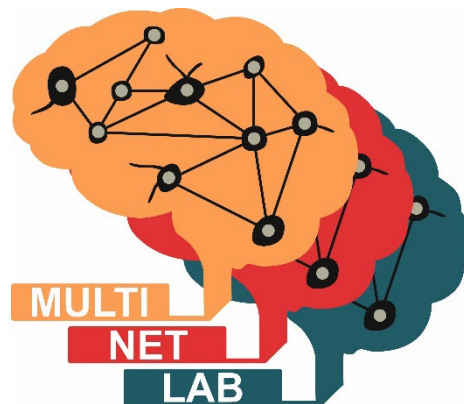


"the network experiment", carlijn kingma, 2016  
[www.carlijnkingma.com](http://www.carlijnkingma.com)

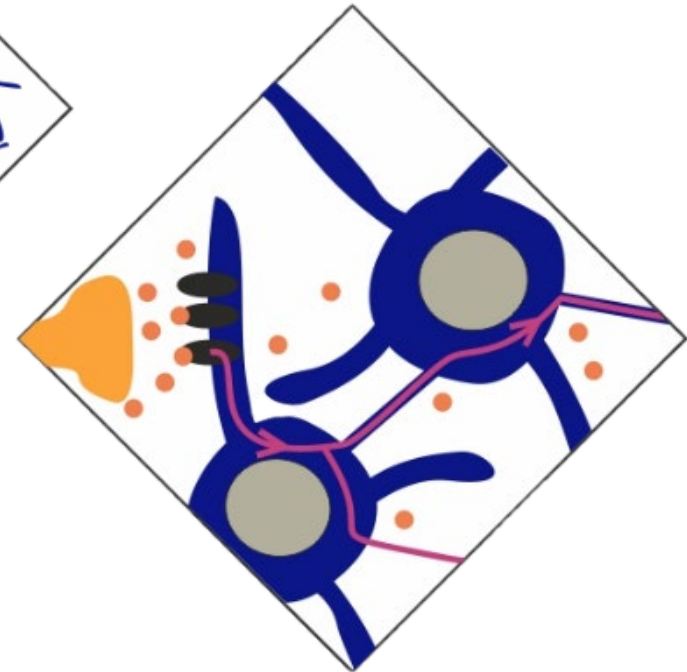
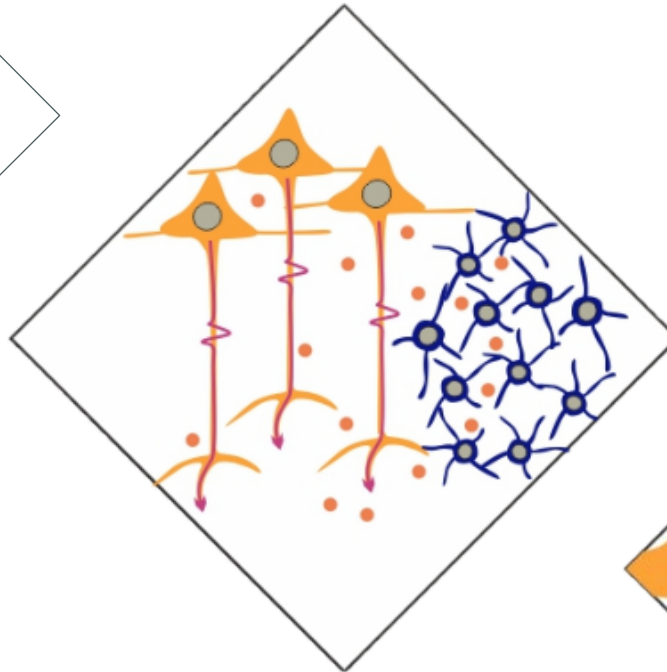
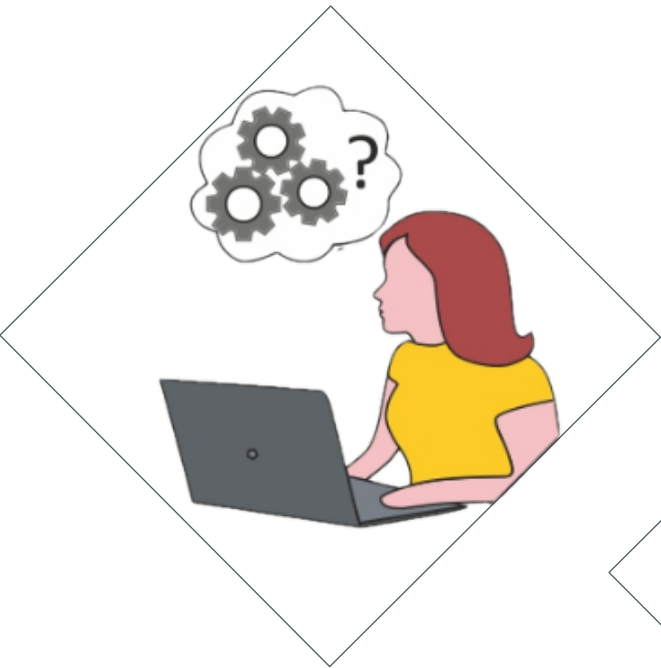


Amsterdam UMC

linda douw  
2025/06/05

multiscale  
network  
neuroscience:

connecting cells to  
circuits to networks in  
brain tumor patients



most common primary brain tumor

6 annual cases per 100,000

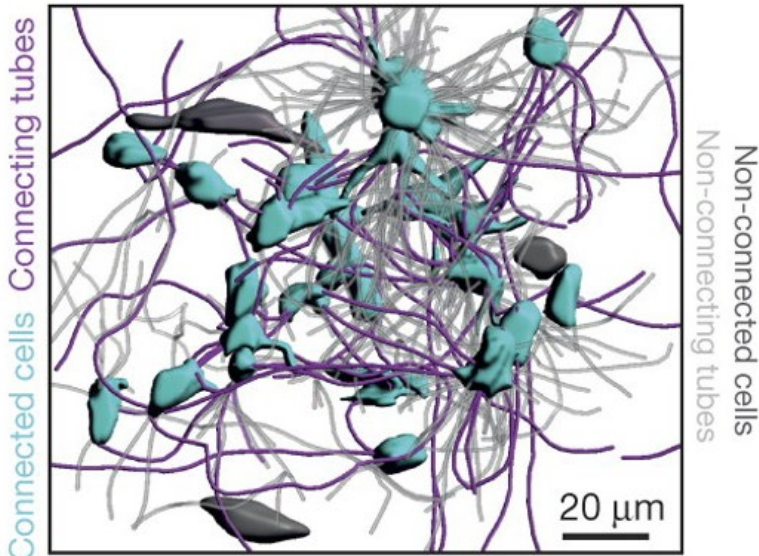
# glioma

prognosis is dismal

cognitive dysfunction

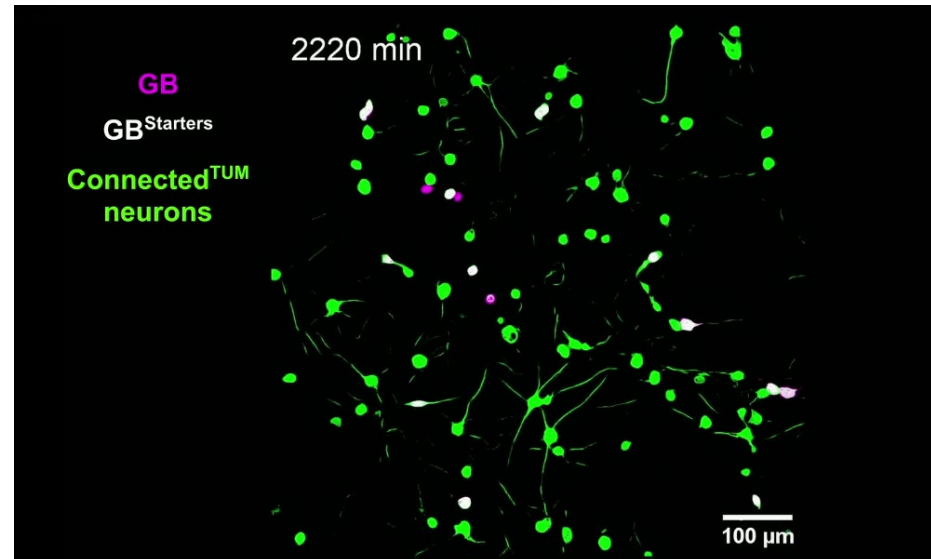
unique multiscale research

tumor cells form a network



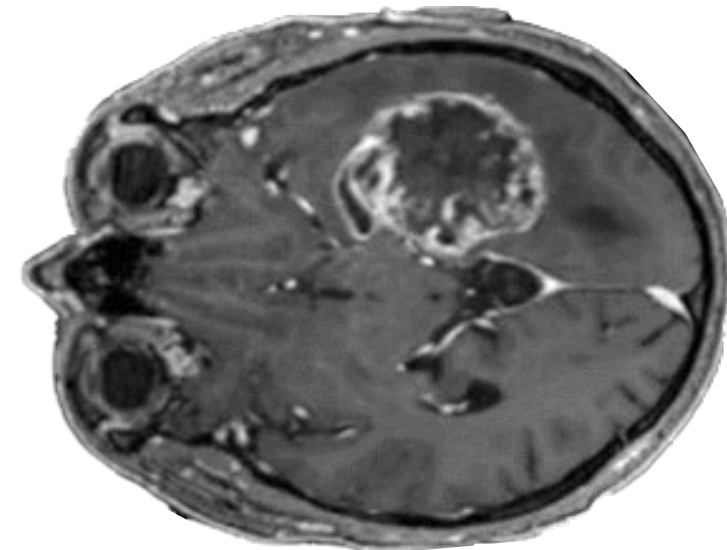
osswald et al (2015) nature

tumor cells connect to brain cells

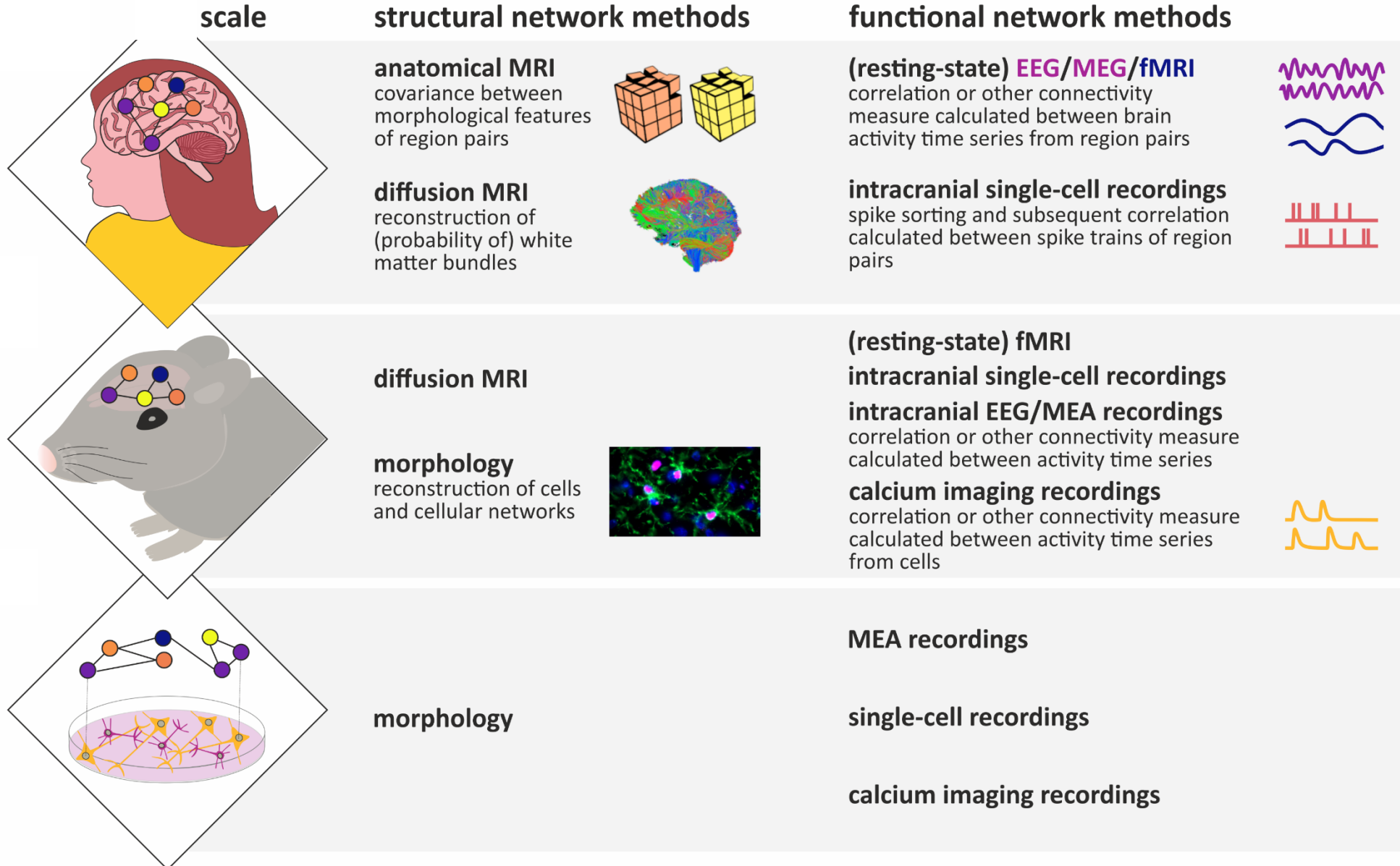


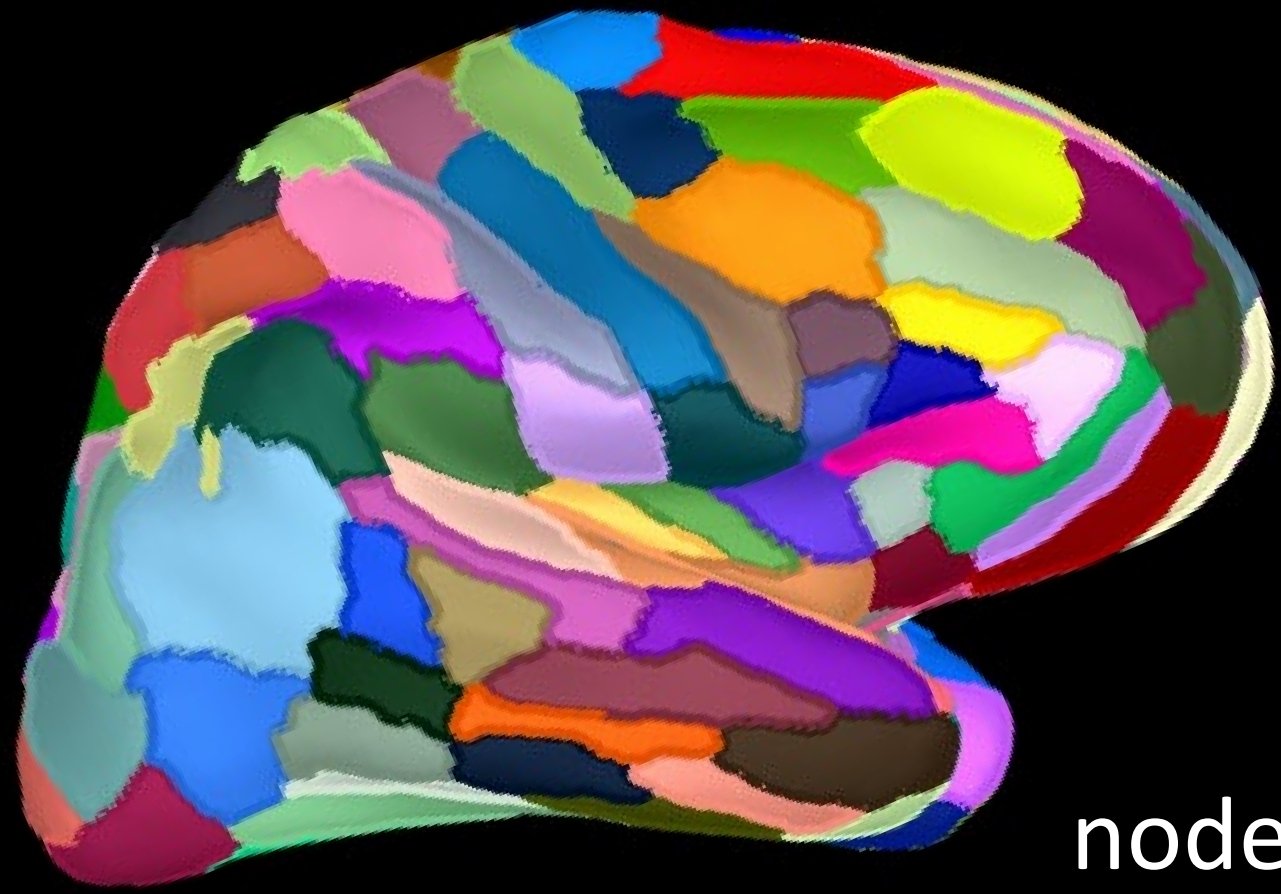
tetzlaff et al 2025 cell

global network disturbances

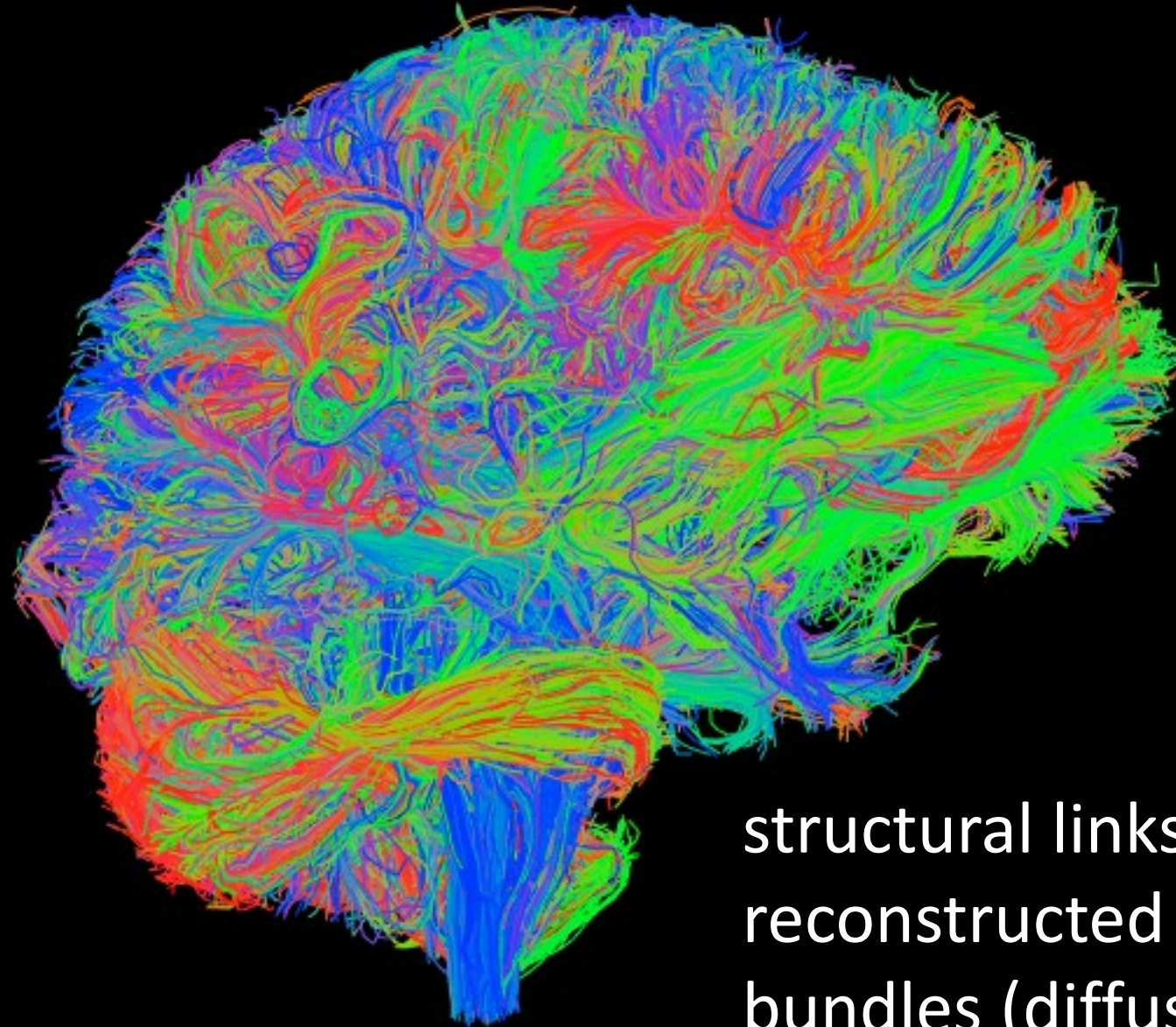


# how do we construct brain networks at multiple scales?





nodes



structural links:  
reconstructed white matter  
bundles (diffusion MRI)

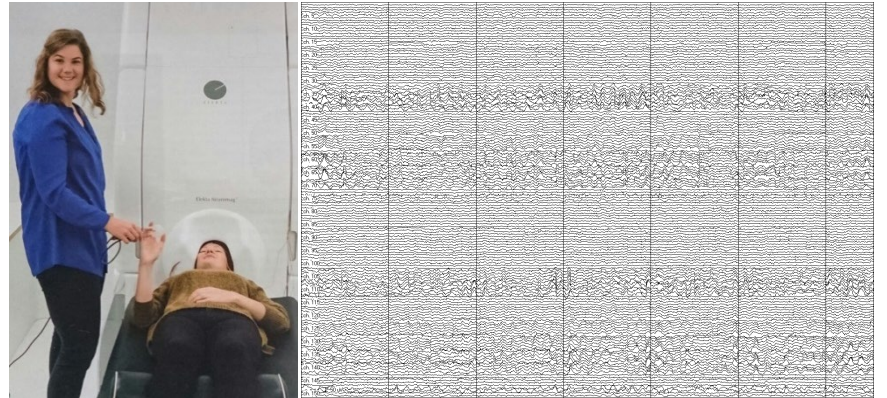
# electroencephalography (EEG)

EEG:  $\Delta$ volt



# magnetoencephalography (MEG)

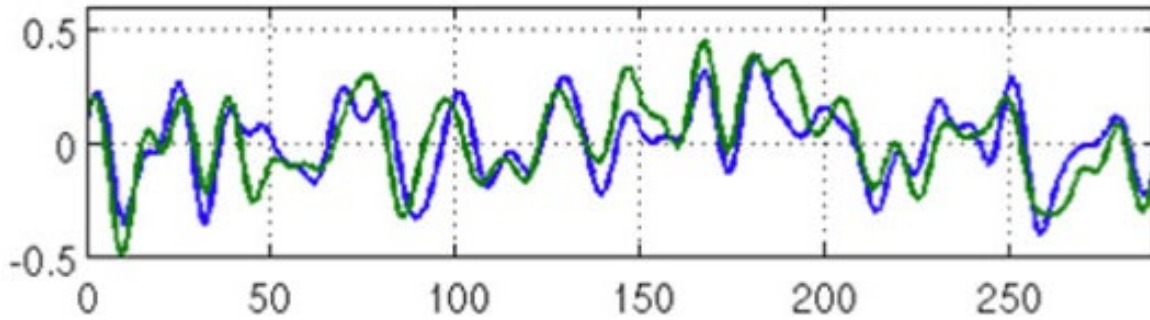
MEG:  $\Delta$ tesla



functional links: synchronization between time series of brain activity (functional connectivity)

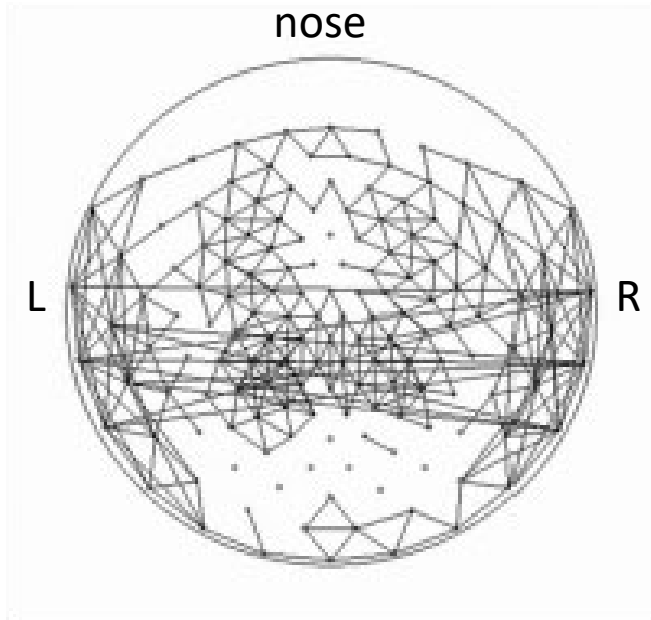
# resting-state functional MRI (rsfMRI)

