Personalized modeling of brain responses to noninvasive stimulation

Fariba Karimi[1,2], Taylor H. Newton[1], Melanie Steiner[1], Javier García Ordóñez[1], Elena Beanato[3], Friedhelm C. Hummel[3,4], Niels Kuster[1,2], Esra Neufeld[1]

[1]Foundation for Research on Information Technologies in Society (IT'IS), Zurich, Switzerland

[2]Department of Information Technology and Electrical Engineering, Swiss Federal Institute of Technolgoy (ETH), Zurich, Switzerland

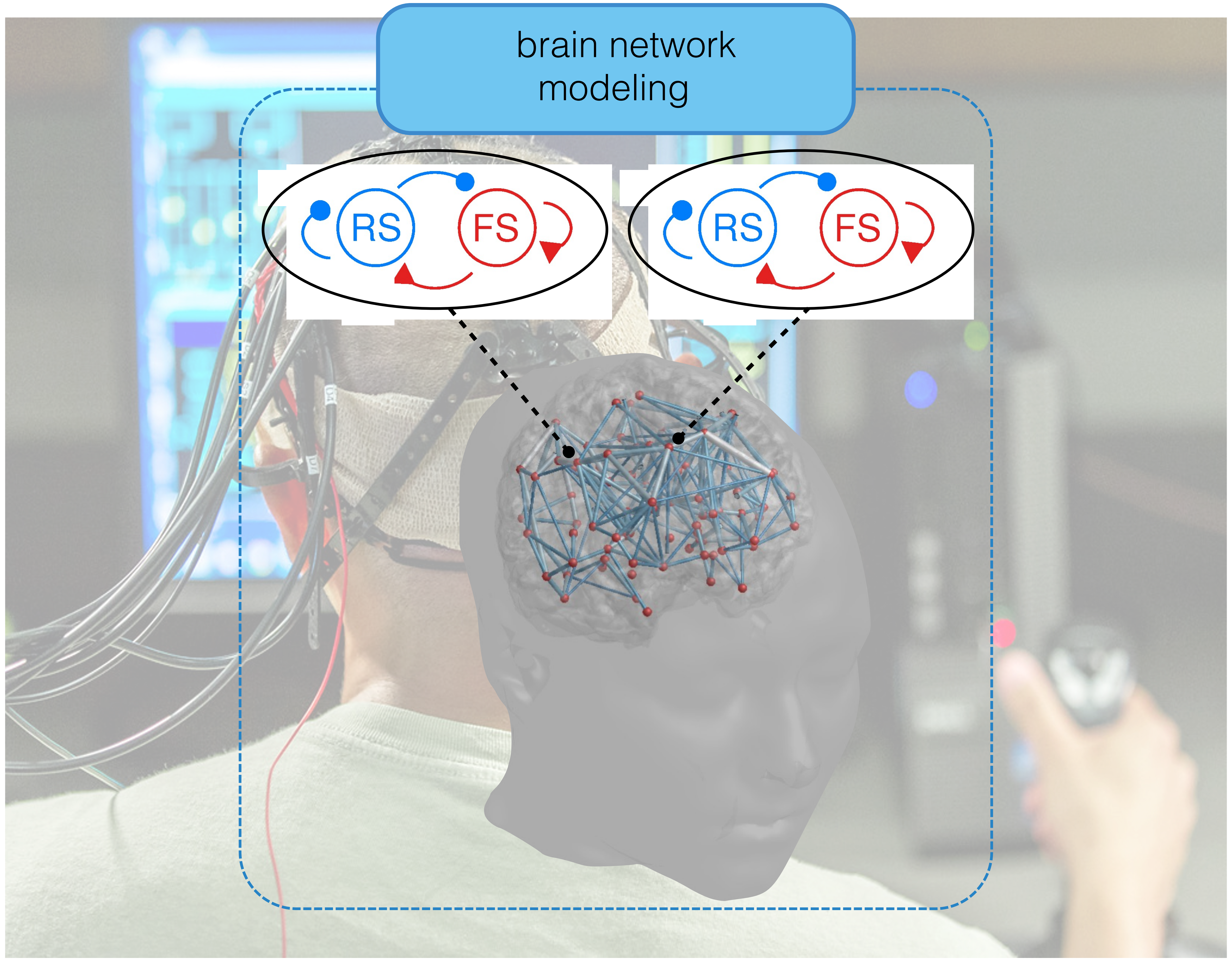
[3]Ecole Polytechnique Fédérale de Lausanne (EPFL), Geneva and Sion, Switzerland

[4]Clinical Neuroscience, University Medical School of Geneva, Geneva, Switzerland

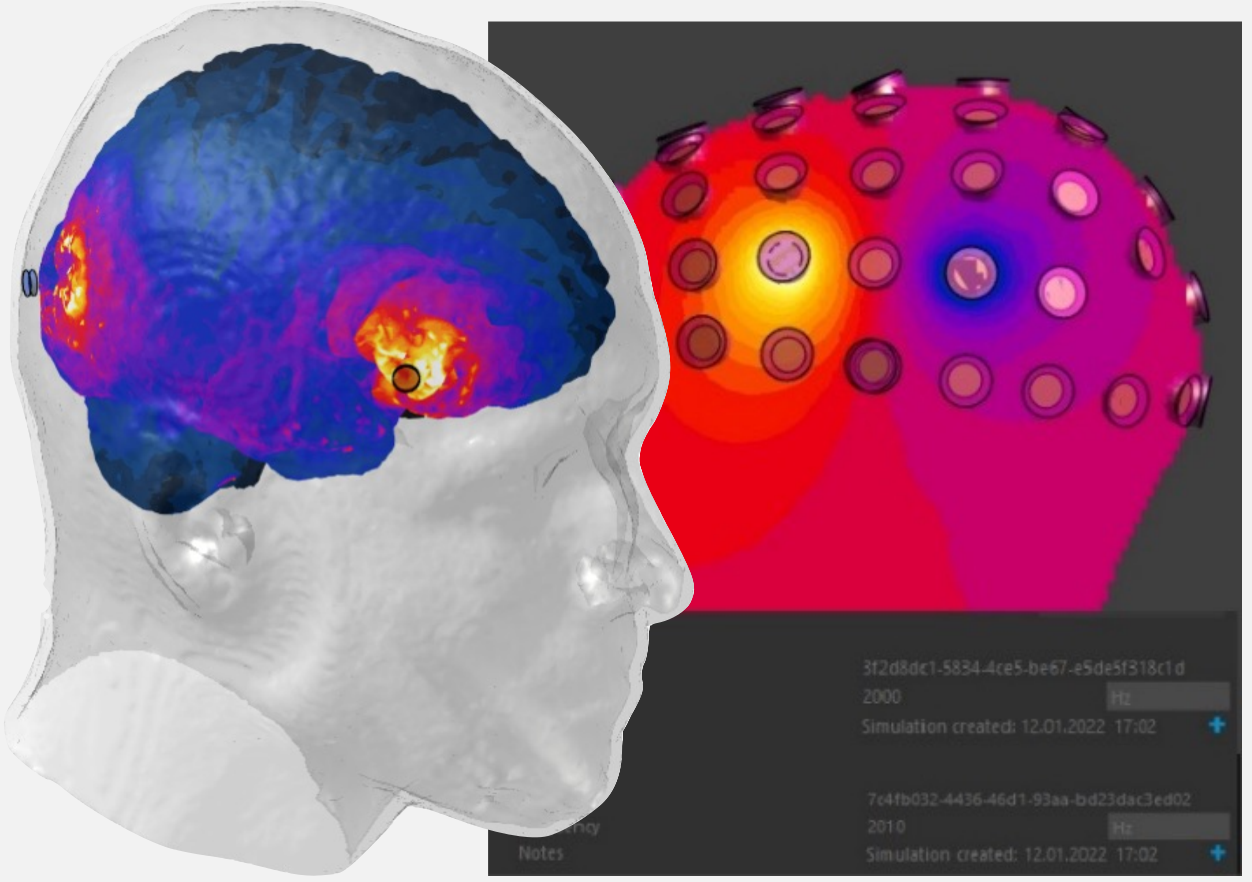
ZMT Workshop, Brain Stimulation 2025, Kobe

Motivation

- Neurological/psychiatric disorders: epilepsy, **stroke, spinal cord injury**, Parkinson‘s/Alzheimer’s disease, depression…
- Electromagnetic (EM) brain stimulation provides a powerful therapeutic approach for brain disorders
- But a one-size-fits-all does not capture significant variation in anatomy & physiology → personalization required

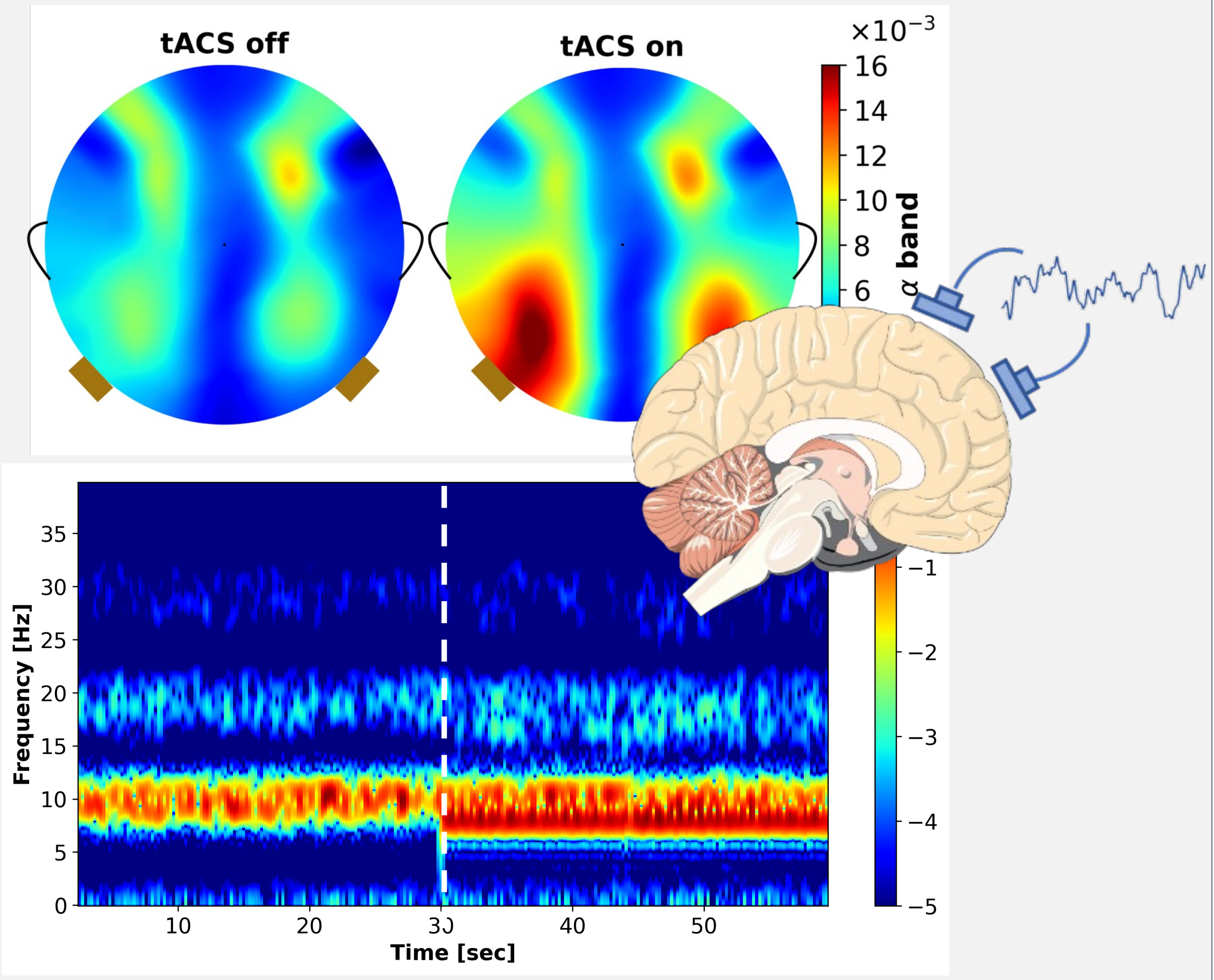


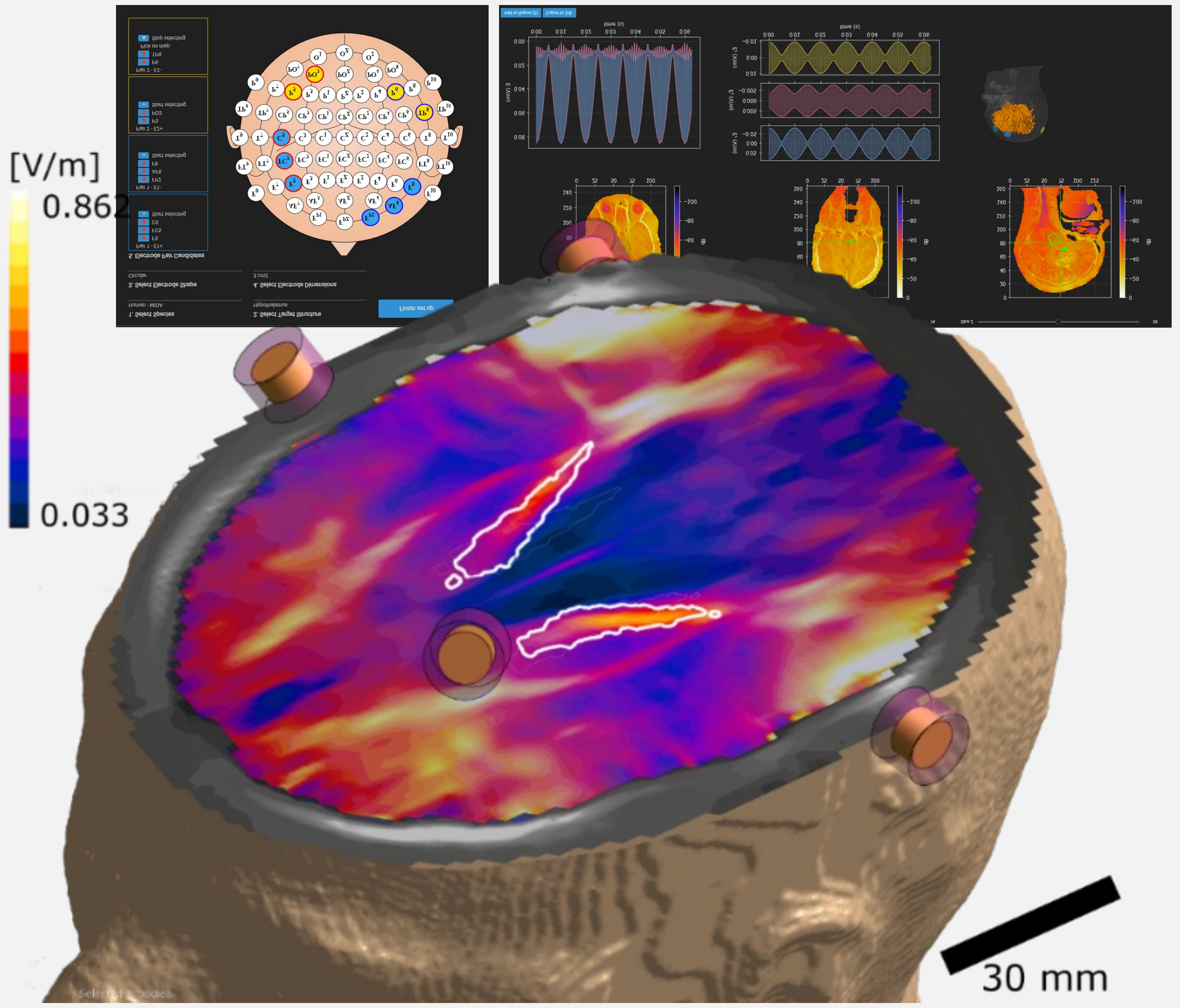
From Targeted Exposure to Optimized Functional Responses



- EM exposures are computed over the space of candidate stimulation configurations → targeted field distributions

- coupled functional responses are simulated, then characterized using dimensionality reduction





- targeted exposure – neural activity coupling permits optimization of functional responses

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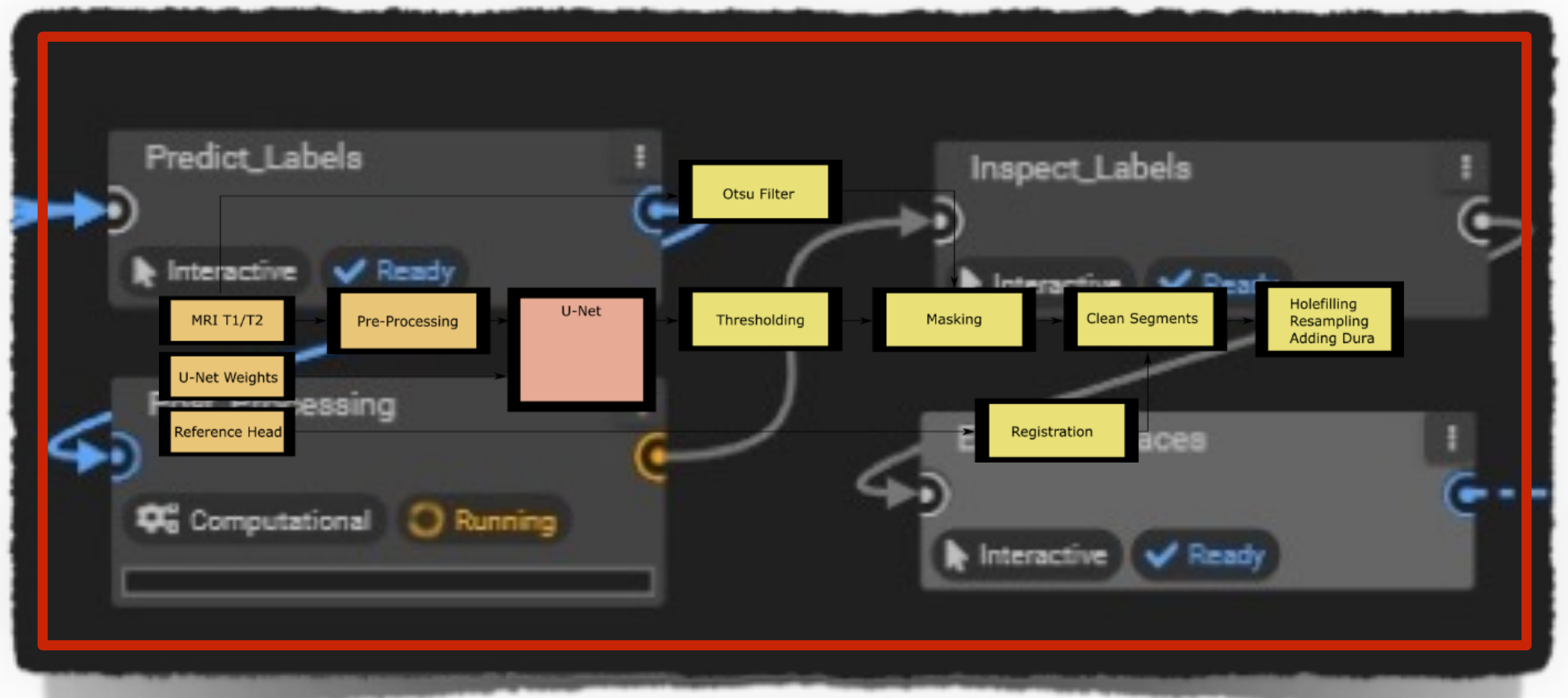
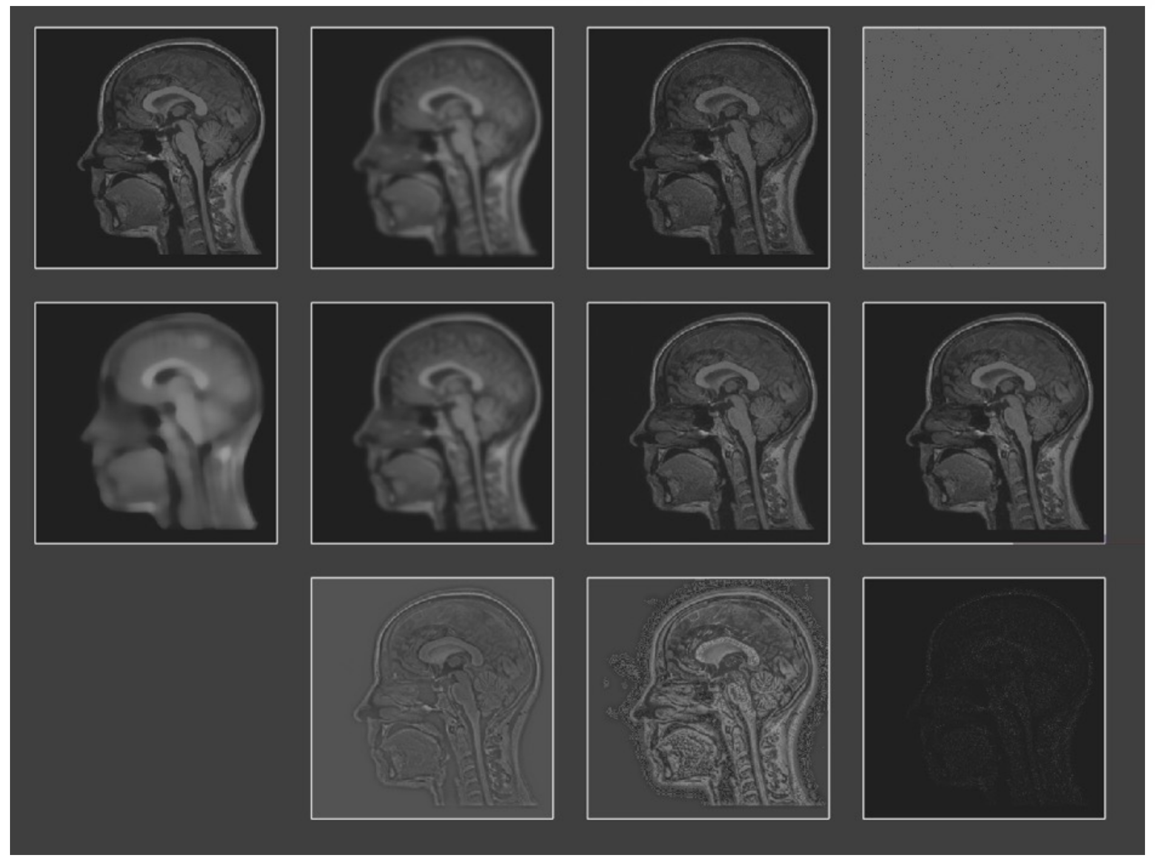
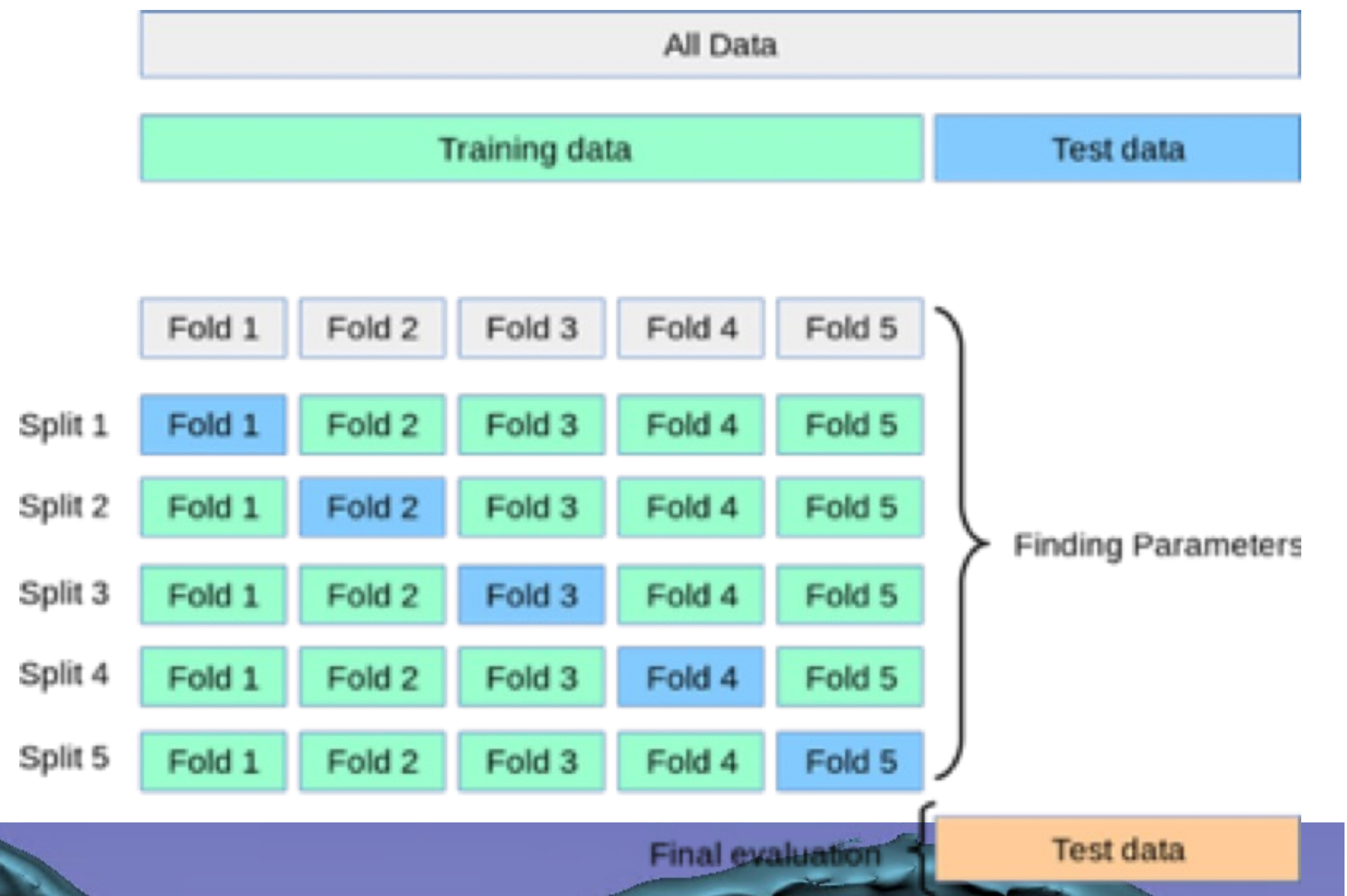
Automated Model Generation

- Segmantic pipeline
  - AI & CV
  - data augmentation, ensemble prediction (best of the best networks)
- postprocessing
  - further improves segmentation quality
  - inserts additional tissue regions
- brain parcellation
  - hybrid AI-registration
- superior segmentation quality and realism, in no time
  - 40 tissues
  - seconds to minutes vs. hours
  - robust







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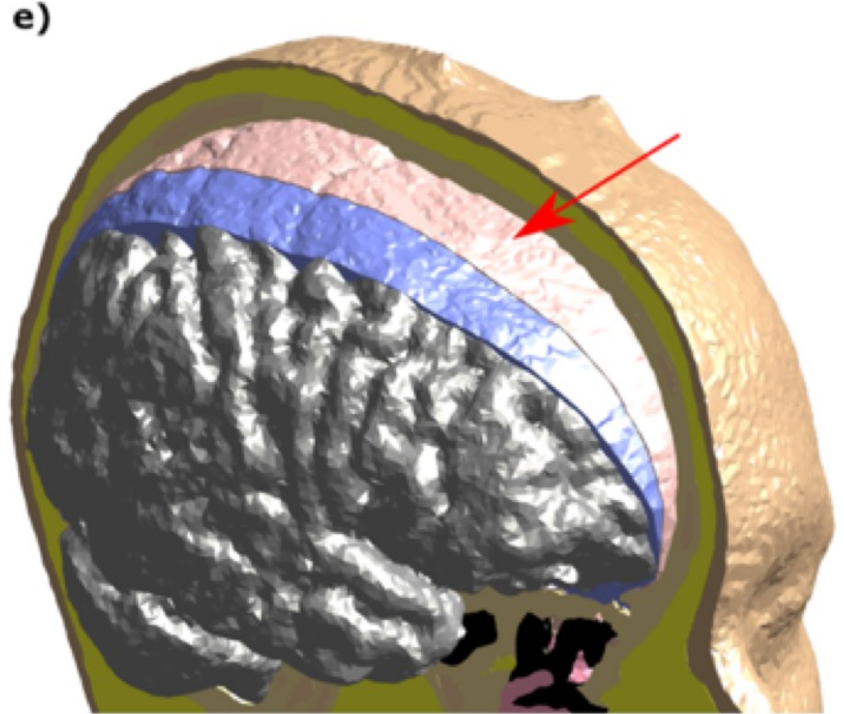

