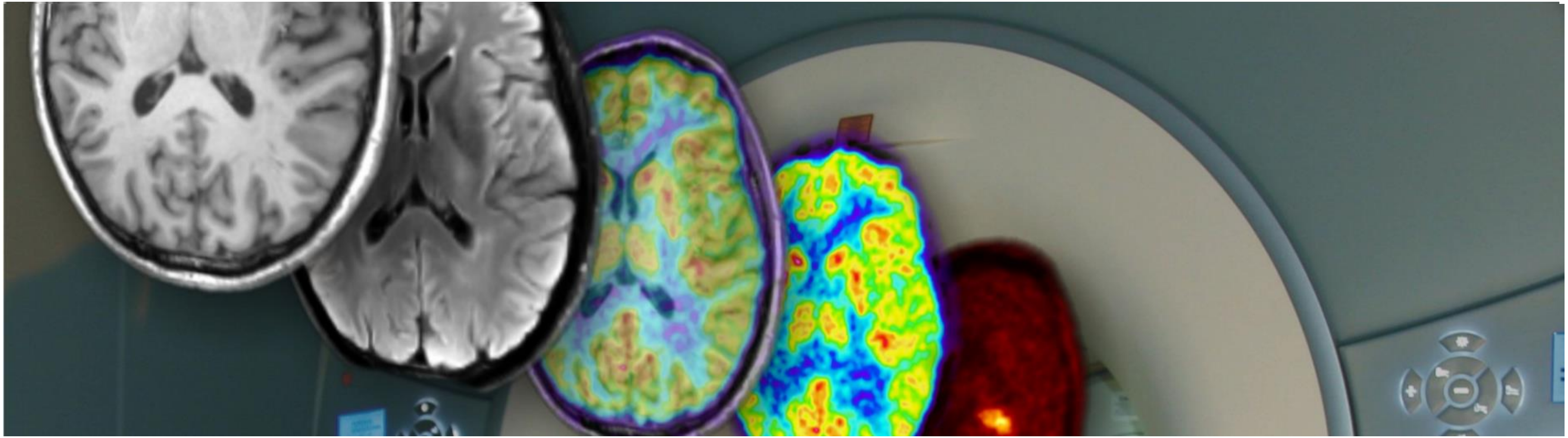

GGSB-PLUS: Perspectives 2023

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Health as a Global Challenge: GGSB-PLUS

- Through globalisation, mankind has developed into a globally interconnected and interacting community…..
- ….. As the current COVID-19 crisis has impressively demonstrated.
- Health is no longer seen in isolation in a national context, but rather as a global challenge that can only be solved at a higher level, through international cooperation, in a long-term and sustainable manner.
- The improvement of patient care through scientific progress and the early diagnosis and therapy of disease patterns made possible by this must no longer be reserved for a few countries.
- GGSB-PLUS will attempt to address this challenge

Health as a Global Challenge: GGSB-PLUS

- Application submitted to BMBF from various institutes of the Research Centre Jülich (FZJ).
- Intended to contribute to bridging national borders for resources and knowledge in order to address the topic of health in a targeted manner and to develop solutions for the treatment of diseases across national borders.
- The already existing "Georgian-German Science Bridge" (GGSB) between the FZJ and various universities in Georgia is an ideal platform for this project.
- A proven tool of the GGSB for improving networking and scientific exchange are the so-called SMART|Labs, of which two laboratories have already been established in Georgia (SMART|AtmoSim_Lab with the research focus on air pollutants; SMART|EDM_Lab with the research focus on basic physics research).
- Within the framework of our application project GGSB-PLUS, another SMART|Lab for Biomedical Imaging is to be established

Health as a Global Challenge: GGSB-PLUS

- SMART|Lab for Biomedical Imaging will focus on:
    - ➢Water mapping with MRI (INM-4)
    - ➢Tumour diagnostics with PET and hybrid MR-PET (INM-4; UKAachen)
    - ➢Early diagnosis using machine learning (IAS-8; KIU; TSU; GTU)
    - ➢Development of therapeutic probes for diagnostics and therapy (INM-5)
    - ➢Training and transfer to therapy centres (GGSB)

Health as a Global Challenge: GGSB-PLUS

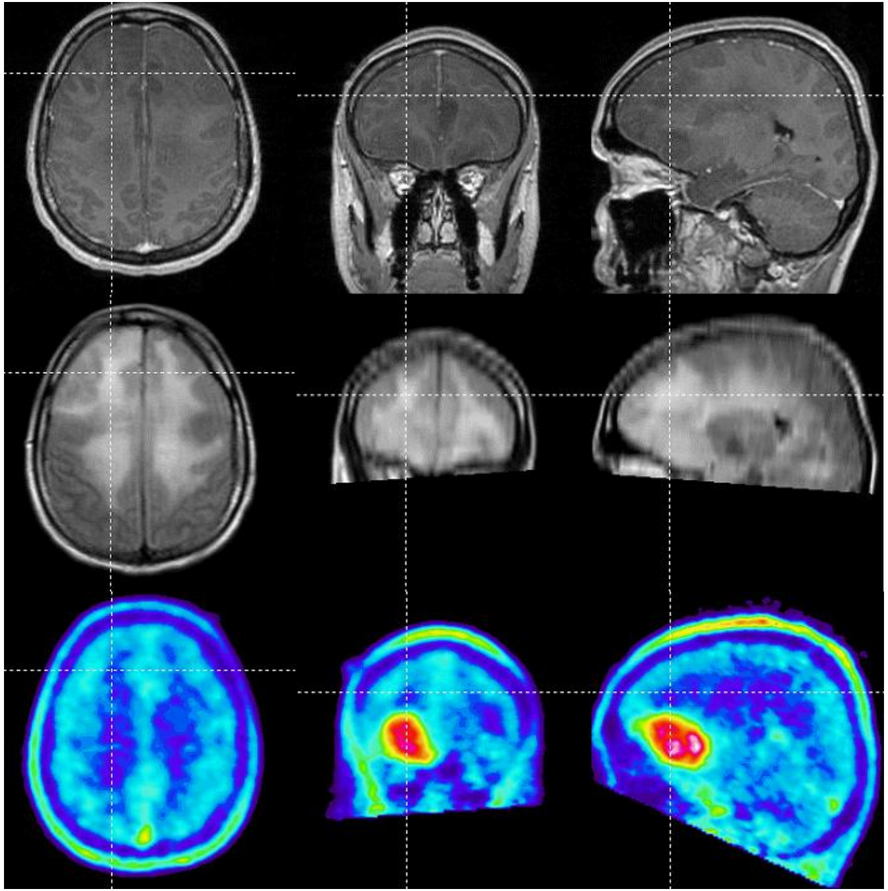
- The Biomedical Imaging SMART|Lab will focus on imaging tumours using:
  - MRI (quantitative MRI)
  - PET
  - Development of radioactive tracers and drugs
- Through the joint research projects of the FZJ and the Georgian partners KIU, TSU and GTU carried out within the framework of the Biomedical Imaging SMART|Lab, the existing platform for technology and knowledge transfer is to be expanded, leading to substantial structural improvements in Georgia.
- In addition, this should support bilateral exchange and lead to scientific feedback, which will thus also have a positive impact on the German research and education landscape.

Health as a Global Challenge: GGSB-PLUS

- FZJ has first-class expertise in diagnostic imaging and radiotracer production - which will benefit Georgia through the SMART|Lab for Biomedcal Imaging, especially for the development of the radiotherapy centre in Kutaisi planned by the Kutaisi International University (KIU), as this centre is will be a unique resource for the entire Caucasus region.
- This extremely ambitious project would sustainably benefit from the knowledge of the German partners.
- The technical know-how of the German partners, especially in the field of imaging, tracer production and particle physics, will be shared with the Hadron Therapy Centre (HTC).
- Precise knowledge of the spatial location of the tumour to be irradiated is crucial.
- **Comprehensive Imaging Centre** to be discussed.

Health as a Global Challenge: GGSB-PLUS

Brain Tumour ?



