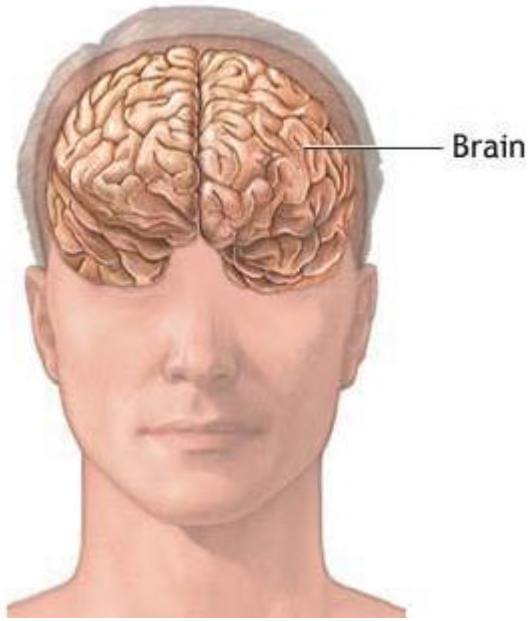
Medical/Bio Research Topics Ⅱ: Week 15 (14.12.2023)

Final evaluation and summary
(최종 평가 및 요약)

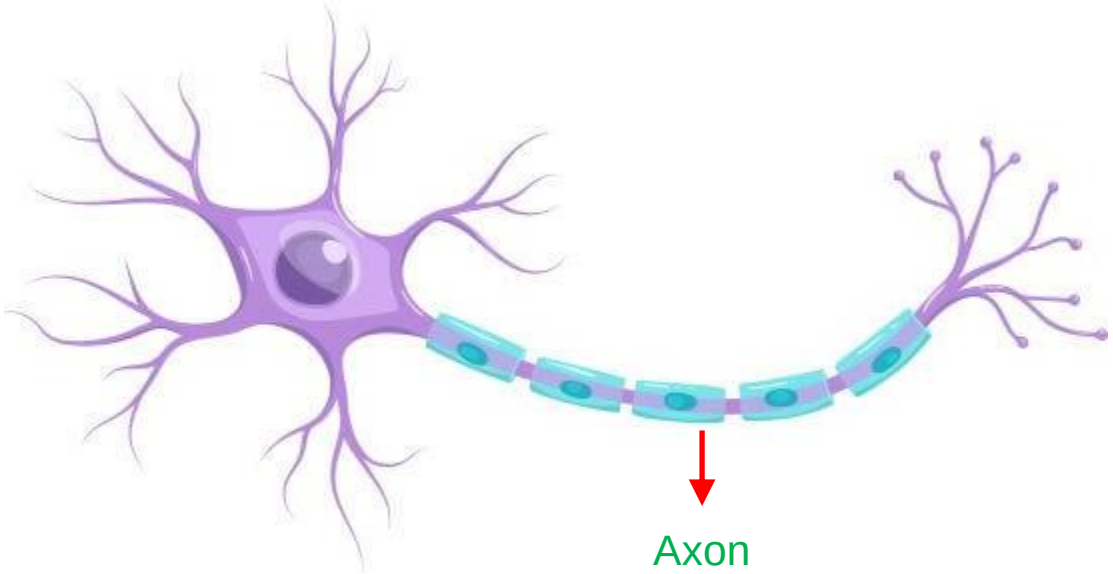
Brain

- Center of the nervous system
- Located in the head

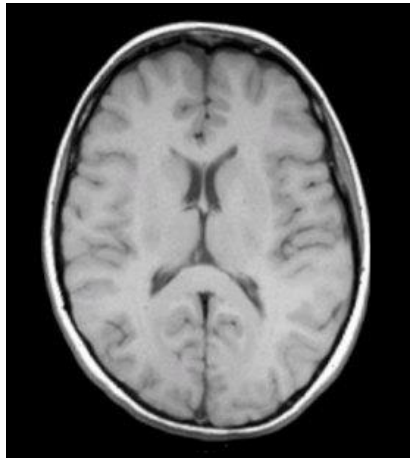


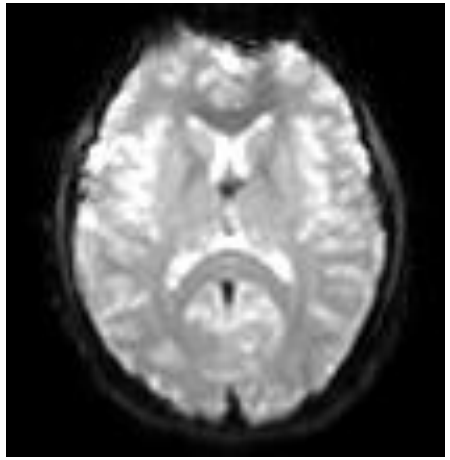
[https://medlineplus.gov/ency/imagepages/8738.htm]

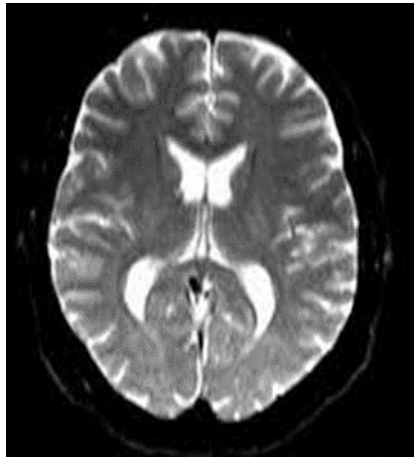
- Composed of tens of billions of neurons
  - Interconnected neurons communicate with each other by axons

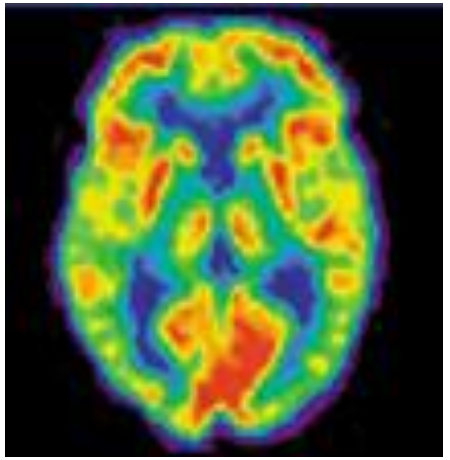


Brain Imaging







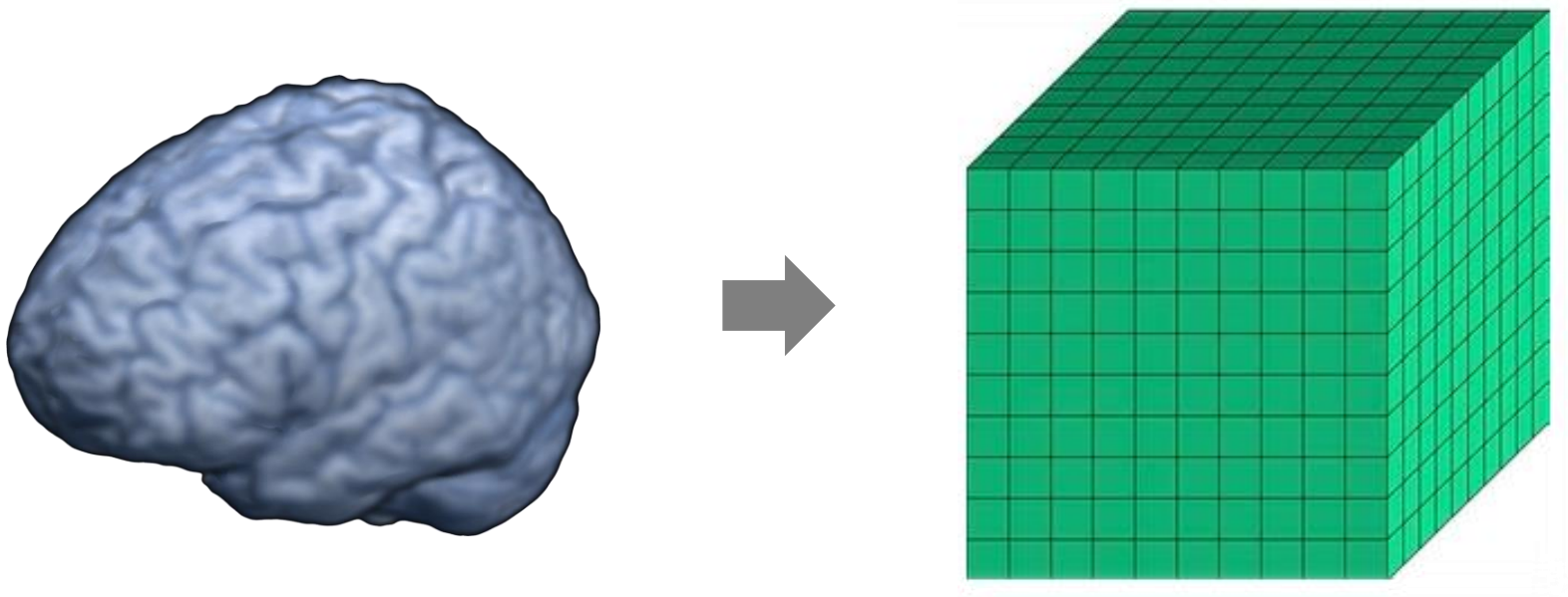


CT | **Structural MRI** | **Functional MRI** | **Diffusion-weighted MRI** | **PET**

CT, Computed Tomography (컴퓨터단층촬영)
MRI, Magnetic Resonance Imaging (자기공명영상)
PET, Positron Emission Tomography (양전자방출단층촬영)

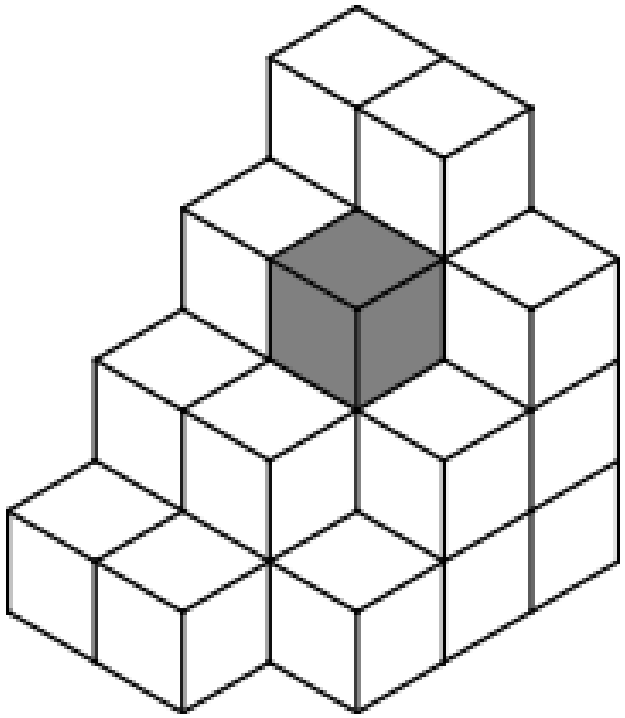
- Various techniques for imaging the structure or function of the brain
  - Computed Tomography (CT)
  - Magnetic Resonance Imaging (MRI)
    - Structural MRI (sMRI)
    - Functional MRI (fMRI)
    - Diffusion-weighted MRI (dMRI)
  - Positron Emission Tomography (PET)

- Volumetric description of the brain as a 3D array [Larobina and Murino, 2014]
  - Representation of the structure or function of the brain in the form of an array of voxels



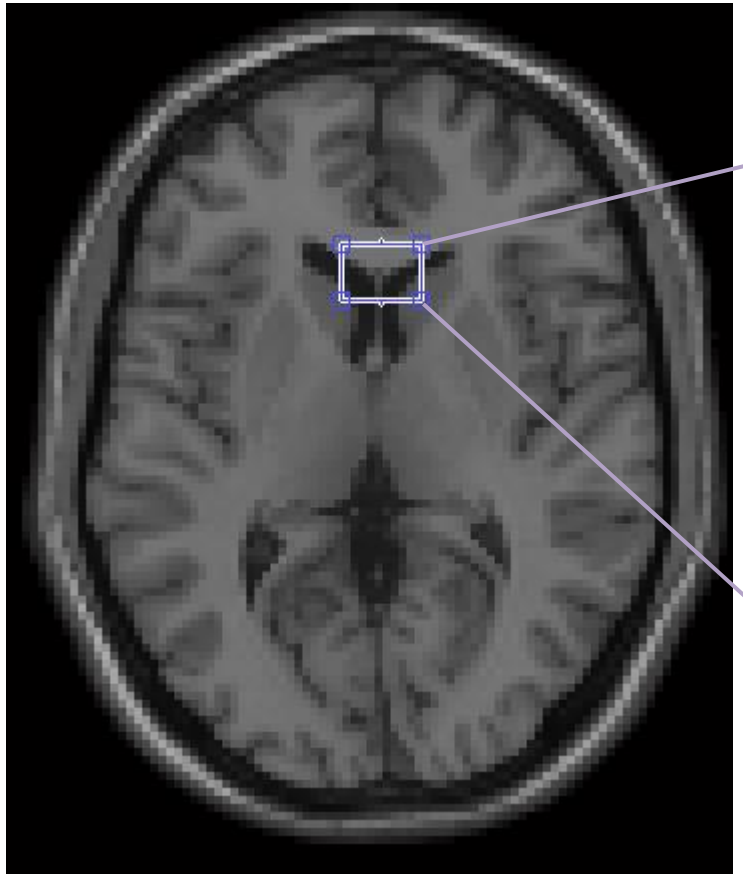
  - Discrete representation resulting from a sampling/reconstruction process that maps numerical values to positions of the space

- Voxel: volume element or volumetric pixel
  - Analogous to a pixel in 2D space

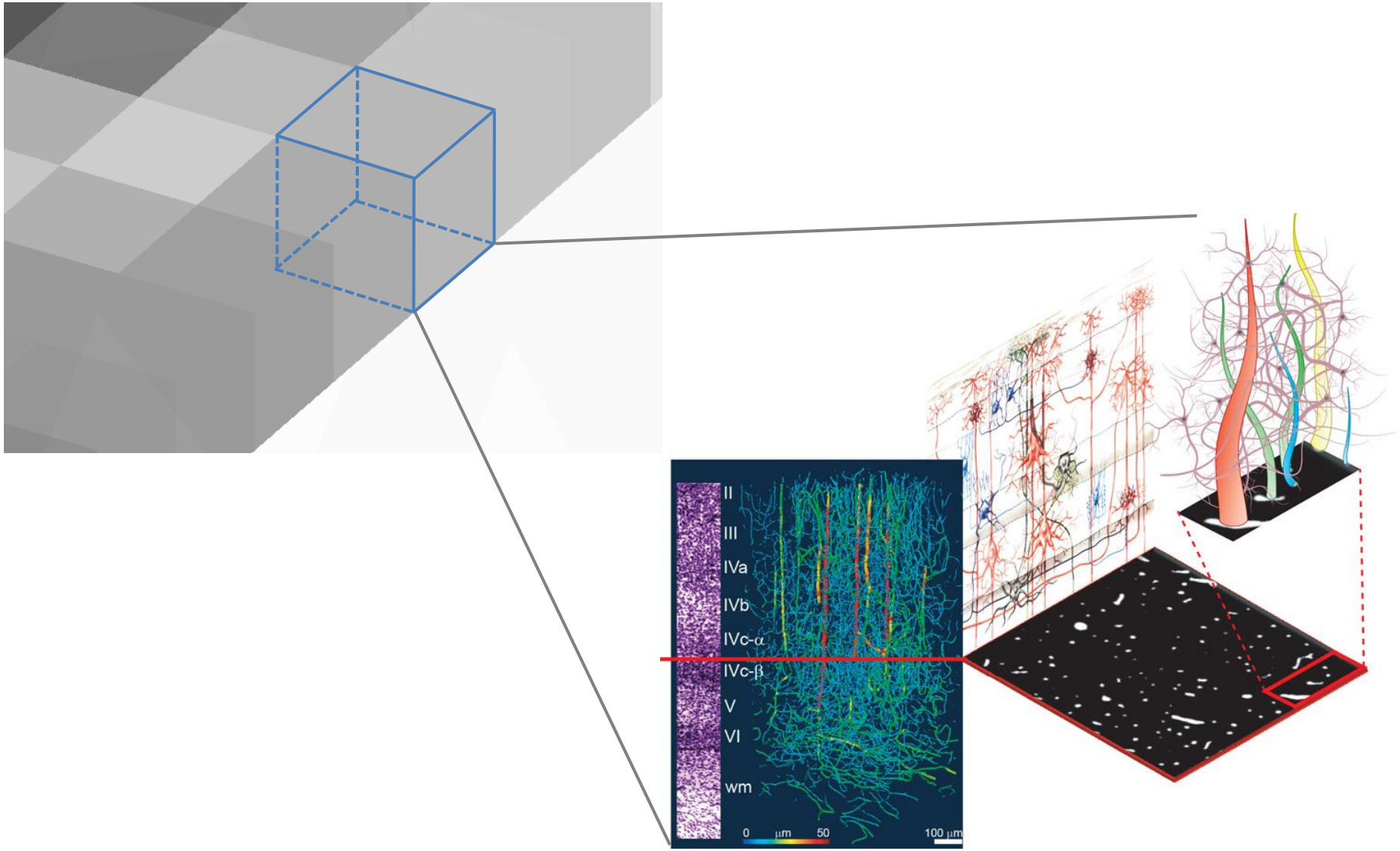


[https://en.wikipedia.org/wiki/Voxel]

– Sub-volume box with a constant value inside



0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
0.41	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.44
0.16	0.28	0.40	0.45	0.45	0.43	0.43	0.41	0.29	0.15
0.12	0.12	0.17	0.33	0.29	0.37	0.24	0.13	0.12	0.13
0.12	0.11	0.12	0.15	0.31	0.18	0.11	0.11	0.17	0.31
0.18	0.12	0.11	0.11	0.27	0.11	0.11	0.14	0.31	0.33
0.32	0.12	0.11	0.11	0.22	0.11	0.11	0.24	0.32	0.33

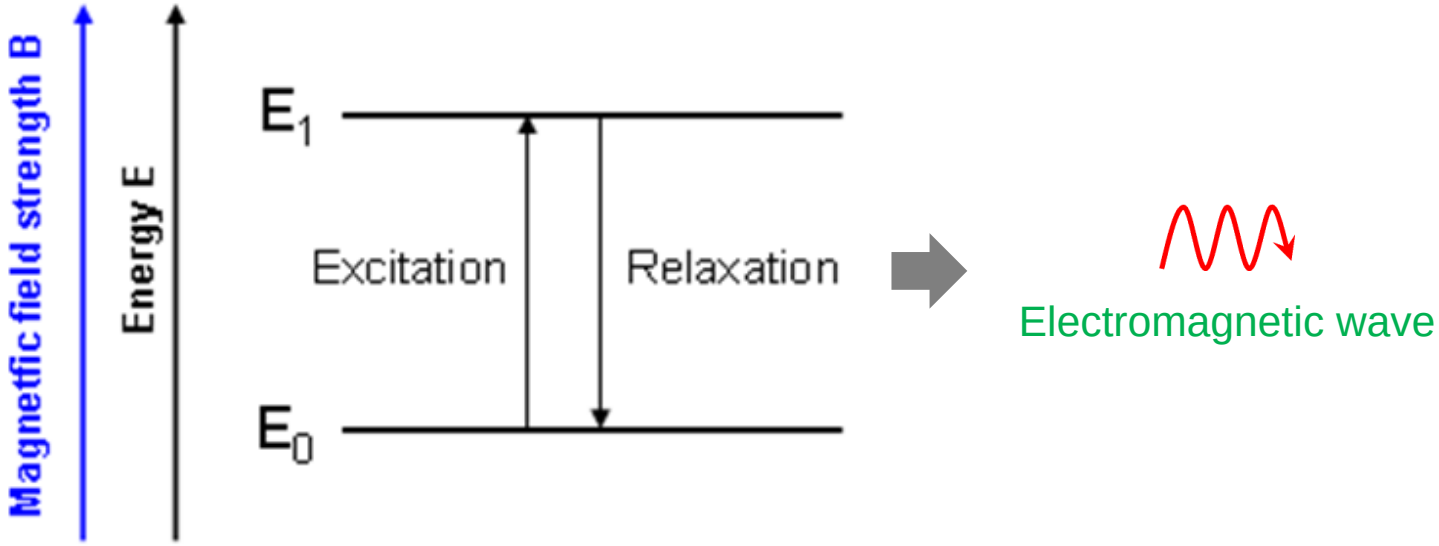


[Logothetis, 2008]

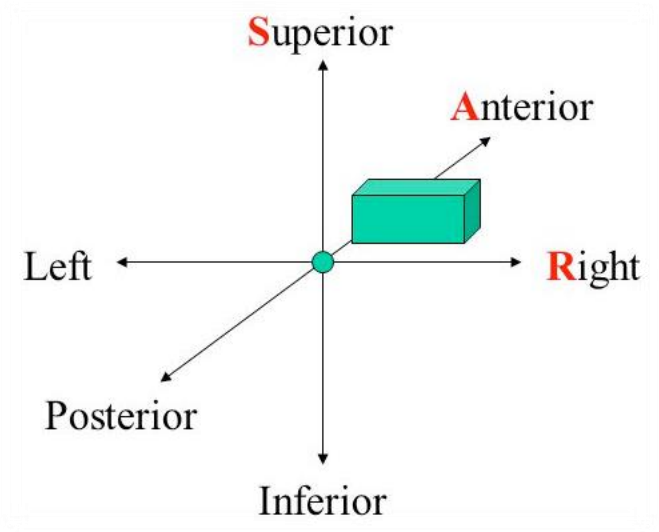
Neuronal and vascular contents within a voxel

