Review

Harnessing Artificial Intelligence for Diagnosis, Treatment and Research of Multiple Sclerosis

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Harnessing Artificial Intelligence for Diagnosis, Treatment and Research of Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system affecting over 2.8 million people around the world. Artificial intelligence (AI) is becoming increasingly utilized in many areas including patient care for MS. AI is revolutionizing the diagnosis and treatment of MS by enhancing the accuracy and efficiency of both processes. AI algorithms, particularly those based on machine learning, are being used to analyse medical imaging data, such as MRI scans, to detect early signs of MS, monitor disease progression and assess patient treatment response with greater precision. AI can help identify subtle changes in the brain and spinal cord that may be missed by human clinicians, leading to earlier diagnosis and more personalized treatment plans. Additionally, AI is being employed to predict disease outcomes which could allow clinicians to tailor therapies for individual patients based on their unique disease characteristics. In drug development, AI is accelerating the identification of potential therapeutic targets and the optimization of clinical trial designs, potentially leading to faster development of new treatments for MS. AI is also playing a critical role in MS fundamental research by promoting efficient analysis of vast amounts of single-cell data. Through these advancements, AI could improve the overall management of MS, offering more timely interventions and better patient outcomes. In this review we discuss these topics and whether the influence of AI on diagnosis, treatment and research of MS can change the future of this field.

Keywords: multiple sclerosis; artificial intelligence; machine learning; image analysis; risk prediction models; personalized treatment; drug discovery; single-cell analysis

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) affecting the brain, spinal cord and optic nerve. Over 2.8 million people have MS worldwide with female preponderance and most diagnosed between the ages of 18 to 40 years [1]. People with MS (PwMS) commonly present periods of relapses followed by remissions and experience debilitating and neurological symptoms as the disease worsens [2]. This occurs when the immune system attacks the myelin surrounding nerve fibres, resulting in disrupted nerve signal transmission and subsequent injury and lesion formation in the brain. Disease-modifying therapies (DMT) have become the cornerstone treatment for reducing inflammation and relapses, subsiding new lesion formation and slowing disease progression [3]. Although MS is a complex chronic disease with no cure, advancements in research into the causes, early diagnosis and DMT have significantly improved disease management and quality of life for PwMS.

Artificial intelligence (AI) is a rapidly evolving technology that is transforming the healthcare industry and is quickly becoming an integral part of our daily lives. It involves the ability for

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machines to learn, analyse, comprehend, reason, solve problems and make decisions that are otherwise performed by humans [4]. AI is changing the landscape for diagnosis and treatment of PwMS by employing machines to analyse medical imaging data, such as MRI scans, to detect early signs of MS and monitor disease progression with greater precision. In this review we discuss how accurately AI algorithms determine MS prognosis compared to clinicians and its efficiency to predict disease outcomes. Furthermore, AI could be exploited to provide personalised treatment plans for MS patients that tailor therapies specifically to each patients' disease characteristics. In addition, we explore the role for AI in drug development and single cell analysis to accelerate the search of potential therapeutic targets that could lead to new DMT for PwMS. Through these advancements, AI could improve overall management of MS, offering improved timely interventions and better outcomes for patients.

2. AI-Assisted Medical Data Analysis for MS Diagnosis and Monitoring

PwMS commonly experience symptoms of fatigue, sleeping difficulty, vision impairment, limb pain and tingling, bladder and bowel issues and ambulatory impairment, though MS is clinically diagnosed by evidence of relapses or lesions in the brain [5,6]. Evaluation of lesion size and numbers using cerebral magnetic resonance imaging (MRI) is part of the daily clinical routine that is not only crucial for diagnosis but also monitoring disease progression and treatment response. Multiple studies have integrated AI into disease diagnosis and prognosis with many showing promising results. AI models have been trained to differentiate between MS and healthy MRI-scanned brains where one study found 91% accuracy when using a sea-horse optimiser algorithm while another reported 98% sensitivity, specificity and accuracy with an improved convolutional neural network (CNN) that combined parametric rectified linear unit and dropout method [7–9]. Relapse-remitting MS (RRMS) is the most common form of MS diagnosed in about 85% of PwMS and is caused by periods of symptom flare-ups followed by recovery [10]. When MRI data from RRMS patients were trained in a CNN, 95% accuracy was obtained for white and grey matter lesions while this reduced to 82% accuracy for T2 lesions [11]. Similarly, Coronado et al., applied multispectral MRI data from RRMS patients in a deep learning CNN which provided accurate segmentation of gadolinium-enhancing lesions when five multispectral contrast images were used and lesion volume was greater than 70 mm^3 [12]. However, another automated deep learning neural network called CLAIMS detected leukocortical and subpial lesions with 70-83% sensitivity when using only T1 weighted contrast images and provided more accurate results compared to T2 weighted contrasts [13]. These differences could be attributed to the strength of the MRI machine as CLAIMS used a 7T MRI scanner which provided ultra-high resolution T2 weighted and T1 weighted 3D magnetization-prepared 2 rapid gradient-echos (MP2RAGE) while the former study acquired MRI data at 3T. This shows that AI accuracy and efficiency could be impacted by the quality of MRI data.

