Review Article

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Deep learning in imaging analysis for multiple sclerosis: Diagnosis and monitoring

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Abstract

Multiple sclerosis (MS) is an autoimmune disease that affects various parts of the central nervous system and often occurs in young population (between 20-40 years old). Given that MS is a lifelong disease and there is currently no definitive treatment for MS, early diagnosis, initiation of treatment with the most appropriate medication, and patient monitoring are three challenging factors in determining the status of MS patients. Magnetic resonance imaging (MRI) and optical coherence tomography (OCT) are two important and useful imaging methods in all the three aspects of diagnosing, monitoring, and determining the effectiveness of treatment in MS patients. In recent years, the use of artificial intelligence in analyzing MRI and OCT data in these aspects has been rapidly increasing. In this article, we reviewed and discussed the usage of deep learning as a class of machine learning and a method of artificial intelligence for analyzing data obtained from MRI and OCT in MS patients.

Keywords: Multiple sclerosis, Imaging analysis, Deep learning.

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Multiple sclerosis (MS) is a disease of the central nervous system (CNS) that occurs due to a malfunction of the immune system and can lead to a wide range of symptoms by affecting different areas of the CNS. This disease usually affects the younger generation and is more common in women. It is considered the most common non-traumatic cause of disability in young people (1, 2). In recent years, it seems that the incidence of this disease is increasing, making it a serious healthcare problem (3).

Specific criteria have been introduced for the diagnosis of the disease. For the first time in 1983, Charles Poser introduced these criteria (4), which have been continuously revised since then. The last published criteria are from 2017 (5), though these criteria were also carefully examined recently and will probably undergo some changes. The basis of the criteria is to diagnose patients with MS as early and as easily as possible. In this criterion, in addition to clinical symptoms and emphasis on time and place, a number of paraclinical methods have also been used in the diagnosis. The first and most important of these is magnetic resonance imaging (MRI), which includes MRI of the brain and spinal cord. The second is oligoclonal bands in the cerebrospinal fluid, which indicate the presence of an active disease in the nervous system with the production of antibodies in the cerebrospinal fluid. It seems that other modalities, including optical coherence tomography (OCT), should be added to these modalities for better and earlier diagnosis (6). Early diagnosis, initiation of the best medication, and monitoring of the disease are now the three most important challenges in diagnosis and treatment that can greatly help patients' conditions (7). It has now been determined that, in addition to clinical data, other modalities, including imaging methods, are very effective and efficient in both diagnosis and monitoring of the disease. Among these methods, MRI (8) and OCT (9) can be mentioned in particular.

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In the criteria presented for the diagnosis of MS, MRI plays an important role. Studies are all trying to improve the accuracy and sensitivity of using this modality in diagnosing the disease (10). MRI also plays an important role in the follow-up and monitoring of the disease, and several of its parameters are directly related to the likelihood of disease progression (11). In recent years, the role of OCT in disease monitoring has also been emphasized and its relationship with disease progression has been discussed (12). In addition, considering the involvement of the optic nerve as one of the key sites in the diagnosis of the disease and the role of OCT in the diagnosis of MS has also been highlighted (13). However, the volume of data used by these methods in the daily practice of physicians is small. This smallness is due to the limited time available to physicians and, at the same time, the inability of humans to process large amounts of information. This has led to the use of various artificial intelligence methods in analyzing data obtained from these methods in different aspects, including diagnosis, monitoring of the disease, and evaluating the effectiveness of drugs; the extent of this usage and its various aspects is progressively increasing (14-16). In this review article, we will discuss the use of deep learning as one of the artificial intelligence and machine learning methods in analyzing data obtained from MRI and OCT. Before that, however, we need to see what each of these modalities tells us about MS and how these modalities can be used for the aforementioned purposes. The novelty of this review lies in its integrated analysis of deep learning applications on both MRI and OCT modalities in MS, which has rarely been jointly reviewed before. In addition, how different deep learning methods can help analyze data from these imaging modalities, MRI and OCT, will be investigated.

