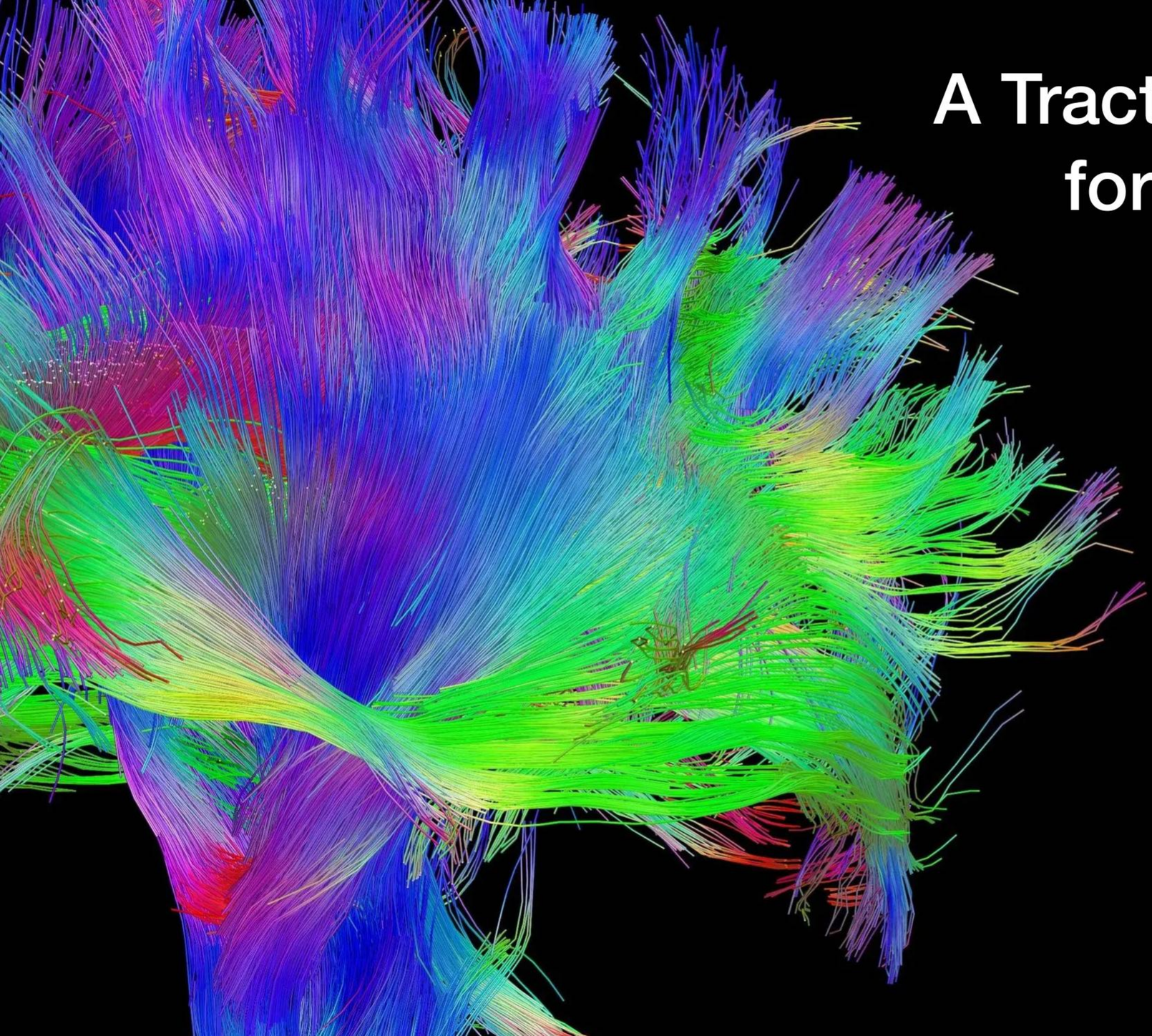


A Tract Density Biomarker for Survival Prediction in Glioblastoma

Joan Falcó-Roget
Jan K. Argasiński

Jagiellonian University in Krakow
Sano - Centre for Computational Medicine

Neuro-Oncology

28(2), 564–579, 2026 | https://doi.org/10.1093/neuonc/noaf234 | Advance Access publication October 16, 2025

A non-local diffusion magnetic resonance imaging tract density biomarker to stratify, predict, and interpret survival rates in human glioblastoma

Joan Falcó-Roget, Gianpaolo Antonio Basile†, Anna Janus†, Sara Lillo, Letterio S. Politi, Jan K. Argasinski, and Alberto Cacciola

All author affiliations are listed at the end of the article

Corresponding Authors: Joan Falcó-Roget, Computational Neuroscience Group, Sano Centre for Computational Medicine, Czarnowiejska 36 building C5, 30-054 Kraków, Poland (joan.falcoroget@gmail.com); Alberto Cacciola, MD, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, 20072 Milan, Italy; IRCCS Humanitas Research Hospital, Rozzano, 20089 Milan, Italy (alberto.cacciola@hunimed.eu).

†These authors contributed equally to this work.

Abstract

Background. Glioblastoma (GBM) is a lethal tumor, actively growing and invading neighboring neural tissue. GBMs appear functionally connected to distributed and spatially distant regions rather than representing an isolated and passive lesion disrupting the brain circuitry. Moreover, increasing evidence suggests that white matter serves as the morphological substrate for GBM to progress and migrate to distant areas in the human brain.

Methods. We hypothesized that the subset of white matter tracts intersecting the tumors depicts the physical substrate for large-scale neuron-glioma interactions and would therefore inform prognosis. Using normative models, we design, analyze, interpret, and test a Lesion-Tract Density Index (L-TDI) marker that considers the distributed white matter pathways interacting with the tumor in 2 independent cohorts of $N = 367$ and $N = 496$ patients, respectively.

