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Original article

Cognition beyond relapses: cognitive progression independent of relapse activity reflects early smoldering neurodegeneration in multiple sclerosis

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ABSTRACT

Background: Progression independent of relapse activity (PIRA) is frequent in relapsing-remitting MS patients (RRMS). While often studied in terms of physical disability, cognitive decline occurring without relapses, termed “cognitive PIRA”, has also been reported. Cortical/deep gray matter atrophy reflect both clinical PIRA and cognition. This study investigated whether early global/region-specific brain atrophy predicts long-term cognitive decline due to PIRA in RRMS.

Methods: A retrospective cohort study was conducted on RRMS patients followed over time at the Verona MS Centre to evaluate the relationship between clinical/radiological data at diagnosis (T0) and 2 years after (T2) with cognitive PIRA after 20 years of MS. Patients underwent 1.5T MRI scans at T0 and T2 (regional cortical/subcortical volumes, cortical thickness, lesion burden) and multiple neuropsychological assessments at the end of follow-up. Significant cognitive decline was defined using reliable change indices and attributed PIRA if no relapses occurred within ±9 months the time between the assessments showing the decline. Random forest models evaluated early predictors of cognitive PIRA.

Results: 115 RRMS patients were followed for 19.1 ± 5.4 years. Fifty-seven (49.6 %) patients exhibited significant cognitive decline, most of whom (80.7 %) were classified as cognitive PIRA. Global cortical thickness emerged as the feature with the highest relative importance in Random Forest models. Baseline thalamic volume and longitudinal atrophy in the middle frontal gyrus ranked among the most informative regional features contributing to model performance.

Conclusions: Cognitive PIRA accounted for most long-term cognitive decline in RRMS. In a predictive machine-learning framework, early measures of brain atrophy contributed most to the identification of individuals who later developed cognitive PIRA. These findings suggest that cognitive PIRA reflects MS silent disease activity and smoldering processes.

Abbreviations: BRB-NT, Brief Repeatable Battery of Neuropsychological Tests; BVMT-R, Brief Visuospatial Memory Test-Revised; CI, cognitive impairment; CLs, cortical lesions; CTh, cortical thickness; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; EOS, end of study; GM, gray matter; IQR, interquartile range; MRI, magnetic resonance imaging; MS, multiple sclerosis; PASAT, paced auditory serial addition task; PIRA, progression independent of relapse activity; PIRMA, progression independent of relapse and MRI activity; PRLs, paramagnetic rim lesions; RAW, relapse-associated worsening; RCI, reliable change index; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SDMT, symbol digit modalities test; SELs, slowly expanding lesions; WMLs, white matter lesions.

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1. Introduction

Multiple sclerosis (MS) is the most common chronic immune-mediated neurological disease in young adults, characterized by inflammation, demyelination, and neurodegeneration processes accumulating over time (Filippi et al., 2018). Traditionally, disease severity in MS has been primarily associated with clinical relapses (relapse-associated worsening, RAW) and with inflammatory lesions detectable on MRI, resulting in disability accumulation. However, emerging evidence has demonstrated that substantial disability in relapsing-remitting MS (RRMS) occurs in the absence of clinical relapses, a phenomenon referred to as "progression independent of relapse activity" (PIRA; Kappos et al. 2020).

PIRA may occur from the earliest disease stages, often more frequently than RAW, and is associated with worse long-term prognosis and sustained disability worsening in most patients (Lublin et al., 2022; Portaccio et al., 2022; Tur et al., 2023).

MS patients with PIRA showed accelerated brain atrophy, particularly in the cerebral cortex and deep gray matter (GM; Cagol et al., 2022). Despite the lack of association with traditional MRI markers of disease activity (i.e., new white matter, WM, lesions), PIRA seems to reflect the so-called "smoldering MS", in terms of its chronic activity (Hemond et al., 2024): a higher presence of paramagnetic rim lesions (PRLs) reflects PIRA (Reeves et al., 2024). The pathophysiological causes of PIRA are still unclear, although it is likely that PIRA is linked to increased diffuse neuroaxonal loss (Cagol et al., 2022).

These findings underscore the importance of recognizing subtle manifestations of PIRA in clinical practice.

The concept of PIRA has traditionally focused on disease worsening, only considering the accumulation of physical disability, measured using the Expanded Disability Status Scale (EDSS) and the presence/absence of relapses; however, MS is characterized by many other important aspects that are not adequately reflected in the EDSS. Among these, cognition is neglected from the traditional PIRA model (Ziccardi et al., 2024a) and is not routinely considered as a potential result of the "smoldering MS" (Scalfari et al., 2024), given the fact that MS is often perceived as a condition that primarily causes physical disability, rather than cognitive impairment (CI) (Giovannoni et al., 2022). However, cognitive alterations affect up to 65 % of MS patients, emerging since the beginning of the disease and worsening over time, with a dramatic impact on quality of life, social relationships, and vocational status (Benedict et al., 2020); then, they should be a core focus of disease monitoring.

Similar to disability accumulation, cognitive functioning can gradually lose efficiency and be unnoticed by patients and/or physicians (Cree et al., 2019), significantly declining independently of relapses. This concept, referred to as "cognitive PIRA", has only recently gained attention; however, it has been demonstrated that cognitive PIRA represents most of the meaningful cognitive decline in MS, compared to that associated with relapses, and happens also independently from EDSS worsening (Fuchs et al., 2024). Of note, cognitive worsening has been reported in all MS patients, also independently from the PIRA condition based on the EDSS evolution: a similar cognitive decline was registered in PIRA and neurologically stable patients (Glanz et al., 2025).

