Chapter

# Perspective Chapter: Artificial Intelligence in Multiple Sclerosis

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## Abstract

In recent times, the words artificial intelligence, machine learning, and deep learning have been making a lot of buzz in different domains and especially in the healthcare sector. In disease areas like multiple sclerosis (MS), these intelligent systems have great potential in aiding the detection and prediction of disease progression and disability, identification of disease subtypes, monitoring, treatment, and novel drug-target identification. The different imaging techniques used to date in multiple sclerosis, various algorithms such as convolutional neural network, Support Vector Machine, long short-term memory networks, JAYA, Random Forest, Naive Bayesian, Sustain, DeepDTnet, and DTINet used in the various domains of multiple sclerosis are explored, along with used cases. Hence it is important for healthcare professionals to have knowledge on artificial intelligence for achieving better healthcare outcomes.

**Keywords:** AI, disease detection, machine learning, monitoring, MS, treatment

## 1. Introduction

Artificial intelligence (AI) is progressively being deployed in healthcare, as it becomes more prevalent in recent business and daily activities [1]. AI in healthcare can aid healthcare practitioners with a variety of patient care and administrative operations, helping to strengthen current approaches and overcome difficulties more quickly [2]. Although AI and medical breakthroughs are beneficial to the medical sector, healthcare companies' policies might vary substantially. The most frequent type of AI in healthcare is machine learning (ML). This wide strategy, which is the foundation of several AI and healthcare tools, has several versions. Personalized medicine has been the most widely used application of classical machine learning in the health sector [3]. Supervised learning of AI in healthcare uses machine learning and personalized medicine tools that include data with outcomes for training. The most often used tools of AI in relation to MS disease are ML as well as deep learning (DL) methods [4].

Multiple sclerosis (MS) is a chronic demyelinating autoimmune disorder affecting the central nervous system (CNS) and is prevalent in young adults. Optic neuritis, cerebellar signs, and sensory impairments are common clinical characteristics of MS, especially in recurrent or early phases. Spasticity, ataxia, muscle weakness, and descending tract dysfunctions are all signs of progression [5–7]. With clinical presentation, MS is diagnosed by CNS magnetic resonance imaging (MRI) and cerebrospinal fluid investigation. Earlier studies of AI approaches in distinguishing MS affected from healthy subjects or differential diagnoses yielded intriguing results related to diagnostic effectiveness [8]. For the identification of MS lesions in MRI images and the prognosis in MS cases, many AI-based algorithms were suggested [8]. In addition, AI has been used in several trials to anticipate physical as well as cognitive impairment in MS cases [8]. Other data employed in AI tools include Optical coherence tomography, serological, and motor function findings, in addition to MRI findings [9]. The present chapter enables us to understand the role of AI in the detection, prediction, identification of subtypes, monitoring, imaging techniques, drug discovery in MS.

## 2. Understanding MS using imaging techniques

The development of localized demyelinated lesions known as plaques, which may be detected on standard MRI scans, is the most common characteristic of MS. Now, the focus is mostly on sophisticated MRI techniques that can more reliably disclose the underlying pathology in lesions and seemingly normal CNS structures. The frequently employed imaging techniques for identifying the microscopic progression of pathologies in CNS with high accuracy and precision are Quantitative magnetization transfer imaging (QMTI), proton MRI spectroscopy (MRS), functional MRI (fMRI), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), relaxometry, and myelin water fraction (MWF) [10].

Of these, QMTI is considered the advanced technique that detects the association of free protons in edematous fluid with protons linked to myelin membrane constituent molecules. It can also provide information regarding the tissue matrix integrity in MS pathogenesis [11–13]. This technique uses magnetization transfer ratio (MTR) mapping analysis to determine myelin content quantitatively as in normal-appearing white matter changes. Also, magnetization transfer rate (Ksat) and longitudinal relaxation time under MT saturation pulse (T1sat), as well as the computation of T1 longitudinal relaxation time, are used in the QMTI approach to infer neurodegenerative processes. Using QMTI-T1 variables to investigate the degree of lesions in the normal-appearing white matter (NAWM), pathological factors such as neuroinflammation, demyelination, regeneration, gliosis, edema, and axonal degeneration can be monitored more precisely. This method provides for a more accurate evaluation of therapeutic approaches [14–17].

