Chapter 28

Machine Learning in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is characterized by inflammatory activity and neurodegeneration, leading to the accumulation of damage to the central nervous system resulting in the accumulation of disability. MRI depicts an important part of the pathology of this disease and therefore plays a key part in diagnosis and disease monitoring. Still, major challenges exist with regard to the differential diagnosis, adequate monitoring of disease progression, quantification of CNS damage, and prediction of disease progression. Machine learning techniques have been employed in an attempt to overcome these challenges. This chapter aims to give an overview of how machine learning techniques are employed in MS with applications for diagnostic classification, lesion segmentation, improved visualization of relevant brain pathology, characterization of neurodegeneration, and prognostic subtyping.

Key words Multiple sclerosis, Machine learning, Artificial intelligence, Deep learning, Neuroimaging

1 Introduction to MS

Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS) affecting women more than men, usually starting in young adulthood with a prevalence of >100 per 100,000 individuals in the Western world and rising [1].

1.1 Disease Characteristics

The most striking feature is the appearance of focal inflammatory lesions in the CNS visible on MR imaging of the brain (Fig. 1) and/or spinal cord that may give rise to partially reversible loss of motor, sensory, and cognitive function depending on lesion location and the magnitude of damage to local nerve tissue. As the disease and resulting damage to the central nervous system accumulate, irreversible disability progresses over time. Although tempting, not all of the accumulated disability can be explained by focal inflammatory lesions [2]. Diffuse neurodegeneration in the CNS is another histopathological feature deemed responsible for gradually accumulating disability, especially in the later stages of the disease. This neurodegeneration is thought to result from a process

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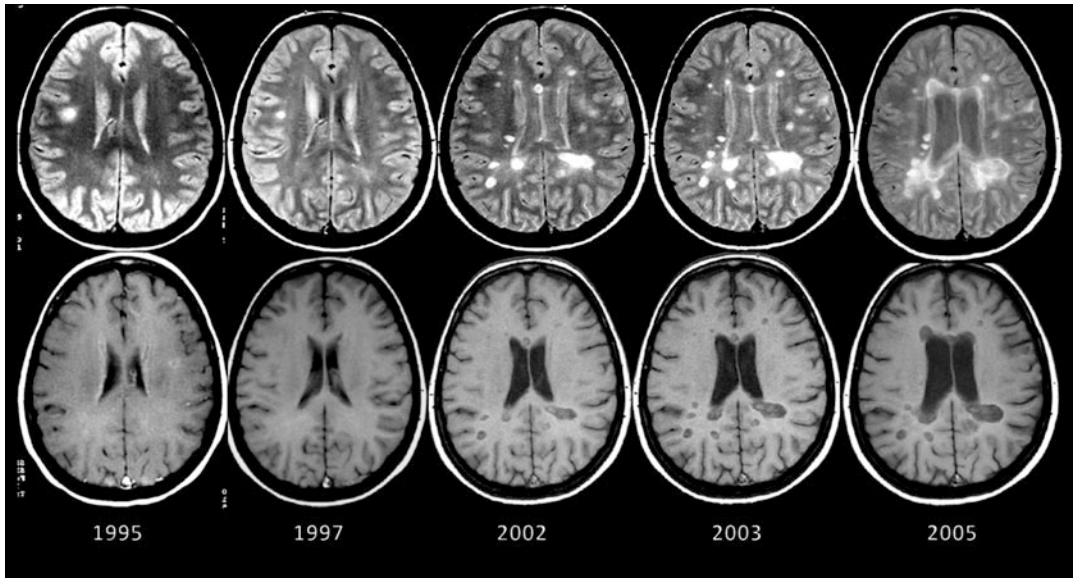


Fig. 1 PD-weighted MR images (top row) showing the occurrence of MS typical T2/PD hyperintense lesions over time. T1-weighted images (bottom row) showing enlargement of sulci and ventricles over time consistent with brain atrophy and hypointensity of multiple lesions due to local tissue loss. (Figure kindly provided by Dr. Alex Rovira (Hospital Universitari Vall d'Hebron, Barcelona))

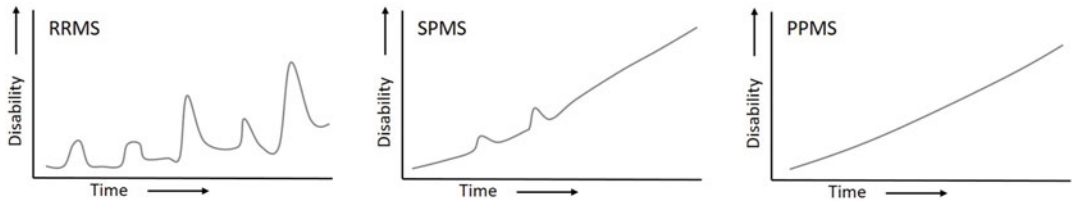


Fig. 2 MS subtypes based on the development of disability over time

that is partially separate from focal inflammation and can be visualized as initially subtle progressive brain atrophy on conventional MRI (Fig. 1) or by advanced MRI techniques that measure brain tissue integrity.

Based on the clinical course, MS is categorized in three main subtypes (Fig. 2). The most common subtype is relapsing remitting MS (RRMS), characterized by relapsing and remitting bouts of symptoms and limited disability. The RRMS subtype gradually transitions into the secondary progressive subtype (SPMS), characterized by gradually accumulating disability. Primary progressive MS (PPMS) is characterized by the gradual accumulation of disability from disease onset and is a common subtype in (male) patients with an older age at onset.

