Institut de
Neurosciences
des Systèmes

Aix Marseille université

Inserm

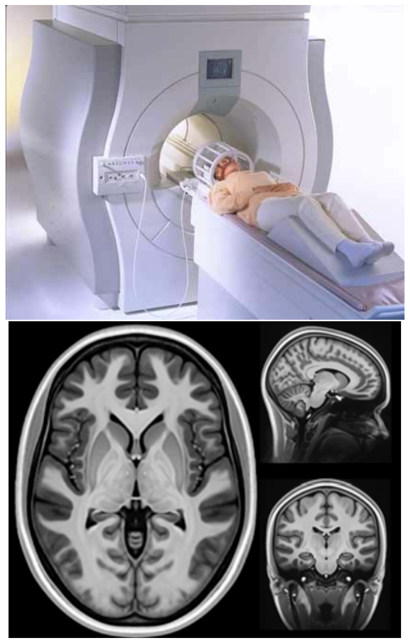
THE VIRTUAL BRAIN

VIKTOR JIRSA

EBRAINS

Institut de
Neurosciences
des Systèmes

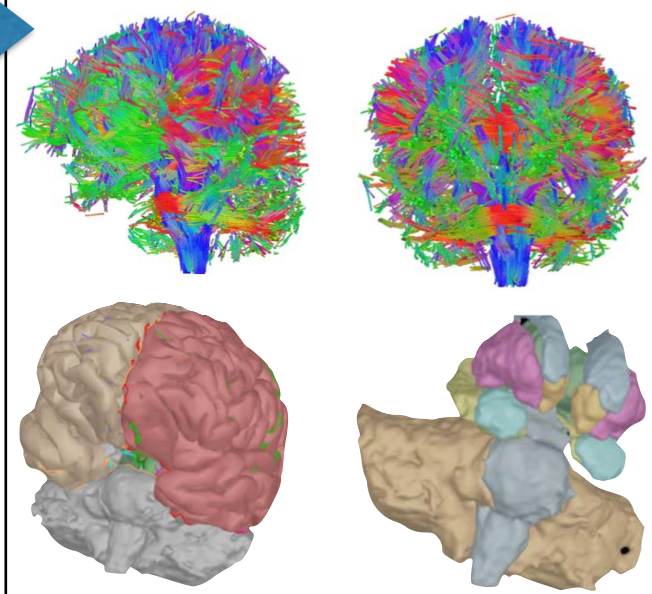
Simulating the Virtual Epileptic Patient (VEP)



Non-invasive imaging

1990s

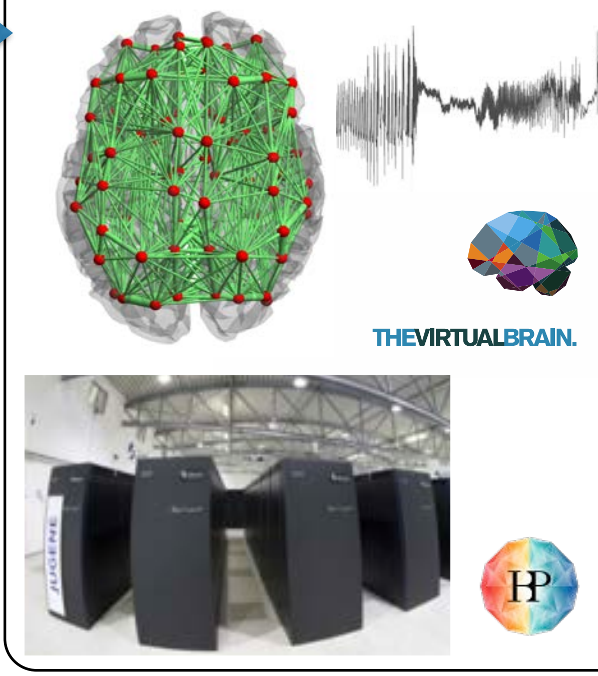
Magnetic Resonance
Spectrography (MRI)
Diffusion Imaging (DTI, DSI)



Networks & Connectomics

2000s

Network theory
Graph theoretical analyses
Connectome



In-silico multiscale brains

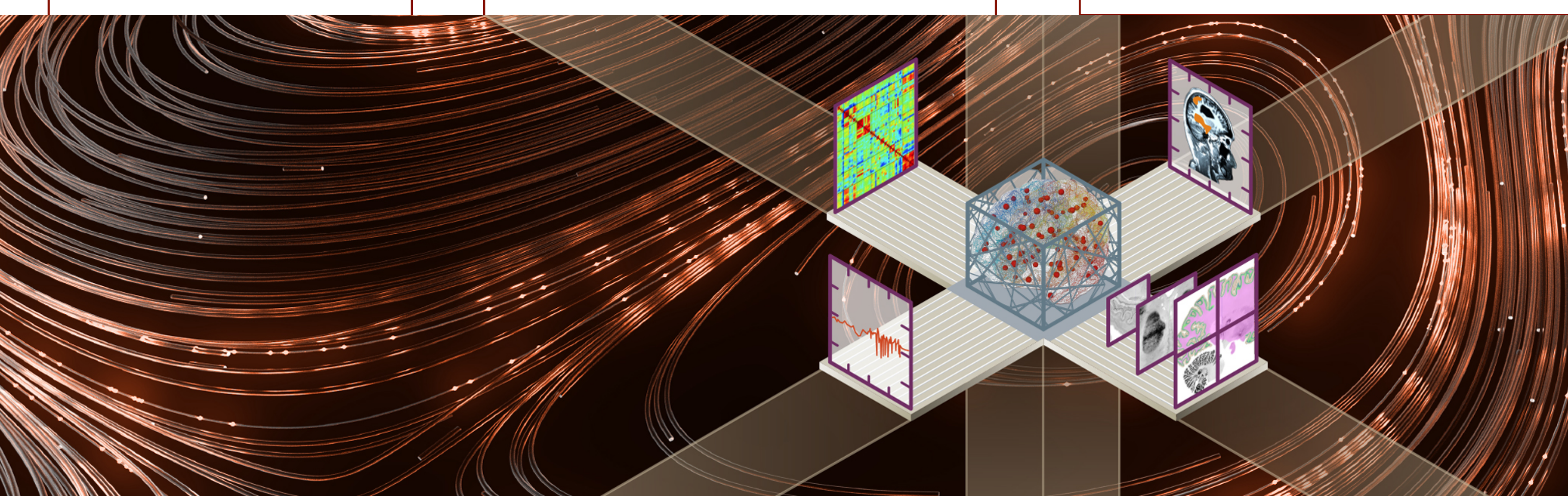
2010s

Large-scale brain network modeling
Multiscale
High Performance Computation

Personalized brain models

2020s

Clinical trial EPINOV
Personalized Medicine
Bio-inspired computation



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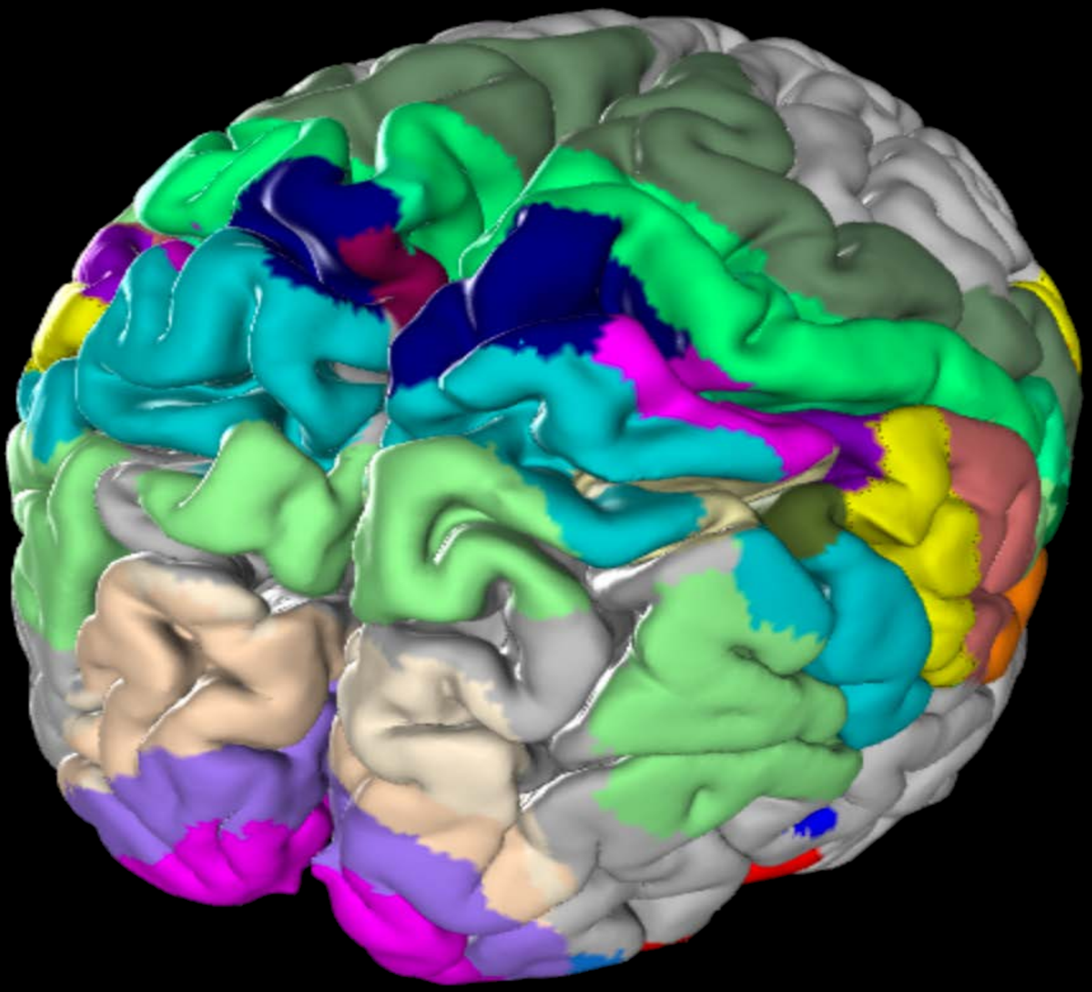
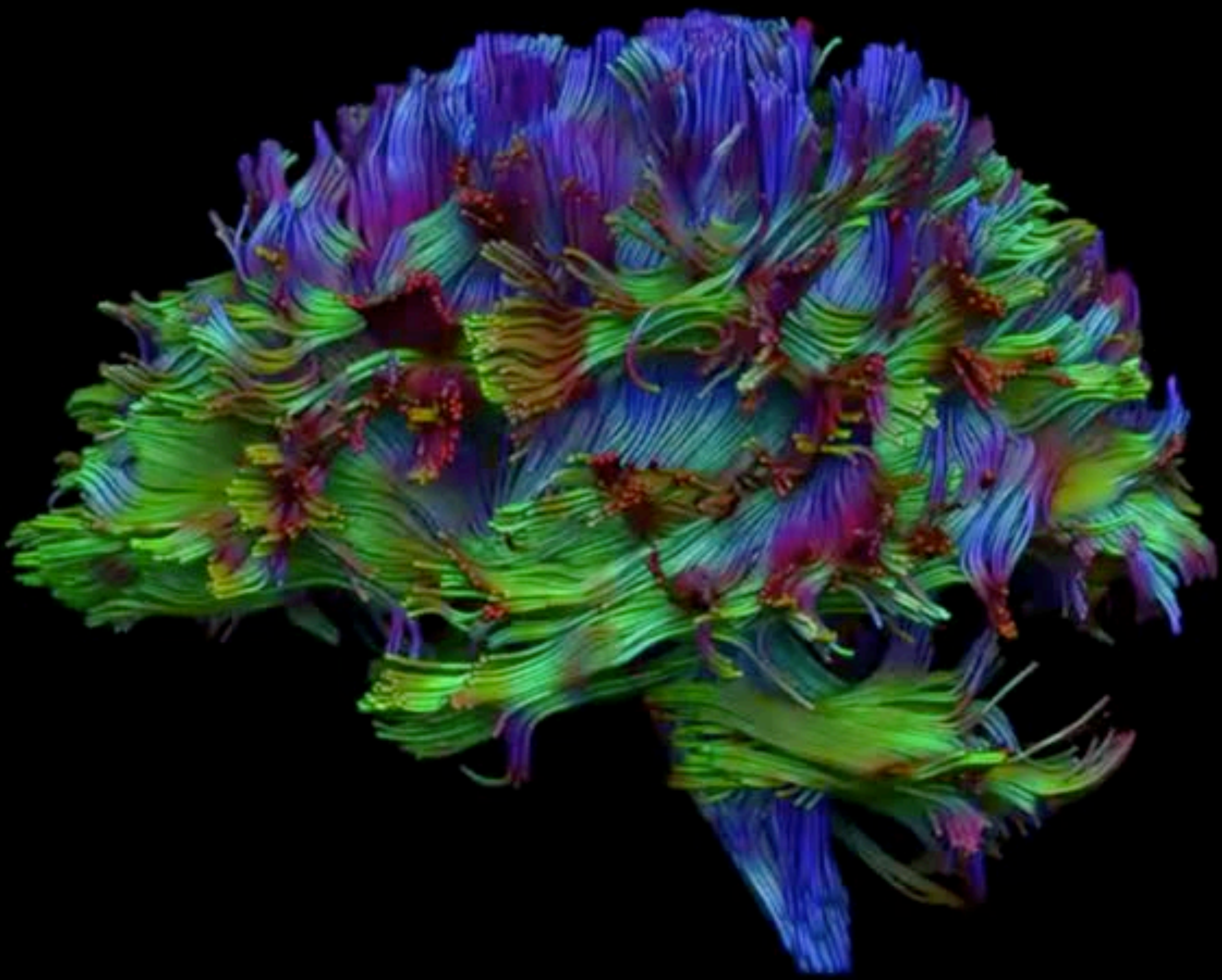
The Virtual Brain (TVB)

Brain structure

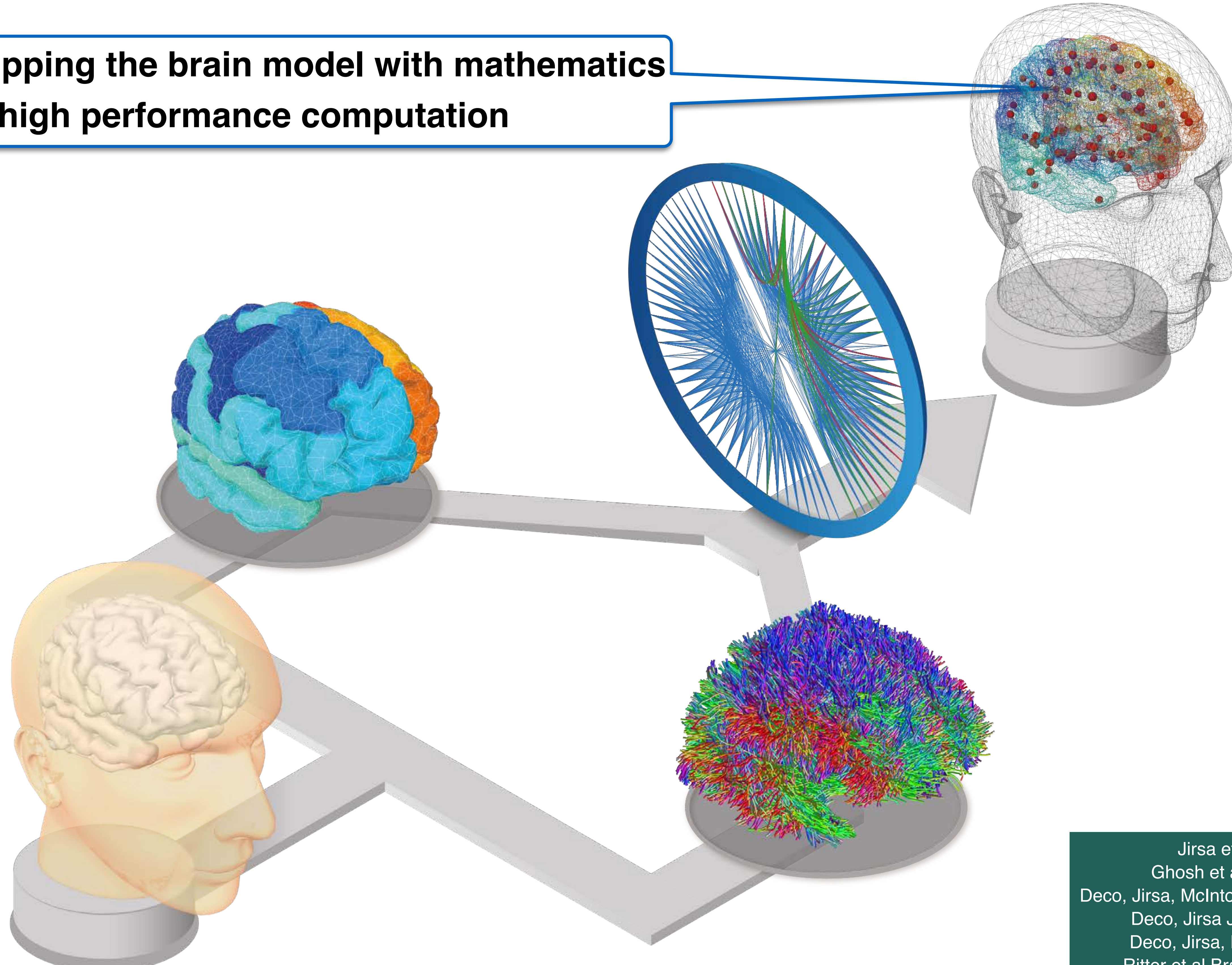


Brain Connectome



Building The Virtual Brain (TVB)

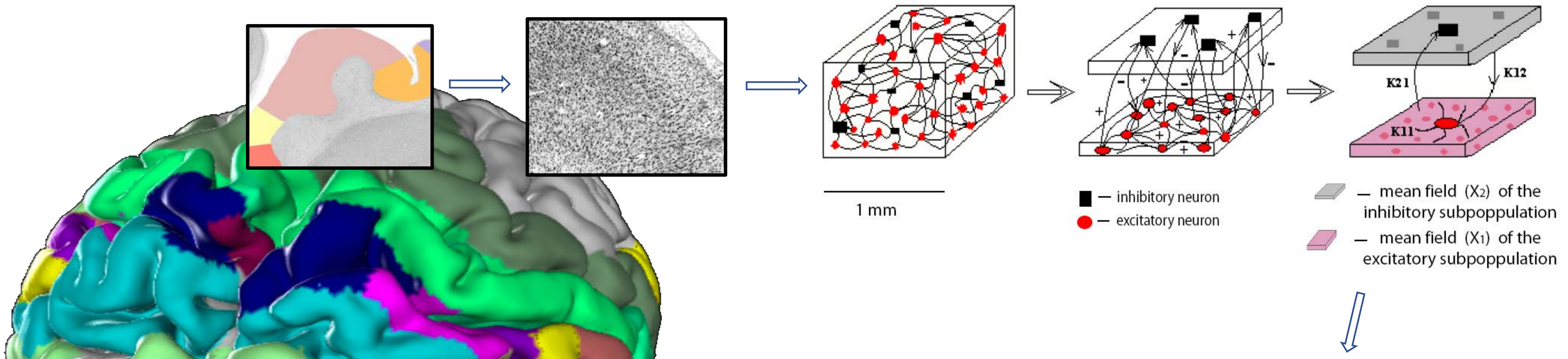
Equipping the brain model with mathematics and high performance computation



Jirsa et al IEEE 2002
Ghosh et al. PLoS CB 2008
Deco, Jirsa, McIntosh Nat Rev Neurosci 2011
Deco, Jirsa Journ Neurosci 2012
Deco, Jirsa, McIntosh TINS 2013
Ritter et al Brain Connectivity 2013

Building The Virtual Brain (TVB)

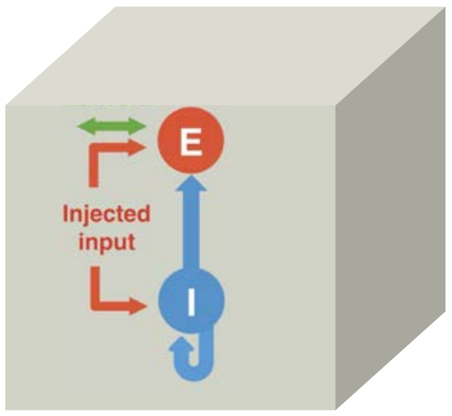
Brain regions



Neural Mass as network node

AMPA, NMDA

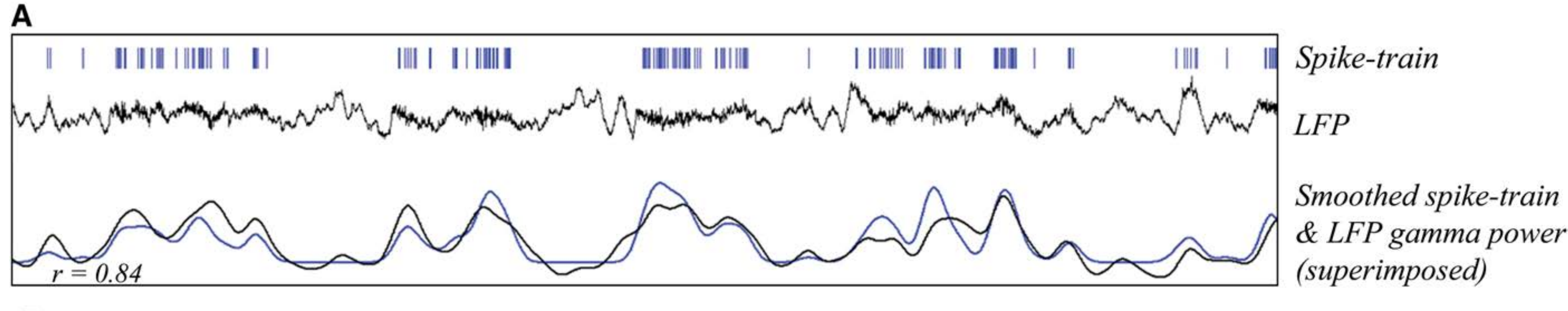
GABA



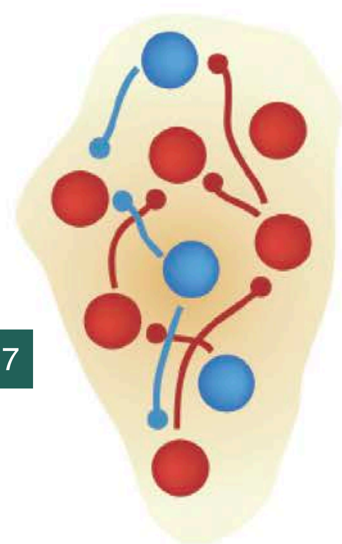
Deco, Jirsa, McIntosh Nature Rev Neurosci 2011

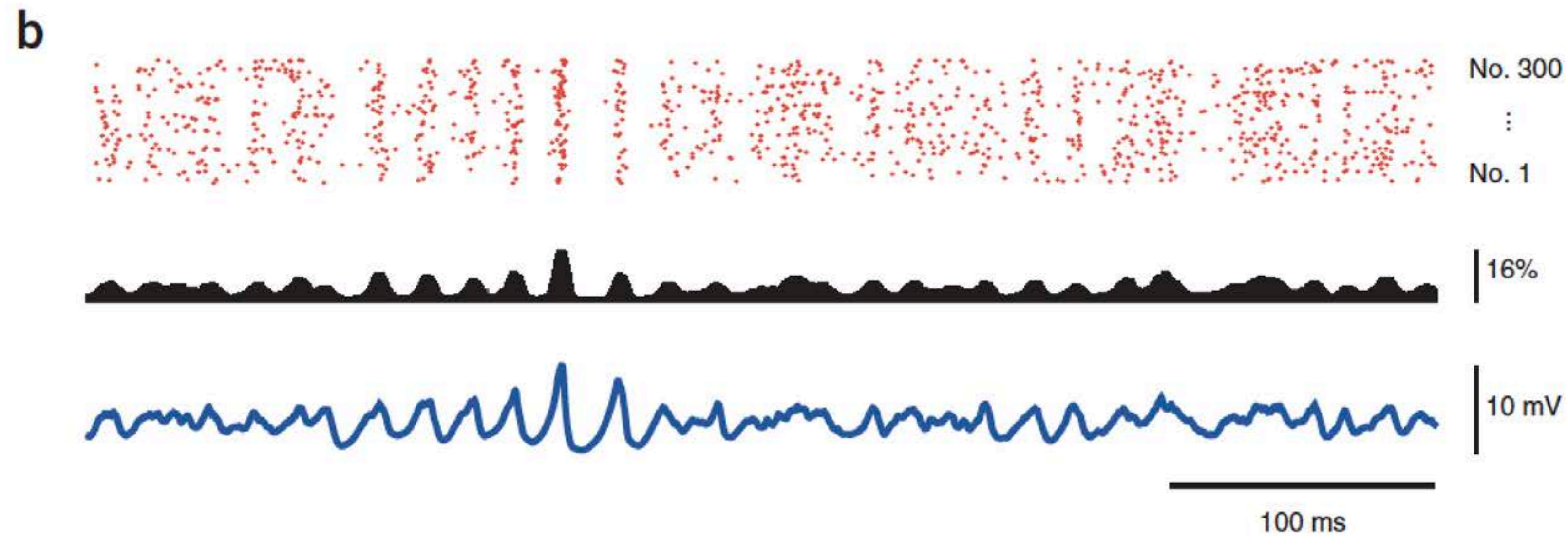
Oscillations in large-scale brain networks