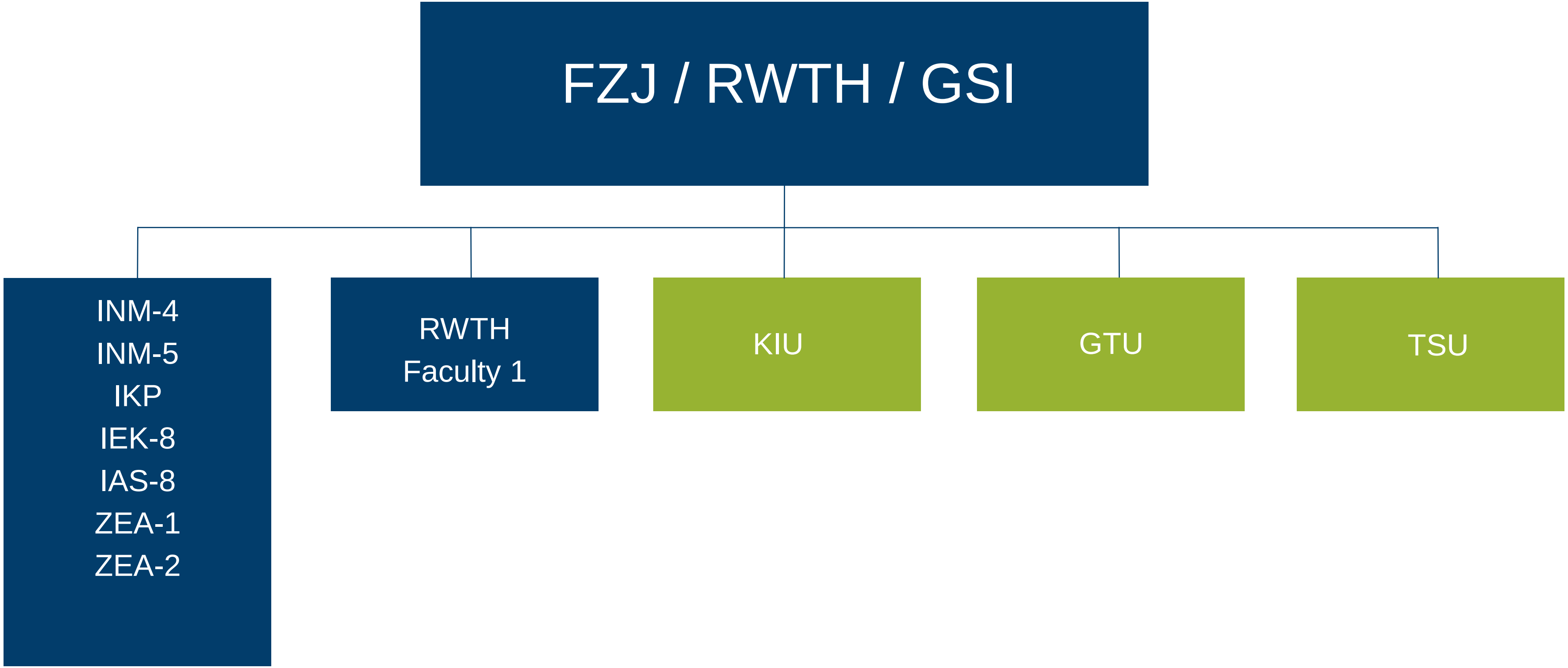
MR-T1 (CA)

MR-FLAIR

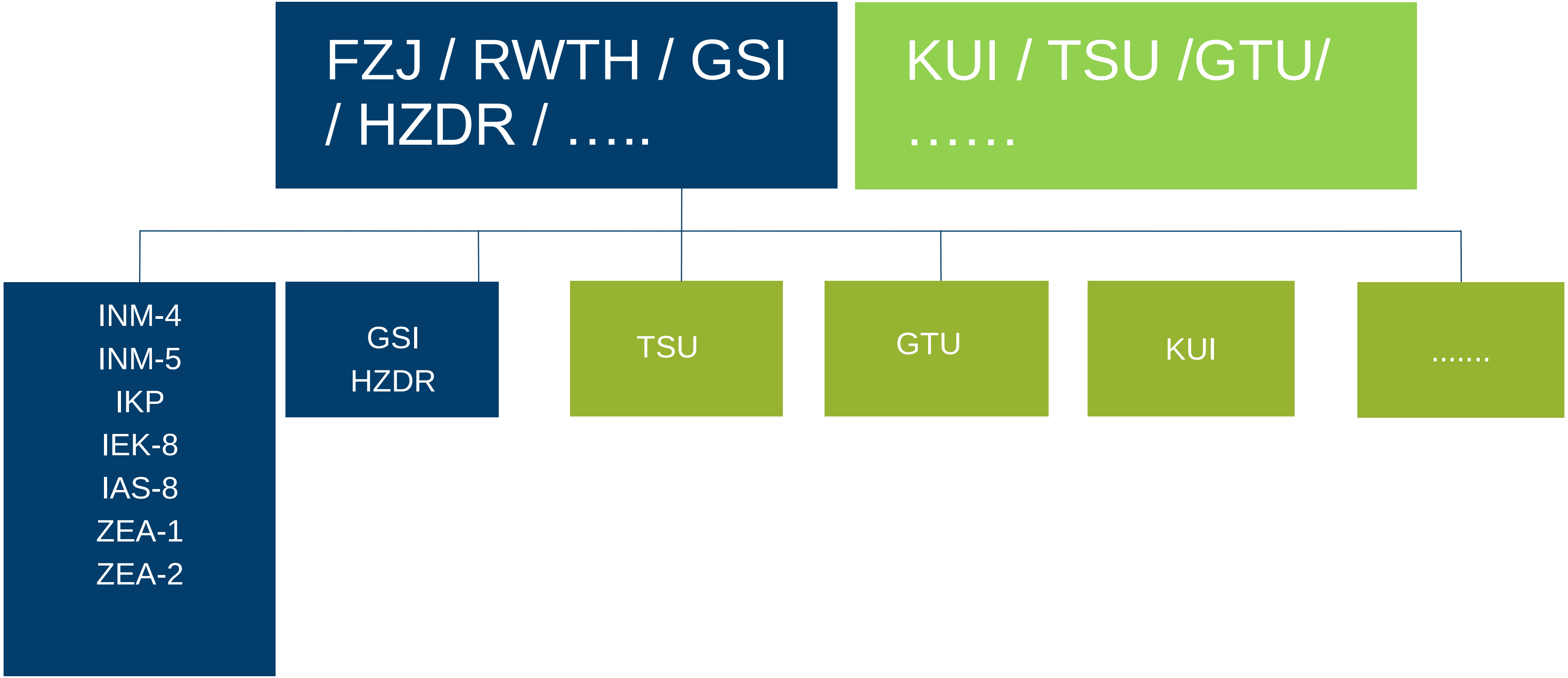
FET-PET

Astrocytoma Grade II

GGSB-PLUS [Planned and Submitted in 2020]



GGSB-PLUS [as planned in 2022]



GGSB-PLUS: Smart|Lab Biomedical Imaging

Research Areas

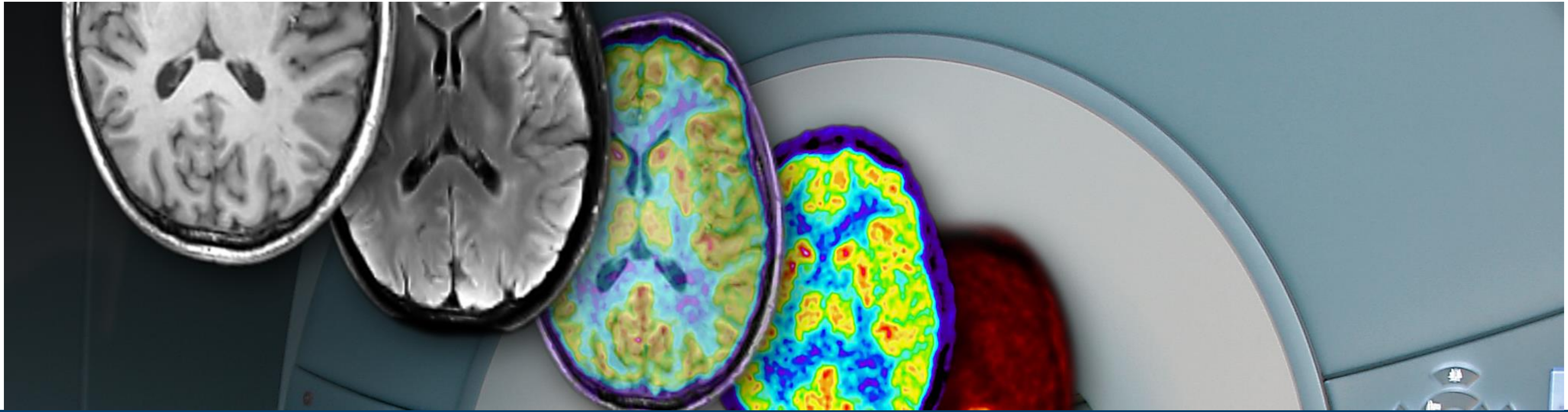
- Biomedical Imaging
  - MRI / PET
  - Tracers
- Novel Machine Learning Software
- Clinical Translation - HTC