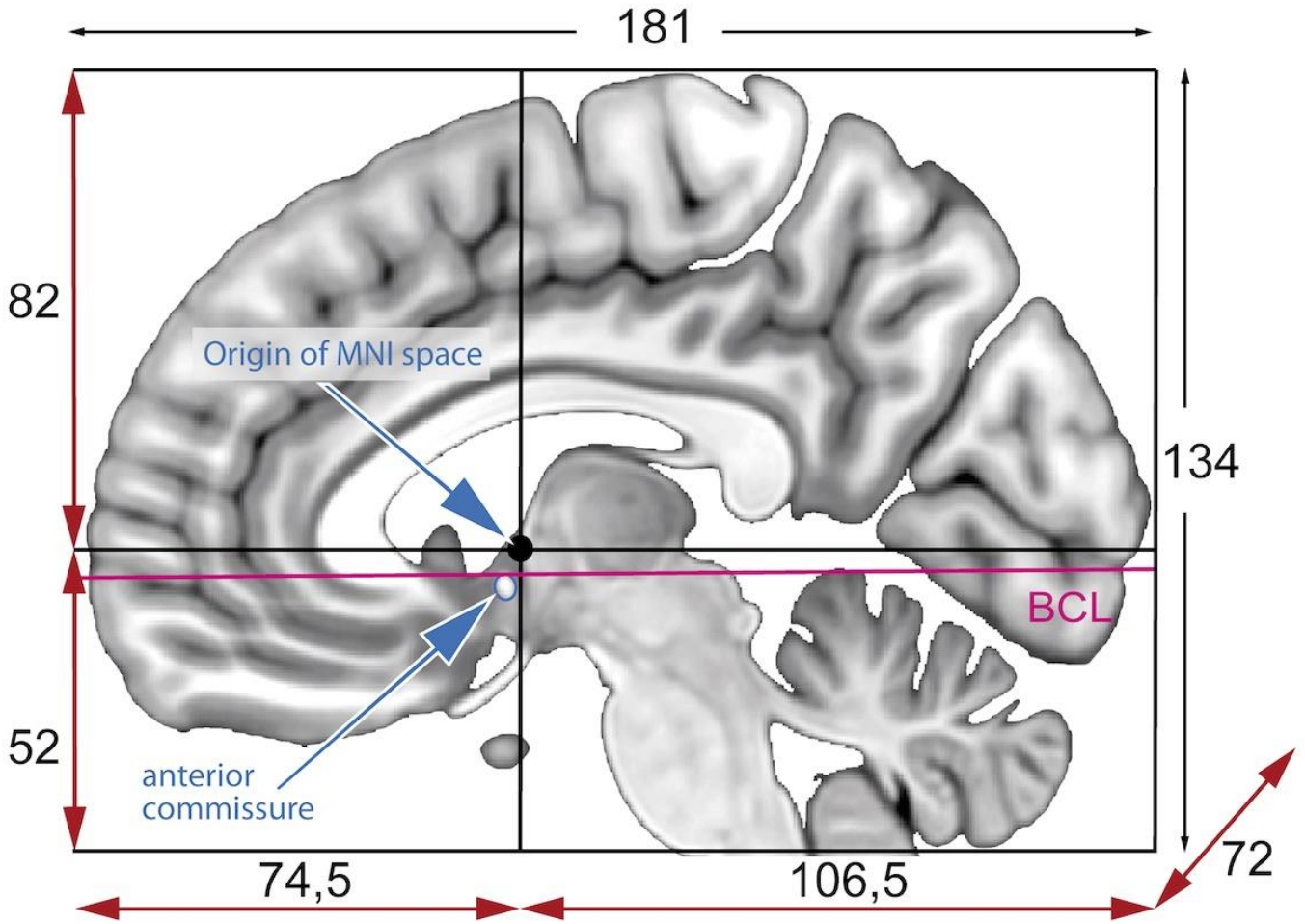
Brain MRI

- Medical application of nuclear magnetic resonance (NMR)
  - Generates different contrasts between tissues based on the relaxation properties of hydrogen nuclei therein



- Coordinate system
  - Reference frame in a 3D space that assigns *x*, *y*, and *z* coordinates to anatomical regions
  - Montreal Neurological Institute (MNI) coordinate system
    [https://www.fieldtriptoolbox.org/faq/coordsys/]
    - Origin in the anterior commissure
    - *X*-axis from left to right
    - *Y*-axis from posterior to anterior
    - *Z*-axis points from inferior to superior
    - Used if the geometry is spatially warped to the MNI152 template brain (average of 152 T1-weighted MRI scans from young adults)





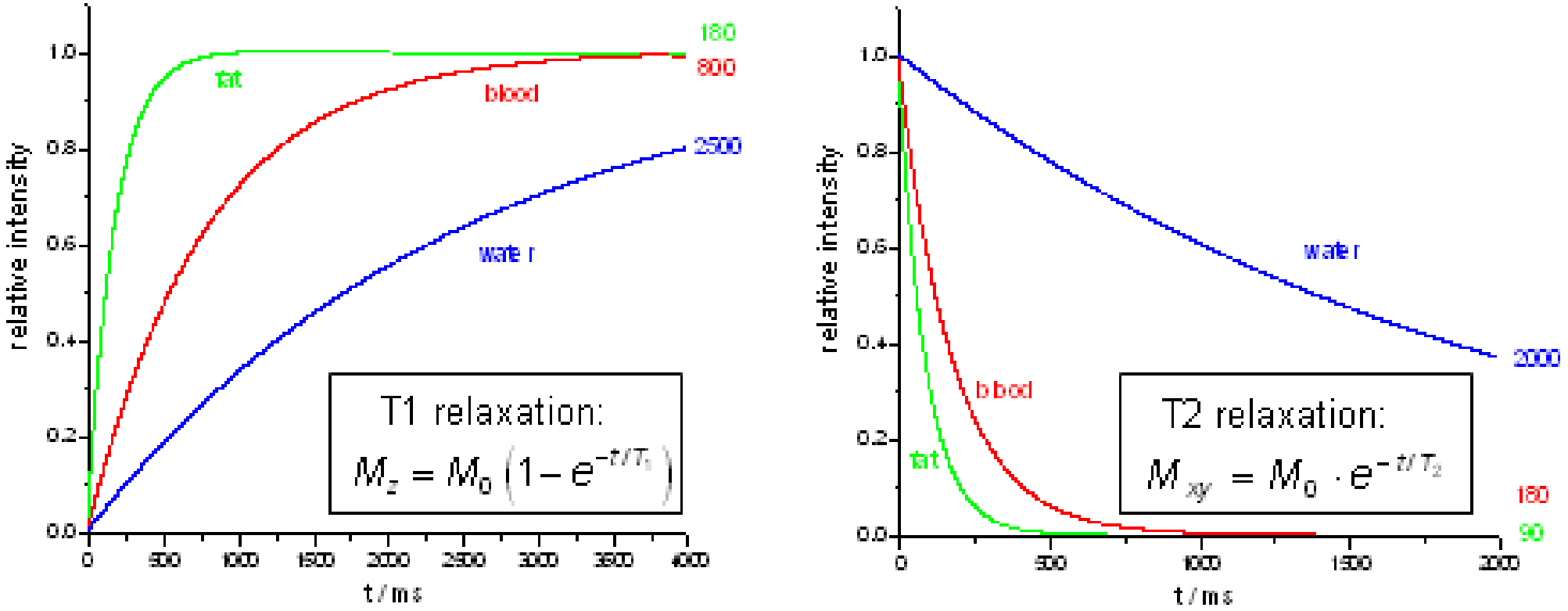
[https://carpentries-incubator.github.io/SDC-BIDS-sMRI/03-Image_Spatial_Normalization/index.html]

MNI coordinate system

- File format
  - Provides a standardized way to store the information describing an image in a computer file [Larobina and Murino, 2014]
  - Major file formats
    - Digital Imaging and Communications in Medicine (DICOM)
      - Default file fomat for acquisition
    - Neuroimaging Informatics Technology Initiative (NIfTI)
      - Default file format for analysis

Structural MRI (sMRI)

- MRI technique primarily for examining the anatomy and pathology of the brain
  - T1-weighted
    - Predominately determined by T1 differences between tissues
  - T2-weighted
    - Predominately determined by T2 differences between tissues
  - Fluid Attenuated Inversion Recovery (FLAIR)
    - Dampens ventricular cerebrospinal fluid signals, causing the highest signals from certain brain parenchymal abnormalities



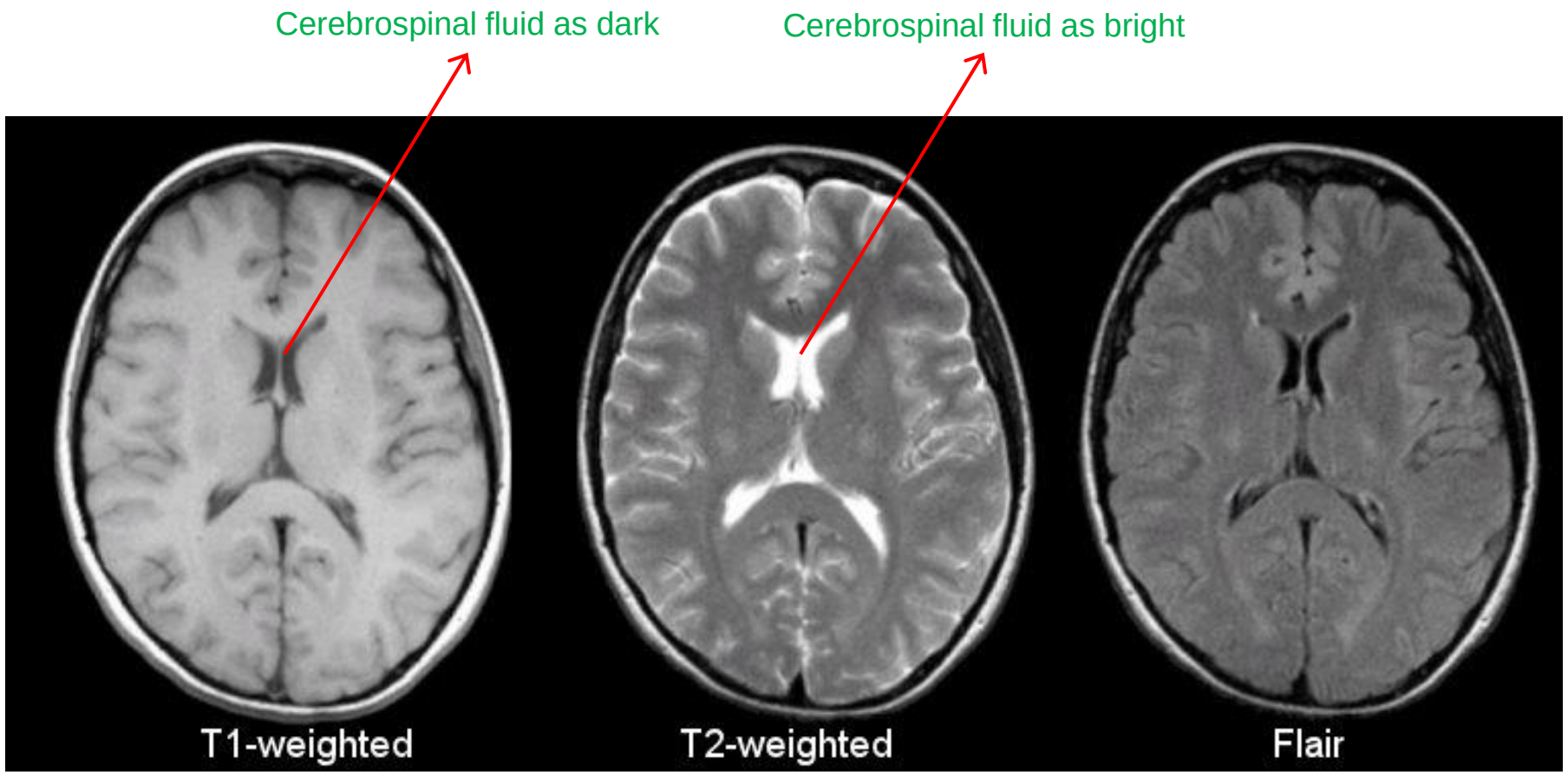
[Pollacco, 2016]

Differences in T1 and T2 relaxation times between tissues

Tissue	T1-Weighted	T2-Weighted	Flair
CSF	Dark	Bright	Dark
White Matter	Light	Dark Gray	Dark Gray
Cortex	Gray	Light Gray	Light Gray
Fat (within bone marrow)	Bright	Light	Light
Inflammation (infection, demyelination)	Dark	Bright	Bright

[https://case.edu/med/neurology/NR/MRI Basics.htm]

Different contrasts of the brain

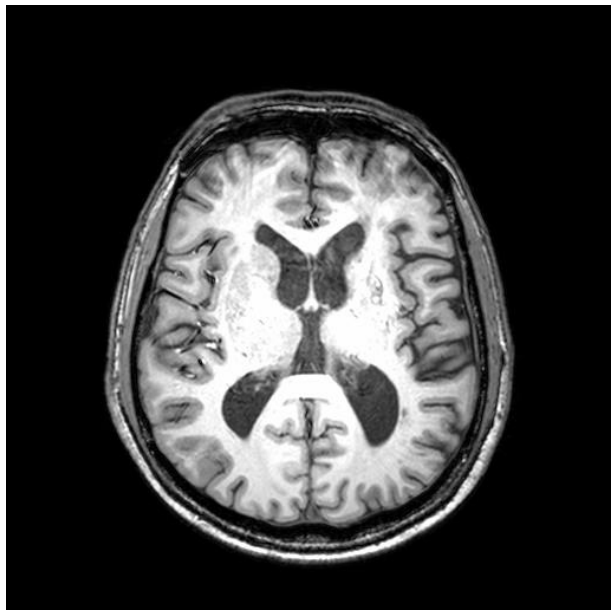


[https://case.edu/med/neurology/NR/MRI Basics.htm]

Comparison between T1-weighted, T2-weighted, and FLAIR images

• T1-weighted contrast

- White matter (nerve fibres) has a very short T1 and relaxes rapidly
- Cerebrospinal fluid has a long T1 and relaxes slowly
- Grey matter (neuron congregations) has an intermediate T1 and relaxes at an intermediate rate



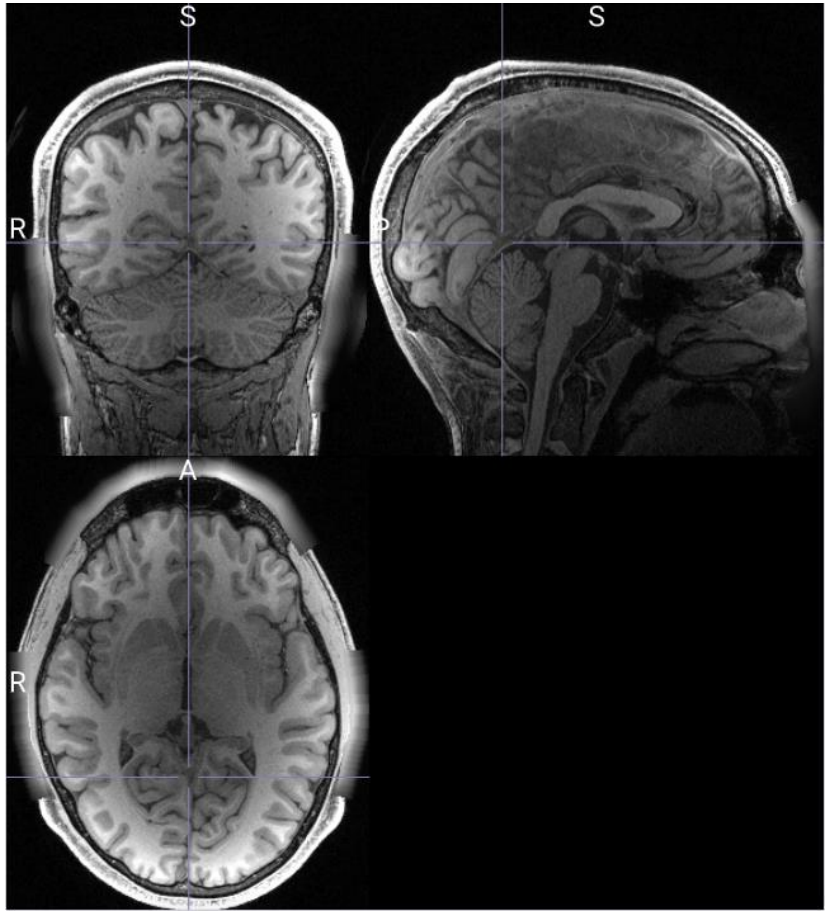
Producing an image
at a time when the curves are widely separated
between the tissues

- White matter contributes to lighter voxels
- Cerebrospinal fluid contributes to darker voxels
- Grey matter contributes to voxels with intermediate shades of grey

sMRI Data Processing

- Numerous steps to clean and standardise sMRI data before brain morphometry
  - Correction for intensity non-uniformity (bias field)
  - Segmentation
    - Classifies an image into the non-brain and brain and, furthermore, the brain into different tissues usually including grey matter, white matter, and cerebrospinal fluid
  - Normalisation
    - Transforms an image from a native space to the standard space