MRI

MRI plays a fundamental role in the diagnosis and treatment of MS. Without MRI, it is virtually impossible to differentiate between MS and other diseases that can mimic it (17). According to the criteria, the plaques seen on MRI must have certain characteristics. These plaques are oval in shape and larger than 3 mm in size (18) (figure 1). The location of the plaques is also very important. The sites that suggest this disease include the periventricular, infratentorial, spinal, and juxtacortical (19), and more recently the optic nerve has been added to these sites (13). In addition, MRI plays a key role in monitoring the disease in terms of progression and the effectiveness of the drug (20). The presence of new or enhancing plaques can be considered an indication of disease activity and treatment failure (21). Although the main emphasis in daily practice may be on the formation of new or enhancing plaques, it is possible to measure brain volume, the degree of atrophy, as well as the lesion load using special software (22). In particular, the decrease in brain volume is not necessarily accompanied by an increase in the number of plaques and can be considered an independent criterion for disease progression (23). Furthermore, MRI is key in the diagnosis of drug-induced complications such as progressive multifocal leukoencephalopathy (PML) (24). All of these highlight the importance of MRI in the diagnosis and monitoring of MS. Meanwhile, it should be noted that advanced imaging is now being used in research. These MRIs, such as functional MRI (fMRI) or brain magnetic resonance spectroscopy (MRS), have played an important role in our understanding of the disease and its progression, though they are not yet used in routine treatment and practice.

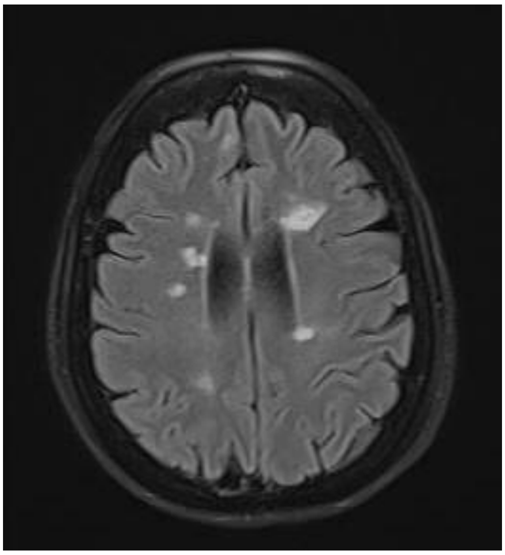

Figure 1. Brain MRI of a 34-year-old female reveals periventricular lesions suggesting the diagnosis of MS

OCT

Another modality that is increasingly being used in various aspects of MS is OCT (figure 2). OCT is an imaging modality that allows us to observe the entire thickness of the retina. For this reason, OCT is a convenient and non-invasive method for measuring peri-papillary retinal nerve fiber layer (RNFL) thickness, ganglion cell layer and inner plexiform layer (GCLIPL) thickness, and macular cube volume (25). Multiple sclerosis is one of the diseases whose changes are clearly visible on OCT (12, 26, 27). In addition to involving the brain and spinal cord, MS can also directly involve the optic nerve (28). Although in the 2017 McDonald criteria (5), optic nerve involvement is not one of the determining areas for the diagnosis of MS, adding optic nerve involvement to other areas seems to be of great potential assistance in better and faster diagnosis of MS (13). Optic nerve plaques can be identified by methods such as orbital MRI, visual evoked potential (VEP) (29) and finally OCT. Since VEP is very dependent on the performing technician, OCT is of particular importance as an objective method that is not dependent on the performing person. In drug monitoring, this method can be used to investigate the side effects of sphingosine-1-phosphate receptor modulators. It is known that these drugs can lead to macular edema, which is asymptomatic in some cases and is not detected during routine eye examinations (30). However, OCT is a suitable method for diagnosing macular edema and can also detect asymptomatic cases (31). OCT findings are also directly related to the degree of neurodegeneration and brain atrophy (32, 33).