rsfMRI:  $\Delta$ BOLD

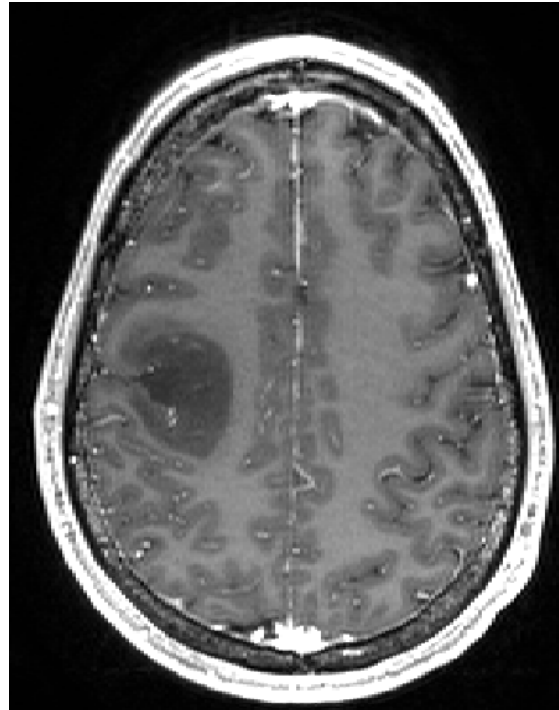


# focal lesions like glioma associate with global network disturbances

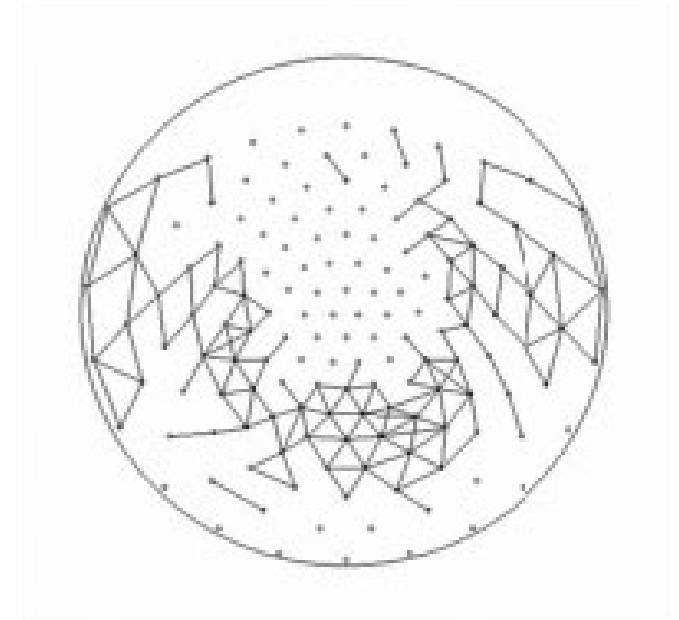
healthy control's network



patient MRI



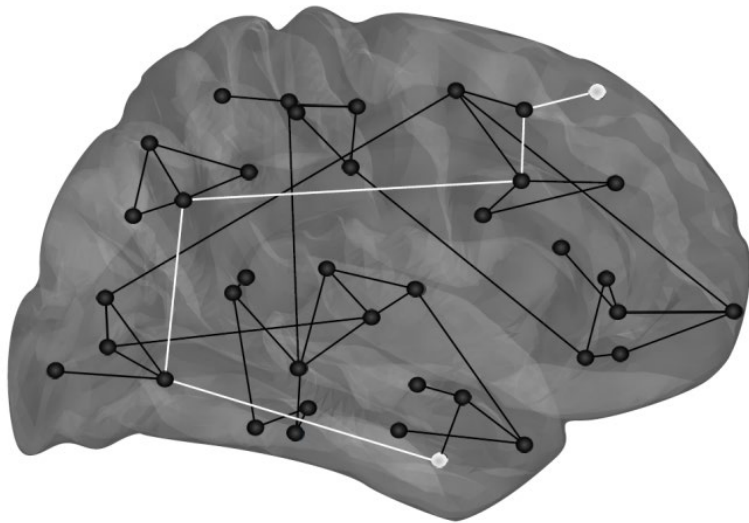
patient's network



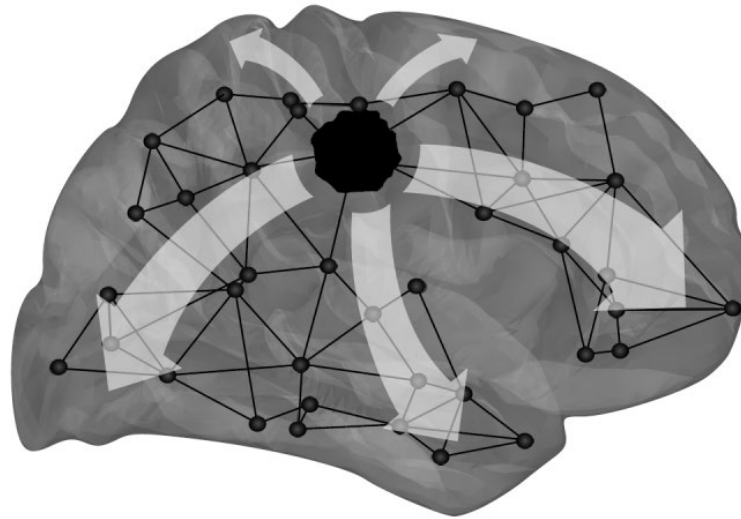
$\gamma$  band, smallest part of the entire signal

# glioma patients have pathologically high network segregation, but low integration

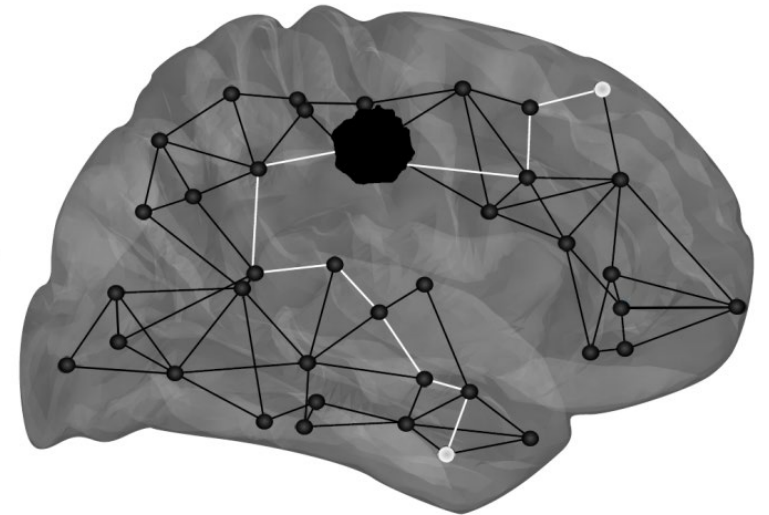
the healthy, small-world, modular brain network



globally higher (pathological) connectivity, clustering and modular segregation associate with seizure vulnerability and poorer prognosis



loss of network integration and hub connectivity, particularly when unifying different frequencies into a multilayer network, relate to cognitive deficits

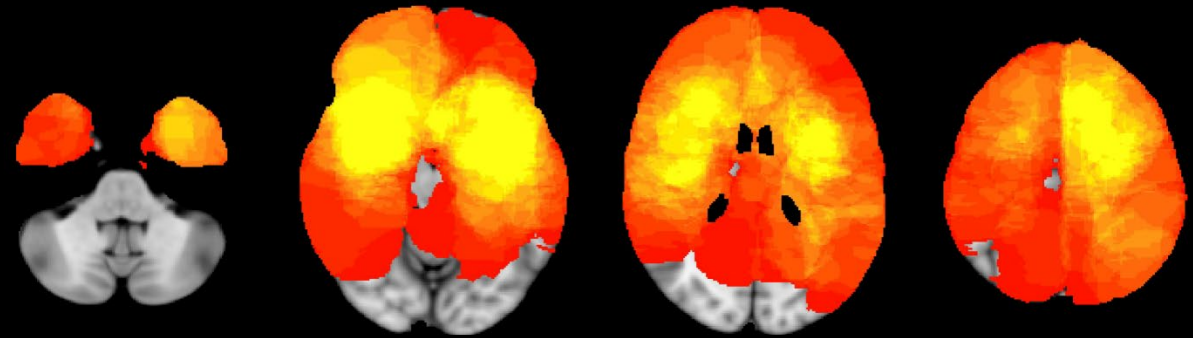


MEG, rsfMRI, dMRI | various node sets | various measures

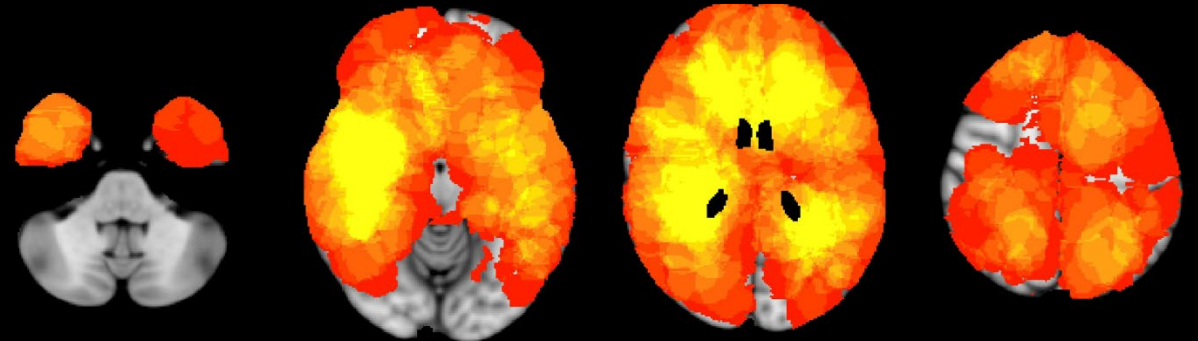
douw et al (2008) experimental neurology; douw et al (2010) bmc neuroscience; wang et al (2010) phys rev e; douw et al (2011) neuroscience; van dellen et al (2012) pLoS one; derks et al (2014) curr opin oncology; carbo et al (2017) scientific reports; derks et al (2017) neuroimage:clinical; derks et al (2019) brain & behavior; derks et al (2021) brain connectivity; numan et al. (2022) brain; van lingen et al (2023) brain imaging and behavior; zimmermann et al (2024) journal of neuro-oncology

but glioma does not occur uniformly across the brain (network)

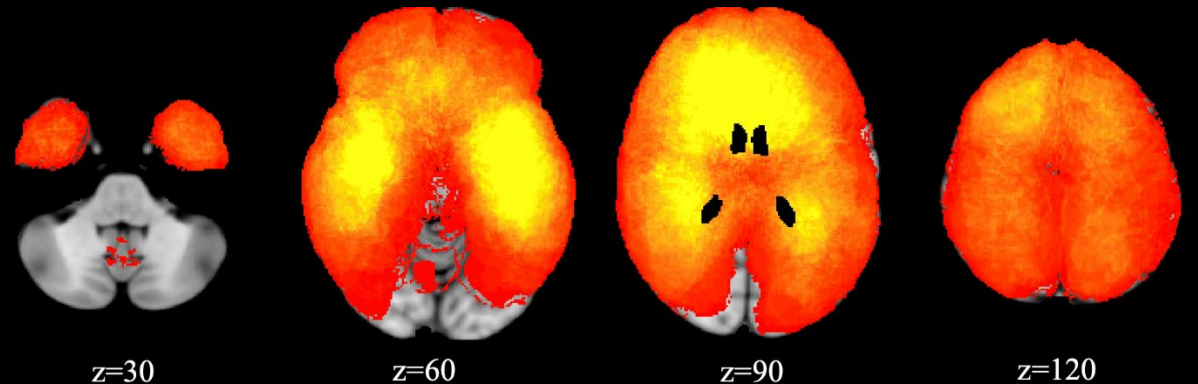
amsterdam cohort (n=83)



boston cohort (n=121)



publically available tcga cohort (n=209)

