Multimodal Patho-Connectomics: Towards personalize medicine

Ragini Verma

Center for Biomedical Image Computing and Analytics
Radiology
University of Pennsylvania

Connectomics for Pathology

- Imaging
  - Connectivity
  - Volume
  - Distance
- Genetic
- Behavioral
- Clinical

Using more than one source of information

Personalized Medicine

interaction between symptoms

Biomarkers: diagnosis, treatment, prevention, progression

therapeutics, genetics, molecular, imaging, clinical information

Parse heterogeneity, link scale and modality, identify “targets”

computational pattern extraction, modeling & integration

standard inputs, quantifiable outputs

big data instead of big mess

Focal Pathology: Subject-specific analysis

DTI is increasingly used for planning

- Identify WM tracts, especially eloquent ones (arcuate, CST, OR)

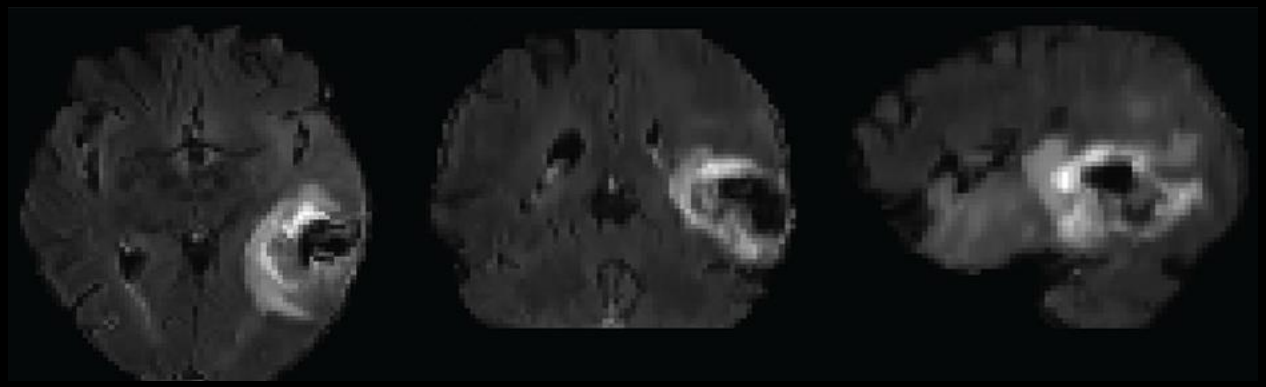
Pre-operatively

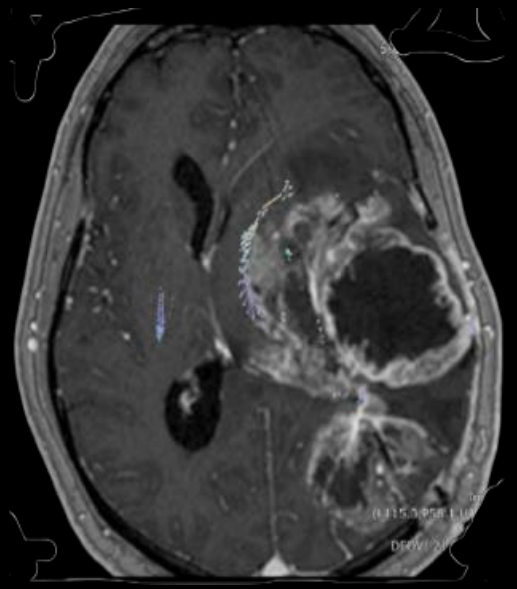
- Aid in choice of optimal resection margin by avoiding damage to tracts associated with eloquent function

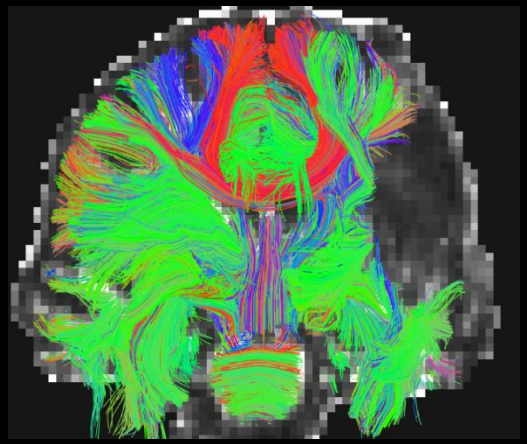
Post-operatively

- Tissue is differentially affected by the tumor (proximity, tissue type) – apply radiation preferentially

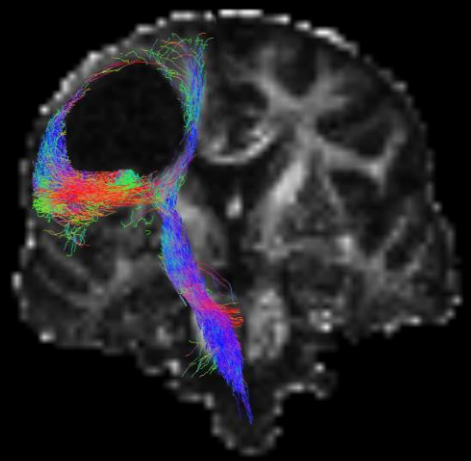
Tumors: as personalized as it gets





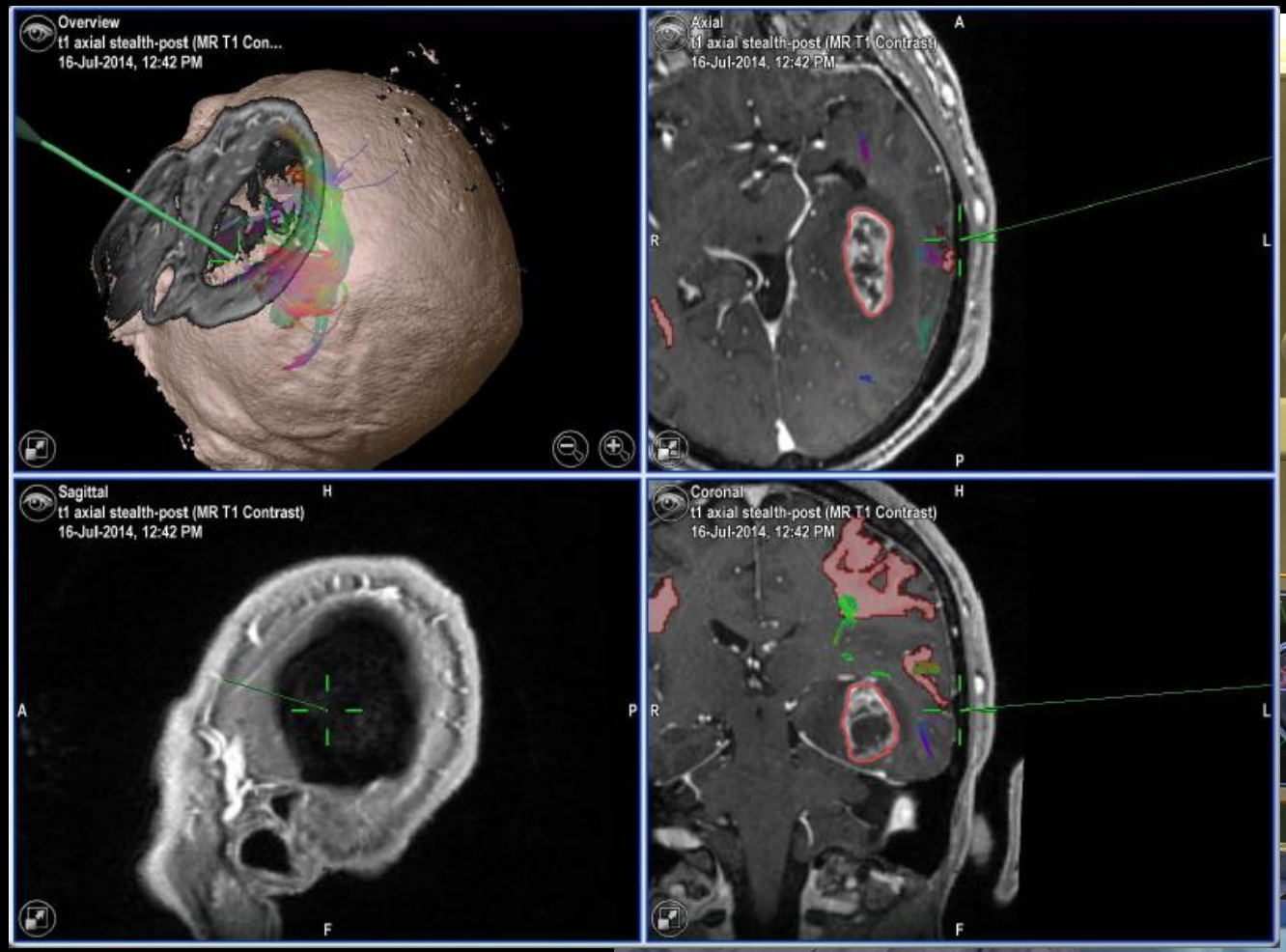


Infiltration



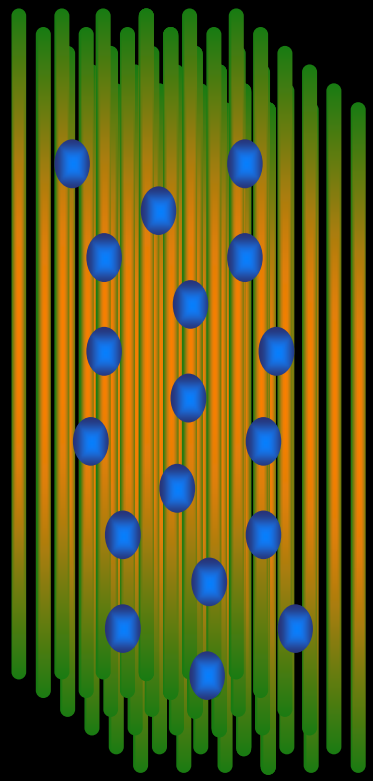
Mass effect

Existing Plans

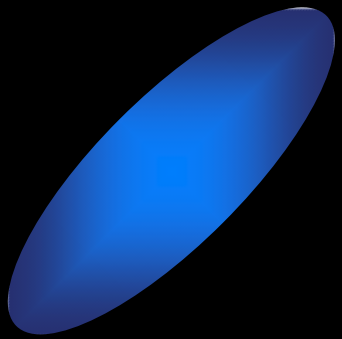


Steven Brem
Leif-Erik Bohman

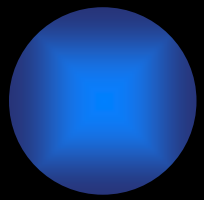
Why is edema such a big problem?



