Practical framework for processing and kinetic modelling for brain PET images

Turku PET Centre Brain Imaging Course 2024

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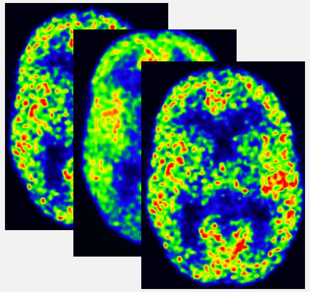
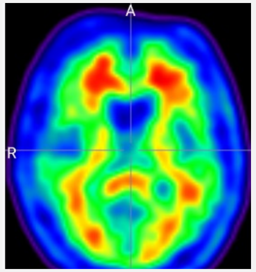
PROCESSING DEPENDS ON SEVERAL FACTORS

- Radioligand

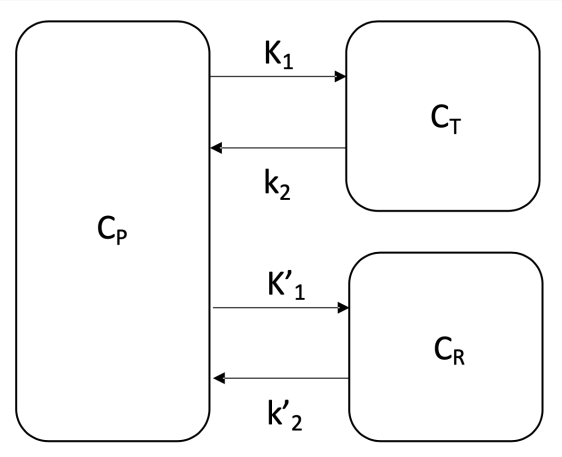


Dynamic 4D data
subsequent time intervals (frames)



Static 3D data

- Pharmacokinetic model
  - Input funtion for modelling
    - arterial input
    - reference region



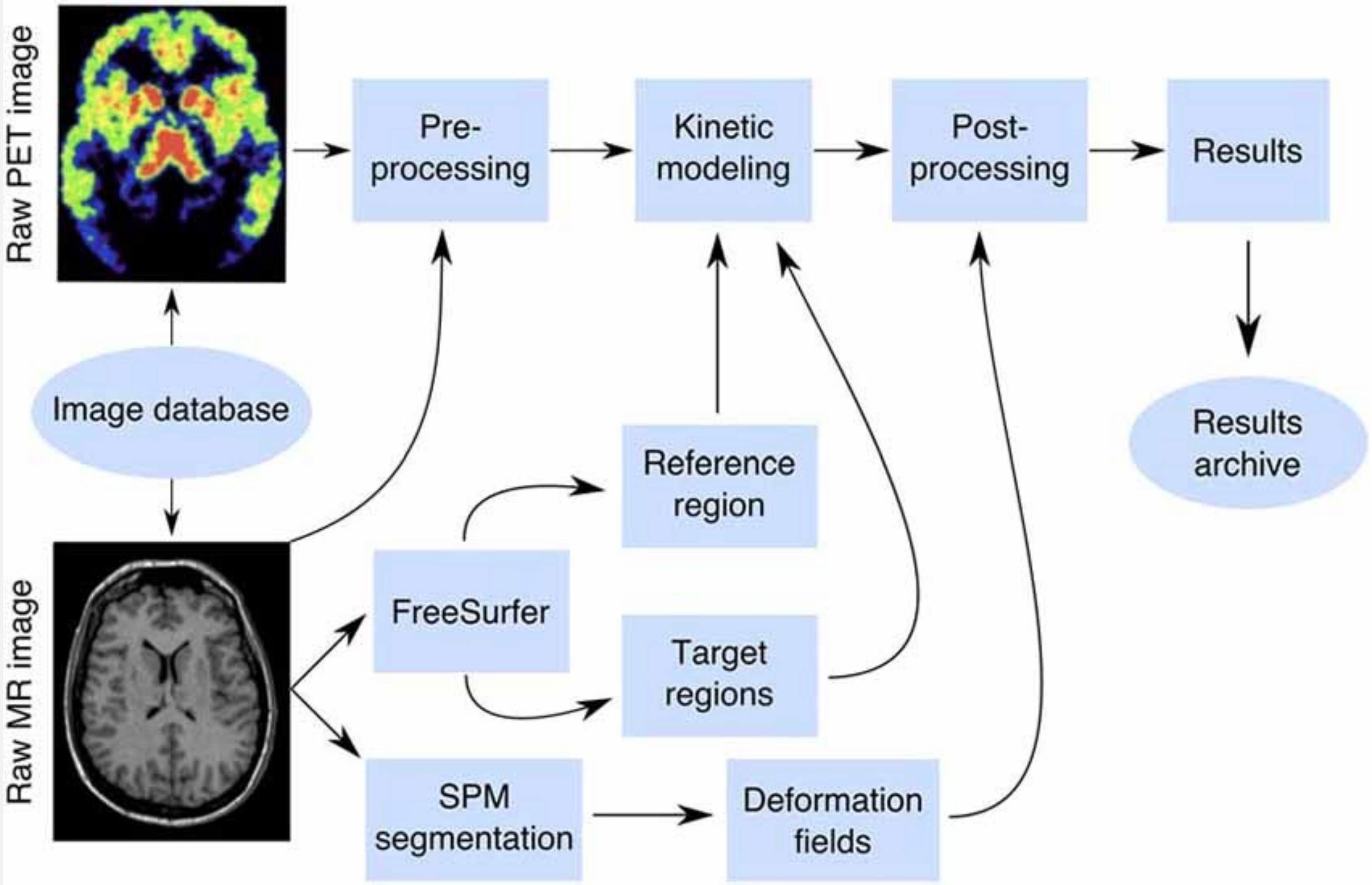
AUTOMATED PROCESSING

Easy interface & automated data processing

- Usable for wide range of different PET radioligands
- Currently limited to human brain data

- Reduced manual (re)work
  - Scripts / batch processing offer increased reproducibility and reliability
  - version control with GitHub
- Integration with Turku PET centre AIVO database

BRAIN IMAGING PIPELINE (MAGIA)



PET & MRI IMAGE PREPROCESSING

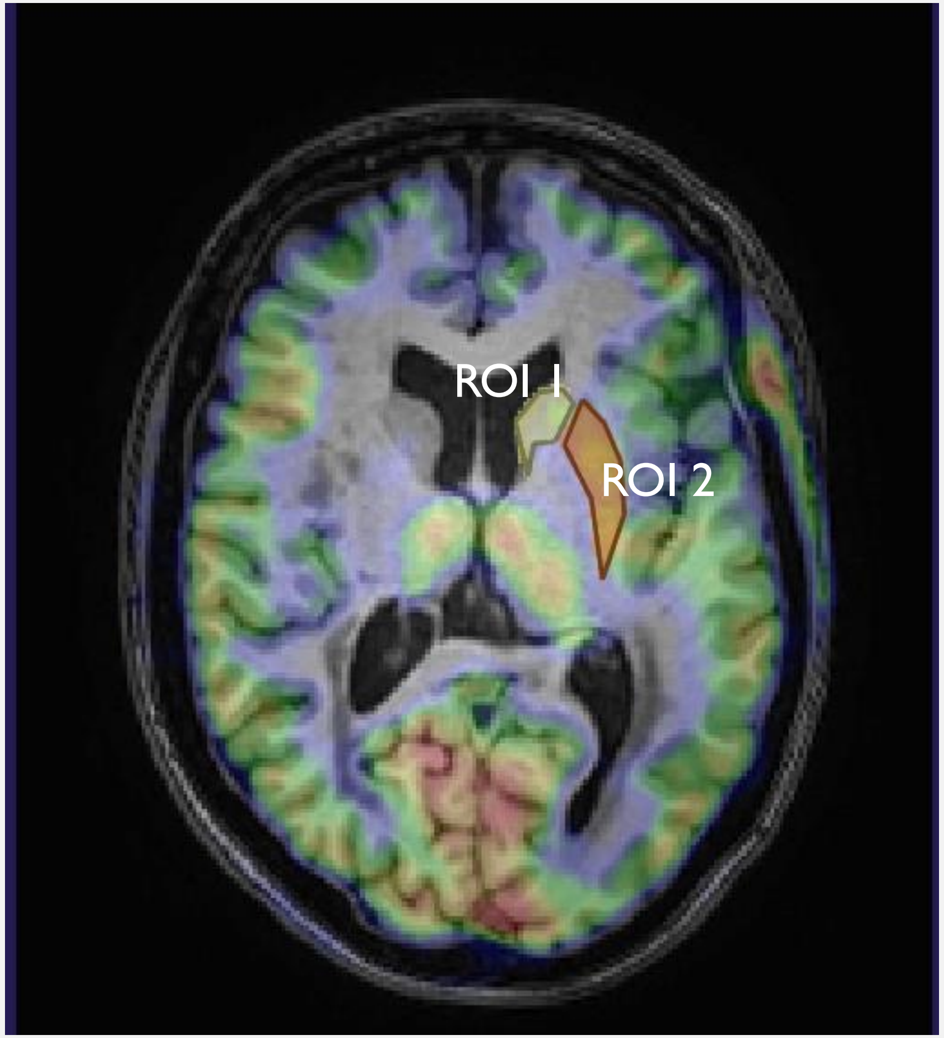
- PET (& MRI) dicom or nifti raw data structure:

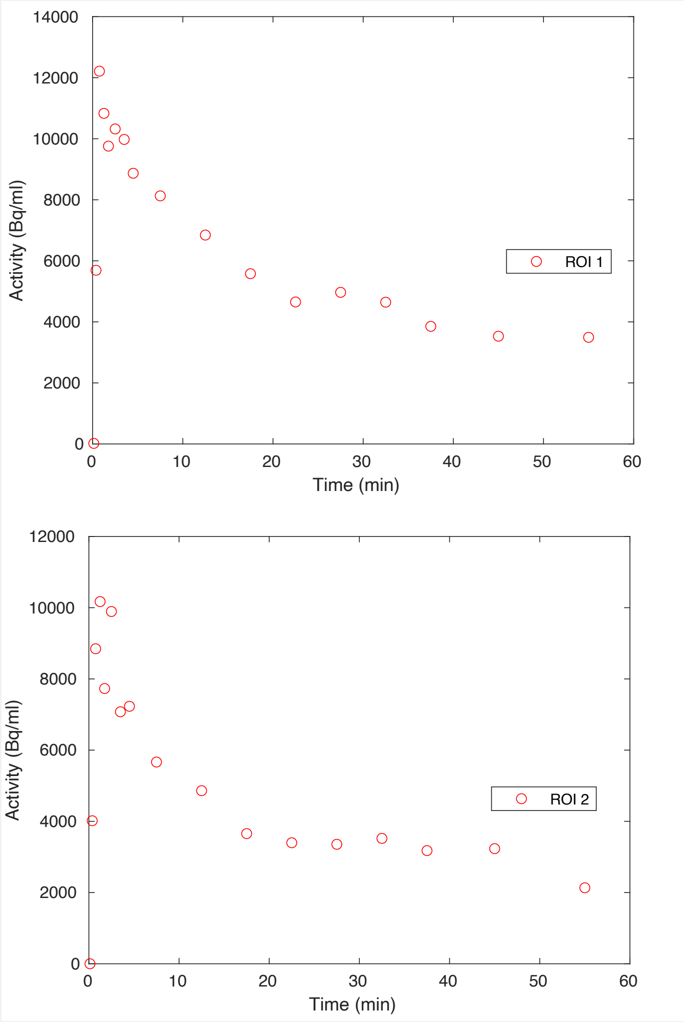
```
PETdatafolder/ID/PET/nii/pet_ID.nii
MRIdatafolder/ID/T1/ID.nii
```

← Format follows loosely PET BIDS (brain imaging data structure)

- 4D PET framewise realignment (motion correction)
- PET ⟷ T1 MR image co-registration
- T1 MRI tissue segmentation / normalisation parameter calculation / smoothing

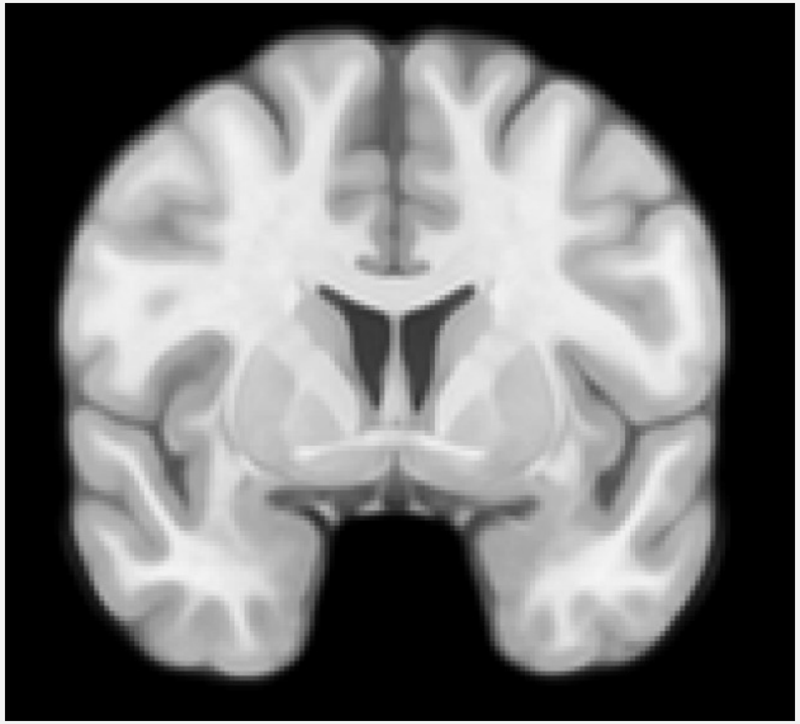
ROI-DELINEATION



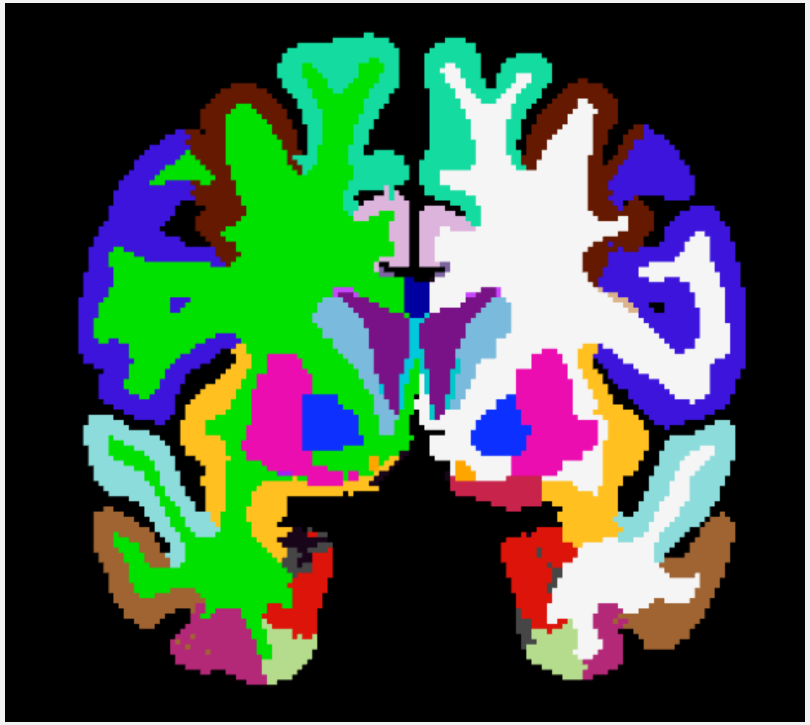


ROI DELINEATION (MRI)

Input:
T1w MRI



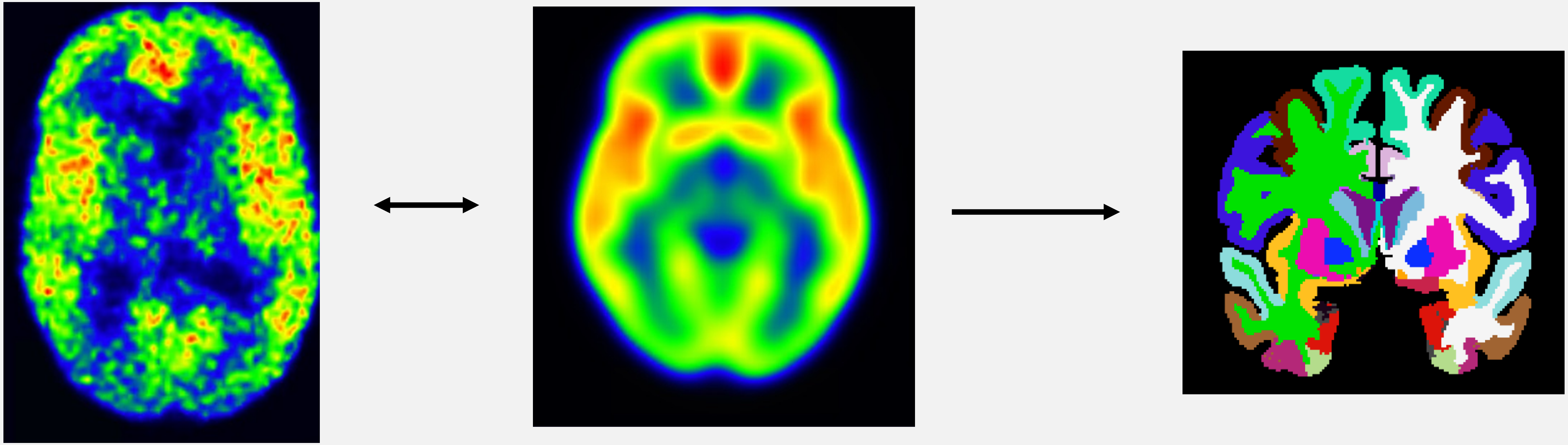
Output:
FreeSurfer parcellation in native subject space



ROI DELINEATION (PET-TEMPLATE)

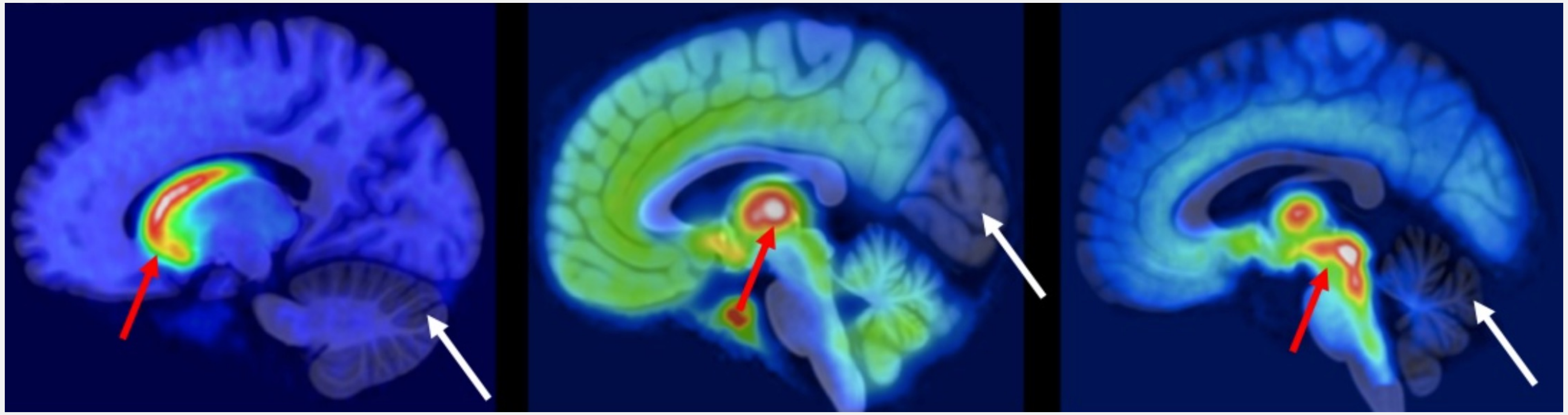
Inputs:
- PET mean image (motion corrected)
- Radioligand template image in MNI space
- ROI mask images in MNI space

