UNIVERSITÀ DI TORINO
Dipartimento Neuroscienze "Rita Levi Montalcini"

2023 - 2027
DIPARTIMENTO DI ECCELLENZA
Ministero dell'Università e della Ricerca

IronAD project

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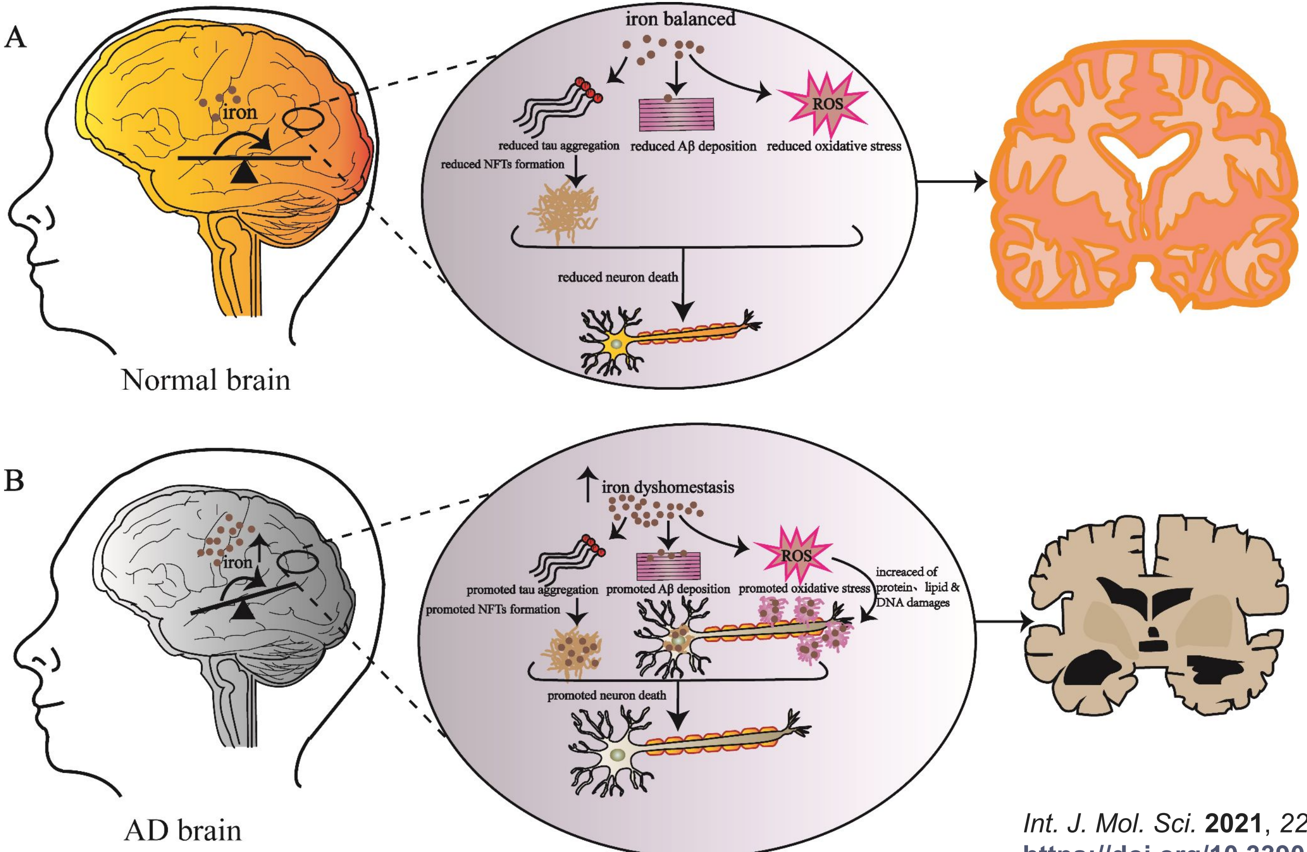
CN1-Spoke 8 – In silico Medicine & Omics data

WP8.2 Digital Twins & in-silico trials

Outline

- Background
- Aims
- Datasets
- Tools for Neuroimaging processing
- Preliminary results
- Goals to be achieved by the end of the project.

Background: iron homeostasis



Int. J. Mol. Sci. **2021**, *22*(22), 12442;
https://doi.org/10.3390/ijms222212442

Background: iron homeostasis

frontiers in Aging Neuroscience
REVIEW
published: 22 March 2022
doi: 10.3389/fnagi.2022.830569

Iron Dyshomeostasis and Ferroptosis: A New Alzheimer's Disease Hypothesis?