Results. First, we show that the tract density within this white matter map robustly stratifies survival rates due to widespread white matter involvement. Second, we demonstrate why tract density-based markers offer critical and necessary insights into the morphology, location, and evolution of human GBM by proving how the proposed L-TDI implicitly considers tumor volume, white matter density, and location. We provide further evidence that the non-uniform distribution of GBMs and their differential prognosis emerge from white matter morphology. Third, we validate the L-TDI marker with multiple Cox survival models and analyze its contribution in relation to other covariates of interest (eg, MGMT promoter methylation). Lastly, by using a simple logistic model, we predict patient death at 12 months with balanced accuracies of 68% and 65%, and areas under the curve of 0.74 and 0.73 when training

EUROPEAN ASSOCIATION OF NEURO-ONCOLOGY

20TH MEETING & EDUCATIONAL DAY EANO 2025
PRAGUE, CZECH REPUBLIC · OCTOBER 16-19

A Normative Human Glioblastoma Connectome Constructed From Tumor Connected Brain Regions Improves Survival Rates Estimation

A Janus, J Falcó-Roget, S Lillo, L Politi, J Argasinski, A Cacciola

Computational Neuroscience Lab @ Sano – Centre for Computational Medicine
International Research Foundation, Kraków

WWW.EANO.EU

A circuit-based white matter density neuroimaging biomarker to stratify, predict, and interpret survival rates in human glioblastoma

Joan Falcó-Roget, Gianpaolo Antonio Basile*, Anna Janus*, Sara Lillo, Letterio Salvatore Politi, Jan K. Argasinski, Alberto Cacciola

Computational Neuroscience Lab @ Sano – Centre for Computational Medicine
International Research Foundation, Kraków

*Equal contribution

WWW.EANO.EU

Bayesian Filtered Generation of Post-surgical Brain Connectomes on Tumor Patients

communications biology

Article

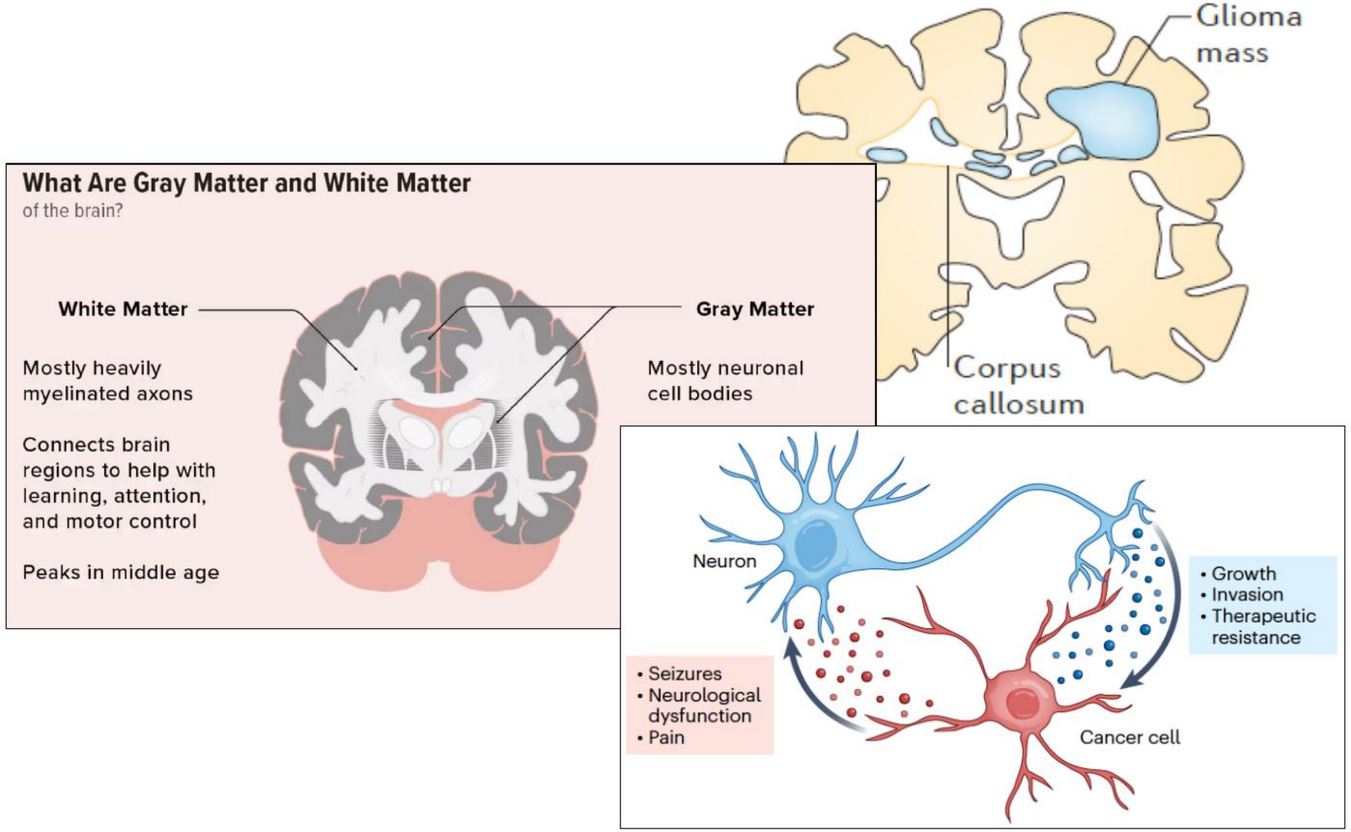
https://doi.org/10.1038/s42003-024-06119-3

Functional and structural reorganization in brain tumors: a machine learning approach using desynchronized functional oscillations

this was originally presented by Joan Falcó-Roget

Introduction: A connectionist framework for GBM

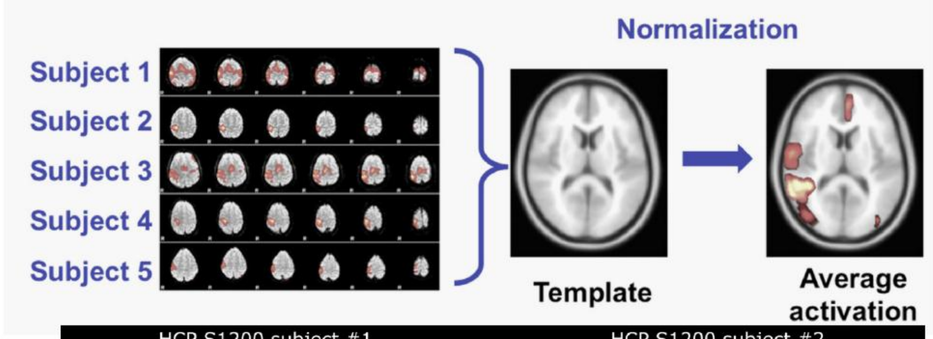
- Glioblastoma (GBM) cells establish functional links with neurons
- Growth, proliferation, and migration must consider the white matter scaffold
- Two interdependent complex networks:
  - 1) the brain
  - 2) the neuron-glioma
- **<u>Our aim:</u>**
  Map the GBM circuit and its relationship with prognosis using non-invasive methods