Nir et al Current Biology 2007



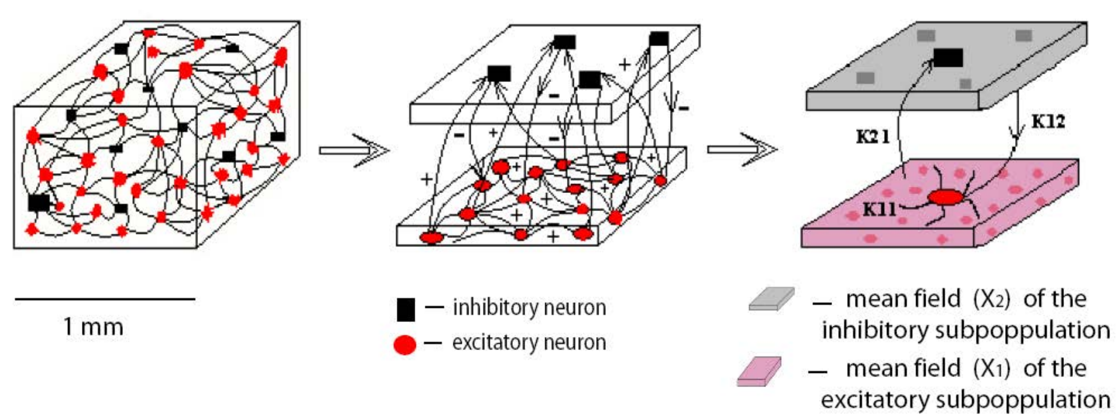
Palmigiano et al. Nat Neurosci 2017

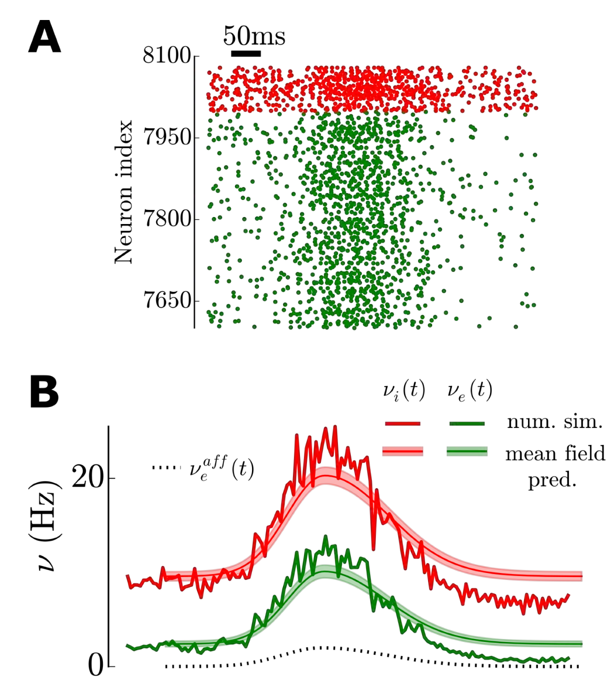




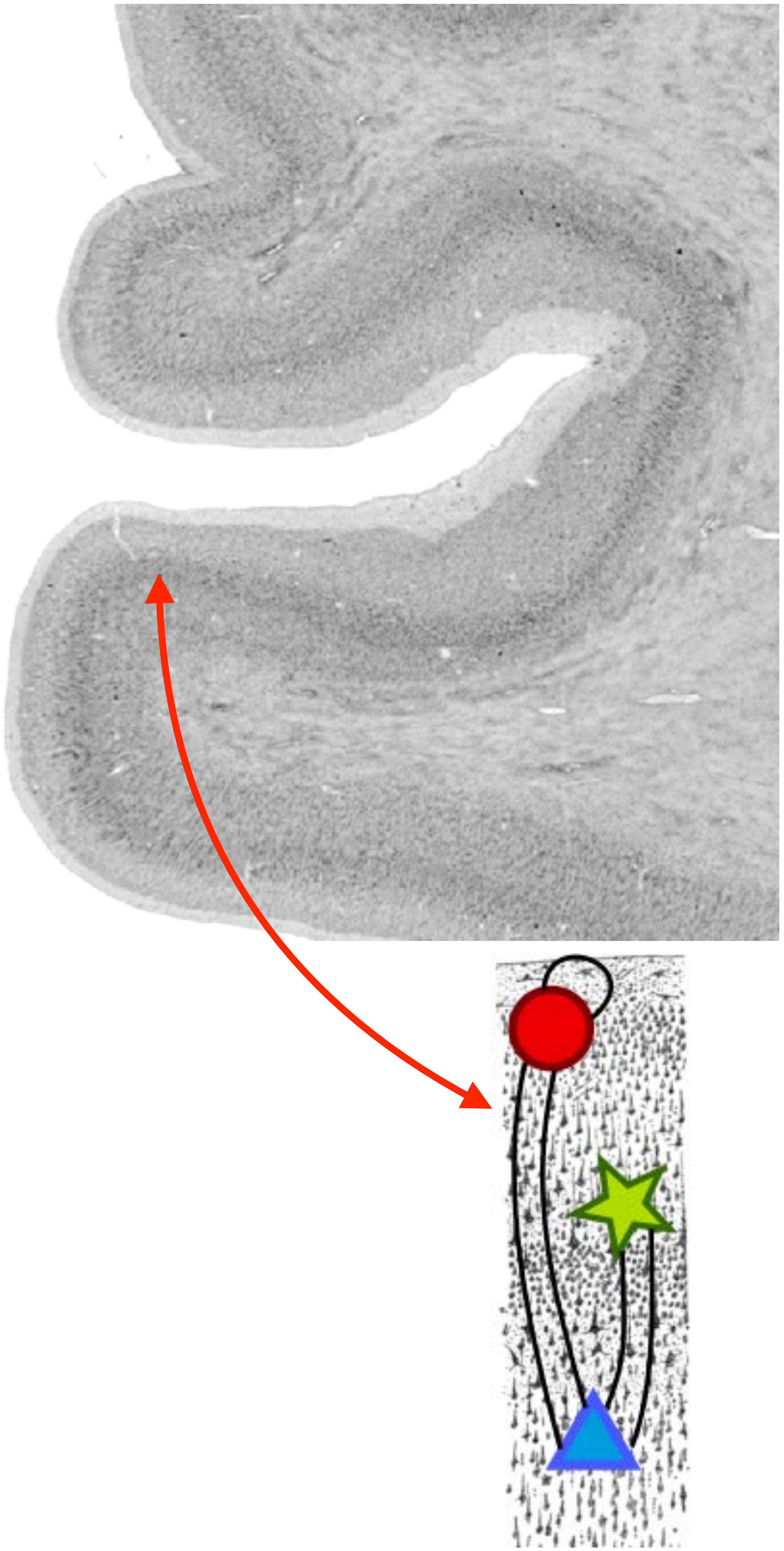
Network node: Mean fields

Wendling et al Europ Journ Neurosci 2002
Stefanescu & Jirsa PLoS CB 2008
Zerlaut & Destexhe J Comp Neurosci 2017



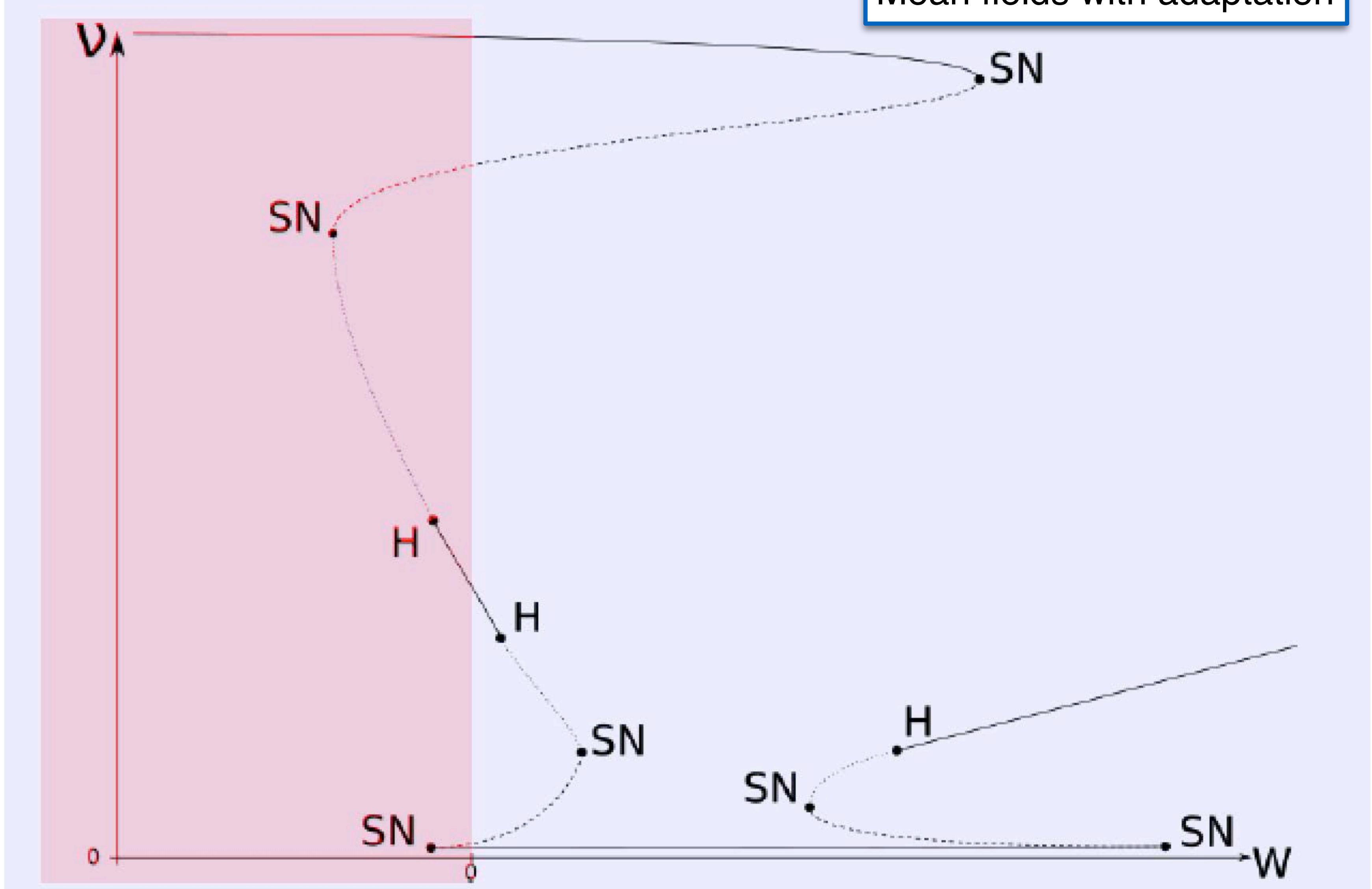


Neural masses through mean fields



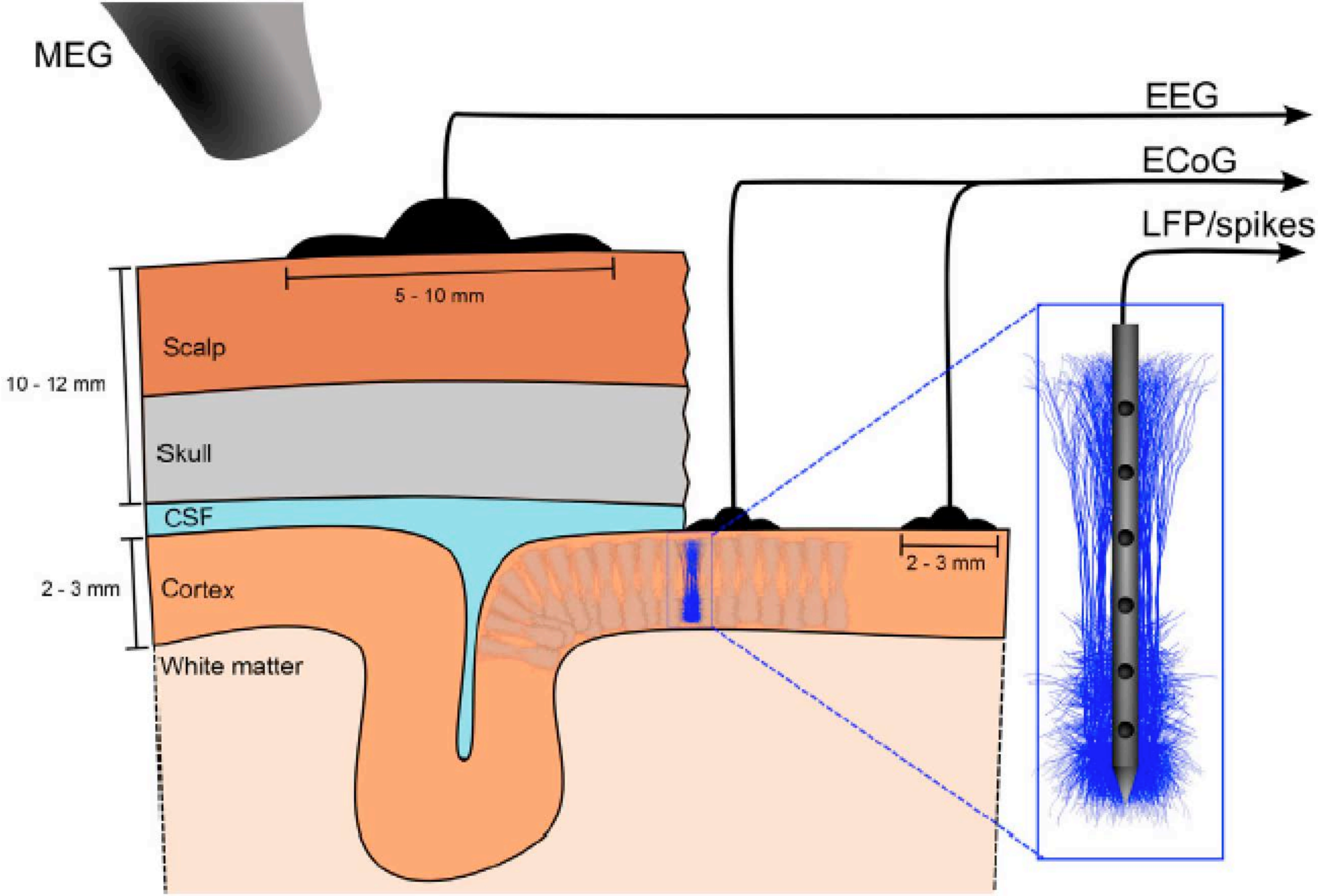
$$
\forall \mu,\lambda,\eta \in \{e,i\}^3, \quad
\begin{cases}
T\dfrac{\partial \nu_\mu}{\partial t} = (\mathcal{F}_\mu - \nu_\mu) + \dfrac{1}{2} c_{\lambda\eta} \dfrac{\partial^2 \mathcal{F}_\mu}{\partial \nu_\lambda \partial \nu_\eta} \\[2ex]
T\dfrac{\partial c_{\lambda\eta}}{\partial t} = A_{\lambda\eta} + (\mathcal{F}_\lambda - \nu_\lambda)(\mathcal{F}_\eta - \nu_\eta) + c_{\lambda\mu}\dfrac{\partial \mathcal{F}_\mu}{\partial \nu_\lambda} + c_{\mu\eta}\dfrac{\partial \mathcal{F}_\mu}{\partial \nu_\eta} - 2c_{\lambda\eta} \quad \text{with } A_{\lambda\eta} = \begin{cases} \dfrac{\mathcal{F}_\lambda (1/T - \mathcal{F}_\lambda)}{N_\lambda} & \text{if } \lambda = \eta \\ 0 & \text{otherwise} \end{cases} \\[2ex]
\dfrac{\partial W}{\partial t} = -\dfrac{W}{\tau_w} + b * \nu_e + a * (\mu_V(\nu_e, \nu_I, W) - E_L)
\end{cases}
$$

Mean fields with adaptation



Zerlaut & Destexhe J Comp Neurosci 2017;
Kusch, Jirsa, & Destexhe (in preparation)

Multiscale virtual brain modeling for network dynamics

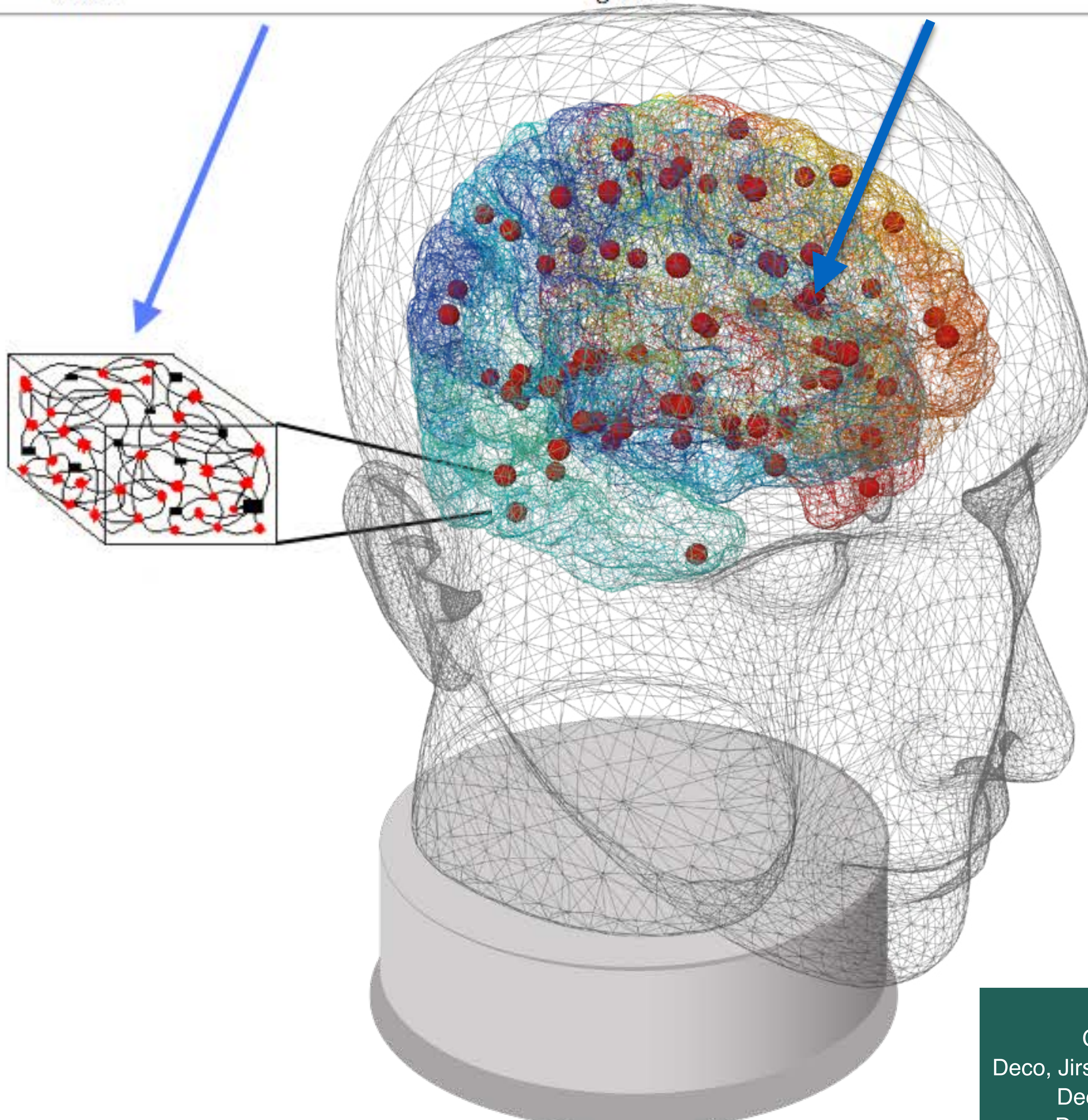


Einevoll et al Neuron 2019

Building personalized large-scale brain networks

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

Field potential



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Ritter et al Brain Connectivity 2013

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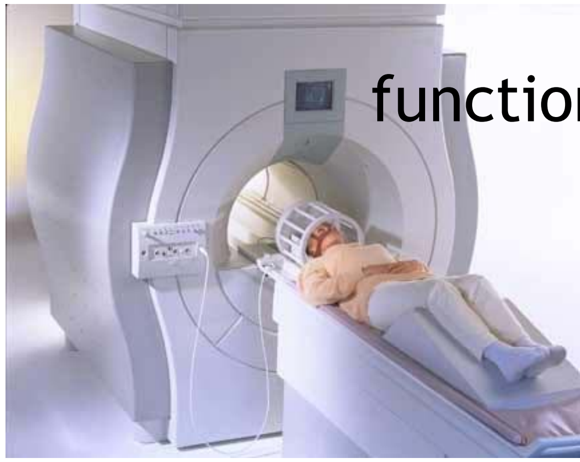
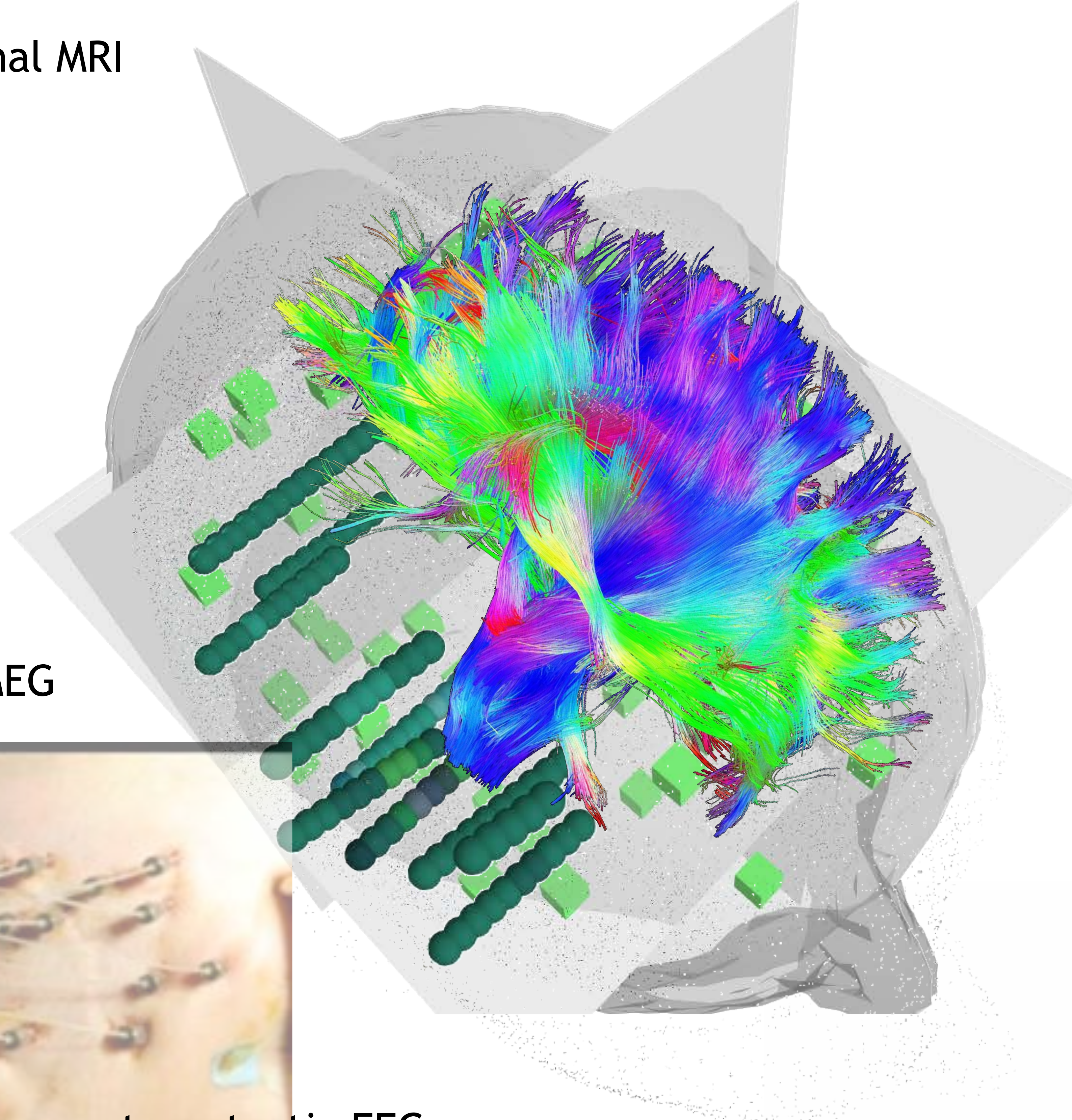
Concepts: Connectome-based brain networks



functional MRI

MEG

stereotactic EEG

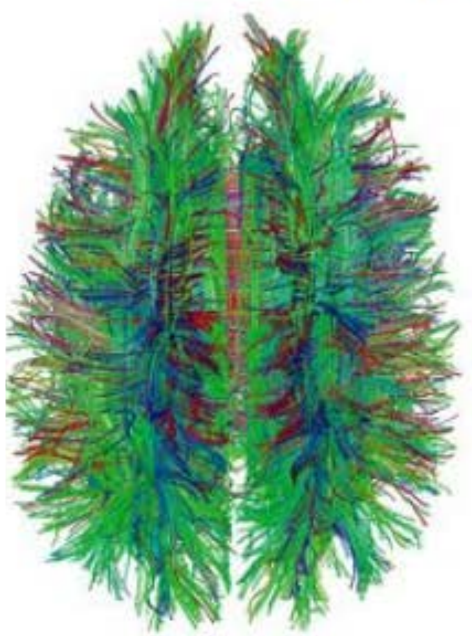


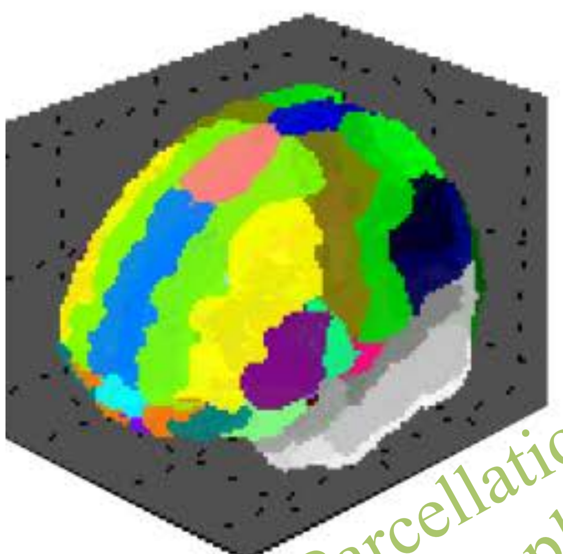
Deco, Jirsa, McIntosh Nature Rev Neurosci 2011

THEVIRTUALBRAIN.