Feixue Wang[1,2], Jiandong Wang[1,2], Ying Shen[1,2], Hao Li[3], Wolf-Dieter Rausch[4] and Xiaobo Huang[1,2]*

NeuroImage 244 (2021) 118584
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/neuroimage

The effect of beta-amyloid and tau protein aggregations on magnetic susceptibility of anterior hippocampal laminae in Alzheimer's diseases

Text

Zhiyong Zhao[a], Lei Zhang[b,c], Qingqing Wen[a], Wanrong Luo[a], Weihao Zheng[a], Tingting Liu[a], Yi Zhang[a], Keqing Zhu[b,c,**], Dan Wu[a,*]

frontiers in Aging Neuroscience
ORIGINAL RESEARCH
published: 22 February 2021
doi: 10.3389/fnagi.2021.607858

Machine Learning Profiling of Alzheimer's Disease Patients Based on Current Cerebrospinal Fluid Markers and Iron Content in Biofluids

Eleonora Ficiarà[1], Silvia Boschi[1,2], Shoeb Ansari[1], Federico D'Agata[1], Ornella Abollino[3], Paola Caroppo[4], Giuseppe Di Fede[4], Antonio Indaco[4], Innocenzo Rainero[1] and Caterina Guiot[1]*

Iron homeostasis can be disturbed by:

- genetic factors
- environmental factors
- aging

iron metabolism diseases, including many neurodegenerative diseases such as **Alzheimer's disease (AD).**

Aims

1. *Evaluate the relationship between the presence/accumulation of iron and morphological abnormalities in healthy subjects and those with AD, in order to use this characteristic as a potential biomarker for the early diagnosis of AD.*
2. *Analysis of candidate genes of interest for AD.*

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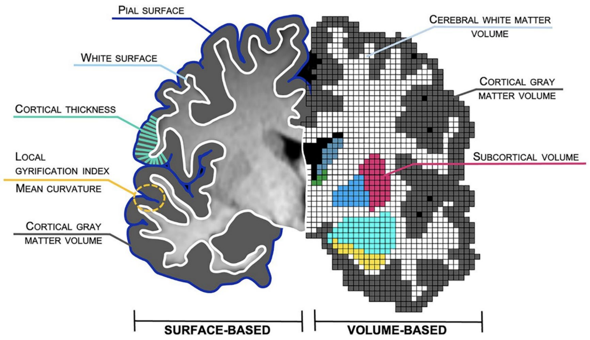
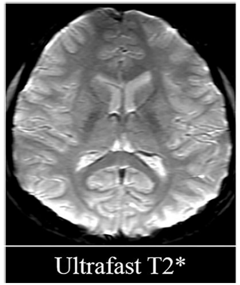
Methods

Atrophy assessed by VBM and SBM



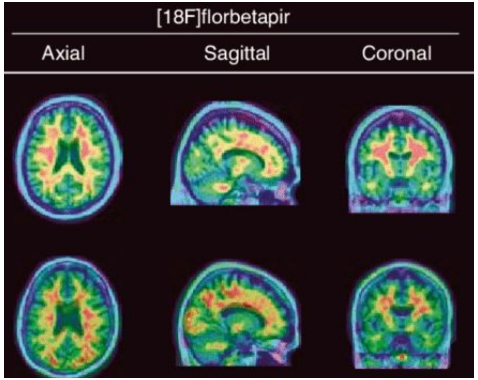
Backhausen, L.L., *Neuropsychol Rev* 32, 400–418 (2022). https://doi.org/10.1007/s11065-021-09496-2

Iron concentration assessed by T2* MRI



https://andreaforneris.com/web/protocollo-encefalo-standard-in-rm-in-un-minuto/

Metabolism analysis assessed by PET



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3468774/

Aims

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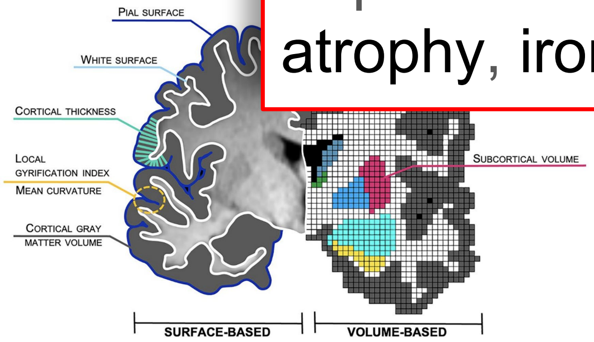
Methods

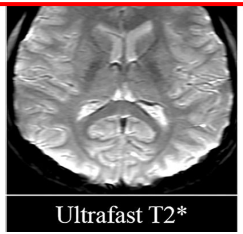
Atrophy assessed by
VBM a

Metabolism analysis
y PET

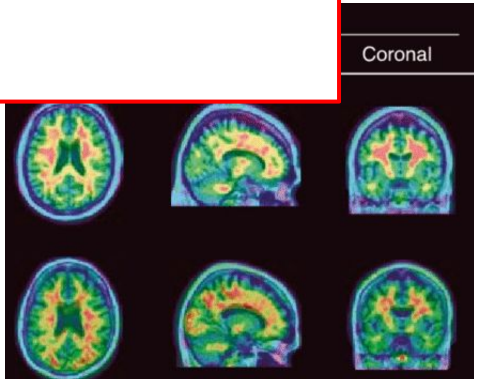
Expected results: overlapping patterns between atrophy, iron concentration and PET.



