Cortical thickness and surface area as biomarkers to differentiate multiple sclerosis and neuromyelitis optica: a multivariate pattern classification study

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Objectives

- To differentiate people with MS and NMO with measures from grey matter: cortical thickness and surface area, and volumes of deep grey matter nuclei
- To investigate the pattern in which the above measures change in each disorder with multivariate statistical techniques

Introduction

Grey matter (GM) is affected in both multiple sclerosis (MS) and neuromyelitis optica (NMO) with different underlying mechanisms, and therefore it has been successfully used as a biomarker to discriminate NMO from MS (e.g. lesions detected with double-inversion recovery technique). However, it is still not clear whether the pattern in which GM changes occur in MS and NMO could be used to differentiate these two disorders. We use cortical thickness and cortical surface area as two independent measures that could provide imoprtant information to differerntiate MS from NMO. Since it is important to have reproducible findings, we included two cohorts from two different countries.

Setting and participants

We included 97 subjects in two groups of people with MS and NMO, from the cohorts in Tehran, Iran (25 patients with MS, and 30 patients with NMO) and Padua, Italy (24 patients with MS and 18 patients with NMO). Diagnosis was made for patients with MS based on 2005 revised McDonald criteria, and for patients with NMO according to 2006 Wingerchuk's criteria.
All patients underwent neurological examination to determine Expanded Disability Status Scale (EDSS). We performed MRI scan including high-resolution T1 (3D- MPRAGE) and FLAIR with 1.5T in Padua and 3T scanners in Tehran.

Image analysis(1)

We calculated cortical thickness and area in 50 regions according to LONI probabilistic atlas (LPBA40). Cortical thickness was calculated with diffeomorphic based estimation of thickness in ANTs (DiReCT).

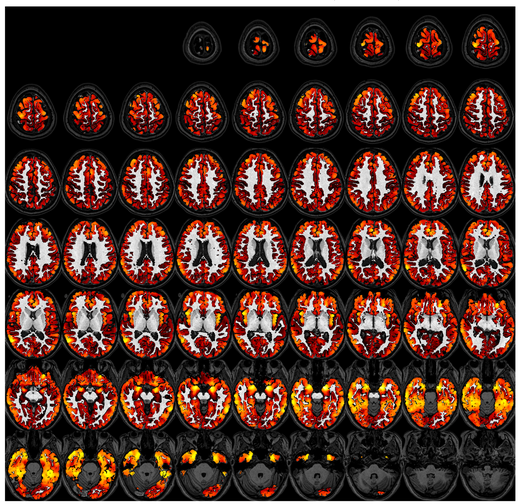

Figure 1: Cortical thickness map in a patient with NMO

Image analysis(2)

To calculate **cortical volume** in each region of LPBA40 atlas we used Atropos to segment GM, and then calculated volumes. Cortical surface was then calculated in each region as follows:

$$Surface\,area = \frac{Volume}{Thickness} \quad (1)$$

We used FSL FIRST software to segment **deep grey matter nuclei**. FIRST uses a probabilistic Bayesian model on shape and intensity to automatically segment subcortical structures. Volumes of each structure were then calculated.

Statistical analysis

We used random forest technique as the method for classification. We randomly assigned each subject (from both cohorts) to training and test sets, so that each of sets will contain half of all patients. Next, we trained random forests on the training set and cross-validated on the left out half. This procedure was iterated for 5000 times. Mean and standard deviation for accuracy of 5000 trained and cross-validated models were calculated. Accuracy is defined as the sum of true positives (patients with MS classified as MS) and true negatives (patients with NMO classified as NMO) divided by all patients in the test set. To calculate the statistical significance of our classifier against null hypothesis (a random classifier) we used permutation testing P-value is defined as the number of times the random classifier has equal or more accuracy than the obtained accuracy from correct labels (MS or NMO) divided by 5000.

Results

Disease and demographic characteristics are shown in Figure 1. Classifier with cortical volume gave 60% classification accuracy, which was not different from a random classifier (P-value > 0.05).Classifier with cortical thickness gave 62% (standard deviation = 0.11, p-value=0.03) accuracy. Feature importance as calculated inside random forest method is shown in Figure 2. Three most important regions to distinguish between two groups are: Left precuneus, left insular cortex, and the right fusiform gyrus.
The mean accuracy of the classifier with surface areas was 68% (standard deviation = 0.13, P-value=0.03). Importance of each region in discrimination between two groups is shown in Figure 3. The three most important regions are: Left parahippocampal gyrus, right middle orbitofrontal gyrus, and right middle frontal gyrus.
The mean accuracy of the classifier when using subcortical volumes was 72% (standard deviation = 0.13, p-value = 0.03). Most important regions for differentiation were: the left thalamus, right pallidum, and right thalamus (Figure 4 and 5).
When using a combination of all measures from cortical thickness, surface and subcortical volumes, the mean accuracy reached 74% (standard deviation = 0.10, P-value = 0.03) (Figure 6).