1.2 Treatment of MS

Suppression of CNS inflammation is the main target of treatment and has greatly improved over the past three decades. The earlier treatments are mainly based on molecules that suppress the CNS inflammatory response by interfering with cell signaling molecules that regulate the immune response (immunomodulation).

Interferon was the first immunomodulatory molecule to be approved for the treatment of RRMS in the last decade of the previous century, reducing relapse rate with approximately 30% as well as reducing the occurrence of inflammatory lesions on MRI [3, 4]. Other immunomodulatory molecules with similar efficacy have been developed and approved for the treatment of RRMS since the beginning of this century and include glatiramer acetate, dimethyl fumarate, and teriflunomide [5, 6]. These therapies are mostly well-tolerated with a low risk of serious adverse events.

Newer treatments are generally based on monoclonal antibodies that can directly block receptors on immune cells (immunosuppressive), disabling them to cause inflammation in the CNS, and include fingolimod, alemtuzumab, ocrelizumab, natalizumab, and siponimod [7–11]. These treatments are generally more effective than aforementioned immunomodulatory treatments with a reduction of the number of relapses with 50–80% and a more effective reduction of new active lesions on MRI. The downside of the latter treatments is the increased occurrence of more serious adverse events that include cardiovascular disease, autoimmune disease, and especially progressive multifocal leukoencephalopathy (PML). PML is caused by an infection of the CNS with the JC virus and the most dramatic and potentially lethal adverse event associated with the use of natalizumab, fingolimod, and, in very rare cases, dimethyl fumarate. Although comparatively less effective, the "immunomodulatory" treatments are recommended as "first-line" treatments due to their more favorable profile with regard to serious adverse events.

The quest for more effective and tolerable MS treatments that are also effective in patients with progressive MS is ongoing. New treatments that are currently being evaluated include vidofludimus calcium/IMU-838 [12], a dihydroorotate dehydrogenase inhibitor that attenuates pro-inflammatory cytokine release by B- and T-cells, and tolebrutinib, an inhibitor of the enzyme "Bruton's tyrosine kinase" that drives CNS inflammation [13].

1.3 Diagnosis of MS

Proof of dissemination of inflammatory activity within the CNS in time and space is the underlying principle for diagnosing MS. This follows the successive bouts of focal inflammation in different parts of the CNS unique to the disease. Initially, these two criteria were fulfilled based on clinical course, in which at least two separate episodes of clinical disability (dissemination in time) related to separate locations in the CNS (dissemination in space) needed to be proven [14]. A first or multiple episodes of symptoms/signs

related to one location in the CNS is referred to as a clinically isolated syndrome (CIS). When a second episode occurs related to another location of the CNS, clinically definite MS (CDMS) can be diagnosed. Using this clinical diagnostic scheme, a definite diagnosis of MS could take years to be made and would take too long in the current era of effective treatment that need to be considered at an early stage of the disease. This has led to the incorporation of brain MRI findings in the diagnostic criteria following the same principles [15, 16]. In the diagnostic setting, the MR imaging protocol should at least include a FLAIR and T2 sequence of the brain to adequately detect and locate inflammatory lesions and a T1-weighted sequence of the brain after intravenous gadolinium contrast administration to detect active inflammatory lesions exhibiting leakage of contrast material into the local brain parenchyma. A T1 without contrast and DWI sequences of the brain is usually included for differential diagnostic purposes. T2-/PD-weighted and post-contrast T1-weighted sequences of the spinal cord are optional, when brain imaging is insufficient to make the diagnosis [17]. *See* Table 1 for an overview of the most frequently used MRI sequences for the diagnosis and monitoring of MS.

To fulfill the MRI criterion for dissemination in space, multiple inflammatory lesions should be demonstrated on brain or spinal cord MRI in two out of four typical CNS locations (i.e., juxta-/intra-cortical, periventricular, infratentorial, spinal cord). The dissemination in time criterion is fulfilled by demonstrating one or more new lesions on subsequent MRI scans and/or the simultaneous presence of lesions that do and do not enhance after gadolinium administration on any single scan. Further refinement of the diagnostic criteria has made it possible to make a diagnosis within 3–12 months of symptom onset for the vast majority cases with typical MS [18, 19].

1.4 Disease Monitoring

Disease progression is monitored by self-reporting of MS-associated symptoms, neurological assessment for MS-associated signs, and the detection of new lesions on MRI of the brain and/or spinal cord. Routine brain MRI is usually acquired each year and includes T2/PD and FLAIR sequences for the detection of new lesions. A DWI sequence of the brain is included to differentiate potential PML from MS lesions depending on the initiated treatment. More frequent MR imaging, T1-weighted post-contrast brain sequences, and imaging of the spinal cord are optional depending on clinical signs and symptoms and timing of treatment initiation [17]. *See* Table 1 for an overview of MRI sequences that are typically acquired for the monitoring of disease activity.

