# NEW TECHNOLOGIES APPLIED TO CLINICAL PRACTICE FOR OBTAINING BIOMARKERS OF ATROPHY AND LESIONS IN MAGNETIC RESONANCE IMAGES OF PATIENTS WITH MULTIPLE SCLEROSIS (BIOMARKEM.CAT)

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## 1. Summary


### Background

Recent studies have shown that magnetic resonance markers can be useful in predicting the clinical course of multiple sclerosis (MS), both in terms of natural history and response to therapy. These markers include the presence of new lesions, as well as the loss of brain volume in follow-up magnetic resonance scans. However, to transfer these research studies to clinical practice, there is a need for technologies and computer tools capable of providing accurate and robust measurements for the atrophy and evolution of MS lesions in a reproducible and efficient manner.

### Main goal

The main objective of the BiomarkEM.cat project has been to develop, validate and implement fully automated and robust tools to measure biomarkers of brain tissues and lesions in magnetic resonance images of patients with multiple sclerosis.

### Scientific objectives

- Development of new tools to provide MRI biomarkers of brain volume.
- Development of new tools for the automated segmentation of MS lesions in cross-sectional studies and new lesions in longitudinal studies.
- Complete automation and generalization of the tools for three magnetic resonance machines (Siemens, Philips and General Electric), including 1.5T and 3T images.
- Evaluation and validation of magnetic resonance biomarkers in studies with longitudinal data. Correlation with the measures of clinical experts.

### Methodology

The project coordinated by the University of Girona, and with the participation of the Vall d'Hebron Hospital and the Biomedical Research Institute of Girona (IDIBGI), which includes the Dr. Josep Trueta Hospital and the Santa Caterina Hospital, has been carried out by a multidisciplinary team of computer scientists, radiologists and neurologists with a strong background and experience in the field. The project has consisted of the following fundamental blocks: 1) Data collection, 2) Development of tools to obtain biomarkers of atrophy, 3) Development of tools for the extraction of

lesion biomarkers, 4) Validation of tools and study of the correlation, and 5) Proof of concept.

**Population and sample size of the study**

The project had two validation cohorts. The first one included 10 healthy subjects and 10 patients with MS who underwent scans in a short period of time (less than 4 weeks) at the 3 MRI machines available in the medical centers participating in the project. These patients had two scans (one baseline and a second one after one year) on each machine. The second validation cohort included 3 subcohorts of 20 patients with MS each acquired with a different MRI scanner (60 MS patients in total). The data collection of each subcohort was homogeneous, also including the baseline images and the 12-month follow-up in order to analyze the longitudinal studies. The 3 subcohorts were merged into one during the proof of concept to make a quantitative analysis of the results of the tools developed with respect to the manual annotations of the experts.

**Results**

Set of automatic and universal computer tools, tested on three magnetic resonance scanner machines (Siemens, Philips and General Electric), including 1.5T and 3T images. The tools have been integrated into the hospital centers to improve the evaluation of the evolution of MS.

## 2. Results

At the beginning of the project, the radiological and magnetic resonance protocol was defined jointly with radiologists and neurologists, and was used throughout the project's image acquisition: axial 3DT1 or isotropic sagittal 1x1x1, and T2-w, PD-w, and FLAIR in 2D axial to 3 mm. The 1.5T magnetic resonance data were used for the two IDIBGI hospitals (Hospital Dr. Josep Trueta and Hospital Sta. Caterina, Philips and GE scanners, respectively) and 3T (Siemens) for the Hospital Vall d'Hebron (Barcelona) in order to perform a better analysis of the tools developed. It was also agreed that the manual annotations of the lesions would all be carried out at the Vall d'Hebron Hospital, where they have experts with many years of experience, thus avoiding variability in annotations made by different experts.

During the first year of the project, research began on the two main lines of development within the project: automatic tools for tissue segmentation and tools for segmentation of multiple sclerosis lesions. One of the first indispensable stages was to analyze and study the best preprocesses that should be applied to these magnetic resonance images, evaluating the effect of the main preprocesses in the algorithms of tissue and lesion segmentation, such as skull-stripping (skull removal), bias-field, correction of intensities (normalization within the same scan) and the equalization of intensities between different scanners or longitudinal studies. Different state-of-the-art techniques were analyzed and evaluated, such as BET, BSE, SPM and ROBEX for skull stripping, N3, N4 and SPM for bias field correction and two techniques for the equalization of histograms (Nyul et al. of WhiteStripe). These algorithms were evaluated with the data sets of the project, as well as in different public databases such as those in different international competitions and workshops.