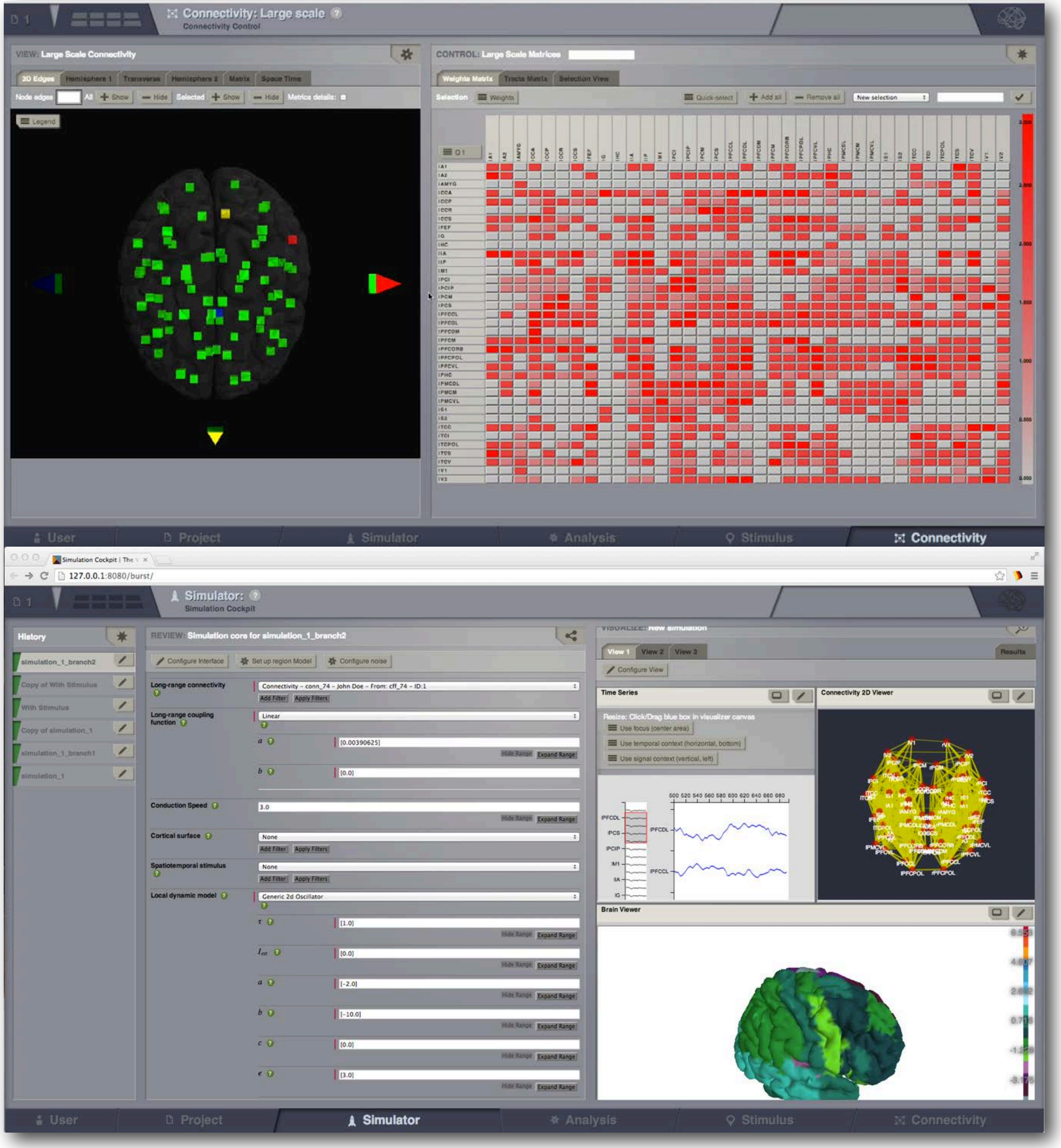
The Virtual Brain (TVB) platform release in 2012

DTI/ Tractography





Parcellation Template



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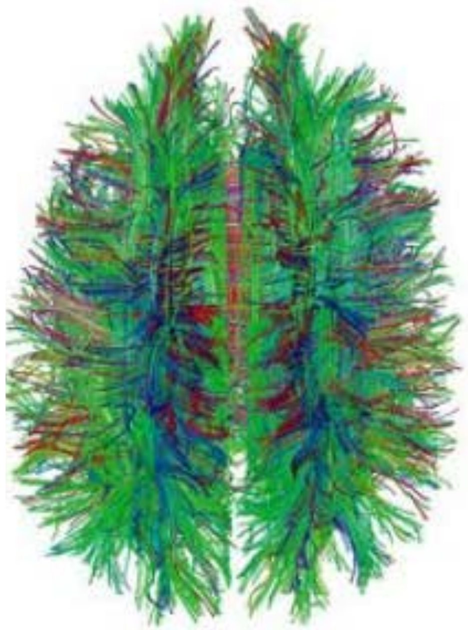
Ritter et al Brain Connectivity 2013

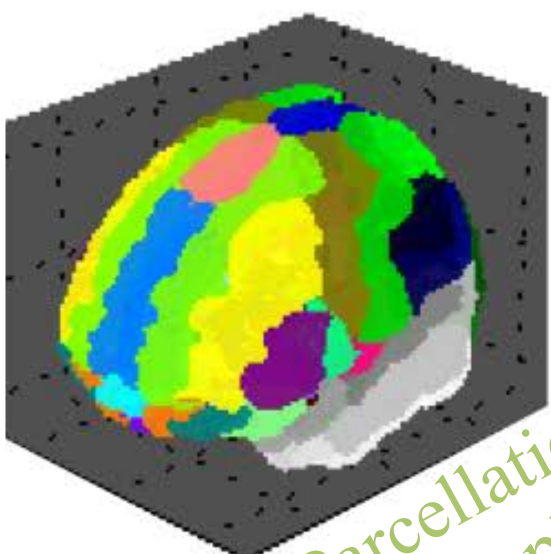
Sanz Leon et al Front NeuroInformatics 2013; Neuroimage 2015

THEVIRTUALBRAIN.

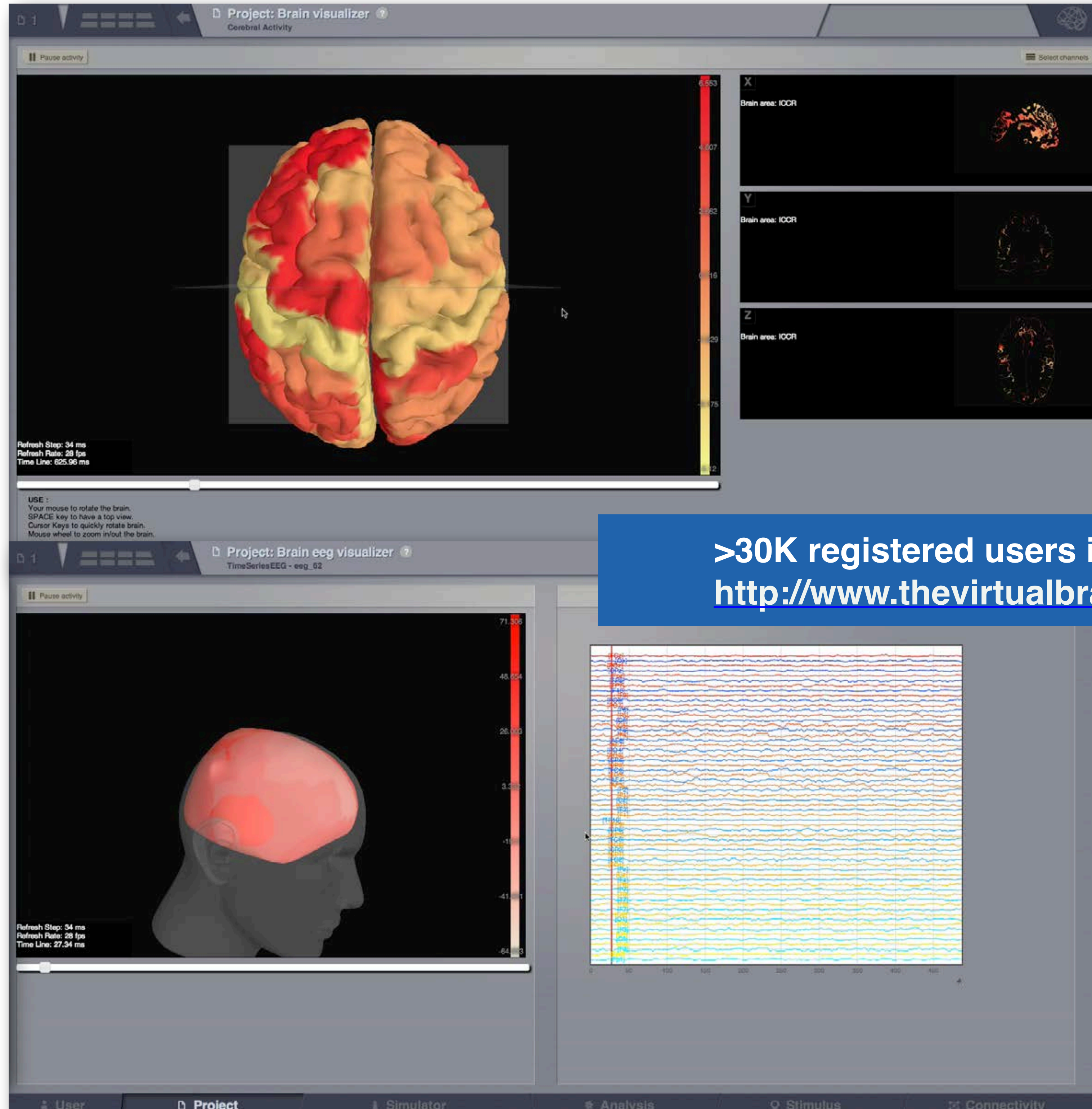
The Virtual Brain (TVB) platform release in 2012

DTI/ Tractography





Parcellation Template



>30K registered users in 2020
http://www.thevirtualbrain.org

Jirsa et al IEEE 2002
Ghosh et al. PLoS CB 2008
Deco, Jirsa, McIntosh Nat Rev Neurosci 2011
Deco, Jirsa Journ Neurosci 2012
Deco, Jirsa, McIntosh TINS 2013
Ritter et al Brain Connectivity 2013

Sanz Leon et al Front NeuroInformatics 2013; Neuroimage 2015

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The Virtual Mouse Brain (TVMB)

