QuanTIM Webinar

Methodologies To Improve The Role Of White Matter Hyperintensities As Neuroimaging Biomarker Of Alzheimer's Disease

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Milan, June 20th 2025

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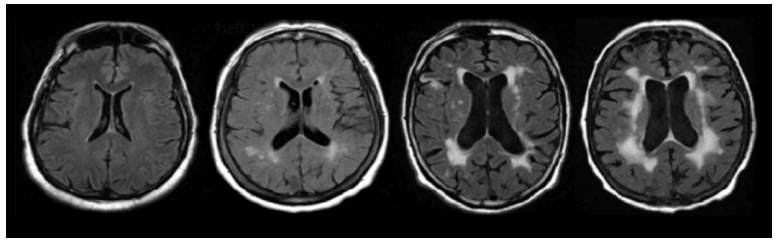
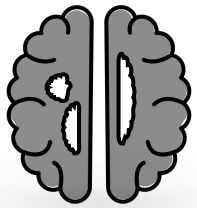
Focus

Chutinet et al., 2014



White Matter Hyperintensities (WMHs): areas of abnormal signal intensity on brain magnetic resonance imaging (MRI).



- Associated to pathological changes in the white matter axonal microstructure [1].
- Associated to alterations in the interstitial fluid mobility and increased water content [1].

[1] Wardlaw et al. (2015).

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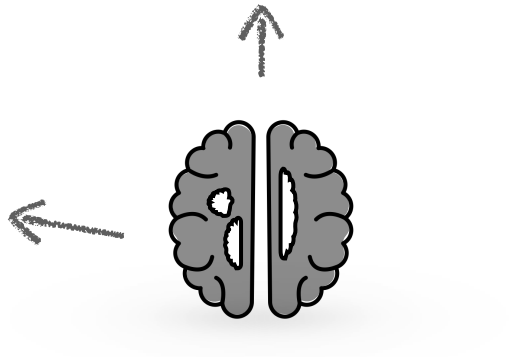
Focus

White Matter Hyperintensities (WMHs): areas of abnormal signal intensity on brain magnetic resonance imaging (MRI).

- Advancing age
- Diabetes
- Hypercholesterolemia/hypertension
- **SMALL VESSEL DISEASE (SVD)**
  ➔ condition responsible for vascular dementia.



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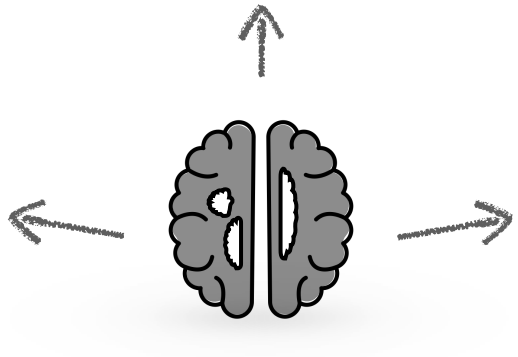

- Increased risk of stroke
- Association with cognitive decline and vascular dementia
- Association with neurodegeneration

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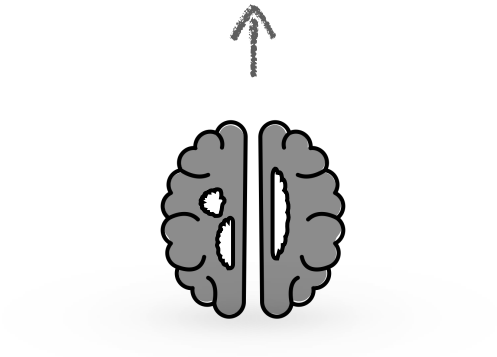

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association with
VASCULAR FACTORS

WIDELY RECOGNISED

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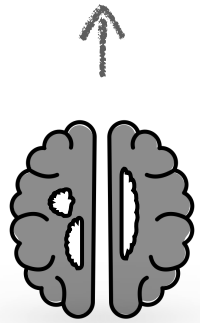

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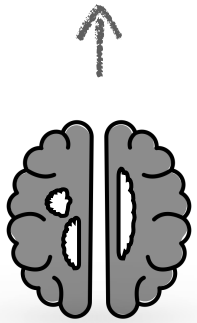

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association with **VASCULAR FACTORS**

WIDELY RECOGNISED

CURRENTLY DEBATED (despite numerous evidence)

association with **NEURODEGENERATION**

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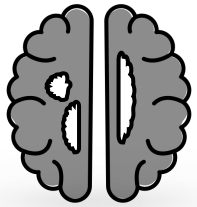
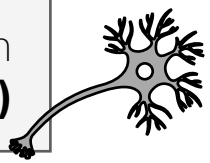
Background



CURRENTLY DEBATED (despite numerous evidence)

association with
ALZHEIMER'S (AD)



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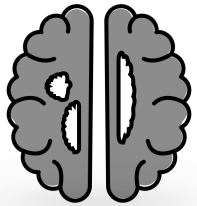

- **Increased WMH load** in symptomatic patients as compared to healthy elderly [1];
- **Increased WMH load** associated with a decreased time of conversion from mild cognitive impairment to AD [2];
- WMH **volume** more **highly predictive** of pre-clinical AD than standard cognitive tests [3].

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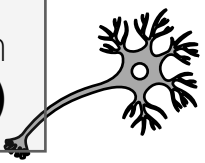

[1] Dubois et al. (2007);
[2] Dadar et al. (2019);
[3] Kandel et al. (2016).

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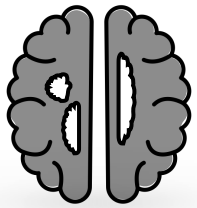
Background

STUDIES ARE:
(i) SCARCE; (ii) LEVERAGE IMAGING-DERIVED MESURES.



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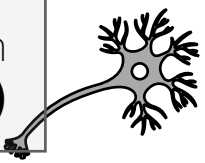

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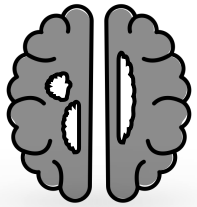

SCIENTIFIC QUESTION

"Can the comprehensive 3D features of WMHs, such as spatial location and signal intensity, significantly enhance the disease identification?"

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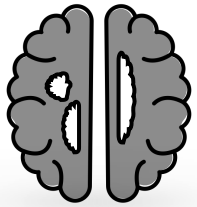

SCIENTIFIC QUESTION

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AIM

Develop a deep learning (DL)-based classification model for AD and assess the level of explainability of WMHs through XAI techniques.

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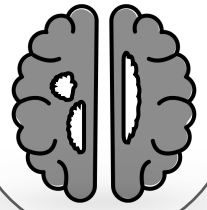

MAIN-WP

"WMH clinical application and relevance"

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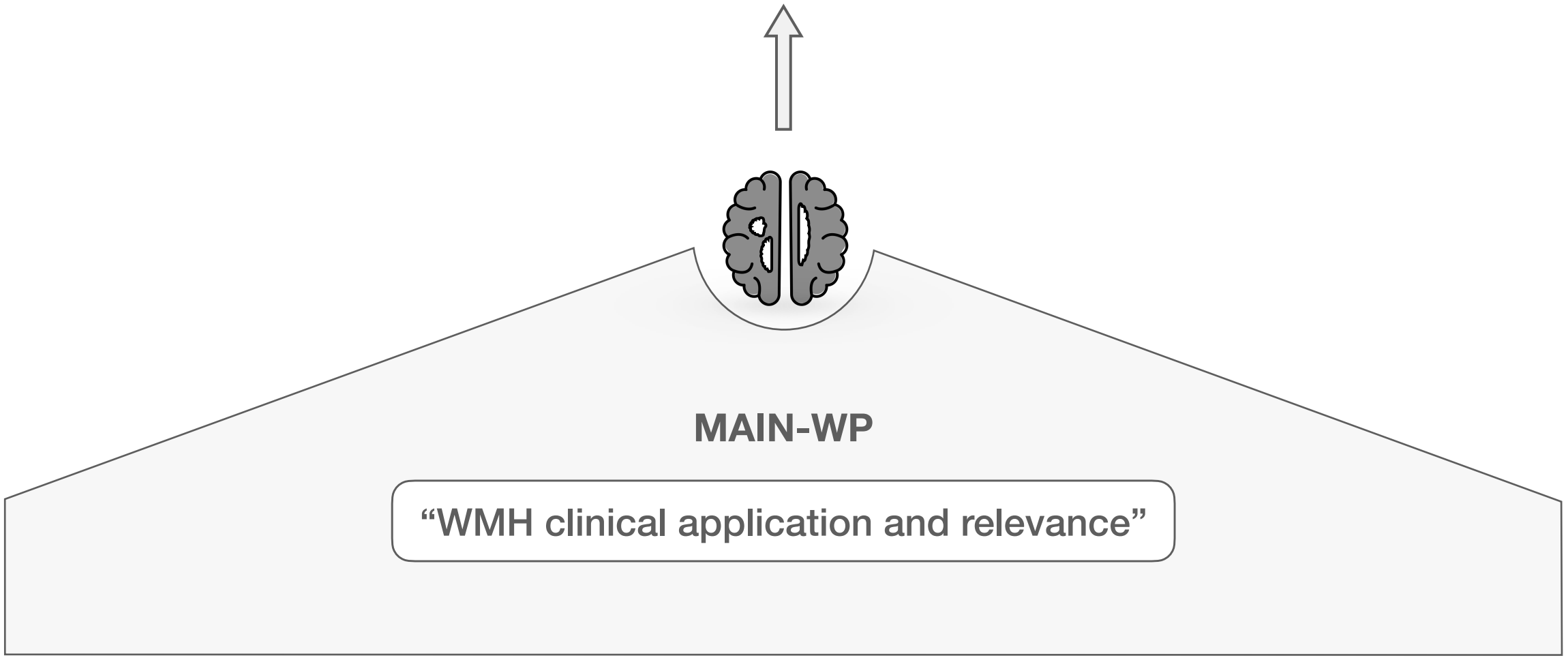
Background

To achieve this goal, two key elements are necessary.



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Background

- Large and **multi centric MRI databases** (focused on WMHs).

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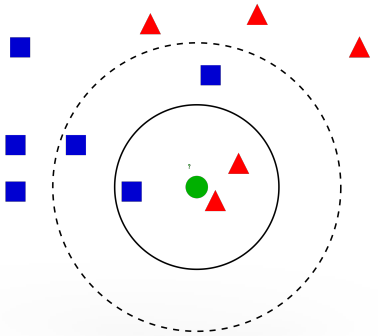
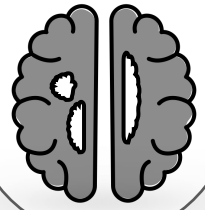
Background

To achieve this goal, two key elements are necessary.

- Large and **multi centric MRI databases** (focused on WMHs).

- Accurate and reliable **algorithms to automatically segment WMHs**.





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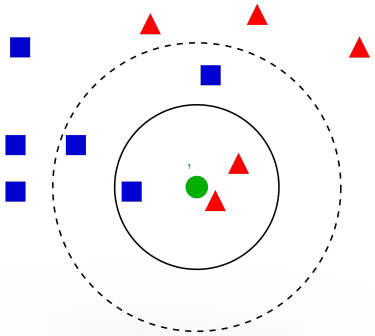

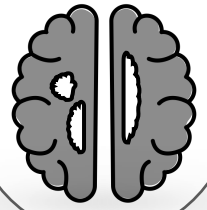

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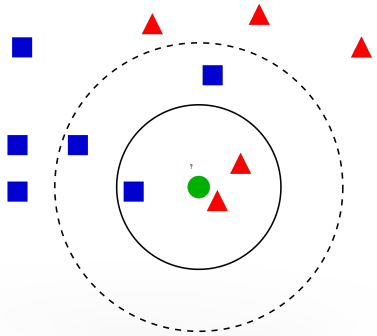
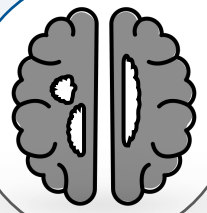
PhD overview

WP-1

"Harmonisation of WMH Measures"

Accurate and reliable **algorithms to automatically segment WMHs**.





MAIN-WP

"WMH clinical application and relevance"

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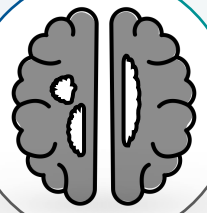
PhD overview

WP-1

"Harmonisation of WMH Measures"

WP-2

"QSM repeatability and potentials in segmenting white matter lesions"



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PhD overview

WP-1

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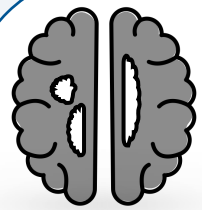

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WP1 – Introduction (1)

“WHY DO WE NEED TO HARMONISE MRI DATA?”

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⇨ Presence of inter-site and inter-scanner variability in MRI.

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WP1 – Introduction (1)

“WHY DO WE NEED TO HARMONISE MRI DATA?”

⇨ Presence of inter-site and inter-scanner variability in MRI.

SCANNER-RELATED FACTORS:

- Inhomogeneities in the static magnetic field;
- Gradient nonlinearities;
- Differences in the utilised image reconstruction algorithms.

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WP1 – Introduction (1)

“WHY DO WE NEED TO HARMONISE MRI DATA?”

⇨ Presence of inter-site and inter-scanner variability in MRI.

⇨ Little impact on visual diagnosis.

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WP1 – Introduction (1)

“WHY DO WE NEED TO HARMONISE MRI DATA?”

Presence of inter-site and inter-scanner variability in MRI.

- Little impact on visual diagnosis.
- Significant impact on automatic image analysis techniques.

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WP1 – Introduction (1)

“WHY DO WE NEED TO HARMONISE MRI DATA?”

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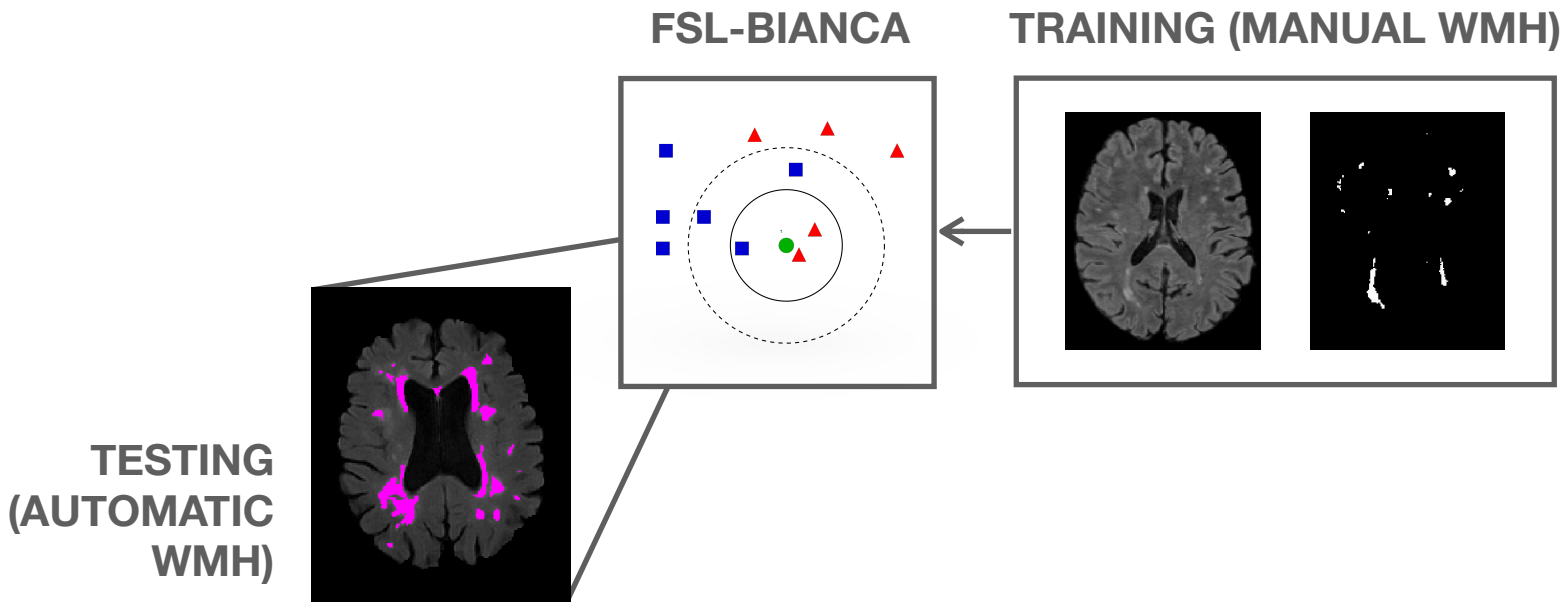
WP1 – Introduction (1)

"WHY DO WE NEED TO HARMONISE MRI DATA?"