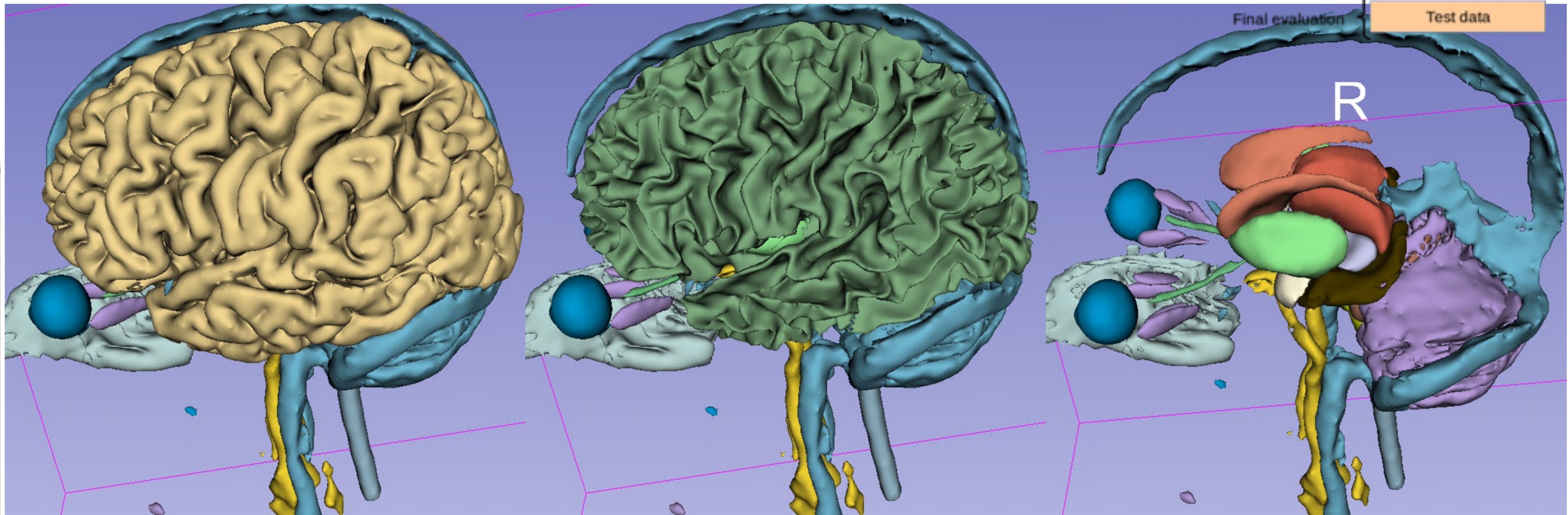

Automated Model Generation

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- postprocessing
  - further improves segmentation quality
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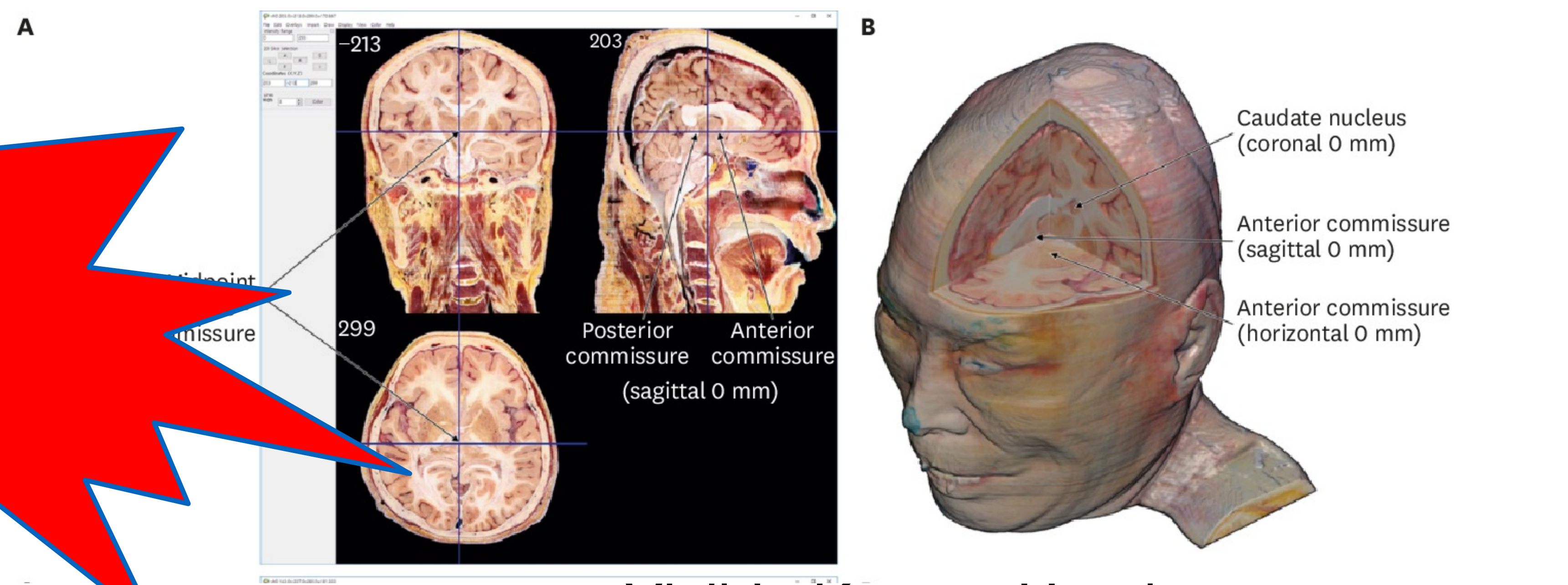
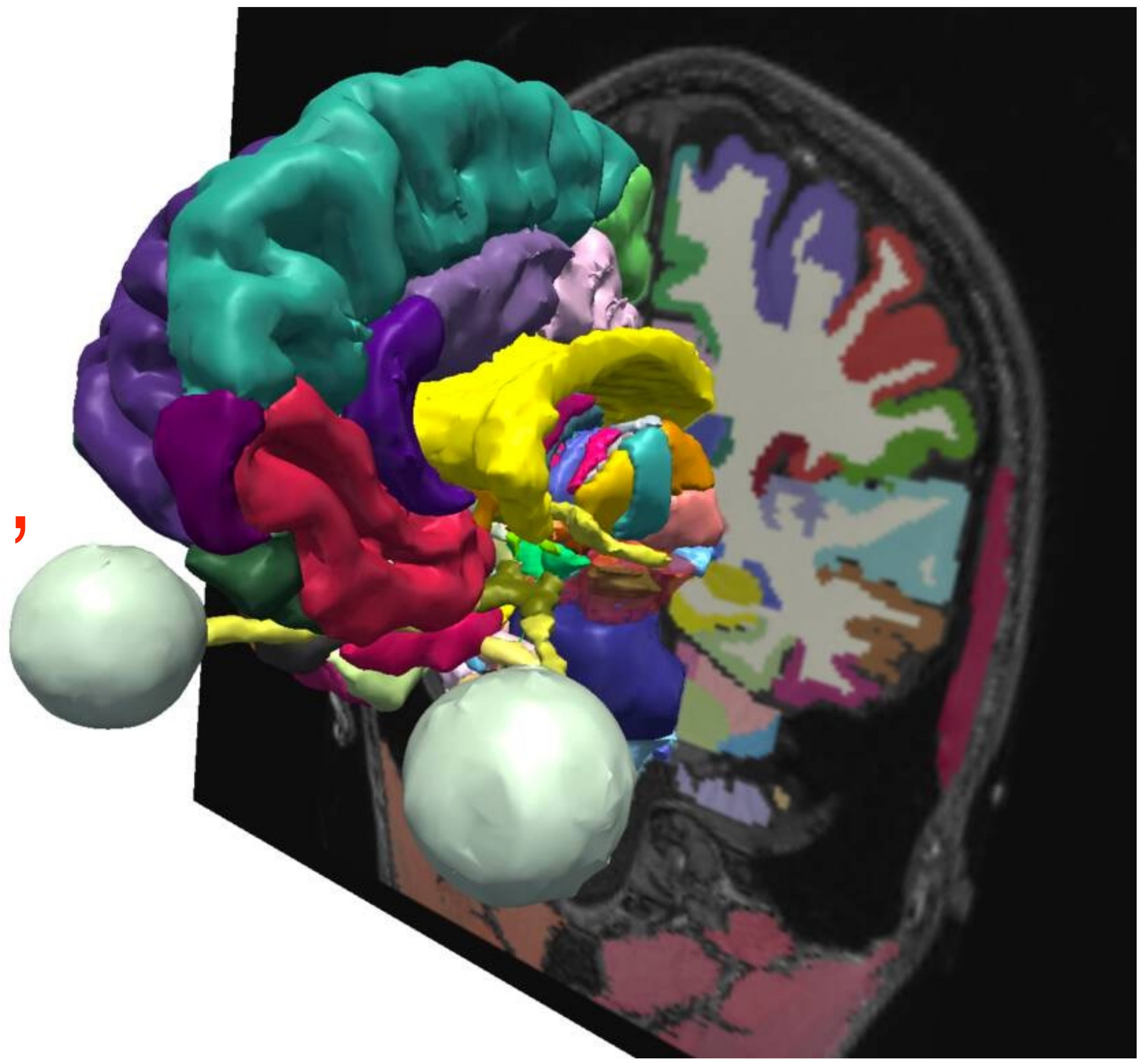
- brain parcellation
  - hybrid AI-registration
- superior segmentation quality and realism, in no time
  - 30 tissues
  - seconds to minutes vs. hours
  - robust

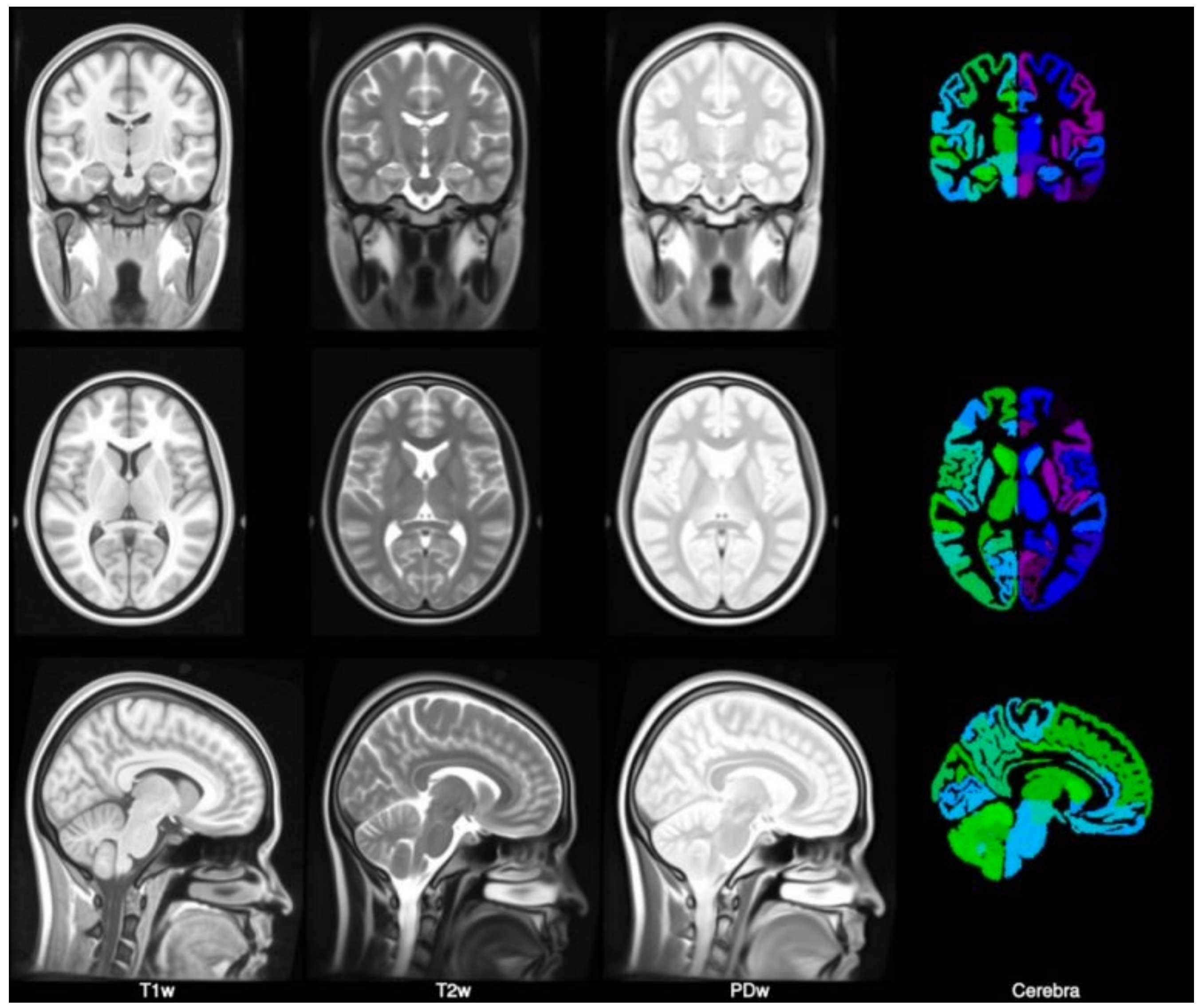
Now in Sim4Life!



Visible Korean Head

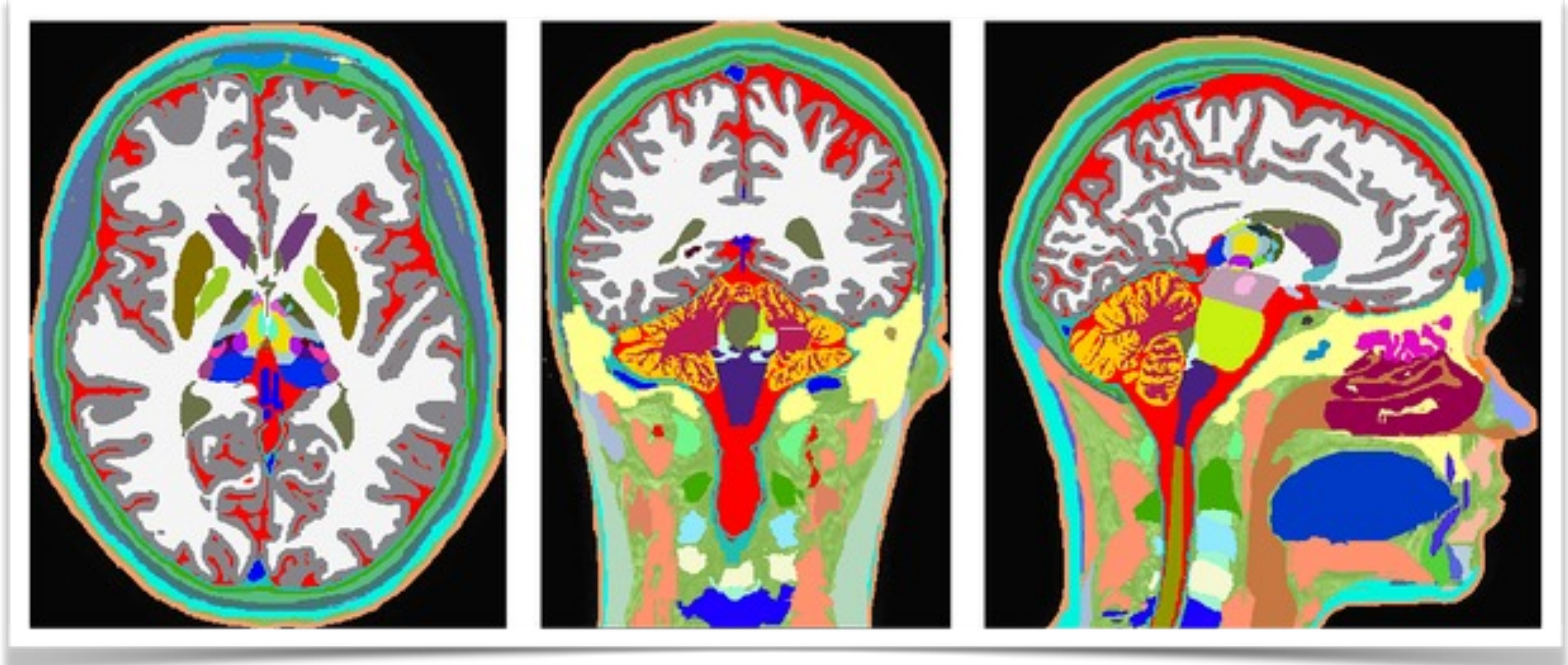


SP/NAC Brain Atlas



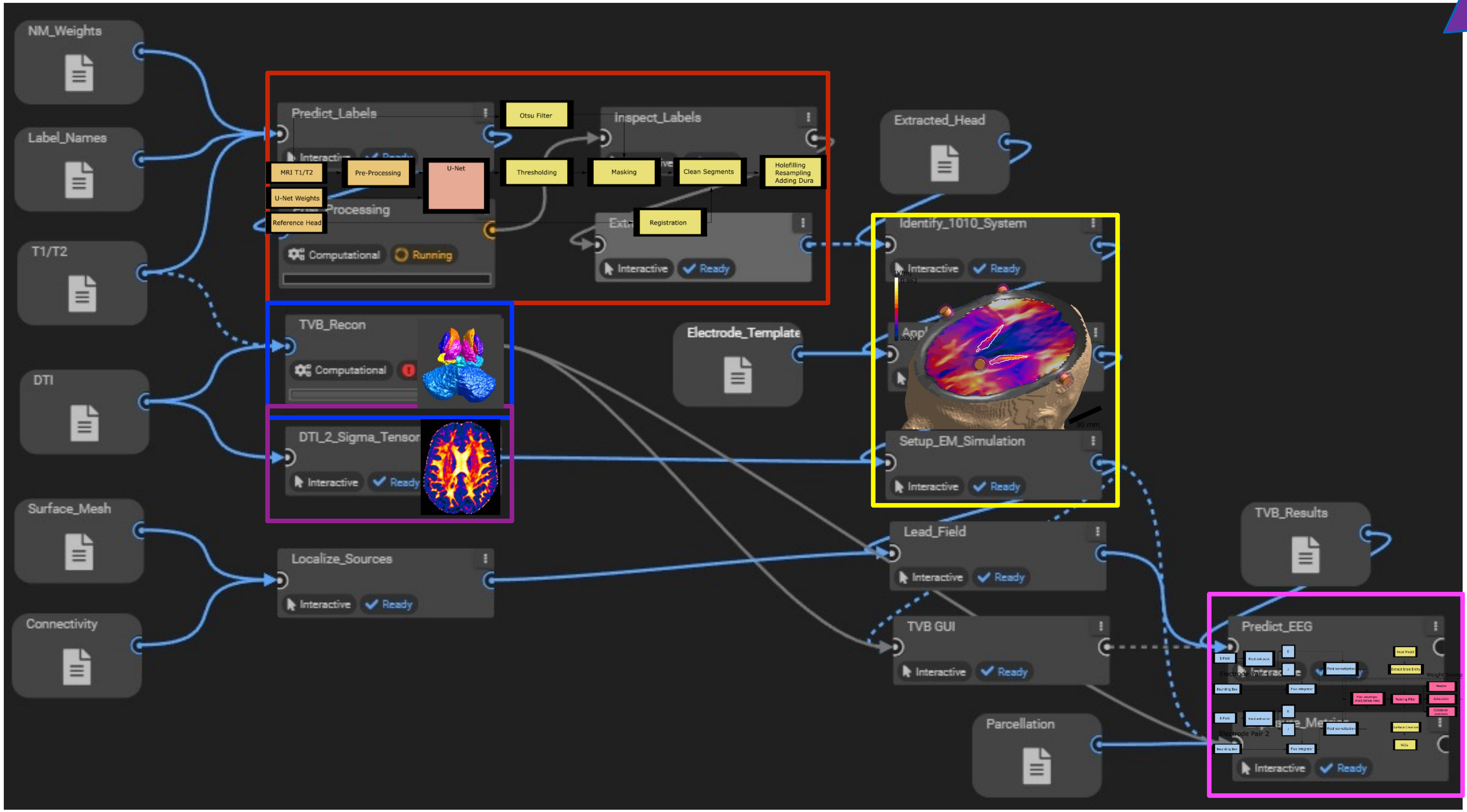
ICBM 152 (CerebrA)

MIDA Head Model



The Pipeline on o2S2PARC: Overview

Coming to S4L Web!



Automated Mo el Generation

Personalized Conductivity Mapping

E-Field Exposure Simulation

Temporal Interference Evaluation

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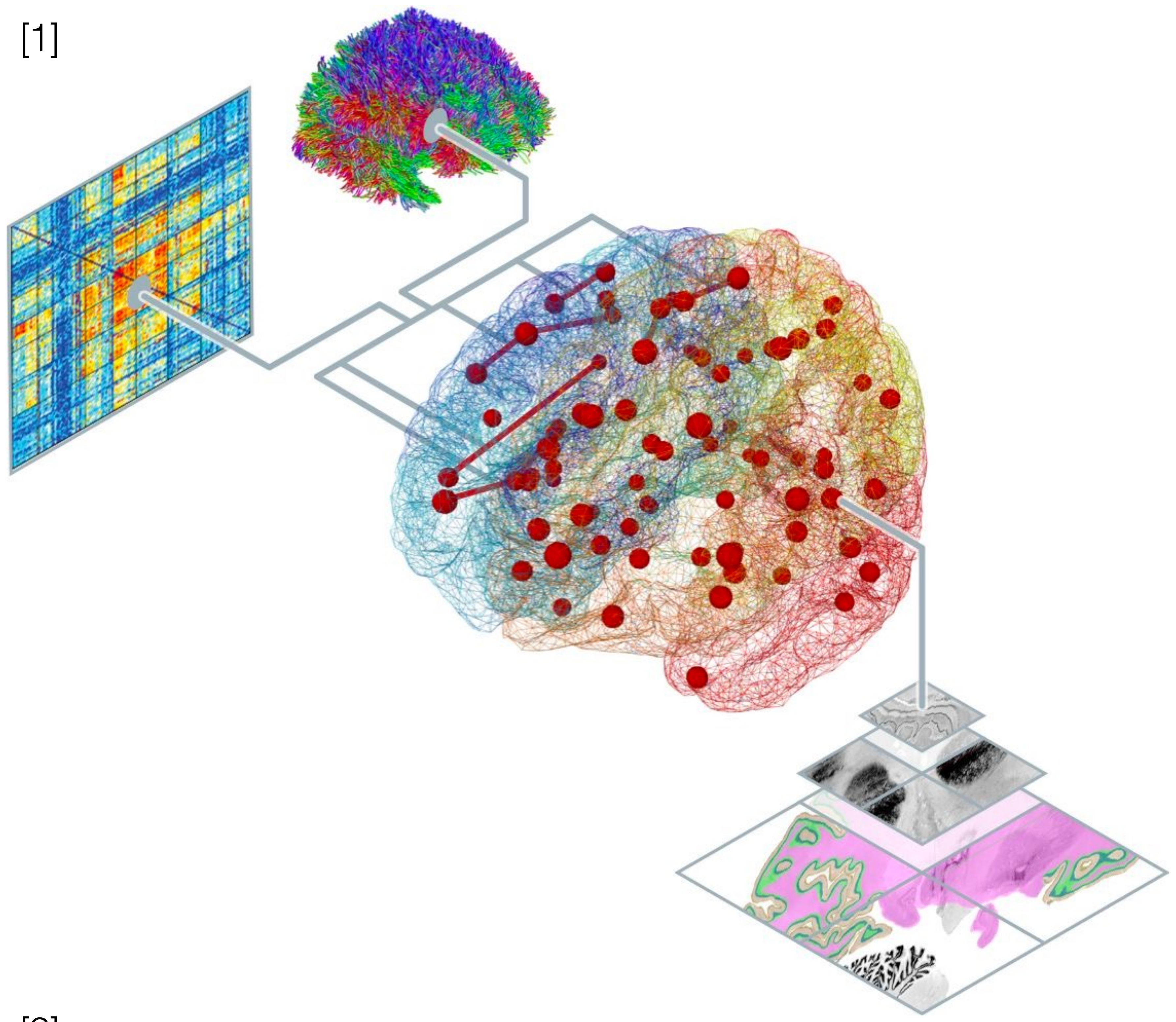
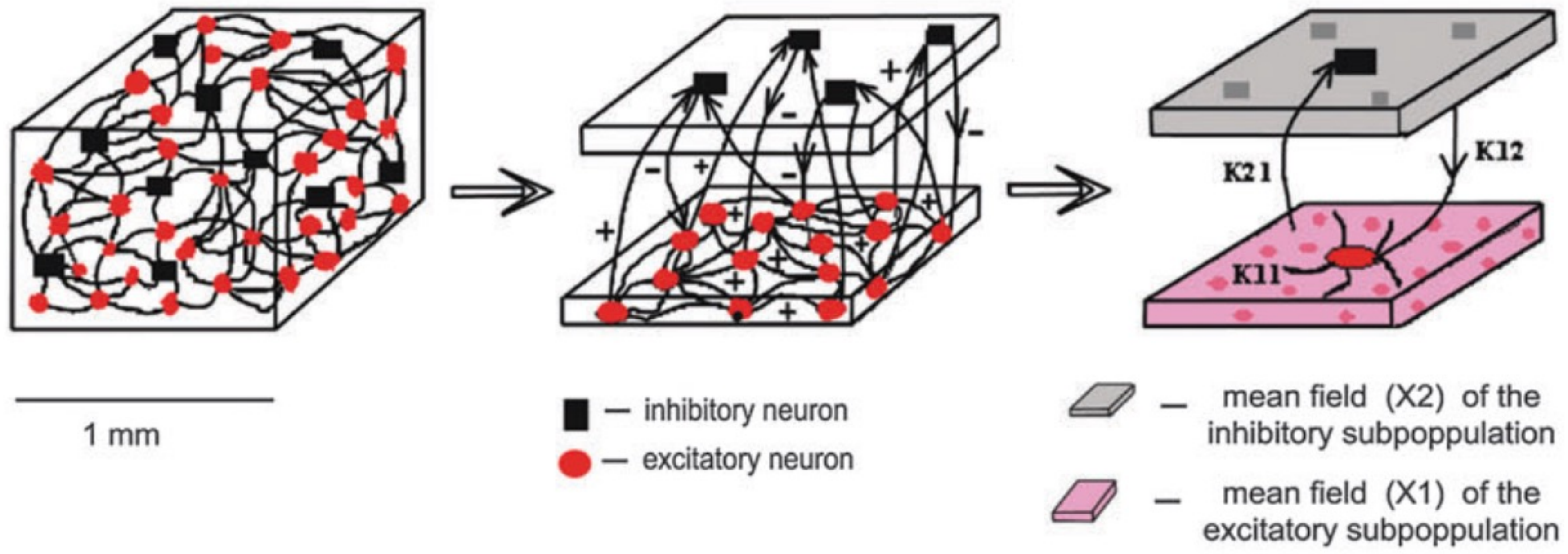
Brain Network Responses to tES

- mean field models: low dimensional representation of the average activity of a neuronal population
  - neural mass models (NMM): one-dimensional nodes
  - neural field models: captures spatial dependence
- coupling NMM-based description of brain activity to EM stimulation input closes the loop between stimulus and response → advanced/personalized tES schemes; effect-driven
- gaps in the standard approach:
  - lead field matrix personalization
  - EM exposure coupling control paradigms

[1]



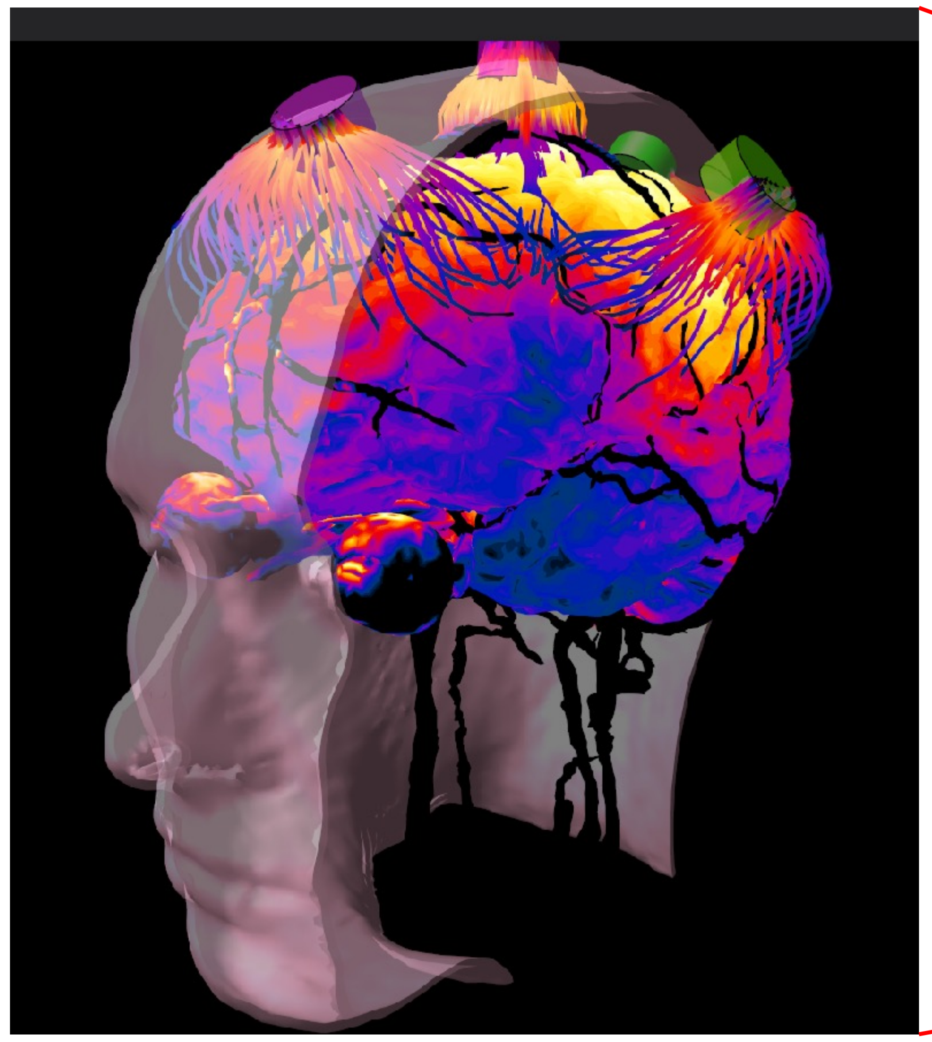
[2]

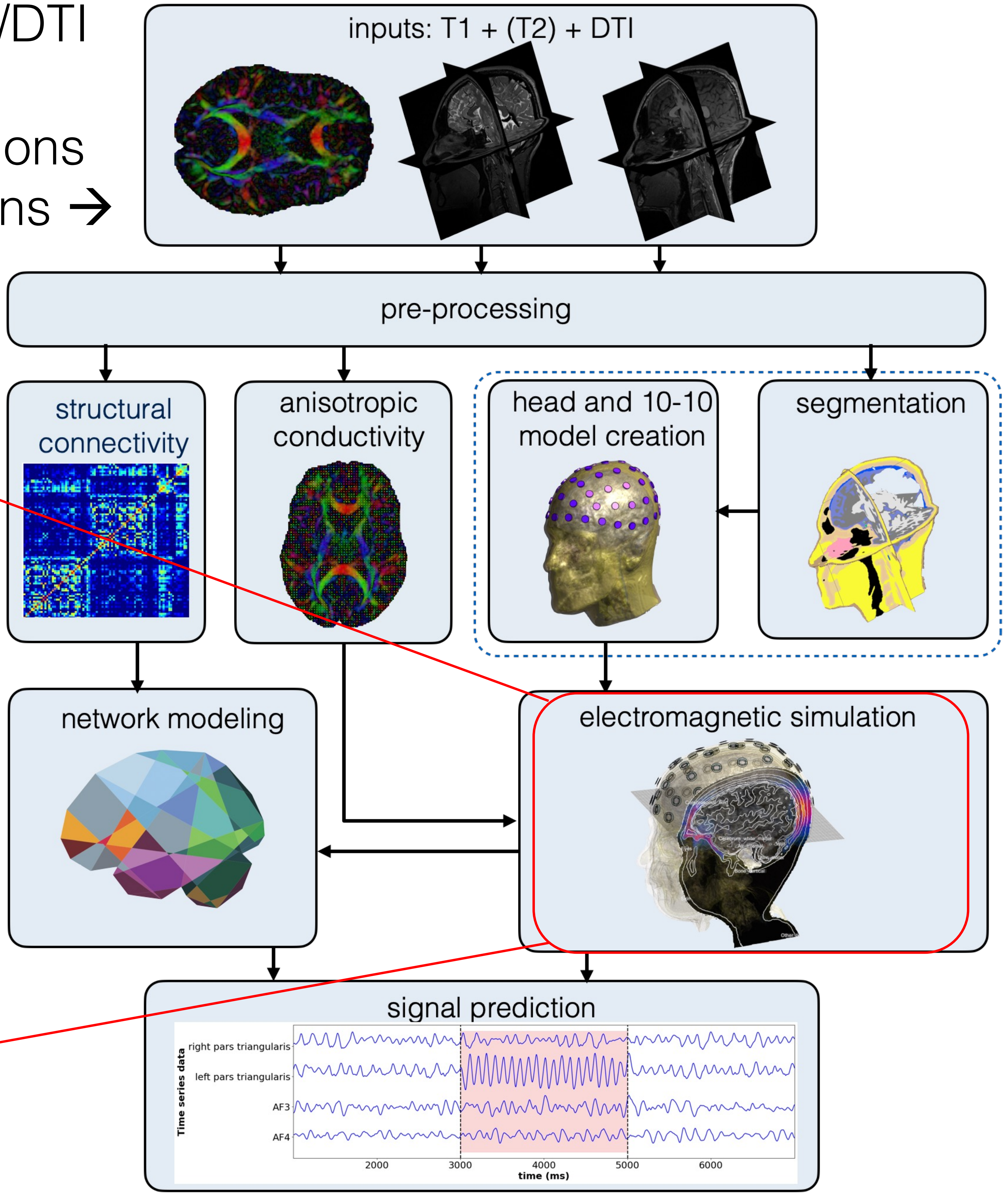


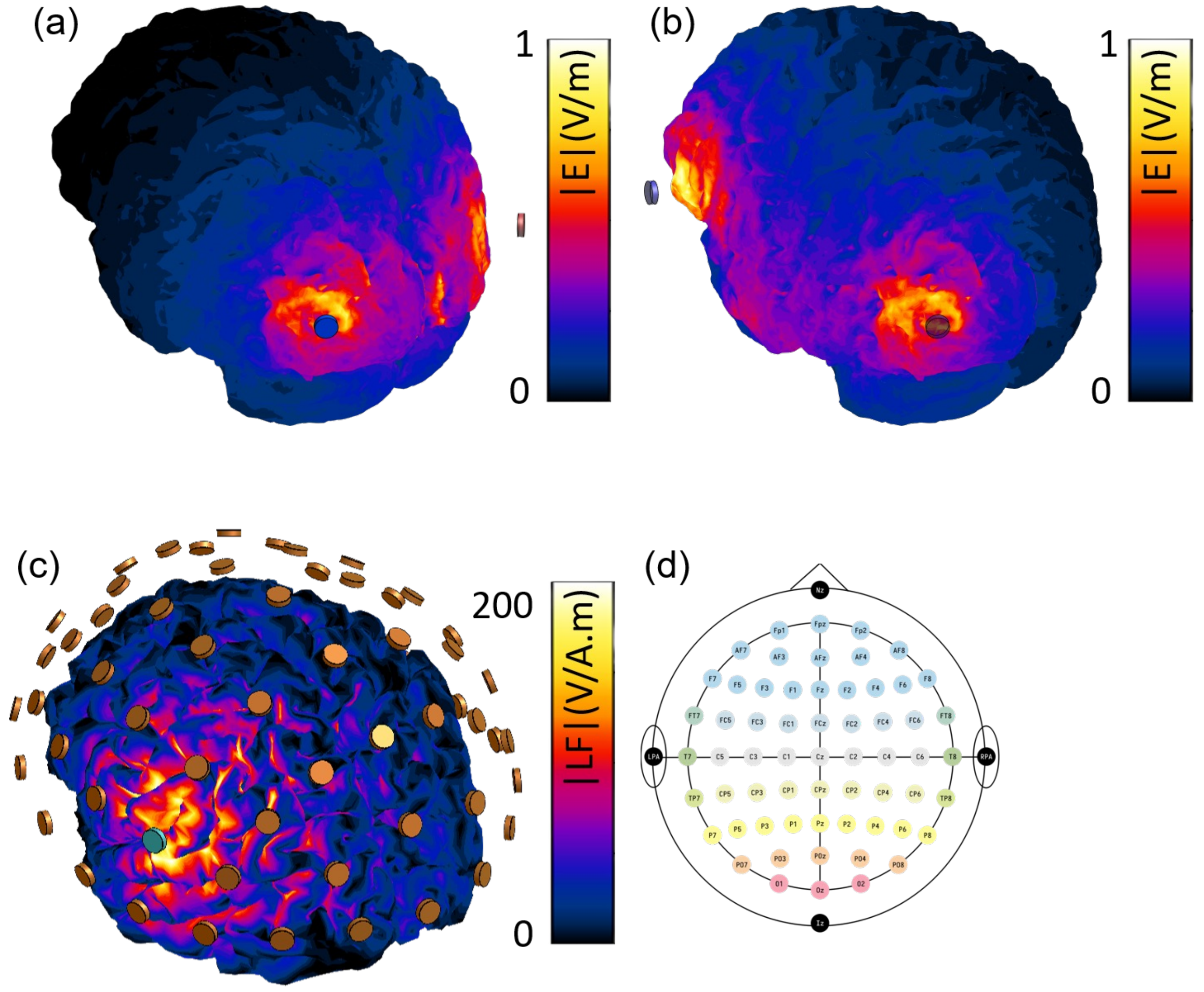
[1] www.ebrains.eu
[2] Stefanescu, Roxana A., and Viktor K. Jirsa. (2008)

Brain Network Responses to tES

- brain modeling pipeline: MRI/DTI inputs → AI-based model reconstruction → EM simulations → coupled network simulations → *in silico* signal generation







(a-b) Cortical E-field distribution induced by transcranial alternating current stimulation applied via 10-10 EEG system. (c) Visualization of a lead field matrix row (corresponding to the FC5 electrode, colored in light blue). (d) 10-10 EEG system representation.