Axon Bundle



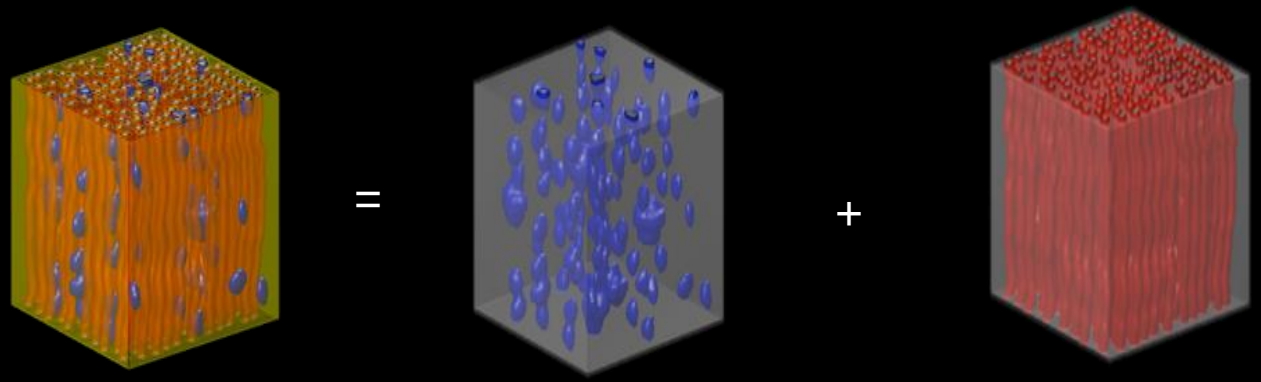
Actual structure



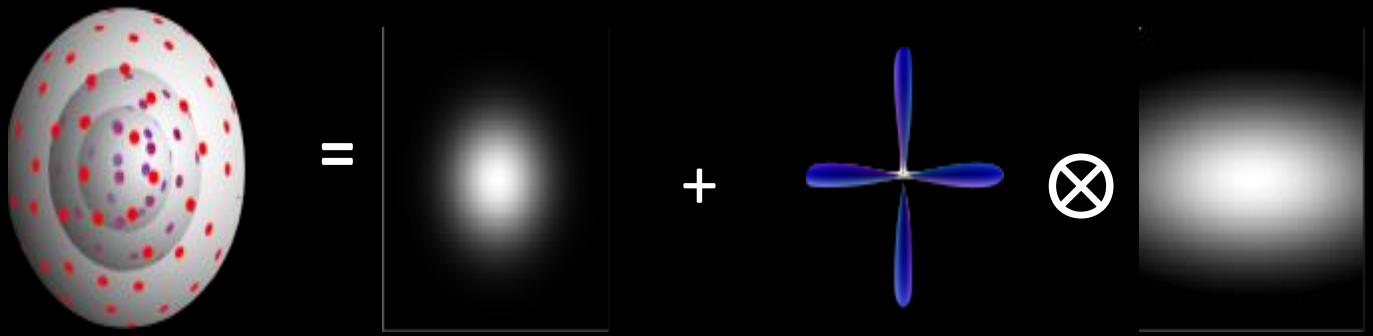
Perceived

Addressing the problem of edema

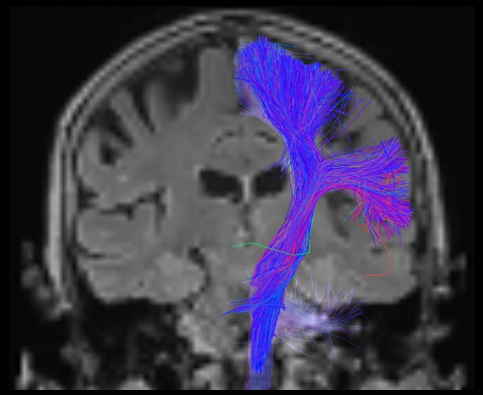
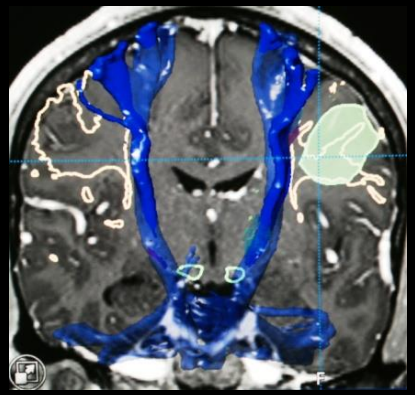
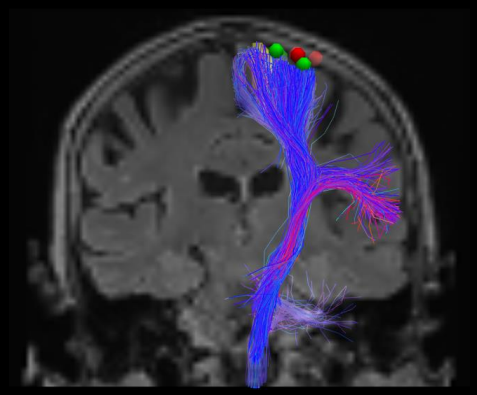
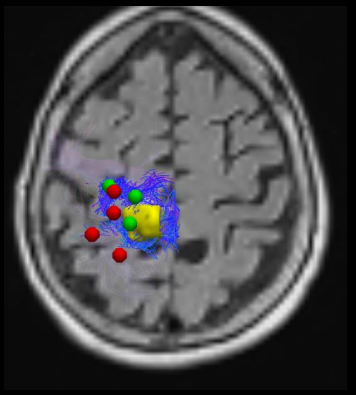
White Matter Tissue structure



