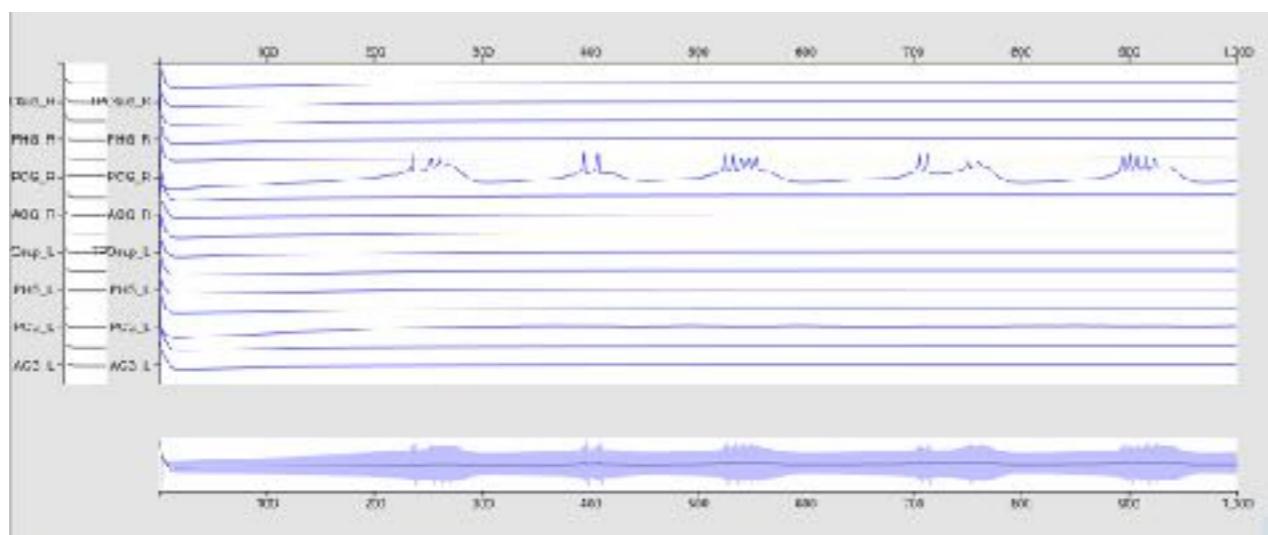
OSCILLATIONS @ $> G_c$



$G = 0.01$



Local
 G
Global



$G = 0.07$

DISEASE PROGRESSION AND G RANGES

$G = 0.017$



$G = 0.04$

$G = 0.018$



$G = 0.07$

$G = 0.018$



$G = 0.07$

$G = 0.019$



$G = 0.02$

Local
 G
Global