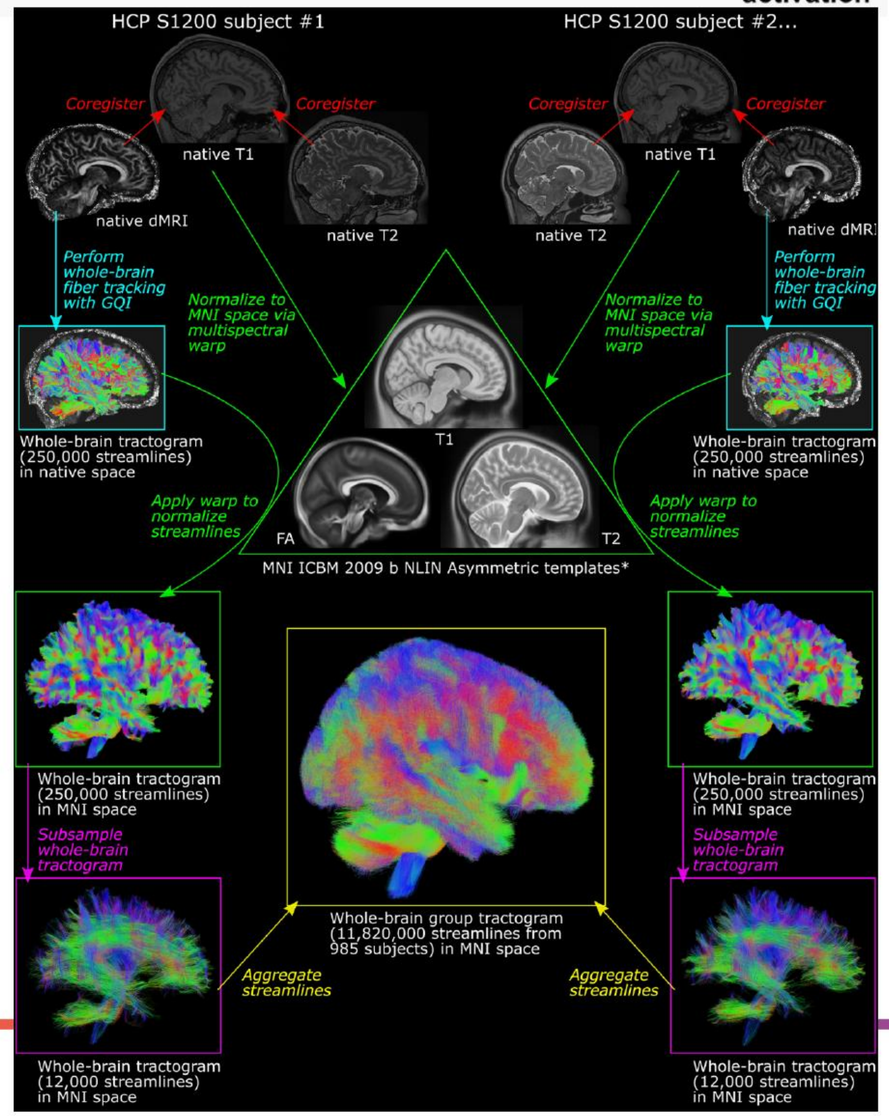


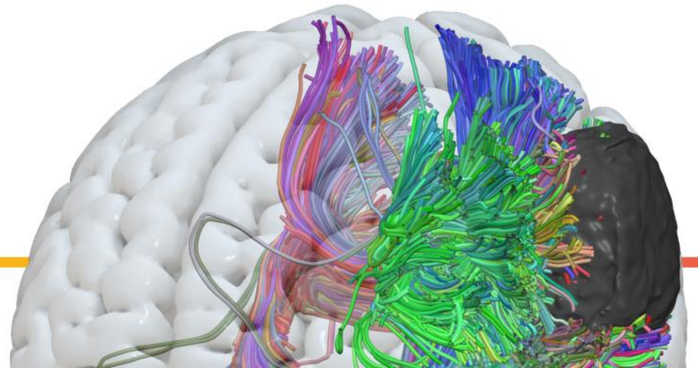
Cuddapah, et al. *Nat. Rev. Neuro.* (2014); Monje & Winckler. *Nat. Neuro. (2025)*

Methods: NeuroImaging

- Two independent cohorts: N=367 and N=496
- Clinical: Age, Sex, MGMT promoter status, EOR
- Normalized multimodal structural MRI
- Normative tractography (11.8M streamlines)
- ***Lesion-tract density index*** (L-TDI: white contour)
- Tract density index (TDI: black contour)





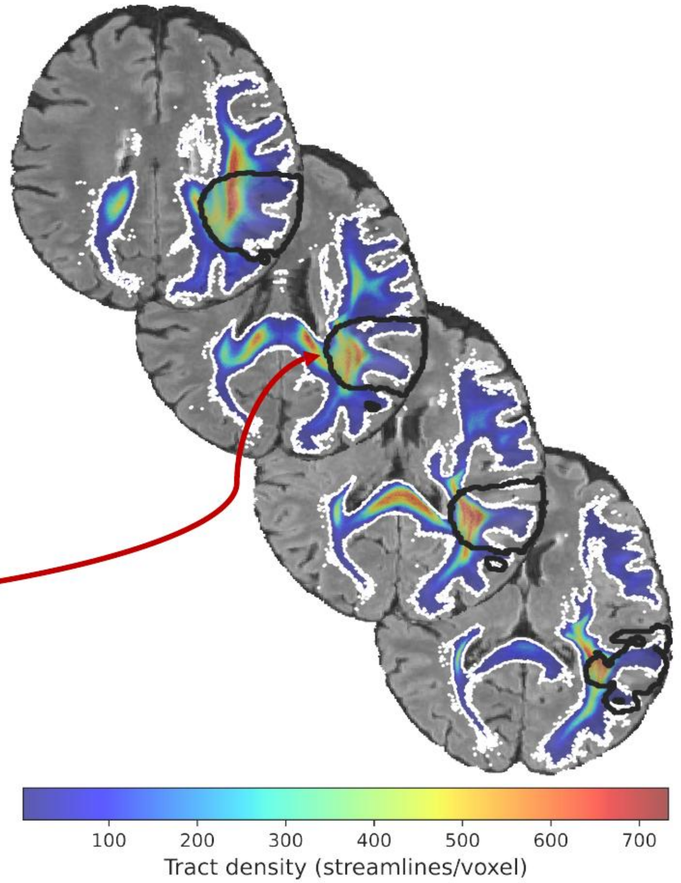


Elias, et al. *Sci. Data.* (2024)