Acquisition

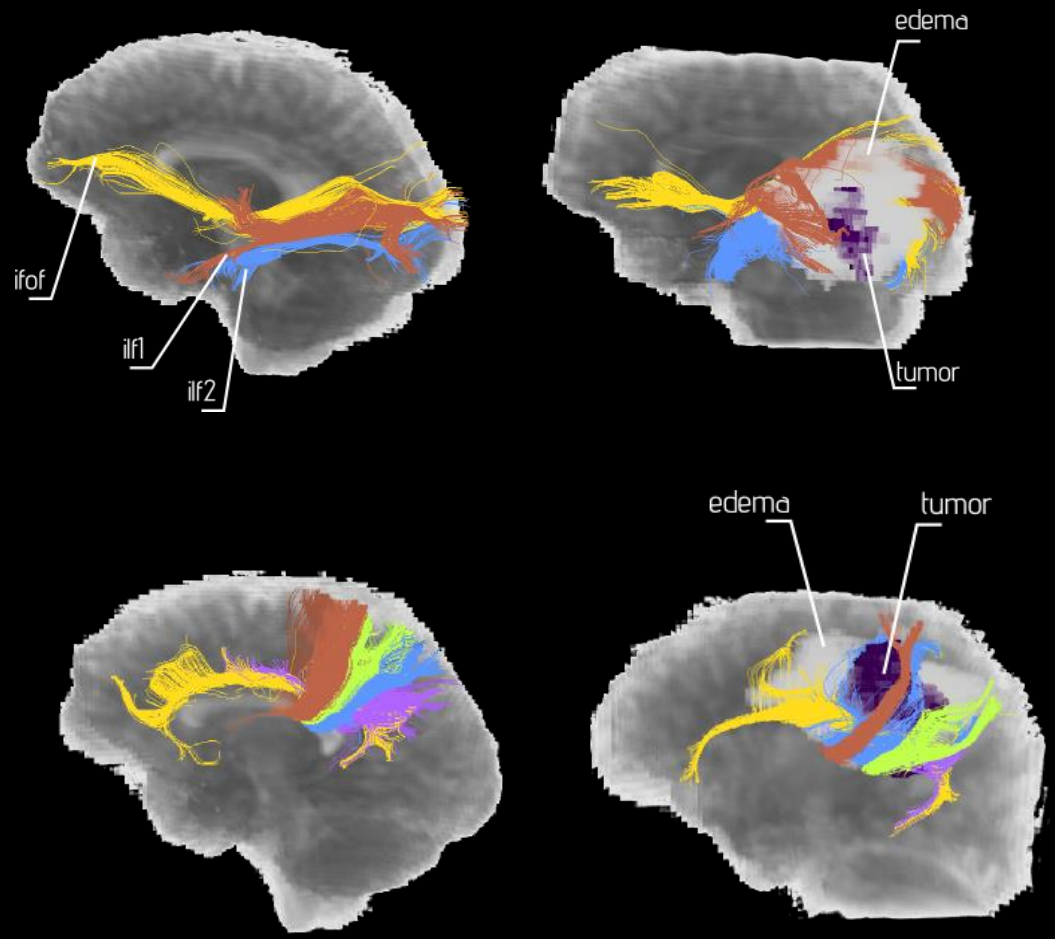


Tracking through edema …

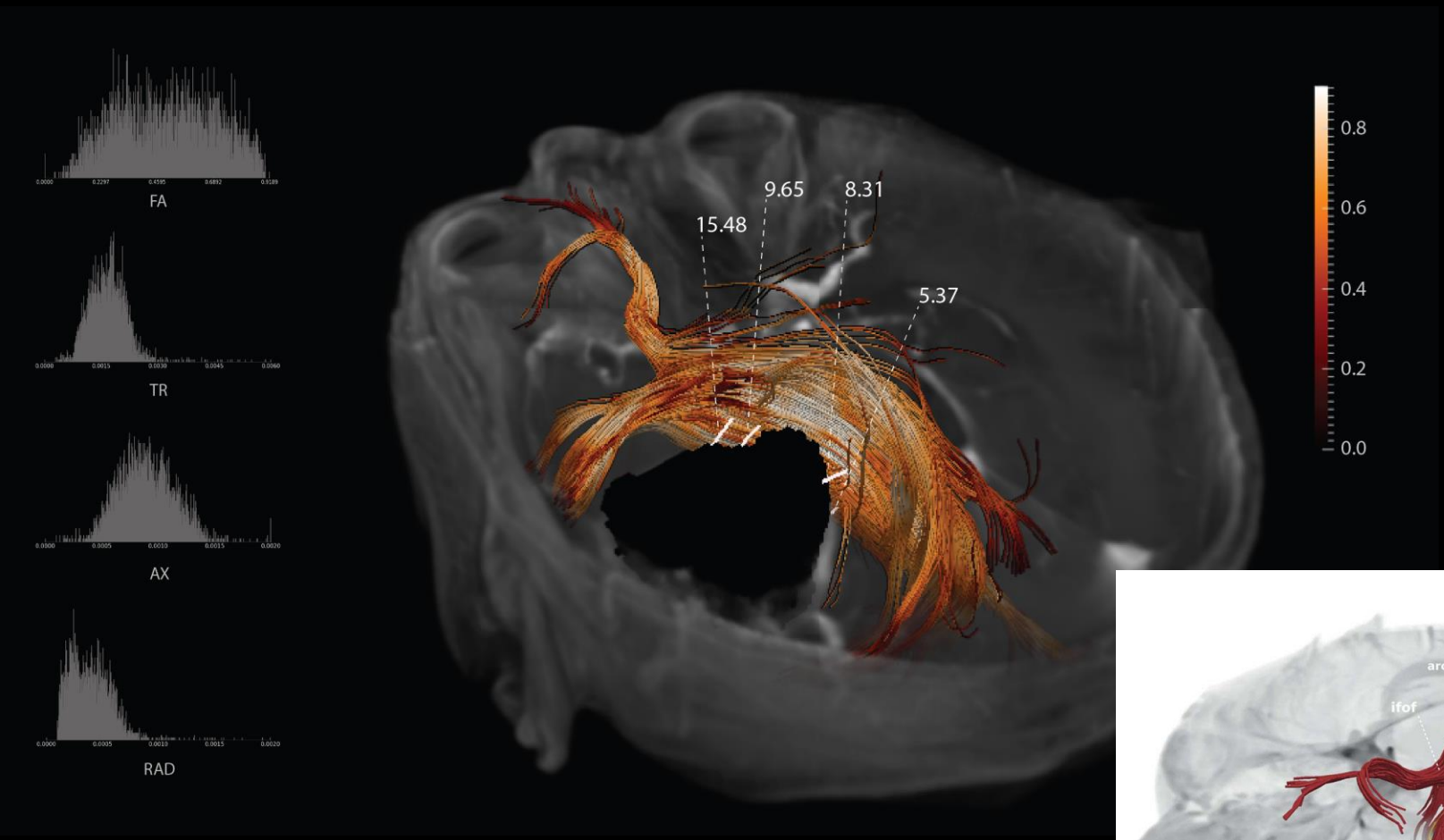





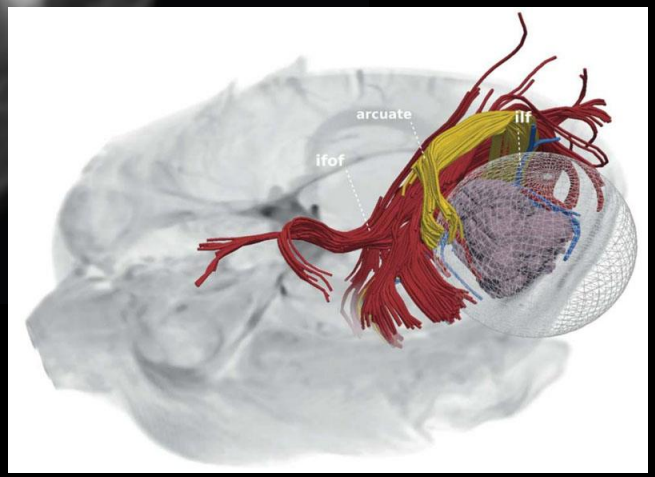
Multiple modalities for validation

Tract Extraction in the presence of tumor

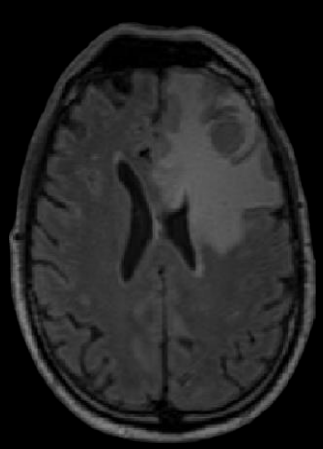


Augmenting an Existing Plan

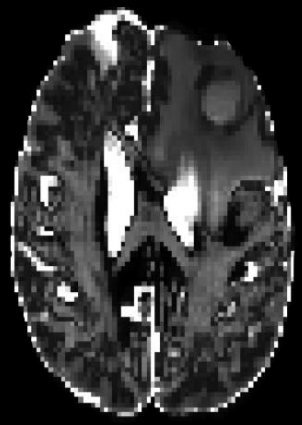




Peritumoral Tissue Characterization



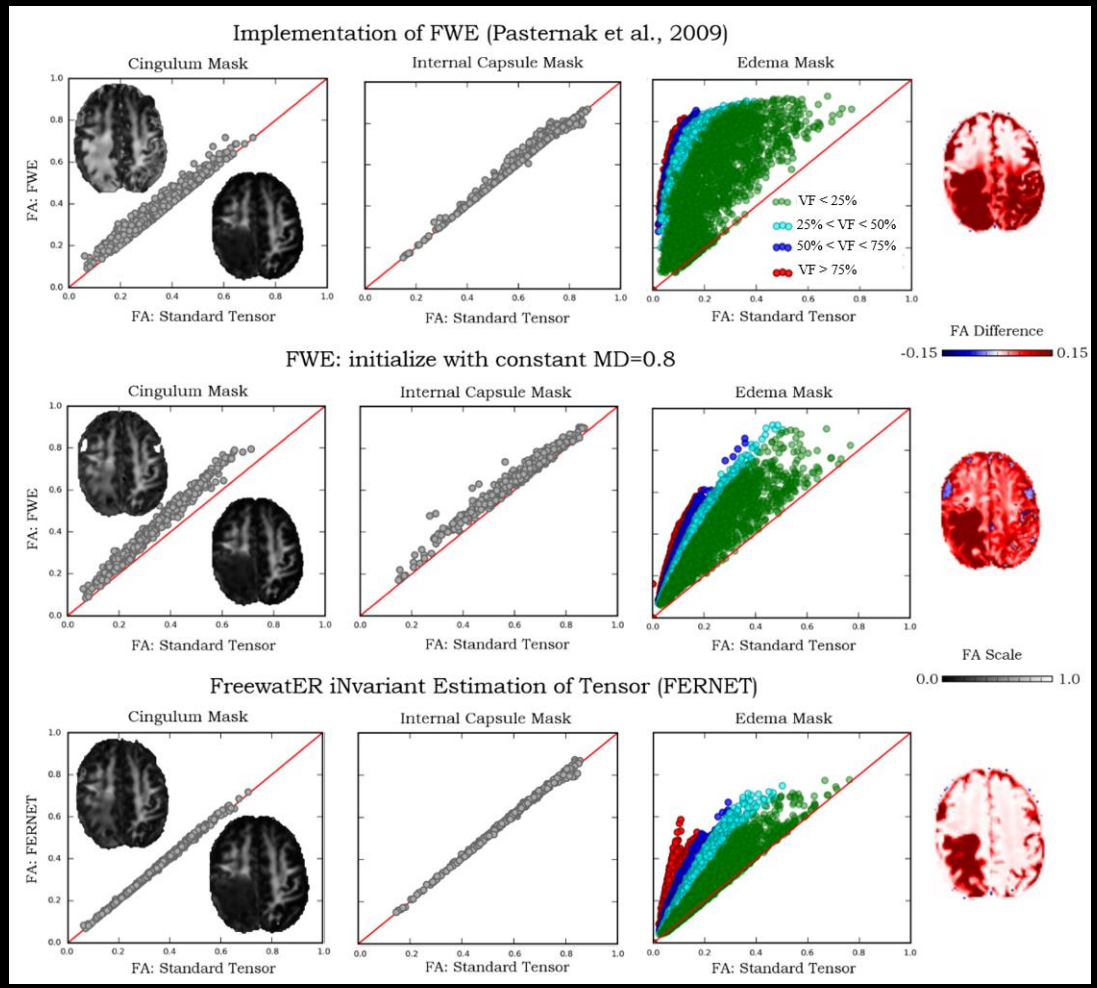
FLAIR



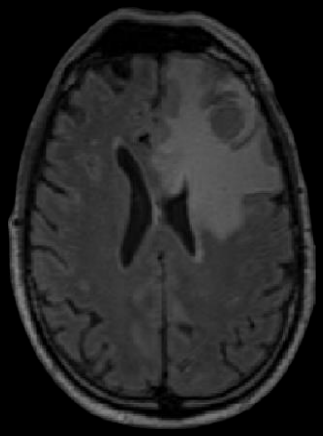
Free Water Map

Marker of peritumoral tissue heterogeneity

Living with clinical data



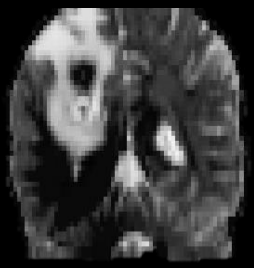
Peritumoral Tissue Characterization



FLAIR

Free Water Map

GBM

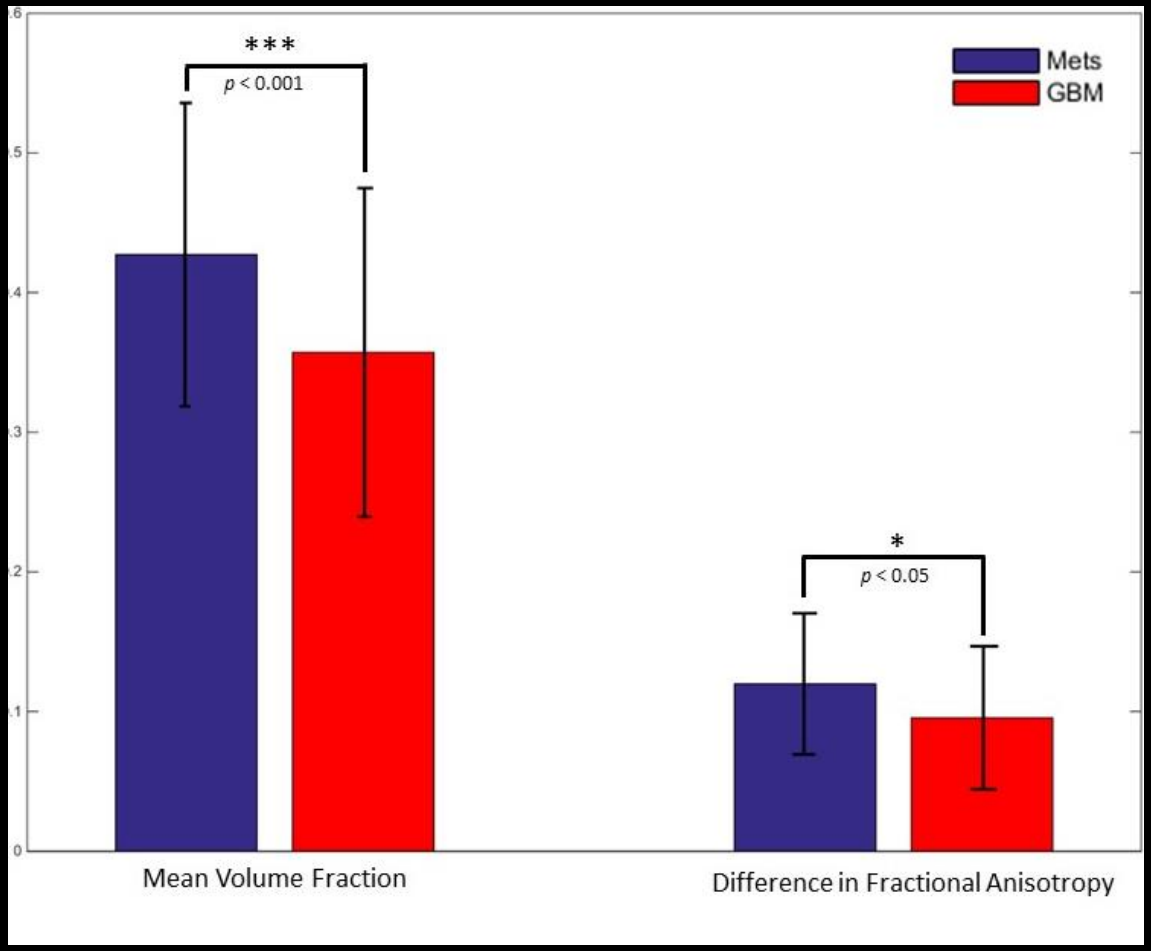


Met

Non-GBM

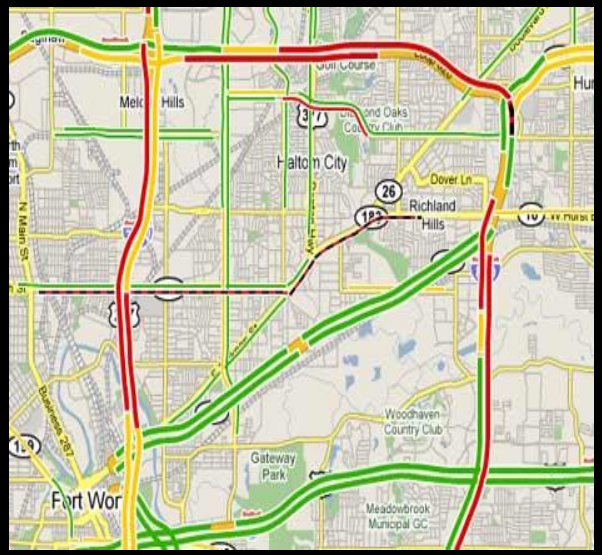
Rec-GBM

Heterogeneity of Water

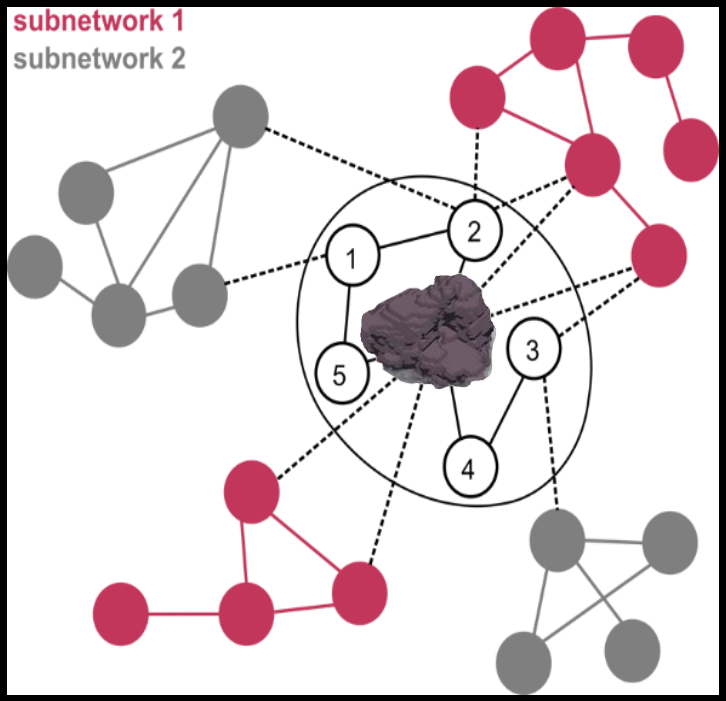


Far reaching effects of accident

Effects of resection/radiation



Tumor/trauma effects global information processing



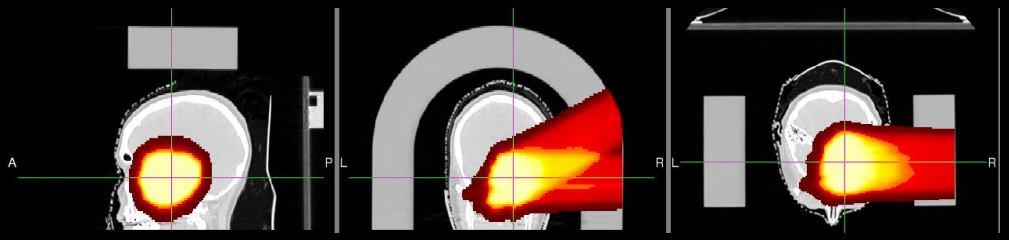
can we quantify effect of resection / treatment

in workings of distant processes

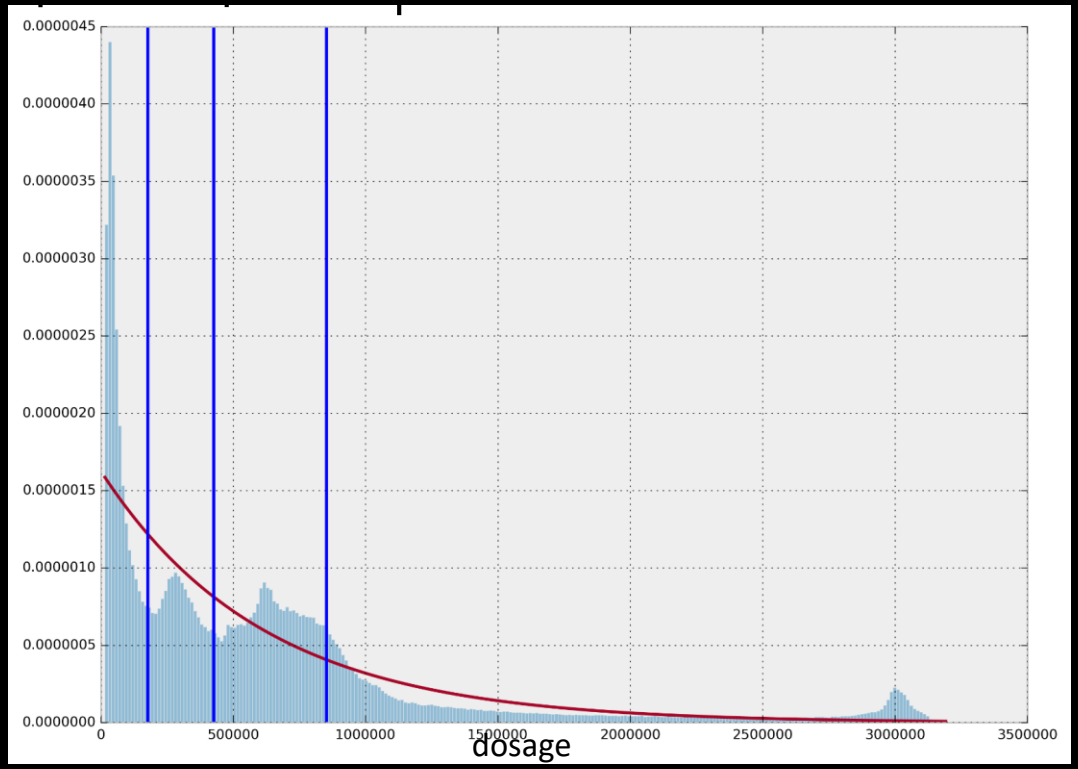
functions that are not localized around resection volume/ area radiated