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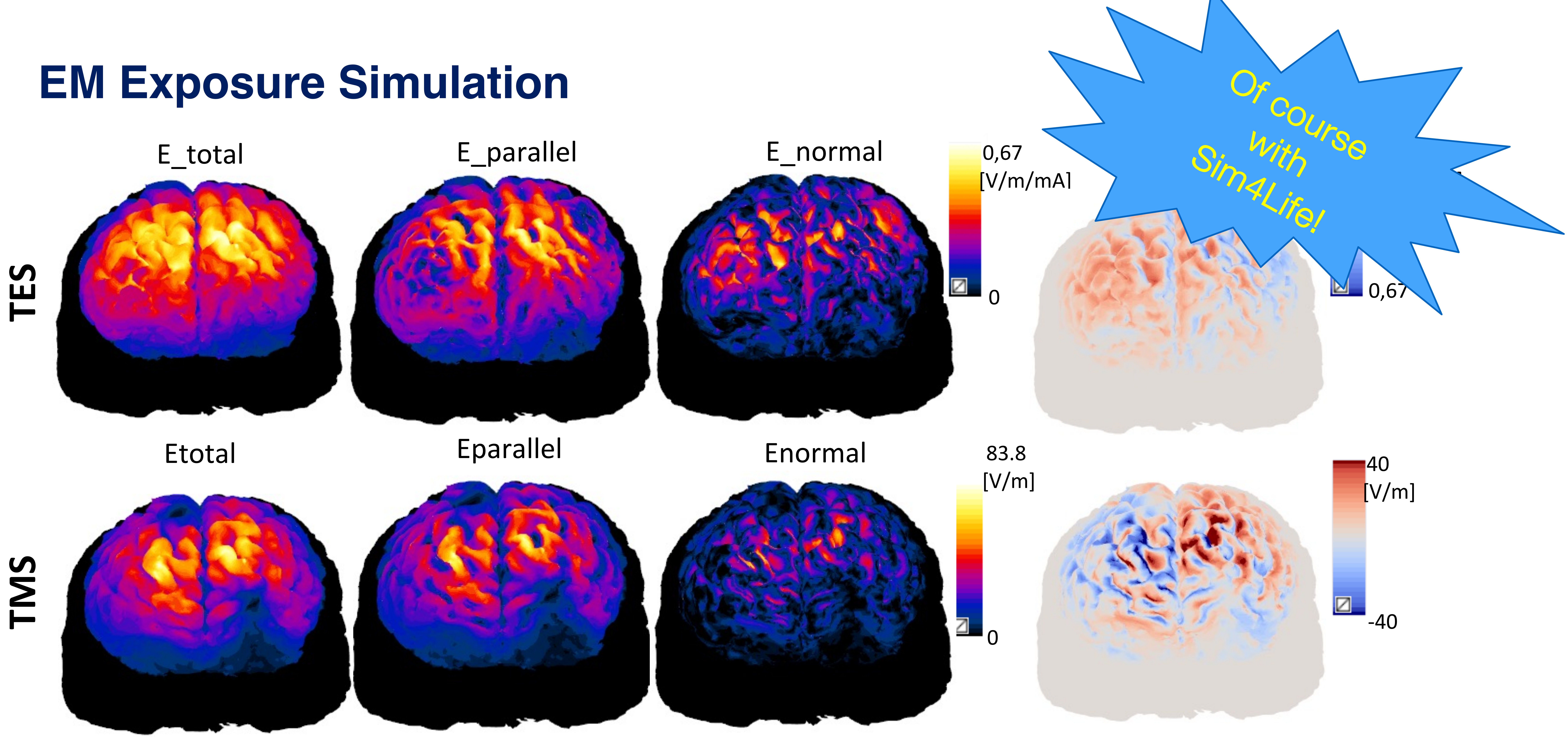
EM Exposure Simulation



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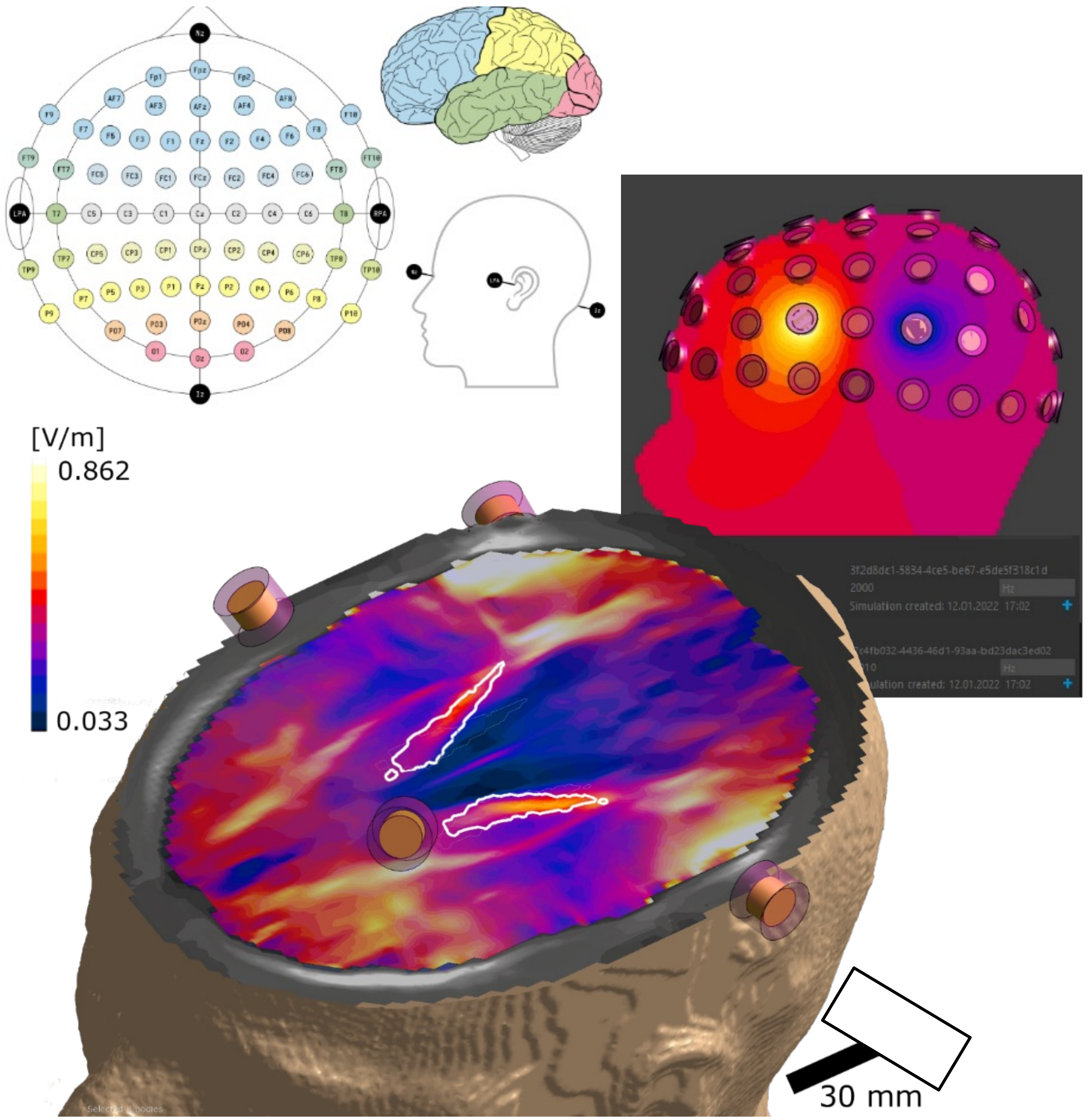
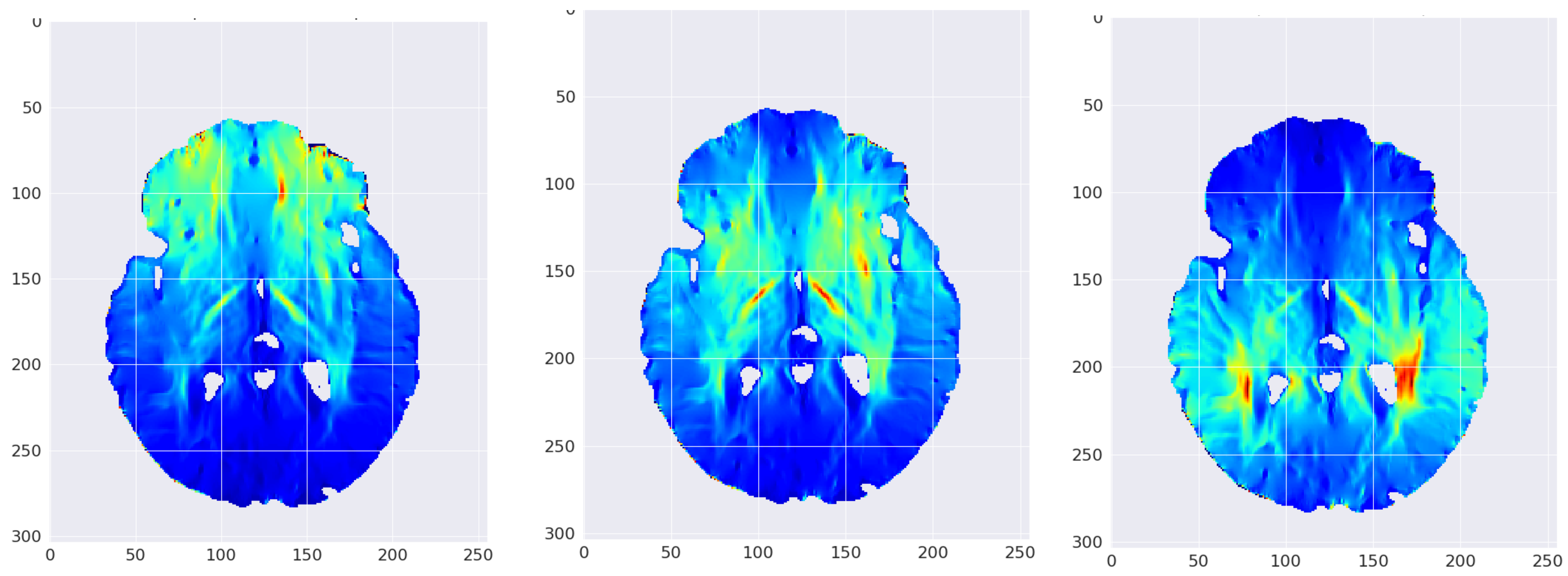
Field Library Generation

- automatic simulation setup and generation of EM field library
    - rapid generation of a large library of exposure configurations





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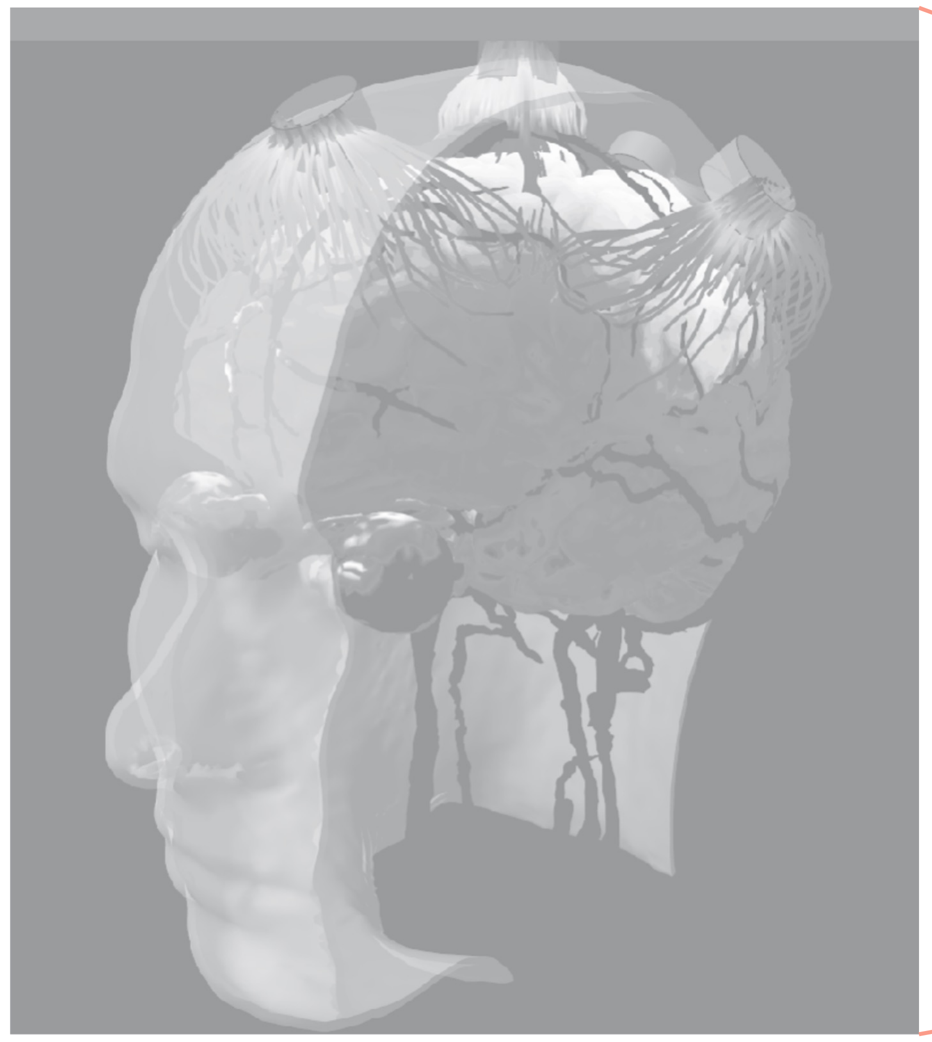
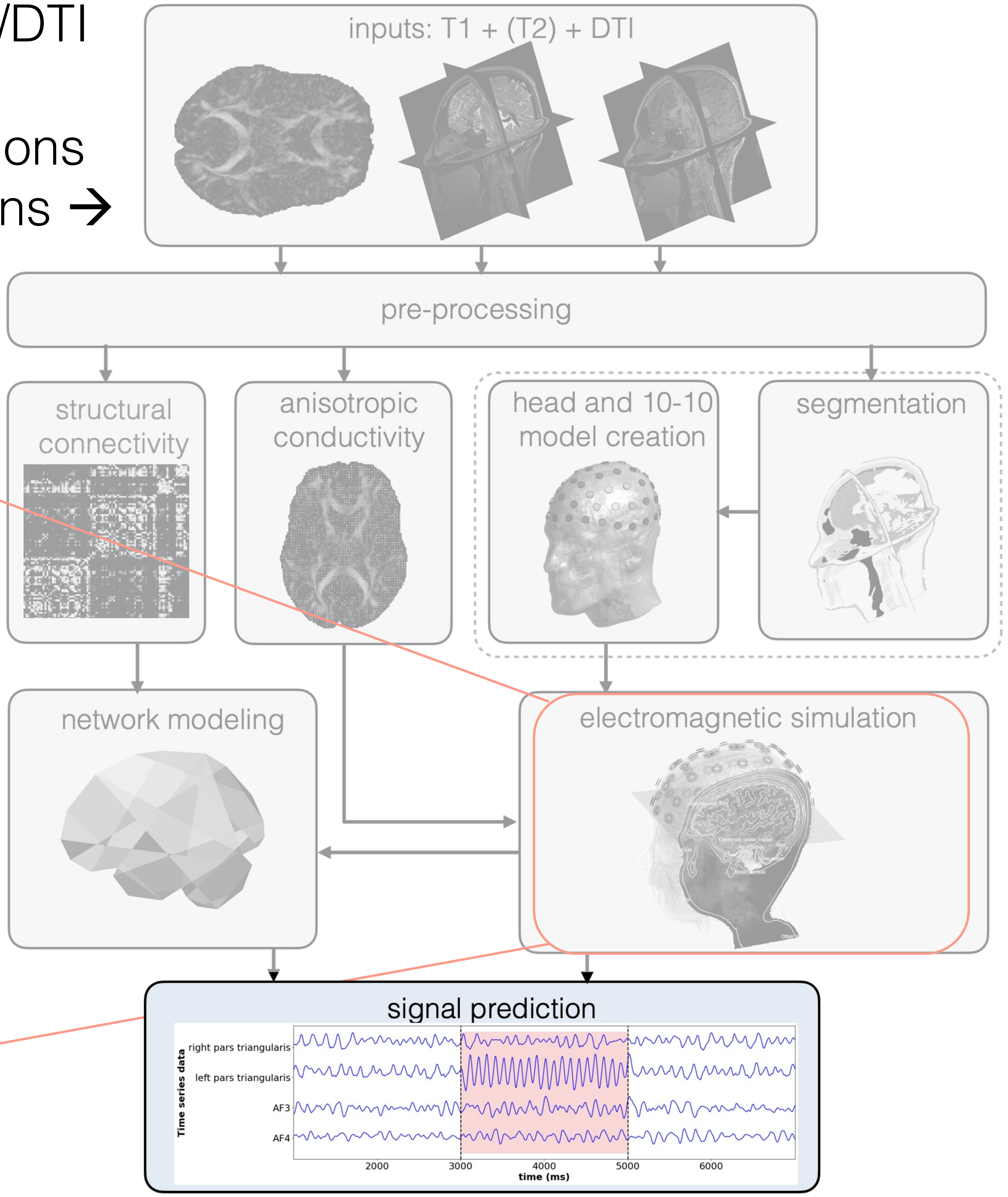
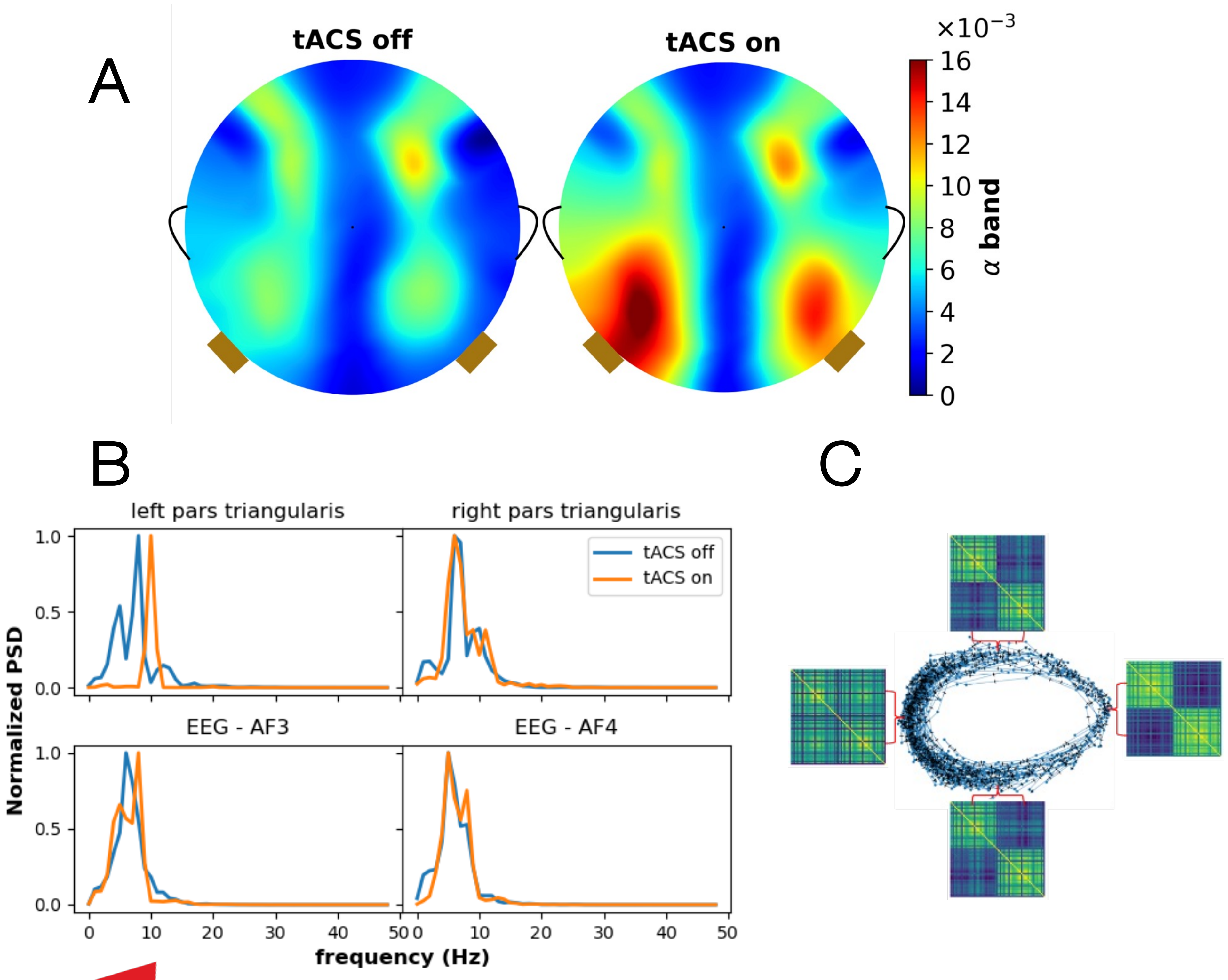




- network response: A) topographic EEG alpha band power map; B) normalized PSD for raw activity of two brain regions and two EEG channels; C) PCA of dynamic functional connectivity states



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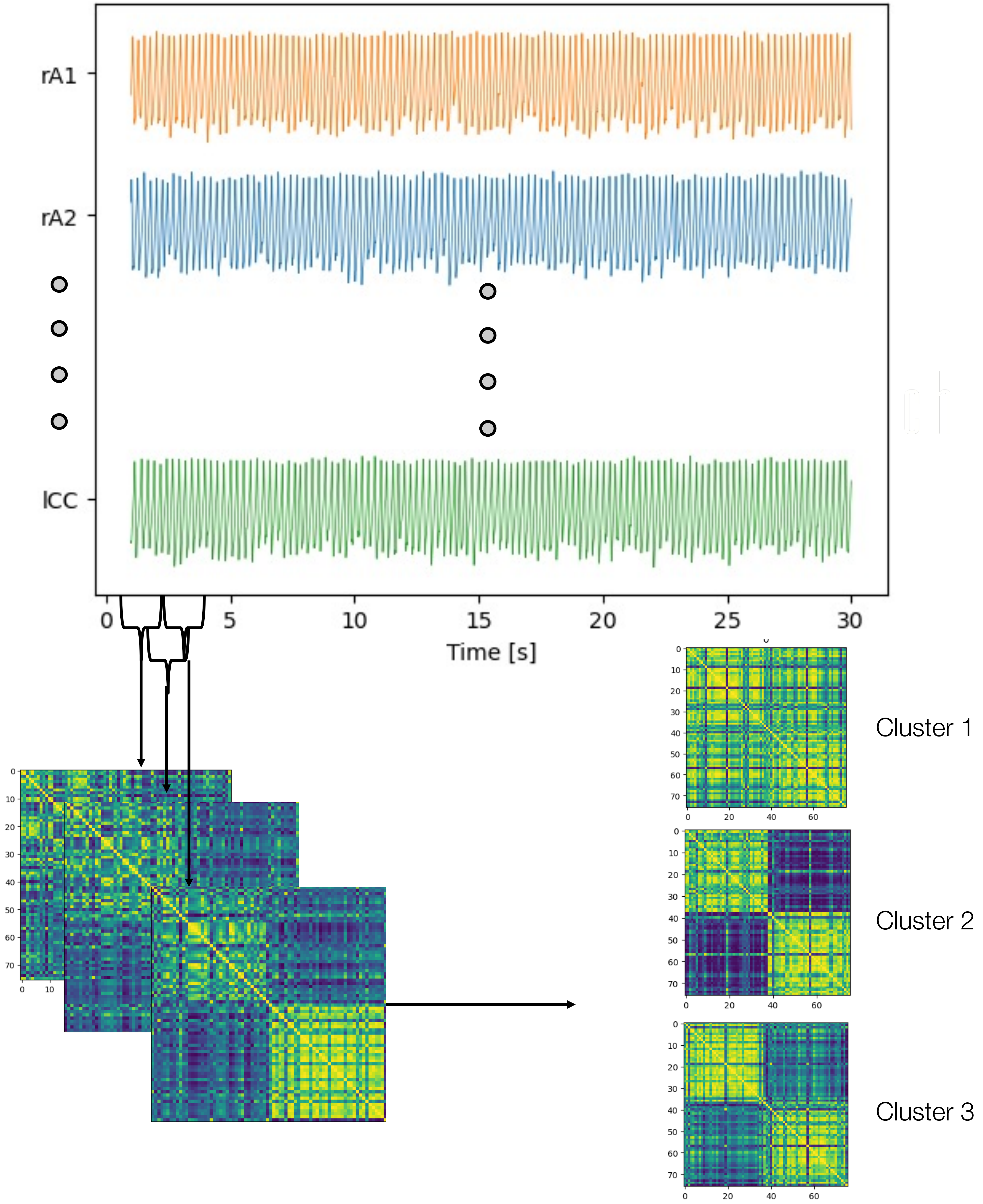
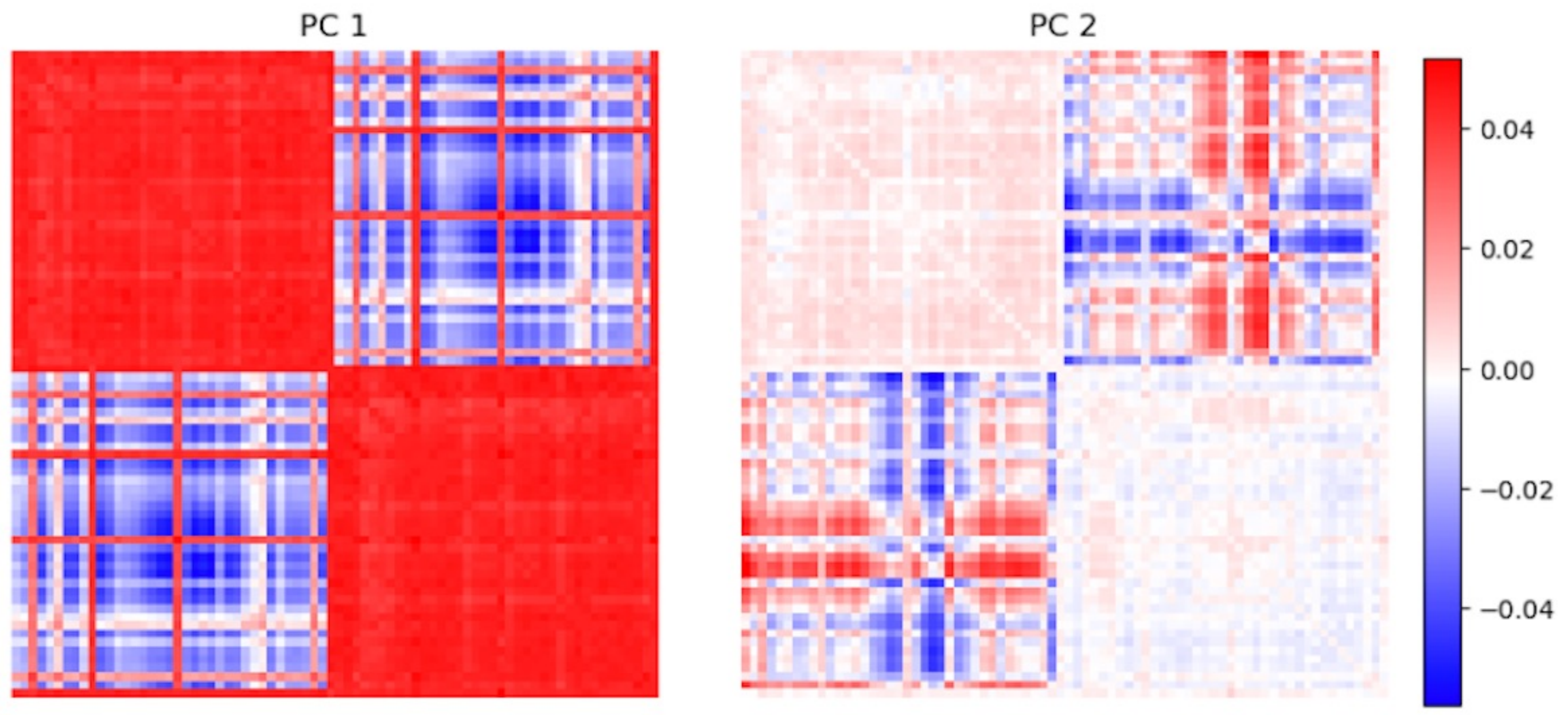
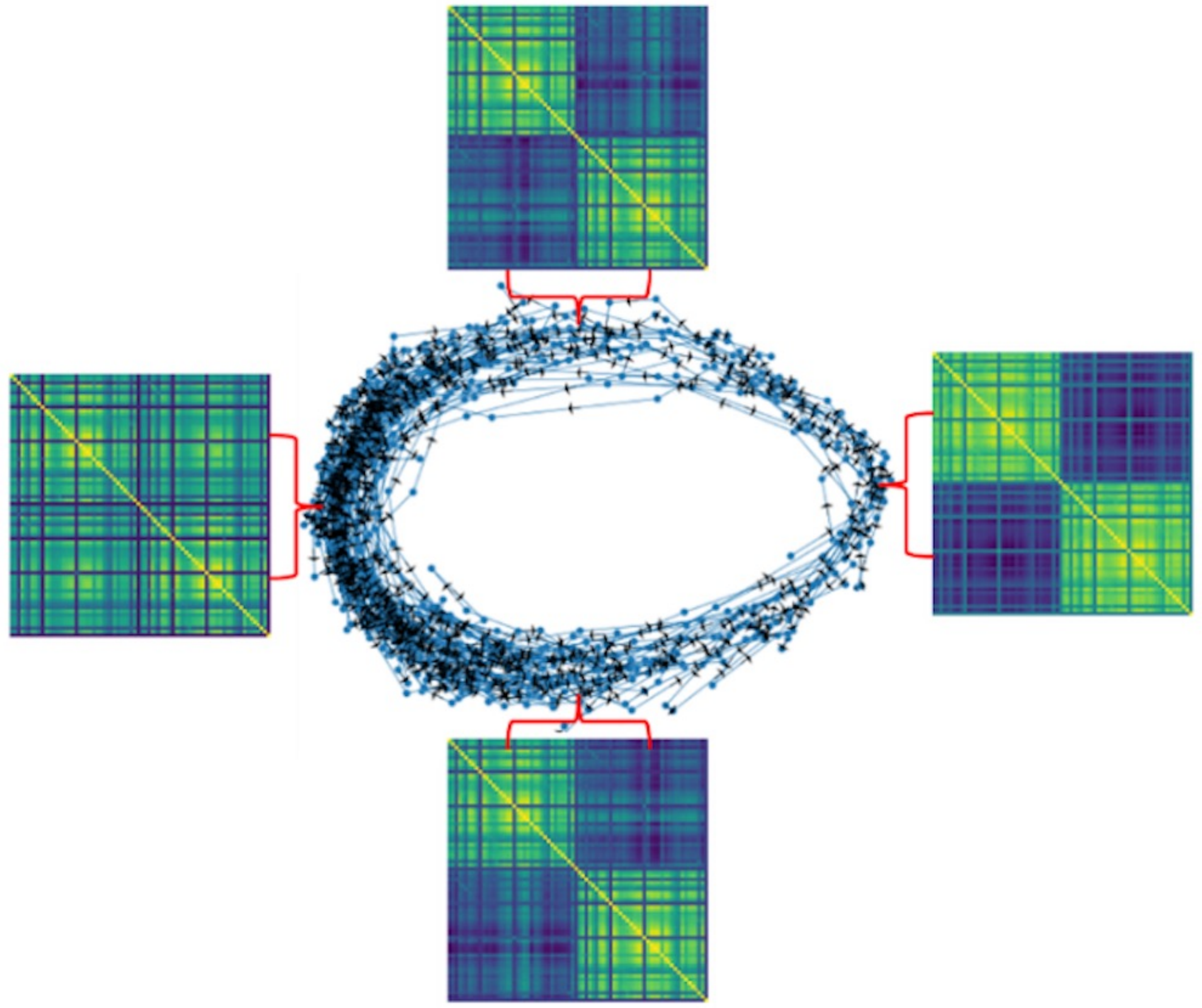
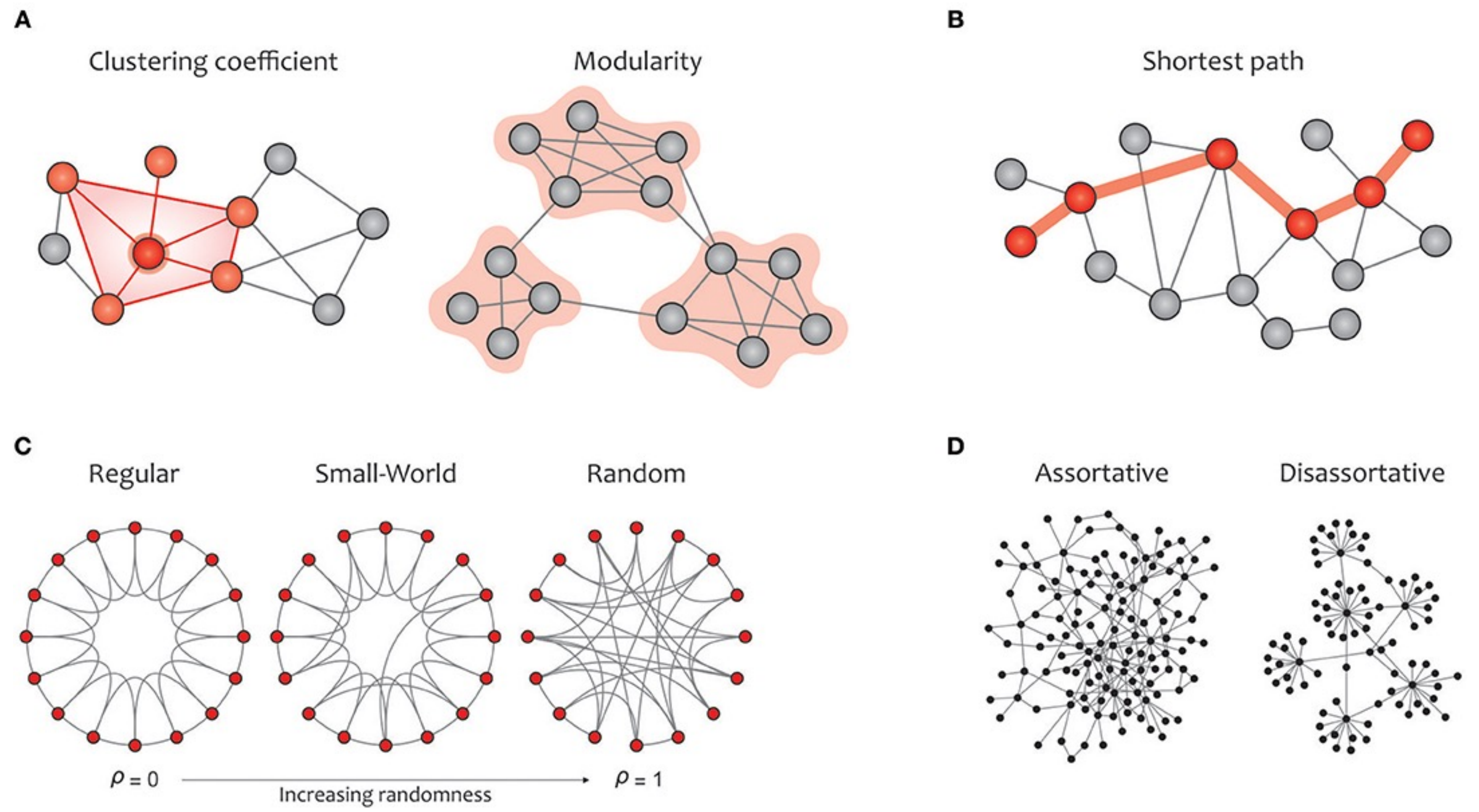
Dynamical Functional Connectivity (DFC) Analysis