Imaging of the retinal nerve fiber layer (RNFL) and retinal ganglion cells (GCL) has also been suggested for the diagnosis of MS through optical coherence tomography scan (OCT) [18].

## 3. Role of AI in MS: prediction, detection, and diagnosis of MS

Artificial intelligence (AI) algorithms are a type of machine learning algorithm that has shown great promise in the prediction, detection, and diagnosis of multiple sclerosis (MS). Here are some examples of AI algorithms with potential applications in MS detection, diagnosis, and prediction. The list of algorithms is not limited to the below-mentioned.

### 3.1 Convolutional neural networks (CNNs)

CNNs are a type of deep learning algorithm used to analyze MRI images and detect MS lesions. These algorithms use a series of convolutional layers to identify features in the images, which are then used to classify the images with or without

MS [19]. The layers of CNN architecture include convolution layers, pooling layers, and fully connected layers. The convolution layer is responsible for the extraction of features from an image. This allows the determination of any abnormalities that are occurring within the image. The pooling layer reduces the dimensionality of the feature maps by down-sampling them, reducing computational complexity before being charted into the final network output [20]. In simpler words, the image becomes smaller, which ultimately reduces the processing time for the subsequent steps executed in the next layer of the neural network [21]. Moreover, recent research interests have involved the development of a novel 14-layer convolutional neural network, for the detection of MS, involving advanced techniques such as dropout, batch normalization, and stochastic pooling. This method has proven to be superior in line with sensitivity, specificity, and accuracy than the traditional AI methods, which are Multiscale AM-FM [22], ARF [23], BWT-logistic regression (LR) [24], 4-level HWT [25], and MBD [26] potentially used for image analysis.

Another novel automated methodology, with higher sensitivity, for the detection of new lesions in images of MS patients has been explored. This algorithm is called 'Fully convolutional neural networks' [FCNNs]. Here, dual streams of FCNNs have been utilized. The initial FCNN network discovers probable candidates, while the second FCNN attempts to detect newer lesions, decreasing the number of false positives. This algorithm helps assess the changes in the lesion volume over two different time points with a faster turnaround time when compared to the manual approach [27]. So, these automated processes are important because they avoid unnecessary exposure to MRI. As per previous studies, it has been emphasized that clinical and radiological results for patients who have not been diagnosed as individuals with MS need to undergo a follow-up MRI of the brain [28]. Overall, in recent times, the convolutional neural network (CNN) has increasingly received attention in image denoising or in other words, deblurring tasks. Image denoising occurs frequently in real-time low-level vision applications. Image denoising continues to be an important subject in the fields of image processing and artificial intelligence because of its ill-posed nature and huge realistic impact [29].

### 3.2 Support vector machines

Support vector machine (SVM) is a machine learning algorithm that works through regression, classification, and outlier detection of data [30]. The way SVM algorithm in general works is by differentiating two given classes with a hyperplane generation, which divides the classes after the data input, which is transformed mathematically into a high-dimensional space [31]. In a nutshell, this algorithm has been utilized to establish automated disease classifiers [31].

This algorithm has provided high accuracy (98.89%), sensitivity, and positive predictive value for MS diagnosis [32]. There have been instances where plasma levels of nutritional factors such as selenium, vitamin B12, and vitamin D3 as potential markers for MS diagnosis have been explored. Several different algorithm methods were tested as a diagnostic method for nutritional factors based on the MS disease relationship. Out of the several machine learning algorithms, SVM, along with Radial-basis function (RBF) kernel methods, yielded higher accuracy, sensitivity, and predictive values. Basically, these methods work on data analysis and subsequent classification of the same, to determine whether an individual is normal or with MS condition. Some of the other algorithms used in similar aspects are decision tree (DT) and K-nearest neighbor (KNN) [32].

It has been emphasized in existing literature that an early detection or prediction of MS is important for improving the survival of an individual with MS. In lieu of this, many machine learning algorithms have been explored with an expectation to have lesser prediction errors and more accurate classifications of potential MS cases from normal healthy individuals. A few of these algorithms are Naive Bayes (NB), decision trees, random forest (RF), nearest neighbor, AdaBoost, support vector machine (SVM), RBF network, and multilayer perceptron [33].