Indeed, the lesion location is another contributing factor as AI models have been exclusively trained to identify white matter lesions in MR images by setting known lesion detection parameters [14,15]. Additionally, Eshaghi and colleagues developed an unsupervised machine learning (ML) algorithm called Subtype and Staging Inference (SuStaIn) to identify lesions and abnormal patterns of grey and normal-appearing white matter MRI which enabled accurate identification of MS subtypes [16]. Furthermore, the combinatorial inclusion of clinical data such as Expanded Disability Status Scale (EDSS), walking and finger dexterity results with MRI in SuStaIn predicted disease progression [16]. Another study also combined MRI with age and EDSS score in a deep learning predictor to identify 2-year clinical disability probability in MS patients [17]. These findings indicate the capability for AI to predict MS disease progression using multiple forms of clinical data. Interestingly, retinal imaging known as optical coherence tomography (OCT) can also be utilised to diagnose MS as the 2008 Optic Neuritis Treatment Trial showed a correlation between decreased visual acuity and MRI lesions [18]. AI models trained to identify discriminating results in the OCT of the retinal structure from healthy and MS patients revealed high accuracy, sensitivity and specificity for MS diagnosis [19–22]. Interestingly, myelin content in the brain, usually measured by positron

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emission tomography, has been predicted with Generative Adversarial Networks using multimodal MR images [23]. This shows that AI can be trained to identify and diagnose MS using various forms of medical data.

Studies have also shown the ability for AI models to identify non-active and active brain lesions in MRI data, which provides vital information about MS disease progression. Gadolinium T1-weighted MRI is commonly used to detect active lesions and when trained with deep learning AI models, 95% accuracy was achieved for differentiating active and non-active plaques [24]. However, accuracy is reduced when using non-contrast FLAIR MRI [25]. One study showed ML models accurately identified active and non-active lesions in diffusion-weighted images, an advanced form of MRI [26]. Even thalamic volume loss, known to be a marker for neurodegeneration, was detected in 7 seconds by a deep learning model called DeepGRAI using T2-FLAIR MRI [27]. Furthermore, an experiment revealed that AI assisted MR image analysis for lesions significantly reduced reporting time compared to radiologists at initial and six-week follow-up [28]. Another study also reported greater accuracy for lesion detection with their AI tool, iQ-MS, showing 93.3% sensitivity compared to radiology reports which had 58.3% sensitivity even though specificity was equal between both [29]. The accuracy and speed by which AI can identify MS pathology is remarkable and proven to be better than clinicians.

An additional method used to identify MS that has not been experimented with AI is histopathology. This involves assessing MS plaques and lesions for immune cell infiltration and myelin degradation [5]. Our literature search found no published studies utilising AI to predict MS based on histopathology but may be a future direction to identify MS subtypes. Cancer studies have already developed deep learning algorithms to detect tumours on histological slides which demonstrated high accuracy and reduced time for diagnosis as well as high throughput analysis compared to pathologists [30–34]. In similarity, AI could be trained to scrutinise MS histopathology slides to detect subtle changes in the brain and spinal cord that could be missed by humans. Compared to cancer, MS histology requires brain biopsy under general anaesthesia or from post-mortem tissue. Thus, AI-assisted analysis of these slides could be implemented to identify MS subtypes and new markers for MS which can increase our knowledge about MS pathogenesis and lead to potential new therapeutic targets [35]. More research is required to establish an ideal method to combine AI with MS histopathology for meticulous and efficient image analysis beyond the human eye.

