

fellowship project

# the molecules of behavior

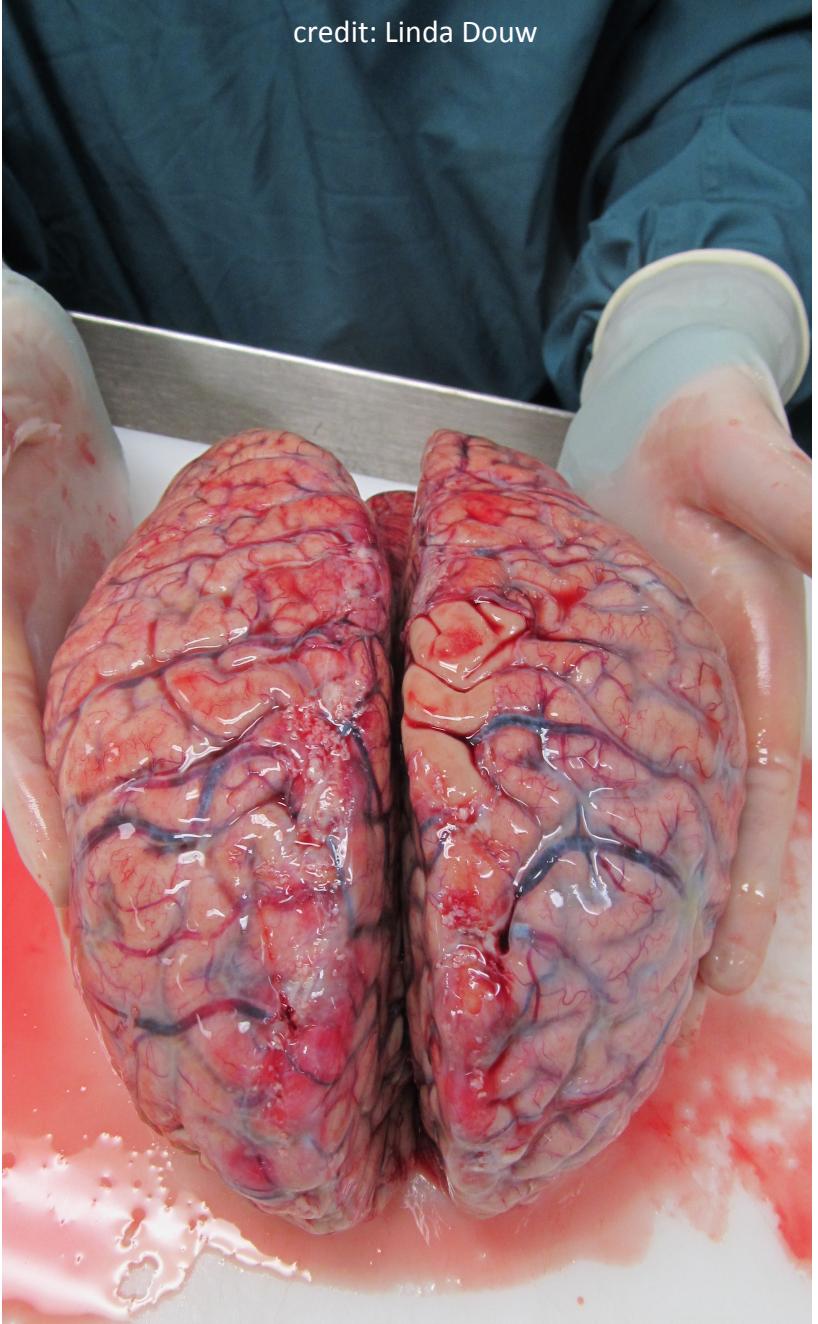
how brain tumors link cellular biology to  
large-scale brain networks and cognition