Another scenario in which the SVM algorithm has been utilized for diagnosing MS is using optical coherence tomography [OCT] data. The retinal structure-based neurodegeneration OCT data parameters used for the analysis are macular thickness and peripapillary region. In fact, analyzing the OCT data for its potential usage as a biomarker in the diagnosis of MS has been an upcoming area in MS research. Usually, MacDonald's Criteria is used for the diagnosis of MS. However, this method may take a longer number of years to arrive at a firm diagnosis from the onset of the disease. In such an instance, it is required to have a more robust and accelerated system that can aid in the early detection of MS, and it is at this juncture that AI-ML-based algorithms play a significant role in executing the same [9].

Another example of the application of an SVM-based technique for diagnosing MS involves MS characterization based on lowered or higher plasma levels of antioxidant or anti-inflammatory biomarkers such as zinc, adiponectin, TRAP, and SH groups and advanced oxidation protein products (AOPP). Here again, the SVM algorithm works by classifying individuals with or without MS based on the higher or lower levels of the above-specified plasma biomarkers data. As a fact, this algorithm has shown higher training and validation accuracy [34].

Application of SVM technique for MS diagnosis based on MRI images has been employed. It has been used to classify based on (a) lesion volume and (b) preprocessed FLAIR (fluid-attenuated inversion recovery) data, which is an advanced form of MRI sequence, perceived to be helpful in the evaluation of MS plaques, lacunar infarction, etc. SVM algorithm, in conjecture with other algorithms such as CNN and layer-wise relevance propagation [LRP], has been used in the diagnosis MS with MRI images. LRP algorithm deals with more understanding and visualizing the intricate inner mechanism of neural networks. To understand LRP better, let us take a hypothetical example where the neural network has predicted a brain lesion from an image of brain tissue. Then, LRP provides a projection of which pixels in the original image had attributed toward the prediction and extent of the same [35]. As a matter of fact, the FLAIR lesion load, which is considered to be one of the significant biomarkers for MS, when combined with the SVM technique, has produced more accurate and robust diagnostic outcomes [36].

### 3.3 Long short-term memory (LSTM) networks

LSTMs are another type of recurrent neural network-based algorithm, with potential usage in the prediction of the course of MS, based on patient data. This algorithm is trained with clinical data of MS patients and then deployed to newer patient data. In a nutshell, this algorithm analyzes the clinical data of a new patient and provides predictions on whether the patient will progress for example from an initial relapsing-remitting (RR) to the secondary progressive (SP) stage of disease, or not [37]. The variations in clinical data across different time frames, including how they affect prediction outcome, have been employed as feed for classifiers in some research [37–40]. LSTM networks, in particular, enhanced reliability for predictions over extended time periods when used to analyze patient medical history. Since all the data of a patient were combined into a single time series, the amount of data accessible for this strategy was significantly reduced. However, the positive predictive value grew significantly, but at the expense of a decreased sensitivity, or the rate of correctly identifying patients who were becoming worse [37], which would take more time with a human approach, and this tool may help Physicians to save time as well as make decision-making.

### 3.4 JAYA algorithm

JAYA algorithm is basically used to find the most ideal result for a specific issue. An imaging perspective, this algorithm optimizes MRI parameters, providing better image quality. This algorithm is utilized to spot different tumor types or lesions of varied grades and structures, enabling the treating physician to recognize the tumor or concerned pathological areas and segmentalize more rapidly. Segmentation, in the context of brain MRI, is used for seeing and measuring anatomical aspects of the brain, defining pathological areas, etc. In simpler words, this algorithm is employed for segmenting and extracting abnormal brain portions in brain MRI input data, enabling physicians to arrive at faster and more accurate conclusions and allowing better surgical or treatment planning [41, 42].

So, in the context of MS, the JAYA algorithm and two other techniques, namely MLP and FRFE, have been applied to diagnose MS based on brain MRI images with potentially identifying the MS plaques [43].

### 3.5 Random forest algorithm

RF is another robust algorithm that provides more accurate predictions [44]. This algorithm, in the context of MS, can be applied for MS diagnosis and disease progression monitoring. Off-late speech patterns have been explored as potential indicators for detecting the presence of neurological disorders [45].