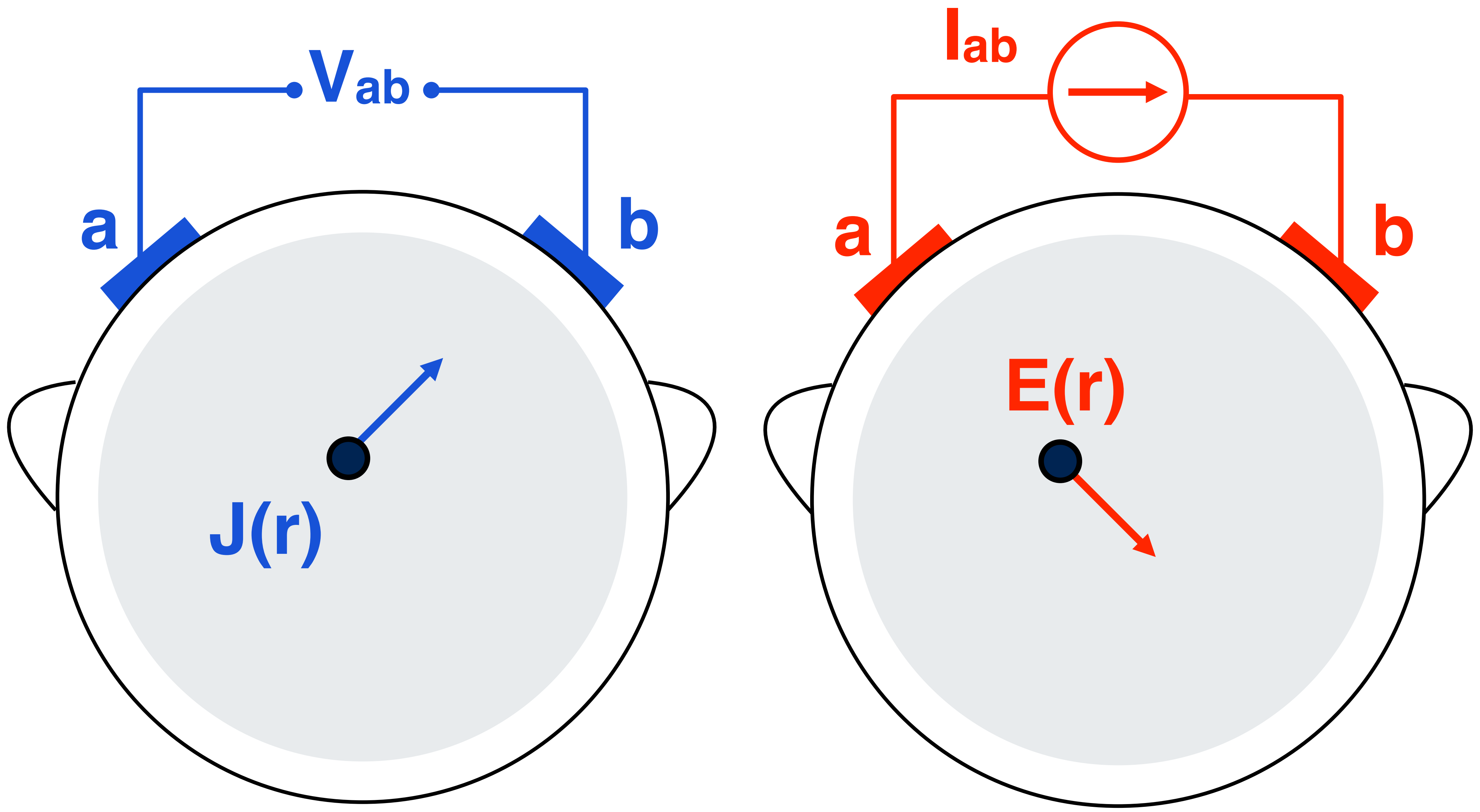


Typical global measures (Farahani, Karwowski, and Lighthall, “Application of Graph Theory for Identifying Connectivity Patterns in Human Brain Networks.”)



Personalized Lead Field Matrices

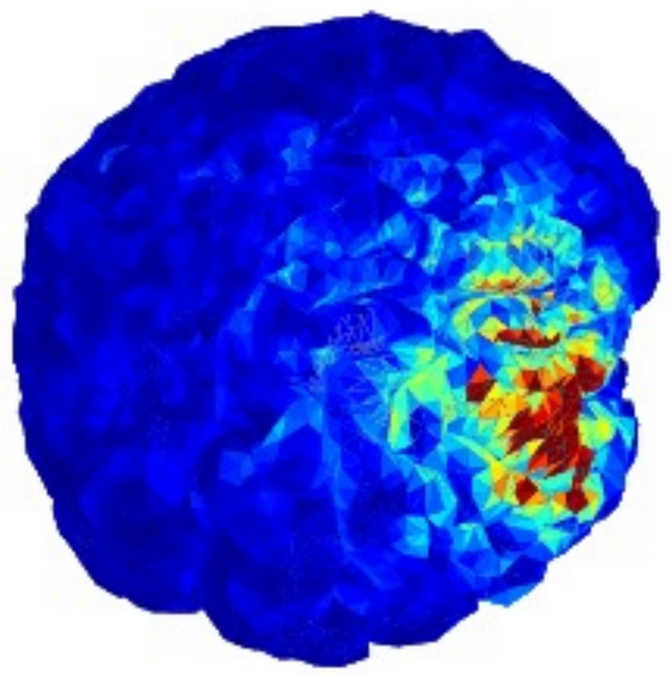
- personalized source-to-sensor mapping (lead field matrix, *M*)
- direct calculation is computationally intensive
  - simulate each dipole as a current source to compute induced voltage on "*n*" EEG electrodes
- reciprocity-based approach
  - apply current between EEG electrodes and compute electric field at sources just once
  - determine a basis (*n-1*) of electrode E-fields
  - simulate desired non-invasive stimulation
  - sample E-field at 'node' locations to obtain *E(r)* → lead field matrix (*n-1* x *#sources*): $M = -E(r)/I_{ab}$



$$V_{ab}\, I_{ab} = -J(r)E(r)$$

#simulation = #sources (~10k)

#simulation = #sensors (~100)



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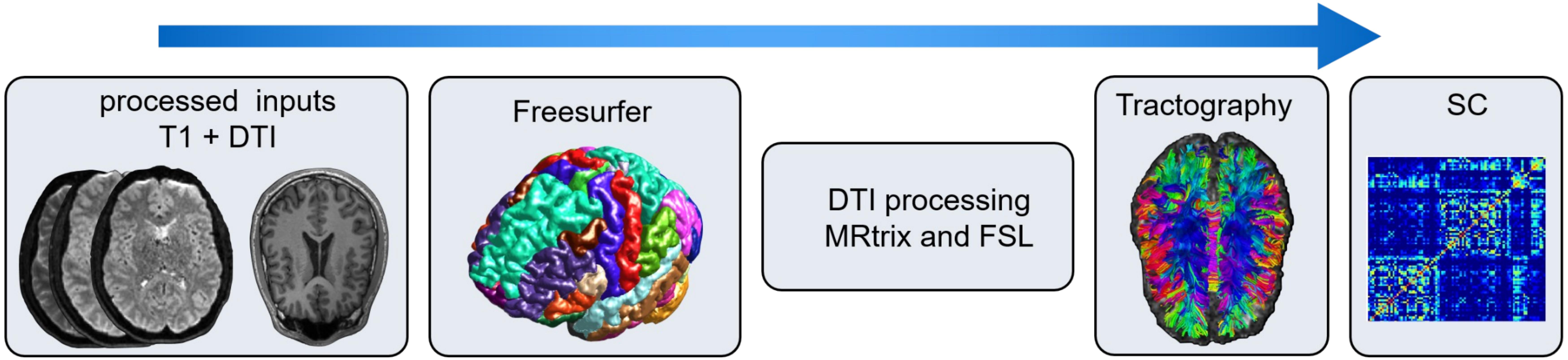
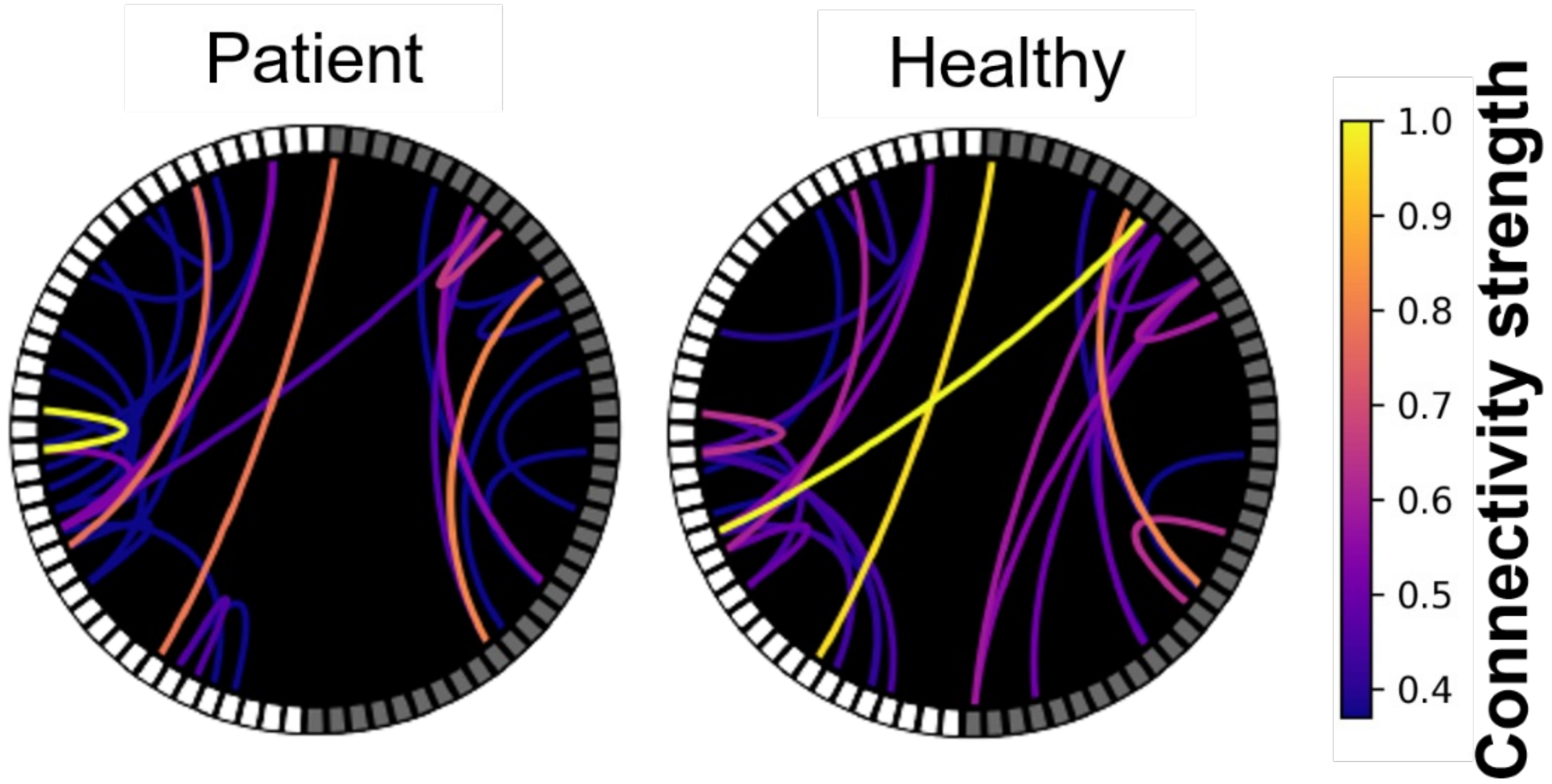
Network Personalization

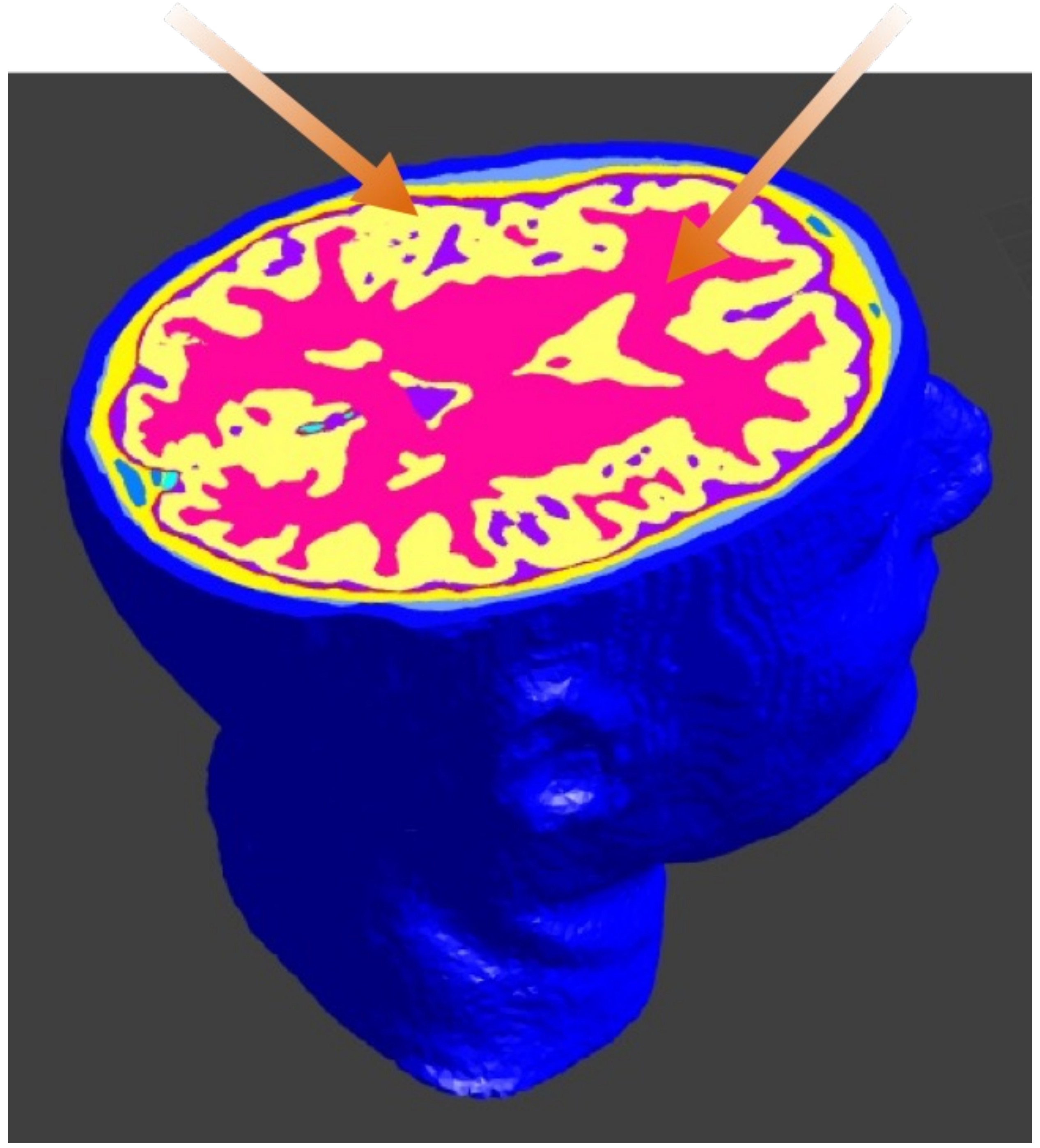


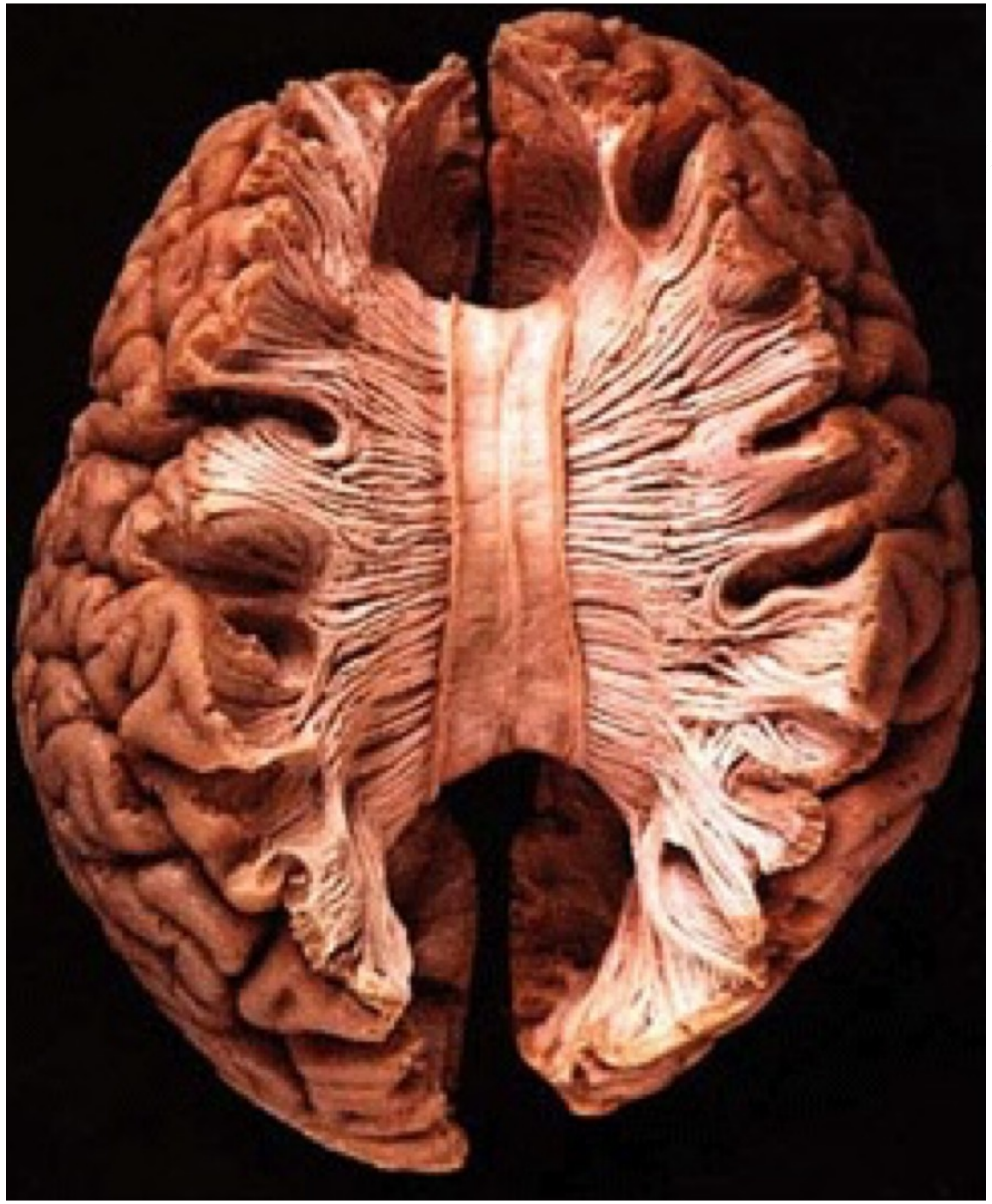


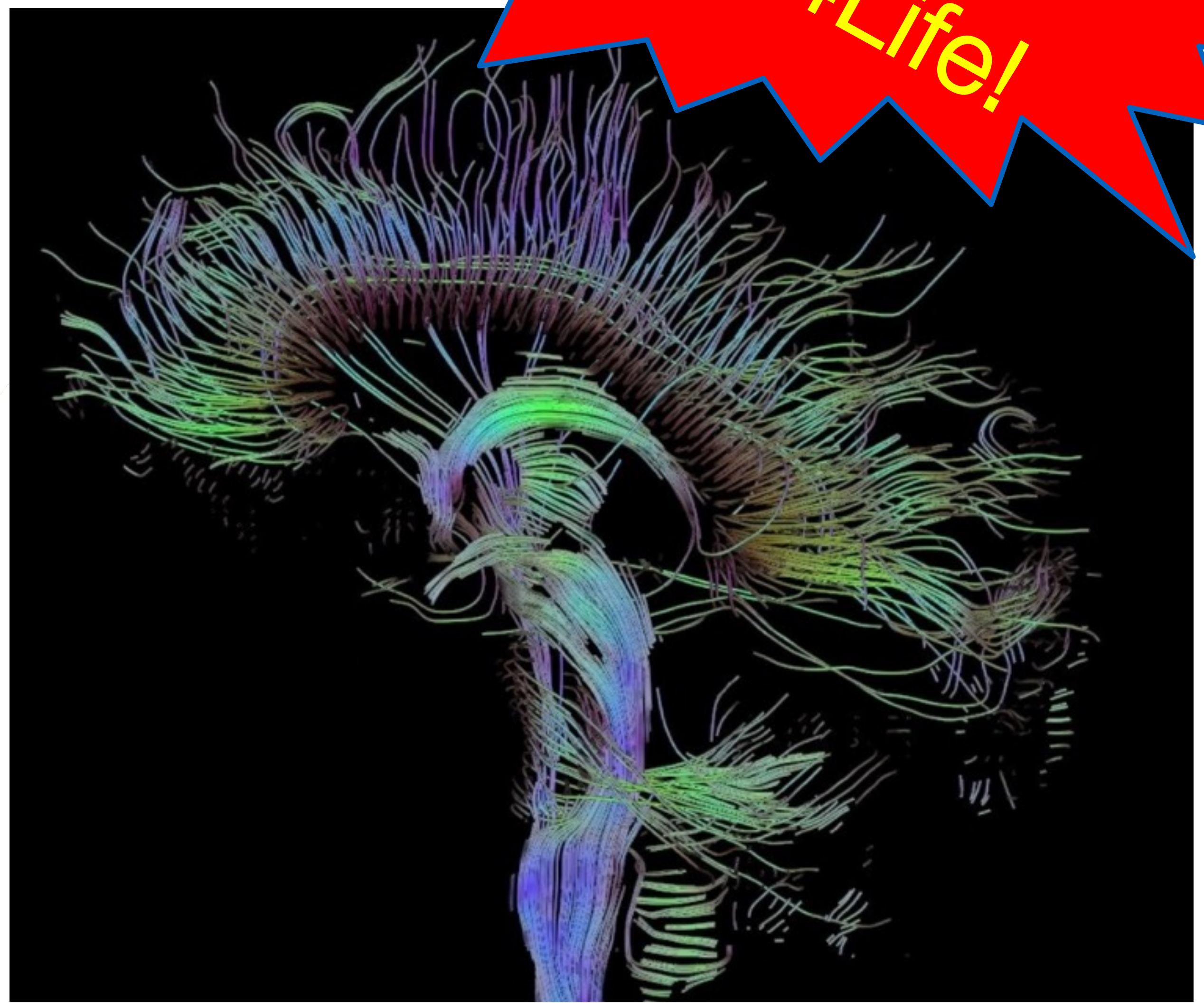
- Fiber tractography can be used to infer the connection strengths (SC) between nodes in a brain-wide NMM
- Left: SC for a stroke patient versus a healthy subject; each rectangle at the circle's perimeter represents a brain region. Note the missing connections in the stroke patient due to cortical lesions.

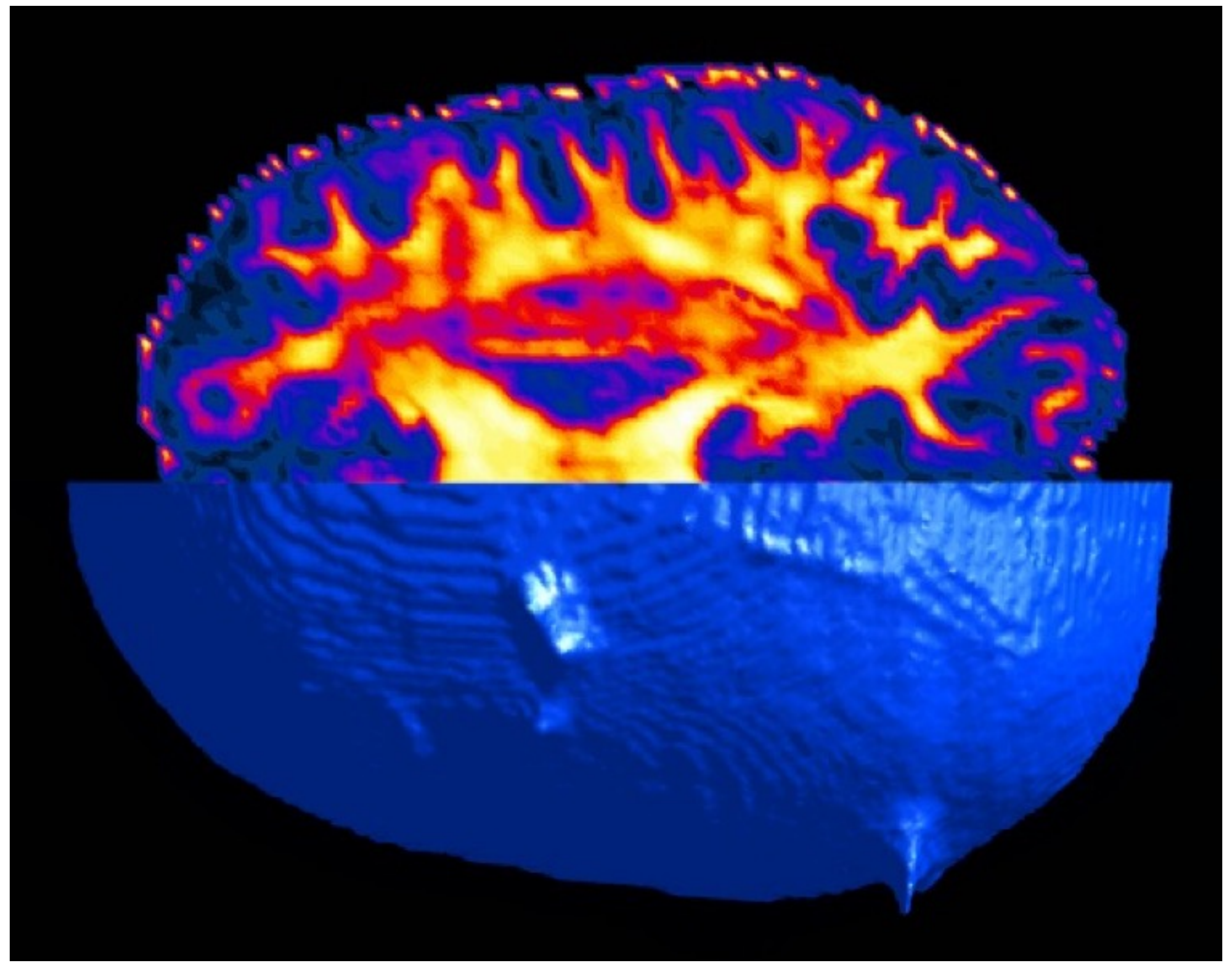
DTI-based Conductivity Maps for White Matter

Now in Sim4Life!