today's title

time, space and scale  
in the brain connectome  
tying it all together

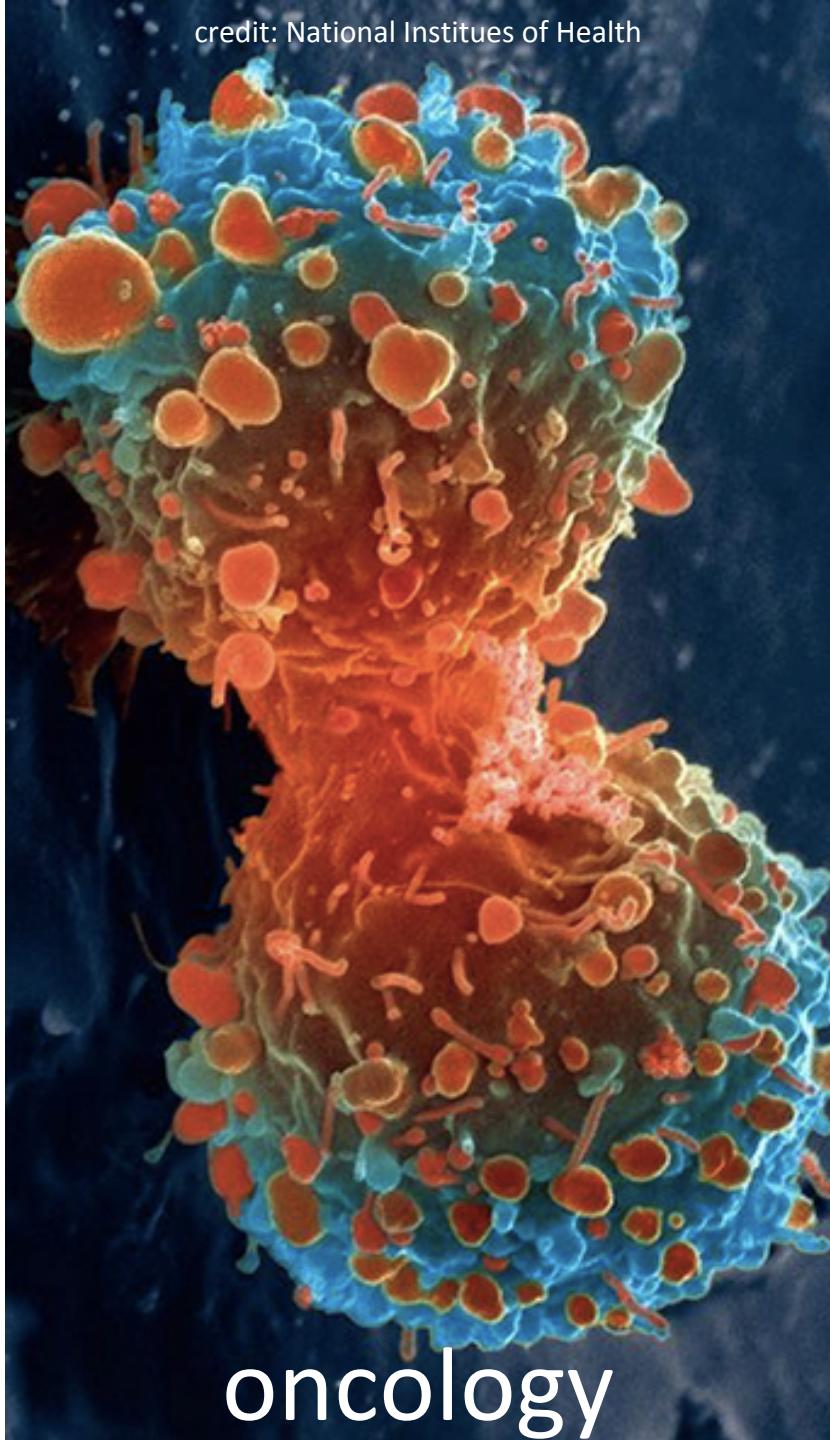
linda douw

credit: Linda Douw



neuroscience

credit: National Institutes of Health



oncology

# glioma

primary brain tumor

incidence 7-19/100,000

median survival 14 m – 9 y

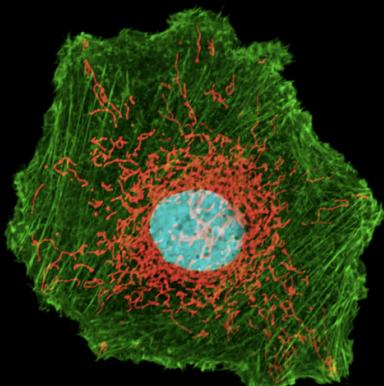
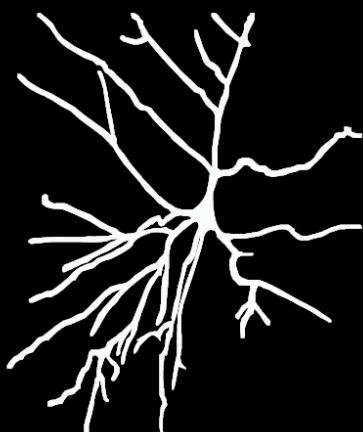
100% mortality rate

poorly understood cognitive deficits

“molecules”

≈

neurons and/or  
glioma cells



“behavior”

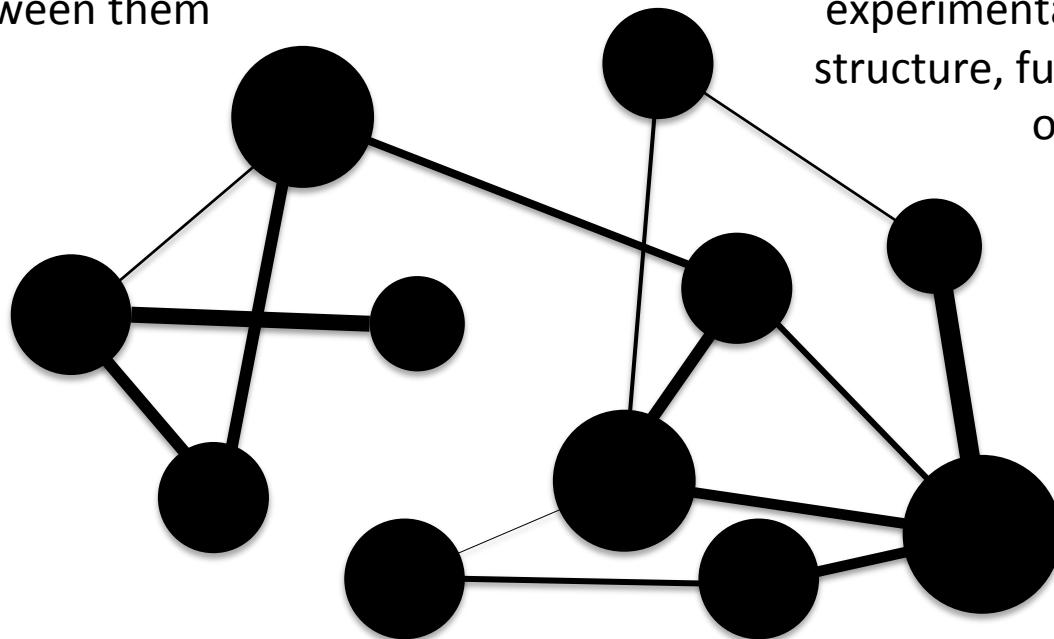
≈

cognition



# graph theory

1 | deals with any system that can be represented by nodes and connections between them



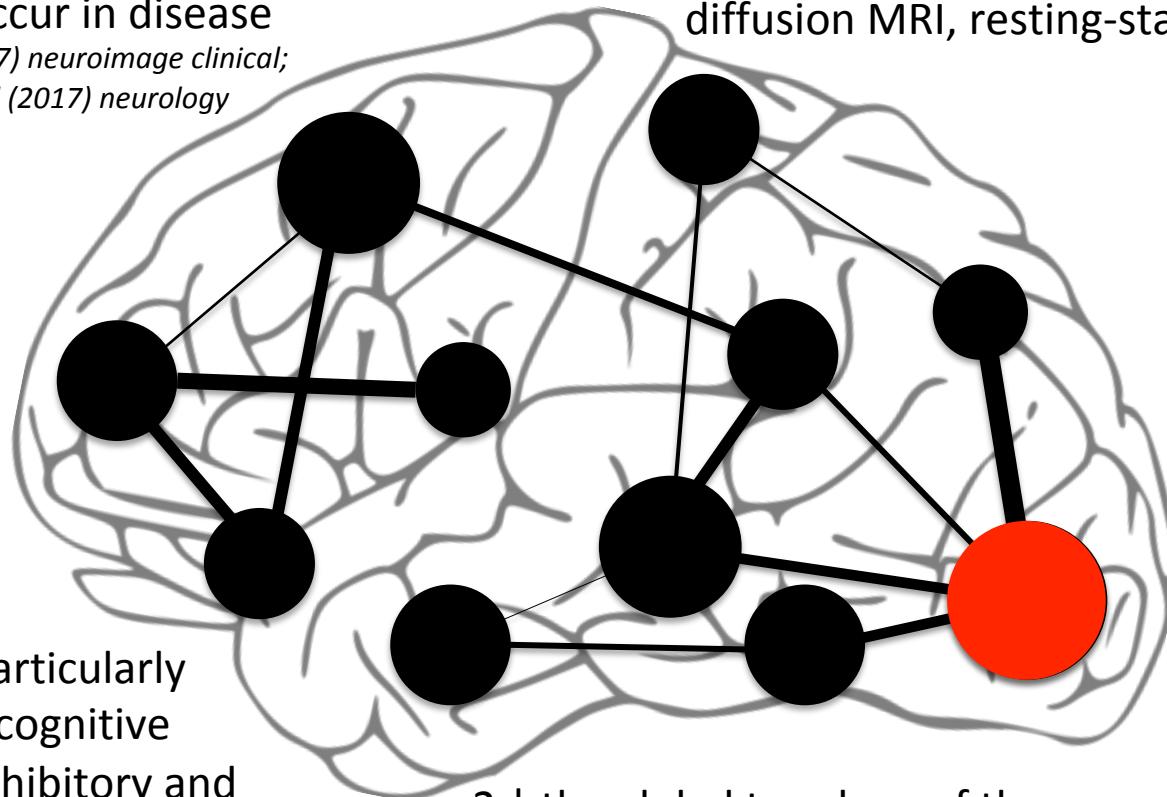
2 | well-vetted theoretical and experimental knowledge on the structure, function and dynamics of systems