Radiation Therapy

Parsing dose maps



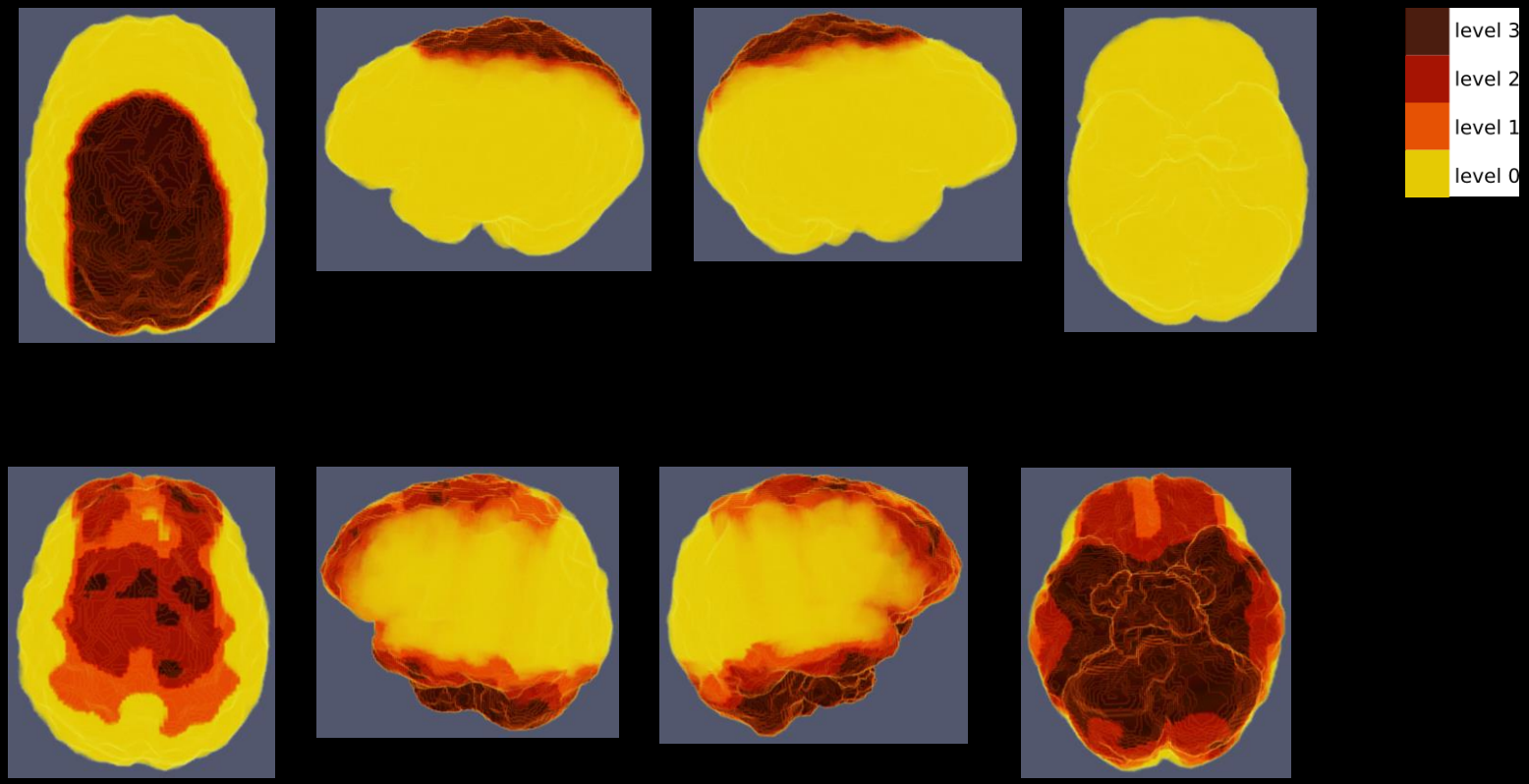
level 0
level 1
level 2
level 3



Radiation Therapy

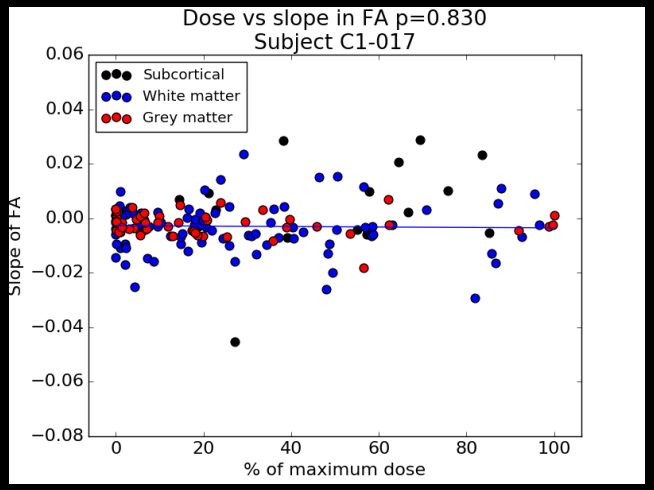
variation of dose maps

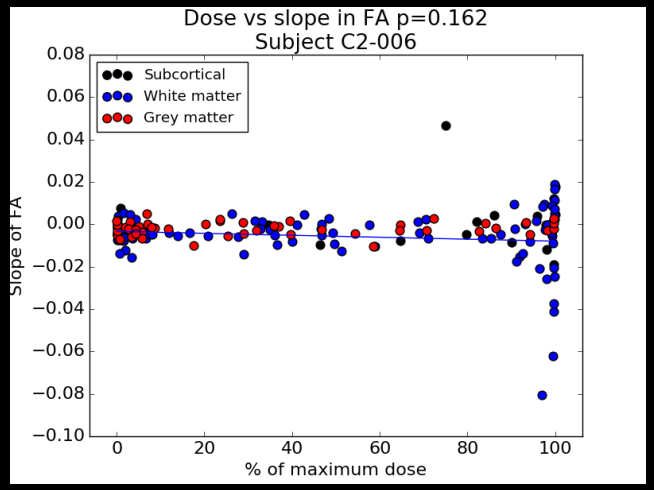
variation in dose maps

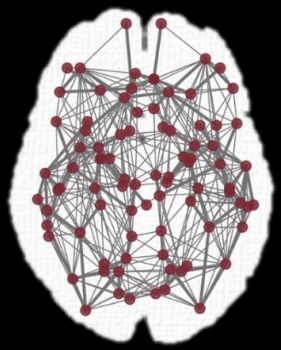


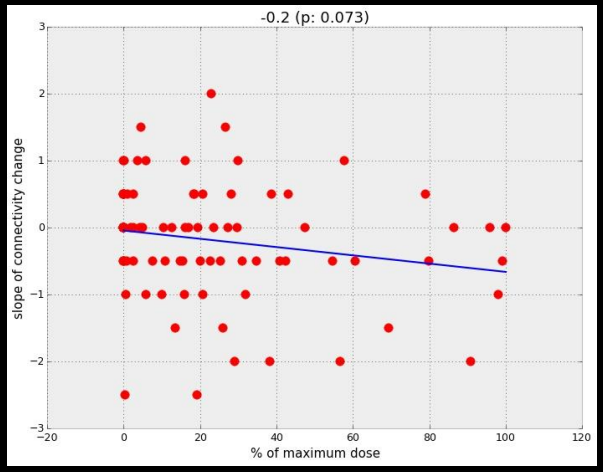
Radiation Therapy

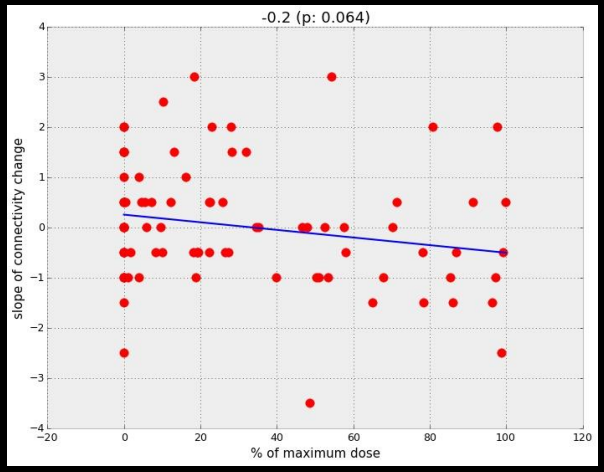
Effect on diffusion measures





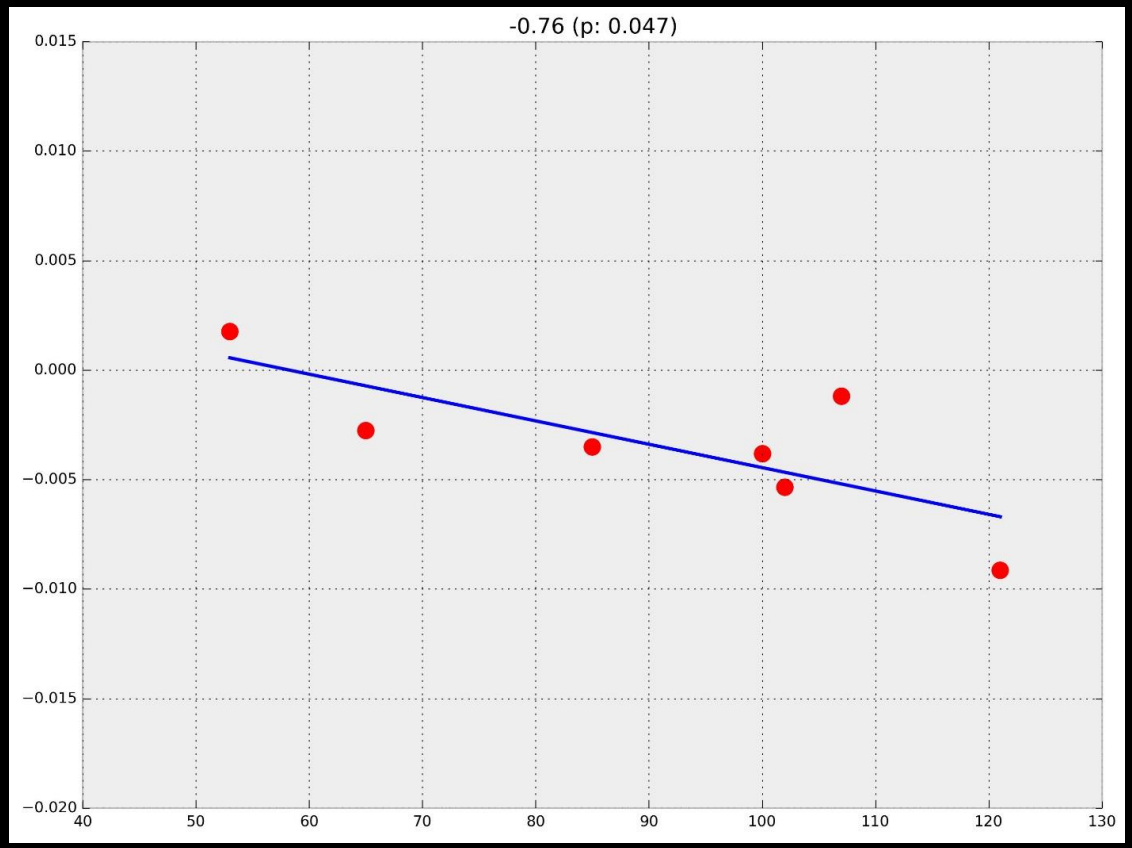






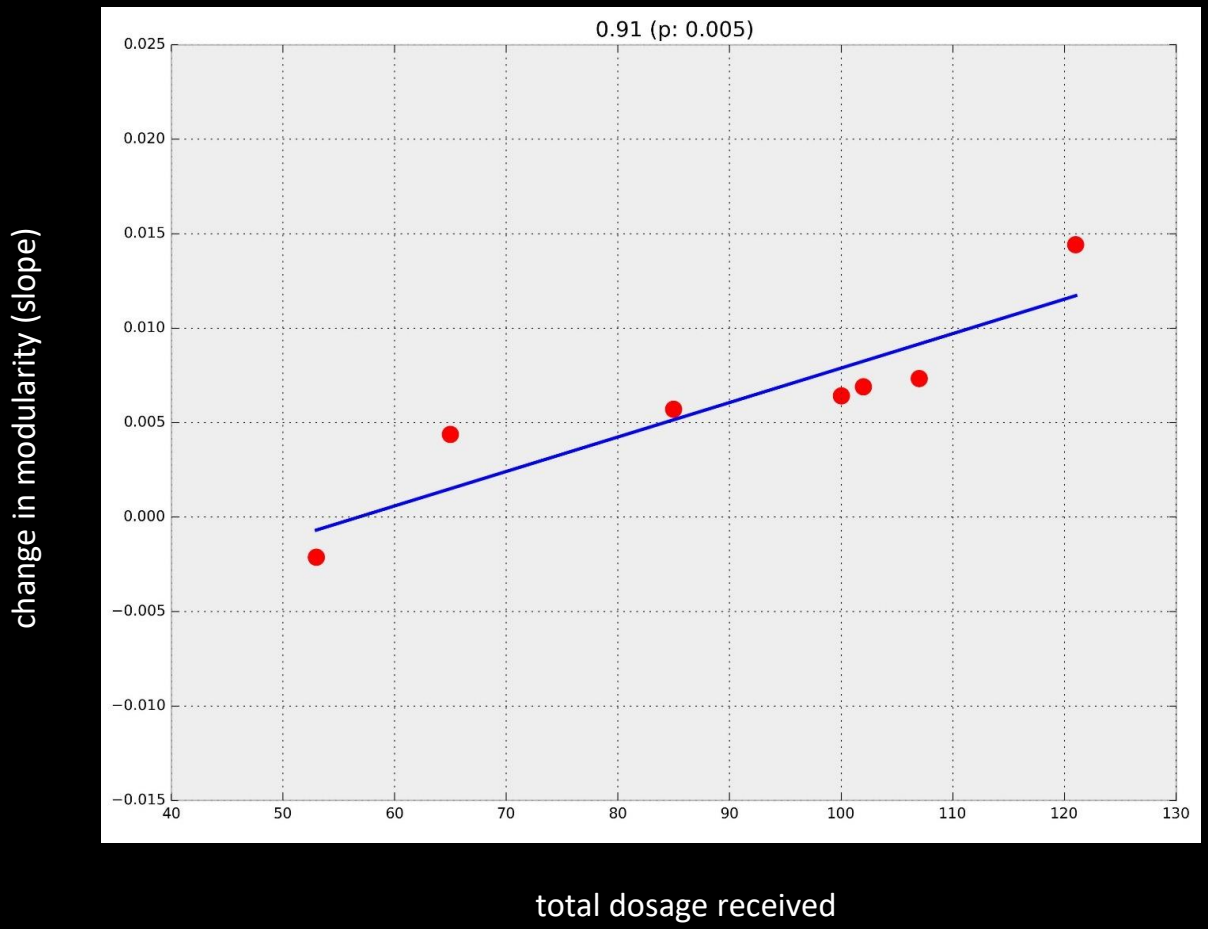
Radiation Therapy

Global change in connectivity with radiation

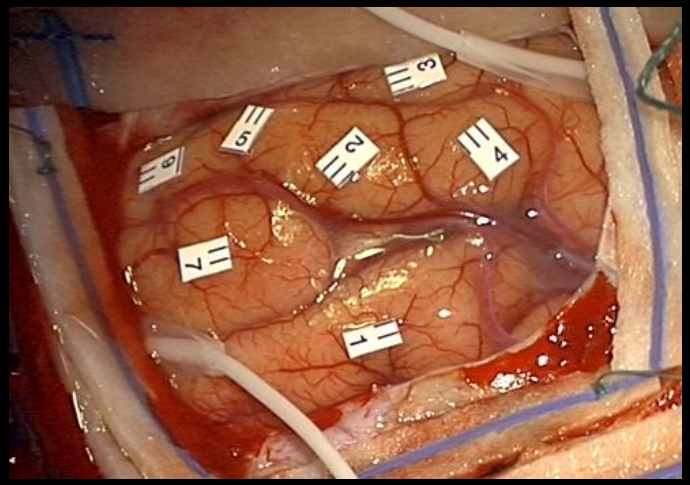


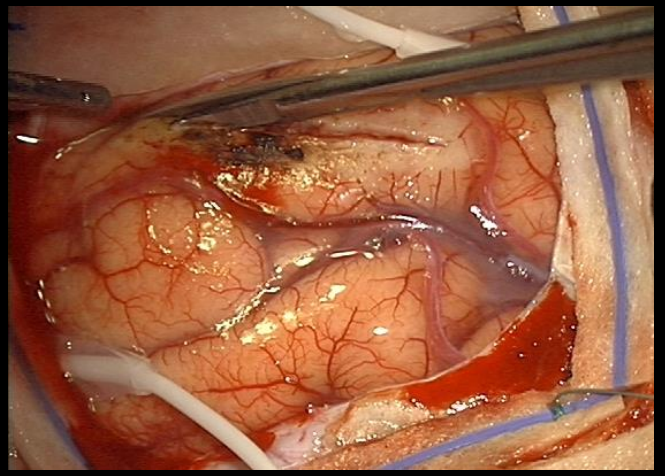
Radiation Therapy

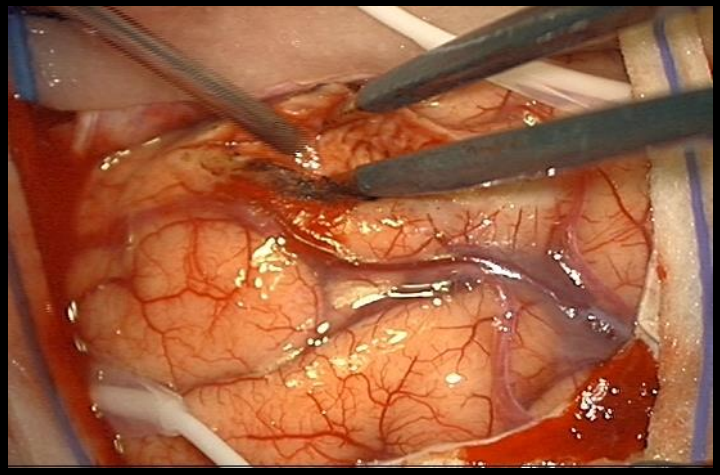
Global change in connectivity with radiation

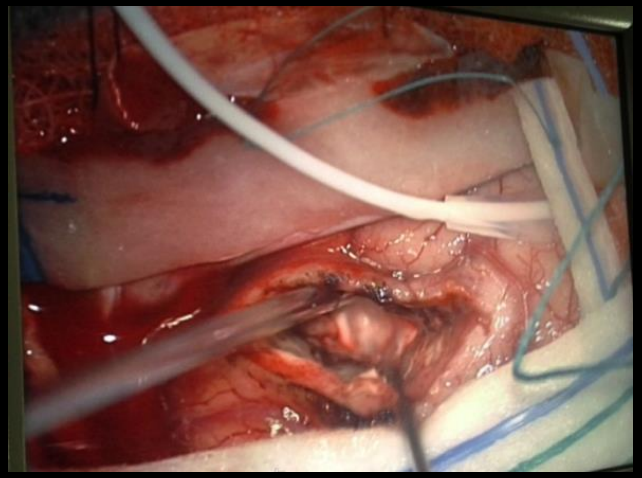