Although both WM and GM pathologies are associated with cognitive alterations in MS, focal and diffuse GM damage are considered key pathological substrates of cognitive deficits. Cortical lesions reflect the presence of cognitive alterations (Calabrese et al., 2009) and predict longitudinal cognitive worsening (Calabrese et al., 2012), even in the long-term (Ziccardi et al., 2023). Moreover, greater cortical and deep GM atrophy is observed in more cognitively-impaired patients and predicts subsequent decline over time (Calabrese et al., 2009, 2010; Filippi et al., 2013; Eijlers et al., 2018): this process appears to be driven predominantly by specific brain regions (Preziosa et al., 2016; Stellmann et al., 2021; Ziccardi et al., 2024b).

In addition, when MRI activity is also considered, most patients with cognitive PIRA show no evidence of new T2 brain lesions during the same period. This pattern of cognitive decline, occurring without clinical relapses and MRI activity, is referred to as "cognitive progression independent of relapse and MRI activity" (cognitive PIRMA; Ziccardi et al., 2025).

The progression of cognitive decline in MS may begin early and is only weakly associated with inflammatory activity, such as the appearance of new/enlarging T2 lesions (Giovannoni et al., 2022). Interestingly, patients with cognitive PIRMA, despite the stability of WM lesion burden, often exhibit a higher presence of baseline PRLs, which are thought to reflect chronic compartmentalized inflammation (Boccia et al., 2025). PRLs also appear to differentiate patients based on their ability to recover from cognitive decline, suggesting their potential as a marker of cognitive PIRA (Reeves et al., 2024).

In this context, routine cognitive assessments can help detect disease progression that may not be apparent through standard clinical/radiological evaluations (Fuchs et al., 2024; Ziccardi et al., 2025). Together, these findings underscore the importance of recognizing cognitive PIRA/PIRMA as manifestations of insidious neurodegenerative processes rather than acute inflammatory events, and highlight the leading contributor role of smoldering inflammation/neurodegeneration in driving cognitive deterioration.

While changes in cognitive function may signal underlying MS activity, the prognostic value of markers of cognitive PIRA remains insufficiently understood.

The present study specifically investigates whether regional brain atrophy occurring during the early stages of MS predicts long-term cognitive decline, independent of relapse activity. By leveraging a uniquely long follow-up duration and MRI data acquired at diagnosis and two years later, we assessed the baseline regional brain volumes and their longitudinal evolution. These imaging markers are then related to neuropsychological outcomes after nearly two decades of disease. Through the application of machine-learning–based predictive models, we evaluated the relative contribution of focal and diffuse damage in selected brain regions to the prediction of future cognitive PIRA, while accounting for conventional clinical and radiological parameters. This approach highlights MRI features that contribute most to model performance in a long-term predictive framework and may support risk stratification of cognitive outcomes in multiple sclerosis.

2. Materials and methods

2.1. Study design and participants

In this retrospective longitudinal study, individuals with RRMS followed at the MS Center of the University Hospital of Verona (Verona, Italy) were enrolled. We included a subsample of patients from a previous project (Ziccardi et al., 2024b): all patients from the previous publication had availability of MRI scans, including a 3D volumetric T1 sequence, conducted at diagnosis (T0) and two years later (T2), as well as an average of 20-year ongoing clinical follow-up period by a neurologist with substantial experience in managing MS (M.C.), and repeated neuropsychological assessments performed with a long-term distance from diagnosis, in which the last represented the end of study (EOS). For the present work, we added the following inclusion criteria: (i) diagnosis of RRMS at the EOS, based on the latest diagnostic criteria (Thompson et al., 2018); and (ii) multiple complete neuropsychological evaluations to evaluate cognitive decline. Exclusion criteria were: (i) presence of any neurological conditions other than MS; (ii) any psychiatric (including depression) or other neurological disorders; (iii) substance abuse; and (iv) sensory or motor impairments (such as hearing loss, important upper limb dysfunction, or visual deficits) that could compromise cognitive assessment.

The study was approved by the local Ethics Committee and carried out in accordance with the Declaration of Helsinki (2013). All participants provided informed consent.

2.2. Neuropsychological assessment and monitoring

After a follow-up period from diagnosis, patients underwent multiple comprehensive neuropsychological assessments in a clinically stable phase, concomitantly with a neurological examination, using the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT; Amato et al., 2006), the Stroop Test (Caffarra et al., 2002), the Phonemic Semantic and Alternate Verbal Fluency Test (Costa et al., 2014), the Modified Five Point Test (Cattelani et al., 2011), and the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997).

Firstly, cognitive decline was assessed using a reliable change index (RCI) methodology , a strict approach designed to ensure the detection of genuine cognitive change, exceeding expected variability due to measurement error and practice effects, employing a more conservative and stringent threshold for reliable change than the commonly used group-level standard criterion (Fuchs et al., 2024; Ziccardi et al., 2025; Portaccio et al., 2024). To evaluate meaningful cognitive decline, we considered those tests for which RCIs have been published in an Italian sample (Portaccio et al., 2024): the Symbol Digit Modalities Test (SDMT), the BVMT-R, and the Paced Auditory Serial Addition Task (PASAT).

Then, we established whether those meaningful cognitive decline events occurred in association with or independently from relapse activity (cognitive PIRA). We used a conservative definition to be sure to catch real cognitive PIRA, which was already proposed in previous publications: cognitive decline was classified as PIRA if no relapses were observed ±9 months before/after the period between the assessments showing the decline, otherwise they were considered as relapse-associated worsening (RAW) (Fuchs et al., 2024; Ziccardi et al., 2025). This approach is more conservative than the 3-months before and after period of observation traditionally used to evaluate absence of relapses for PIRA (Müller et al., 2023); moreover, given the fact that usually in clinical practice the frequency of neurological evaluations is higher compared to that of cognitive assessments, we aimed to be more confident defining patients free from activity according to multiple neurological examinations (using a reference period of 6 months or less would have referred only to a single neurological evaluation, limiting the probability to catch relapses in that time).