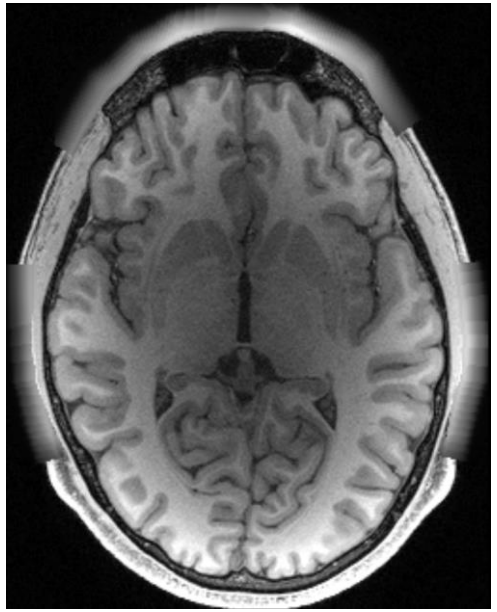
Input

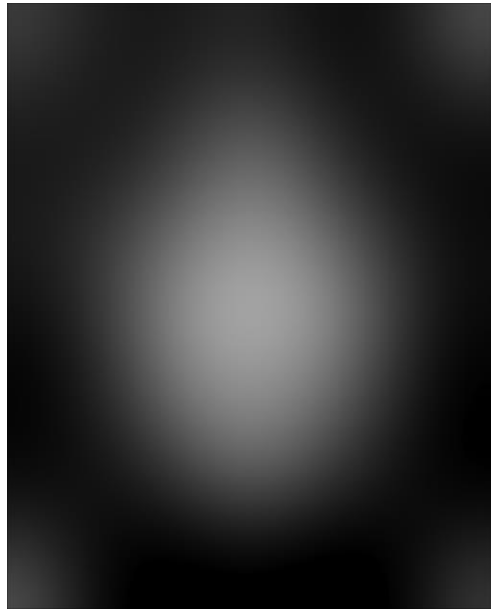


T1-weighted image

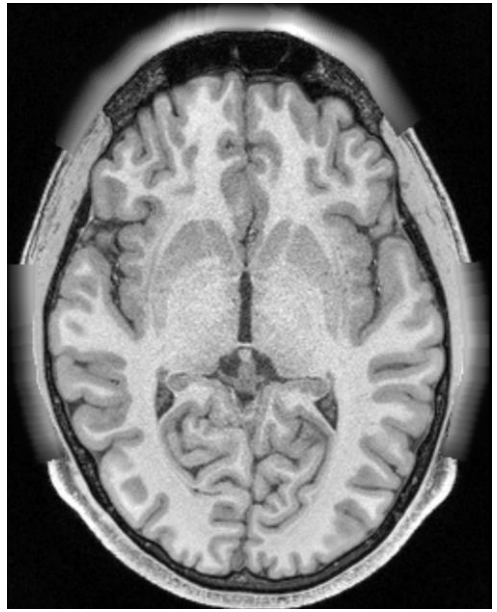
Output

Correction for intensity non-uniformity



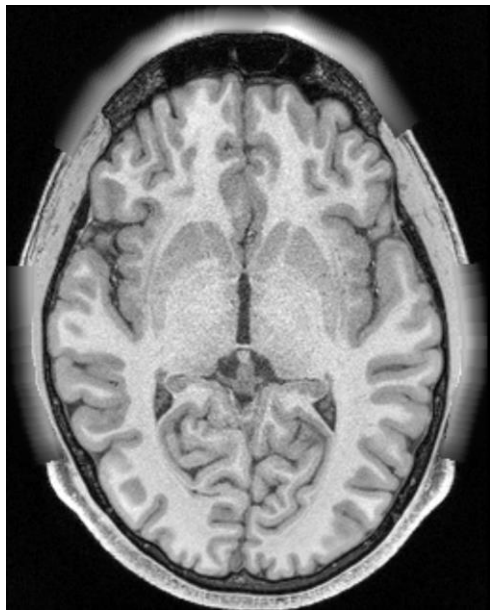


Intensity non-uniformity



Output

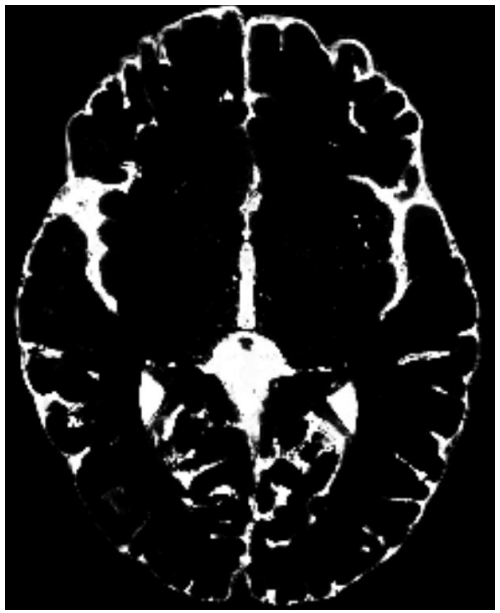
Segmentation



Segmentation

Grey matter

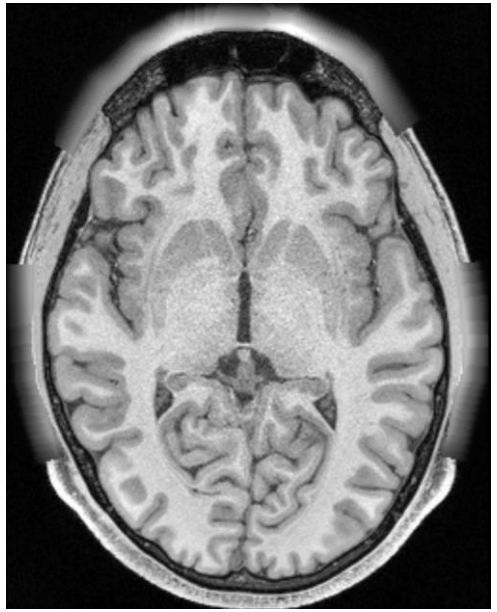
White matter



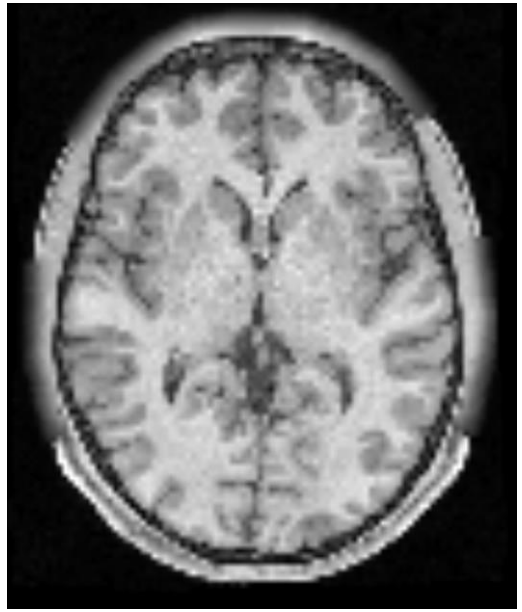
Cerebrospinal fluid

Output

Normalisation



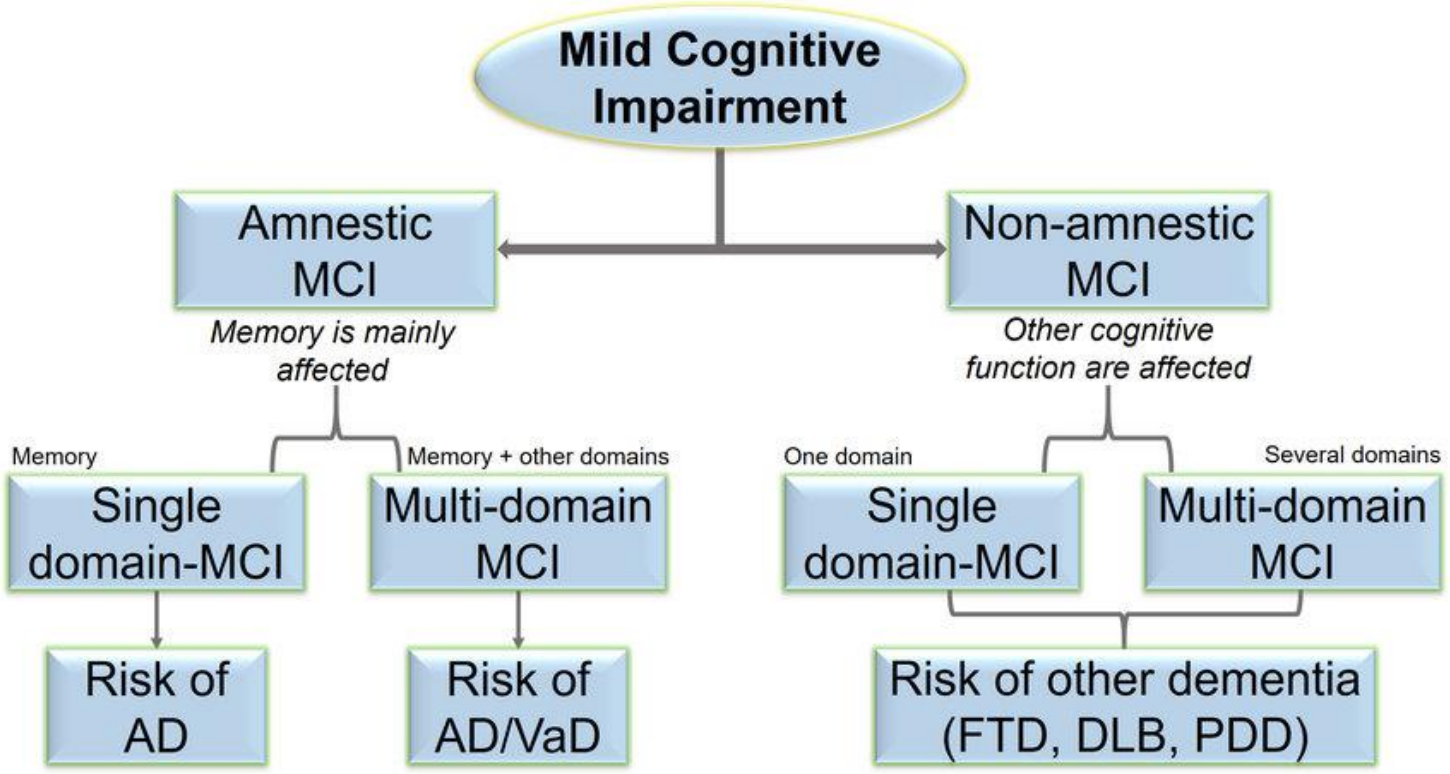
Normalisation



[Database 1] Alzheimer's Disease Neuroimaging Initiative (ADNI)

- https://adni.loni.usc.edu/
- Alzheimer’s disease
  - Neurodegenerative disease
  - Involves cell death caused by the accumulation of amyloid beta (Aβ) and hyperphosphorylated tau
  - Most recognizable by cognitive symptoms
  - Most common cause of dementia

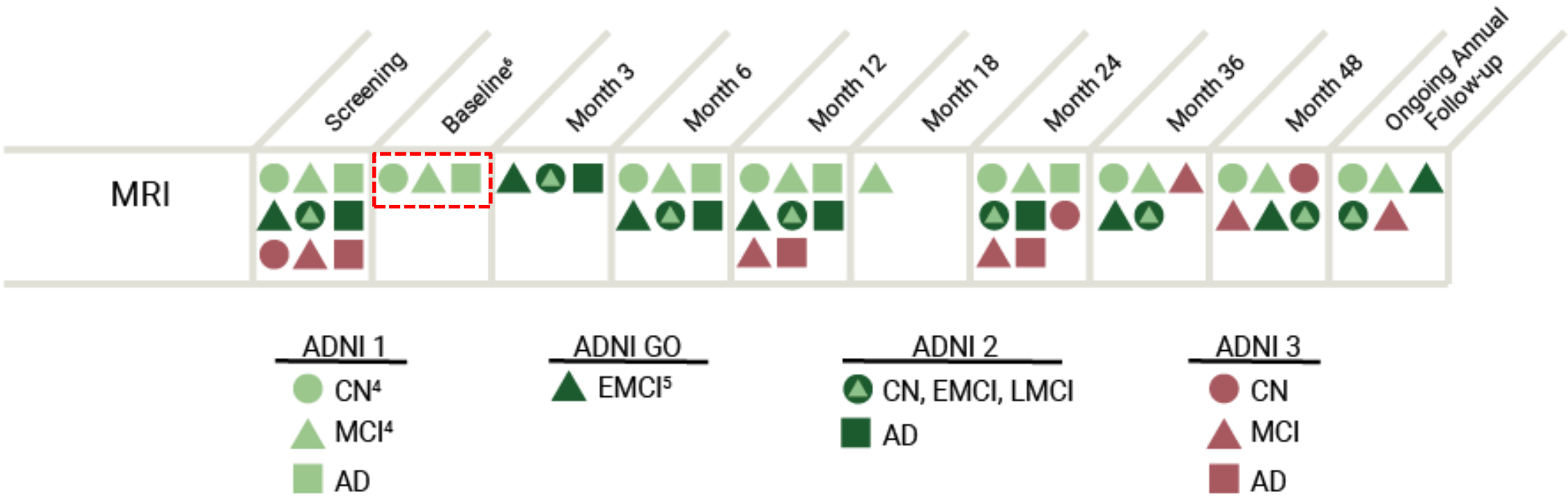
- Mild cognitive impairment (MCI)
  - Intermediate stage between normal ageing and dementia



MCI, mild cognitive impairment
AD, Alzheimer's disease
VaD, vascular dementia
FTD, frontotemporal dementia
DLB, dementia with Lewy bodies
PDD, dementia in Parkinson's disease

[Giau et al., 2019]

Subtypes of MCI and their risk for neurodegenerative diseases

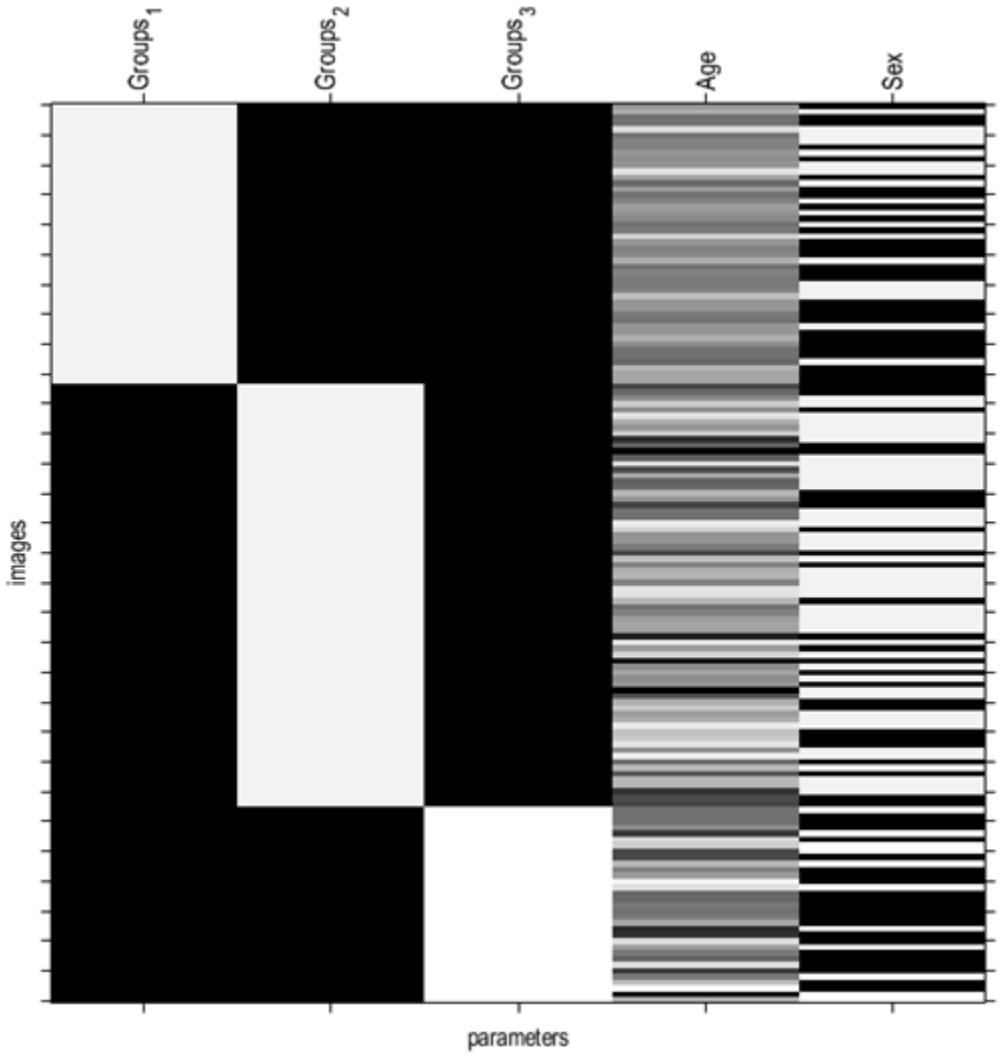


[https://adni.loni.usc.edu/data-samples/data-types/mri/]

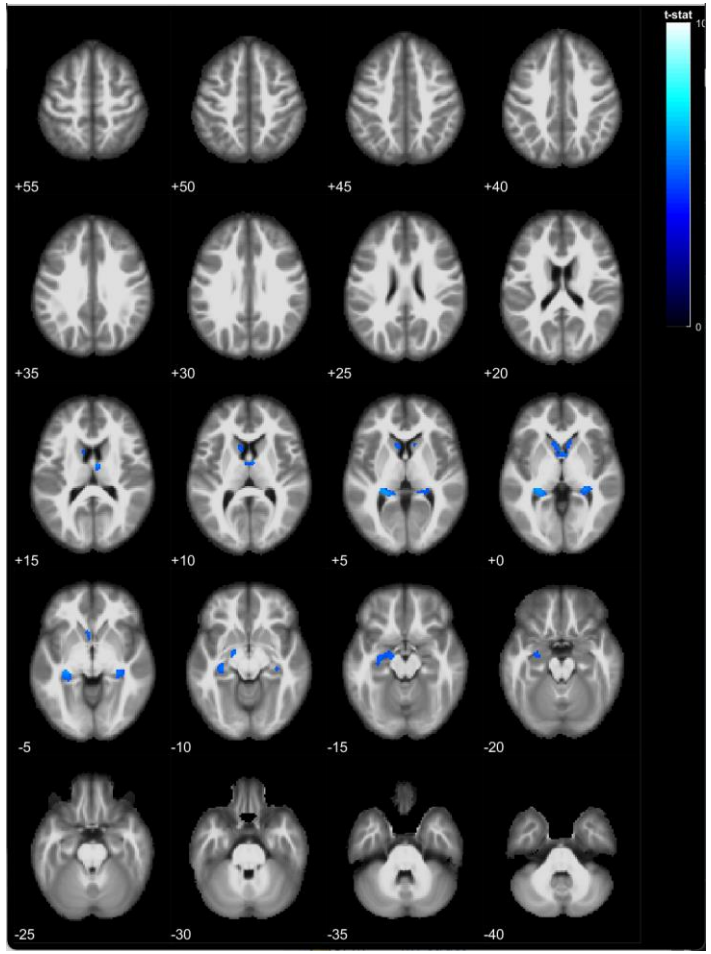
Collection of MRI data in ADNI

- Dataset: ADNI 1 study baseline dataset
  - CN (healthy elderly individuals): $n = 47$
  - MCI (individuals with mild cognitive impairment): $n = 71$
  - AD (individuals with Alzheimer's disease): $n = 33$

- Group comparison of grey matter/white matter volume



Two-sample *t*-test: CN > MCI

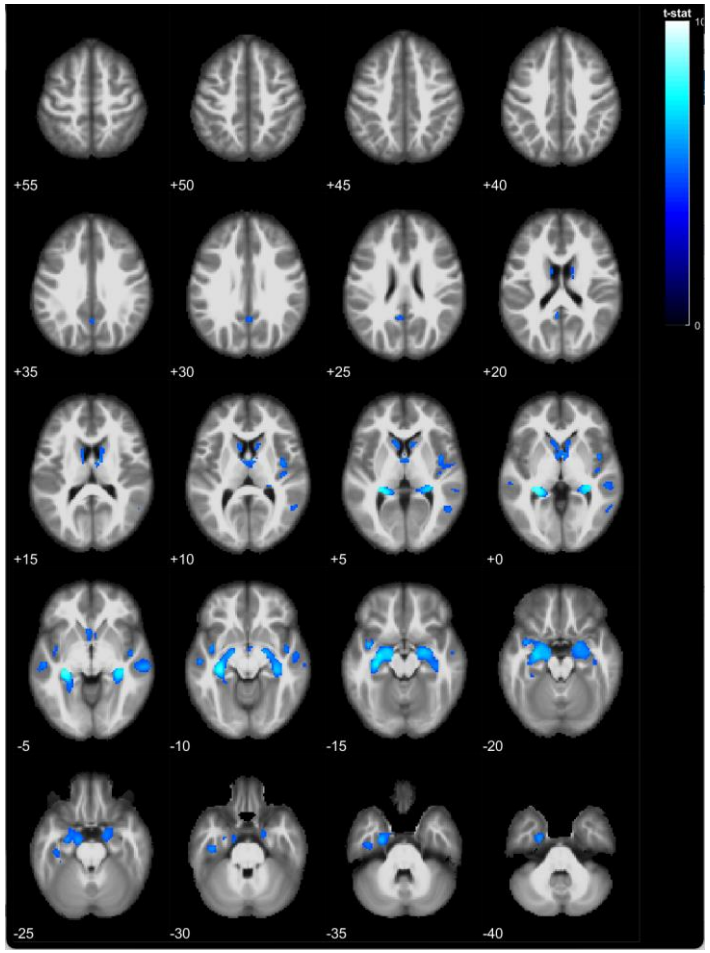


Grey matter volume

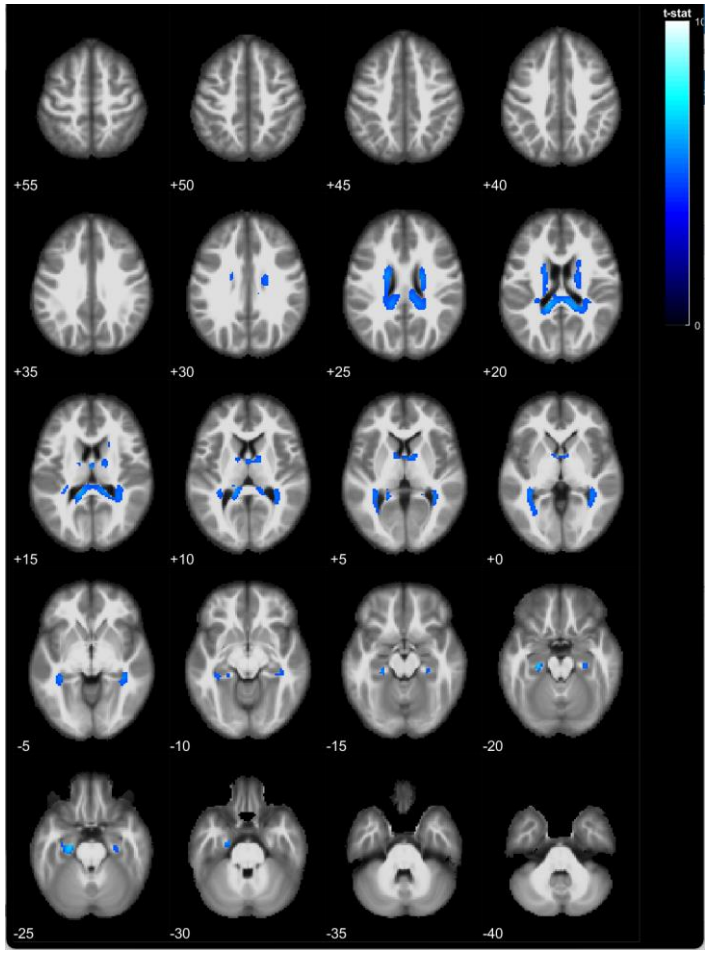
White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and FWE corrected $p = 0.05$ at the voxel level

