

AI in Radiology: Where are we today in Multiple Sclerosis Imaging?

KI in der Radiologie: Wo stehen wir in der MS-Bildgebung?

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ABSTRACT

Background MR imaging is an essential component in managing patients with Multiple sclerosis (MS). This holds true for the initial diagnosis as well as for assessing the clinical course of MS. In recent years, a growing number of computer tools were developed to analyze imaging data in MS. This review gives an overview of the most important applications with special emphasis on artificial intelligence (AI).

Methods Relevant studies were identified through a literature search in recognized databases, and through parsing the references in studies found this way. Literature published as of November 2019 was included with a special focus on recent studies from 2018 and 2019.

Results There are a number of studies which focus on optimizing lesion visualization and lesion segmentation. Some of these studies accomplished these tasks with high accuracy, enabling a reproducible quantitative analysis of lesion loads. Some studies took a radiomics approach and aimed at predicting clinical endpoints such as the conversion from a

clinically isolated syndrome to definite MS. Moreover, recent studies investigated synthetic imaging, i. e. imaging data that is not measured during an MR scan but generated by a computer algorithm to optimize the contrast between MS lesions and brain parenchyma.

Conclusion Computer-based image analysis and AI are hot topics in imaging MS. Some applications are ready for use in clinical routine. A major challenge for the future is to improve prediction of expected disease courses and thereby helping to find optimal treatment decisions on an individual level. With technical improvements, more questions arise about the integration of new tools into the radiological workflow.

Key Points:

- Computer algorithms have a growing impact on analyzing MR imaging in MS.
- Artificial intelligence is more and more commonly employed in such computer tools.
- Applications include lesion segmentation, prediction of clinical parameters and image synthesizing.

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ZUSAMMENFASSUNG

Hintergrund MRT-Untersuchungen sind ein zentraler Baustein in der Diagnostik bei Multipler Sklerose (MS). Dies gilt sowohl für das Erstereignis wie auch für die Verlaufsbeurteilung. In den vergangenen Jahren wurden zunehmend Algorithmen zur Analyse von MRT-Daten bei MS entwickelt. Diese Übersichtsarbeit stellt die wesentlichen Anwendungsfelder unter besonderer Berücksichtigung von Algorithmen aus dem Bereich der Künstlichen Intelligenz (KI) vor.

Methoden Relevante Studien wurden durch eine Literatursuche in anerkannten Datenbanken sowie durch Querverweise in so gefundenen Studien identifiziert. Dabei wurde Literatur berücksichtigt, die bis November 2019 erschienen war, ein besonderes Augenmerk lag auf kürzlich erschienenen Studien aus den Jahren 2018 und 2019.

Ergebnisse Viele Studien haben Lösungen zur optimierten Läsionsvisualisierung oder der Segmentierung von Läsionen entwickelt. Hier liegen bereits Werkzeuge vor, die diese Aufgaben mit hoher Genauigkeit bewerkstelligen können und damit mittelbar eine reproduzierbare, quantitative Auswertung der Läsionslast ermöglichen. Einige Arbeiten gingen

einem Radiomics-Ansatz nach und untersuchten die Vorhersage klinischer Endpunkte, z. B. die Konversion von einem klinisch isolierten Syndrom zu definitiver MS. Zuletzt liegen erste Arbeiten vor, die synthetisch erstellte Bildgebung untersuchen, also solche Bilder, die basierend auf tatsächlich gemessenen MRT-Sequenzen von Maschinenlernalgorithmen generiert werden und die Kontraste zwischen Läsionen und normalem Hirnparenchym optimieren.

Schlussfolgerung Computerunterstützte Bildanalyse und KI sind hochaktuelle Themen in der MS-Bildgebung. Einzelne

Anwendungen sind dabei bereits jetzt prinzipiell in der klinischen Routine einsetzbar. Eine wesentliche Herausforderung für die Zukunft besteht vor allem darin, bessere Prädiktionen klinischer Verläufe und entsprechende Hilfestellungen in der Findung einer optimalen Therapie auf patientenindividueller Ebene bereitzustellen. Außerdem rücken durch die Erfolge auf technologischer Ebene zunehmend Fragen über die Integration in klinisch-radiologische Abläufe in den Vordergrund.