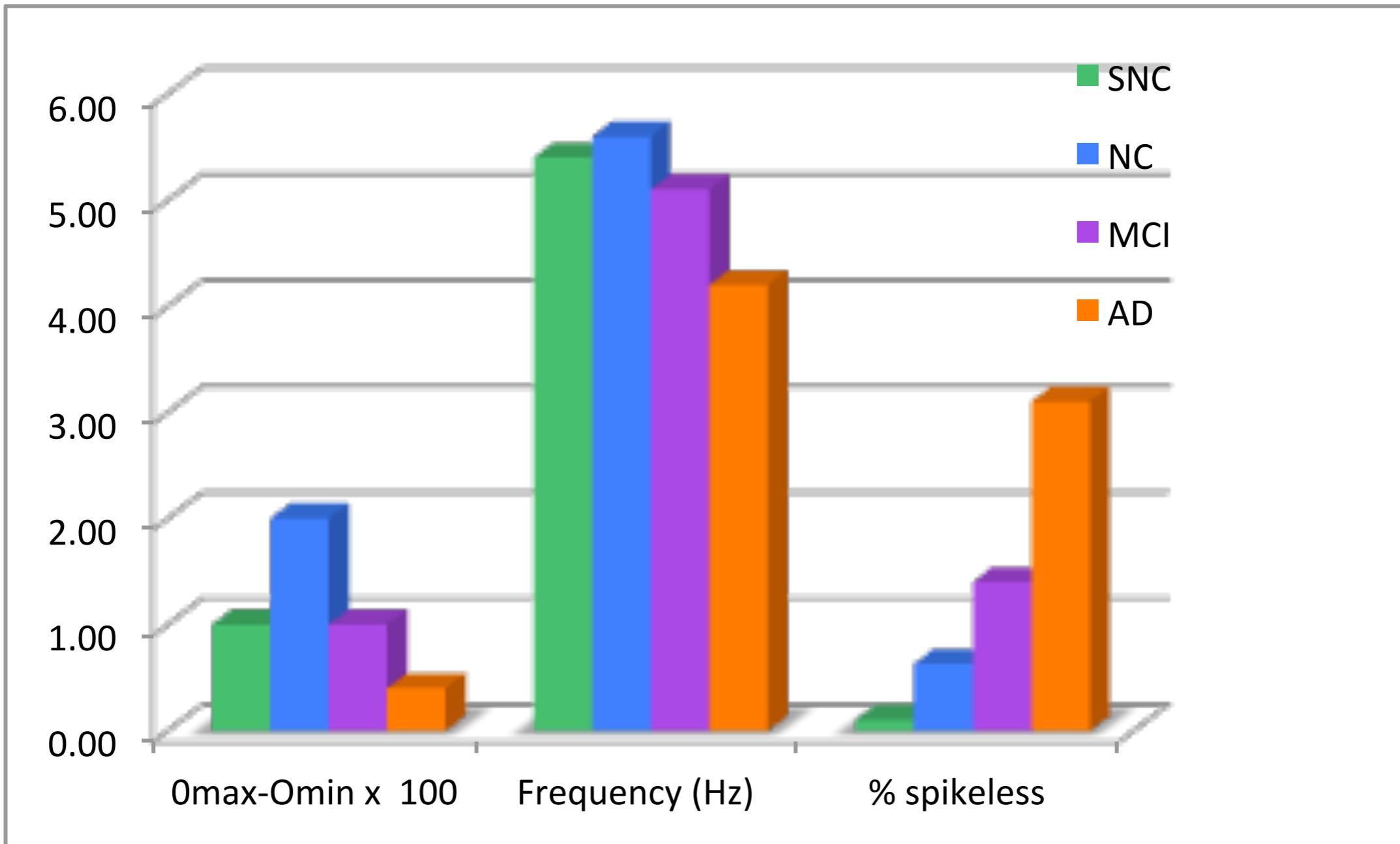
SNC

NC

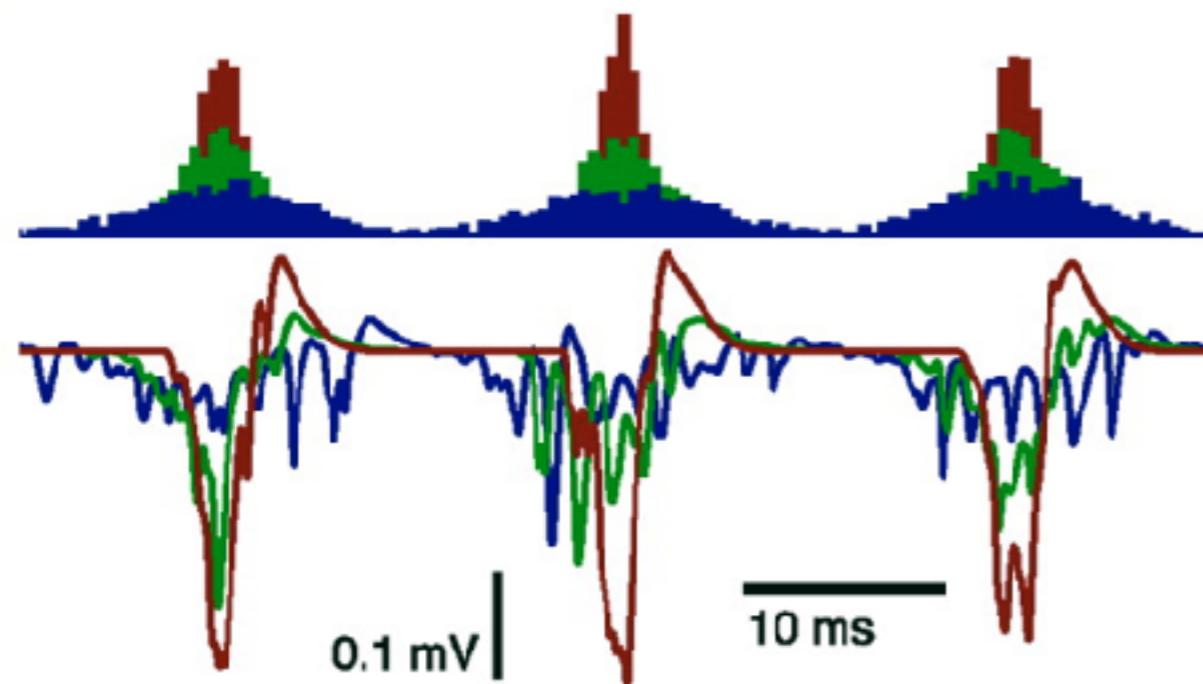
MCI

AD

ADDITIONAL METRICS

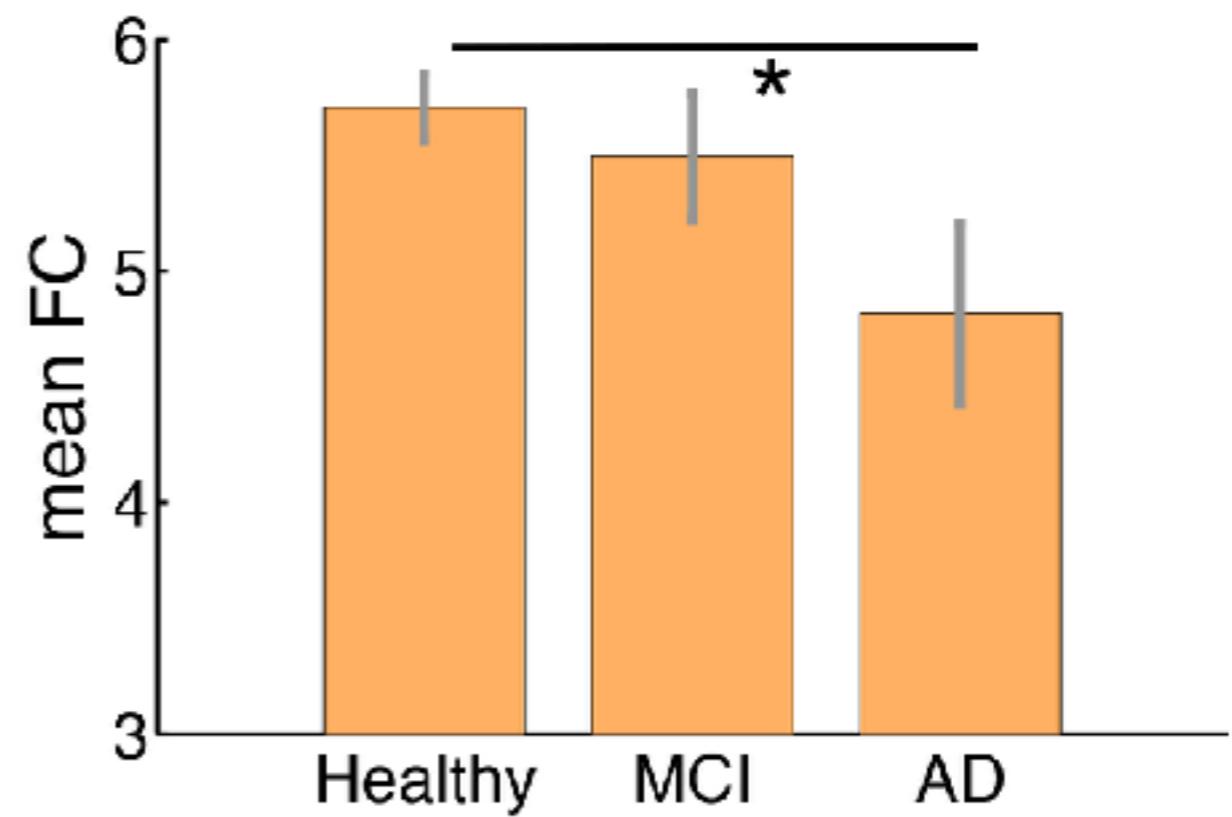


WHY SHOULD WE CARE?



Schomburg et al., 2012

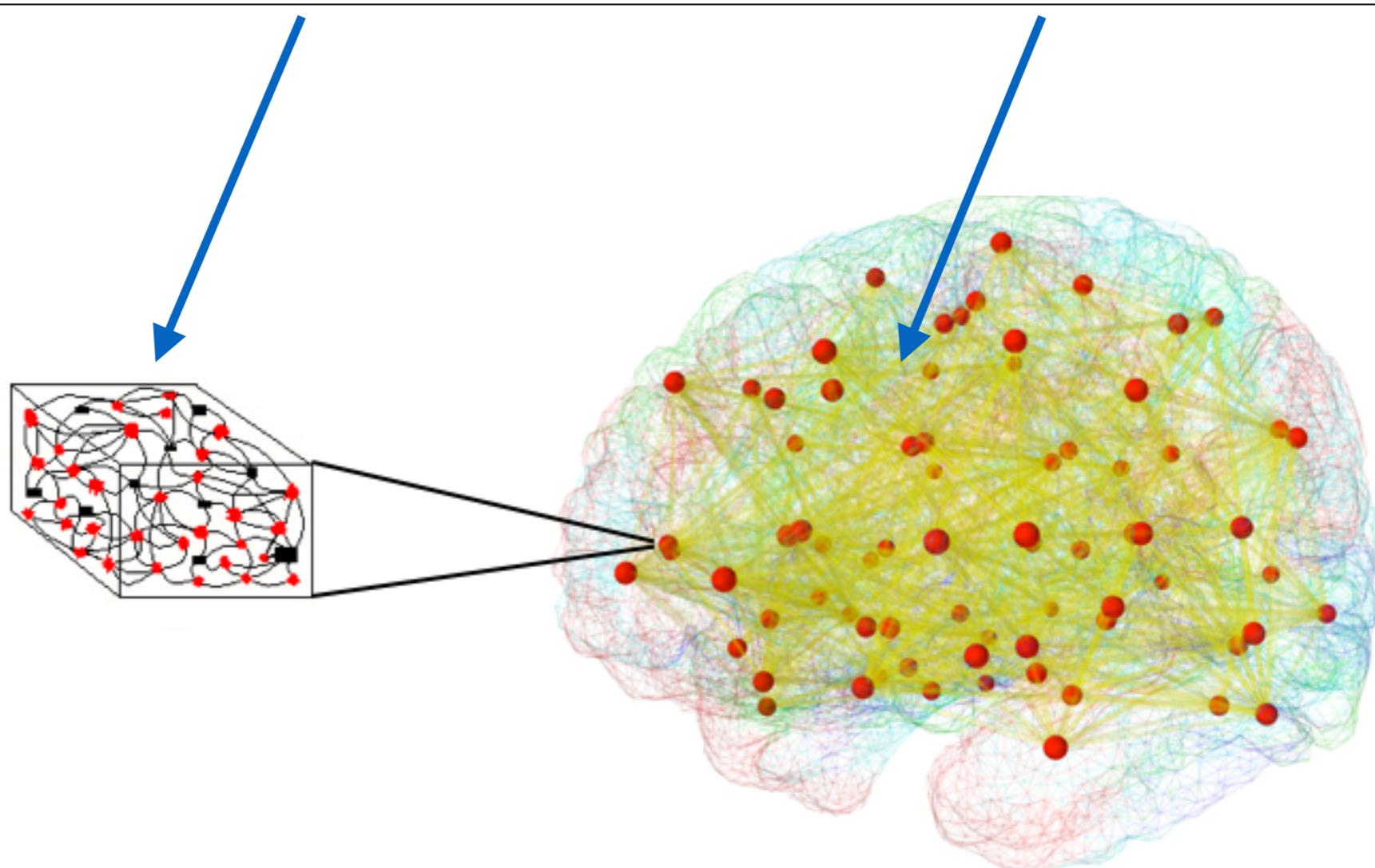
Bases for brain synchrony!