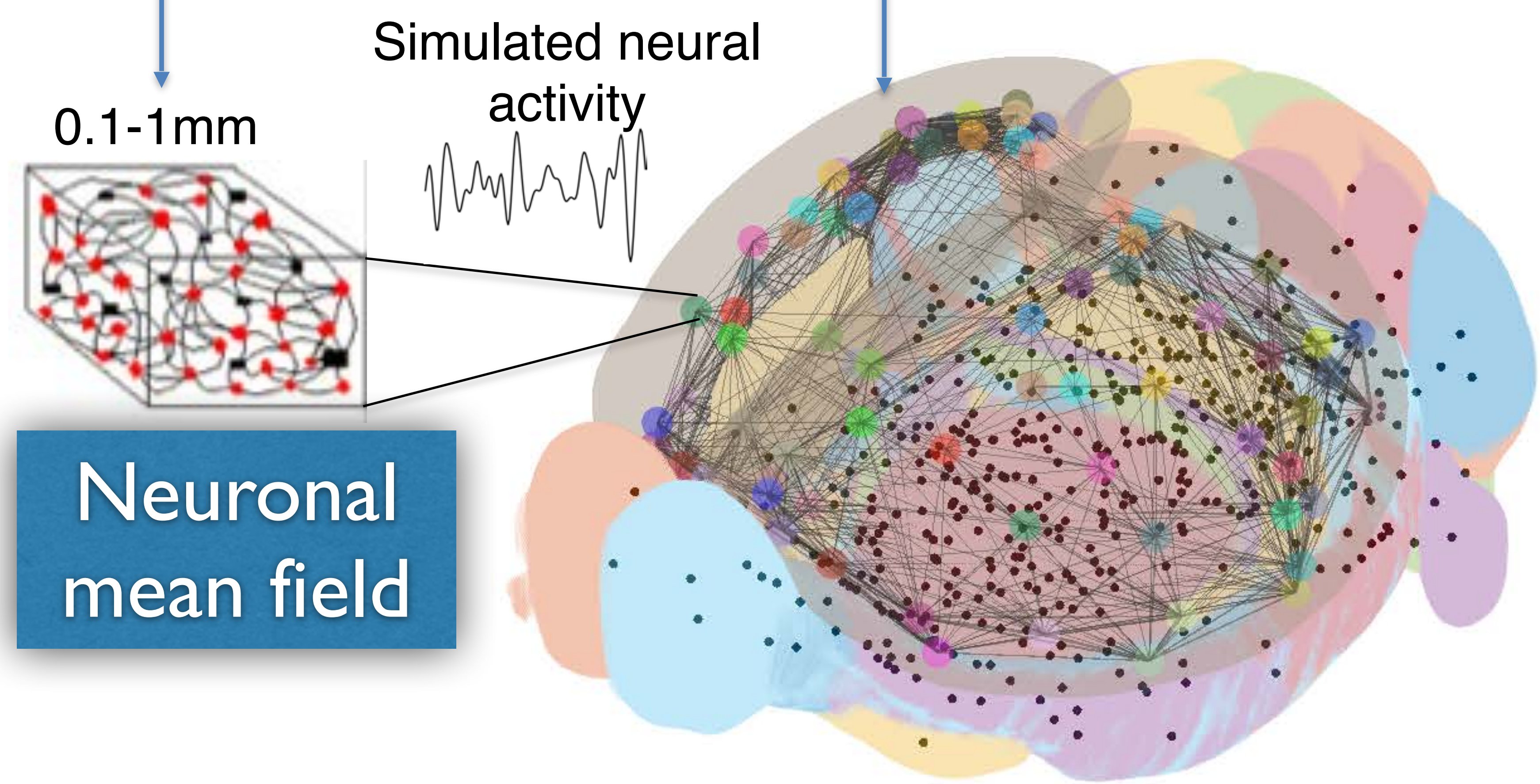
Local dynamics

Global dynamics

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

Field potential

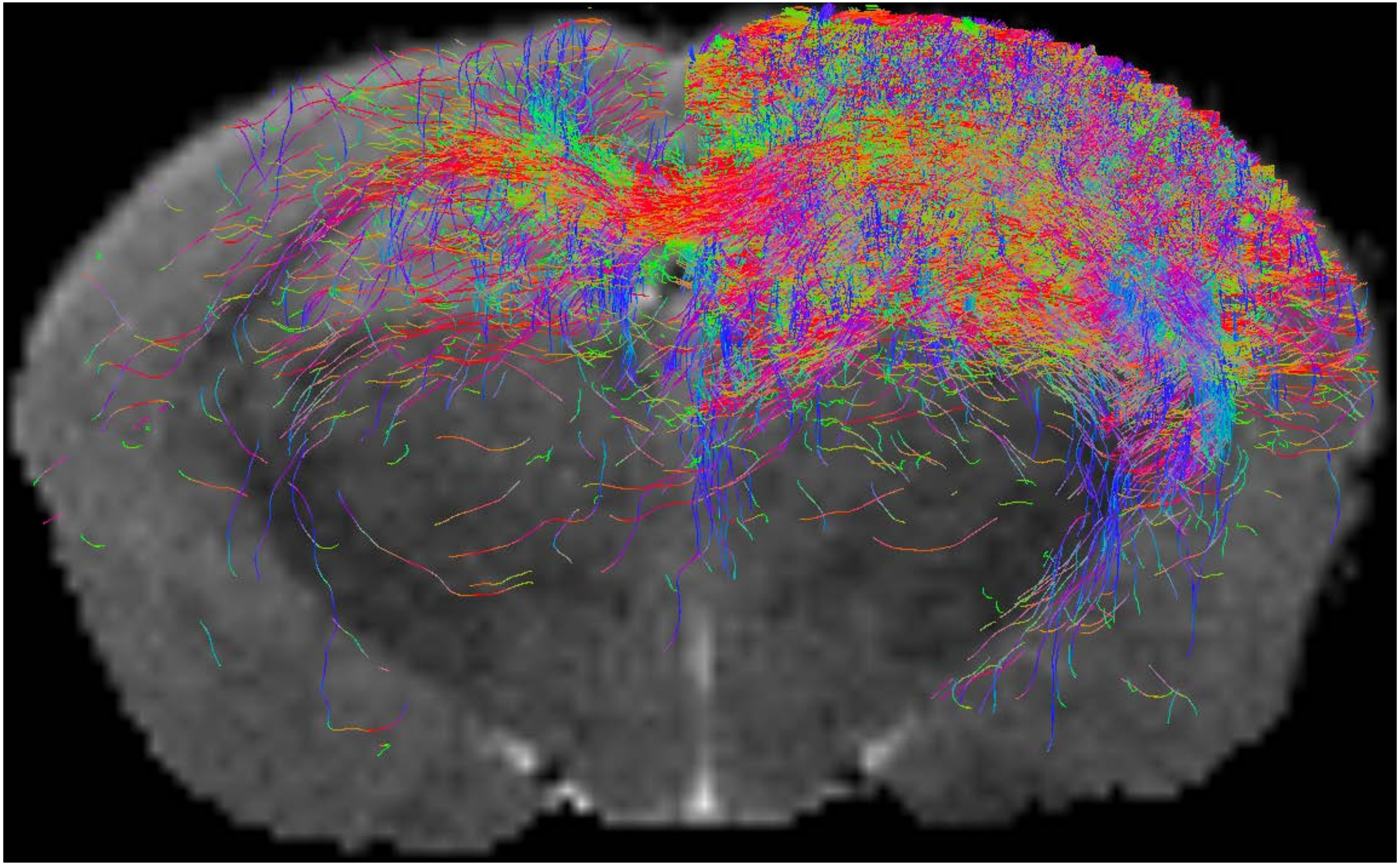
Intrinsic activity



Human Brain Project

Melozzi et al ENeuro 2017, PNAS 2019

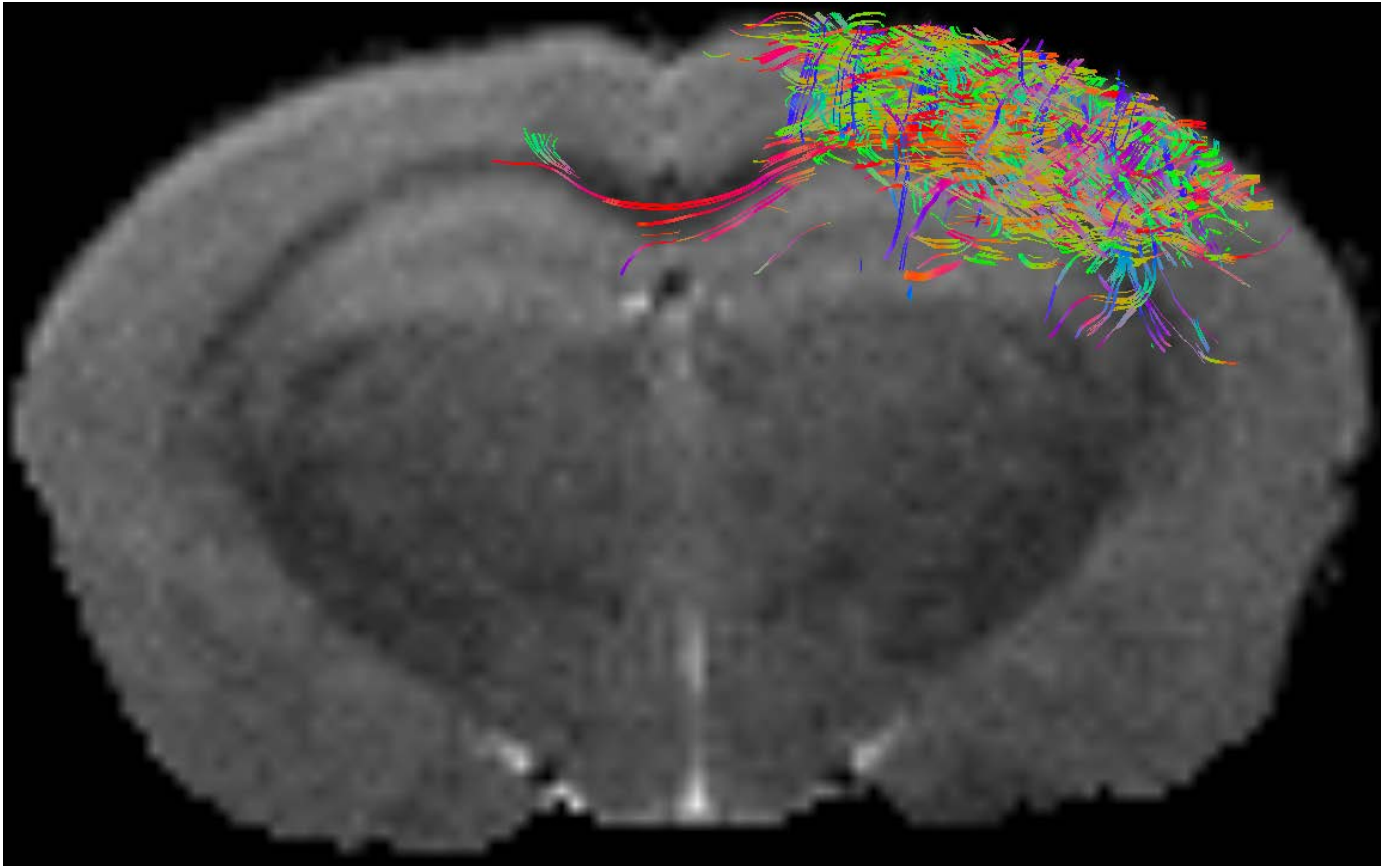
Probabilistic Tractography



Human Brain Project

Melozzi et al ENeuro 2017, PNAS 2019

Deterministic Tractography



Human Brain Project

Melozzi et al ENeuro 2017, PNAS 2019

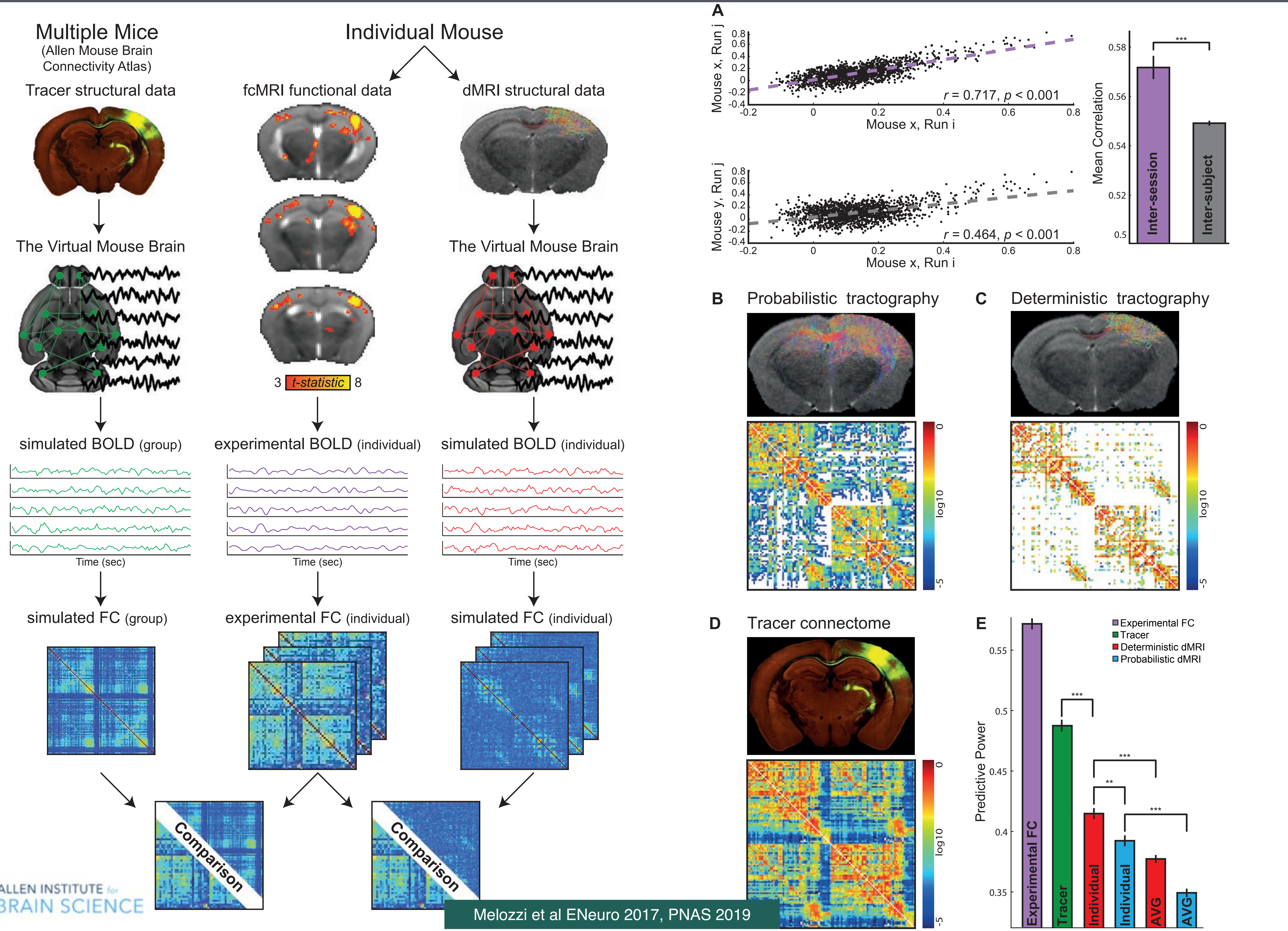
Allen Atlas

Human Brain Project

ALLEN INSTITUTE for BRAIN SCIENCE

Melozzi et al ENeuro 2017, PNAS 2019

The Virtual Mouse Brain (TVMB) modeling - validation



Melozzi et al ENeuro 2017, PNAS 2019

ALLEN INSTITUTE for BRAIN SCIENCE

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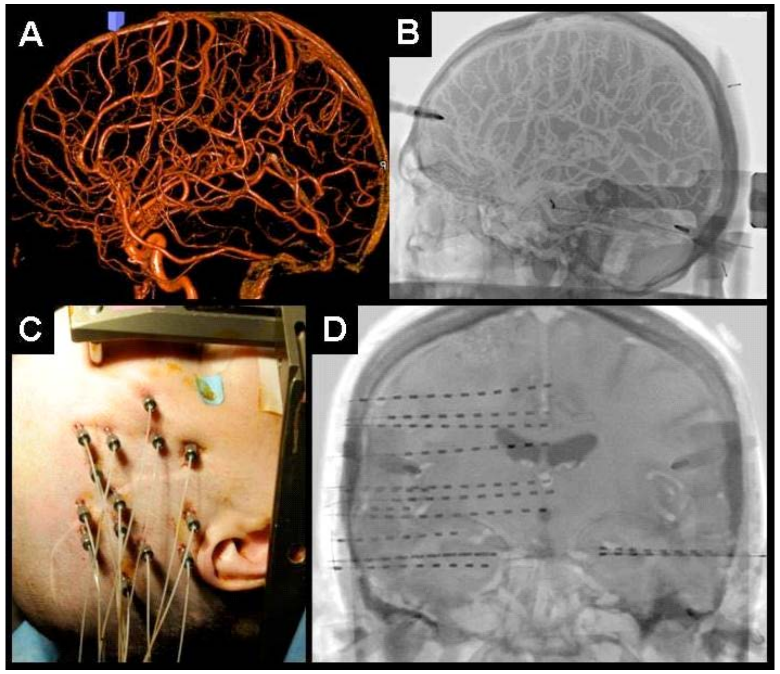
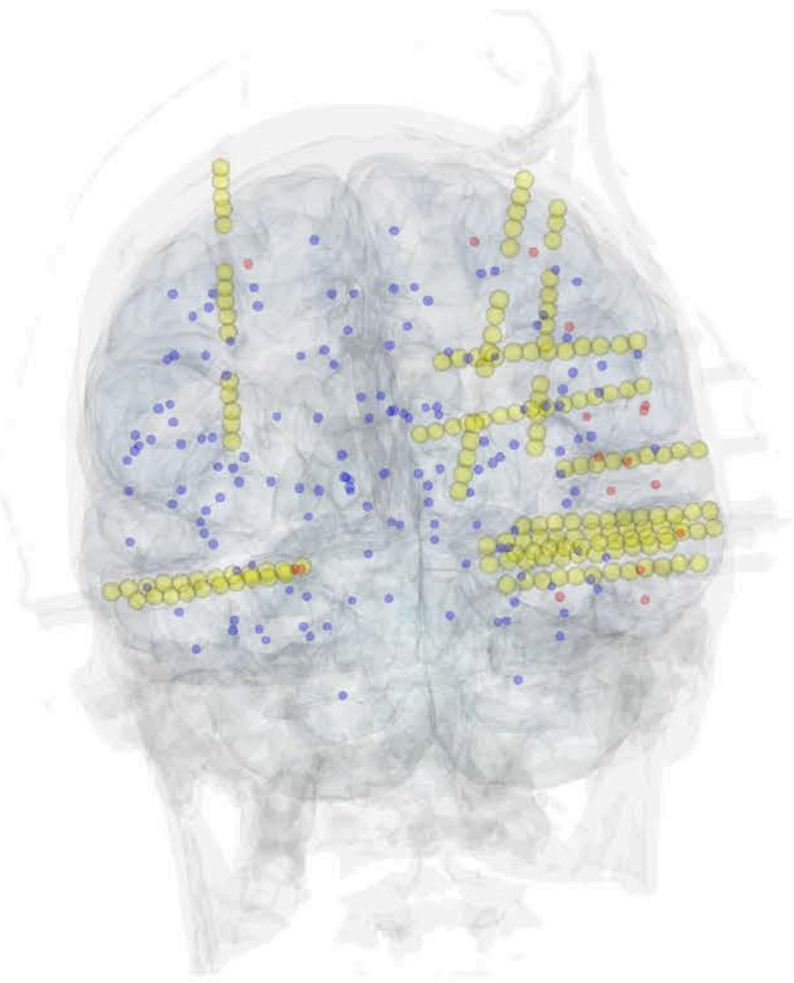
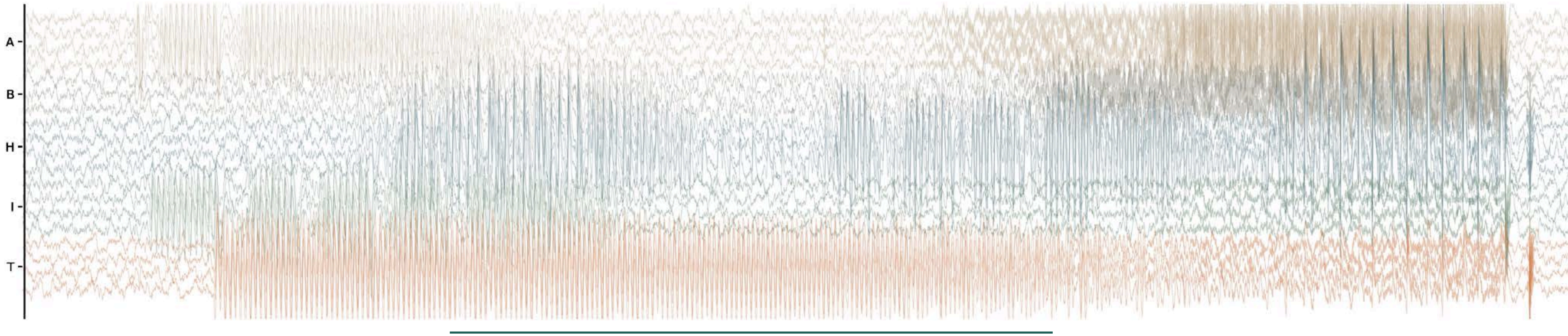
TRANSLATION

APPLICATIONS IN EPILEPSY

Simulation: Complex seizure







Simulating the Virtual Epileptic Patient (VEP)

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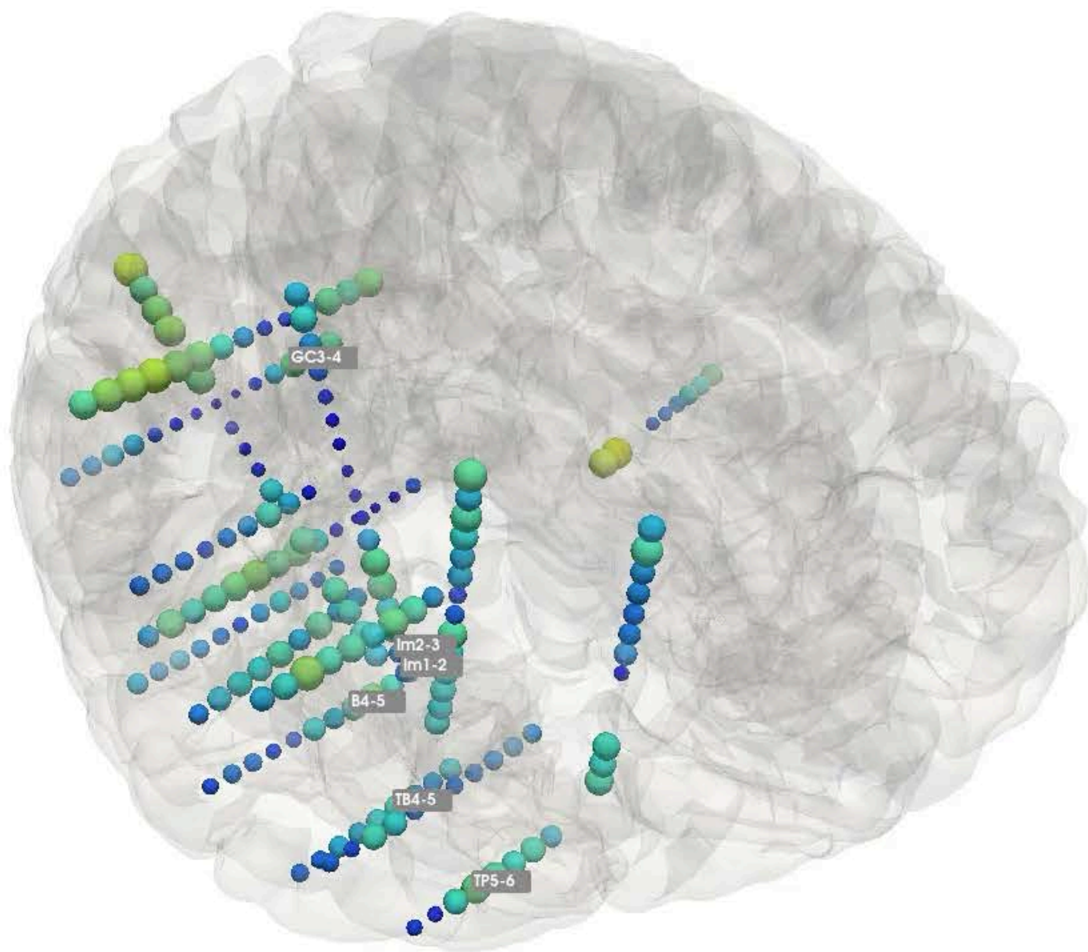
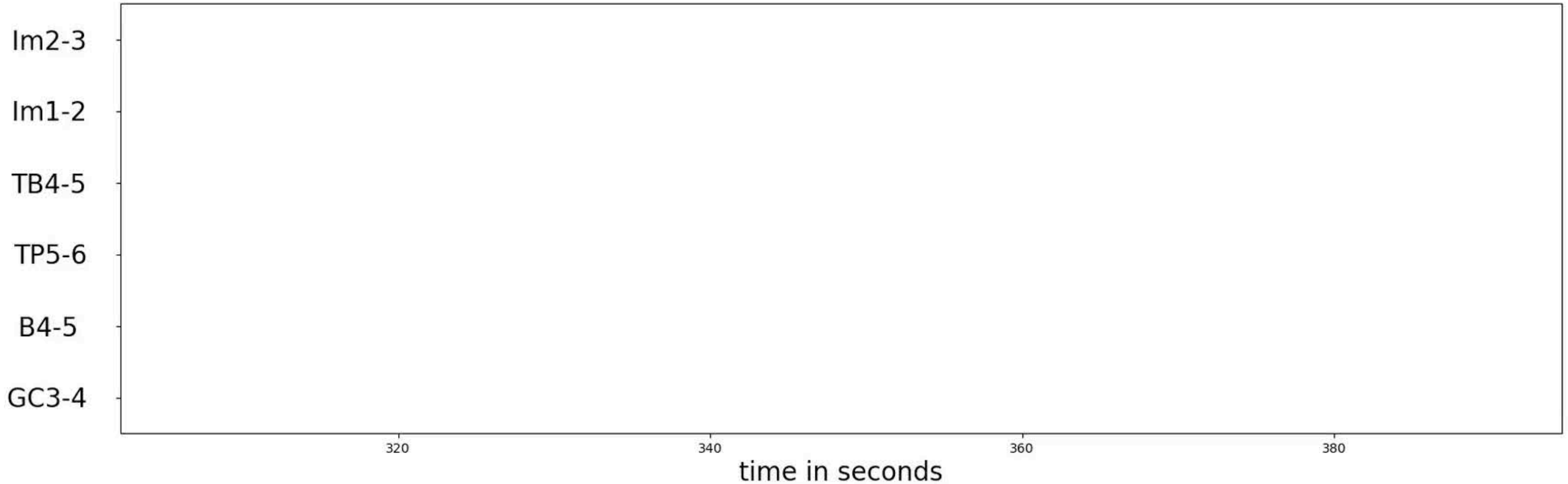
Sensor level





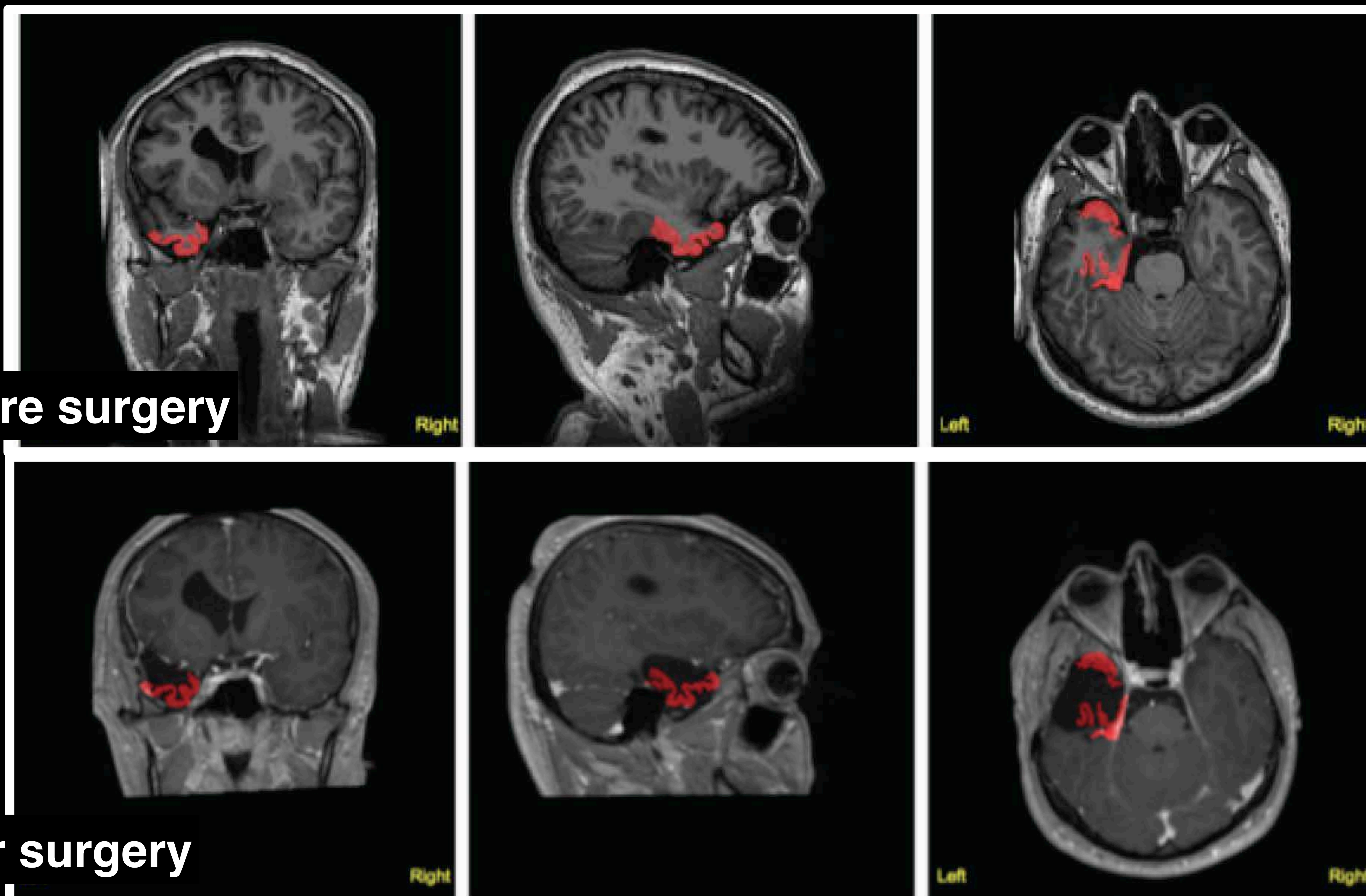
Epilepsy surgery guided by VEP

epinov

UN PROJET RHU

« Brain surgery is a very personal matter… »

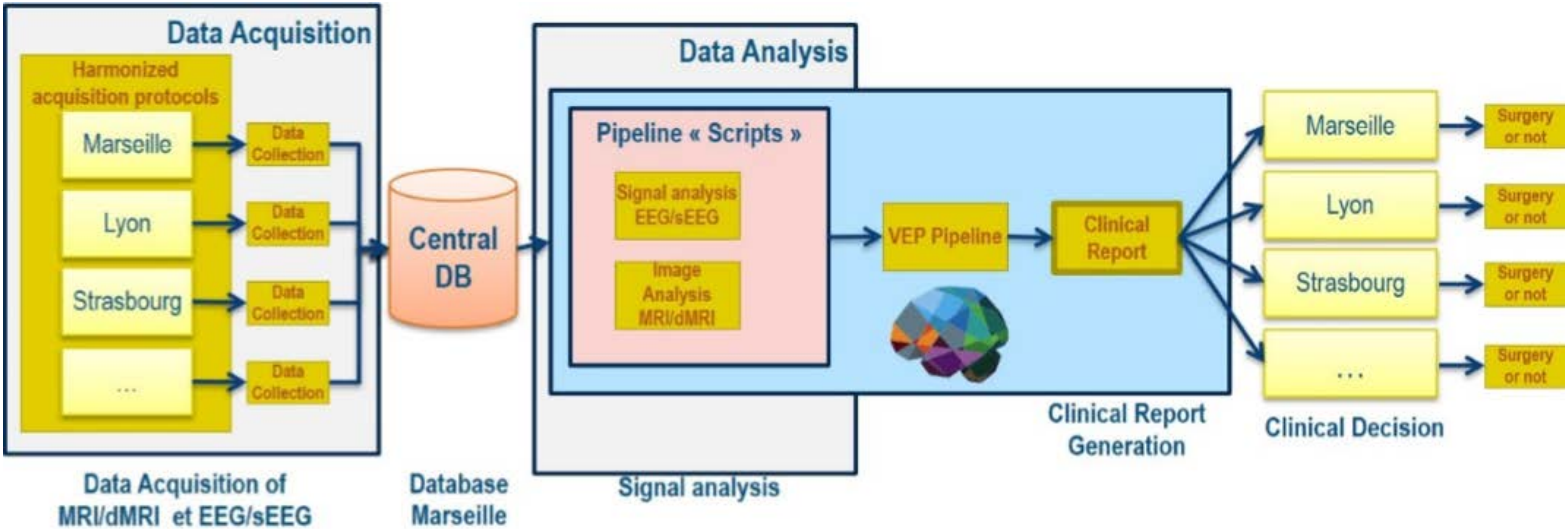
VEP Clinical trial 2019 - 2022: 400 prospective patients



Before surgery

After surgery

VEP: Prospective validation in clinical trial (400 patients, 2019-2022)



<u>Clinical trial:</u>
randomized parallel-group study trial
(Coordinator F. Bartolomei; Scientific Director V. Jirsa)

<u>Objective:</u>
evaluate the role of personalized **Virtual Epileptic Patient brain models** for surgery planning and outcome

13 French clinical centers
400 prospective patients during 2019 – 2022

VEP: retrospective validation for retrospective cohort (> 50 patients)

State of the art

Clinical trial EPINOV ongoing in France

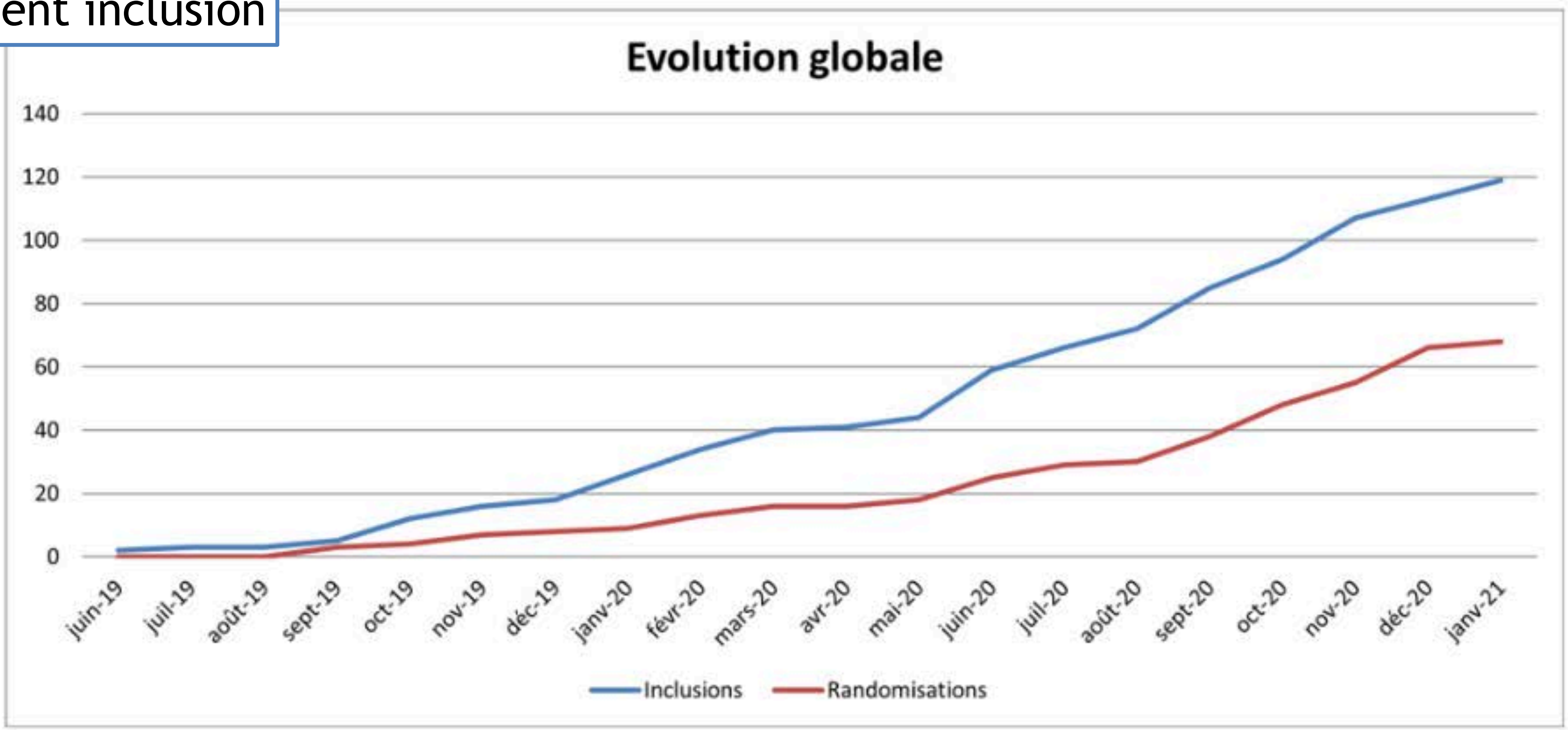
(13 epilepsy centers, 400 prospective patients in total)

epinov

UN PROJET RHU

02/2021: 128 patients included, data of 75 have been randomized

Patient inclusion



Proix et al. Brain 2017; Nature Comm 2018

VEP: retrospective validation for retrospective cohort (> 50 patients)

epinov
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VEP performance parameters

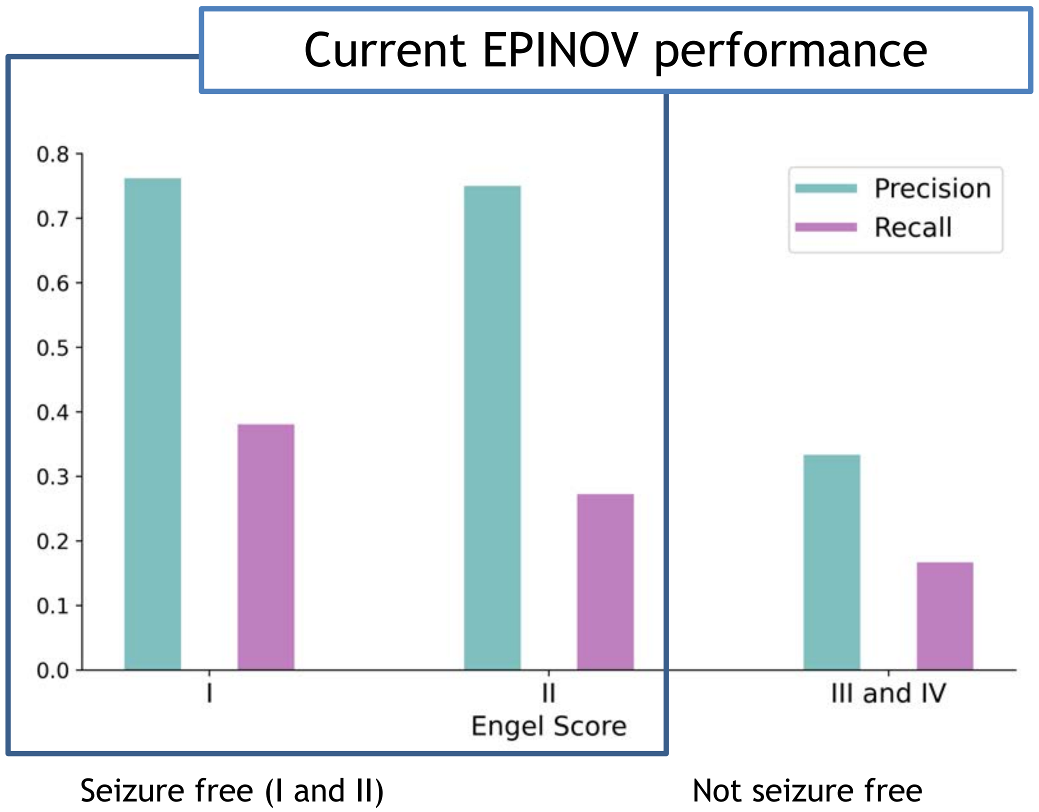
VEP was tested against clinical gold standard in cohort of 50 patients
Precision: 0.65
Recall: 0.75
AUC: 0.89