Methods: NeuroImaging

- Two independent cohorts: N=367 and N=496
- Clinical: Age, Sex, MGMT promoter status, EOR
- Normalized multimodal structural MRI
- Normative tractography (11.8M streamlines)
- ***Lesion-tract density index*** (L-TDI: white contour)
- Tract density index (TDI: black contour)

$$\text{Tract density index} = \frac{1}{\text{Size}(\textbf{tumor})} \sum_{\text{voxel} \in \textbf{tumor}} \textbf{Tract density}$$



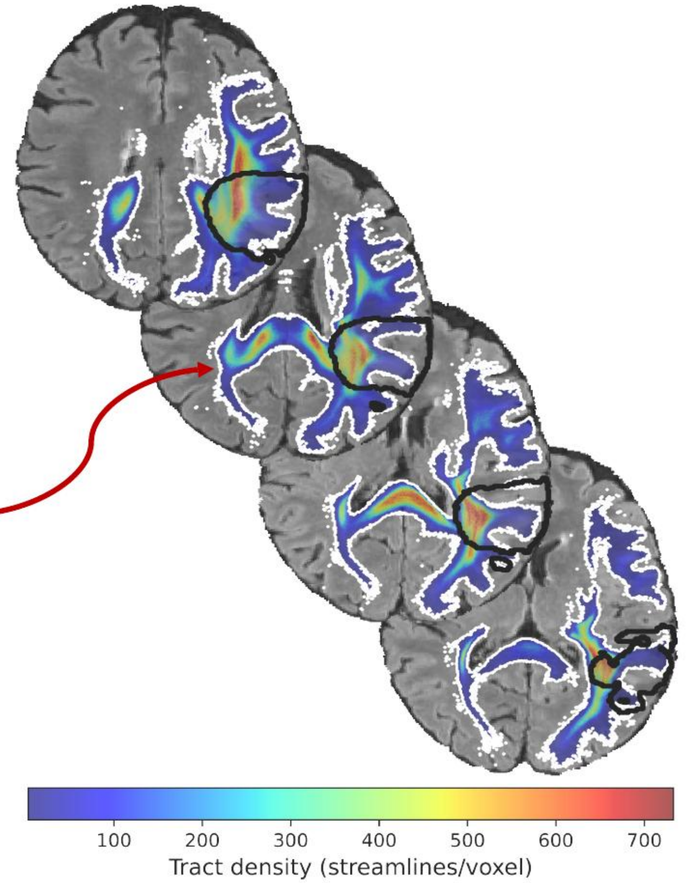
Salvalaggio, et al. *JAMA Neurol.* (2023);

Methods: NeuroImaging

- Two independent cohorts: N=367 and N=496
- Clinical: Age, Sex, MGMT promoter status, EOR
- Normalized multimodal structural MRI
- Normative tractography (11.8M streamlines)

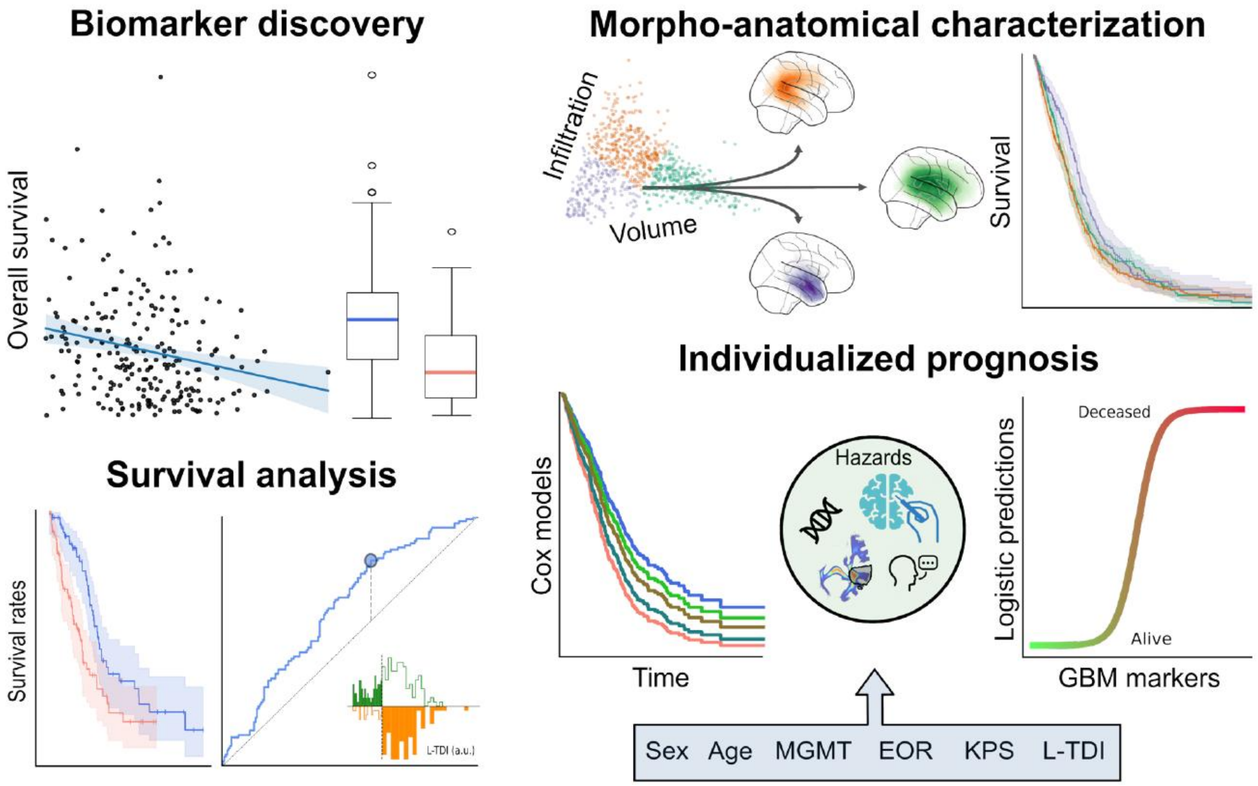
- ***Lesion-tract density index*** (L-TDI: white contour)
- Tract density index (TDI: black contour)

$$\text{Lesion-tract density index} = \frac{1}{\text{Size(L-TDM)}} \sum_{\text{voxel} \in \text{L-TDM}} \text{Tract density}_{\text{voxel}}$$