STEP 3: INCREASING NOISE

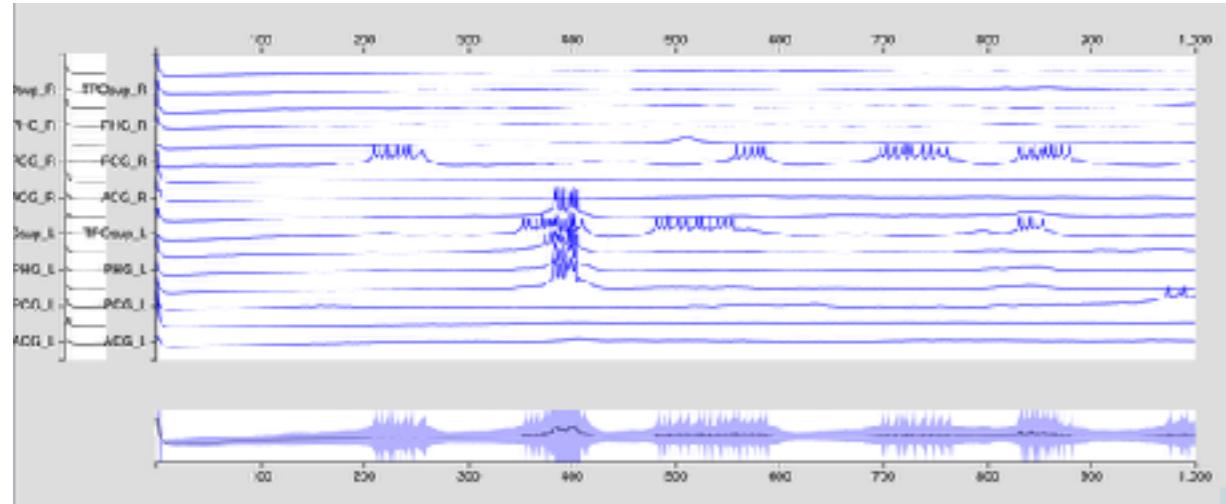
$$\dot{\psi}(x,t) = N(\psi(x,t)) + \int_{local} g(x - x')S(\psi(x',t))dx' + \int_{global} G(x, x')S(\psi(x',t - \frac{|x - x'|}{v}))dx' + \text{noise}$$