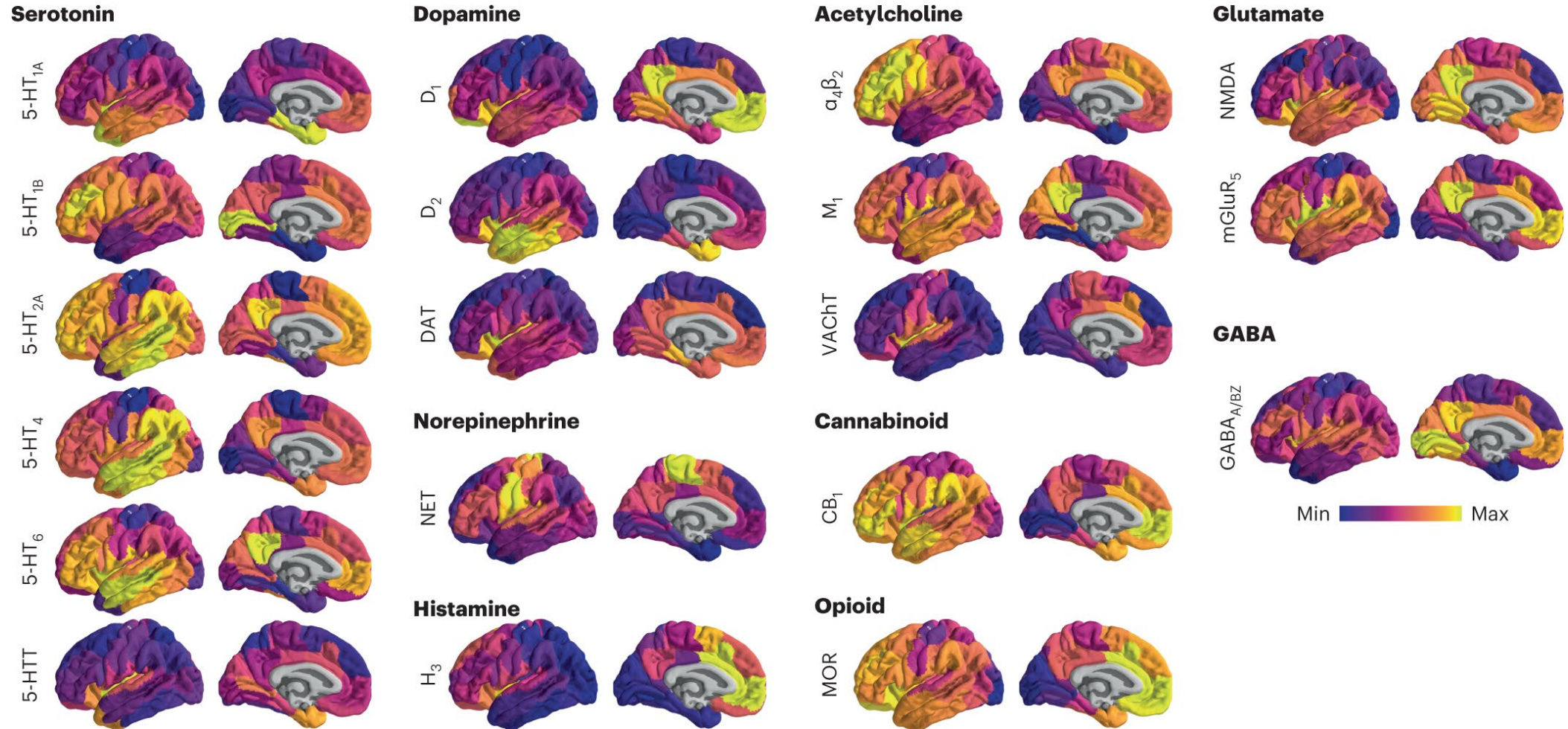


low occurrence  high occurrence

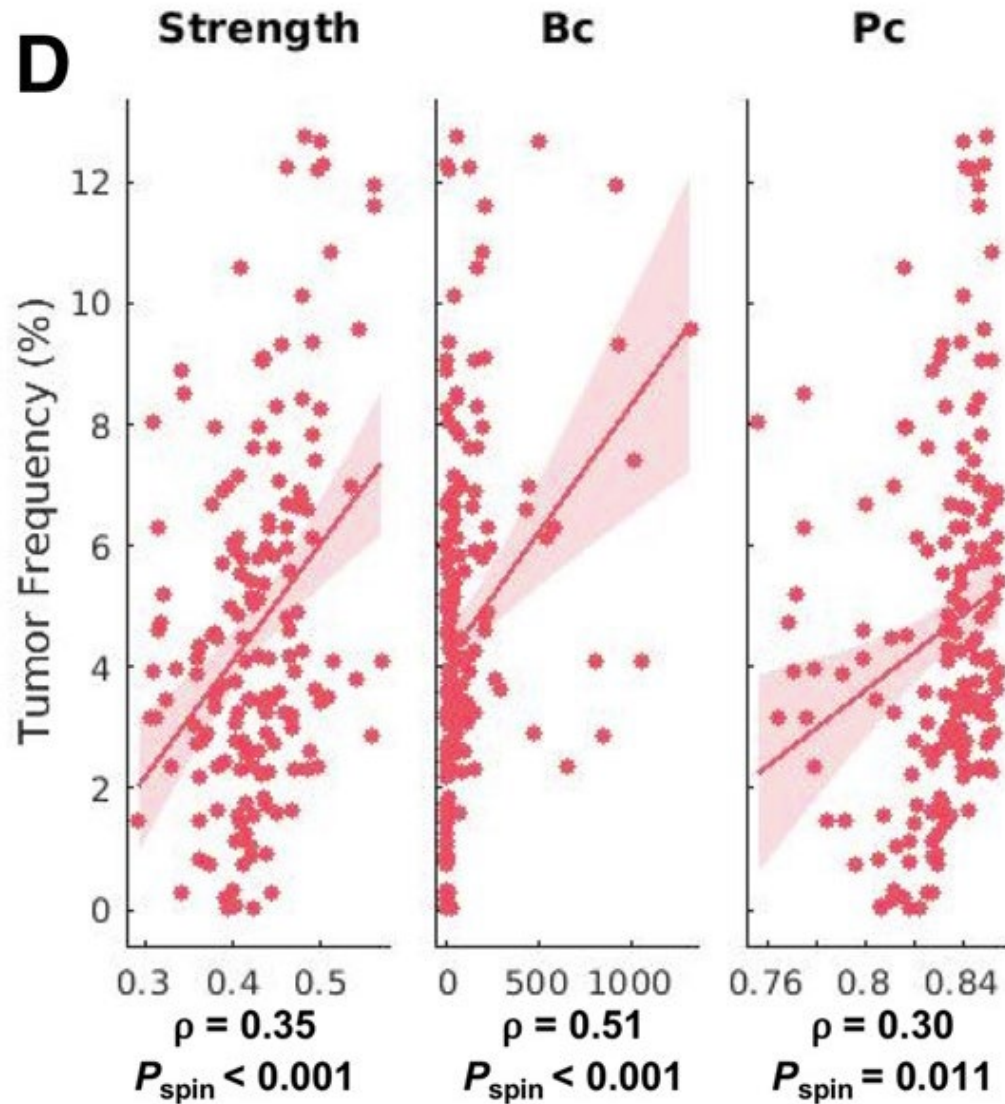
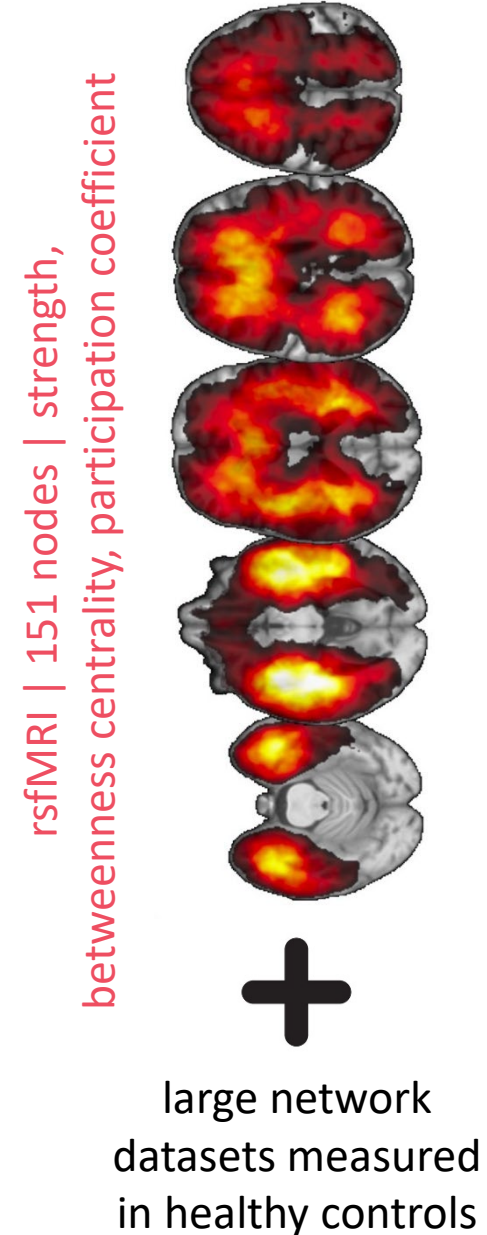


tianne numan

# nodal properties of the macroscale brain network correlate spatially with cellular characteristics in collated datasets

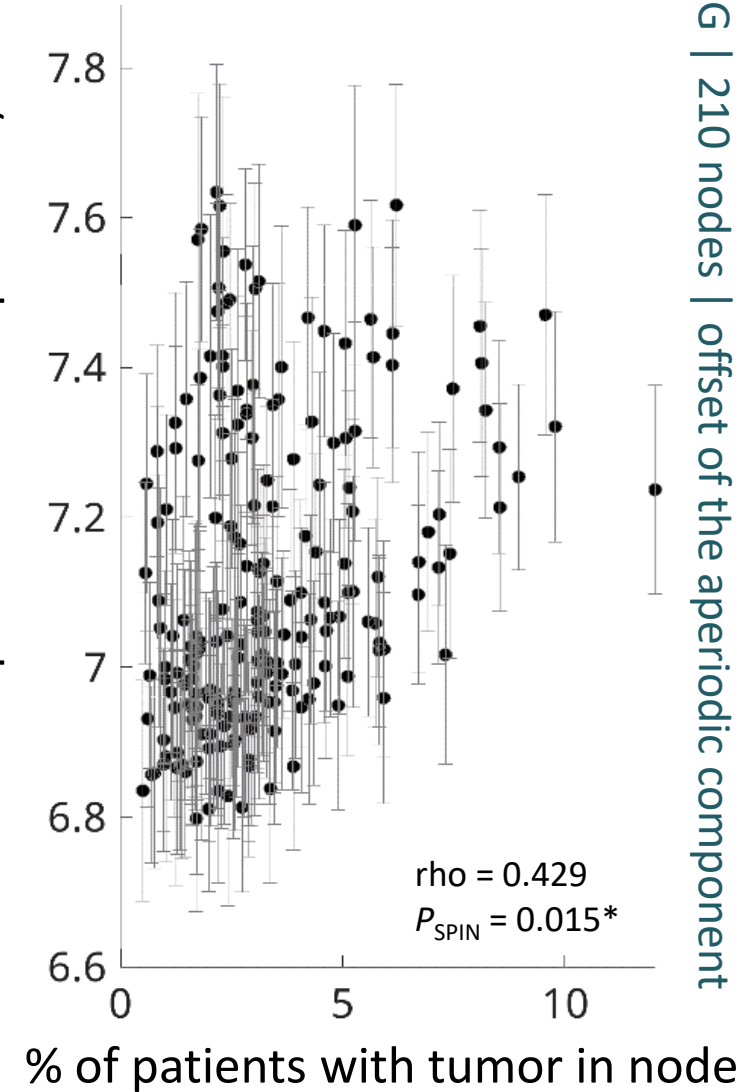


# glioma occurrence coincides with greater hubness and higher brain activity



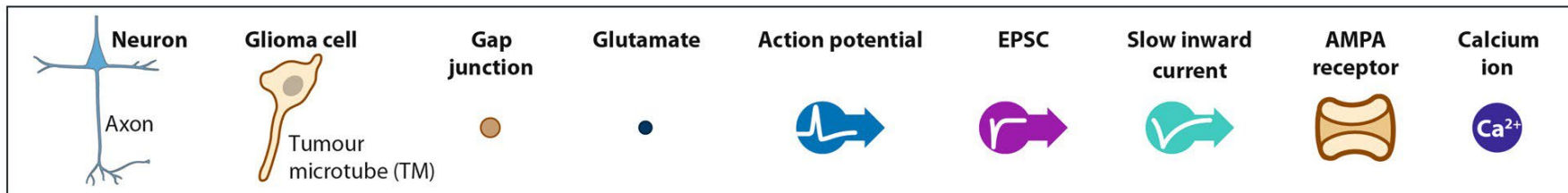
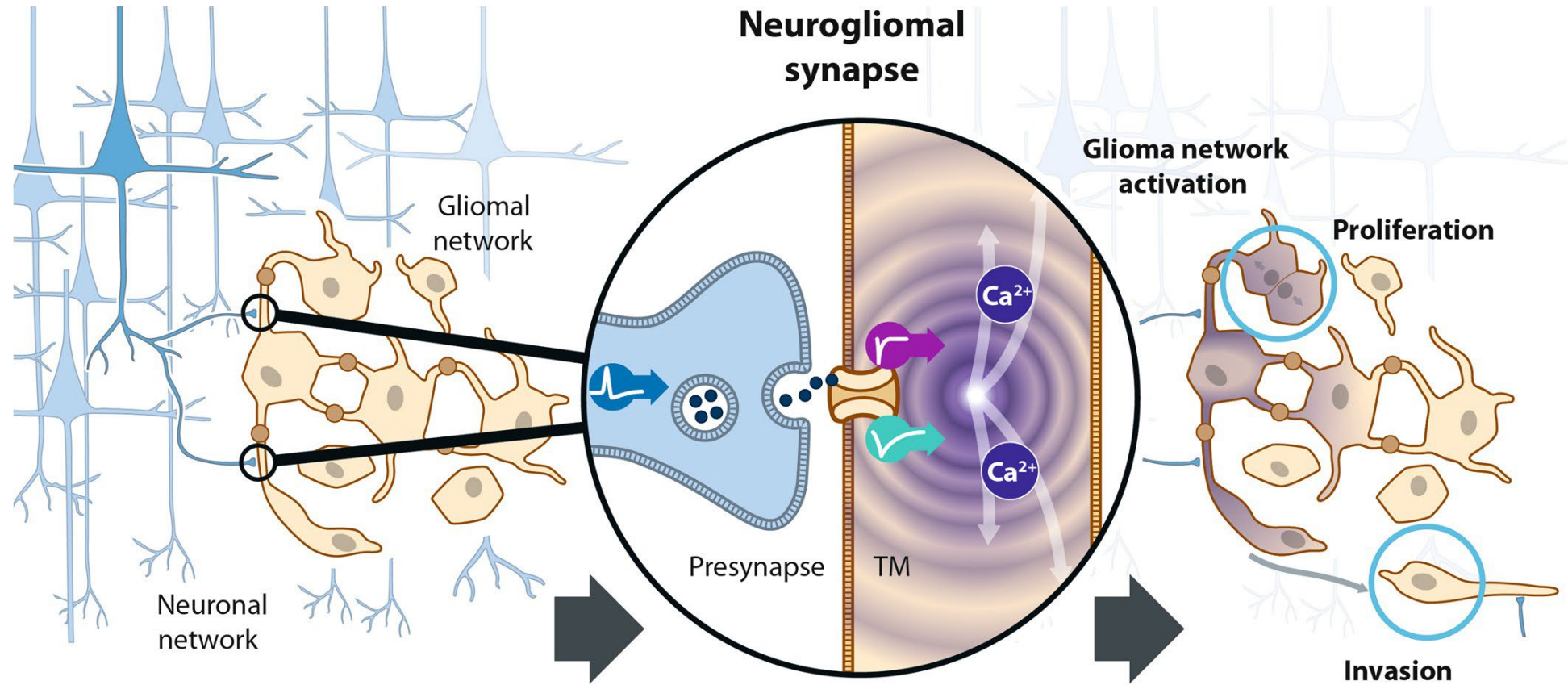
mandal et al (2020) brain

nodal healthy brain activity  
(offset calculated on the aperiodic  
component of MEG spectrum)



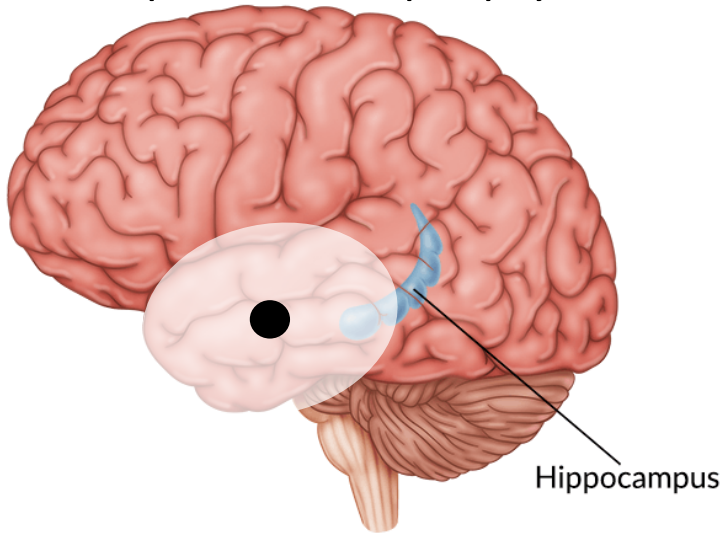
numan et al (2022) brain

# higher brain activity actually causes tumor growth



# but how do scales correlate in the same individual?

temporal lobe epilepsy

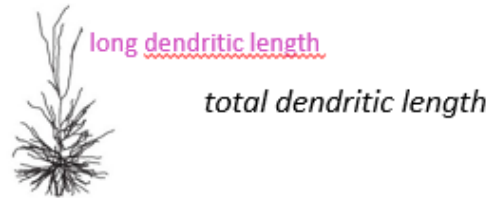


A micro-scale

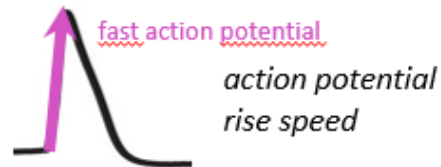
- resected node  
middle temporal gyrus
- other nodes