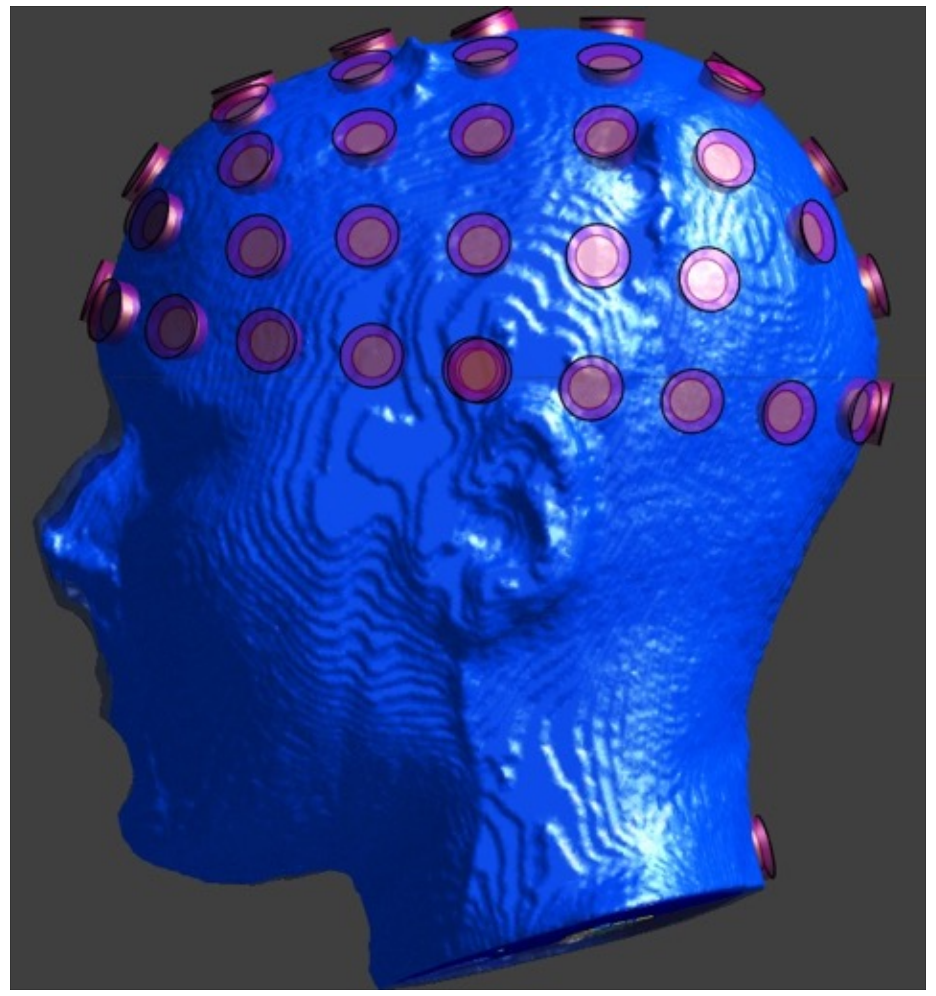


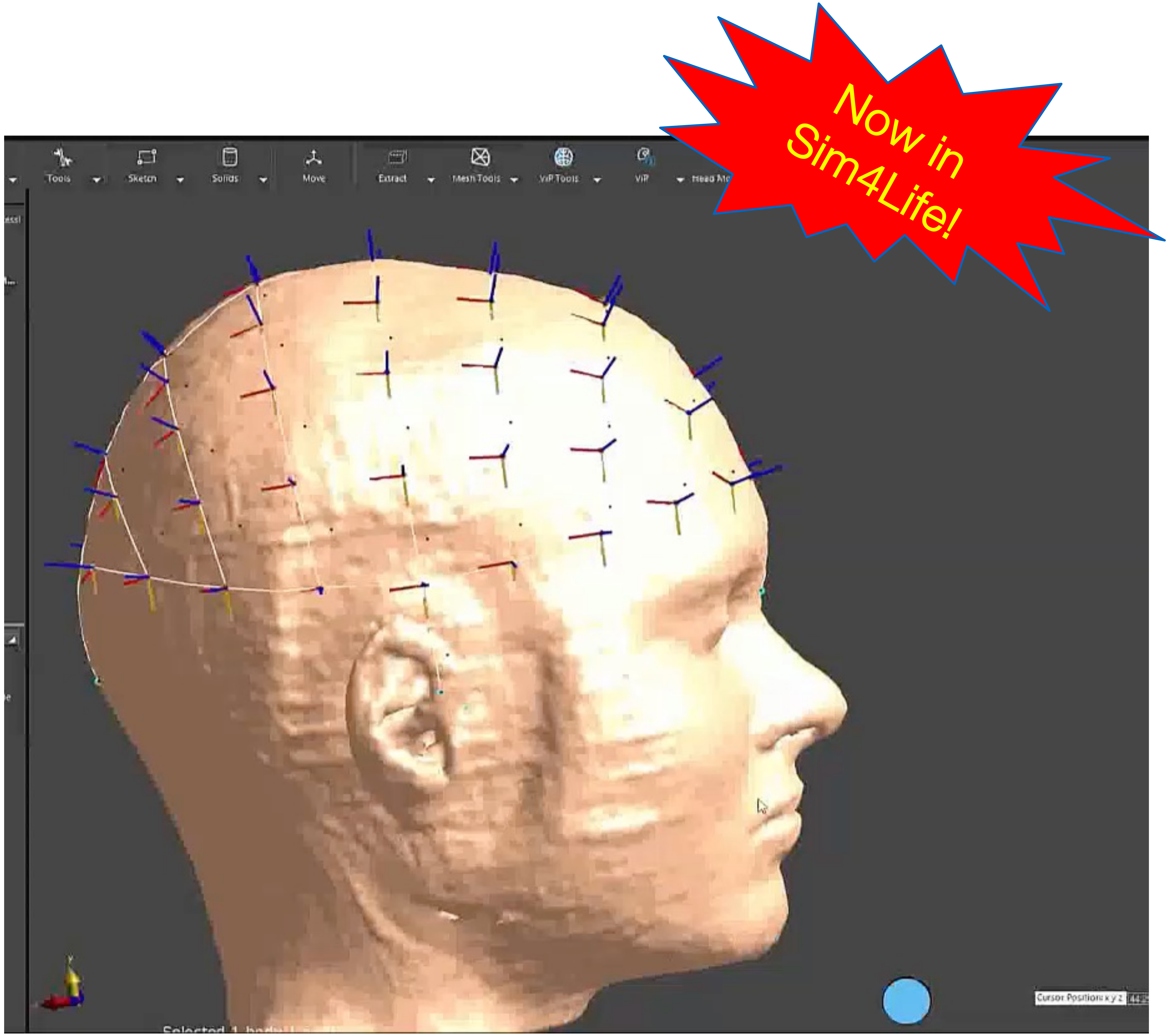
-
- DTI → anisotropic conductivity map*

* Tuch et al, "Conductivity mapping of biological tissue using diffusion MRI."

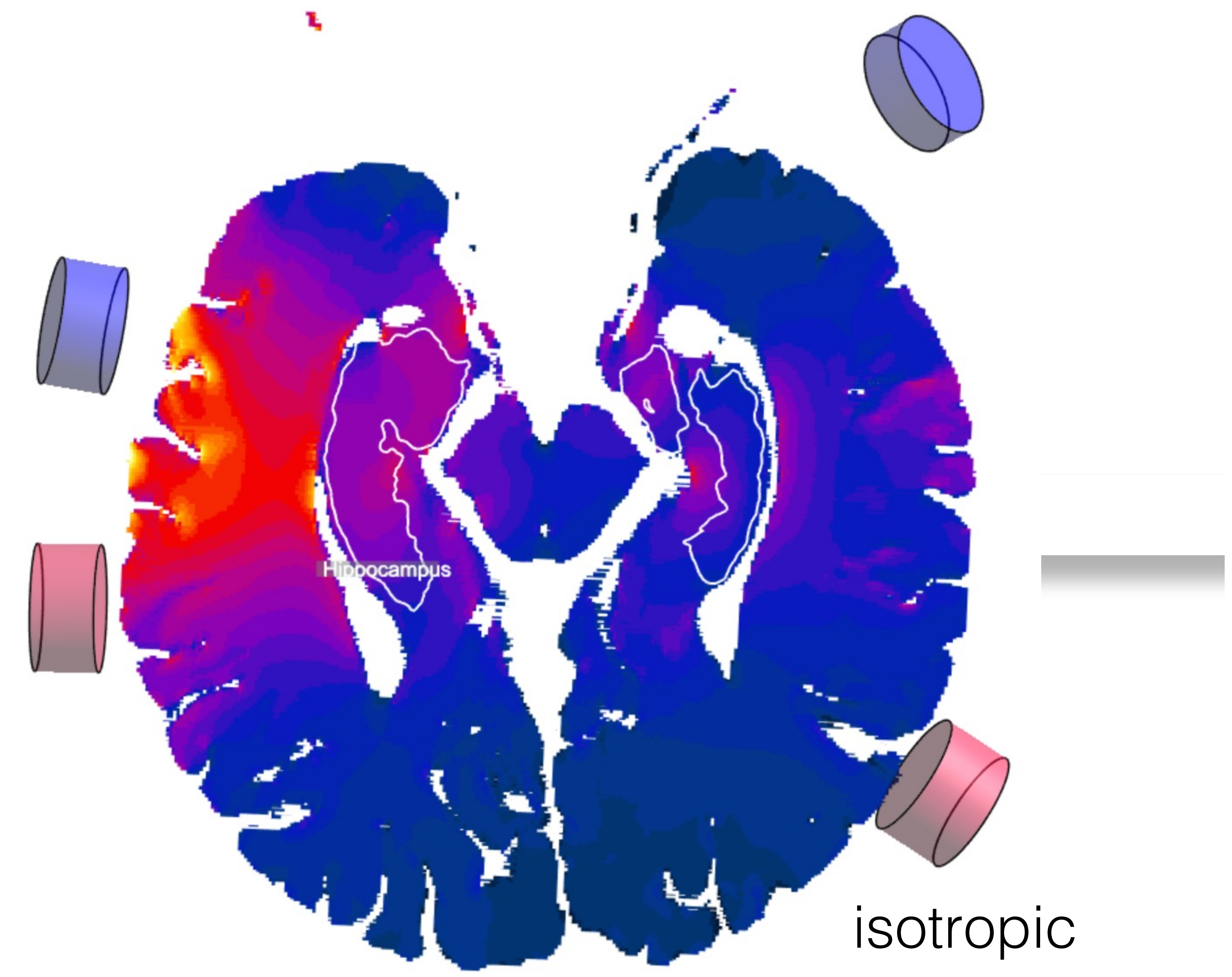
Electrode Placement

- AI identifies 4 fiducial points
  - nasion
  - inion
  - LPA
  - RPA
- automatic 10-10 system identification
- electrode placement

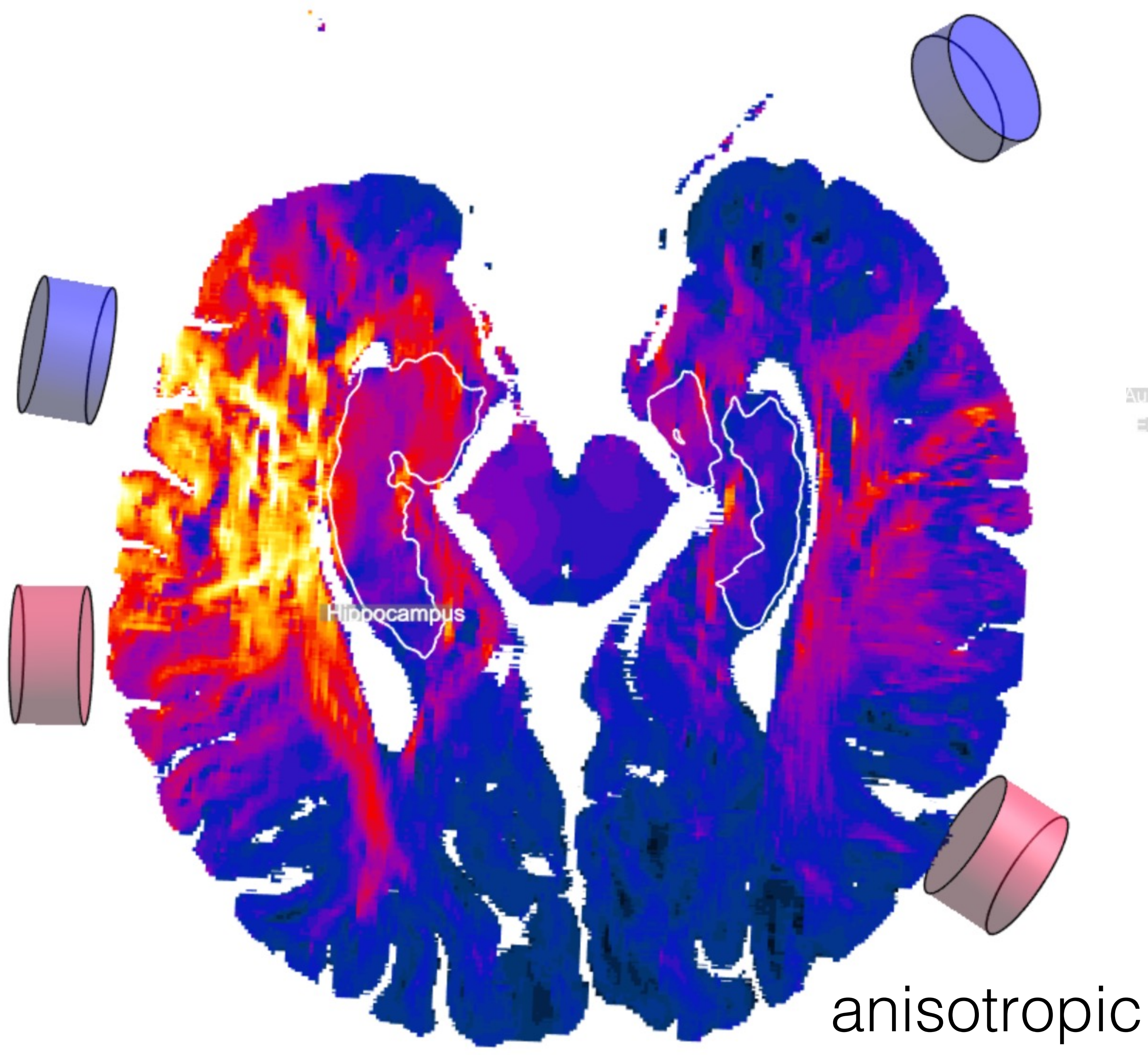




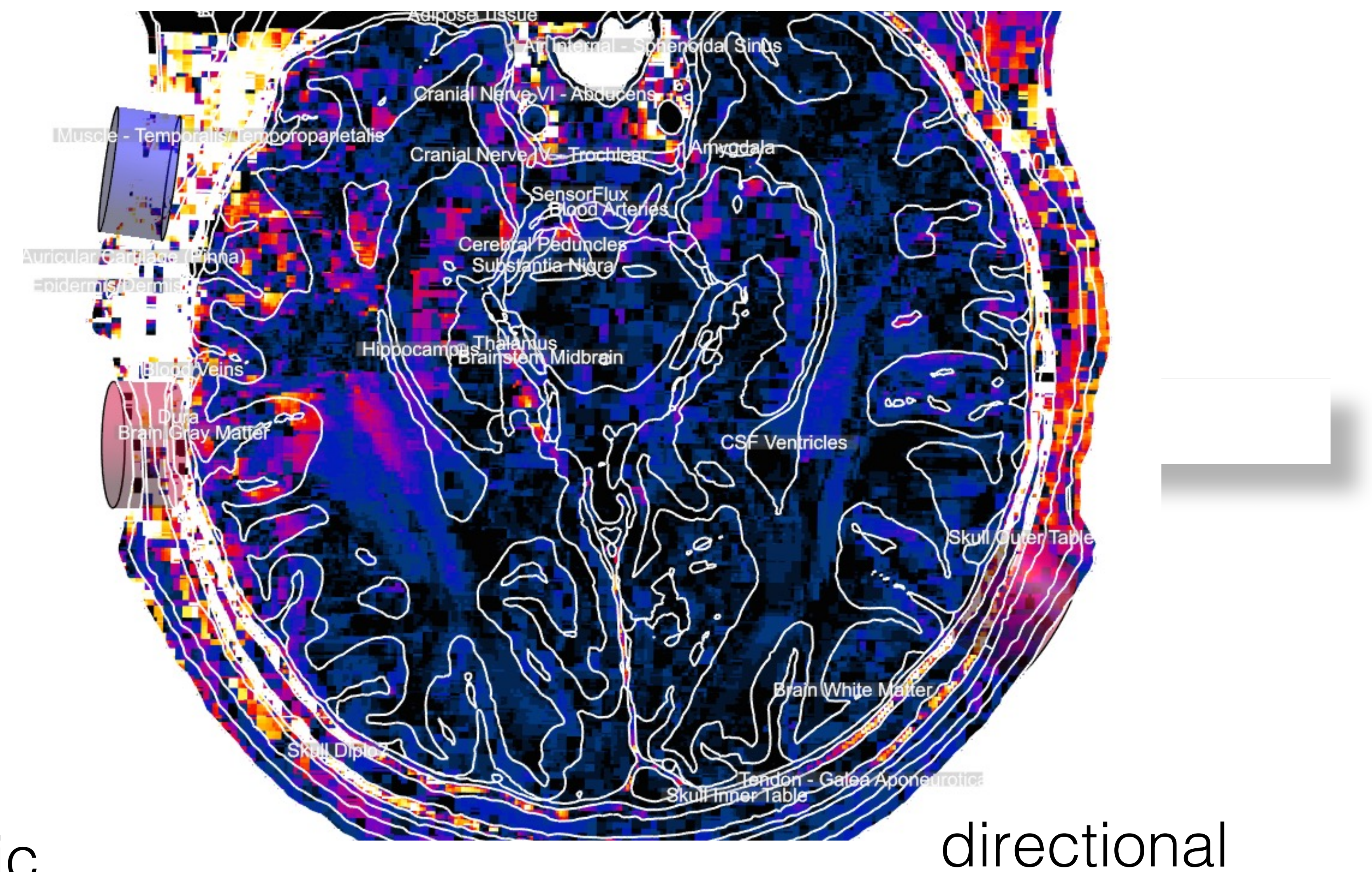
Tissue Anisotropy



isotropic



anisotropic



directional

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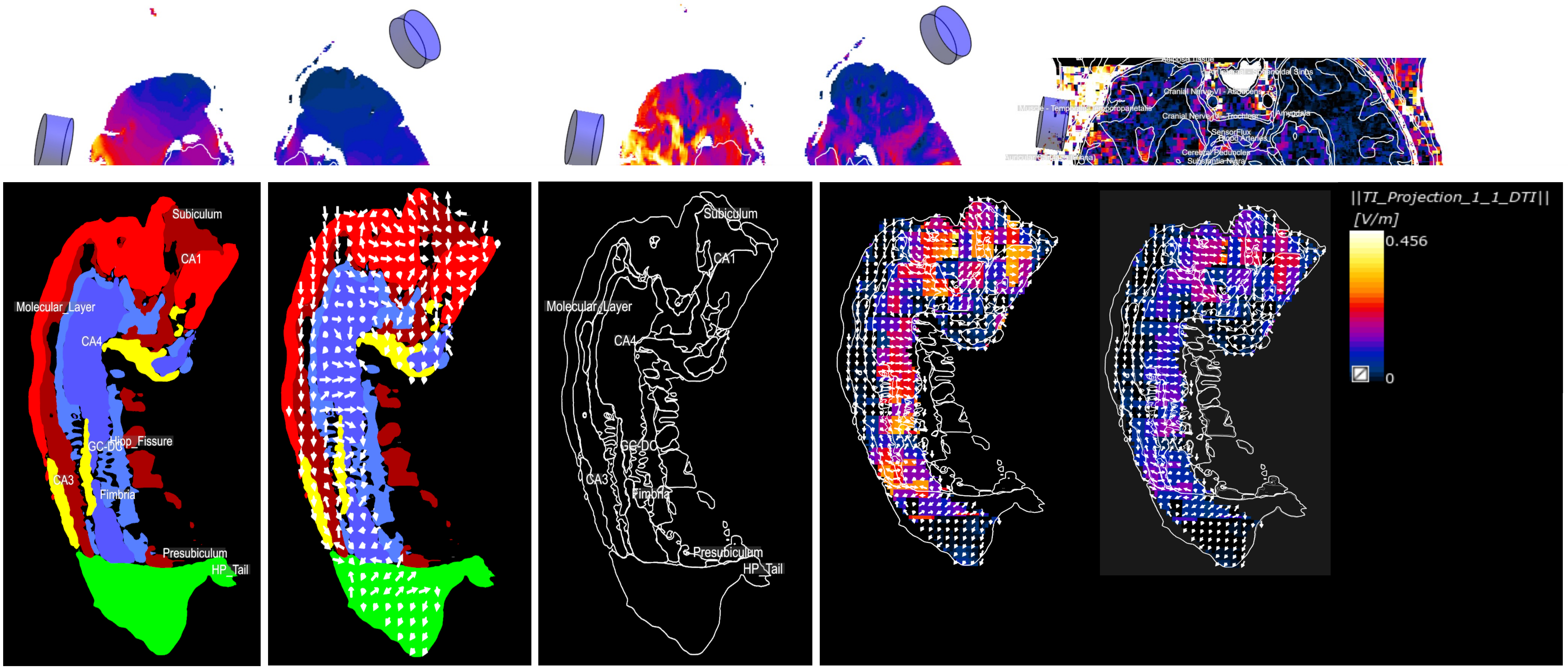
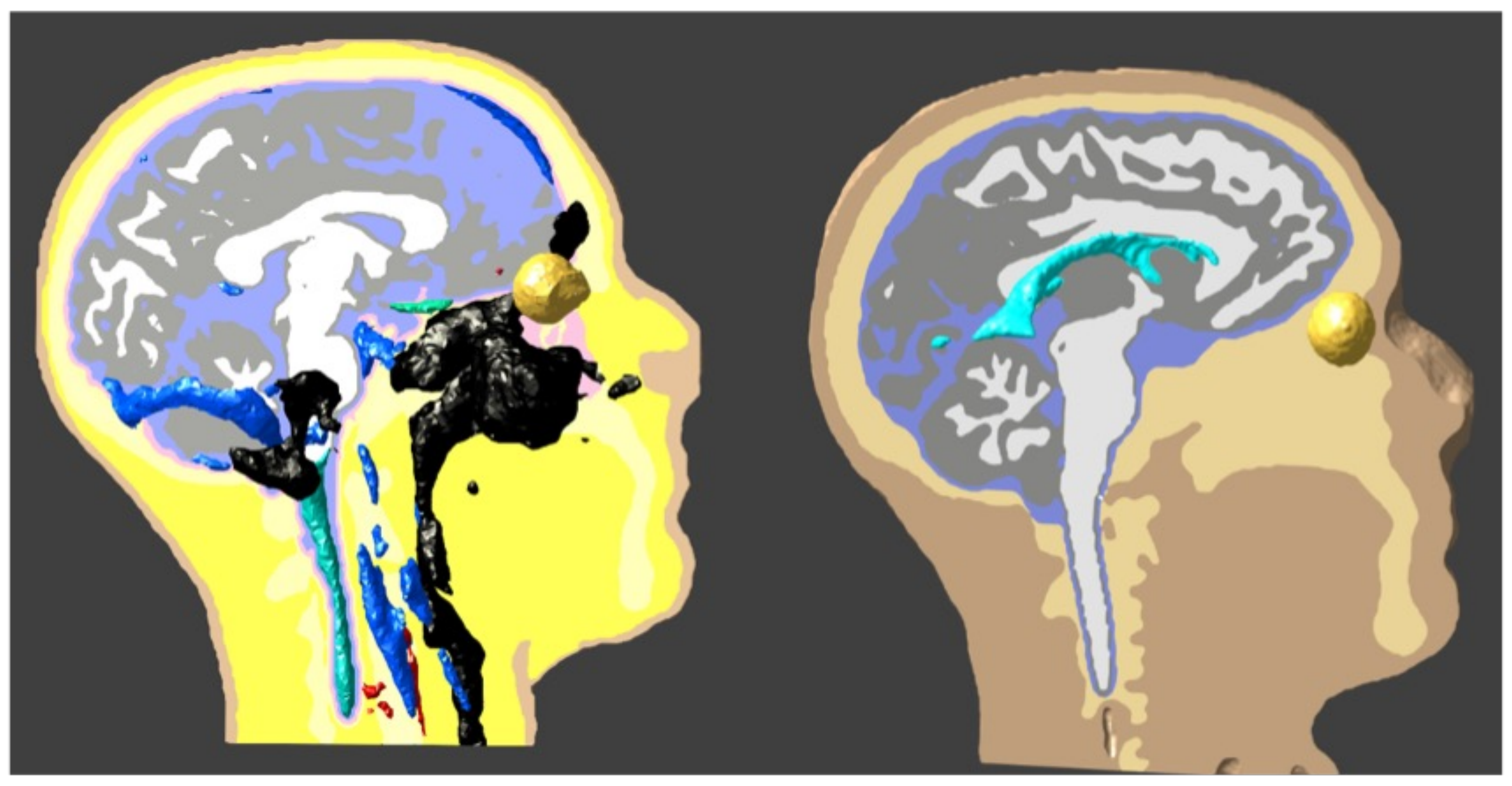
Tissue Anisotropy



Labels DTI Directions Contours TI Directional Projection

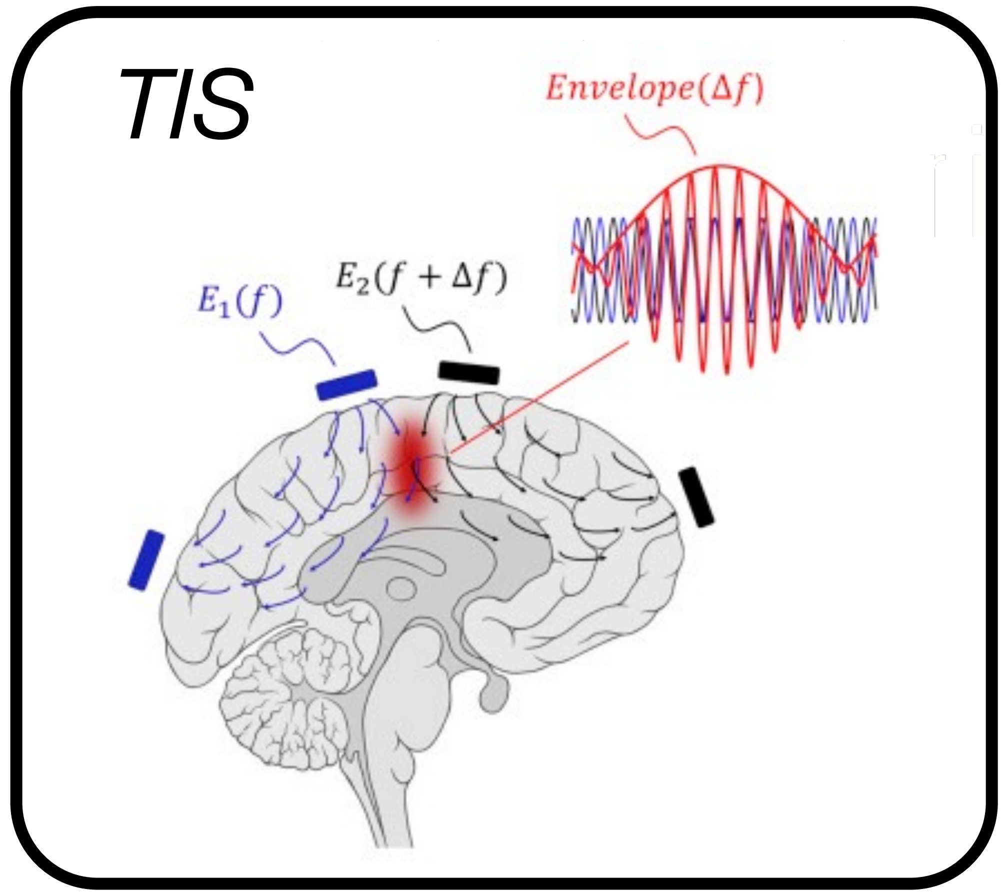
Restoring Healthy Brain Patterns

personalized head & brain models

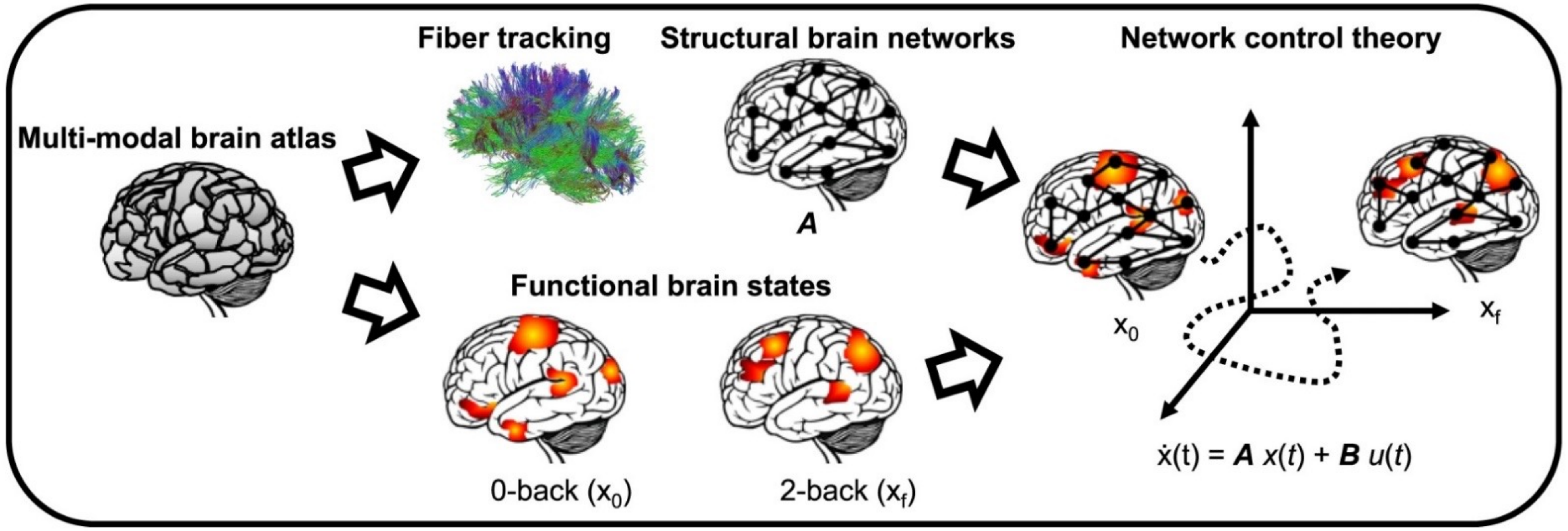


optimal non-invasive exposure

Grossman *et al.* (2017)

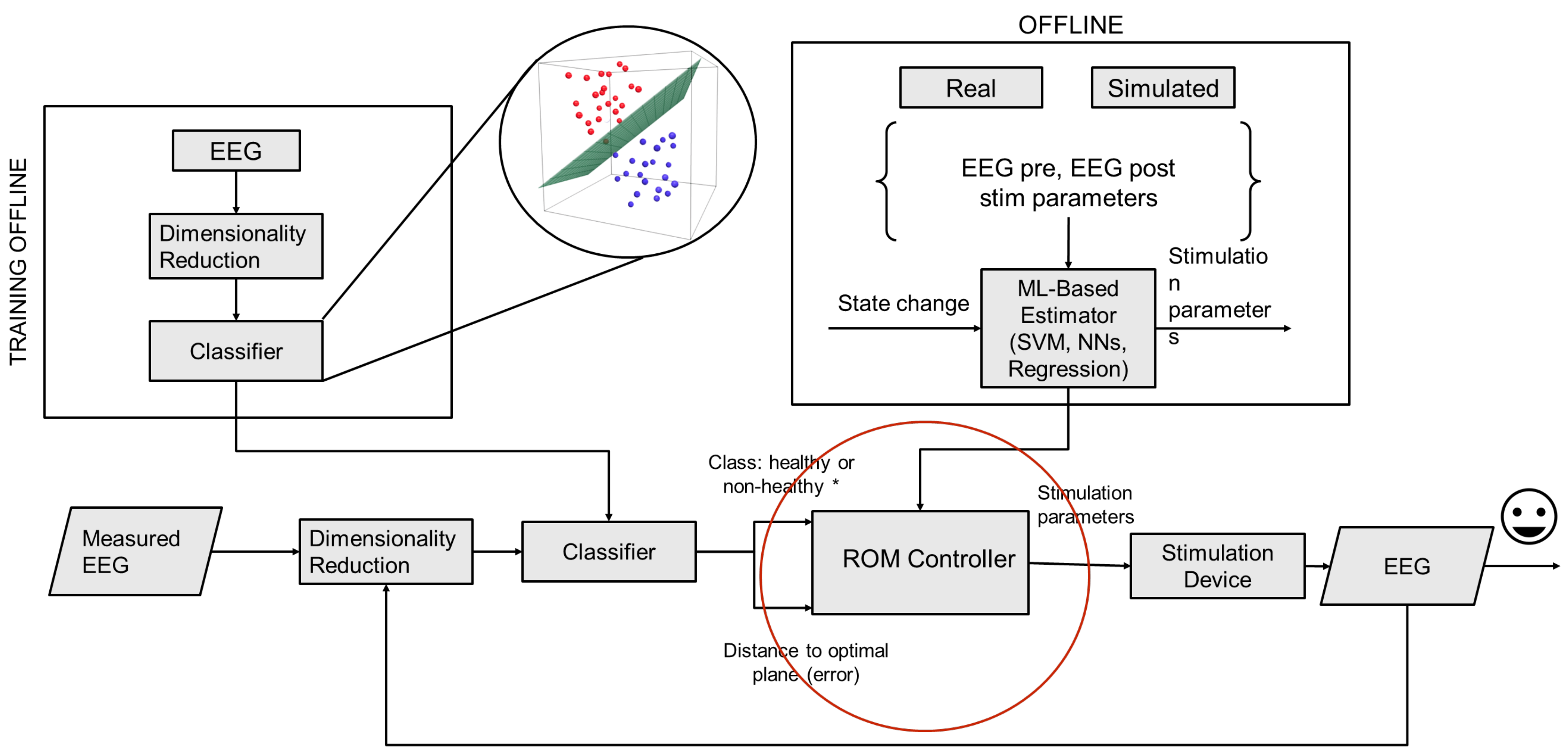


closed-loop network control



Braun *et al.* (2021)