Two-sample *t*-test: CN > AD



Grey matter volume

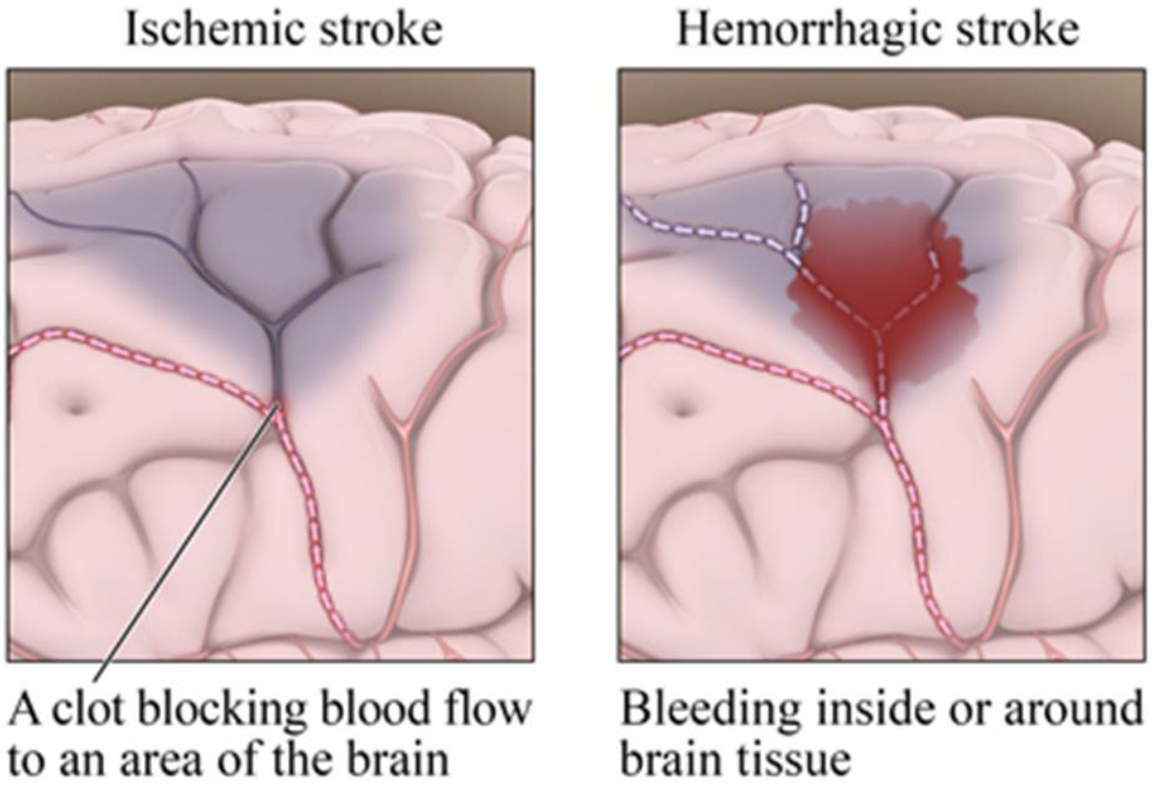


White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and FWE corrected $p = 0.05$ at the voxel level

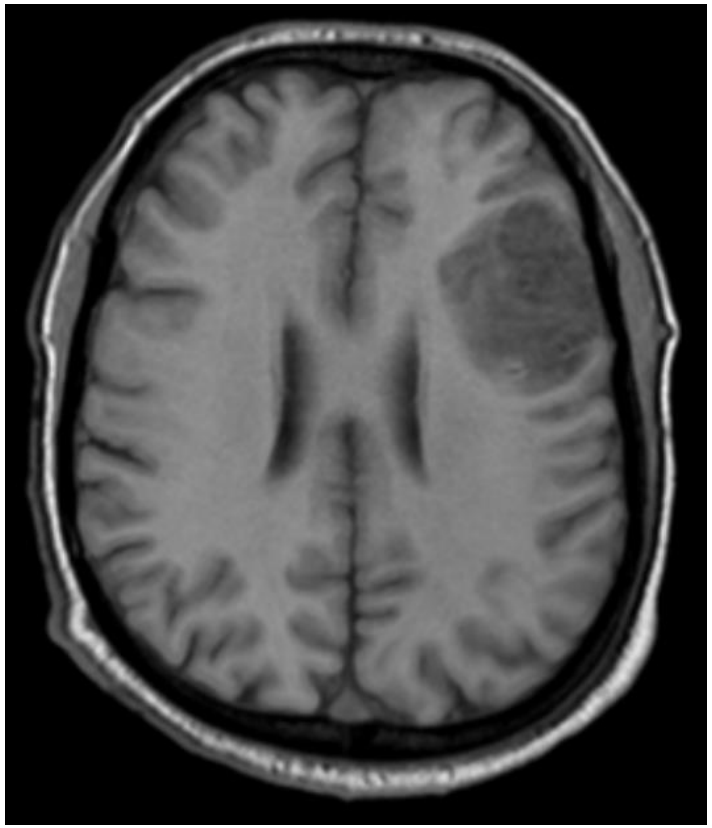
[Database 2] Anatomical Tracings of Lesions After Stroke (ATLAS) v2.0

- https://fcon_1000.projects.nitrc.org/indi/retro/atlas.html
- Stroke
  - Cerebrovascular disease
  - Involves cell death caused by poor blood flow
  - Two types of stroke
    - Ischemic stroke
      - Caused by interrupted or reduced blood flow to the brain
    - Hemorrhagic stroke
      - Caused by bleeding in the brain

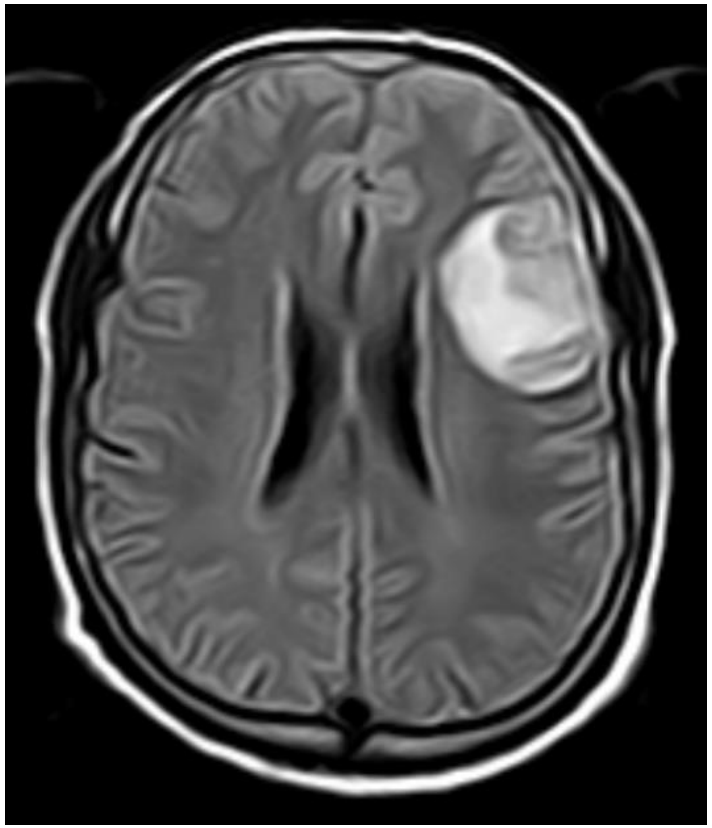


[https://myhealth.alberta.ca/Health/Pages/conditions.aspx?hwid=tp12720]

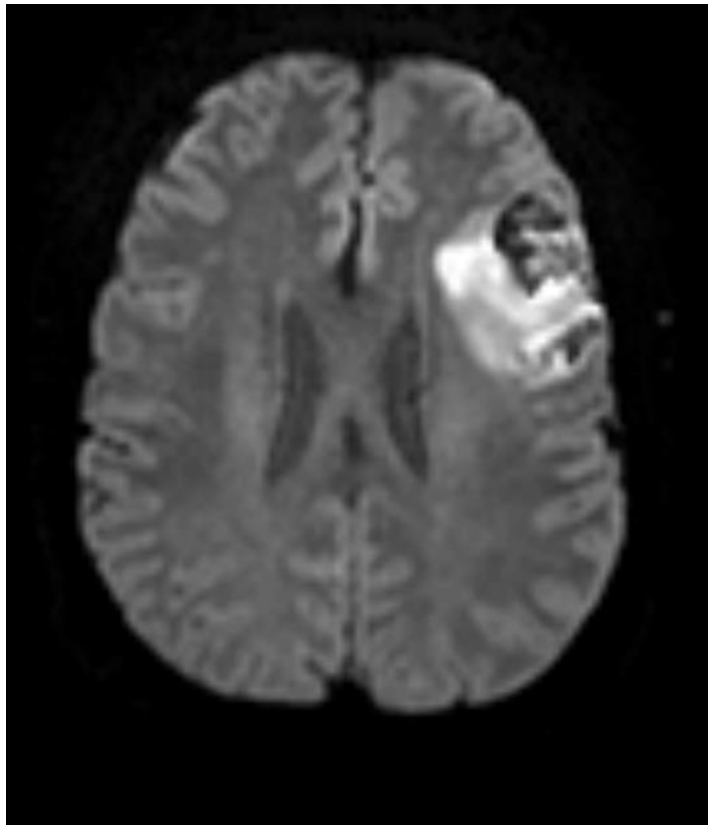
Ischemic vs. hemorragic stroke



T1-weighted



FLAIR



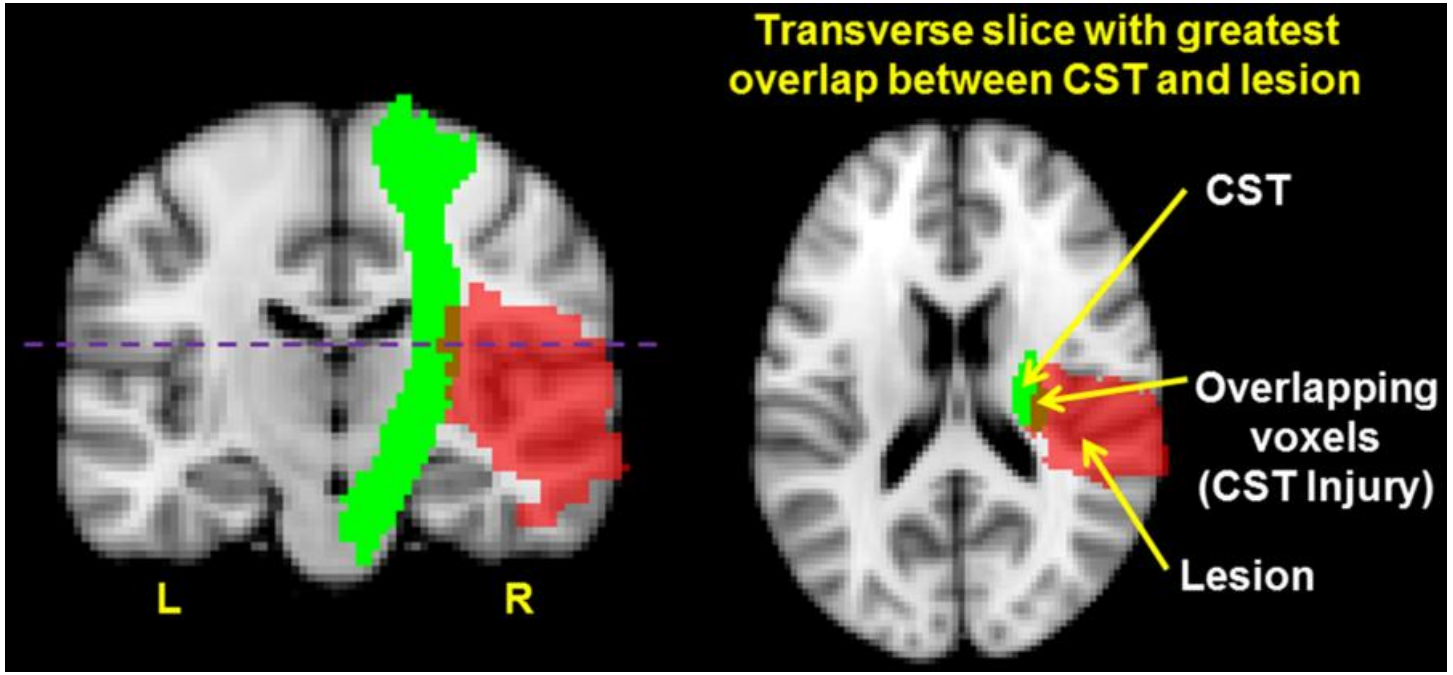
Diffusion-weighted

[https://www.mayoclinic.org/diseases-conditions/stroke/diagnosis-treatment/drc-20350119]

Stroke lesion displayed as altered signals in MRI

- Lesion segmentation
  - Critical for the quantification of lesion burden
    - Lesion size
    - Lesion location
    - Lesion load
  - Manual segmentation remains the gold standard, but it is time-consuming, subjective, and requires neuroanatomical expertise

$$\text{CST Injury} = \left(\frac{\text{Number of overlapping voxels between the CST and lesion for the transverse slice}}{\text{Total number of CST voxels for the transverse slice}}\right) \times 100\%$$



[Lam et al., 2020]

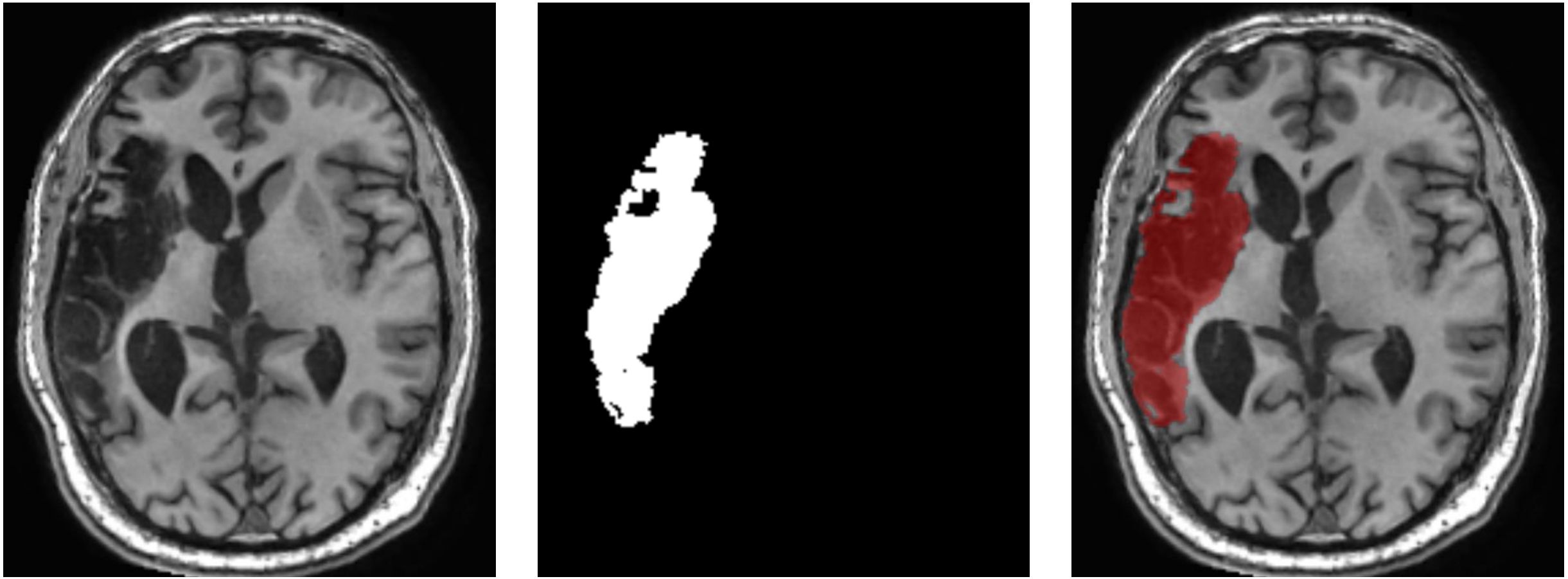
Computation of a corticospinal tract lesion load

- Dataset: ATLAS v2.0 training dataset (*n* = 655)

	Subjects with One Lesion			Subjects with Multiple Lesions		
	Left	Right	Other	Unilateral	Bilateral	Other
Training data (n = 655)	173 (26.4%)	187 (28.5%)	46 (7.0%)	47 (7.2%)	121 (18.5%)	81 (12.4%)

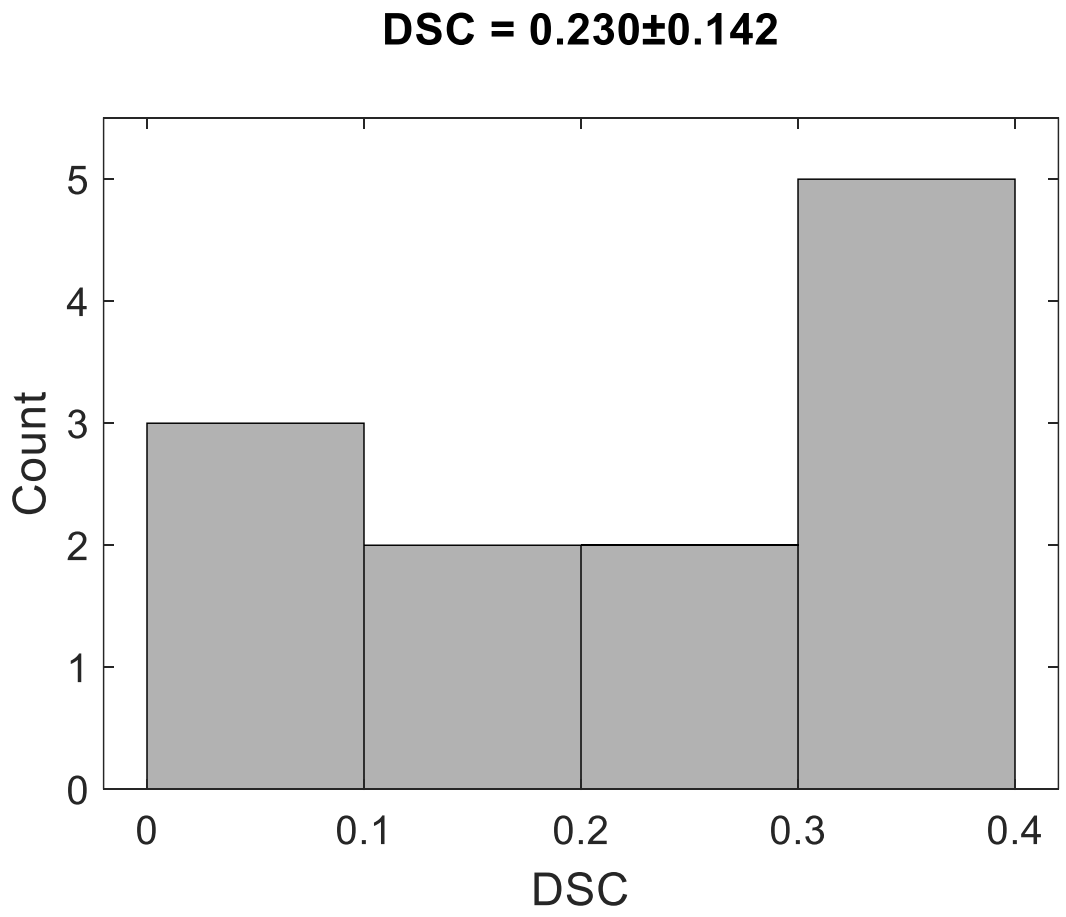
[Liew et al., 2022]

- Training dataset: $n = 600$
  - T1-weighted MRI scans
  - Lesion masks
- Test dataset: $n = 55$
  - T1-weighted MRI scans
  - Hidden lesion masks
- Lesion segmentation performance
  - Dice similarity coefficient (DSC) [Dice, 1945]

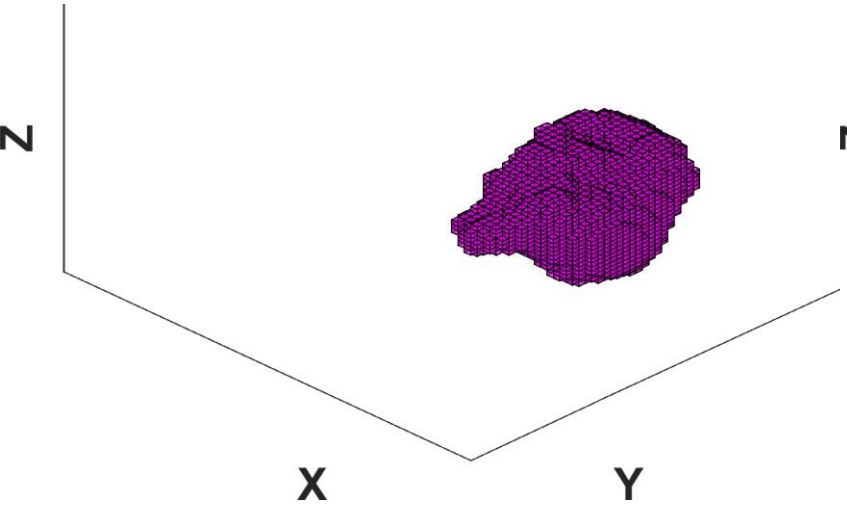


Example pair of a T1-weighted MRI scan and a lesion mask

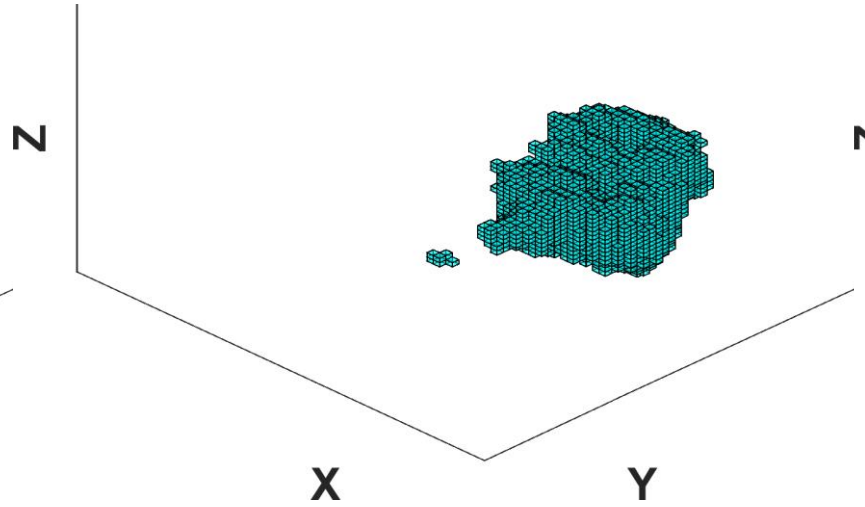
- Deep learning-based lesion segmentation
  - Performance of lesion segmentation for the test dataset