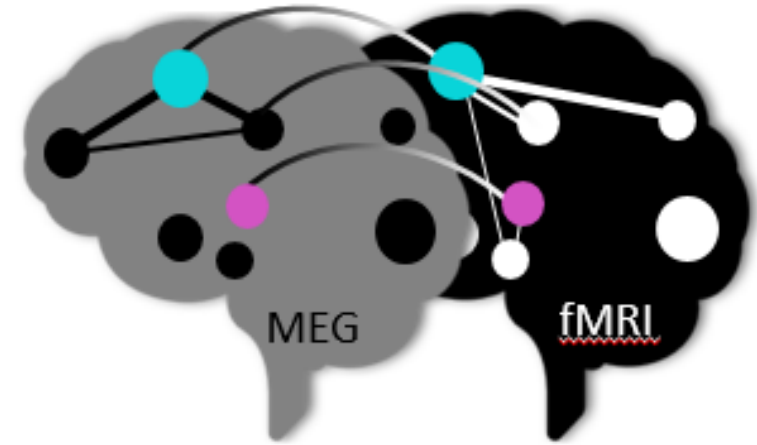
**biocytin-labelling**



**whole-cell recording**

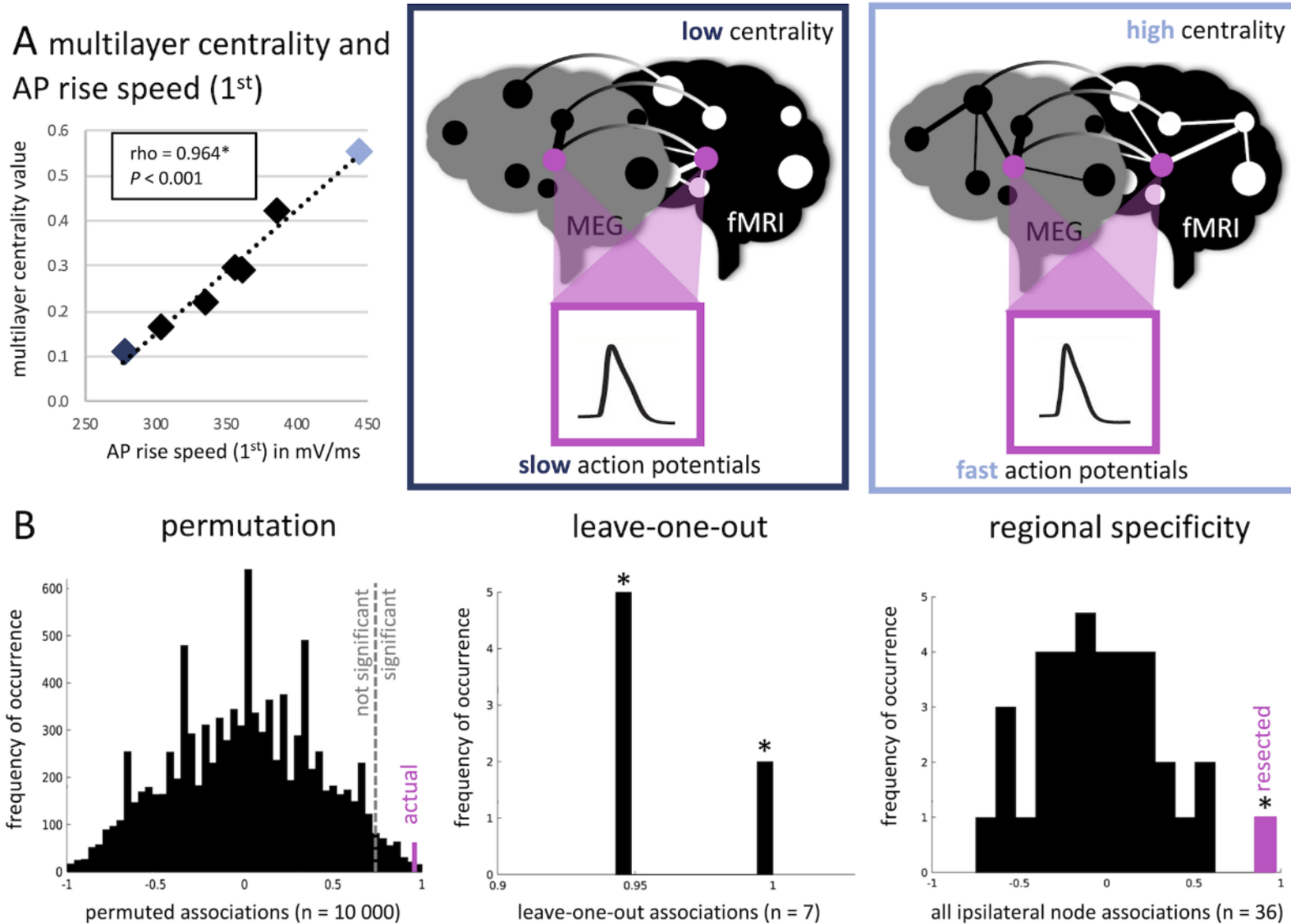


low versus high multilayer centrality



- multilayer eigenvector centrality
- rsfMRI layer, MEG layer (theta 4-8 Hz)
  - interconnected multiplex
  - MST to normalize across layers

# integrative properties go hand in hand across scales

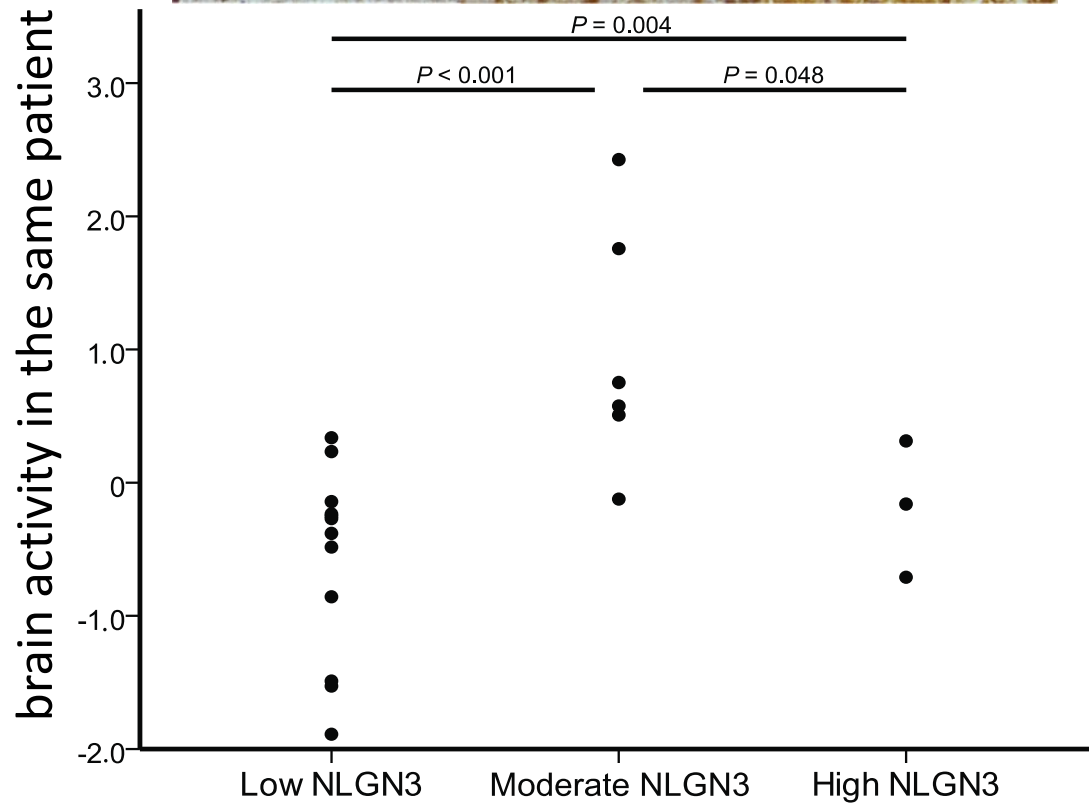
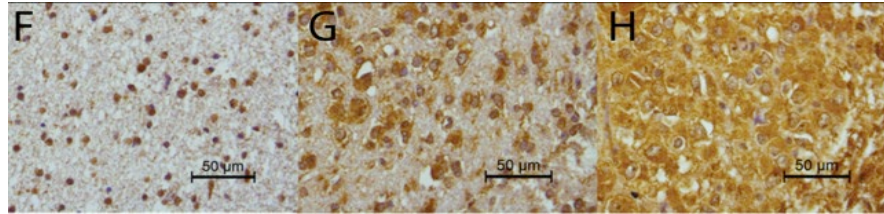


# ... also in glioma patients

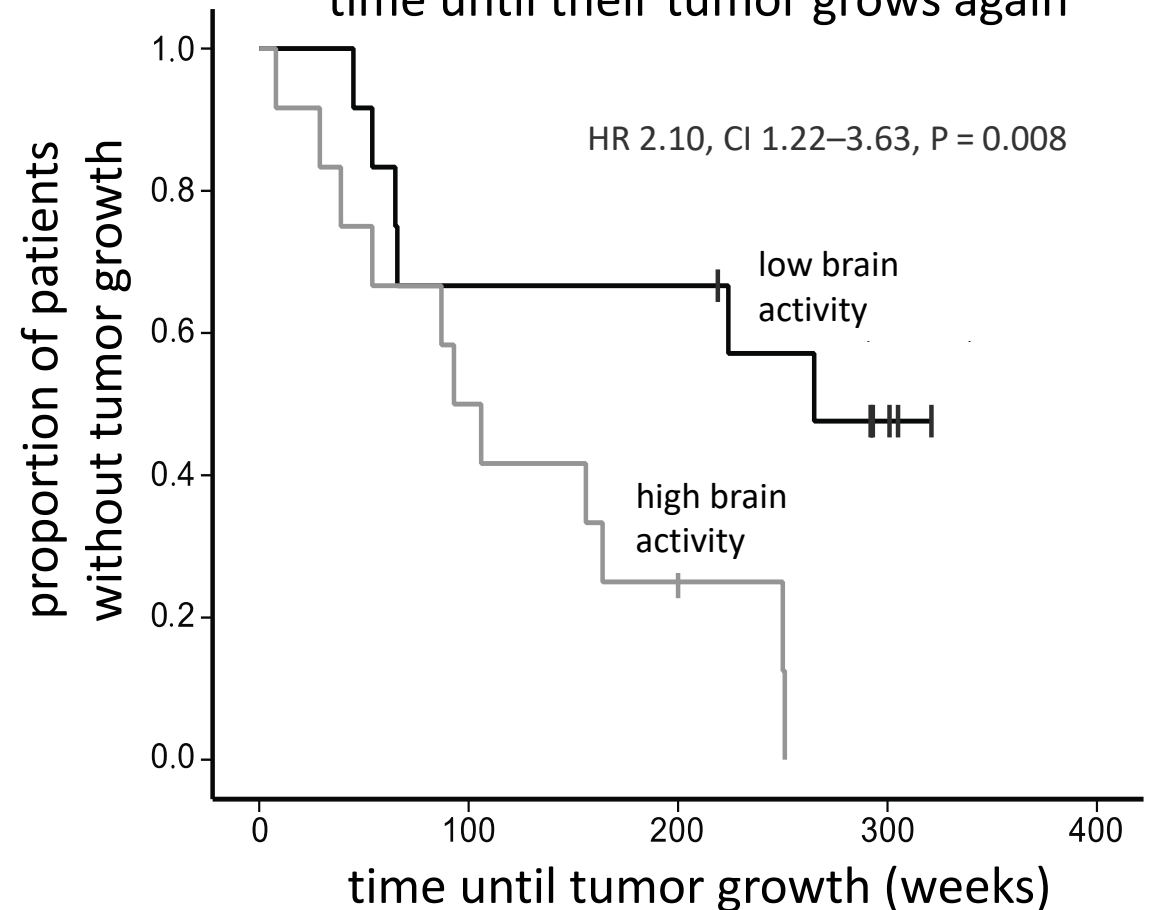
jolanda  
derks



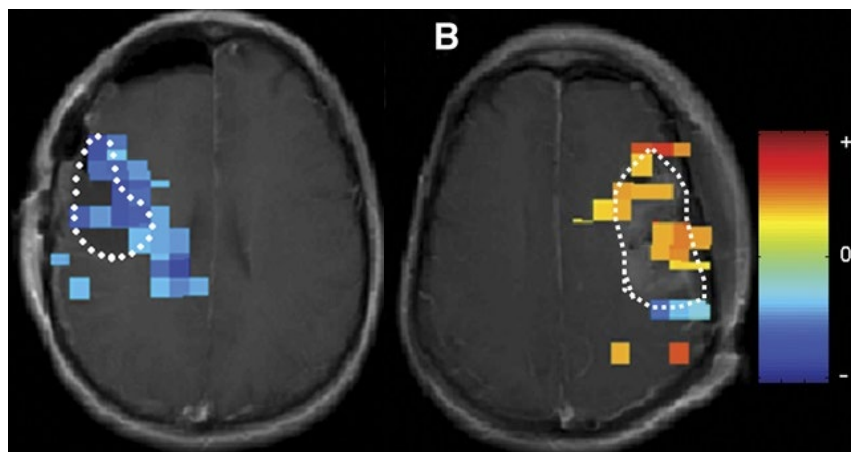
neuroligin-3 measured in the tumor tissue as a proxy of tumor-brain network integration



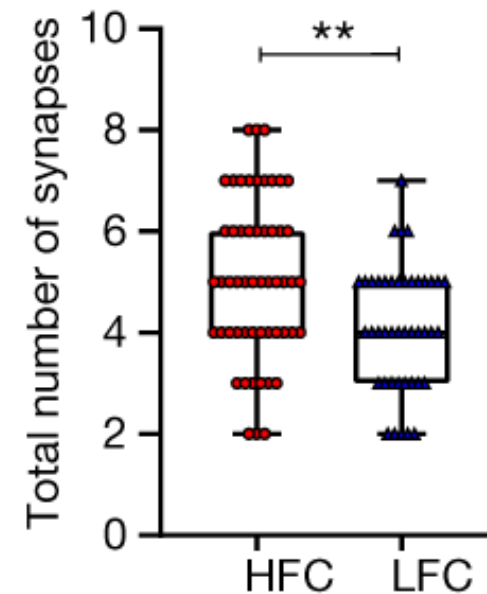
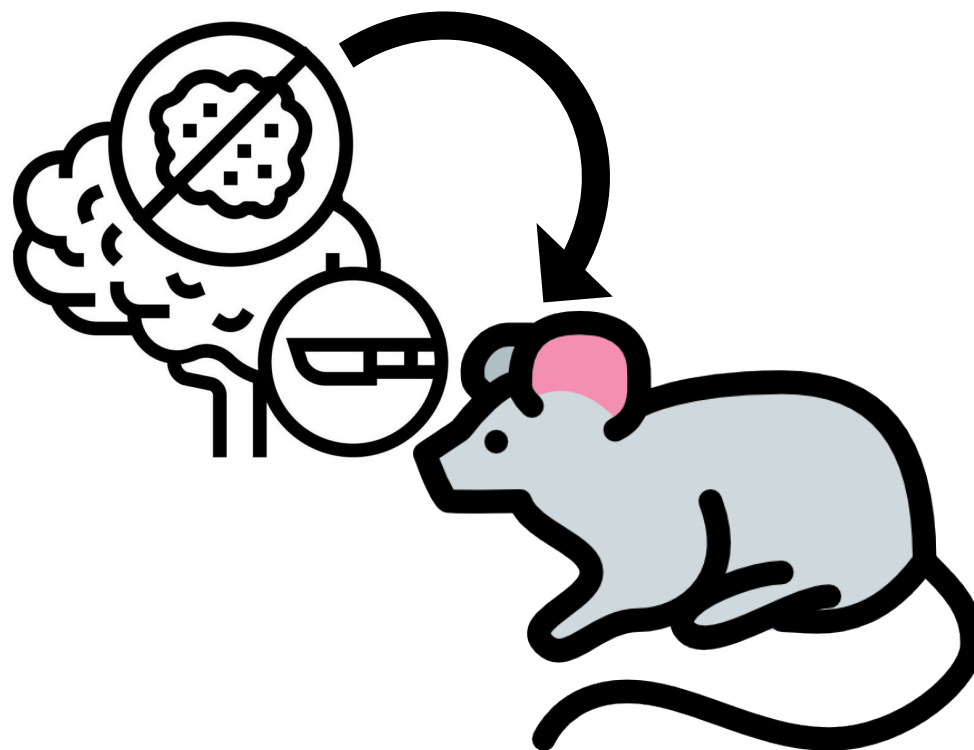
patients with low brain activity (and lower tumor-brain integration) have twice as much time until their tumor grows again



there is a causal link between high MEG tumor connectivity and more tumor-neuron connections