3 | unifying theory that may facilitate (clinical) neuroscience

# the brain network or 'connectome'

4 | hubs and their connections are also most dysfunctional when cognitive deficits occur in disease

*derkx et al (2017) neuroimage clinical;  
meijer et al (2017) neurology*



3 | hubs are particularly conducive to cognitive impact of both inhibitory and excitatory perturbation

*fitzsimmons et al (under review);  
quaak et al (in preparation)*

1 | can be measured in humans using non-invasive macroscopic techniques like diffusion MRI, resting-state fMRI, EEG, MEG

2 | the global topology of the connectome correlates with cognitive (dys)function in health and disease and may become a predictive marker of decline

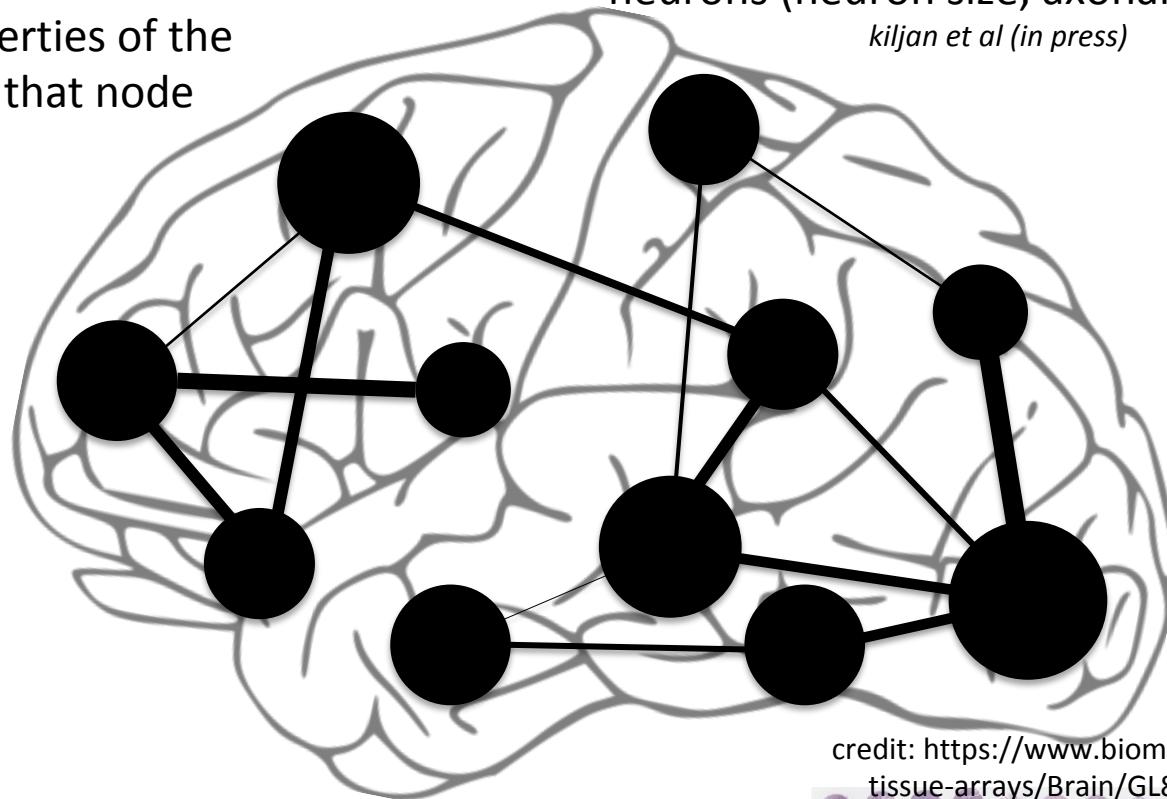
*carbo et al (2017) scientific reports*

# the unique window of opportunity

2 | translate macroscopic  
nodal properties to  
microscopic properties of the  
neurons within that node

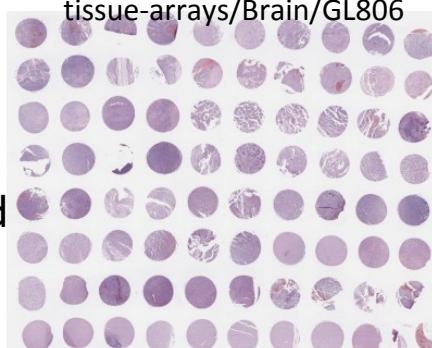
3 | macroscopic hubness correlates with morphology of  
neurons (neuron size, axonal density) ...

