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Opportunities for Understanding MS Mechanisms and Progression With MRI Using Large-Scale Data Sharing and Artificial Intelligence

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Abstract

Multiple sclerosis (MS) patients have heterogeneous clinical presentations, symptoms and progression over time, making MS difficult to assess and comprehend in vivo. The combination of large-scale data-sharing and artificial intelligence creates new opportunities for monitoring and understanding MS using magnetic resonance imaging (MRI).

First, development of validated MS-specific image analysis methods can be boosted by verified reference, test and benchmark imaging data. Using detailed expert annotations, artificial intelligence algorithms can be trained on such MS-specific data. Second, understanding disease processes could be greatly advanced through shared data of large MS cohorts with clinical, demographic and treatment information. Relevant patterns in such data that may be imperceptible to a human observer could be detected through artificial intelligence techniques. This applies from image analysis (lesions, atrophy or functional network changes) to large multi-domain datasets (imaging, cognition, clinical disability, genetics, etc.).

After reviewing data-sharing and artificial intelligence, this paper highlights three areas that offer strong opportunities for making advances in the next few years: crowdsourcing, personal data protection, and organized analysis challenges. Difficulties as well as specific recommendations to overcome them are discussed, in order to best leverage data sharing and artificial intelligence to improve image analysis, imaging and the understanding of MS.

1 Introduction

Multiple sclerosis (MS), is highly heterogeneous across patients in terms of symptoms, sites of damage, degree of recovery, and development of the disease across time. This makes the disease more difficult to comprehend. Relevant patterns may be imperceptible to a human observer, but by analyzing large amounts of imaging data from MS patients with sophisticated artificial intelligence techniques, urgently required advances in understanding MS disease pathological heterogeneity may be made.

Furthermore, to tracking of disease progression in individual MS patients, MRI markers are needed. This could benefit from MS-specific image analysis methods, because existing generalized methods tend to exhibit poorer performance in cases with MS[1], as has been demonstrated quantitatively for segmentation of deep grey matter (GM) structures[2]. Large amounts of MS imaging data, with expert annotations as appropriate, can be used to train and validate more accurate measurement and analysis tools specifically for MS.

Against this background, we review the possibilities of data-sharing and artificial intelligence for improved applications of MRI to study MS, addressing both the need to understand MS disease processes and the need for MS-dedicated quantitative measurement and analysis techniques for MRI assessments. We first survey relevant existing efforts regarding data-sharing and artificial intelligence, and then highlight three areas of interest in bringing the field forward: crowd-sourcing, personal data protection, and organized analysis challenges (see Figure 1 for the methods used to create this manuscript). Specific recommendations aim to achieve the best outcomes for MS patients.

2 Data-sharing

2.1 Data-sharing in MS: Non-imaging

The multicenter collection of MS clinical data provides valuable information on disease prevalence, current treatment patterns and general distribution of patients' outcomes. Thus, clinical registries including data from several MS centers have been strongly promoted in the last decades. National and regional MS registries exist in most countries, especially in Europe[3] and North America[4]. Data collected by national initiatives have often been included in computerized platforms, such as the European Register for Multiple Sclerosis (EUReMS)[5] or the MSBase[6]. Collaborative research studies have used these data to define the value of

prognostic indicators in different patient populations[7], to investigate the influence of demographic and geographic factors on MS clinical course[8], and to evaluate the comparative efficacy of different drugs[9] (additional references in eAppendix 1 [https://doi.org/10.5061/dryad.2fqz612p9]).