LFP

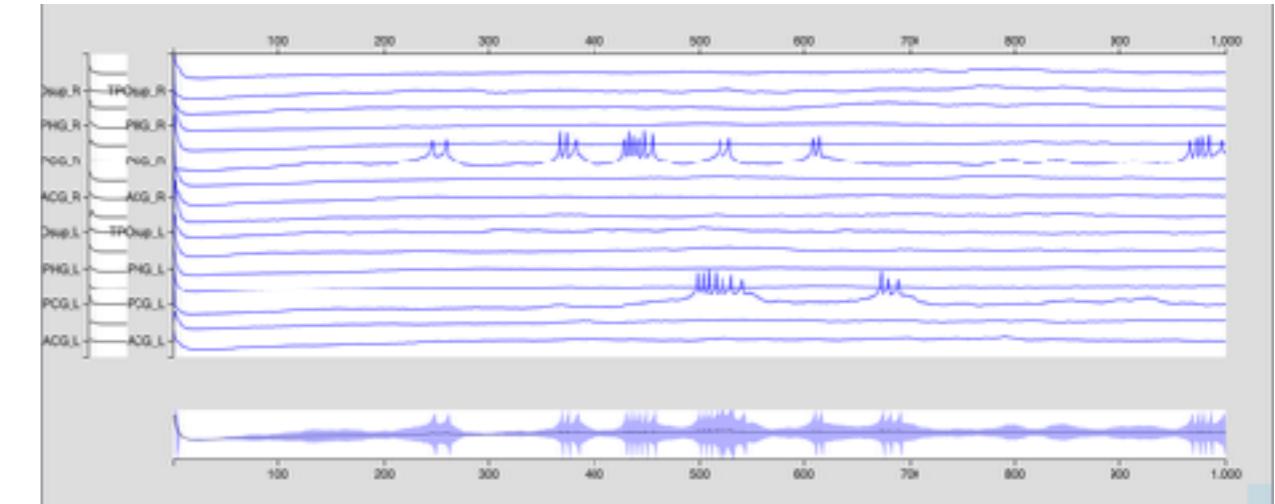


SYNCHRONY

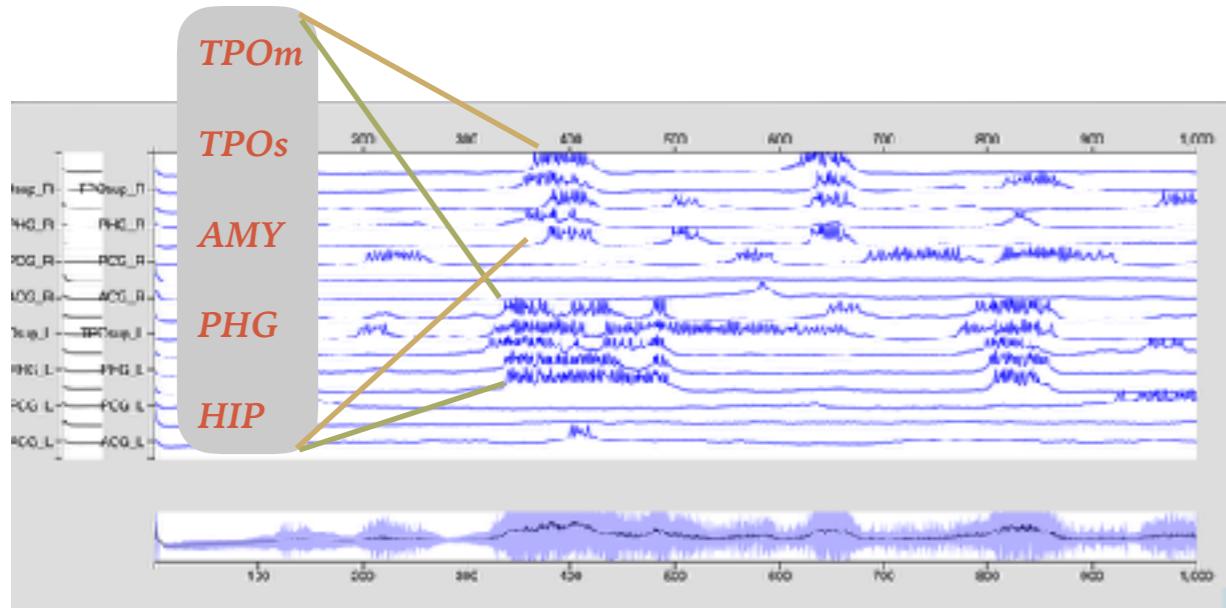
Normal Cognition



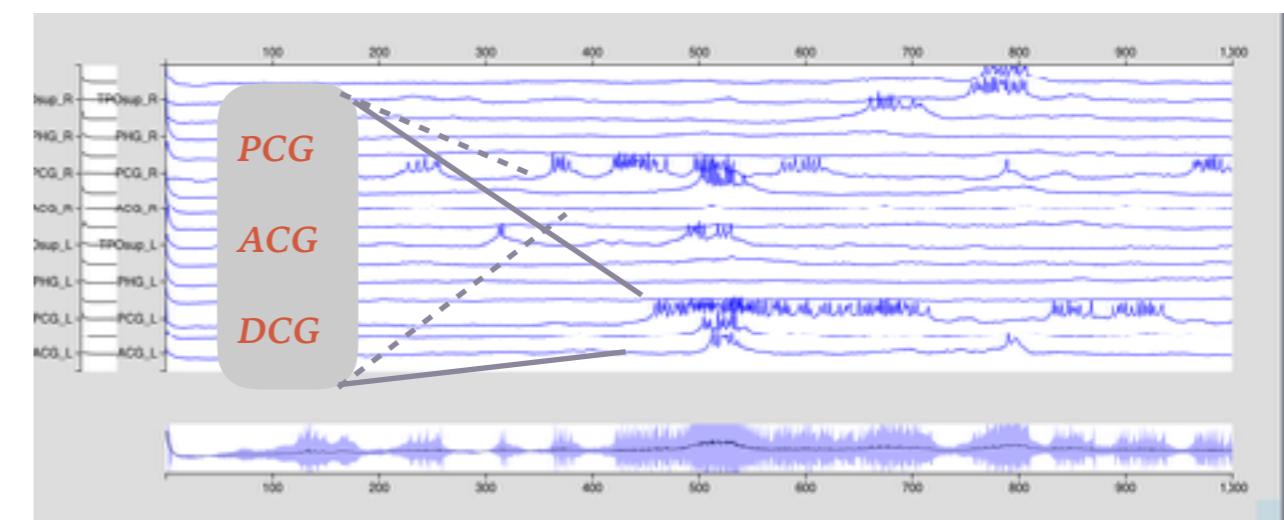
Alzheimer Disease