Backhausen, L.L., *Neuropsychol Rev* 32, 400–418 (2022). https://doi.org/10.1007/s11065-021-09496-2



https://andreaforneris.com/web/protocollo-encefalo-standard-in-rm-in-un-minuto/



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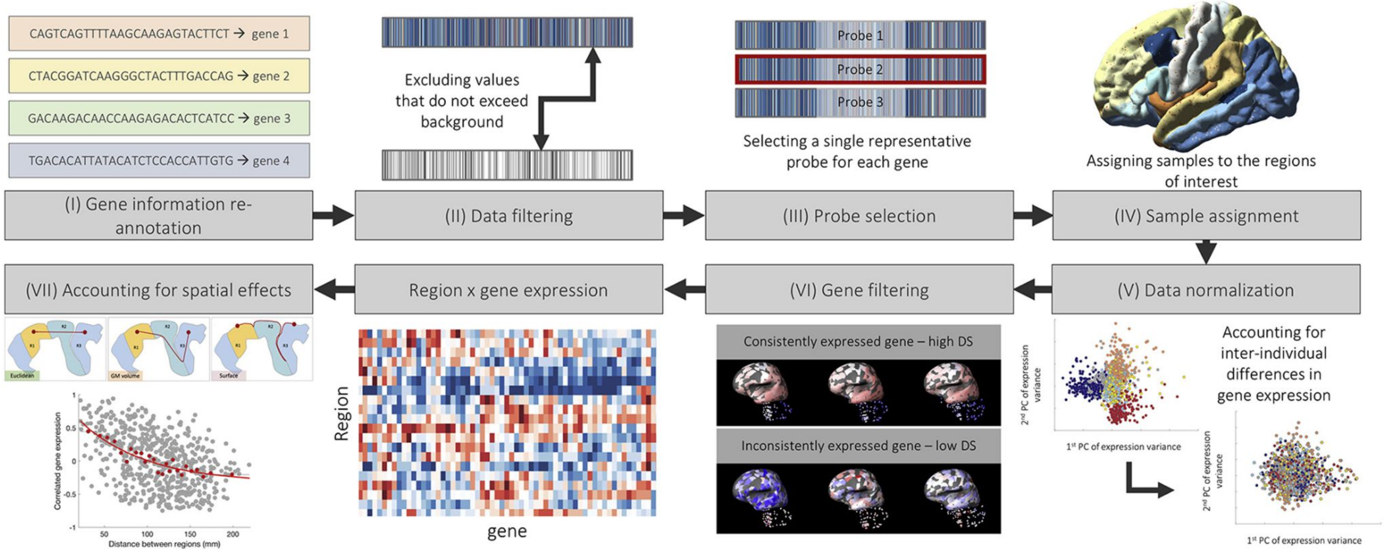


Aurina Arnatkevičiūtė, Ben D. Fulcher, Alex Fornito, A practical guide to linking brain-wide gene expression and neuroimaging data, NeuroImage, Volume 189, 2019

IMAGES DATASETS

ADNI
ALZHEIMER'S DISEASE
NEUROIMAGING INITIATIVE

6000 subjects

ADNI is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD).

https://adni.loni.usc.edu/

aibl

3045 subjects

The Australian Imaging, Biomarker and Lifestyle (**AIBL**) Flagship Study of Ageing is an ongoing observational cohort study helping researchers unlock new insights into the onset and progression of Alzheimer's disease.

