

NODE

#7

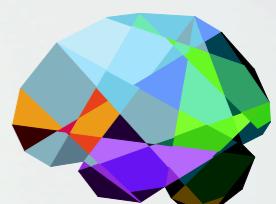
WORKSHOP

AUGUST 7-8, 2018 | MONTREAL, CANADA

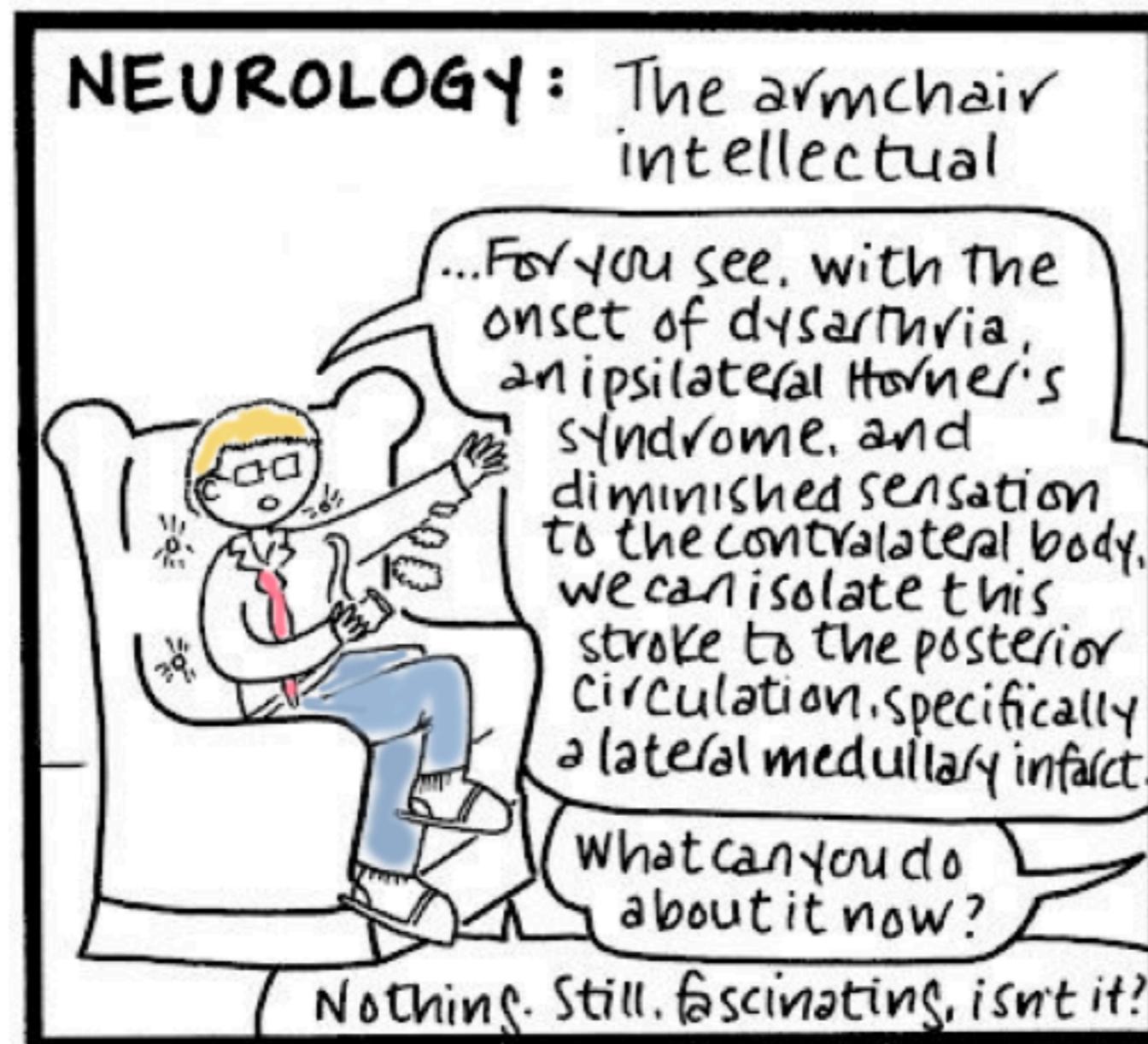
**Clinical Applications of TVB: From Stroke
to Alzheimer's Disease**

Generating The Virtual Patient Brain

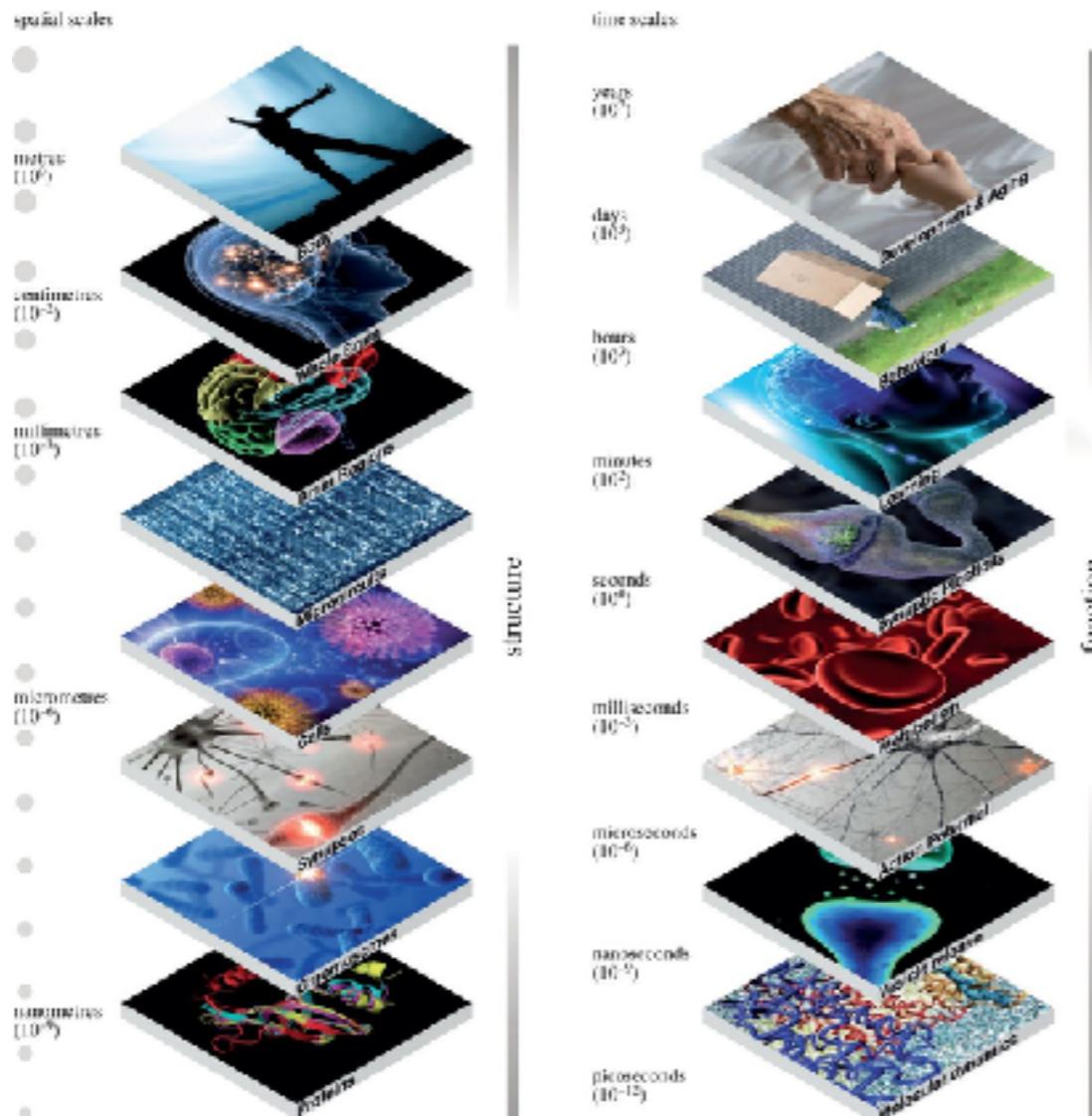
ANA SOLODKIN, UC IRVINE HEALTH/NEUROLOGY



SEARCHING FOR CURES



PRECISION MEDICINE: BIOMARKERS

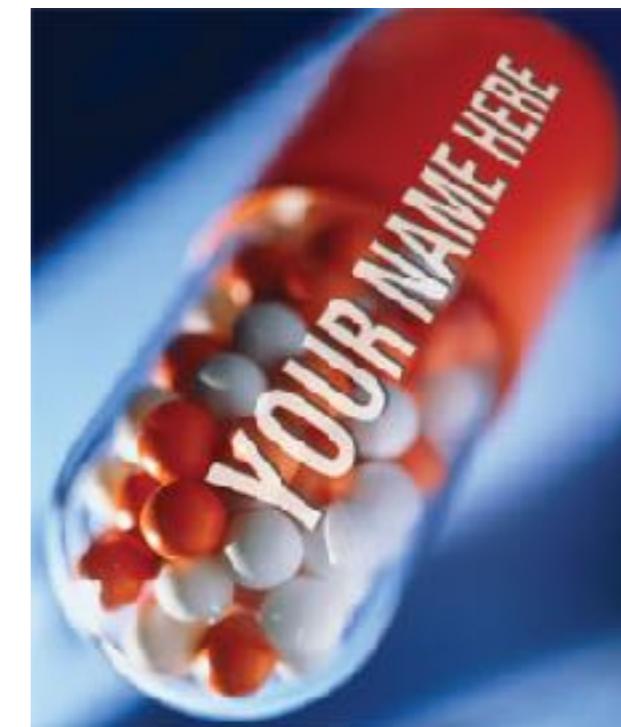


Directly related to basic pathological mechanisms:

Multi-scale



Individualized



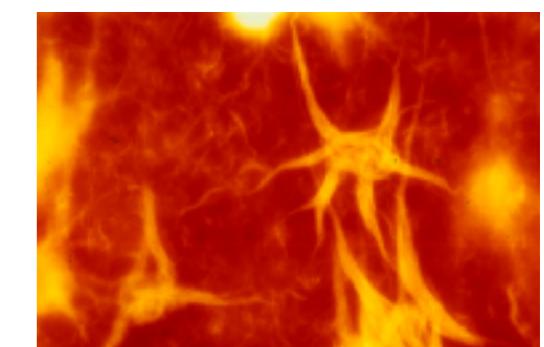
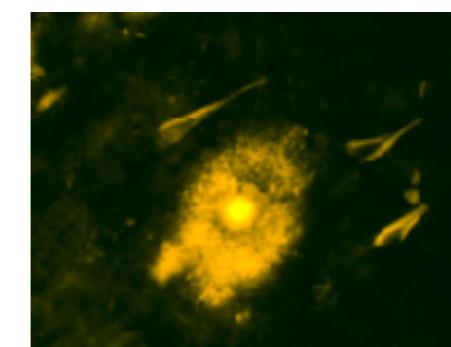
Associated to Clinical Phenotype

STROKE VS. ALZHEIMER'S DISEASE

Stroke



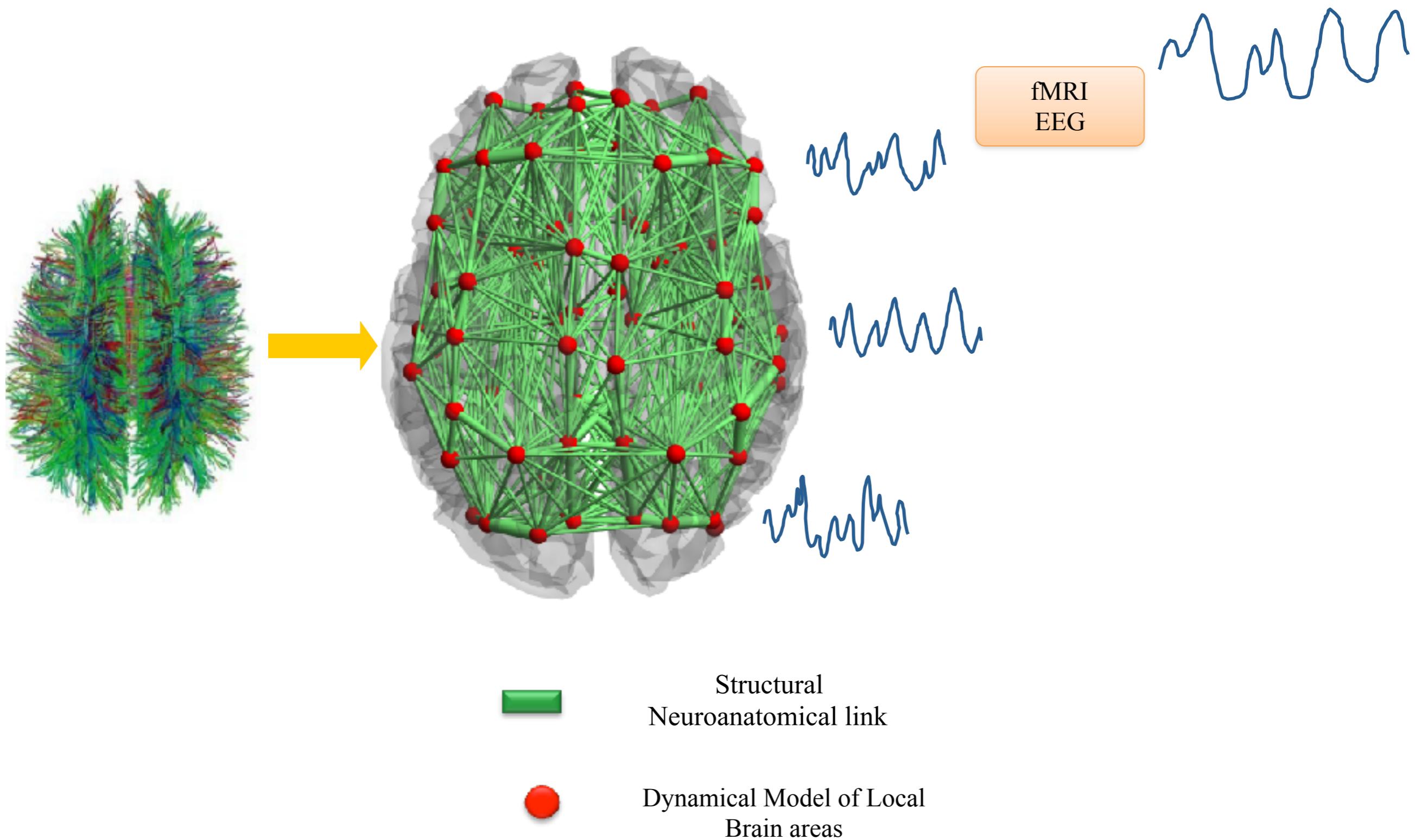
Alzheimer's Disease



STROKE VS. ALZHEIMER'S DISEASE

Stroke	Alzheimer's Disease
Cause #1 of disability; #3 cause of mortality	Prevalence increasing exponentially
Sudden damage (blood flow interruption)	Progressive damage (NP and NFTs)
Damage according to vascular territory	Starts in limbic ventromedial temporal (MCI)
Any age	Older population
Some functional recovery	Progressive deterioration
Who will recover?	Who will convert to MCI-AD?
Post-stroke treatment	Pre-AD (or MCI) treatment

