LESION PATTERN IN MULTIPLE SCLEROSIS: A DEEP LEARNING EXPLORATION APPROACH.

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Introduction. Multiple Sclerosis (MS) is an autoimmune, neurodegenerative disease presenting central nervous system damage. White matter lesions, as visualized by conventional magnetic resonance imaging, are an established biomarker of the disease and are clinically useful for assessing and follow-up of the disease course, but with some limits(1,2). Although there are selective areas of occurrence, lesions have not yet been characterized in terms of established and recognizable patterns of spatial dissemination with a biological/clinical/behavioral counterpart.
Group classification of MS has been based on both clinic and imaging and is an ongoing work, with diagnostic and classification criteria periodically updated with new knowledge. The importance of this grouping is crucial because it is the adopted model for treatment and follow-up.
Clustering algorithms can figure out useful information for grouping and classification, according to a variety of data similarity metrics and data grouping schemes(3). To let the samples be properly assigned to different groups (called clusters), meaningful feature values of the samples need to be obtained first. However, in medical imaging, i.e. 3D-MRI brain scans, the data we get is often of high dimensions and usually contains noise, making the clustering difficult to succeed.
Recently, due to the emergence of powerful deep neural networks, deep learning based approaches have been introduced to produce better data representations and achieve appealing performance improvements for clustering algorithms.

Objectives. In this study we took an exploratory approach, based on deep learning, to find lesion pattern groupings on patients affected by MS.

Methods. Participants with MS and availability of brain MRI data and the corresponding maps of white matter lesions, were extracted from the MS research database of the Functional Neuroimaging Lab, Human Neurosciences Department, Sapienza University of Rome. There were two main analysis steps: representation learning and clustering.
In the representation learning, a U-Net is trained to segment the lesions. The high dimensional inputs were fed into the network's encoder, generating a low dimensional embedding. This vector was further fed to the network's decoder that tries to recover the lesions segmentation. Then a principal components analysis (PCA) is applied to select from the embedding a reduced feature space, representing the directions of maximum variance in the data, eliminating redundant and correlated extracted features.
The learned representations are then fed to a classic K-means algorithm to do clustering. The learned low dimensional representation vector contains key information of the given input and therefore expected to yield

better clustering results. We chose to explore K={2,3,4,5} at the baseline session for every subject.
In order to find a clinical/behavioral counterpart for the resulting grouping, we performed multinomial logistic regression testing to predict clustering, with the use of some the most established parameters characterizing MS, which are: clinical form (Revised McDonald criteria 2010(4)), disease duration, type of onset, expanded disability status scale (EDSS), two cognitive tests (PASAT and SDMT), ambulation test (25-Feet Walk Test), hand-dexterity index for dominant and nondominant handedness (9-hole peg test), all inserted in the model; age, sex and fatigue status scale (FSS) considered as confounders. In a second step, the same model was applied with age, sex and FSS as covariates. Finally we estimated two more models, considering clinical- only and behavioral-only parameters, respectively.
Results. 299 subjects with 1 up to 9 lesion masks, obtained in an equal number of MRI sessions for a total of 707 exam sessions, were included. In the annexed Table we show the performance of the U-net in segmenting, when compared to the ground truth - that is the manually segmented lesions. This guarantees the quality of the embedding in representing the features that are useful for lesion identification.
The multinomial logistic regression model with a binomial logit function showed an association of the k=2, clustering with age (OR 0.932, 95%CI[0.894, 0.970]). Moreover, at k=3 there was a significant association with sex (OR 28.875, 95%CI[7.935, 148.531]), at k=4 with both age (OR 1.059, 95%CI[1.009, 1.117]) and sex (OR 21.625, 95%CI[6.065, 108.357]) and at k=5 with disease duration (OR 1.119, 95%CI[1.045,1.216]).
Conclusions. The goal of the applied pipeline was not the segmentation, but to exploit the lesion segmentation process of the brain for estimation of the most meaningful features that characterize the lesions, to be fed to a clustering algorithm for extracting the groupings. Those preliminary results suggest a high performance of lesion segmentation. Every deriving level of grouping, based upon the lesion pattern of the brain, might reveal both disease-specific (clinical) and not disease-specific (demographic) information. Further exploration is warranted to address the full potential of this approach.

Table : Segmentation performance

Accuracy	Sensitivity	Specificity
99.98 ± 0.02	89.14 ± 6.11	99.99 ± 0.01

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