Another consideration for the future of AI in MS is the ability to differentiate MS lesions from other brain lesions associated with stroke, tumours and infectious diseases as this could lead to misdiagnoses. Numerous cases have been reported whereby MRI lesions are recognised as gliomas or MS plaques leading to the wrong diagnosis and treatment for MS or late detection for cancer patients [36–38]. Indeed, AI provides more accurate diagnosis for MS compared to clinicians but there are still cases where it is difficult for ML to differentiate MS lesions from other neurodegenerative diseases [39]. Hence other methods are required to confirm diagnosis such as reviewing patient symptoms and close follow-up, analysing cerebrospinal fluid (CSF) or a CNS biopsy and performing positron emission tomography (PET) scan or magnetic resonance spectroscopy (MRS) [36,38]. MRS improves analysis of lesions as it measures biochemical changes in normal appearing white brain matter and is often used in conjunction with MRI to better assess MS prognosis [40,41]. A study used MS and brain tumour MRS data and applied various ML methods to distinguish MS lesions from tumours [42]. Remarkably the results showed that an artificial neural network had 100% accuracy, specificity and sensitivity for differentiating MS lesions and brain tumours. This confirms that AI can identify different diseases, possibly better than clinicians, providing early and accurate diagnosis for patients thus expediting their treatment. Ultimately, this section showcases significant results of accurate and efficient MS diagnosis and disease prognosis using AI which presents a positive and promising outlook on implementing AI in the future for patient care.

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3. AI-Modelling to Predict Risk of MS, Progression of MS and Treatment Response

Given the diverse clinical presentations and unpredictable disease progression in MS, it is imperative to mitigate long-term disability. Traditional diagnostic frameworks encounter challenges due to the subjective nature of symptom reporting and constrained healthcare accessibility, particularly in resource-limited settings [43]. The emergence of AI and ML has introduced innovative approaches to early disease prediction [44]. AI-driven diagnostic systems offer promising solutions by enhancing clinical accuracy and supporting evidence-based decision-making [45].

One of the primary contributions of AI in MS diagnosis is its ability to manage diagnostic uncertainty through fuzzy logic. Patients may provide imprecise or incomplete descriptions of their conditions, introducing variability into the diagnostic process [46]. Fuzzy logic overcomes this issue by assigning degrees of membership to symptoms, facilitating a more refined interpretation of patient-reported data [46]. This enhances the reliability of diagnostic assessments despite subjective input variability. Another contribution of AI is the ability of Expert Systems to replicate human reasoning, leveraging structured knowledge bases and predefined inference rules. These systems integrate well-established clinical indicators of MS such as optic neuritis, brainstem dysfunction, and spinal cord involvement [47]. Expert Systems can identify high-risk individuals through evaluation of symptoms and demographic data which prevents diagnostic delays and clinical referrals [46].

In a recent study, ML techniques, a subtype of AI tools, were used to differentiate between MS patients and healthy individuals in which socio-demographic characteristics and environmental factors were gathered from 100 MS patients and 100 controls [48]. Six ML models were evaluated for their ability to predict MS: Naive Bayes (NB), Support Vector Machine (SVM), Least Square Support Vector Machine (LSSVM), Random Forest (RF), Logistic Regression (LR), and Linear Discriminant Analysis (LDA). NB reported high sensitivity (79%) but lower specificity, while SVM performed well in non-linear scenarios with kernel functions [48]. RF was the most robust model, achieving the highest accuracy (68%) whilst identifying key predictors such as age between 20-40 and females [48]. Performance metrics like sensitivity and specificity can identify the strengths and limitations of each model, highlighting the ability of ML in analysing complex clinical datasets for MS [49].

The predictive ability of ML and AI in MS is enhanced by the well-established pathological processes such as immune system dysfunction and BBB disruption. Levels of innate immune cells are altered in the CSF and the BBB disruption facilitates infiltration of proteins and immune cells which exacerbates the inflammatory and demyelinating processes [50,51]. By identifying routine blood markers, AI models can classify certain individuals at heightened risk of MS [52]. Hybrid approaches that combine ML predictions with human expertise offer an innovative solution to the limitations of standalone systems. Studies involving medical students as evaluators have shown that human predictions improve significantly when combined with algorithmic outputs such as predictions from RF model [53]. These results suggest that human intuition and algorithmic classification can complement each other to enhance the reliability of MS progression forecasts [53].