2.2 Data-sharing in neuro-MRI: Non-MS

Data sharing in MRI is becoming increasingly prevalent, large-scale and open in the neuroimaging community. Table 1 lists several prominent examples, including Alzheimer's Disease Neuroimaging Initiative (ADNI), which in the neuroimaging field is a template for data acquisition and fostering of methodological developments. These datasets are associated with a range of access policies (from free, unrestricted downloads to collaboration-only agreements) and cover various sizes, demographics and pathologies. They provide access to large, diverse, groups of subjects including rare diseases and a wider range of disease stages (including prodromal cases) than is possible from single studies. In addition, the increasingly large numbers provide greater statistical power and the opportunity to apply state-of-the-art deep learning techniques. They also allow common standards to be applied in the evaluation of methodological tools, as pioneered by the MICCAI challenges (e67). As such they provide the community with fair and open comparisons of methods, a richer set of data on which to test hypotheses, and greater ability for assessing reliability and repeatability. There are also benefits for those involved in creating and managing such datasets, since the process of designing, piloting and pre-processing provides impetus for novel developments in acquisition and analysis, demonstrated by state-of-the-art methodologies developed within the Human Connectome Project. In addition, there are benefits in visibility, engagement, and publications. Challenges still exist (e.g., IT infrastructure, access policies, ethics policies, etc.) but currently many such datasets are already accessible, with a range of solutions to these problems, thus offering options for the creation of new datasets focusing on MS. The datasets listed also highlight that standardized MR acquisition protocols can harmonize data only to a certain extent. Therefore, alternative approaches such as synthetic MRI, should also be investigated (additional references in eAppendix 1).

2.3 Data-sharing of MRI in MS

MRI is one of the most important tools for diagnosing and monitoring MS[10]. However, MRI data collected by clinical MS registries usually includes just conventional measures and/or metadata regarding fulfilment of diagnostic criteria[5, 6]. Recent collaborations (e.g., the publicly funded German Competence Network Multiple Sclerosis (e68) or the privately funded MS PATHS[11]) promoted the use of relatively standard conventional MRI protocols (typical T1-weighted, proton density-weighted, and T2-weighted or FLAIR images), but did not include advanced MRI techniques (such as quantitative mapping techniques of tissue properties, tractography, spectroscopy, functional MRI, etc.). Table 2 lists MS Registries identified from public sources that collect MRI information.

As an example, one can take the Italian Neuroimaging Network Initiative (INNI) (e69)[12]. This has recently been established among four sites leading MRI research in MS in Italy, with the support of the Italian MS Society. INNI's major goal is to determine and validate novel MRI biomarkers, including biomarkers based on more advanced, non-conventional imaging techniques, to be utilized as predictors and/or outcomes in future MS studies. INNI aims also to standardize MRI procedures of acquisition and analysis in MS at a national level.

A large population of MS patients and healthy controls (more than 1,800 subjects and more than 3,000 MRI exams) has been collected in the INNI platform so far. Although MRI data had to meet some minimum requirements in order to be included[12], a full standardization of acquisition protocols was not requested from sites, at least in the first phase of the project.

The main challenges faced at the beginning of the INNI initiative were related to ethical approvals, to the creation of the online platform, to ensure proper handling of subjects' anonymity, and to define guidelines to regulate database access levels and their implementation as access procedures[12]. Conversely, most of the subsequent challenges are related to the quality assessment (QA) of the data collected, which will now be used for different research projects at the four promoting sites. Systematic QA (on subjects' positioning, image inhomogeneity, distortions and artefacts, and measurement of contrast-to-noise ratio) has been established to verify source data and ensure maintenance of high quality. QA results will be used to propose effective guidelines on acquisition protocols and scanning options, to improve harmonization of MRI data. Basic analysis (e.g., T2-hyperintense lesion segmentation, T1-hypointense lesion refilling, minimal pre-processing

on diffusion-weighted MRI and resting-state fMRI scans) that may be shared in the INNI platform to harmonize future projects is also being performed in a centralized manner.

2.4   Recommendations on MRI data-sharing in MS

Clearly define variables to be shared. This avoids ambiguity and heterogeneity at a later stage.

Set up proper QA and QC (quality control) procedures to ensure compliance with minimum standards. Preferably quantitative and automated, such procedures guarantee the integrity of the included data.

Implement clear policies and procedures on how access to data can be obtained.

Create a flexible data-sharing system, permitting a manifold use of collected data. By choosing maximally permissive data licenses (within legal and institutional boundaries), combined with clear data storage organization, database management and flexible access choices, data can be flexibly and easily selected, accessed and used for a variety of purposes.