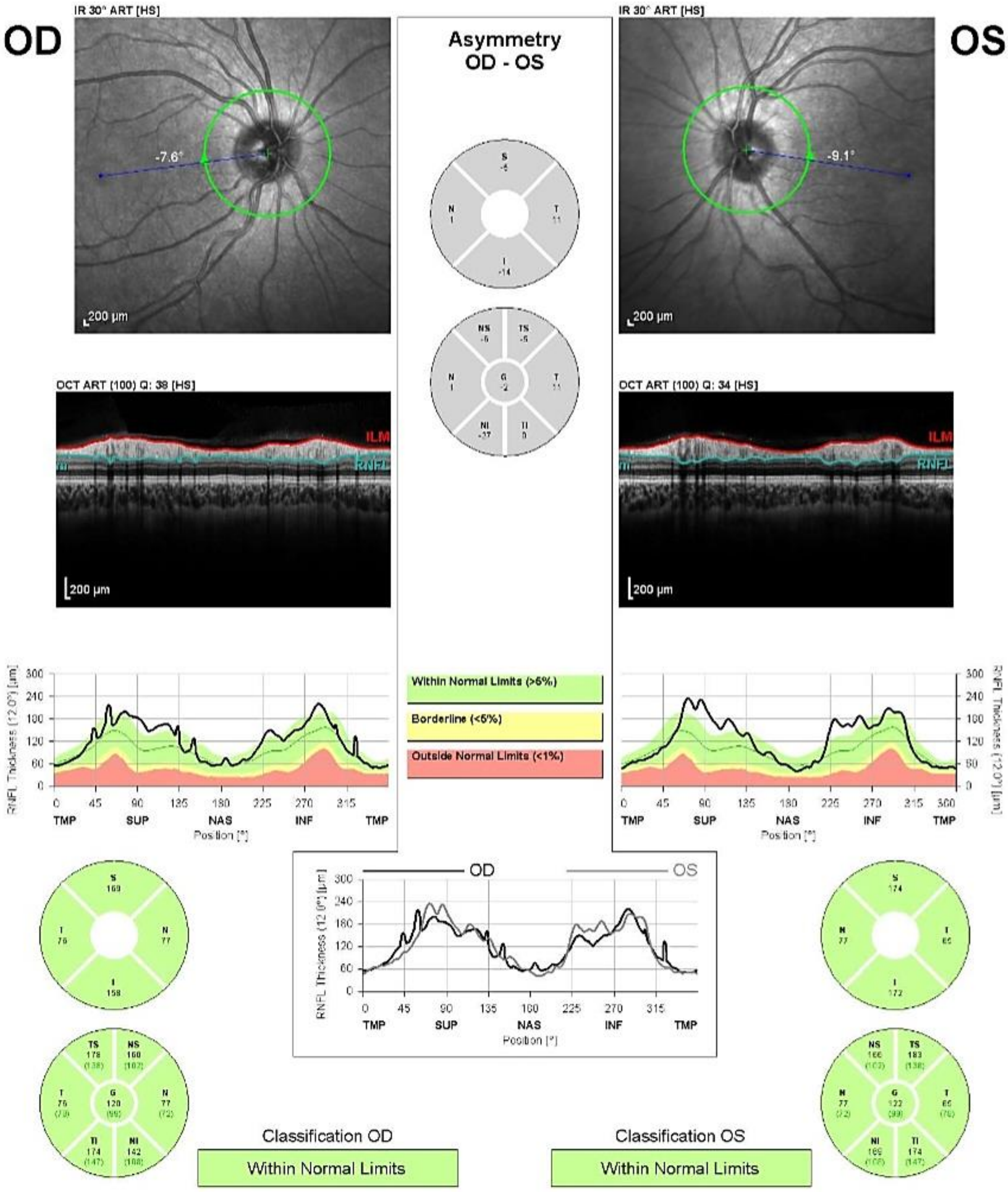

Figure 2. A normal OCT in a patient who has been diagnosed with MS recently.

Use of artificial intelligence in analyzing data related to MRI and OCT

MRI and OCT, as two important imaging modalities, can provide massive data about different aspects of MS. Due to the large volume of this data, its analysis by humans is not only time-consuming but also impossible. Therefore, artificial intelligence (AI) with its characteristics can help us in this analysis, and currently a large volume of articles and studies are dedicated to the use of artificial intelligence in analyzing this data. AI itself includes several models. Deep learning is based on the use of artificial neural networks (ANNs), allowing the use of different layers for data analysis (34), which makes it a very suitable candidate for use in the analysis of MRI and OCT data: data that have a high volume and cannot be analyzed and utilized in daily practice. This high volume of data is due to the high volume of pixels in each image individually, as well as the multiple images that are taken from a patient over time. Therefore, deep learning allows us to examine images both cross-sectionally and longitudinally and over a long period of time. Nevertheless, deep learning itself also has different methods, each of which gives us special possibilities in data analysis, both cross-sectionally and longitudinally. This review article intends to examine these methods separately and explain the role of each in the analysis of imaging data. In addition, the different techniques utilize in deep learning and how each can help in different aspects of image analysis and help in the diagnosis as well as treatment of MS will be described.

Lesion detection and segmentation with convolutional neural networks (CNNs)

In the discussion of MRI, detecting brain lesions and determining the load of these lesions in the brain is very important in the diagnosis and follow-up of patients with MS. However, determining these lesions manually by humans is very time-consuming and can be associated with errors. These drawbacks also greatly limit the use of these methods in the clinic and daily practice, emphasizing the need for methods that are not dependent on humans and can analyze a large volume of image data (35). Therefore, the use of artificial intelligence is increasingly being considered due to its high power and speed in data analysis (14). As mentioned, various artificial intelligence techniques are used to analyze data, including imaging data, such as deep learning as well as its different methods in the determination and segmentation of lesions. One of these methods is Convolutional Neural Networks (CNNs). CNNs is a type of feed-forward neural network that automatically learns various features through a method called kernel optimization (36).