Table 1
Brief overview of sequences that are typically used in clinical practice for the diagnosis and monitoring of MS

	Diagnosis/purpose	Monitoring/purpose
Brain MRI		
Ax T1 (<3 mm 2D or 3D)	*Optional* Detection of T1 hypointense lesions	*Optional* Detection of T1 hypointense lesions
Ax T2 and PD (<3 mm)	*Recommended* Detection and localization of lesions (dissemination in space)	*Recommended* Detection of new lesions
FLAIR (preferably 3D with FS)	*Recommended* Detection and localization of lesions (dissemination in space)	*Recommended* Detection of new lesions
Ax T1 after contrast (<3 mm 2D or 3D)	*Recommended* Detection of (in)active inflammation (dissemination in time)	*Optional* Detection of new active inflammation
DIR	*Optional* Improve detection of (juxta)cortical lesions	*Optional* Detection of new lesions
Ax DWI	*Optional* Characterization of lesions (differential diagnosis)	*Optional* Differentiation of MS versus PML lesions
Optic nerve MRI		
Ax/cor T2 FS or STIR (≤3 mm)	*Optional* Detection of optic neuritis	*Not required*
Ax/cor T1 after contrast (≤3 mm)	*Optional* Detection of active optic neuritis	*Not required*
Spinal cord MRI		
Sag T2 and PD (≤3 mm)	*Optional* Detection of spinal cord lesions (dissemination in space)	*Optional* Detection of new spinal cord lesions
Sag T1 after contrast (≤3 mm)	*Optional* Detection of active inflammation (dissemination in time)	*Optional* Detection of new active inflammation

For a detailed description see the 2021 MAGNIMS recommendations [17]. (Note: local preferences may vary)
Ax axial orientation, *Sag* sagittal orientation, *Cor* coronal orientation, *FS* fat suppression, *DWI* diffusion-weighted imaging, *PML* progressive multifocal leukoencephalopathy

1.5 Advanced MR Imaging Techniques

More advanced MRI techniques, like magnetic transfer ratio (MTR), diffusion tensor imaging (DTI), and resting state functional MRI (rsFMRI), are generally not used for the diagnosis and monitoring of MS patients in clinical practice as clinically relevant changes are hard to determine due to considerable biological and

technical (inter-/intra-scanner or inter-/intra-sequence) variability. These advanced sequences have been successfully used in controlled research settings to gain knowledge on the functional and structural dynamics of the MS disease process. MTR and DTI are mainly used to quantify microstructural integrity by measuring spin relaxation times and diffusion of protons within, in general, white matter tracts respectively. RsFMRI uses the BOLD effect to measure functional brain activity in the resting brain and/or in relation to specific tasks.

2 Machine Learning to Aid in the Differential Diagnosis of MS

Although the current diagnostic criteria are highly accurate and efficient in most cases of suspected MS, diagnostic challenges arise when atypical clinical and/or radiological findings occur that may represent other diseases that mimic multiple sclerosis. To aid in these diagnostic challenges, machine learning techniques have been employed in an attempt to distinguish MS from other diseases.

2.1 Differentiation of MS from Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) has previously been considered a variant of multiple sclerosis due to similarities in clinical presentation and presence of inflammatory lesions in the optic nerve, the spinal cord, and, especially in later stages, the brain. NMOSD has only recently been identified as a separate disease entity [20], especially with the identification of elevated antibodies against aquaporin-4, a water channel involved in water homeostasis in the CNS, and antibodies against myelin oligodendrocyte glycoprotein (MOG), a constituent of the normal myelin sheath. Although the clinical and radiological differences are known, the differential diagnosis remains a challenge due to the considerable overlap with MS.

Various machine learning models have been developed to differentiate between MS and NMOSD using decision trees based on expert findings of MRI of the orbits, brain, and spine [21], random forest analysis on radiomic features of brain lesions [22], CNN on brain MR images [23, 24], and LASSO binary logistic regression on the combination of radiomic features from spinal cord scans and clinical variables [25]. Performance of these models had AUCs varying between 0.712 and 0.935.

2.2 Differentiating MS from Other Diseases

A variety of other inflammatory autoimmune diseases and vascular diseases can present with similar brain MRI findings as MS. These diseases are usually easier to distinguish from MS using clinical variables such as age and disease course. However, MRI findings of the brain and spinal cord can still pose a challenge for radiologists who are not experienced with these pathologies.

Using support vector machine analysis on MRI-based radiomic features of brain lesions, Luo et al. created a model able to distinguish brain lesions in RRMS from systemic lupus erythematosus patient with an AUC of 0.967 [26].

In a broader effort, Rauschecker et al. [27] have created a machine learning model to provide a neuroradiological differential diagnosis for a range of brain diseases including MS. In their approach, they first detected and segmented brain lesions from brain MRI scans using a U-Net-based deep learning algorithm. They subsequently extracted 18 location-, spatial-, and signal-based quantitative imaging features using multiple pulse sequences from the segmented lesions. A Bayesian classifier was then used to combine these 18 image features with 5 clinical features for the prediction of the underlying brain disease. This classifier was able to make an accurate top three differential diagnosis in 91% of cases, with a similar performance as specialized academic neuroradiologists (86%, $P = 0.20$). More interestingly, this classifier outperformed neuroradiology fellows (77%, $P = 0.003$), general radiologists (57%, $P < 0.001$), and radiology residents (56%, $P < 0.001$). However, the datasets used were small (total $N = 86$ for training and $N = 92$ for testing, with N typically around 5 for each diagnostic class), and the performance for MS and related disorders like migraine was less favorable.

2.3 Future Considerations

Taken together, these studies show that machine learning has the capability to assist in the differential diagnosis of MS and can be especially helpful for radiologists that are not specialized in neuroradiology.

Most of the aforementioned ML models that could aid in differential diagnosis have focused on the differentiation between MS and NMOSD. Although interesting from a scientific point of view, this distinction is not the only diagnostic challenge from a clinical point of view. The main challenge for radiologists that are not experienced with these disease entities is the distinction between demyelinating lesions due to MS and vascular lesions and should be the focus of future studies.