*kiljan et al (in press)*



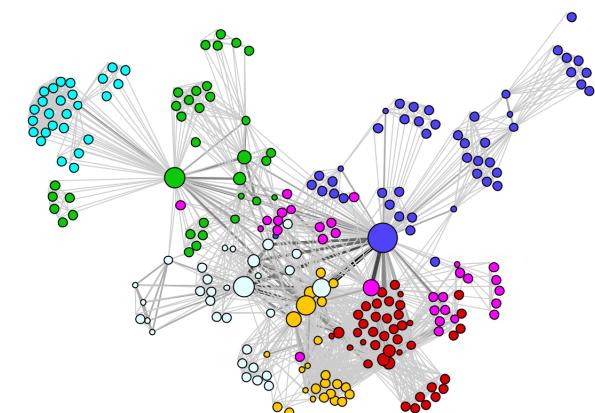
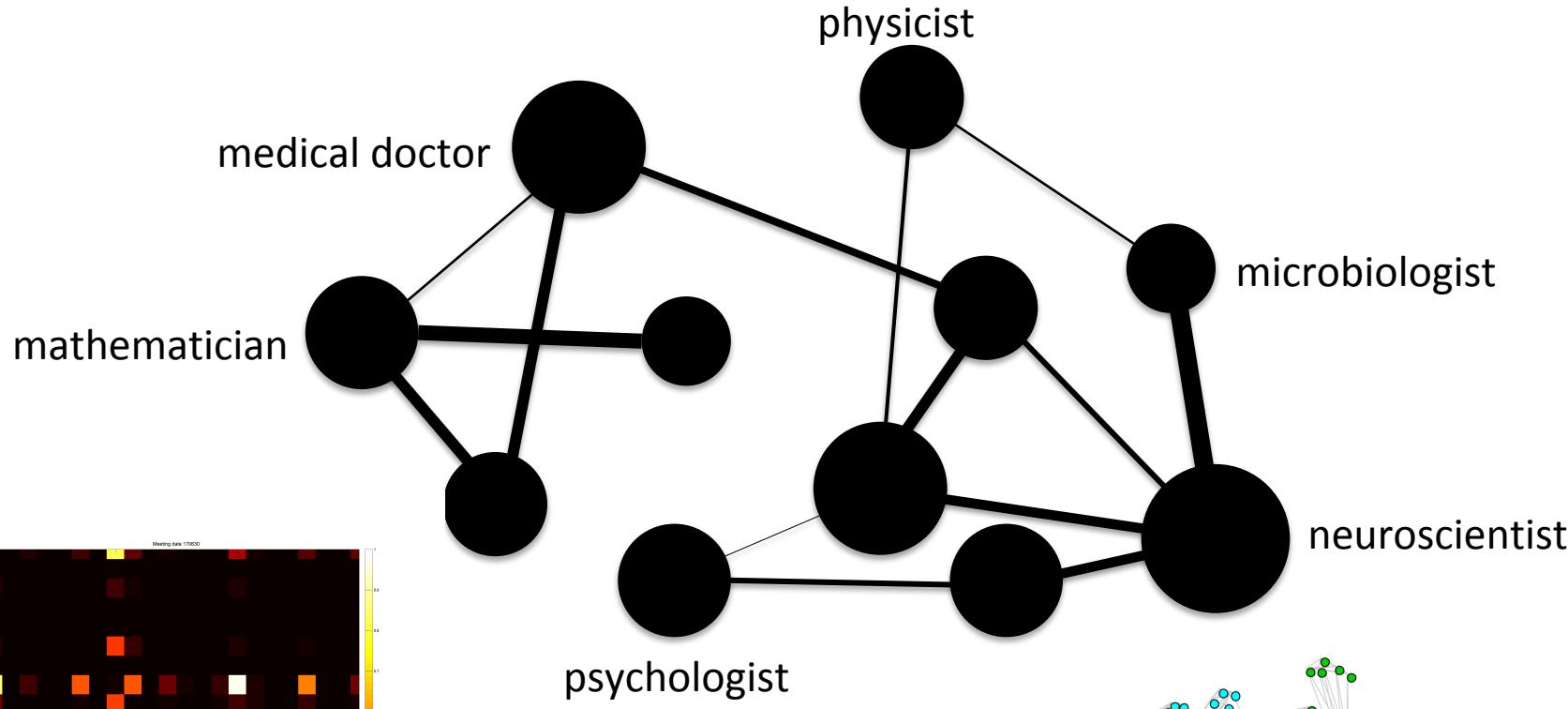
1 | glioma patients undergo tumor  
resection and postmortem section,  
which includes both tumor tissue and  
peritumor/healthy tissue

credit: [https://www.biomax.us/  
tissue-arrays/Brain/GL806](https://www.biomax.us/tissue-arrays/Brain/GL806)