3   Artificial intelligence

3.1   Artificial intelligence in medical image analysis beyond MS

Artificial intelligence can be roughly divided into "classical" machine learning techniques such as support vector machines, and (newer) deep learning techniques based on convolutional neural networks. Classical machine learning approaches typically make predictions using classifiers trained not directly on images, but on features extracted from images[13]. While this can be advantageous, it precludes the discovery of features not perceptible to or appreciated by the human observer. Deep learning, when applied to classification or segmentation of images[14], instead analyzes image data directly, without prior feature selection. This has given rise to excellent classifier performance in a range of medical imaging applications[13]. However, as shown for example by Ghafoorian and colleagues[15], at least given the current limitations regarding sizes of available datasets and networks, performance may be further improved by incorporating well-chosen features extracted from the images using domain knowledge and "classical" image analysis techniques. Specifically, in their work, they incorporate measures reflecting location in the brain to improve segmentation of age-related white matter hyperintensities[15].

3.2 Artificial intelligence in imaging of MS

Existing studies applying artificial intelligence in MS imaging can generally be divided into descriptive and predictive experiments. Descriptive studies use cross-sectional data sets in order to segment from MRI WM lesions[16] or specifically contrast-enhancing lesions[17], identify imaging patterns based on MS phenotype or clinical or cognitive disease severity[18], or perform an automated diagnosis using uni- or multi-modal information[19]. Predictive studies, on the other hand, detect patterns in baseline data that allow for predicting future disease outcome or severity by incorporating clinical follow-up information[20, 21]. The majority of studies to date used classic machine learning techniques such as Support Vector Machines or Random Forests, where features have to be defined and extracted from the data *a priori*, while more recent studies also use deep learning methods allowing automated detection of relevant features in the data. Deep learning has now been used not only to segment WM lesions[22-24] or their enhancing subset[17], but also to quantify lesion changes[25, 26], to detect the central vein sign[27], classify different lesion types based on diffusion basis spectrum imaging[28], to predict Gd-enhancement from other image types[29], to perform MRI-based diagnosis[30, 31], to segment and analyze non-lesion structures[32, 33], to analyze myelin water fraction[34] or quantitative susceptibility mapping data[35], to synthesize absent image types[36], to perform automatic QC[37], to improve image quality[38], or to correct intensity differences between scanners[39] (additional references in eAppendix 1).

3.3 Challenges of artificial intelligence in MS imaging

Although showing impressive performance, state-of-the-art deep learning methods (convolutional neural networks) rely solely on the use of local intensity patterns and contextual features to guide the image analysis process. Importantly, they lack high-level abstract thinking and have limited understanding of human anatomy and physiology. Learning from relatively small and noisy datasets, learning systems are commonly unable to extrapolate and handle uncertain situations. Furthermore, in precision medicine applications, fully automatic, robust and quick measurements are required for every single subject. Three important categories of current limitations of learning systems are:

1) Inputs: The main limitation of many machine learning models is the strong dependence on (good) training data. While human raters may intuitively extrapolate from a few examples to new cases that may be very different, a supervised (deep) learning model

has to be fed with sufficient examples to cover the whole range of heterogeneity in the population, disease and scanning parameters. Differences in imaging devices, acquisition parameters, tissue contrasts, artefacts, and *noise* patterns can degrade algorithm performance if not handled appropriately. To overcome between-scanner or between-acquisition image differences, many approaches for post-processing based data harmonization have been proposed, including traveling phantoms[40], which requires physical travel of objects or subjects[39], limiting scalability; data augmentation[41], which requires sufficiently accurate signal simulating models; and domain adaptation[42], which has shown promising results. Ultimately, the most robust results may come from combinations of the above, together with basic steps such as intensity normalization (additional references in eAppendix 1).

Given the relatively low prevalence of MS, lack of training data is an issue of particular relevance here. Insufficient variability in training data can lead to overfitted models that do not perform well on new data, and single-center data-sets seldom exceed a few hundred MS cases. This effect can be reduced with regularization, augmentation and cross-validation, but not fully removed. Therefore, pooling data from different sources is advantageous, but this introduces new challenges due to differences between centers, scanners and scanning protocols, which require standardizing and post-processing.