Previous literature has reported that speech discrepancies occur in MS. This feature aids in not only early diagnosis but also in monitoring of MS disease progression. One of the recent research studies involved this concept by making the individual read a text, recording, and storing the same. Then, this algorithm analyzes and provides potential output using the speech recordings derived from MS patients. So here, the algorithm analyzes the speech recordings of healthy and MS patients, which means that the acoustic variables are evaluated statistically, and along with the patient's biometric and health status data, a potential diagnosis and disease progression status of the patient can be derived [45].

### 3.6 Naive Bayesian networks

Naive Bayesian networks (NBNs) are simple and effective algorithms for disease predictions. It serves like a prediction or probabilistic model for diseases [46]. Bayesian networks are increasingly used as classifiers [47]. So, in MS, Bayesian algorithms analyze a set of clinical and imaging data, which in turn aids in the identification of subtypes. It determines the probability of each patient belonging to a particular MS subtype [47, 48]. Studies suggest that one of the strengths of Bayesian networks is that they can include the gathered knowledge of experts in situations where data are limited and continue to yield significant and accurate decision-support systems [49]. Hence, in this manner, it aids in achieving better clinical outcomes.

### 3.7 Sustain algorithm

In the field of MS subtype identification, artificial intelligence has a very pivotal role. A newly developed AI algorithm called SUSTAIN has the ability to identify new subtypes of MS. This algorithm basically has the ability to discover data-driven-based subtypes in chronic disorders [48]. In fact SUSTAIN has been utilized in neurodegenerative diseases like Alzheimer's disease, multiple sclerosis, frontotemporal dementia, and progressive lung disease [50].

So, this unsupervised machine learning method groups people with MS into disease subtype categories based on MRI scans, and the algorithm gives a score based on the extent of pathology seen on the MRI scan, subsequently bifurcating the patients into varied categories on certain discrete findings. The uniqueness of SUSTAIN Algorithm is that it can delineate temporal and phenotypic heterogeneity. A set of subtypes is identified by this algorithm, and the subtypes are defined by observing patterns of variations in a group or set of features, for instance, MRI deviations. All of this allows for predicting which MRI-based subtype responds to which particular treatment better, along with taking into account the worsening of Expanded Disability Status Scale (EDSS) as well. So, ultimately, getting the right treatment for the right patient at the right time is achieved [48].

## 4. Treatment, monitoring, and novel drug-target identification

AI can support decision-making, identify the best course of treatment for a patient, including individualized medications, supervise the collection of clinical data, and use it to ensure subsequent drug development and assist in moving drugs from the research lab to the patients [51, 52]. Various applications of AI in new drug development have been depicted in **Figure 1**. Machine learning (ML) techniques are data-driven methods for creating models of prediction that can recognize patterns and connections in data with relatively little assistance from humans [53, 54]. The use of ML in multiple sclerosis is currently used primarily for categorizing patients into various disease stages [53–55] or for anticipating the transition of disease stage, as