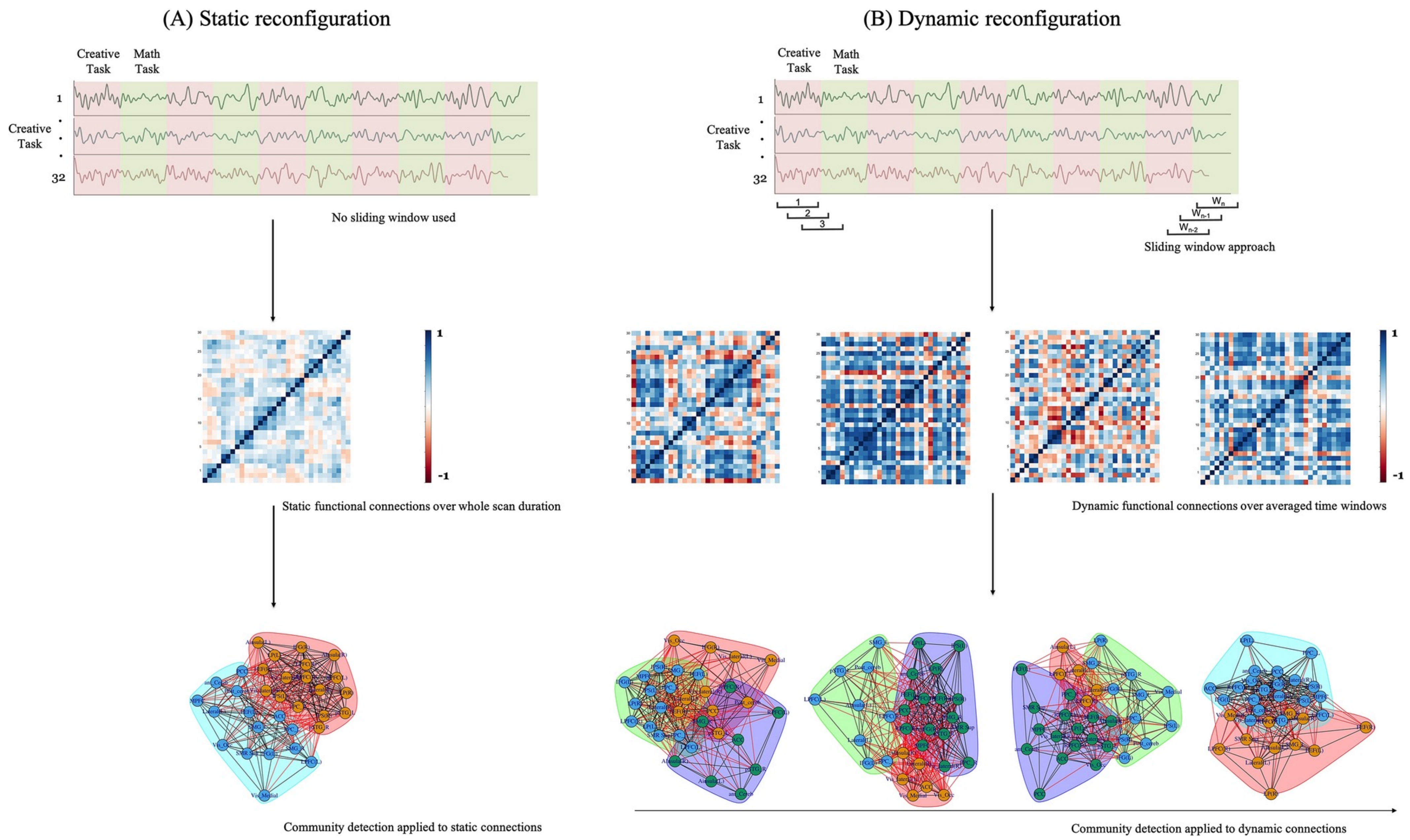
State-Synchronized Control



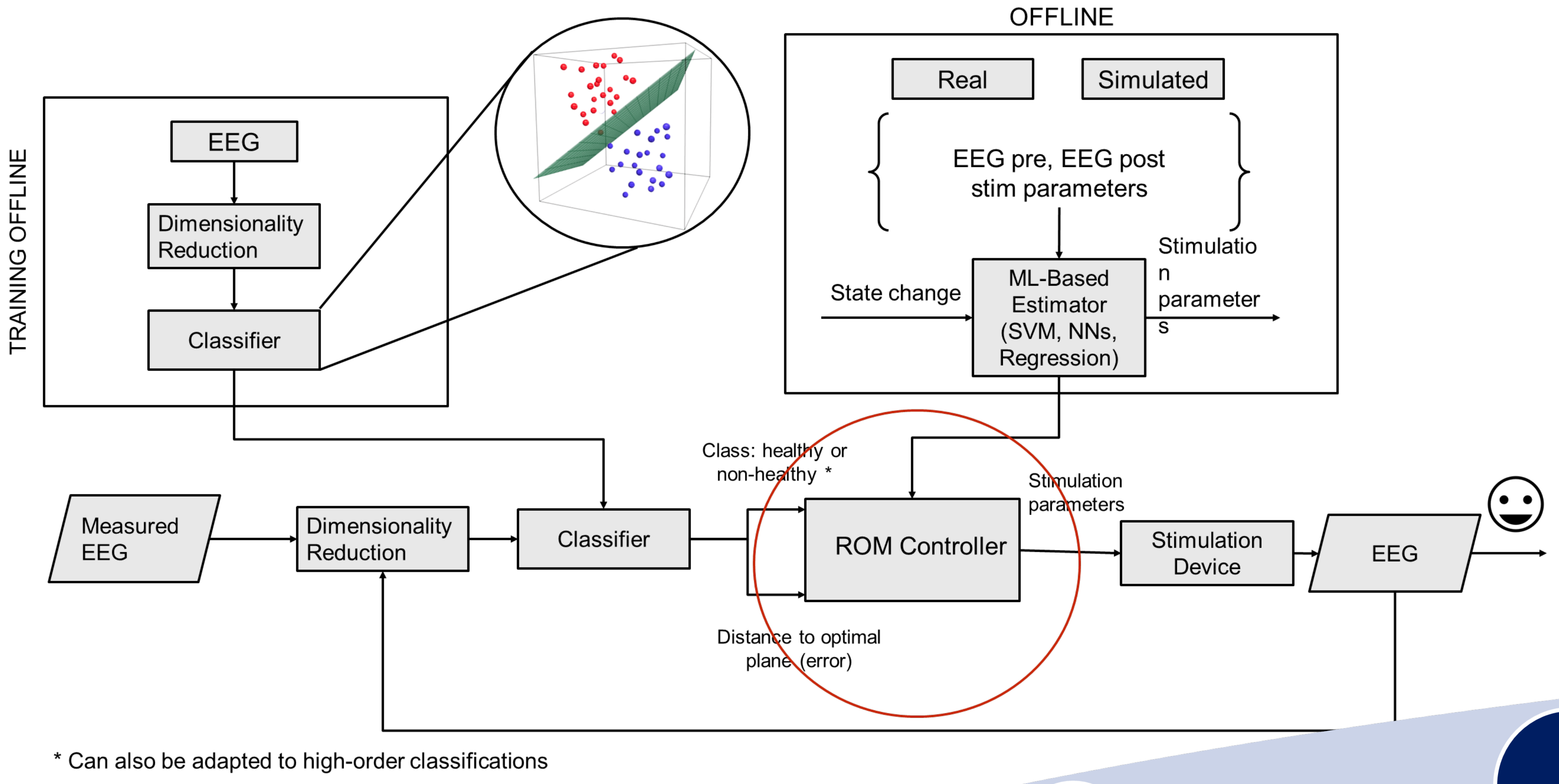
* Can also be adapted to high-order classifications

- State-driven control architectures for closed-loop neurostimulator design

- High-level brain fluidity metrics (e.g., dynamic functional connectivity) can be used to quantify “healthy” activity patterns

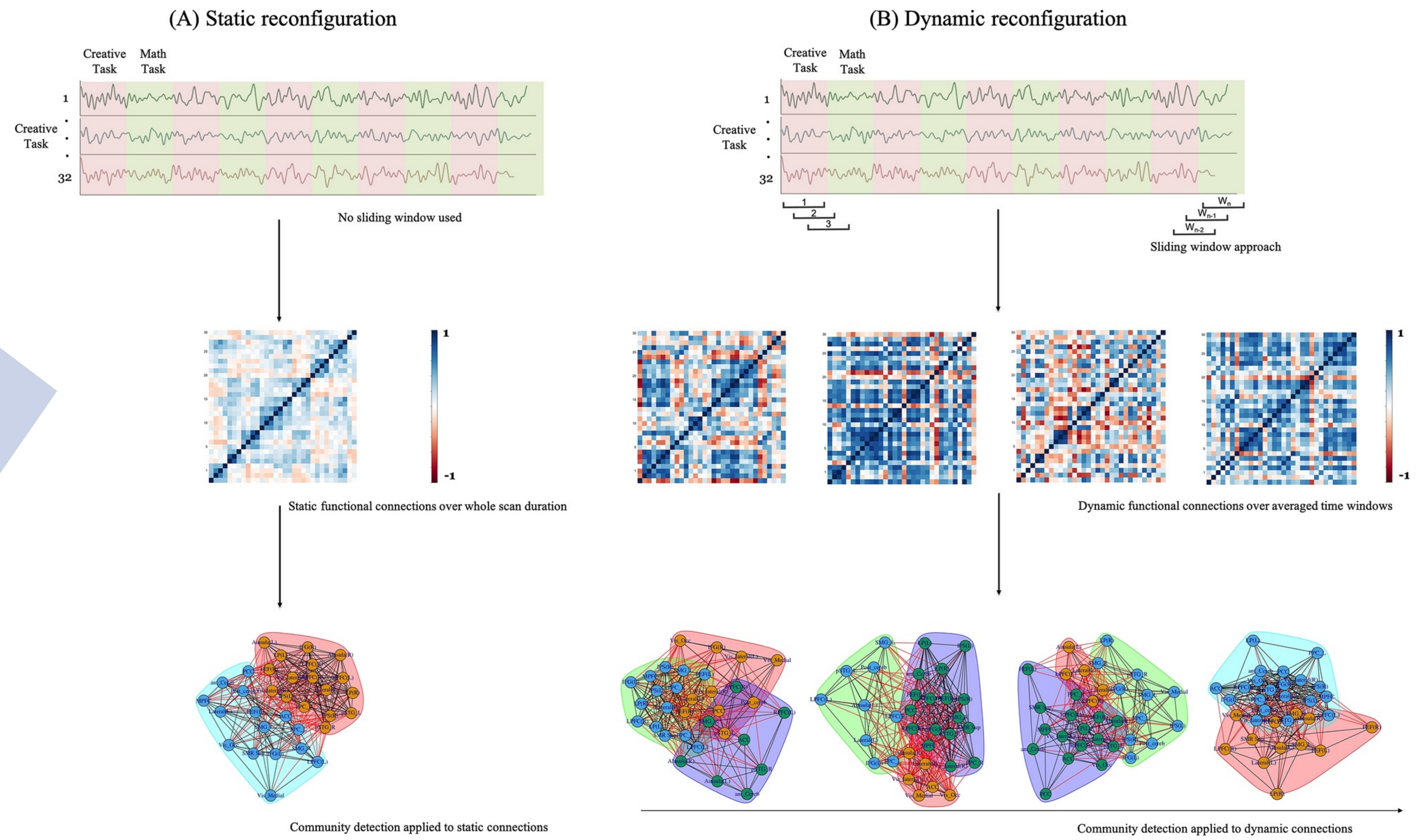


State-Synchronized Control

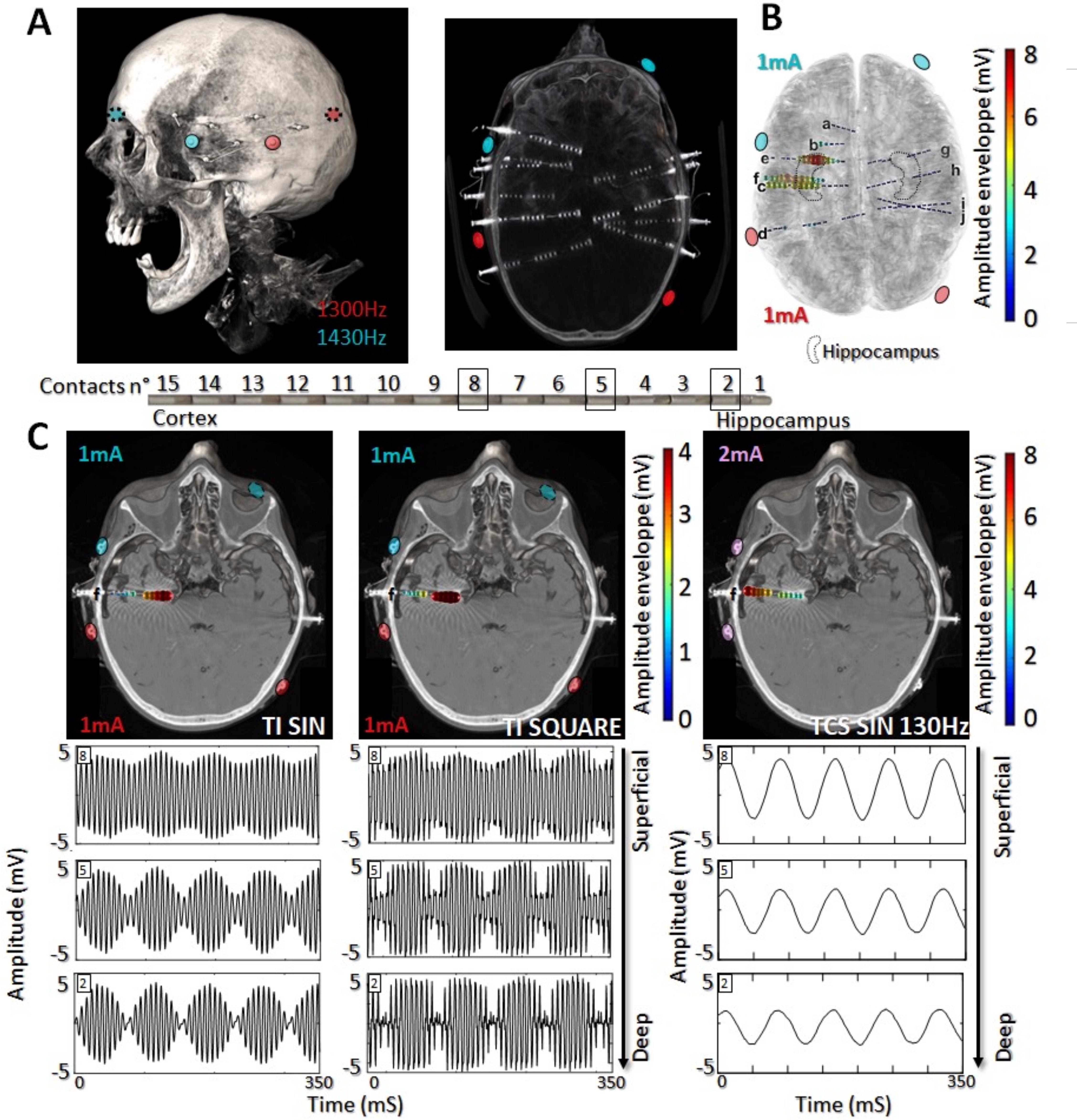


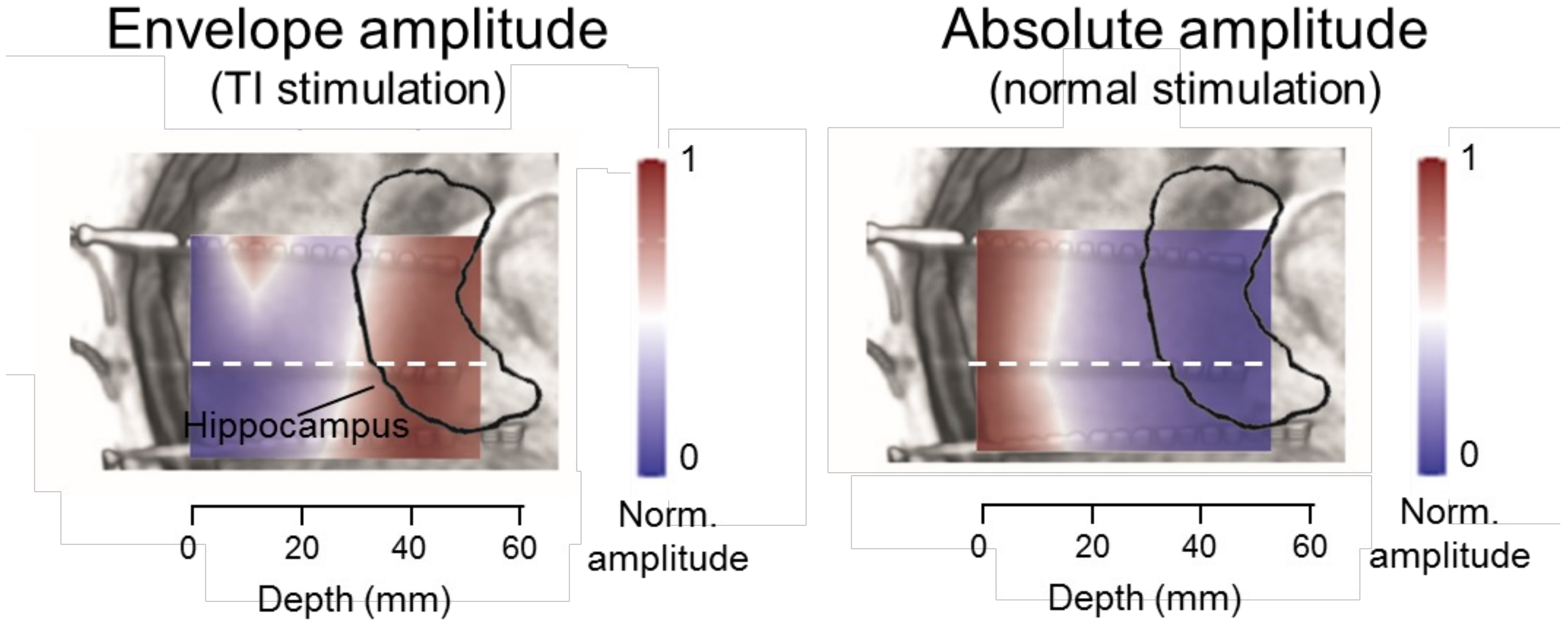
- Characterization of the healthy and pathological state
- Distance metrics to define how to drive brain to health state
- Define the base parameters for the stimulation of each patient
- Refine the parameters depending on the current state and the distance to the predefined healthy state

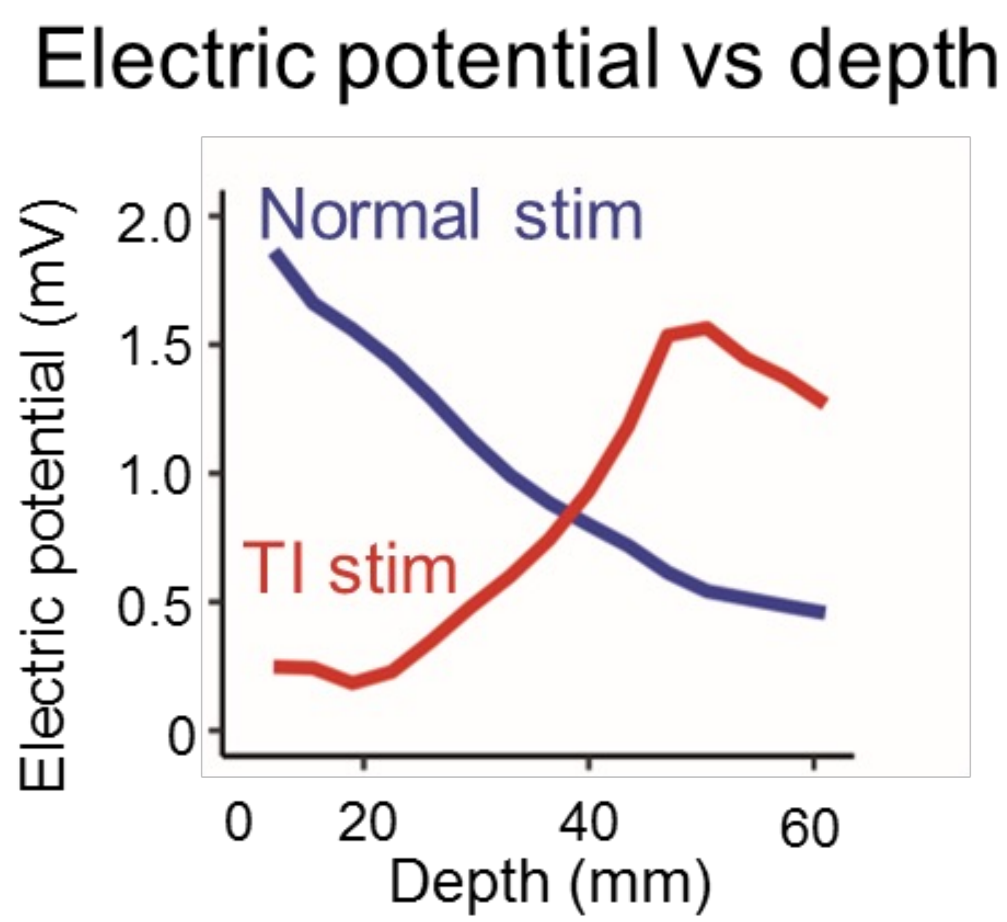
- High-level brain fluidity metrics (e.g., dynamic functional connectivity) can be used to quantify “healthy” activity patterns



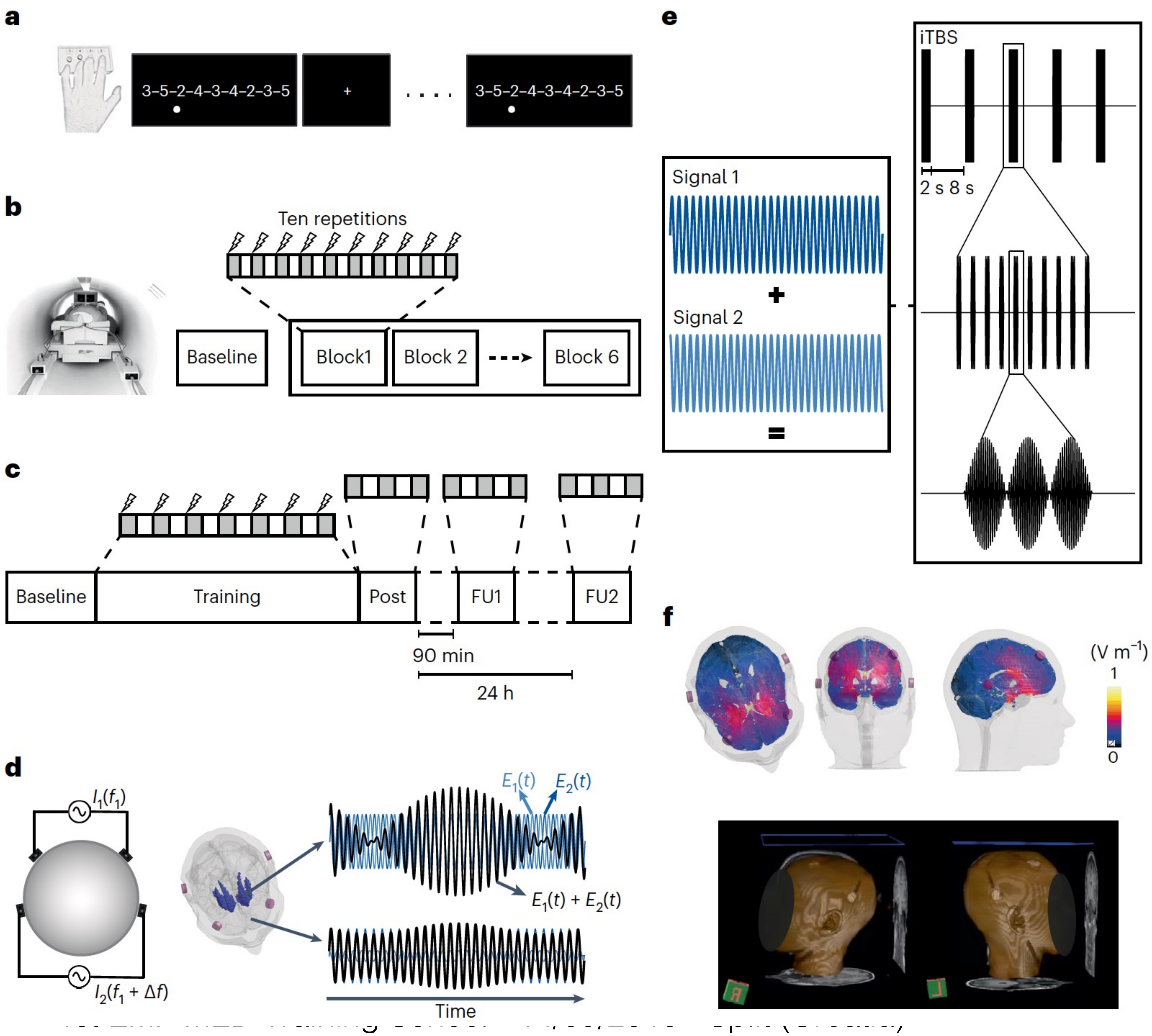
Experimental Validation of Exposure Predictions

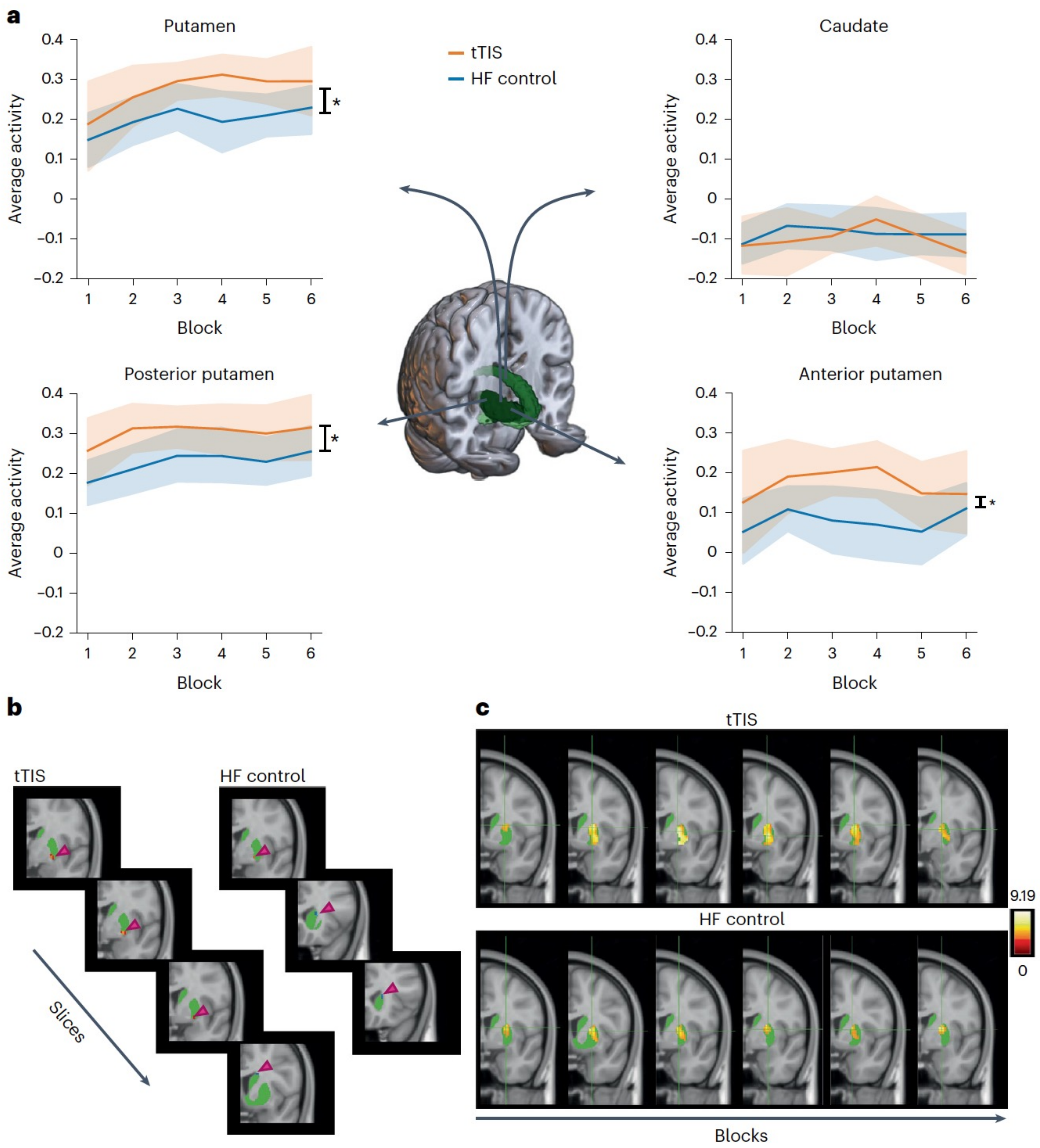






Noninvasive theta-burst stimulation of the human striatum enhances striatal activity and motor skill learning





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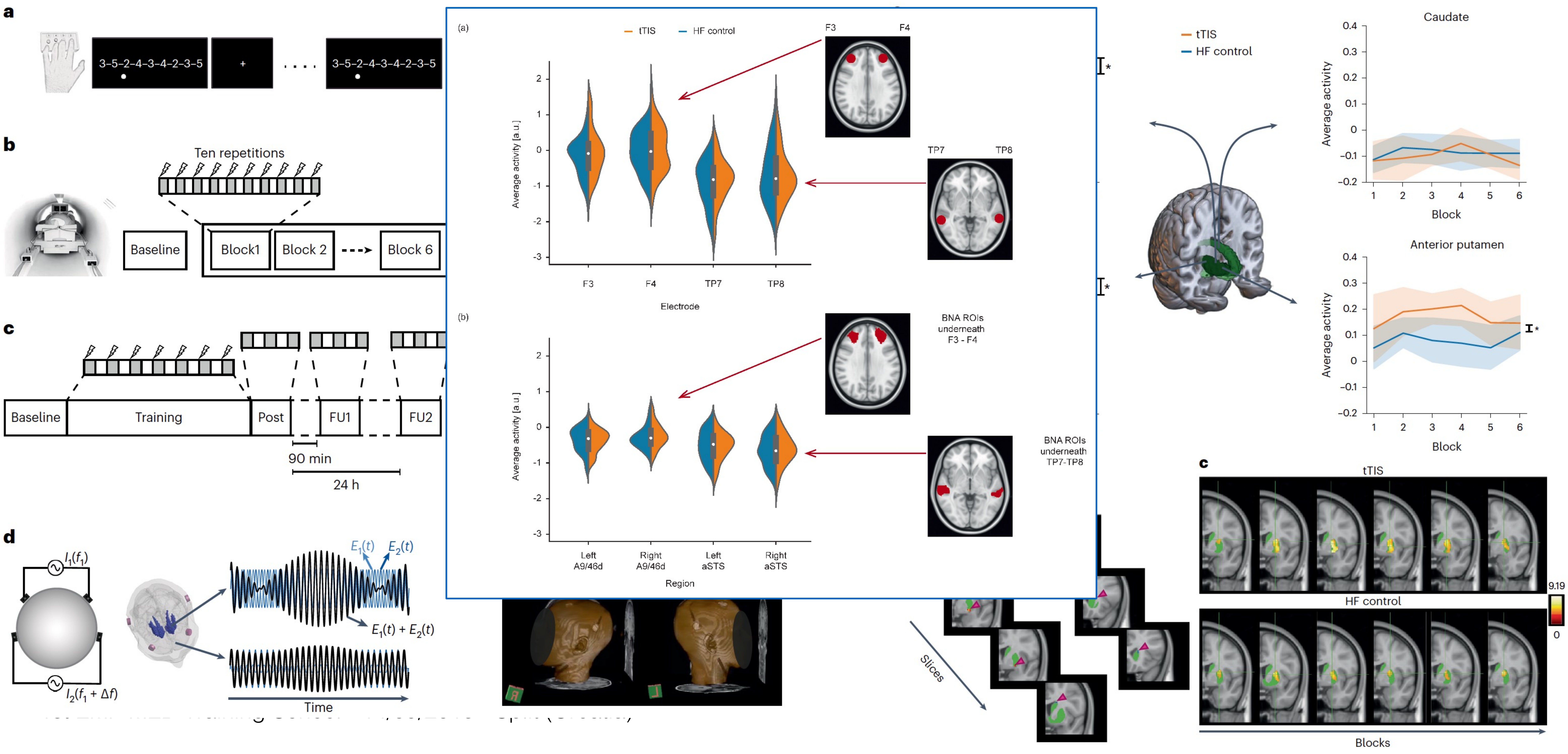