REVERSE ENGINEERING: SIMULATIONS



THE VIRTUAL BRAIN

BASIC ELEMENTS



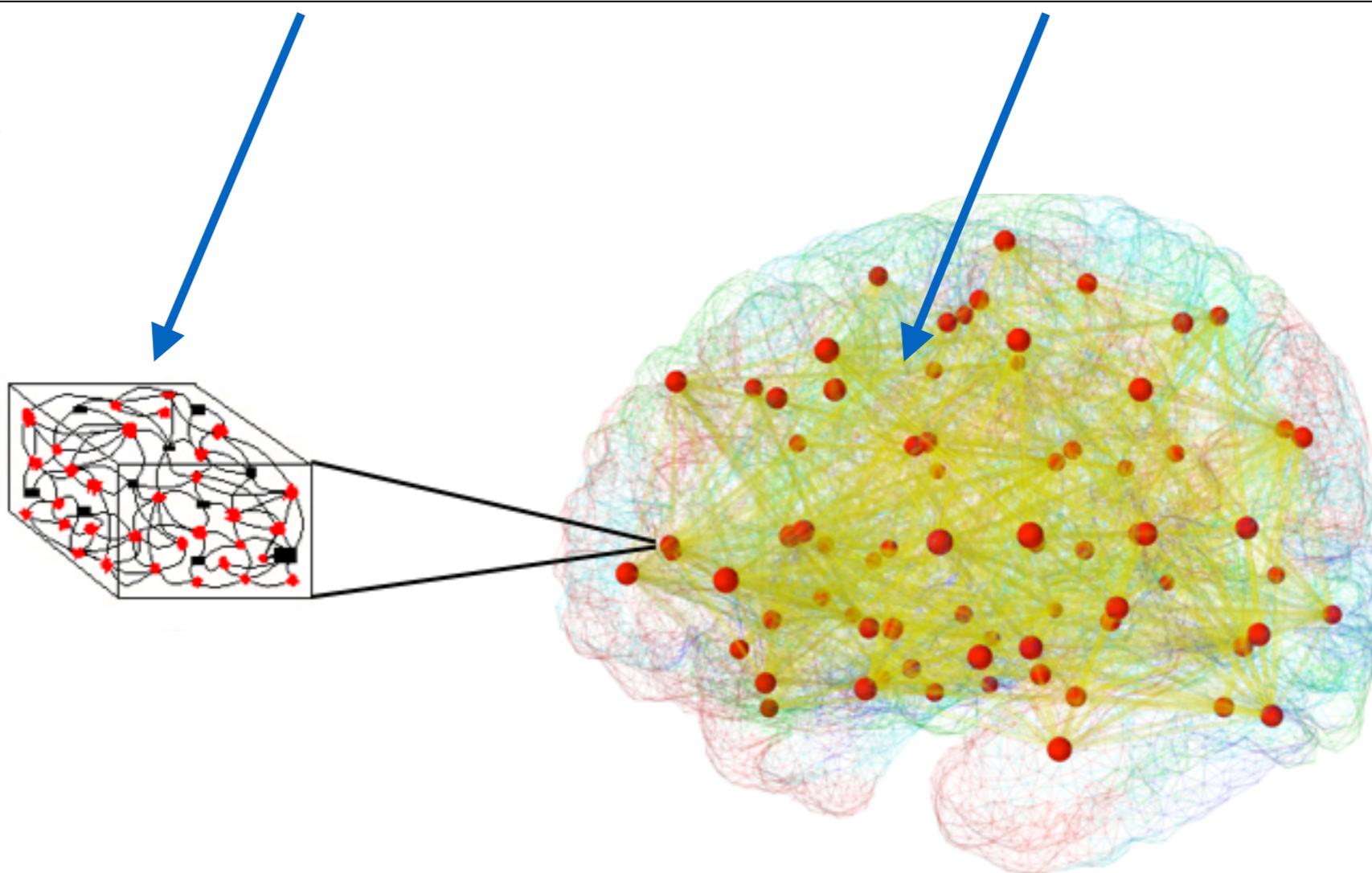
THE VIRTUAL BRAIN.

MULTI-SCALE INTEGRATION

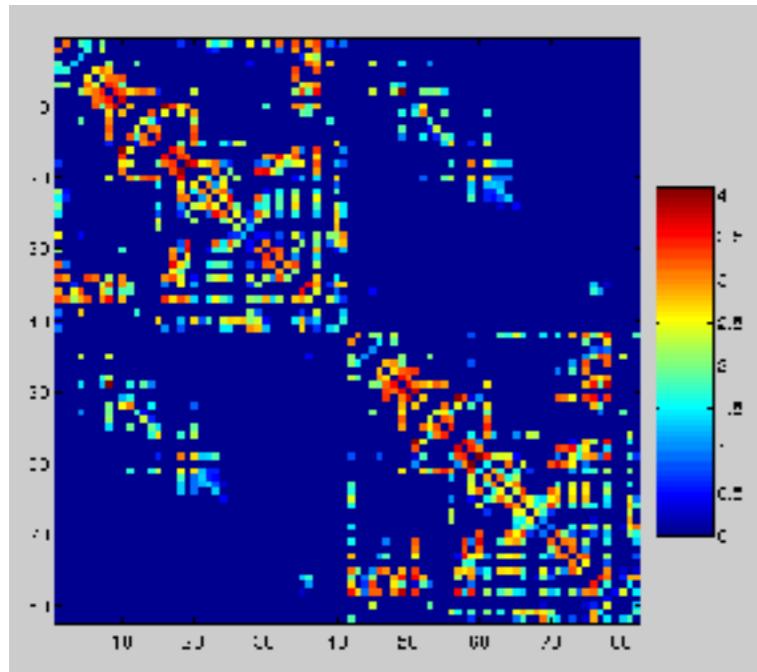
$$\dot{\psi}(x,t) = N(\psi(x,t)) + \int_{local} g(x - x')S(\psi(x',t))dx' + \int_{global} G(x,x')S(\psi(x',t - \frac{|x - x'|}{v}))dx' + \text{noise}$$



Neuronal Activity



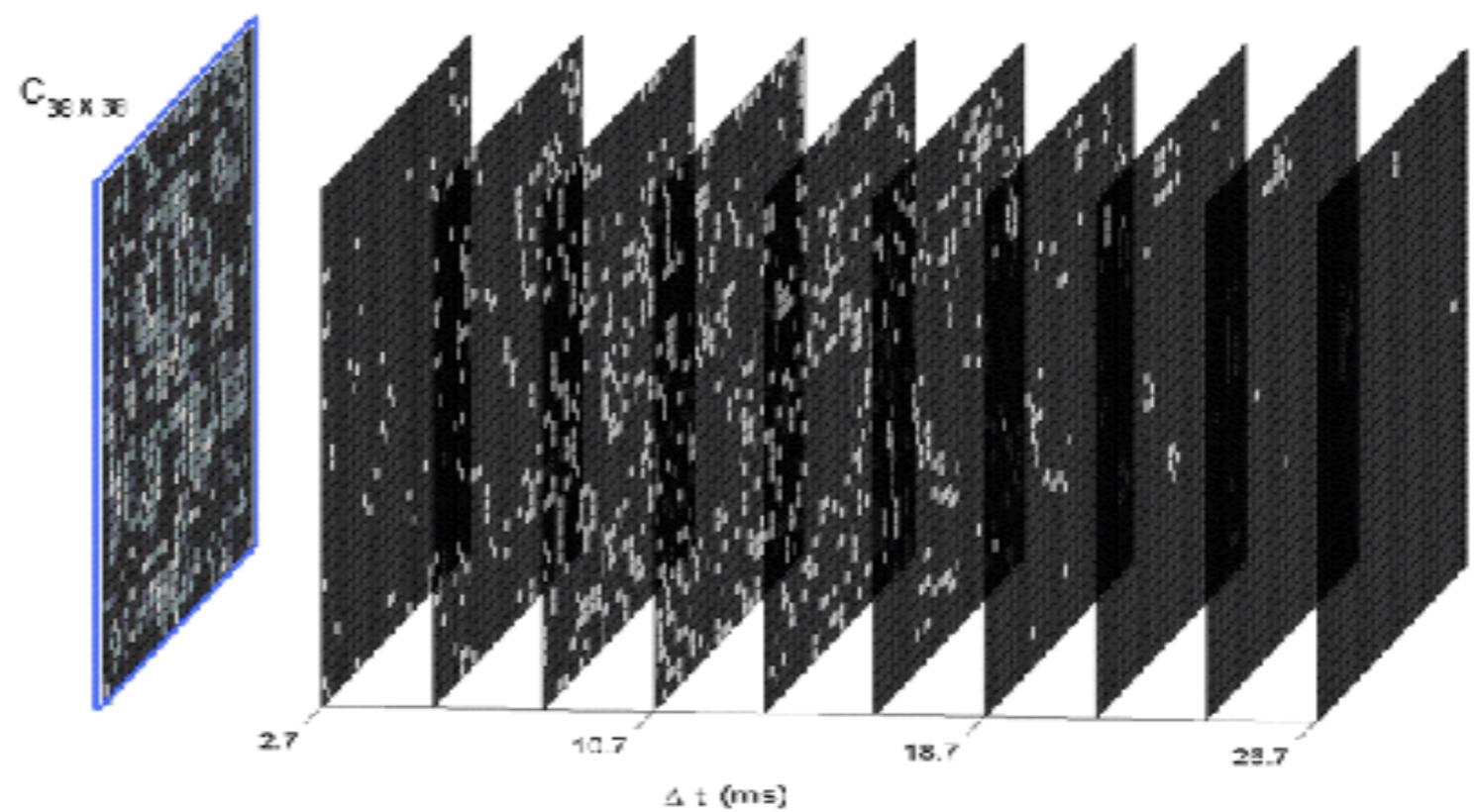
GLOBAL PARAMETERS: DERIVED FROM SC



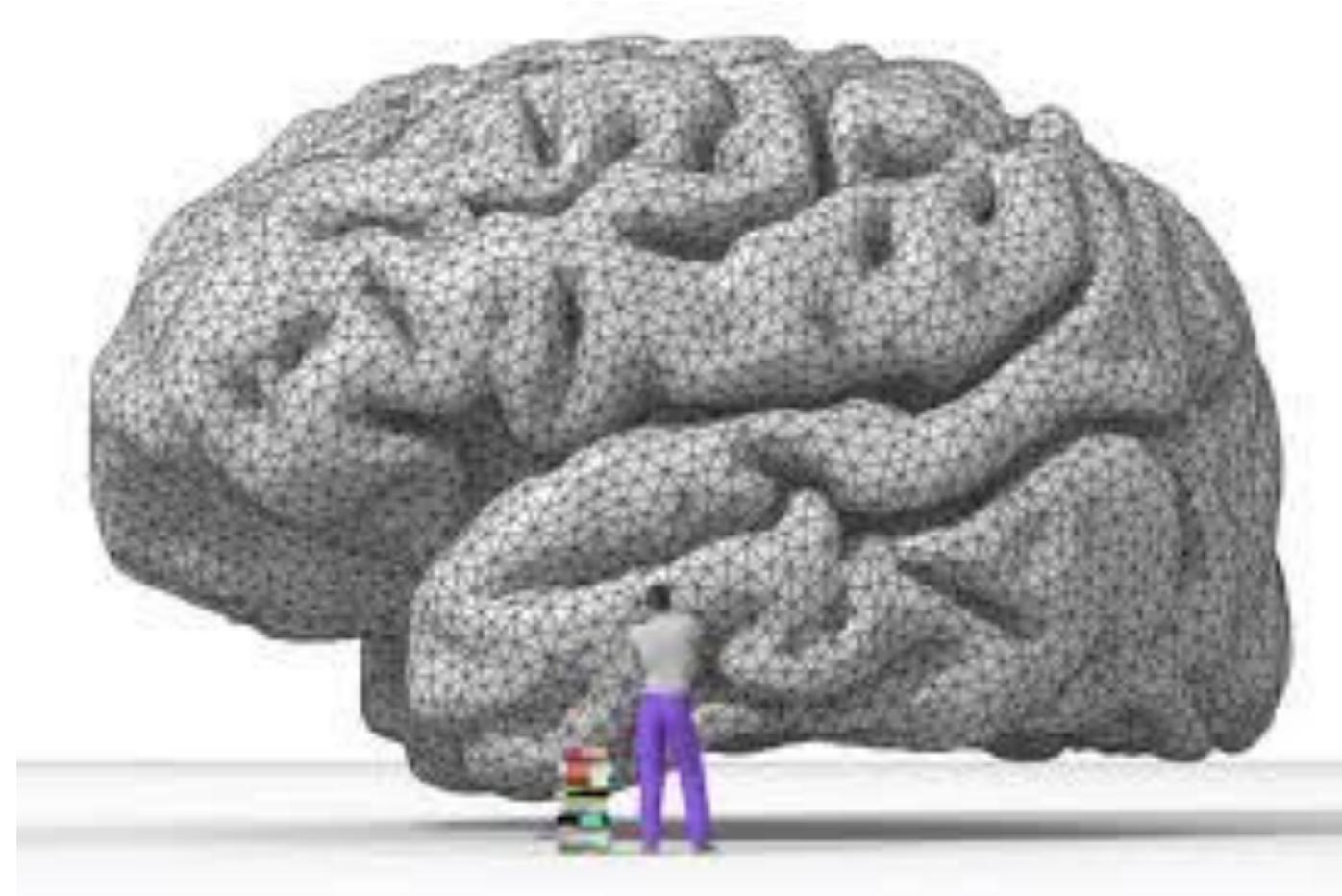
Metrics:

- *Pathway Weights*

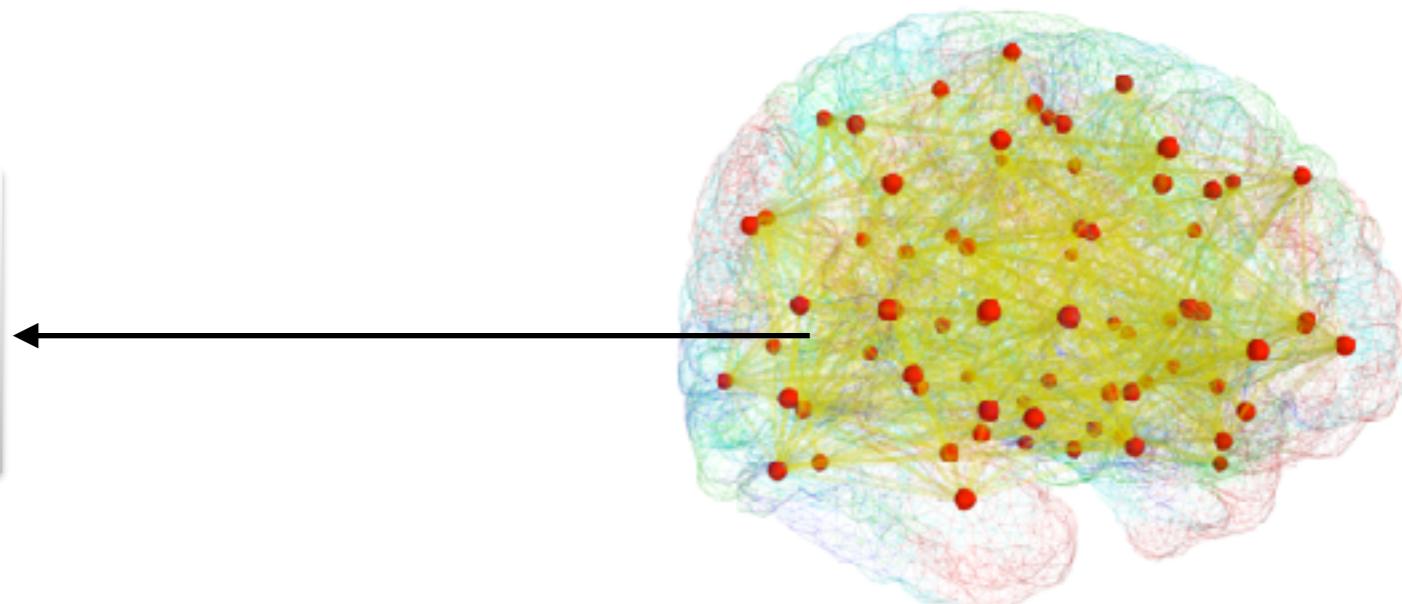
Tracks networks across



GLOBAL PARAMETERS

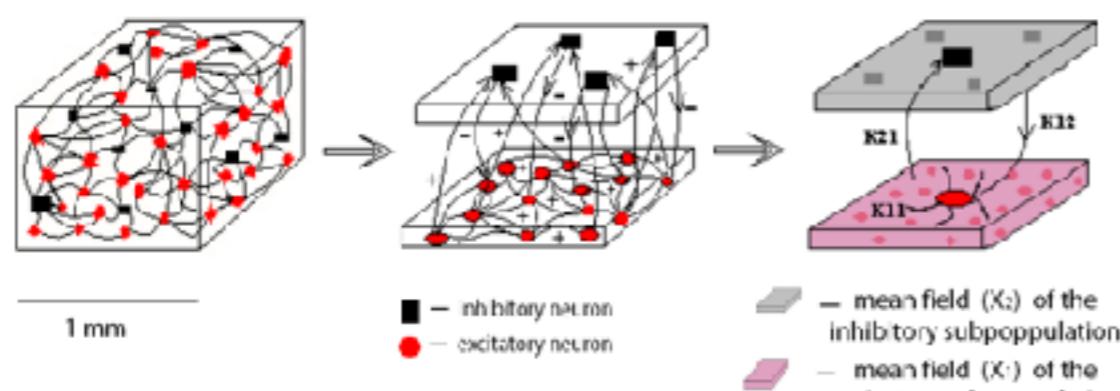


Global Variables:
Conduction Velocity
Long-range Coupling

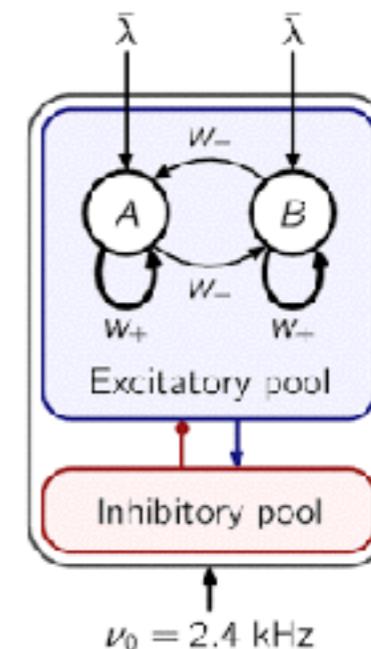


LOCAL MODELS: MEAN FIELD APPROXIMATION

Stroke



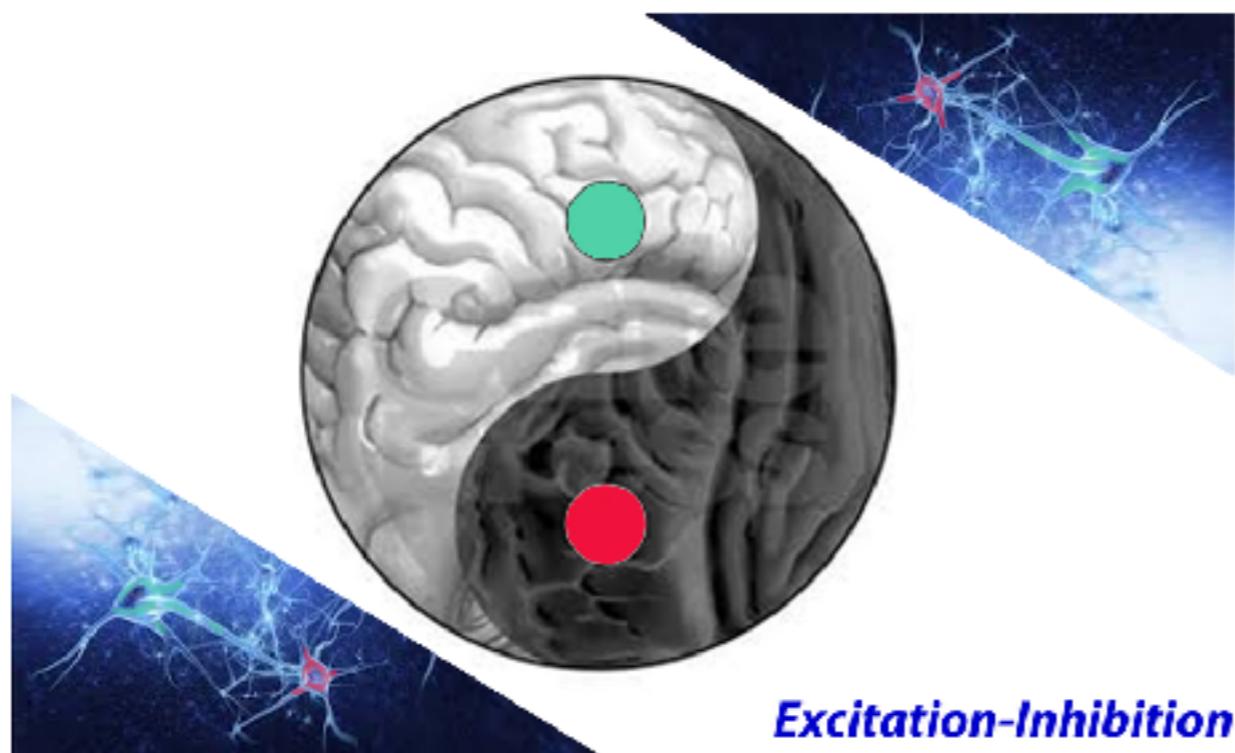
Alzheimer's Disease



- *Stefanescu-Jirsa 3D*
- *Models Local field Potentials*

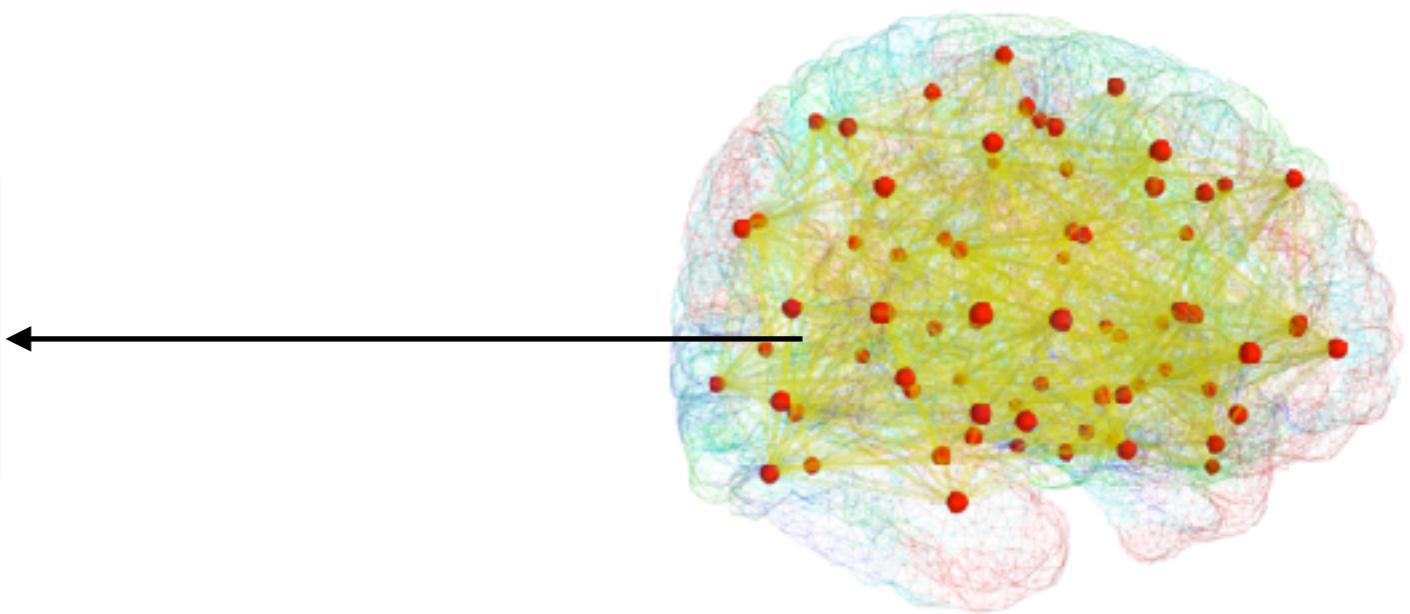
- *Reduced Wong-Wang*
- *Models Neuronal Firing rates*

LOCAL PARAMETERS



Excitation-Inhibition

Local Parameters:
K₁₂, K₂₁, K₁₁
(excitatory-inhibitory
coupling)



THE VIRTUAL BRAIN

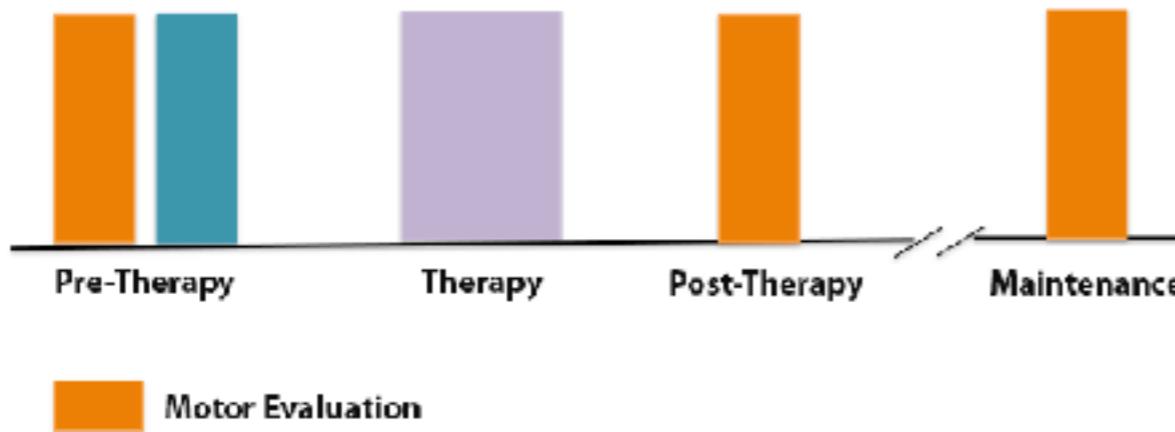


SPECIFIC IMPLEMENTATION

THE VIRTUAL BRAIN.