Platforms

- **HTC**
- **Computational Resources**
- **Cyclotrons**
- ….
- Machine Learning
- Animal Laboratory
- Novel 7T BrainPET Insert

Applications / Topics

- Tumours
- Health



Advanced multimodal quantitative characterisation of brain tumours and oedema

Mitglied der Helmholtz-Gemeinschaft

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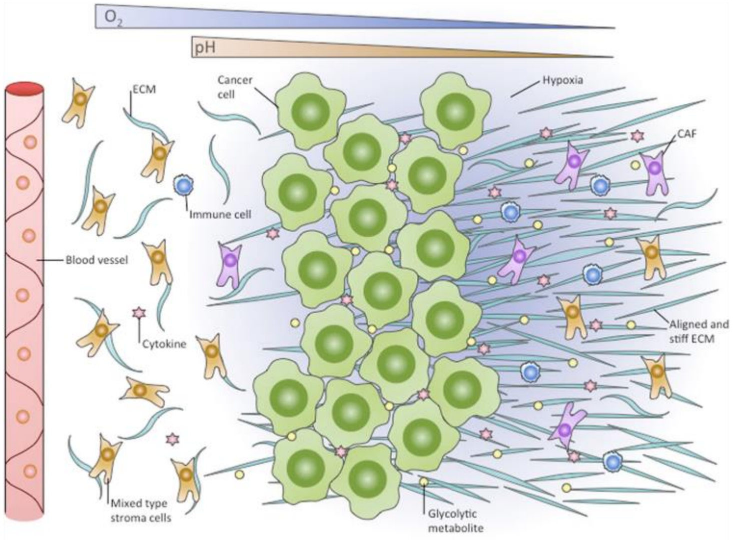
Multimodal qMRI: general considerations

- Advantages of quantitative vs contrast-weighted imaging in characterising tumour evolution (see Hattingen)
- MRI methods such as MPRAGE, FLAIR have high diagnostic usefulness in oncology but the changes in the underlying parameters are neither carefully investigated not properly understood!
- **qMRI can characterise physiologically meaningful parameters: water content, pH, temperature, perfusion, oxygen extraction fraction, CMRO2, iron content, tissue conductivity (free ion concentration)**
- Brain tumours cause clear structural and biophysical changes in their environment (structure of extracellular matrix, pH, vasculature, water content, …)
- Practically all qMRI parameters reflect aspects of these changes
- Relevant histological correlations not sufficiently investigated

Multimodal qMRI: MRI aspects

- **Correlations between parameters are potentially more sensitive to microstructure than single parameters**
  - e.g. water-T_1 or water-conductivity or T_2-diffusion or T_1-MT etc.
  - Different tissue aspects can be investigated. e.g. diffusion restrictions and pH showing hypoxia, necrosis and tumour cell migration



Aligned and stiff ECM: diffusion restrictions
Hypoxia: pH changes

https://en.wikipedia.org/wiki/Tumor_hypoxia#/media/File:Tumour_stroma_and_extracellular_matrix_in_hypoxia.svg

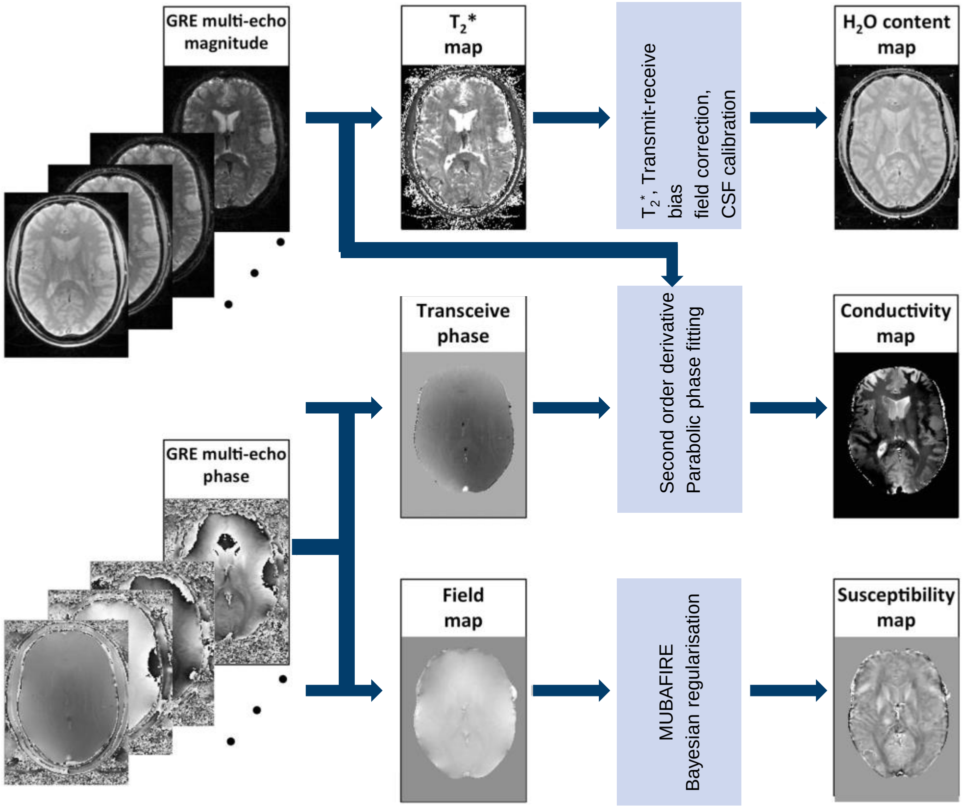
Multimodal qMRI: subprotocol 1

- **Water content**
- **T_2^* changes as surrogate of T_2 changes**
- **Conductivity (Na / K / Cl concentrations)**
- **Susceptibility (oxygen extraction fraction, tissue iron content)**

- Simultaneous parameters, intrinsically coregistered
- **5 min measurement time**

Oros-Peusquens et al. NIMA 2014
Oros-Peusquens et al. Methods 2017
Oros-Peusquens et al. Frontiers Neurology 2019
Liao*, Oros-Peusquens* et al. Sci Reps 2018

Multimodal qMRI: subprotocol 1



4 coregistered simultaneously acquired quantitative maps for tumour qMRI fingerprinting.

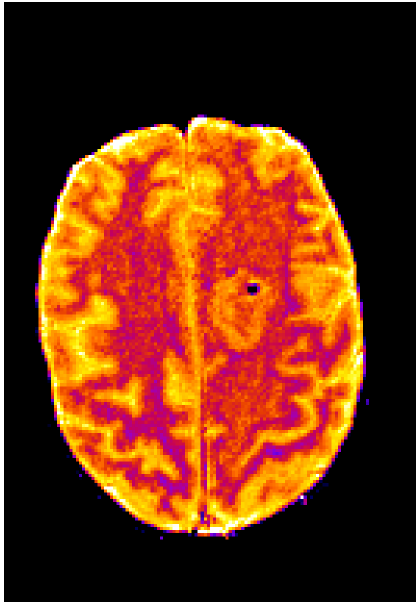
Correlations between parameters also meaningful:

H_2O- ??: possibly cellular bound water

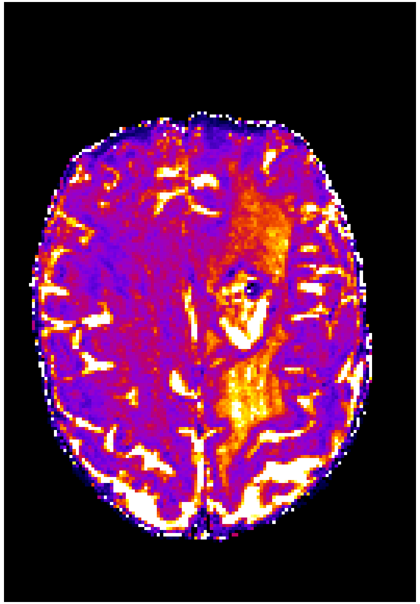
χ – R_2^*: iron chemical form and microscopic distribution