Introduction

Multiple sclerosis (MS) is a neurological disease characterized by autoimmune-mediated episodes in many patients, particularly in the early stages of the disease [1]. MRI examinations reveal corresponding parenchyma lesions of the central nervous system. On the one hand, this means that imaging plays an important role in the diagnosis according to the current McDonald criteria [2], and on the other hand, imaging of inflammatory lesions allows the progression of the disease activity to be observed. In addition to lesion diagnosis, other MRI parameters such as atrophy rates [3] are increasingly used to characterize the course of the disease. Accordingly, MRI examinations have been established as an important tool for monitoring the effectiveness of immunomodulatory therapy. Imaging evidence of disease activity opens up the possibility of a change in therapy even before clinically detectable deterioration [4].

The evaluation of MRI imaging in MS is therefore a very common task in the (neuro)radiological routine. The questions relevant for monitoring the course of the disease are clearly defined (How has the lesion burden developed? Are there signs of increasing atrophy?), and codified accordingly in the NEDA criteria (No Evidence of Disease Activity) [3]. As a result of this standardization as well as the high quantity of MRI data sets collected, MS has become one of the pathologies for which computer-assisted evaluation of imaging is increasingly important. With the growing popularity of deep learning [5] and a generally expanded interest in artificial intelligence (AI), this development has further accelerated.

The aim of this study is to provide an overview of recently published examples of the application of computer algorithms in the context of MS imaging. The main focus is on studies from the field of AI [6].

Technical Background

Conventional CAD (computer-aided diagnosis) applications employ an algorithm programmed explicitly with expert knowledge in order to solve a specific problem. In contrast, machine learning provides a rough architecture of the algorithm, but the exact design is “learned” from it. This requires training data which are used to gradually configure the parameters of the algorithm. With respect to this review article, three types of machine learn-

ing algorithms are of particular importance: support-vector machines, random forest models and artificial neural networks.

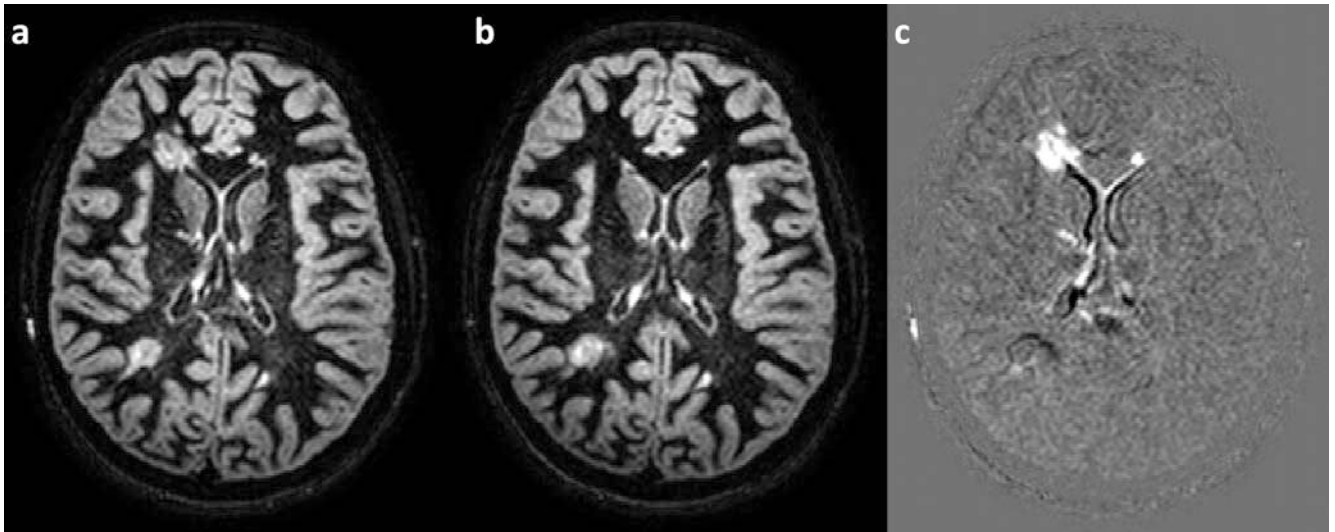
Support-vector machines (SVM) are designed for classification problems, but can also be used for regression tasks [7]. For this purpose, the training data are interpreted as points in a data space. In the simplest case, this would be one plane, i. e. an x-y diagram. In this example, a straight line is then calculated that separates these data points according to their class. In general, where the data is available as a complex vector, a higher-dimensional analog of such a separation line is calculated accordingly.