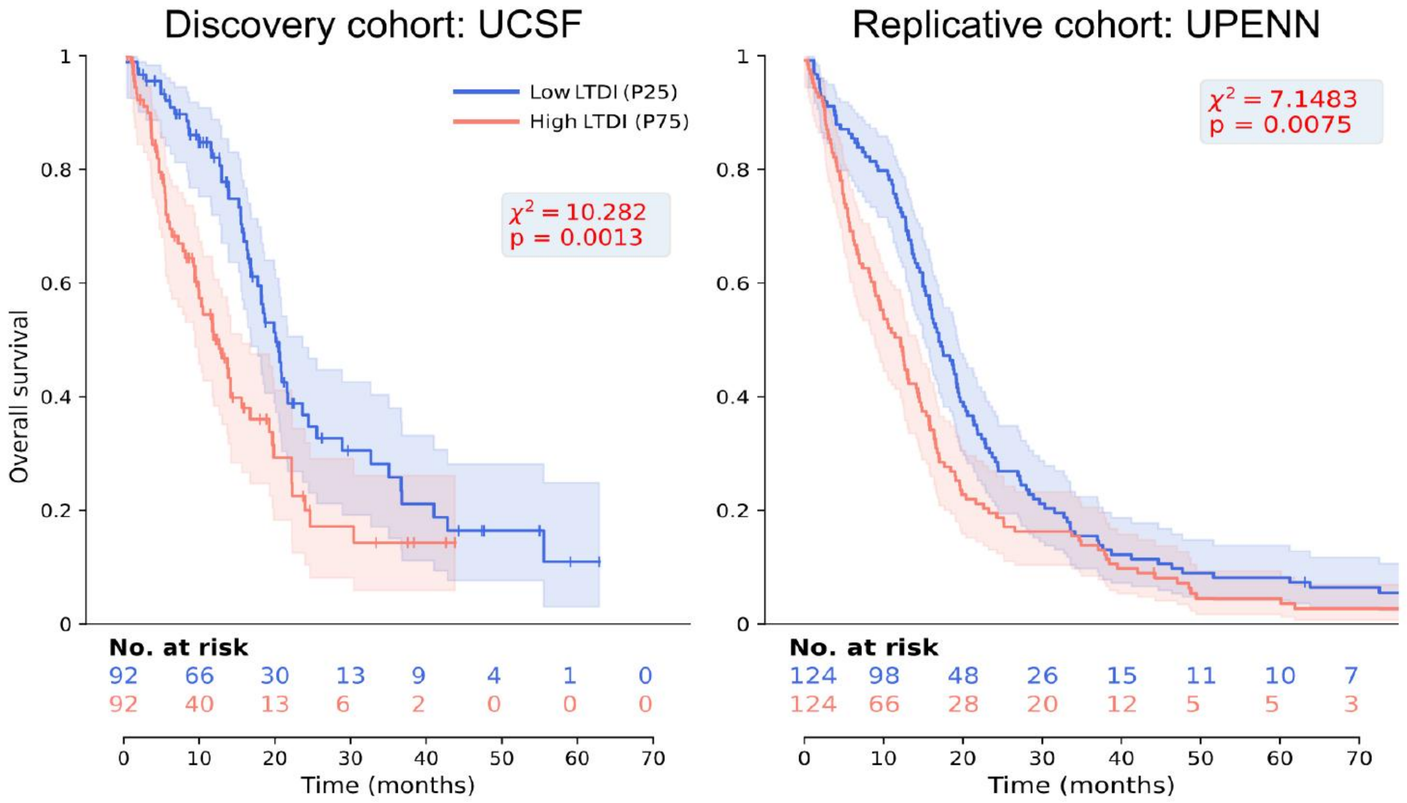


Methods: Connectomics-informed survival analysis

- Univariate analysis
- Interpretability
- Cox multivariate analysis
- Survival predictions



Results: Strata from the lesion-tract density index (L-TDI)



MEDIAN SURVIVAL

Discovery cohort (p<0.0001*)

Low L-TDI: 17.88 [11.14, 21.06]

High L-TDI: 9.58 [4.15, 13.74]

Replicative cohort (p=0.0009*)

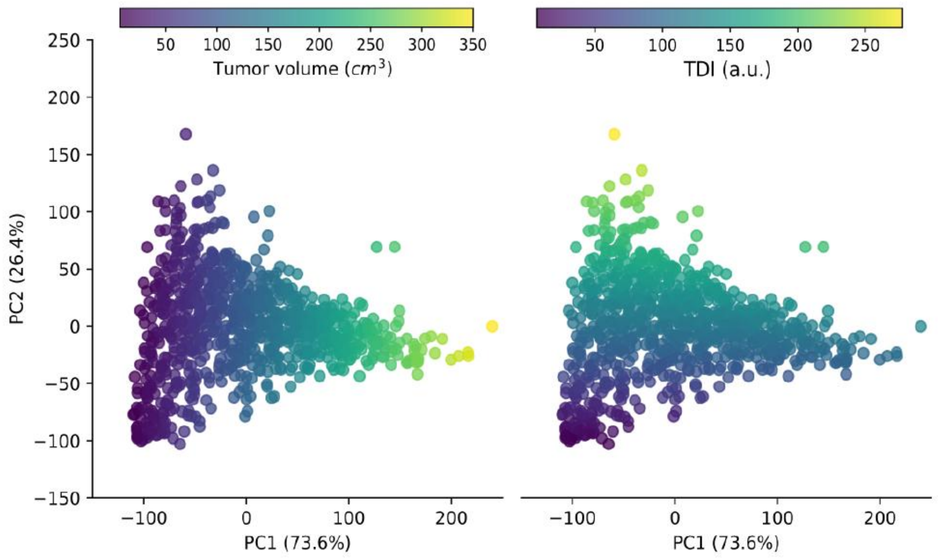
Low L-TDI: 19.89 [11.21, 24.39]

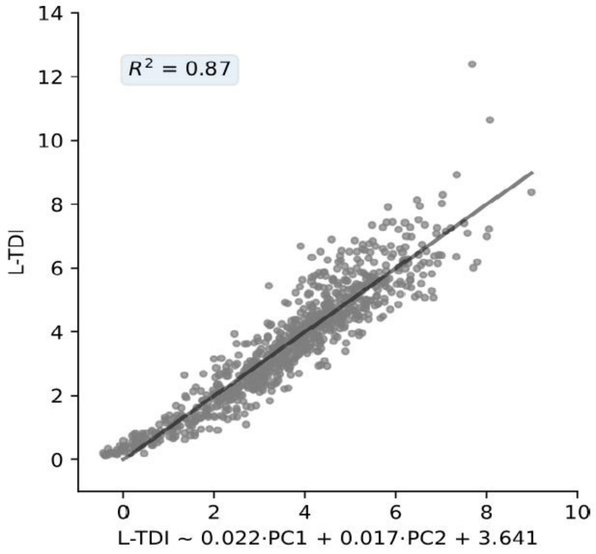
High L-TDI: 15.74 [4.96, 19.00]