https://aibl.org.au/

OASIS
OPEN ACCESS SERIES
OF IMAGING STUDIES

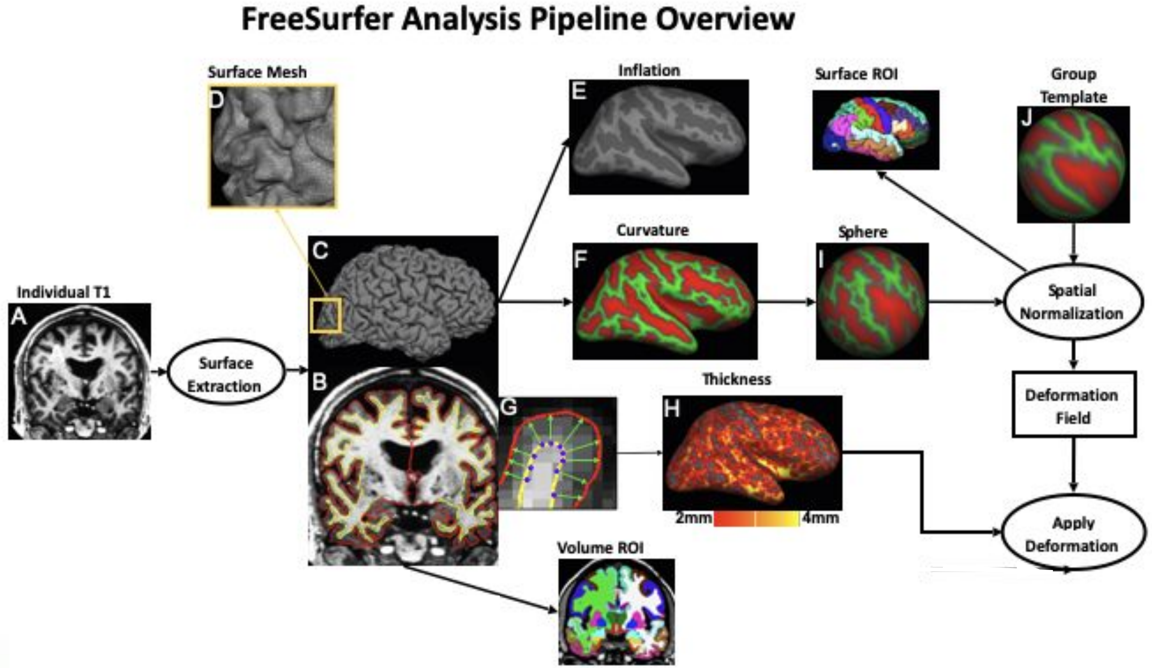
2600 subjects

OASIS-3 is a longitudinal multimodal neuroimaging, clinical, cognitive, and biomarker dataset for normal aging and Alzheimer's Disease.

https://www.oasis-brains.org/

TOOLS
Softwares

FreeSurfer



Freesurfer pipeline (T1w):

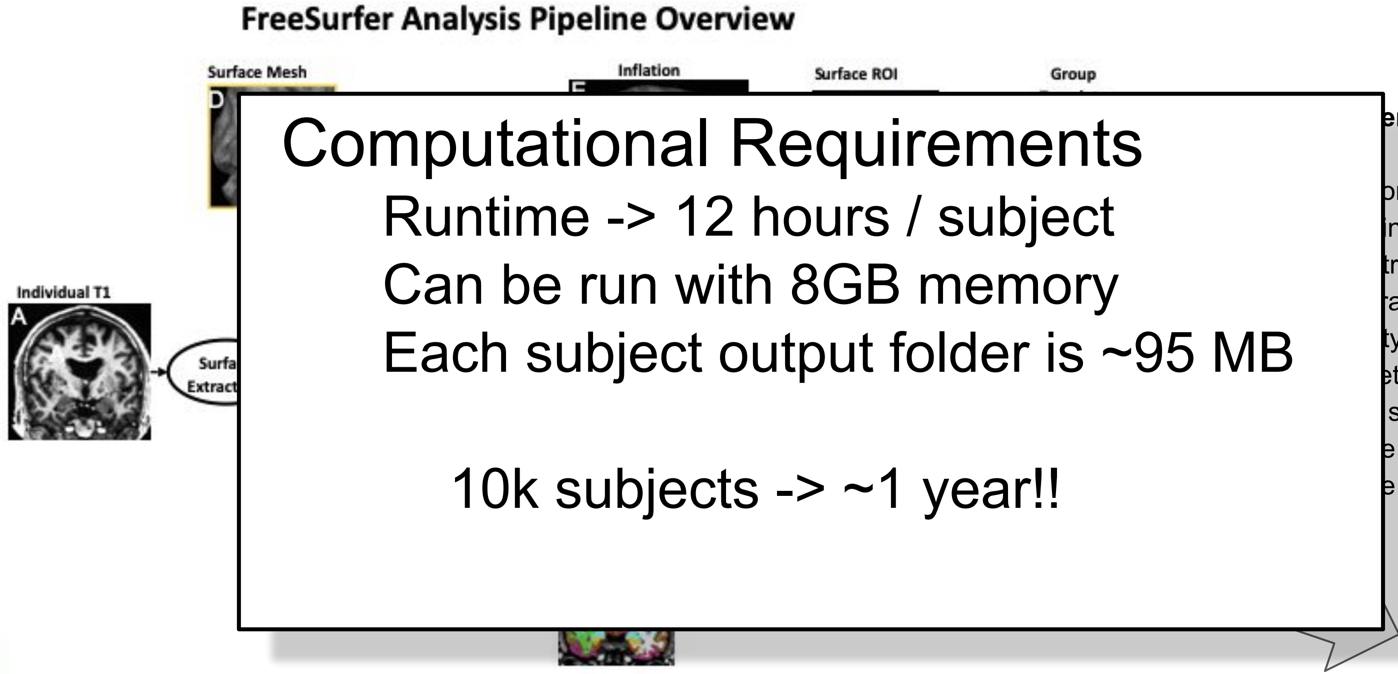
1. Data conversion from DICOM to Nii.gz
2. T1W1 input
3. Skull stripping
4. Registration (spatial normalization)
4. Intensity normalization
5. Volumetric labeling
6. Tissue segmentation
7. Surface atlas registration
8. Surface Extraction

Singularity container

https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview

TOOLS
Softwares

FreeSurfer



Computational Requirements

Runtime -> 12 hours / subject
Can be run with 8GB memory
Each subject output folder is ~95 MB

10k subjects -> ~1 year!!

er pipeline (T1w):

onversion from DICOM to Nii.gz
input
tripping
ration (spatial normalization)
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segmentation
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Singularity container