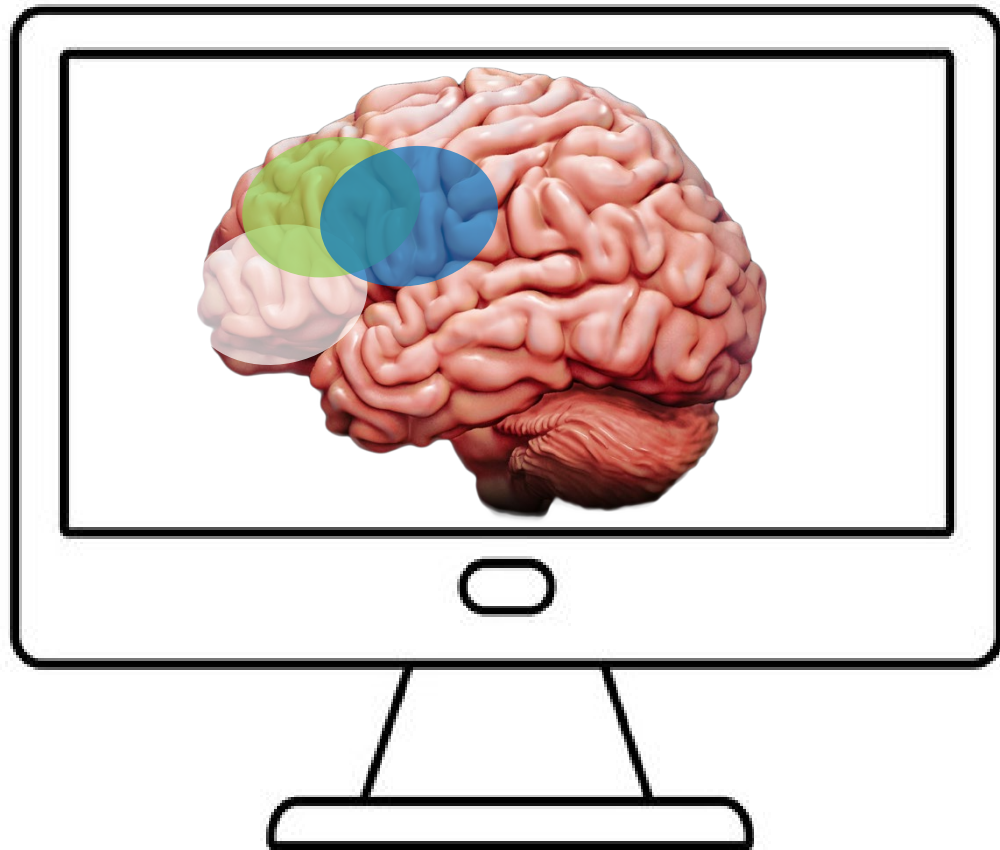
low functional connectivity (LFC)      high functional connectivity (HFC)



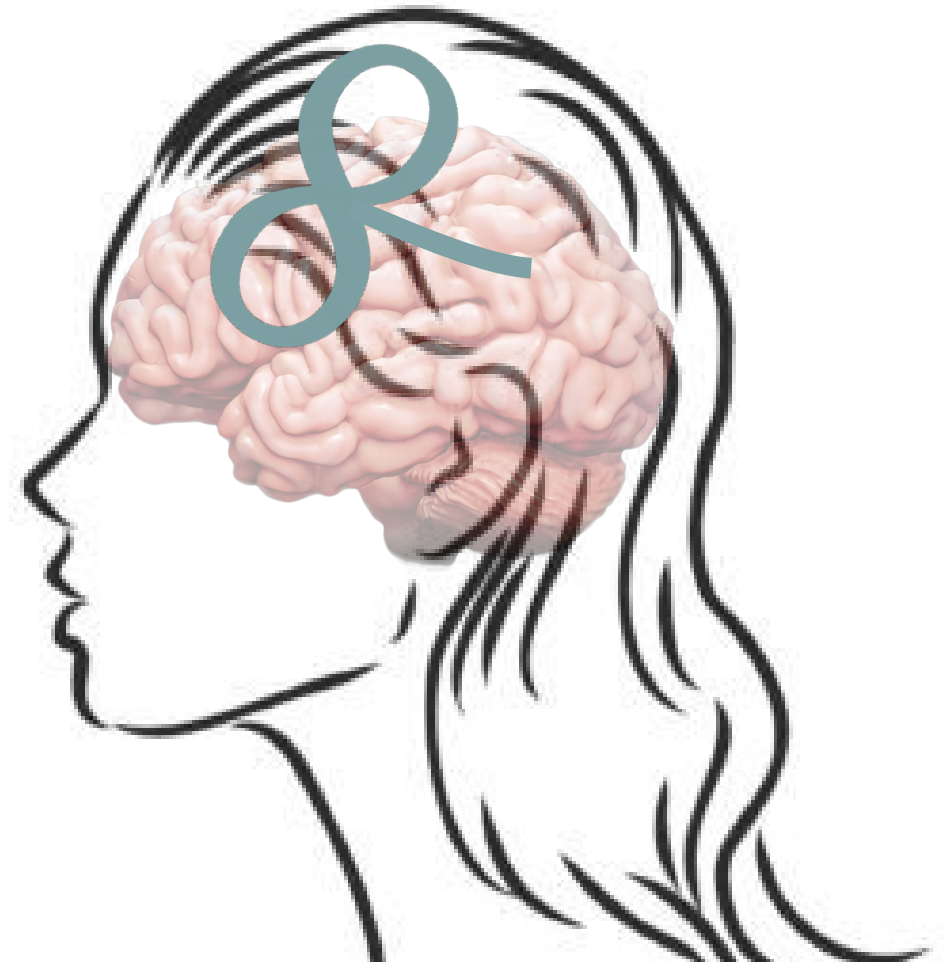
MEG | 1000s of nodes | functional connectivity

so what can we do with these multiscale network insights?

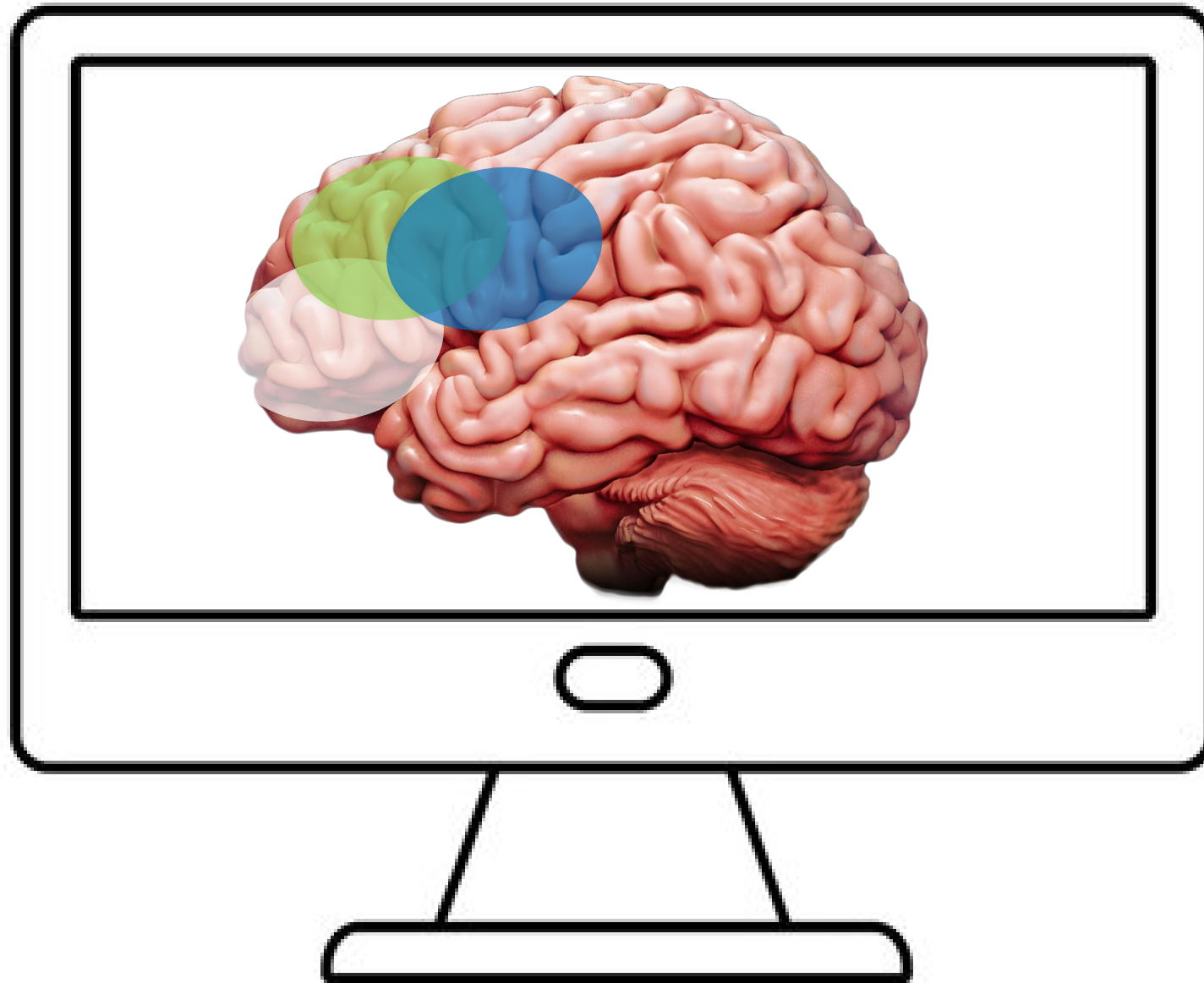
virtual  
neurosurgery



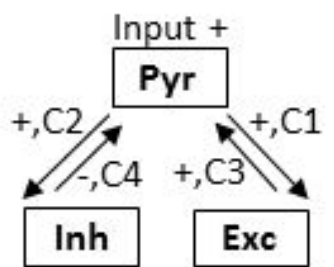
personalized non-invasive  
brain stimulation



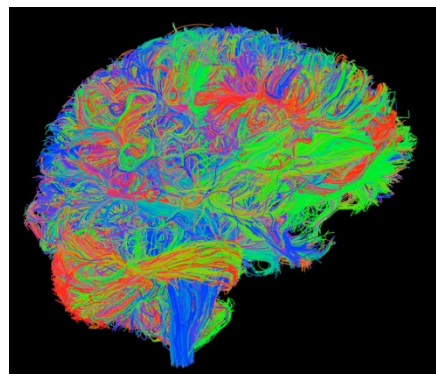
# virtual neurosurgery



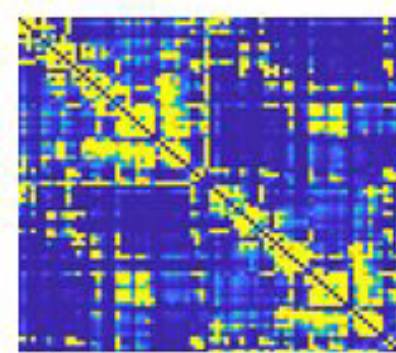
# individualized computational modeling of functional connectivity



each brain region is represented by a single neural mass



tractography determines structural connectivity between brain regions

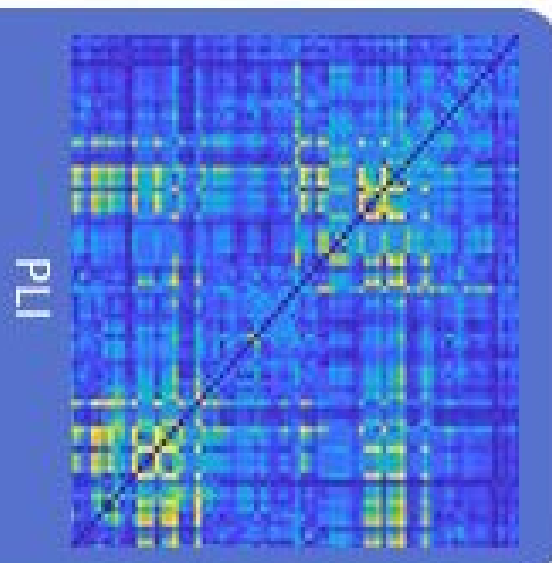
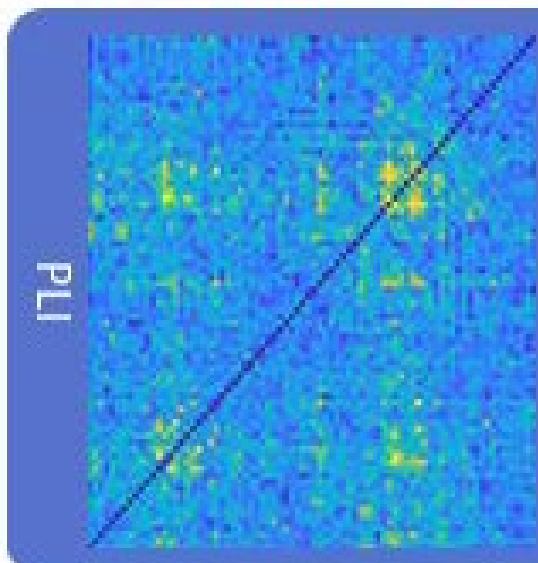