Presence of inter-site and inter-scanner variability in MRI.

Variability **tackled** in a former study **(Bordin et al., 2021)**, that evaluated the Brain Intensity AbNormality Classification Algorithm (BIANCA) for the automatic segmentation of WMH lesions.



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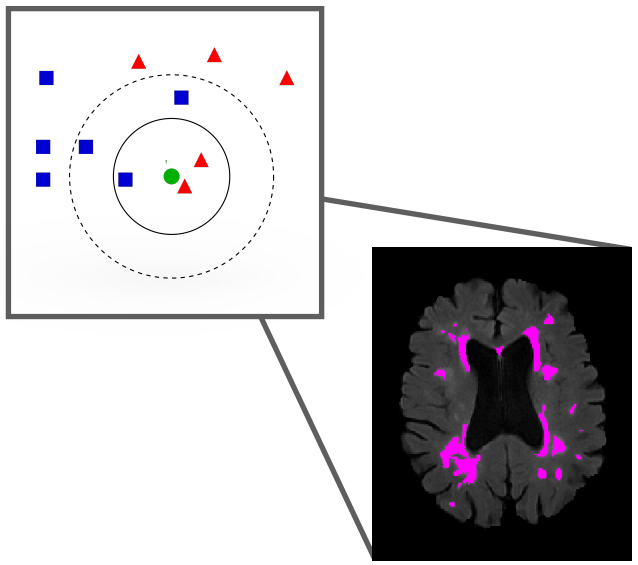
WP1 – Introduction (2)

FSL-BIANCA



SOLUTION

Set of recommendations relative to the image pre-processing and algorithm training.

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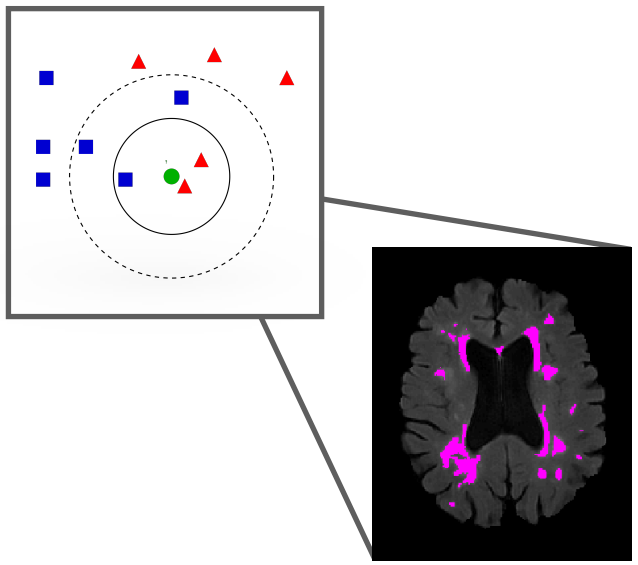

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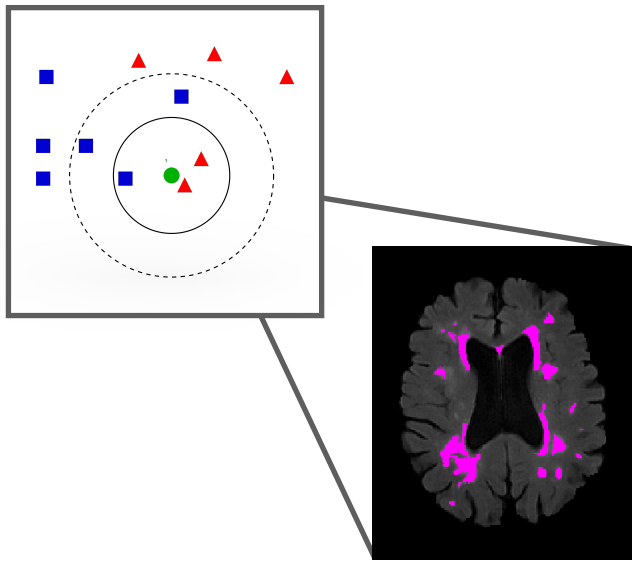

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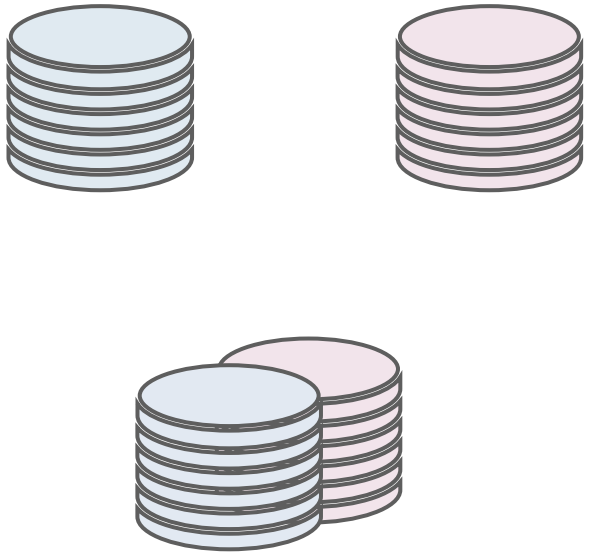

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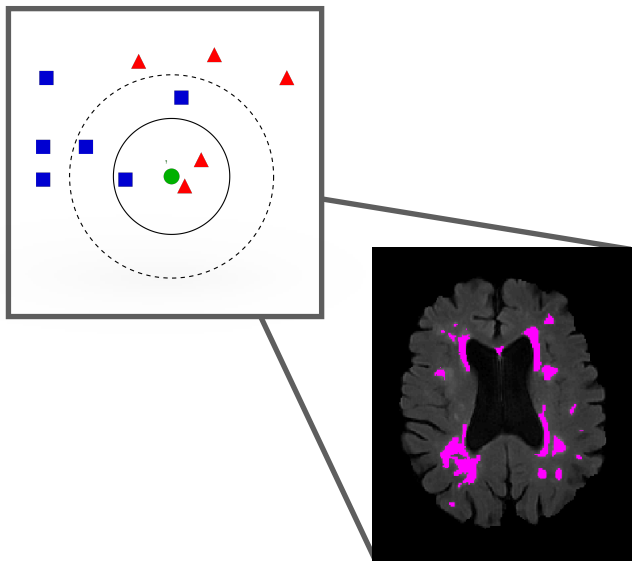

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UK Biobank (UKB)

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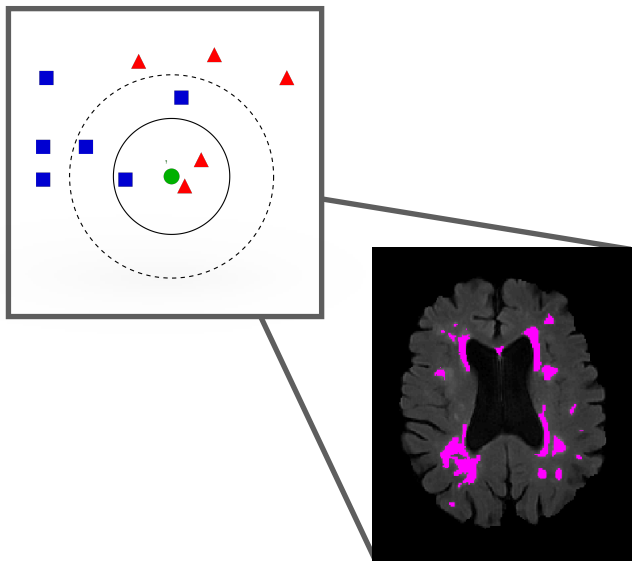

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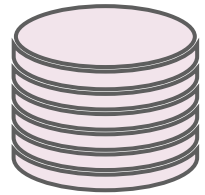

UK Biobank (UKB)

BIANCA(WH, UKB)

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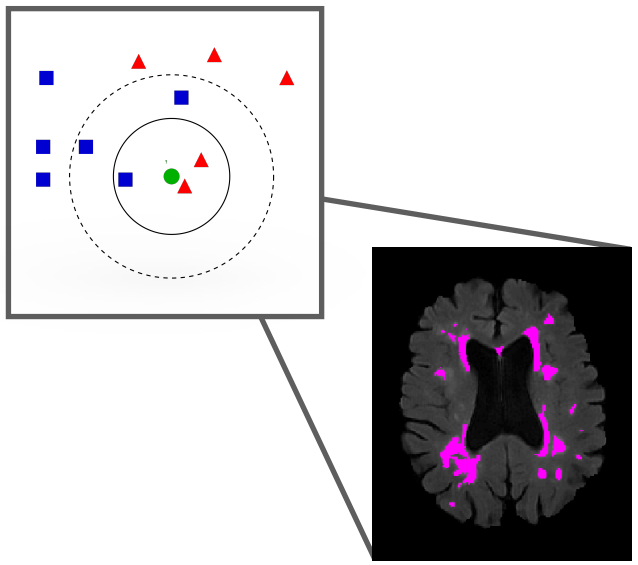

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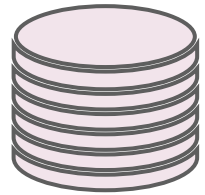

UK Biobank (UKB)

BIANCA(WH, UKB)

Simple harmonisation strategy.

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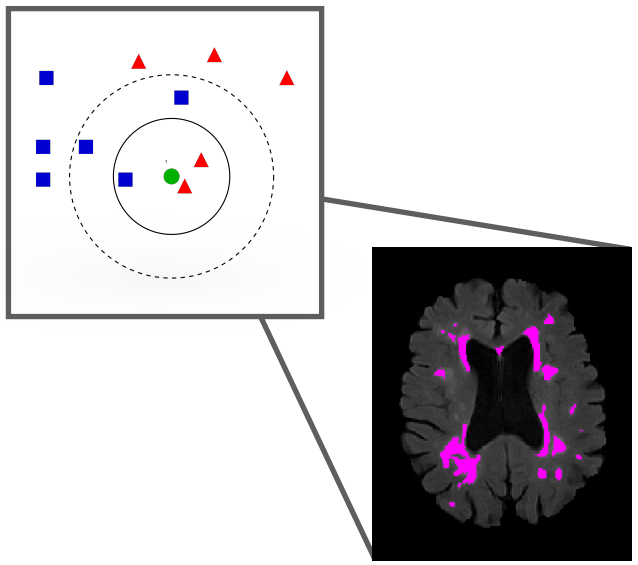
WP1 – Introduction (2)

FSL-BIANCA



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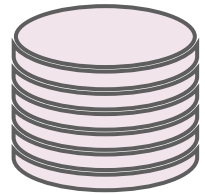

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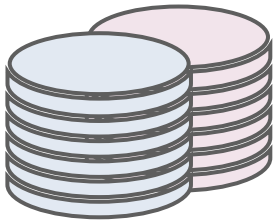

BIANCA(WH, UKB)

Simple harmonisation strategy.

Has never been tested on external datasets.

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WP1 – Aim & Methods (1)

AIM

Validating BIANCA(WH, UKB) on novel imaging datasets of normal aging subjects.

OASIS-3 (OS-1) **OASIS-3 (OS-2)** **ADNI3 (AD-3)**

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WP1 – Aim & Methods (1)

AIM

Validating BIANCA(WH, UKB) on novel imaging datasets of normal aging subjects.

OASIS-3 (OS-1) **OASIS-3 (OS-2)** **ADNI3 (AD-3)**

Respectively, with 15, 15 and 30 **manually annotated subjects**.

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WP1 – Aim & Methods (1)

AIM

Validating BIANCA(WH, UKB) on novel imaging datasets of normal aging subjects.

OASIS-3 (OS-1) **OASIS-3 (OS-2)** **ADNI3 (AD-3)**

1) Validating **segmentation performance,** by calculating the overlap metrics between manual and automatic WMH mask (e.g., **Dice Similarity Index – DSI**) and comparing results for the following cases:

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WP1 – Aim & Methods (1)

AIM

Validating BIANCA(WH, UKB) on novel imaging datasets of normal aging subjects.

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Training on **BIANCA(WH, UKB)** – testing on **OS-1, OS-2** and **AD-3**.

SITE-SPECIFIC

Training on **OS-1, OS-2** and **AD-3** – testing on **OS-1, OS-2** and **AD-3** (independently).

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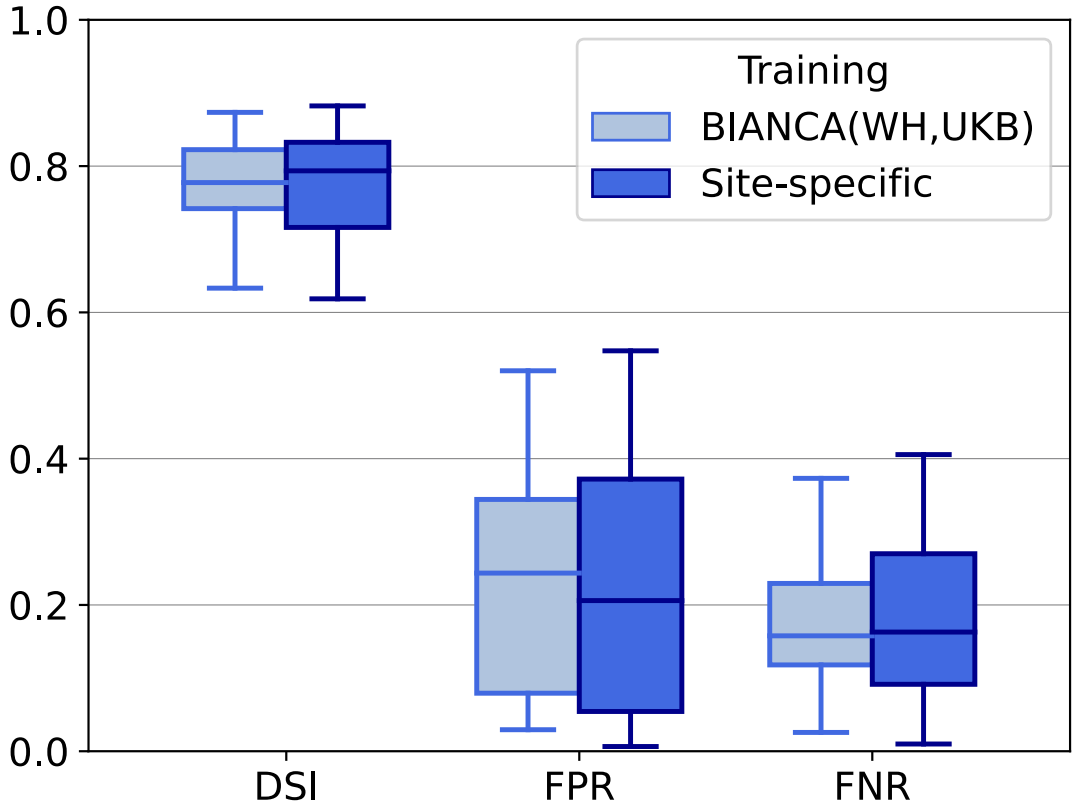
WP1 – Results (1)

1) Validating **segmentation performance:** NEW against SITE-SPECIFIC:



No significant difference between BIANCA(WH, UKB) and the site-specific training across **all metrics**.