Generalizability to the general population and MRI scanners is clearly the most important hurdle before these models can be introduced in clinical practice. In addition, these studies are generally limited to a small subset of differential diagnoses, which could lead to tunnel vision when relying on these tools in clinical practice.

3 Machine Learning for Lesion Segmentation and Quantification

Although lesions do not fully relate to the accumulation of clinical disability over time [2], lesion volume is still regarded as an important outcome measure in MS research and clinical trials, requiring accurate lesion segmentation. Manual lesion segmentation on MR images is highly labor-intensive and time-consuming, for which automated segmentation is an obvious solution, especially for 3D scans. Over the years, many (semi-)automated lesion segmentation techniques have been developed, including semi-automated seed growing and unsupervised K-means clustering techniques. In the recent years, convolutional neural networks have been shown to work particularly well in lesion segmentation tasks [28].

3.1 Cross-Sectional Lesion Segmentation

A large number of ML-based models have been developed that provide cross-sectional automated lesion segmentation in MS [29–38] using a variety of ML architecture designs. Critical evaluation and comparison of these large and increasing number of lesion segmentation methods is necessary to determine the best performing methods and their added value to existing methods using large test datasets made available in various challenges organized by the Medical Image Computing and Computer Assisted Intervention Society (MICCAI http://www.miccai.org/) and the International Symposium on Biomedical Imaging (ISBI, https://biomedicalimaging.org/) [28, 39]. Previous MS lesion segmentation challenges showed that segmentation algorithms could attain an average Dice score of 0.59 and an average surface distance of 0.91 for the segmentation of cross-sectional images in the MICCAI 2016 challenge [28] and an average Dice score of 0.670 and average symmetric surface distance of 2.16 for the segmentation of longitudinal MR images in the ISBI 2015 challenge [39]. Most of these algorithms required multiple input sequences, including T1, T2, PD, and/or FLAIR sequences, whereas only three algorithms required a single FLAIR sequence as input.

Besides segmentation performance, these methods need to be validated in real-world scenario with subjects scanned on MRI machines different from the original training dataset. To achieve this, some level of adjustment/optimization prior to implementation on a given dataset is generally needed. Weeda et al. [40] have compared methods with and without local optimization for *cross-sectional* segmentation of MS lesions using several freely available tools including LST [33], NicMSlesions [41], and BIANCA [31] (Fig. 3). Optimization to the local dataset improved performance for all these methods, while retraining with manually labelled representative MR images provided the best performance.

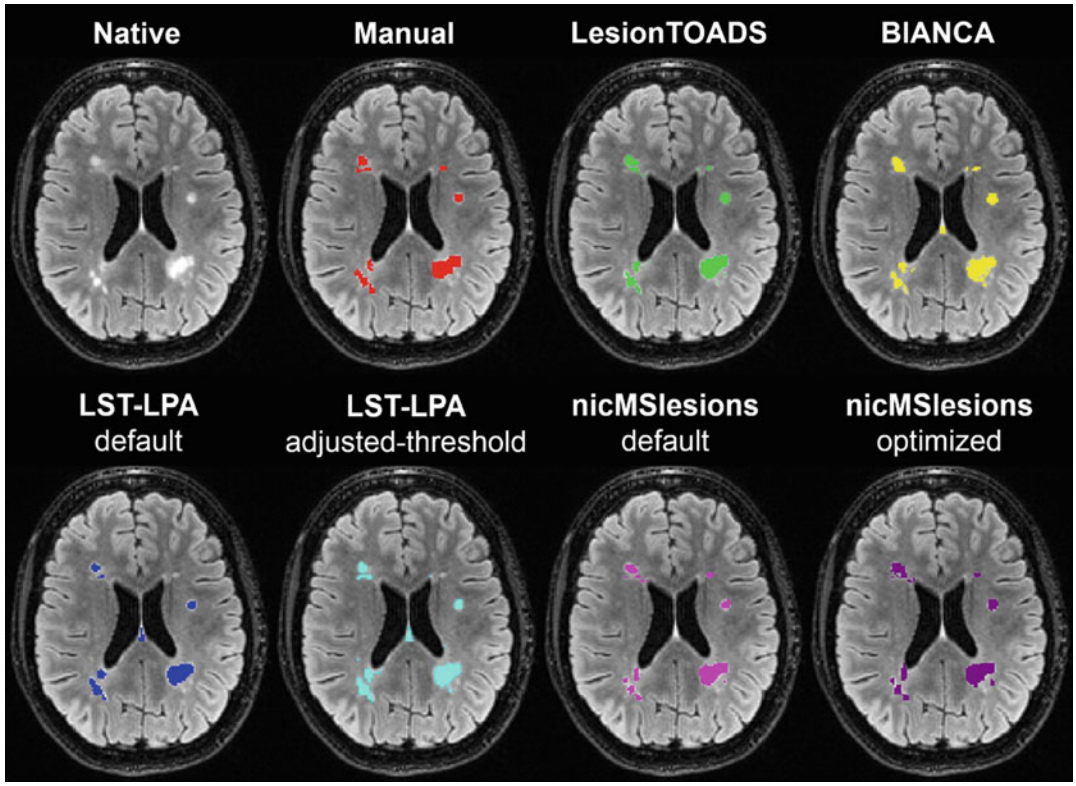


Fig. 3 Output examples of four lesion segmentation algorithms and manual segmentation overlaid over FLAIR images of the brain. (Figure adapted from Weeda et al. [40], reprinted with permission from Elsevier)

3.2 Detection of New MS Lesions

The detection of new lesions *longitudinally* is a highly important clinical monitoring task to demonstrate new inflammatory activity in the CNS that may prompt initiation or change of treatment for an individual MS patient. This requires tedious and time-consuming visual comparison of FLAIR images, especially in patients with a high number of confluent lesions. Initially, the aim of any treatment was to have no evidence of disease activity (NEDA). This proved to be unrealistic, as a low number of new lesions over time could be observed in patients treated with various treatment modalities [42]. Additional studies have shown that long-term clinical disability does not increase with two or less new lesions within 1 year and no contrast-enhancing lesions (minimal evidence of disease activity (MEDA)).