VEP was tested against surgery outcome in cohort of 50 retrospective patients **p<0.05
Mann-Whitney U-test

Nature of misclassifications

Physiological rhythms mimic seizures
Propagation network identified
Variability in seizure classes
Variability in clinical hypothesis

Engel score:
Convergence with VEP correlates with better postsurgical outcome



Proix et al. Brain 2017; Nature Comm 2018

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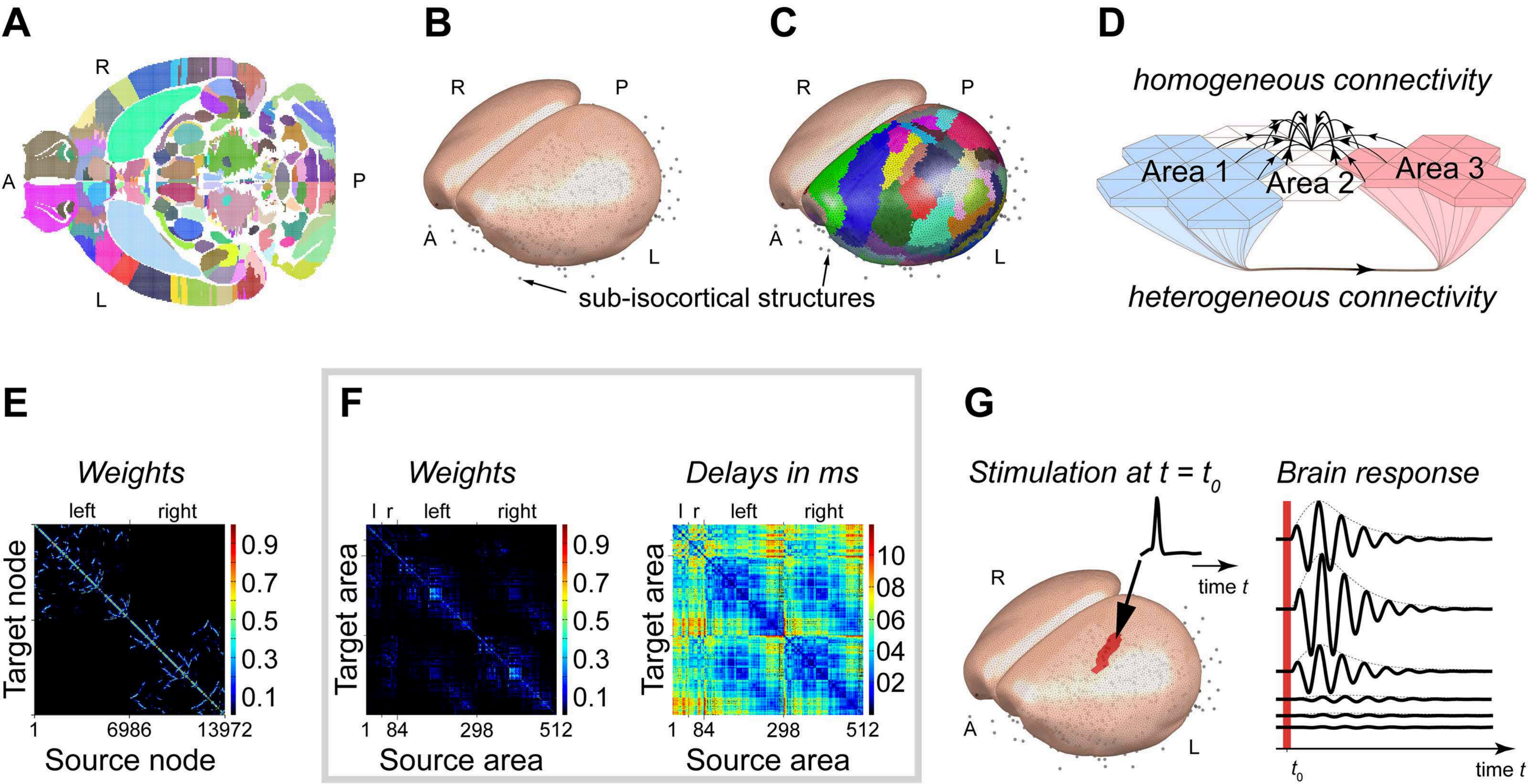
STIMULATION

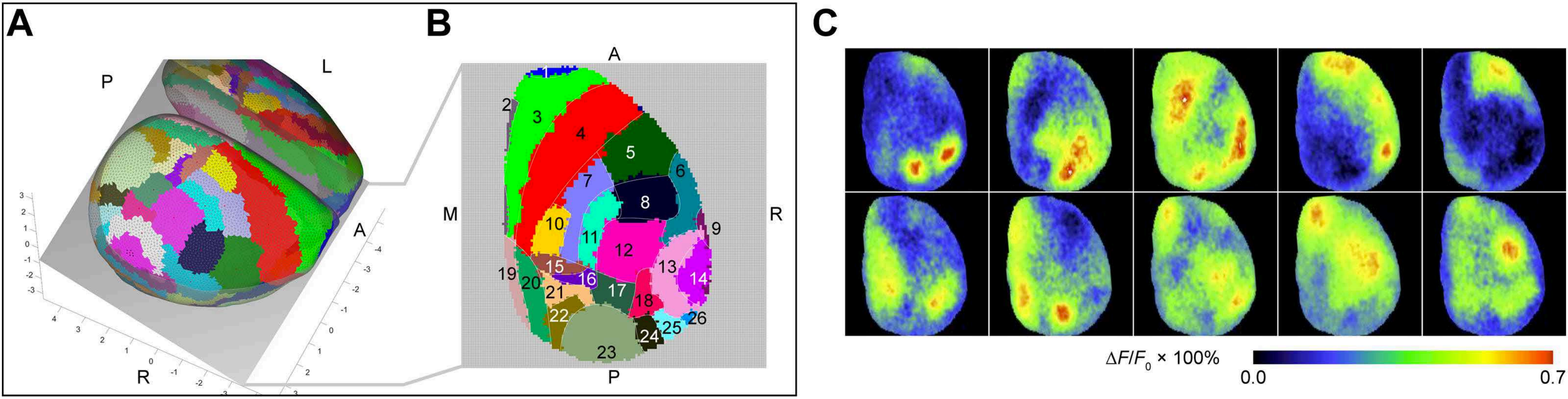
MANIPULATION TVB NON-INVASIVELY

Stimulation in the Mouse



Spiegler, A., Abadchi, J. K., Mohajerani, M., & Jirsa, V. K. (2020).
In silico exploration of mouse brain dynamics by focal stimulation reflects the organization of functional networks and sensory processing.
Network Neuroscience, 4(3), 807–851. https://doi.org/10.1162/netn_a_00152

Stimulation in the Mouse



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In silico exploration of mouse brain dynamics by focal stimulation reflects the organization of functional networks and sensory processing.
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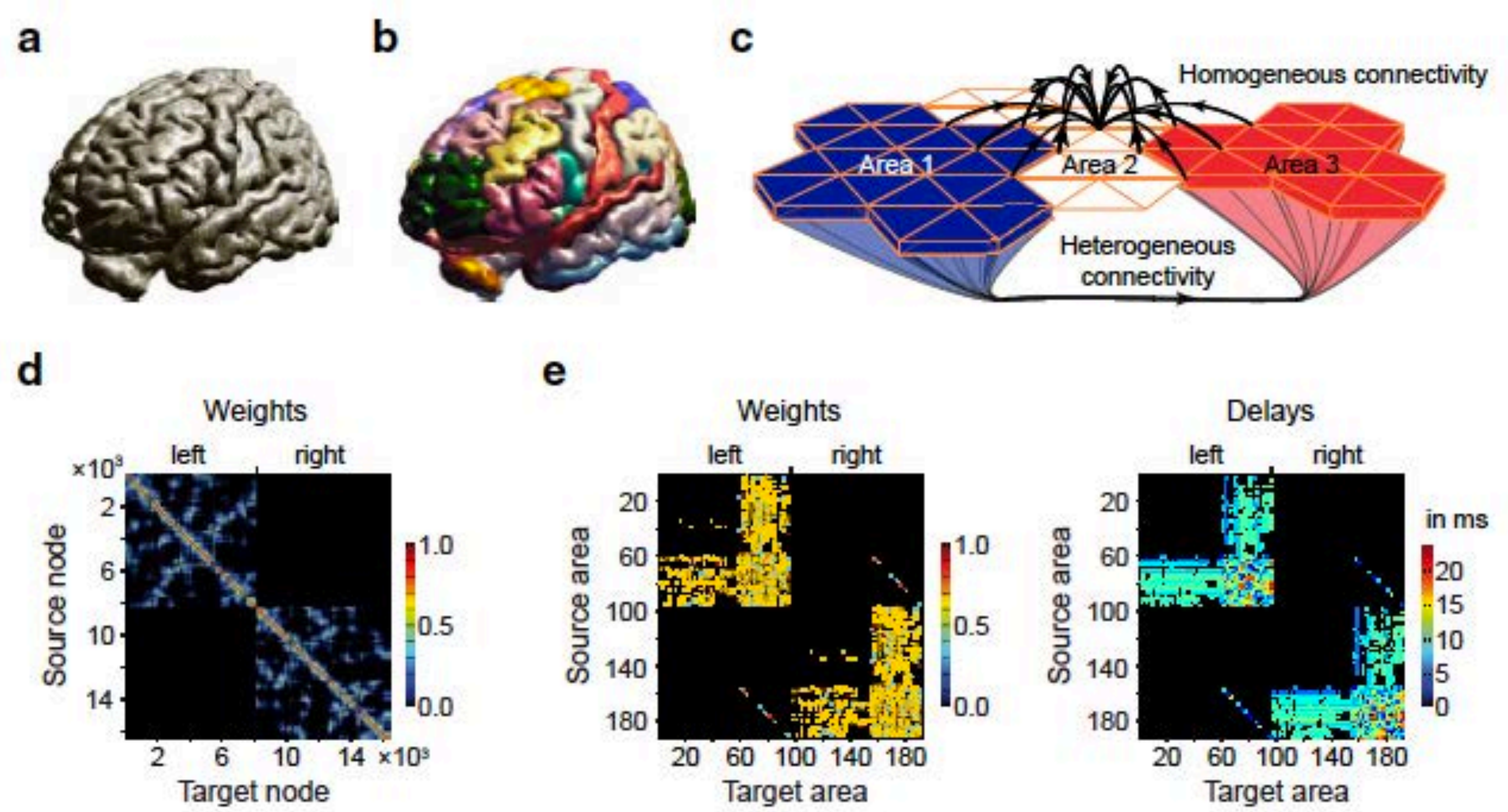
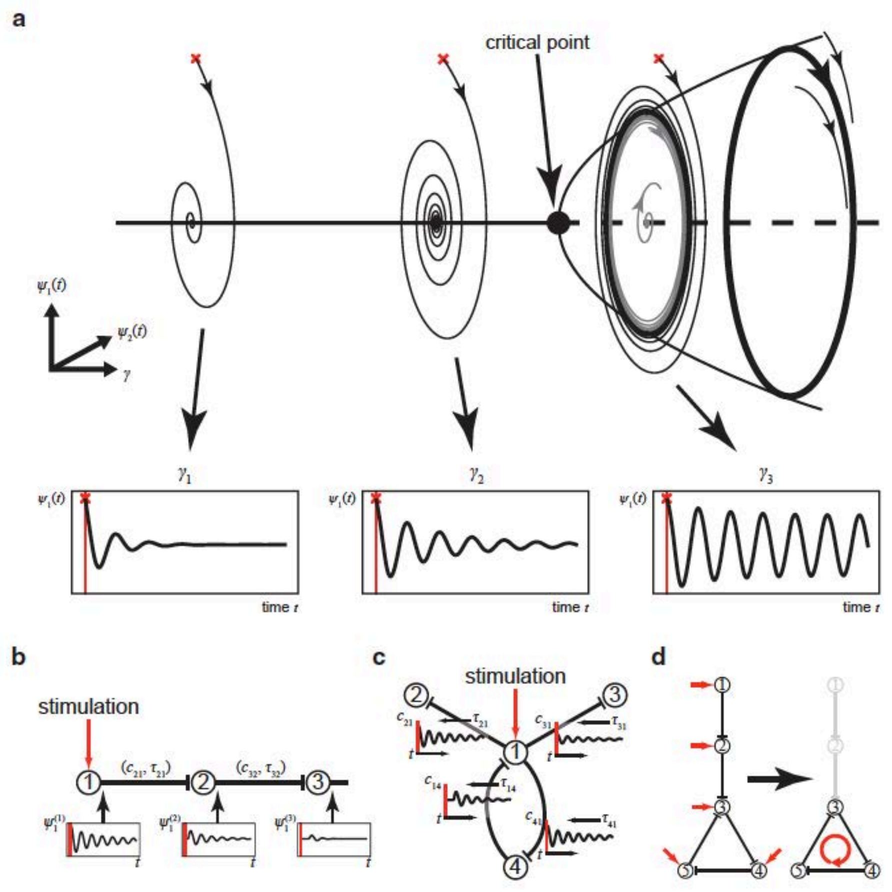
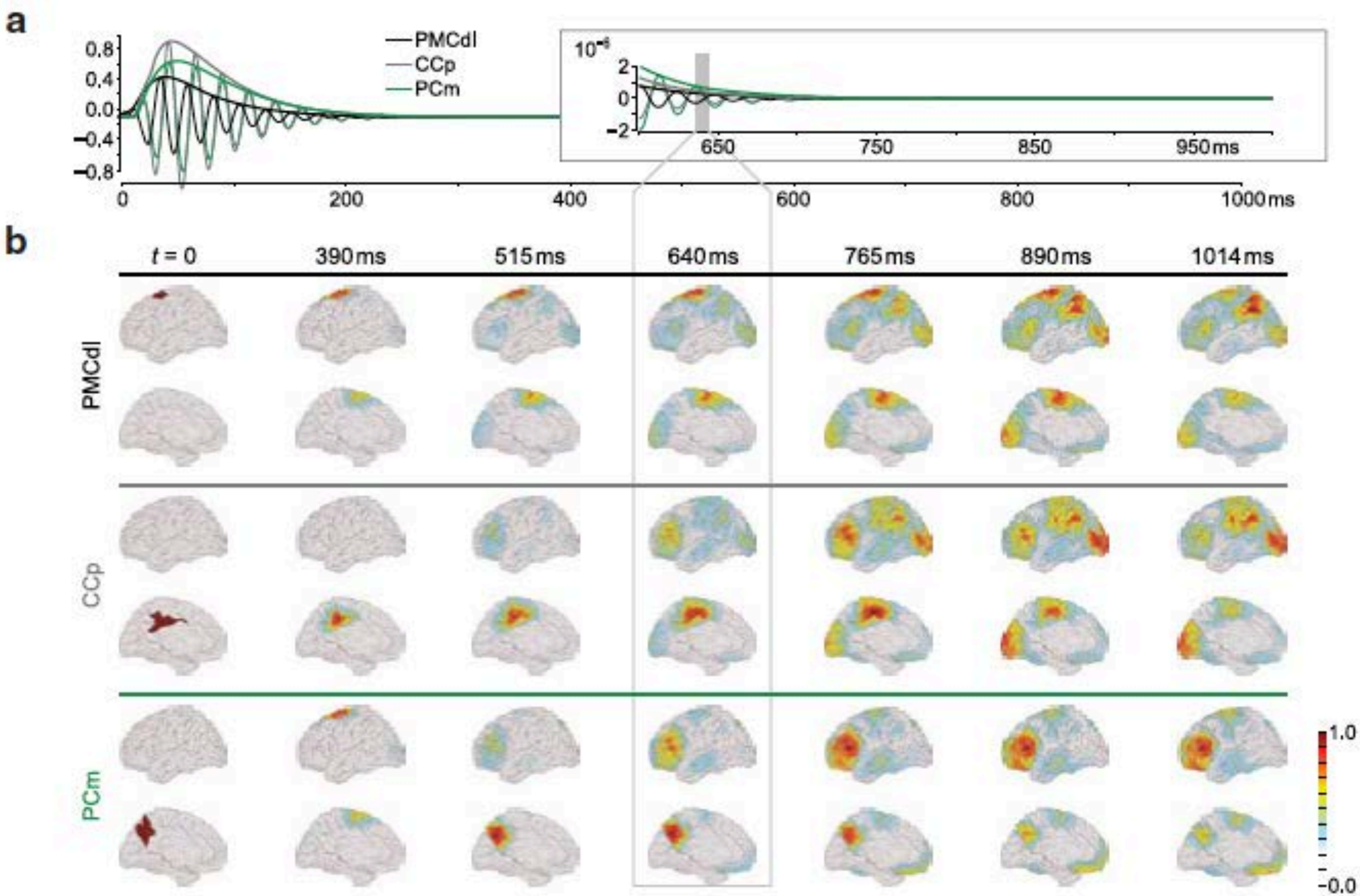
Stimulation in the Human: brain region





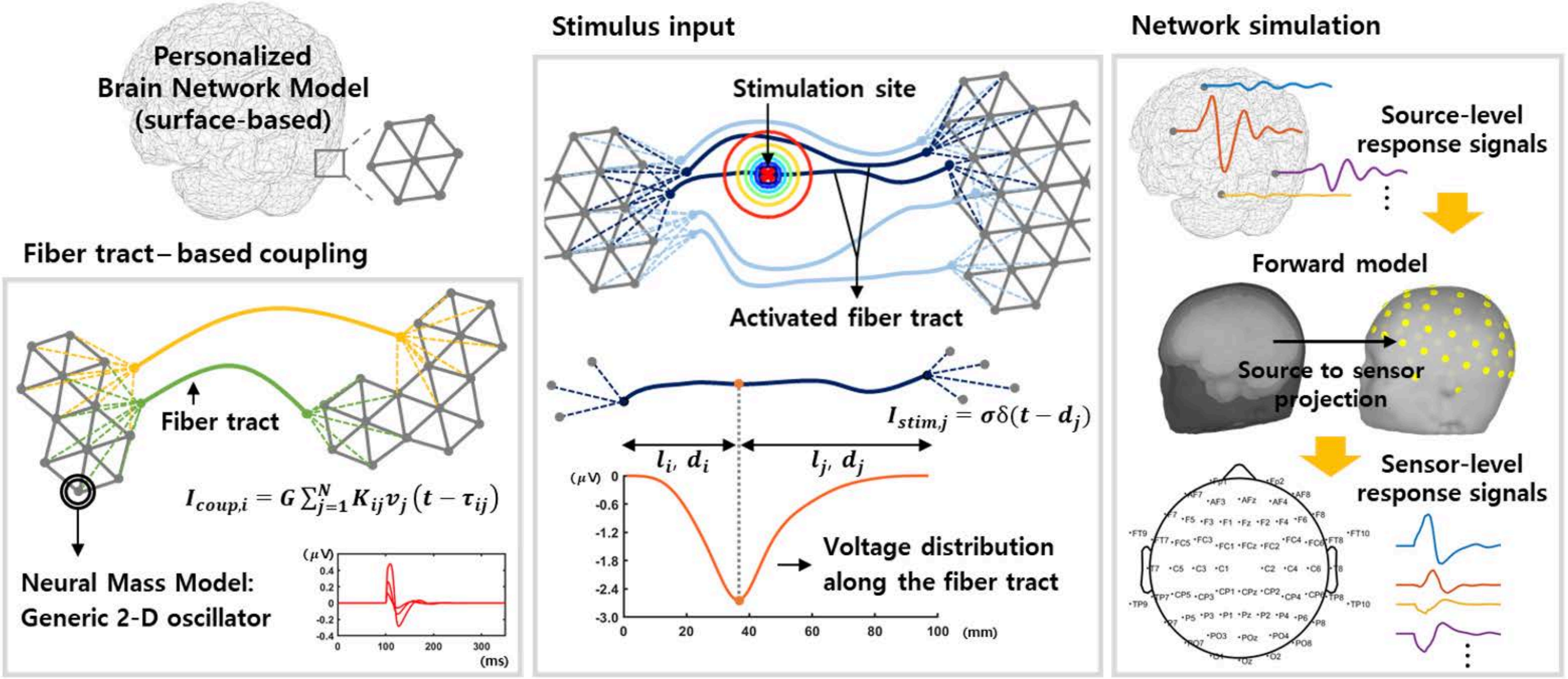
Spiegler et al., Selective Activation of Resting-State Networks following Focal Stimulation in a Connectome-Based Network Model of the Human Brain. eNeuro 2016

Stimulation in the Human: brain region



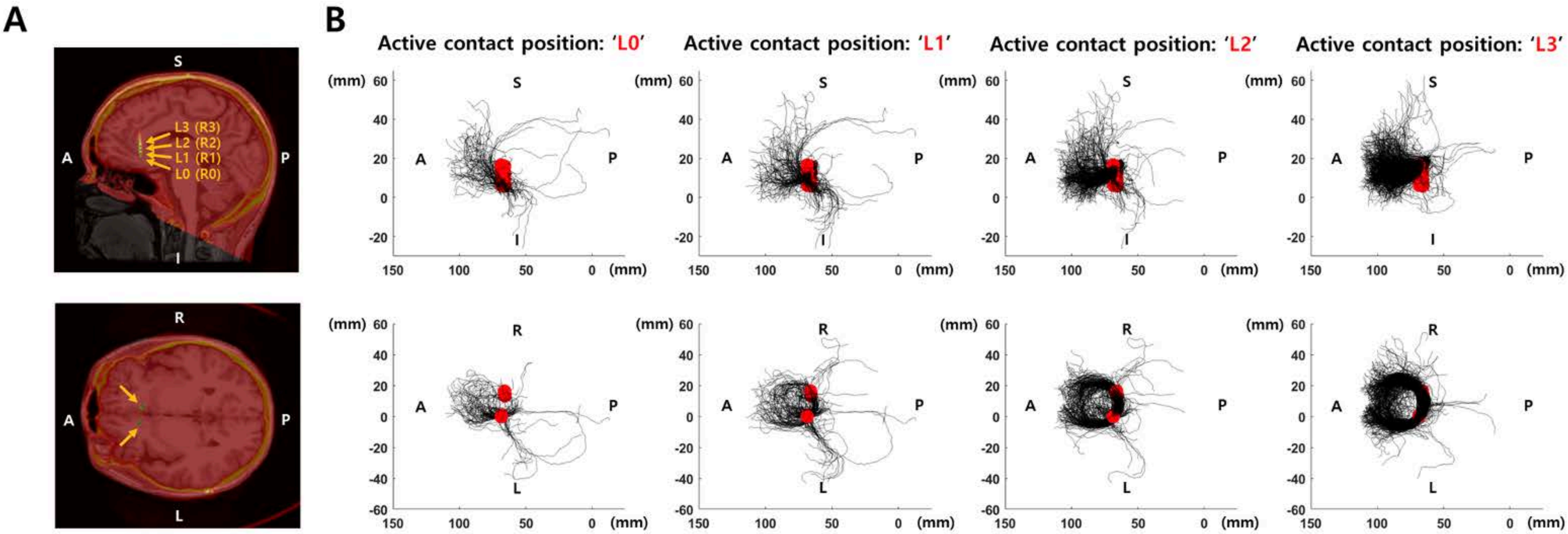
Spiegler et al., Selective Activation of Resting-State Networks following Focal Stimulation in a Connectome-Based Network Model of the Human Brain. eNeuro 2016

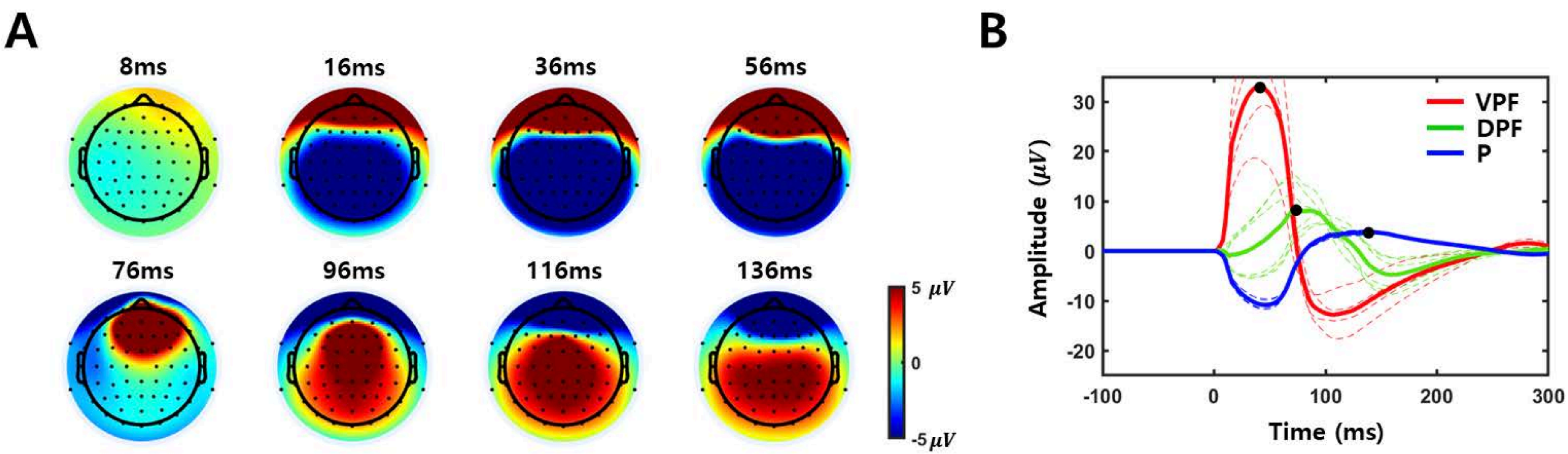
Stimulation in the Human: fibre tracts



An et al (in preparation)