In the study by Gaber et al., a fully CNN (FCNN) model was developed for the segmentation of brain lesions that are seen as hyperintense lesions on T2 MRI. They used 1000 MRI samples from patients with relapsing-remitting MS (RRMS) to create this model. The model they designed not only automatically segmented brain lesions but also classified all brain tissues. The results obtained by this model were highly accurate. The data obtained were from different centers, and this model was able to achieve the mentioned goals with high accuracy in all these data, which added to the value of their work (37). Their study found that the use of this method is accurate in MRI lesions segmentation. Thus, it was quickly used specifically in the segmentation of brain lesions that have special characteristics. One of these lesions was cortical plaques. Cortical lesions have received plenty of attention in recent years. It has been shown that these lesions are directly related to the prognosis of the disease (38). However, identifying these lesions, especially with conventional MRI, is very difficult and time-consuming (39).

In another study, deep learning was attempted to be used to identify cortical lesions in scans acquired by 7 Tesla MRI. This model was more accurate and successful in identifying leukocortical and subpial lesions than intracortical lesions. This result indicates that this model needs further correction and may be an effective method for detecting cortical lesions in MS patients in the future (40). Another study examined the effect of training set size on the accuracy required in lesion segmentation and reported that this value is 10 for examining the volume of white matter, gray matter, and cerebrospinal fluid, while being 50 for lesion segmentation (41).

Unlike the above methods, which segment and identify plaques on a single MRI image (snapshot), studies have attempted to identify new plaques on serial MRIs. Identifying new lesions is of great importance in monitoring patients and changing their medication if necessary. Comparing serial MRI scans to find new plaques can be difficult and time-consuming. Small plaques can also be easily missed, and the detection of new lesions can vary from one observer to another. To address these problems, Salem et al. utilized FCNN to detect new lesions in T2-weighted MRI scans taken from serially acquired patients. In this study, MRI scans from 60 patients were examined, 36 of which contained new plaques. The network consisted of two parts. The first part used U-Net blocks that learned the deformation fields (DFs) and nonlinearly registered the baseline image to the follow-up image for each input modality. The learned DFs together with the baseline and follow-up images were then fed into the second part of the network, where another U-Net detected and segmented the new T2 lesions. The advantage of this method was in combining these two networks together, whereby it was shown that the combination of these two networks can identify new lesions in serial MRIs significantly better than other methods (42). Another study combined U-Net, attention gate, and residual learning and tried to identify new lesions in MRI better and more accurately. The use of residual units facilitates the learning process in the network. This helps improve the performance of this network by reducing the number of parameters. The use of attention gate allows the network to focus on salient features with variations in size and shape (43).

In another study, two 3D patch-wise FCNNs were employed. The first FCNN detects possible new lesions while the second FCNN removes those that were incorrectly classified in the first stage. This method also revealed high accuracy in detecting new lesions (44). In addition to new lesions, enhancing lesions are also of great value both in the diagnosis process and in the follow-up process of patients. Therefore, the use of artificial intelligence to detect these lesions can be useful. A study addressed this issue and found that deep learning can also help in determining enhancing lesions (45).

The more sequences used in the study, the greater the chance of detecting enhancing plaques by the CNN method. In a study, it was reported that the use of five sequences, Fluid-attenuated inversion recovery (FLAIR), T1 with and without gadolinium injection, T2 and proton density weighted images, would increase the success of deep learning. Also, the size of the lesion is influential in the success of this model. In the same study, the greatest success of this method was achieved in detecting plaques with a volume of ⩾70 mm^3 (46). In addition to what was stated above, new methods are being developed to facilitate the use of deep learning for segmentation of MS plaques and lesions. In deep learning, training the developed model requires the use of large datasets, which are not always available. Therefore, scientists in this field are looking to achieve this goal in the stated model using fewer samples. One of the methods used is to apply the transfer learning effect from the segmentation of other pathologies to facilitate training with smaller MS datasets. This has been shown to help us apply smaller datasets for learning segmentation (47).

Apart from MRI, deep learning has also been used to analyze OCT data in MS. In one study, this technique was used to examine and segment retinal layers and microcystic macular edema in MS. Meanwhile, it should be noted that previous methods that used graph-based machine learning to segment retinal layers were not only time-consuming but also failed to segment microcystic macular edema (48). In addition to cross-sectional studies of OCT, studies of its changes over time are also of great importance. However, this longitudinal investigation can be difficult and time-consuming with conventional methods, so the use of machine learning is very valuable in achieving this goal. A study addressed this issue and was able to measure OCT changes over time with high accuracy. Changes that can help us understand the progression of the disease (49).