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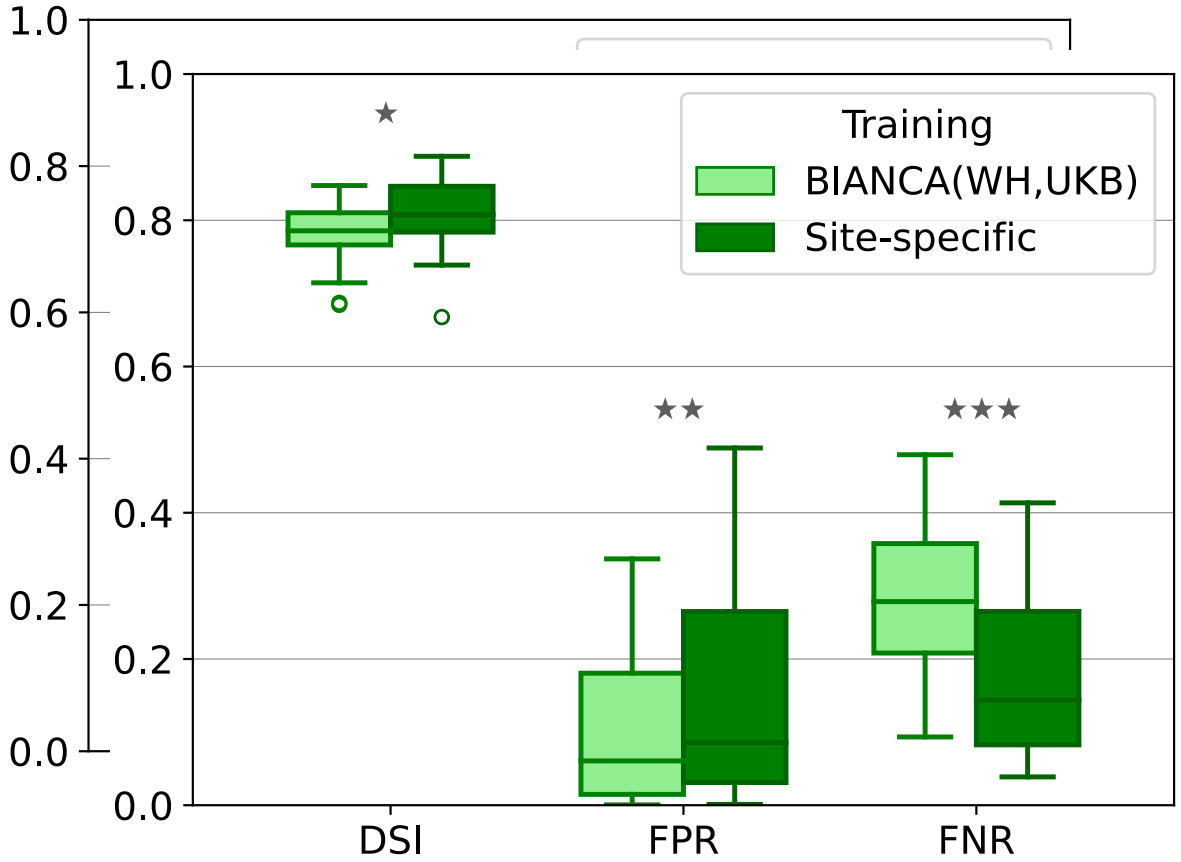
WP1 – Results (1)

1) Validating **segmentation performance:** NEW against SITE-SPECIFIC:



⇨ Higher **DSI** and lower **FNR** values were found for the site-specific training;

⇨ Higher **FPR** for the the site-specific training.

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WP1 – Results (1)

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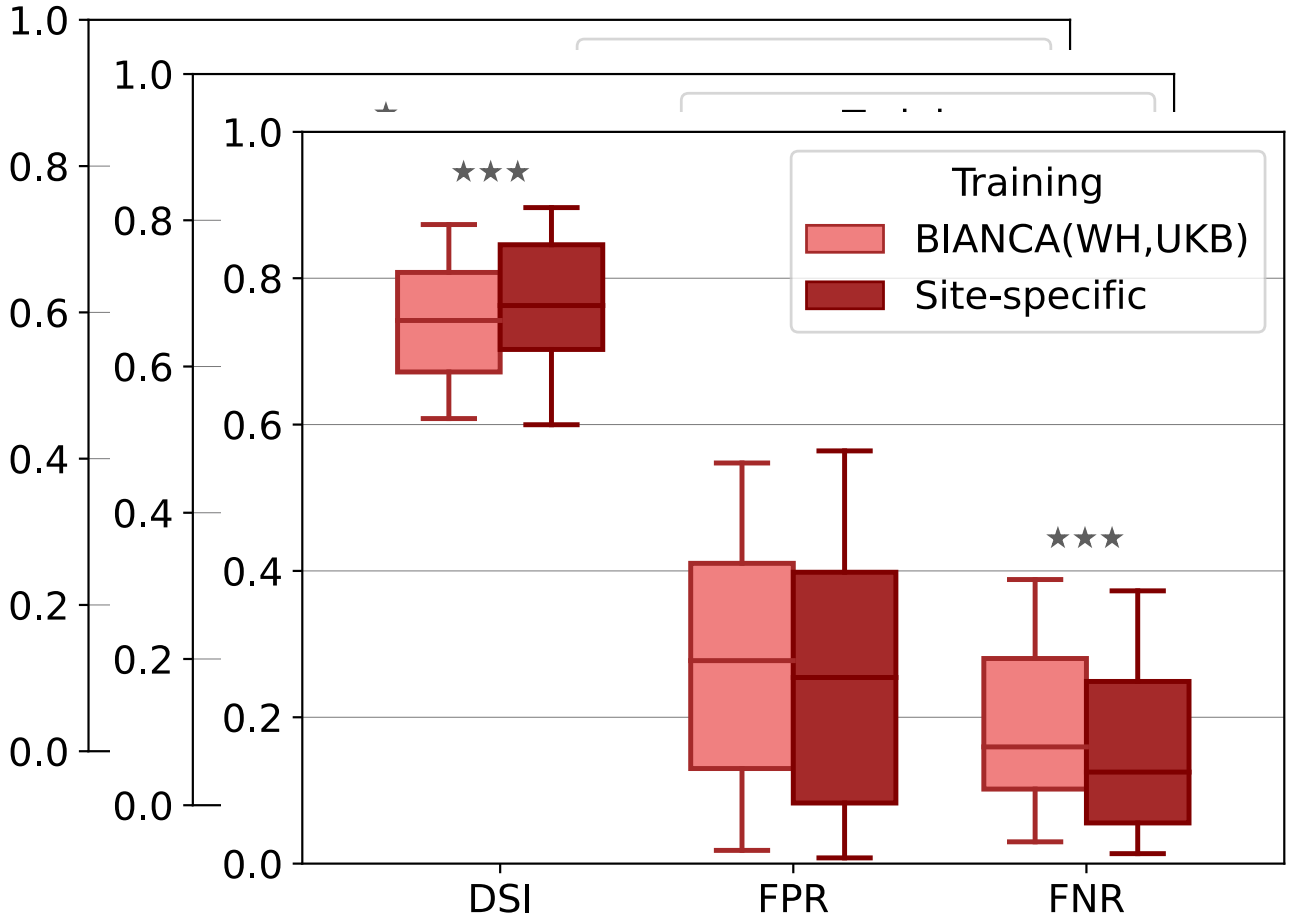

⇨ Higher **DSI** and lower **FNR** values were found for the site-specific training;

⇨ No significant differences for the **FPR**.

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WP1 – Aim & Methods (2)

AIM

Validating BIANCA(WH, UKB) on novel imaging datasets of normal aging subjects.

OASIS-3 (OS-1) **OASIS-3 (OS-2)** **ADNI3 (AD-3)**

2) Validating **harmonisation**, by calculating the consistency of **WMH volume** across datasets with similar health status (measured through the Johnson–Neyman (J-N) procedure).

(*) EXAMPLE PLOTS

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WP1 – Aim & Methods (2)

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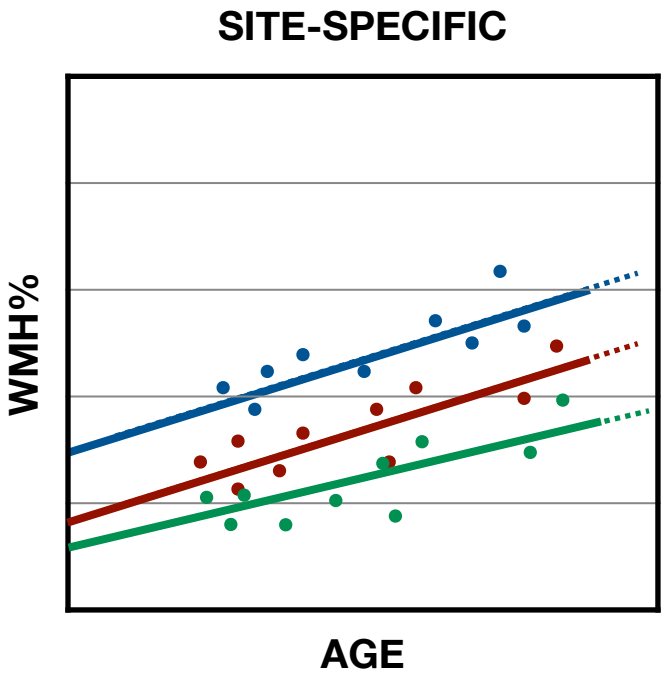

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WP1 – Aim & Methods (2)

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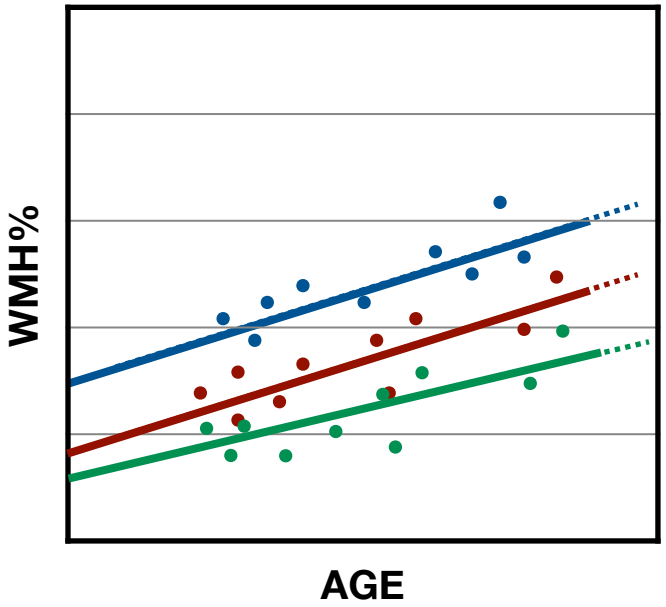
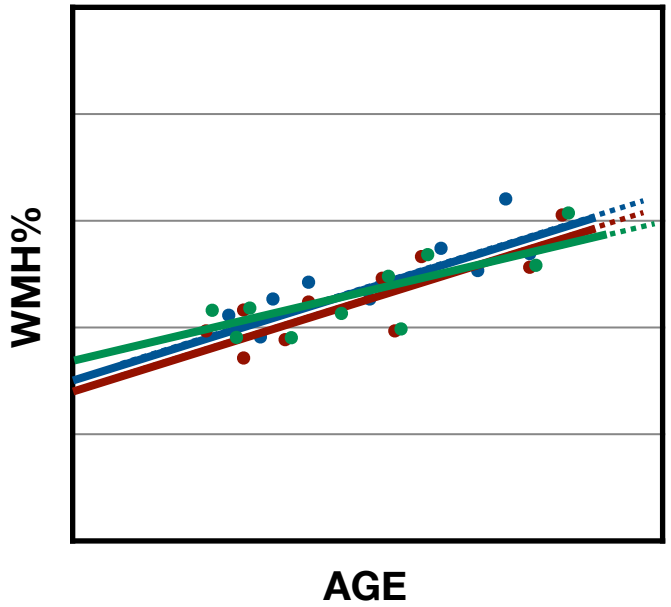
SITE-SPECIFIC



BIANCA(WH, UKB) ?



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WP1 – Aim & Methods (2)

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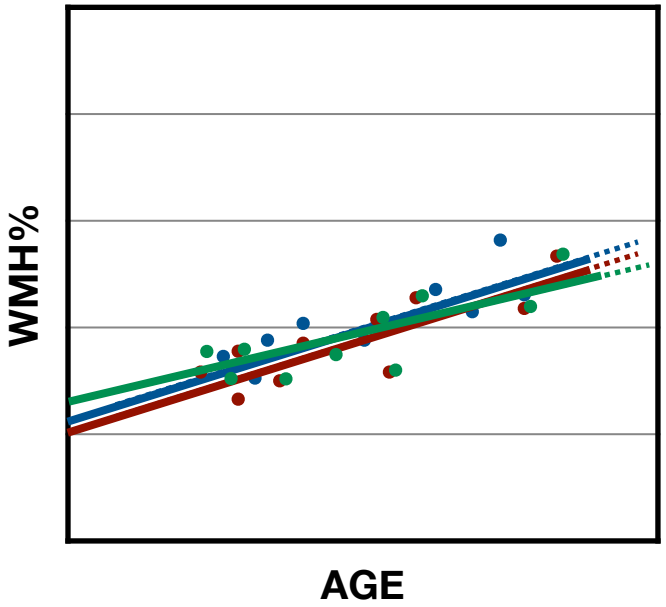
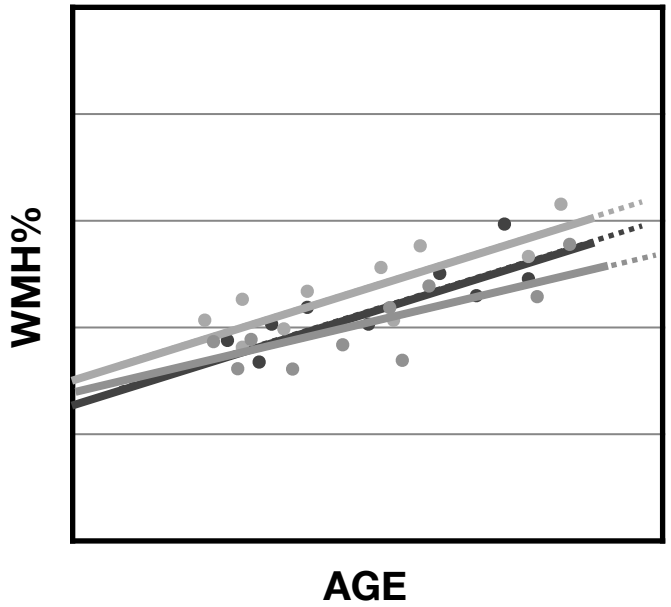


COMBAT ?