Random forest models [8] use a classification algorithm to create a group of uncorrelated decision trees, the convergence of which predicts the result. Using this architecture, such algorithms are likewise tailored to classification problems, but can also solve regression problems.

Artificial neural networks are multi-layered networks of artificial neurons which only remotely resemble their biological models. Ultimately, they only contain an instruction on how to generate an output from several inputs. The parameters within a neural network to be adapted in the learning process are the connection strengths among the individual neurons. The concept “deep learning”, which is frequently used, refers to artificial neural networks that go beyond a few individual layers; however, this concept is not strictly defined [9]. An essential difference between SVM and random-forest models on the one hand and artificial neural networks on the other is that in the former models, the features (i. e. image properties translated into quantitative values) supporting the algorithms are determined in advance. Artificial neural networks, however, are not limited to predefined features, but “learn” relevant image properties independently in the training process.

Literature Search

The studies considered in this review were identified by a literature search using PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) which included articles which had been published as of November 30, 2019. Special attention was paid to recent studies from the years 2018 and 2019. The search terms used included “multiple sclerosis” and “MRI” and “neuroimaging”, respectively, in connection with “artificial intelligence”, “machine learning” and “neural networks”. In addition, the bibliographies of the articles thus were searched for further matching titles.



► **Fig. 1** Example of a DIR-based subtraction map. **a** DIR-image of the follow-up MRI exam. **b** DIR-image of the baseline exam. **c**: Calculated subtraction image based on the two exams. Note that new lesions (e. g. periventricular at the anterior horns) appear as bright structures.

Literature Search Results: Application of AI with respect to Multiple Sclerosis

Lesion Detection and Segmentation

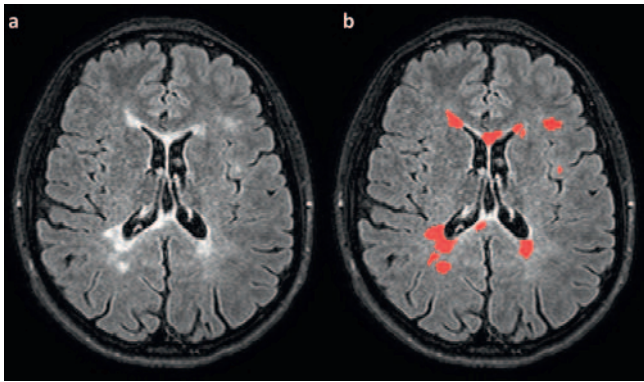
One of the radiological core tasks in the evaluation of MS imaging, the manual analysis of lesion data for new or enlarged lesions, is arduous and prone to errors. In contrast, automatic segmentation offers the possibility of using objective parameters such as directly detecting lesion volumes. Therefore, many studies are concerned with either better visualization or even direct segmentation of these lesions. A strategy for comparing two studies is the generation of subtraction maps [10, 11], a process in which two MRI sequences are co-registered and then the intensity values are subtracted voxel by voxel. Applied to the comparison of a follow-up MRI with a reference examination, maps can be generated that directly visualize newly occurring lesions (► **Fig. 1**). This technique can significantly increase the sensitivity in the detection of new lesions while reducing the time needed to compare the two examinations by a factor of 3 [11]. Subtraction maps, as an example of conventional tools, demonstrate that even relatively simple computer algorithms can significantly support routine radiological work. In projects based directly on this technology, it has been shown that the administration of contrast can no longer contribute to a further increase in sensitivity in the detection of newly occurring lesions [12]. In addition, subtraction maps were used to show the equivalence of an innovative accelerated double inversion recovery (DIR) sequence with a conventionally-acquired DIR sequence [13].