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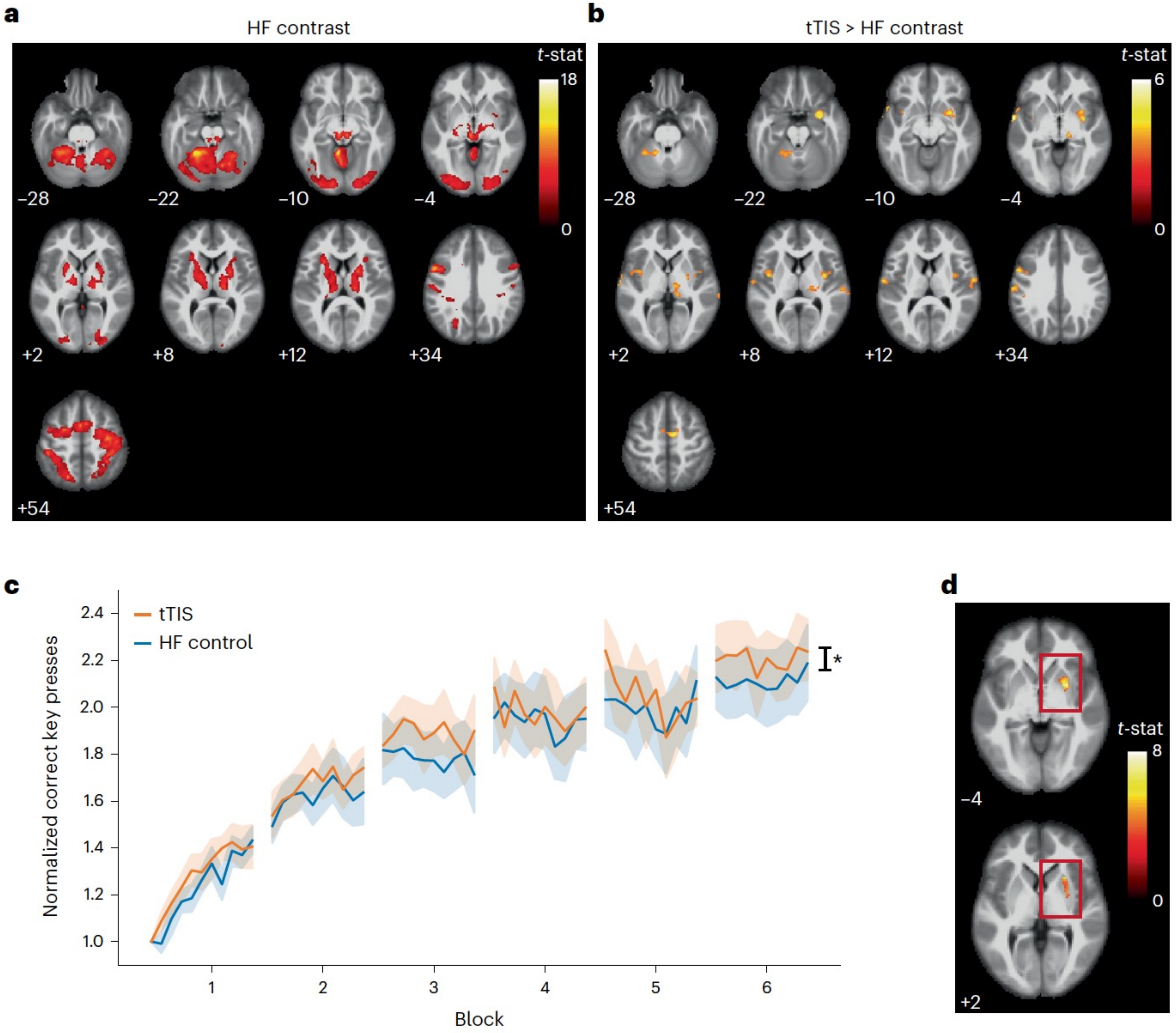

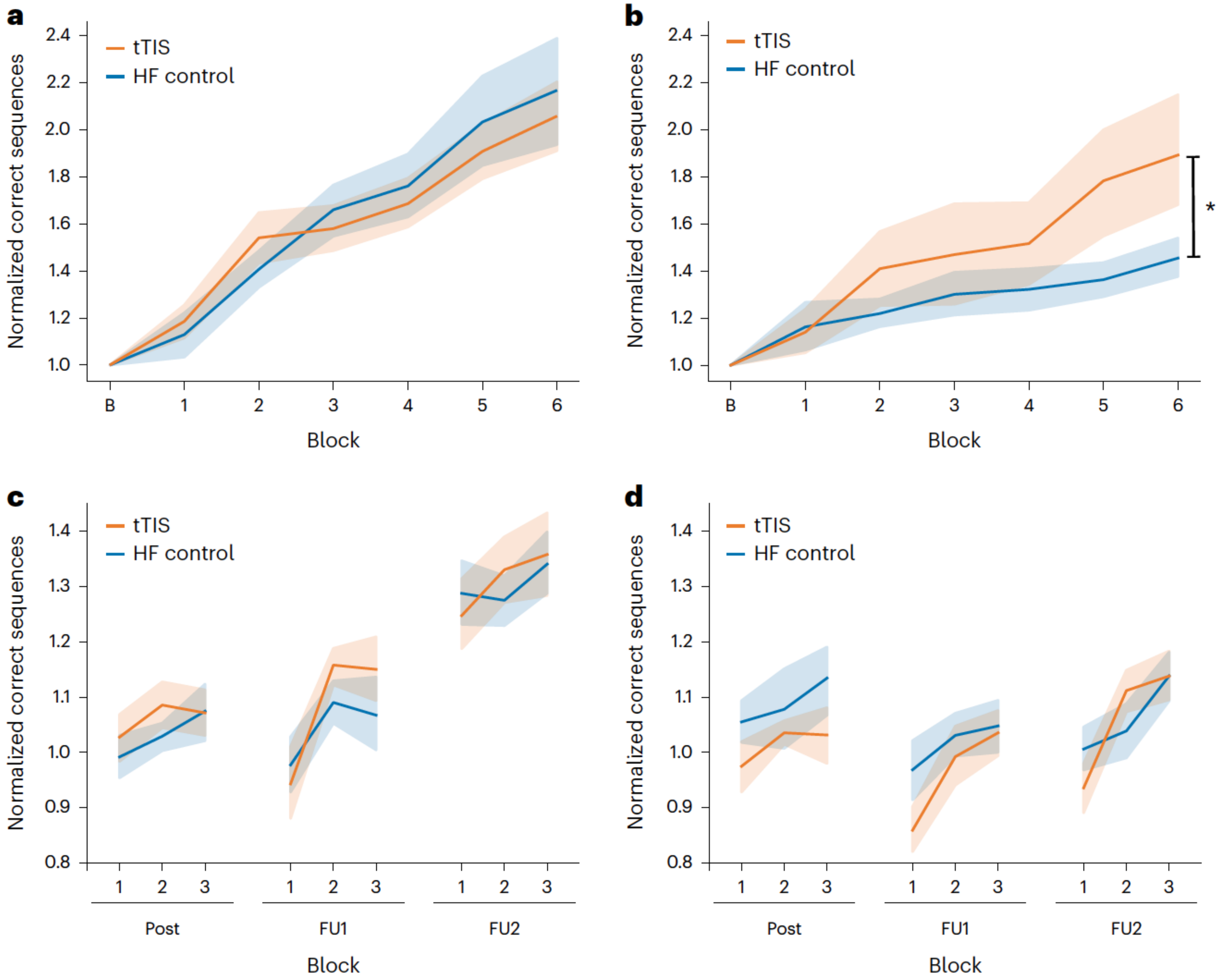

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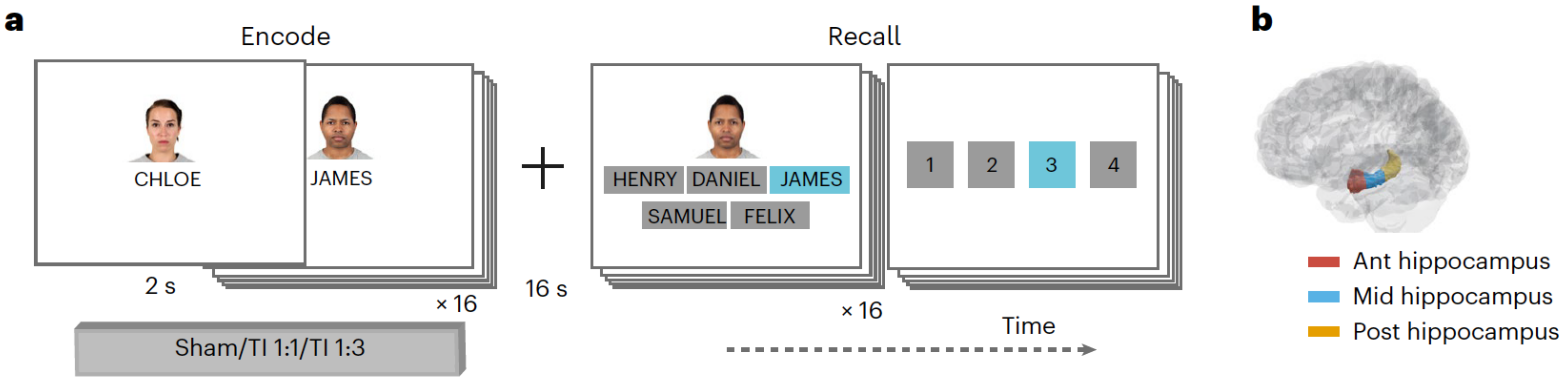
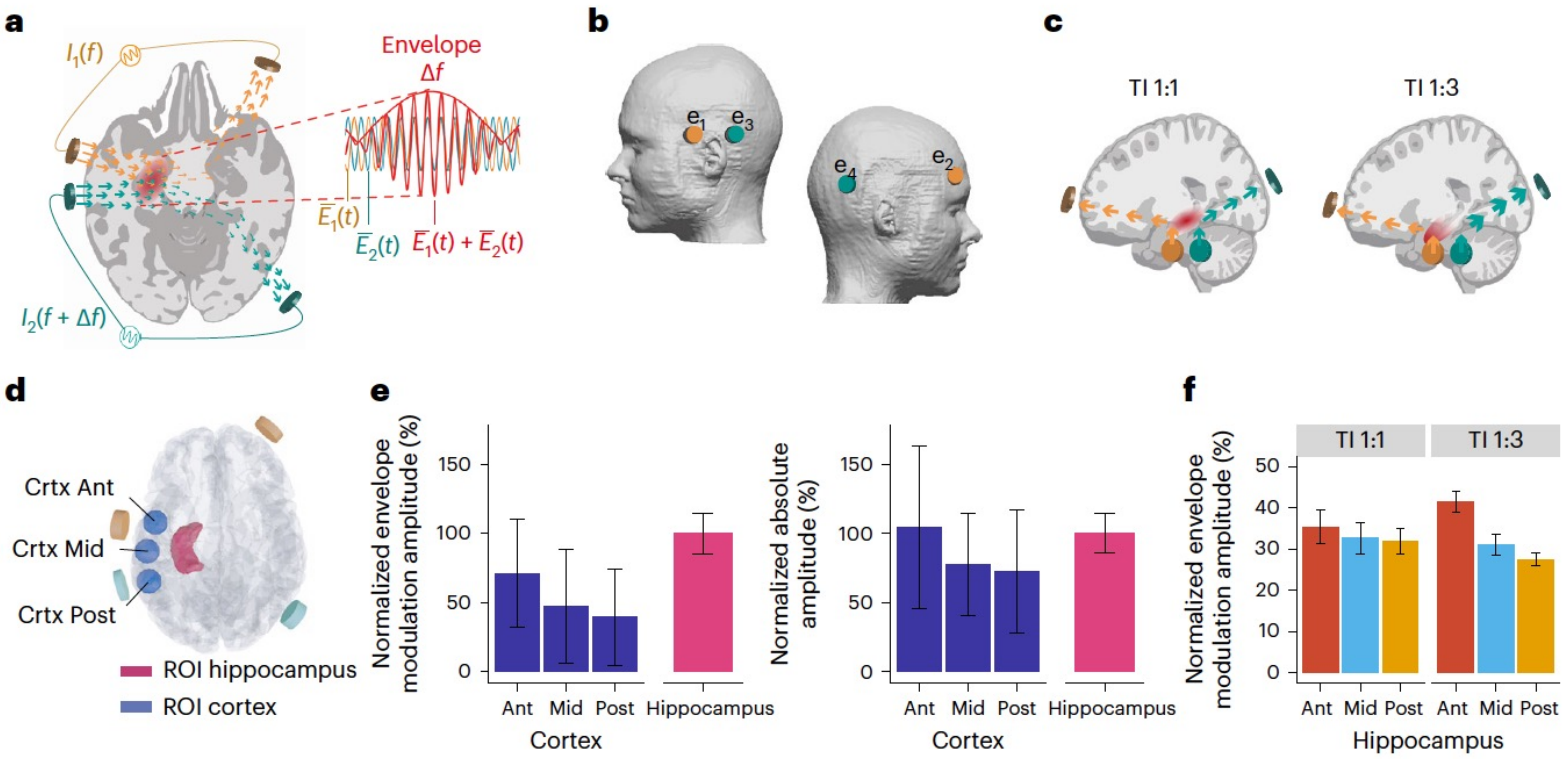
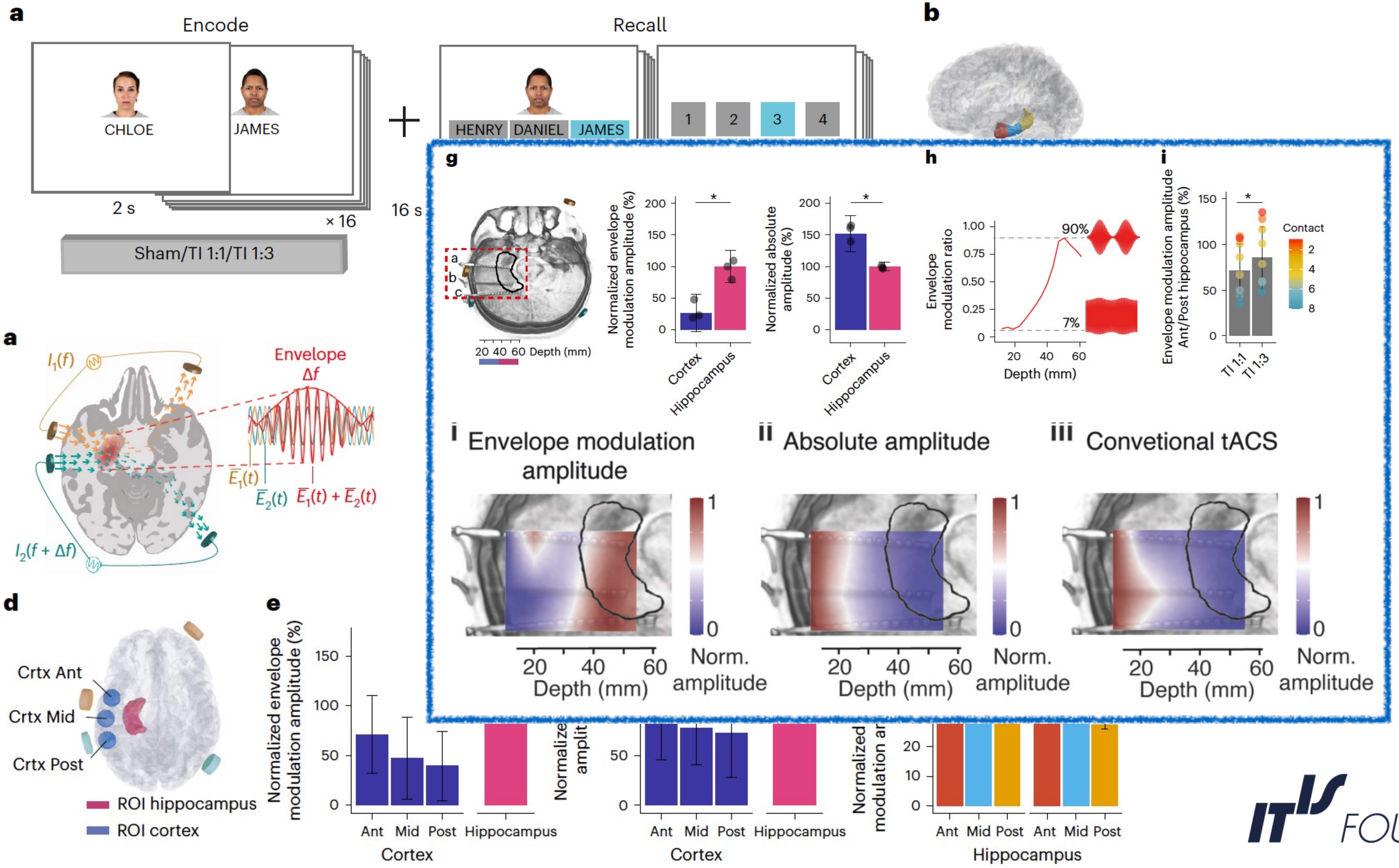
Non-invasive temporal interference electrical stimulation of the human hippocampus



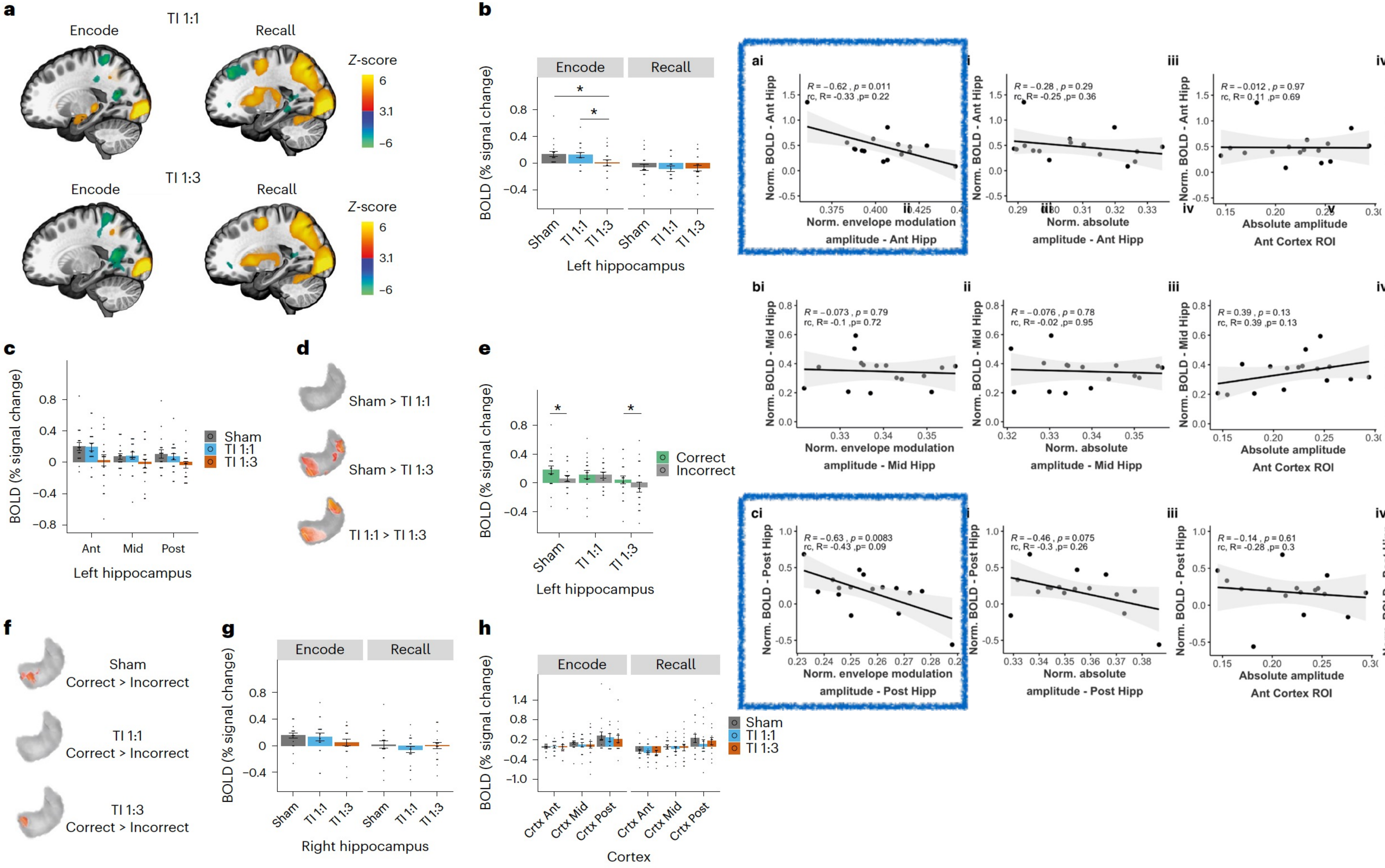


1st E

Non-invasive temporal interference electrical stimulation of the human hippocampus



Non-invasive temporal interference electrical stimulation of the human hippocampus



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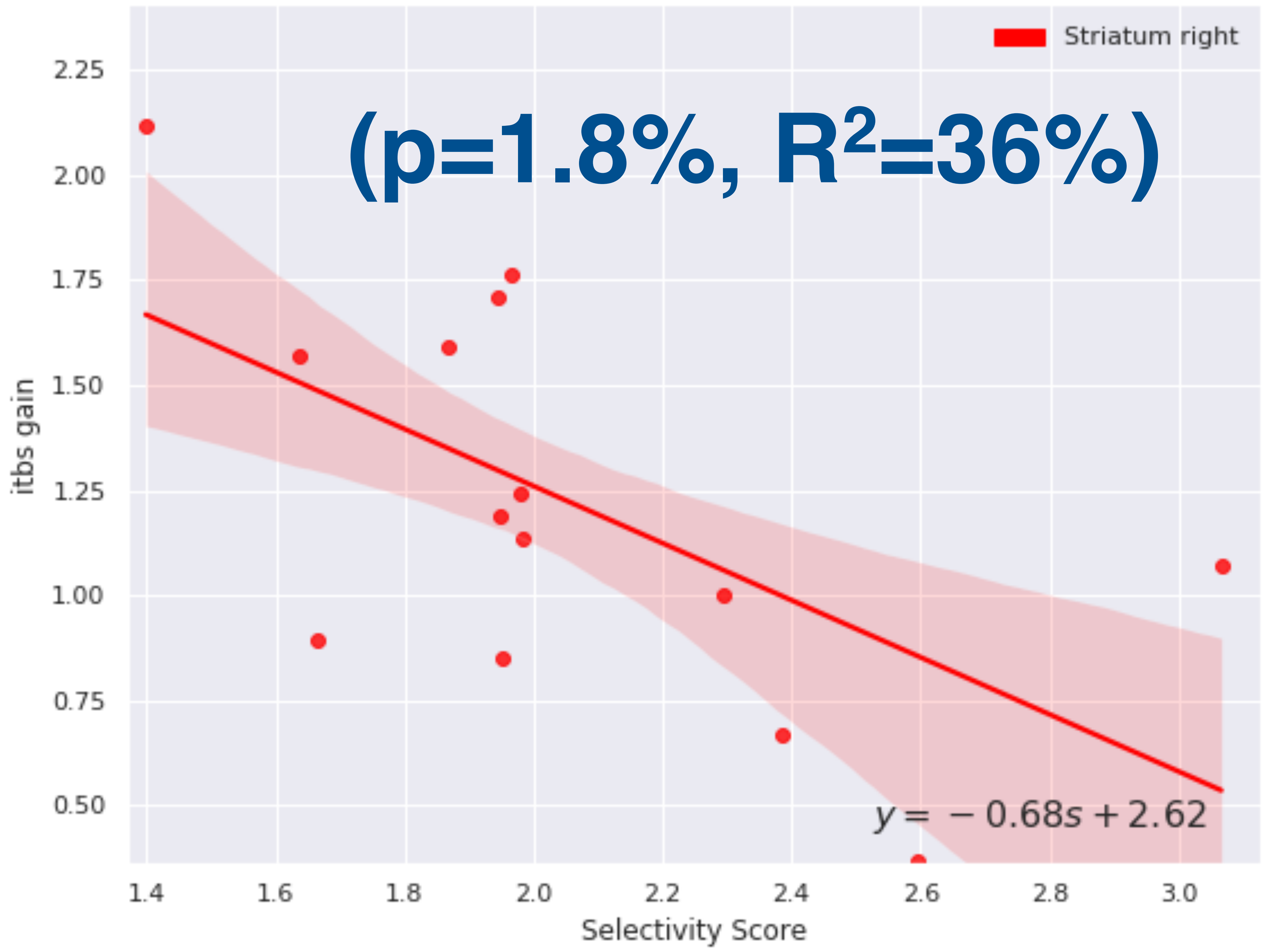
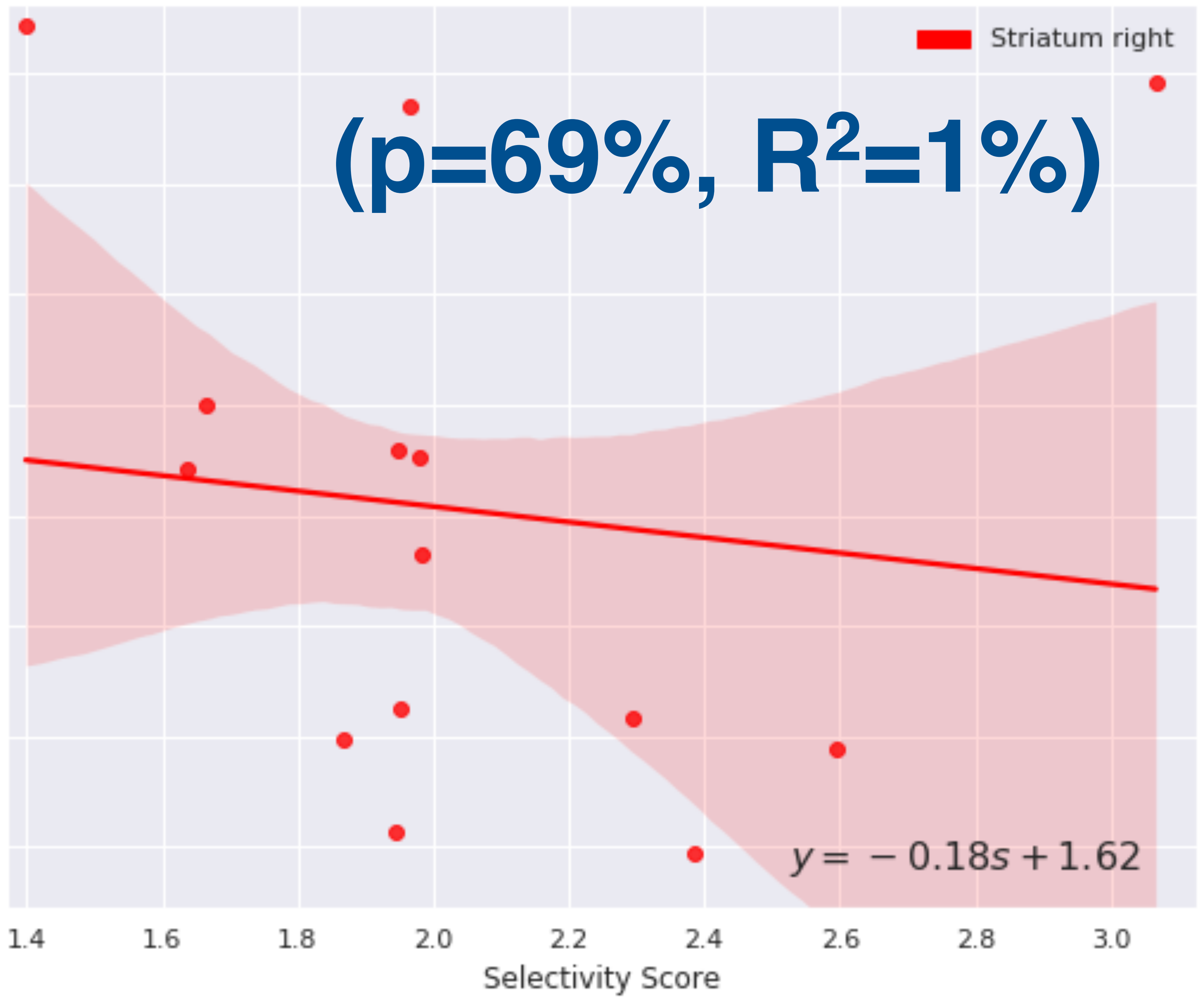
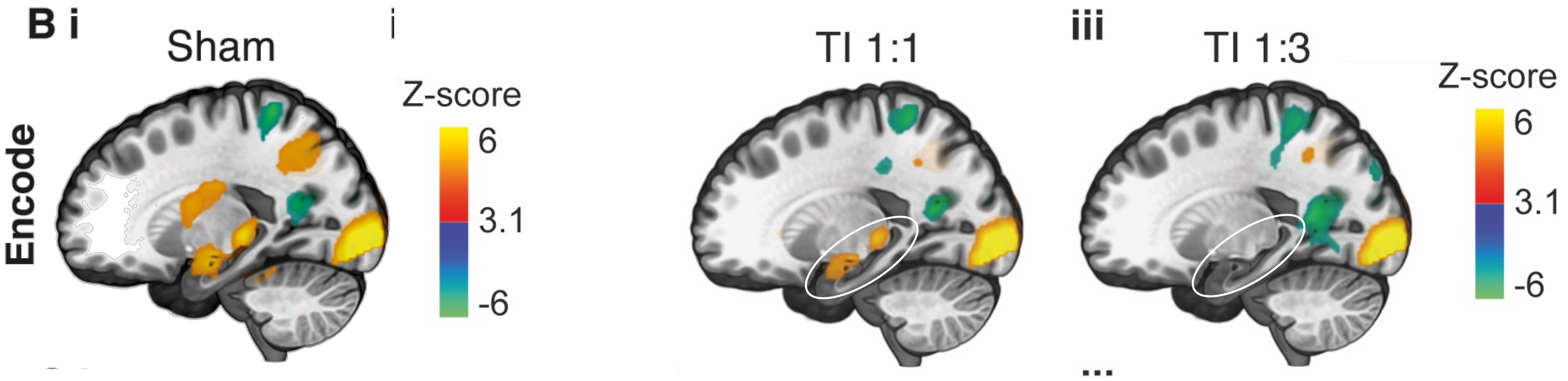
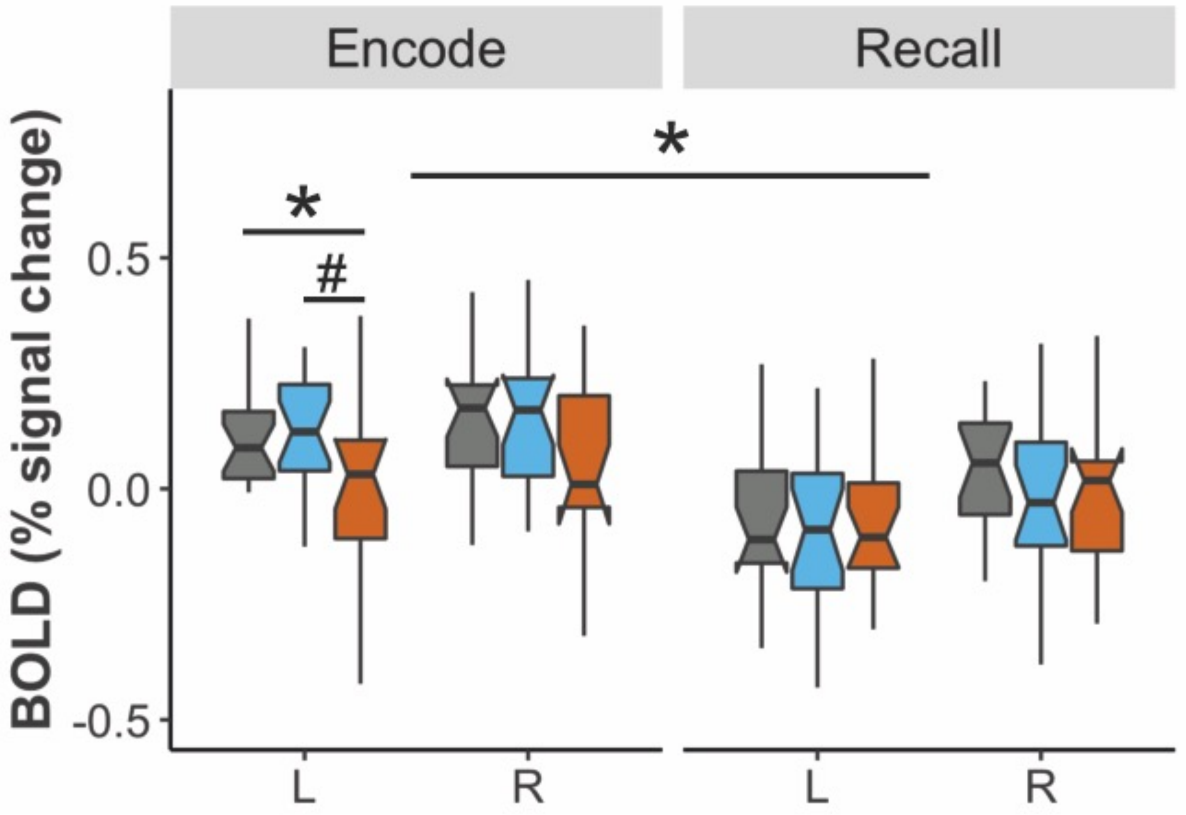
Personalized Selectivity Modeling Predicts Learning Response