Maps from subprotocol 1
Water content and T_2^*

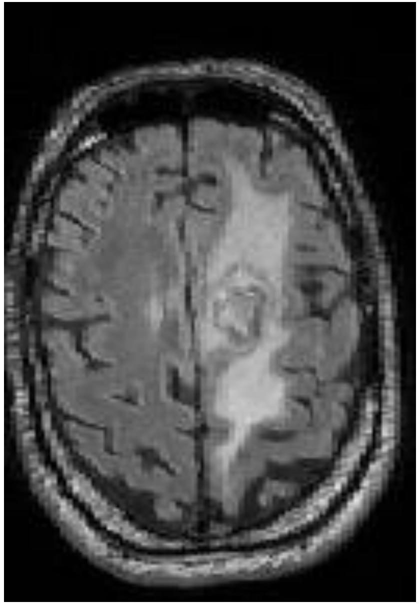
H_2O



T_2*

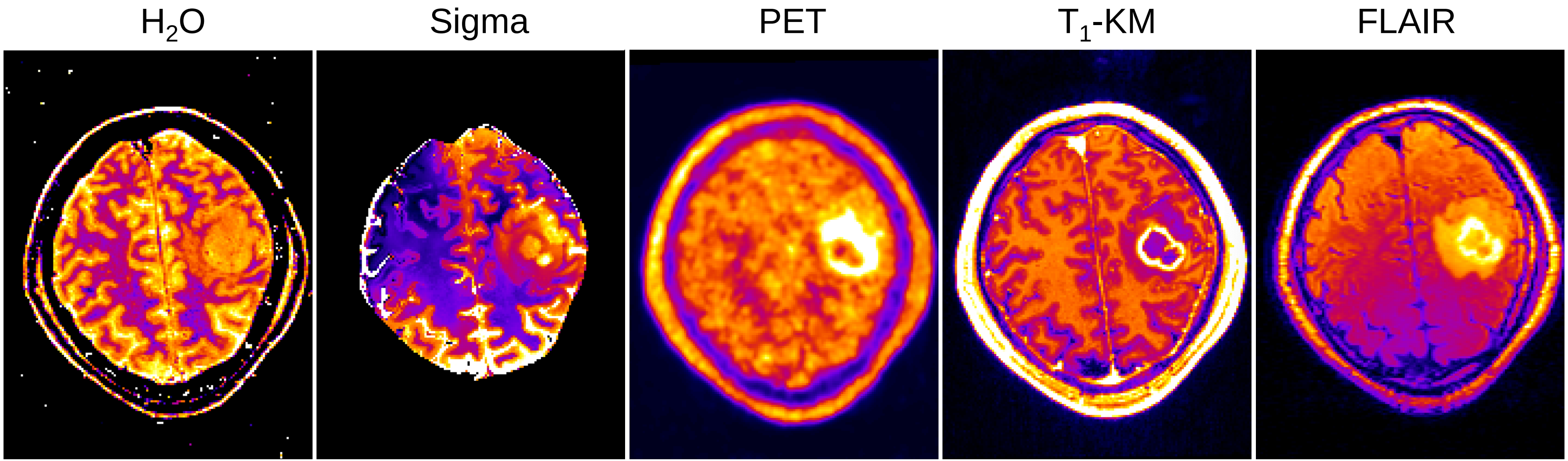


FLAIR



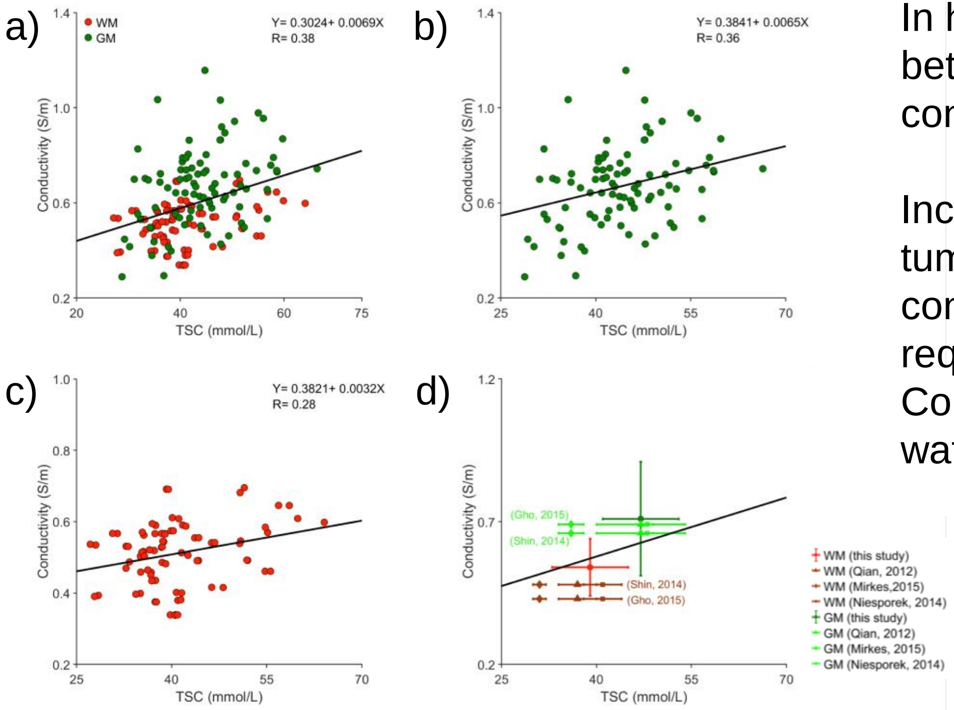
Maps from subprotocol 1

Electric conductivity σ (similar to sodium imaging)



Maps from subprotocol 1

Electric conductivity σ (similar to sodium imaging)

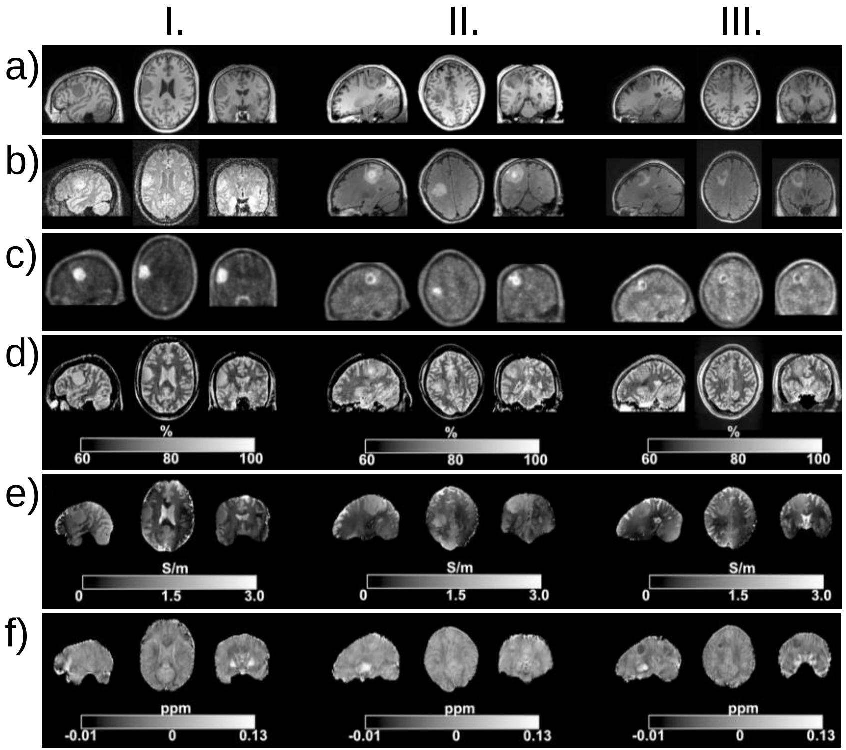


In healthy tissue there is a good correlation between conductivity and total sodium concentration (intra and extracellular)

Increased conductivity in edema and tumour region reflects increased free ion content (Na, K, Cl) quantitatively and requires no special hardware to measure. Correlations with simultaneously measured water content to be further exploited.

MR and PET images from three tumour patients.

Sagittal, transverse and coronal slices through the tumours.