Current applications of longitudinal ML methods for monitoring treatment response remain limited due to several challenges. First, ML models must be optimized in cross-sectional settings before extending their application to longitudinal data [54,55]. Second, AI algorithms require large-scale datasets comprising thousands of subjects, which are difficult to acquire [54]. Third, the emergence of personalized DMT for MS requires precise and reliable tools to assess motor and cognitive disability progression, which ML may contribute to [56].

AI and ML are revolutionizing the prognosis of MS by providing advanced tools that overcome the limitations of conventional approaches. A combination of algorithmic predictions and clinical expertise presents a robust framework for achieving greater accuracy and personalization in patient care. These innovations have the potential to enhance clinical outcomes, refine treatment strategies, and transform the landscape of medical decision-making in MS. AI in MS faces significant challenges, particularly the lack of large, diverse datasets available to train robust models capable of addressing disease variability [57,58]. Open science initiatives and adherence to FAIR principles (Findable, Accessible, Interoperable, Reusable) are critical for fostering collaboration and ensuring broader

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applicability [59]. A recent study by Placido and colleagues utilised the application of AI to predict the risk of pancreatic cancer in large, longitudinal datasets containing 6 million patient records in Denmark and 3 million patient records in the United States [60]. Using a ML model trained on comprehensive electronic health records (EHRs), 1,000 highest-risk patients in a hypothetical population of 1 million were identified, predicting that approximately 320 would develop pancreatic cancer within a 12-month interval [60]. The model also identified high-risk individuals who might not have been flagged by traditional clinical practices, enabling earlier surveillance [60]. While some progress has been made for MS, the availability of large public datasets remains limited [61].

In addition to conventional MRI features, ML models applied to radiomics have garnered interest, particularly in differentiating MS from other neurological disorders with similar radiological features [62,63]. A radiomics-based model was designed to differentiate RRMS from neuropsychiatric systemic lupus erythematosus (NPSLE) using MRI. Radiomics extracts high-dimensional imaging features, including those overlooked by radiologists, to capture subtle differences between diseases [64]. RRMS and NPSLE share features like white matter hyperintensities, radiomics analysis highlighted distinguishing characteristics in lesion morphology, intensity, and texture [65–67]. ML algorithms enhanced the model's accuracy, achieving robust performance with minimal misclassifications [64]. This multi-lesion merging strategy outperformed single-lesion approaches and radiologists, making it a valuable tool for improving differential diagnosis and preventing misclassification [64].

Furthermore, the incorporation of statistical modelling such as Markov model to current AI applications allows prediction of short-term disability progression in MS [68]. In conventional survival models, patients are excluded if they do not reach the disability threshold within the study duration, which limits disease progression data [69]. To overcome these limitations, the Markov model uses the EDSS score to focus on the transitions between distinct states of disability, ensuring all clinical information, including transient changes in disability, is incorporated into the analysis [68]. By analysing sequential EDSS scores with clinical and imaging data, the model can generate a potential progression pathway for individuals [68,70,71]. This allows clinicians and researchers to compare outcomes across different patient profiles and better tailor interventions to individual needs.

4. AI-Assisted Drug Discovery

When it comes to the implementation of AI techniques in MS drug discovery, most methods haven't been widely realised. Drug development is costly, as the development of a new FDA-approved drug can cost upwards of 802 million dollars [72] and is also restrained by the "one gene, one drug, one disease" hypothesis. The frequent failure of randomised control trials, multiple drug-target interactions, unintended side-effects and off-target toxicities also cloud the smooth development of new therapies [72]. AI techniques such as deep-learning and machine-learning provide a solution to this through drug repurposing and re-organisation of existing data on drugs and their targets. Other techniques more geared towards prediction have been employed in other diseases which has laid the groundwork for its potential application in MS drug discovery [73,74].