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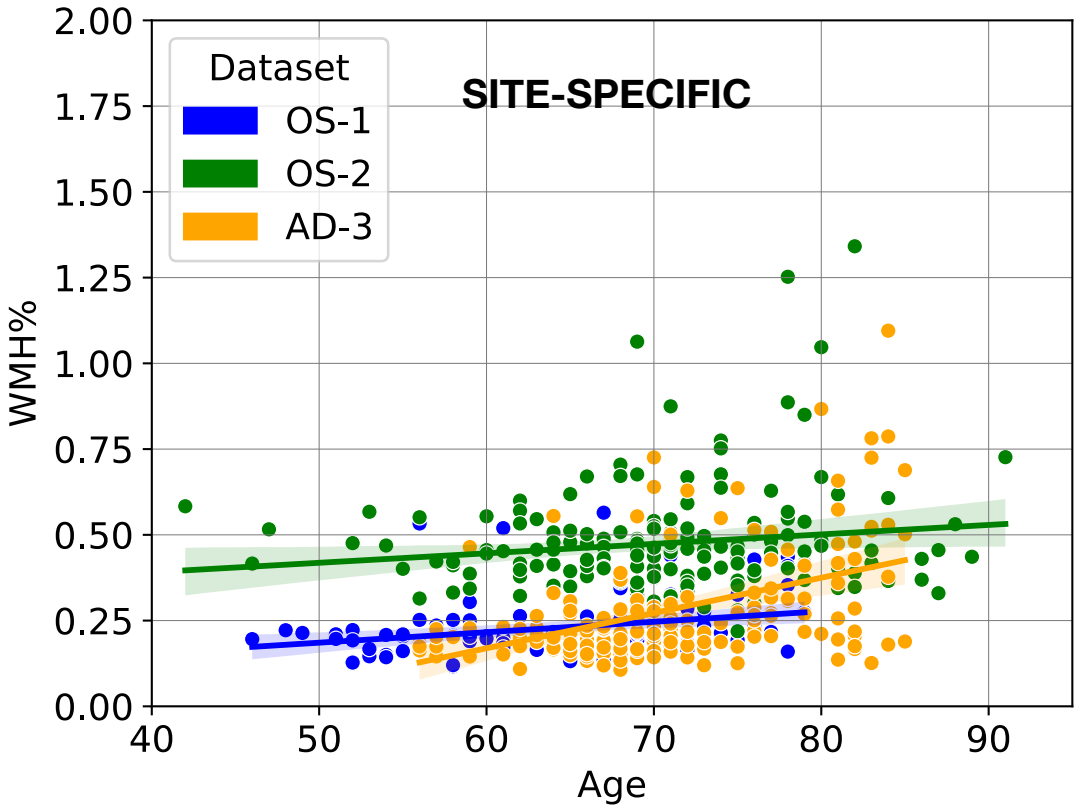
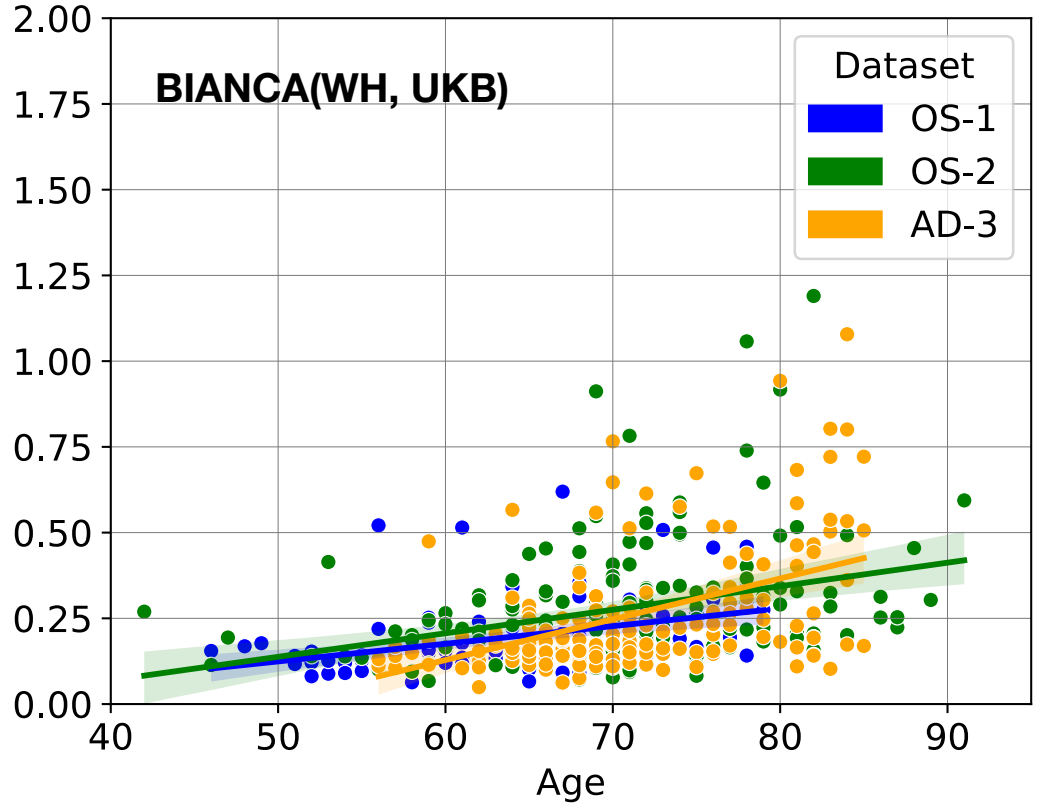
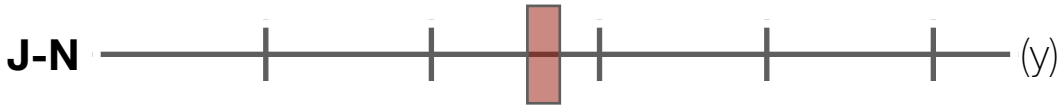
WP1 – Results (2)







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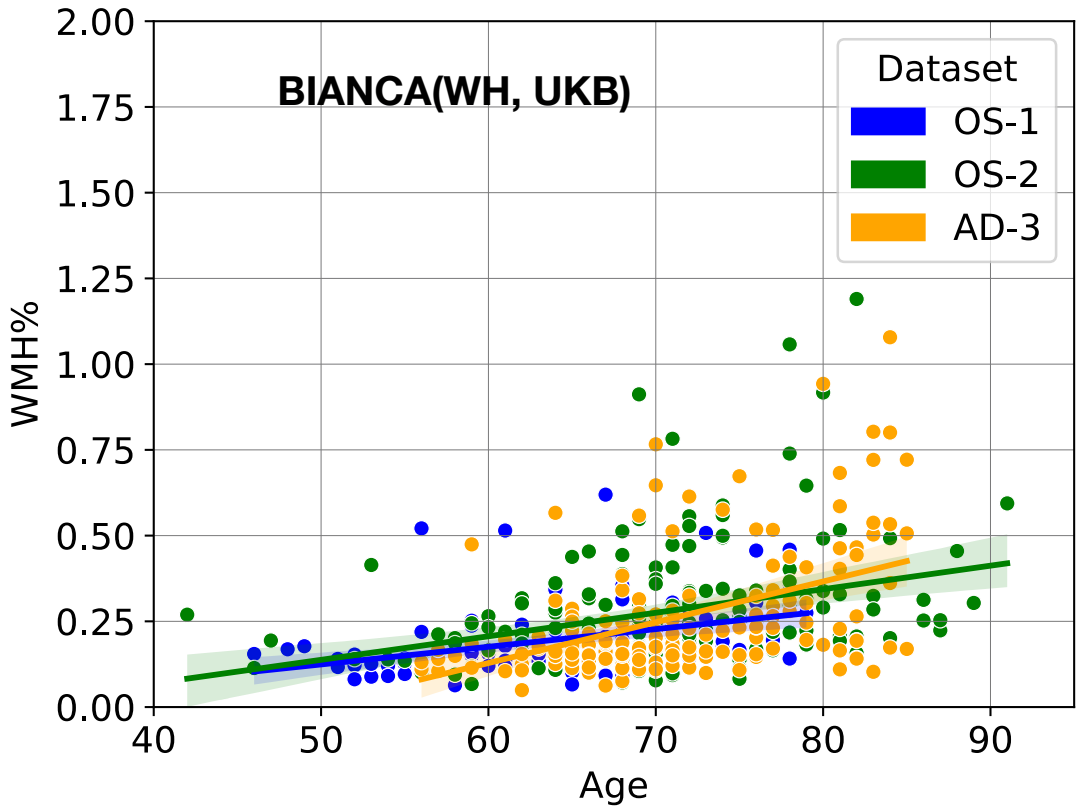
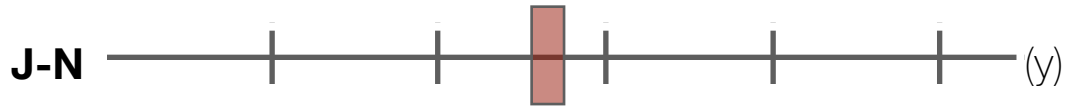
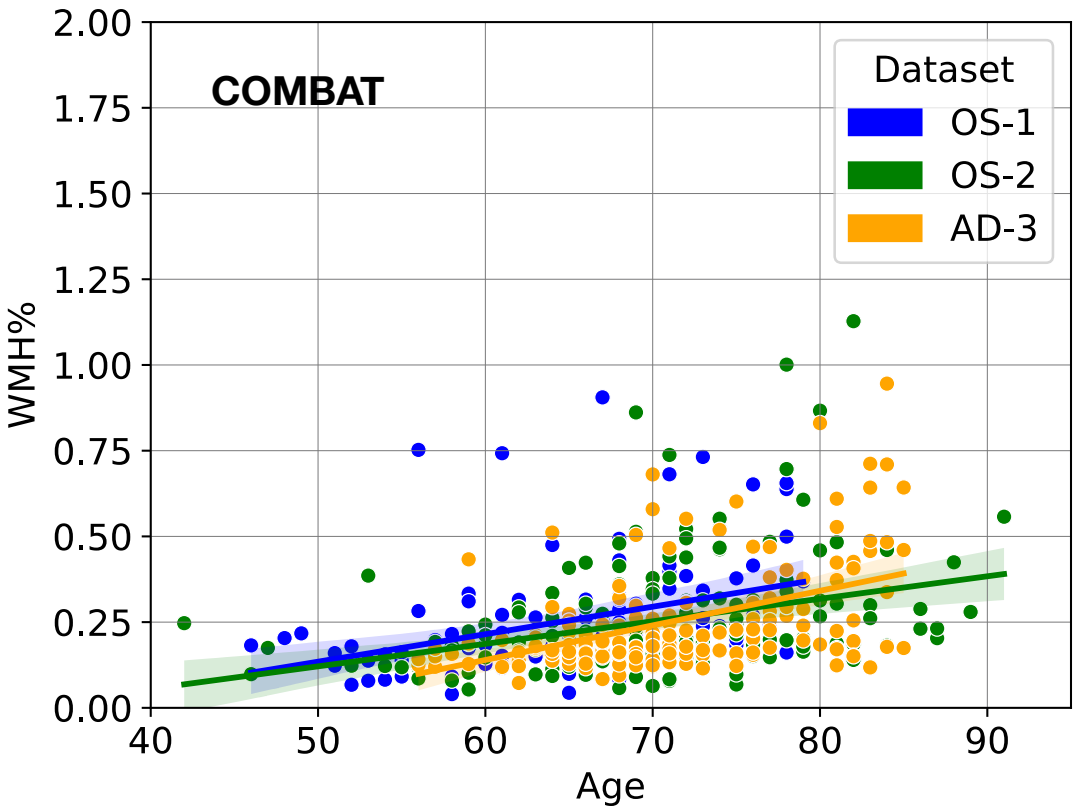
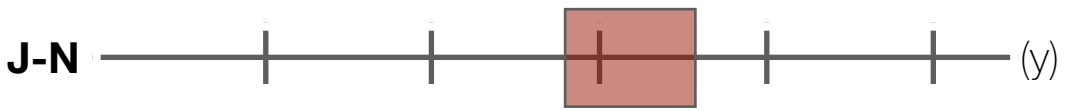
WP1 – Results (2)





66.57–67.56





68.41–76.95

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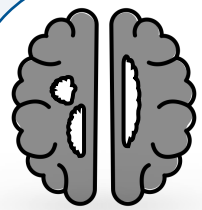
WP1 – Conclusions

WP1

"Harmonisation of WMH Measures"



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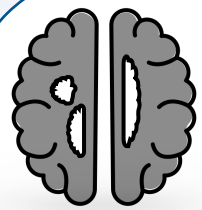
WP1 – Conclusions

WP1

“Harmonisation of WMH Measures”



- BIANCA(WH, UKB)’s performance suggest it could serve as a **viable alternative to the optimal training strategy**.

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WP1 – Conclusions

WP1

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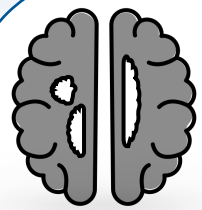

- BIANCA(WH, UKB)’s performance suggest it could serve as a **viable alternative to the optimal training strategy**.
- Despite lacking the complexity of ComBat, BIANCA(WH, UKB) still **managed to effectively integrate WMH measures across datasets**.

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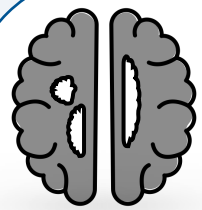
WP1 – Conclusions

WP1

“Harmonisation of WMH Measures”



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- Despite lacking the complexity of ComBat, BIANCA(WH, UKB) still **managed to effectively integrate WMH measures across datasets**.

BIANCA(WH, UKB) is **usable in multi-centric studies** where manual rating is impractical.

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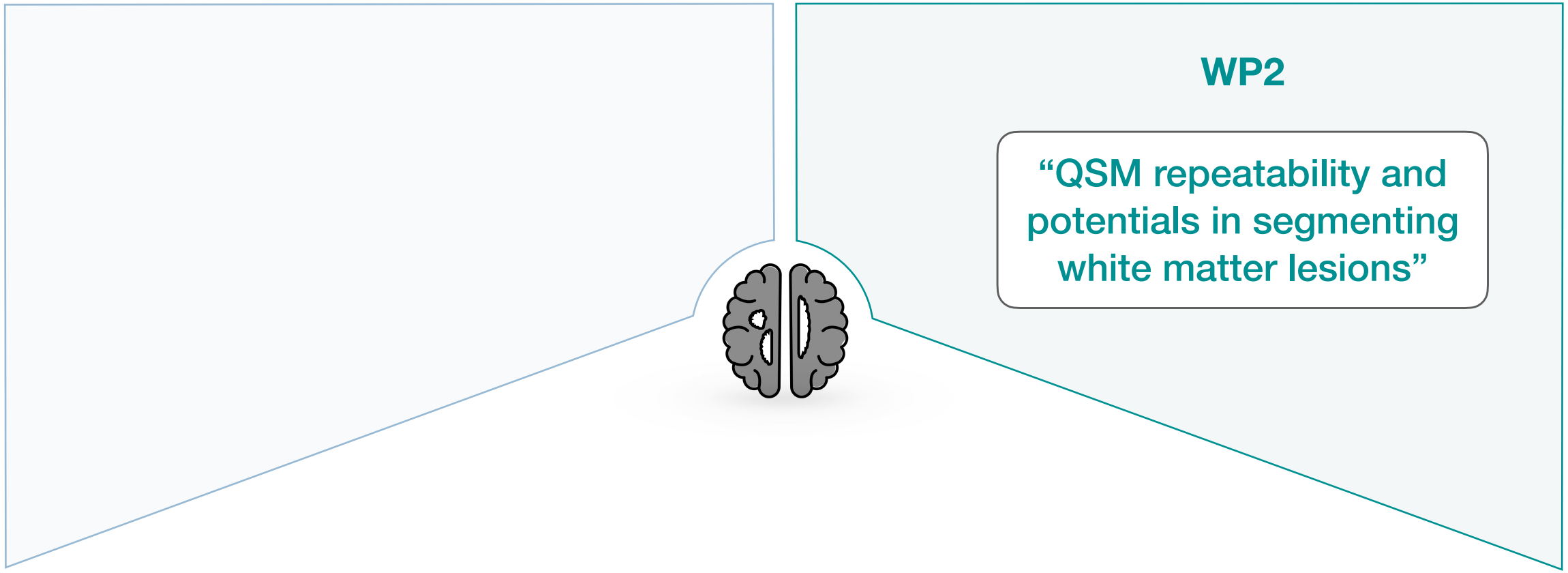
PhD overview



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WP2 – Introduction (1)

“WHY DO WE NEED MULTIMODALITY?”