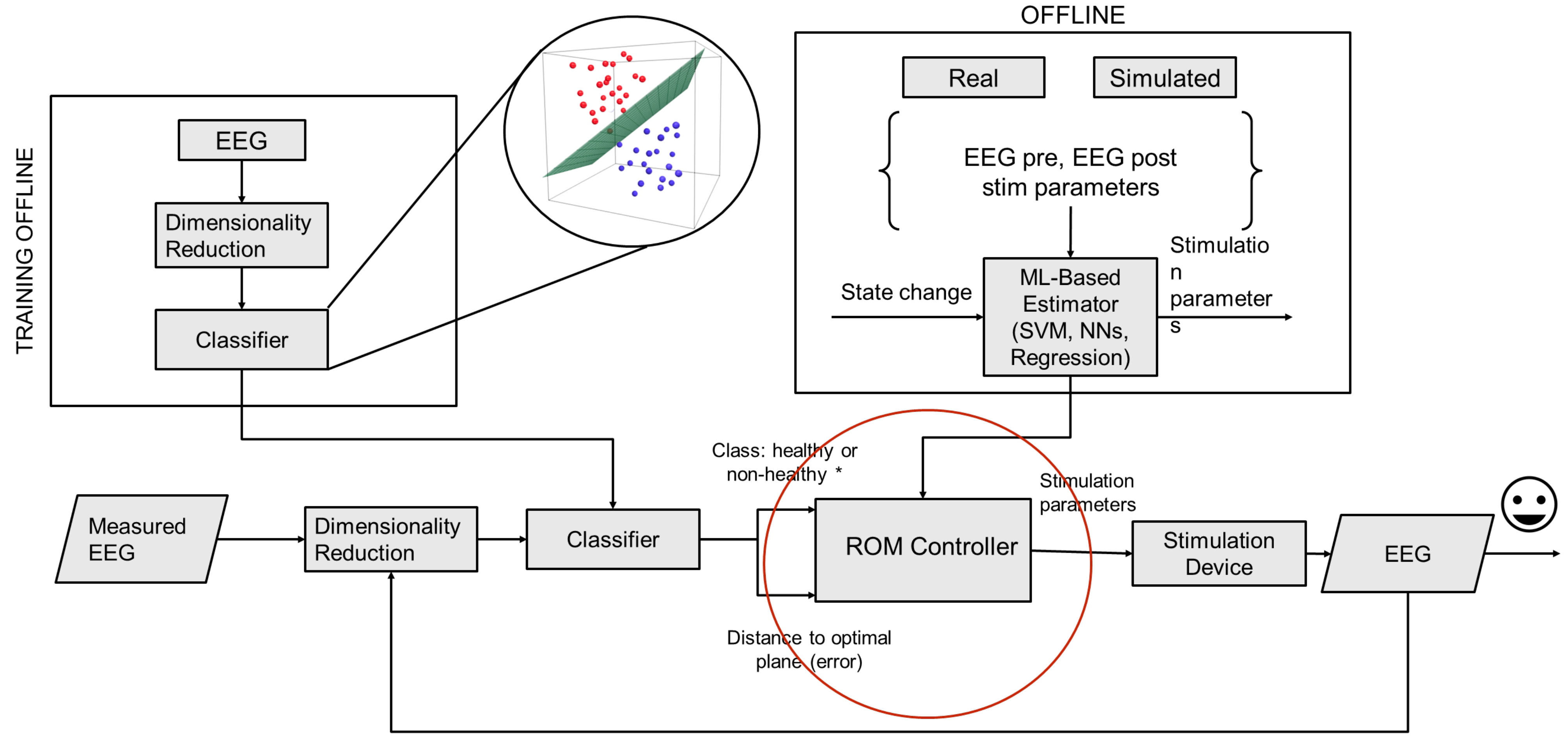




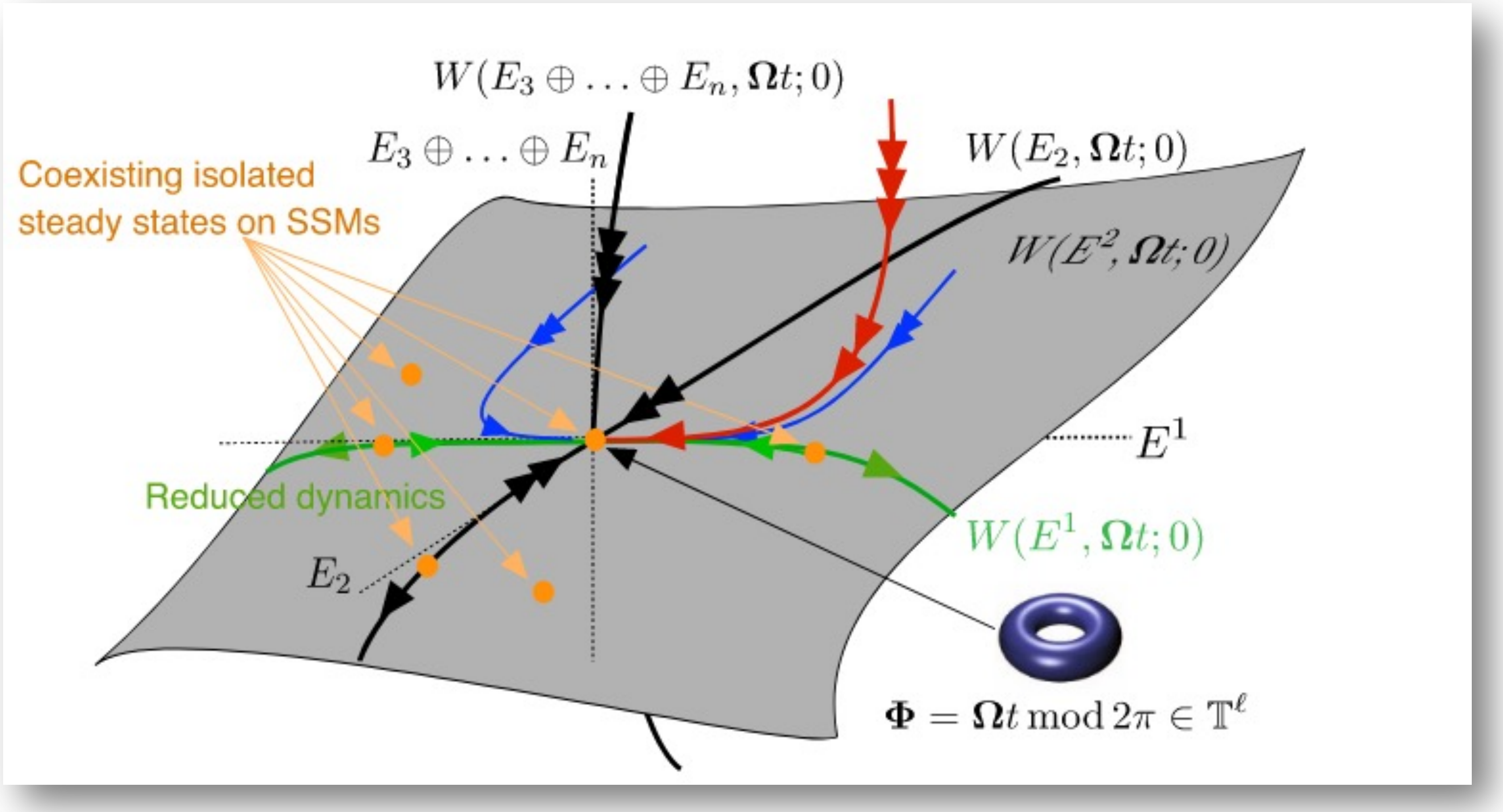


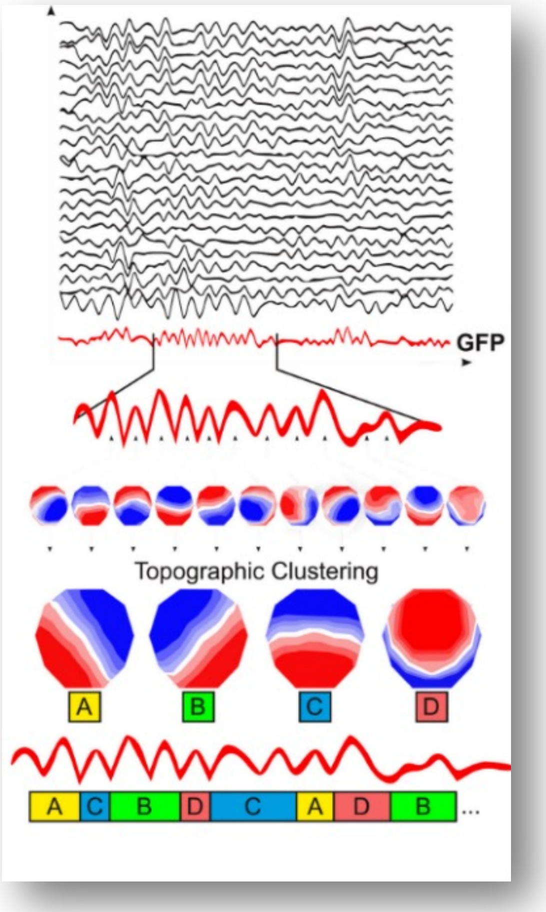


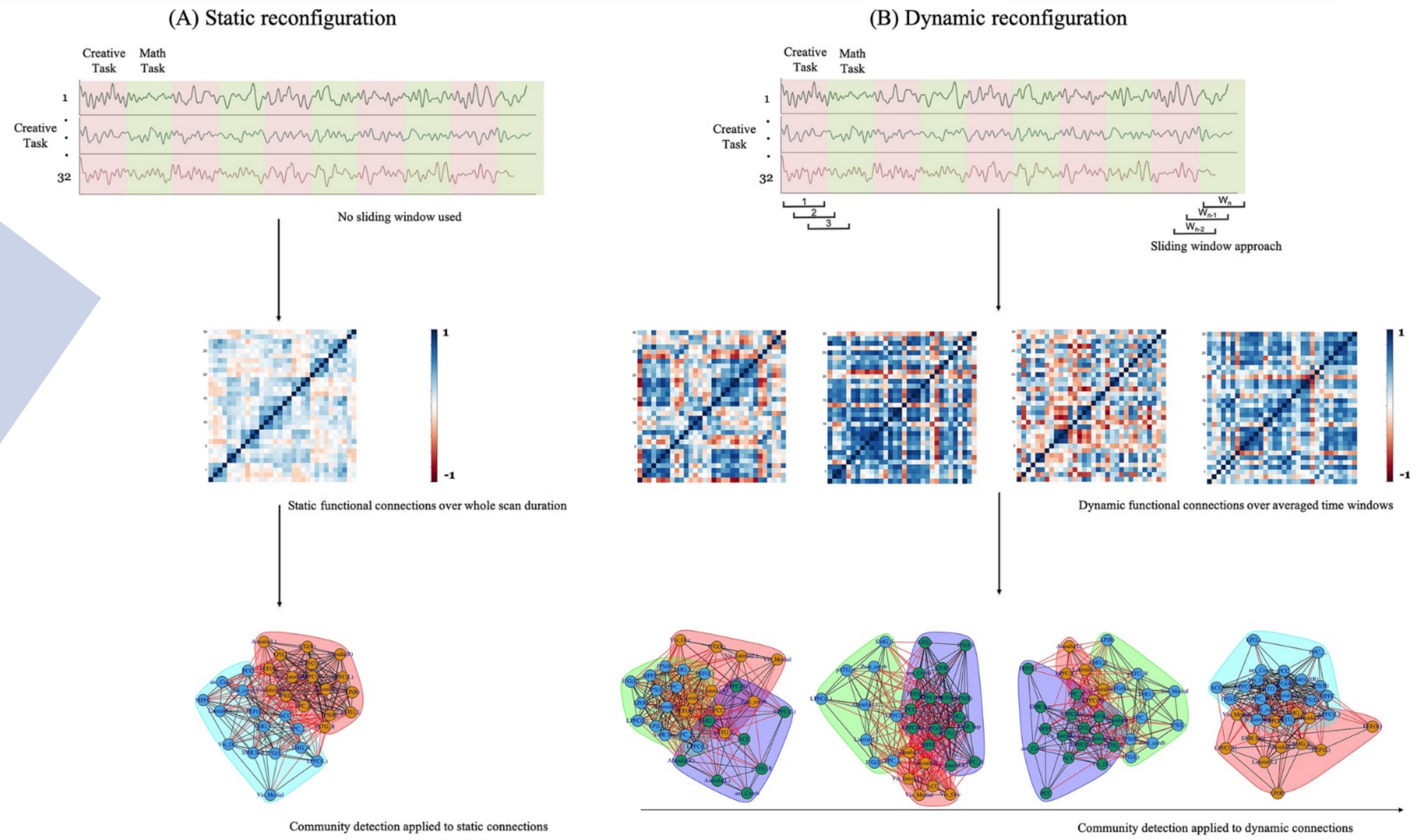
Towards State-Driven Control



* Can also be adapted to high-order classifications







Characterization of the healthy and pathological state

Distance **metrics** to define how to drive brain to health state

Define the **base parameters** for the stimulation of each patient

Refine the parameters depending on the current state and the distance to the predefined healthy state

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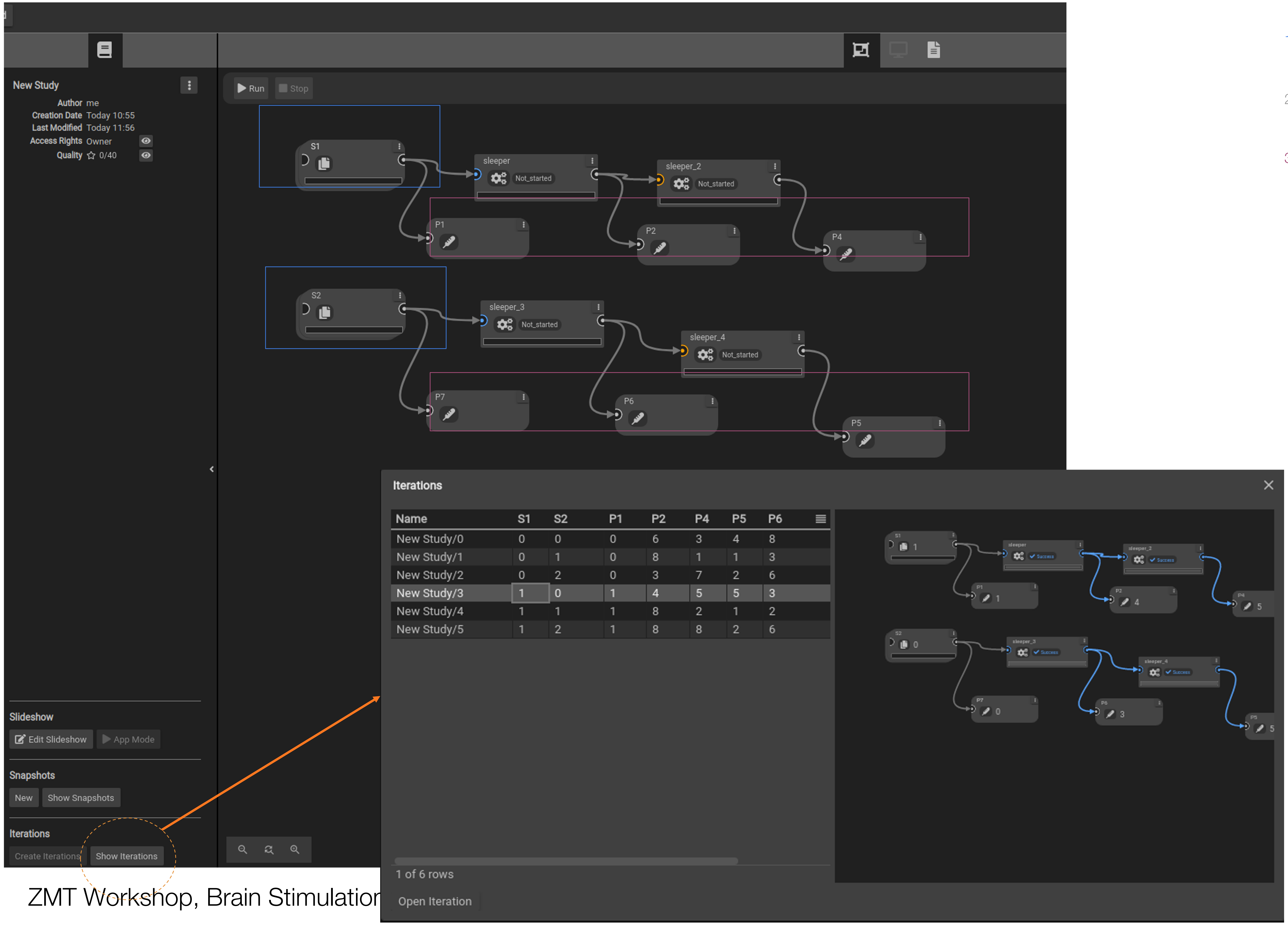
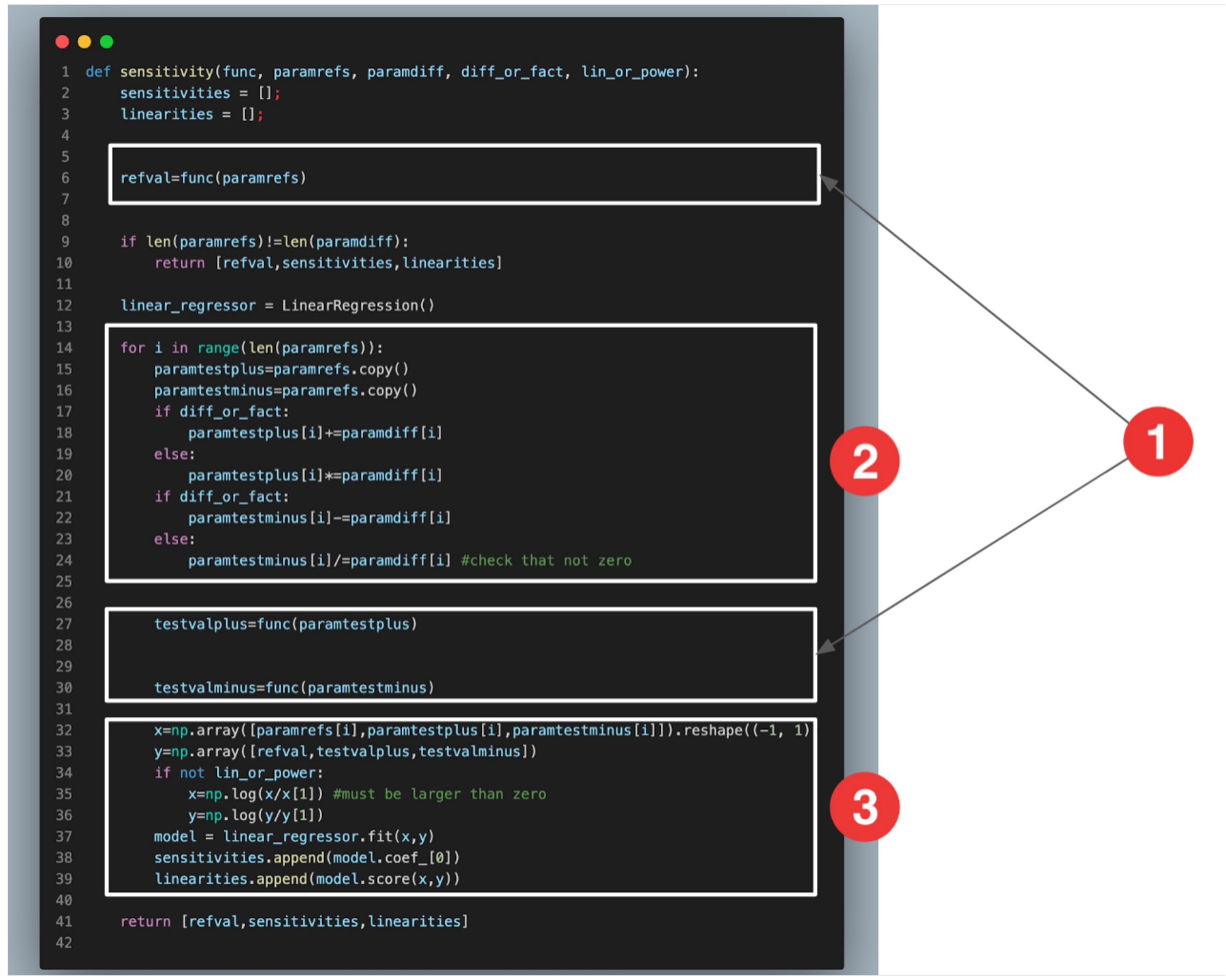
Parameterized Studies



1. Iterat
2. Comput
3. Probes

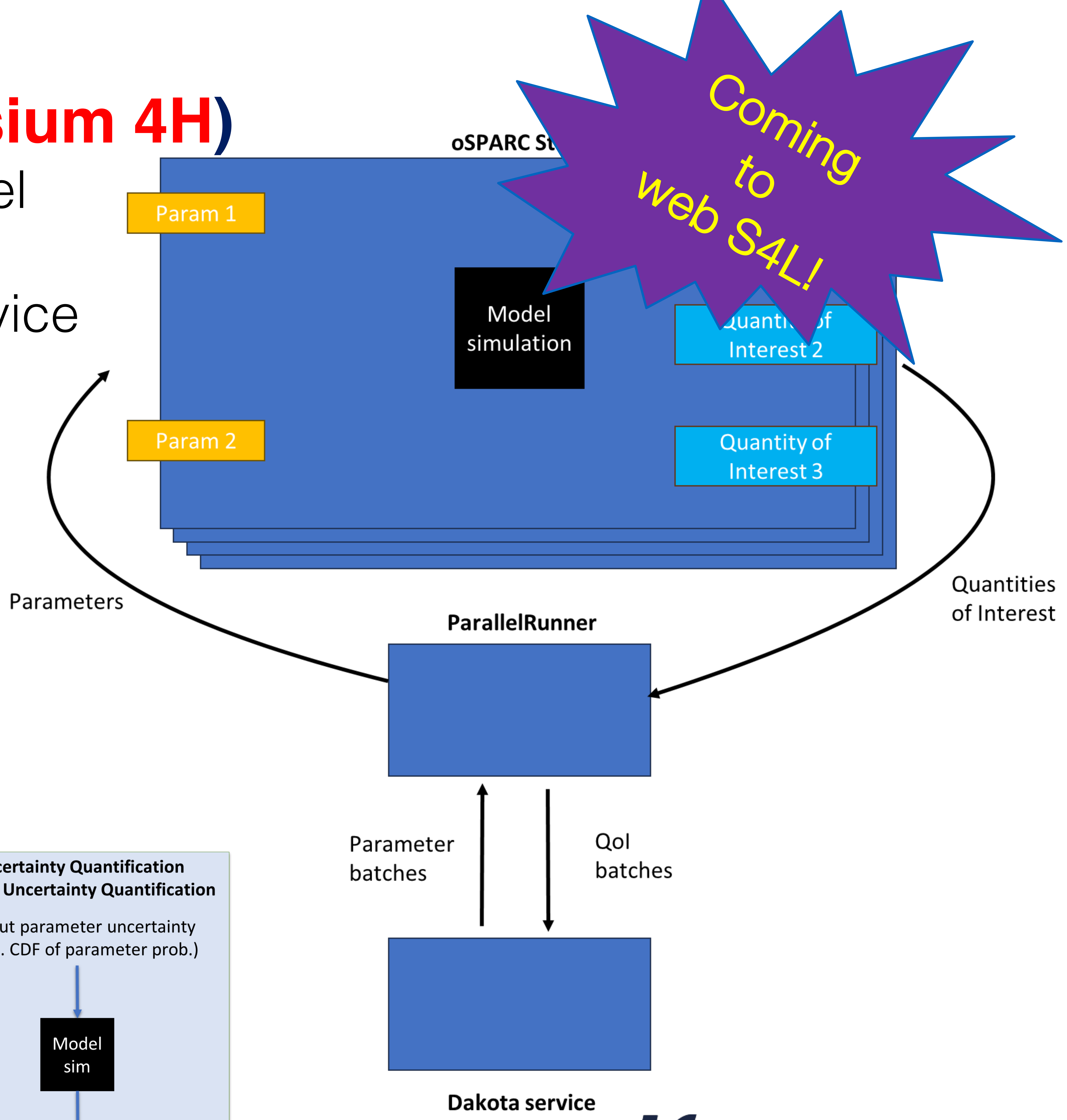


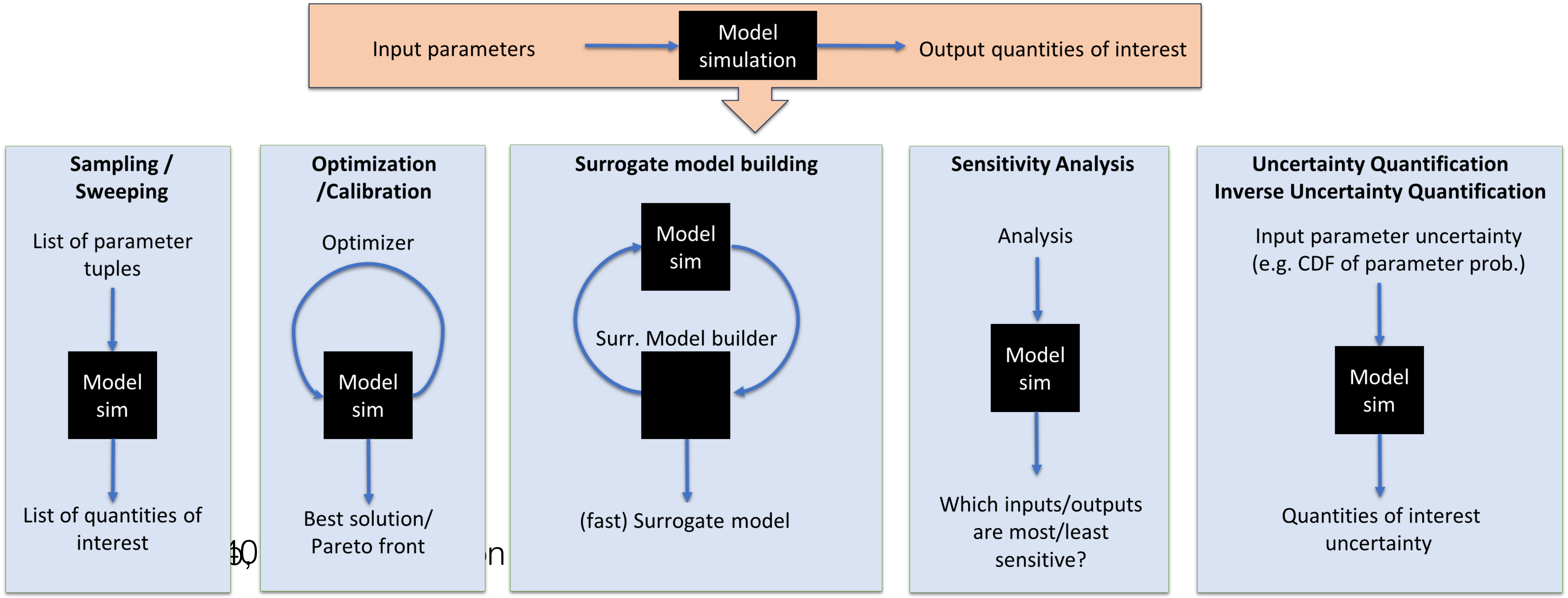
```python
def sensitivity(func, paramrefs, paramdiff, diff_or_fact, lin_or_power):
    sensitivities = [];
    linearities = [];

    refval=func(paramrefs)

    if len(paramrefs)!=len(paramdiff):
        return [refval,sensitivities,linearities]

    linear_regressor = LinearRegression()

    for i in range(len(paramrefs)):
        paramtestplus=paramrefs.copy()
        paramtestminus=paramrefs.copy()
        if diff_or_fact:
            paramtestplus[i]+=paramdiff[i]
        else:
            paramtestplus[i]*=paramdiff[i]
        if diff_or_fact:
            paramtestminus[i]-=paramdiff[i]
        else:
            paramtestminus[i]/=paramdiff[i] #check that not zero

        testvalplus=func(paramtestplus)


        testvalminus=func(paramtestminus)

        x=np.array([paramrefs[i],paramtestplus[i],paramtestminus[i]]).reshape((-1, 1))
        y=np.array([refval,testvalplus,testvalminus])
        if not lin_or_power:
            x=np.log(x/x[1]) #must be larger than zero
            y=np.log(y/y[1])
        model = linear_regressor.fit(x,y)
        sensitivities.append(model.coef_[0])
        linearities.append(model.score(x,y))

    return [refval,sensitivities,linearities]
```

Meta-Modeling Framework (Symposium 4H)

- parametrized pipelines evaluated in parallel
  - cloud-inherent scalability
- Dakota (Sandia National Laboratories) service
  - optimization
  - uncertainty analysis
  - design of experiments
  - risk & failure analysis
  - sensitivity analysis
  - parameter estimation
  - surrogate modeling

DAKOTA
Explore and predict with confidence.





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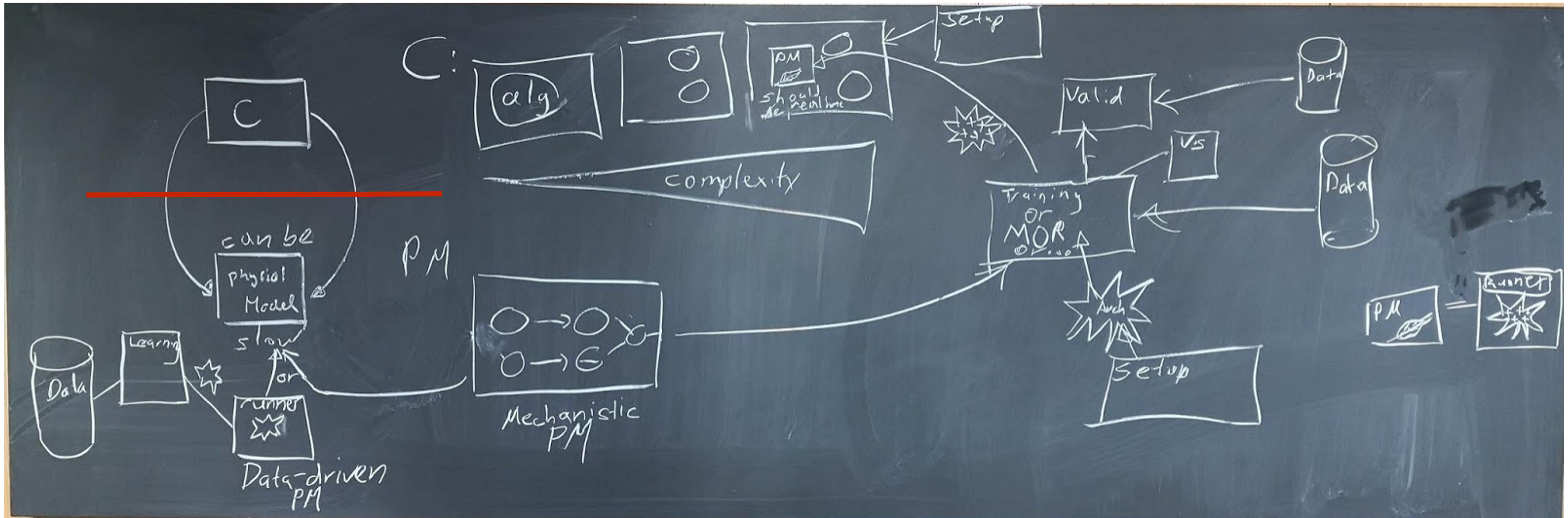
In Development: Control Framework

- modular, mutually agnostic combination of (predefined) control strategies and simulations of the controlled physiology
- minimal but sufficient coupling and control API
  - can be voluntarily satisfied by o2S2PARC
  - service that satisfy this API can automatically be used as
    * part of coupled multi-physics/physiology modeling
    * for closed-loop control simulations
- SuMo / MOR to establish light-weight, internal models for intelligent (i.e., model-based) control



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Conclusions

- Sim4Life is the platform for the modeling of neuromodulation and neural sensing
  - leading EM, FUS, NEURO (across scales), T... simulators capable of handling complex anatomical environments
  - the most realistic anatomical population (incl. pre-functionalization)
  - image-based, personalized modeling and treatment planning
  - and much more
- browser-based and cloud-hosted web version of Sim4Life
  - collaborate and publish, access scalable resources on demand, GUI- and API-based usage supported
  - released soon: integrate with powerful 3rd party services and applications (e.g., for computational neurosciences), build advanced pipelines, publish guided applications (e.g., for treatment planning)
- continuously expanding, innovative functionality
  - new: rapid stimulation predictors, leading AI for head model creation (incl. 10-10 system placement & brain atlas registration)
  - coming soon: powerful meta-modeling framework (SuMo-based), model-predictive control framework