DeepDTnet was developed as a deep learning method for identifying new targets and for repurposing existing therapies [72]. It was successfully applied to MS drug discovery, validating topotecan as a new inhibitor of ROR-γt, a hormone receptor that regulates inflammation in the pathogenesis of MS, in a ligand-dependent manner. To validate this interaction, it used a heterogeneous drug-gene-disease network composed of 15 chemical, genomic, phenotypic and cellular network profiles. The network was trained on 732 existing U.S. FDA-approved, small-molecule drugs. Topotecan also had a therapeutic effect on mice in in-vivo experiments. The model was particularly viable as the low dimensionality of the t-SNE vectors created provided information on all drug targets, without erroneous exclusions. It also was able to use positive-unlabelled matrix completion to exclude negative sample input, when two drugs shared a target. The model covered four dominant target families in MS drug discovery: GPCRs, kinases, NRs and ICs [72].

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Another machine-learning pathway, justified with Leave-One-Out-Cross Validation (LOOCV) was similarly employed to perform drug repositioning and to understand the defective pathways that underpin MS [75]. Two publicly available microarray datasets were acquired from naïve $CD4^{+}$T cells, using 54, 675 probes and 113 samples from healthy and MS samples. A second, independent microarray data set was used for validation purposes, comprised of 20 samples and similarly derived from T cells. For the second data set, MS samples were taken from relapsed patients. From this, an expanded list of predictive genes was generated to reflect biological pathways involved in the pathology of MS. Posterior gene discriminatory power, paired with LOOCV and a distance-based classifier was used to identify a smaller subset of gene signatures with predictive accuracy, and to remove redundancies caused by study's under-determined phenotype prediction problem. This subset was tested against the independent dataset to confirm druggable targets. Viral infections and processes such as Th17 cell differentiation and CD28 co-stimulation were considered relevant in the progression of MS [75]. This information led to the discovery of new therapeutic targets associated with these processes, such as Trichostatin A and other histone deacetylase (HDAC) inhibitors.

In addition to the discovery-based applications, AI can assist in the testing the broader effects of new therapies. A network model of the genes that underpin T-cell activation in healthy patients compared to MS patients was developed. The network model used data obtained through the assessment of gene expression levels from 20 genes using a quantitative real-time PCR. The analysis involved a cohort of 104 subjects, composed MS patients and healthy controls. The model combines this gene expression data, results from PBMC stimulation studies, Jagged-1 and IFN-β stimulation assays to uncover how certain molecular interactions contribute to T-cell activation in MS. A MS mouse model was also used to validate Jagged-1 receptors as therapeutic targets, which reduce inflammation by influencing T-cell differentiation. 13 new biologically significant, and targetable links, including Jagged-1, were identified in their network [76].

Additional recent literature outlines other AI techniques and models which may be appropriate for future application in MS drug discovery. For instance, a novel Bayesian formulation combined dimensionality reduction, matrix factorisation and binary classification [75]. The model was built by encoding the chemical similarity between drug compounds and genomic similarity between target proteins. A variational approximation was applied to allow for efficient approximation of the complex structure of these drug-target relationships. The joint Bayesian formulation was used to project drugs and targets into a subspace and then chemoinformatic and bioinformatic techniques were employed to find similarities, inferring new drug-target interactions [73], for further testing in-vitro or in-vivo. Drug-target interactions have also been explored under the bipartite model concept, "NetLapRLS" [74]. In an effort to analyse both well-known, labelled information and unidentified yet potentially useful information in the system, a semi-supervised learning model was used, including heterogeneous publicly available biological datasets. This included a chemical structure similarity matrix and a genomic similarity matrix which were enhanced by a set of known drug-protein interactions. This study was able to predict certain drug-target interactions involving enzymes, ion channels, GPCRs, and nuclear receptors [74]. The team was also able to verify some of these more strongly predicted interactions using existing KEGG databases to prove the efficacy of the method.

Other examples include a more specific analysis of the bioactivity and structure of the potential molecular drug candidates. Chemical ranking methods have also been an object of investigation, as a means to comb through extensive, existing molecular databases for viable candidates for pharmaceutical application- a task that is difficult due to the high volume of data [77]. Computational docking has also been surveyed for its potential in evaluating drug candidates [78]. It involves predicting the best orientation and conformation of a molecule, and possible drug candidate, when attached to a protein of interest. A list of binding poses is assessed and then given a rank using a scoring function. The result is a list of ranked, potential ligands in order of stability which allows for the algorithm's high throughput production of feasible drug candidates.