2.3. MRI acquisition and analysis

MRI was applied to quantify early white matter lesions, cortical lesions, and global/regional brain volumes/atrophy at baseline (T0) and after two years (T2) using a 1.5T scanner. MRI sequences and procedure have already been described in previous studies (Ziccardi et al., 2023, 2024b) and are provided as Supplementary Material.

2.4. Statistical analysis

The dependent variable was the presence or absence of cognitive PIRA (cognitive stable patients vs cognitive PIRA patients), while a range of clinical, lesion-related, and global/regional brain thickness and volume measures served as independent variables. Random Forest classifiers were applied to predict cognitive PIRA. Random Forest models were trained and evaluated using a stratified 10-fold cross-validation procedure. Model performance metrics and variable importance scores were aggregated across folds and summarized using median values. The variability of variable importance across cross-validation folds was quantified using the interquartile range (IQR) [Q1–Q3]. Variable importance measures derived from the Random Forest models are reported descriptively as relative, model-specific contributions within a predictive framework and do not represent effect sizes, directions of association, or measures of statistical significance.

Table 1
Patients demographic and clinical characteristics.

	MS sample (n = 115)
Clinical data	
RRMS at EOS, n (%)	115 (100 %)
Females, n (%)	85 (73.9 %)
Age at T0, years	30.9 ± 9.2
Age at EOS, years	47.4 ± 10.0
Disease duration at EOS, years	19.1 ± 5.4
Education, years	13.8 ± 3.8
EDSS at T0, median [IQR]	1.5 [2.0]
EDSS at EOS, median [IQR]	3.0 [3.0]
Neuropsychological data	
Period of observation with cognitive assessments, years	4.7 ± 2.6
Number of cognitive assessments, median [IQR]	3 [1]
Time between cognitive assessments, years	2.4 ± 1.1
MRI data	
Years between T0 MRI and diagnosis, median [IQR]	0 [0]
Global CTh at T0 (mm)	2.72 ± 0.32
Global CTh at T2 (mm)	2.69 ± 0.32
WMLs class at T0, median	4–9
New WMLs at T2, median [IQR]	0 [1.0]
CLs number at T0, median [IQR]	1 [3.0]
New CLs at T2, median [IQR]	0 [0]

Continuous data are reported as mean±SD. WMLs classes: 0, 1–3, 4–9, >10.
Abbreviations: RRMS = relapsing-remitting multiple sclerosis, EOS = end of study, EDSS = Expanded Disability Status Scale, CTh = cortical thickness, WMLs = white matter lesions, CLs = cortical lesions.

Multiple models were trained with different sets of predictors to evaluate the relative contribution of anatomical and temporal features to the classification task. Firstly, we performed different models (clinical and MRI global together, only MRI global, only MRI regional) using data at T0; secondly, using data of weighted changes at T2 compared to T0 [(T2-T0)/T0].

All analyses were conducted with a fixed random seed to ensure reproducibility. Statistical computations were conducted using Python (https://www.python.org, version 3.12), Stata (StataCorp, College Station, TX, USA, version 16.0), and RStudio (https://www.r-project.org, version 2024.12.1).

3. Results

115 RRMS patients (73.9 % females) were enrolled in the present study. Mean±SD clinical follow-up since the disease onset was 19.0 ± 5.4 years (Table 1 for clinical/demographic sample characteristics).

Considering neuropsychological monitoring over time, 57 individuals (49.6 %) met the criteria for cognitive decline based on RCIs. Of these, 46 (80.7 %) showed no concomitant relapses and were classified as cognitive PIRA, while 11 (19.3 %) showed a cognitive worsening associated with relapses (RAW).

3.1. Predicting cognitive PIRA using clinical and global MRI variables at diagnosis (T0)

Firstly, we considered clinical and global MRI data acquired at diagnosis (T0). The median [IQR] time interval between MRI acquisition and diagnosis was 0 [0] years. Across Random Forest models with 10-fold cross-validation, global cortical thickness consistently showed the highest median relative importance among T0 variables, accounting for 36.6 % of the total importance [IQR: 35.7–36.9 %], indicating a stable and dominant contribution to predictive performance within the examined feature set. While in a model performed only considering MRI data at diagnosis (global cortical thickness, number of WM/cortical lesions), global cortical thickness reached an importance of 74.9 % [IQR: 74.2–76.0 %] (Fig. 1).

