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Forecasting the information computational efficiency for multiple sclerosis using a machine learning-based approach on a massive multi-focal magnetic resonance imaging dataset

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Abstract

The Symbol Digit Modalities Test (SDMT) has been suggested as a reliable screening tool for information processing speed (IPS) deficiencies, which are common in MS patients. Understanding the mechanisms underlying cognitive problems in multiple sclerosis has significantly improved because to magnetic resonance imaging (MRI). It is yet unknown, nevertheless, which structural MRI signals have the most correlation with cognitive function. We extracted multimodal data (demographic, clinical, neuropsychological, and structural MRIs) from 540 MS patients using the multicenter 3T-MRI data set of the Italian Neuroimaging Network Initiative. Our objective was to evaluate, using machine learning techniques, how brain MRI structural volumes, in conjunction with clinical and demographic characteristics, contribute to the prediction of IPS abnormalities. In order to achieve dependable generalization performance, we trained and evaluated the eXtreme Gradient Boosting (XGBoost) model using a strict validation scheme. Based on SDMT scores, we performed a regression and classification exercise, feeding each model with various feature combinations. The model trained with the volumes of the thalamus, cortical gray matter, hippocampus, and lesions obtained an area under the receiver operating characteristic curve of 0.74 for the classification task. A mean absolute error of 0.95 was attained by the model trained with cortical gray matter and thalamus volumes, EDSS, nucleus accumbens, lesions, and putamen volumes, as well as age, for the regression task. Our findings demonstrated that one of the most significant predictors of cognitive function in multiple sclerosis is damage to cortical gray matter and other deep and ancient gray matter regions, including the thalamus and hippocampus.

Keywords: Symbol Digit Modalities Test (SDMT), eXtreme Gradient Boosting (XGBoost), Information processing speed (IPS)

1. Introduction

The most prevalent nontraumatic debilitating illness affecting young adults is multiple sclerosis (MS), a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system. Regardless of their clinical profile, a significant number of MS patients have cognitive impairments, primarily in the areas of episodic

memory and information processing speed (IPS). Sometimes disregarded, cognitive impairment (CI) has a significant detrimental effect on social interactions, work status, and, more generally, the patients' everyday lives and quality of life. As a result, many people now think that normal clinical evaluations should involve tracking MS patients' cognitive health. Numerous neuropsychological (NP) batteries have been created and approved to assess CI in MS. However, the lack of neuropsychologists as well as the lack of time and space for such equipment makes it difficult to monitor CI in ordinary clinical practice. Short batteries, like the Brief International Cognitive Assessment for Multiple Sclerosis, or a single test with a high sensitivity and predictive value could be used to assess MS patients. Because of its convenience (taking only a few minutes to administer), reliability, sensitivity, ecology, and predictive value, the Symbol Digit Modalities tool (SDMT), which largely evaluates IPS, has been suggested as a reliable screening tool for CI in MS.

Magnetic resonance imaging (MRI) has significantly advanced our knowledge of the mechanisms behind CI in MS patients by demonstrating the pertinent role of ventricular enlargement, whole brain and grey matter (GM) atrophy, and white matter (WM) lesion burden. In the case of GM atrophy specifically, global, cortical, and deep and archaic GM damage are the most significant contributors to CI. It is yet unknown, though, which structural MRI signals are most strongly associated with MS patients' cognitive function. Actually, only one or a small number of particular brain areas have been examined in relation to CI in MS patients. Since CI has been linked, as anticipated, to damage to numerous brain regions, it is still necessary to identify which brain regions are most relevant or which combination of them is more predictive of CI in MS for the purposes of monitoring and treatment implications, as well as at the individual subject level. A method that combines several MRI-derived metrics to deduce patterns of brain damage linked to cognitive function ought to more accurately depict the intricacy of CI in MS, which is probably supported by a number of interrelated biological processes. Furthermore, the cognitive test has reliability issues, particularly if it is repeated over time. Therefore, it would also be very helpful in a therapeutic environment to choose a small number of very specific imaging and/or non-imaging indicators that could predict an MS patient's cognitive status at the subject level.