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WP2 – Introduction (1)

“WHY DO WE NEED MULTIMODALITY?”

Shown to improve BIANCA performance according to:

- Griffanti et al., 2016,
- Bordin et al., 2021.

Particularly valuable, as harmonisation techniques, can sometimes lead to a **decrease in model performance** (Bordin et al., 2021).

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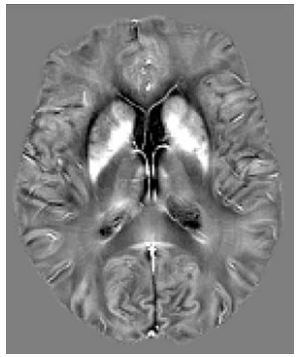
SOLUTION Explore an additional MRI contrast.



QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM)

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WP2 – Introduction (1)

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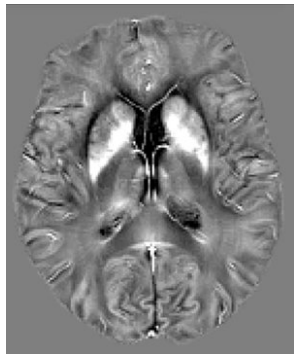
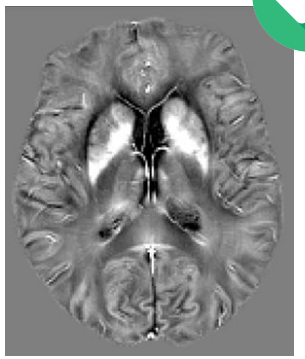


QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM)

- Quantifies the spatial distribution of **magnetic susceptibility** within an object or tissue [1,2].
- Not directly extracted from the MRI scanner but **reconstructed** from the phase signal acquired during Gradient Echo (GRE) sequences.

[1] Vinayagamani et al. (2021),
[2] Li et al. (2011).

WP2 – Introduction (2)



QUANTITATIVE SUSCEPTIBILITY MAPPING

- Known to provide valuable information on **myelin density**, WM microstructural changes and axonal integrity [*].

- It has the potential to be included in the current WMH segmentation, yet **received scarce interest** in this context.

ANALYTICAL FRAMEWORK II

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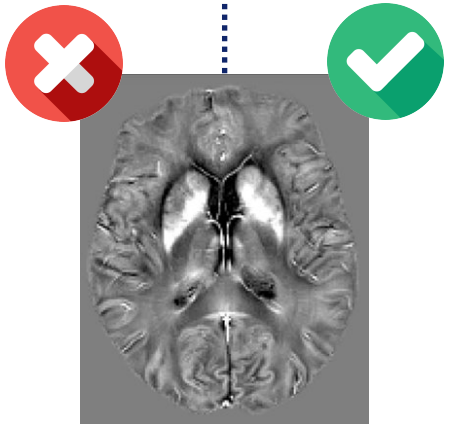
WP2 – Introduction (2)

- Presence of **variability** in the susceptibility measurements extracted using different:
  - Magnetic field strengths;
  - Acquisition parameters;
  - Reconstruction algorithms.
- Numerous studies evaluated the reproducibility (across scanners/sites) of QSM.
- No studies focused on scan-rescan repeatability, especially considering a varying number of echo times (nTEs) to carry out the reconstruction.



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ANALYTICAL FRAMEWORK I

ANALYTICAL FRAMEWORK II

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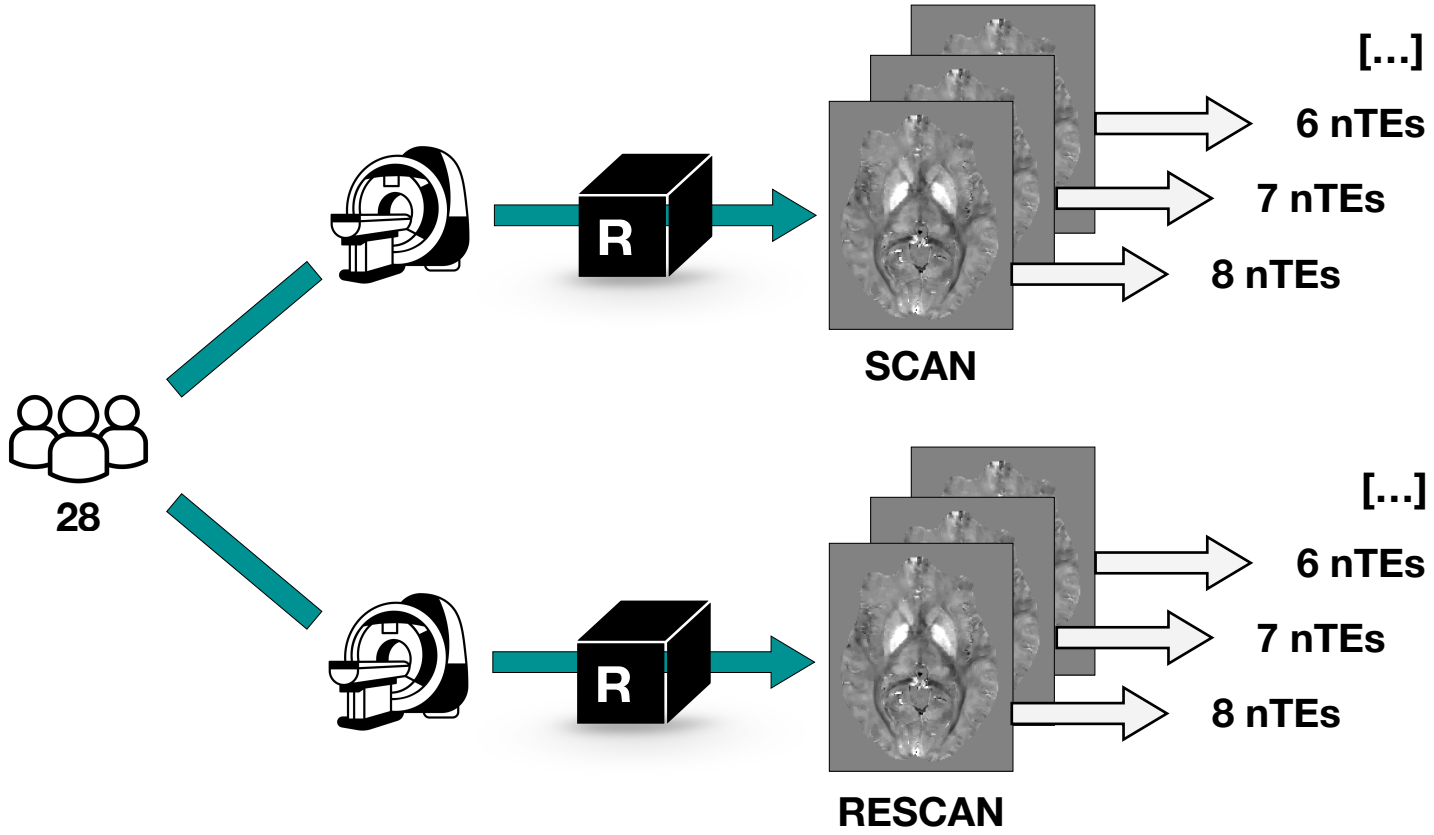
WP2 – Aim & Methods (1)

ANALYTICAL FRAMEWORK I

On a dataset of healthy volunteers, investigate the scan-rescan repeatability of QSM and its dependence on **nTEs** used to carry out reconstructions.



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WP2 – Extra (2)

ANALYTICAL FRAMEWORK I

In a dataset of healthy volunteers, investigate the scan-rescan repeatability of QSM and its dependence on the number of echoes times (**nTEs**) used to carry out reconstruction.

(i) **ROI-based analysis**

ICC between the scan and rescan **mean QSM value** extracted across single Region of Interest (**ROI**);

7 BRAIN NUCLEI

(ii) **Voxel-wise analysis**

ICC between the scan and rescan voxel-wise **QSM value** across a binary mask of all **ROIs**;

(**) Both analysis repeated at different nTEs.

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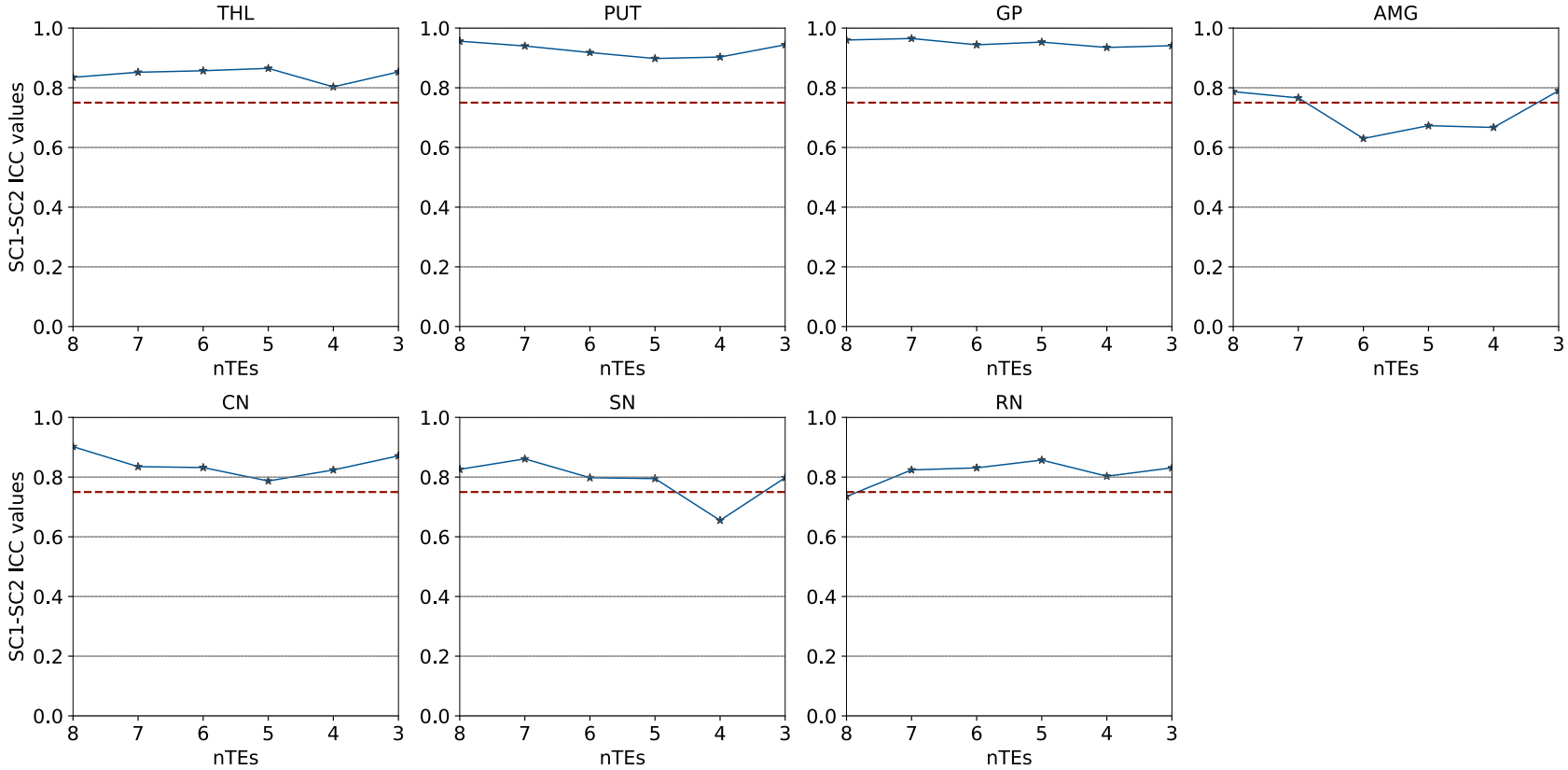
WP2 – Results (1)

ROI-based analysis

Repeatability is influenced by the number of echo times used to derive the final susceptibility estimates, with **more echoes** generally resulting in **more consistent outcomes** and small structures displaying the highest variability.



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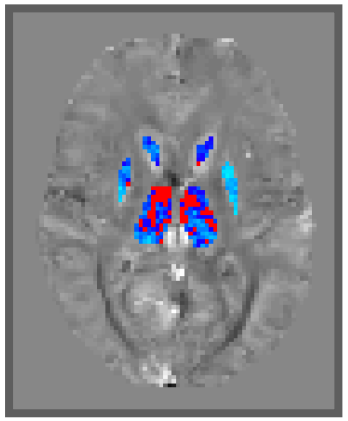
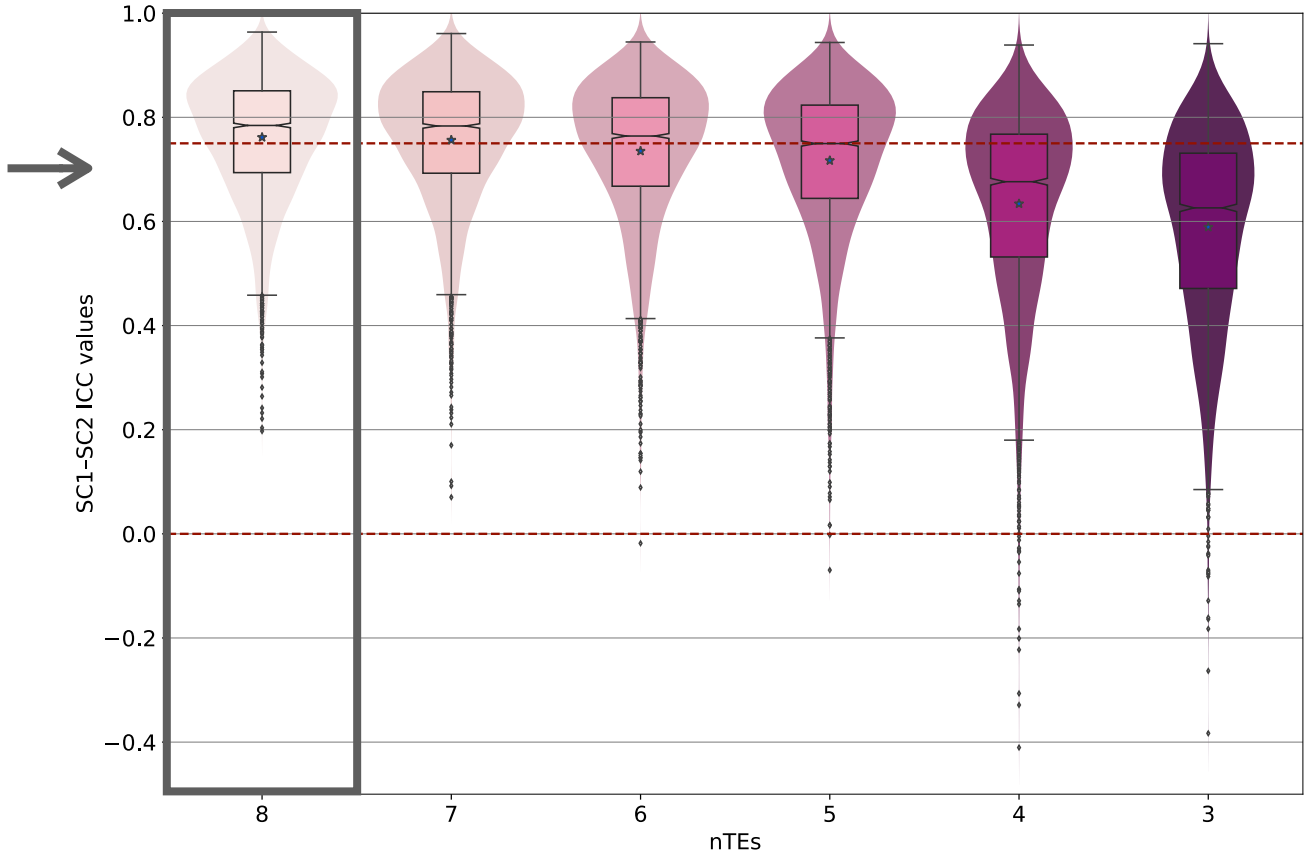
WP2 – Results (1)

Voxel-wise analysis

Even at the voxel level, repeatability is influenced by the number of echo times used to derive the final susceptibility estimates, with **more echoes** generally resulting in **more consistent outcomes.**



8 nTEs



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WP2 – Aim & Methods (3)

ANALYTICAL FRAMEWORK II

On a dataset of **multiple sclerosis (MS) patients**, evaluate the possibility of including QSM among the imaging modalities used by BIANCA to segment white matter lesions (WMLs).