Stimulation in the Human: fibre tracts





An et al (in preparation)

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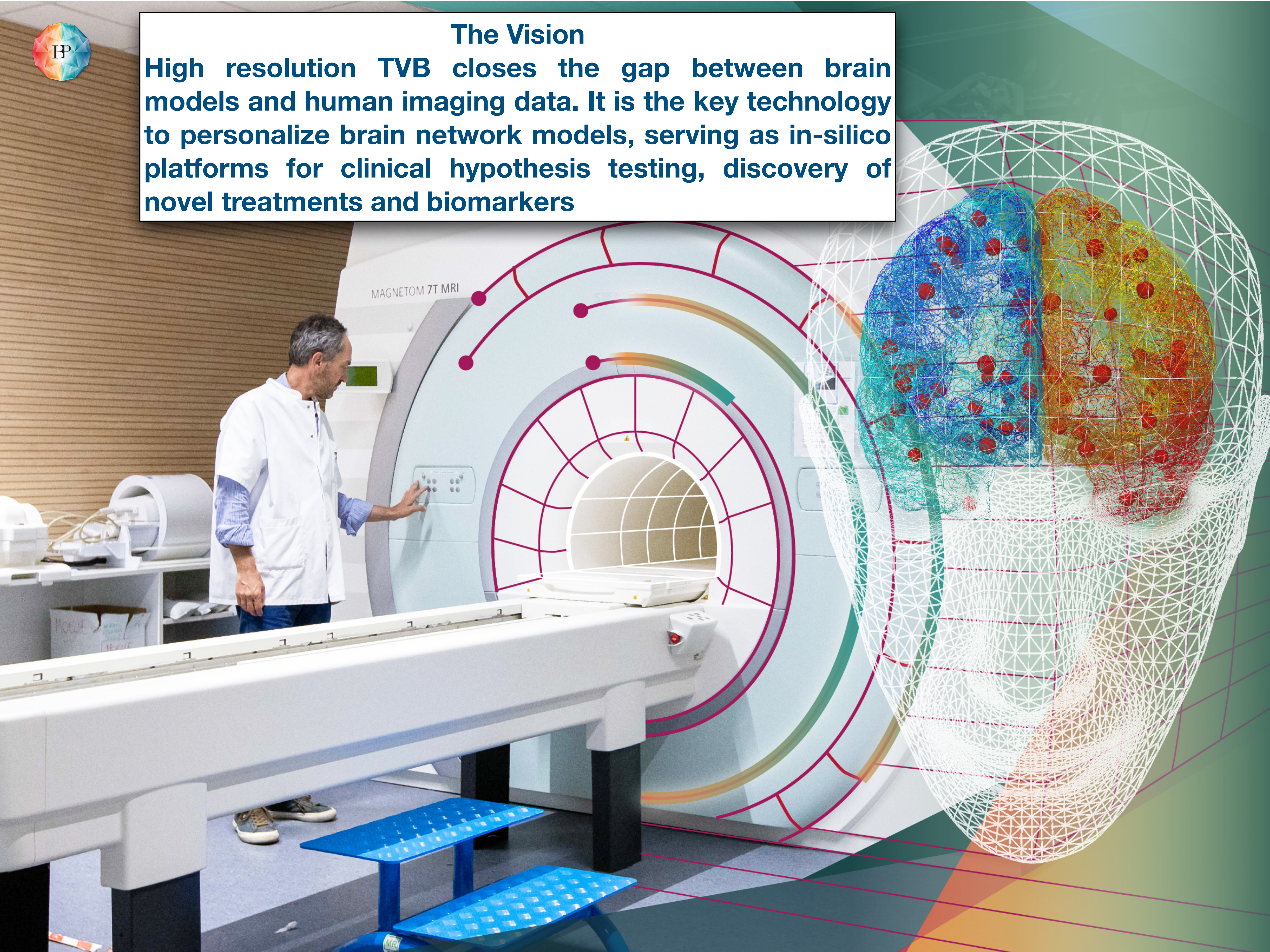
OUTLOOK

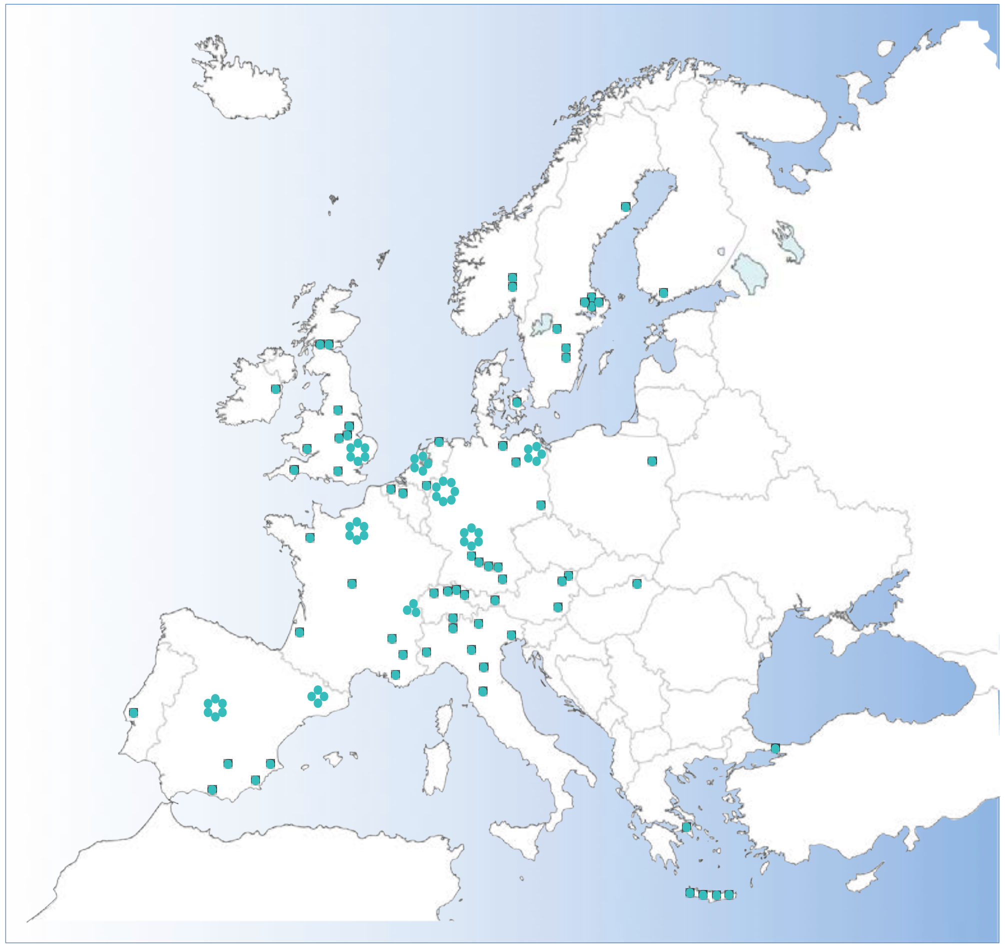
HIGH-RESOLUTION TVB AND BRAIN DISEASE

The Vision

High resolution TVB closes the gap between brain models and human imaging data. It is the key technology to personalize brain network models, serving as in-silico platforms for clinical hypothesis testing, discovery of novel treatments and biomarkers



Human Brain Project



« Understanding the brain »

« Healing the brain »

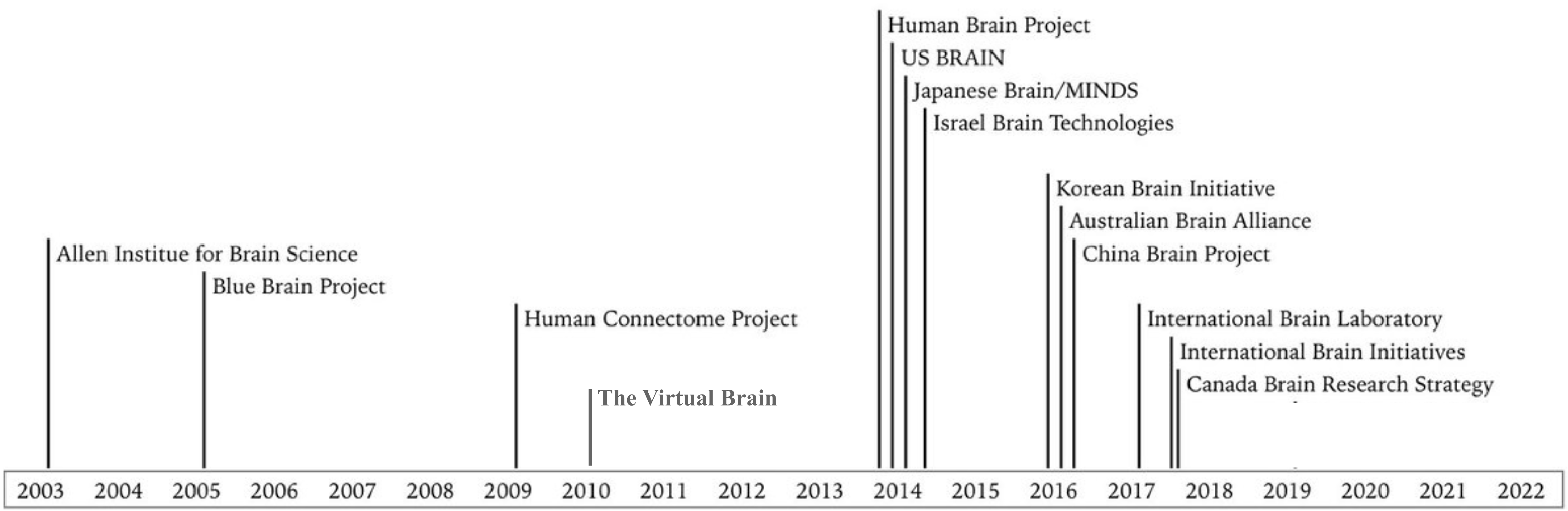
« Modeling the brain »

Basic science, health & technology

The strongest driving force for neuroscience today is the societal demands for treatment of brain disease

Cost of dementia alone will surpass all of cancer

2015: number of people in age group 60-64 surpassed number in age group 20-24



Service Categories All Services

SERVICE CATEGORY
Data and Knowledge

SERVICE CATEGORY
Atlases

SERVICE CATEGORY
Simulation

SERVICE CATEGORY
Brain-Inspired Technologies

SERVICE CATEGORY
Medical Data Analytics

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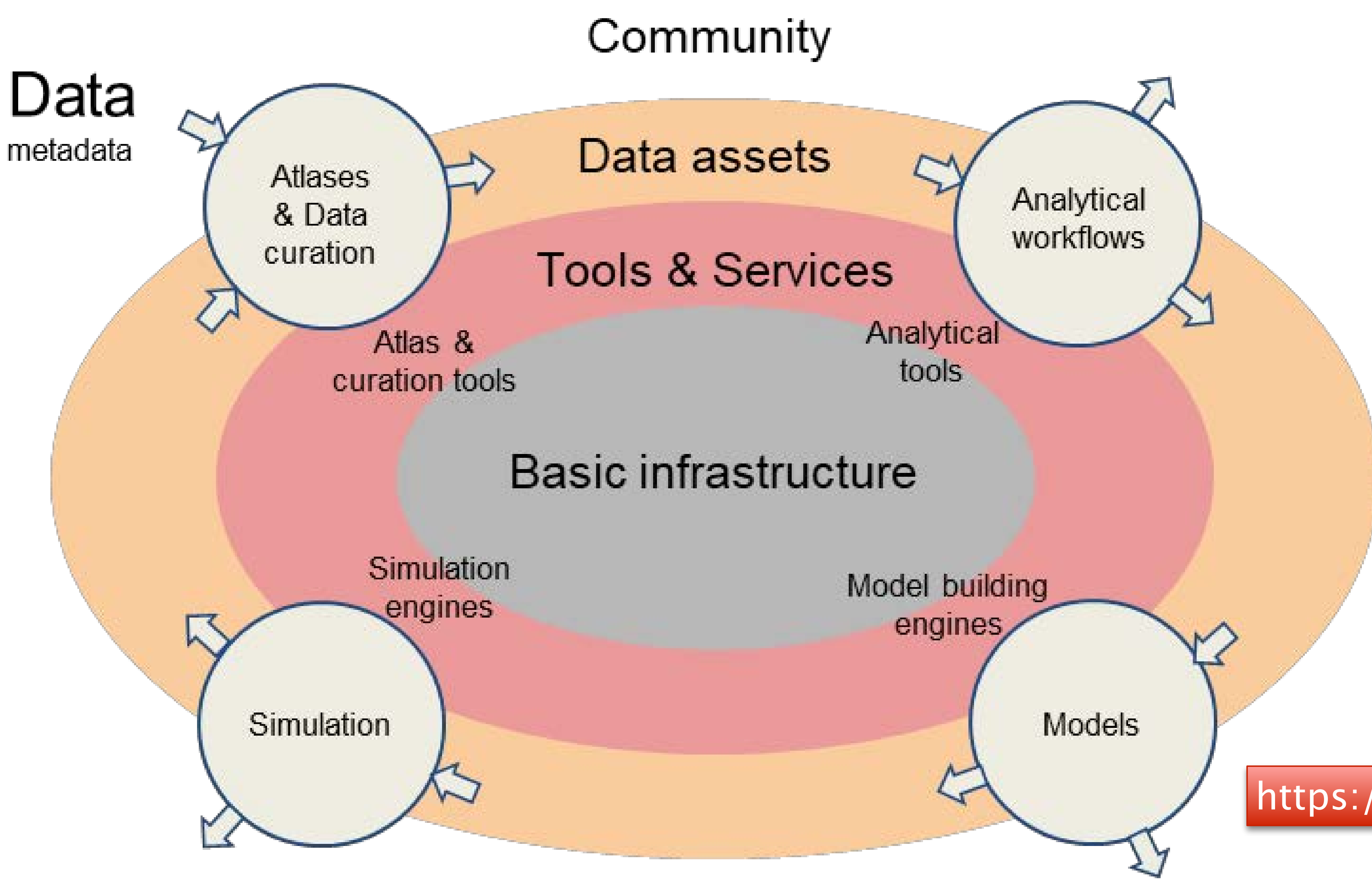
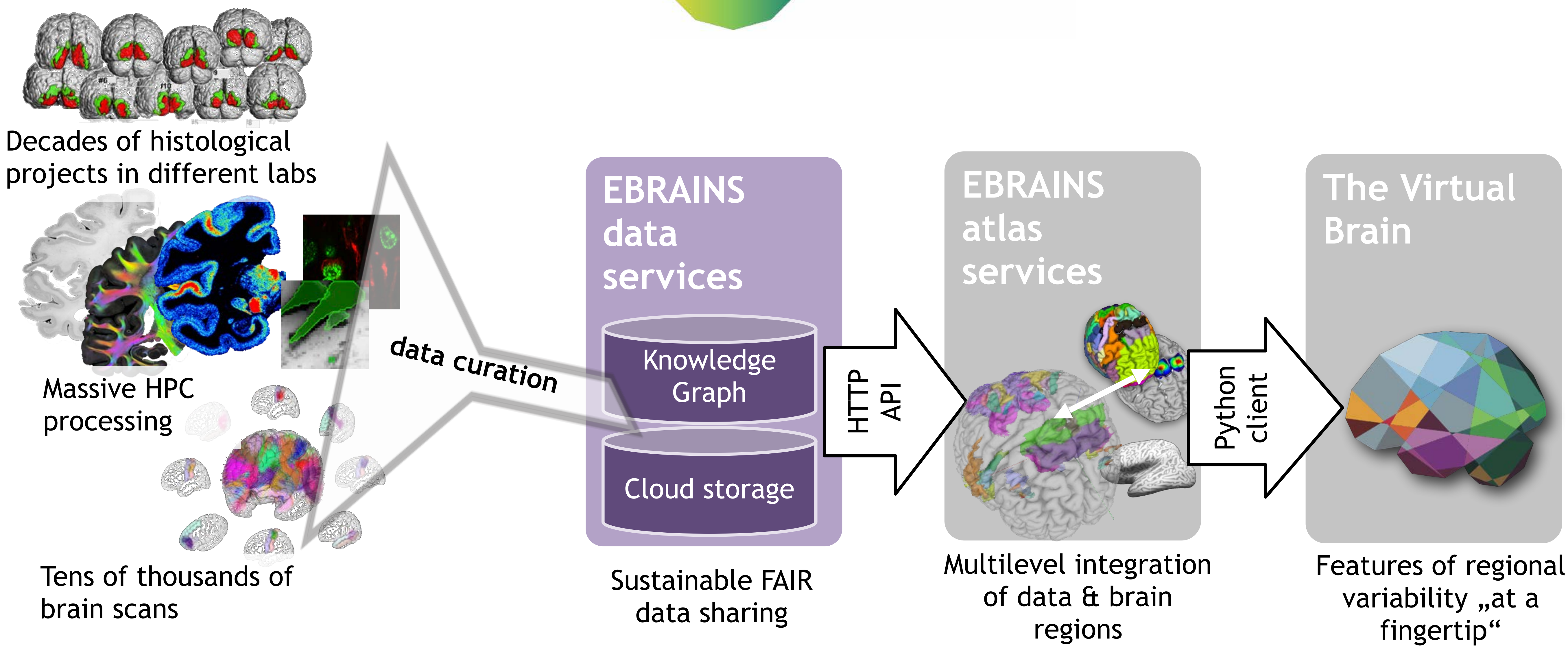
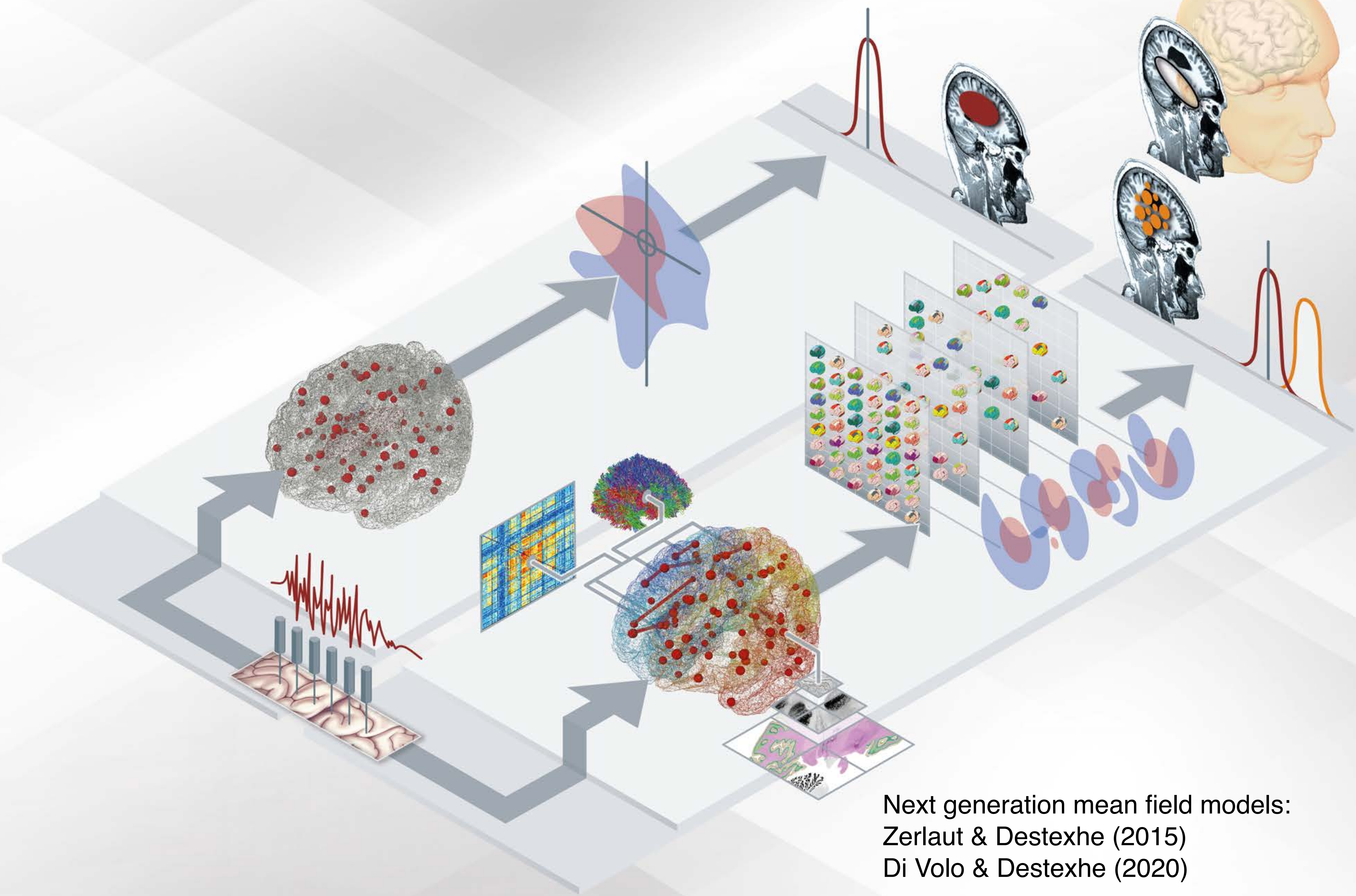


https://ebrains.eu

Human Brain Project

EBRAINS





Next generation mean field models:
Zerlaut & Destexhe (2015)
Di Volo & Destexhe (2020)

Current Generation - Virtual Epileptic Patient (VEP)

State of the art

Network size: 100-200 network nodes

Connectivity: personalized white matter connectome

Average region size: 20cm2

Minimal fiber lengths: 3-5cm

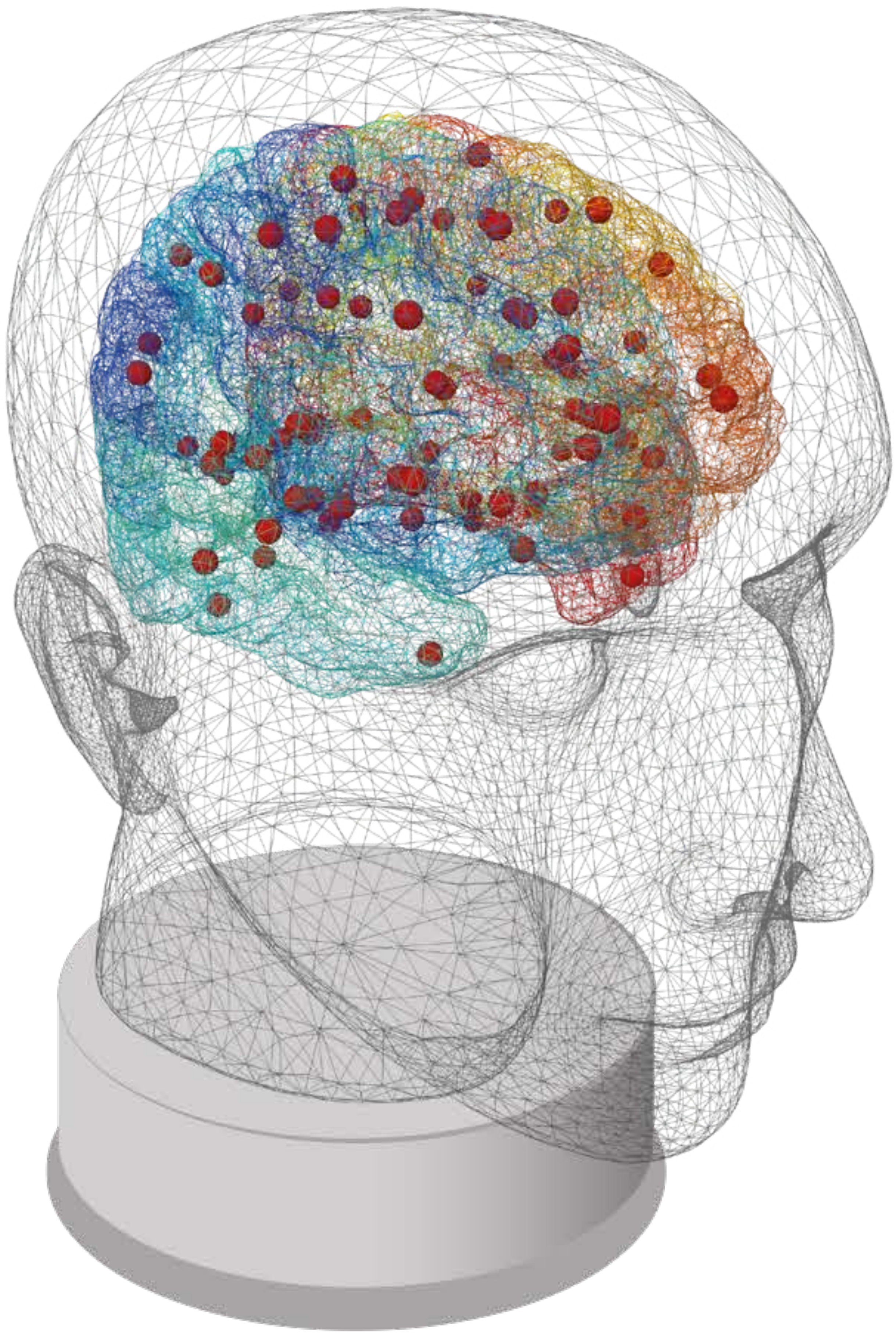
Challenges

Impossibility to integrate high-resolution data

Source-to-sensor mapping is sub-optimal

Dynamic range of seizure variability is limited

Saggio et al eLife (2020); Sip et al PLoS CB (2021)