Effect on surrounding healthy tissue

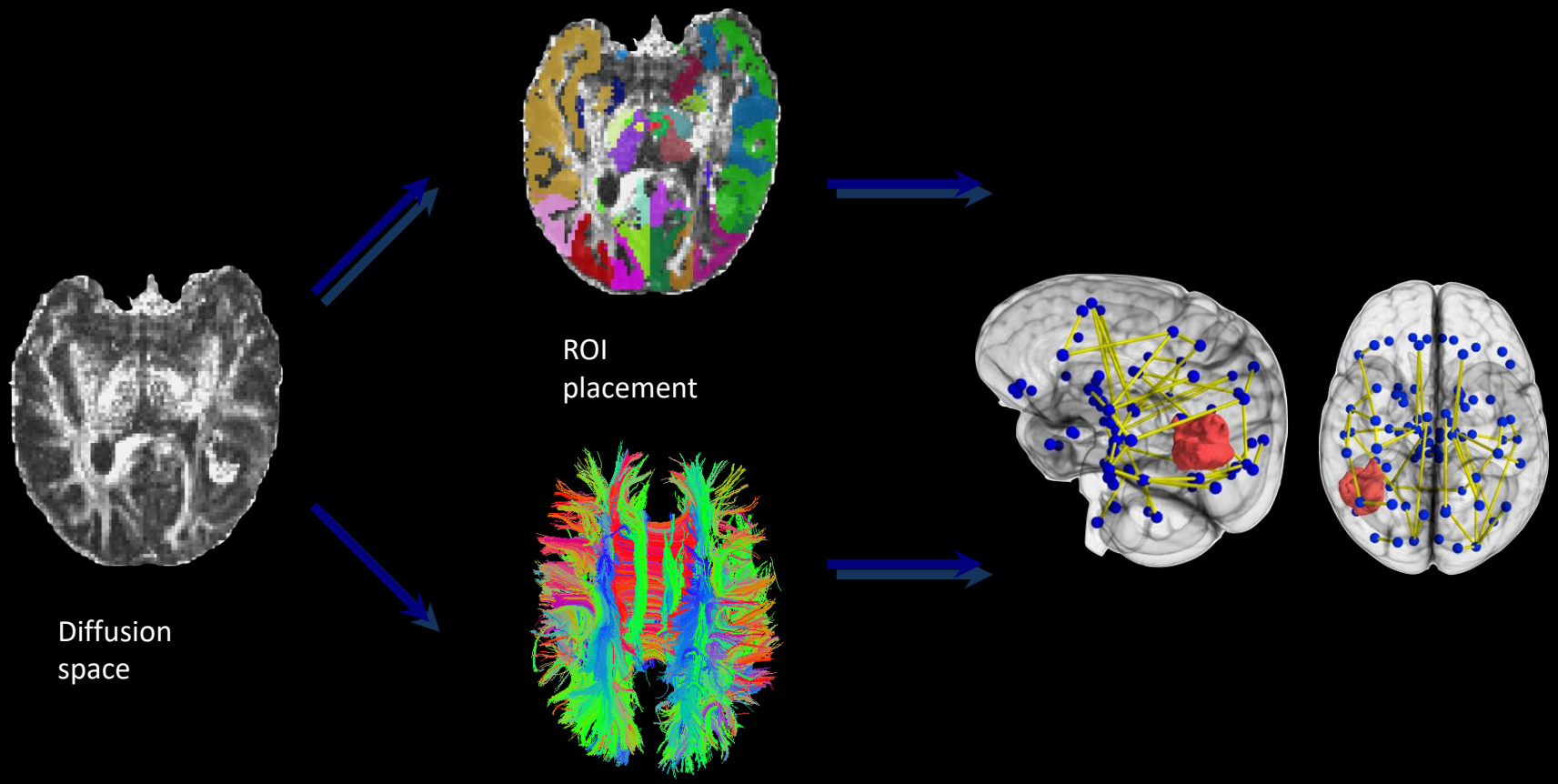




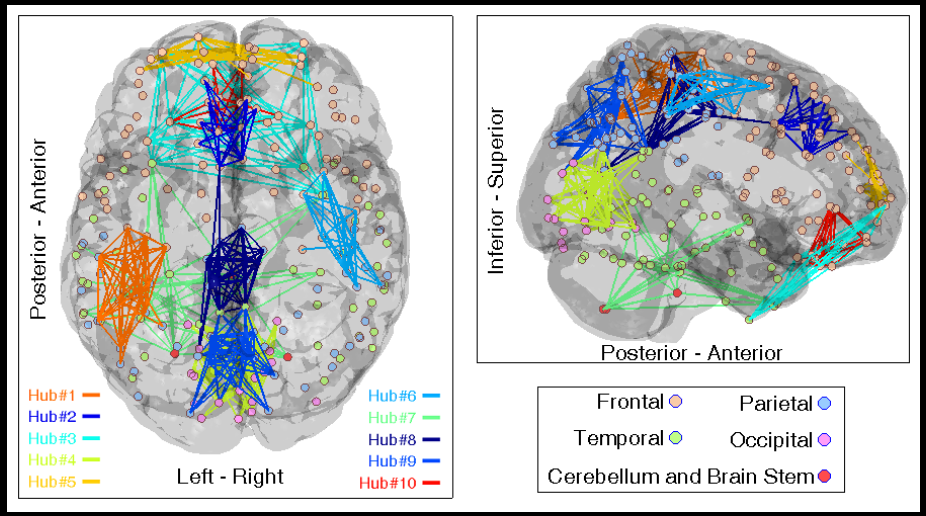




Tumor Connectome



Tumor/trauma effects global information processing

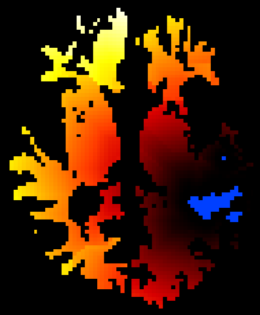


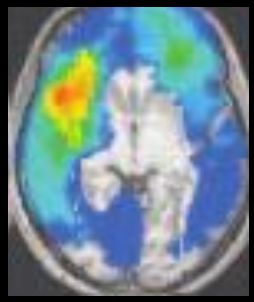
determine the damage score around the tumor to determine extent / effect of resection/radiation

Longitudinally: Determine how the vulnerability / damage score changes with treatment

Identify vulnerability of subnetworks

Design a *vulnerability map* of a *tumor connectome* quantifying importance of regions to functional systems

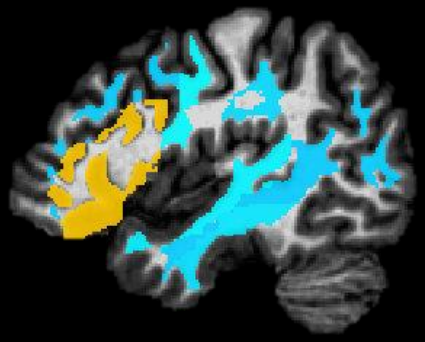


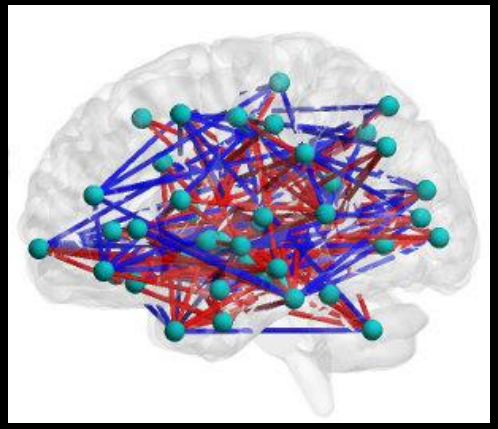


Atlas of Vulnerability:
connectomic resection/radiation marker
to quantify the effect on brain connectivity

Diffuse Differences ….