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Many ML based techniques are currently being examined, in MS and in other diseases. Most involve the repurposing of existing drugs, the evaluation of drug efficacy, analysis of drug-protein interactions, and the optimisation of the bioactivity of molecules based on, for instance, their structure. It seems clear that there is strong potential for the optimisation of these techniques further to suit the unique pathogenic profile of MS.

5. AI-Assisted Personalized Medicine Approach to MS Care

Disease course and response to DMT can vary significantly, meaning the management of each person's MS must be adaptive and tailored to individual needs. This approach is referred to as personalised medicine where an individual's genetics, environment and lifestyle are incorporated in the management of their MS [79]. More recently a role for AI in personalised medicine for MS has emerged including using AI models to process and analyse large patient specific datasets including genetic profiles, biomarkers and clinical history to tailor treatment plans. AI-assisted analyses of these data sets could be used to develop digital patient pathways to inform clinical decision-making. There is also a role for AI in strengthening knowledge about MS and facilitating accessible communication between clinicians and PwMS to improve treatment adherence and overall health outcomes.

The development of AI assisted digital patient pathways could help support personalised treatment decision making. Large language models (LLM) could be used to process and analyse large datasets such as patient records, and treatment guidelines could aid in selecting DMT that are likely to be the most effective [79]. An extensive integrative framework for the design of a digital patient pathway for MS has been described [80]. Few studies have put into practise such systems likely due to concerns about privacy and the ethical implications of collecting and storing sensitive health information are significant. A digital twin is a virtual copy of a real patient and ML algorithms provided with ongoing data could suggest a treatment regime that will give the digital twin the best health outcome [81]. A recent study used clinical information to create a digital twin for MS patients and four types of ML models were trained to predict their disability status. The most accurate model was the Gradient Boosted classifier that was able to predict the transition of patients to moderate disability within 0-12 months. Analysis of these data could inform timely decision making around clinical interventions [81]. The future for digital twins in MS management involves long-term evaluation of the performance of such ML models. It has been suggested that multi-omics could be used to identify disease biomarkers in a large population and potentially reveal new therapeutic targets for personalised treatment [81].

Personalised medicine for MS involves improving the prediction of treatment response using available clinical data, a process that could be more accurate using AI. Additionally, there are very few biomarkers that can predict an individual's response to various DMT. In the present study deep learning models, that were a form of neural network, were trained to estimate an individual's treatment effect on disability progression [82]. Clinical information including demographics, EDSS scores and MRI lesion and volumetric measures were used. The models compared disability progression, using EDSS scores, for a patient under treatment or placebo to estimate an individual treatment effect. The model was able to identify and rank treatment effect among people with primary progressive MS receiving anti-CD20 antibody treatment. Similarly, the model could identify a subgroup of people more likely to respond to laquinimod, a medication with broad effects on leukocytes whose treatment effect was considered insufficient for drug approval [82]. This approach could be used to predict how specific treatments will impact an individual's disease progression. In the case of new medications for MS like laquinimod, results could inform selection criteria to increase the efficiency of clinical trials for drug development and approval. The study was limited to predicting treatment effect over two to four years where long-term observational data could identify those who may benefit from longer exposure to treatment.

Patient adherence can greatly influence the success of treatment meaning effective communication between clinicians and PwMS and their caregivers is crucial. AI, specifically LLM, could be used to translate medical terminology into more accessible language and communicate

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crucial information about treatments to PwMS [83]. In addition, LLM could be used to tailor educational materials to the knowledge background of each person and provide tailored responses when professionals are not available. In a cohort of PwMS, responses to frequently asked questions provided by an AI chatbot, Chat-GPT, were perceived to be more empathetic than responses from neurologists [84]. However, those who received higher education were less likely to prefer Chat-GPT responses emphasising the importance of tailored communication that addresses the needs of each PwMS. AI could also facilitate effective communication between health care professionals involved in MS management via the translation of clinical data. Ophthalmology notes translated by Open AI ChatGPT-4.0 were considered more comprehensive and useful than original notes [85]. This highlights the potential use for AI in tailoring responses to individual characteristics to aid in MS care, although the implementation of these responses should consider human involvement. AI models could be used to complement clinicians in delivery of education to PwMS however improved accuracy and validation of such models is required. AI models are promising in the field of personalised MS management but require further validation in the context of MS care and education.