T_1-weighted MPRAGE

proton FLAIR

FET-PET

quantitative water content (colour bar: water content in percentage)

electrical conductivity (colour bar: conductivity in S/m.

quantitative susceptibility images:
colour bar: susceptibility in ppm

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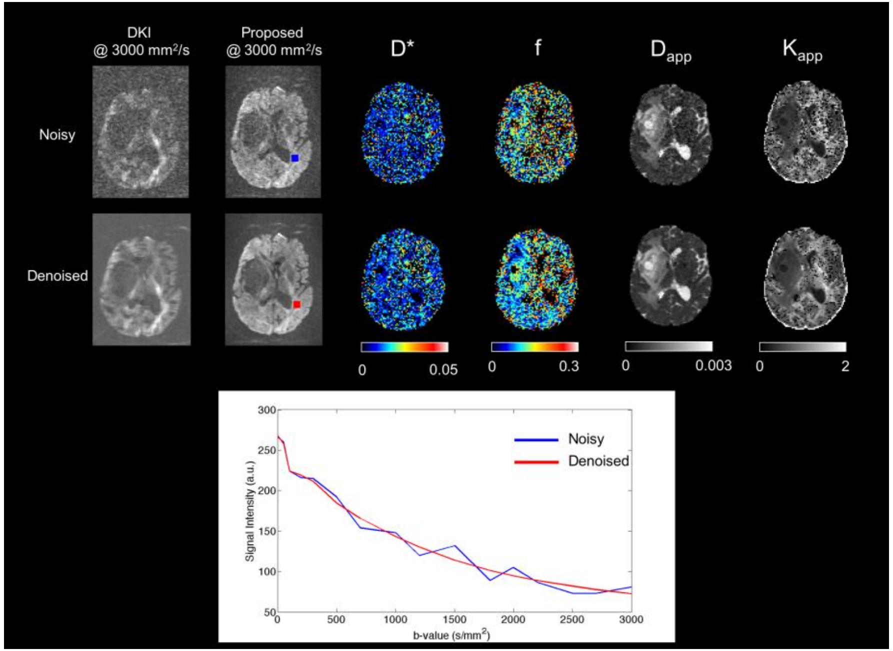
Multimodal qMRI: subprotocol 2

- **Diffusion**
- **Covers three diffusion regimes**
- **Pseudoperfusion (IVIM)**
- **Fast tissue diffusion (similar to ADC)**
- **Slow tissue diffusion (kurtosis)**

- Simultaneous parameters, intrinsically coregistered
- Longer measurement time allows for full slow diffusion characterisation. More sensitive than kurtosis. Potential for grading.
- Diffusion hyperintensities (slow diffusion) detected in about 50% of patients and characterised quantitatively

- **5-8 min measurement time**

Short acquisition, noisy images.

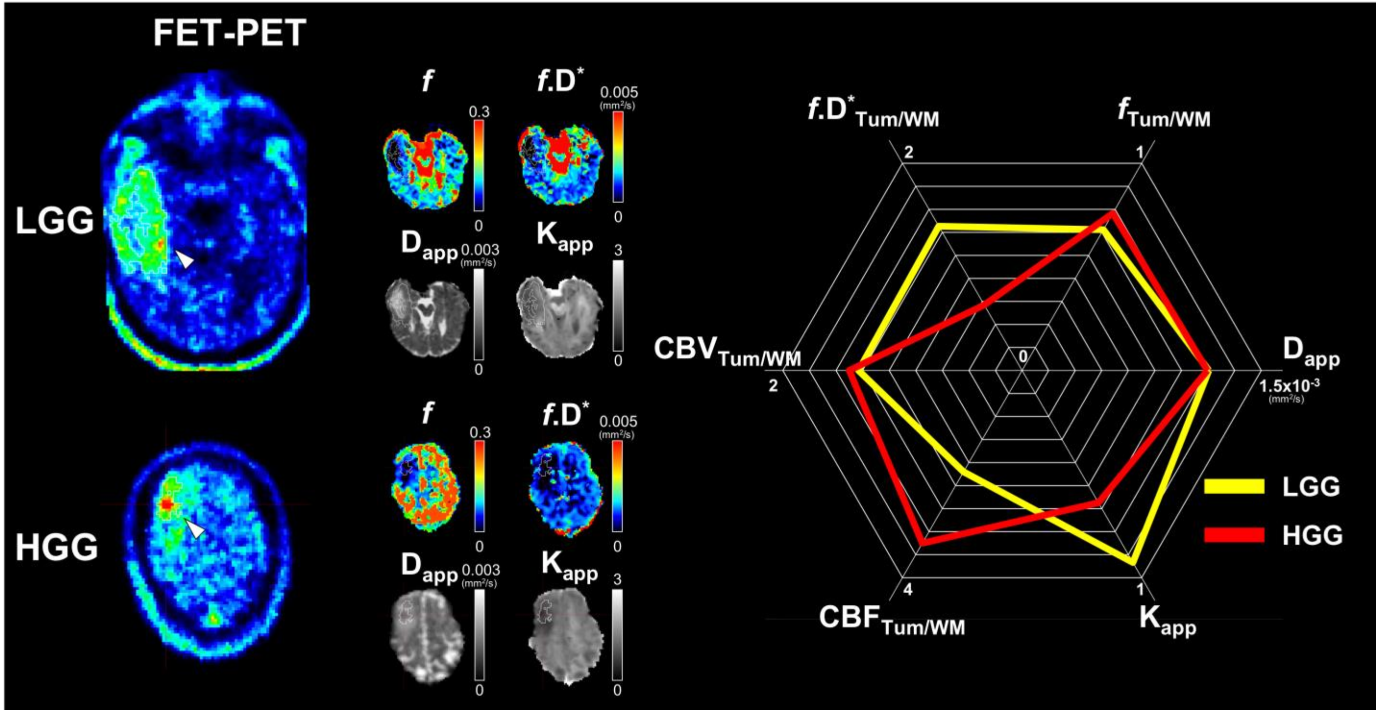


Denoising algorithm developed.

ADC and kurtosis maps with good anatomical detail.

Pseudoperfusion maps very noisy,
but fit at whole-tumour level very reliable.

Subprotocol 2: diffusion fingerprint



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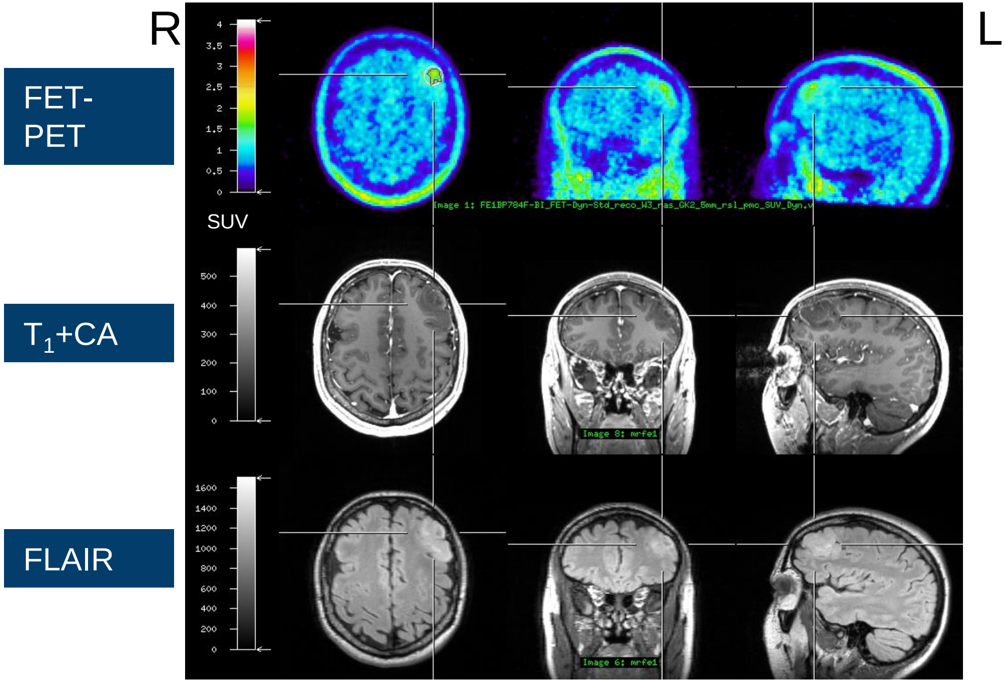
Multimodal qMRI: subprotocol 3

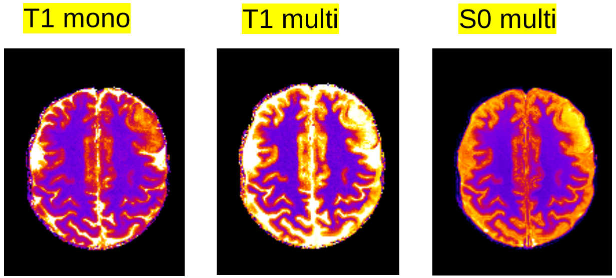
- **Multi-exponential T1 Mapping**
- **Based on single-slice TAPIR**
- **High accuracy and precision T_1 mapping**
- **Extremely high resolution of T_1 contrasts (ultra-high temporal resolution): visualisation of anatomical details even with reduced T_1 contrast.**

- Multicomponent T_1 analysis
- **4-6 min measurement time** (TAPIR + TAPIR-IE)