Advanced statistical techniques are needed to predict CI in individual patients using MRI data. The analysis of high-dimensional data with a hidden complicated pattern has shown great promise in recent years thanks to machine learning (ML) techniques. The use of these cutting-edge technologies in neuroimaging research can aid in understanding the behavior of biological systems and in predicting future behavior or unobserved events. ML approaches have so far been used in a number of studies to help with MS diagnosis, classify MS patients according to the most prevalent clinical phenotypes, or predict physical disability. To the best of our knowledge, just one recent study used machine learning approaches to examine the connection between MS patients' cognitive status and neuroimaging data. The results of earlier studies may have been excessively hopeful due to the limited sample size and certain methodological restrictions (i.e., feature selection not done in the training/validation set only).

We postulated that machine learning approaches may be used to determine which brain structural MRI volumes, in conjunction with clinical and demographic information, are the most reliable indicators of MS patients' cognitive status as measured by SDMT score. We conduct a study with the following features to look into our hypotheses: In order to obtain a robust, dependable, and generalizable prediction of the cognitive performance in MS, (1) a large multicenter multimodal data set comprising high-quality clinical, NP, and 3T MRI data is used; (2) appropriate and "state of the art" methodology is applied for the harmonization of MRI data acquired in various centers; and (3) ML algorithms are implemented and used in accordance with a strict validation scheme.

2. Materials and methods

The study comprised 540 MS patients whose MRI and NP exam results were part of the Italian Neuroimaging Network Initiative (INNI) repository. NP, clinical, demographic, and 3T structural and functional MRI data sets are gathered at INNI, a multicenter multimodal repository funded by a specific research funding from the Italian MS Foundation. The four founding centers currently oversee the INNI project. According to earlier research, the centers are now referred to as A, B, C, and D in any particular order.

The following inclusion criteria were used to select MS patients from the INNI repository for the current cross-sectional study: (1) having access to complete clinical and demographic data, such as sex, age, years of education, disease onset, disease course, and clinical disability as measured by the Expanded Disability Status Scale; (2) having access to axial T2-weighted (T2w) and anatomical, isotropic, 3D-T1-weighted (3D-T1w) scans; and (3) gathering clinical and NP data within 180 days from the reference MRI scans.

2.1 Assessment of NP and neurology

At each participating site, skilled neurologists and neuropsychologists conducted a neurological evaluation and an NP assessment on all enrolled MS patients. The primary data about the history and progression of the disease as well as the clinical disability scores were included in the neurological evaluation. Specifically, we extracted the disease duration and the EDSS score from the clinical data that was accessible in the INNI repository.

A thorough NP examination based on the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) is part of the INNI protocol. We chose the SDMT among the BRB-N tests to investigate the IPS, the cognitive domain most frequently impacted by MS. It consists of a time-limited symbol substitution exercise, and the score is determined by how many responses are right (range 0–110). Therefore, better performance is indicated by higher SDMT scores. The Z-scores and demographic-and education-adjusted scores were determined in this investigation using the available normative data, which are based on a sample of 200 healthy Italian individuals.

2.2 MRI analysis

The 3T MR system at each INNI facility was used to scan all MS patients. 3D-T1w and T2w pictures were used in this investigation. With the exception of the 3D-T1w scans from center A, which were obtained using two distinct sequences, all MRI data sets were obtained at each center using the same scanner and methodology. Therefore, we treat the pictures of center A as belonging to two distinct groups in order to properly apply post-acquisition harmonization procedures.

At each of the participating locations, skilled researchers used a local thresholding segmentation technique to semi-automatically segment focal WM hyperintensities of the entire brain in T2w images. The total T2w lesion volume (T2LV), which would serve as a predictor in the machine learning analysis, was then calculated for every patient.

Every 3D-T1w MRI scan underwent two preprocessing steps. In the initial step, the lesion filling tool was utilized to refill lesions in the 3D-T1w images utilizing focal WM lesion masks. In order to enable precise tissue segmentation and assessment of brain subregional volumes, the lesions were filled with intensities that matched the surrounding normal-appearing WM. The second step involved estimating and correcting intensity inhomogeneity (bias field) in lesions-refilled 3D-T1w images using the tried-and-true N4 approach from the Advanced Normalization Tools (ANTs) toolbox version 1.9.