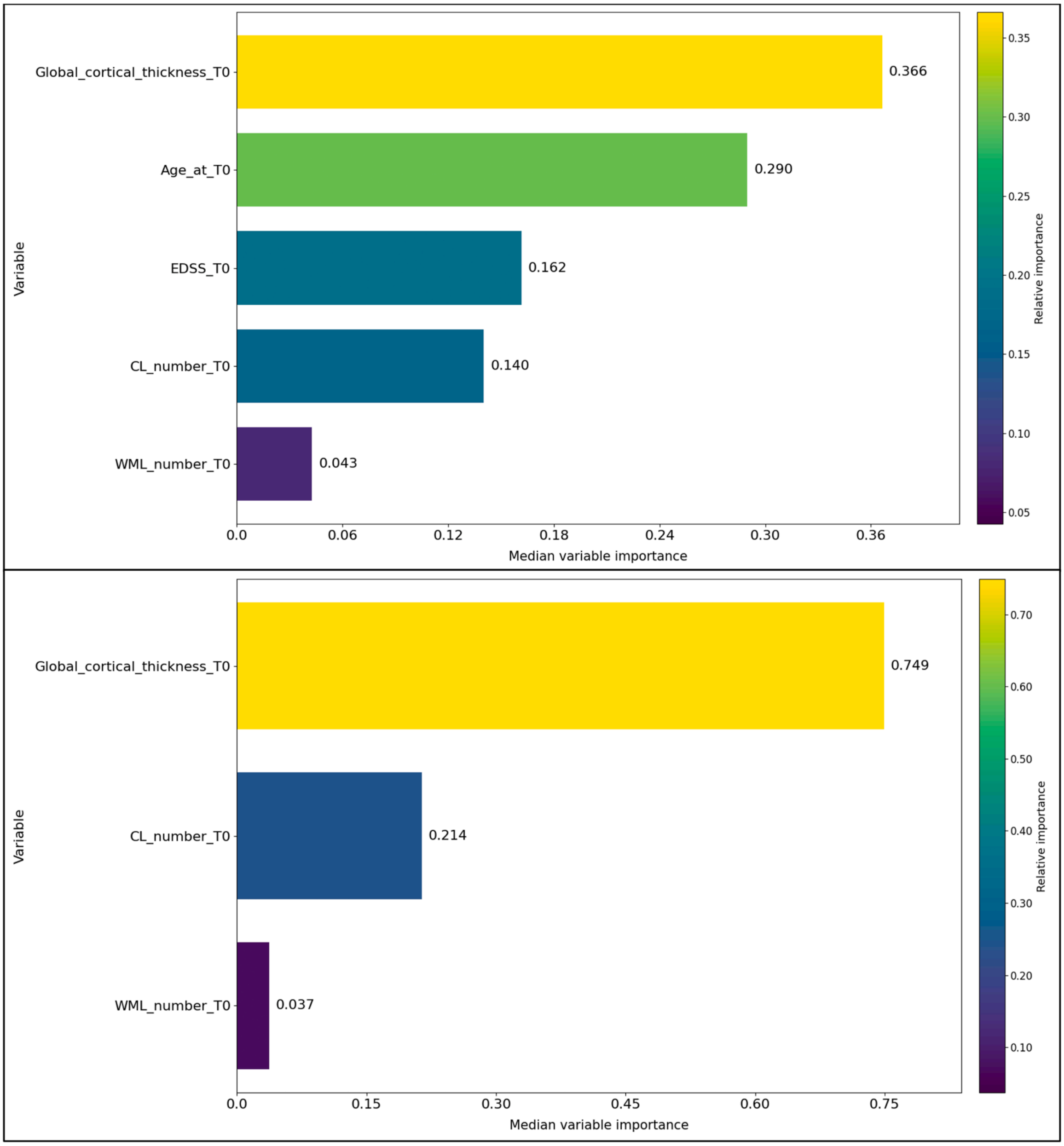

Fig. 1. The random forest model considers the importance of clinical and MRI global data available at diagnosis (T0) in predicting future cognitive PIRA. The figures show the importance of each variable at T0 in predicting the accumulation of future cognitive PIRA. Specifically, above is a model considering both clinical and global MRI data; below is a model focusing on global MRI markers, excluding clinical variables.
Abbreviation: EDSS = Expanded Disability Status Scale, CL = Cortical Lesion, WML = White Matter Lesion.

3.2. Predicting cognitive PIRA using regional MRI cortical thickness and deep GM volumes at T0

Given the strong predictive value of global cortical thickness in the previous models, we further explored this result by applying a Random Forest model focused on regional GM volumes/thicknesses at T0.

Results showed that the thalamic volume at diagnosis ranked highest among regional features in terms of relative importance in the Random Forest model (7.3 %) [IQR: 6.8–7.6 %], followed by inferior temporal gyrus (4.9 %) [IQR: 4.7–5.3 %], cerebellum (4.9 %) [IQR: 4.3–5.4 %], postcentral gyrus (4.4 %) [IQR: 4.3–4.8 %], putamen (4.2 %) [IQR: 4.1–4.4 %], calcarine (4.2 %) [IQR: 4.1–4.4 %], inferior occipital gyrus (4.2 %) [IQR: 3.6–4.3 %], caudate (4.1 %) [IQR: 3.9–4.3 %], cingulate (4.0 %) [IQR: 3.6–4.5 %], superior frontal gyrus (4.0 %) [IQR: 3.8–4.2 %], and pallidum (4.0 %) [IQR: 3.8–4.0 %] (Fig. 2).

3.3. Predicting cognitive PIRA using clinical and global MRI variables change two years after diagnosis (T2)

We then analyzed clinical and MRI data acquired at T2 in comparison with baseline (T0) to capture early longitudinal changes. Across Random Forest models with 10-fold cross-validation, reduction in global cortical thickness between T0 and T2, weighted for baseline values, consistently showed the highest median relative importance for predicting cognitive PIRA. In a model including clinical measures and global MRI changes at T2, global cortical thickness change accounted for 40.5 % of the total importance [IQR: 39.9–41.7 %], exceeding the contributions of age, EDSS, and new lesion counts. In a model restricted to MRI-derived