Oros-Peusquens et al. ISMRM 2019 and in preparation

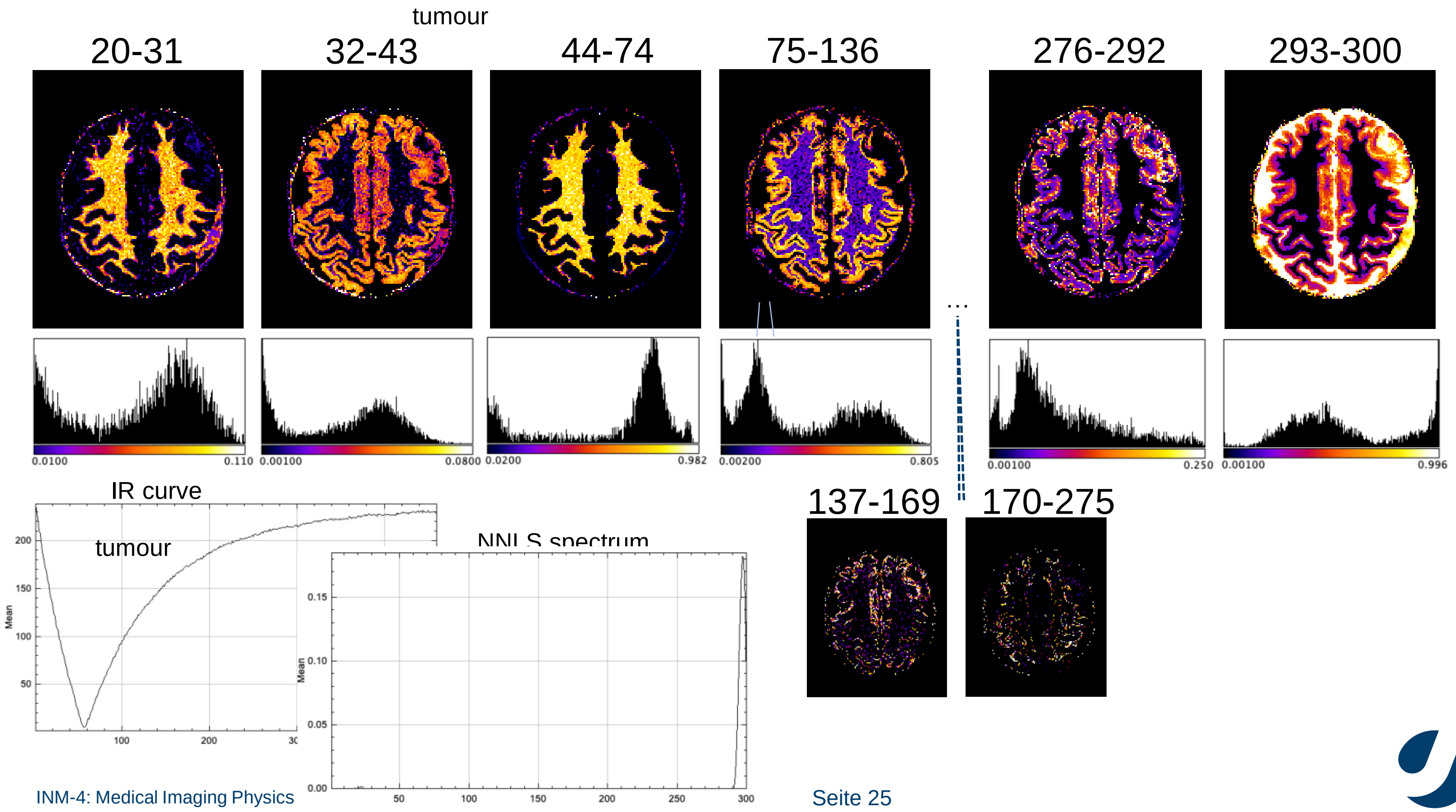
Subprotocol 2: diffusion fingerprint





Increased T_1 in tumour area

Tumour-specific components with v long T_1



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SMART|Bioimaging_Lab: Imaging

N. JON SHAH, HANNO SCHARR AND RAMAZ BOTCHORISHVILI

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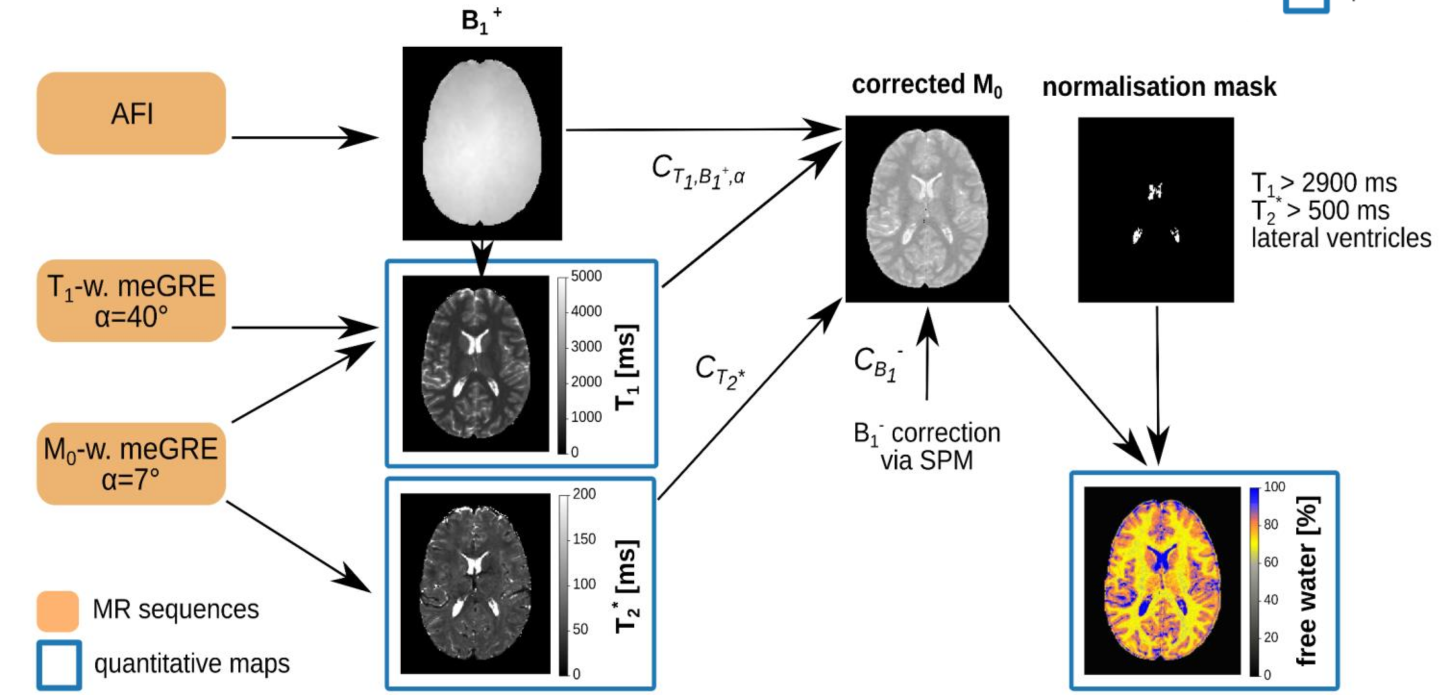
qMRI (Water Mapping)

3D Two-Point (3D2P) VFA Method

- meGRE signal equation: $S(\mathrm{TE}) = M_0 \cdot C_{T_2^*}^{-1} \cdot C_{T_1, B_1^+, \alpha}^{-1} \cdot C_{B_1^-}^{-1}$

MR sequences

quantitative maps

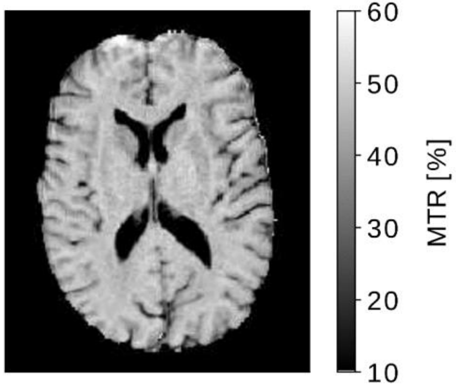


Schall et al. (2018), PLOS ONE 13(8):1-21

Semi-Quantitative Magnetisation Transfer (qMT) Parameters

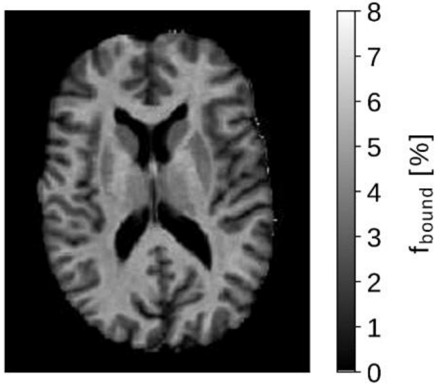
- **Magnetisation transfer ratio**

$$\mathrm{MTR} = \frac{(M_0 - M_{\mathrm{MT}})}{M_0}$$



- **Bound proton fraction**

$$f_{\mathrm{bound}} = \frac{M_{\mathrm{MT}}}{M_0 + M_{\mathrm{MT}}} \approx \frac{\mathrm{MTR}}{T_1^{\mathrm{free}}} \cdot 1\mathrm{s}$$