The early development related to tissue segmentation and entailed studies to analyze the effect of lesion filling, as well as the automation of this step together with the automatic segmentation of lesions [NI- CL15]. As a result of these studies, a new tissue segmentation proposal was developed using information from FLAIR and T1-w modalities, which internally incorporated an automatic detection of candidate regions to be lesion and a lesion filling process to improve the results of tissue segmentation. These results were published in the journal Medical Image Analysis, one of the most important in the field of medical image analysis and processing [MIA17].The quantification of longitudinal changes (atrophy rate) per patient using this tool was also analyzed. In general, the results analyzed by the medical experts participating in the project were very positive, correlating with the clinical values of the patients. Within the project, new algorithms were also developed to quantify the volumetry of the subcortical regions (gray matter of the brain) that are also used as local markers of atrophy in different neurodegenerative diseases. This line of research included the analysis of the effect of lesions on volumetric quantification [AAIM16, NI-CL17], as well as the proposal of new tools to obtain more precise measurements of these subcortical regions [MIA2018, NI-CL19].

The development part of the project related to the segmentation of lesions and obtaining the corresponding markers included different contributions. Firstly, the development of an unsupervised proposal for the automatic segmentation of lesions in

cross-sectional studies [NRAD2015], where new post-processing was proposed to help reducing the number of FP of these automatic segmentation tools. Subsequently, a new proposal for segmentation of lesions was also made, in this case a supervised strategy based on the use of pioneering techniques of artificial intelligence (deep learning). This development and the results obtained were published in the best journal of this research field, Neuroimage Journal [NI 2017]. This tool has had a great international impact winning and leading the results of different international competitions (Challenges of the MICCAI 2008 and MICCAI 2016). The two tools for segmentation of lesions in cross-sectional studies were thoroughly evaluated with the project data, having very positive results, with high sensitivity values and, most importantly, a small number of false positives (around 15%-20%), a feature that is highly desired by medical experts. Great correlation was also shown with the lesional volume noted by the medical experts in all the analyzed cases, superior for example to other tools of the state of the art of segmentation of lesions known internationally as LST. The developed tools were installed in the hospital centers through dockers (software containers) that allow great portability to different platforms and operating systems (Windows, MAC, Linux) and also the creation of simple interfaces to be used for example in hospital environments.

Techniques for the segmentation of new lesions in longitudinal studies were also developed within the project. Specifically, a new proposal based on the subtraction of images that incorporated the information of the deformation field obtained through a non-rigid registry between the two temporal studies of the same patient [AJNR16]. One of the main contributions of this work was the proposal of new post-processing rules aimed at reducing the detection of false positives of new lesions: 1) global and local rules based on intensity, and 2) deformation fields obtained through non-rigid registration. These deformation fields were used both to improve the detection of new lesions using this information, and to incorporate new post-processing rules. In this sense, regional metrics calculated from the deformation field (Divergence, Jacobian, Concentricity) of each candidate lesion were integrated, allowing to improve the differentiation between correct and false positive detections.

This tool to detect new lesions was subsequently improved with a supervised post-processing stage that allowed improving the number of false positives detected by the tool [NI-CL 2018]. These markers of new lesions, number of new lesions and change in

volume, were evaluated using the longitudinal data sets of the project, comparing them quantitatively and correlating with the manual annotations made by the medical experts participating in the project. It should also be noted that the tools were evaluated with healthy subjects who did not present new lesions to evaluate the possible detection of false positives. The results of this investigation demonstrated the ability of the tool to not detect false positives in these healthy cases, maintaining a very good sensitivity in the detection of new lesions in patients with multiple sclerosis

All these tools generated within the BiomarkEM.cat project have also had an international impact, highlighting the segmentation of lesions based on Deep Learning techniques, which has been used by numerous research centers and hospitals worldwide. It should be noted that many of the tools developed have been made available to the scientific community for use and evaluation through free code or dockers with GNU GPL 3.0 license.

Within the BiomarkEM.cat project, two postdoctoral researchers and a doctoral student who will complete his doctoral thesis during the first semester of 2019 were hired, as well as different technicians in the hospital centers.

## 3. Relevance and possible future implications

The main impact of the project has been the development of different computerized tools that allow biomarkers to be obtained automatically through the analysis of magnetic resonance images. Specifically, tools were developed for the segmentation and quantification of brain tissue, brain structures (e.g. subcortical structures) and multiple sclerosis lesions in the white matter. In addition, specific techniques were developed to obtain information on changes in longitudinal studies, such as the quantification of the appearance of new lesions that is a great prognostic marker of the disease.

The results obtained in the project have been highly valued by the medical experts participating in the project, who use the tools in Vall d'Hebron Hospital in Barcelona, and Trueta and Santa Caterina Hospitals in Girona. The contributions and

breakthroughs resulting from the project have been recognized in scientific publications not only Q1, but some of them in the first decile.

