Quantifying longitudinal microstructural tissue changes in MS lesions with a unified metric derived from multiparametric quantitative MRI

Giuseppe Battaglia[1], Sara Alampi[1], Giordano Gentile[1,2], Alessandro Cagol[3,4,5,6], Ludovico Luchetti[1,2], Mario Ocampo-Pineda[3,4,5], Alessia Bianchi[1], Valentina Damato[7,8], Ludwig Kappos[4,5], Cristina Granziera[3,4,5], Nicola De Stefano[1,2], Marco Battaglini[1,2*], Rosa Cortese[1*]

[1]Department of Medicine, Surgery and Neuroscience, University of Siena, 53100 Siena, Italy. [2]Siena Imaging SRL, 53100 Siena, Italy. [3]Translational Imaging in Neurology (ThINk) Basel, Department of Biomedical Engineering, Faculty of Medicine, University Hospital Basel and University of Basel, Switzerland. [4]Multiple Sclerosis Centre, Departments of Neurology, Clinical Research and Biomedicine, University Hospital and University Basel, Switzerland. [5]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital Basel and University of Basel, Switzerland. [6]Dipartimento di Scienze della Salute, Università degli Studi di Genova, Genoa, Italy. [7]Department NEUROFARBA, University of Florence, Italy. [8]Careggi University Hospital of Florence, Italy.
*joint last authors.

Finanziato dall'Unione europea NextGenerationEU | Ministero dell'Università e della Ricerca | Italiadomani | Università degli Studi Firenze

INTRODUCTION

Advanced quantitative MRI **(qMRI) provides tissue-specific measures sensitive to microstructural changes**, such as myelin and axonal damage [1]. While different qMRI modalities highlight complementary pathological features within white matter lesions (WMLs) in MS, integrating them to track tissue changes over time remains challenging.

OBJECTIVES

To develop a unified voxel-wise method that integrates longitudinal qMRI data to characterize microstructural changes in WML and surrounding tissue, and assess its relevance via associations with chronic inflammation, neurodegeneration, and disability accumulation.

METHODS

Study population: We studied **41 people with MS** from the INsIDER Basel cohort, who underwent a 3T MRI at 2 timepoints. Clinical and MRI details available in Table 1.

Sex	Age (mean±SD)	Disease duration (mean±SD)	EDSS (median[range])	cEDSS/y (mean±SD)
26F + 15M	45.23±14.83 years	9.87±11.68 years	2.0[0.0, 6.5]	0.08±0.29
qMRIs		**cMRIs**	**Follow up (mean±SD)**	
T1map, QSM, MWF		T1w, FLAIR	2.00±0.07 years	

Table 1. Data information. Abbreviations: myelin water fraction (MWF), quantitative susceptibility mapping (QSM), annualized EDSS change (cEDSS/y), conventional MRI (cMRI), standard deviation (SD).

Data processing: After identifying WMLs on FLAIR and black holes (BH) on T1w, external portion (EP) and perilesional tissue (PT) regions were segmented (Figure 1). Paramagnetic Rim Lesions (PRLs) were identified using Chimap/phase imaging. Brain atrophy was quantified via percentage brain volume change (PBVC) using FSL SIENA tool [2].

Mahalonobis map: A novel map that captures multiparametric microstructural abnormalities over time was generated by computing Mahalanobis distance in qMRI change maps between lesions and a reference region (Figure 2). The Mahalanobis distance can be interpreted as the Euclidean distance where differences are weighted according to the covariance of the data. The higher the distance from the reference region distribution (i.e., the higher abnormality), the higher the magnitude of the Mahalanobis map.

Statistics: To evaluate differences across lesion regions, generalized linear mixed-effect models were used, with covariates adjustement (age, sex, follow up interval, lesion volume), mean Mahalanobis distance as dependent variable, region as regressor and subject as random factor. The same model was applied to assess differences in chronic inflammation state (PRL vs non-PRL) and to evaluate associations with brain atrophy or disease accumulation, with PBVC or cEDSS/y as regressors, respectively.