- **Magnetisation exchange rate**

$$k_{ex} \approx \frac{\mathrm{MTR}}{T_1^{\mathrm{sat}}} \cdot 1\mathrm{s} \,/\, f_{\mathrm{bound}} \approx \frac{T_1^{\mathrm{free}}}{T_1^{\mathrm{sat}}}$$

in addition to H_2O, T_1 and T_2^*

Current Activities in DL / AI

MR Group

Image reconstruction

published paper

DFG grant application passed first round

Image Reconstruction of Sparsely Sampled Data

Joint MR-PET image reconstruction

grant application in AUS submitted

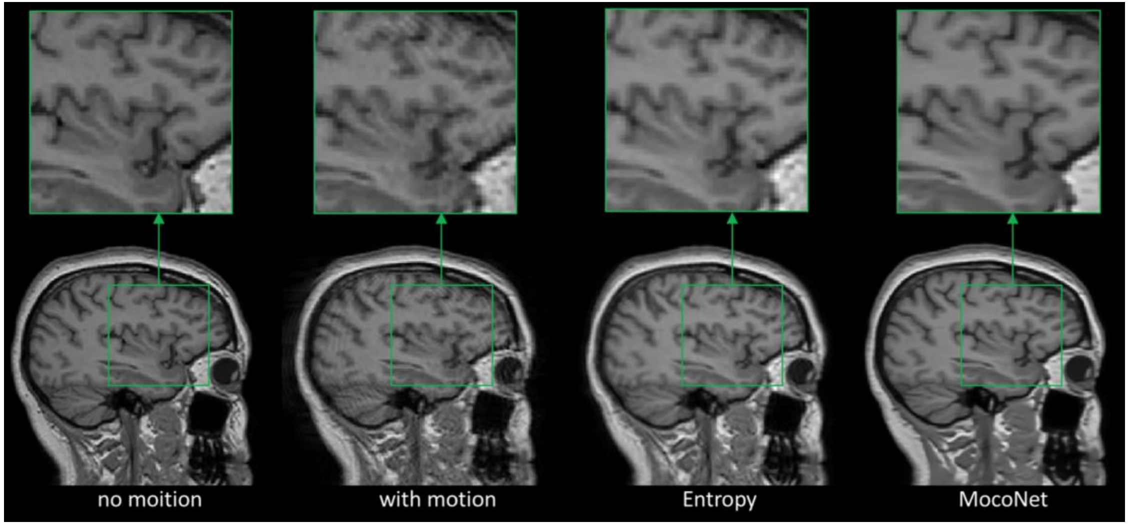
MRFingerprinting

being planned

Motion correction

paper, patents

spin-off planned – AUS lead partner



Machine-LEARNING for ULTRA-FAST MRI

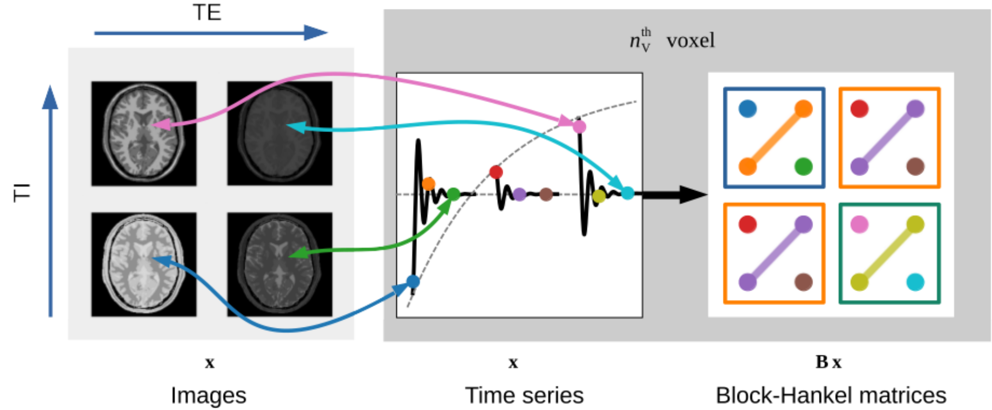
Conventional fully sampled sequential imaging

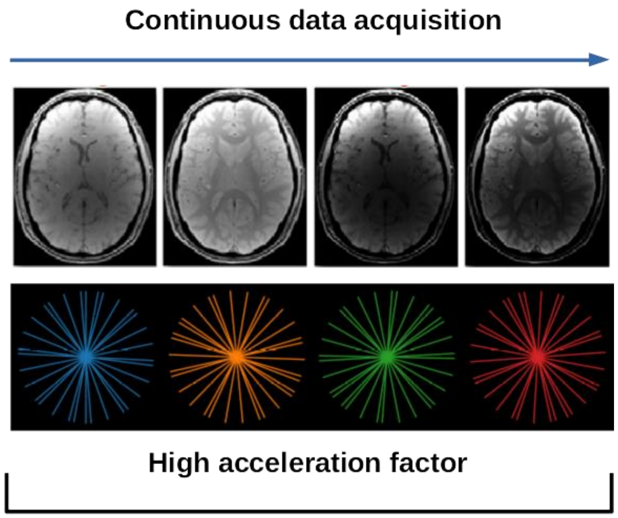
- Long measurement time & motion sensitivity

Proposed undersampled continuous imaging

- Joint reconstruction of all time points
- Machine learning to apply temporal signal model

$$\min_{\mathbf{x}} \quad \lambda_{\mathrm{W}} \|\mathbf{W}\,\mathbf{x}\|_{1,2} + \lambda_{\mathrm{B}} \|\mathbf{B}\,\mathbf{x}\|_{1,*} \qquad \text{s.t.} \qquad \|\mathbf{FCx} - \mathbf{d}\|_2 \le \epsilon$$

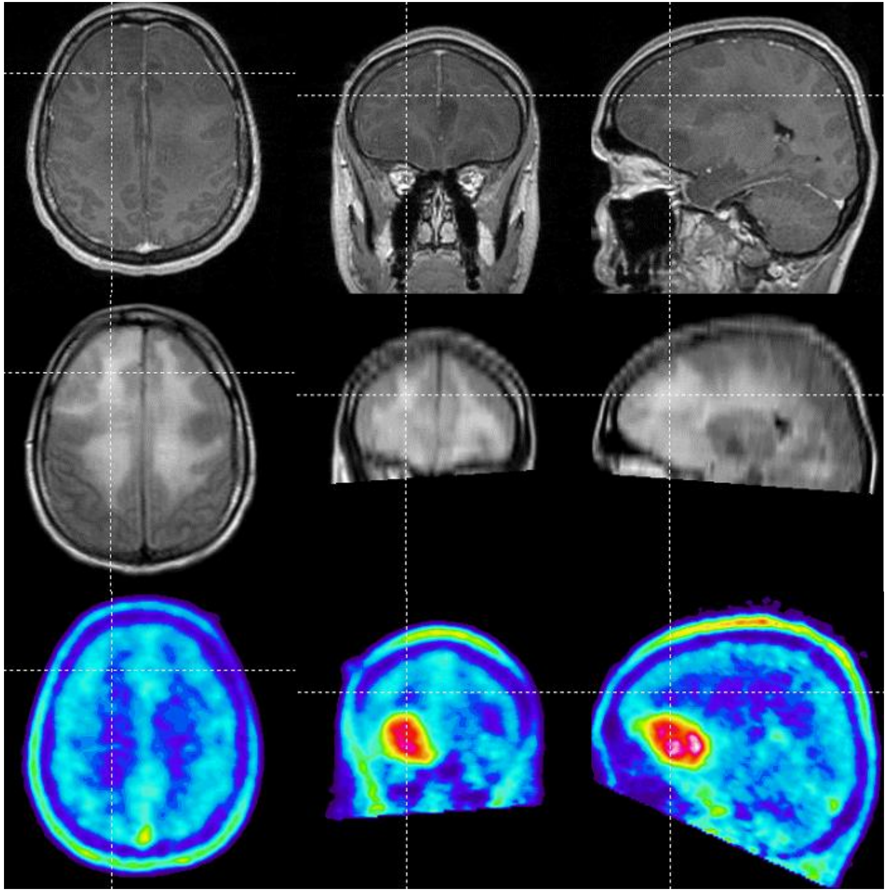




Joint reconstruction with temporal model

Tumour diagnostics (medical imaging)

Brain Tumour ?