Table 1. Studies which have used CNN for lesion detection and segmentation

Ref.	Aim of study	Image modality	Dataset	Method	Outcome
Gabr et al., 2020	Segmentation of brain lesions	dual echo, FLAIR, and T1-w images	Approximately 1000 MRIs	FCNN	DSC was 0.95 for WM, 0.96 for GM, 0.99 for CSF, and 0.82 for T2 lesions
La Rosa et al., 2022	Segmentation of cortical lesions	0.5 mm isotropic MP2RAGE acquired four times (MP2RAGE×4), 0.7 mm MP2RAGE, 0.5 mm T2 *-weighted GRE, 0.5 mm T2 *-weighted EPI and 0.75 × 0.75 × 0.9 mm3 MP2RAGE	80 scans	FCNN	Detection rate was 83% for leukocortical lesions, and 70% for subpial lesions. But it reached 53% for intracortical lesions.
Narayana et al., 2020	segmentation accuracy of brain MRI	dual turbo spin echo, FLAIR, and T1 -w	1008 patients	FCNN	DSC values varied from 0.00 to 0.86±0.016 for T2 lesions, 0.87±009 to 0.94±0.004 for GM, 0.86±0.08 to 0.94±0.005 for WM, and 0.91±0.009 to 0.96±0.003 for CSF

Ref.	Aim of study	Image modality	Dataset	Method	Outcome
Salem et al. , 2020	the presence of new T2-w lesions in longitudinal MRIs	T1-w, T2-w, PD-w, and FLAIR	60 patients	FCNN	A mean DSC of 0.83 with a true positive rate of 83.09% and a false positive detection rate of 9.36%
Sarica et al., 2022	detecting new lesions	3D FLAIR MR images	100 patients		DSC were obtained as a mean of 48 and 44.30%.
Salem et al., 2022	the presence of new lesions on brain MRI scans	3D T2-FLAIR images	100 patients, each with two-time points	FCNN	DSC of 0.42 with a detection F1-score of 0.5.
Greselin et al. , 2024	detection of contrast-enhancing lesions	T1-w before and after gadolinium injection, and FLAIR images.	372 scans from 280 MS patients	FCNN	DSC and True Positive and False Positive Rates were 0.76, 0.93, and 0.02, respectively
Coronado et al., 2021	segmenting gadolinium-enhancing lesions	FLAIR, T2-w, proton density-w, and pre- and post-contrast T1-w images	1006 RRMS patients	FCNN	DSC/TPR/FPR values averaged over all the enhancing lesion sizes were 0.77/0.90/0.23
Wahlig et al., 2023	Evaluates the effect of transfer learning from segmentation of another pathology to facilitate use of smaller MS-specific training datasets.	FLAIR, T1 post-contrast imaging	149 patients	FCNN	For new lesion segmentation, a fine-tuned model demonstrated similar sensitivity (0.49±0.05) and improved PPV (0.60±0.05) compared to a de-novo model. For enhancement segmentation it improved overall performance (sensitivity 0.74±0.06, PPV 0.69±0.05).
He et al., 2019	Segmentation of both the retinal layers and MME	OCT	35 macular OCT scans	FCNN	The proposed framework obtains retinal surfaces with sub-pixel surface accuracy comparable to the other methods and MMEs with better accuracy than the state-of-the-art method.
He et al. 2023	longitudinal OCT segmentation network	OCT	2,037 Cirrus scans from 176 subjects and 347 Spectralis scans from 70 subjects	FCNN	Deep-Backward obtained the best stability in measuring longitudinal changes for MS (varied from 0.141(0.079) for OPL-Macula to 0.859 (0.561) for RNFL-Macula)

Abbreviations: CSF: Cerebrospinal fluid, DSC: Dice similarity coefficient, FCNN: Fully Convolutional Neural Network , FLAIR: Fluid-attenuated inversion recovery, FPR: False positive rate, GM: Gray matter, GRE: Gradient echo sequences, MP2RAGE: Magnetization Prepared 2 Rapid Acquisition Gradient Echoes, MS: Multiple Sclerosis, OCT: Optical coherence tomography , OPL: Outer plexiform layer , PPV: Positive predictive value, RNFL: Retinal nerve fiber layer, RRMS: Relapsing Remitting MS, TPR: True positive rate, w: weighted, WM: White matter, 3 D: 3 Dimensional