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WP2 – Aim & Methods (3)

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(i) **Preliminary analysis**

Comparison of **voxel-wise values** between normal-appearing white matter (NAWM) and WMLs using an independent t-test.

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WP2 – Aim & Methods (3)

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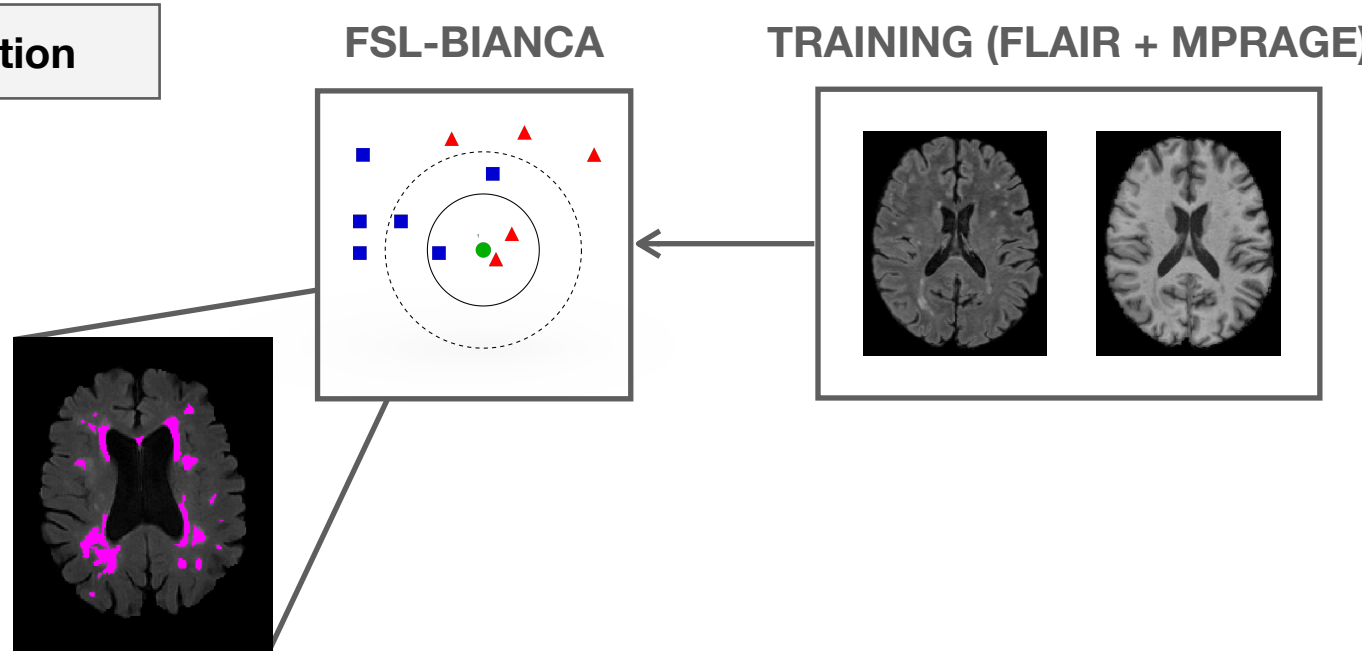
- **(ii) Segmentation**



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WP2 – Aim & Methods (3)

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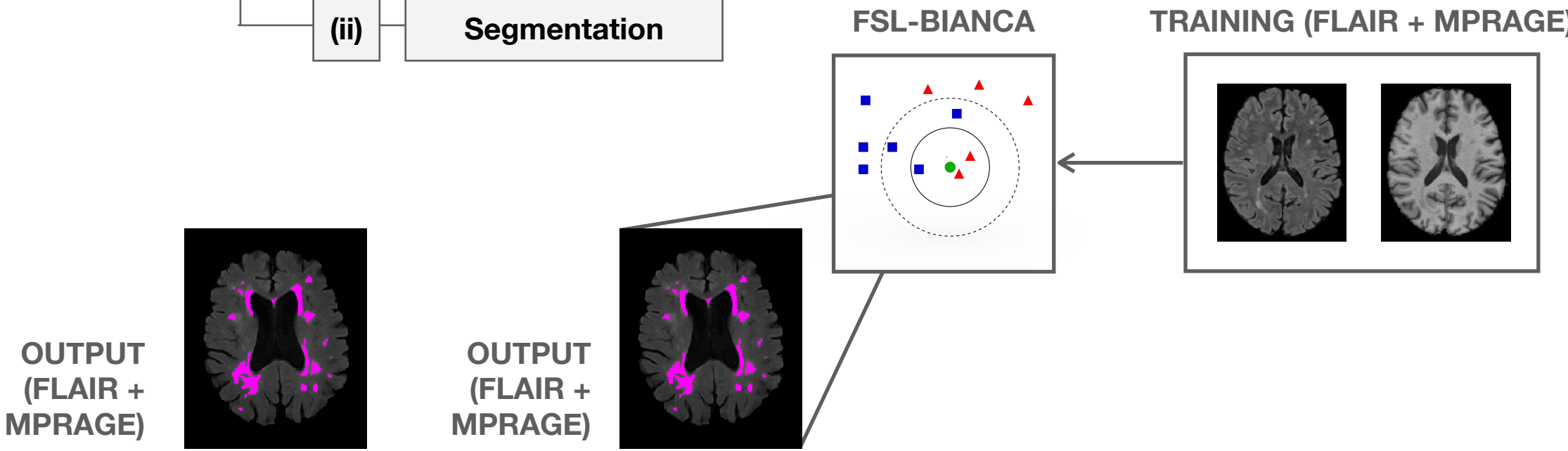

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WP2 – Aim & Methods (3)

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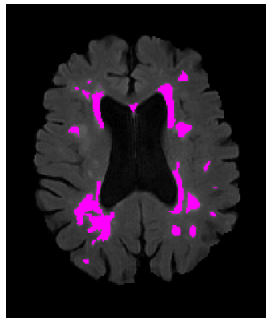

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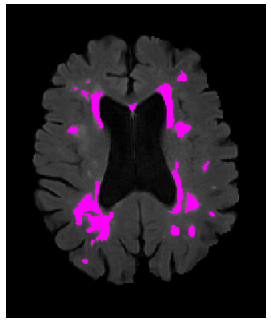

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WP2 – Aim & Methods (3)

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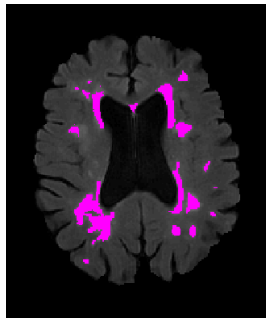

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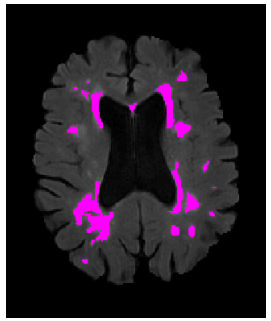

The obtained results were **compared** in terms of **DSI** with respect to manual annotation.

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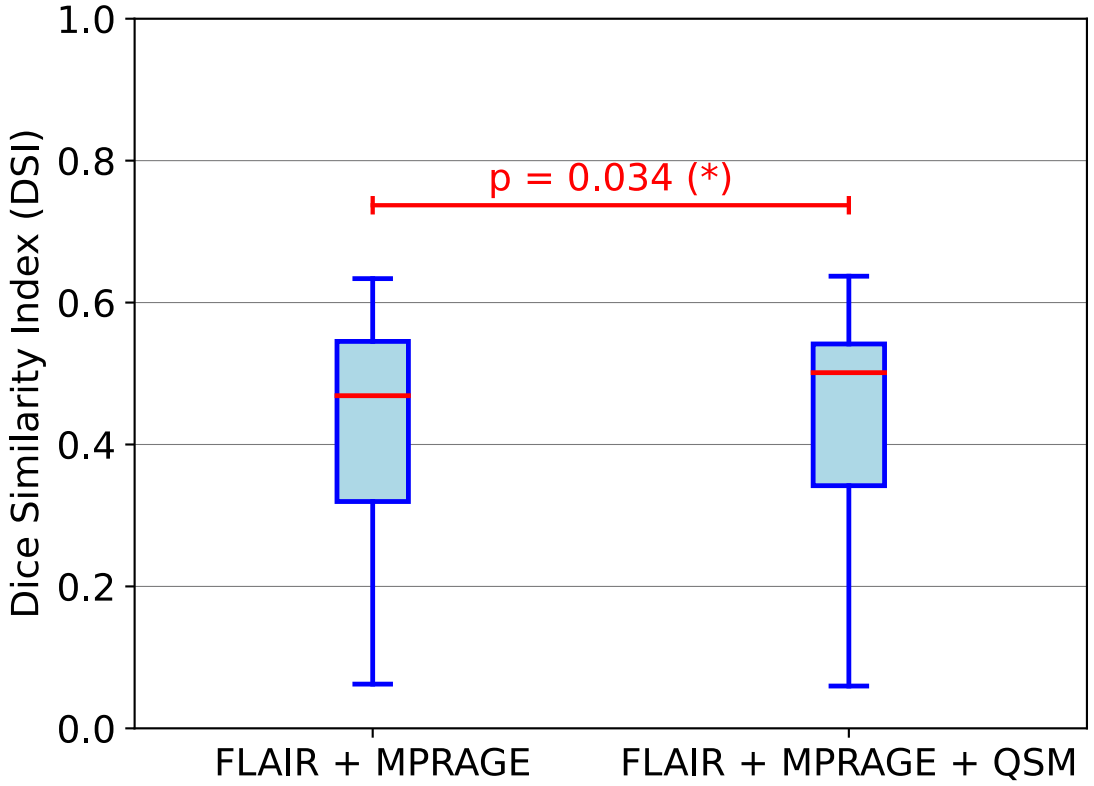
WP2 – Results (3)

Preliminary analysis

Almost all subjects (i.e., 14 out of 17) showed p-values < 0.001, indicating the presence of significant differences (i.e., **QSM CONTRAST**) between the susceptibility values of WMLs and NAWM.

Segmentation



Presence of a significant difference between the two set of modalities, with a **preference for including QSM**.

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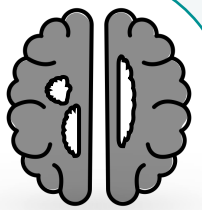
WP2 – Conclusions

- The **good level of repeatability** found at high nTEs suggest that QSM could be used to segment WMLs without introducing biases in the results.
- QSM seem **effective in enhancing** lesion **segmentation** (at least for MS-related WMLs).



WP2

"QSM repeatability and potentials in segmenting white matter lesions"

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WP2 – Conclusions

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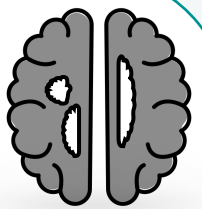
⇩

However, further investigation on larger datasets focused specifically on WMHs is needed.



WP2

"QSM repeatability and potentials in segmenting white matter lesions"

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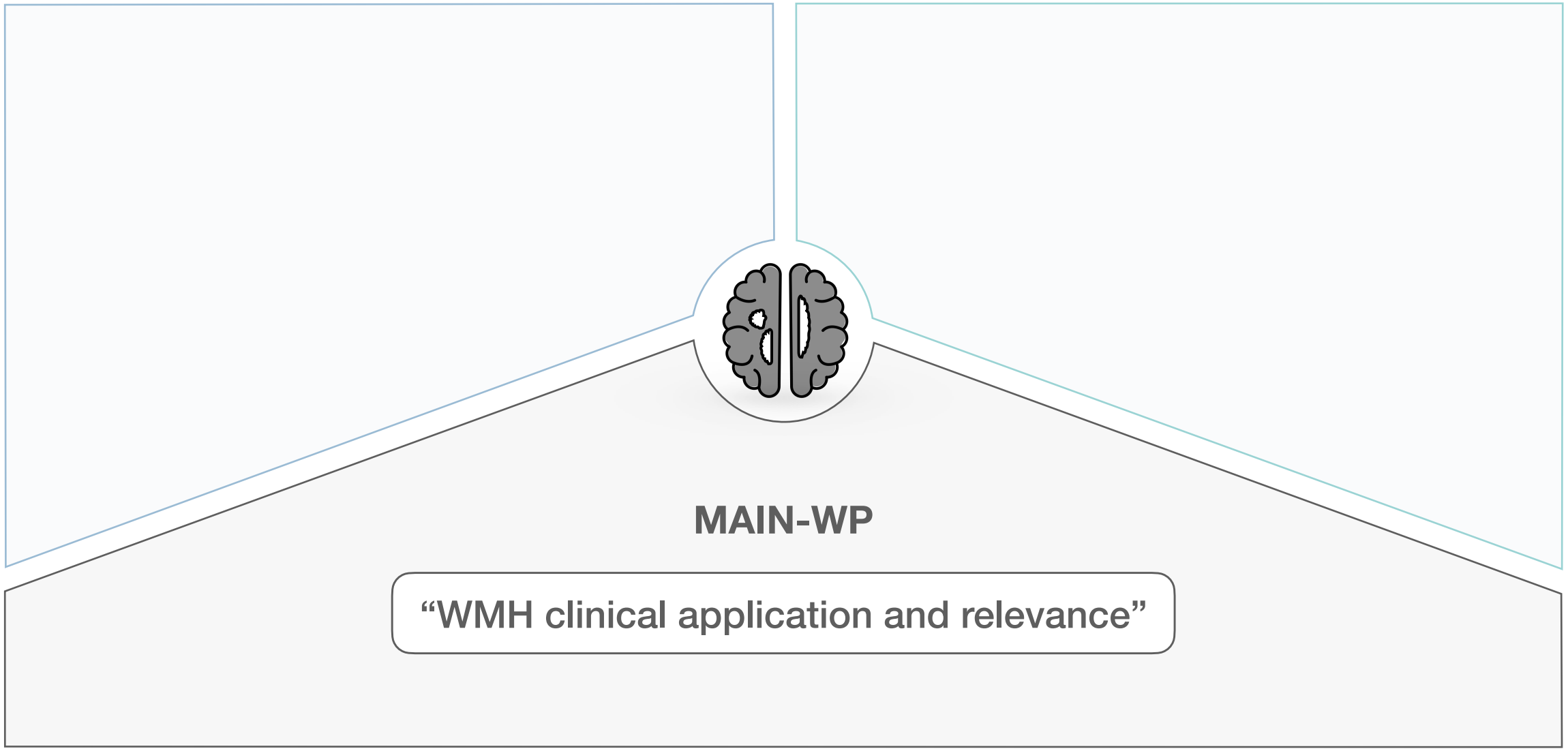
PhD overview



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MAIN-WP – Introduction (1)

SCIENTIFIC QUESTION

"Can the comprehensive 3D features of WMHs, such as spatial location and signal intensity, significantly enhance the disease identification?"

AIM

Develop a deep learning (DL)-based classification model for AD and assess the level of explainability of WMHs through XAI techniques.