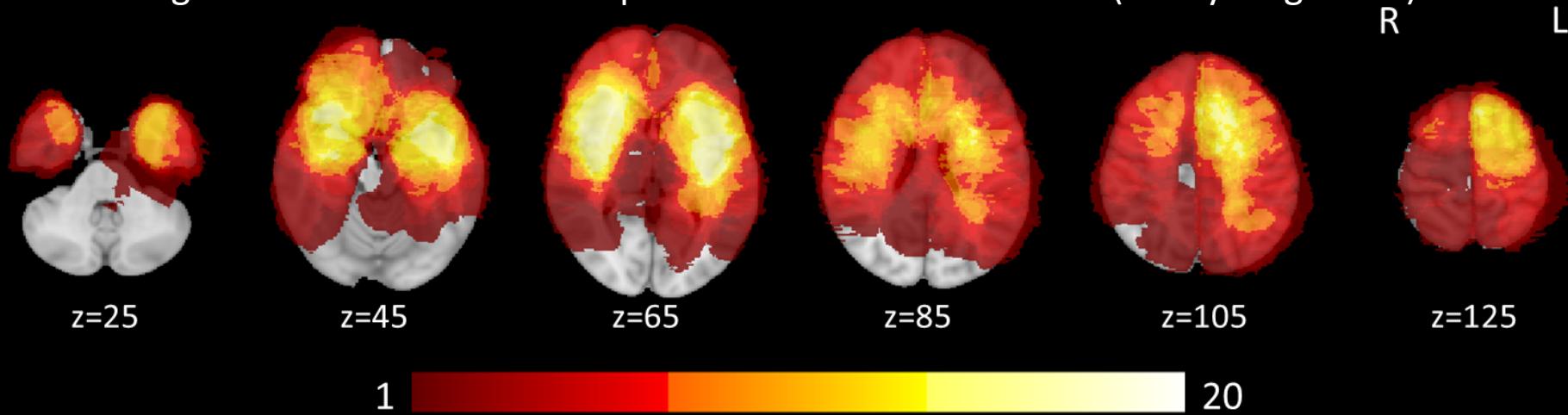
credit: Linda  
Douw

# unexpected yield part 1 | establishing a translational, multidisciplinary team

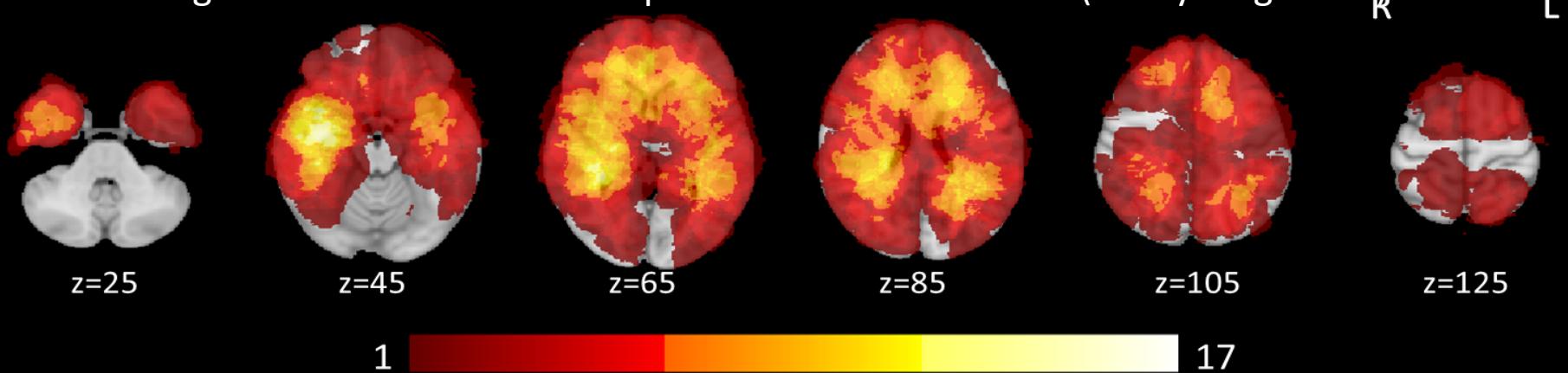


# glioma does not occur randomly

glioma occurrence heatmap in Amsterdam cohort n=83 (newly diagnosed)

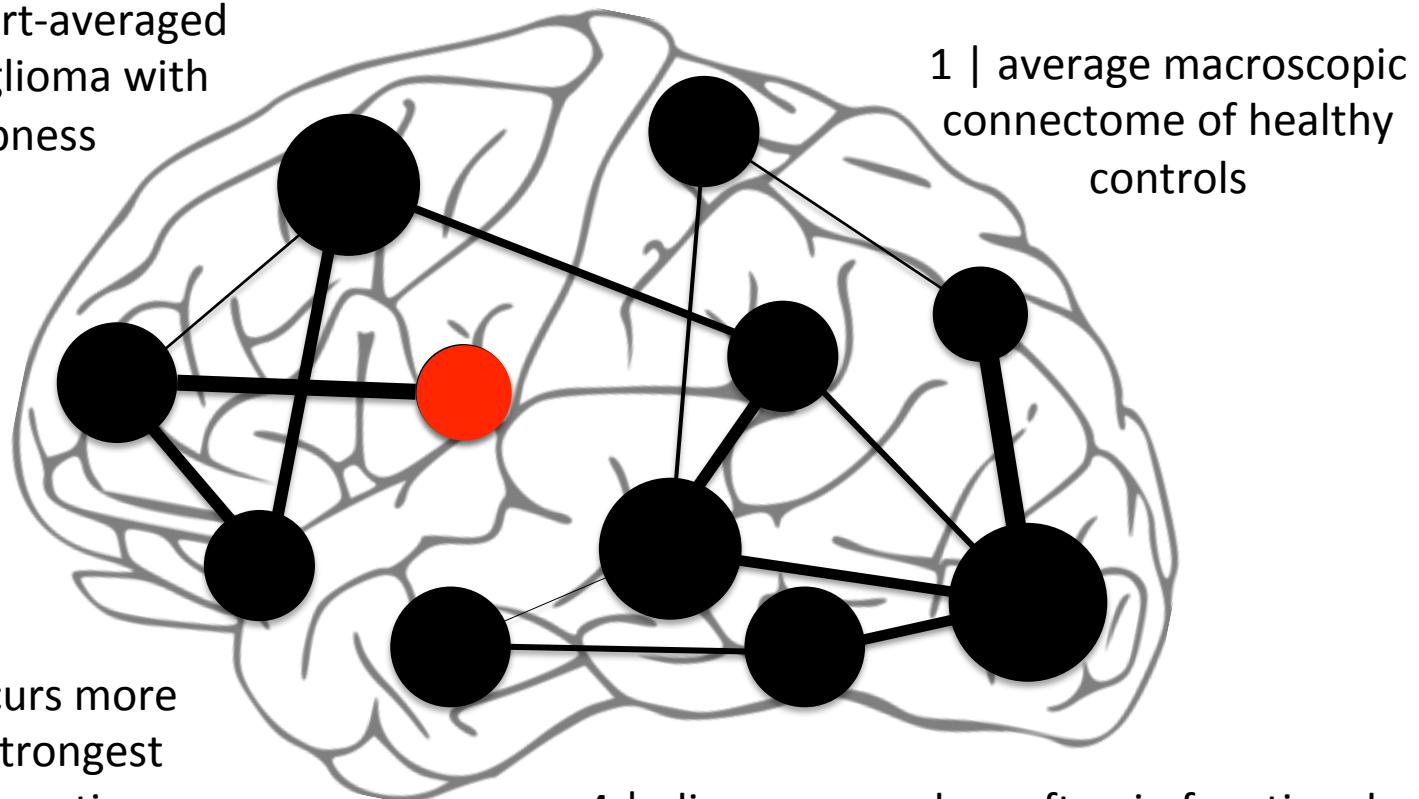


glioma occurrence heatmap in Boston cohort n=120 (newly diagnosed)