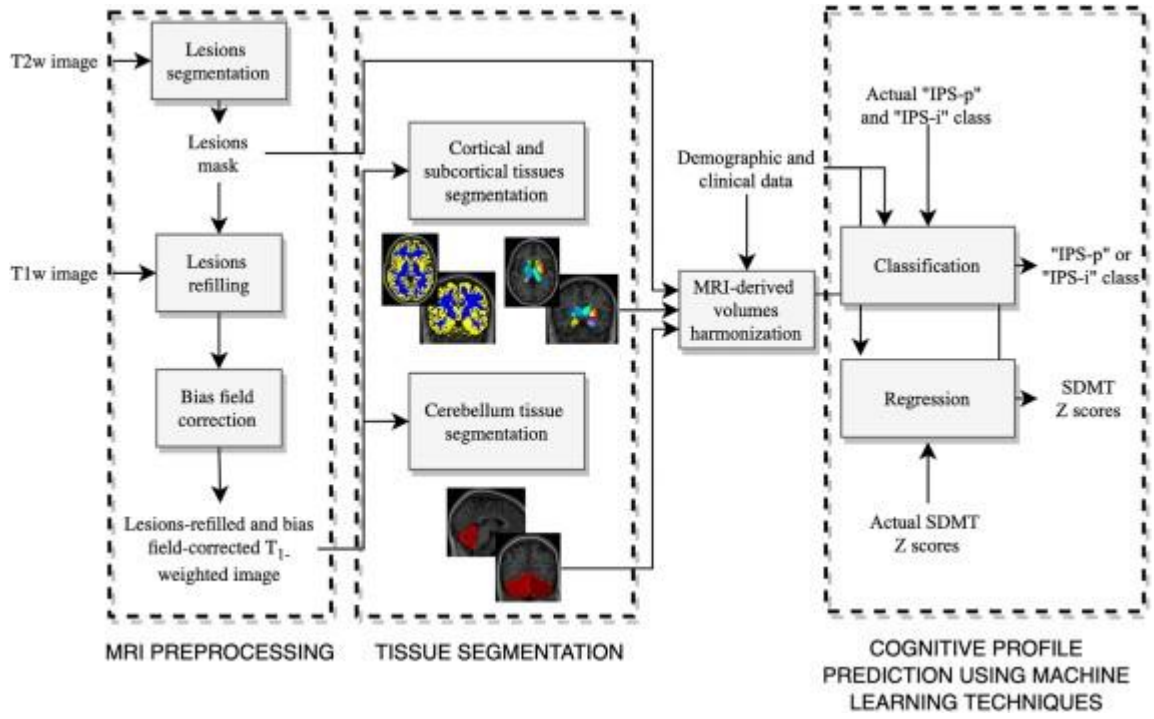

Fig: 1 An overview of the complete machine learning (ML) analysis and magnetic resonance imaging (MRI) processing

2.3 Segmenting tissues

Using FSL v.6.0.3 scripts on lesions-refilled and bias field-corrected 3DT1w images, brain tissue segmentation was performed. Specifically, we employed (i) the SIENA-XL package's cross-sectional pipeline to calculate the volumes of the entire brain, cortical GM, WM, thalamus, basal ganglia, hippocampus, and amygdala, and (ii) FIRST scripts for cerebellar segmentation with specified settings. To lessen subject-to-subject variability associated to head size, all segmented volumes—including the T2LV acquired during preprocessing—were calculated in cm3 and multiplied by the SIENAX scaling factor. We took into account the average volume of the left and right structures for the subcortical and cerebellar volumes.

2.4 Harmonization of volumes acquired from MRI

The comparability of the pictures across centers, scanners, and imaging sequences is crucial to the effectiveness of pooling multicenter MR scans and MRI-derived metrics, such as cortical and subcortical volumes. Indeed, due to variations in scanner manufacturers and imaging procedure heterogeneity, MR pictures can vary greatly between scans. To reduce the "center-effect" on MRIs while maintaining between-subject biological variability, we harmonized our multicenter MRI-derived volumes data prior to pooling them. We specifically employed the Neuro-Com-Bat package v. 0.1.dev0, a user-friendly and open-source Python module that can be incorporated into any processing pipeline that is currently in place. Age, gender, education, length of illness, EDSS score, clinical phenotype, and SDMT are among the demographic, clinical, and NP characteristics that are known to affect the MRI-derived volumes for each MS patient. These factors were therefore taken into account as a source of inter-subject biological variability during the harmonization procedure. To prevent any possible data leaking, the harmonization procedure was carried out following the separation of the test and training/validation sets.

The existence of the "center effect" on MRI-derived volumes prior to and following the harmonization step was then assessed using an analysis of covariance (ANCOVA) for both training/validation and test sets, taking into account the effects of various demographic and clinical data. Harmonized MRI-derived volumes were employed in all ensuing studies.