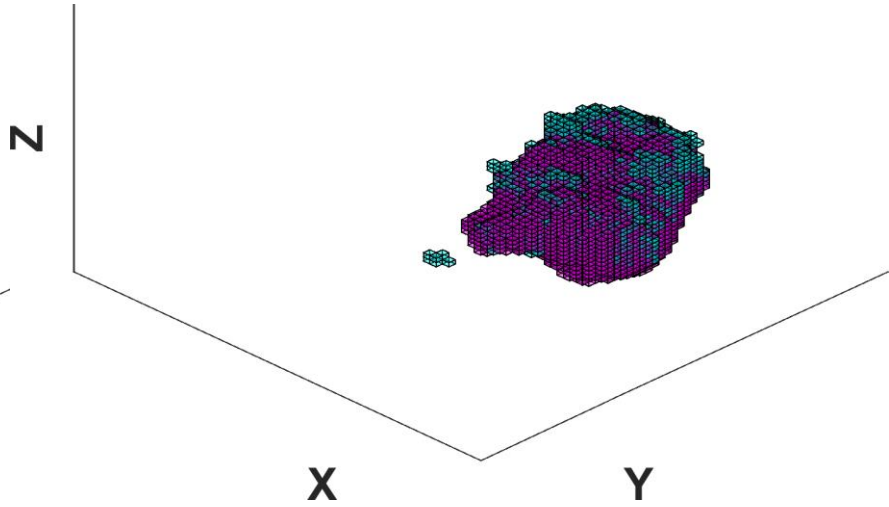
DSC = 0.860 (6,815 voxels vs. 5,904 voxels)



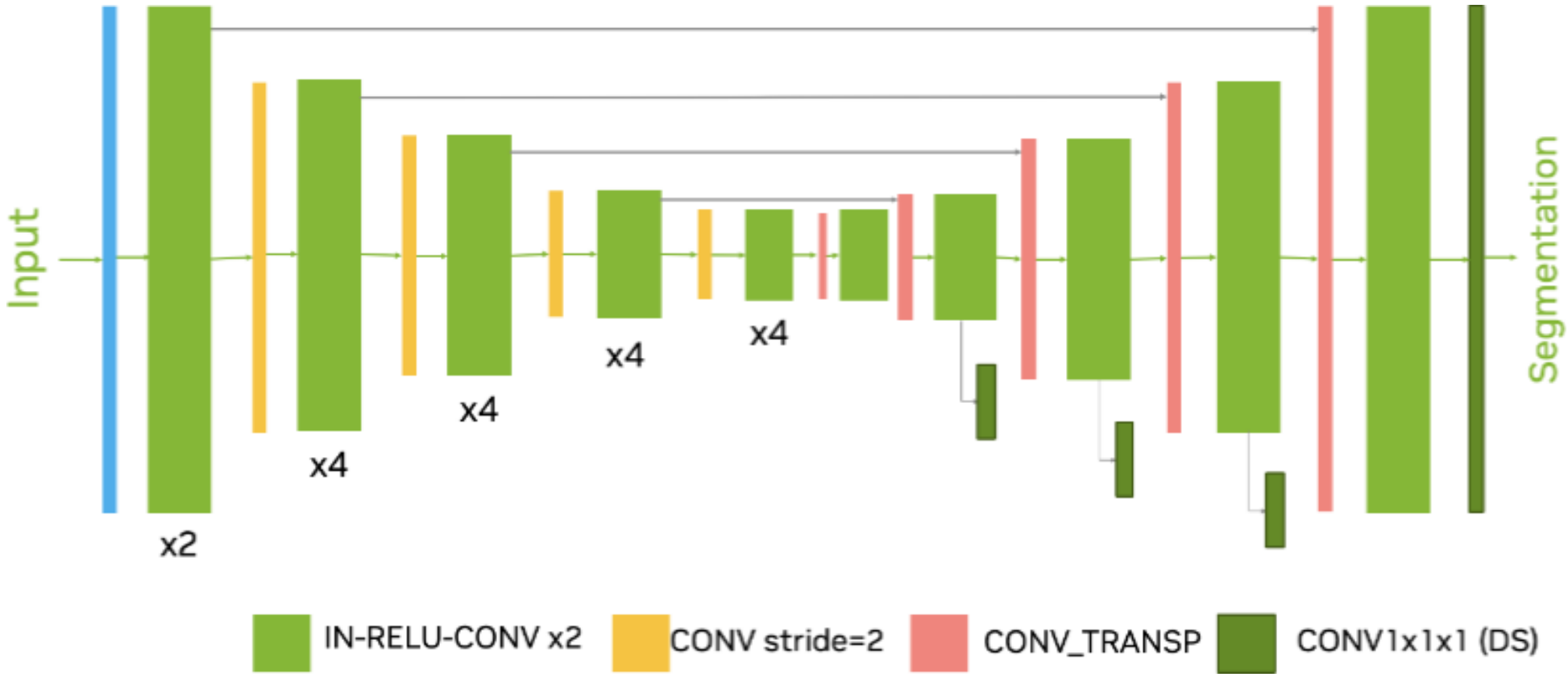
Actual



Predicted



Actual vs. Predicted



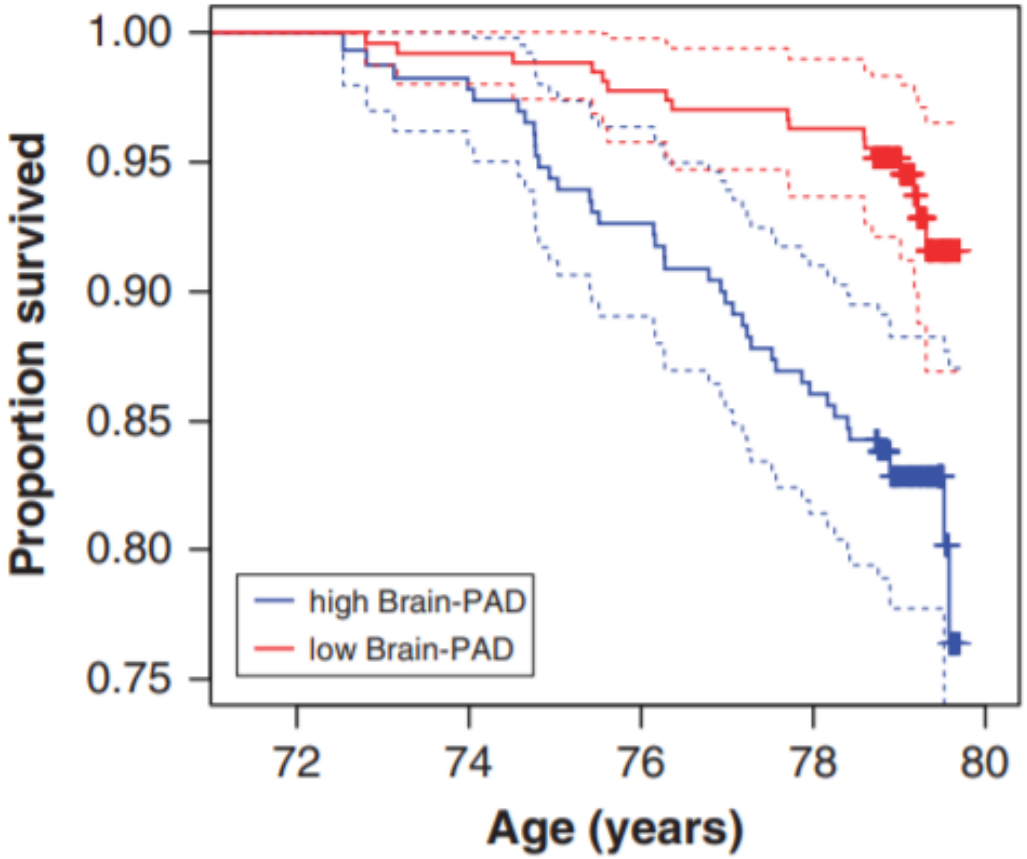
[Siddique et al., 2022]

SegResNet

[Database 3] Human Connectome Project (HCP)

- https://www.humanconnectome.org/
- Ageing
  - Process of becoming older
  - Two types of age
    - Chronological age
      - Number of years an individual has been alive
    - Biological age
      - How old an individual's cells and tissues appear to be based on their current condition

- Brain age
  - Biological age usually estimated with information derived from brain MRI data
  - Sums up the progression of ageing processes in the brain
- Brain age gap (BAG)
  - Difference between brain age and chronological age
  - Indicates whether an individual's brain appears to have aged more or less than the population average for their actual chronological age
    - BAG > 0: accelerated ageing
    - BAG < 0: resilience to ageing

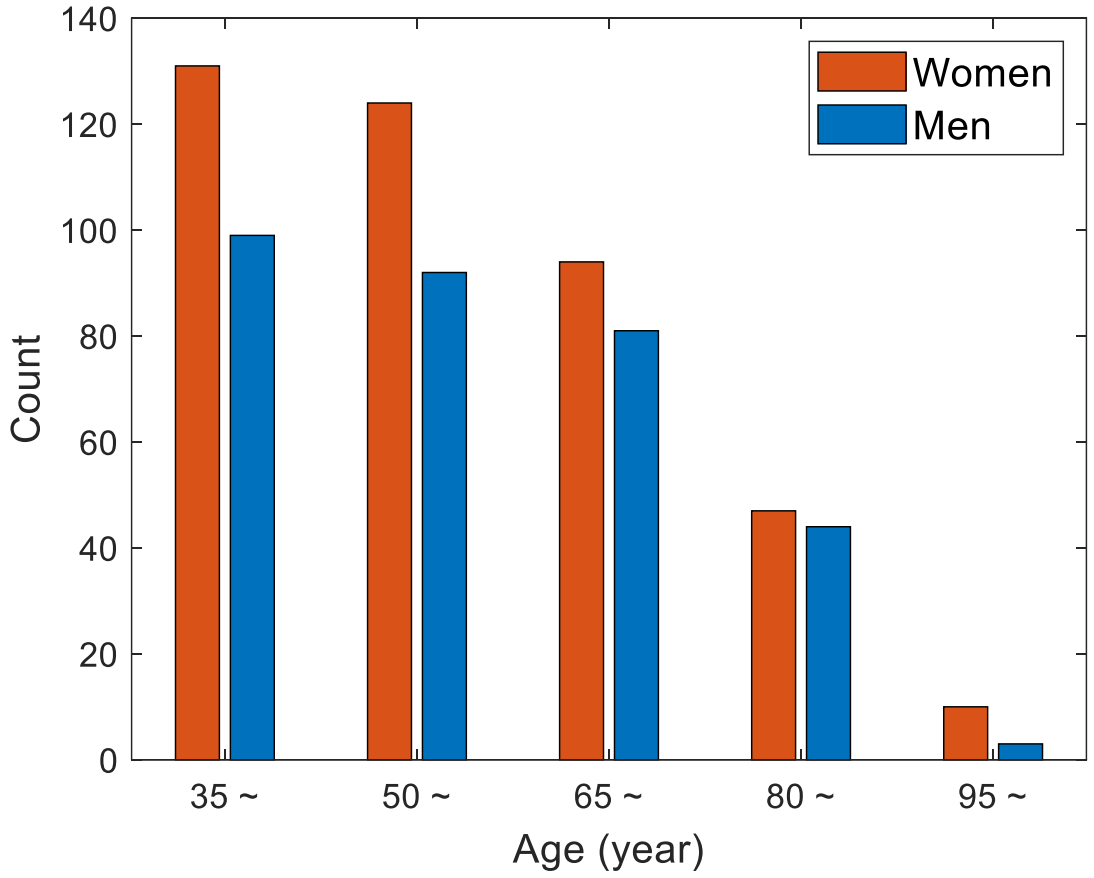


[Cole et al., 2017]

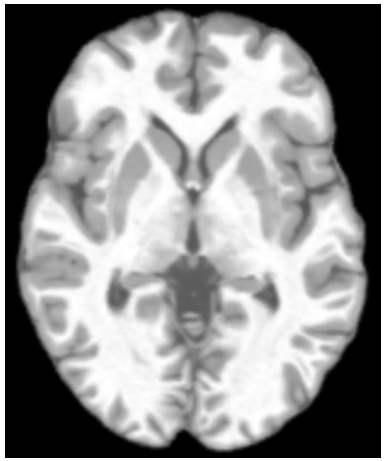
Larger proportion of survival in individuals with lower BAG than those with higher BAG

- Brain age estimation
  - Critical for the use of brain age as a biomarker of ageing
  - Based on a normative model that describes population-level trajectories of the relationship between brain structure and age

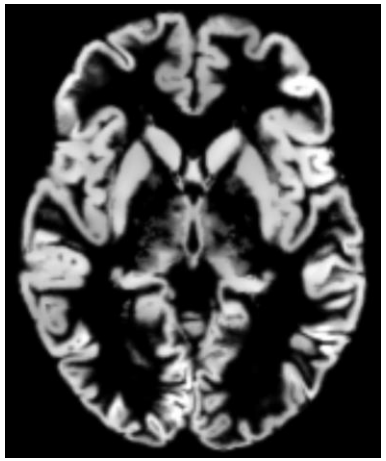
- Dataset: HCP Aging (HCP-A) dataset (n = 725)



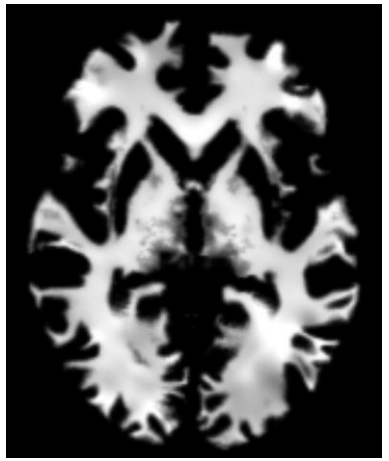
- Training dataset: n = 650
  - Preprocessed images of T1-weighted MRI scans
    - Brain/grey matter probability/white matter probability images
  - Individuals' ages
- Test dataset: n = 75
  - Preprocessed images of T1-weighted MRI scans
    - Brain/grey matter probability/white matter probability images
  - Individuals' hidden ages
- Brain age estimation performance
  - Mean absolute error (MAE)



Brain image



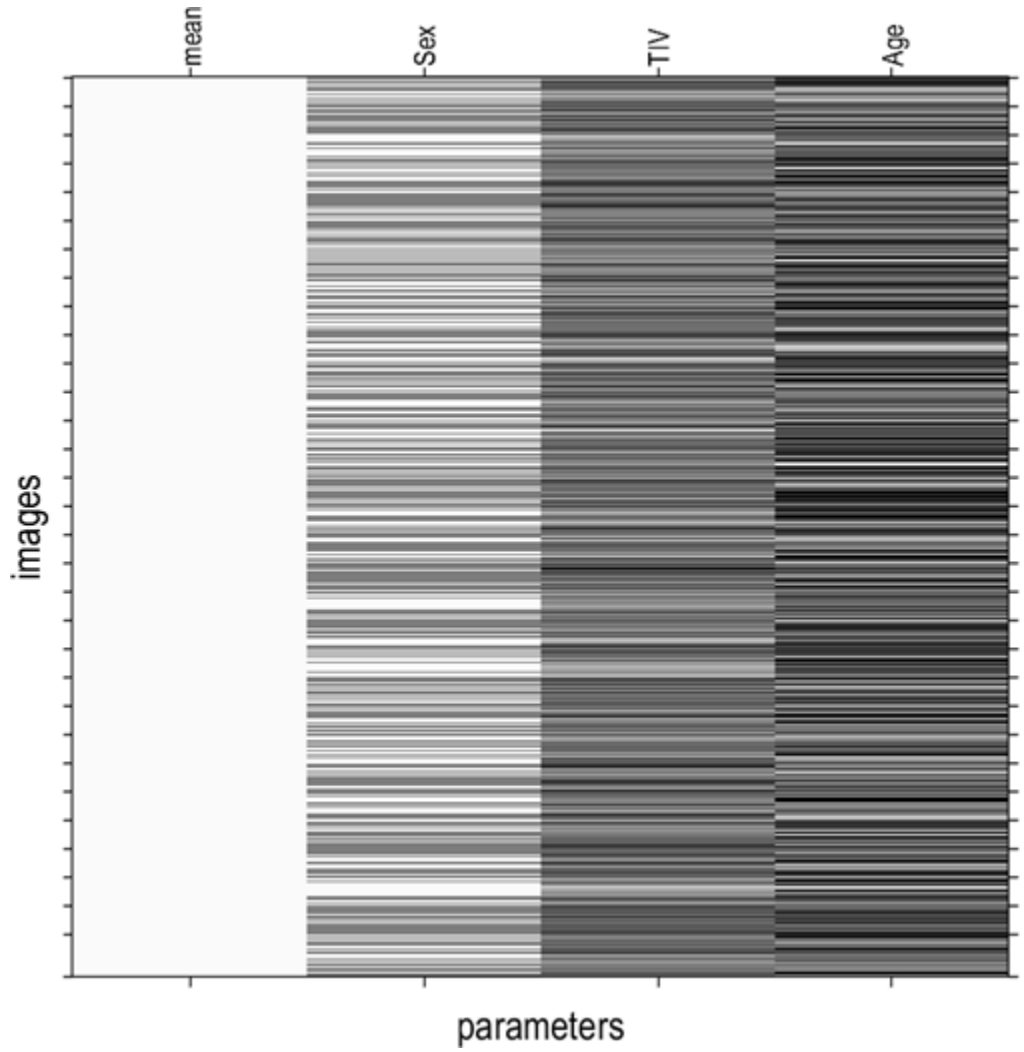
Grey matter
probability image



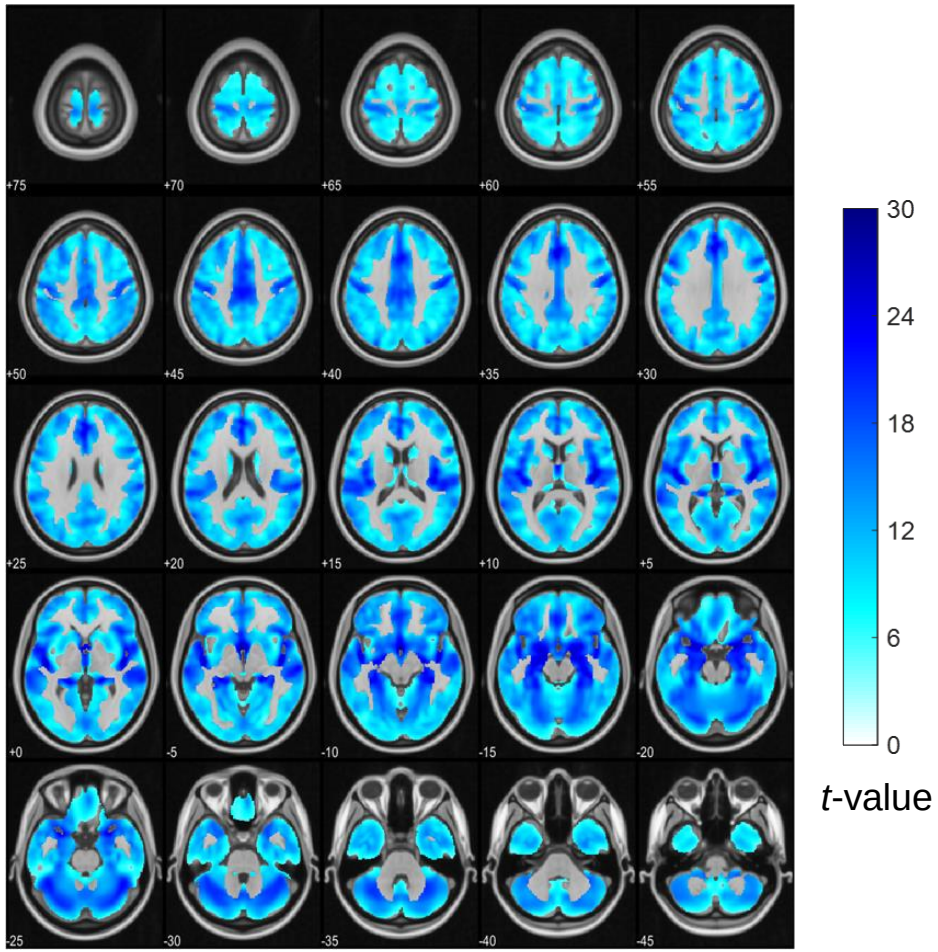
White matter
probability image

Input data for brain age estimation

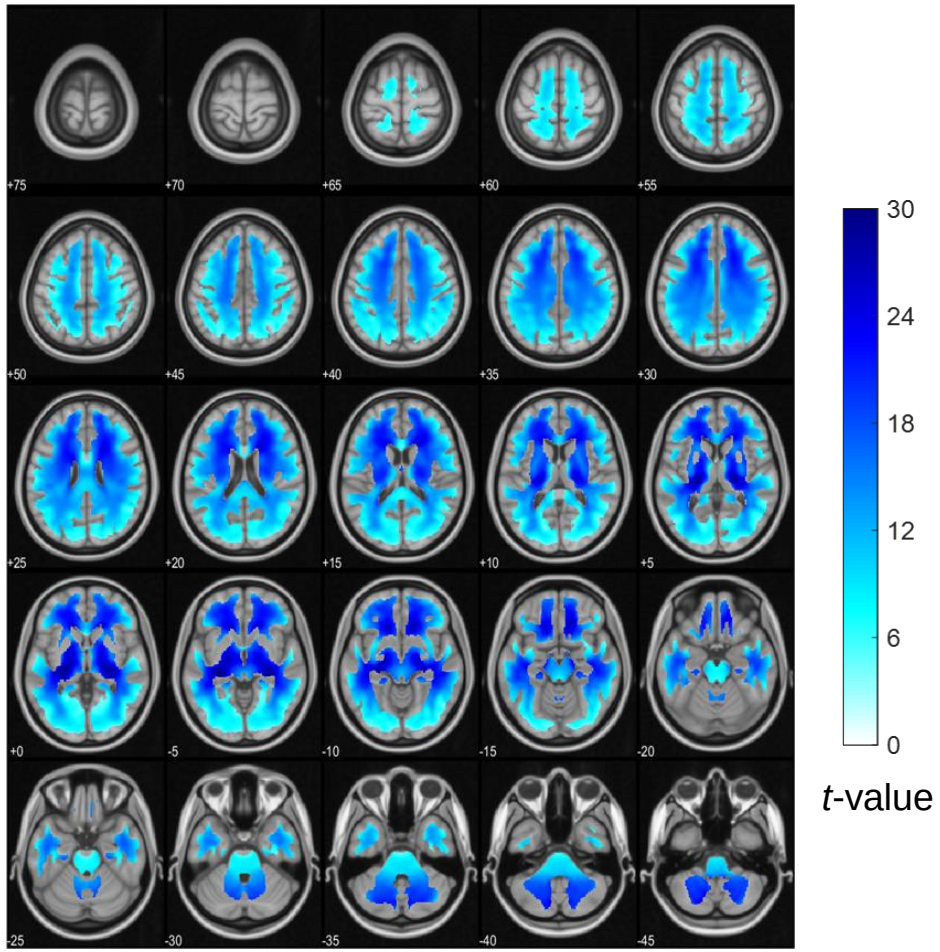
- Age correlation of grey matter/white matter volume