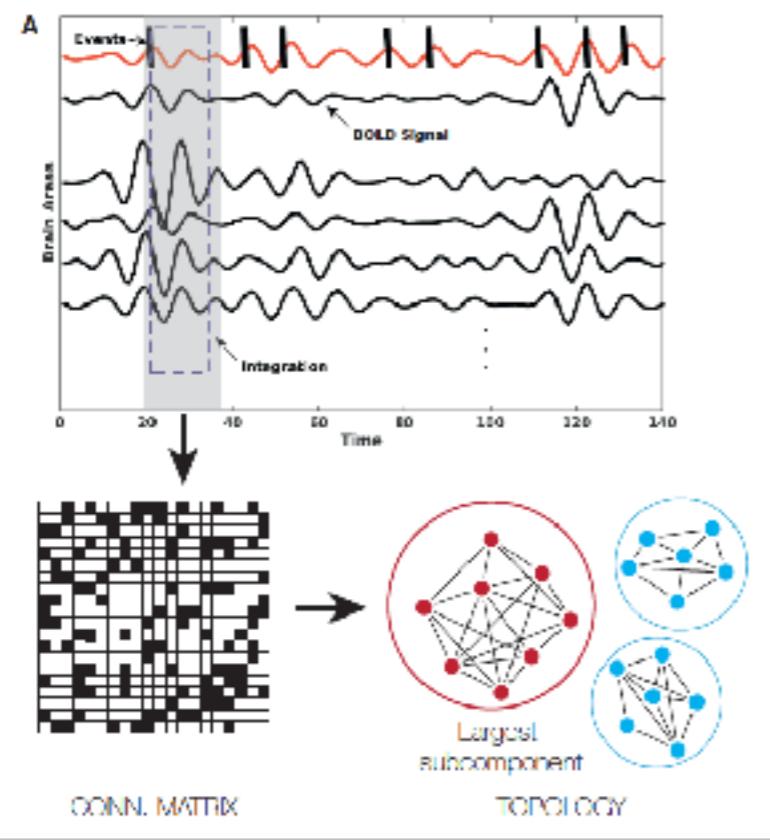
$$D = 0.01$$



$$D = 0.1$$



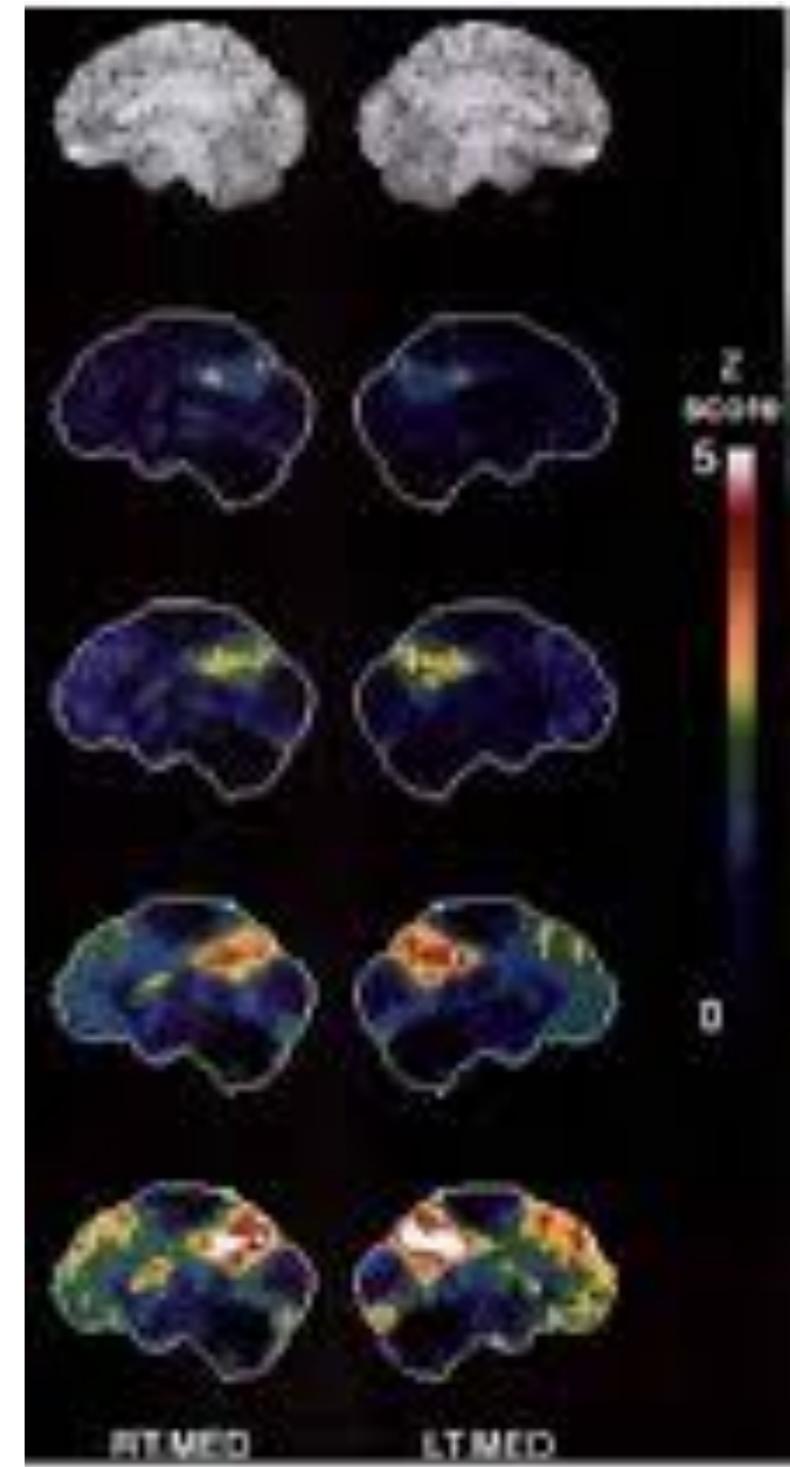
BRAIN IGNITORS



Deco and Kringelbach, Neuron 2017
Deneux and Grinvald, Cer. Cor. 2017