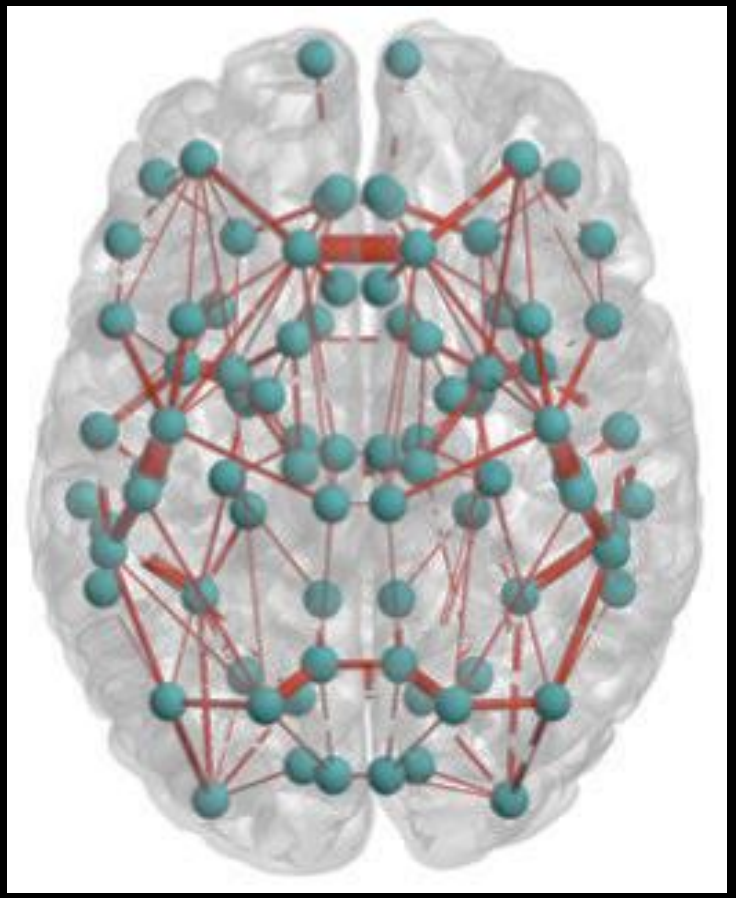
TBI
population



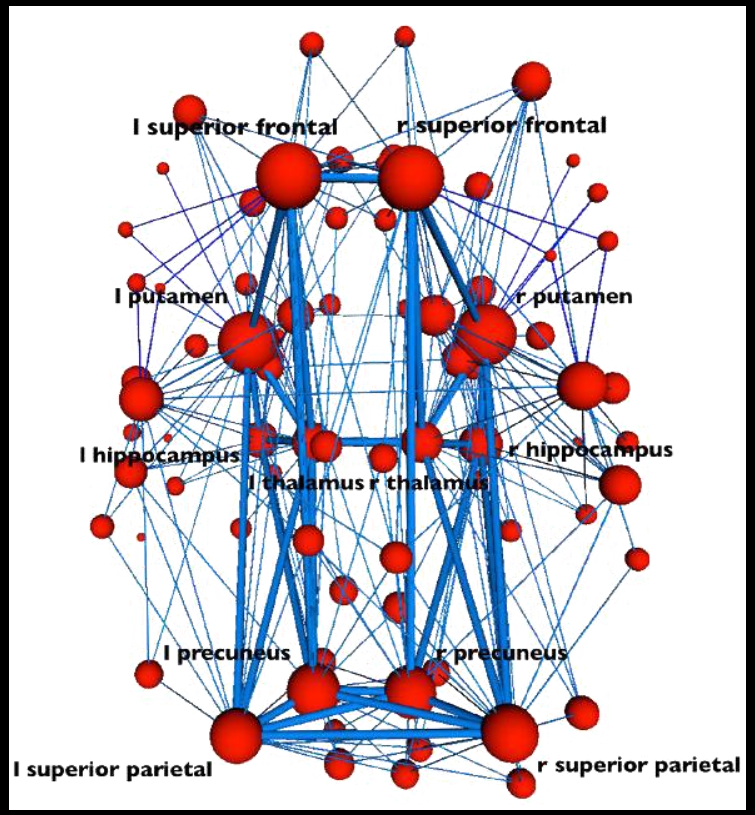


Brain: information processing unit

identify contribution of edges to communication: “importance”



Tunc, Selmaz et al. submitted HBM



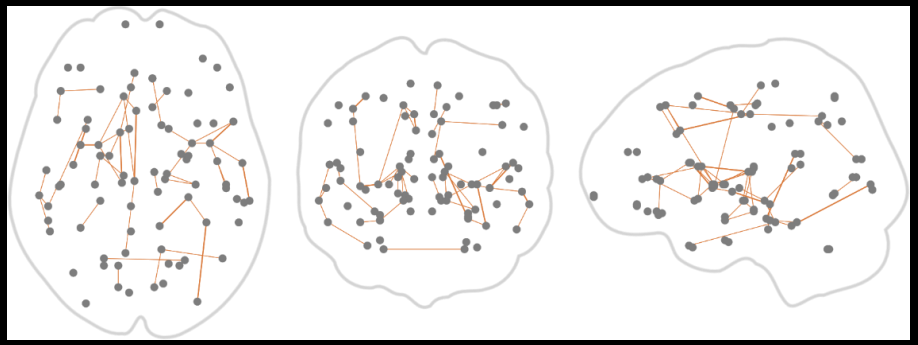
van den Heuvel et al. The J. Neuroscience, 2011

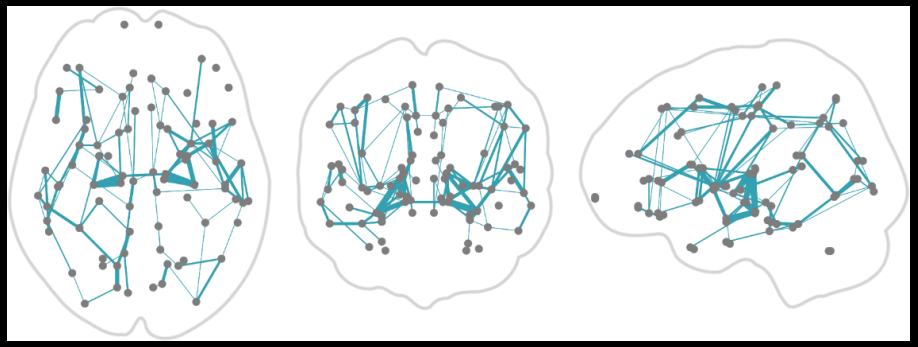
Global measure of brain injury

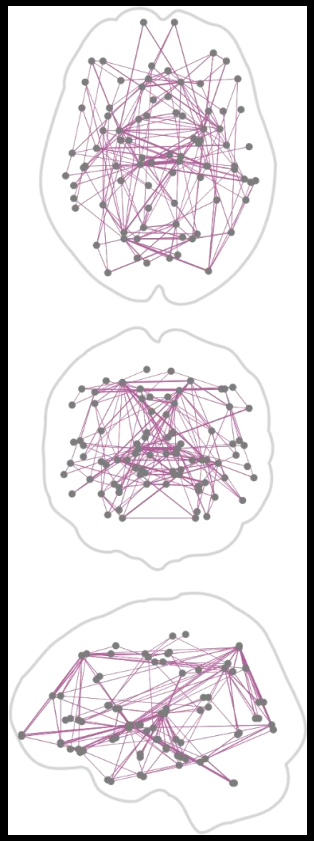
importance

controls

patients







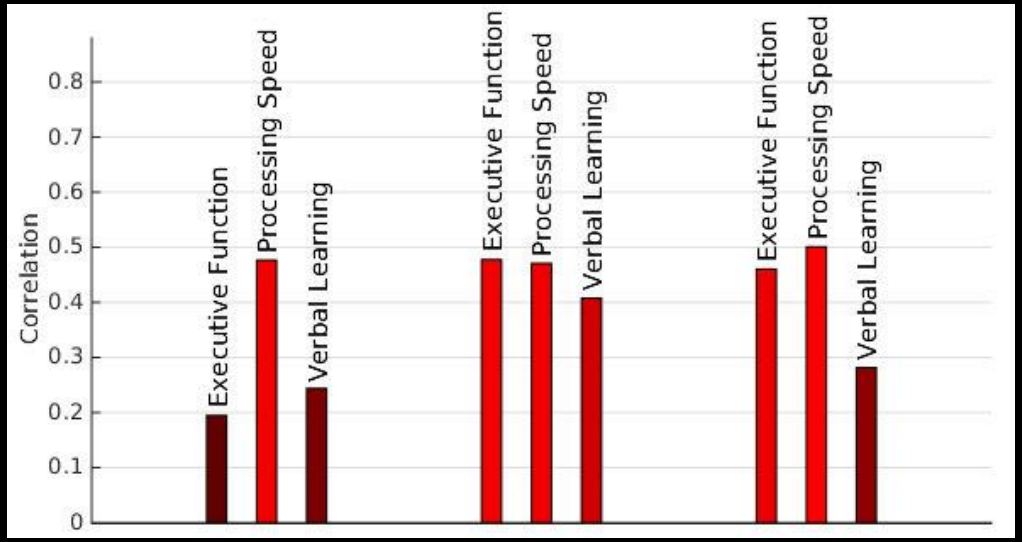
Tunc *et al.* HBM

Global Brain Injury Scale

TBI < CNT

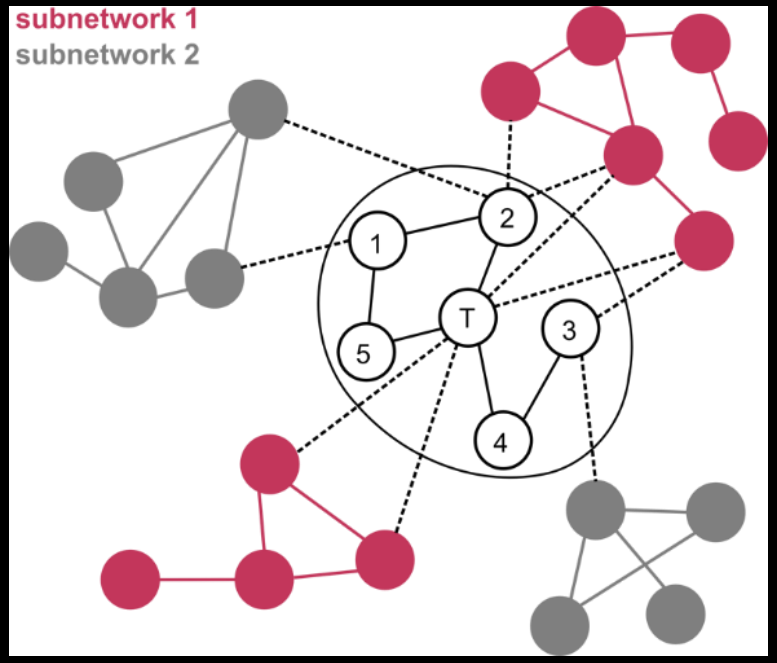
	# subjects	t	p-val
TBI (combined) / Controls	79/33	-3.98	0.000143
TBI (3-months) / Controls	33/33	-3.24	0.00201
TBI (6-months) / Controls	24/33	-2.65	0.0116
TBI (9-months) / Controls	22/33	-2.59	0.0136