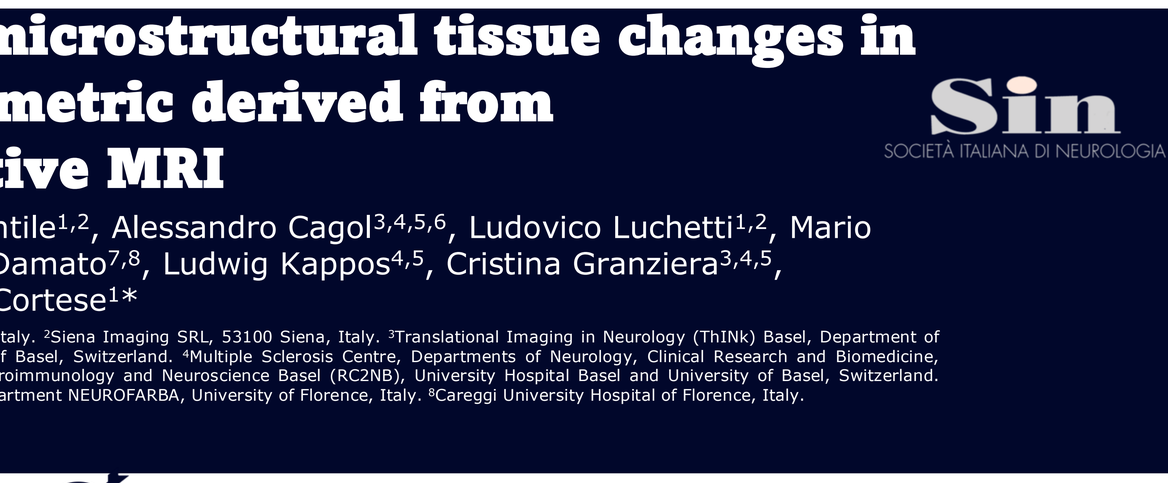

Figure 1. Lesion regions identification scheme. First, **WML** mask was identified segmenting FLAIR-hyperintensities. Then T1-hypointenisietes in WML mask were identified as black hole (**BH**) region. Finally, external portion (**EP**) was defined the as region between BH and lesion edge, while peri-lesional tissue (**PT**) region as 2 mm-ring beyond lesion edge.