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PILOT STUDY

MAIN STUDY

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PILOT STUDY	
DL model	EfficientNetB0
XAI model	Occlusion Sensitivity
Dataset	OASIS-3 (n=251)
Data dimensionality	2D
MRI modalities	FLAIR
WMH masks	Manual (n=8)

MAIN STUDY	
DL model	ResNet50
XAI model	Grad-CAM
Dataset	ADNI3 (n=611)
Data dimensionality	3D
MRI modalities	i) FLAIR; ii) FLAIR + T1-weighted
WMH masks	BIANCA(WH, UKB) (n=611)

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WP1

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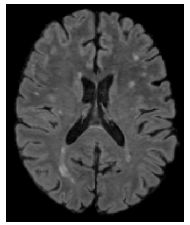
MAIN-WP – Methods (1)

PILOT STUDY



FLAIR

251

EfficientNetB0 → GAP → ReLU activation (FC layer (1024)) → ReLU activation (FC layer (1024)) → ReLU activation (FC layer (512)) → Sigmoid activation (Classifier)

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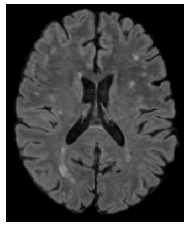
MAIN-WP – Methods (1)

PILOT STUDY

Target areas for XAI are: WMHs and Normally appearing Tissue (NT).



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251

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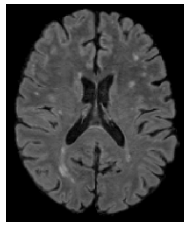
MAIN-WP – Methods (1)

PILOT STUDY



FLAIR

251

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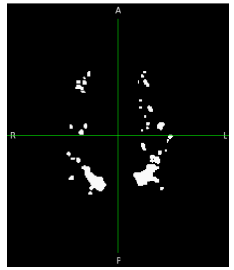
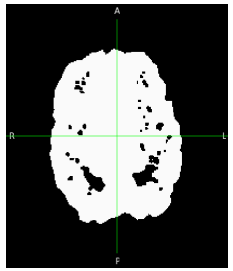
8

XAI ALGORITHM

EXPLAINABILITY HEATMAP



RV (WMHs)



RV (NT)

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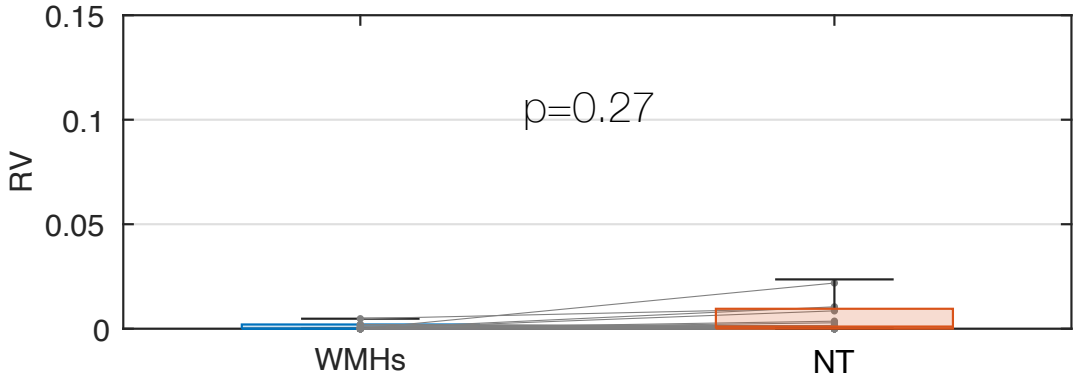
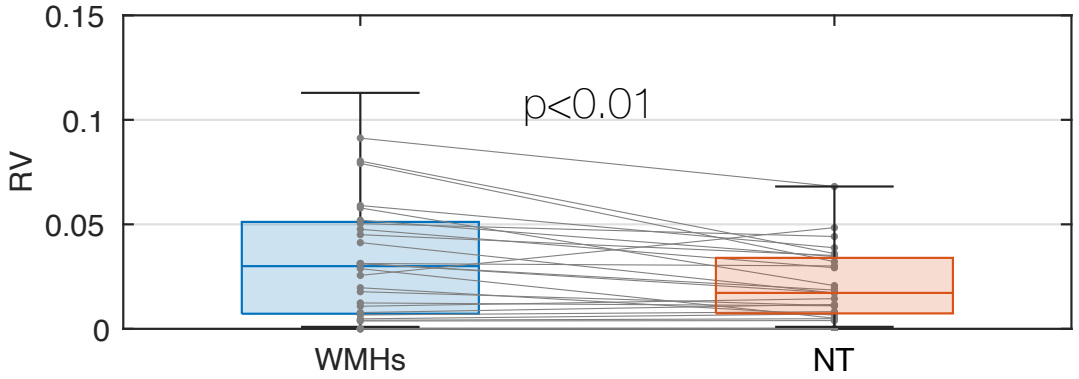
MAIN-WP – Results (1)

Healthy Controls (HC) – correctly classified



No significant difference between tissue types in the RV of the HC subjects.

Alzheimer's Disease (AD) – correctly classified



WMHs are characterised by higher RV (i.e., are considered more by the model) with respect to normally appearing tissue.

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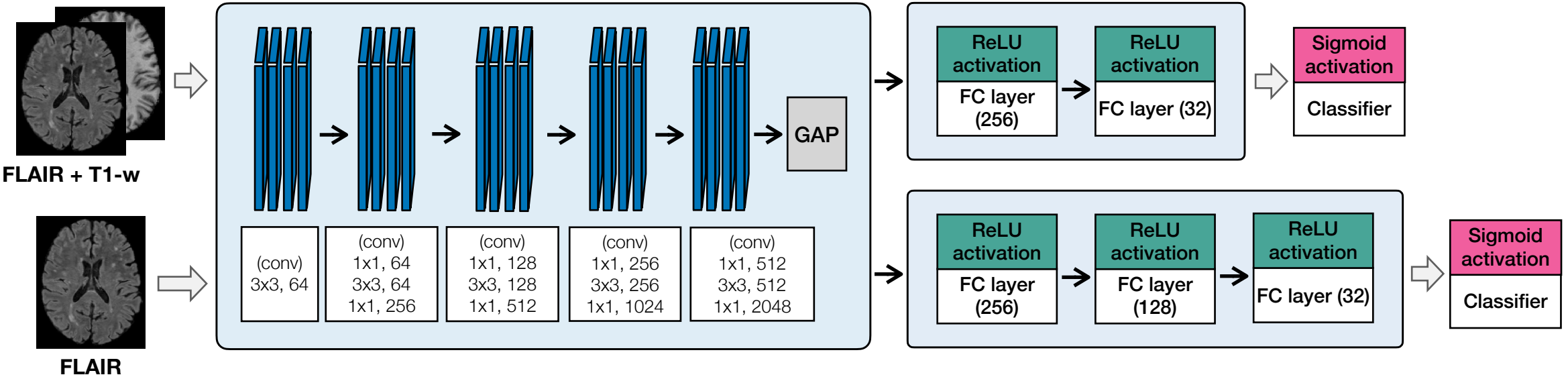
MAIN-WP – Methods (2)

MAIN STUDY



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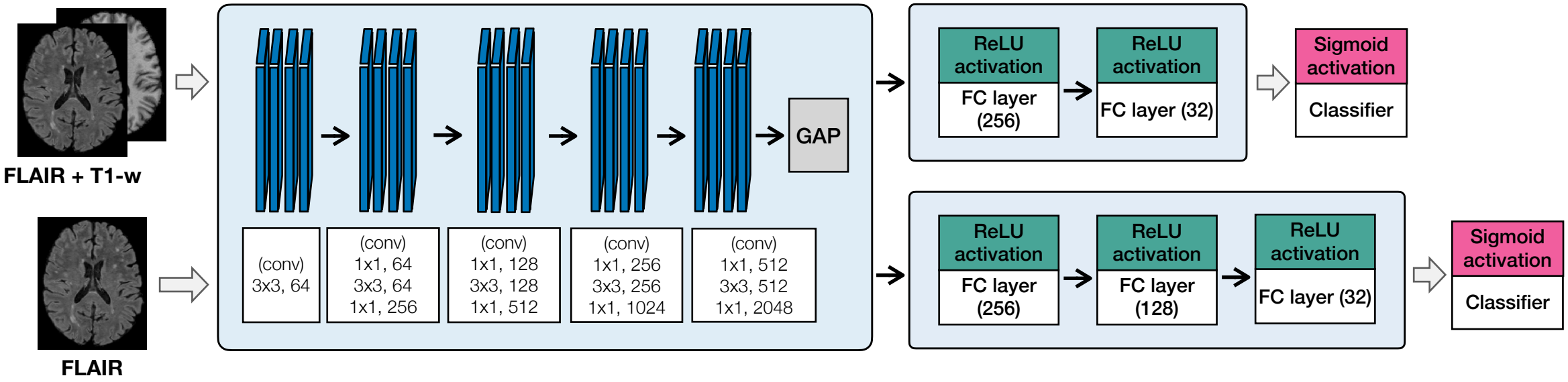
MAIN-WP – Methods (2)

MAIN STUDY

Target areas for XAI are: WMHs, NAWM and 8 cerebral grey matter areas representing a well-established biomarker of AD – the medial temporal lobe (MTL) [1,2].



[1] Cutsuridis and Yoshida. (2017).
[2] Frisoni et al. (2010).

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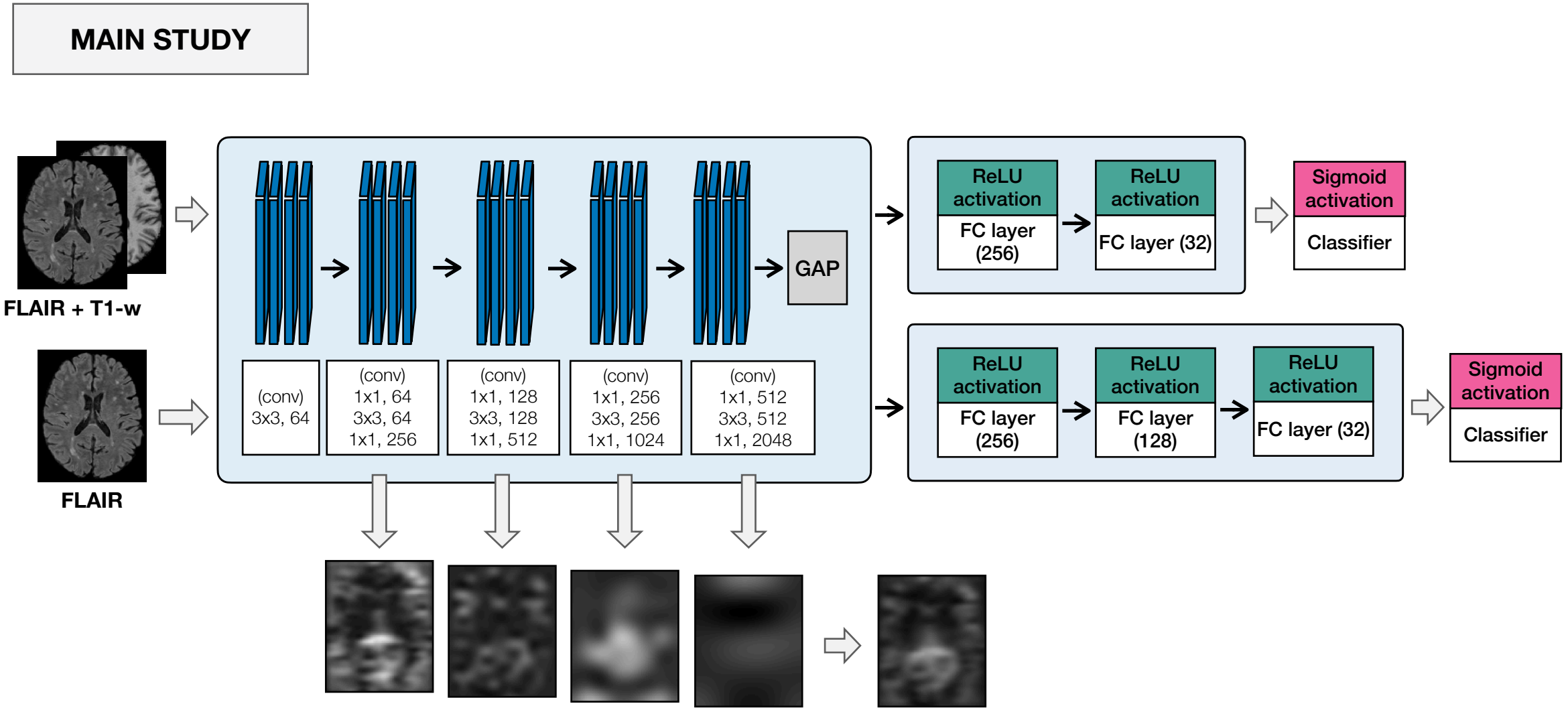
MAIN-WP – Methods (2)



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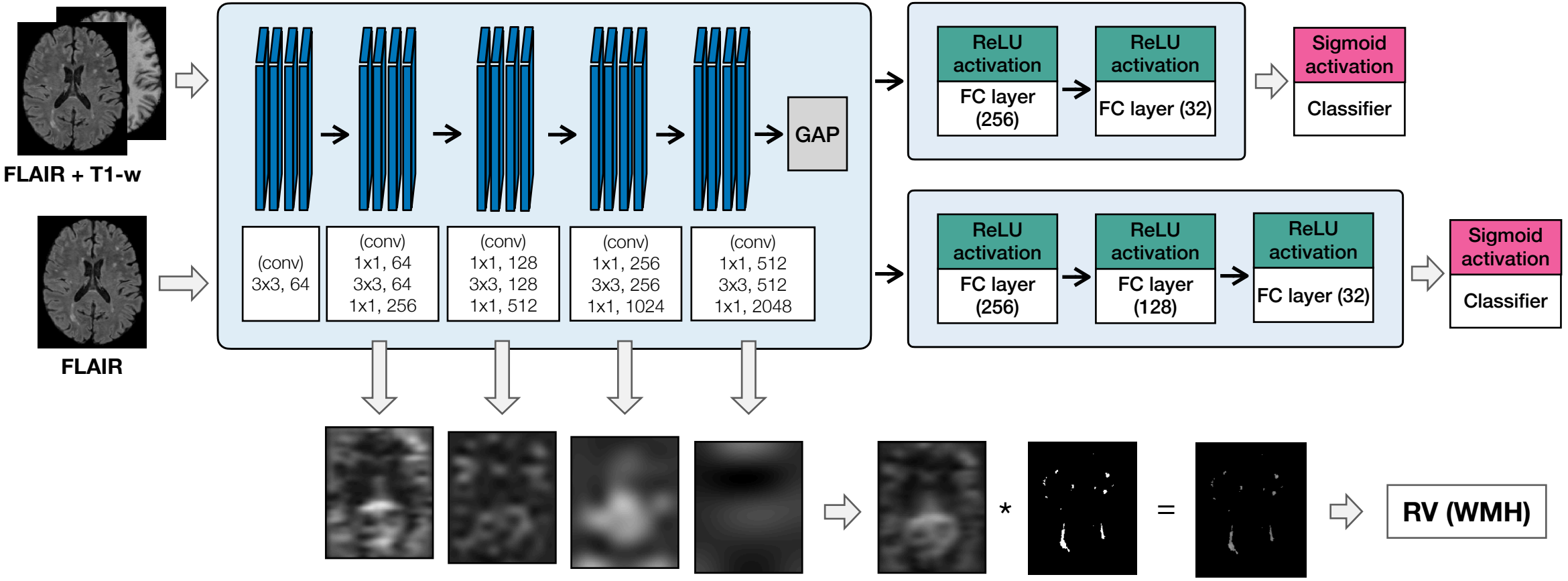
MAIN-WP – Methods (2)