For many years lesion segmentation has been studied using various techniques; a compilation of earlier publications can be found, for example, in Schmidt et al. [14]. This paper also presented a proprietary tool for segmentation of MS lesions, which as well as studies presented here are based on conventional programming methods. In a recent review article, Danelakis et al. specifically address the topic of lesion segmentation and also consider AI

studies [15]. An example of such a recent study is by Li et al. [16] which is based on a so-called U-Net [17]. This is a particular type of deep learning network that has proven to be particularly powerful for segmentation tasks. The paper by Li et al. concerns the segmentation of white matter hyperintensity associated with cerebral microangiopathy. Since segmentation of microangiopathic lesions and MS lesions are very similar tasks, this algorithm can also be applied to MRI examinations with adapted MS training data. ► **Fig. 2** shows an example of segmentation obtained in this way. A recent study by Gabr et al. [18] likewise used a U-Net for segmenting MS data sets. The special feature of this paper is that it is based on a very large collective of more than 1000 MRI examinations conducted in the course of a multi-center phase 3 study. In addition, this study also presents the segmentation of brain volume by means of a U-Net which also allows the automated determination of atrophy rates.

Integration of Clinical Data

The procedures described so far address questions inherent to imaging. In contrast, many studies also pursue the goal of using machine learning methods to capture information in image data that is not directly accessible to radiological-visual evaluation, thus enabling new issues to be addressed [19]. MRI imaging can help to make a reliable diagnosis at a very early stage (depending on the constellation present at the first manifestation) [2]. However, there is often a situation where a clinical event is considered a possible first episode of MS, but no definitive diagnosis can yet be made. Such a constellation is called a clinically isolated syndrome (CIS) [20]. Frequently a CIS develops into a positive case of MS [21]. Patients with a high risk of conversion should at least be closely monitored and, if necessary, receive immunomodulatory treatment at a very early stage [22, 23]. Therefore, prediction of individual conversion risk is clinically highly relevant. Several studies have investigated whether AI procedures can now be used to predict subsequent conversion or non-conversion in CIS



► **Fig. 2** Example of an automatically generated lesion segmentation. **a** FLAIR sequence from an MRI exam in a 27 year old patient with known relapsing-remitting MS. **b** The same image together with a lesion segmentation, shown as red overlay. This segmentation was generated by a deep learning network developed by Li et al. [17].

patients based on initial imaging. Zhang et al. [24] used a random forest model based on brightness and shape features of the lesions in the initial MRI examination. Only shape properties of the lesions contributed to improved prediction, especially those that directly or indirectly describe the ovality of the lesions. However, features based on the intensity distribution of the lesions did not improve the prediction accuracy. Berndfeldt et al. [25] investigated the same question using an SVM method, including lesion geometry, clinical and demographic data, as well as gray matter volume. This study also demonstrated a significant contribution of lesion geometry to classification accuracy. These results reflect the fact that MS lesions often appear ovoid (“Dawson finger”). Thus, the decision making of these tools correlates with already known lesion properties, which makes the behavior of the algorithms transparently reasonable.

Other issues already addressed for radiomics work were the differentiation of MS and diseases of the neuromyelitis optica spectrum [28–30] and the differentiation of MS patients from healthy control subjects. Studies based on deep learning also exist on the latter topic [31–33]. In this regard, Eitel et al. [34] also examined which characteristics the algorithm uses for classification and showed that in addition to typical lesions, areas that appear normal, such as the thalamus, can also contribute to a lesser extent to the algorithm’s decision. Likewise, in other studies such as by Weygandt et al. [35] and Yoo et al. [31] healthy-appearing areas contributed to the predictive value of the algorithm. Hackmack et al., in an earlier study based on an SVM procedure [36], investigated the benefits of very complex and thus abstract features obtained by so-called wavelet transformations. These results impressively demonstrate that AI can make image data usable beyond the information that can be interpreted visually and radiologically. In another study, Hackmack et al. were able to show a correlation between the spatial information of MRI scans and symptom manifestation in MS patients [37]. The visual radiological evaluation of MS lesions, on the other hand, faces the so-called “clinical-radiological paradox”, namely the experience

that lesion load and distribution, as recorded conventionally, does not allow any statement on disease severity.