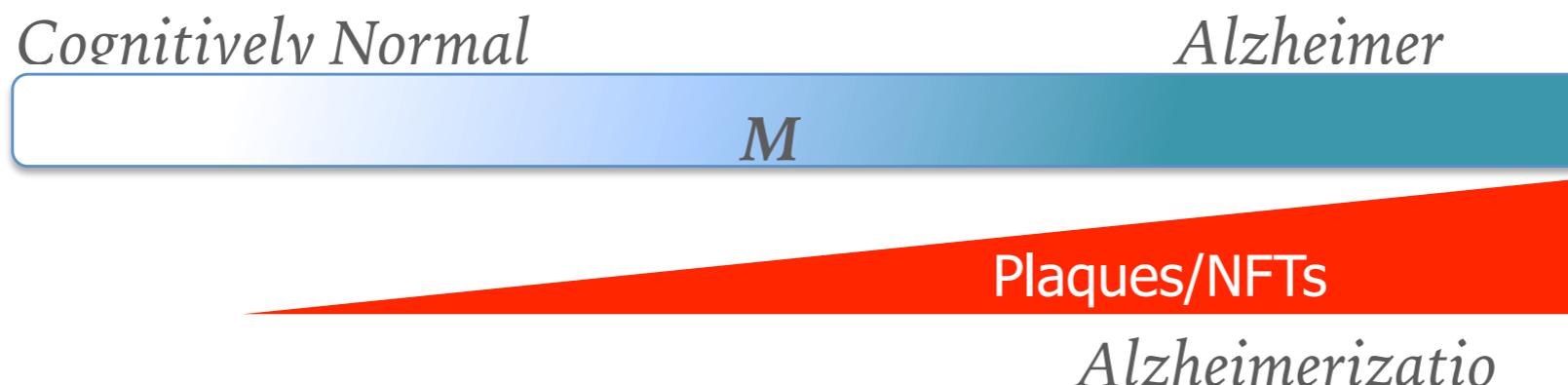
SUBJECTS

- STROKE: 20 chronic stroke and 10 healthy controls.
 - *Motor assessment pre-therapy, post-therapy and after 1 year.*



Falcon et al., eNeuro, 2016

- AD: 35 MCI, 16 AD and 73 healthy controls.
 - *Extensive Cognitive Neuropsychological Assessment*

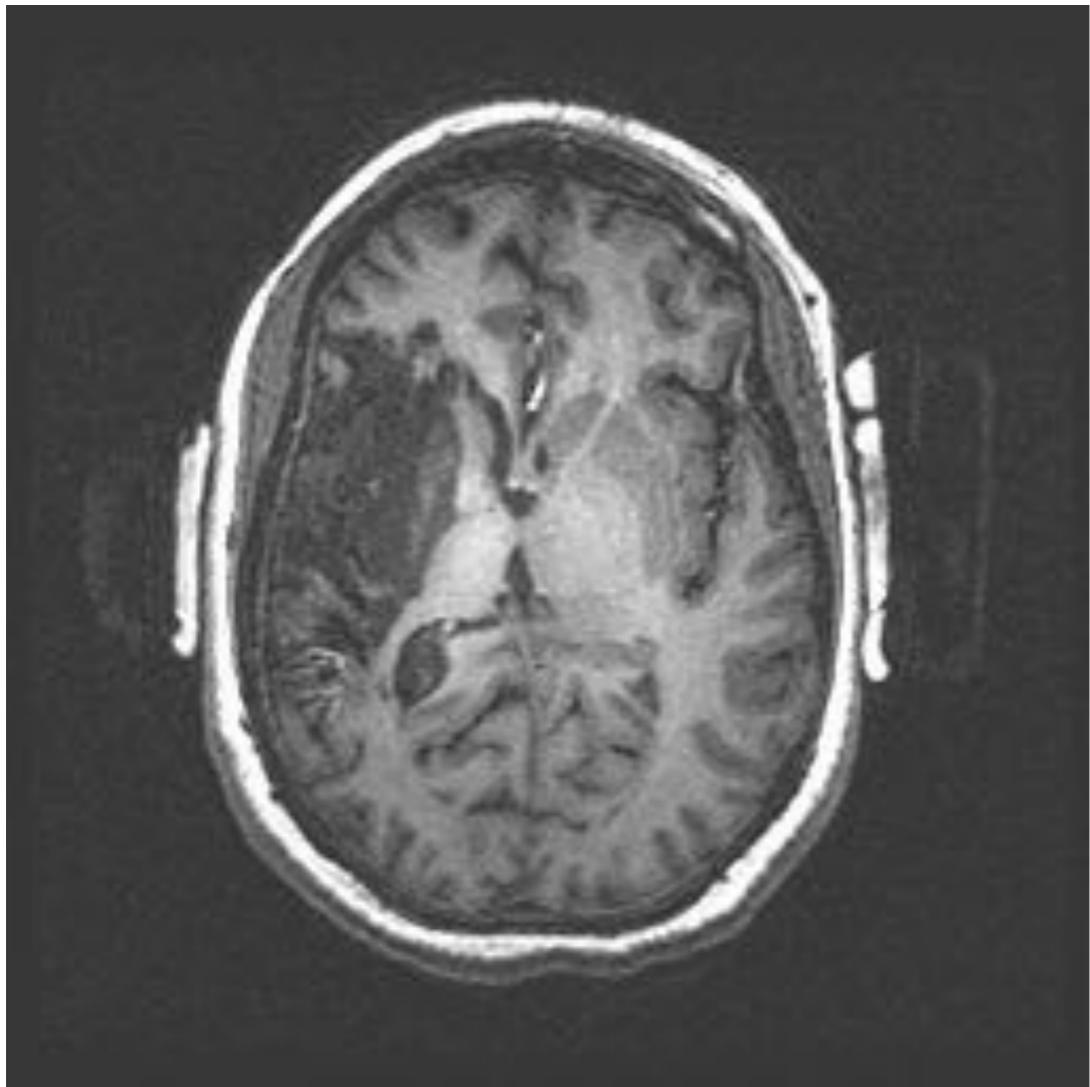


Zimmermann et al., NeuroImage Clinical, 2018

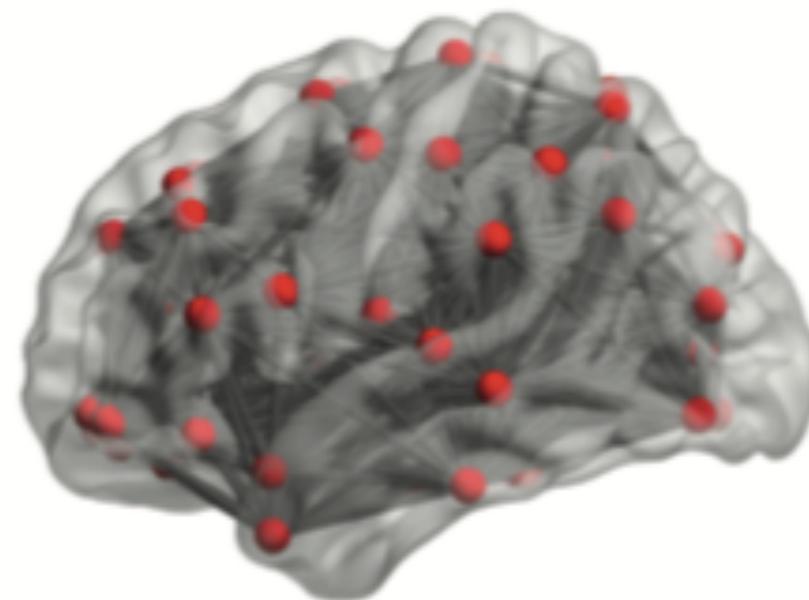
GENERAL METHODS

- Methods:
 - *MRI (T1w, rsfMRI, DTI): At baseline*
 - *Generation of Individual Structural Connectivity matrix (DTI- MRI).*
 - *Generation of Individual Functional Connectivity matrix (rBOLD-MRI).*
 - *TVB:*
 - Selection of Local model
 - Parameter Space Exploration and Estimation
 - Generation of BOLD simulation
 - *Comparison between simulated and empirical TS.*
- Correlation with Clinical Phenotype

EXPERIMENTAL DESIGN: STROKE

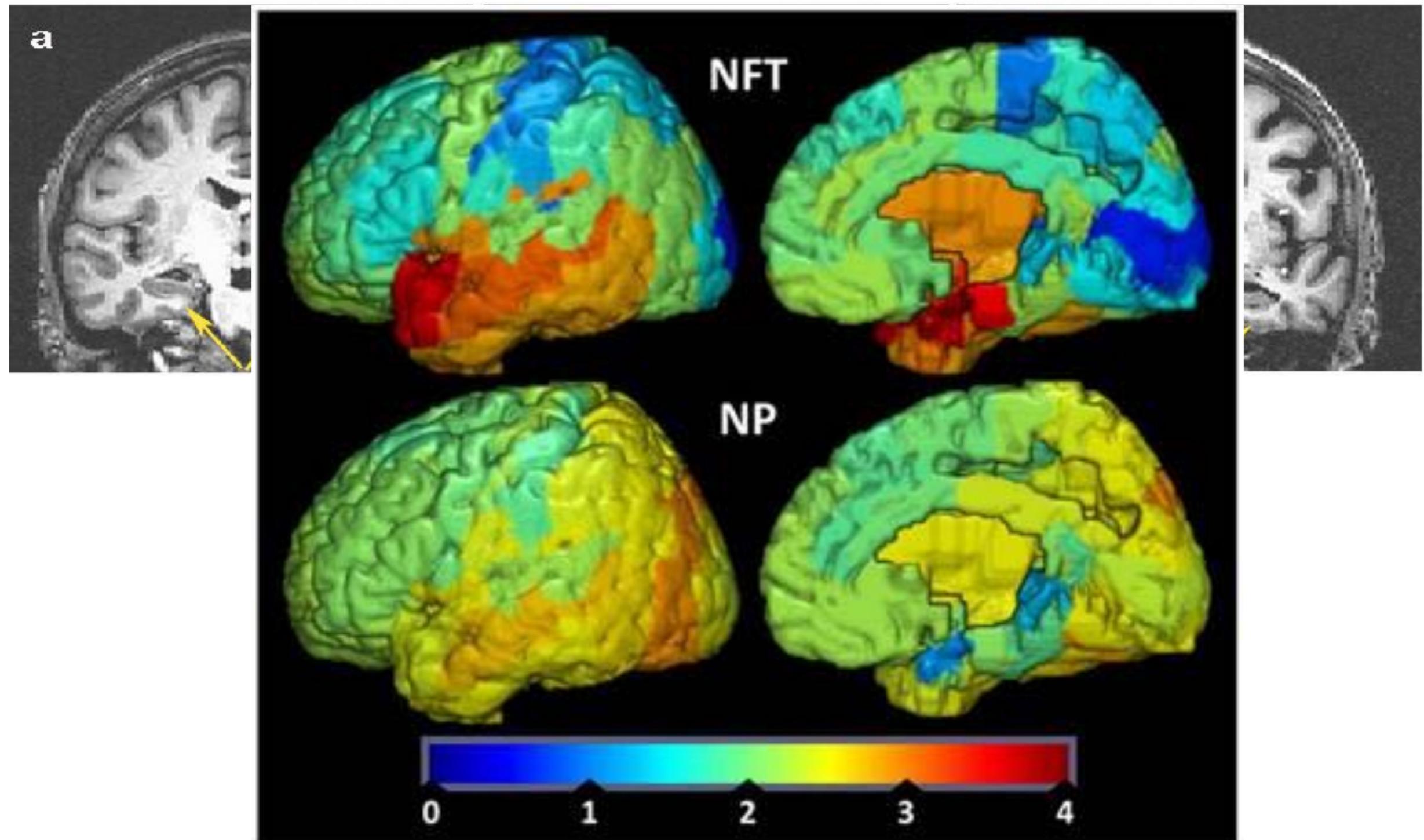


Whole Network



- Stroke:
 - *Whole Brain Simulation*

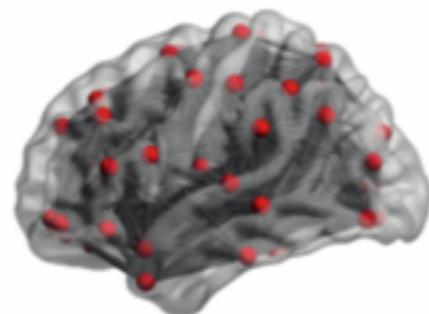
EXPERIMENTAL DESIGN: ALZHEIMER'S



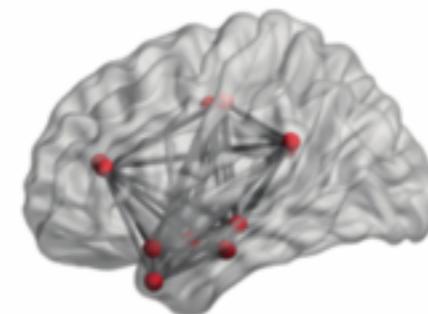
MODELING MODES

- Alzheimer's Disease
 - *Whole Brain Simulation*
 - *Limbic sub-network*
 - *Whole “embedded” brain*