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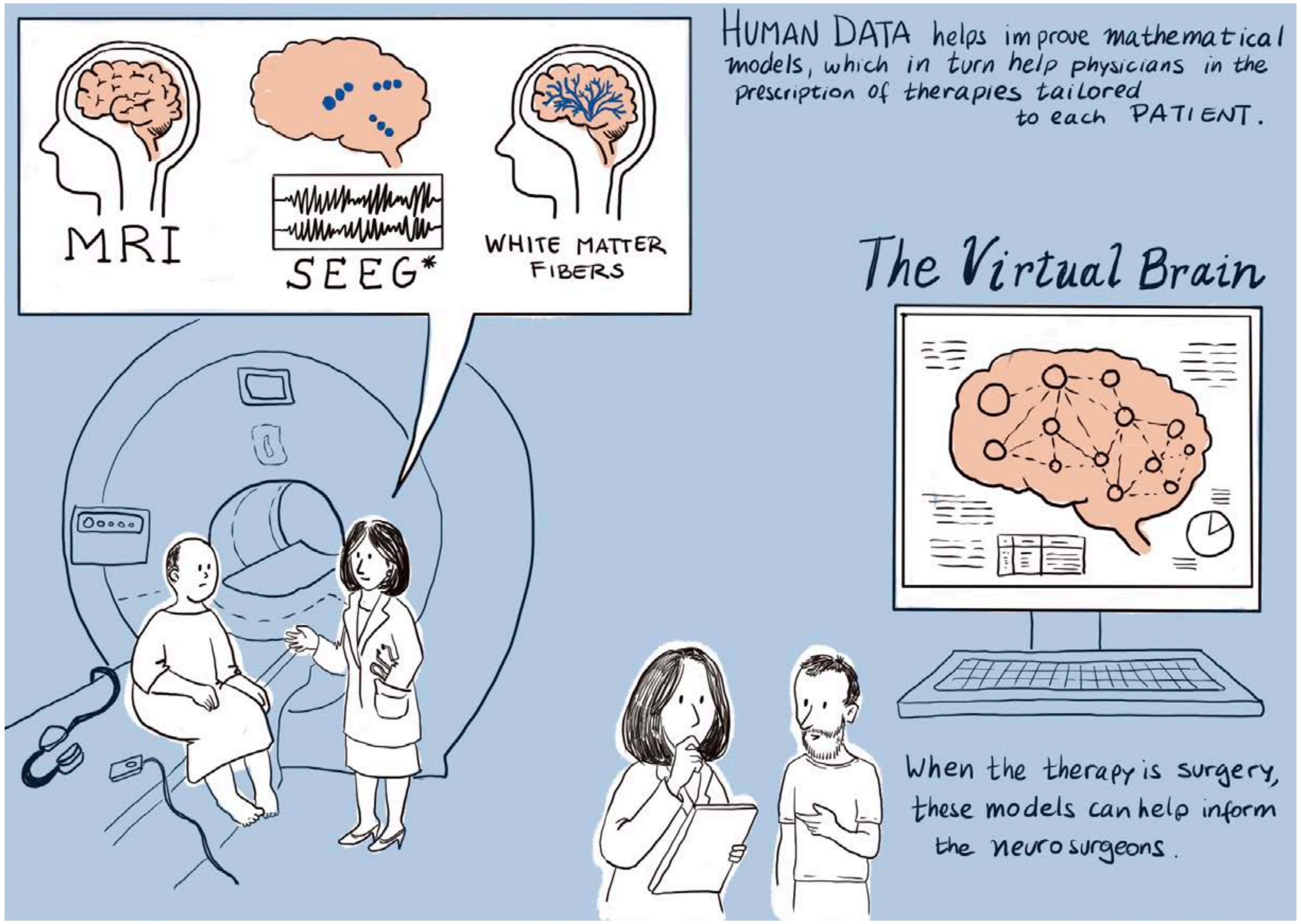
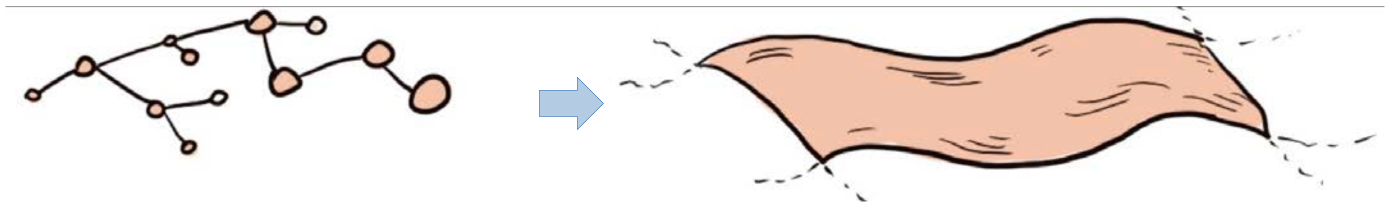


Transition from discrete to continuous models



Next Generation - Virtual Epileptic Patient (VEP) coming now

Low and high-resolution meshes span cortical surface

Network size:

Low-resolution mesh: 20,000 nodes

High-resolution mesh: 260,000 nodes

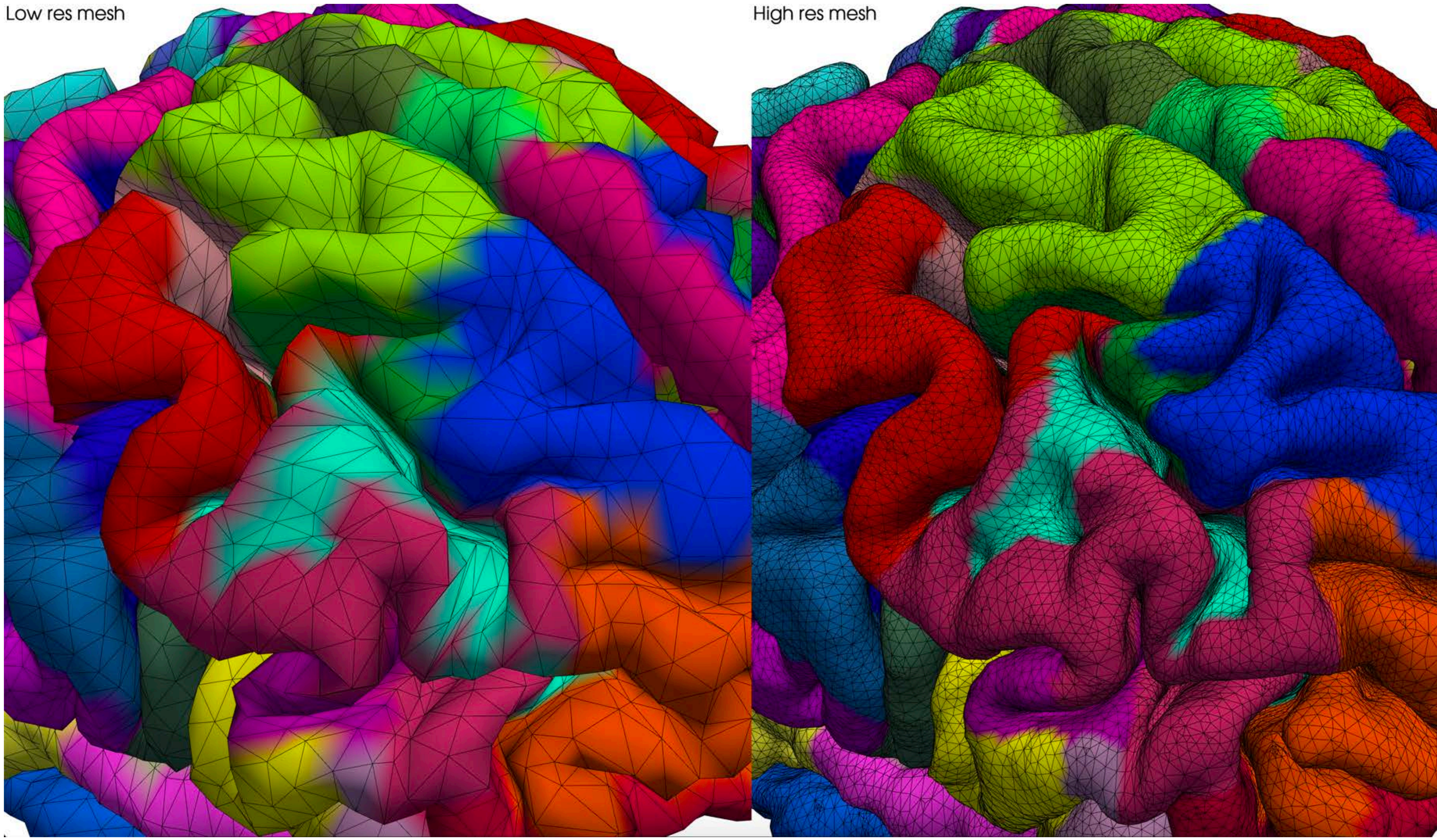
Connectivity:

- High-resolution intracortical
- High-resolution corticocortical
- personalized connectome from DTI

Average region size:

2-3mm2 (high resolution)

Minimal fiber lengths:
1mm



Informative prior of individual brain data is most predictive (Hashemi et al (under review))

Next Generation - Virtual Epileptic Patient (VEP) coming now

Network size:

Low-resolution mesh:
20,000 nodes

High-resolution mesh:
260,000 nodes

Connectivity:

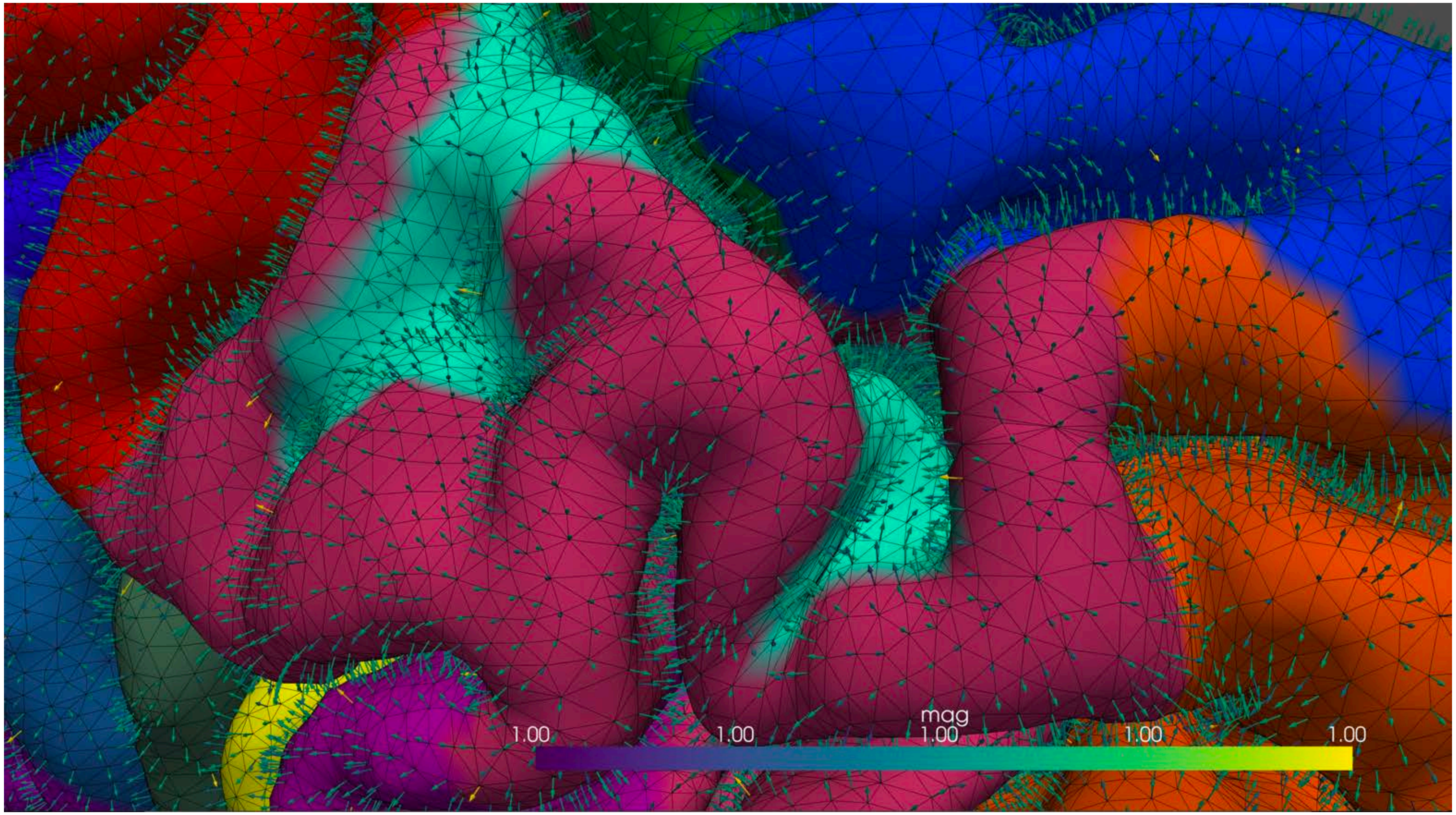
- High-resolution intracortical
- High-resolution corticocortical
- personalized connectome from DTI

Average region size:

2-3mm2 (high resolution)

Minimal fiber lengths:
1mm

Dipolar momenta are oriented perpendicular to cortical surface



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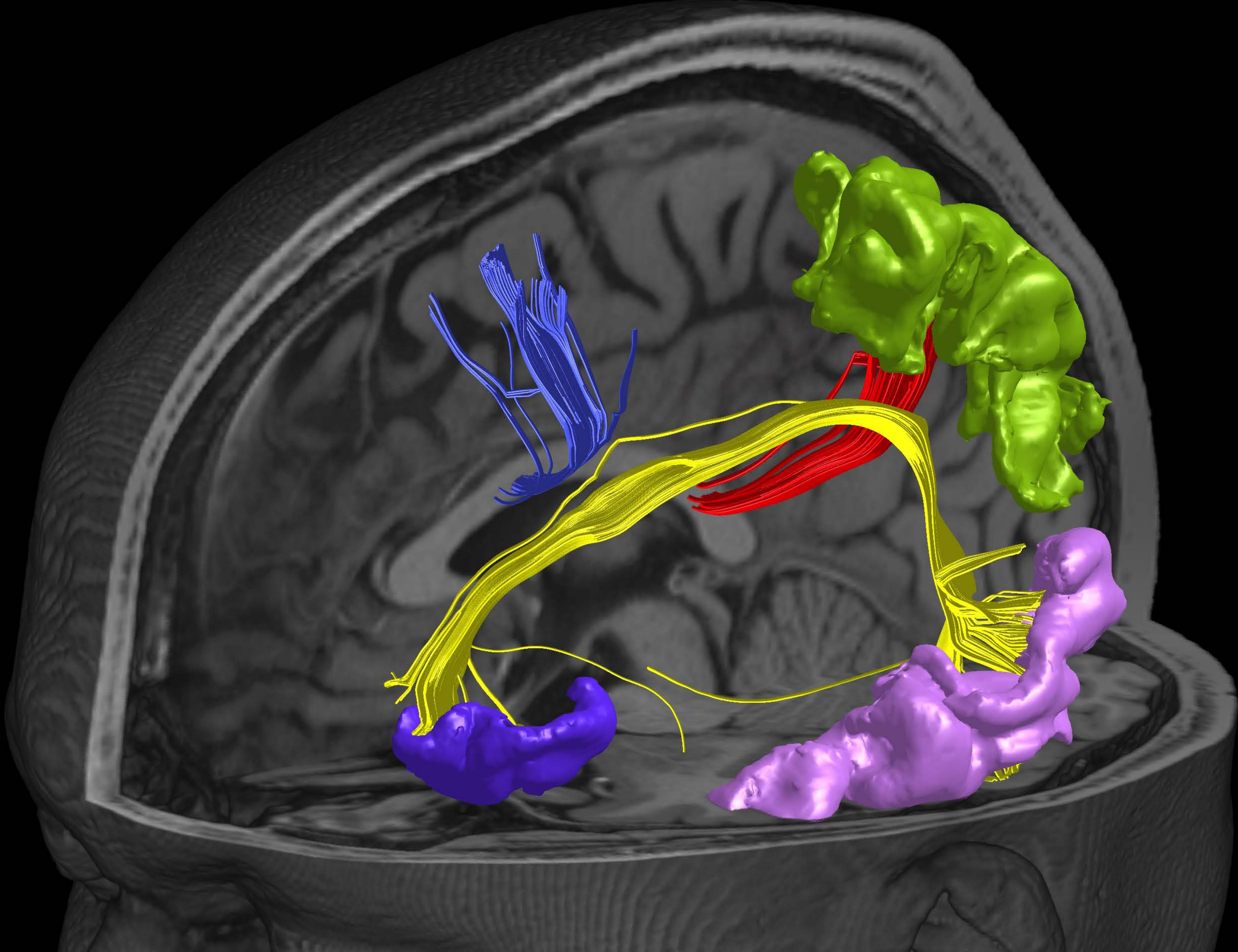

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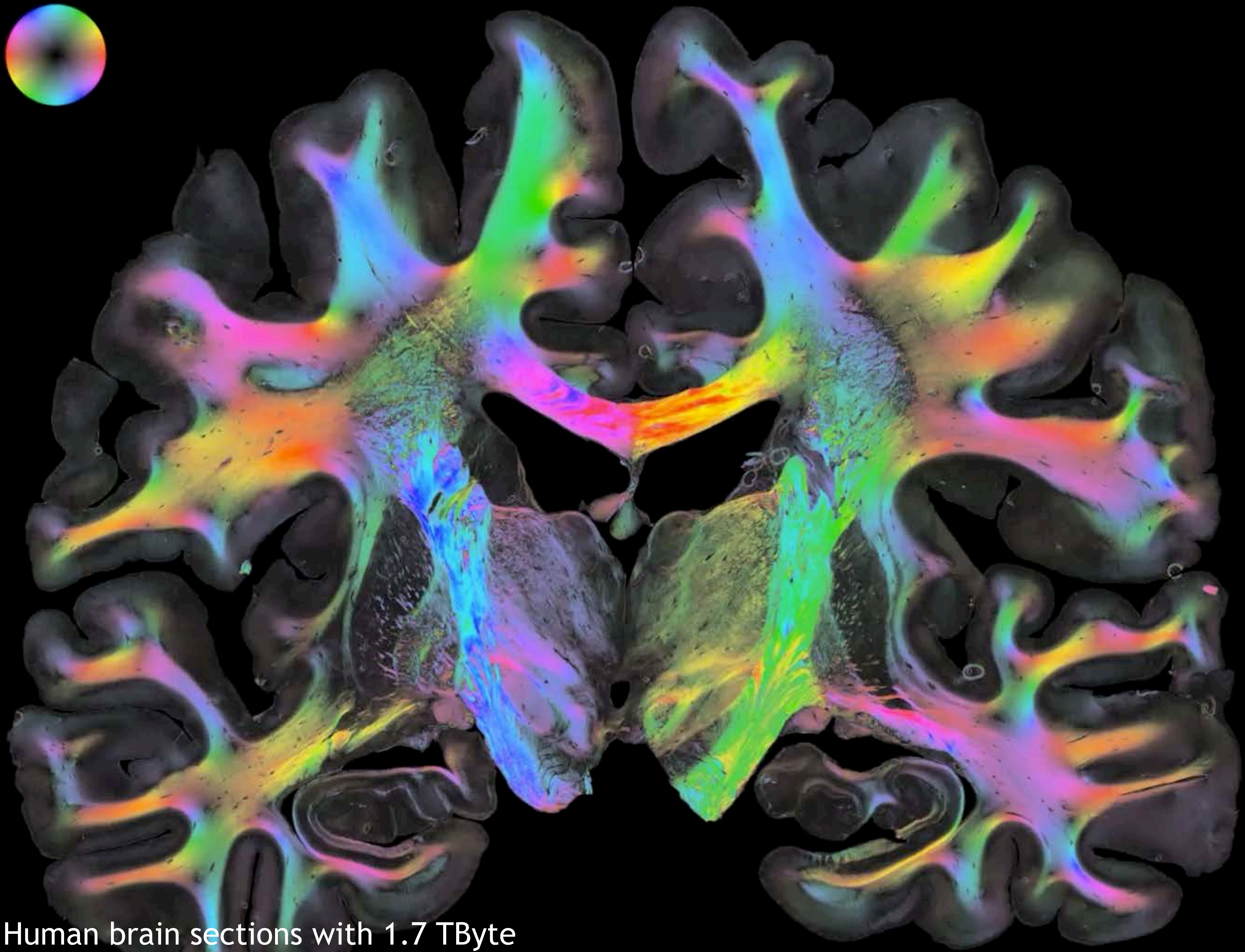
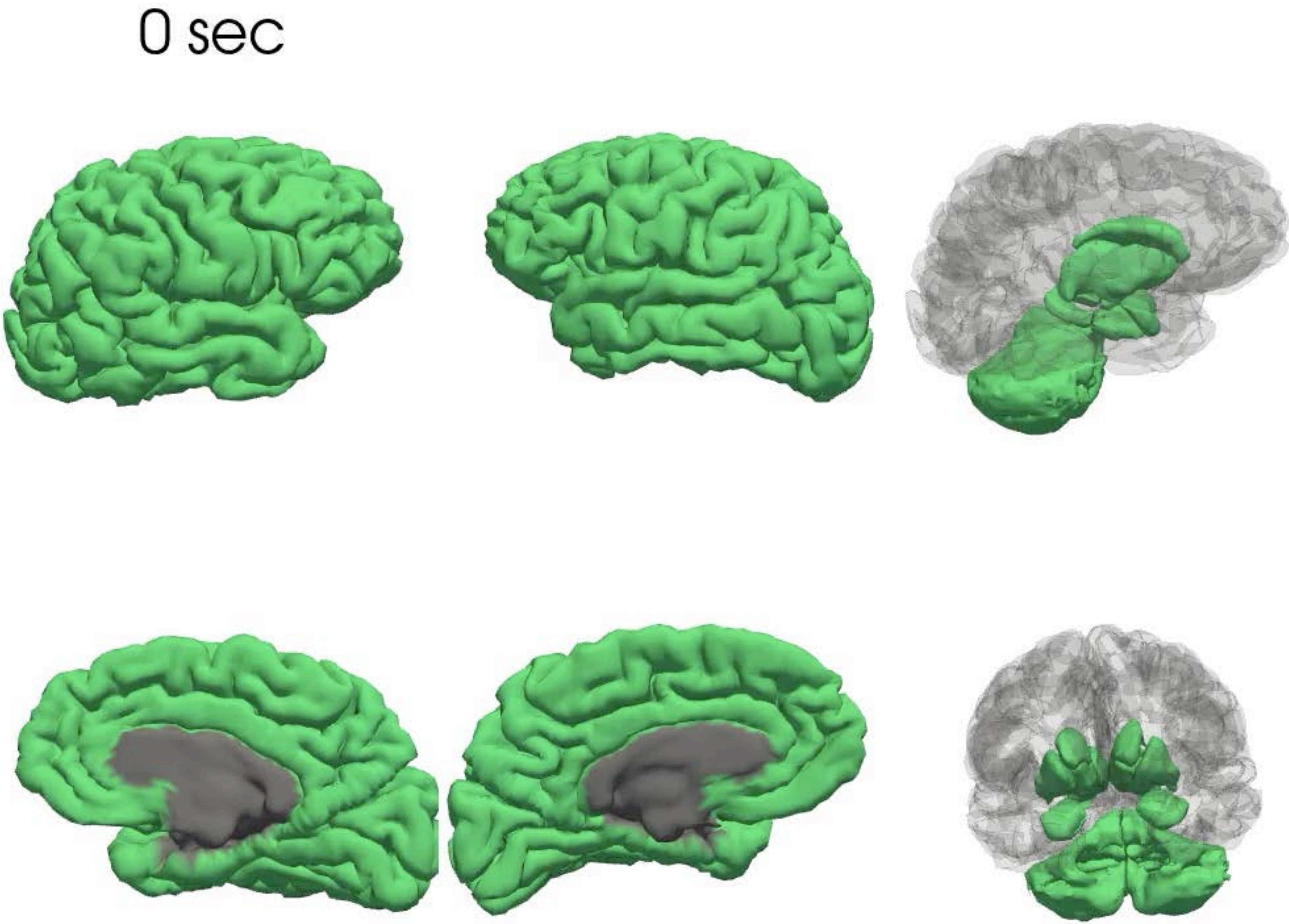
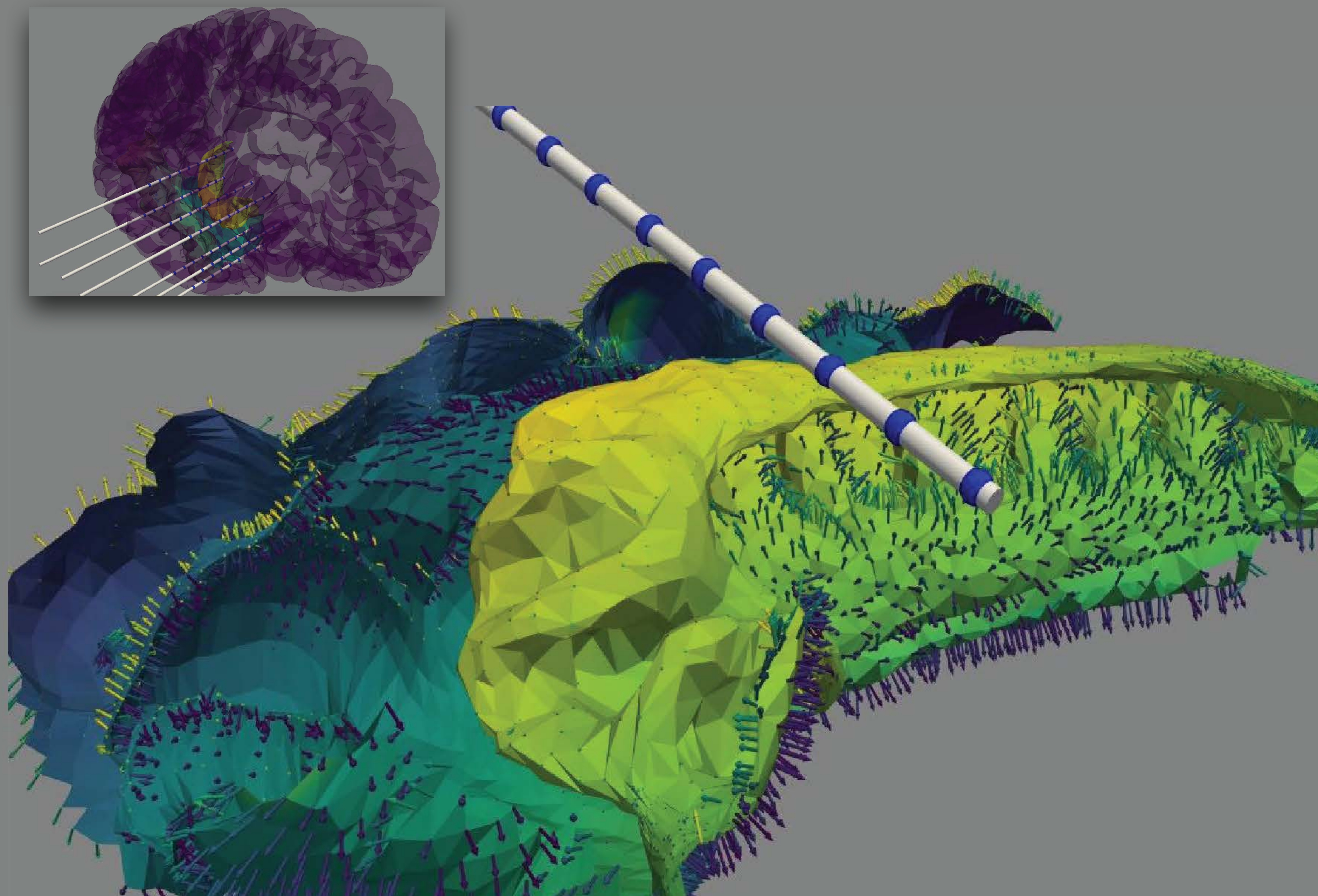