Disease progression tracking using recurrent neural networks (RNNs)

RNN is another method employed in deep learning. The basis of RNN is based on the recurrent unit. This unit is formed by creating a loop between the current condition and previous factors, and causes the artificial neural network to learn how the previous conditions are involved in creating the current condition. Therefore, this model can be very effective on determining the course and future of diseases. Unlike other deep learning methods that examine and analyze a snapshot of data at a specific time, this model can examine data and their changes longitudinally and by considering different times. Such an ability makes it suitable for examining the prognosis and the rate of disease progression in chronic diseases. Of course, in most cases, different deep learning methods are used in combination with each other. Therefore, many of the models used are combined and apply all of these methods. Predicting the future and disease progression in MS is very crucial in determining the type of treatment for patients. If we know where the disease is headed, then we can determine a more effective treatment for the patient from the beginning. This method is now done according to various risk factors. Risk factors including demographic, radiological and imaging characteristics of the patient are all effective on this decision-making (50). However, the use of more data and the estimation of disease progression can be done with higher accuracy and speed by artificial intelligence. It has been found that the use of machine learning can be effective on predicting various aspects of disease progression, including predicting the conversion of clinically isolated syndrome (CIS) to MS, cognitive situation, disease activity and degree of disability (51). Studies in this field and using the RNN method have been conducted in MS. In a study conducted by Brouwer et al. and published in 2021, information from 6682 patients in the MS base database was used. An attempt was made to predict the disease progression in these patients using this deep learning method. In this study, the model was able to predict disease progression within 2 years with a receiver operating characteristic area under the curve (ROC-AUC) of 0.85 (52). In another paper, a combination of different deep learning methods was used to predict disease progression. They first pretrained the model on data from 3830 MS patients collected from 6 different trials and then applied it to predict the course as well as disability of primary progressive MS (PPMS) patients who were randomly assigned to one of two anti-CD20 or placebo treatments (53). In addition to demographic and MRI findings, recent studies have also applied deep learning methods to predict disease progression on OCT data. For this purpose, they used a combination of different methods used in deep learning. They found that not only OCT is involved in the early diagnosis of MS, but it can also be used to predict the course of the disease. The same study revealed that RNFL thickness can be used as a suitable biomarker for MS (54).

Table 2. Studies which have used RNNs for tracking disease progression

Ref	Aim of study	Image modality	Datasets	Method	Outcome
Brouwer et al., 2021	to predict the disease progression	-	6682 patients (clinical data)	RNN	ROC-AUC of 0.85
Falet et al., 2022	to predict disease progression	-	3830 PPMS patients (clinical data)	RNN	the average treatment effect was larger for the 50% and 30% predicted to be most responsive, in comparison with 0.743 for the entire group.
Montolío et al., 2021	to predict disease progression	OCT scans	A total of 104 healthy controls and 108 MS patients	RNN	accuracy: 81.7%; sensitivity: 81.1%; specificity: 82.2%; precision: 78.9%; AUC: 0.8165

Abbreviations: MS: Multiple sclerosis, PPMS: Primary progressive multiple sclerosis, OCT: Optical coherence tomography, RNN: Recurrent Neural Network, ROC-AUC: Receiver Operating Characteristic Area under the Curve

Studies indicating the evaluation of treatment response using autoencoders

Autoencoders are a type of artificial neural network employed to compress large amounts of data into a specific number of features. This method first encodes the input data to prepare them for the second stage. In the second stage, the data is decoded and made suitable for analysis by other machine learning methods. This reduces the dimensionality of the data and changes the data from higher dimensions to lower dimensions. It is clear that this can help to optimally utilize machine learning in dealing with big data such as data obtained from MRI images (55). If we want to detect small changes between images, we need high-resolution images that have high dimensions of data themselves. Thus, the data obtained from these images should be transformed to lower dimensions, which can be done with artificial neural networks such as autoencoders (56). It is clear that such a method can be very helpful in the assessment of MS, especially in examining the response to treatment. To this aim, we need to compare imaging data over time, and these changes can be so subtle that they remain invisible to human eyes and they cannot be analyzed correctly with traditional and human methods. We also encounter a large volume of data, which can be very difficult and time-consuming to analyze and compare. Therefore, this method has also been attempted to be used in assessing the response to treatment in MS.