structural connectivity matrix determines coupling between neural masses



simulation yields a time series per brain region

empirical functional matrix



simulated functional matrix

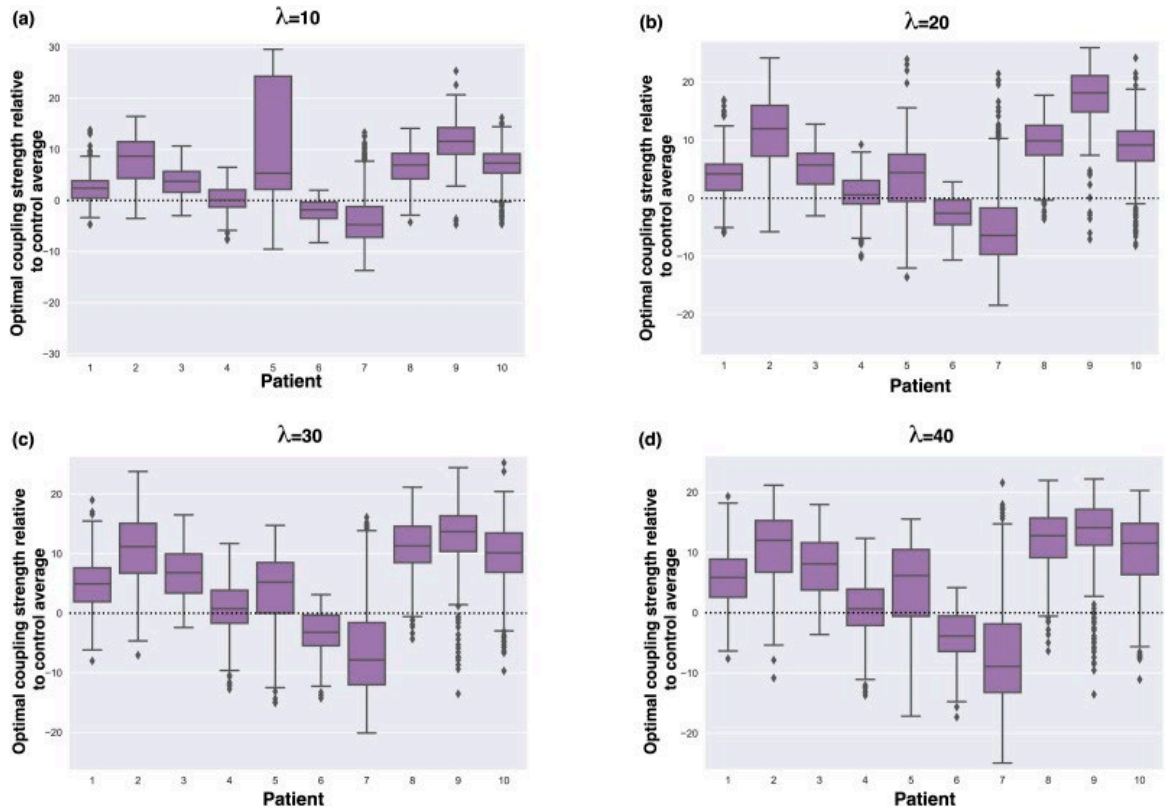


shanna kulik

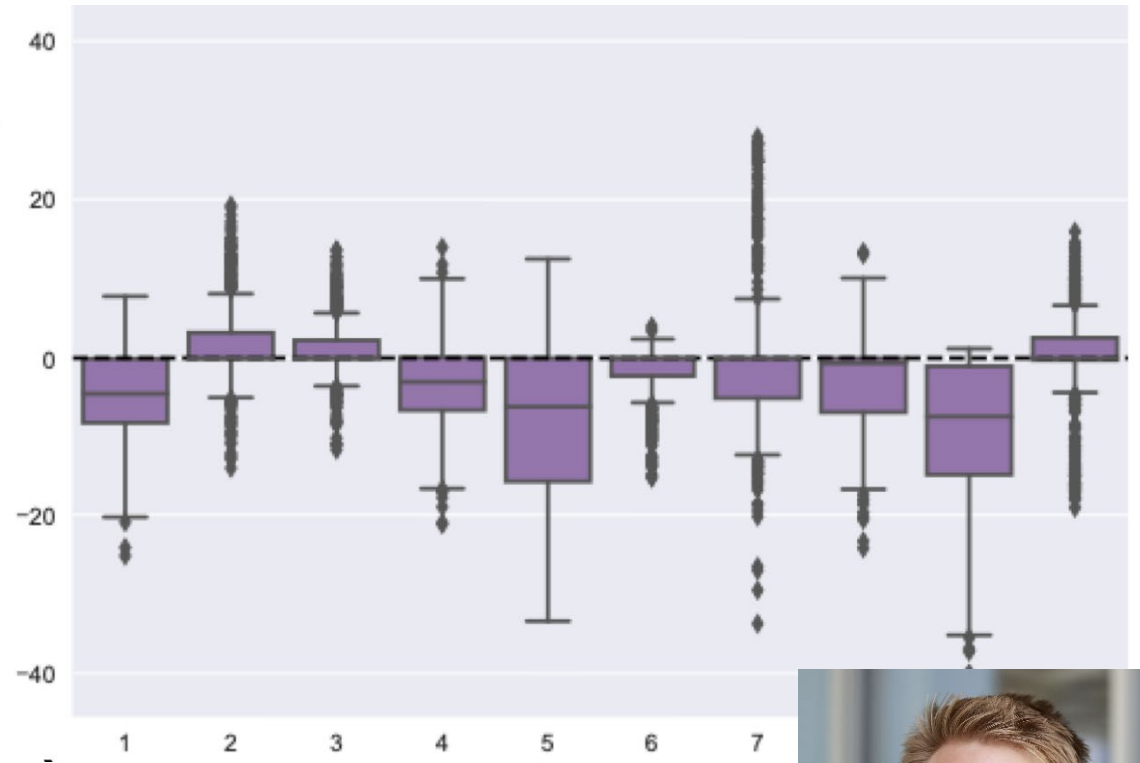
# modeling tumor resections in glioma patients

we recapitulate the pathologically high regional coupling in most patients' individualized models

pathological coupling decreases after virtual resection of the tumor areas



Relative coupling strength change after functional connectivity



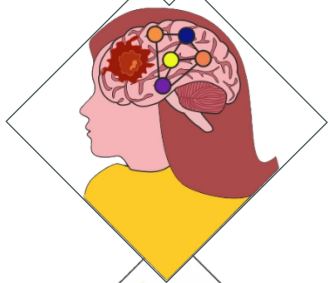
christoffer alexandersen



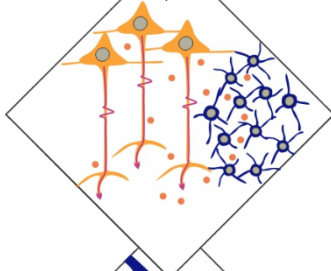
# personalized non-invasive brain stimulation



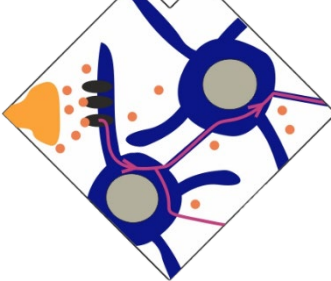
improves symptoms like depression and cognitive deficits



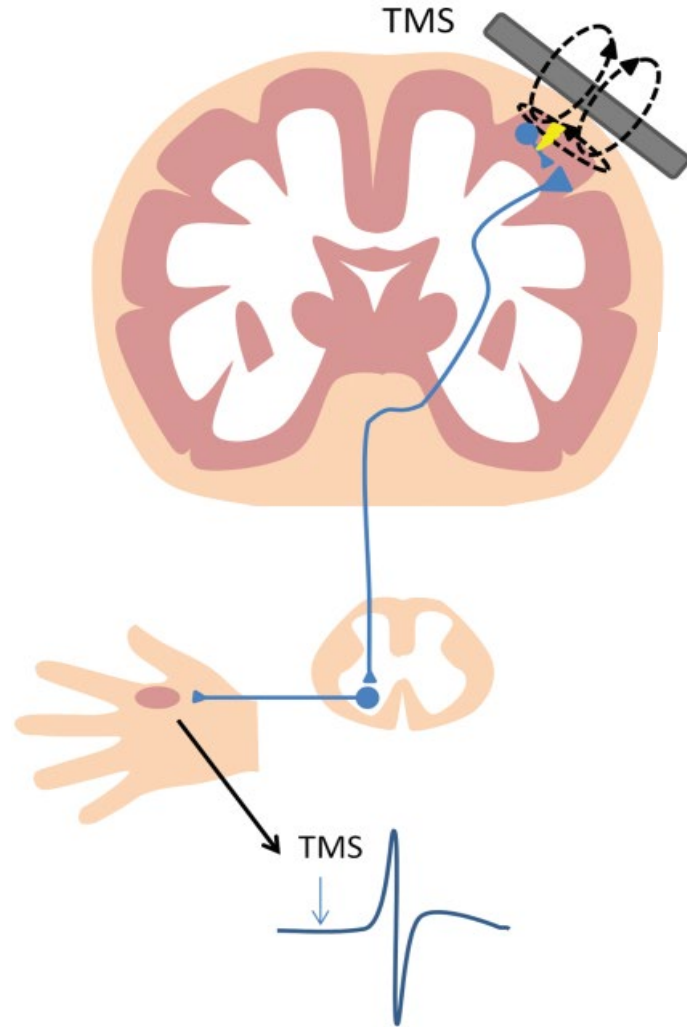
alters network topology, also at a distance



impacts circuit activity



transcranial magnetic stimulation (TMS) induces action potentials



# what does it look like?

maxine operates the  
stimulation machinery,  
increasing or decreasing the  
simulation intensity  
depending on the  
(non)visible motor response

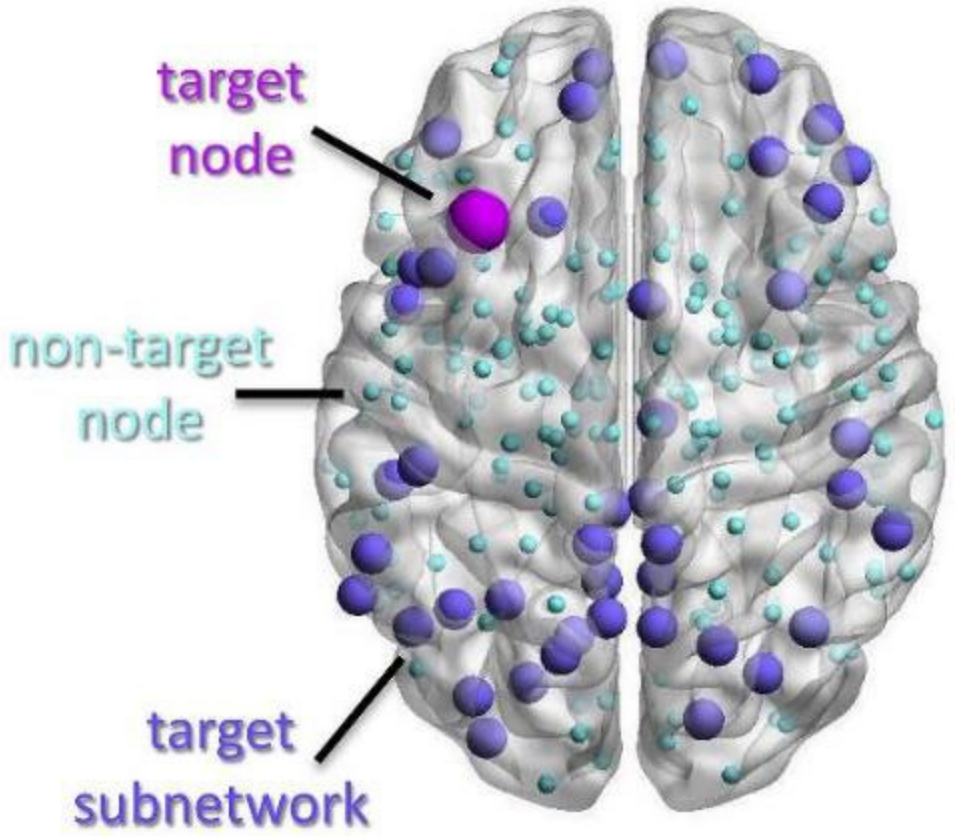
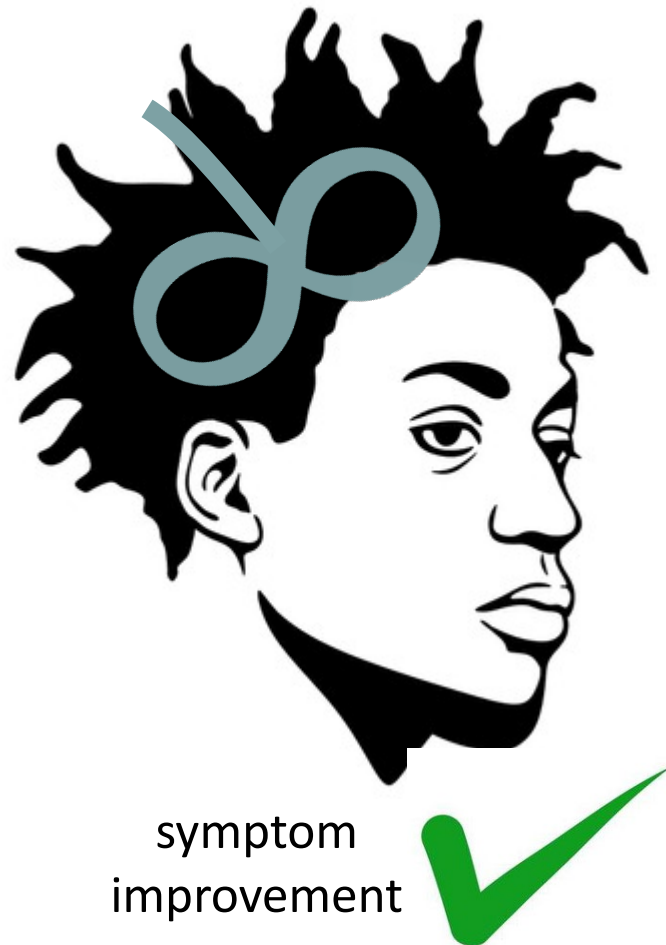


lucas operates the coil,  
moving and angling it to  
get a motor response

marieke is the “patient”