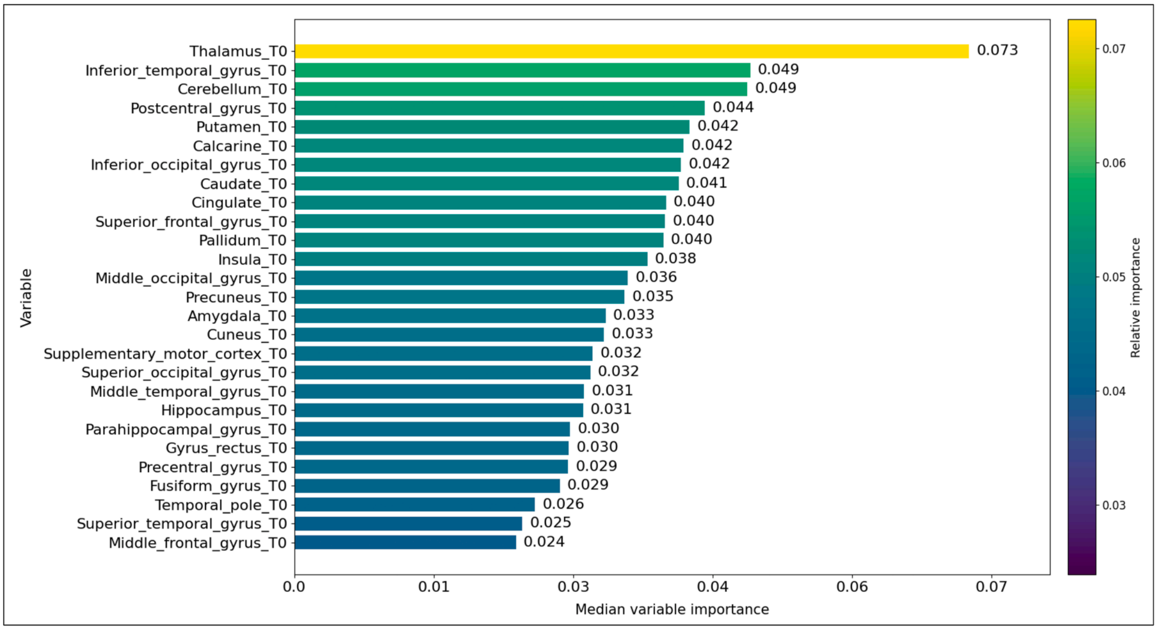

Fig. 2. The random forest model considers the importance of regional MRI data available at diagnosis (T0) in predicting future cognitive PIRA. The figure shows the importance of the thickness/volume of each structure/region at T0 in predicting the accumulation of future cognitive PIRA.

longitudinal measures, global cortical thickness change remained the dominant predictive feature, with a median importance of 79.2 % [IQR: 78.1–80.1 %], contributing substantially more to model performance than the number of new white matter or cortical lesions (Fig. 3).

3.4. Predicting cognitive PIRA using regional MRI atrophy accumulation at T2

Based on the relevance of global cortical thickness reduction, we further explored regional gray matter atrophy at T2 within the Random Forest framework. Among regional measures, atrophy of the middle frontal gyrus showed the highest median relative importance (8.4 %) [IQR: 8.0–9.0 %], followed by the fusiform gyrus (7.4 %) [IQR: 5.9–8.0 %], amygdala (4.6 %) [IQR: 4.4–4.8 %], insula (4.4 %) [IQR: 3.9–4.5 %], and postcentral gyrus (4.0 %) [IQR: 3.6–4.2 %] (Fig. 4).

4. Discussion

The present study aimed to evaluate the occurrence of cognitive PIRA in a RRMS sample followed for a long-term period (20 years) and identify early clinical/MRI predictive markers potentially associated with future development of cognitive PIRA. Similar projects with comparable length of the follow-up, inclusion of regional MRI metrics, and specific PIRA outcomes are rare.

First, our results supported the idea that cognitive PIRA was responsible for most cognitive decline events occurring in RRMS. These findings suggest that most cognitive decline in RRMS patients progresses silently, without clinically evident physical relapses, and is independent from neurological progression, in line with previous evidence (Fuchs et al., 2024; Glanz et al., 2025; Ziccardi et al., 2025).

A relevant study at the end of the previous century showed that gadolinium-enhancing lesions predict recovery from cognitive decline (Foong et al., 1998). This corroborates the fact that cognitive PIRA and RAW are not only differently prevalent in MS, but they are biologically different and reflect separate pathological processes: acute inflammation associated with resolving cognitive change (cognitive RAW) vs smoldering processes leading to silent cognitive progression and consistent cognitive decline (cognitive PIRA).

It is essential to note that cognitive PIRA remains undetectable without formal neuropsychological testing and the application of RCIs. This is particularly relevant, especially considering that early CI is a window of opportunity for cognitive rehabilitation (Ziccardi et al., 2024c).

Second, using a machine-learning–based predictive approach, we found that early measures of global cortical and subcortical damage contributed most to the identification of patients who later developed cognitive PIRA. Global cortical thickness/atrophy were the most relevant predictors of future cognitive PIRA, highlighting the early signs of neurodegeneration as a marker of long-term cognitive vulnerability, contributing more to model performance compared to clinical variables and focal inflammatory damage (both WM/cortical lesion burden).

Our results support a previous study, which demonstrated that PIRA patients had an increased rate of brain volume loss, mainly driven by that in the cerebral cortex (Cagol et al., 2022). Additional studies suggested that PIRA typically occurs in a neurodegenerative environment (Kappos et al., 2020; Cree et al., 2019).

Conversely, our findings show that clinical variables and lesion-based MRI features (WM/cortical lesions) showed lower relative importance within the Random Forest models compared with measures of cortical atrophy, indicating a smaller contribution to predictive performance in this specific modelling framework, suggesting that subtle cognitive decline may be inefficiently reflected by clinical variables and lesion burden, which instead better reflect acute inflammatory activity and RAW (Kappos et al., 2020; Cagol et al., 2022; Ciccarelli et al., 2024).

Notably, MRI data were collected at the earliest stages of MS, suggesting that neurodegenerative processes are detectable from the beginning of the disease, are clinically relevant, and represent a promising predictive marker for future silent cognitive progression.