3. Cognitive performance prediction with machine learning techniques

Following MRI preprocessing, tissue segmentation, and harmonization of MRI-derived volumes, we used sophisticated machine learning algorithms to forecast MS patients' cognitive function. In fact, as shown below, we evaluated the potentials of several feature combinations supplied as input in order to do both a classification and a regression task.

Classification task: Based on their SDMT Z-scores, MS patients were split into two subgroups: "IPSpreserved (IPS-p)" and "IPS-impaired (IPS-i)." The criterion for IPS deficit was set at 1 SD below the mean, or SDMT Z scores ≤~1.0. Consequently, 255 MS patients were assigned to IPS-i and 285 to IPS-p. We predicted the patient's class designation in this exercise (IPS-p vs. IPS-i).

We trained, validated, and tested the eXtreme Gradient Boosting (XGBoost) for both the classification and regression tasks. A popular end-to-end tree boosting technique that is scalable, XGBoost achieves cutting-edge results on a variety of contemporary machine learning tasks. Its recursive tree-based decision system's high potential interpretability is one of its main advantages.

We looked at (1) a priori knowledge-based feature sets in conjunction with (2) a data-driven approach where we automatically choose the optimal feature combination without preconfigured sets in order to analyze the contribution of both imaging and non-imaging features to SDMT performance and to evaluate the most contributing features. We constructed several combinations of demographic, clinical, and MRI-derived features for the a priori sets of data. We began with a basic model that only contained demographic and clinical aspects and progressively increased its complexity to arrive at a full model that contained all variables. These various feature combinations were deduced from the literature and clinical experience of highly skilled MS neurologists. In a nutshell, we first looked at a model that included demographic data with the primary clinical characteristics of MS research, namely the EDSS score and the duration of the condition. Metrics from structural neuroimaging, such as brain volumes and T2-WM lesion volume (which accounts for the degree of WM lesions), were gradually added to the analysis to further examine the effects of various structural changes on cognitive function. Age, sex, and education were included in each feature combination to account for the possible residual effect of these characteristics on cognitive performance, even though this was controlled by the use of normative data. The important gain, or performance boost, that each feature contributes is estimated by the XGBoost algorithm.

Therefore, we used the top n features in the feature ranking that was produced with the combination "All" using n = 1, 2, …, 16 to iteratively retrain a new XGBoost model. The characteristics with the highest importance gain were then added one at a time, and we saw the possible improvement in performance. Following Occam's razor principle and minimizing potential overfitting, we chose the feature set with the fewest features when performance was equivalent. The best feature set was ultimately chosen based on the best performance (from a priori and data-driven techniques).

3.1 Experimental tests

The Oracle Grid Engine scheduler was used to extract advanced neuroimaging features from a Dell PowerEdge T620 workstation that has two 8-core Intel Xeon E5–2640 v2 processors, for a total of 32 CPU threads and 128 GB of RAM. The quantification of cerebral and cerebellar features took roughly 20 and 15 minutes, respectively, for a single-core CPU to process for each participant.

The following modules were used in the custom Python code (v. 3.8.1) for the pipelines' training, validation, and testing: graphviz v.0.15, matplotlib v.3.3.4, numpy v.1.18.1, pandas v.1.0.2, pingouin v.0.3.5, scikit-learn v.0.22.2.post, seaborn v.0.11.0, and xgboost v.1.2.1. Specifically, we employed the XGBClassifier and XGBRegressor estimators for the regression and classification tasks, respectively. Training, validation, and testing took roughly five days to complete on a single core of a Linux workstation with a 64 GB RAM and a 4-core (eight threads) Intel i7-7700K CPU.

4. Results

Prior to data harmonization, ANCOVA results revealed substantially significant variations in MRI-derived volumes between various INNI centers (p-values <10~3 for all structures in the training/validation set and p-values <10}2 for all structures in the test set, with the exception of NT2LV and NCaudmV). While the volumes of the entire brain and subcortical regions displayed less noticeable variations, the cortical GM, WM, and cerebellar volumes specifically displayed the most significant variances. Volume disparities between groups were either eliminated (ANCOVA test p-values >.05) or significantly decreased (the partial η2 coefficients pertaining to the group effects were reduced) in all structures for the training/validation and test sets following data harmonization.

