

# AI-detected brain atrophy patterns associated with Progression Independent of Relapse Activity in MS

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## BACKGROUND

**Progression independent of relapse activity (PIRA)** represents the main driver of clinical disability accrual in multiple sclerosis (MS). Mechanisms underlying PIRA are still uncertain. However, most of the putative pathological substrata of disease progression hesitate in neuronal damage/loss, which appear visible in vivo on MRI as **brain atrophy (BA)**. However, it is still difficult to quantify **global BA** and characterize **regional BA patterns** at a subject-level in the clinical practice. Also, **functional** and **microstructural** implications of regional BA remain largely unclear.

## AIMS

The **primary goal** of this study was to quantify the **global BA** and identify the **regional BA patterns associated with PIRA** using Artificial Intelligence (AI) in a real-world setting.

**Secondarily**, we aimed to assess the **functional** and **microstructural connectivity** correlated to PIRA-associated BA patterns.

## METHODS

We included **24 MS patients** treated with Natalizumab presenting **PIRA** (n=14) and **clinically stable (CS)** (n=10) disease. Patients underwent a motor and cognitive evaluation (through **EDSS** and **SDMT**) and a brain 1.5T MRI scan (including **MPRAGE**, **3D-FLAIR**, **RS-fMRI** and **DTI** sequences). Brain volumetrics was analyzed through an **AI software (Pixyl)** detecting **global and regional BA** (20 brain regions of which 15 of cortical/deep gray matter (GM) Fig. 2). **Comparisons** of clinical/MRI volumetric measures between PIRA and CS groups were performed using Wilcoxon sum rank/Fisher's exact test. We then assessed the **Default Mode Network (DMN) RS-FC** correlated to the regional BA patterns associated to PIRA by a **seed-based analysis** (CONN-toolbox). Finally, we evaluated the microstructural damage of PIRA-associated BA patterns through **tract-based spatial statistics (TBSS)**.

## RESULTS

Age, sex, disease and treatment duration resulted comparable between the two groups (Table 1). PIRA group showed a higher proportion of patients with global/total white matter (WM) atrophy than CS (Fig. 3A). No differences were found for total GM atrophy, however when analyzing the single GM regions, PIRA group showed a greater proportion of patients with **left thalamus atrophy (leftTA)** (88% vs. 40%; **p-value = 0.03241**) compared to CS (Fig. 3B). From FC analysis, patients with leftTA resulted to have a **RS-FC alteration** of the Default Mode Network (DMN) compared to those with no leftTA. In particular, leftTA group showed an **abnormal anticorrelated activity** ( $p < 0.0001$ , FWE-corrected) (Fig. 5A) between the main posterior component of the DMN (**posterior cingulate gyrus (PCG)**) and a **cortical area** including the **fusiform** and **parahippocampal gyri** (Fig. 4B).

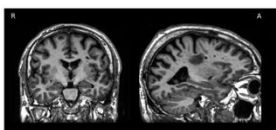


Figure 1. Brain 1.5T MRI 3D-T1 MPRAGE



Figure 2. Brain regions considered for volumetrics analysis by Pixyl

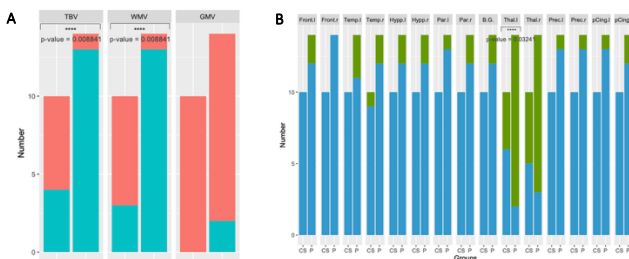


Figure 3. (A) Proportions of patients with total brain/WM/GM atrophy (blue) in PIRA (P) vs clinically stable (CS) group. (B) Proportions of patients with atrophy (green) in the 15 cortical/deep GM regions analyzed by Pixyl in Pvs. CS group. \*Fisher's exact test