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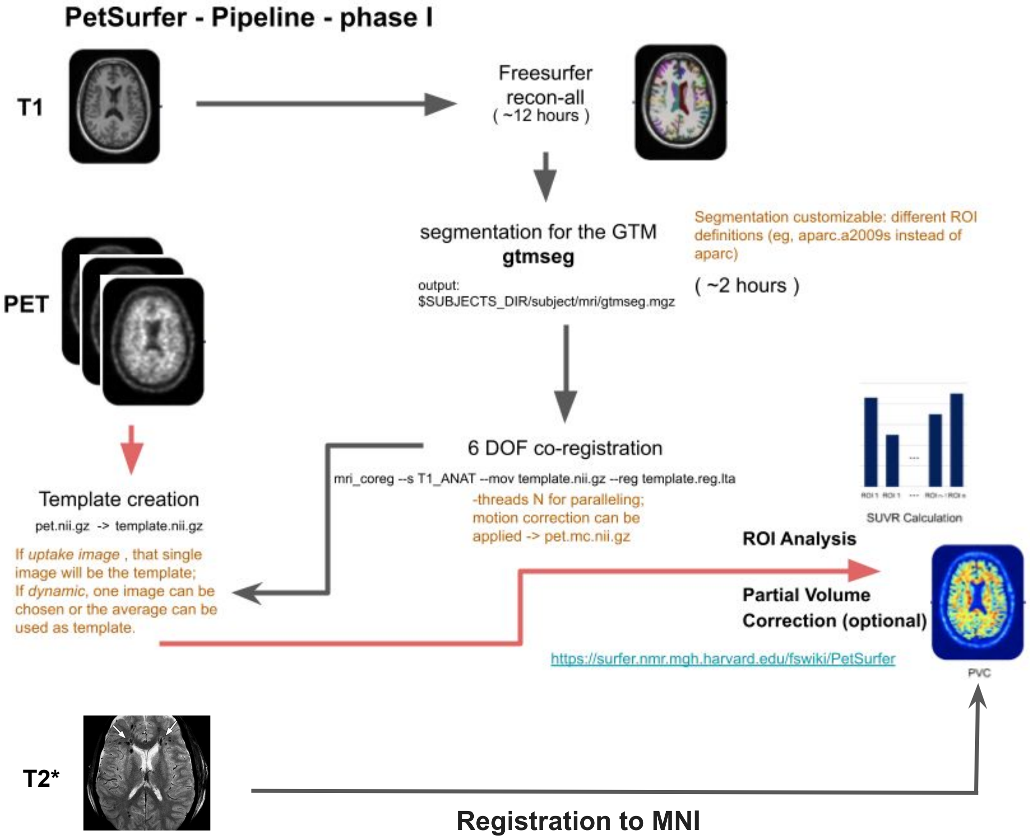


PetSurfer

1. Template creation
2. Partial volume correction
3. Motion correction across PET frames
4. Co-registration PET images with T1
5. Intensity normalization

Singularity container

PET and T2* pipeline: workflow showing the preprocessing steps for the PET data analysis, using the PetSurfer pipeline (https://surfer.nmr.mgh.harvard.edu/fswiki/PetSurfer). The output will be superimposed to the T2* maps to detect the iron deposition related to metabolic abnormalities.

PRELIMINARY RESULTS

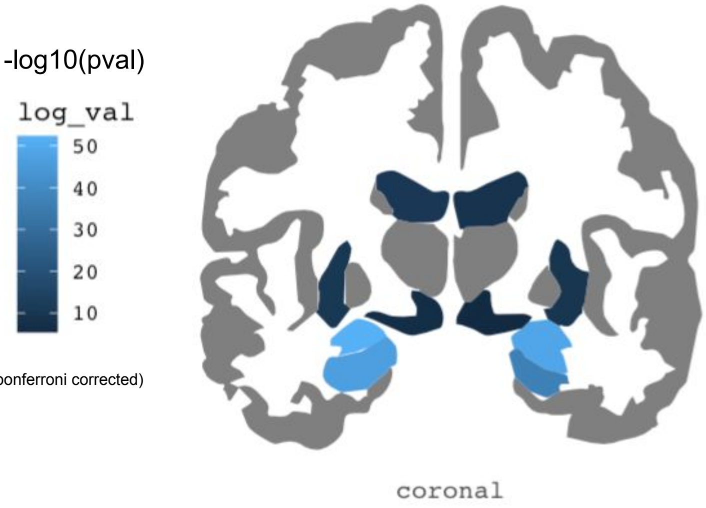
- 206 CN / 160 AD including T1w, T2* e β amiloide PET (AV45) from ADNI
- Building up T1 e PET pipeline
- Building up VM on Cloud CINECA
- Running the T1 pipeline using FreeSurfer on Cloud CINECA