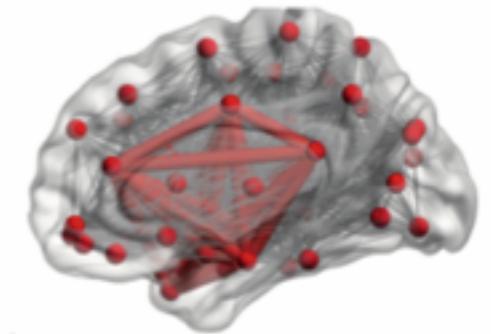
Whole Network



LBC



Embedded LBC



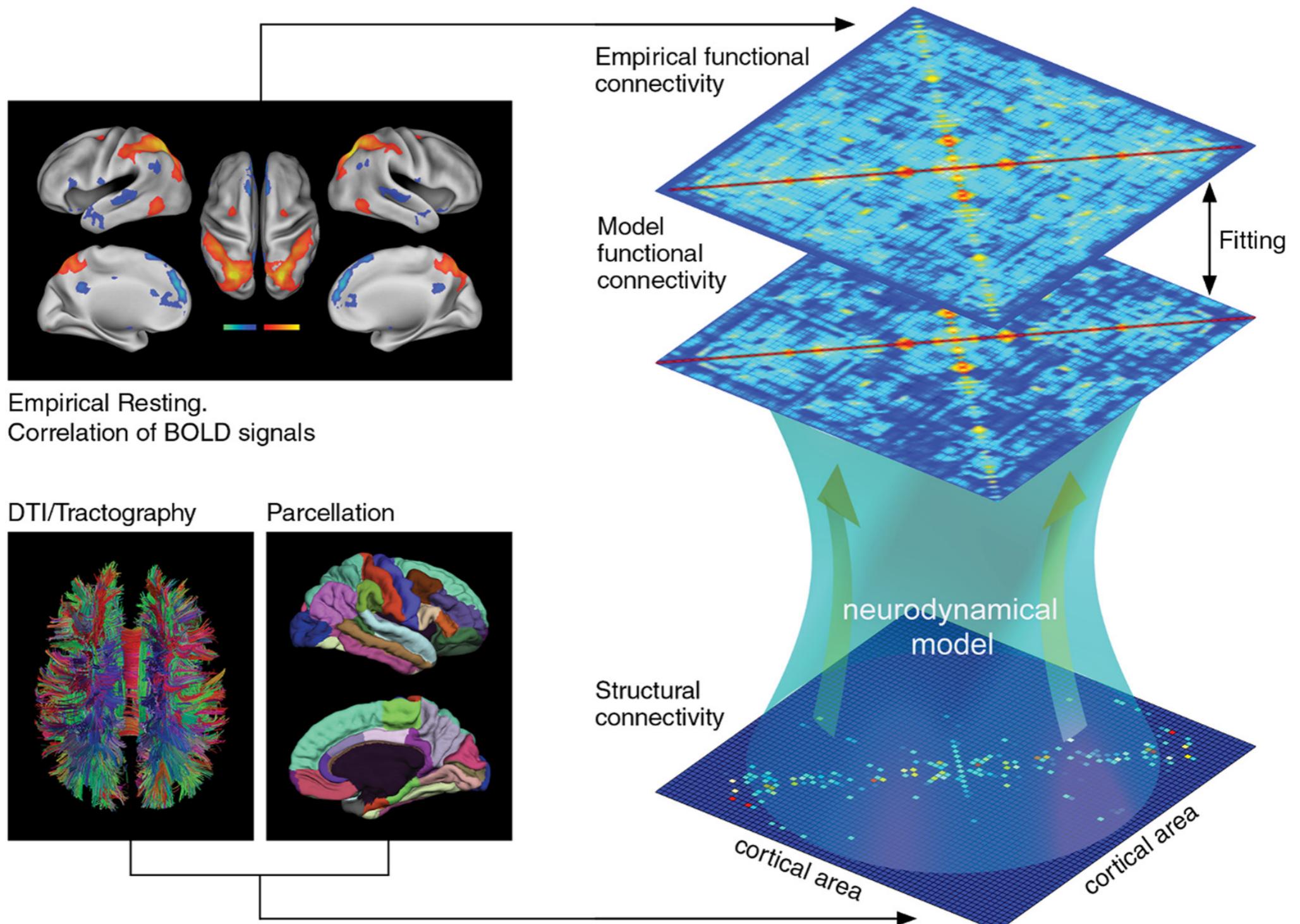
THE VIRTUAL BRAIN



PRAGMATICS

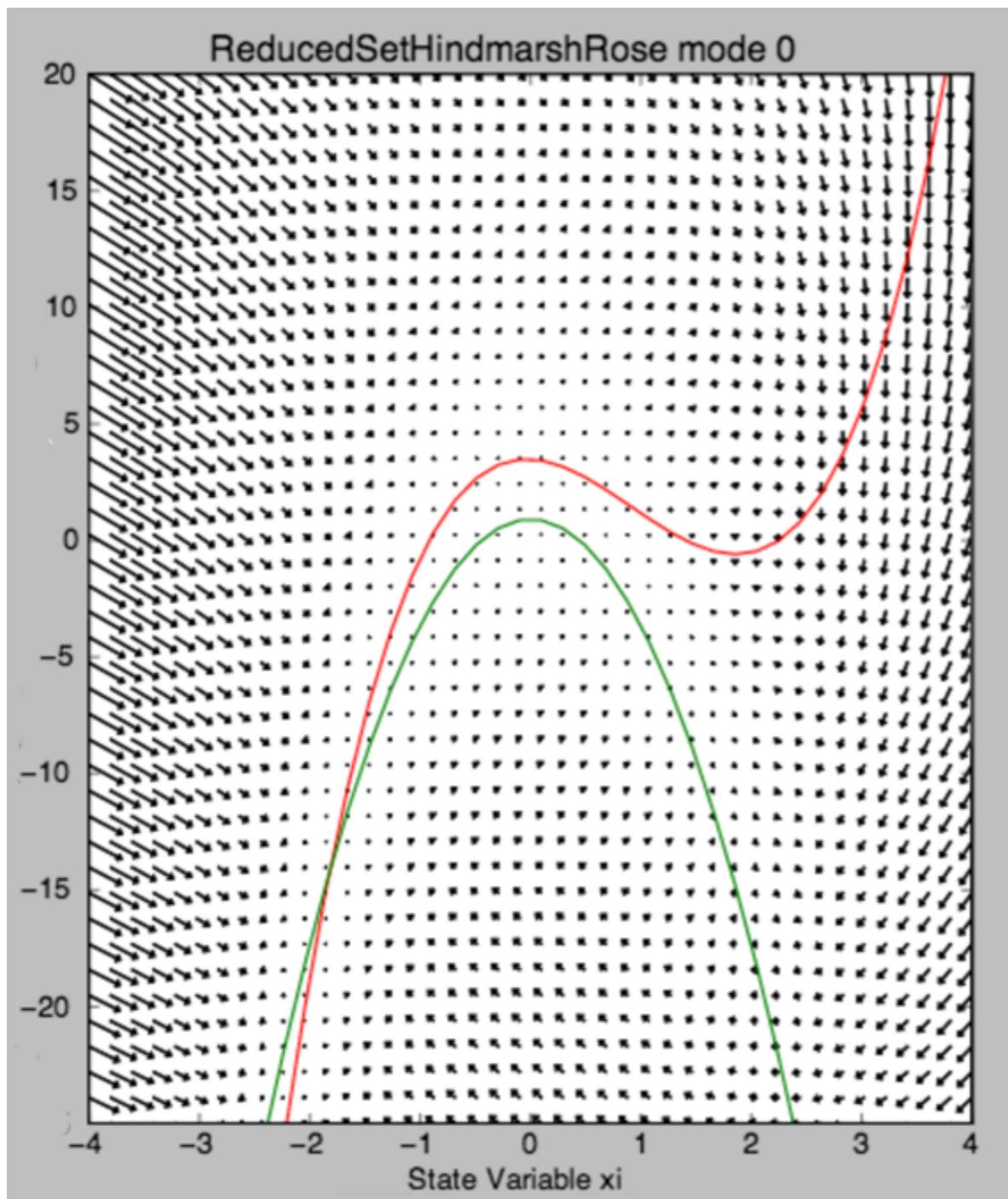
THE VIRTUAL BRAIN.

TVB WORKFLOW



Deco, Jirsa & McIntosh, *Nat Neurosci Reviews* 2011
Deco, Jirsa & McIntosh, *TINS* 2013

PARAMETER EXPLORATION AND ESTIMATION

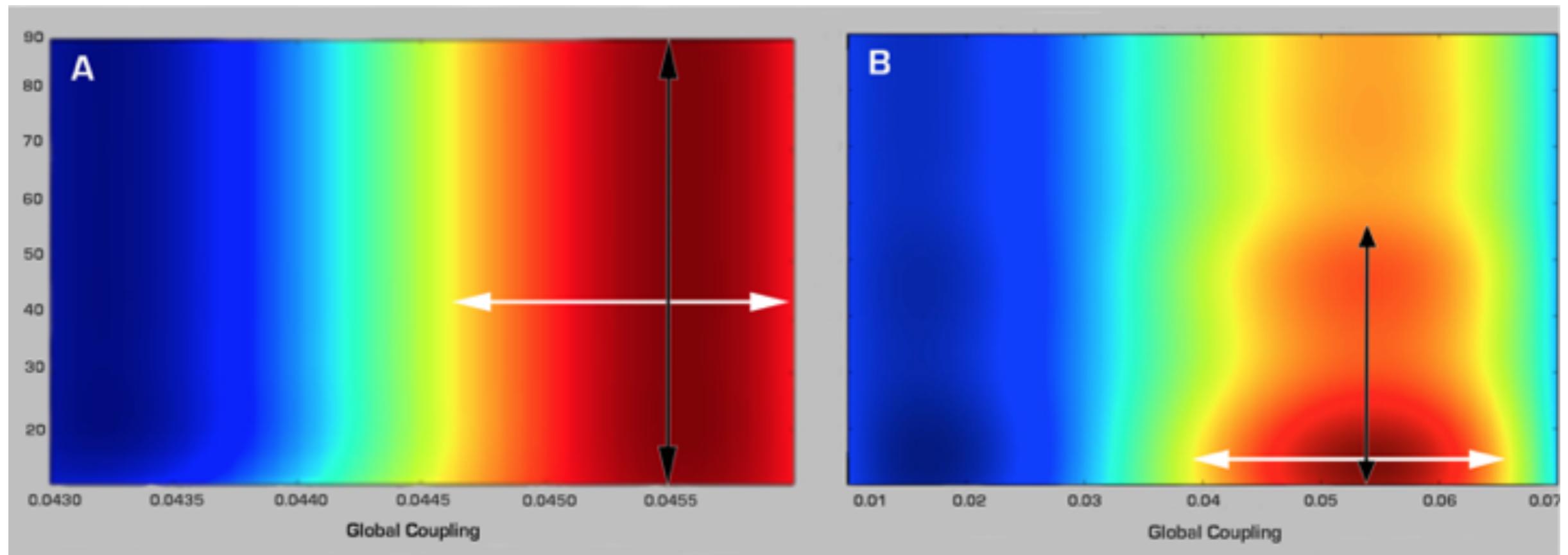


Configure parameters:

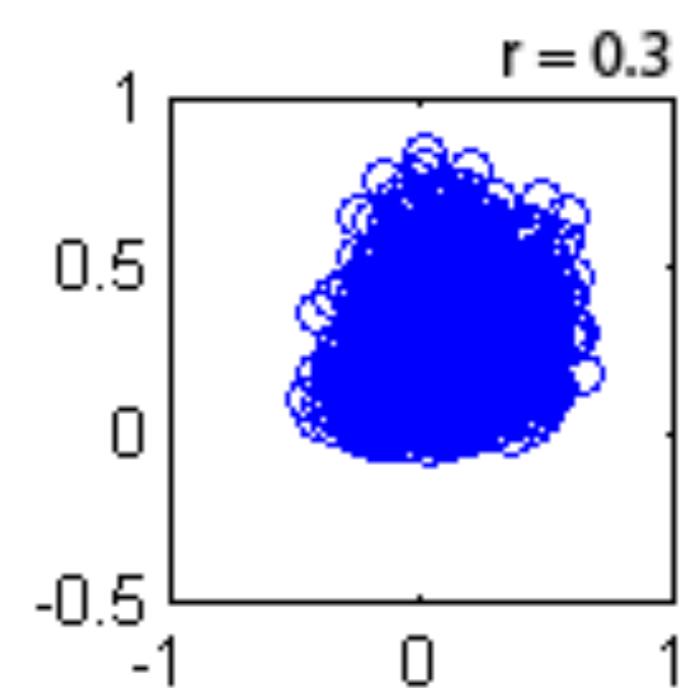
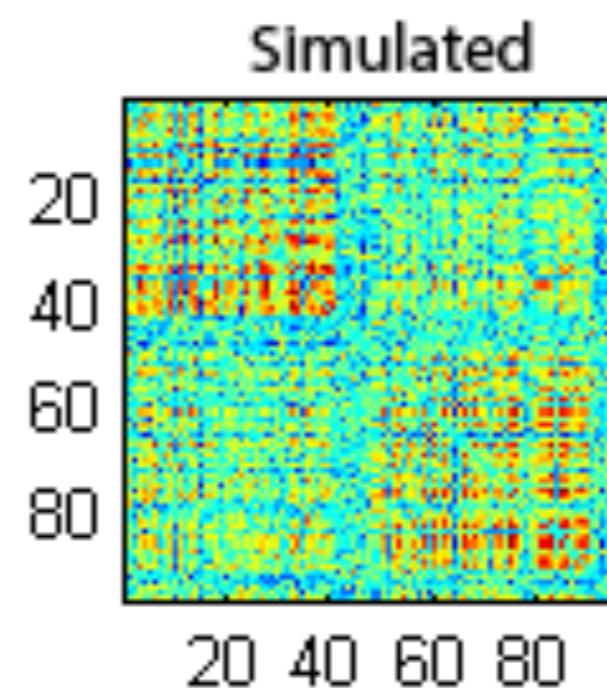
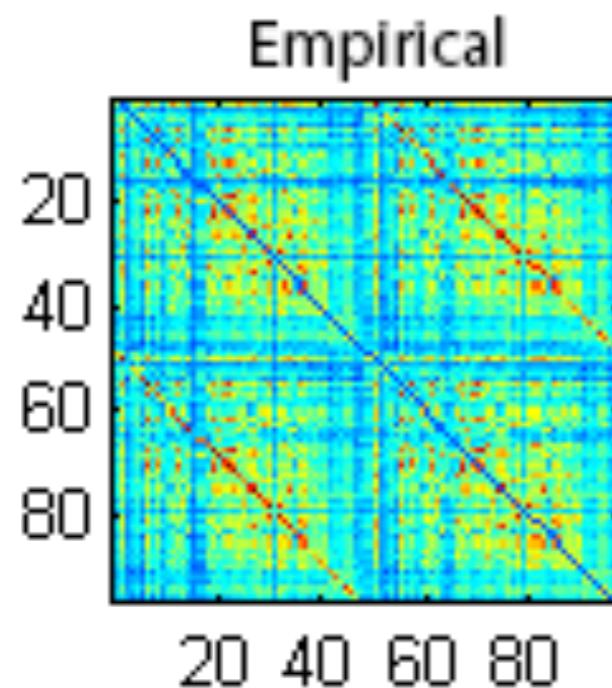
Reset parameters for node(s)

Parameter	Value
r	0.006
a	1
b	3
c	1
d	5
s	4
x ₀	-1.6
K ₁₁	0.5
K ₁₂	0.1
K ₂₁	0.15
sigma	0.3
mu	3.3

GLOBAL VARIANCE: HEAT MAPS



SIMULATION: VALIDATION VS. EMPIRICAL SIGNALS



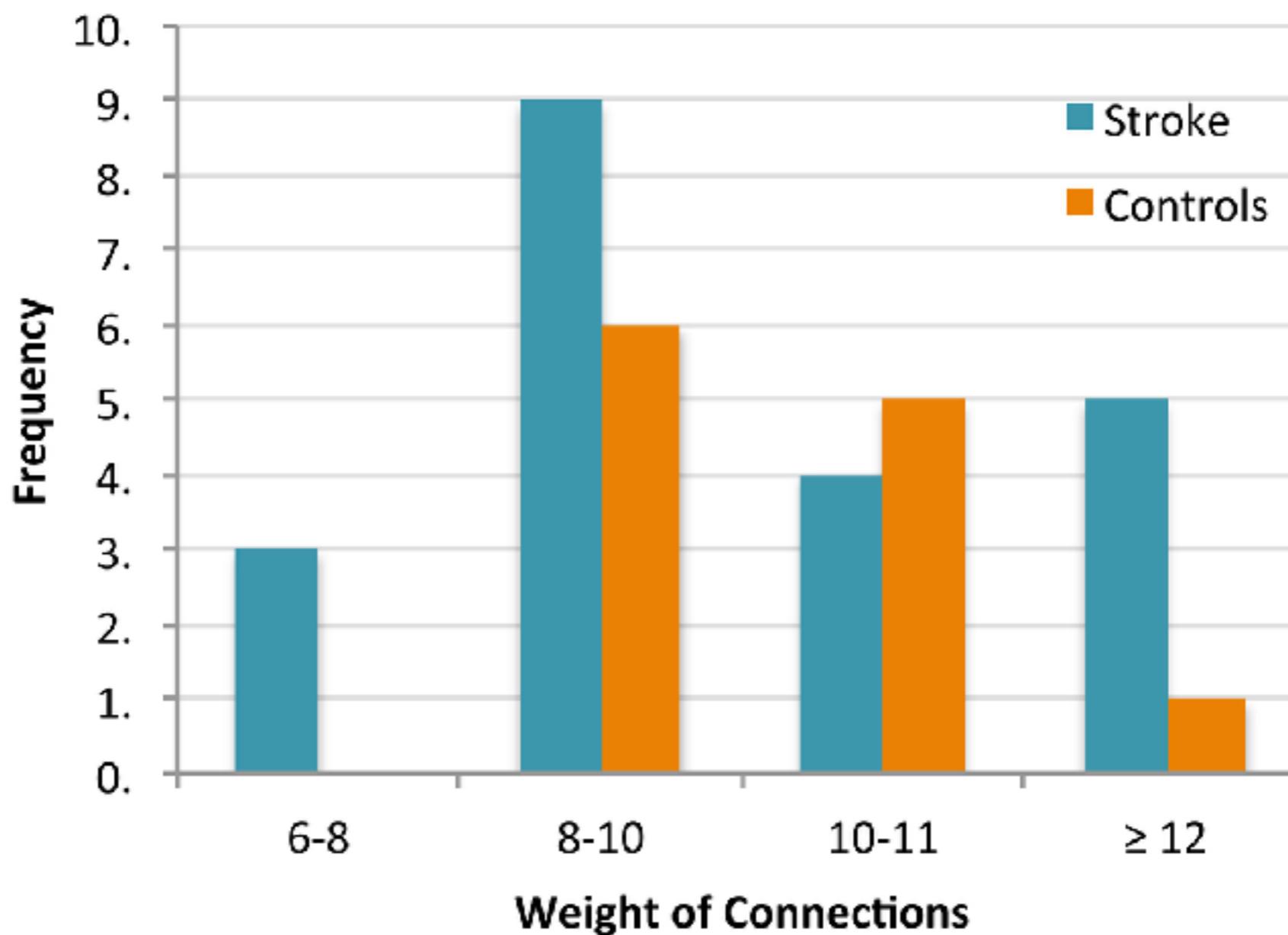
PARAMETER ESTIMATION

STROKE



THE VIRTUAL BRAIN.

SANITY CHECK: STRUCTURAL CONNECTOMES



TVB PARAMETERS AFTER STROKE

Group	Parameter	Range	Mean	SD	Wilcoxon rank sum (p)
Control	<i>Long-range</i>				
	Global coupling	0.044-0.047	0.053	0.009	
	Conduction velocity	45-100	63.9	9.9	
	<i>Local</i>				
	K ₁₂	0.12-0.55	0.49	0.338	
	K ₂₁	0.3-0.9	0.804	0.17	
	K ₁₁	0.6-0.95	0.833	0.142	
Stroke	<i>Long-range</i>				
	Global Coupling	0.04-0.09	0.061	0.016	0.013
	Conduction velocity	12-80	46	21	0.05
	<i>Local</i>				
	K ₁₂	0.1-0.8	0.369	0.257	0.17
	K ₂₁	0.1-0.9	0.674	0.302	0.01
	K ₁₁	0.1-0.99	0.613	0.301	0.1

BIOPHYSICAL INTERPRETATION

- Long-range Parameters:

- *Global Coupling: Increased*
- *Conduction Velocity: Decreased*

That is, global dynamics were reduced in favor of local dynamics

- Local SJ3D Parameters:

- *K_{21} Decreased: Excitatory over inhibitory coupling*

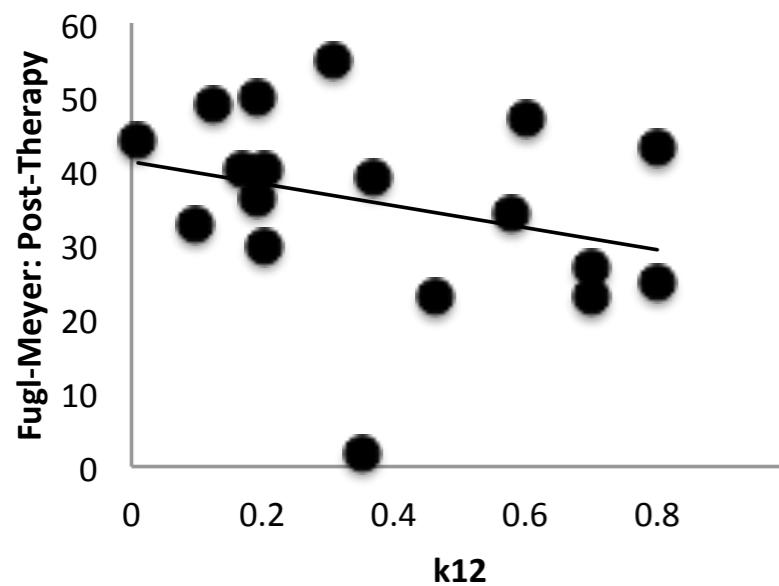
That is, excitability of inhibitory populations at the local level decreased

CORRELATION WITH CLINICAL PHENOTYPE

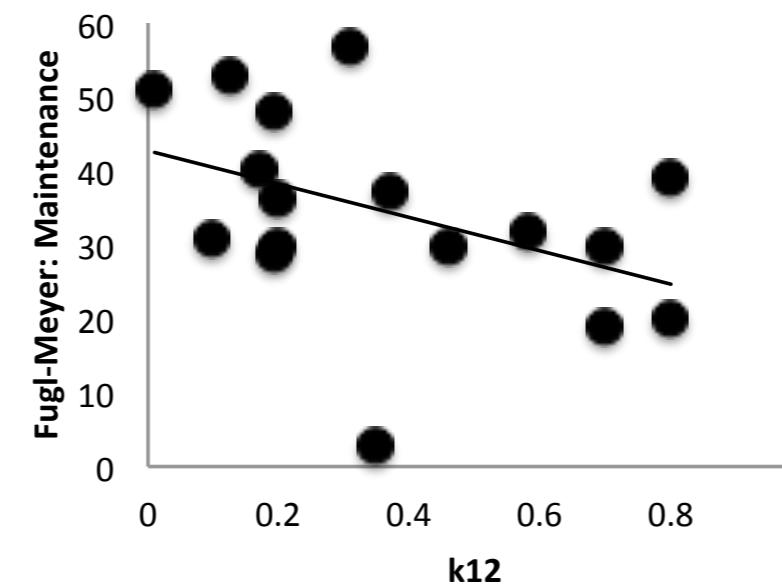
Multiple regression analysis

*Stroke outcome measures = independent variables
TVB parameters = dependent variables*