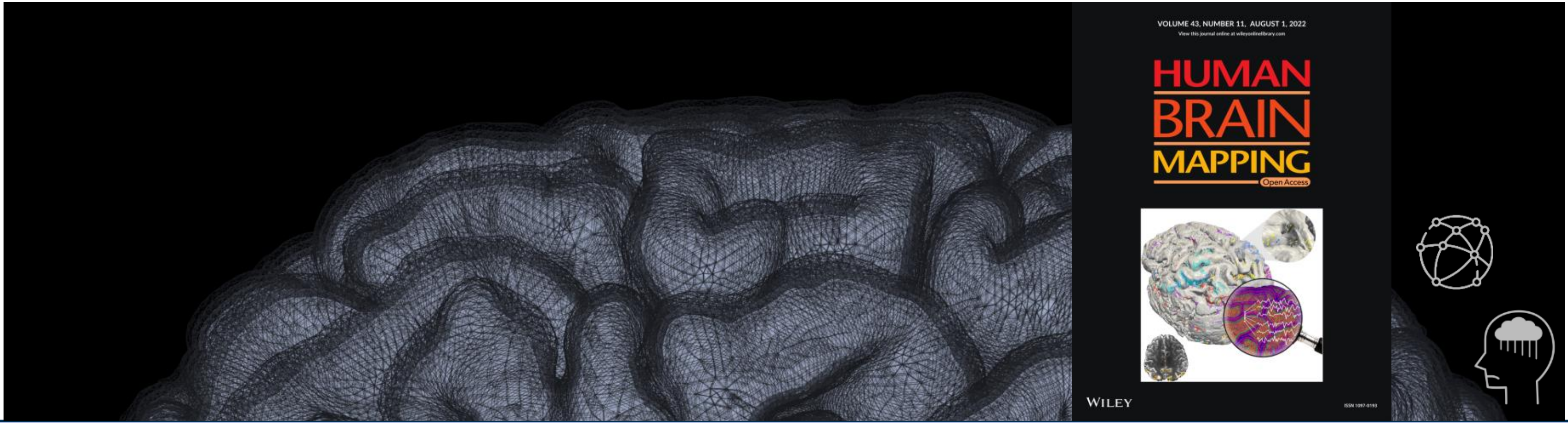


MR-T1 (CA)

MR-FLAIR

FET-PET

Astrocytoma Grade II

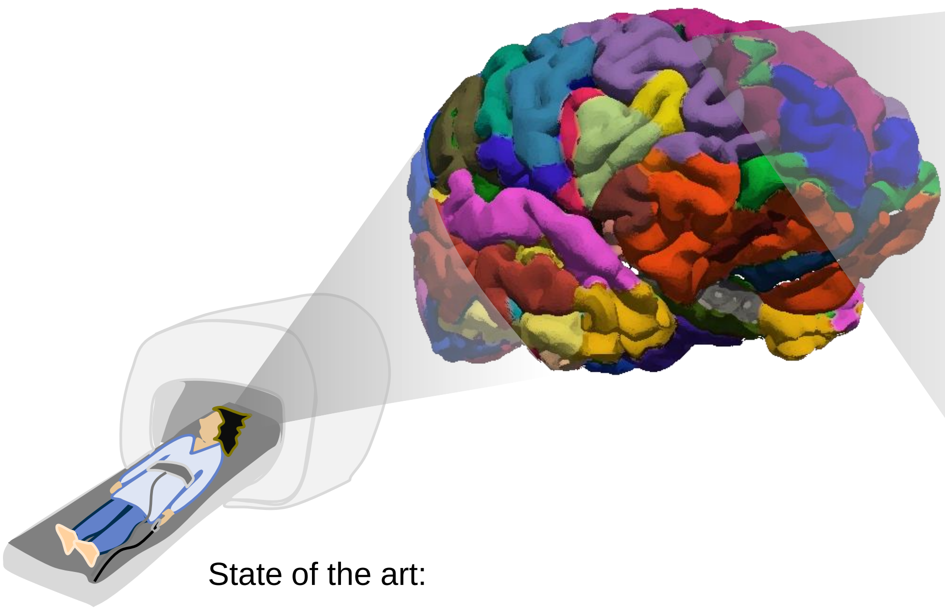


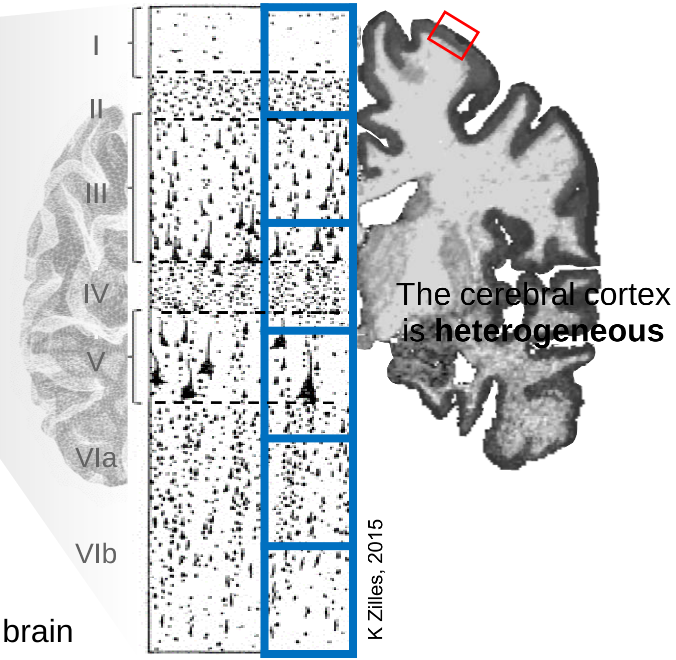
Early diagnosis using machine learning

High-resolution fMRI

Why does it matter?

Studying this cortical dimension (depth) provides additional information in functional studies (“laminar fMRI” or “depth-dependent fMRI”).



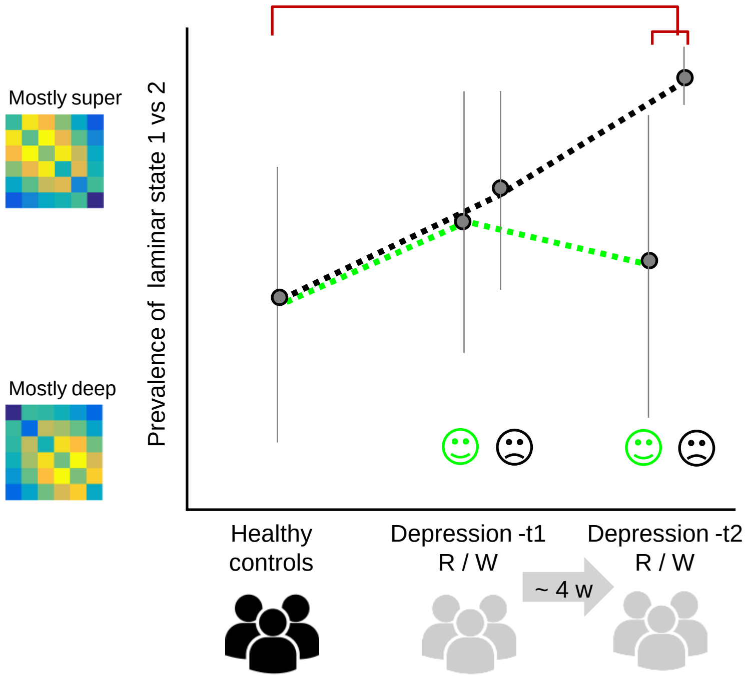


State of the art:

- Measure fMRI signal from almost every voxel in the brain
- Average the signal of voxels within each ROI
- Report ROI-to-ROI connectivity

LAMINAR DYNAMIC CONNECTIVITY IN MAJOR DEPRESSION (EPIK)

DIFFERENCES IN CORTICAL-STATE PREVALENCE



- After treatment, patients who recover or worsen show a significantly different laminar connectivity preference.
- Patients who worsen are significantly different from healthy controls, but patients who recover are not.

The evolution of depression may be related to changes in the connectivity along the cortical depth.

Pais-Rodain et al. In preparation

Student Profiles

Physics:	All rounders
Medicine:	Work in neuroscience studies
IT:	Sequence programming / Machine learning
Engineering:	Radiofrequency coils / MR-PET hardware