The majority of published machine learning studies in MS used research data rather than clinical data, which has limitations: patients were filtered through inclusion criteria; the number of subjects and scans is limited by the obtained funding; and more severe patients are more likely to drop out, biasing data towards more benign cases. Clinical data is more representative of the general (disease) population but is typically more heterogeneous and requires additional patient consent.

2) Labels: Training with high-quality labels is crucial to attaining good performance of machine learning systems. Labels can be the person's diagnosis or other overall features, or typically in image analysis tasks, manual outlines of anatomical structures or pathological entities like MS lesions. Distinguishing MS lesions in the white matter from other white matter lesions and from normal-appearing white matter requires skill and expertise. The variability of labeling protocols and inter- and intra-rater variability, introduce errors when training machine learning systems. Such errors degrade the performance of learning systems and limit to what extent that performance can be validated. Those errors could be quantified by expanding training sets, based on common protocols applied by larger

numbers of raters, and subsequently overcome by modelling or machine learning approaches.

3) Uncertainty & Confidence: Algorithms commonly solve a categorical hard problem, but clinical decisions are rarely categorical, and involve intrinsic uncertainty. The introduction of biomarker- and subject-specific error-bars, and the development of novel ways to convey and introduce this information into the clinical workflow, will present challenges to clinical adoption. Recent work addresses that uncertainty for MS lesion detection and segmentation[43]. Other areas of medicine with inherently uncertain predictions may suggest ways of introducing this uncertainty into the clinical workflow in the context of MS imaging (additional references in eAppendix 1).

3.4 Recommendations on machine learning in MS imaging

Compile large, annotated datasets for training. To obtain sufficient amounts of training data, large-scale data-sharing of MS imaging data is required; both for homogeneous datasets (for generating new knowledge), and heterogeneous datasets (for deriving more generalizable classifiers).

Create methods that are robust to data variability. Harmonize data using both classical and machine learning techniques to improve robustness to unseen datasets.

Include non-research data in training. Train machine learning methods also on data acquired in a real-life clinical setting, to increase robustness to heterogeneity and to improve applicability in the clinical population.

Create high-quality labels. Validating algorithms for clinical use will require large multi-center labeling efforts yielding, depending on the aims, consensus-based "ground truth" labels or collections of individual raters' labels.

Allow more subtle information in labels than global yes/no answers. The use of soft labels (e.g. image wide disease classification) to model the intrinsic anatomical and pathological variability should also be investigated.

Incorporate the uncertainty of classifier predictions. Algorithms should learn the intrinsic uncertainty and confidence of every decision they make. Diagnostic and prognostic guidelines should be modified to enable clinical usage of biomarker- and subject-specific uncertainty metrics.

4 Opportunity 1: Crowd-sourcing

4.1 Crowd-sourcing in research

The first highlighted opportunity here is "crowd-sourcing". Crowd-sourcing, not to be confused with "crowd-funding", refers to people donating their time and skills to complete certain tasks. In the context of scientific research, it is sometimes called "citizen science". Its premise is that there are many enthusiastic members of the general public who are willing to donate some of their time to science. By making it easy for them to contribute, the scientific community can reward their enthusiasm and willingness by letting them really help the field forward. Successful projects have been conducted this way, including examples in astronomy on differentiating different galaxy types (Galaxy Zoo (e70)), in organic chemistry on the topic of protein folding (Foldit, a game with tens of thousands of players (e71)), in biology on identifying bat calls (Bat Detective (e72)), and in paleontology on dinosaur limb bone measurements (Open Dinosaur Project (e73)). The potential for brain imaging applications has been noticed, and a successful approach to interface-building, data management and analysis has been described. SPINE (e74), Open Neuroimaging Laboratory (e75), and OpenNeuro (e76) are examples of web-based infrastructures for crowd-sourced brain imaging research.