correlations with phenotype

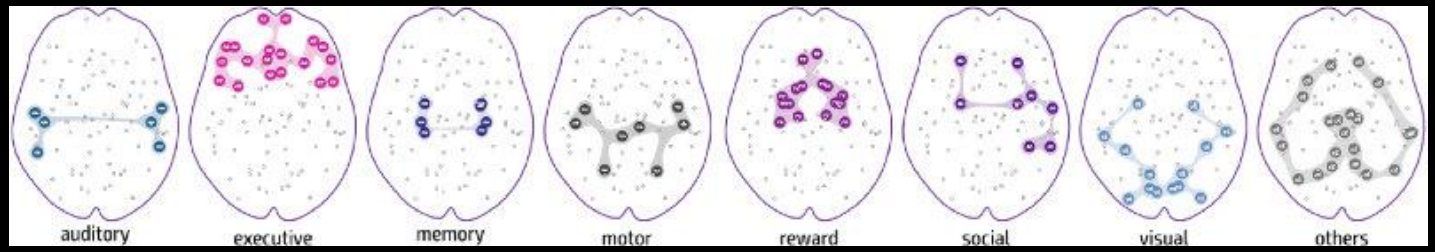


Solmaz *et al.* unpublished

Dominant Patterns of Connectivity in Pathology



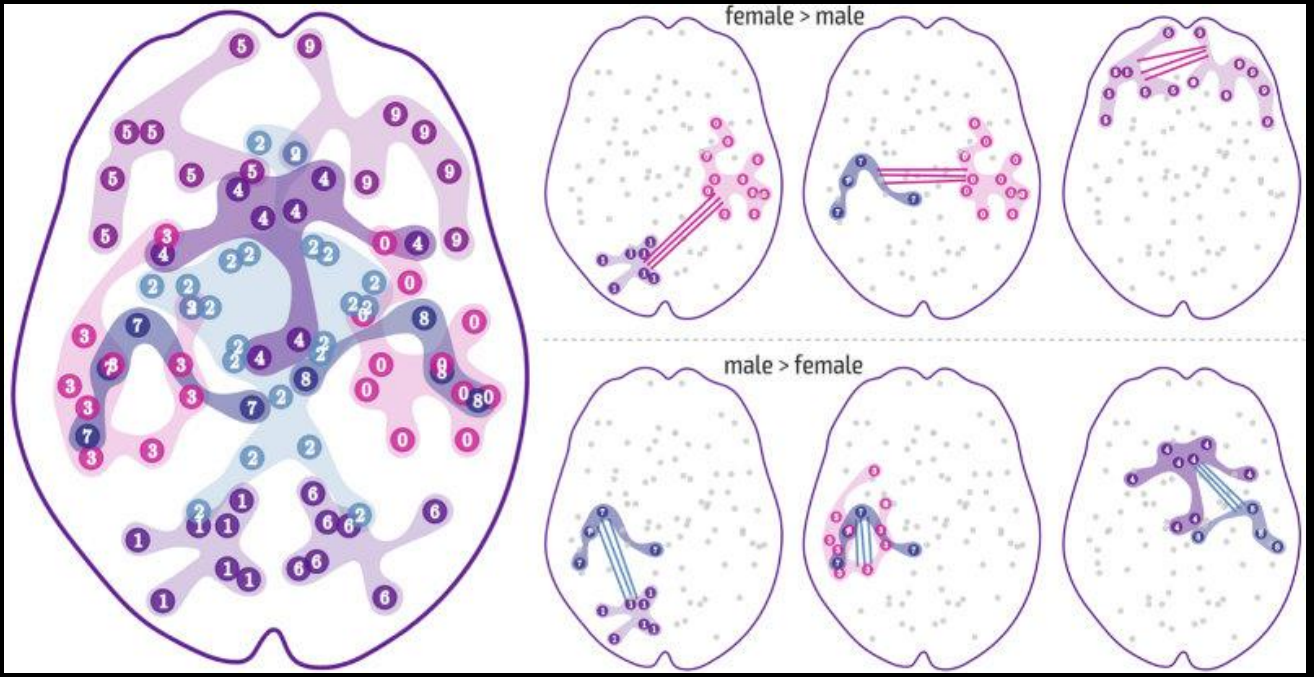
Functionality-based subnetworks



Auditory	Banks Of Superior Temporal Sulcus, Superior Temporal, Transverse Temporal
Executive	Caudal Middle Frontal, Medial Orbitofrontal, Pars Triangularis, Frontal Pole, Caudal Anterior Cingulate, Pars Opercularis, Pars Orbitalis, Rostral Anterior Cingulate, Rostral Middle Frontal
Memory	Hippocampus, Entorhinal, Parahippocampal, Amygdala
Motor	Paracentral, Post Central, Precentral, Cerebellum
Reward	Caudate, Putamen, Pallidum, Hippocampus, Nucleus Accumbens, Ventral Dc, Amygdala, Medial Orbitofrontal
Social	Amygdala, Fusiform (Right), Banks Of The Superior Temporal Sulcus (Right), Superior Temporal (Right), Insula (Right), Lateral Orbitofrontal
Visual	Cuneus, Entorhinal, Fusiform, Inferior Temporal, Lateral Occipital, Lingual, Pericalcarine

Tunç *et al.* 2016

Sex Differences



	Mean (SD)		Statistical Analysis	
Connectivity	Male	Female	Statistic (t)	*p* Value (FDR)
motor - executive	27.50 (7.58)	23.11 (5.93)	3.75	0.003
motor - auditory	23.13 (7.70)	19.67 (6.76)	4.79	0.000
reward - auditory	18.00 (6.36)	19.00 (6.49)	-3.66 [f]	0.003
memory - auditory	22.43 (7.94)	22.95 (7.58)	-2.82 [f]	0.045

Tunç *et al.* 2016

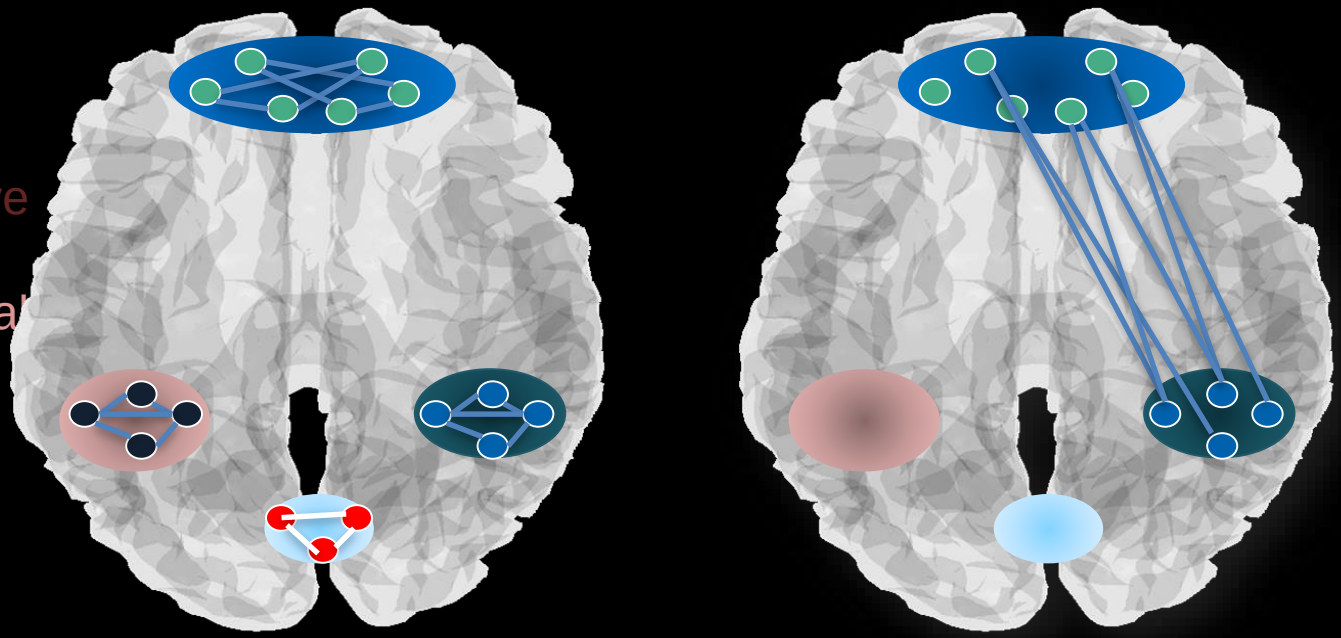
Data driven subnetworks

$$\mathbf{S}^{(m)} \approx \sum_{i=1}^{k} \lambda_{ii}^{(m)} u_i u_i^T + \sum_{i=1}^{k} \sum_{\substack{j=1 \\ j>i}}^{k} \lambda_{ij}^{(m)} \left(u_i u_j^T + u_j u_i^T \right)$$

Intra-connectivity

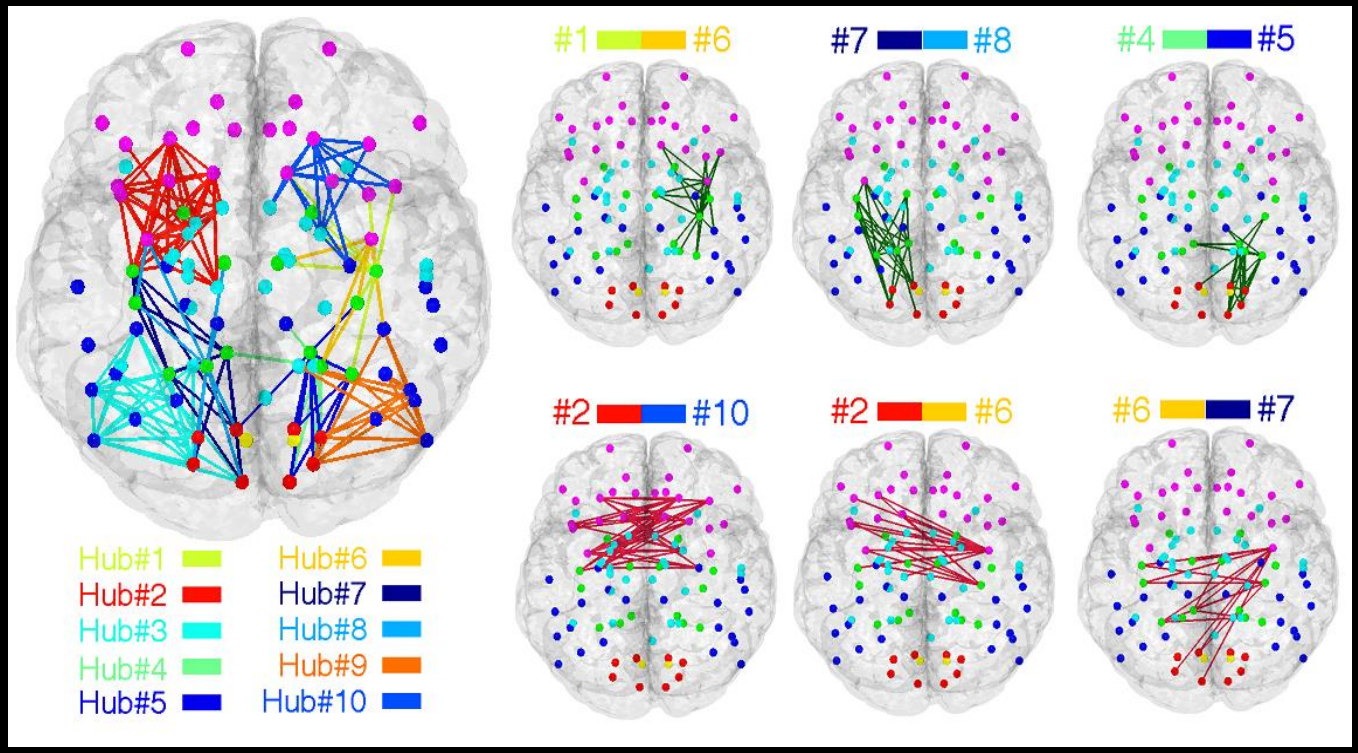
Inter-connectivity

Non-negative
Symmetric
Non-diagonal



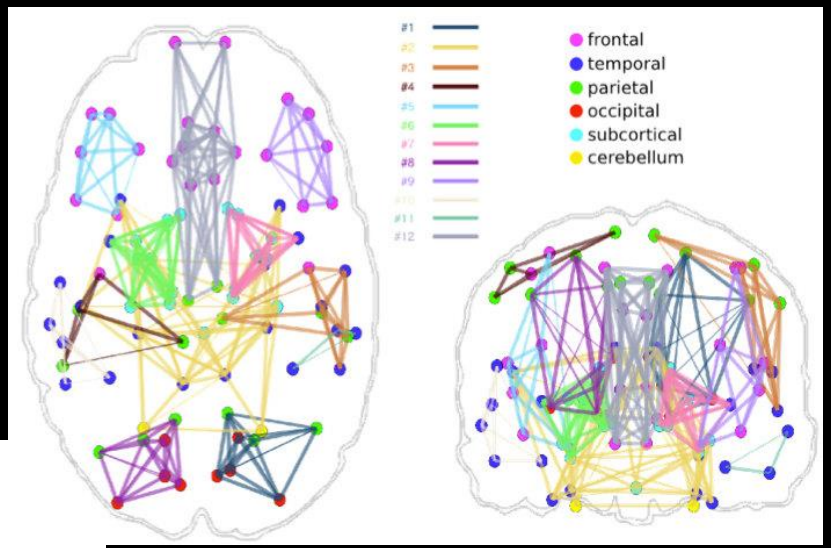
Gender Sub-networks

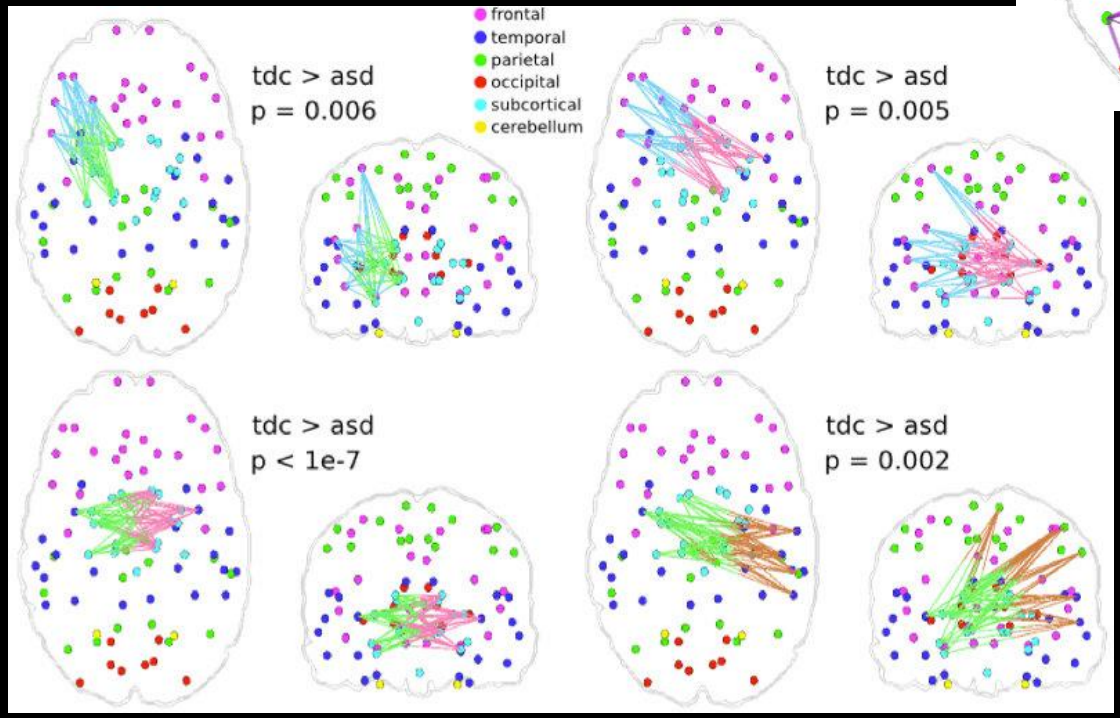
DTI-based connectivity in a healthy population 8-23 years of age