Synthetic Image Generation

A more recent application of artificial intelligence is the generation of synthetic sequences that are predicted by neural networks using existing imaging [38]. Finck et al. used such an approach to generate a double inversion recovery (DIR) sequence from a FLAIR (FLuid Attenuated Inversion Recovery), a T2-weighted and a T1-weighted sequence [39]. DIR sequences show a particularly high lesion-to-parenchyma contrast and display cortical lesions better than conventional sequences [40–42]. Disadvantages of the DIR sequence are a high technical effort and a certain susceptibility to artifacts, thus it has not found its way into routine MRI protocols, with the exception of a few centers. Synthetic generation from standard sequences could bypass these disadvantages and thus help DIR sequences to become more widespread. In the aforementioned study, the synthetic sequence was found to be slightly behind the real acquired DIR sequence, but to represent MS lesions significantly better than the (real acquired) FLAIR sequence. In a variant of the Turing test, neuroradiologists were not able to distinguish between a real acquired and a synthetic DIR sequence [38]. ► **Fig. 3** presents an example of a synthetic DIR sequence.

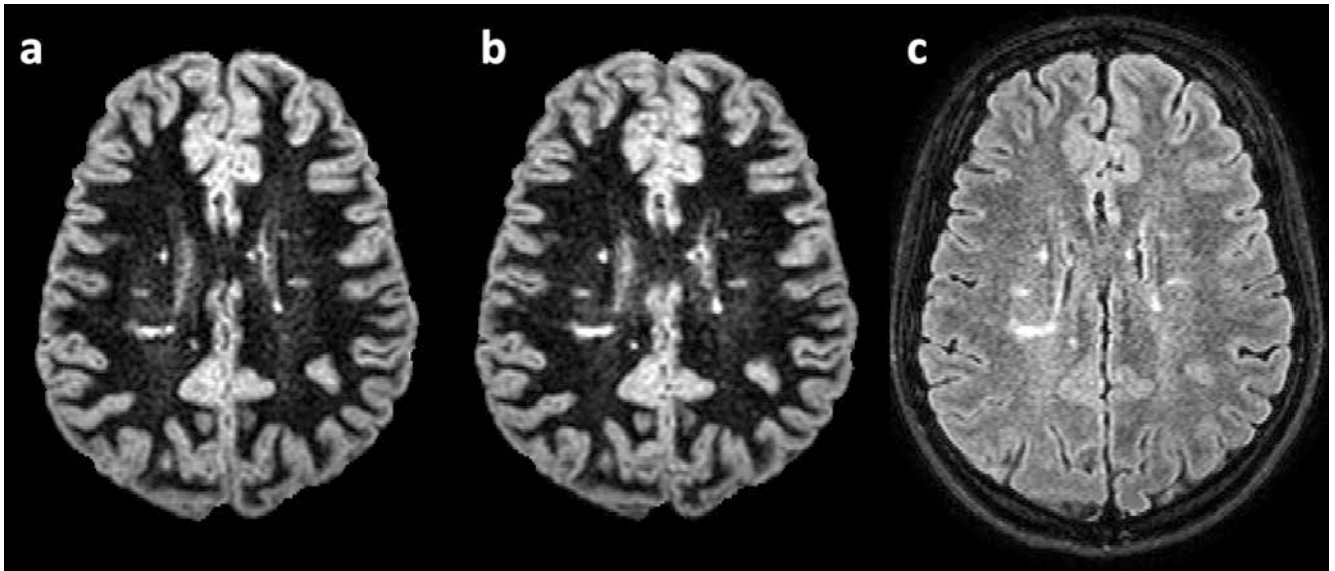
Discussion and Outlook

The use of AI in MS is supported by several factors: MS is a common disease and people with MS receive regular MRI scans. For this reason, large numbers of MRI examinations are carried out, especially at specialty centers. However, a sufficient number of data sets is essential for to ensure effective machine learning. It is therefore not surprising that although there are a large number of studies for lesion diagnostics, none are available for the detection of relatively rare therapeutic complications such as PML (progressive multifocal leukoencephalopathy).