While the potential benefits of crowd-sourcing to the researchers are clear, the benefits to the participants (the "crowd") may be less obvious. There is the potential gratification of contributing to science, and in the case of MS research, these volunteers may be people with an interest in brain imaging or neuroscience, or they may personally know someone who suffers from MS and want to help develop a solution. Furthermore, well-designed crowd-sourcing activities can also carry the reward of being entertaining to perform. The field of "gamification" is a rapidly developing area of research and development in its own right which has already been applied in the radiological field[44], which creates important opportunities for helping volunteers enjoy participating in crowd-sourced research and remain committed to finishing their contribution.

4.2 Potential for crowd-sourcing in MS imaging

For processing large amounts of image data on a regular basis, as in a clinical setting, automation of analysis methods is key. The training that goes into such automated methods, whether based on deep learning or using other approaches, obviously plays a large role in their performance. Ideally, reference labels, e.g., of specific imaging features

such as MS lesions or particular anatomical structures, would be generated by intensively trained expert raters. However, if this is not possible, for example due to the associated costs, crowd-sourcing such training labels could provide a realistic alternative, if properly used. A potential issue concerns the quality of crowd-sourced image annotations. For the example of image segmentation, this has been addressed. Specifically, Bogovic and colleagues[45] demonstrated that for cerebellar parcellation, it is possible to achieve high-quality labels from a group of non-expert raters.

This suggests that, provided that training and quality assurance procedures are adequately employed, a large group of non-expert volunteers could create reference labels on a large enough dataset to train deep learning or other methods robust to data variability. Nevertheless, as the task becomes more complex, the degree of communication required between the participants in order to achieve an adequate performance is likely to increase, with the risk of the efforts becoming an outsourcing initiative instead of a crowd-sourcing one. Thus, the project to be carried out should be clearly defined in terms of tasks and expectations, with the inclusion of tutorials and support by an experienced professional in the field.

Besides providing training labels for image segmentation, crowd-sourcing may also assist in other tasks such as (providing training labels for) image artifact detection, quality control, or disease classification. Especially niche applications such as MS imaging, where the costs of expert training labels can be prohibitive, can provide a "sweet spot" where crowd-sourcing can make a crucial contribution that advances the field. A first such approach has been proposed recently[46].

4.3 Recommendations for crowd-sourcing in MS imaging

Ensure high-quality instruction of volunteers. In order to help the crowd participate effectively, especially for longer and more complex tasks, comprehensive tutorials are essential.

Define clear tasks and expectations. In order to allow volunteers to experience making contributions to research, their tasks should be clearly defined, and generally limited in scope and time investment.

Enforce rigorous quality control. In order to ensure high quality of the crowd-sourced contributions, quality control procedures such as repeatability and agreement with experts on selected samples are essential.

5   Opportunity 2: Solutions to personal data protection and consent requirements

5.1   Personal data protection and consent in the GDPR framework

When sharing data, protecting personal data is a crucial guarantee to the participants. Since MAGNIMS Study Group is a European collaboration, the expertise available on data protection laws in other jurisdictions is limited and we therefore focus here mainly on the situation in the EU. Personal data protection is required by law in the EU with very specific rules set out in the General Data Protection Regulation (GDPR (e77)). While the specific legal requirements vary, concerns about preserving confidentiality of data of participants exist around the globe, and different legal frameworks to address these concerns exist in different countries. Differences between GDPR and the US HIPAA framework include the more limited scope of the latter, and have been discussed in detail elsewhere[47]. Personal data is understood as any information relating to an identified or identifiable natural person. An identifiable natural person is one who can be identified, either directly or indirectly. Now to determine whether someone is identifiable, all the means reasonably likely to be used have to be taken into account, and for each of these, the costs and the amount of time required for identification, the available technology at the time of the processing and expected technological developments have to be assessed. This is important because GDPR holds the controller, i.e. the researcher's organization, accountable. Security of personal data must be demonstrated through the existence of both technical and organizational measures (e77). GDPR places the persons whose data it concerns (referred to as "data subjects") in full control of what happens to their data. If personal data are meant to be shared and/or the possibility of identification cannot be excluded, written informed consent must be obtained from all participants for data sharing, including whether data will be shared with countries where EU regulations do not apply. Furthermore, procedures must be in place for removal of data when participants ask for that removal. It must be noted that the data protection authorities consider coded or pseudonymized data as personal data. If personal data are to be shared written data protection agreements are necessary to demonstrate compliance with the GDPR.