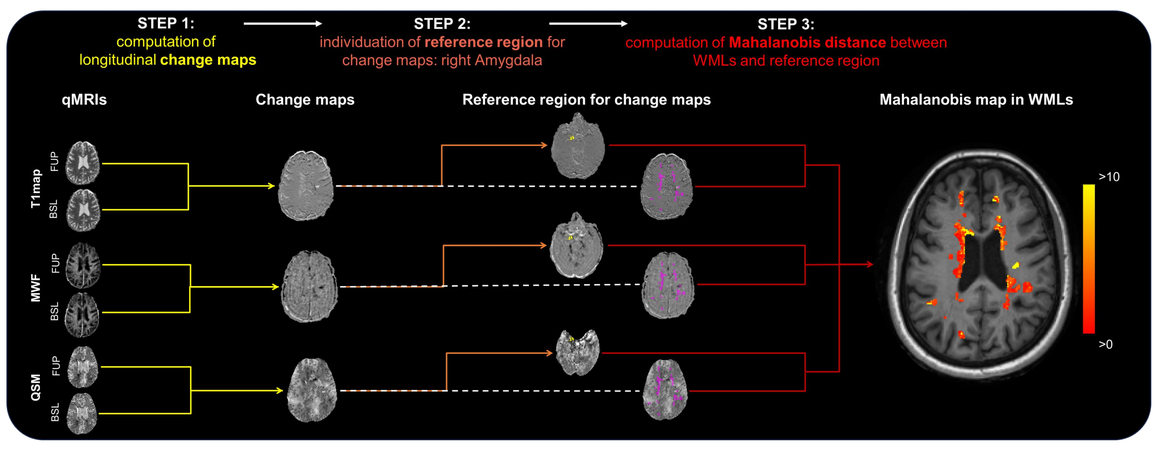

Figure 2. Longitudinal microstructural abnormality mapping scheme. Step 1) computation of longitudinal (BSL: baseline, FUP: follow up) change maps from qMRIs. Step 2) Individuate the most time invariant anatomical region common to all sequences. Step 3) compute Mahalanobis distance in change maps between WMLs voxels and the reference region distribution.

RESULTS

A total of 804 WMLs with BH were analysed, of which 71 (9%) PRLs. When considering all WMLs, **Mahalanobis maps** revealed **an "inside-out" gradient of microstructural abnormalities**, with the highest values in BH and decreasing in EP and PT (mean:4.8±6.7, 3.1±3.3, 1.2±1.5 respectively, p<0.01; WML: 3.3±3.5) (Figure 3A). **PRLs had higher Mahalanobis values than non-PRLs** within BH and EP (p<0.01) (Figure 3B).

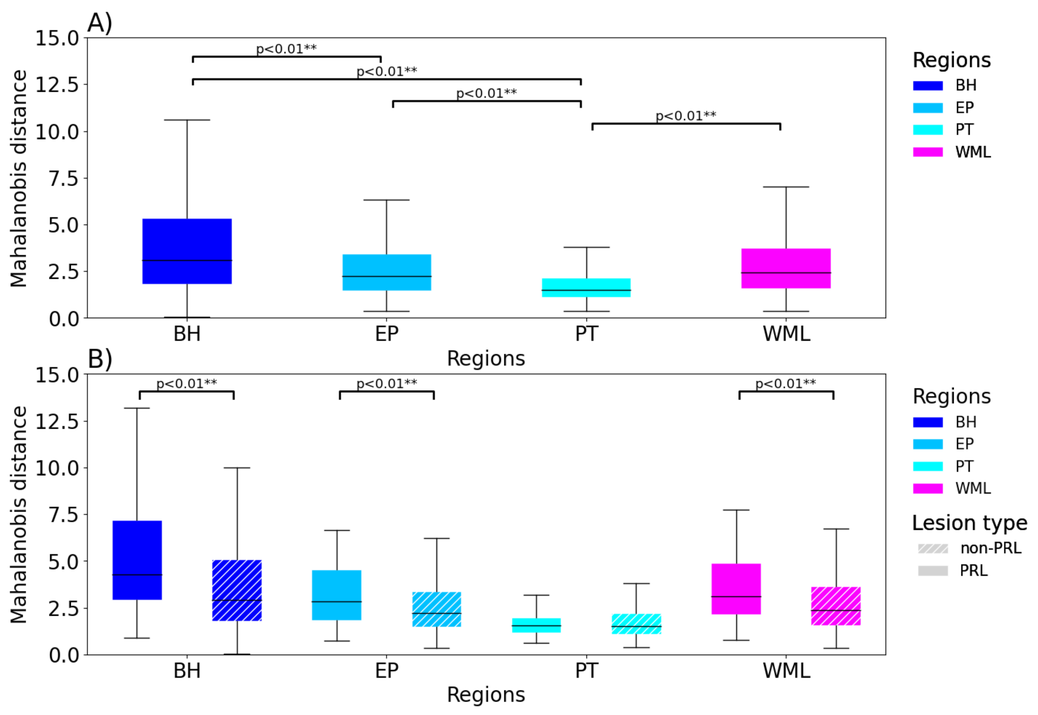

Figure 3. A) Boxplots of Mahalanobis distance in lesion regions unstrarified (A) and stratified in PRLs and non-PRLs (B). Abbreviations: black hole (BH), external portion (EP), perilesional tissue (PT), white matter lesion (WML).