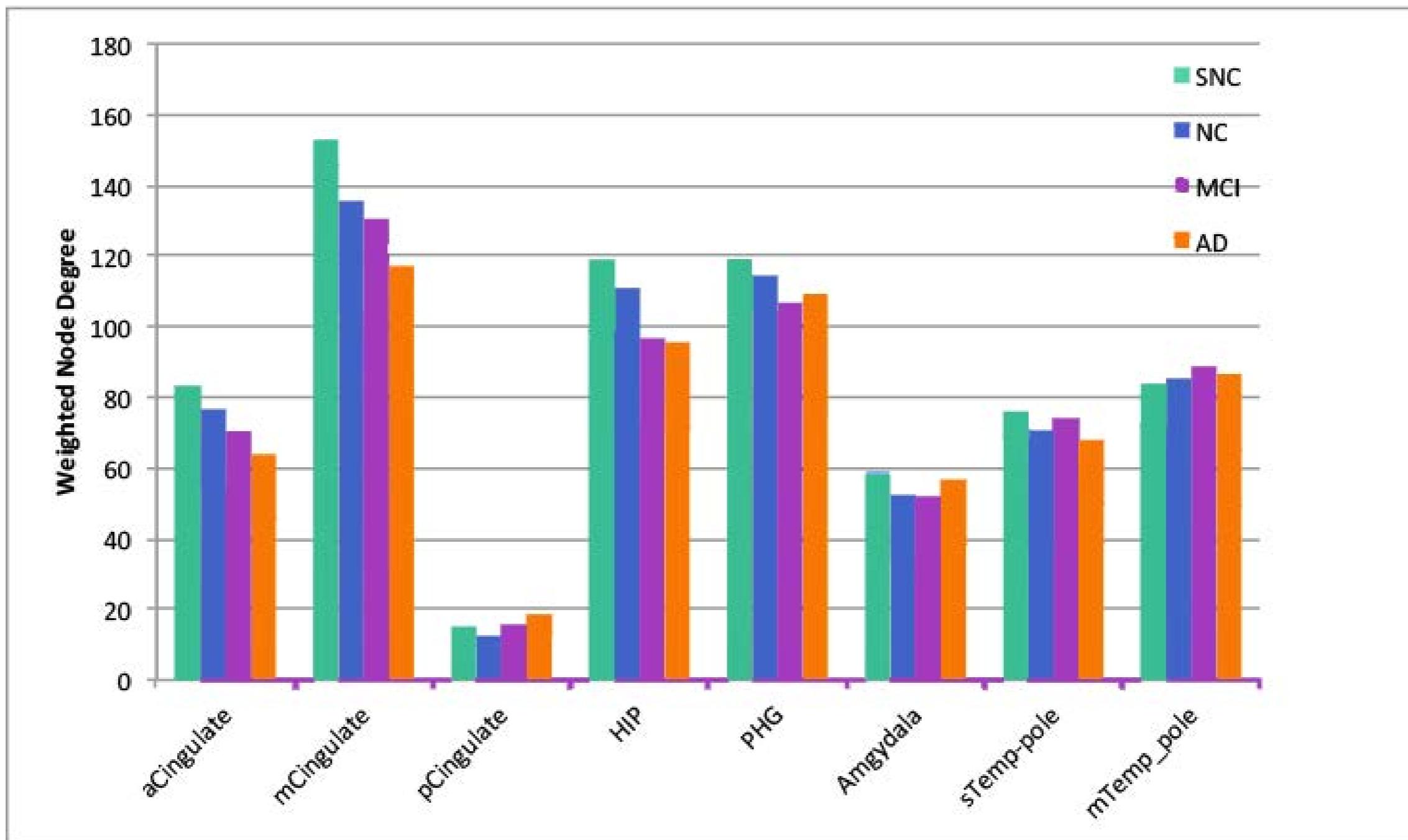
Intrinsic Ignition

- Evoked or at rest
- Single regional activity influences global computation
- Hierarchical information processing