Output:
- Spatially normalised PET image, or ROI masks in native space



REFERENCE REGION EXTRACTION

Red = high specific binding   Dark blue = low specific binding

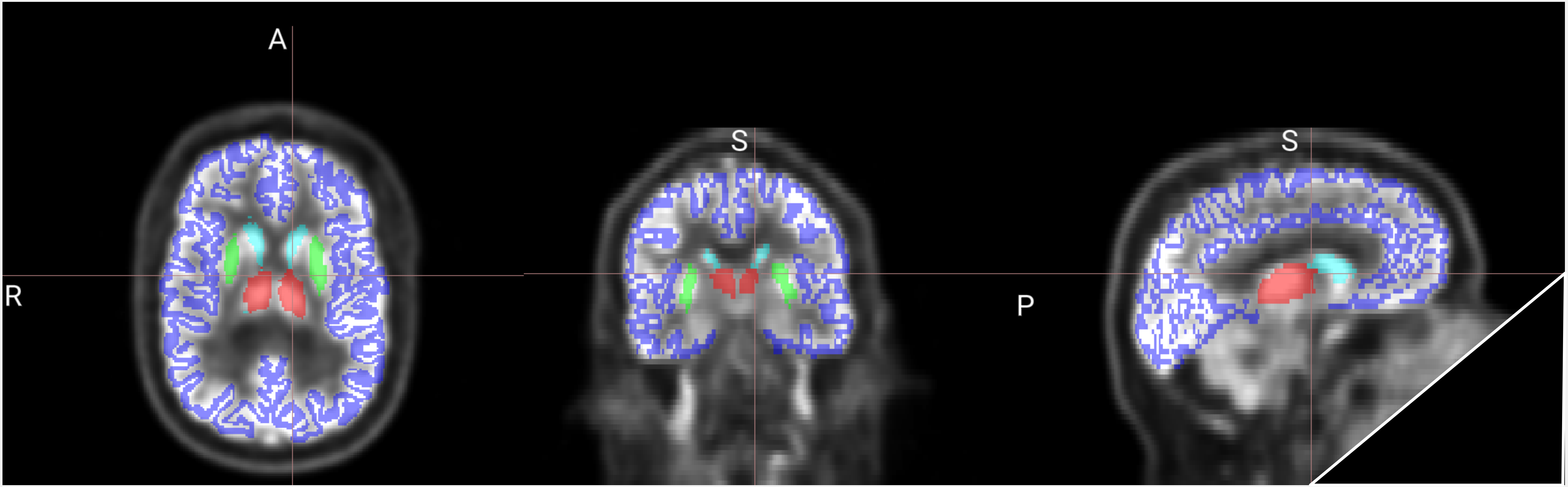


[^{11}C]raclopride / dopamine D2-receptors

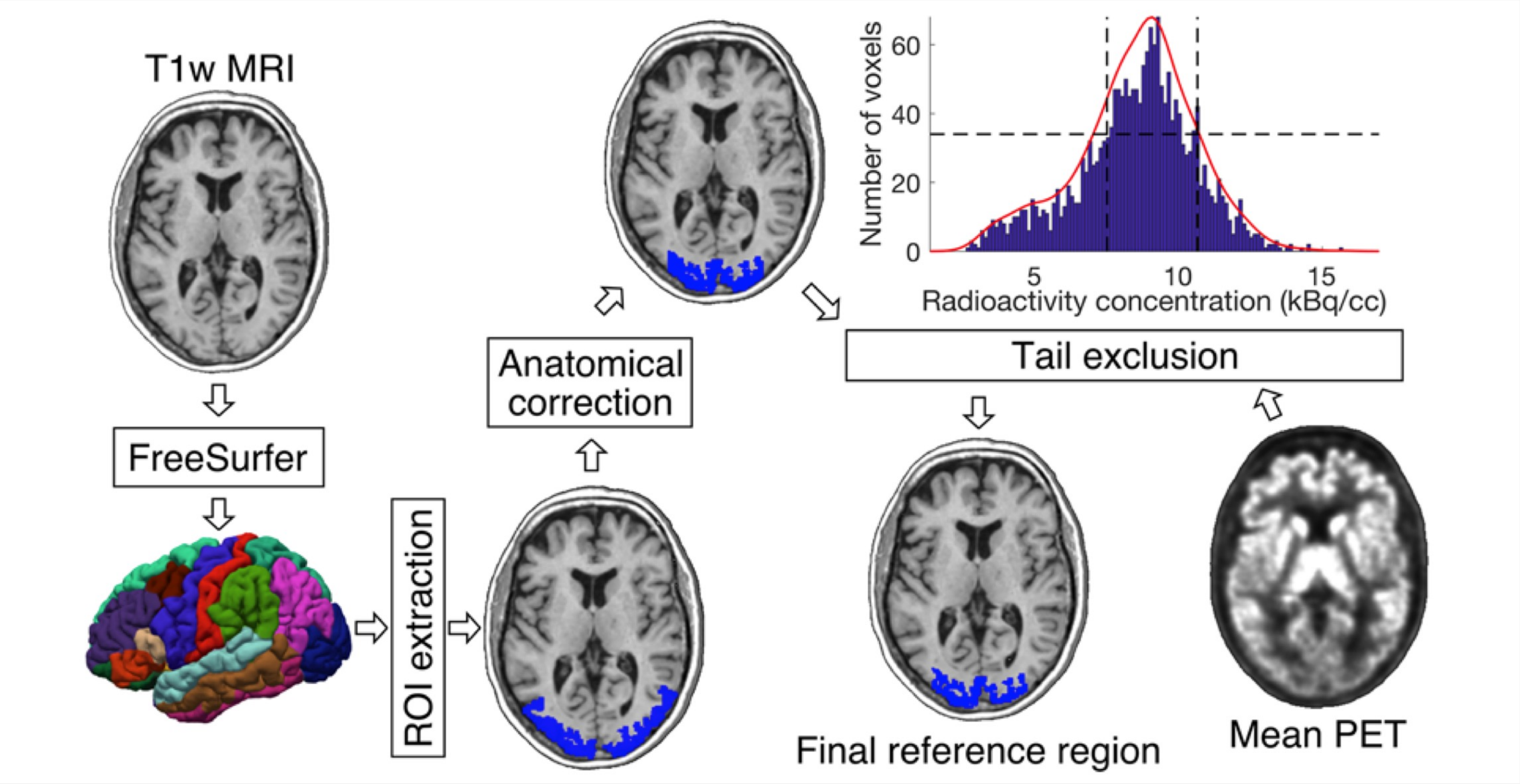
[^{11}C]carfentanil / μ-opioid receptors

[^{11}C]madam / serotonin transporter

ROI & REFERENCE DELINEATION (QC)