In addition, as previously mentioned, international recognition has also been received, occupying highly important positions in different international challenges. To highlight the participation in the MSSEG Challenge of automatic segmentation of lesions that was held in conjunction with the international congress MICCAI 2016 (the most important in medical image analysis). This was the first Challenge where multiple sclerosis lesion segmentation tools were evaluated in a scenario similar to the one proposed in our research project. A study with multi-center cases (database of 38 patients) acquired with 4 different MRI scans and with 1.5T and 3T images. Our team participated in the competition with the two lesion segmentation tools developed within the project (one unsupervised and another supervised, Deep Learning). Thirteen research centers from around the world participated in the competition, and the results of our tools were very positive (1$^{st}$ and 3$^{rd}$ positions). The results of this competition were published in 2018 in the journal Nature Scientific Reports (JCR Q1).

One of the tools that has had the most impact is the segmentation of lesions based on Deep Learning techniques, a work published in the prestigious journal NeuroImage, (docker: https://github.com/NIC-VICOROB/nicMSlesions), which in addition to being integrated into collaborating hospitals, it has also been used by numerous research centers and other hospitals at international level. This docker and others developed within the project have been made public in the scientific community under the GNU GPL 3.0 license (see https://github.com/NIC-VICOROB). This has been another impact derived from the project that may have future implications, since spreading research internationally, sharing tools through free code, improves the visibility of research and facilitates collaborations with different research centers around the world.

This impact allowed us to sign several collaboration agreements with different international institutions, to explore lines of research related to the subject dealt with in the BiomarkEM.cat project.

All the tools used to obtain markers can generate valuation and knowledge transfer. Within the project, the technology that has generated most interest is the one used for the segmentation of new lesions, as well as the strategy based on Deep Learning for

the segmentation and volumetric quantification of lesions in cross-sectional studies. In this regard, a collaboration has been established with the international company OLEA Medical for the use of its software development kit (SDK) to integrate the new lesions detection tool, which can be the seed for a possible transfer of knowledge and valorization of the different tools developed within the BiomarkEM.cat project.

These medical imaging markers should be the basis for the future creation of predictive models of multiple sclerosis, a challenge that the research team that has participated in this project of *La Fundació la Marató de TV3* intends to face in the near future. The sector of the medical imaging requires new technologies and solutions to take the final step towards the development and use of these predictive models that can change the diagnosis, monitoring and prognosis of patients with multiple sclerosis, optimizing the decisions made by medical experts.

## 4. Literature generated

The project has generated different publications in indexed journals and in international conferences and congresses.

JCR Journals:

**[NI-CL 2019]** S. Valverde, M. Salem, M. Cabezas, D. Pareto, J. C. Vilanova, Ll. Ramió-Torrentà, À. Rovira, and J. Salvi, A. Oliver, X. Lladó. "One-shot domain adaptation in multiple sclerosis lesion segmentation using convolutional neural networks". NeuroImage: Clinical, To appear. [JCR N IF 3.869, Q1(3/14)]

**[NI-CL 2019]** S. González-Villà, A. Oliver, Y. Huo, X. Lladó, B.A. Landman. "Intensity-based Multi-atlas Segmentation in the Presence of Multiple Sclerosis Lesions". NeuroImage: Clinical. To appear, 2019. [JCR N IF 3.869, Q1(3/14)]

**[MIA 2018]** K. Kushibar, S. Valverde, S. González-Villà, J. Bernal, M. Cabezas, A. Oliver, X. Lladó. "Automated sub-cortical brain structure segmentation combining spatial and deep convolutional features". Medical Image Analysis, 48, pp-177-186, 2018. [JCR CSAI IF 5.356, Q1(6/105)]

**[NI-CL 2018]** M. Salem, M. Cabezas, S. Valverde, D. Pareto, A. Oliver, J. Salvi, À. Rovira, and X. Lladó. "A supervised framework with intensity subtraction and deformation field features for the detection of new T2-w lesions in multiple sclerosis". NeuroImage: Clinical, vol. 17C, pp. 607-615, 2018. [JCR N IF 3.869, Q1(3/14)]

**[NI-Cl 2017]** S. González-Villà, S. Valverde, M. Cabezas, D. Pareto, J.C. Vilanova, Ll. Ramió-Torrentà, À. Rovira, A. Oliver, X. Lladó. "Evaluating the effect of multiple sclerosis lesions on automatic brain structure segmentation". NeuroImage: Clinical, vol. 15., pp. 228-238, 2017. [JCR N IF 3.869, Q1(3/14)]

**[NI 2017]** S. Valverde, M. Cabezas, E. Roura, S. González-Villà, D. Pareto, J.C. Vilanova, Ll. Ramió-Torrentà, À. Rovira, A. Oliver, and X. Lladó. "Improving automated multiple sclerosis lesion segmentation with a cascaded 3D convolutional neural network approach". NeuroImage, vol 155, pp. 159-168, 2017. [JCR NI IF 5.426, Q1(1/14)]