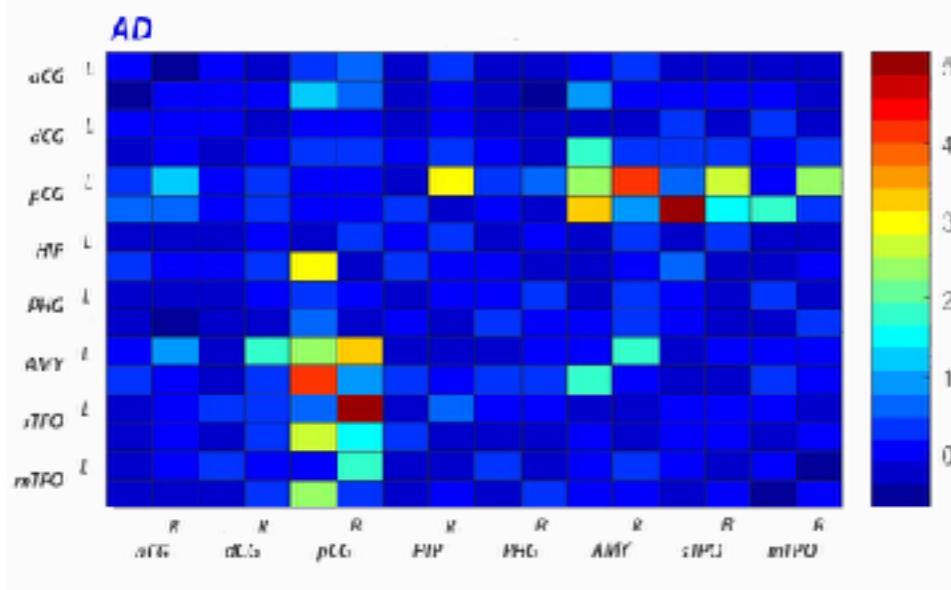
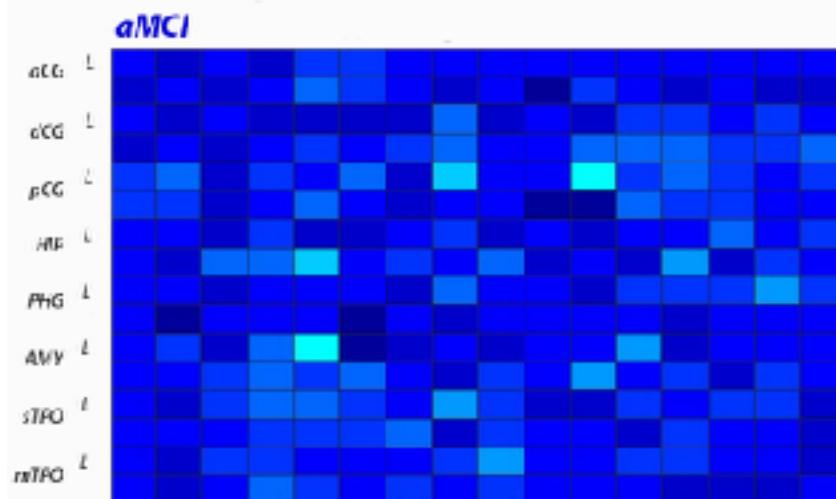
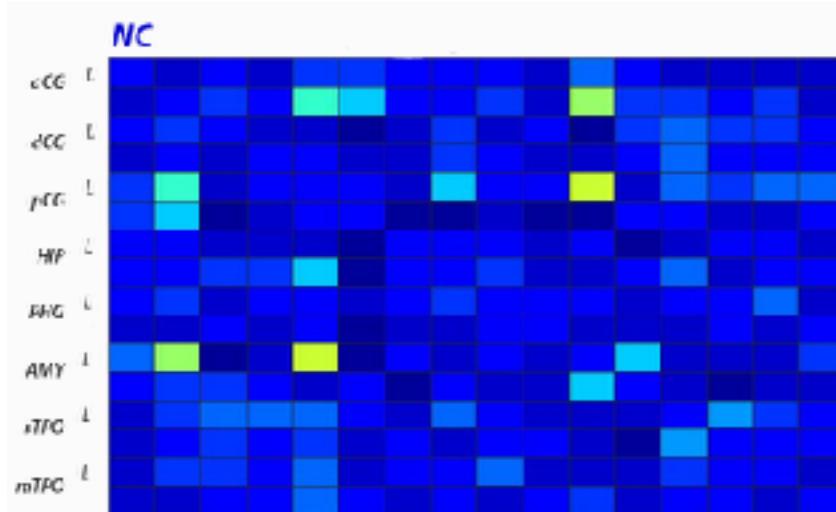