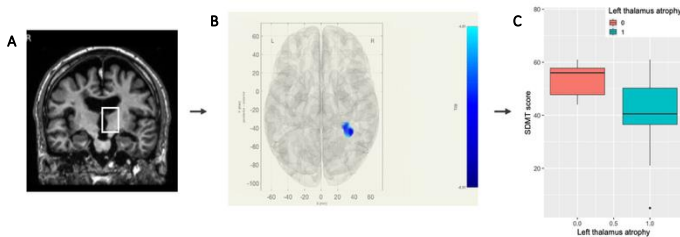


Figure 4. (A) Left thalamus atrophy (leftTA) detected by Pixyl. (B) Cortical area (in blue) showing an abnormal RS-FC with posterior cingulate gyrus (PCG) in leftTA vs. no leftTA group. (C) Box-plot showing SDMT score in leftTA vs. no leftTA group. \*Wilcoxon sum rank test

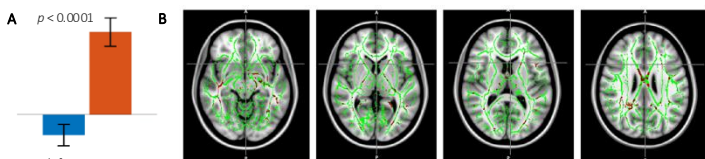


Figure 5. (A) Anticorrelated activity between PCG and the cortical area (shown in Fig. 4B) in leftTA vs. no leftTA group. (B) Fractional anisotropy (FA) map showing areas with decreased FA (in red) in leftTA compared to no leftTA group.

	PIRA (P)	Clinically stable (CS)	Comparison P vs CS
Age <sup>1</sup> median (range)	40.5 (27-54)	40 (27-52)	*W = 61, p-value = 0.6176
Sex female (%)	10 (71)	8 (80)	*p-value = 1
Disease duration <sup>2</sup> years - median (IQR)	12 (9-25.2)	13 (12-14.75)	*W = 67.5, p-value = 0.9064
Time on treatment <sup>3</sup> years - median (IQR)	9 (8-11.7)	10 (8-11)	*W = 69.5, p-value = 1
EDSS score baseline median (IQR)	1.7 (1.5-3)	1.5 (1.5-2.4)	*W = 54, p-value = 0.3493
EDSS score follow-up <sup>4</sup> median (IQR)	4.2 (3.6-4.6)	1.5 (0.4-2)	*W = 5.5, p-value = 0.0001602
SDMT score <sup>5</sup> median (IQR)	41 (35.5-53.7)	50 (42.5-56.6)	*W = 95, p-value = 0.1509
T2LT <sup>6</sup> Median (IQR)	16.4 (8.6-30.8)	4.5 (2.2-11.5)	*W = 27, p-value = 0.01073

Table 1. Clinical characteristics and T2 lesion load (T2LT)

<sup>1</sup>Age follow up (B1), <sup>2</sup>on diagnosis to 1, <sup>3</sup>on treatment start (B4-B10) to 1, <sup>4</sup>at 12 confirm edms 6 mo (B2), <sup>5</sup>EDSS score follow-up, <sup>6</sup>EDSS score at baseline/Time on treatment. \*Wilcoxon sum rank test, \*Fisher's exact test

Interestingly, patients with leftTA had a lower **SDMT score** comparing to those with no leftTA (median = 40.5 vs 56; **p-value = 0.01824**) (Fig. 4C).

Considering the involvement of the fusiform (for symbols/numbers recognition) and parahippocampal (for working memory) gyri in the SDMT, an alteration of FC in those areas could partially explain a decreased performance in the leftTA group. From TBSS analysis, patients with leftTA showed a greater microstructural damage ( $p < 0.05$ ), more evident in the posterior thalamic radiations (Fig. 5B).

## CONCLUSIONS

AI enables to identify **regional BA patterns** associated to **clinical phenotypes**. PIRA is associated with **leftTA**, which correlates to a **RS-FC alteration** of the **DMN**, possibly linked to a decreased cognitive performance. Studies with larger sample size are needed to confirm these results.