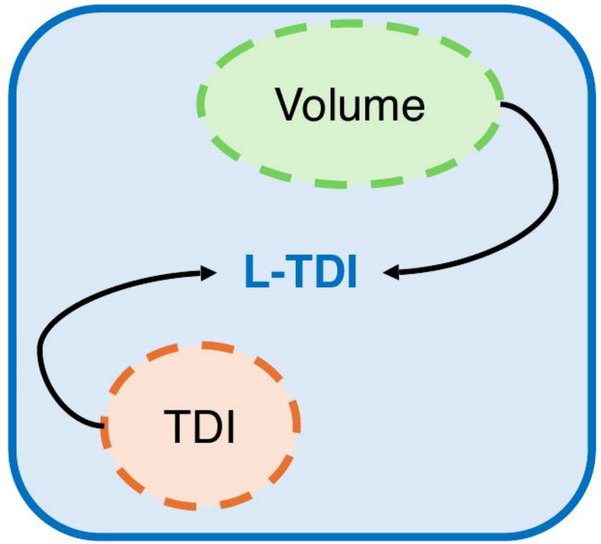
*Two-sided Mann-Whitney U-test

Results: The morpho-anatomy of Glioblastomas

- **L-TDI** = **TDI** + **volume** *(it implicitly considers tumor volume and local fiber density)*

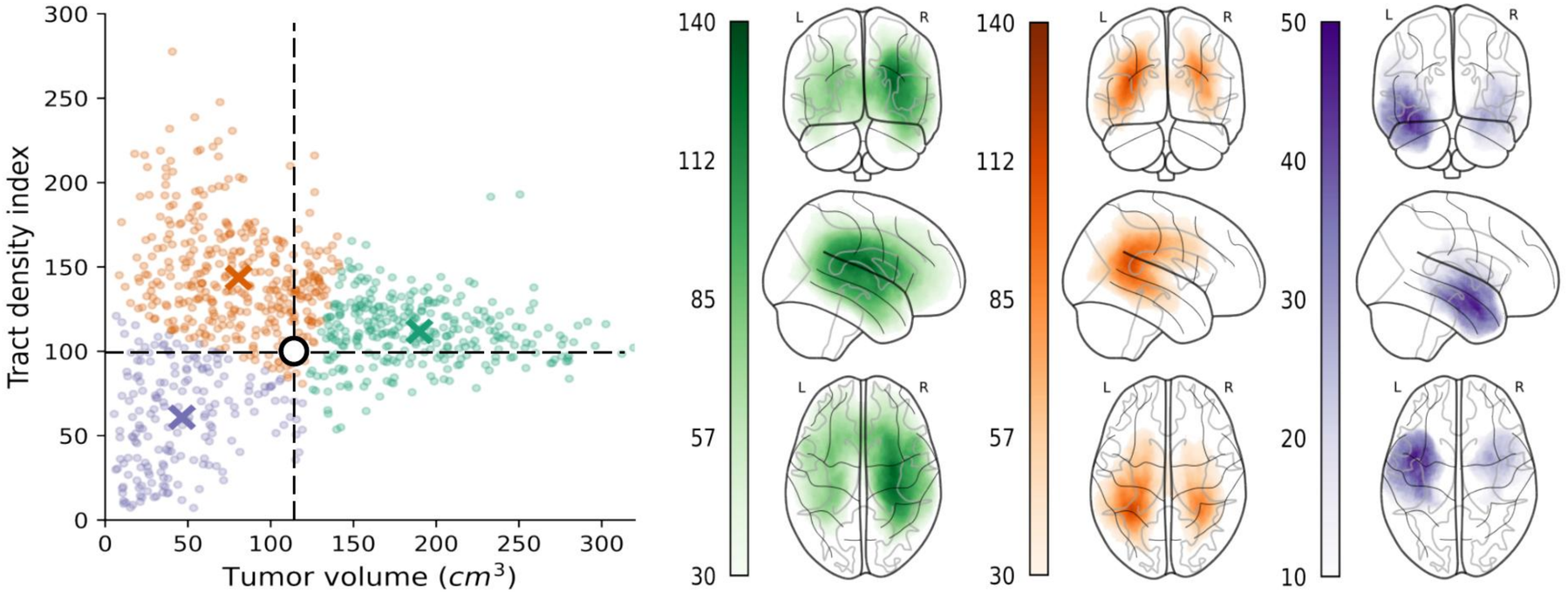






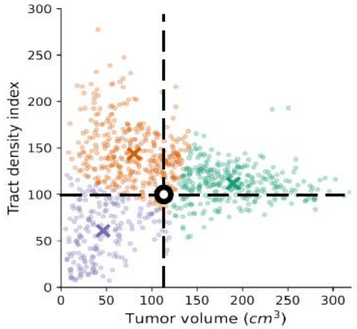
Results: The morpho-anatomy of GBMs

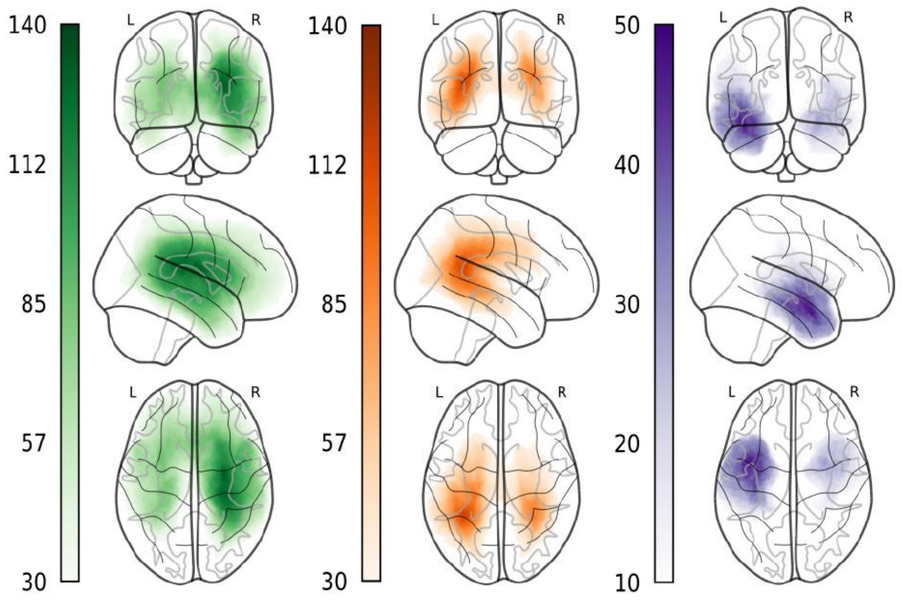
- L-TDI assigns a unique pair of (TDI, volume) coordinates within the human brain