Human brain sections with 1.7 TByte
Runs on JURECA @ JSC, Axer et al., Juelich

Next Generation - Virtual Epileptic Patient (VEP) coming now



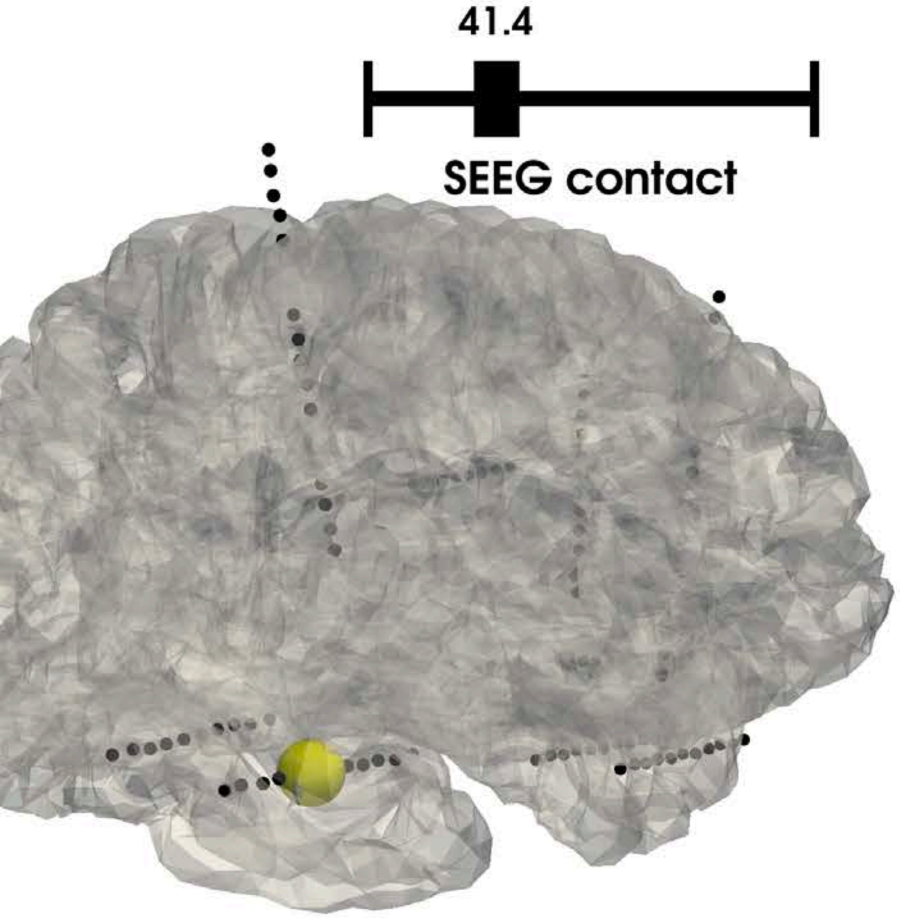
Next Generation - Virtual Epileptic Patient (VEP) coming now



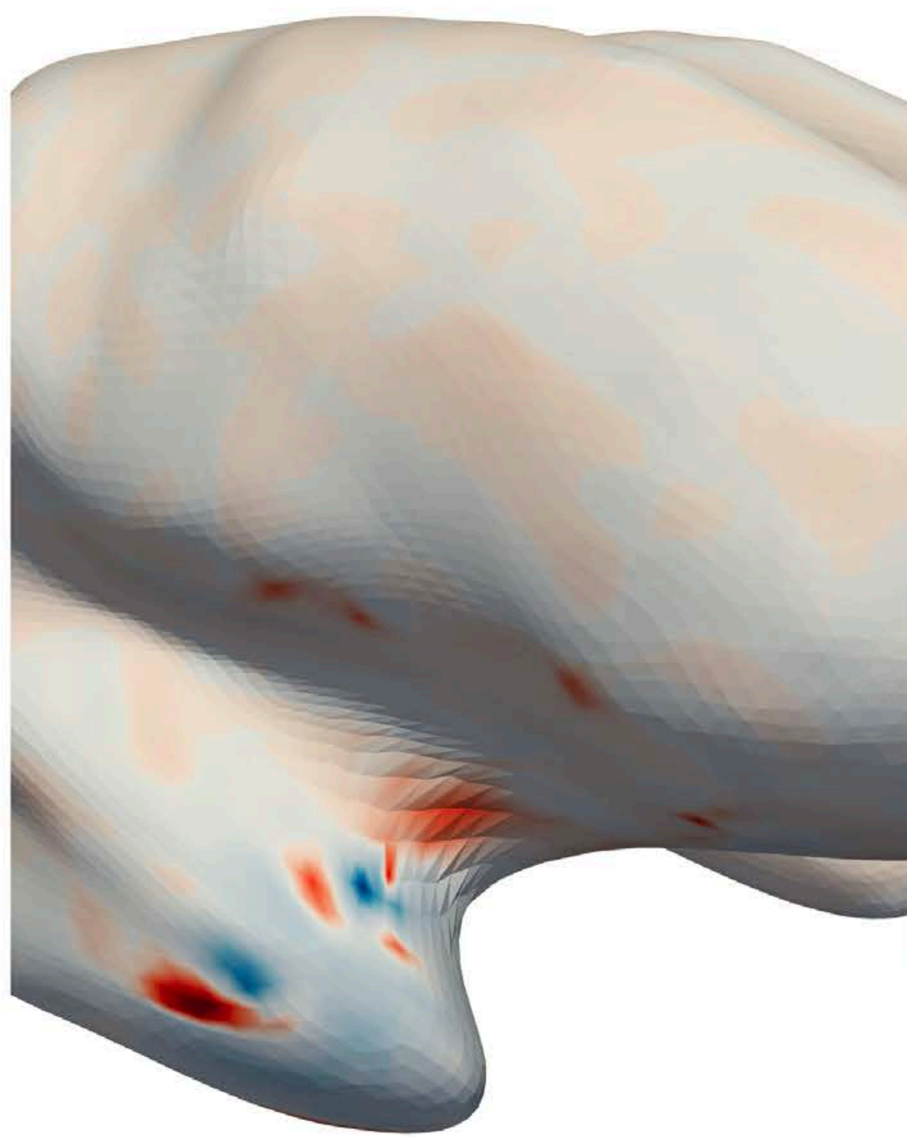
Next Generation - Virtual Epileptic Patient (VEP) coming now

Model inversion using gain matrices of the source-to-sensor forward solution

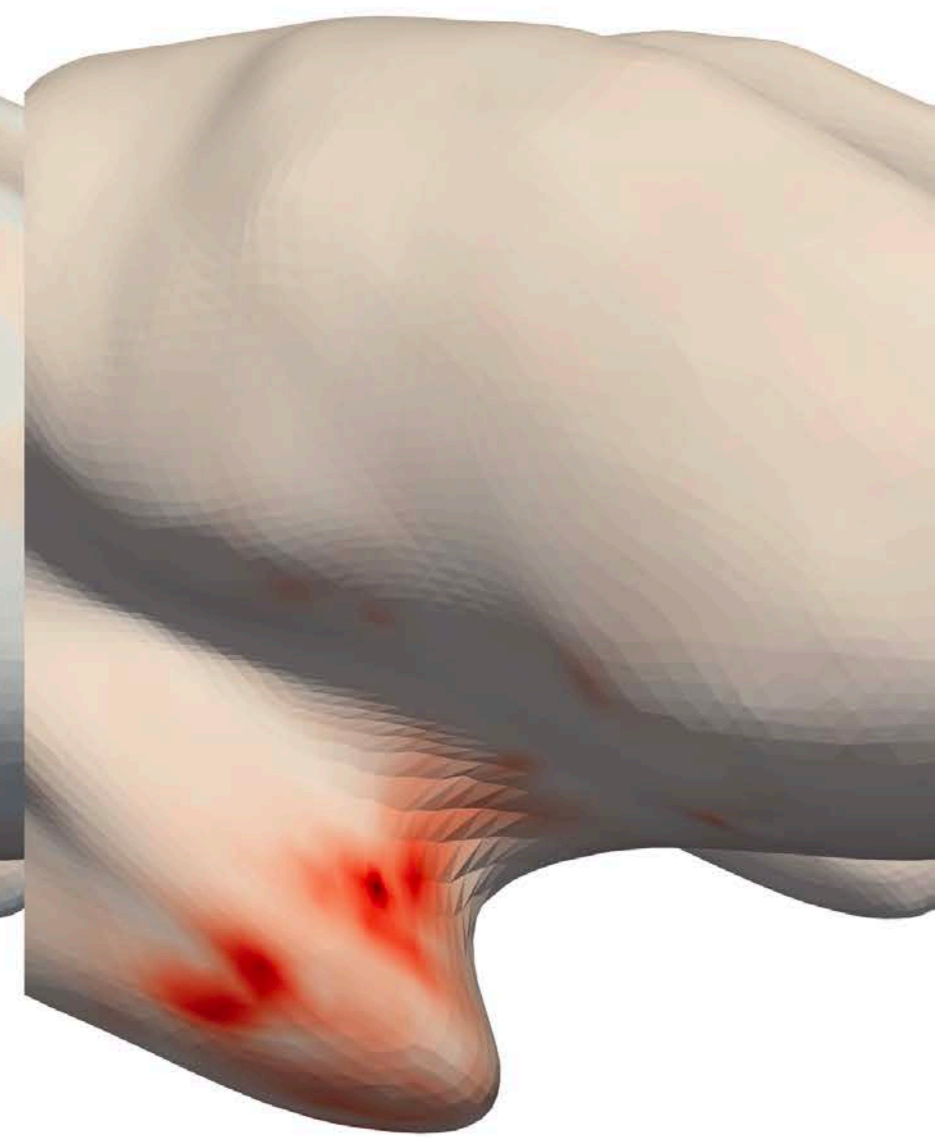
A7



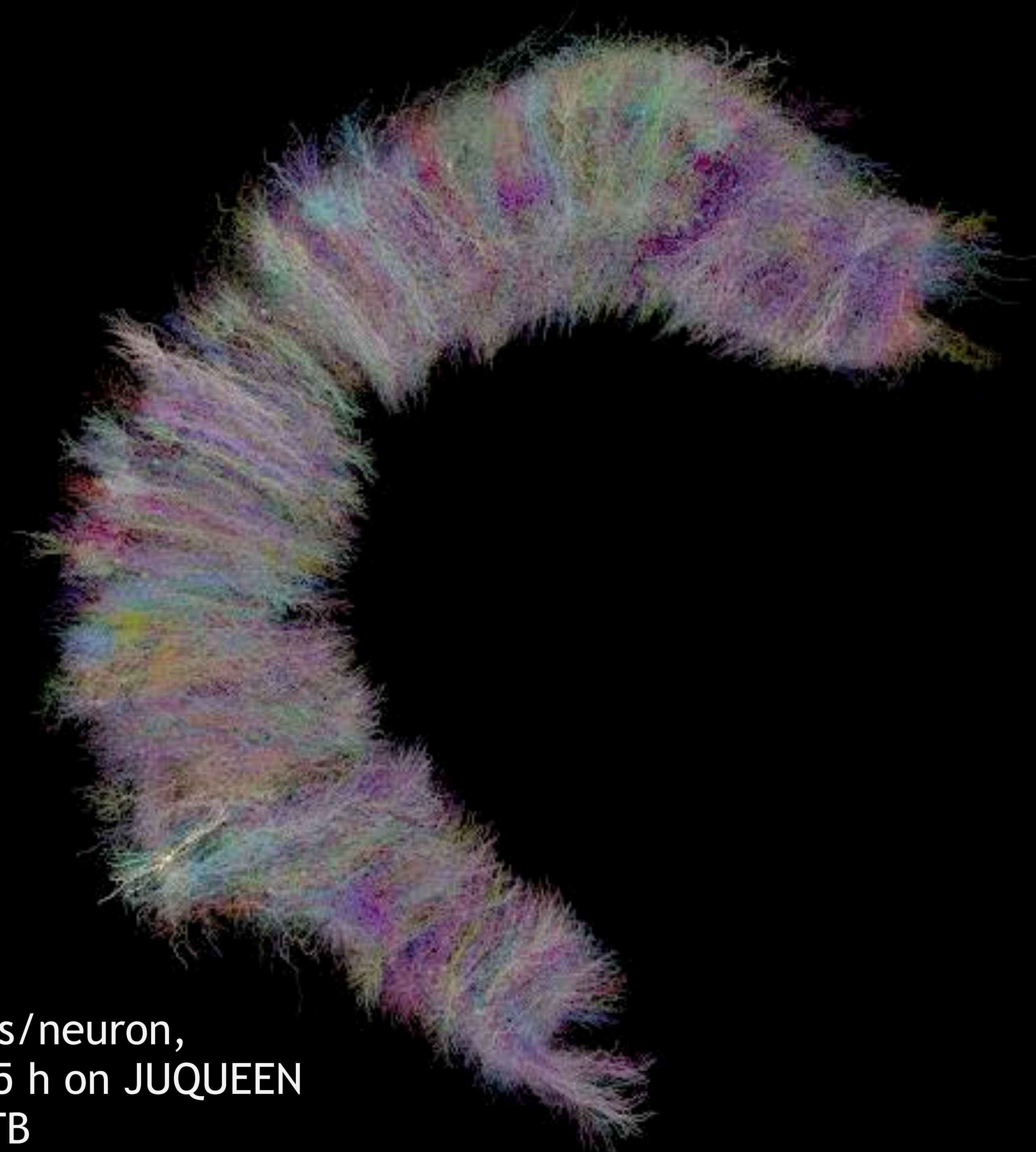
Dipole mapping



Distance mapping only

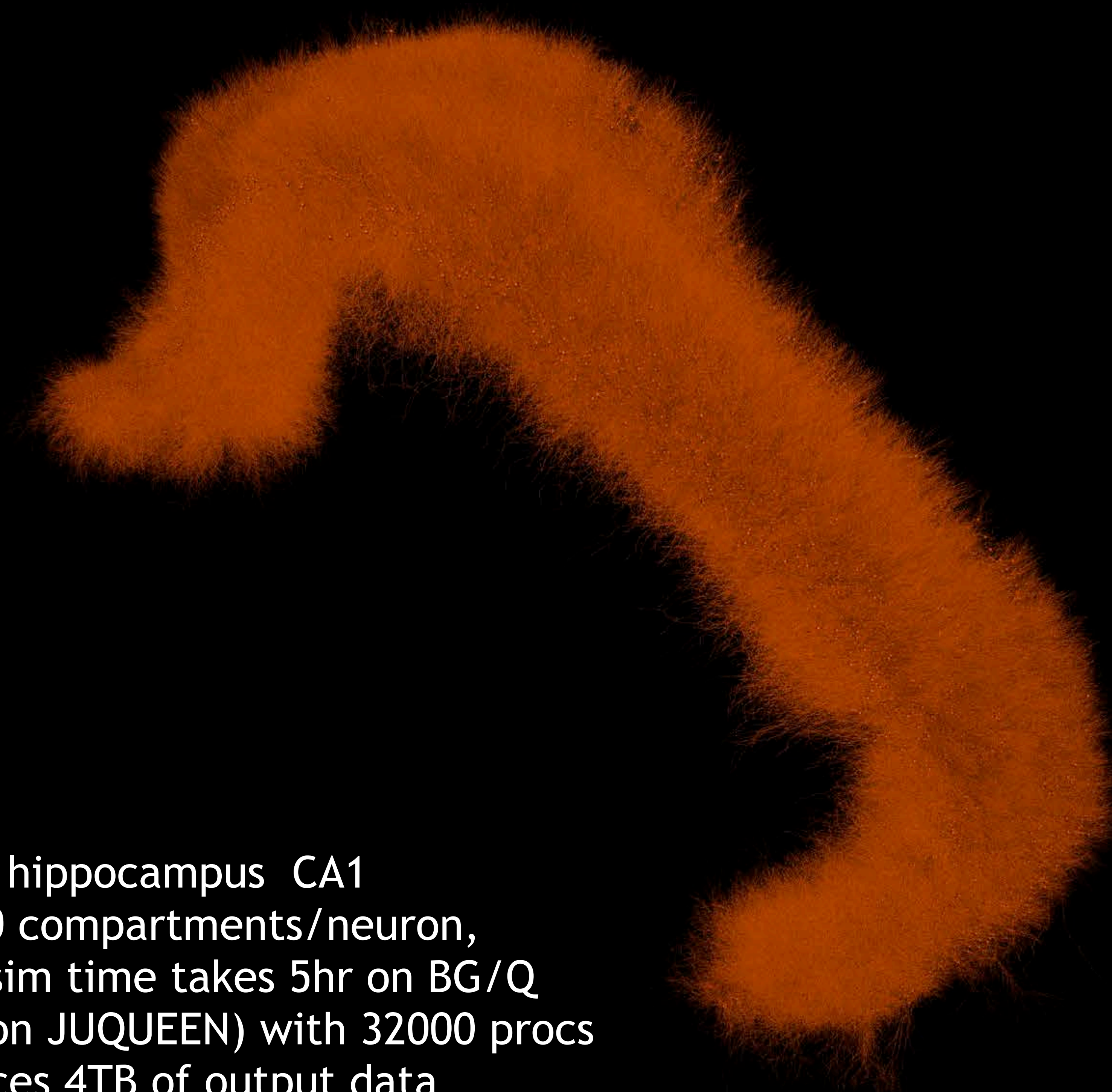


Next Generation - Virtual Epileptic Patient (VEP) coming now



mouse, CA1 region
~1'000 compartments/neuron,
1" simulation needs 5 h on JUQUEEN
generates approx. 4TB

Next Generation - Virtual Epileptic Patient (VEP) coming now



Mouse hippocampus CA1
~1’000 compartments/neuron,
1” of sim time takes 5hr on BG/Q
(runs on JUQUEEN) with 32000 procs
produces 4TB of output data
Migliore et al., Palermo, SP6

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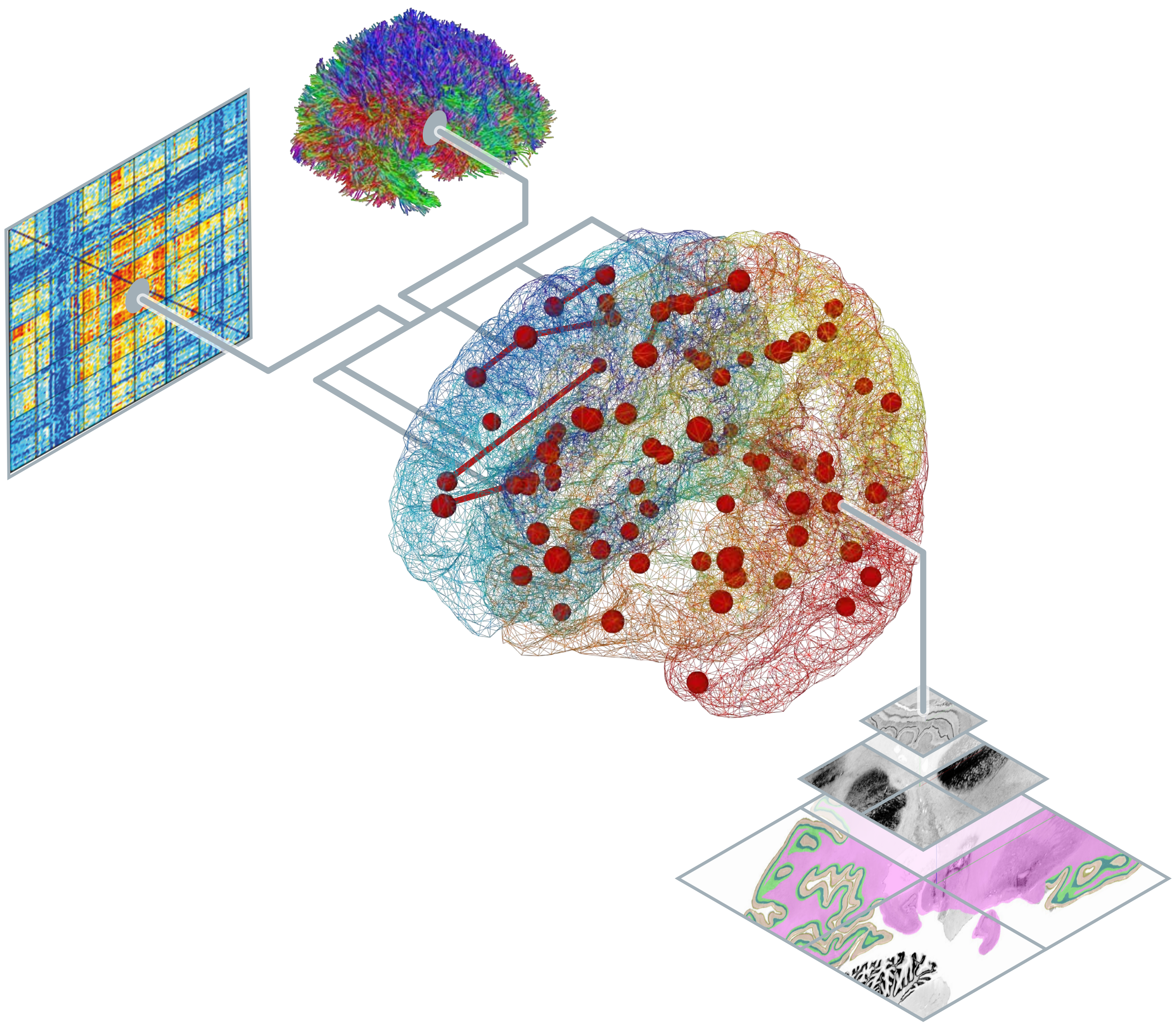
IN CONCLUSION

Final thoughts



The Virtual Brain closes the gap between model and brain imaging.

Personalized in-silico brain modeling platforms enable search for novel clinical solutions.

EBRAINS provides an eco-system, in which a new form of scientific (‘industrialized’) collaboration is possible.

McIntosh AR & Jirsa VK (2019). The hidden repertoire of brain dynamics and dysfunction. Network Neuroscience, 3(4), 994–1008

Jirsa VK (2020) Structured Flows on Manifolds as guiding concepts in brain science.
In: Viol K., Schöller H., Aichhorn W. (eds) Selbstorganisation - ein Paradigma für die Humanwissenschaften. Springer

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THANK YOU

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Lionel Kusch

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THANK YOU

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ACCÉLÉRONS LE TRANSFERT DE TECHNOLOGIES

A*Midex
Initiative d'excellence Aix-Marseille

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Agence Nationale de la Recherche
ANR