# does general occurrence of glioma relate to hubness?

2 | overlay cohort-averaged occurrence of glioma with nodal hubness



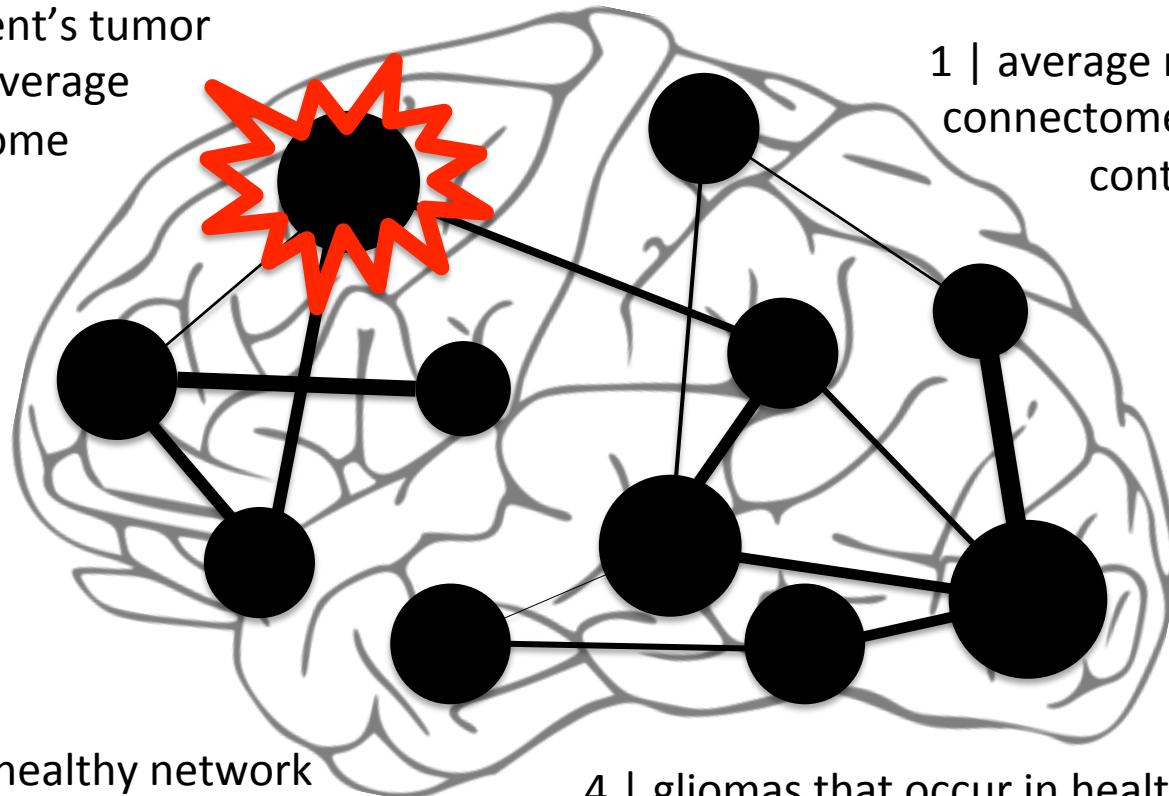
3 | glioma occurs more often in the strongest structural connections  
*numan et al (under review)*

1 | average macroscopic connectome of healthy controls

4 | glioma occurs less often in functional hubs, while there was association between glioma occurrence and structural hubs  
*numan et al (under review)*

# does individual glioma location in the connectome relate to cognition?

2 | overlay patient's tumor mask with average connectome



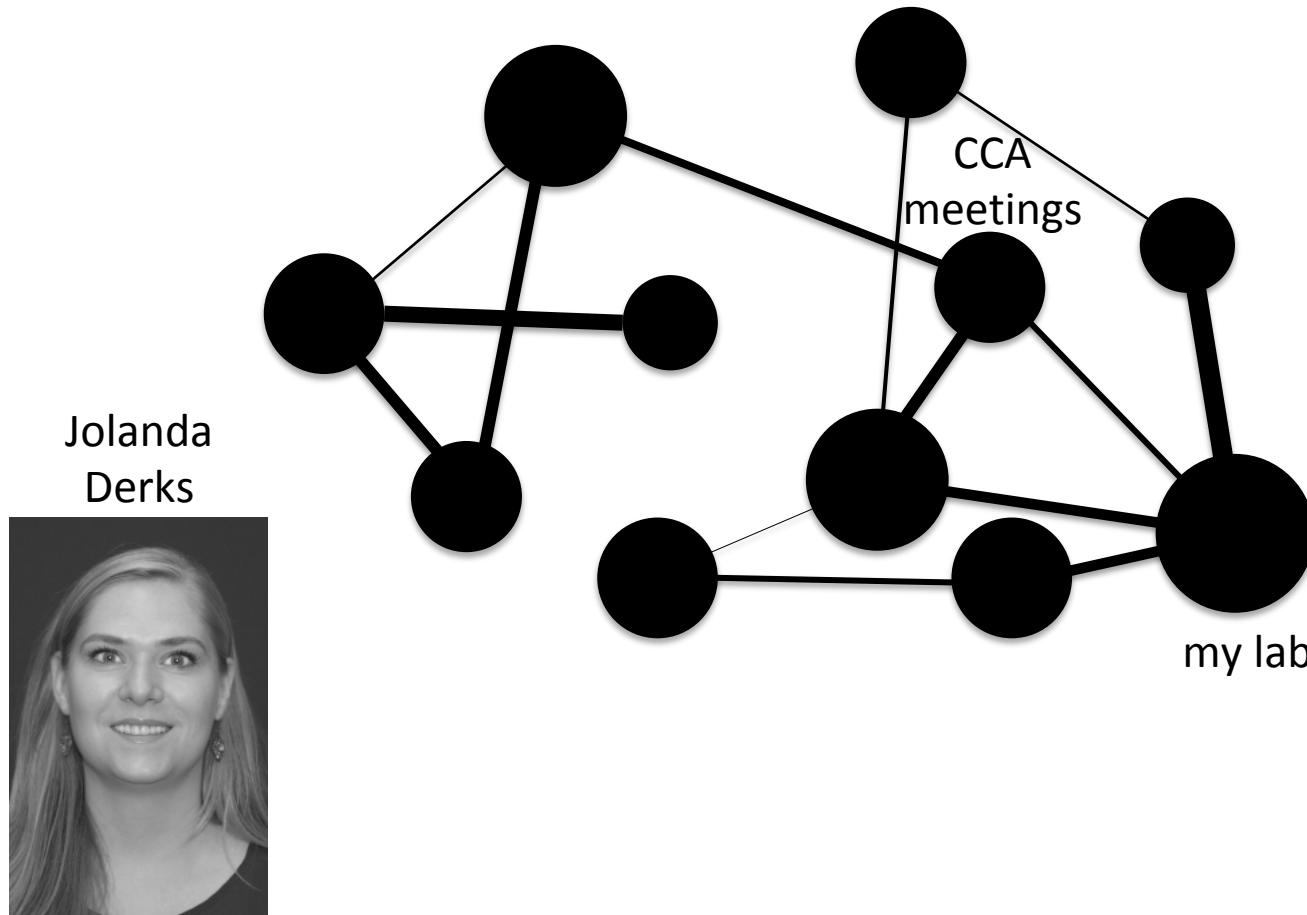
1 | average macroscopic connectome of healthy controls

3 | extract healthy network characteristic (in this case: hubness) of patient's tumor location, under the hypothesis that gliomas in hub nodes present with more cognitive deficits