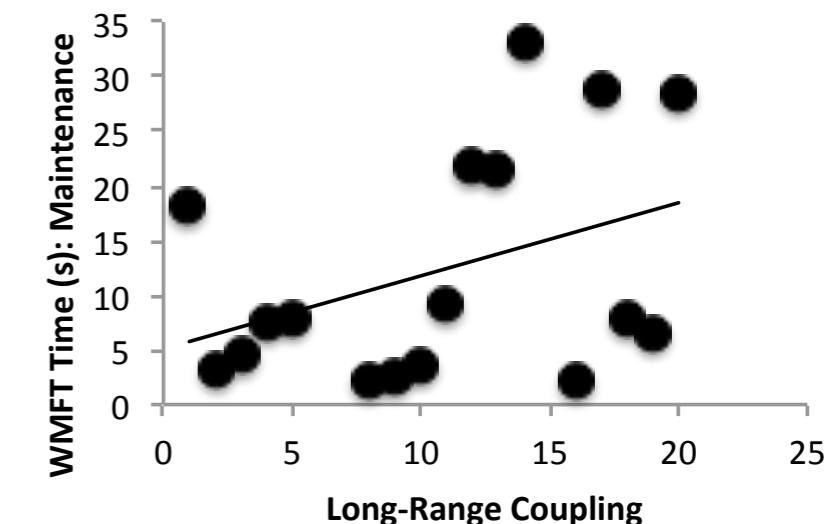
A. K12 vs Fugl-Meyer



B. K12 vs Fugl-Meyer

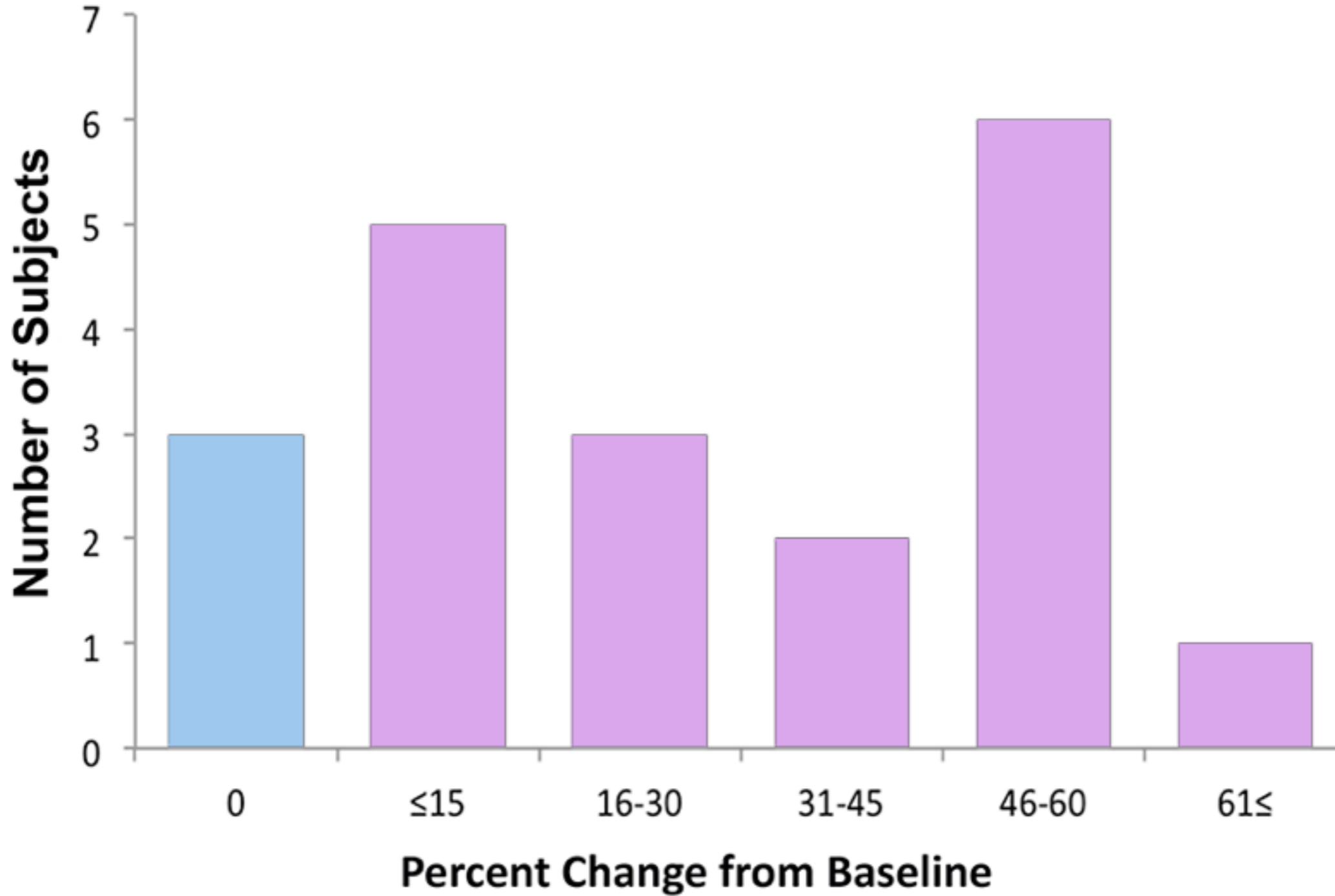


C. Long-Range Coupling vs WMFT



That is, some TVB parameters reflect changes in brain dynamics after therapy.

THE VIRTUAL THERAPY



Falcon, Jirsa & Solodkin, 2016

PARAMETER ESTIMATION

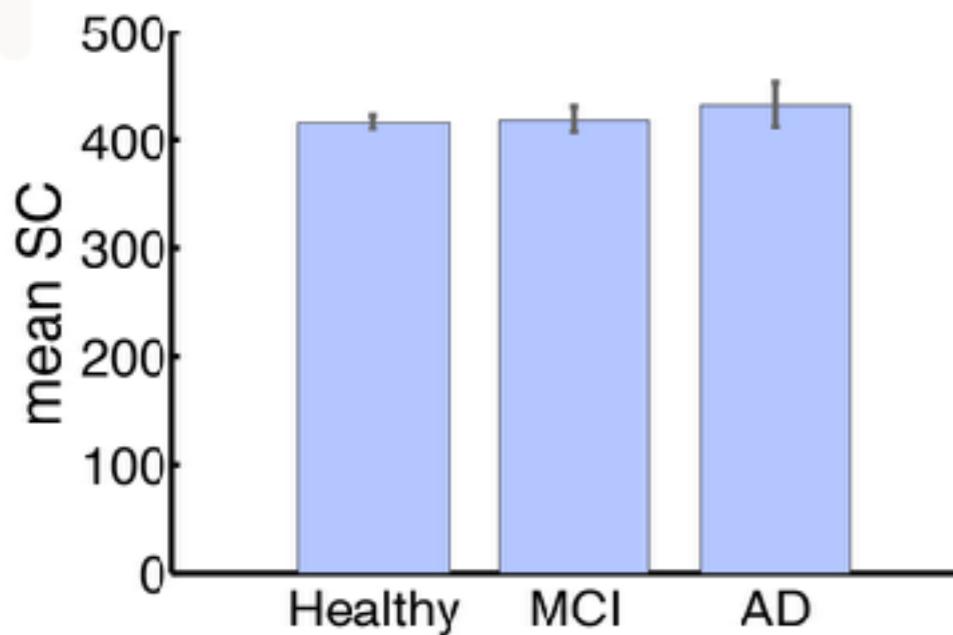


ALZHEIMER'S DISEASE

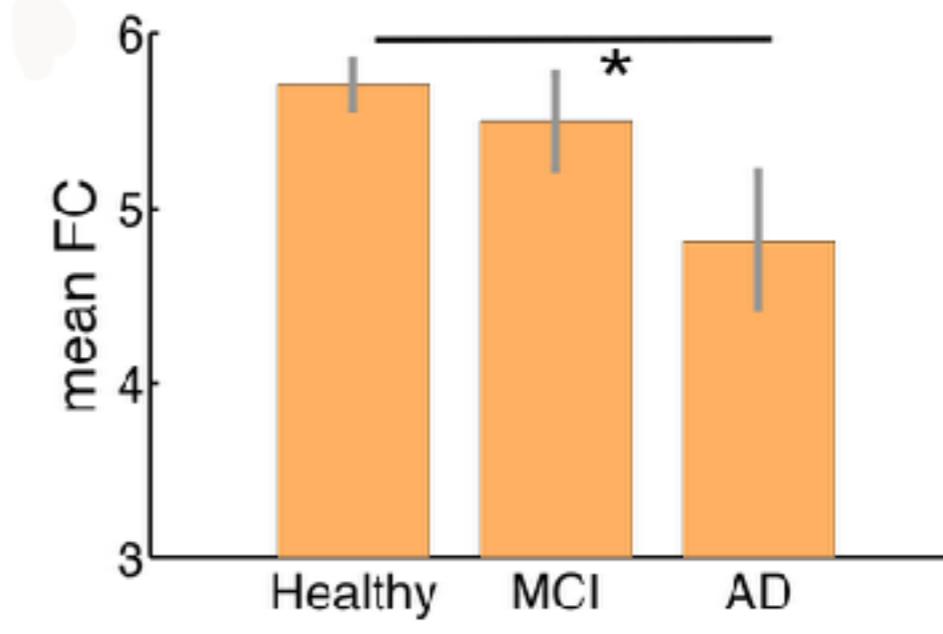
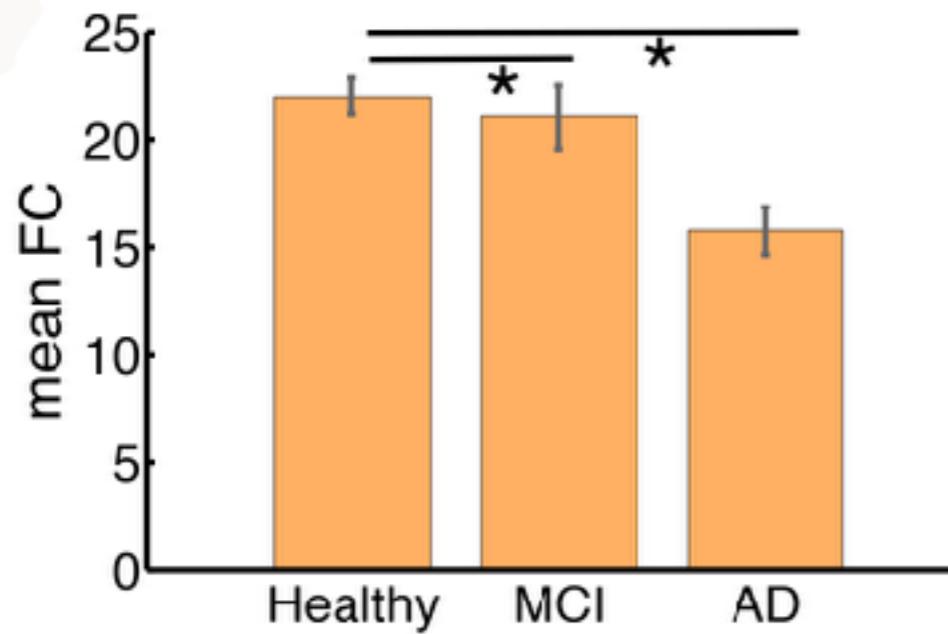
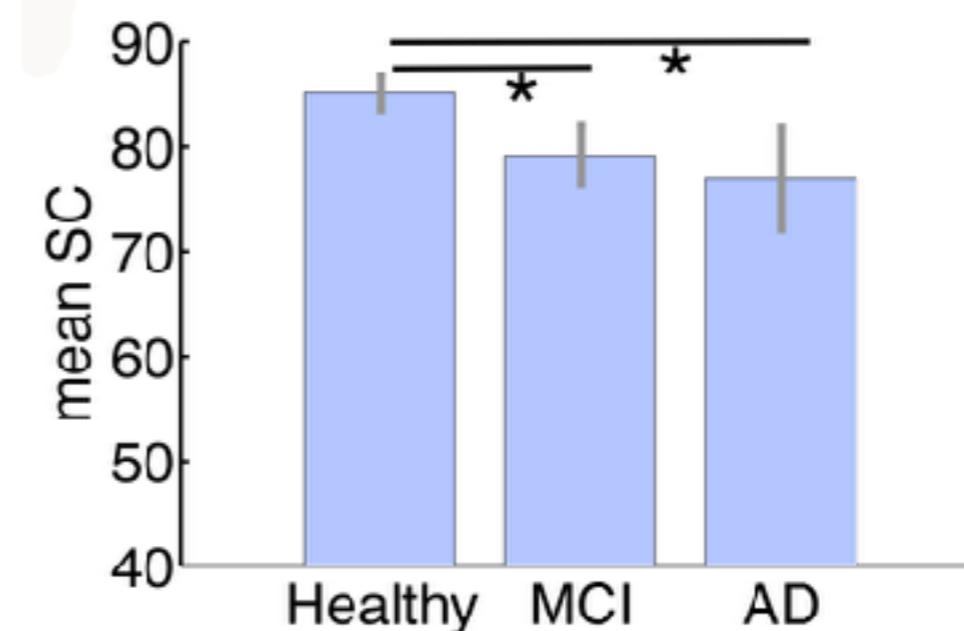
THE VIRTUAL BRAIN.

STRUCTURAL AND FUNCTIONAL CONNECTOMES

Whole Network



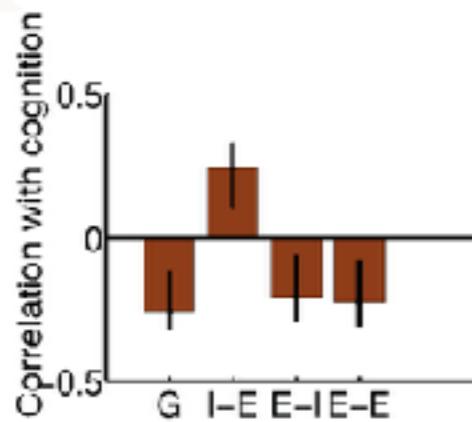
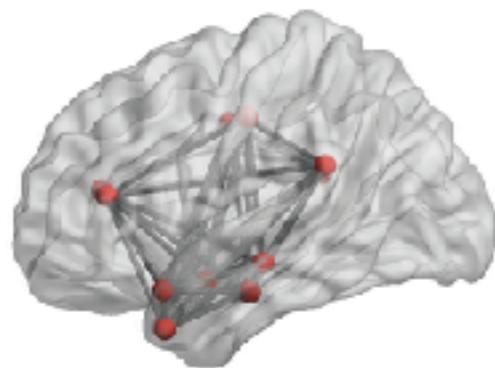
LimbicSubNet



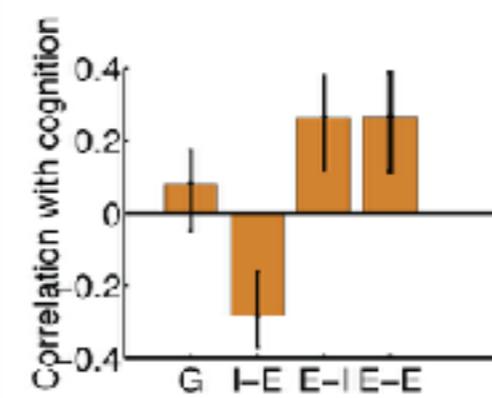
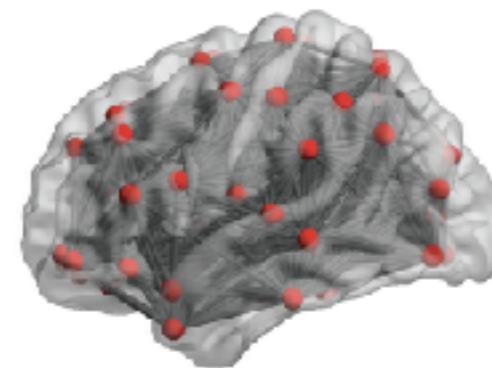
Zimmermann et al., *NeuroImage Clinical*, 2018

SENSITIVITY OF MODELING “MODES”