Various machine learning models have been created to detect *new* MS lesions on subsequent MR images based on fusion or subtraction of subsequent segmentation maps [33, 43–48] or end-to-end training of a combined registration and segmentation network on serial MRI scans [48]. Evaluation of these and new machine learning tools are expected following the recent MICCAI challenge (https://portal.fli-iam.irisa.fr/msseg-2/).

A recent study has compared the number of new lesions detected by visual assessment (highest sensitivity/accuracy: 69/67), automated assessment (highest sensitivity/accuracy: 84/64), and visual verification of the automated assessments (sensitivity/accuracy: 86/NA) on a single-center cohort of 100 MS patients [49]. The automated methods detected a higher number of new MS lesions than visual assessment. Visual verification of automated assessments revealed a high number of false positive new lesions when using automated assessments only and a high number of false negative new MS lesions with only visual assessments. Evidently, automated tools for new lesion detection require further development before they can be implemented in clinical practice *without supervision*. More importantly, this study showed that *visually supervised* automated methods are currently able to improve the detection of new MS lesions in current clinical practice. This would warrant clinical implementation, provided that the clinical tool allows swift and efficient visual supervision and correction and has a reasonable tradeoff between false negative and false positive rates erring slightly to the false positive side.

3.3 Clinical Implementation of ML Tools for Lesion Segmentation and Detection

Commercial image analysis packages meant for implementation in clinical care have incorporated automated lesion segmentation algorithms to provide cross-sectional and longitudinal assessments of lesion volume rather than (new) lesion counts. Although this may provide more precise monitoring of the patient's overall lesion burden, the utility of these tools should be critically evaluated on at least the following points: (1) knowledge of the robustness of the lesion segmentation algorithm to inter-scanner variability and various MR artifacts; (2) proven clinically relevant cut-off points of the provided measurements that are related to relevant future disability progression; and (3) implementation of a mandatory visual check of provided lesion counts and volumes.

4 Machine Learning to Improve Detection of Tissue Properties from Conventional MRI Sequences

MR imaging is the modality of choice for the diagnosis and monitoring of MS patients in clinical trials and daily clinical practice, due to its availability. Scan protocols in daily clinical practice are usually limited to the most essential conventional sequences to limit burden on patients and to limit financial cost. Machine learning can be employed to enhance these conventional sequences to visualize initially inconspicuous relevant tissue properties.

4.1 Synthetic DIR Sequences

Cortical lesions are an important part of MS pathology, specific to the disease, associated with disease progression [50, 51] and have recently been included in the radiological diagnostic criteria [52]. These cortical lesions are generally inconspicuous on commonly used FLAIR and T2-/PD-weighted MR images. The double inversion recovery MRI sequence (DIR) is uniquely capable of visualizing these cortical lesions by combined suppression of the MR signal from cerebrospinal fluid and white matter [53]. DIR sequences are generally not used in daily clinical practice or clinical trials due to the long acquisition time and lack of availability on most MR systems. Models based on generative adversarial networks have been trained to generate synthetic DIR images from conventional and routinely acquired T1, T2, and FLAIR images [54] and T1 and PD/T2 [55]. These synthetic DIR images were able to improve the detection of juxtacortical lesions (12.3 ± 10.8 vs 7.2 ± 5.6, $P < 0.001$) [54] and cortical lesions ($N = 626$ vs 696) [56] compared to conventional MRI sequences. Although not as sensitive as the original DIR images, synthetic DIR images are sensitive enough to improve diagnosis and prognostication in routine clinical setting.

4.2 Prediction of Contrast-Enhancing Lesions

Besides a very low risk of nephrogenic systemic fibrosis [57], gadolinium-based contrast agents are generally safe when used for imaging purposes. However, gadolinium is known to accumulate in the brain after repeated IV gadolinium administrations. Although no adverse effects have been demonstrated to date, this is a cause for concern in the medical community as the long-term effects are still unknown. Because of this, prediction of the presence of active inflammatory contrast-enhancing lesions without the use of contrast agents is desirable. Using a large multicenter dataset, Narayana et al. have developed a deep learning model capable of predicting contrast-enhancing lesions using T1, T2, and FLAIR images with sensitivity and specificity of 78% and 73%, respectively, for patient-wise detection of enhancement using fivefold cross-validation [58].

4.3 Visualization of Tissue Myelin Content from MR Images

Demyelination is one of the pathological hallmarks of MS that cannot be directly quantified by MR imaging. In vivo quantification can be useful for monitoring inflicted damage by inflammation and the efficacy of myelin repair mechanisms. PET imaging is capable of visualizing and quantifying myelin using the radiotracer [(11)C] PIB [59], but is not generally available, expensive, and invasive. A recent study has used [(11)C]PIB PET images from MS patients to train a CF-SAGAN-based model to successfully predict myelin content changes from MTR, DTI, T2, and T1 MRI sequences [60] (Fig. 4).