Moreover, the regional brain atrophy metrics reported in this study were derived from standard T1-weighted volumetric sequences acquired on 1.5T MRI. These measures did not require advanced MRI acquisition protocols or complex post-processing techniques, and were obtained using conventional neuroimaging pipelines. As such, they may be feasibly integrated into routine clinical settings in the future, enhancing the early identification of patients at risk for cognitive PIRA without the need for highly specialized technical resources.

In addition to global GM damage, we also examined regional measures of cortical/deep GM atrophy to determine which brain structures

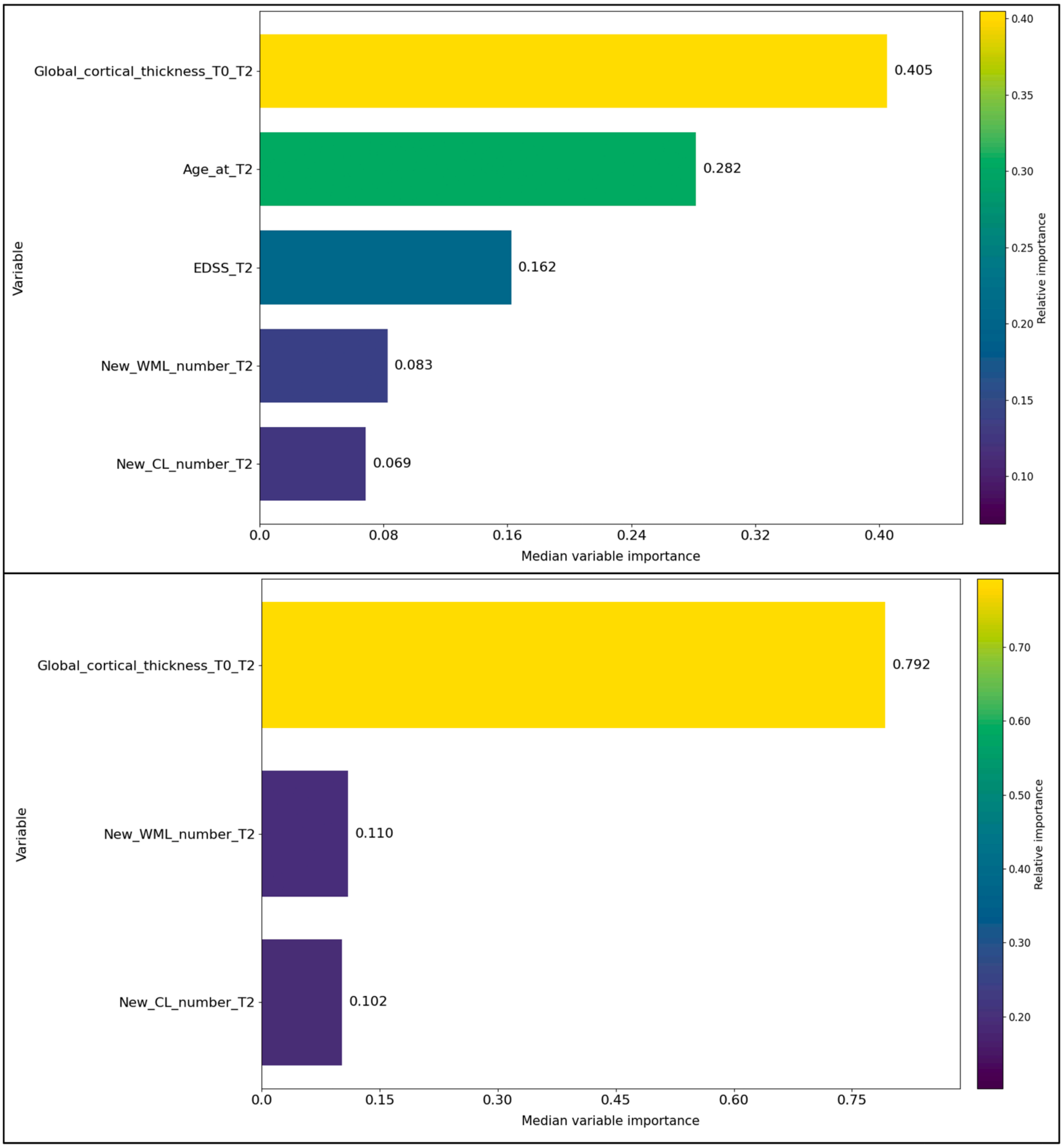

Fig. 3. The random forest model considers the importance of clinical and MRI global data available two years after diagnosis (T2) in predicting future cognitive PIRA. The figures show the importance of each variable in predicting the accumulation of future cognitive PIRA. Specifically, above is a model considering both clinical and global MRI data; below is a model focusing on global MRI markers, excluding clinical variables.
Abbreviation: EDSS = Expanded Disability Status Scale, WML = White Matter Lesion, CL = Cortical Lesion.

played a predominant role in predicting cognitive PIRA. Based on volumetric/thickness measures at diagnosis, the thalamus emerged as the structure with the highest relevance for future cognitive PIRA development. The thalamus is a crucial hub for cognition, as consistently demonstrated in the literature (Schoonheim et al., 2015): it is highly susceptible to neurodegenerative processes (Cagol et al., 2022), and its damage has been repeatedly associated with cognitive deficits (Eijlers et al., 2018; Preziosa et al., 2016). Thalamic atrophy is recognized as one of the most reliable MRI predictors of CI (Conti et al., 2021). Notably, a recent study identified thalamic volume at diagnosis as the strongest MRI predictor for clinical PIRA and PIRMA events accumulated 5 years after diagnosis (Marastoni et al., 2025).