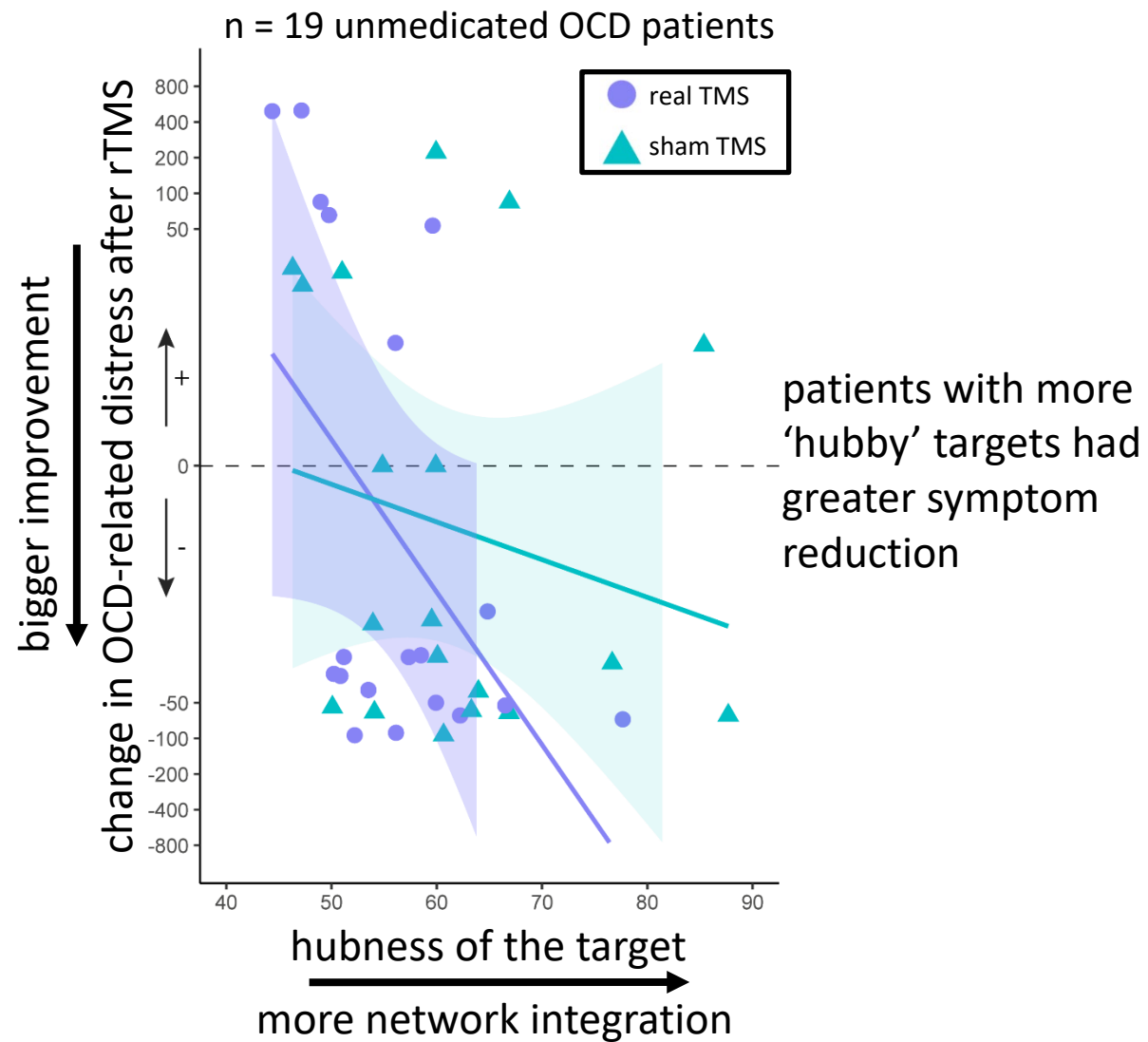
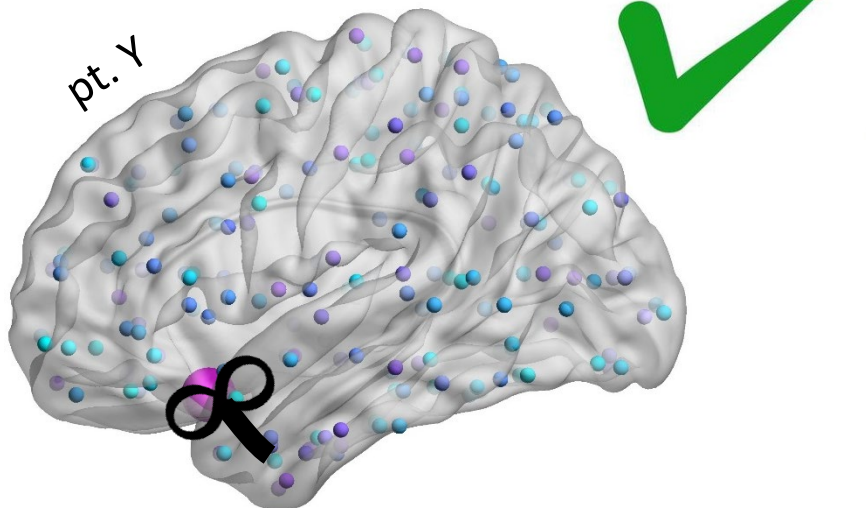
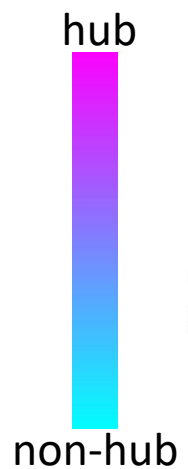
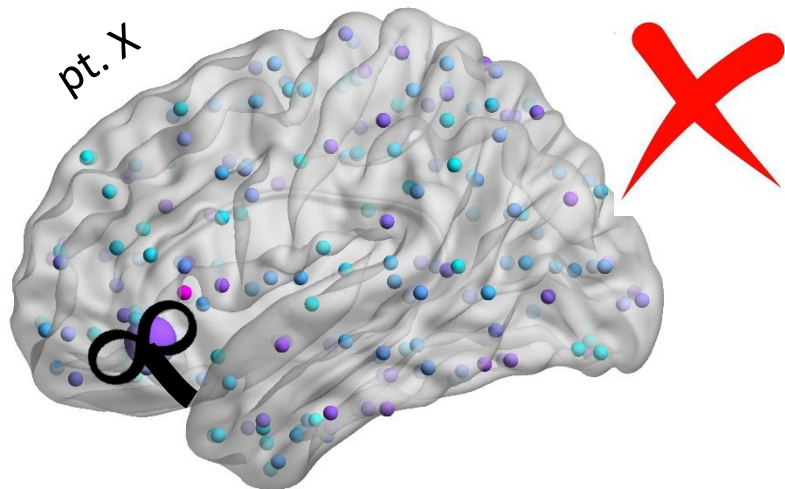
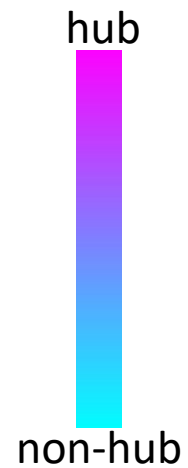
TMS is currently clinically used for depression, obsessive compulsive disorder, migraine to restore lower network integration

can personalized network properties of the target node explain variations in clinical response?

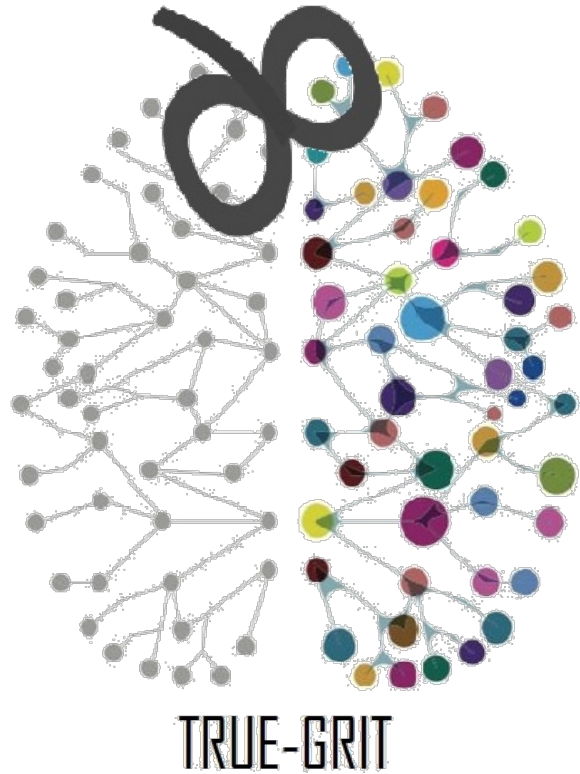


does TMS targeted at the biggest hub cause the most effect in terms of restoring network integration?

# TMS efficacy and hubness of the target region



# network-based targeting with TMS to improve cognitive complaints in glioma patients



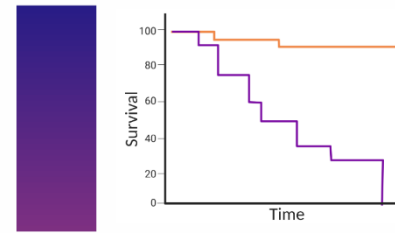
- frontal glioma patients with cognitive complaints
- target node = most strongly connected parietal node
- rTMS sessions 3x per week, for 7 weeks
- cognitive strategy training to boost the TMS
- n=4 so far!



maxine gorter

# how else can we use these multiscale network neuroscience insights to improve patient care?

## prognostication



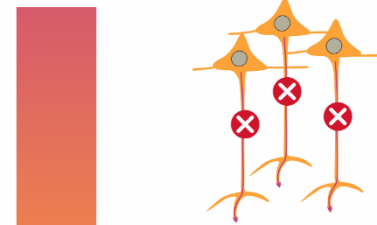
- functional decline
- cognitive deterioration
- progression-free survival
- overall survival

## resective strategy



- preoperative and peri-operative functional mapping
- determining the epileptogenic zone
- selection of patients for awake craniotomy

## disease-modifying treatment



- (hyper)activity antagonists
- inhibitory (non-invasive) brain stimulation

## disease and treatment monitoring

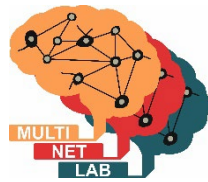


- disease monitoring, e.g. differentiating between tumor progression and radionecrosis
- monitoring treatment efficiency

## symptom management



- tailored (non-invasive) brain stimulation
- response prediction of interventions aimed at symptom management



[www.multinetlab.com](http://www.multinetlab.com)



[multinetlab-amsterdam](https://github.com/multinetlab-amsterdam)



[l.douw@amsterdamumc.nl](mailto:l.douw@amsterdamumc.nl)



[lindadouw.bsky.social](https://lindadouw.bsky.social)



Athinoula A. Martinos Center  
For Biomedical Imaging



Amsterdam Neuroscience



MASSACHUSETTS GENERAL HOSPITAL



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Society in Science



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KWF



EpilepsieNL

Brigit Thomassen, Jaap Reijneveld, Marike van Lingen, Linda Douw, Dorien Maas, Eva Koderman, Lucas Baudouin, Iza Oostra, Rachel Smith, Mona Zimmermann, Maxine Gorter, Marieke Blom  
not pictured: Lucas Breedt, Floris Tjihuis

**MULTINET alumni**

- Vera Belgers
- Jolanda Derks
- Shanna Kulik
- Tianne Numan

**University of Amsterdam**

- Matthan Caan
- Vera Keil
- Anouk Schrantee

**Brain Tumor Center Amsterdam**

**Brain Tumor Center Amsterdam**

- Martin Klein
- Mathilde Kouwenhoven

- Don van den Bergh
- Tessa Blanken

- Denny Borsboom
- Maarten Marsman

**UMC Utrecht**

- Fernando Santos
- Edwin van Dellen

**Oxford University**

- Christoffer Alexandersen
- Alain Goriely

**Martinos Center/Harvard Medical School/ MGH**

- Elizabeth Gerstner
- Julie Miller

**UCSF**

- Steve Stufflebeam
- Srikantan Nagarajan

- Jennie Taylor
- Christina Weyer-Jamora

**VU Amsterdam**

- Christian Bick
- Natalia Goriounova

- Christiaan de Kock
- Huib Mansvelder

**CERVO research center Canada**

- Prejaas Tewarie

**Anatomy & Neurosciences**

- Wilma van de Berg
- Jeroen Geurts

- Odile van den Heuvel
- Laura Jonkman

- Menno Schoonheim
- Chris Vriend

- Ysbrand van der Werf

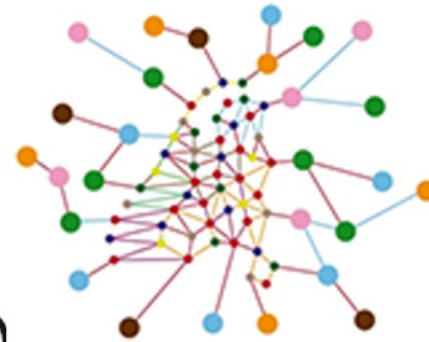
**Clinical Neurophysiology**

- Arjan Hillebrand
- Ida Nissen

- Kees Stam

**Radiology & Nuclear Medicine**

- Frederik Barkhof



NetSci

Dutch Network Science Society

join our community and  
(self)nominate a young talent for  
our prize (coming soon!)