In PRLs only, **higher Mahalanobis values were associated with lower PBVC** (BH: b=-1.98; EP: b=-0.98; WML: b=-1.12) (Figure 4). In non-PRLs, no associations with atrophy were found. In all lesion types, no associations with disability accumulation were found.

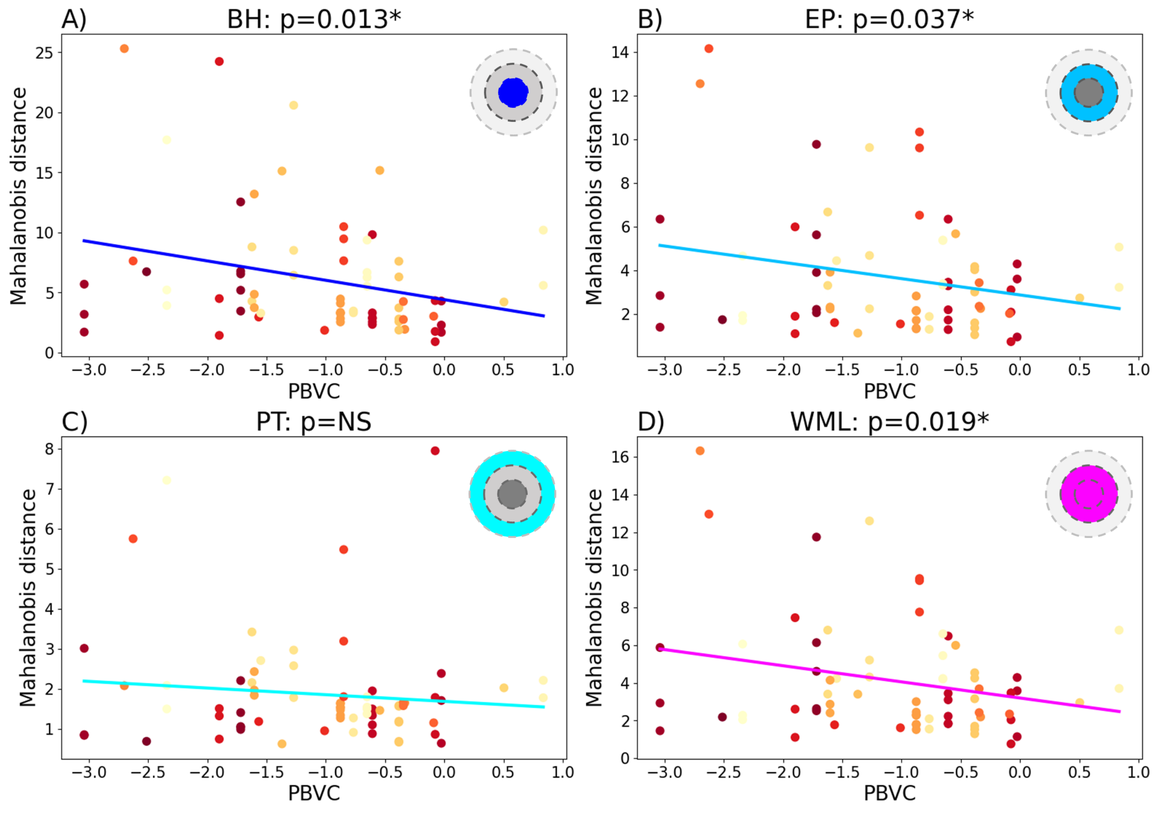

Figure 4. Scatter plot showing associations between PBVC (x axis) and Mahalanobis distance (y axis) in each WML region (A-C) and in WMLs (D). Each line represents the regression as obtained from the linear model, each dot correspond to a WML, and the color of dots indicate different subjects. Abbreviations: non-significant (NS), black hole (BH), external portion (EP), perilesional tissue (PT), white matter lesion (WML).