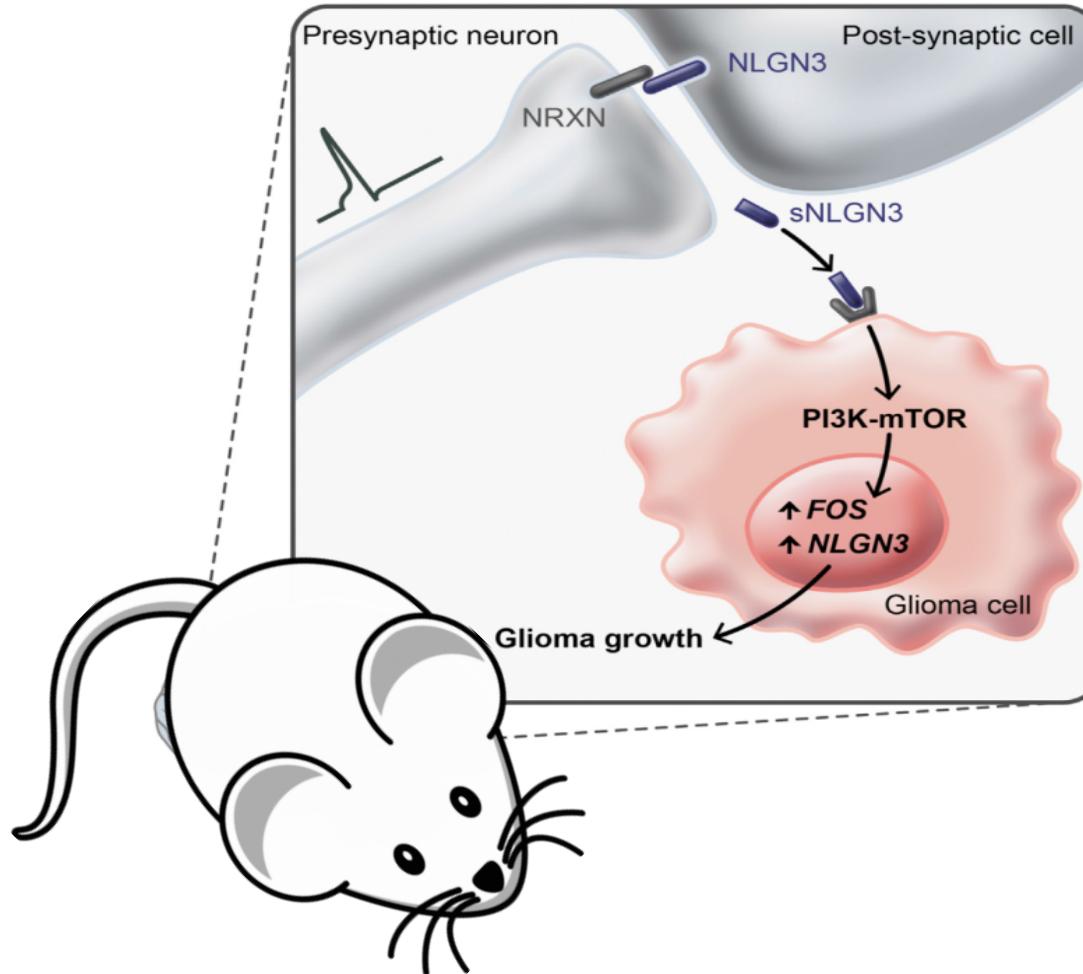
4 | gliomas that occur in healthy hub locations are bigger, which mediates the relationship between greater hubness and poorer cognitive functioning

*numan et al (under review)*

# unexpected yield part 2 | openness to inspiration is key



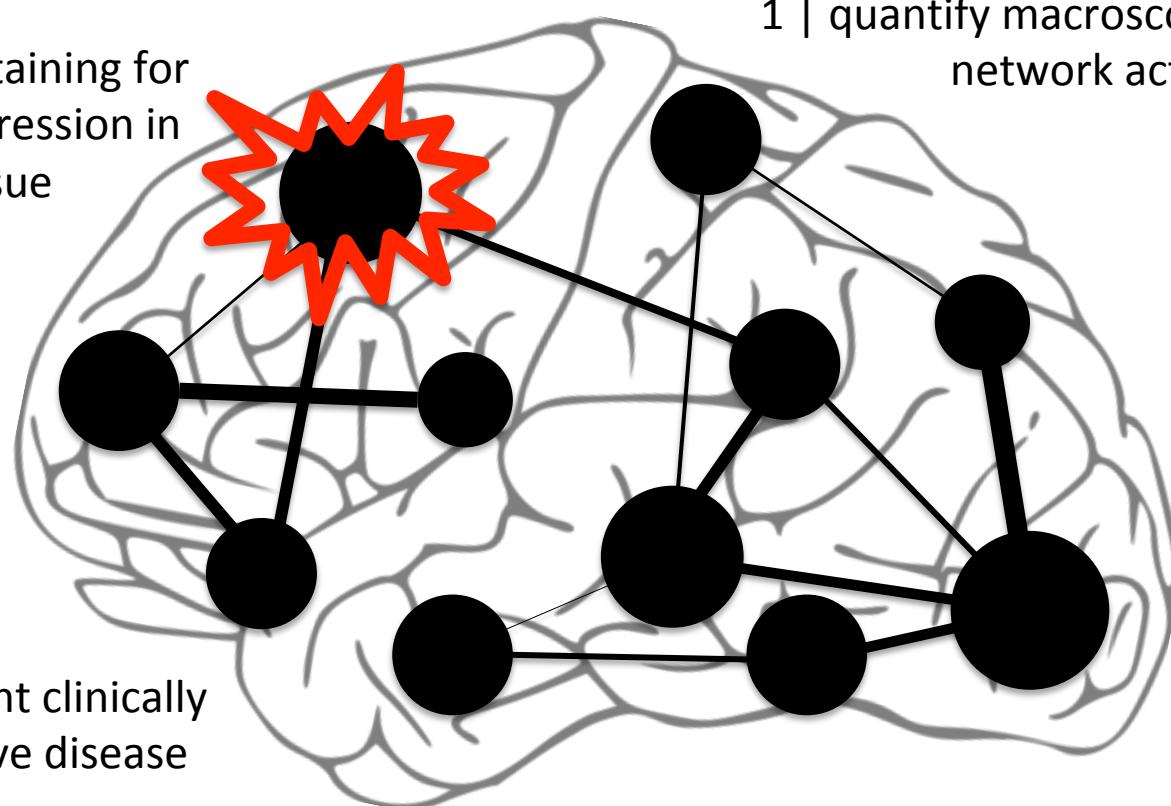
# neuronal activity promotes glioma growth through neuroligin-3 secretion and directly