Normally, this assessment is performed in three ways: clinical, imaging, and laboratory. Clinically, the success of the drug is considered in reducing disease attacks and preventing disease progression. For this purpose, more precise measurement parameters have been tried. If EDSS

(57) was used for a long time to assess disease progression, now, with the increase in our understanding of the disease and the emergence of new concepts such as progression independent of relapse activity (PIRA) (58) and smoldering associated worsening (SAW) (59), other functions besides the patient's motor function are also considered to assess disease progression, where cognitive and neuropsychological examinations are also employed for this purpose. In addition to clinical data, imaging has long played an important role in assessing the effect of treatment. In addition to imaging data, OCT data can also be effective on assessing disease progression, and as mentioned, recent studies have presented a direct relationship between the amount of brain atrophy and OCT. In recent years, biomarkers have also received much attention and their role in assessing disease progression plus the effect of drugs has been investigated (60). The list of these biomarkers is growing day by day, and some of them, such as NfL, are directly related to the rate of relapse (61) while others, such as glial fibrillary acid protein (GFAP) (62), are directly linked to the rate of disease progression. With the growth of technology and the widespread use of smartphones, digital biomarkers are also increasingly used. These technologies provide the physician with massive data from the patient, including walking speed, various physical changes, limb movements, fatigue, and cognitive problems (63-66).

Vijayarajan et al. utilized autoencoders method along with a pre-trained classifier to identify lesions and their segmentation in MRI. It is clear that considering the role of MRI in assessing the effectiveness of drugs, this assessment can be helpful (67). As mentioned, digital biomarkers can also be helpful in assessing the progression of the disease and the effectiveness of treatment. One of the problems of MS patients is falling. Investigating the factors involved and predicting falling can be of great importance. However, these factors can be very different and have a large volume, and at the same time depend on the person's gait style and daily activities, all of which can only be collected through digital technologies that collect this data using different sensors. It is clear that the volume of this data will be very large and methods should be used to convert high-dimensional data to lower dimensions. The Autoencoder method is considered a suitable model for this task due to its characteristics (68).

Table 3. Studies which have used autoencoders for treatment response assessment

Ref	Aim of study	Image modality	Datasets	Method	Outcome
Rajangam et al. 2017	Identify lesions and their segmentation in MRI	FLAIR	292 images	Autoencoders And pre-trained classifier	an accuracy of 94%
Mosquera-Lopez et al., 2021	Investigating the factors involved and predicting falling	-	25 MS patients (clinical data)	Autoencoders	a sensitivity of 92.14%, and false-positive rate of 0.65 false alarms per day

Abbreviations: FLAIR: Fluid-attenuated inversion recovery, MRI: Magnetic Resonance Imaging, MS: Multiple sclerosis

Predictive modeling for relapse using deep learning

Disease progression has been elaborated more than anything else in this review article. The reality is that the biggest problem in dealing with a patient with MS is disease progression and the resulting disability. However, disability is not simply due to disease progression; relapses can also be disabling. These relapses can be associated with irreversible disability (69). Therefore, it is important to develop a model that can predict the likelihood of relapse in an MS patient. Since such a model requires huge data, artificial intelligence and deep learning can be very helpful in its development. So far, few attempts have been made to do so, and a few of them will be mentioned here. In a study, the data collected from positron emission tomography (PET) scan and MRI imaging methods was used to predict relapse rates. They first employed a multi-branch FCNN to segment brain lesions obtained from MRI and PET scan data, and then measured the volume of the lesions. They then evaluated different models for predicting the number of attacks and ultimately selected the best one. They found that this model created with high accuracy can be effective on predicting the number of attacks (70). In another study, researchers also tried to investigate the possibility of predicting the formation of active plaques. The formation of active plaques can be associated with the risk of attacks; therefore, it is very valuable and is actually considered a type of radiological attack of the disease that is sometimes accompanied by clinical manifestations. They tried to build a model to predict the formation of active plaques with data obtained from 82 patients. Six different classifier algorithms were used in this model. Accordingly, 107 radiomics features and 11 robust features were identified for each lesion. Finally, it was indicated that the formation of active plaques can be estimated with high accuracy based on the identified features (71).

Table 4. Studies which have tried to introduce predictive models for relapse using deep learning

Ref	Aim of study	Image modality	Datasets	Method	Outcome	Practical result
Du et al. 2023	predict relapse rates	PET scans and MRI (T1 and T2) imaging	25 patients	FCNN	Dice Similarity Coefficient (DSC) of 0.81 and a precision of 0.86.	They found that this model created with high accuracy can be effective on predicting the number of attacks
Khajetash et al. 2023	investigate the possibility of predicting the formation of active plaques	T2 FLAIR images	82 patients	Six different classifier algorithms	an AUC, sensitivity, and specificity of 0.85, 0.82, and 0.66, respectively	

Abbreviations: AUC: Area under the curve, DSC: Dice Similarity Coefficient, FCNN: Fully Convolutional Neural Network, FLAIR: Fluid attenuated inversion recovery, MRI: Magnetic resonance imaging, PET: Positron emission tomography.