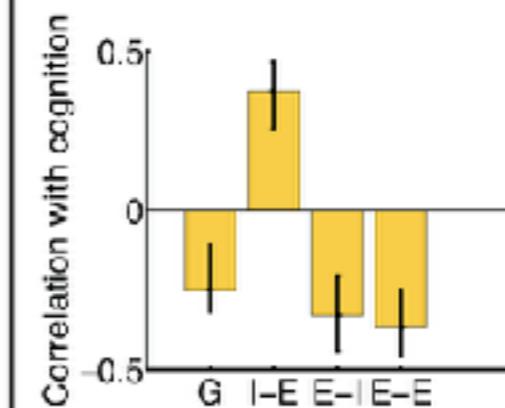
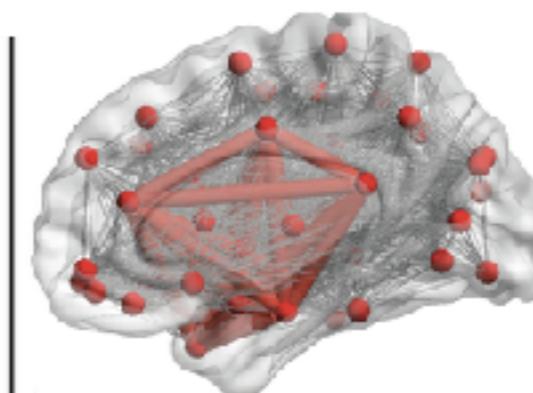
LimbicSubNet



Whole Network

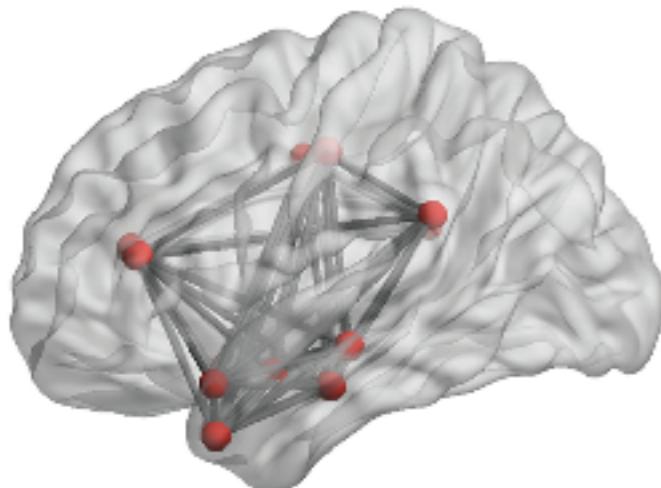


Embedded
LimbicSubNet



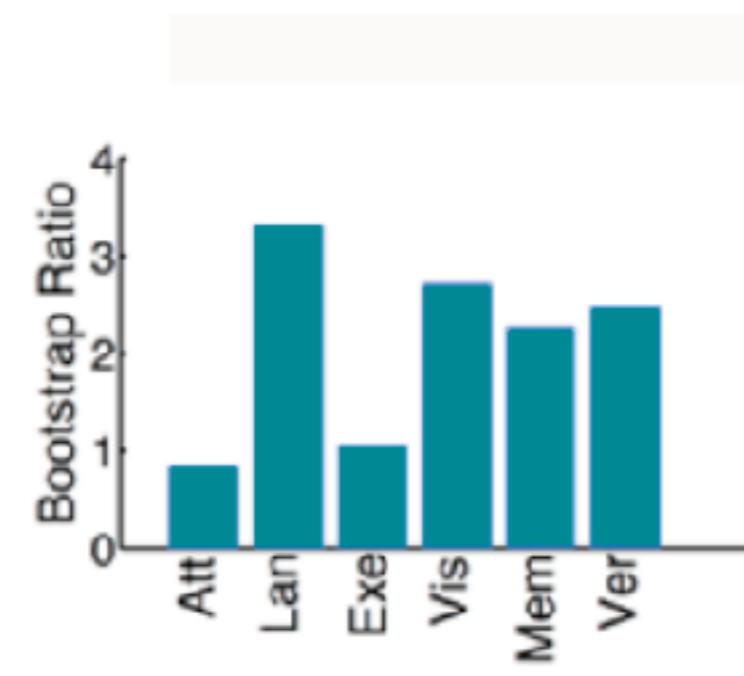
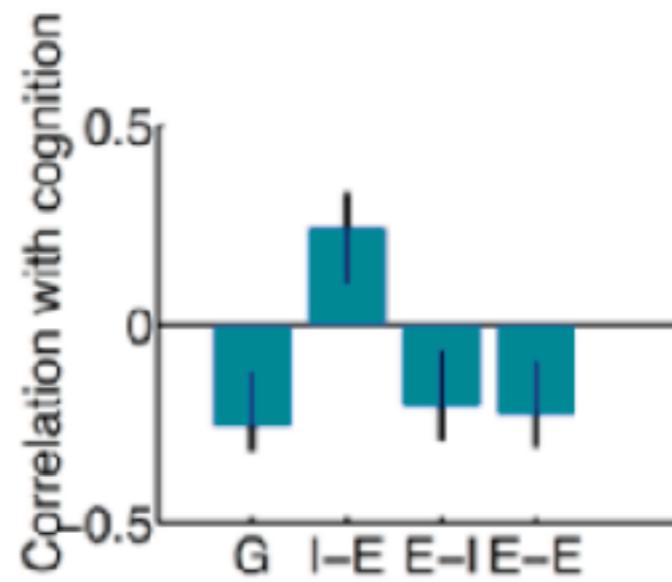
LimbicSubNet and Embedded Networks had stronger relation to Cognitive performance

CORRELATION WITH CLINICAL PHENOTYPE

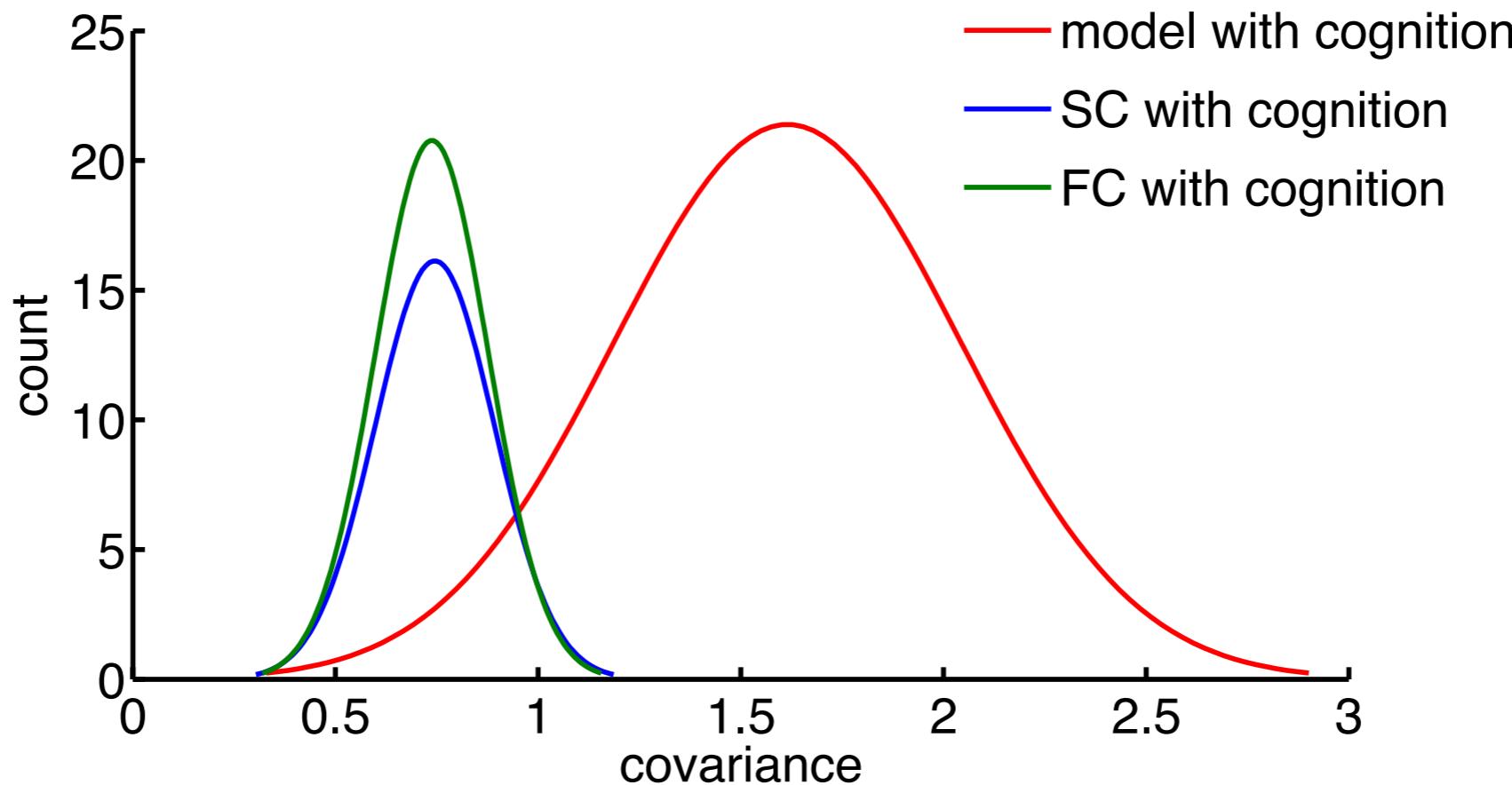


Better Cognitive Performance:

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



TVB vs. CONNECTOMICS



Prediction of cognitive function was significantly better using the model parameters than the person's own structural or functional connectomes (bootstrap estimation of covariance).

SUMMARY

- ▶ Multi scale: Ideal for Clinical Research and Translation
- ▶ Biologically interpretable
- ▶ Individualized: The Virtual Therapy
- ▶ Open source and ready to install
- ▶ Depends on quality of structural connectome and it is non-directional
- ▶ Parameter values are relative not absolute: No literal interpretation
- ▶ Research tool with a steep learning curve

WHAT DOES IT TAKE TO DO TVB CLINICAL MODELING?

- ▶ Embrace the disease of interest
 - ▶ Get acquainted with its pathological mechanisms
 - ▶ Meet patients (ex. shadow Neurologist)!
 - ▶ Develop working hypotheses
 - ▶ Avoid falling on the “hacking craze”.



Thanks!

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Duke Shereen

Viktor Jirsa

Lia Domide

Petra Ritter

Mark Mapstone

Michael Breakspear

Randy McIntosh

El Cerebro Virtual

Le Cerveau Virtuel

Das Virtuelle Gehirn

Il Cervello Virtuale

El Cervell Virtual

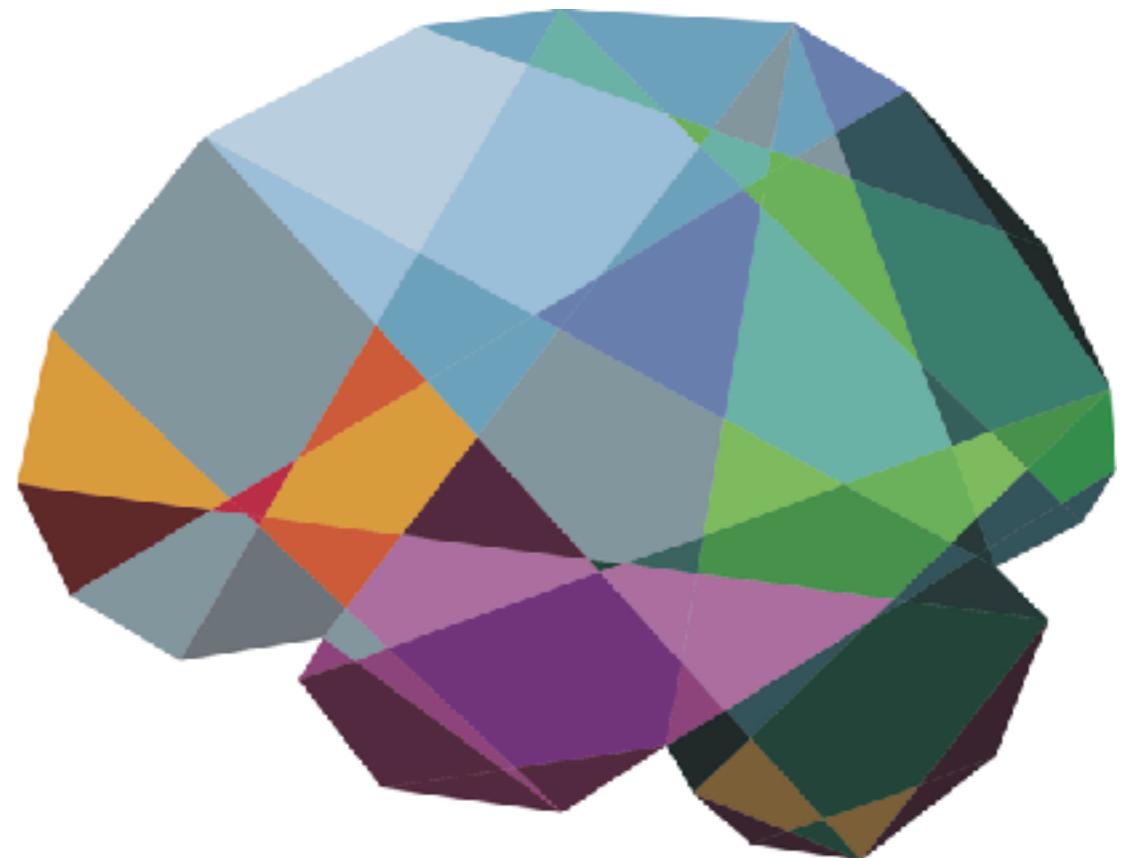
המוח וירטואלי

Creierul Virtual

Virtuální Mozek

虛擬大腦

Ο εικονικός εγκέφαλος



THE VIRTUAL BRAIN.