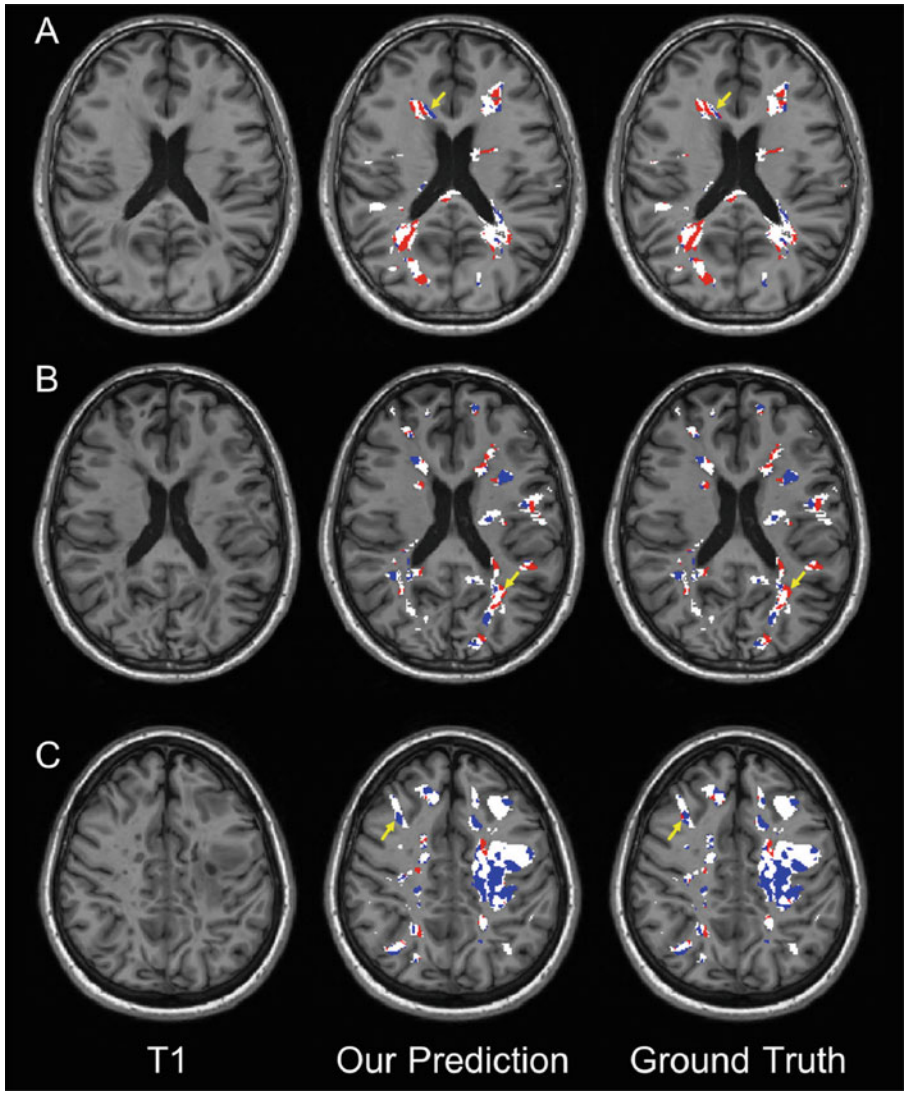


Fig. 4 Examples of lesional myelin content changes showing T1-weighted images (left column), the predicted change in myelin content by the MR-based model proposed by Wei et al. (middle column), and the ground truth change in myelin content based on [(11)C]PIB PET imaging (right column). Demyelinating (red) and remyelinating (in blue) voxels are indicated on top of the lesion mask (white). (Figure adapted from Wei et al. [60], reprinted with permission from Elsevier)

5 Machine Learning to Characterize Neurodegeneration in MS

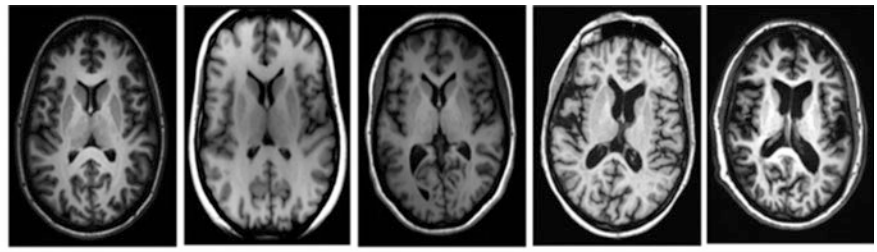
In daily clinical practice, treatment changes in the course of the disease are mainly based on new inflammatory/demyelinating activity visible as new or enhancing lesions on brain MRI scans. In contrast, the partially unrelated but clinically relevant neurodegenerative aspect of the MS disease process is generally

underappreciated in monitoring and treatment decisions. The reason for this is the absence of simple, reliable, and easily interpretable measures that reflect the degree of neurodegeneration in individual patients.

Overall brain volume measured on MR images is currently the most important tool to quantify neurodegeneration in MS. However, brain volume measurements have not been implemented in routine clinical care as universal clinically relevant cut-off points for brain volume loss have not been identified due to considerable technical, biological, and, specifically, age-related variations [61].