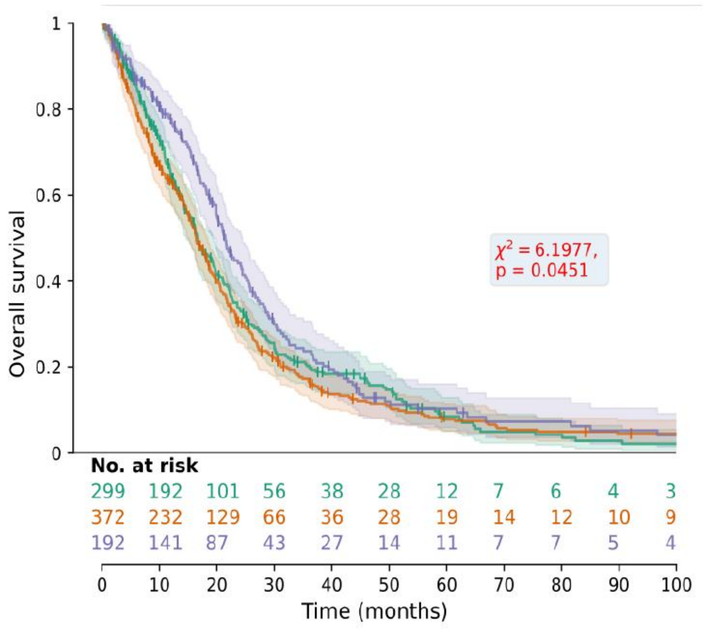


Results: The morpho-anatomy of GBMs

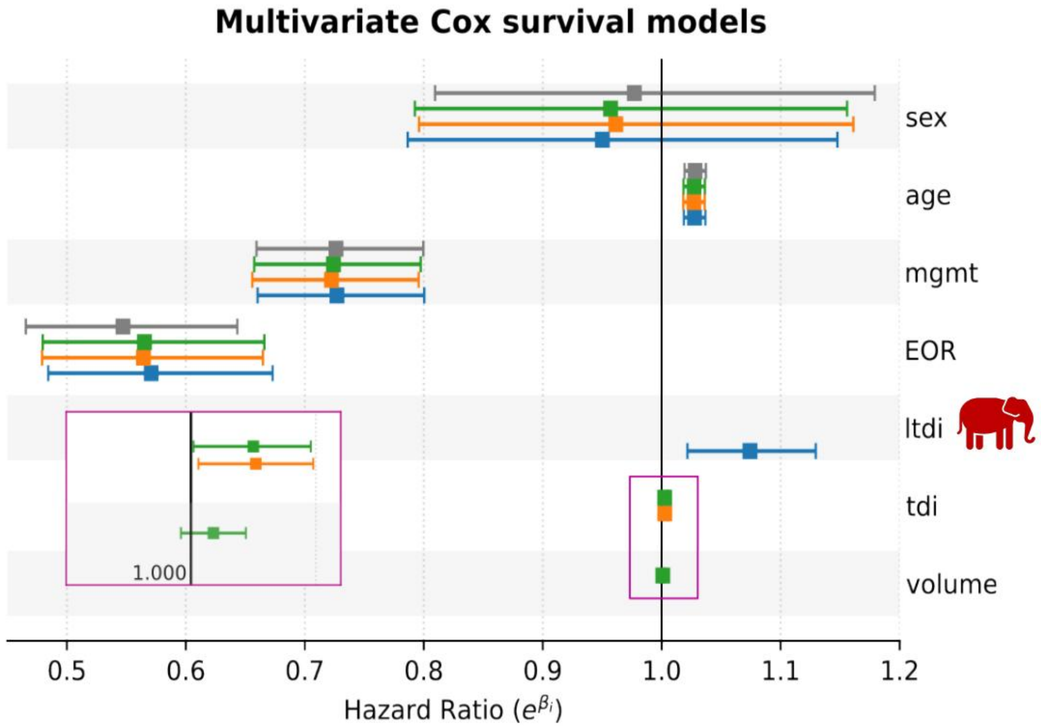
- L-TDI assigns a unique pair of (TDI, volume) coordinates within the human brain