ADNI: 160 AD, 206 CN

Volumes: AD < CN

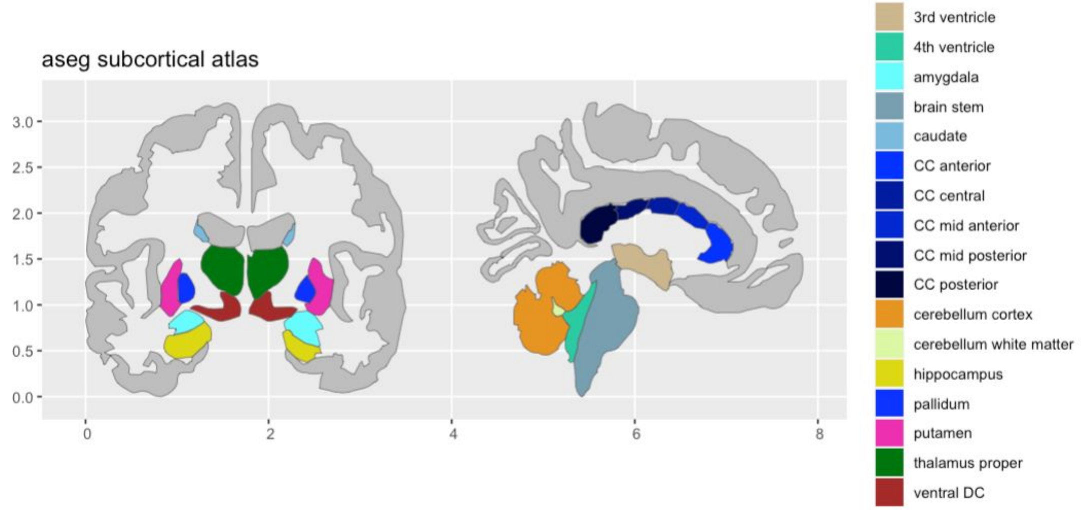
(corrected for age, sex, TIV)

-log10(pval)



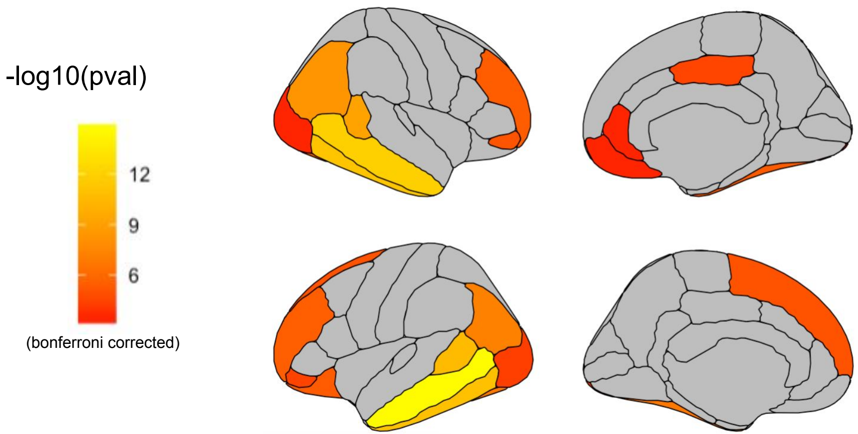
(bonferroni corrected)

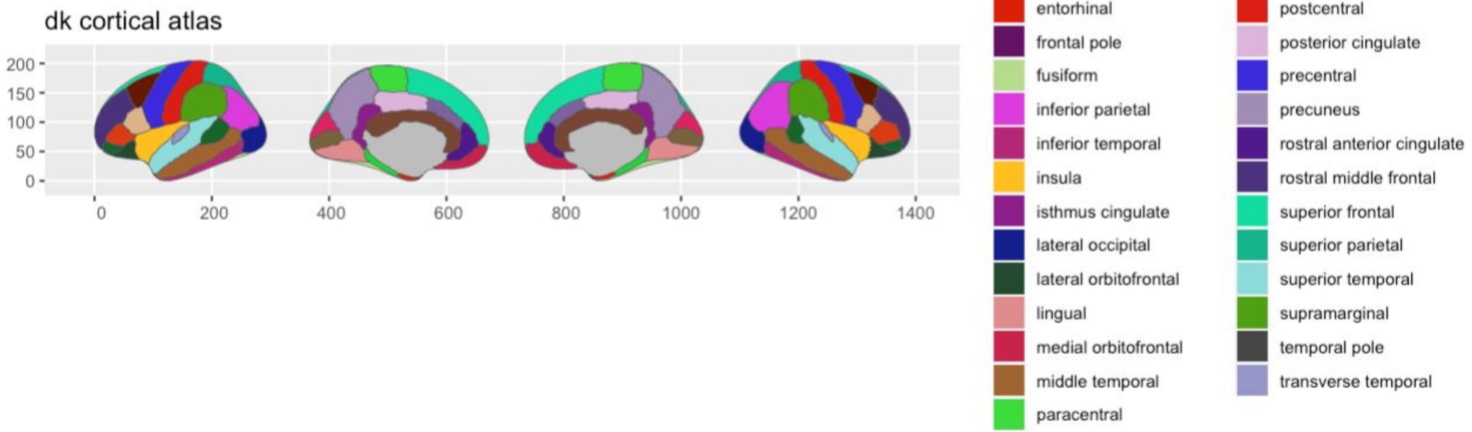
Atlas for ROI nomenclature



Cortical surface area: AD < CN

(corrected for age, sex, TIV)





Achievements by the ended of the project and UPDATES

- ❑ PET pipeline to run on CINECA
- ❑ T2* - PET β amiloide comparison
- ❑ Apply predictive models (ML) using longitudinal data

- ❑ RAC approved 06/21/2024:
  - ❑ 100.000 core-hours on Leonardo DCGP and 20 TB of storage

Thank you!