Along with the thalamus, other regions with high predictive value for cognitive PIRA included inferior temporal gyrus, cerebellum, post-central gyrus, putamen, calcarine, inferior occipital gyrus, caudate, cingulate, superior frontal gyrus, and pallidum. Within the Random Forest models, putamen, caudate, and pallidum, together with the thalamus, showed the highest relative importance among deep gray matter structures for predicting cognitive PIRA: several studies reported reduced subcortical GM volumes in MS patients with CI, reinforcing their relevance in cognitive functioning (Eijlers et al., 2018; Conti et al., 2021). The cerebellum also plays a key role in cognition, due to its dense connectivity with frontal, parietal, and limbic cortices (Schmahmann and Sherman, 1998): cerebellar demyelination and neurodegeneration are common in MS, especially in patients with cognitive deficits (Preziosa et al., 2016), making it one of the most valuable predictors of CI (Conti et al., 2021). The cingulate is known to support multiple cognitive processes: damage in this area is linked to CI (Ziccardi et al., 2024b), and patients with PIRA showed reduced cingulate volumes (Cagol et al., 2022). In addition, the superior frontal gyrus, as a part of

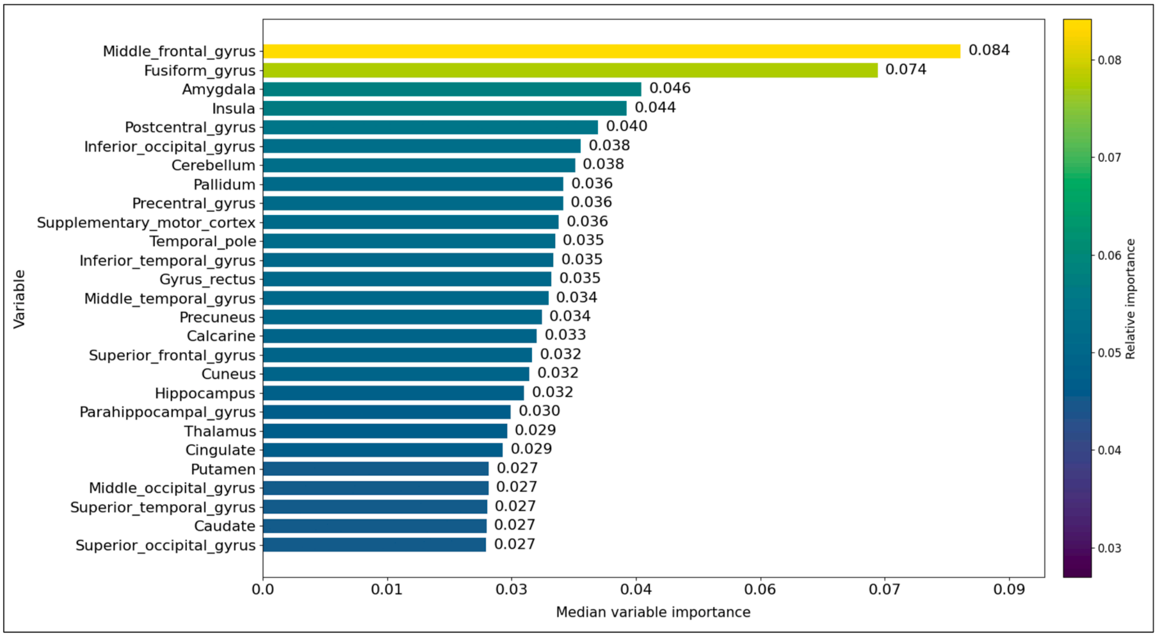

Fig. 4. The random forest model considers the importance of regional MRI atrophy data available two years after diagnosis (T2) in predicting future cognitive PIRA. The figure shows the importance of the atrophy in each structure/region from T0 to T2, weighted for the T0 baseline value in predicting future cognitive PIRA.

the dorsolateral prefrontal cortex, is involved in higher-level cognitive processes (du Boisgueheneuc et al., 2006; Hu et al., 2016): MS-related atrophy in this region can contribute to cognitive difficulties (Stellmann et al., 2021; Ziccardi et al., 2024b). Lastly, early atrophy in specific cortical areas (i.e., postcentral gyrus) has been identified as a major risk factor for long-term CI (Ziccardi et al., 2024b).

Furthermore, our results showed that the middle frontal gyrus was the brain region in which the volume reduction (weighted for baseline values) reached the highest importance with future cognitive PIRA. As for the superior frontal gyrus, the middle frontal gyrus is also included in the dorsolateral prefrontal cortex and is important for higher-level cognitive processes (Ridderinkhof et al., 2004): its potential relevance is consistent with previous studies identifying frontal regions as vulnerable substrates for cognitive dysfunction in MS (Calabrese et al., 2010). In particular, middle frontal gyrus thickness at diagnosis emerged as a major determinant for PIRA occurring within 5 years (Marastoni et al., 2025).

Other regions whose early atrophy was relevant for cognitive PIRA prediction included the fusiform gyrus, amygdala, inferior occipital gyrus, and insula, in addition to the postcentral gyrus, which was already found important considering their baseline volume at diagnosis.

In particular, the fusiform gyrus reached an importance almost comparable to the middle frontal gyrus: this is in line with literature showing this component is involved in cognitive processes, especially in visual memory (Lageman et al., 2025). Moreover, the insula is also involved in many different cognitive processes: insular damage in MS has been associated with cognitive difficulties (Ziccardi et al., 2024b) and with PIRA (Cagol et al., 2022).