5.1 Brain Age Determination from MR Images

Neurodegenerative processes are known to change the macroscopic structure of the brain with increasing age. Similar brain structure changes are observed as a result of various neurodegenerative brain diseases, including MS. Such MS-related atrophic changes occur at a faster pace as would be expected in normal aging individuals. This has given rise to the "brain age" paradigm, in which accelerated aging of the brain is considered as a marker of MS-related neurodegeneration [62]. Machine learning models based on large populations of healthy aging individuals have been developed to determine biological brain age from T1-weighted MR images of the brain [63–65]. Subtraction of this predicted brain age from the actual calendar age results in the brain-predicted age difference (brain-PAD) or brain age gap (BAG) as an indicator of premature aging of the brain. Key advantages of brain-PAD/BAG over brain volume measurement are that these measures incorporate image characteristics across the entire brain (not only the segmented brain tissue as in brain volume measurement), provide an intuitive easily interpretable metric, are more robust to acquisition-related image variations, and, most importantly, are specific for the individual patient by inherently adjusting for age. Initial studies on brain age in MS found that the estimated brain age is between 4 and 6 years higher than chronological age in comparison to healthy controls and that a higher relative brain age is associated with a higher degree of disability [65, 66]. A large retrospective multicenter study of brain age in MS showed that brain age is approximately 10 years higher than chronological age in MS, is increased in MS compared to HC, predicts current as well as future disability, and is mainly driven by brain atrophy [67] (Fig. 5). Recent developments in brain age models were made to reliably predict brain age using FLAIR sequences instead of the usual T1-weighted sequences (Colman et al., 2021; ISMRM 2022), ensuring flexible implementation in retrospective research settings and general clinical practice. Further studies are needed to further elucidate changes in brain age over time, the relationship of brain age with a wider range of measures of cognitive and physical disability, the influence of non-MS-related factors on brain age, the pathological substrate of brain



Group	Healthy control	CIS	RRMS	SPMS	PPMS
Sex	Female	Female	Female	Female	Female
Age (yrs)	30.4	31.0	31.1	48.6	49.0
Brain-predicted age (yrs)	29.6	31.7	40.3	67.3	63.9
Brain-PAD (yrs)	-0.8	+0.7	+9.2	+18.6	+14.9
Years since diagnosis	-	0	7.6	13.6	3.0
EDSS score	-	0.0	2.0	6.5	2.0

Fig. 5 Examples of increasing differences between brain-predicted age and chronological age (brain-PAD) in a healthy control, three RRMS onset patients with increasing disease durations, and a PPMS patient with a very high brain-PAD with relatively short time since diagnosis. (Figure adapted from Cole et al. [67], CC BY 4.0)

age in MS, and the effect of treatment on brain age. In the future, these brain age models may provide a useful clinical tool to quantify and monitor neurodegeneration in routine clinical care of MS patients.

5.2 Evolution of Brain Atrophy Over Time

Although overall progressive WM and GM atrophy is a well-known feature of MS, less is known on the evolution of atrophy in different brain regions over time. Event-based modelling [68, 69] has been used to elucidate the sequence in which GM atrophy affects various brain structures in repeated MRIs of 1417 subjects including healthy controls and all subtypes of MS [70, 71]. The posterior cingulate cortex and precuneus were the first regions to become atrophic, followed by the middle cingulate cortex, brainstem, and thalamus in patients with clinically isolated syndrome and relapse-onset MS. A similar pattern of sequential atrophy was found in PPMS with the involvement of the thalamus, cuneus, precuneus, and pallidum, followed by the brainstem and posterior cingulate cortex. Patients were then categorized according to the event stage defined by their individual atrophy pattern. Using a linear mixed effect model, progression of event stages was found to be related to the rate of disability progression proving that these atrophy stages represent clinically relevant GM pathology.

6 Machine Learning to Predict Disease Progression

The efficacy in reducing inflammatory activity, and thus preventing disability, varies across treatments and is generally speaking inversely related to side effects. Choosing the treatment with the

right tradeoff between efficacy and side effects is challenging as the disability accumulation over time can vary greatly among patients. Demographic variables, presence of oligoclonal bands, and the number of, especially infratentorial, T2 lesions at baseline brain MRI are known to be predictive of future disability progression and the likelihood of clinical relapse in the future [72]. Still, prediction of future disease progression remains a challenge in daily clinical practice especially when these risk factors are not unequivocally present. Several definitions of disease progression exist and include demonstration of short-term inflammatory activity (prediction of time to next relapse or progression from CIS to CDMS), changes in disability status using standardized clinical evaluations (EDSS progression or time to a certain clinical threshold), or progression from RRMS to SPMS.

6.1 Prediction of Disease Progression

ML techniques have successfully created models to predict worsening of disability based on CNN-based analysis of lesion maps, MR images, and age at baseline [73] and by combining clinical disability status and MRI-derived lesion volume and brain atrophy using SVM classifiers [74]. The latter study showed that the predictive properties of the SVM model improved when adding changes in MRI measurements over the first year.

A number of studies have successfully predicted a second relapse or conversion from CIS to CDMS by analyzing clinical and demographic data, lesion-specific quantitative geometric features, and gray matter-to-whole brain volume ratios using support vector machines [75]; clinical characteristics as well as global and local measures of GM/WM volume, lesion volume, and cortical thickness using support vector machines in combination with recursive feature elimination [76]; and lesion shape features derived from computer-assisted manual segmentation using a random forest classifier [77]. Pareto et al. created a model based on regional gray matter volume and T1 hypointensities obtained from the baseline T1-weighted MR images, but were not able to accurately predict conversion from CIS to CDMS [78].