4.1 Classification task

Specifically, the following feature combinations produced the greatest results, with an AUROC of 0.74 (0.01): Whole brain + les and Auto 4. The latter combination was thought to be the best collection of predictors for the cognitive class because it had fewer indicators but the same greatest performance. When compared to the classification performance achieved with the XGBoost model trained using simply the most significant predictor—the thalamus volume—this set demonstrated an increase in AUROC of 2.78%. Next, using the unseen test set data, the final XGBoost classifier—which had been trained using the volumes of the thalamus, cortical GM, hippocampus, and lesions—obtained an AUROC of 0.69 (0.03).

4.2 Regression task

The XGBoost regressor trained with cortical GM and thalamus volumes, EDSS, nucleus accumbens, lesions, putamen volumes, and age had the best performance (MAE = 0.95 (0.01) [mean (SD)]). When compared to a regression using an XGBoost model built using only the best predictor, namely the cortical GM volume, this feature combination, which was selected automatically during the training phase, demonstrated a decrease in MAE score of 10.38%. Lastly, this model received an MAE score of 1.02 (0.01) [mean (SD)] after being evaluated on the unseen test data.

5. Discussion

In this study, we used machine learning approaches to forecast an indicator of MS patients' cognitive health, namely the SDMT score. We combined the data from the demographic, clinical, and MRI-derived volume data of 540 MS patients from the vast, multicenter INNI repository to undertake a regression work (SDMT score prediction) as well as a classification task (IPS-p vs. IPS-i MS patients). A combination hold-out/CV strategy was used to train, validate, and test an XGBoost estimator (80% of subjects in the training/validation sets and 20% in the test set). The model was trained and verified in the training/validation set by optimizing hyperparameters and selecting features using a nested CV technique that was tailored for the classification job. Furthermore, the nested CV process was carried out ten times using various random splits because the choices could change based on how the training and validation data are divided in each fold. Our findings demonstrated that every feature combination performed well. The classification task's XGBoost classifier, which was trained using the volumes of the thalamus, cortical GM, hippocampus, and lesions, obtained an AUROC score of 0.74 (0.01) on the validation set and 0.69 (0.03) on the data from the (unseen) test set. Conversely, the XGBoost regressor developed with cortical GM and thalamus quantities, EDSS, nucleus accumbens, lesions, putamen volumes, and age performed the best in the regression task, achieving an MAE of 0.95 (0.01) in the validation set and an MAE of 1.02 (0.01) on the (unseen) test set.

Our results demonstrate that the widespread structural brain architecture damage associated with MS pathology may foretell effects on MS patients' cognitive state that are insufficiently explicable by clinical data alone. In addition to the model with the highest performance, we wanted to identify the smallest feature set that could predict the SDMT score the best and was less likely to overfit. For instance, we chose the feature combination with less features (thalamus, cortical GM, hippocampal volumes, and T2LV) for the classification task after observing two models with the same highest performance (i.e., AUROC = 0.74 (0.01)). In essence, we demonstrated that the thalamus, cortical GM, hippocampal volumes, and T2 lesion volume provide a dense representation of all clinical/demographic and MRI-related data in the classification task.

In keeping with earlier research, we believe this to be a significant finding. It is well established that a key basis for CI is cortical atrophy, namely in a specific circumscribed area of the prefrontal, parietal, and temporal cortex. Since the thalamus is an important "cognitive hub" with numerous afferent and efferent connections to the cerebral cortex and midbrain, its degeneration is likely to contribute to IPS dysfunction and, in turn, to a general cognitive dysfunction. However, it is also well known that in MS populations with a somewhat long disease duration, such as our sample (mean 10.8 years, SD 8.7 years), there is a strong correlation between the thalamic volume and the whole-brain volume. For instance, this could explain why combinations involving the volume of particular, localized brain regions or the entire brain might be just as beneficial.

In addition to the thalamus, it has been discovered that the hippocampus and other pertinent "cognitive structures" play a role in cognitive failure in MS patients. A predilected location for demyelinated lesions, the hippocampus is directly related to memory and learning processes. Cognitive function is impacted by the cortical-thalamic-hippocampal disturbance in MS patients with mild to moderate CI.