ASSESSING IRON OVERLOAD AND ABNORMAL MORPHOLOGIES IN NORMAL VS AD BRAIN BASED ON COMPARISON BETWEEN PET & RMI IMAGING BASED ON AVAILABLE LARGE DATASETS

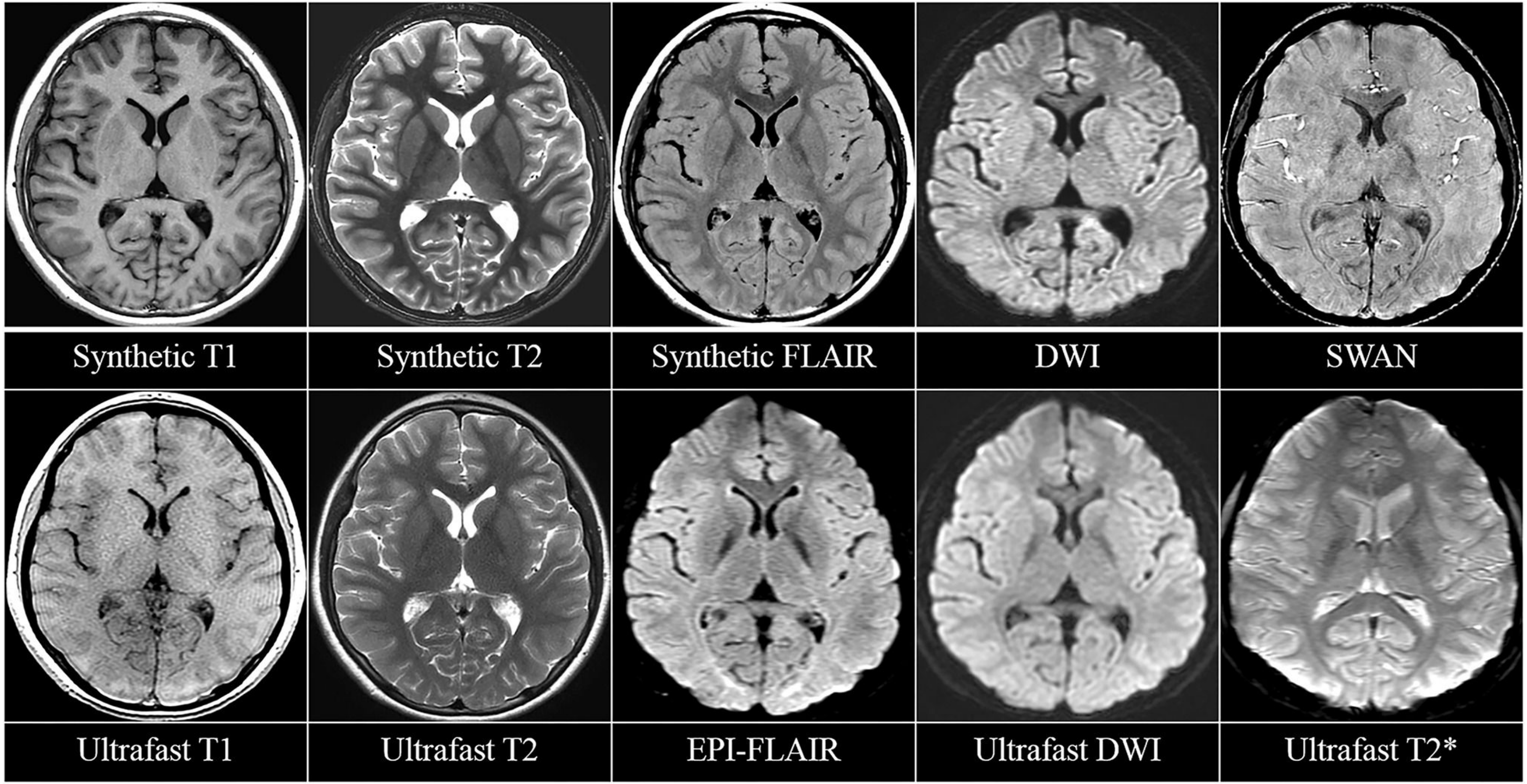
FOCUS:

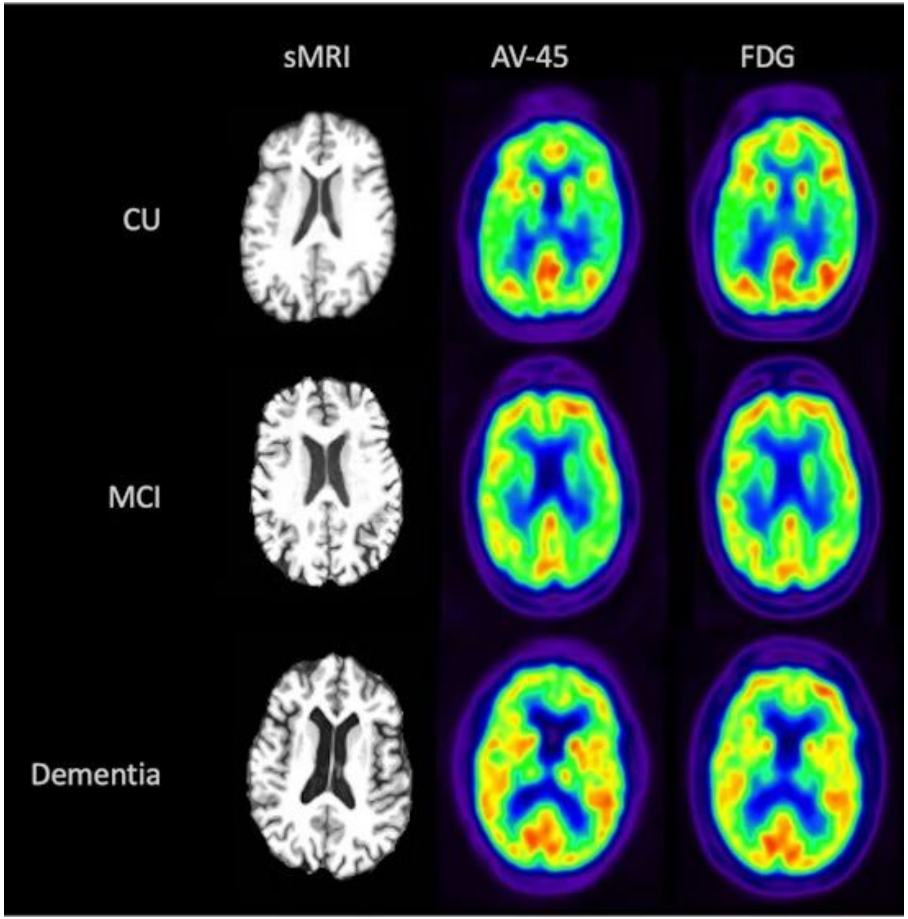
-ABETA PLAQUES ARE DETECTABLE BY PET AND ARE EXPECTED TO BE SUPERPOSED TO IRON DEPOSITION SITES

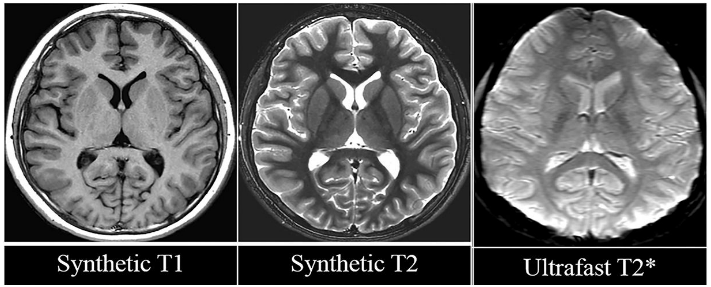
-MRI IMAGES ARE MORE EASILY AVAILABLE AND SOME SPECIFIC SEQUENCES ARE EXPECTED TO BE SENSITIVE FOR THE MAGNETIC PROPERTIES OF SMALL IRON DEPOSITS

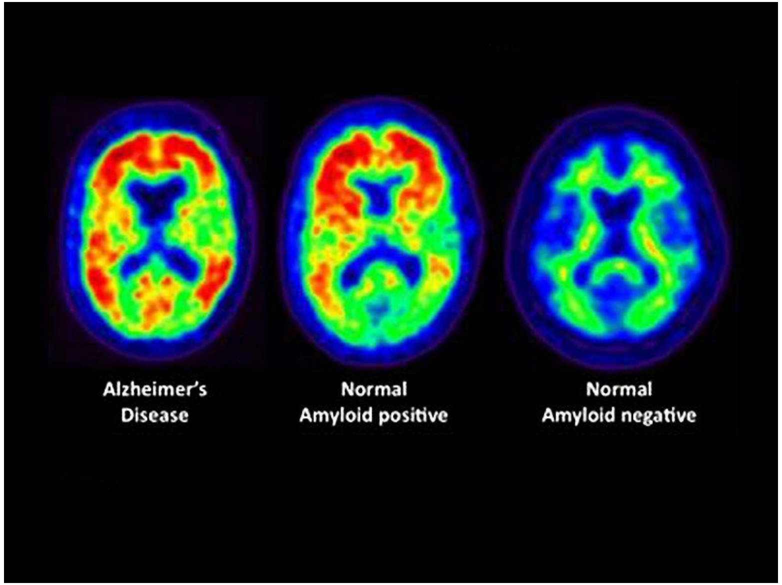
-MORPHOLOGICAL DIFFERENCES IN BRAIN REGIONS, E.G. HIPPOCAMPAL SHRINKING AND/OR ABNORMAL SULCAL FEATURES DETACTABLE FROM MRI IN CONTROL AND AD PATIENTS

MRI-pet tools: t1, t2, pet ab-tau




sMRI
AV-45
FDG
CU
MCI
Dementia


Synthetic T1
Synthetic T2
Ultrafast T2*


Alzheimer's
Disease
Normal
Amyloid positive
Normal
Amyloid negative