6.2 Stratification of Patients at Risk of Disease Progression

Although the aforementioned models provide valuable insights into the predictive properties of clinical and radiological variables, the value to individual patients in daily clinical practice is still limited. An important downside of these models is the assumption that the predictive properties of baseline variables are monotonous among patients, whereas these predictive properties may well vary over time and between patients. Recent studies have applied the SuStaIn model [79] to identify MS subtypes based on clinical and radiological variables with the underlying assumption that these variables evolve over time. Using this technique on MRI-derived GM volumes in various brain regions, white matter volume, total brain lesion volume, and T1/T2 ratio within brain structures of

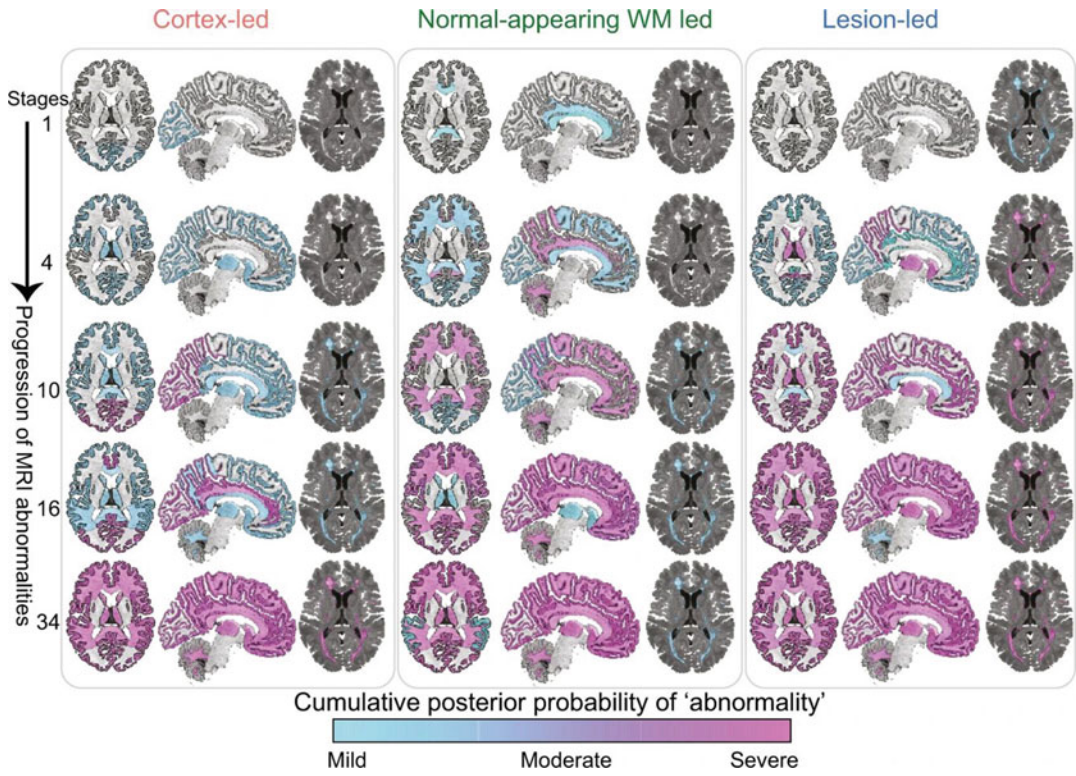


Fig. 6 Evolution of MRI abnormalities in each of the three MRI-based subtypes revealed by the SuStaIn analysis by Eshaghi et al. For each subtype, the left two columns depict the probability of regional brain atrophy, and the right column depicts the probability of lesion occurrence in the various stages of MRI abnormality progression. (Figure adapted from Eshaghi et al. [81], CC BY 4.0)

6322 MS patients, Eshaghi et al. were able to define "cortex-led," "normal-appearing white matter-led," and "lesion-led MS" subtypes in the earliest stages of the disease [80, 81] (Fig. 6). Further analysis in the validation dataset ($N = 3068$) revealed that the lesion-led subtype had a significantly higher risk of disability progression, relapse rate, and treatment response in the following 24 weeks compared to the other two subtypes. Similar findings were made in a separate study on 425 MS patients analyzing GW matter volume in various brain regions, and T2 lesion volume using SuStaIn revealed a subtype characterized by early deep GM atrophy and lesion appearance and a subtype characterized by early cortical GM volume loss that were consistent over time [82]. The subtype with early deep GM atrophy was associated with earlier disability progression and cognitive impairment compared to the subtype with earlier cortical volume loss. Taken together, these studies show that SuStaIn modelling can reveal previously unknown subtypes of MS that are biologically and clinically relevant. The SuStaIn models can be used to stratify individual patients and therefore has the potential for implementation in daily clinical practice after

adaptation of the model to include robust measurements that can be derived from MRI scans acquired in daily clinical practice.

7 Concluding Remarks

As covered in this chapter, ML techniques provide new insights and possibilities with regard to differential diagnosis, lesion segmentation and quantification, enhanced detection of relevant pathology on MRI, characterization of neurodegeneration, and prediction of disease progression in MS. In general, challenges still exist with regard to generalizability to the general population, robustness across images acquired from different MRI scanners, and validation that the ML technique provides biologically and clinically relevant information. Implementation of various ML tools in clinical practice is ongoing, but should provide insight in their robustness across scanners, clearly defined clinically relevant cut-off points for each provided outcome, and an efficient interface that allows the user to check the quality of the analyses when appropriate.

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