Minoshima et al., 1997

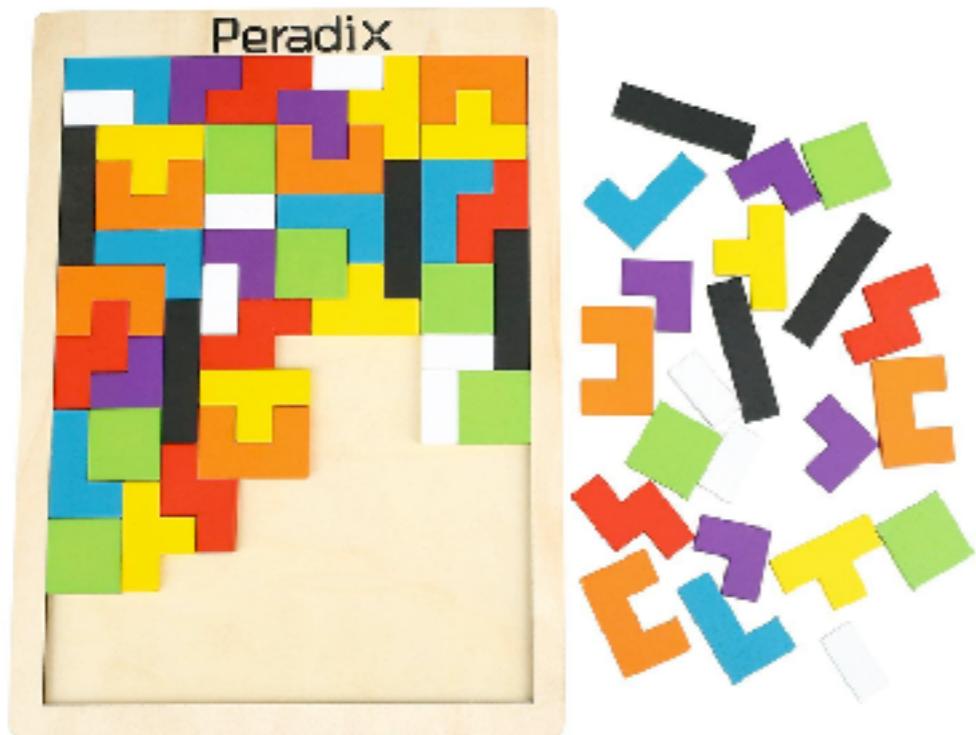
WEIGHTS OF STRUCTURAL CONNECTIONS



COMPARING SNC TO OTHER GROUPS



BIOMARKER IDENTIFICATION



Determination of useful Biomarkers

WHAT DID WE LEARN?

- TVB
 - Multiscale (from cellular to whole brain analysis)
 - Translatable (bed to bench)
 - Individualized (DWI)
 - Open source
- Alzheimer disease
 - Parameters related to clinical phenotype
 - Good for testing effects of therapies?
 - + Focus from wellness to disease!



Thanks!

James S. McDonnell Foundation

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Viktor Jirsa
Mark Mapstone
Michael Breakspear
Randy McIntosh
Petra Ritter
Lia Domide
Laura Ng
Stanley Chen
Duke Shereen

El Cerebro Virtual

Le Cerveau Virtuel

Das Virtuelle Gehirn

Il Cervello Virtuale

El Cervell Virtual

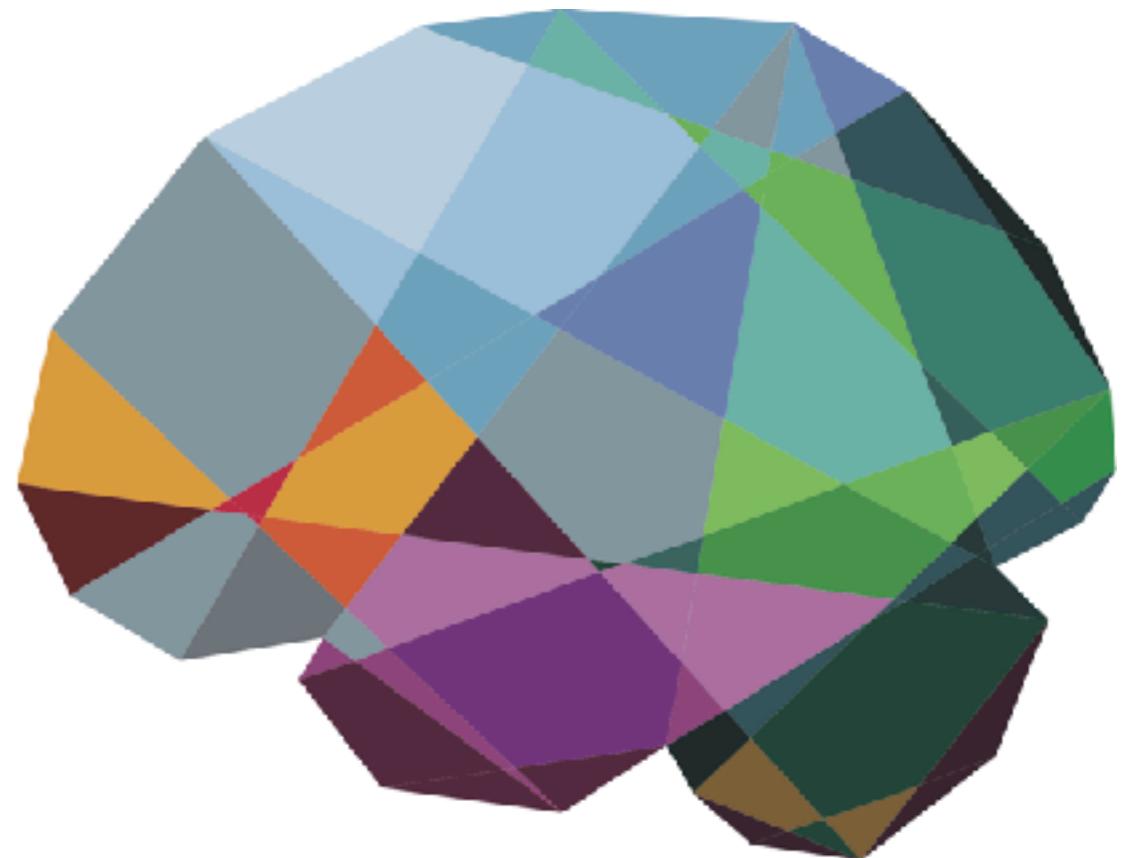
המוח וירטואלי

Creierul Virtual

Virtuální Mozek

虛擬大腦

Ο εικονικός εγκέφαλος



THE VIRTUAL BRAIN.