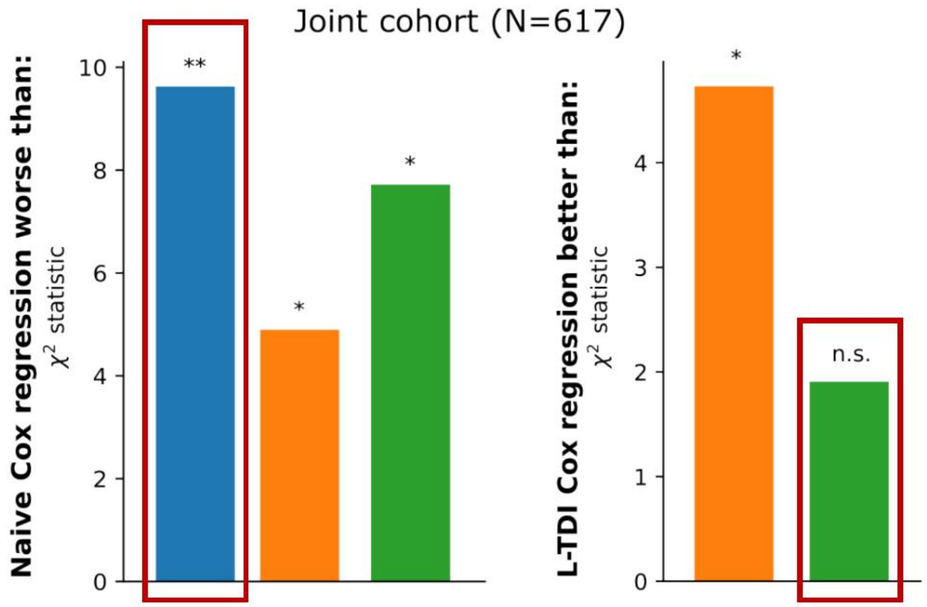






Results: A biomarker that improves survival analyses

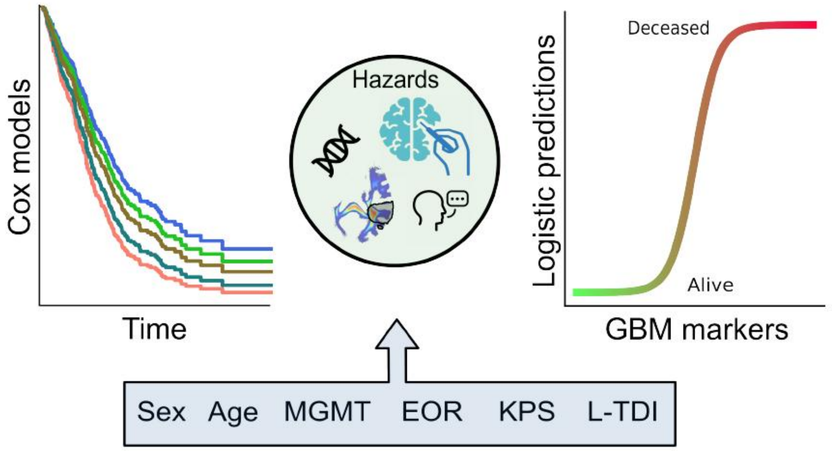


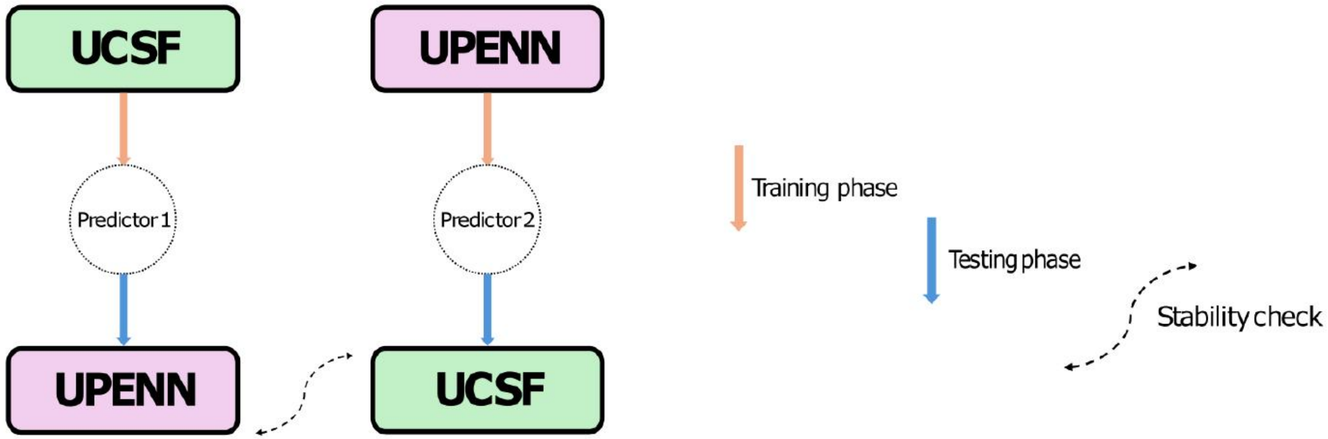


L-TDI TDI TDI+Volume Naive

Log-likelihood ratio tests (*p<0.05; **p<0.01; ***p<0.001)

Individualized prognosis

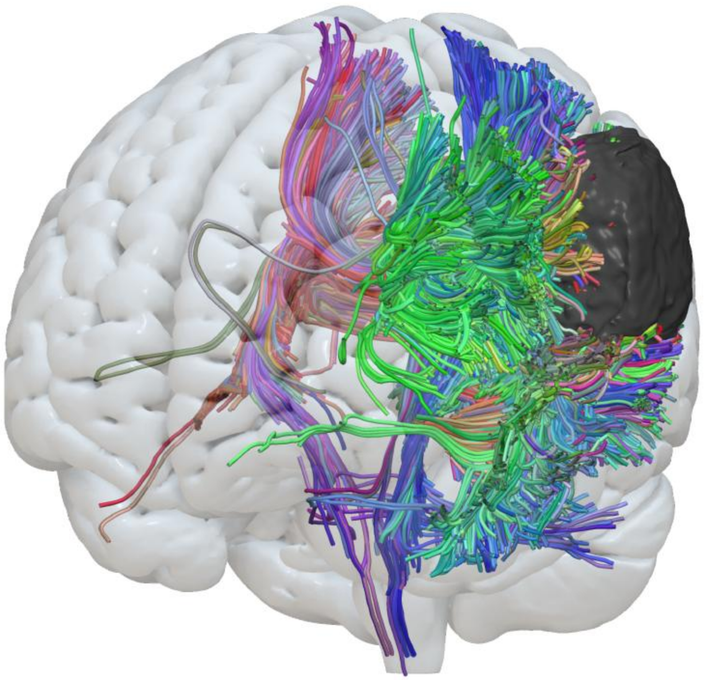




		TRAIN (12 months)					
Area under the curve (AUC)		UCSF			UPENN		
Model		L-TDI	TDI	Naive	L-TDI	TDI	Naïve
TEST (12 months)	UCSF	N.A.			0.7433	0.7088	0.7220
	UPENN	0.7327	0.7039	0.7077	N.A.		
Balanced accuracy (bACC)		UCSF			UPENN		
Model		L-TDI	TDI	Naive	L-TDI	TDI	Naïve
TEST (12 months)	UCSF	N.A.			0.6498	0.6463	0.6418
	UPENN	0.6753	0.656	0.6661	N.A.		

Conclusions

- We introduce a fast, robust, and interpretable tractography-based marker to stratify GBM survival
- We model GBM as a distributed lesion embedded within the brain's white matter scaffold
- We reinterpret GBM morphology and anatomy through a connectomics framework
- We demonstrate how connectomics can enhance AI/ML survival prediction models



Acknowledgements

Joan Falcó-Roget ***(Sano - Centre for Computational Medicine and Jagiellonian University, Kraków)***

Alberto Cacciola *(Humanitas University and IRCCS Humanitas Research Hospital, Milan)*
Anna Janus *(Jagiellonian University, Kraków and Sano - Centre for Computational Medicine)*
Sara Lillo *(National Center for Oncological Hadrontherapy and University of Pavia, Pavia)*
Letterio Salvatore Politi *(Humanitas University and IRCCS Humanitas Research Hospital, Milan)*
Gianpaolo Antonio Basile *(University of Messina, Messina)*

Jan K. Argasinski ***(Jagiellonian University, Kraków*** *and Sano - Centre for Computational Medicine**)***

Funding:
NCN (UMO-2024/53/N/NZ4/03513);
EU Horizon 2020 (857533); FNP (MAB PLUS/2019/13);
Minister of Science and Higher Education (MEiN/2023/DIR/3796)