The provision of a large data set can significantly influence the development of artificial intelligence. Particularly prominent in this regard is the Alzheimer’s Disease Neuroimaging Initiative (ADNI), the database of which supports numerous machine learning studies on degenerative diseases.

Of the above topics, lesion segmentation is the most intensively studied. The algorithms used here have matured considerably, and some are even CE-certified as commercial products or approved by the FDA. Thus, tools are available that in principle can now support routine radiological work. The results of these techniques can also be integrated into structured findings [43], so that a largely automated workflow for standardized analysis of MRI lesion load appears technically immediately accessible.

However, the prediction of clinical parameters is not yet as advanced. An important task for future computer algorithms would be the prediction of clinical progression of the disease. The above-mentioned studies on the prediction of conversion in CIS patients can be seen as a first step in this direction. The study by Hackmack et al. on better correlation of imaging and clinical manifestation



► **Fig. 3** Example of a synthetically generated DIR sequence. **a** Synthetically generated DIR image (based on acquired FLAIR-, T1- and T2-weighted sequences). **b** Corresponding DIR sequence acquired during the same exam. **c**: Corresponding FLAIR sequence.

shows a promising application potential made available by computer algorithms.

Starting therapy early is particularly important for MS [44, 45], therefore reliable early prediction of the expected course could influence therapy decisions. In view of an ever-increasing arsenal of available medications [46], it would also be particularly useful to know the extent machine learning can help to identify the most suitable therapy for individual patients. At the latest it seems increasingly unlikely that this task can be solved by algorithms solely based on imaging; instead, clinical data will increasingly have to be integrated into an algorithm as additional input parameters for such issues. When interpreting AI studies, it is particularly important that the quality of an algorithm depends largely on the learning cohort. Here clinical expertise is particularly necessary with regard to the quality of the labels. For example, several of the projects presented above still refer to the 2010 version of the McDonald criteria. However, if the updated version (2017) were to be used as a label, some patients previously diagnosed with CIS would already be considered definitively MS at baseline (especially due to the inclusion of CSF diagnostics). These algorithms can therefore not easily be used to predict according to the current McDonald criteria.

With the generation of DIR sequences, an example was presented of how synthetic imaging can be used to make efficient use of real acquired data. MRI protocols have some redundancy in the presentation of MS lesions in that lesions are usually presented in multiple sequences. Here it would be an important starting point to investigate what a “minimal” MRI protocol could look like, i. e. the smallest possible set of sequences from which other image contrasts could then be generated synthetically.

In recent years, the utility of contrast agents in MS imaging has been questioned with respect to maximizing the sensitivity of lesion detection [12, 47]. At the same time, discussion of intracranial gadolinium deposits [48] makes many patients increasingly

skeptical about the use of contrast media. There are already some studies that have investigated the distinction between contrast-enhancing and non-enhancing lesions using other MRI parameters (e. g. diffusion imaging) [49]. In this context, it appears to be a particularly interesting goal to synthesize a T1-weighted sequence after contrast administration based on native imaging. One such study was recently presented by Kleesiek et al. for gliomas [50].

In summary, many application examples of AI in the processing of imaging data can be identified with respect to MS. There are solutions for segmentation tasks that are already available in everyday radiology. In addition to technical features, the focus is increasingly on practical aspects, including primarily the integration of appropriate software into existing IT infrastructures and access to the required computing capacity. In addition, since only commercial products can achieve certification for use in routine clinical practice, the question of how such programs are funded will have a significant impact on their actual dissemination.

Conflict of Interest

The authors declare that they have no conflict of interest.

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