MAIN STUDY



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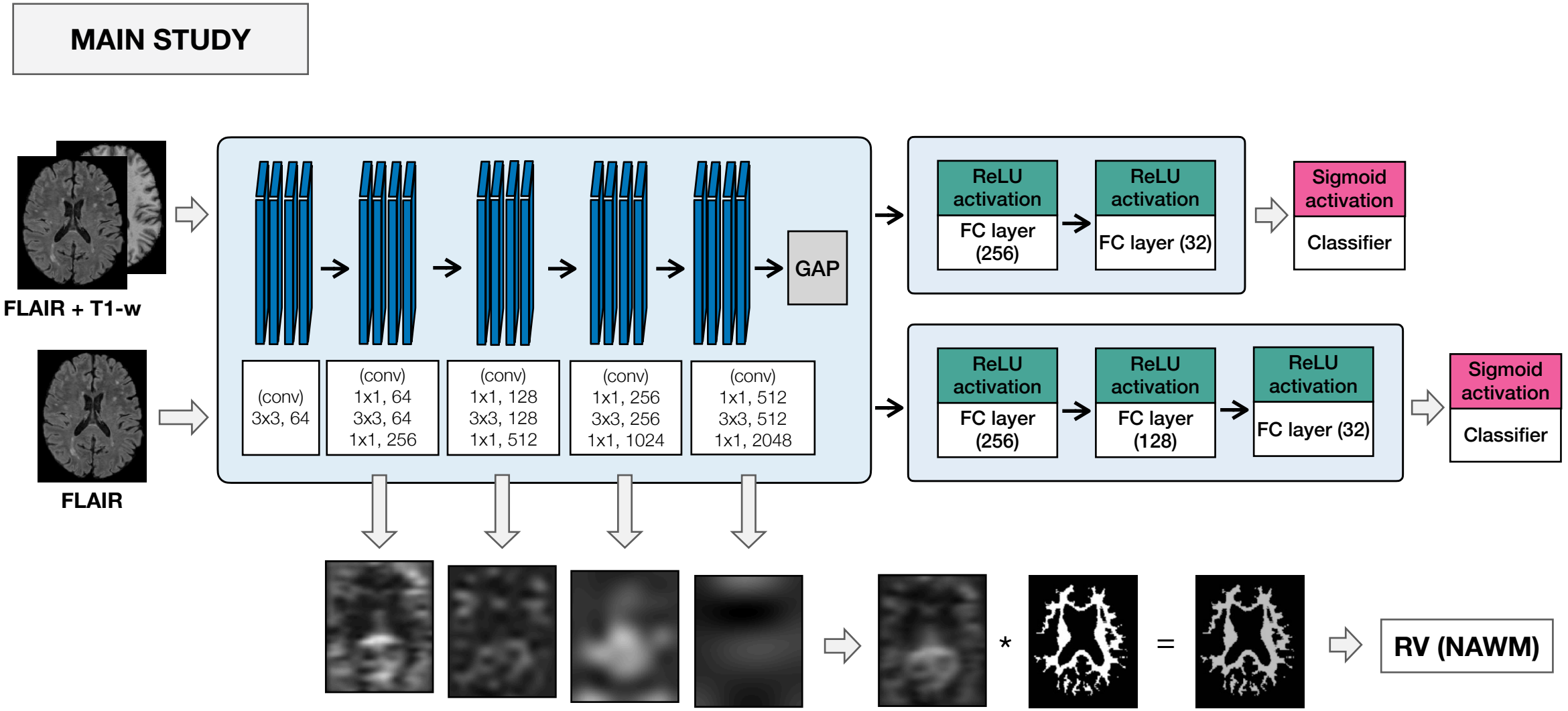
MAIN-WP – Methods (2)



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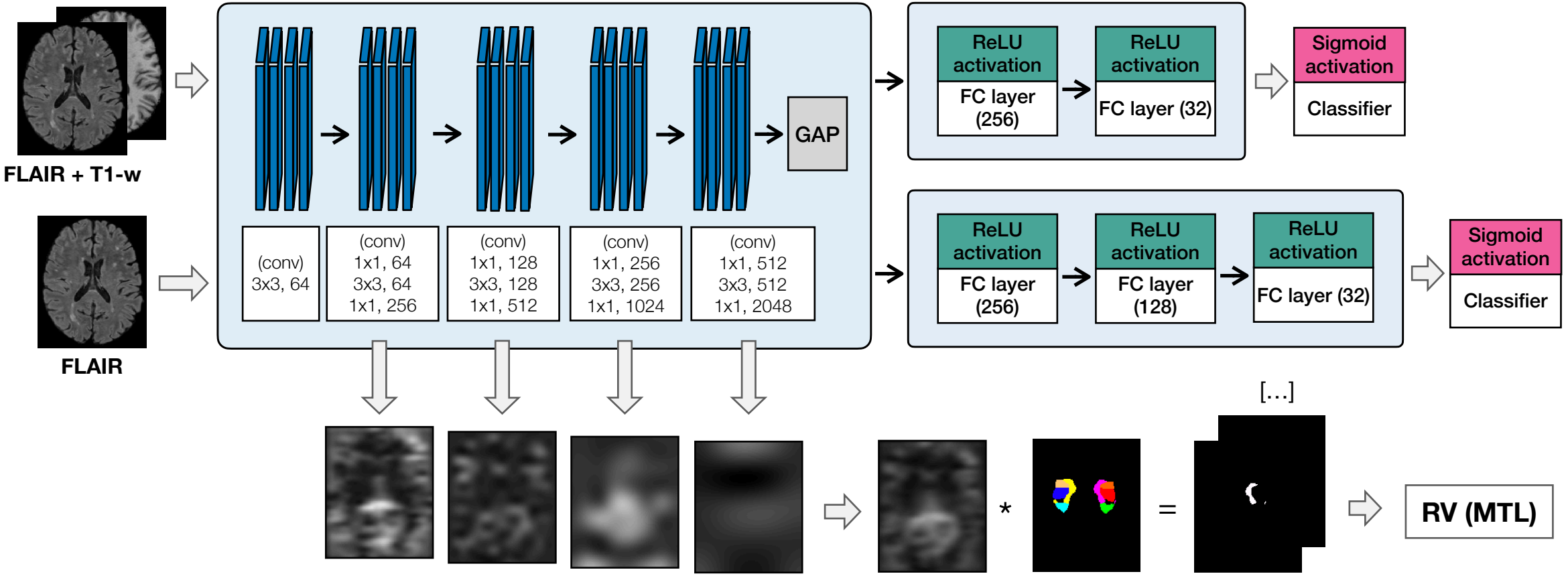
MAIN-WP – Methods (2)

MAIN STUDY



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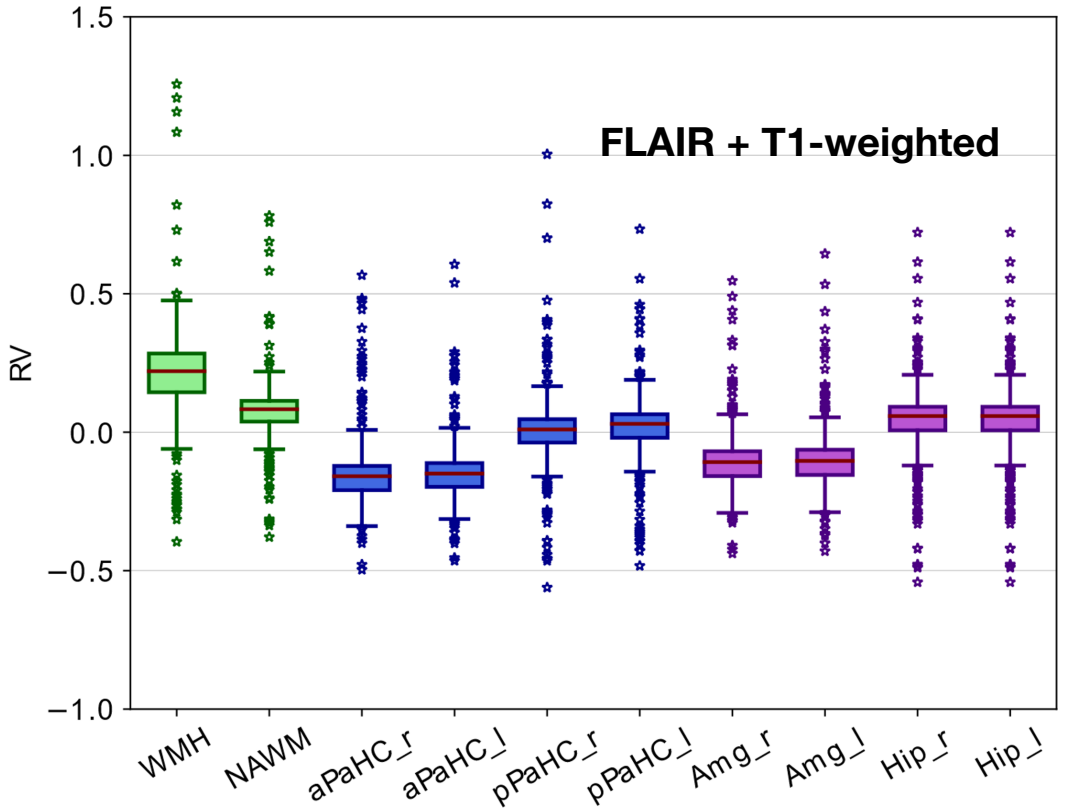
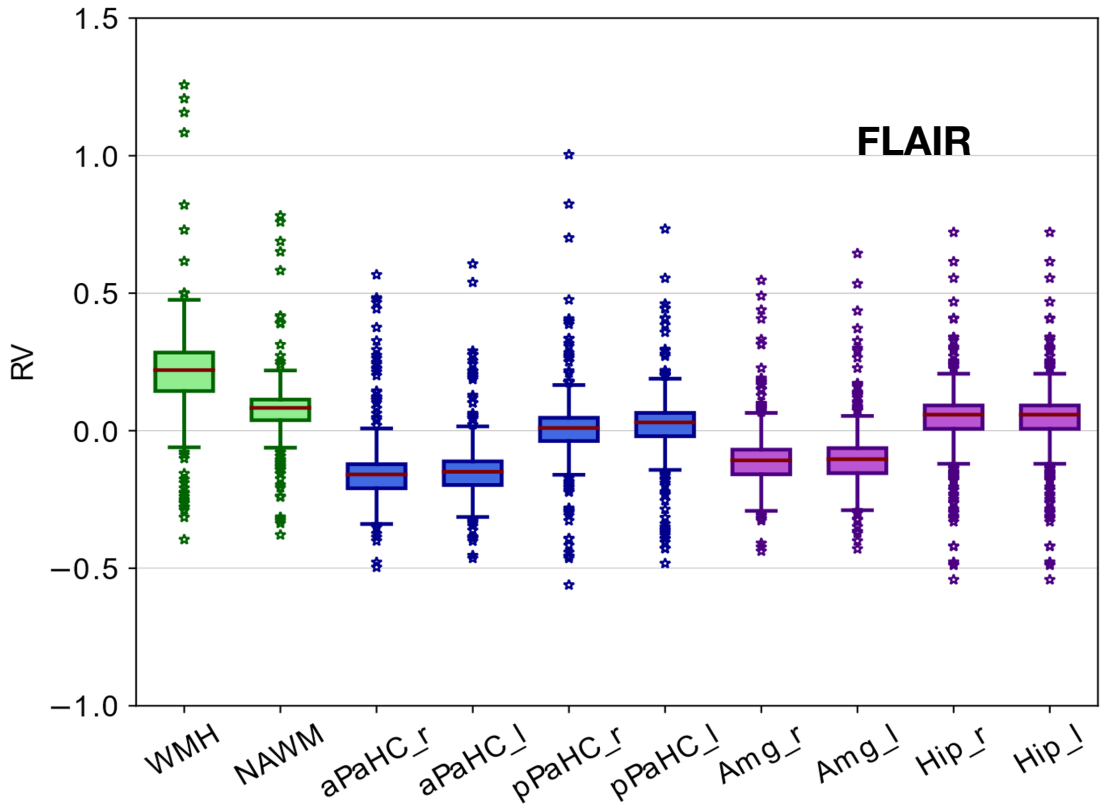
MAIN-WP – Results (2)





ANOVA test: p-value < 0.001 for post-hoc relative to WMHs.

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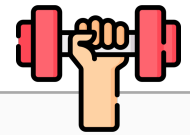
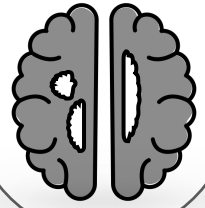
MAIN-WP – Conclusions

- **PILOT:** despite the limited sample size used for XAI, WMHs had higher impact on the final classification compared to the healthy tissue.
- **MAIN:** on a bigger population, WMHs demonstrated higher relevance compared to NAWM and MTL parcels – both for FLAIR + T1-weighted and FLAIR alone.



This reinforces pre-existing results and suggests that multimodality has little impact on explainability.



MAIN-WP

"WMH clinical application and relevance"

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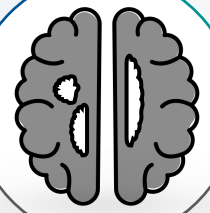
PhD overview

WP-1

"Harmonisation of WMH Measures"

WP-2

"QSM repeatability and potentials in segmenting white matter lesions"



MAIN-WP

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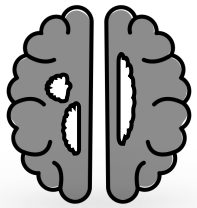
Discussion & Conclusions



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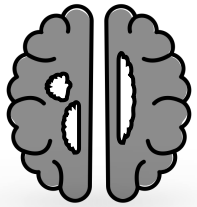
Discussion & Conclusions

- **Extensive validation of BIANCA(WH, UKB)** – an openly available training set (https://git.fmrib.ox.ac.uk/open-science/analysis/wmh_harmonisation/-/tree/master/) that allows to reduce the measurement bias when segmenting WMHs from multi-centric data.

- Useful in contexts where manual rating is impractical (e.g., **MAIN-WP**).

- *Usability limitation: there must be a correspondence between the imaging modalities used in BIANCA(WH, UKB) and those used for testing.*



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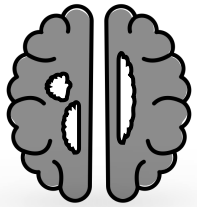

- The inclusion of **QSM has emerged as a valuable asset** for lesion segmentation in a specific application context (MS-lesions), but *results cannot be generalised due to limited sample size.*
- Additionally, despite the **promising repeatability** demonstrated by QSM, *large-scale databases focused on vascular lesions (WMHs) were lacking in the current work.*

⇩

Expanding the dataset and scope would lay the foundations for translating QSM into the current segmentation pipeline.

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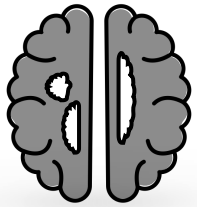
Discussion & Conclusions

- The **relevance characterising WMHs was consistent** across both the conducted analyses (i.e., PILOT- and MAIN-STUDY), despite using different DL models and different XAI approaches.

⇩

This suggests a certain degree of reliability in our findings



- *The results are promising in terms of the original goal of this work:* ***to evaluate the possibility of enhancing the AD identification through WMHs.***

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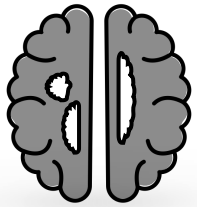

FUTURE DEVELOPMENTS

- Development of approaches that integrate **imaging-derived measures** and **raw MRI data**. This could allow for a more comprehensive investigation into the relative efficacy of WMHs in AD diagnosis.

- Extending this analysis to a cohort of preclinical subjects would provide invaluable insights into the early stages of the disease.

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QuanTIM Webinar

Thanks for the attention!!

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Milan, June 20th 2025