Overall, our findings are consistent with and reinforce the conclusions of a recent study, which demonstrated that MS patients who experience clinical PIRA show significantly greater cortical atrophy. This atrophy is particularly pronounced in key brain regions, including frontal, temporal, and parietal lobes: these areas are critically involved in higher cognitive functions, motor control, and sensory processing, which may help explain the more severe clinical outcomes observed in patients with PIRA compared to those whose disease remains stable (Cagol et al., 2022). By corroborating these results, our study adds further evidence to the growing recognition that neurodegeneration in MS can progress independently of acute inflammatory relapses, highlighting the importance of monitoring cortical atrophy as a marker of disease progression.

We are aware that the present study is not free from limitations.

First, this long-term MS cohort was clinically followed over 20 years, but we could not evaluate the cognitive and MRI evolution over the entire follow-up, which would have provided a complete sampling over the whole longitudinal period, resulting in a more comprehensive and adequate description of brain damage evolution and its effect on cognitive PIRA.

Second, in the present study, we focused on global and regional brain volume and atrophy as MRI predictors of cognitive PIRA, expanding findings from previous research on cortical thinning and PIRA accumulation (Cagol et al., 2022). However, the MS scientific community increasingly emphasizes the need for integrated imaging approaches that capture all relevant pathological processes, including new lesion formation, brain atrophy, PRLs, slowly expanding lesions (SELs), and other neurodegenerative markers (Ciccarelli et al., 2024; Guerra and Iaffaldano, 2025). Incorporating such metrics into future clinical trials could enhance the understanding of biological correlates of progression (Guerra and Iaffaldano, 2025).

Third, our analyses did not account for heterogeneity in disease-modifying therapies (DMTs) across the disease course. However, during the first two years from diagnosis, all patients received first-line treatments available at that time (approximately 20 years ago). Additionally, although DMT can have a positive impact on cognition, structured evidence on the potential benefit of DMTs expanding to cognition is limited and not clearly explored (Landmeyer et al., 2020). In fact, to date, there is no approved pharmacological treatment for cognitive impairment in MS (Benedict et al., 2020). Pharmacological studies evaluated DMTs effect on preventing PIRA: the presently available DMTs are effective in reducing relapses, even though they are still largely ineffective on target silent progression (Prosperini et al., 2024).

Fourth, Random Forest variable importance scores quantify the relative contribution of each feature to classification performance within a specific model and dataset. These measures are model-dependent, stochastic, and non-inferential; therefore, they do not represent effect sizes, statistical associations, or causal relationships. Finally, although Random Forest models were trained and evaluated using 10-fold cross-validation, an important limitation concerns the interpretation of variable importance measures. Cross-validation primarily assesses the robustness of predictive performance and does not guarantee stability of feature importance rankings. In this study, we did not formally quantify the variability of importance scores across folds, random seeds, or alternative model specifications. Therefore, reported importance values should be interpreted as descriptive indicators of feature relevance within a cross-validated predictive framework rather than as stable or precise estimates of feature effects.

Future studies will need to focus on overcoming the abovementioned limitations, by further exploring the concept of cognitive PIRA and its pathological drivers, in terms of both neuroradiological and biological markers.

Taken together, our results showed that cognitive PIRA accounted for the majority of meaningful cognitive decline events in this cohort. Within a predictive machine-learning framework, early measures of neurodegeneration contributed more to model performance than clinical variables or focal inflammatory markers. The importance of global cortical and deep GM thickness/atrophy, with reference to cognitive PIRA development, is substantially more relevant than the role played by WM lesions and clinical variables. Early atrophy in specific cortical and subcortical regions, such as the thalamus and the frontal lobe, emerged as the most informative predictors.

Cognition is not only a symptom, but instead, it represents an important and helpful part of the disease diagram, in which it is highly connected with other pathological substrates, including those more subtle: cognitive worsening offers a unique window into the underlying neurodegenerative mechanisms of MS. Therefore, a comprehensive routine cognitive assessment can detect disease progression that might otherwise be entirely overlooked, offering to healthcare professionals the possibility to better tailor early therapeutic and rehabilitative intervention to maintain a better prognosis over disease course.

When silent cognitive decline is recognized correctly, it could reflect silent disease activity and provide insights into smoldering MS progression. The recognition and study of cognitive PIRA might help to bridge the gap between covert pathological changes and radiological markers of brain damage.

These findings challenge the historical emphasis on relapse-associated changes and underscore the need for more refined biomarkers capable of capturing subclinical progression.

Data availability

The corresponding author declares the right to publish these results, full access to the study data, and full responsibility for the integrity and the accuracy of the analyses. Deidentified data that support the findings of this study will be shared on request from a qualified investigator.

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CRediT authorship contribution statement

Stefano Ziccardi: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Tom A Fuchs:** Writing – review & editing, Conceptualization. **Luigi Martinelli:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Teresa Maltempo:** Writing – review & editing. **Francesco Guarnaccia:** Investigation. **Francesco Crescenzo:** Writing – review & editing. **Maddalena Guandalini:** Investigation. **Gian Marco Schiavi:** Investigation. **Albulena Bajrami:** Writing – review & editing. **Agnese Tamanti:** Investigation. **Valentina Camera:** Data curation. **Damiano Marastoni:** Writing – review & editing, Data curation. **Ralph H B Benedict:** Writing – review & editing, Supervision, Conceptualization. **Massimiliano Calabrese:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of competing interest

SZ serves on the editorial board of Frontiers in Aging Neuroscience and Diagnostic.

TAF serves on the editorial board of Frontiers in Neurology, and receives research support from the European Committee for Treatment and Research in Multiple Sclerosis and consulting fees for Click Therapeutics.

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MC serves on the editorial board of Frontiers in Neurology and Diagnostic, received research support from the Progressive MS Alliance, the Italian Minister of Research and the Italian Minister of Health and has served as a consultant for or received research support from Biogen, Celgene/Bristol Meyers Squibb, Sanofi, Roche, Novartis and Merck.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2026.107080.

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