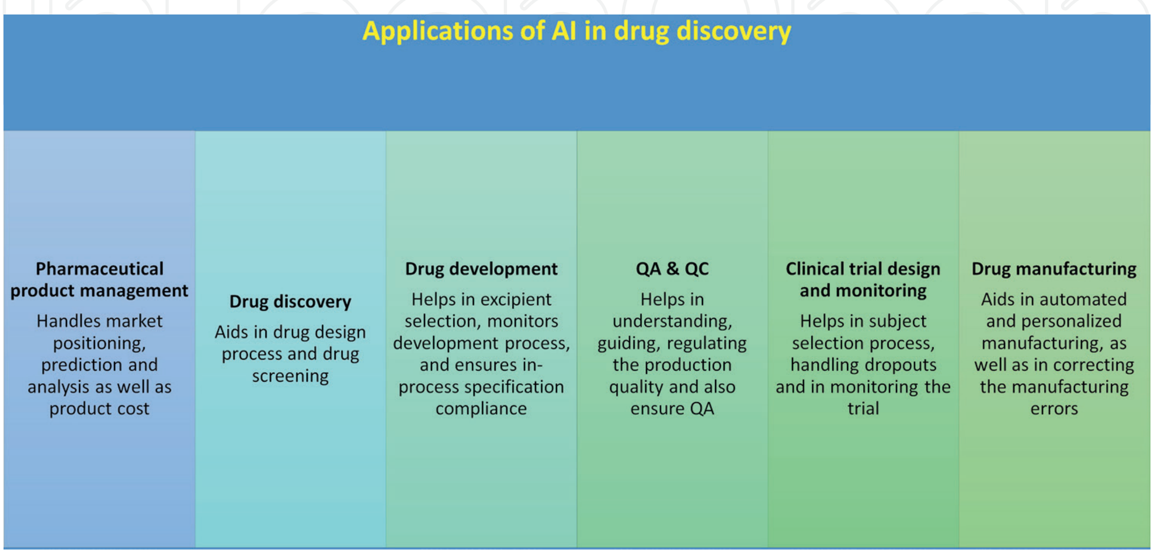


**Figure 1.**
*Scope of AI in drug development process. QA: Quality assurance, QC: Quality control.*

well as development of disability [56–58]. It is crucial to identify the illness subtype in new patients. The anticipated time to disease severity progression, especially requiring support for walking, is another important piece of data or parameter to predict [38]. Researchers utilize multidimensional Bayesian network classifiers as they may represent and take advantage of the relationships between both variables, which is important given that we have to forecast two correlated class variables: illness subtype and time to reach a specified severity level. Due to the interpretability of Bayesian networks, the resulting models can also be verified by doctors using their specialized knowledge. A cutting-edge multi-objective method is used to train the classifiers, aiming to simultaneously maximize the accuracy of both class variables [47].

Statistical techniques like linear regression to predict continuous response or LR over binary response anticipation [59], as well as Cox regression or Kaplan–Meier procedures of survival analysis [60], are typically used in predictive models in investigations of prognostic variables that influence the advancement of disabilities. However, these evaluations do not estimate how well they generalize to data that were not utilized for model fitting. In order to predict the Expanded Disability Status Scores (EDSS) at 10 years, for instance, LR was employed to assess brain atrophy as well as lesion burden as prognostic markers. The quality of fit of the model to the data was measured using R2 values, but no prediction of the model's performance using data that were not utilized for model fitting was given [61]. One study used advanced statistical modeling to evaluate the prognostic impact of different clinical measures on disability progression and came to the conclusion that the relatively poor predictive capacity of baseline factors in MS disease progression modeling was confirmed by the inconsistent ranking of prognostic factor importance. One study followed a model that validates data withheld from training in each cycle of 10-CV [62].

Support vector machines may offer a potential way to forecast the path of MS disease and identify individuals who may benefit from intensive treatment approaches by adding short-term clinical as well as brain MRI data, class imbalance correction measures, and misclassification costs [63]. There has been little investigation of machine learning strategies in MS, despite the fact that various research in predicting the course of disease in MS have been done using logistic regression [64], Markov modeling [65–67], and more recently, a Bayesian modeling approach [68]. In order to forecast the progress of the disease in 51 MS patients, one study investigated a neural network computer classifier. Depending on the situation and conditions, an accuracy of >70% may or may not be regarded as a reasonable standard for machine learning [69]. In a different scenario, it was suggested that precise detection of progressive cases without a significant number of false positives is more important so that these patients can receive more aggressive therapies. Therefore, most clinicians may find the predicted accuracy of 81 percent on progressive and 59 percent on nonprogressive using SVM with an expense of 1.5 to be acceptable for clinical purposes. However, it is up to each doctor and patient to decide on this balance [38]. Many investigations mostly centered on quantitative MRI characteristics and clinical data sets. Incorporating biomarker data is unmet. Based on changes in EDSS values over a 5-year period, there may also be variations in the outcome measure for progressive or nonprogressive cases. The weight of progress measured by an increase in EDSS signifies physical disability. The EDSS scale has come under criticism for being fairly insensitive, especially to declines in visual and cognitive abilities. It should be investigated to do further studies using these parameters.

When it comes to patient's disease condition monitoring, one of the words we may often come across is 'wearables. Though short as a word, 'Wearables' are making an immense impact in the world of remote patient monitoring. “Wearables” refers to smallish electronic devices that can be easily put on and off and also be embraced into garments or anybody-based accessories [70].