**[MIA 2017]** S. Valverde, A. Oliver, E. Roura, S. González-Villà, D. Pareto, J.C. Vilanova, Ll. Ramió-Torrentà, À. Rovira, and X. Lladó. "Automated tissue segmentation of MR brain images in the presence of white matter lesions". Medical Image Analysis, vol 35, pp. 446-457, 2017. [JCR CSAI IF 5.356, Q1(6/105)]

**[AJNR 2016]** M. Cabezas, J.F. Corral, A. Oliver, Y. Diez, M. Tintoré, C. Auger, X. Montalban, X. Lladó, D. Pareto, and À. Rovira. "Improved automatic detection of new T2 lesions in multiple sclerosis using deformation fields". American Journal of Neuroradiology, vol 10, pp. 1816-1823, 2016. [JCR RNMMI IF 3.589, Q1(19/125)]

**[FNINF 2016]** E. Roura, A. Oliver, S. Valverde, S. Gonález-Villà, R. Cervera, N. Bargalló, and X. Lladó. "Automated detection of lupus white matter lesions in MRI images". Frontiers in Neuroinformatics, 10, art 33, 2016. [JCR MCB IF:3.047 Q1(6/56)]

**[AIIM 2016]** S. González-Villà, A. Oliver, S. Valverde, L. Wang, R. Zwiggelaar, and X. Lladó. "A review on brain structures segmentation in magnetic resonance imaging". Artificial Intelligence in Medicine, vol 73, pp. 45-69, 2016. [JCR CSAI IF:2.142 Q2(34/142)]

**[NI-CI 2015]** S. Valverde, A. Oliver, E. Roura, D. Pareto, J.C. Vilanova, Ll. Ramió-Torrentà, J. Sastre-Garriga, X, Montalban, À. Rovira, and X. Lladó. "Quantifying brain tissue volume in multiple sclerosis with automated lesion segmentation and filling". NeuroImage: Clinical, 9, pp 640-647, 2015. [JCR N IF 3.857, Q1(3/14)]

**[FN 2015]** E. Roura, T. Schneider, M. Modat, P. Daga, N. Muhlert, D. Chard, S. Ourselin, X. Lladó, C. Wheeler-Kingshott. "Multi-channel registration of FA and T1w images in the presence of atrophy: application to Multiple Sclerosis". Functional Neurology, 30(4), pp. 245-256, 2015. [JCR N IF 1.855, Q3(187/252)]

**[NRAD 2015]** E. Roura, A. Oliver, M. Cabezas, S. Valverde, D. Pareto, J.C. Vilanova, Ll. Ramió-Torrentà, À. Rovira, and X. Lladó. "A toolbox for multiple sclerosis lesion segmentation". Neuroradiology, 57(10), pp. 1031-1043, 2015. [JCR RNMMI IF 2.485, Q2(41/125)]

In addition to these publications in prestigious journals, the project has generated 22 publications and participations in international conferences and congresses, such as the ECTRIMS (Congress of the European Committee for Treatment and Research in Multiple Sclerosis), and in 3 national conferences such as the SERAM, Congress of the Spanish Society of Medical Radiology, where the advances made in the project were presented.

PhD theses read within the framework of the project:

Roura E. *Automated methods on Magnetic Resonance Brain Imaging in Multiple Sclerosis*.
Co-directed by Dr. X. Lladó and Dr. A. Oliver.
Defense: 1 July 2016.
Qualification: Excellent Cum Laude by Unanimity

Valverde S. *Automated brain tissue segmentation of magnetic resonance images in multiple sclerosis*.
Co-directed by Dr. X. Lladó and Dr. A. Oliver.
Defense: 14 June 2016.
Qualification: Excellent Cum Laude by Unanimity.

**Best PhD thesis award in the University of Girona within the Doctorate program in Technology.**

Ongoing PhD theses:

González, S. *Brain structures in MRI image segmentation of multiple sclerosis patients*.
Co-directed by Dr. Lladó, Dr. Oliver **(Granted from BiomarkEM.cat project)**
Expected completion date: May 2019

Salem, M. *Brain change detection in MRI images*.
Co-directed by Dr. Lladó, X. and Dr. J. Salvi
Expected completion date: December 2019

Bernal, J. *Supervised tissue segmentation in brain MRI images using Deep Learning*.
Co-directed by Dr. Lladó and Dr. Oliver
Expected completion date: 2020

Kushibar, K. 2020. *Deep Learning techniques for MRI Segmentation of brain structures*.
Co-directed by Dr. Lladó and Dr. Oliver
Expected completion date: 2020