# is there synergy between glioma cells, their growth pattern and the connectome?

2 | histological staining for neuroligin-3 expression in tumor tissue

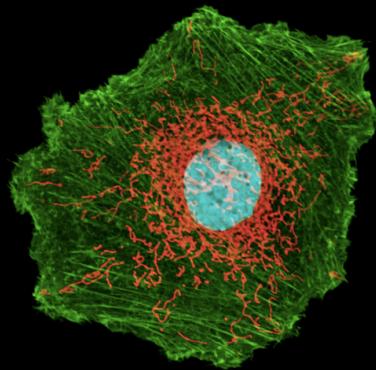
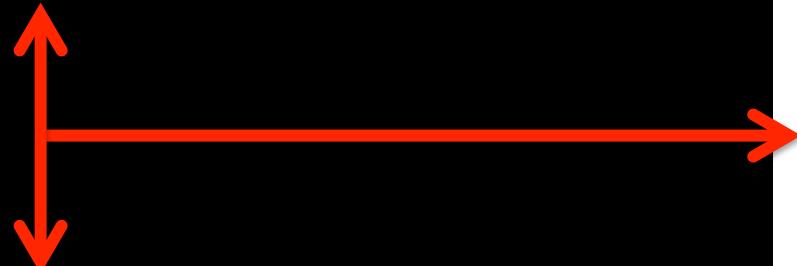
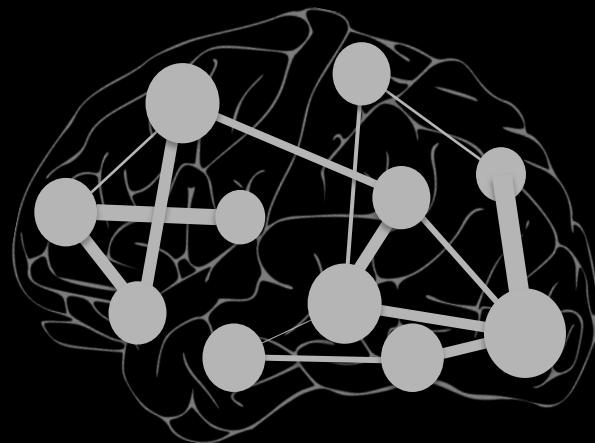
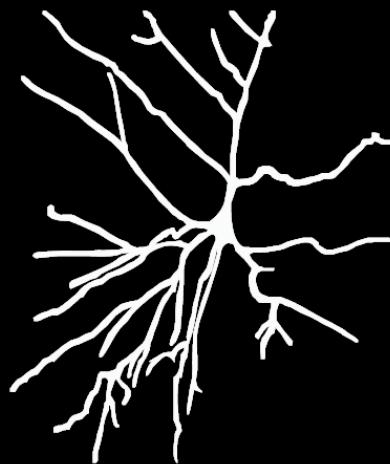
1 | quantify macroscopic peritumor network activity



3 | follow patient clinically until progressive disease

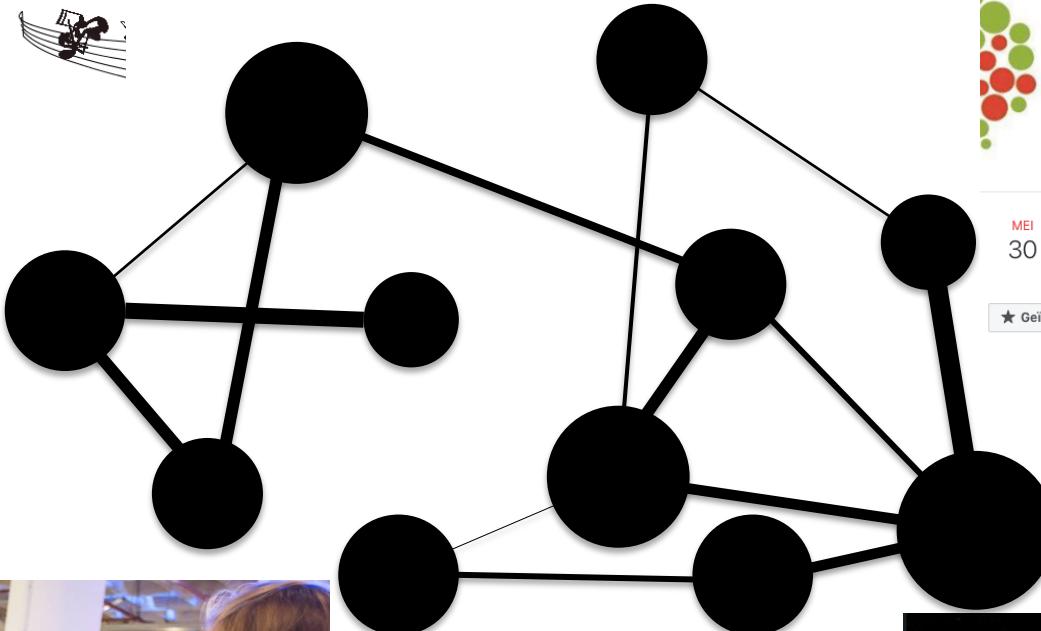
4 | high macroscopic peritumor network activity associates with high neuroligin-3 expression and faster tumor growth

*derkx et al (2018) journal of neuro-oncology*



# unexpected yield part 3 |

## scientists ≈ children ≈ people ≈ patients



MEI  
30

Informatieavond voor hersentumorpatiënten  
Openbaar - Georganiseerd door VUmc Cancer Center  
Amsterdam en Amsterdam UMC - Locatie VUmc

Geïnteresseerd



all patients participating  
in scientific research

**MULTINET lab**

Jolanda Derkx  
Lieke van Dongen  
Gwenda Engels  
Shanna Kulik  
Dagmar Nieboer  
Tianne Numan  
Quirien Oort

**VUmc Anatomy &  
Neurosciences**

Anand Eijlers  
Quinten van Geest  
Jeroen Geurts  
Hanneke Hulst  
Svenja Kiljan  
Kim Meijer  
Geert Schenk  
Menno Schoonheim

**VUmc MEG center**  
Arjan Hillebrand  
Kees Stam

**Brain Tumor Center Amsterdam**

David Noske  
Jaap Reijneveld  
Philip de Witt Hamer

**VU University**

Christiaan de Kock  
Natalia Goriounova  
Huib Mansvelder

**UMC Utrecht**

Edwin van Dellen

**MGH/Martinos Center**

Matthew DeSalvo  
Koene van Dijk  
Elizabeth Gerstner  
Matt Hibert  
Hesheng Liu  
Julie Miller  
Noam Peled  
Steve Stufflebeam

**Dana-Farber Cancer Institute**

Brian Alexander  
Daniel Cagney

**University of Heidelberg**  
Frank Winkler

The  
**Branco Weiss**  
**Fellowship**  
**Society in Science**

 **Amsterdam**  
**Neuroscience**

 **Nationaal Epilepsie Fonds**



Nederlandse Organisatie voor Wetenschappelijk Onderzoek

**[l.douw@vumc.nl](mailto:l.douw@vumc.nl)**