Negative correlation with age



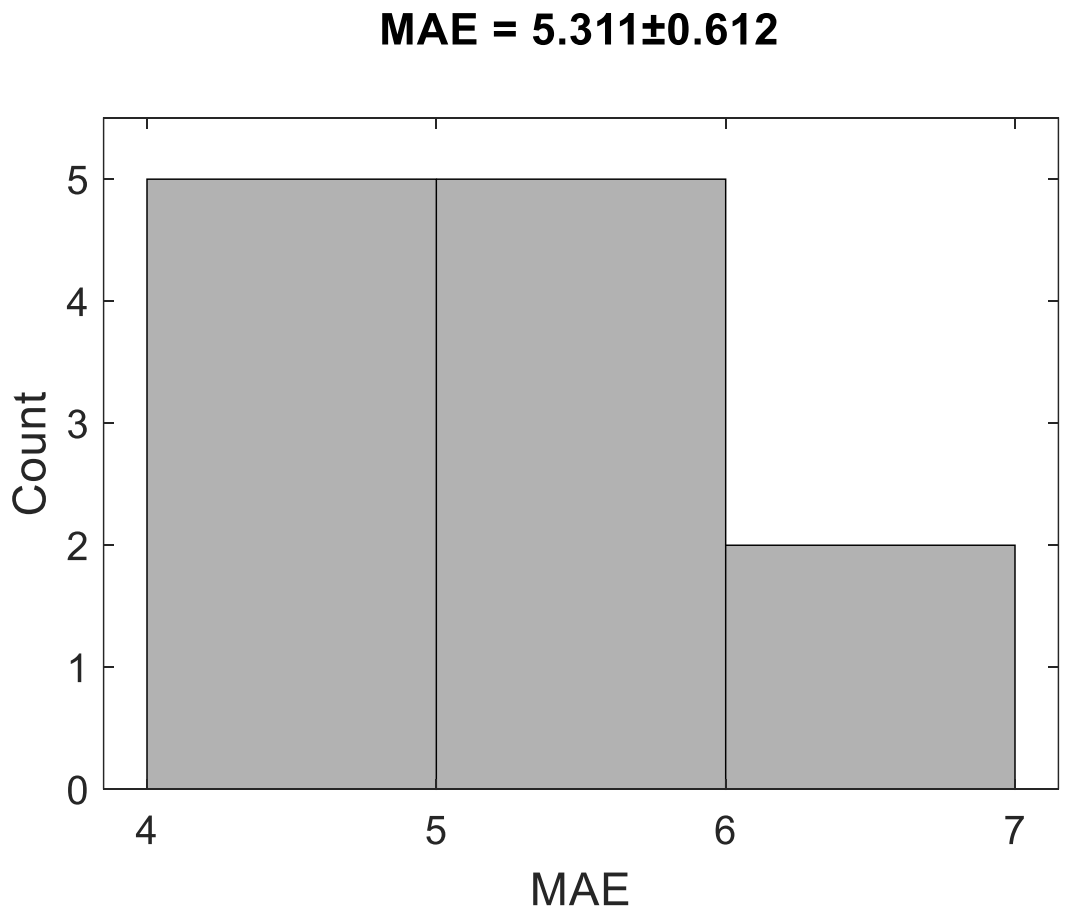
Grey matter volume

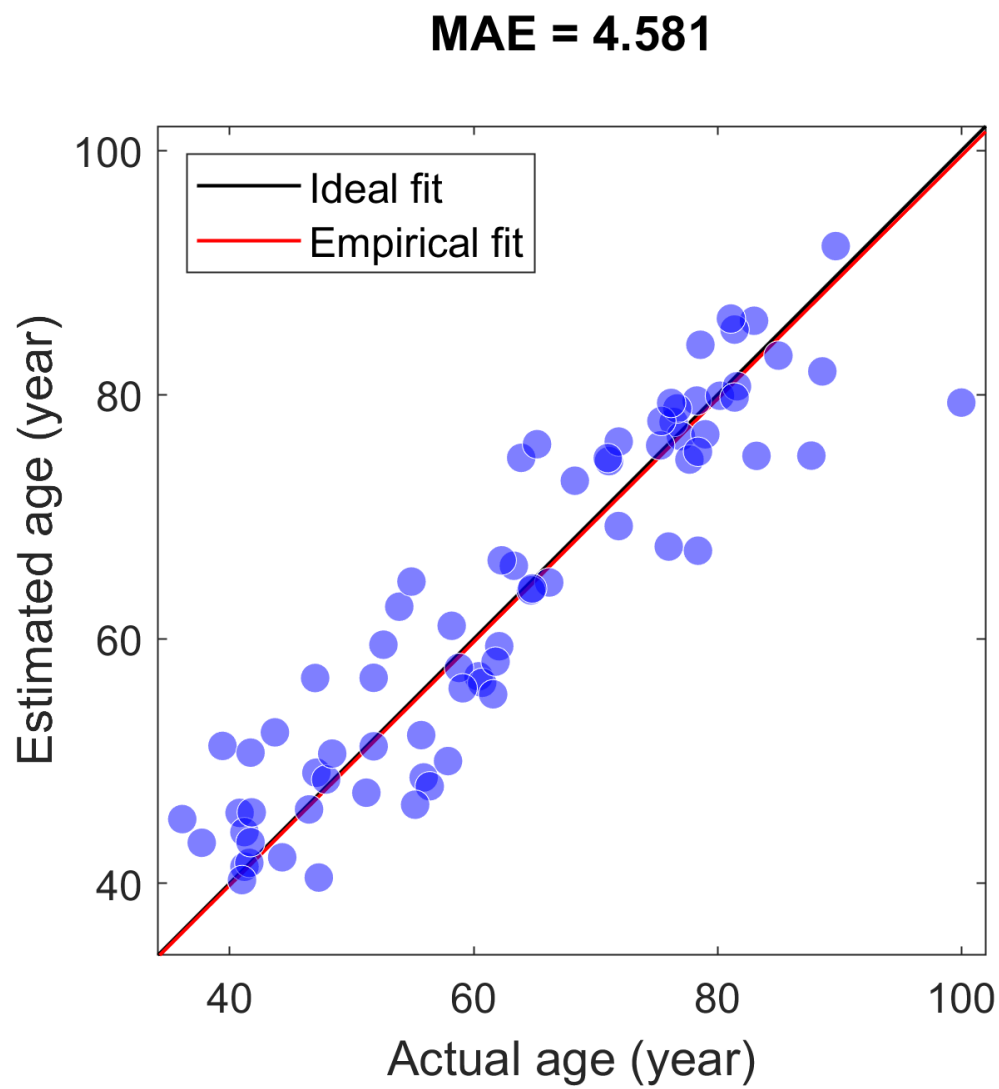


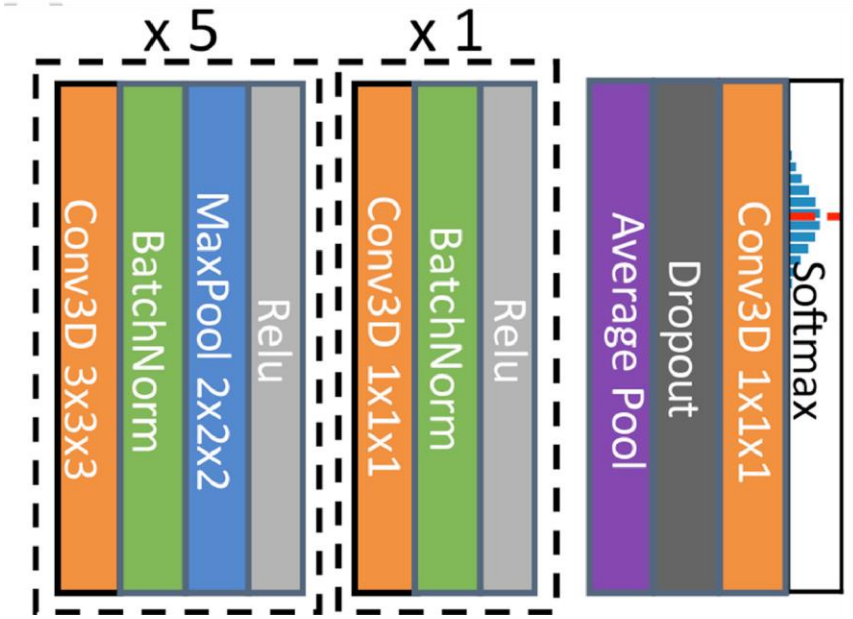
White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and FWE corrected $p = 0.05$ at the voxel level

- Deep learning-based brain age estimation
  - Performance of brain age estimation for the test dataset




MAE = 4.581
Ideal fit
Empirical fit
Estimated age (year)
Actual age (year)
100
80
60
40
40
60
80
100

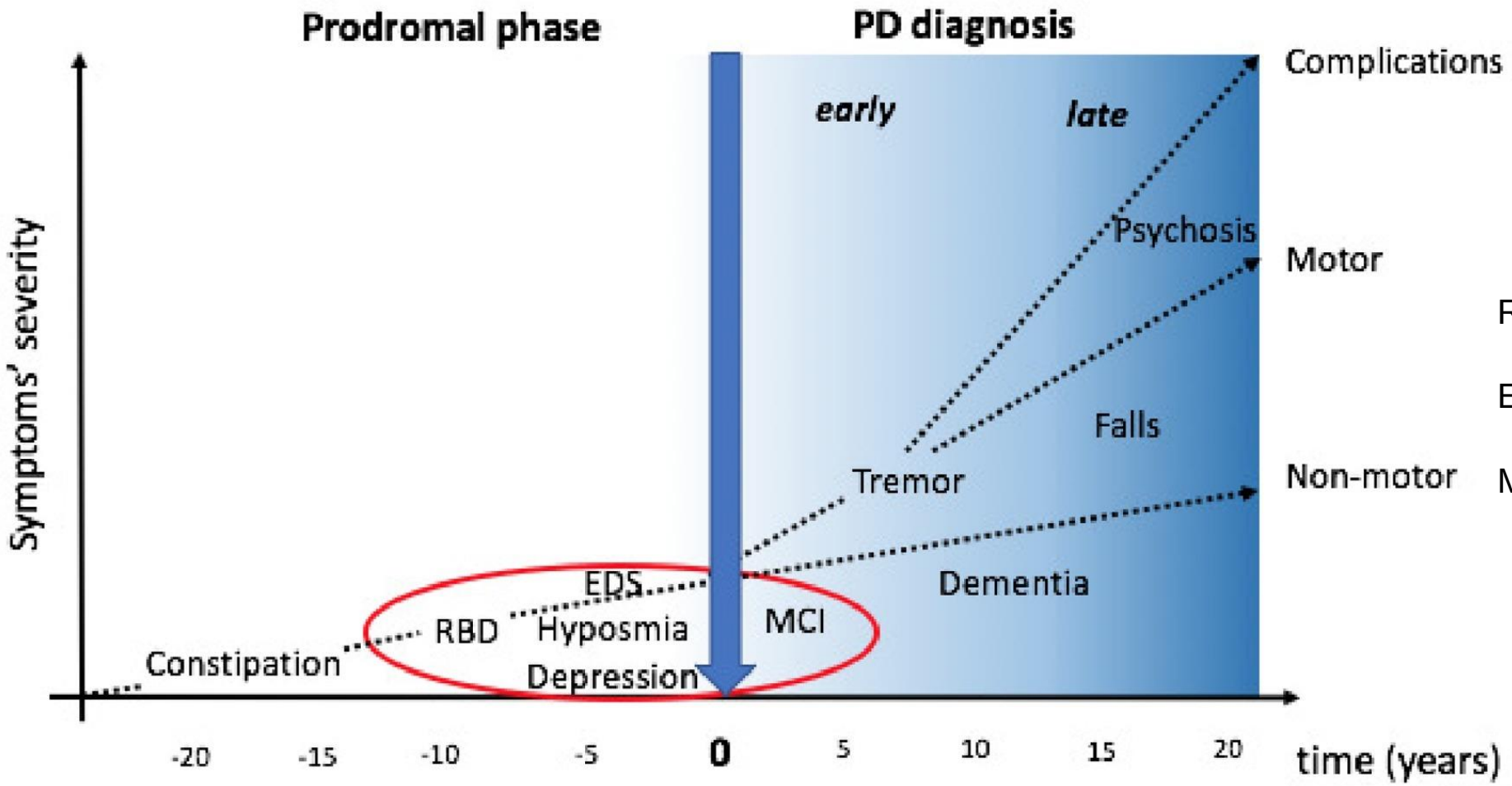


[Peng et al., 2021]

Simple fully convolutional network (SFCN)

[Database 4] Parkinson's Progression Markers Initiative (PPMI)

- https://www.ppmi-info.org/
- Parkinson's disease
  - Neurodegenerative disease
  - Involves the aggregation of α-synuclein proteins into Lewy bodies
  - Most recognizable by motor symptoms
- Prodromal Parkinson's disease
  - Prodromal phase of Parkinson’s disease
  - Disease course modifying treatment may be given proactively



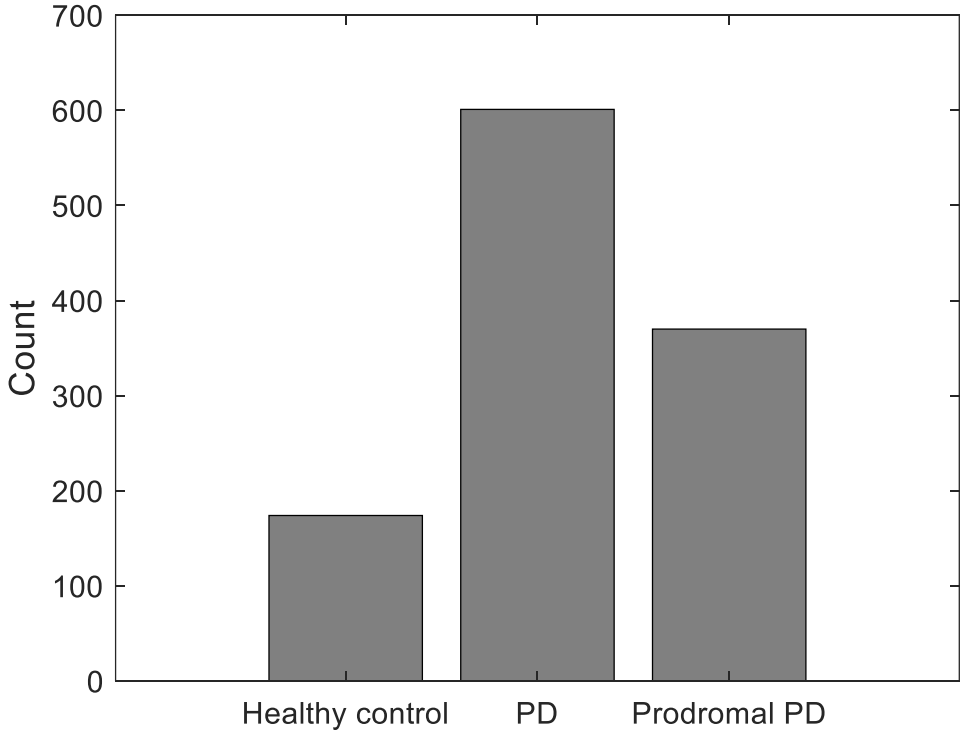
RBD, rapid eye movement sleep behaviour disorder
EDS, excessive daytime sleepiness
MCI, mild cognitive impairment

[Amoroso et al., 2018]

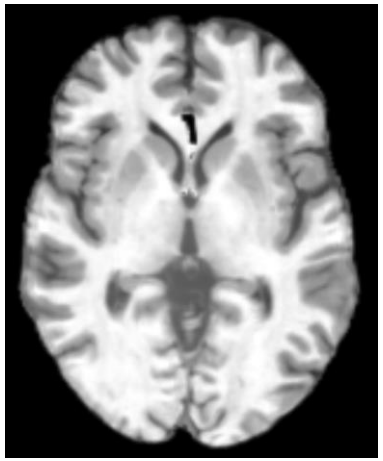
Symptoms characterizing prodromal Parkinson's disease

- Brain disease diagnosis
  - Critical for providing optimal and personalized care
    - Development of an appropriate and effective treatment plan, while avoiding unnecessary or inappropriate treatments
    - Accurate prognosis
    - Prevention of the progression of the disease
  - For Parkinson's disease, diagnosis made by a neurologist or movement disorder specialist based on a combination of clinical evaluation, medical history, and certain criteria remains the gold standard

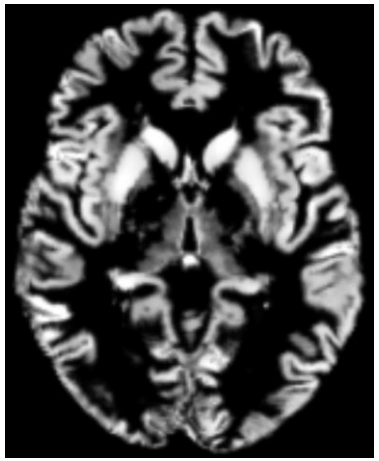
- Dataset: PPMI baseline dataset (*n* = 1,145)
  - HealthyControl (healthy individuals): *n* = 174
  - PD (individuals with Parkinson's disease): *n* = 601
  - ProdromalPD (individuals with prodromal Parkinson's disease): *n* = 370



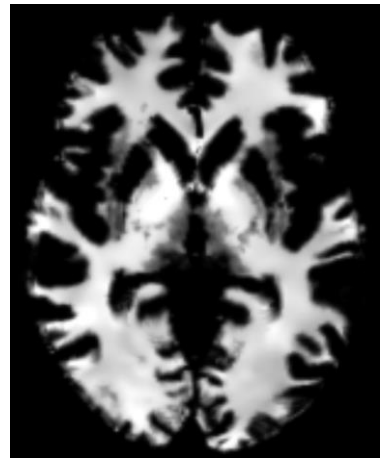
- Training dataset: *n* = 1,030
  - Preprocessed images of T1-weighted MRI scans
    - Brain/grey matter probability/white matter probability images
  - Individuals' class labels
- Test dataset: *n* = 115
  - Preprocessed images of T1-weighted MRI scans
    - Brain/grey matter probability/white matter probability images
  - Individuals' hidden class labels
- Brain disease diagnosis performance
  - Accuracy