5.2   Challenges related to personal data protection and consent

Ensuring protection of personal data while providing adequate access for research purposes is challenging. Full anonymization, meaning that the person cannot be identified from the

data at all, may be difficult to achieve in several cases. In "extreme" groups (rare diseases, extremely tall persons, etc.) some basic information accompanying the imaging data may help reveal the identity of the person. The increasing accumulation of "big data" on people's behavior from many different sources by many companies and organizations, poses another hurdle to achieving full anonymization. New technologies, notably artificial intelligence techniques, allow, e.g., reconstruction of faces from low-resolution pictures[48]. In brain imaging, structural images allow 3D face reconstructions, possibly enabling identification. Face removal and face scrambling[49, 50] do not fully solve this, as these procedures may impact subsequent image analysis, e.g., radiotherapeutical dose distributions or EEG signals, or further brain image analyses[51]. Finally, removed faces can be (partially) reconstructed, and the structure of each brain may soon be enough to identify the person[52].

It may therefore be difficult to reach full anonymization at all. Hence, a second option may be more viable: to request, upfront, informed consent of the persons to share their data in an identifiable or not directly identifiable way. This informed consent should comply with national laws including those based on GDPR, where applicable as well as indicate the various options for planned or as yet unforeseen data sharing, such as with researchers in countries outside the EU, or perhaps with members of the general public through crowd-sourcing initiatives as discussed above. In addition, to further ensure the protection of personal data, an agreement on the use of the personal data must be made between the institutions or organizations sharing the data. An increasingly important way of generating large cohorts is by sharing the data across large groups of many different centers from many countries, which can lead to additional legal uncertainties about personal data protection, data ownership and data usage. The extreme case of this informed consent approach, where legally allowed, would be to ask the participants to consent to sharing their data without restricting that sharing to specific parties or applications.

A third way to share research data is by using an infrastructure that allows researchers to analyze the data remotely[53]. Such "trusted data ecosystems" at their core are similar to a federated database but are much more comprehensive and encompass not just data management but all features necessary to perform analyses on the data including the computing infrastructure and audit trail. An example of such an infrastructure, currently under development in the Netherlands, is the Health-RI infrastructure (e78). The approach taken by Health-RI is that the personal data is on the inside and the platform performs the analyses, so researchers only receive the outcome measures but have no access to the

actual data. Examples focused on federated deep learning, in which model parameters but not data are transferred between sites, are described by Chang and colleagues[54] and by Remedios and colleagues[55]. A limitation of such a federated approach is that the careful scrutiny of analysis pipeline success and inspection of intermediate results, is less directly feasible than in the more standard data-sharing approach, which would hamper not just any particular research project but also use of those data for further methodological improvements. An advantage is that their comprehensive approach, including technological, legal and business layers ensures compliance with regulations, governance, legal issues for data sharing, security issues and accountability.

Thus, the trade-off between protecting privacy and allowing access remains the main challenge that needs to be addressed properly. In this context, "differential privacy" may offer solutions. By limiting how much algorithms can learn from each data point, it prevents algorithms from learning enough to identify individuals, yet allows them to learn the relevant information at the population level[56].

5.3   Recommendations related to personal data protection and consent

Protect personal data. Implement technical, legal and organizational guarantees for protecting personal data. For MRI, these include DICOM anonymization and face removal.

Always request consent for data sharing. Maximize possibilities for re-use by requesting participant's consent for subsequent sharing and aiming for a broad scope of future projects. Invest in standardization of the necessary data protection agreements.

Invest in developing optimized infrastructure. Investigate how the strengths of Trusted Data Ecosystems can be combined with access to raw data and intermediate results.