CONCLUSIONS

Our novel multiparametric approach enables **comprehensive mapping of microstructural changes across MS lesion** compartments, particularly in chronic active lesions. By capturing distinct pathological signatures of abnormalities, it may provide new relevant markers of neurodegeneration as indicated by correlations with brain atrophy.

References

[1] Sanabria-Diaz G, Cagol A, Lu PJ, Barakovic M, Ocampo-Pineda M, Chen X, Weigel M, Ruberte E, Siebenborn NOS, Galbusera R, Schädelin S, Benkert P, Kuhle J, Kappos L, Melie-Garcia L, Granziera C. Advanced MRI Measures of Myelin and Axon Volume Identify Repair in Multiple Sclerosis. Ann Neurol. 2024 Oct 10;97(1):134–48. doi: 10.1002/ana.27102. Epub ahead of print. PMID: 39390658; PMCID: PMC11683175.
[2] Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage. 2002 Sep;17(1):479-89. doi: 10.1006/nimg.2002.1040. PMID: 12482100

DISCLOSURES

S. Alampi is funded by the Italian Ministry of University and Research – Research Project of Relevant National Interest (PRIN), project code: 2022PR3PEY. **A. Cagol** is supported by EUROSTAR E!113682 HORIZON2020 and received speaker honoraria from Novartis and Roche. **A. Bianchi** has received a research grant from the Italian Society of Neurology; she has been awarded a MAGNIMS-ECTRIMS fellowship in 2023; she received speaking honoraria from Biogen. **V. Damato** has received public speaking honoraria and compensation for advisory boards and/or consultations fees from UCB, Alexion, Dianthus, Roche. She declares no competing interest regarding this work. **L. Kappos** has received no personal compensation. His institutions (University Hospital Basel/Stiftung Neuroimmunology and Neuroscience Basel) received payments for steering committee, advisory and data safety monitoring board participation, consultancy services and educational activities from Bayer, Biogen, Bristol Myers Squibb, Celltrion Inc, Clene Nanomedicine Inc., EMD Serono Research and development, Galapagos NV, Genentech, Immunic AG, Janssen, Kiniksa Pharmaceuticals, Merck Healthcare AG, MSD Merck Sharp & Dohme AG, Minoryx Therapeutics S.L., Neurostatus UHB AG, Novartis, Roche, Sanofi, Shionogi BV, Wellmera AG and Zai Lab and received research support from Novartis, Roche and Innosuisse.. **C. Granziera** The University Hospital Basel (USB), as the employer of C.G., has received the following fees which were used exclusively for research support: (i) advisory board and consultancy fees from Actelion, Genzyme-Sanofi, Novartis, GeNeuro and Roche; (ii) speaker fees from Genzyme-Sanofi, Novartis, GeNeuro and Roche; (iii) research support from Siemens, GeNeuro, Roche. Cristina Granziera is supported by the Swiss National Science Foundation (SNSF) grant PP00P3_176984, the Stiftung zur Förderung der gastroenterologischen und allgemeinen klinischen Forschung and the EUROSTAR E!113682 HORIZON2020. **N. De Stefano:** is a consultant for Biogen, Merck, Novartis, Sanofi-Genzyme, Roche, and Teva; has grants or grants pending from FISM and Novartis, is on the speakers' bureaus of Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; and has received travel funds from Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. **R. Cortese** received speaker honoraria/travel support from Roche, Merck Serono, UCB, Sanofi-Genzyme, Alexion, Novartis, and Janssen, and received a research grant from the Italian Ministry of University and Research. **G. Gentile, L. Luchetti, M. Ocampo-Pineda, G. Battaglia, M. Battaglini:** have nothing to disclose.

The study is funded by the Italian Ministry of University and Research – Research Project of Relevant National Interest (PRIN), project code: 2022PR3PEY and by the European Union - Next Generation EU, PNRR MUR M4 C2 Inv. 1.5 of the National Recovery and Resilience Plan (PNRR), project ECS00000017 Tuscany-Health Ecosystem-Spoke6—CUP B63C2200068007.