Brain image



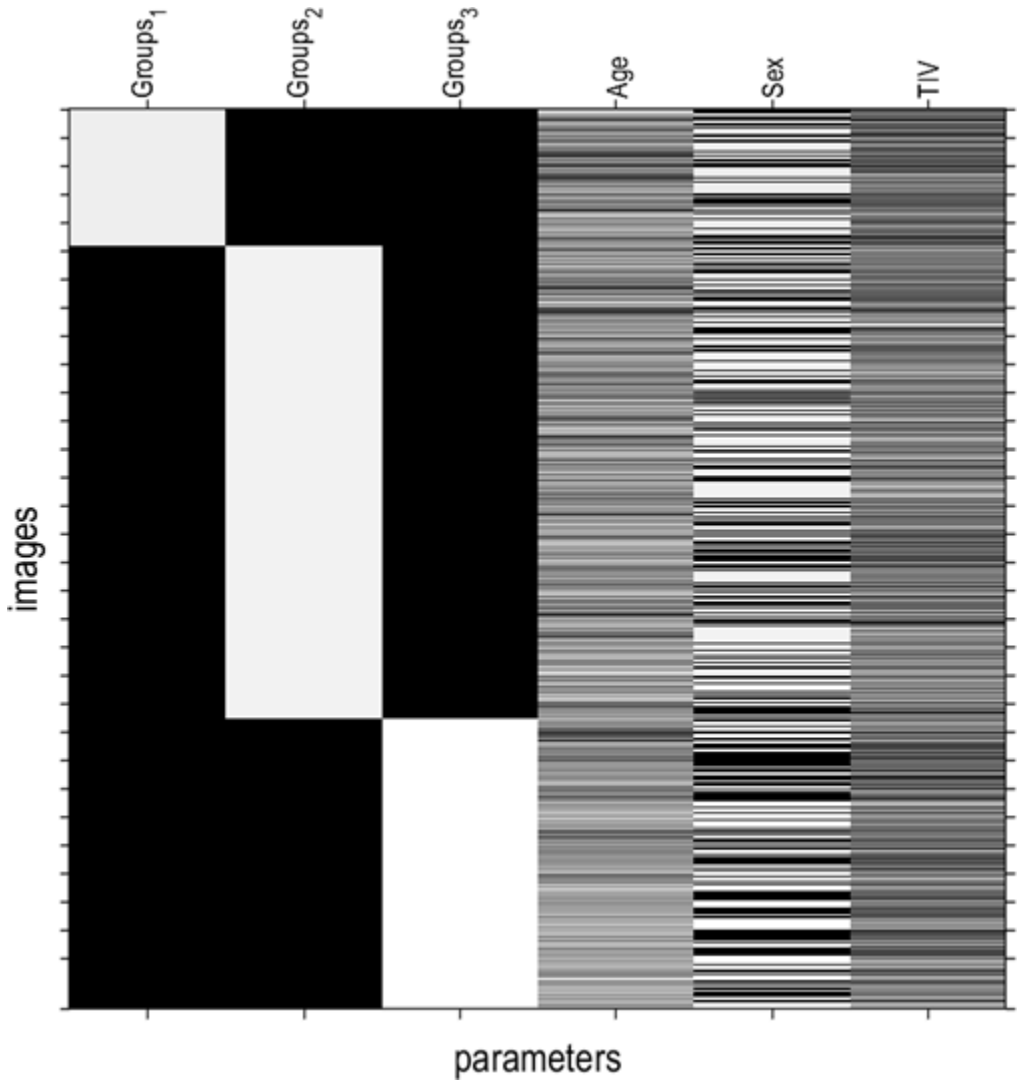
Grey matter
probability image



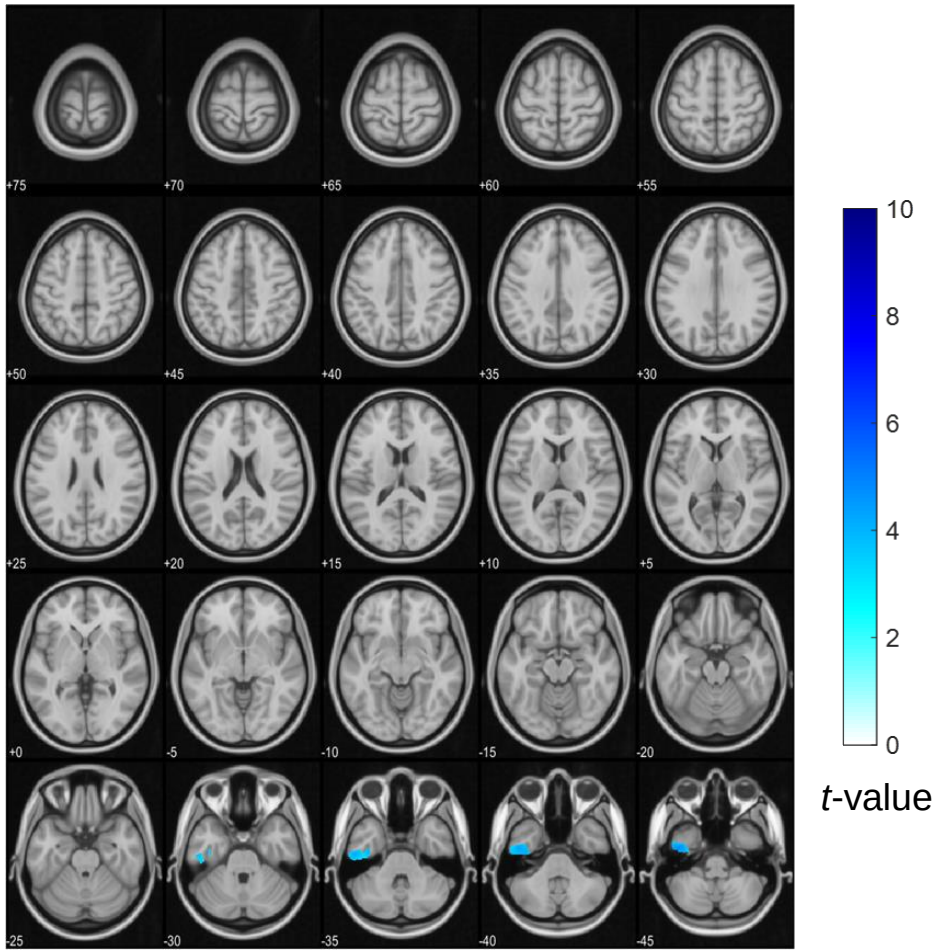
White matter
probability image

Input data for brain disease diagnosis

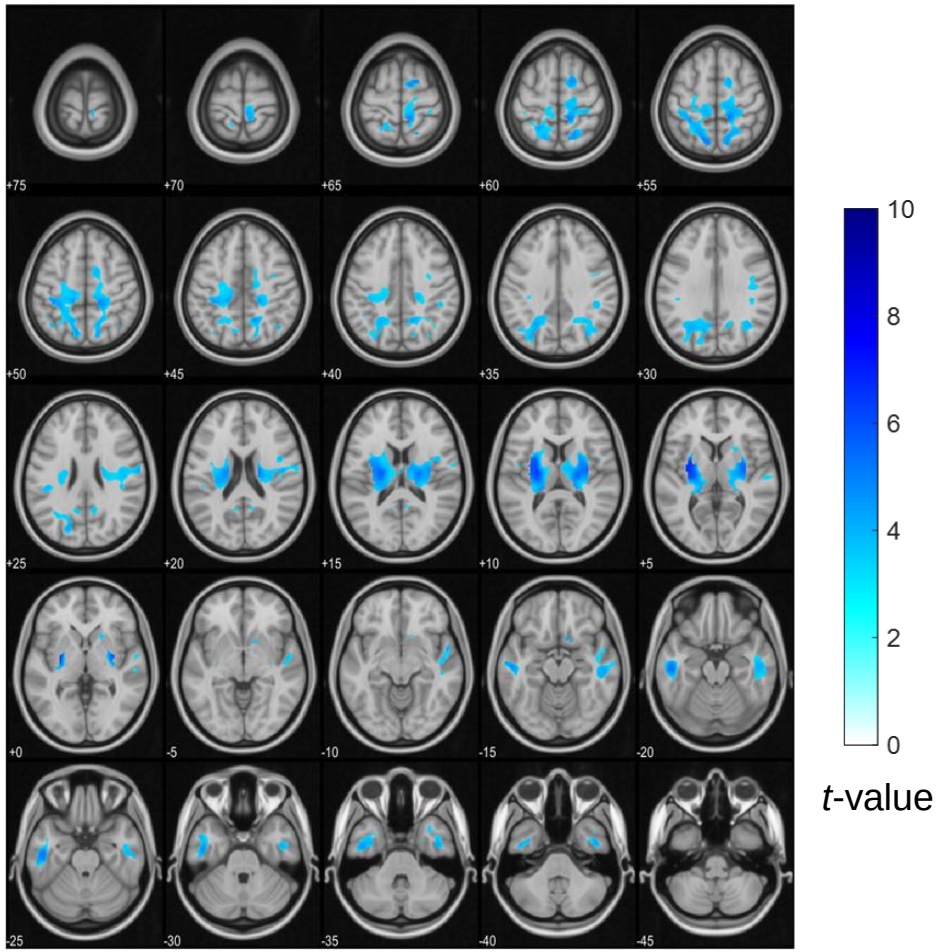
- Group comparison of grey matter/white matter volume



Healthy control > PD



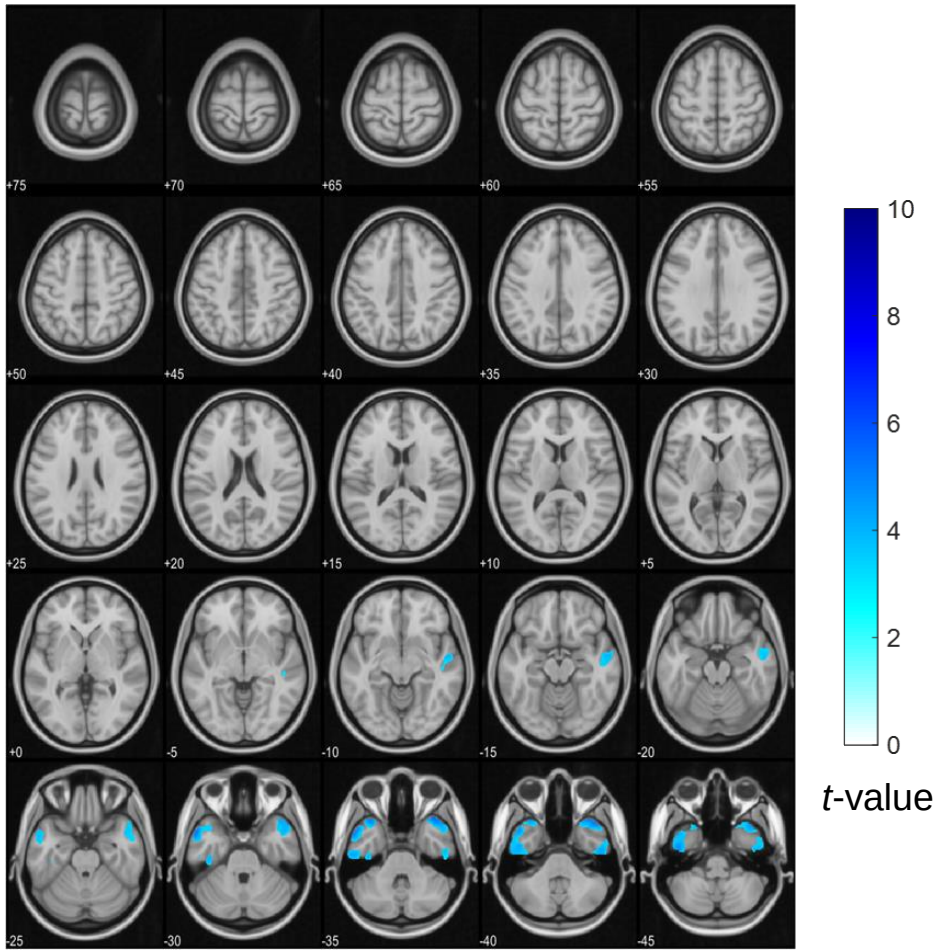
Grey matter volume



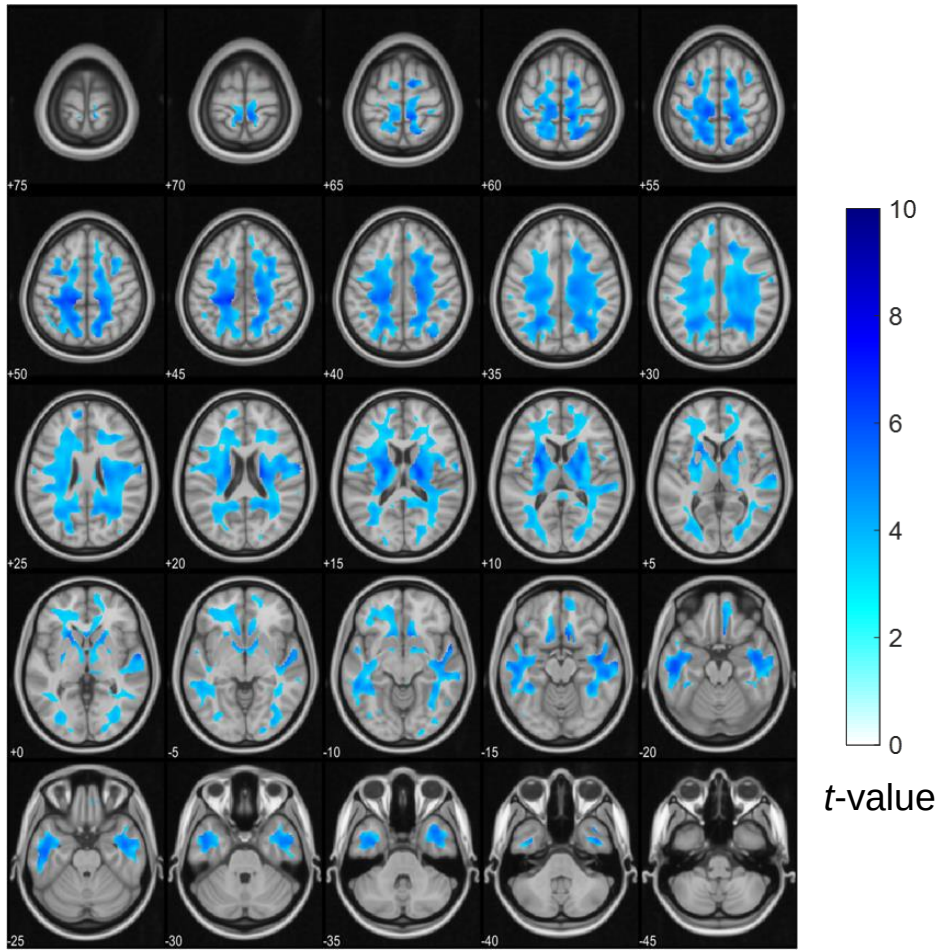
White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and uncorrected $p = 0.001$ at the voxel level

Healthy control > Prodromal PD



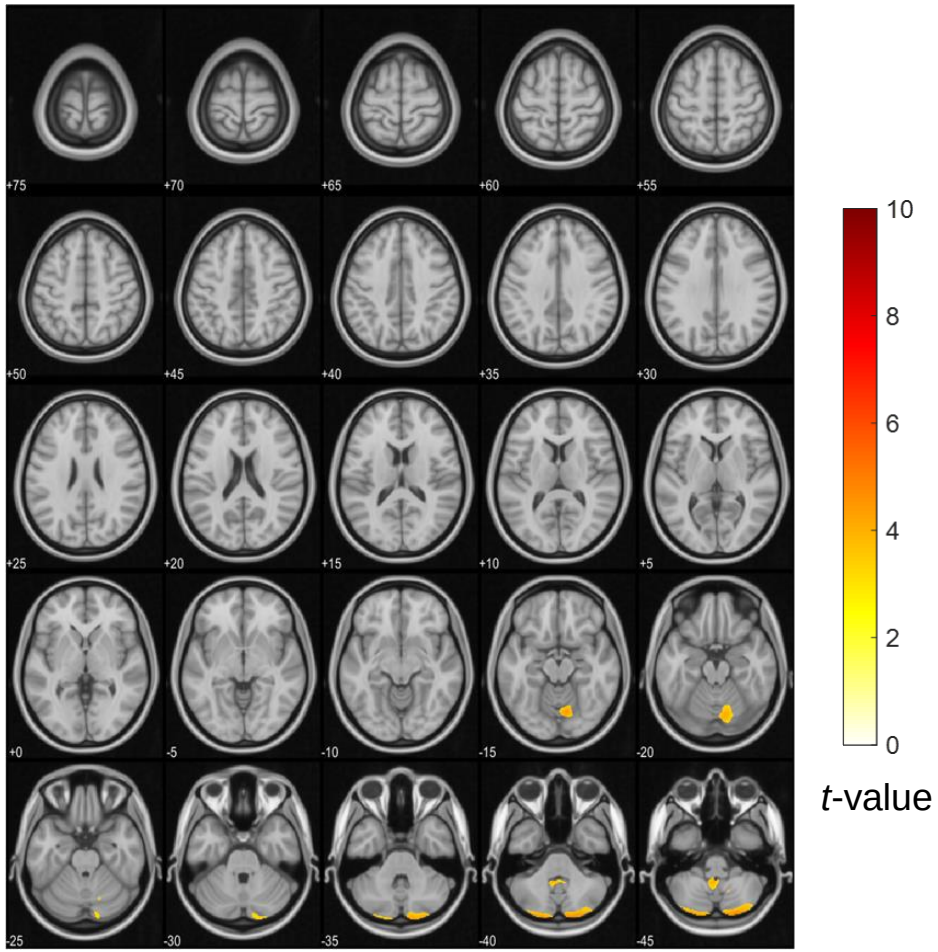
Grey matter volume



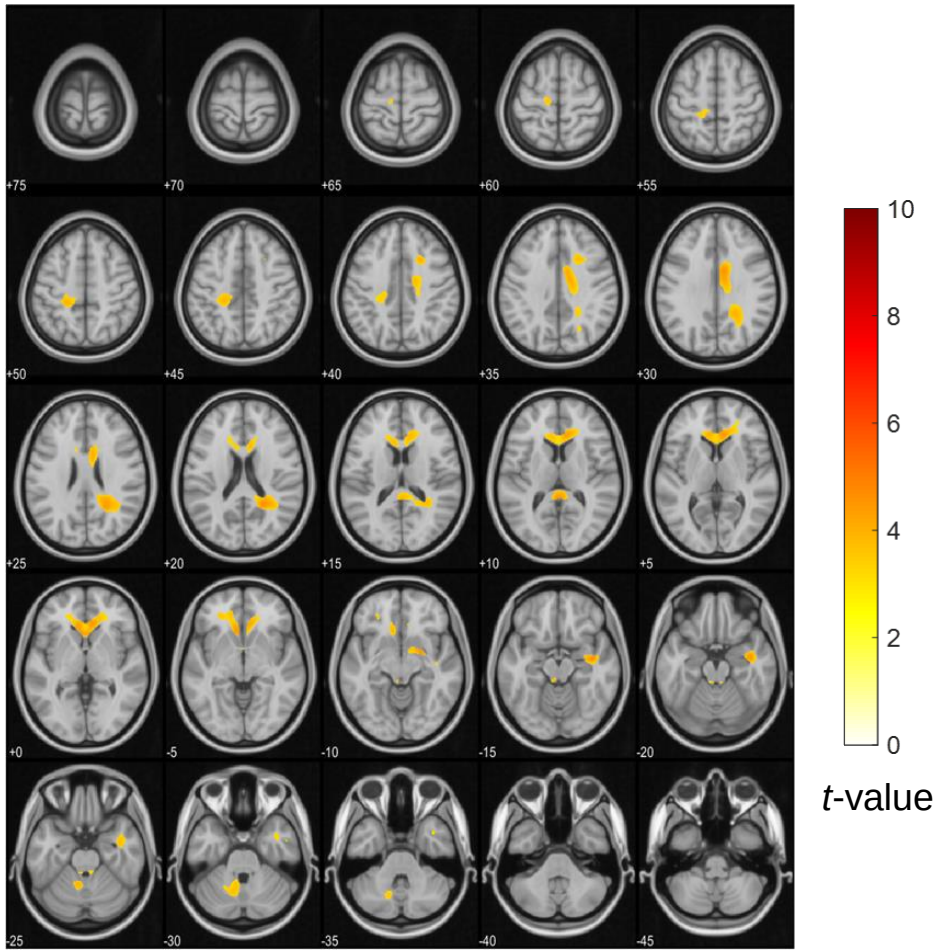
White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and uncorrected $p = 0.001$ at the voxel level