6   Opportunity 3: Organized Analysis Challenges

6.1   Organized Analysis Challenges as a tool for accelerating methodological developments

With image analysis and machine learning algorithms advancing at a rapid pace, there exists a need to understand the performance and limitations of state-of-the-art approaches. Evaluating the performance of an automated algorithm, such as lesion segmentation, is a fundamental part of methods development that can require significant resources. Grand challenges are organized, competitive events that provide data to be analyzed, an analysis objective, ground truth data, and evaluation metrics for achieving the objective (e79). They

provide a means to compare the performance of multiple algorithms, to which a single lab would not typically have access. Furthermore, by providing these critical resources, research labs may participate in the challenge that might not otherwise engage in MS research.

The format of a grand challenge typically involves several key steps. Participating teams are first provided with a training data set that includes both imaging data and the ground truth. For the aforementioned lesion segmentation challenges, this consisted of multi-contrast MRI data from multiple patients, and a set of manual lesion delineations. The training data allow the teams to optimize performance of their algorithms and achieve results consistent with the ground truth. Next, teams are provided with a test data set that includes imaging data but no ground truth. The teams apply their approach to the test data set and submit results for evaluation. Finally, the teams and organizers discuss performance of the different algorithms, as well as the evaluation and related issues.

There have been three segmentation challenges focused specifically on the segmentation of MS brain lesions in the past: the 2008 MICCAI Challenge [e106,57], the 2015 ISBI Longitudinal Challenge[58], and the 2016 MICCAI Challenge[59]. These provide clear examples of what can be achieved through this kind of approach. An enduring key benefit of these challenges, beyond the papers, is that the organizers have continued to make the data available after the meeting, and have set up web-based systems for continually benchmarking new algorithms. In this way, all three challenges continue to actively make an impact aiding software developers to develop improved methods (e80, e81, e82).

These advances notwithstanding, challenges thus far have only released portions of the full data sets for training, with the testing data reserved by the challenge organizers for algorithm evaluation. Furthermore, data use licenses have been restricted to research or educational use. Those previous MS challenges have also focused rather narrowly on different aspects of MS white matter lesion segmentation. For example, the 2015 challenge focused on longitudinal data[58], while the 2016 data focused on multi-centric data, including those acquired at different field strengths[59]. Continued organization of challenges could target benchmarking algorithms for applications directly relevant to patient care, such as clinical trials or patient monitoring. Instead of metrics based on lesion segmentation accuracy, algorithms could be evaluated based on predicting the efficacy of therapies or clinical measures. Besides white matter lesion segmentation, a number of other promising

imaging biomarkers could be tested: Cortical lesions, cortical gray matter measurements, and thalamic volumes have all been found to be promising predictors of disease progression[60]. An MS database with whole-brain labels, currently not available, would aid training and validation of algorithms to more accurately extract such biomarkers. Other grand challenges could examine MR imaging of spinal cord morphology and pathology, and characterization of retinal morphology using optical coherence tomography. In summary, there is ample opportunity for challenges to contribute to further improvements in methods for studying MS, as well as proof from previous years that challenges can be a successful approach.

6.2   Recommendations on Organized Analysis Challenges for MS image analysis

Include additional aspects of MS image analysis other than WM lesions, such as cortical lesions and measures of brain volume.

Evaluate algorithms also against clinical outcomes, instead of just against imaging data.

Ensure challenge datasets contain large numbers of images and labels, to improve robustness and generalizability.

Reduce restrictions on challenge data, to allow more diverse applications and to build more expansive data resources for algorithm development and evaluation.

7   Conclusion

To maximize improvements of both the understanding of MS disease processes and in vivo MRI methods to study those, using "big data" and machine learning, specific recommendations were provided on data sharing, machine learning, crowdsourcing, personal data protection, and organized analysis challenges.

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Name	Location	Role	Contribution
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Figure 1. Methods used to create the current manuscript

Methods used to create the current manuscript
This paper is the outcome of a workshop organized by MAGNIMS Study Group on April 13th, 2018, and subsequent discussions. The panel convened at the workshop was chosen, by consensus among the Steering Committee of MAGNIMS Study Group, from candidate experts both within and outside MAGNIMS to best represent the different aspects to be discussed. Two of the speakers at the workshop, deeming the topic too far removed from their own immediate fields of work, chose not to participate in the subsequent writing of the paper and are hence not included among the authors.
The three target areas for near-future opportunities were identified in consensus between the expert panel members and Steering committee before, during and after the workshop; these were refined especially during the manuscript preparation and writing phase.
The recommendations formulated for each target area were obtained by discussing proposed recommendations and reaching consensus among the group of individual authors as well as the Steering Committee members. By going through multiple rounds of edits, consensus was reached.