6. AI-Assisted Fundamental Research Using Single-Cell Data

The use of AI for single-cell data analysis in MS research offers several advantages, namely increasing the efficiency and standardisation of analysing the vast amounts of data generated by single-cell technologies. Furthermore, the recent appreciation of MS as a disease driven by a patient's immune signature and how this may facilitate precision medicine in MS necessitates efforts to optimise single-cell data analysis by applying ML methods [86]. Common single-cell technologies to study MS include flow cytometry, mass cytometry and single-cell RNA sequencing (scRNA-seq).

The use of AI to perform automated analysis of flow cytometry data is becoming increasingly important as the number of fluorescent parameters used in spectral flow cytometry panels reaches 40 features [87]. Current methods often involve a combination of both manual gating analysis and unsupervised dimensionality reduction and clustering to study cell populations in PwMS. Garcia and colleagues analysed spectral flow cytometry data from 42 RRMS patients before and after ocrelizumab treatment by first manually gating the major T and B cell populations. They subsequently performed unsupervised dimensionality reduction via t-stochastic neighbour embedding (t-SNE) and clustering via the clustering algorithm FlowSOM [88] to identify distinct T cell clusters which they were able to relate to disease clinical activity [89]. Similarly, Waede and colleagues obtained spectral flow cytometry data from 23 RRMS patients and 10 healthy controls [90]. They first performed unsupervised analysis by means of UMAP [91] and both clustering algorithms FlowSOM and X-shift [92] to distinguish major immune cell populations and then manually gated the clusters of interest to quantify their relative proportions within the entire data set. In a landmark study that aimed to define 3 distinct peripheral blood immune signatures of MS, Gross and colleagues used both manual gating and unsupervised dimensionality reduction and clustering via PhenoGraph [93]. They reasoned that the former allowed investigation of small well-defined immune cell subsets whilst the latter enabled identification of complex phenotypes, that is, marker expression of differentiation, activation and maturation for each immune cell [86]. Ultimately, 149 and 235 cellular parameters were identified through manual gating and unsupervised analysis respectively and further unsupervised cluster analysis could characterise 3 distinct immunological subgroups in a cohort of 309 PwMS.

In the field of mass cytometry, Diebold and colleagues adapted CellCnn, a CNN based ML algorithm to identify key immune cell subsets that were most relevant to the therapeutic effects of dimethyl fumarate (DMF) treatment [94]. For the input, mass cytometry data from 31 DMF-treated patients were used with the output being either 'responder' or 'non-responder' depending on the presence or absence of evidence of clinical or radiological activity. Subsequent model training optimised weights to match the training data set phenotype and the trained filter weights represented the molecular profiles of immune cell subsets. One subset of effector memory CD4+ T cells was identified as being most strongly associated with treatment response with a predictive accuracy of

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79.14% (AUC = 0.85) and this finding was confirmed by spectral flow cytometry and automated analysis in a separate cohort (AUC = 0.84) [94].

For the analysis of scRNA-seq data, machine-learning based classifiers can be used to identify different cell populations in datasets as opposed to traditional methods of unsupervised clustering followed by manual inspection of cell populations for identification [95]. Esaulova and colleagues employed a neural network-based classifier with an input of gene counts obtained from published results using brain tissue microglia and an output of microglial cluster assignment [96,97]. They applied this classifier to CSF cells obtained from 2 RRMS patients and 1 patient with anti-MOG disorder and were able to identify a myeloid cell population as a pre-defined microglial cluster [96]. To avoid issues which may arise from using reference atlases based on different biological sources, Ostkamp and colleagues created another neural network-based tool which enabled automated immune cell annotation of scRNA-seq datasets using CSF and found good correlation between their tool's computed values and Seurat computed values, ranging from 0.843 to 0.964 [98].