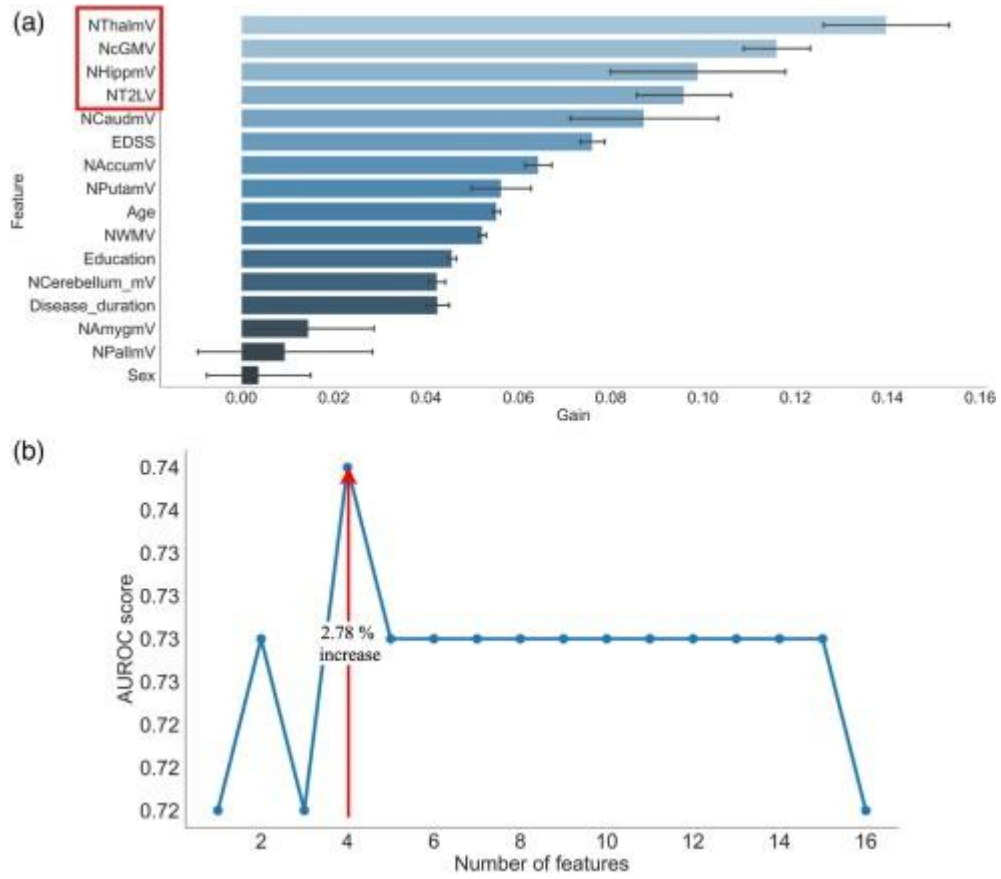

Fig: 2 The XGBoost estimator is used for the automatic feature selection in the classification task.

Area under the ROC curve (AUROC) as a function of feature count and (a) feature rating. Average values from the validation set are presented in both panels using ten iterations of the fivefold nested stratified cross-validation [CV] method. The features in the red rectangle in Panel (a) are those that collectively yield the best AUROC in the validation set, whereas the black lines with caps show the standard deviation.

6. Conclusion

Our ML method performed well in predicting CI in MS utilizing a wide range of brain structural metrics taken from a sizable multicenter 3T-MRI data set. This innovative method shown that when predicting cognitive function in MS, the involvement of certain brain cognitive hubs, such as the thalamus and the hippocampus, is more significant than focal WM loss (i.e., T2LV).

We started by forecasting the cognitive function of a sample of MS patients with any disease profile. Although similar NP profiles have been reported in all MS courses, it is still unclear if distinct MS phenotypes share pathophysiological substrates of CI. Unfortunately, a diverse distribution within the participating institutions and the scarcity of some phenotypes (i.e., benign MS, clinically isolated condition, and primary progressive MS) prevented us from conducting sub-group analyses. Future machine learning research should examine whether structural brain MRI predictors of CI differ among MS phenotypes.

Second, MRI data obtained using imaging techniques established individually by each site is currently available in the INNI repository. The application of established protocols reduced the sample sizes needed to identify disease-related neuroanatomical alterations by up to five times, according to a recent study, and is especially helpful for identifying subtle effects. Standardized acquisition techniques of advanced structural and functional MRI data sets will be promoted as a result of these factors and in accordance with the INNI's primary future objectives.

Lastly, we assessed the correlation between the volumetric data taken from anatomical T1w and T2w scans and the cognitive status as determined by the SDMT score. Future studies should look into factors that predict cognitive performance using different NP tests alone or in combination with other MRI metrics, like diffusion-weighted imaging- and, most importantly, functional MRI-derived metrics.

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