Discussion

MS is a debilitating disease of the central nervous system that mainly affects the younger generation. Therefore, it can have a profound impact on a generation that is supposed to play an important role in society as a human resource. As such, this disease will cause huge costs with the problems it causes (72). These costs will be both on an individual and societal level. Therefore, any solution that helps to diagnose this disease more quickly as well as monitor and improve the conditions of patients can lower these costs for the individual and society. Diagnostic methods play an important role in this, among which MRI and OCT are key players in the diagnosis and long-term evaluation of patients. However, a small amount of data obtained from these diagnostic methods is used in the daily practice of physicians. This is due to both the limited processing capacity of the human brain and the fact that the time required to extract and analyze data is generally very long and is practically beyond the scope of doctors' abilities. The next point is that many relationships between data will remain unknown to the physicians for this reason unless a new way to analyze data is found. Currently, several studies have been conducted to employ imaging data to predict disease prognosis. However, even despite the large volume of these data, many relationships between the parameters involved will remain invisible to physicians. All these factors suggest the necessity of using AI in analyzing these data. Artificial intelligence itself has several methods in analyzing data. In this review, deep learning in analyzing imaging data has been investigated. But AI is never limited to one method in data analysis and tries to use a combination of methods for better analysis. In particular, since other methods such as computer vision are also effective in analyzing image data (73), and therefore this review would be incomplete without considering them, and the authors generally recommend using all of these methods in analyzing data from imaging modalities. This will help to discover more relationships in the data and their role in diagnosing as well as monitoring the disease. In this review, it is shown that deep learning, through its various models, can both help us segment brain lesions and show us how these lesions change over time. As stated in each section, these findings are of great value in treatment. Of course, it should be noted that imaging methods are not limited to MRI and OCT.

Although currently only these two are used in daily practice, these very new studies that use advanced imaging methods also generate a large volume of data. Also, these new imaging methods are moving towards creating more diverse and complex images, which makes their analysis more difficult. Therefore, future studies need to use various AI methods, including deep learning, to analyze them. On the other hand, if we look at the studies that have been carried out in the previous sections, a major flaw in them is their excessive focus on cross-sectional studies and lack of longitudinal studies. Meanwhile, longitudinal studies are essential for monitoring the course of the disease and the effect of drugs on the course of the disease. Thus, these deep learning methods should be used more than ever in these longitudinal studies. The next point is the heterogeneous use of deep learning techniques in the analysis of imaging data. As it has been observed, the FCNN method has been mainly used in these analyses, and the use of methods such as RNN has been significantly limited. Meanwhile, all of these methods have special and unique capabilities and should be used efficiently in the analysis of imaging data. The necessity of using a combination of these methods is another point that has been considered in several studies and has shown that if these methods are used in combination, the conclusions can have higher accuracy. All of these indicate the need for further research and studies. The last point that should be mentioned is the creation of appropriate platforms for the use of these data in the daily practice of physicians. Every physician should have a specific platform for that patient as a physician assistant to deal with their patient. A platform that not only has the ability to upload all patient's information, but also the data can be uploaded digitally by the patient. Depending on the doctor's principal need, which is usually rapid diagnosis, MRI examination for enhancing and new lesions, as well as the course of the disease, these data should be analyzed by AI methods and the result should be displayed on the doctor's dashboard. In this case, AI can be of great help to the physician as an assistant in the treatment process of patients. At the same time, this also helps considerably in personalizing the treatment. Through AI, the best decision can be made for a particular patient, considering the analysis of all the data that is collected about their disease condition.Use of deep learning is not just a data analysis. It can also greatly help in personalizing treatment. If a physician has the ability to use AI as an assistant for data obtained from each patient, whether cross-sectionally or longitudinally, then they can use these data and the results of their analysis in timely diagnosis as well as monitoring of the disease and how it responds to treatment. Deep learning allows us to step beyond some simple points in examining the patient's imaging and to gain a deeper understanding of the disease process. This issue will be given more attention with the introduction of advanced MRIs in the field of treatment. It is essential for physicians to be familiar with AI methods and especially the use of deep learning in analyzing imaging data, which plays a major role in the management of MS patients. In the near future, without such knowledge, it will be practically impossible to treat patients. Attention to creating appropriate platforms that allow doctors to do this analysis is also of high importance, as looking at and familiarizing oneself with the ever-increasing trend of AI advancement makes its use inevitable.

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