There are more advanced techniques of AI-assisted single-cell analysis currently being used in other disease areas that could be applied to MS. Barone and colleagues developed T-REX, an unsupervised ML algorithm that combines UMAP and KNN clustering algorithms and could identify key immune cell subsets representing <0.1% of the population in both spectral flow cytometry and mass cytometry samples [99]. By immunophenotyping cells which localised to regions of significant change in samples obtained over the course of rhinovirus infection, they were able to identify and quantify a small but critical population of virus-specific CD4+ T cells. T-REX also outperformed PhenoGraph and FlowSOM in successfully identifying rare cells undergoing significant change in paired spectral flow cytometry samples [99]. Similarly, T-REX could be applied to MS cytometry datasets and used to monitor how individual patients respond to treatment or change during disease progression, potentially revealing key cell subsets not yet identified due to their low proportions in peripheral blood. Furthermore, the previously mentioned CellCnn algorithm for the analysis of mass cytometry samples can also be applied to flow cytometry and scRNA-seq data, increasing the efficiency of analysing highly multiparametric single-cell datasets obtained from large patient cohorts [100]. In the field of oncology, Fiser and colleagues applied hierarchical clustering analysis (HCA) to flow cytometry samples from 123 patients with acute lymphoblastic leukaemia (ALL) to characterise the leukemic cell population (i.e. minimal residual disease) and subsequently trained a SVM classifier to automatically detect the same population in follow-up samples from the same patient [101]. Similarly, using spectral flow cytometry, our lab previously found that following cladribine treatment, regenerating effector memory $CD4^+$ T cell and central memory $CD8^+$ T cell subsets differed in both functional properties and immunophenotype in RRMS patients [102]. It would be of interest to train such a classifier to identify and quantify important regenerating cell subsets and whether this may inform a patient's response to therapy in a highly personalised fashion.

7. Discussion

Phenomenal progression has been made to incorporate AI in MS research, diagnosis, monitoring and treatment with studies showing improved accuracy, efficiency, accessibility and enhanced knowledge when using ML. Indeed, AI can scrutinise data faster and more thoroughly than humans as studies have shown that AI program ChatGPT was faster to diagnose MS patients than clinicians even though both had similar accuracy scores [103]. Interestingly, another study revealed that ChatGPT displayed greater empathy scores than clinicians by offering more support [84]. The results of these papers raise the question of whether AI are better doctors than humans, especially when patient care and comfort is required. Whether patients would knowingly accept AI over clinicians is unknown. However rather than replacing clinicians with AI, more research is required to understand how AI can be utilised to assist clinicians and PwMS. Because realistically when patients interact face-to-face with clinicians, patient disease and background is better recognized while AI relies on electronic data to understand patient disease prognosis [104].

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Government bodies and private companies are now fuelling money into commercialising AI models to improve health care access for patients. Nevertheless, ethical concerns such as population biases in training data, reduced human accountability, and potential monopolization of AI tools complicate AI integration in patient health care services [59]. Ethical and regulatory barriers complicate the creation and sharing of standardized datasets integrating MRI, biomarkers, and clinical data, which are essential for validating models, especially for neurodegeneration and progression [105,106]. Addressing these issues requires equitable data practices and multidisciplinary collaboration. Indeed, the World Health Organisation has recognised the need for ethics and governance regarding large multi-modal models [107].

Another important consideration for the future of AI in MS is that patient symptom presentations are changing. ML models have been trained to identify the 2017 McDonald diagnostic criteria however patients have identified atypical symptoms that don't fit this, thus AI models must be adapted to these changing factors [108]. Furthermore, AI model performance is highly dependent on training data which can result in biases and overfitting, where the model performs poorly on unseen data. Hence, future directions should mitigate this by cross-validation and utilizing larger diverse datasets.

8. Conclusion

AI is increasingly becoming popular for its easy accessibility and ability to simplify tasks that require extensive knowledge and time. In this review we explored how AI has impacted PwMS whereby AI and ML tools have aided in diagnosing and monitoring MS patient prognosis using clinical data such as MRI, EDSS, OCT and MRS essentially outperforming clinicians. Furthermore, AI-assisted approaches provide information about potential risks for MS and predict whether DMT's can improve patient outcomes. Using AI for drug discovery has shown potential to evaluate drug efficacy and identify if existing drugs can be repurposed for MS, thus accelerating its progress into clinical trials. Furthermore, the effect of AI on personalized treatment adapts specific treatments for patients based on individual characteristics which could improve responses to treatments. Finally, the capability for AI to analyse large single-cell datasets would also aid clinicians and researchers to finding novel therapeutics and targets for disease. So far, our research indicates promising results for AI integration in MS healthcare, however more studies are required to validate these models and ensure patients feel comfortable with AI-assisted support. Relatively soon the diagnosis, monitoring and treatment landscape for PwMS will change with the integration of AI.

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