In MS, the usage of AI-based wearables very much adds onto effective patient monitoring and in turn helps to assess and alter treatment plans for the individual. Gait and cognition are important parameters to be tracked in MS patients and this can be addressed by various intelligent wearables. In fact these wearables can be categorized as software and hardware based. The parameters that can be effectively tracked by these systems are activity levels, fatigue, mood changes, cognitive and mood changes. Adding on as a self-management tool, these systems can aid in timely medication administration and adherence to the same. A few examples of these wearables are ‘ActiGraph’, ‘StepWatch’ to monitor activity levels, in terms of the number of steps taken by MS individuals are increasing or decreasing [71]. ‘myBETAapp by Bayer’, which aims to provide assistance to its autoinjectors BETACONNECT, which helps patients to confidently self-manage their symptoms and dose [72]. ‘MyeReport France’ is a mobile app for reporting adverse reactions in relapsing remitting MS (RRMS) patients [73]. Another app that aids in monitoring balance and cognition is ‘Floodlight’ [74].

Another issue that needs to be effectively monitored is the cognitive level of MS patients. As per extensive literature, cognitive impairment is one of the specific features observed in patients with MS, and it is reported that around 45-70% of individuals with MS have cognitive dysfunction [75]. Hence, this can be a potential biomarker for assessing disease status. Recently, a self-administered AI software-based solution, which comprises 5 minutes computerized tests, has been explored to evaluate cognitive dysfunction in MS patients. It uses MLR (multiple linear regression) classifier algorithm to furnish a predictive score in line with the individual’s cognitive status [76].

In the new drug discovery process, more than 1060 molecules make up the enormous chemical space, which encourages the creation of many different pharmacological compounds. However, new drug discovery is constrained by a dearth of new technology, rendering it a costly and time-consuming endeavor that may be resolved by applying AI [77]. DeepDTnet is an advanced, network-based DL technology for identifying drug targets as well as drug repurposing that forecasts novel molecular targets within existing pharmaceuticals through systematic embedding of 15 different kinds of chemical, genomic, phenotypic, and cellular networks [78]. DeepDTnet outperforms earlier state-of-the-art network-based as well as conventional machine learning algorithms, according to thorough evaluations, and reveals established drug-target interactions [79]. In one instance, researchers discovered that DTINet performed well when predicting novel targets for medications with high degree in the established drug-target network, but poorly when predicting targets for compounds that had a low degree [80]. DeepDTnet, however, has strong performance in foretelling drug-target interactions across both drugs and targets of high and low degrees. DeepDTnet and DTINet were assessed using a comparable dataset that was previously published in order to accurately compare their performance. DeepDTnet was found to be superior to DTINet as well as NeoDTI, a currently developed successor to DTINet, on both the earlier published dataset and a real-time study data validated drug-target network constructed in a study [81, 82]. Positive-unlabeled matrix completeness as well as autoencoder embedding were two novel deepDTnet components that were used to compare DTINet along with NeoDTI. Both autoencoder embedding along with positive and unlabeled (PU) matrix completeness helped deepDTnet perform better together [78]. This is a systematic deep-learning method that incorporates the biggest biomedical network datasets for target discovery, drug repurposing, and experimental testing of discoveries. By doing this, the translational gap that currently exists between the outcomes of preclinical testing in experimental animals and clinical outcomes in patients can be minimized [80]. The importance of automation will increase as a result of the use of the most recent AI-based technologies, which will additionally reduce the time it takes for new drugs to reach the market while also improving product quality, production process safety, and resource utilization [83]. The biggest concern with implementing these technologies is the potential loss of jobs and the tight rules required for AI implementation. However, these tools are simply meant to facilitate work, not to entirely replace people [84].

## 5. Conclusions

Artificial intelligence, machine learning, and deep learning in this era are making a significant impact in the healthcare medical vertical. These advanced intelligent systems are being vastly explored in detection, prediction, monitoring, and drug discovery for various disease areas including neurodegenerative and neuroinflammatory conditions such as MS. Though these systems may have noticeable specificity, sensitivity and accuracy in their assessments, further validations and refinements are required to create an extremely robust system. At this juncture, it needs to be emphasized that AI will not replace physicians, but physicians who are not aware of the same may get replaced!

## Conflict of interest

"The authors declare no conflict of interest."

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