Tables

Table 1: Shared datasets. Please see eReferences for citations of URLs and associated journal papers.

Dataset Name	Age Range (y)	Demo-graphic	Number of Subjects	Modalities	Selected additional data/info	Started	Website / References
ADNI: Alzheimer's Disease Neuroimaging Initiative	55-90	AD + MCI + HC	> 2000	sMRI + dMRI + fMRI + PET	Genetics + clinical + neuropsych tests + biosamples	2004	e83, e84
Harvard Aging Brain Study	65+	Normal Aging	284	sMRI + fMRI + dMRI + PET	Longitudinal	2009	e85, e86
DIAN: Dominantly Inherited Alzheimer Network	18+	Autosomal Dominant AD	430	sMRI + dMRI + fMRI + PET	Repeat visits + biosamples	2008	e87, e88
OpenNeuro (formerly OpenfMRI)	Any	Any	> 1000	Mainly MRI, but also with MEG + EEG + PET	Wide variety of different studies	2013	e76, e89
OASIS: Open Access Series of Imaging Studies	18-96	HC + MCI + AD	1664	sMRI + fMRI + dMRI + PET	Over 1000 with longitudinal data	2007	e90, e91
PPMI: Parkinson Progression Marker Initiative	33-85	PD + HC	~ 1000	sMRI + dMRI + fMRI + PET + SPECT	Biosamples	2010	e92, e93

HCP: Human Connectome Project	22-35	Healthy	1200	sMRI + dMRI + fMRI + some MEG	Siblings and twins; genetic + lifestyle data	2010	e94, e15
dHCP: Developing HCP	20-44 weeks	Fetal + Neonatal (healthy and otherwise)	1500	sMRI + dMRI + fMRI		2013	e95, e96
UK Biobank	48-77	Any	100,000 (currently 25,000)	sMRI + dMRI + fMRI	Genetic, lifestyle and clinical data + non-neuro data	2012	e97, e98
Neurovault	Any	Any	> 1000 studies	fMRI + sMRI + PET	Statistical results from publications	2014	e99, e100
MICCAI Challenges	Any	Any	> 160 separate challenges	Any medical imaging modality, and any body part	Each challenge comes with a modest dataset and some training labels /	2007	e101 (Many papers)

					ground truth		

Table 1: A small selection of open neuroimaging datasets currently available with partial
information on the characteristics of each, highlighting the breadth and diversity.
Abbreviations: AD = Alzheimer's Disease ; MCI = Mild Cognitive Impairment ; HC = Healthy
Controls ; PD = Parkinson's Disease ; sMRI = structural MRI ; dMRI = diffusion MRI ; fMRI =
functional MRI ; PET = Positron Emission Tomography.

Table 2:   MS Registries that collect MRI information

Registry	Start date	Reference
National registry of Croatia	2007	5
National registry of Denmark	1948/1996	5
National registry of France	1976	5
National registry of Germany	2001	5
National registry of Greece	2011	5
National registry of Italy	2001	5
National registry of Norway	1998	5
National registry of Russia	2006	5
National registry of Spain (Catalonia)	2009	5
National registry of Sweden	1997	5
National registry of Switzerland	2012	5
National registry of United Kingdom	2009	5
MSBase	2004	6
Expression, Proteomics, Imaging and Clinical (EPIC)	2004	e105
Kompetenznetz Multiple Sklerose (KKNMS)	2005	e68
Comprehensive Longitudinal Investigation of MS (CLIMB)	2006	e104
Italian Neuroimaging Network Initiative (INNI)	2011	12
OPTIMISE-MS	2017	e103
North American Registry for Care and Research in MS (NARCRMS)	2017	e102

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