Y. Ghanbari

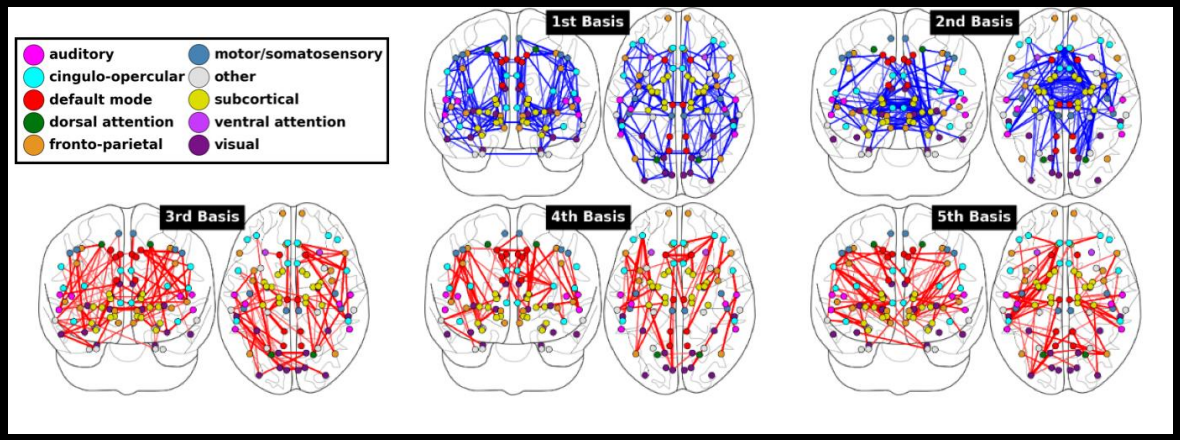
Subnetworks in Autism Spectrum Disorder





Tunç *et al.* 2015

Discriminative Subnetwork Detection – manifold regularization

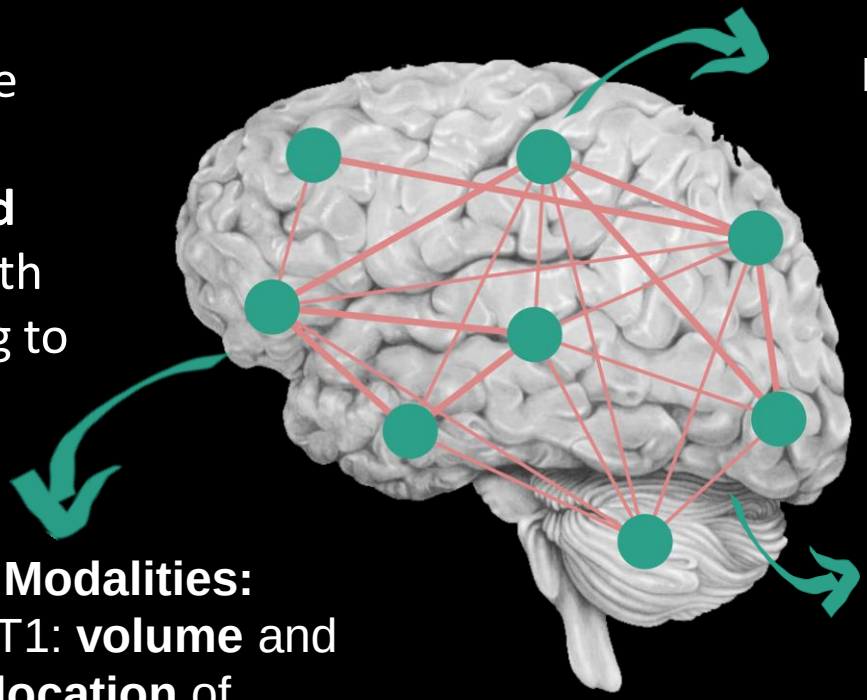


Classifier	Accuracy	Sensitivity	Specificity	BSR
SVM	76.6%	77.2%	75.0%	76.1%
SVM + L1	69.4%	73.4%	59.4%	66.4%
LogReg + L1	67.6%	70.9%	59.4%	65.1%
Proposed NMF + SVM	**82.0%**	**82.3%**	**81.3%**	**81.8%**

- Reconstructive: can be interpreted in a neurobiologically meaningful way
- Discriminative: emphasizes group differences by accounting for label information
- captures the variation in disease severity by respecting the intrinsic manifold structure underlying the data - subjects with similar disease-severity to share similar network representations

Enriched Structural Connectome

Given parcellation of the brain into n regions, construct a **weighted undirected graph** with nodes corresponding to brain regions



Two Modalities:
- ✓ T1: **volume** and **location** of regions
- ✓ DTI: **node strength**

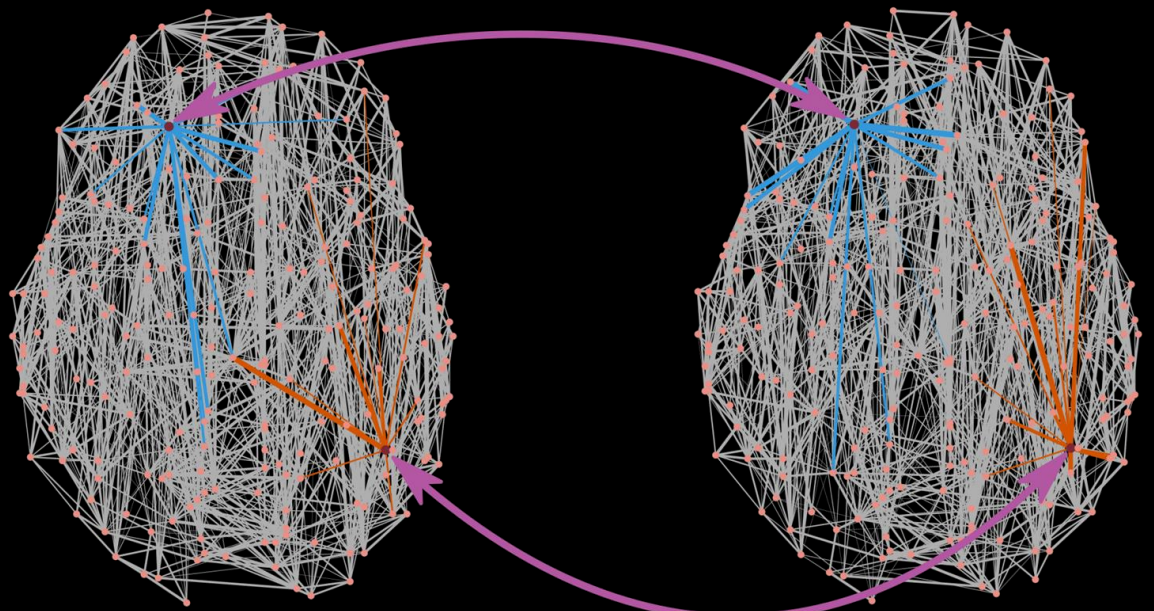
Node Features:
- ✓ Region Volume
- ✓ Spatial Location
- ✓ Node Strength

Edge Feature:
- ✓ Structural Connectivity

Similarity Measure: Graph Matching

Graph Matching:

- ✓ Defines a **similarity measure** between two enriched connectomes
- ✓ Finds a **one-to-one mapping** between their nodes



Enriched connectome of subject 1

Enriched connectome of subject 2

Evaluate graph matching as an instance of the quadratic assignment problem (QAP): find the optimal bijective (one-to-one) mapping between the nodes of the two enriched connectomes

Application: TBI Classification

35 TBI patients
35 Healthy Controls

Siemens 3.0 T Trio
30 Gradient directions
b = 1000 s/mm2
TR/TE = 6500/84
isotropic voxels = 2.2mm

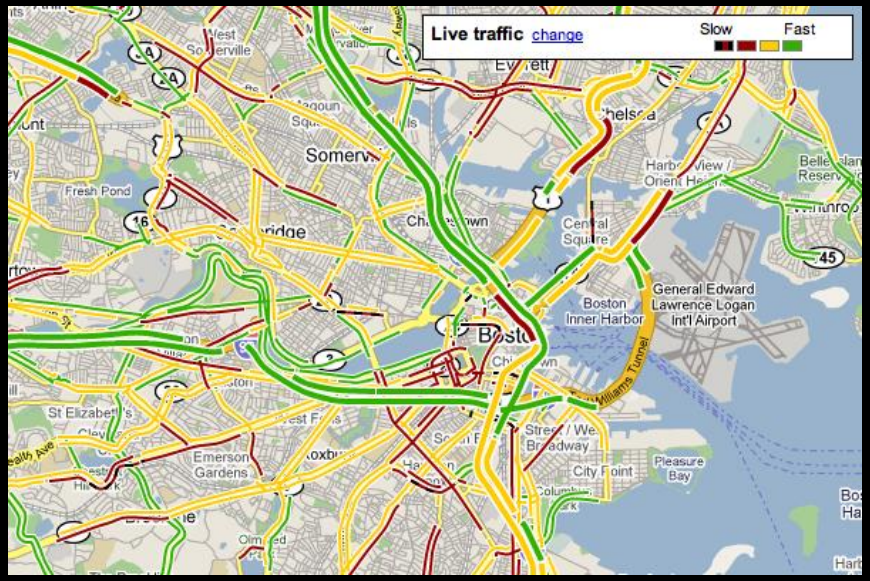
86 Brain Regions
Probabilistic tractography

- Cross validation: nested leave-one-out
- Training: multi-level grid search
- Baseline: a traditional connectome (TC) where edge weights are represented in a vector form without a graph representation (VEC)

Scenario	Accuracy	Sensitivity	Specificity
TC & VEC	61.43	62.86	60
EC & QAP_{PD}	71.43	62.86	80

	Volume	Spatial Location	Node Strength	Combined
Accuracy	61.43	70.00	55.71	81.43

Multi-parametric map of brain pathology



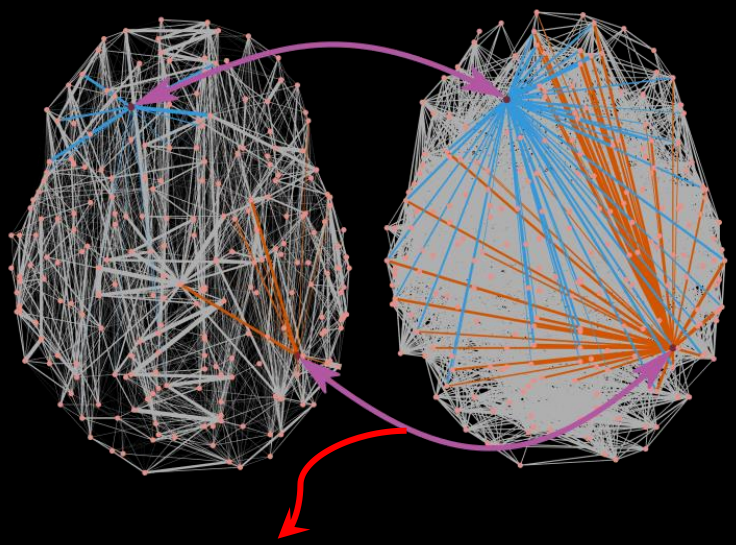
- differences in traffic pattern (new multimodal representation)
- hubs and subnetworks affected (better features)
- re-rerouting (nature of tissue beyond connectivity)

Structure-Function Coupling

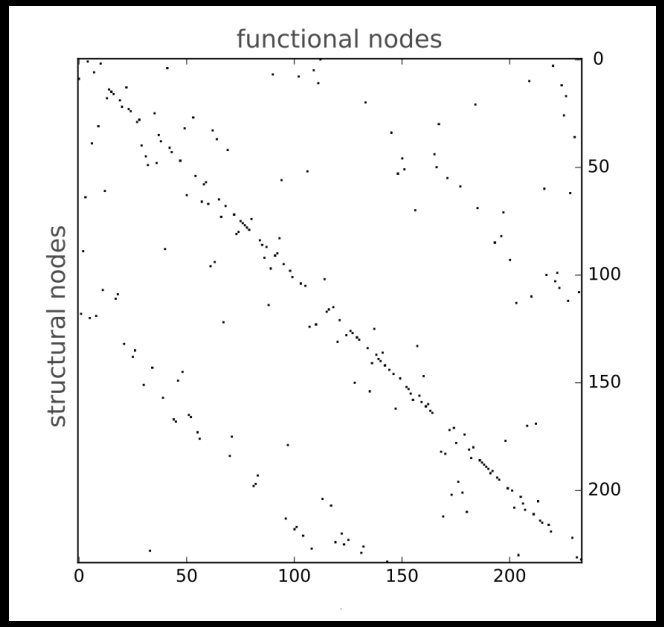
Graph representation of

structural connectome

functional connectome



Used Hungarian algorithm for matching nodes of structural graphs with that of functional graphs



Structure-function matching matrix

Philadelphia Neurodevelopmental Cohort

793 subjects
Age range
[8,22]

234 Brain Regions
Deterministic
tractography

- ✓ Calculate structure function coupling for each subject
- ✓ Permutation test: randomly shuffle edges of the structural graph while preserving the degree distribution

Postdoc Positions available

- Positions in
  - microstructure modeling for the clinic
  - connectomics (graph theory)
  - biomarker (machine learning)
- Technical advances with clinical applications
- Interaction with clinical faculty
- Available immediately
- Contact with CV: ragini.verma@gmail.com
- Located in Dept of Radiology, Upenn, Philadelphia, USA

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Taki Shinohara (Statistics)

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Lisa Desiderio (Radiology, Recruitment)
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