Variables in classifier	Accuracy (p-value)
Cortical volume	60% (not significant)
Cortical thickness	62% (p=0.03)
Cortical surface	72% (p=0.03)
Subcortical volumes	73% (p=0.03)
Combination of all the above	74% (p=0.03)

Table 1: Classification results

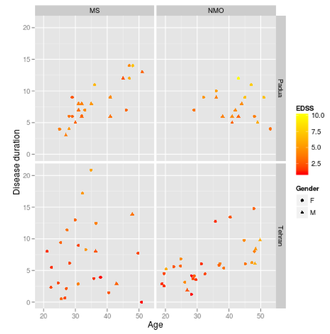

Figure 2: Disease and demographic characteristics in two cohorts from Iran and Italy

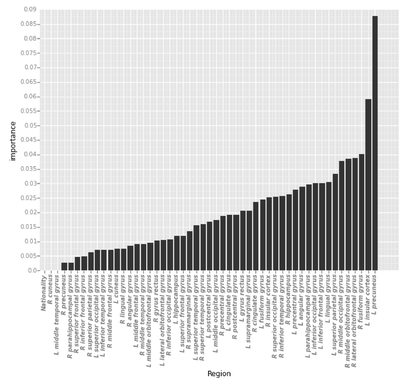

Figure 3: Importance of cortical thickness in each region to differentiate between NMO and MS

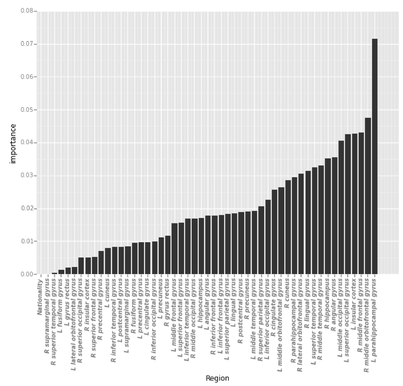

Figure 4: Importance of cortical surface in each region to differentiate between NMO and MS

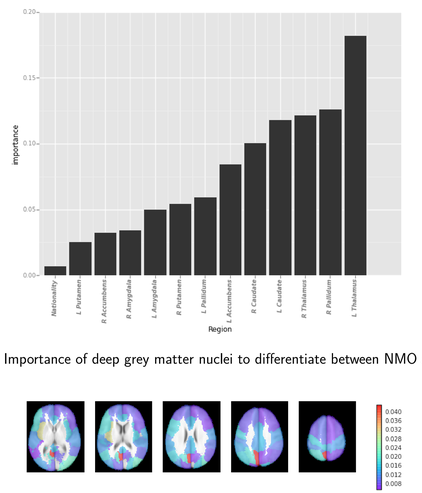

Figure 5: Importance of deep grey matter nuclei to differentiate between NMO and MS

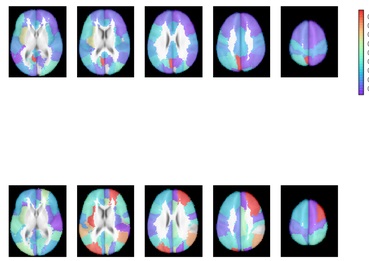

Figure 6: Imortance of cortical thickness (upper row) and surface area (lower row) to differentiate between MS and NMO in each region

Summary of findings

In this study we used multi-parameter classification approaches that combined cortical grey matter measures to investigate subtle differential changes in patients with MS and NMO. The classification was performed with random forests method, which had an accuracy of 62%, 68%, 73% and 74% in models using cortical thickness, cortical surface, subcortical volumes, and combination of all those features, respectively.

Conclusion

Cortical thickness, **cortical surface** and **volumes of deep grey matter nuclei** provide up to 74 percent accuracy in discriminating MS from NMO. The results are reproducible across centers in different countries.

References

[1] Brian B Avants, Nicholas J Tustison, Jue Wu, Philip A Cook, and James C Gee. An open source multivariate framework for n-tissue segmentation with evaluation on public data. *Neuroinformatics*, 9(4):381–400, 2011.

[2] Nicholas J Tustison, Philip A Cook, Arno Klein, Gang Song, Sandhitsu R Das, Jeffrey T Duda, Benjamin M Kandel, Niels van Strien, James R Stone, James C Gee, et al. Large-scale evaluation of ants and freesurfer cortical thickness measurements. *NeuroImage*, 2014.