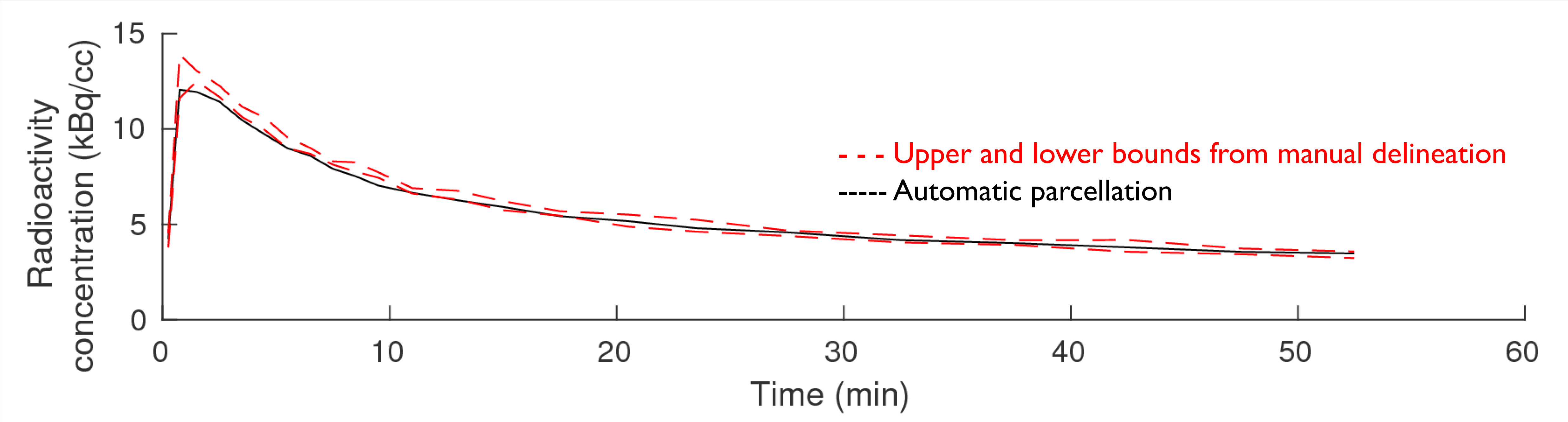
AUTOMATIC REFERENCE REGION EXTRACTION



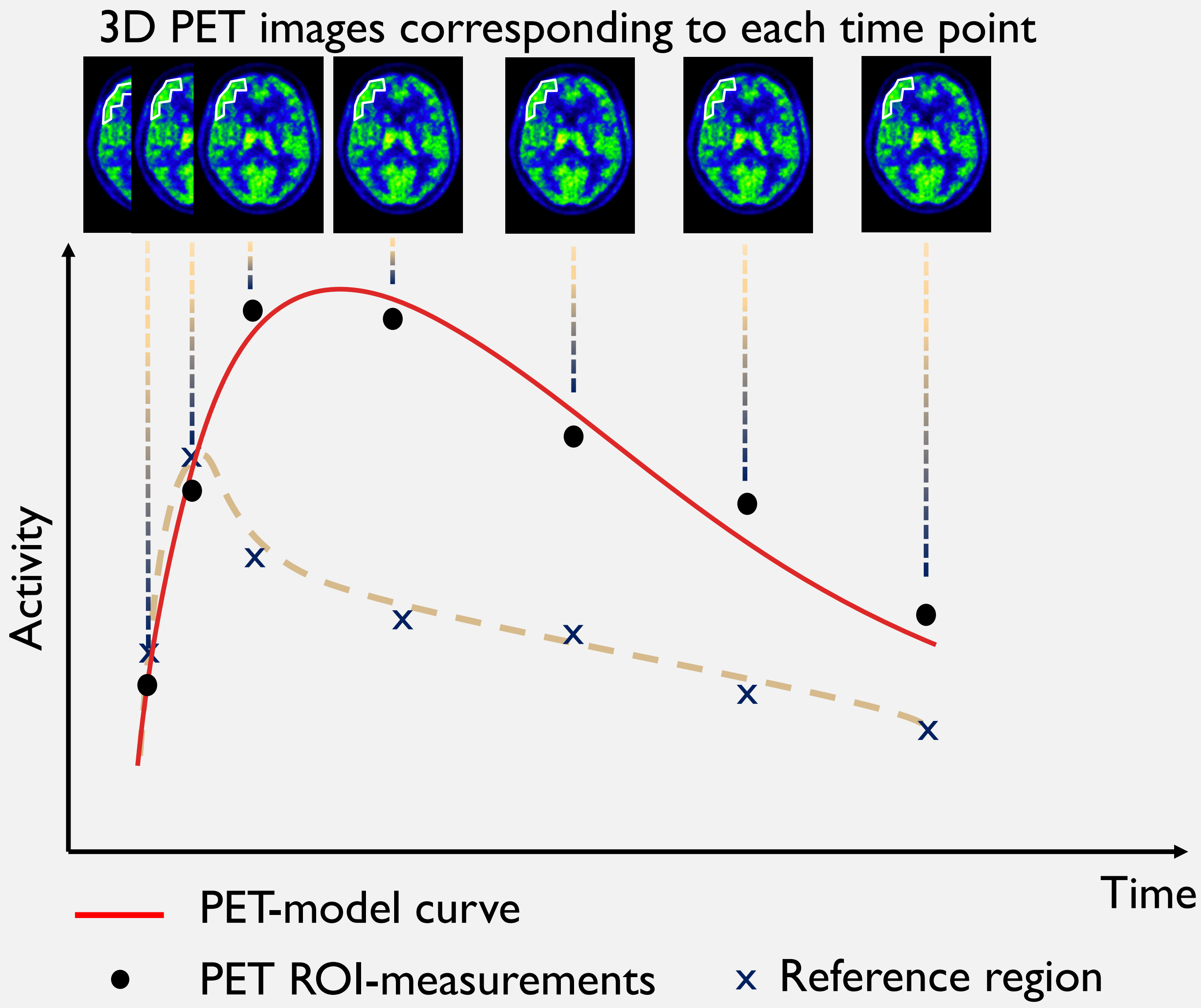
AUTOMATIC REFERENCE REGION EXTRACTION

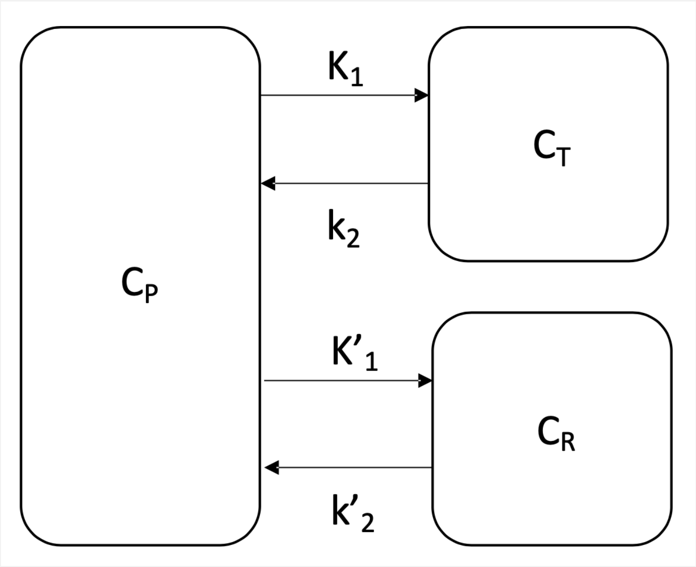
- Magia ROIs compare well with the manually drawn ROIs (Karjalainen et al. 2020)

Example [^{11}C]raclopride cerebellum TAC



ROI-LEVEL PHARMACOKINETIC MODELLING





Simplified reference tissue model (SRTM)

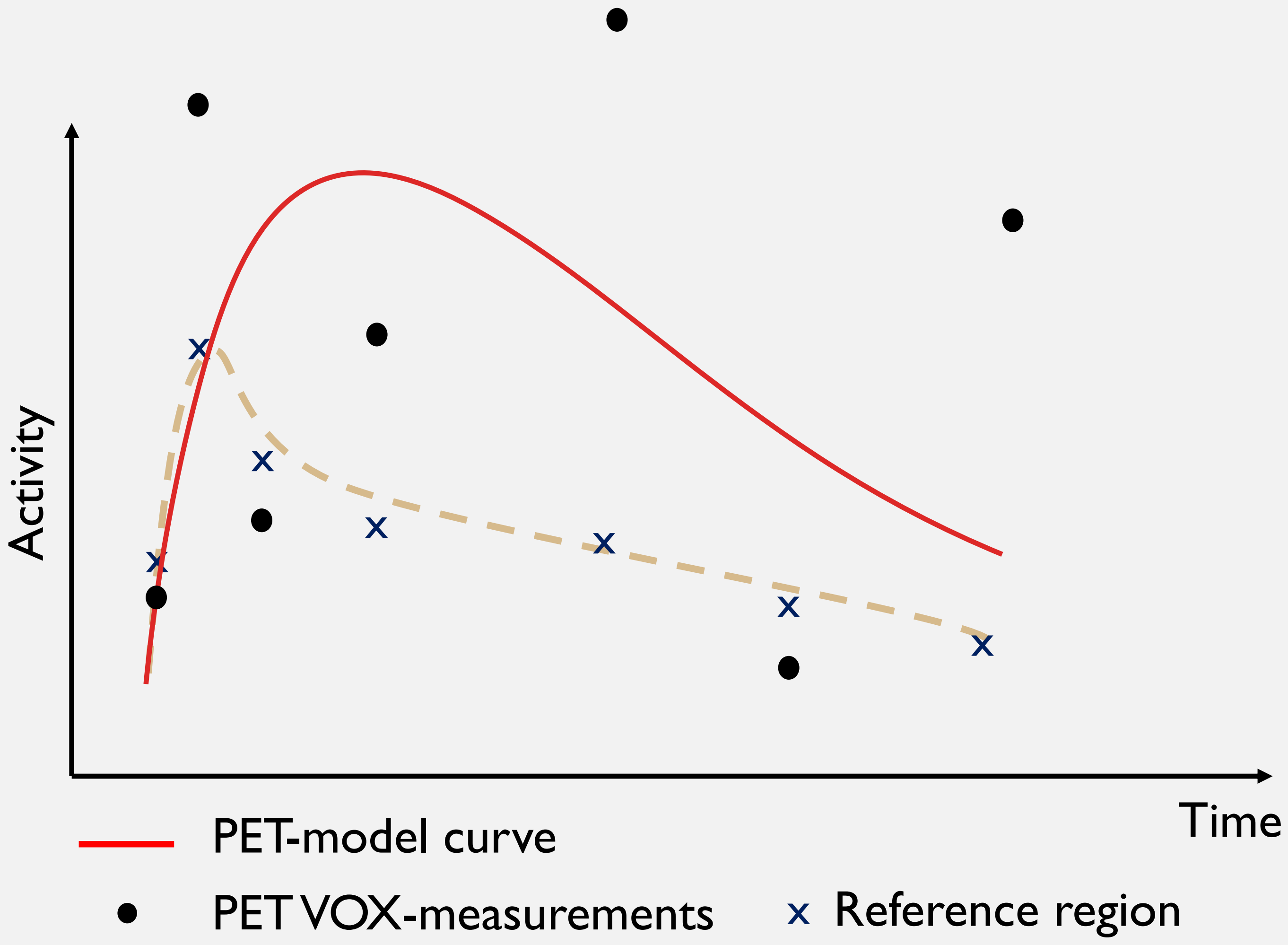
Estimates:

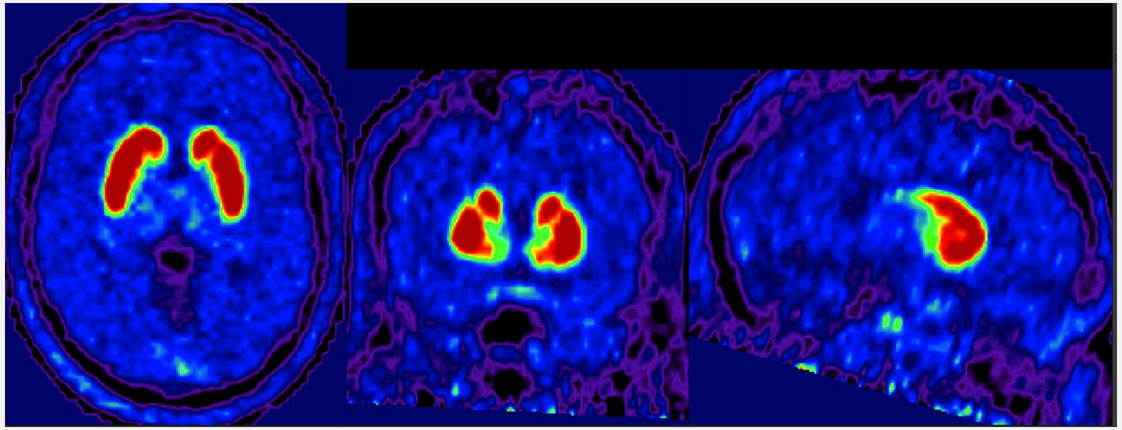
BP_{ND}

$R_1=K_1/K'_1$

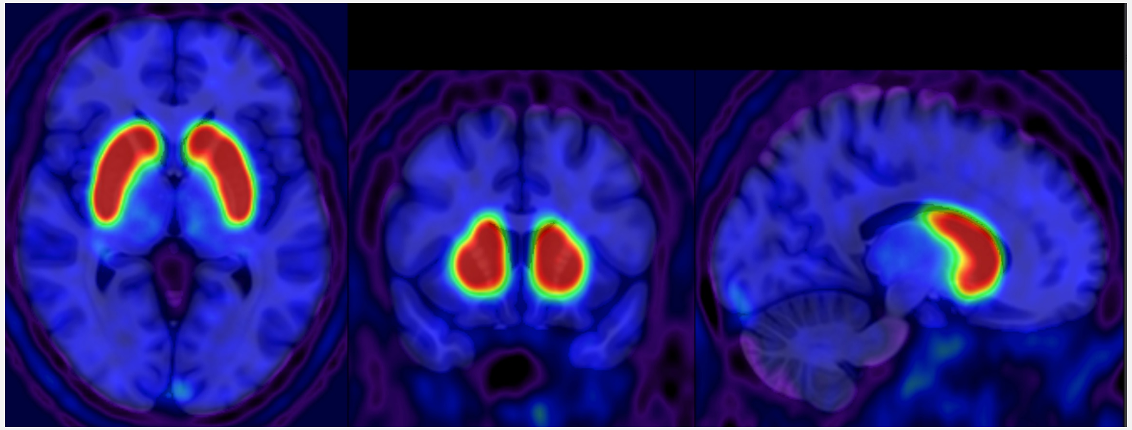
k_2

VOXEL-LEVEL PHARMACOKINETIC MODELLING





SRTM BPnd image in subject native space



SRTM BPnd image in MNI152 space

ROI/VOXEL-LEVEL KINETIC MODELS

Simplified techniques:

- SUV (Standardised Uptake Value) & ROI-reference ratio analysis
- FUR (Fractional Uptake Ratio)

Reference tissue input models:

- Simplified Reference Tissue Model (SRTM) (Lammertsma et al. 1996)
- Logan plot with reference tissue input (Logan et al. 1996)
- Patlak plot with reference tissue input (Patlak & Blasberg 1985)

Arterial input models (requires manual processing):

- Logan plot (Logan et al. 1990)
- Patlak plot (Patlak et al. 1983)
- Ichise's multillinear analysis 1 (Ichise et al. 2003)
- One- and two-tissue compartment model (1TCM, 2TCM)

ARCHIVING

- **Archived result data structure :**

```
PETarchivefolder/ID/method/PET/
PETarchivefolder/ID/method/MRI/
PETarchivefolder/ID/method/results/
```

```
method = model_normalisationtype_ROItype
```

HOW TO USE

```
run_magia(ID, specifications, model_options)
```

Inputs:

- Study ID
- Study specifications: dose, weight, tracer, frames, mri-ID, scanner
- Model options: model name, parameter bounds, …
- Preprocessing specifications: roi-set, reference frame, excluded frames, …
- PET (& MRI) dicom or nifti data stored in a predefined structure

A I V O DATABASE

	Targets	Scan type	n
Structure	Atrophy	T1 MRI	64,556
Amyloid	Beta-amyloid	[11C]-PIB	1,363
	Beta-amyloid	[18F]-flute	132
Function	Glucose uptake	[18F]-FDG	3,363
	Perfusion	[15O]-H2O	4,931
Dopamine	D_2R	[11C]-raclopride	1,355
	Dopamine	[18f]-DOPA	914
	D_2D_3R	[11C]-FLB	377
	Dopamine	[18F]-CFT	244
	DR	[11C]-NNC	115
Opioid	MOR	[11C]-Carfentanil	471
lammation	Inflammation	[11C]-PBR28	192
	Inflammation	[11C]-PK11195	172
Serotonin	5HT1A	[11C]-WAY	135
	SERT	[11C]-MADAM	131

Imaging & Biological data

65 000 subjects & T1w MR images

30 PET tracers (14 000 images)

Register data

Full medical history

Socioeconomic data

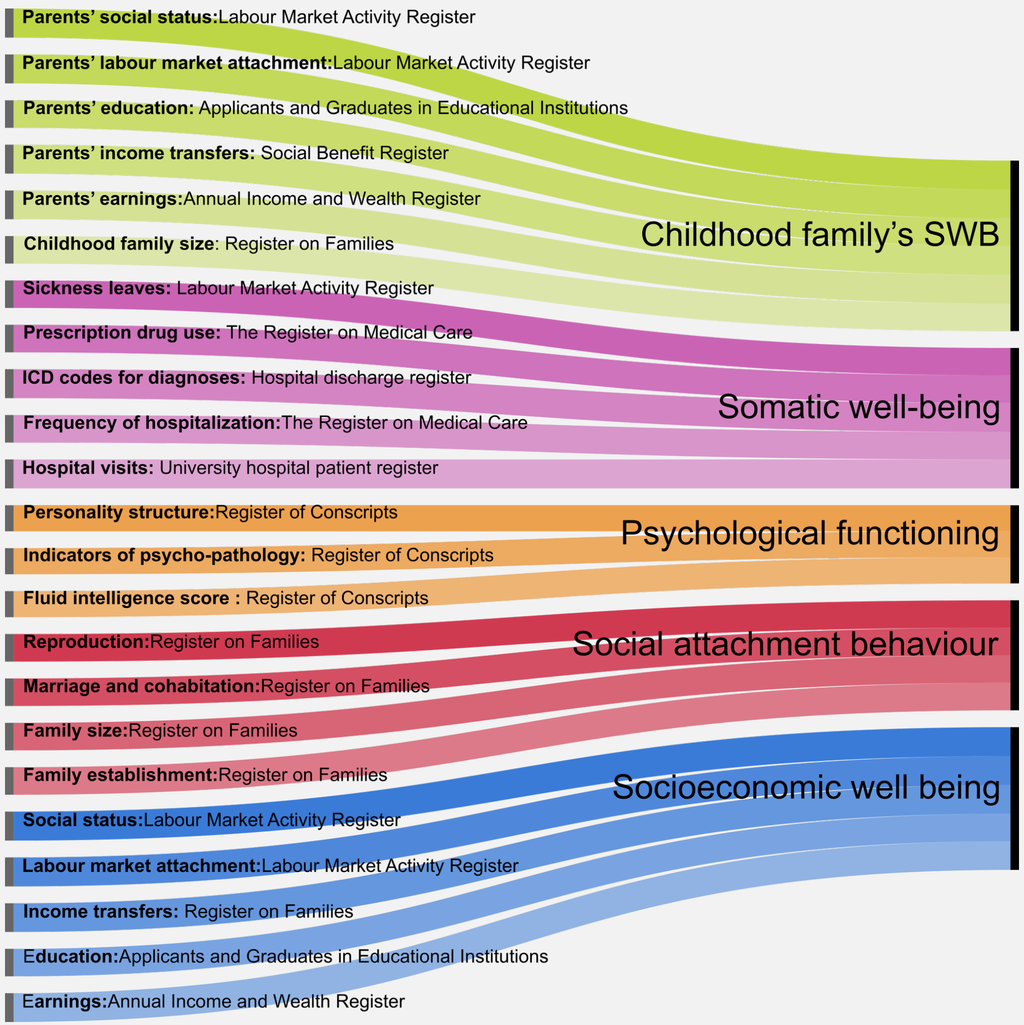
A I V O DATABASE

Example: select all studies of a project named ”Pleasure”

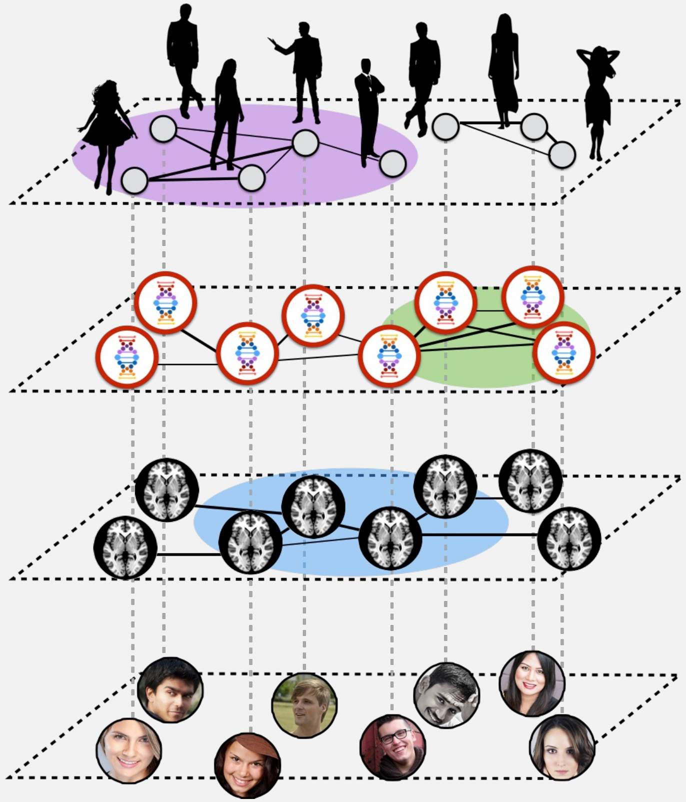
```
subjects =
aivo_get_subjects('project','pleasure');

for i = 1:length(subjects)
    sub = subjects{i};
    run_magia(sub);
end
```