PD > Prodromal PD



Grey matter volume

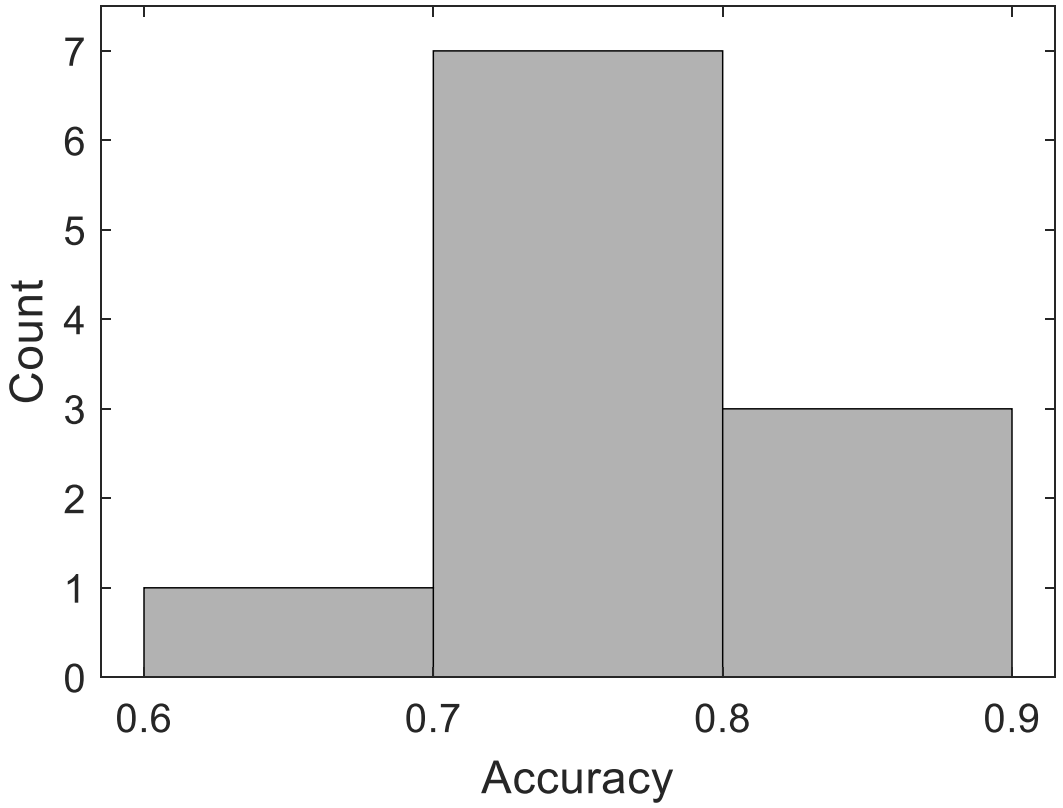


White matter volume

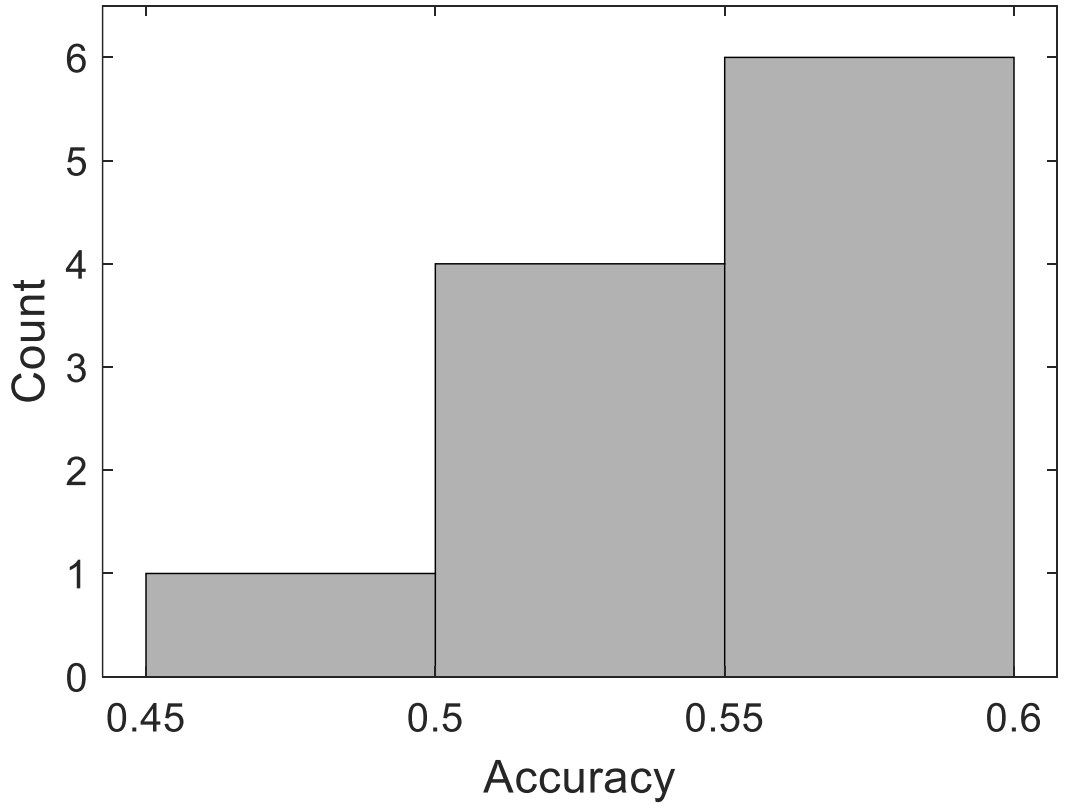
Thresholded at FDR corrected $p = 0.05$ at the cluster level and uncorrected $p = 0.001$ at the voxel level

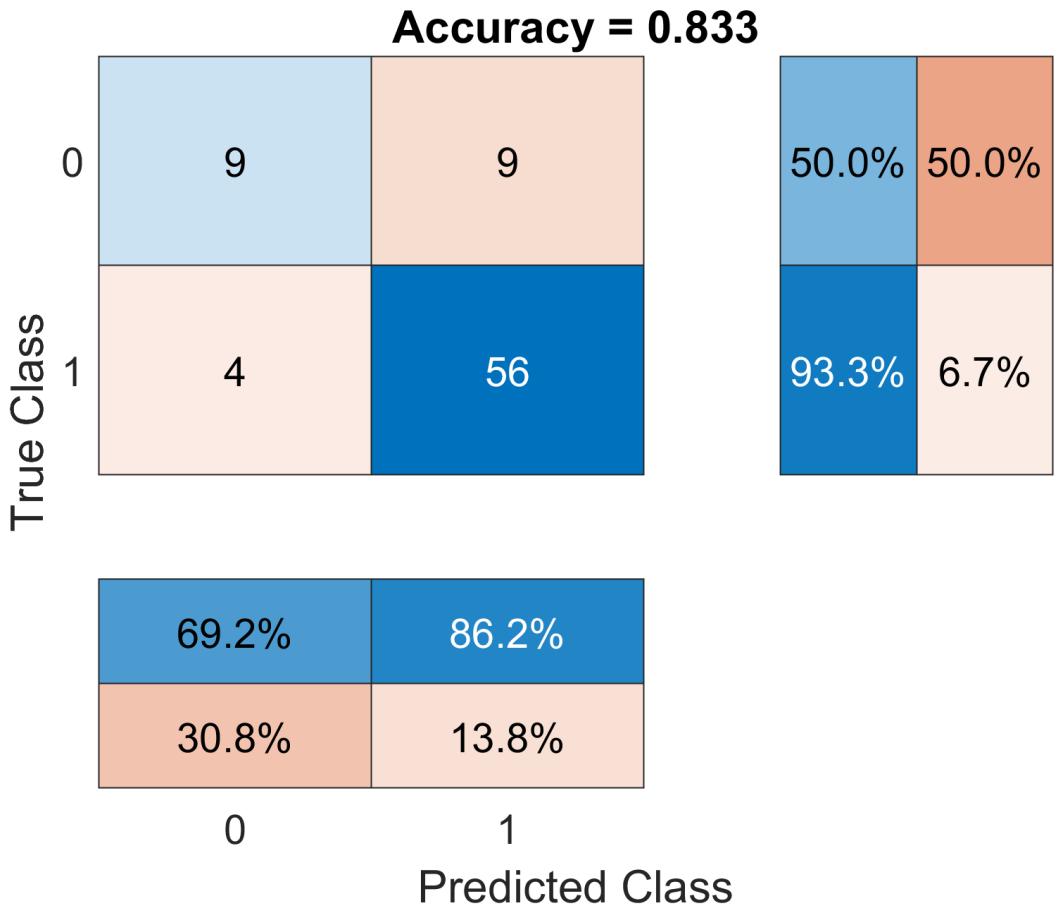
- Deep learning-based brain disease diagnosis
  - Performance of brain disease diagnosis for the test dataset

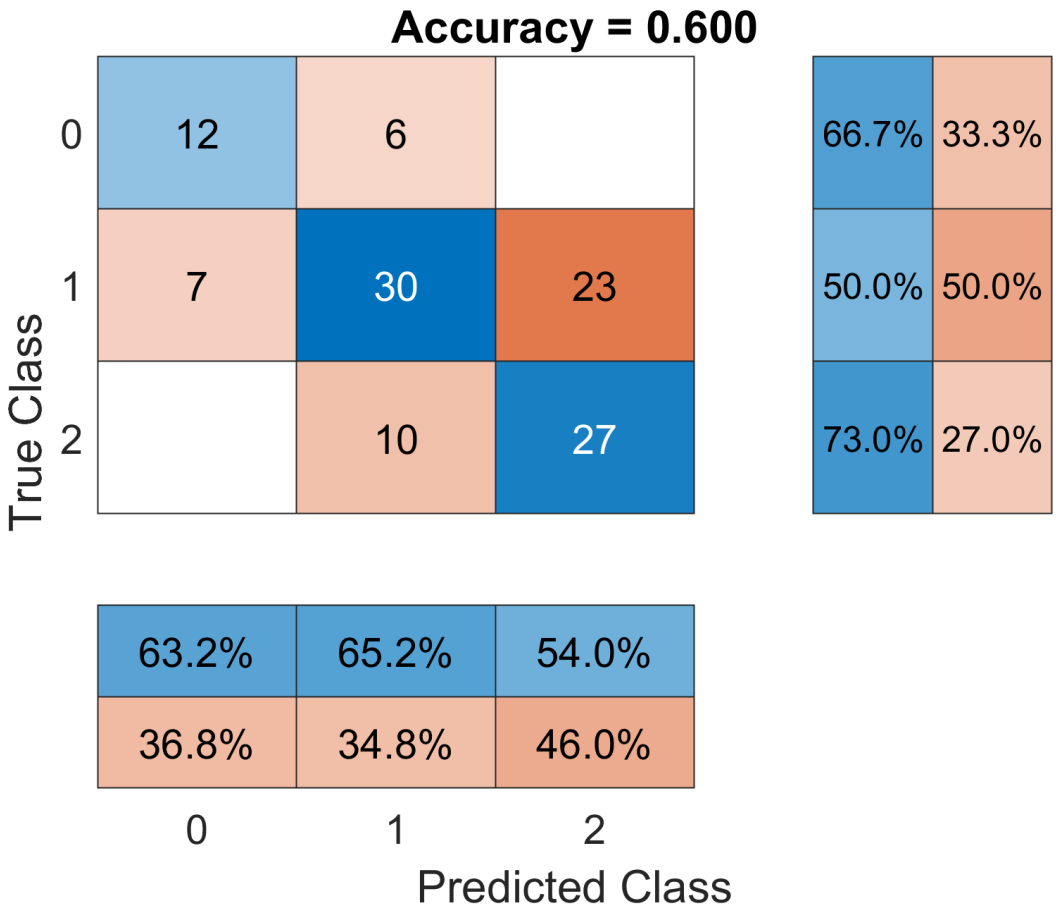
Two-class classification accuracy = 0.752±0.056

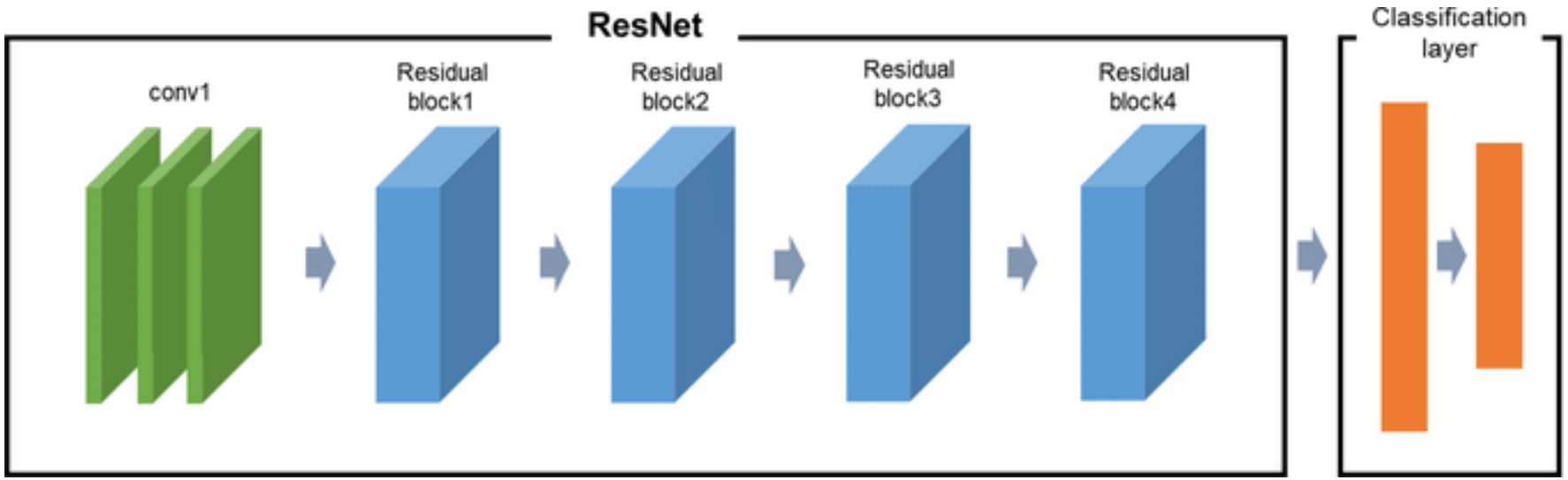


Multiclass classification accuracy = 0.555±0.029




Accuracy = 0.833
True Class
0
1
9
9
4
56
50.0%
50.0%
93.3%
6.7%
69.2%
86.2%
30.8%
13.8%
0
1
Predicted Class

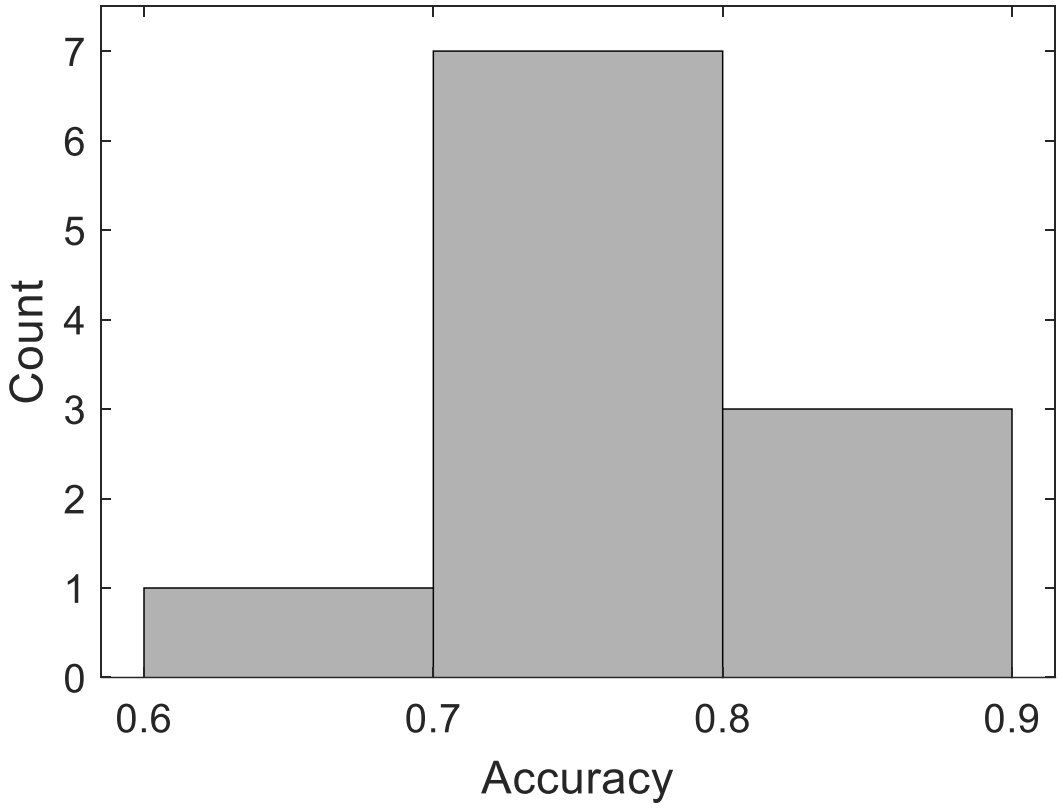

Accuracy = 0.600
True Class
0
1
2
12
6
7
30
23
10
27
66.7%
33.3%
50.0%
50.0%
73.0%
27.0%
63.2%
65.2%
54.0%
36.8%
34.8%
46.0%
0
1
2
Predicted Class



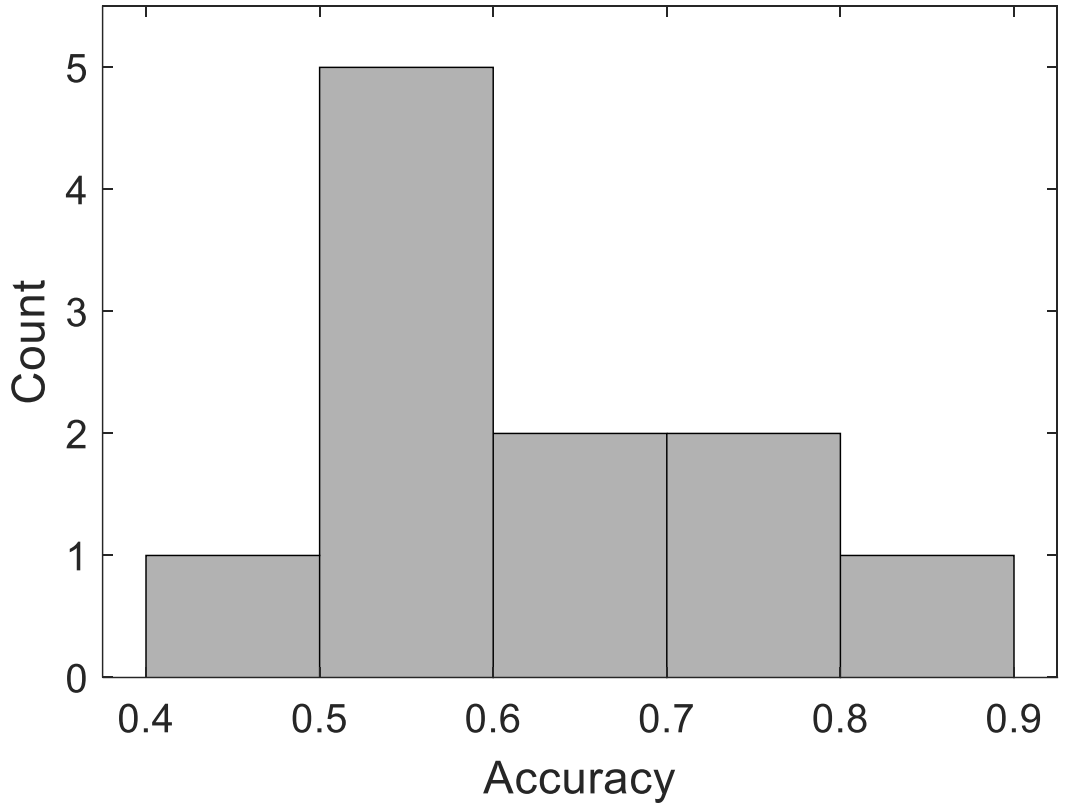
[Shin et al., 2021]

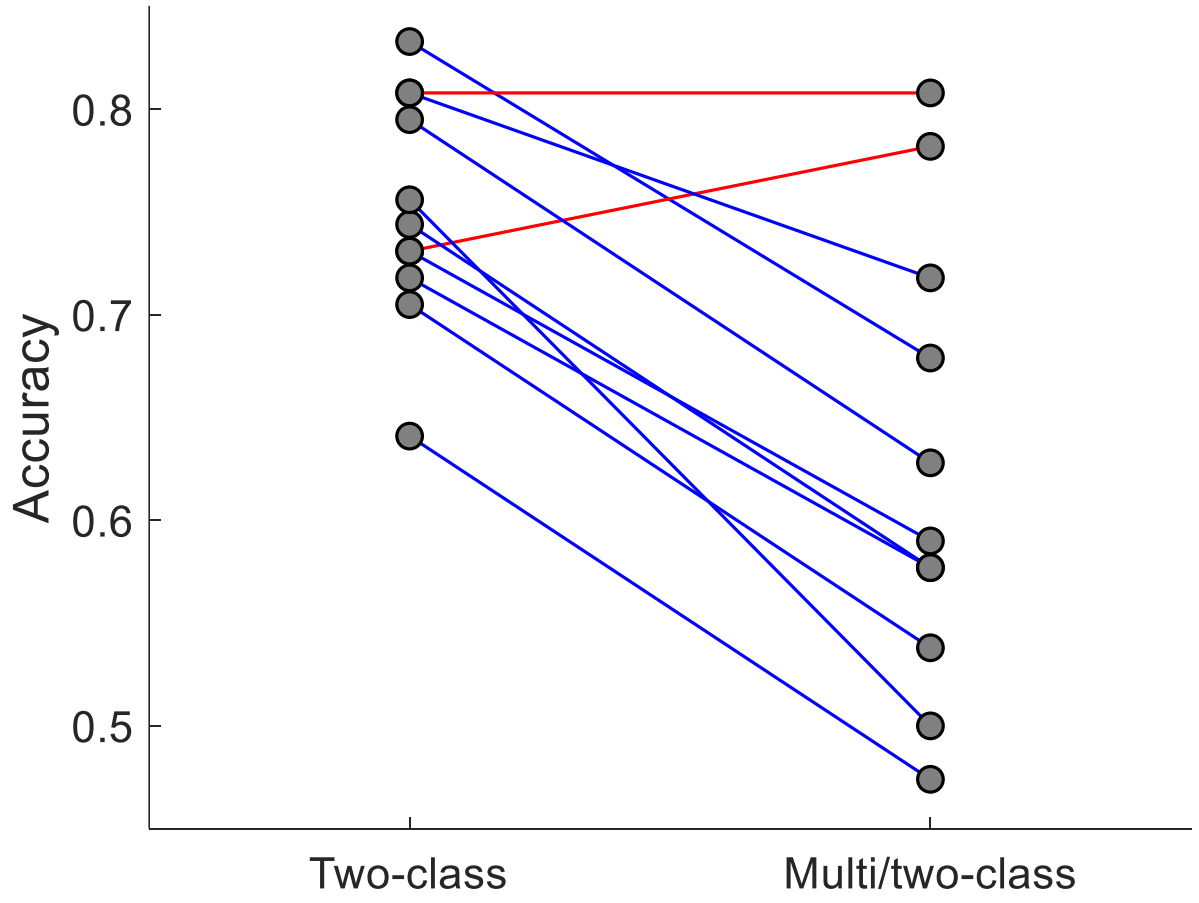
ResNet

Two-class classification accuracy = 0.752±0.056



Multi/two-class classification accuracy = 0.625±0.110




0.8
0.7
0.6
0.5
Accuracy
Two-class
Multi/two-class

ADNI
Alzheimer's Disease Neuroimaging Initiative

HUMAN Connectome PROJECT

Parkinson's Progression Markers Initiative