AIVO DATABASE

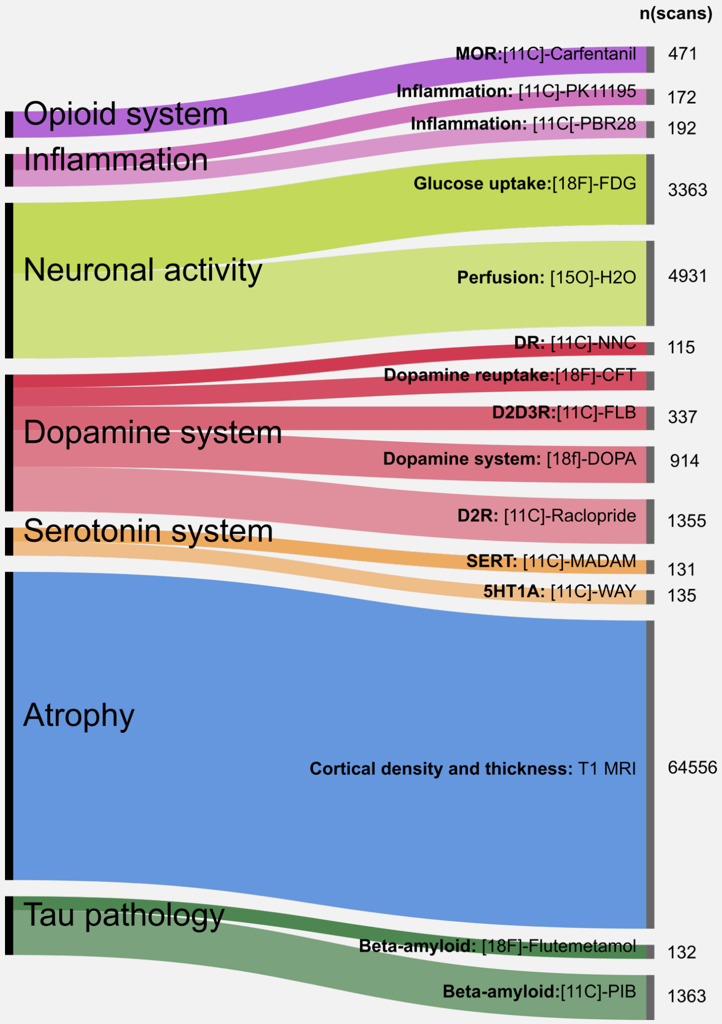
Socioeconomic and medical data



Database

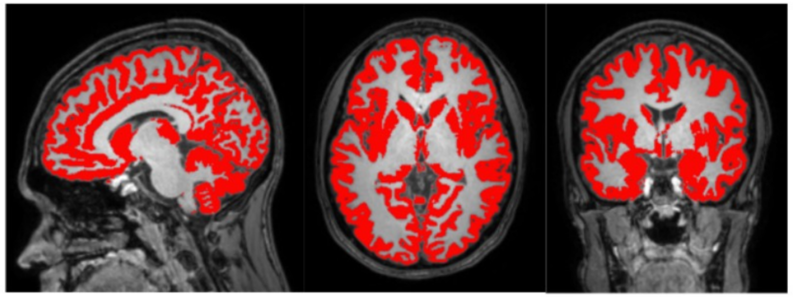


Brain scan data

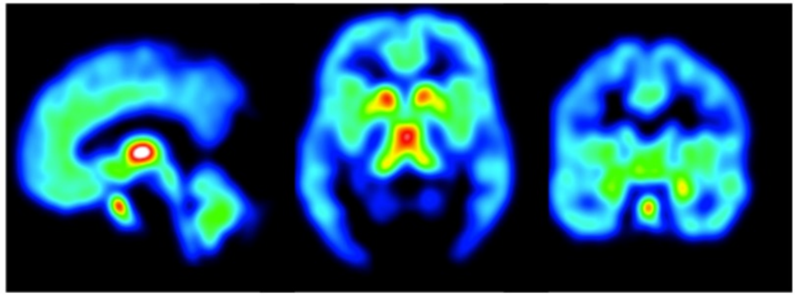


QUALITY CONTROL

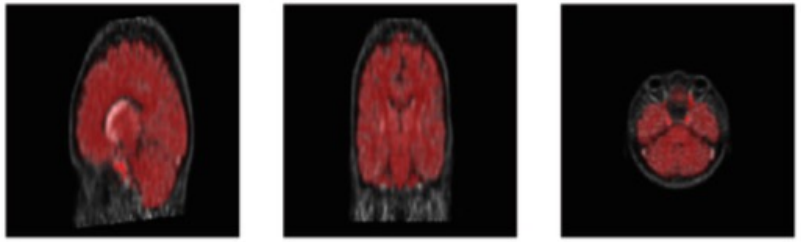
ROI segmentation checkup

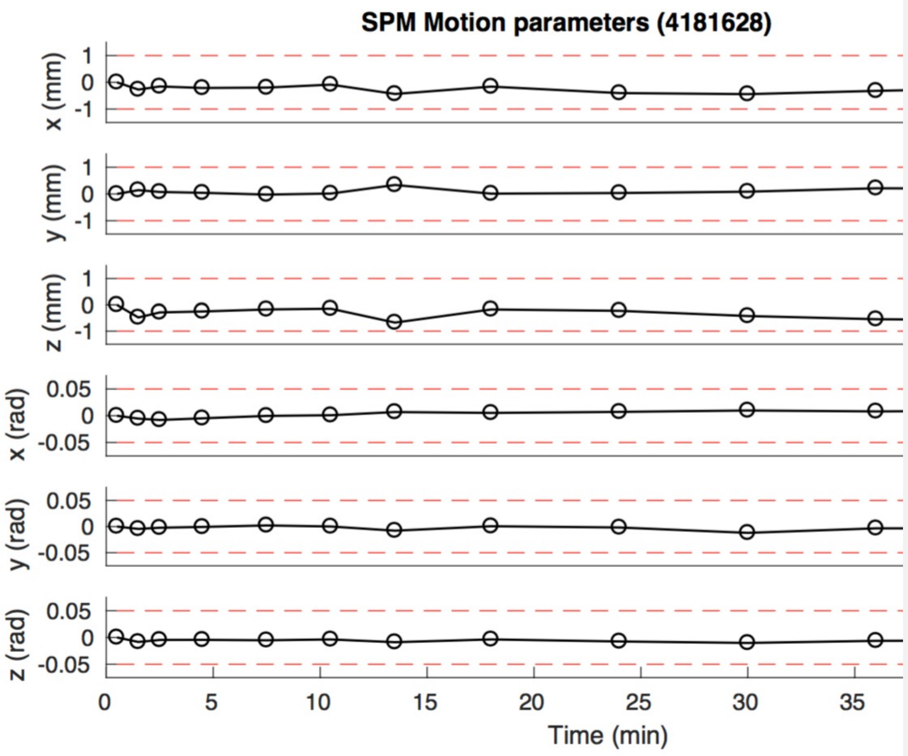


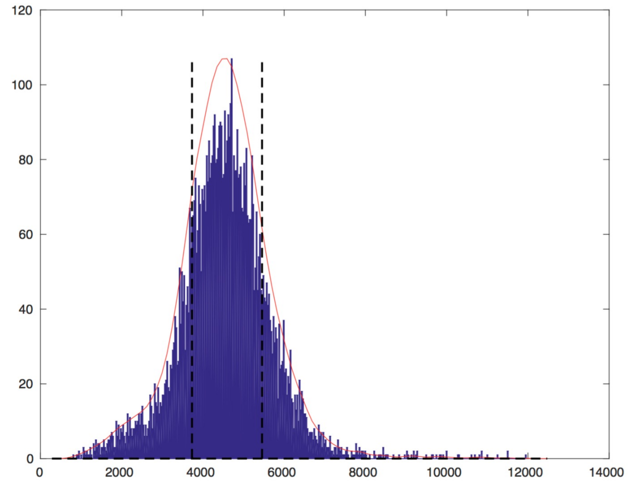
PET Outcome volume checkup



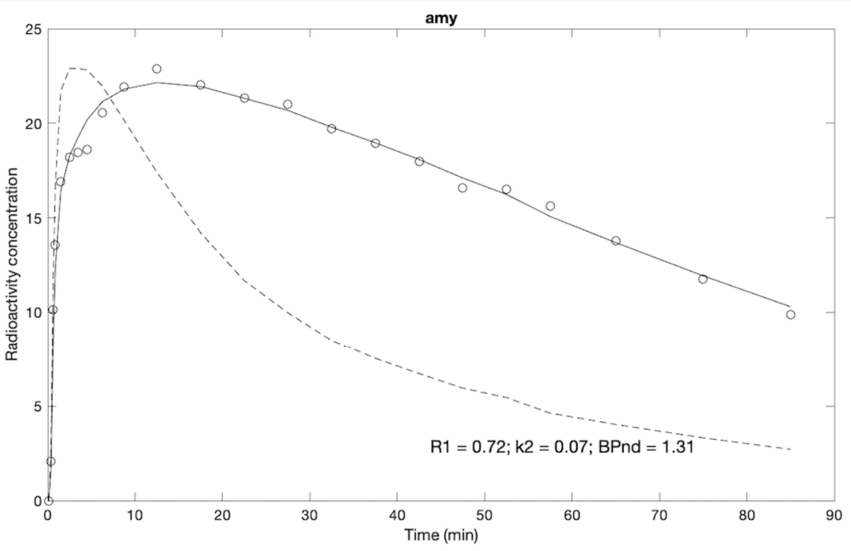
PET-MRI coregistration checkup



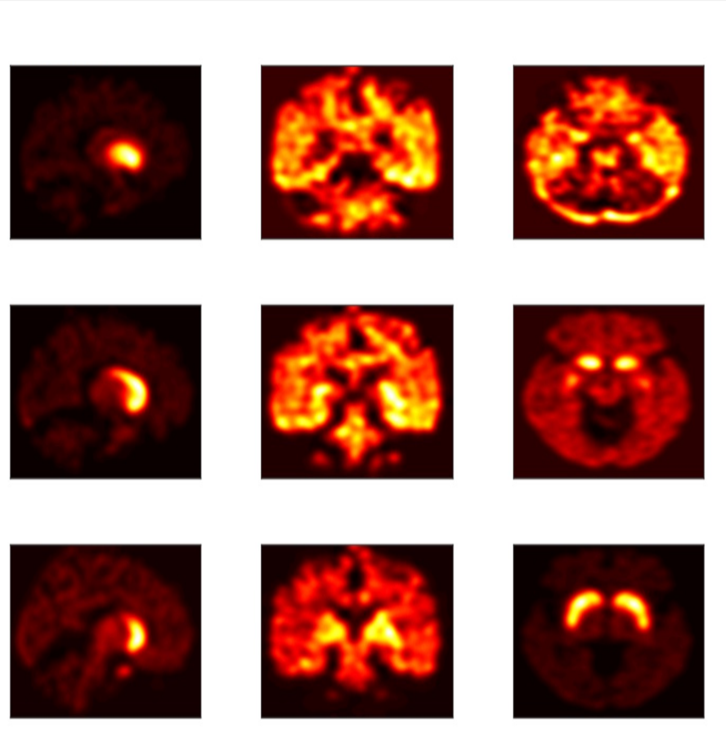




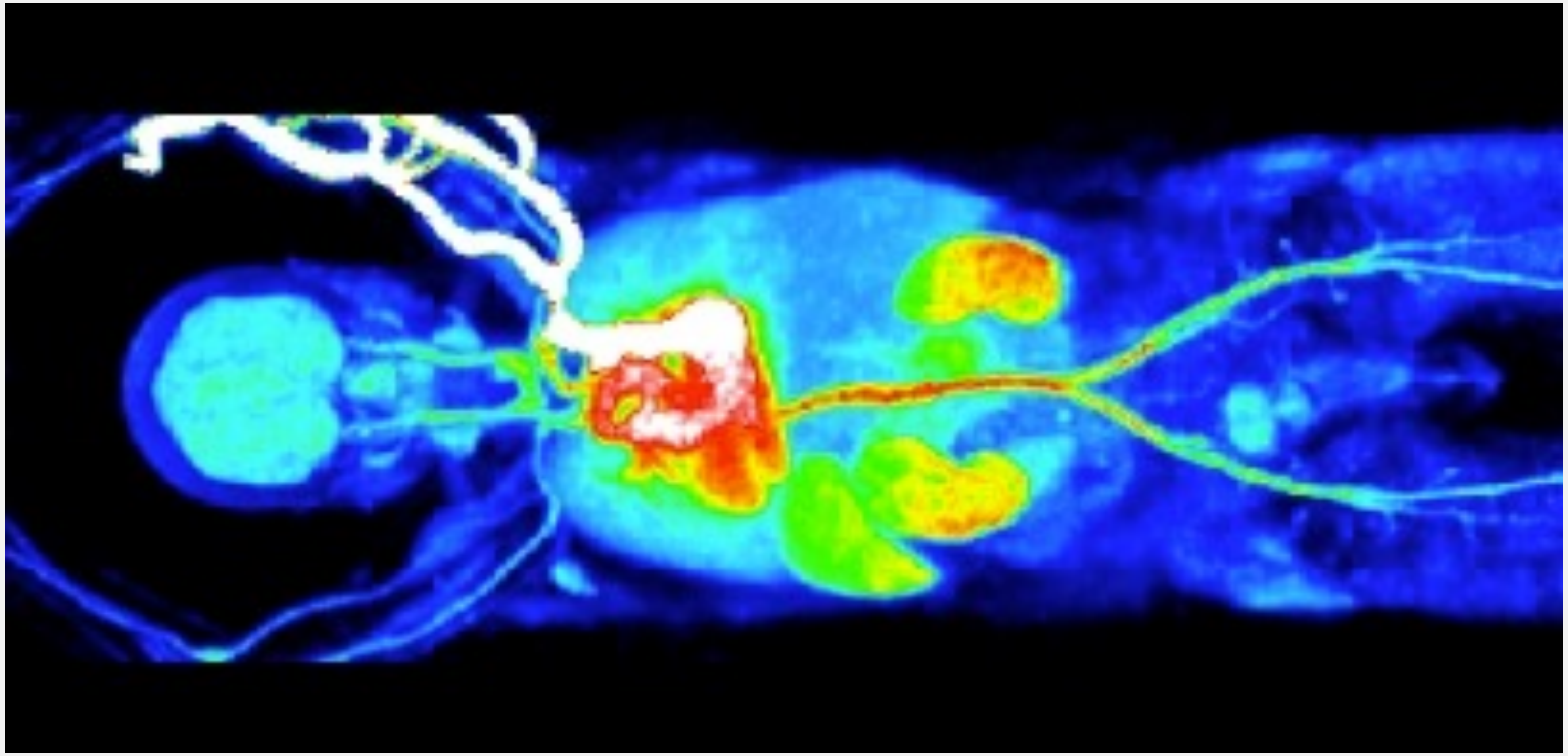
QUALITY CONTROL / OUTPUTS



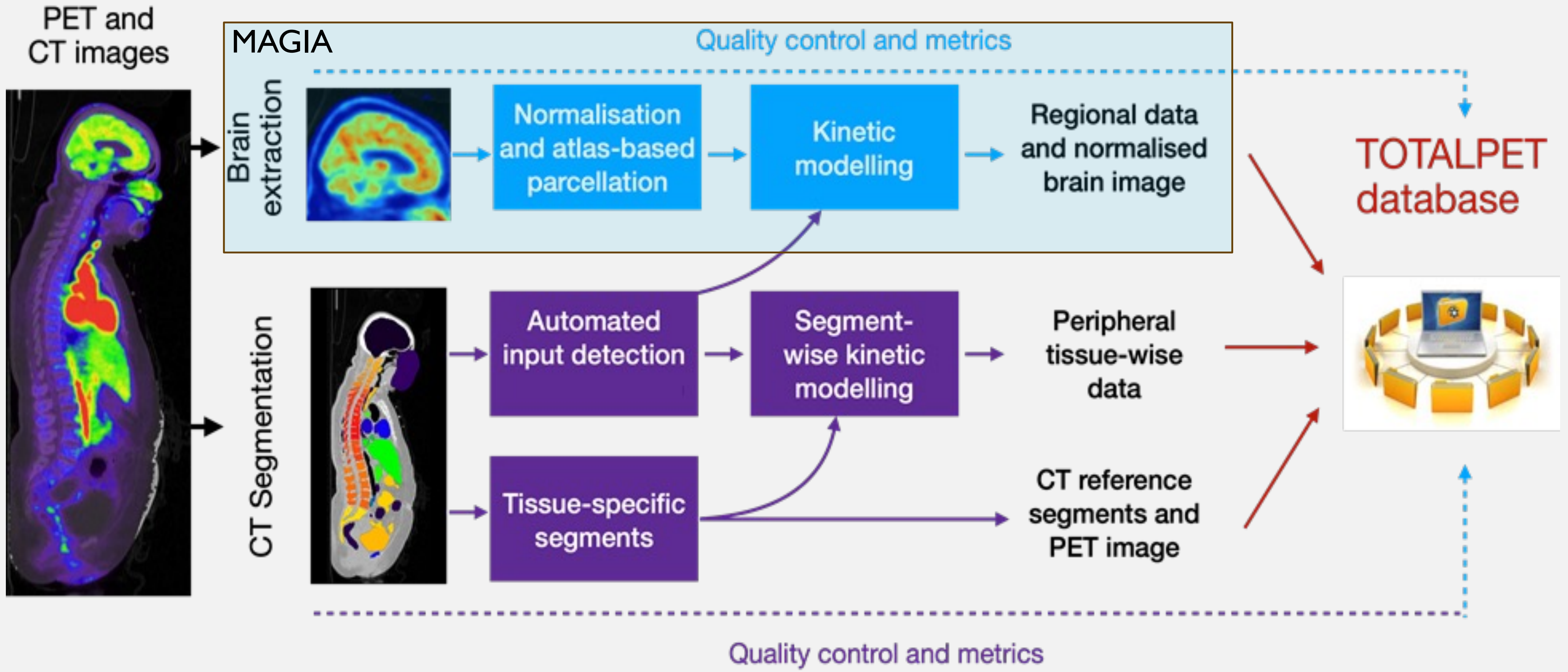
Row	R1	k2	BPnd	vol
amy	0.721	0.067	1.313	4181
cau	0.656	0.046	0.145	9316
amy	0.669	0.005	0.000	140267
dacc	0.880	0.081	1.044	5081
hip	0.672	0.062	1.037	10926
inftemp	0.888	0.080	0.774	27437
ins	1.048	0.088	1.342	16909
medul	0.346	0.007	0.005	5565
midbr	0.628	0.033	0.000	7915
midtemp	0.914	0.081	0.742	27802
nacc	0.849	0.079	1.518	1511
ofc	0.991	0.082	0.876	30532
parsop	1.082	0.083	0.691	11074
pcc	0.992	0.079	0.633	7530
pons	0.445	0.020	0.000	18316
put	0.957	0.062	0.537	12715
racc	1.061	0.104	1.679	5442
supfront	0.944	0.076	0.628	52053
suptemp	0.952	0.079	0.870	28373
tempol	0.670	0.067	1.090	5145
tha	0.808	0.052	0.028	21544



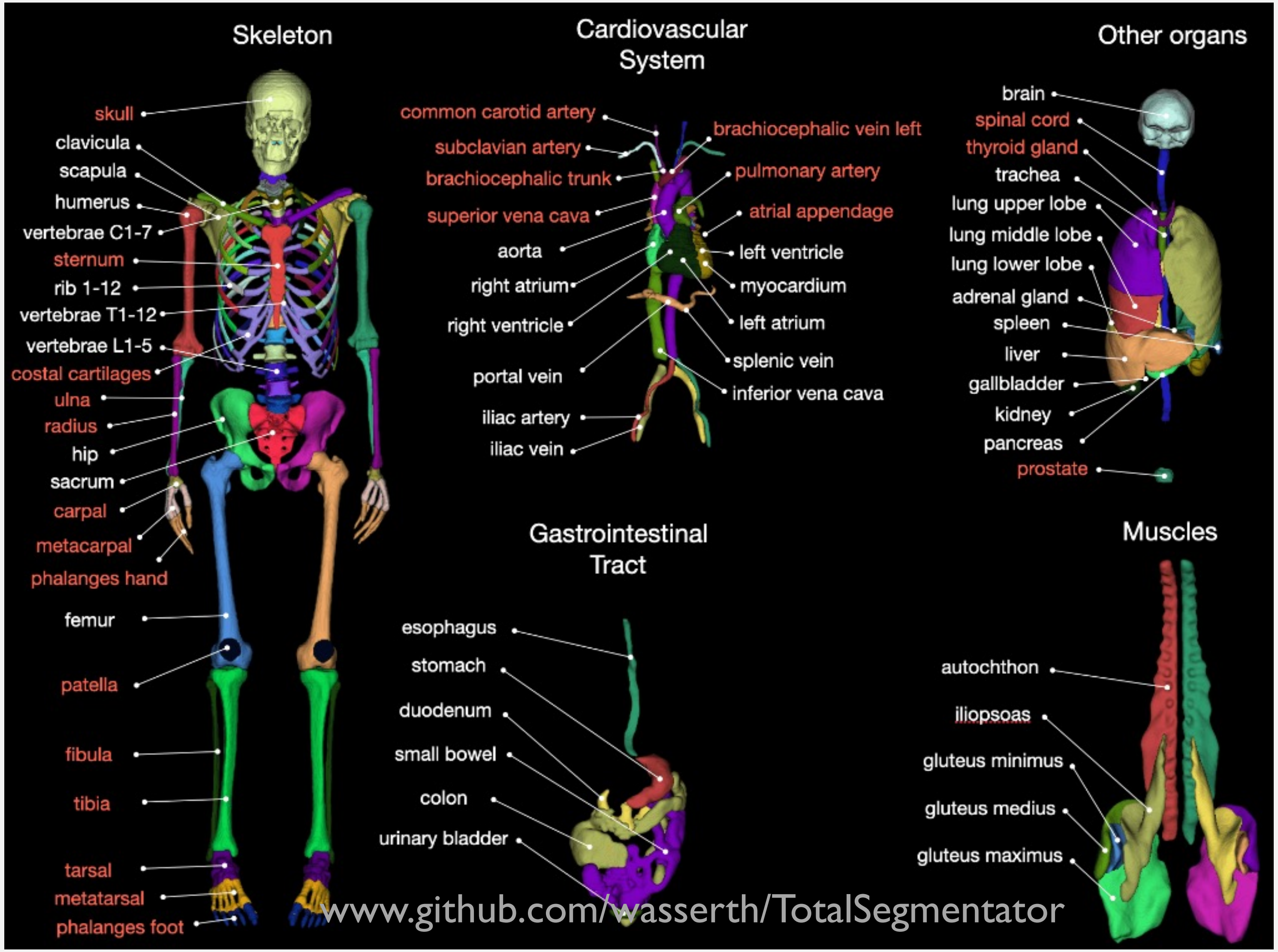
EXTENDING OUTSIDE BRAIN



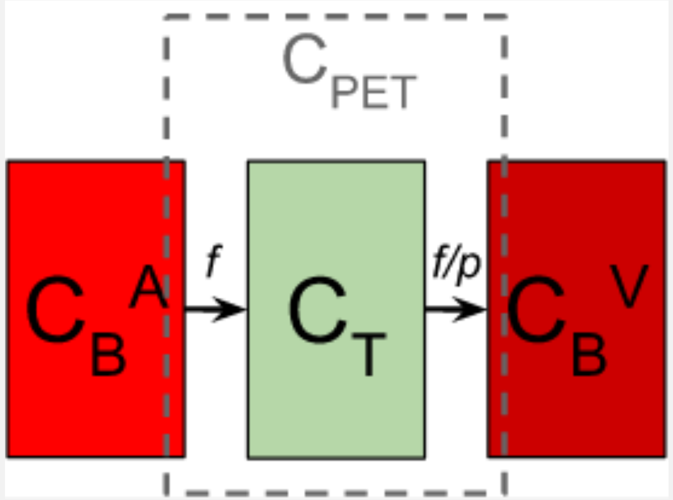
TOTAL BODY PIPELINE (TURBO)



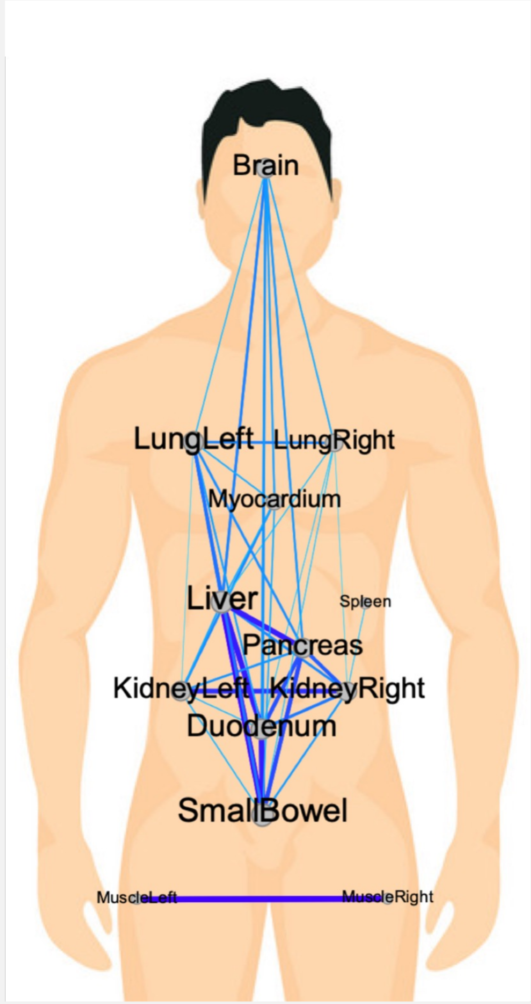
TOTAL BODY SEGMENTATION



TOTAL BODY VOXEL LEVEL MODELLING



1-tissue compartment model



EFFICIENT DATA ANALYSIS

- AIVO and automated frameworks allow efficient preprocessing of PET data:

1. The preprocessing only has to be run only once per study, after which the data is available to be used in the statistical analyses
2. Metadata is easily retrieved from the centralized AIVO-database
3. Allows analysis of large (N >> 100) datasets easily
4. Results and quality control metrics are stored in AIVO

REQUIREMENTS

- MATLAB (version 2016b or newer)
- SPM (Statistical Parametric Mapping, version 12)
- FreeSurfer (v6.0), Totalsegmentator (v2)
  - Supported operating systems: Linux & Mac
- Running may take ~ 8 hours to complete
  - Segmentation step only needs to be executed once

REFERENCES

Karjalainen T, Tuisku J, Santavirta S, et al. Magia: Robust Automated Image Processing and Kinetic Modeling Toolbox for PET Neuroinformatics. *Front Neuroinform*. 2020;14.

PET-BIDS specification:
https://bids-specification.readthedocs.io/en/stable/modality-specific-files/positron-emission-tomography.html

Magia version 1:
www.github.com/tkkarjal/magia

Magia version 2:
www.gitlab.utu.fi/human-emotion-systems-laboratory/magia-v2

Total body TURBO toolbox:
www.gitlab.utu.fi/human-emotion-systems-laboratory/turbo

Turku PET centre modelling reference:
http://www.turkupetcentre.net/petanalysis/modelling_intro.html

OTHER EXAMPLES OF LARGE SCALE DATASET STUDIES

- Tuisku et al. 2019: Effects of age, BMI and sex on the glial cell marker TSPO - a multicentre [^{11}C]PBR28 HRRT PET study
- Nummenmaa et al. 2020: Lowered endogenous mu-opioid receptor availability in subclinical depression and anxiety
- Kantonen et al. 2021: Cerebral μ-opioid and CB_1 receptor systems have distinct roles in human feeding behavior
- Sun et al. 2021: Seasonal Variation in the Brain μ-Opioid Receptor Availability
- Malén et al. 2022: Atlas of type 2 dopamine receptors in the human brain: Age and sex dependent variability in a large PET cohort
- Nummenmaa et al. 2022: μ-opioid receptor availability is associated with sex drive in human males