NeuroImage: Clinical 32 (2021) 102847

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Imaging cortical multiple sclerosis lesions with ultra-high field MRI

Mads A.J. Madsen [a,*], Vanessa Wiggermann [a], Stephan Bramow [b], Jeppe Romme Christensen [b], Finn Sellebjerg [b,d], Hartwig R. Siebner [a,c,d]

[a] Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital - Amager & Hvidovre, Kettegard Allé 30, 2650 Hvidovre, Denmark
[b] Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Valdemar Hansens Vej 1-23, 2600 Glostrup, Denmark
[c] Department of Neurology, Copenhagen University Hospital - Bispebjerg, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark
[d] Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3b, 2200 Copenhagen, Denmark

ARTICLE INFO

Keywords:
Multiple sclerosis
Cortical lesions
7T MRI
Ultra-high field MRI
Systematic review

ABSTRACT

Background: Cortical lesions are abundant in multiple sclerosis (MS), yet difficult to visualize *in vivo*. Ultra-high field (UHF) MRI at 7 T and above provides technological advances suited to optimize the detection of cortical lesions in MS.
Purpose: To provide a narrative and quantitative systematic review of the literature on UHF MRI of cortical lesions in MS.
Methods: A systematic search of all literature on UHF MRI of cortical lesions in MS published before September 2020. Quantitative outcome measures included cortical lesion numbers reported using 3 T and 7 T MRI and between 7 T MRI sequences, along with sensitivity of UHF MRI towards cortical lesions verified by histopathology.
Results: 7 T MRI detected on average 52 ± 26% (mean ± 95% confidence interval) more cortical lesions than the best performing image contrast at 3 T, with the largest increase in type II-IV intracortical lesion detection. Across all studies, the mean cortical lesion number was 17 ± 6 per patient. In progressive MS cohorts, approximately four times more cortical lesions were reported than in CIS/early RRMS, and RRMS. Yet, there was no difference in lesion type ratio between these MS subtypes. Furthermore, superiority of one MRI sequence over another could not be established from available data. *Post-mortem* lesion detection with UHF MRI agreed only modestly with pathological examinations. Mean pro- and retrospective sensitivity was 33 ± 6% and 71 ± 10%, respectively, with the highest sensitivity towards type I and type IV lesions.
Conclusion: UHF MRI improves cortical lesion detection in MS considerably compared to 3 T MRI, particularly for type II-IV lesions. Despite modest sensitivity, 7 T MRI is still capable of visualizing all aspects of cortical lesion pathology and could potentially aid clinicians in diagnosing and monitoring MS, and progressive MS in particular. However, standardization of acquisition and segmentation protocols is needed.

1. Introduction

Multiple sclerosis (MS) is a heterogeneous, chronic, immune-mediated disease of the central nervous system (CNS). It is characterized by widespread inflammation, demyelination and axonal degeneration causing both focal lesions and diffuse tissue alterations (Kutzelnigg et al., 2005). Magnetic resonance imaging (MRI) at field strengths up to 3 T is widely used in the clinical management of MS, playing a key role in diagnosis, monitoring disease course and treatment response. Although conventional, clinical MRI is sensitive to white

Abbreviations: MS, multiple sclerosis; UHF, ultra-high field; CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; CNS, central nervous system; MRI, magnetic resonance imaging; MOG-AD, anti-MOG-IgG; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; DIR, double inversion recovery; CSF, cerebrospinal fluid; FLAIR, fluid attenuated inversion recovery; PSIR, phase sensitive inversion recovery; IR-SWIET, inversion recovery susceptibility weighted imaging with enhanced T2 weighting; PRISMA, preferred reporting items for systematic reviews and meta-analyses; EDSS, expanded disability status scale; eRRMS, early relapsing remitting multiple sclerosis; PMS, progressive multiple sclerosis; w, weighted; MP2RAGE, magnetization prepared 2 rapid gradient echo; NAGM, normal appearing gray matter; FLASH, fast low-angle shot; MTR, magnetization transfer ratio; WHAT, white matter attenuation; SDMT, symbol digit modalities test; BVMT, brief visuospatial memory test; NPI, null point image.

* Corresponding author.
E-mail address: madsjm@drcmr.dk (M.A.J. Madsen).

https://doi.org/10.1016/j.nicl.2021.102847
Received 25 June 2021; Received in revised form 19 August 2021; Accepted 25 August 2021
Available online 6 October 2021

matter lesions, the diagnostic value is limited by various differential diagnoses that may underlie myelin injury in the white matter. Additionally, white matter lesions correlate relatively poorly with clinical disability (Barkhof 1999). In contrast, recent studies highlight subpial demyelination as specific for MS and rare encephalitic syndromes associated with anti-MOG-IgG (MOG-AD) (Moll et al., 2008; Popescu et al., 2010; Fischer et al., 2013; Hoftberger et al., 2020; Takai et al., 2020; Junker et al., 2020). Cortical lesions have been associated with clinical disability, lower age at death (Howell et al., 2011) and earlier conversion to secondary progressive (SP)MS (Scalfari et al., 2018; Pisani et al., 2021). Consequently, both cortical lesions and juxtacortical lesions are now considered in the 2017 revised McDonald criteria (Thompson et al., 2018). However, lesions within the cortical grey matter are difficult to identify with conventional, clinical MRI (Kidd et al., 1999; Geurts, Bo, et al., 2005; Seewann et al., 2011). A number of advances have improved cortical lesion detection at 3 T, but MRI at ultra-high field (UHF, 7 T and above) provides higher signal to noise ratio, allowing for sub-millimeter structural imaging (de Graaf et al., 2013). As the number of UHF MRI scanners increases worldwide, clinical applicability of these machines is increasing. In MS, numerous studies have now assessed the potential of UHF MRI for improving *in vivo* visualization of cortical lesions.

In this review, we provide a brief narrative overview of recent views on cortical pathology in MS, and the current status of cortical lesion detection at 3 T. Thereafter, a systematic overview of the existing literature on imaging of cortical MS lesions with UHF MRI is presented. Specifically, we delineate the extent and distribution of cortical lesions detected with UHF MRI, highlight the utility of different MRI sequences used for lesion detection, and address the sensitivity of 7 T MRI compared to histology. Finally, we discuss various approaches of cortical lesion identification and segmentation, and the potential clinical benefit of UHF MRI for cortical lesion detection.

1.1. Cortical involvement in MS

Pathologically, white matter plaques, i.e. confluent and sharply demarcated demyelinated areas with relative axonal sparing (Lassmann 2005), were initially identified as the hallmark of MS. However, cortical demyelination in MS was also already demonstrated more than a century ago (Hulst and Geurts 2011). In 1962, Brownell and Hughes (1962) showed in a macroscopic study that 21% of lesions were located either in the cortex or at the cortical-white matter boundary. More recent histopathologic studies demonstrated that 69% of the cortical forebrain can be demyelinated and that in primary progressive (PP)MS, the fraction of demyelinated cortex can exceed that of demyelinated white matter (Kutzelnigg et al., 2005).

Already in 1916, Dawson (1916) noted heterogeneity of cortical lesions, but it took until 1999 before staining sensitivity allowed a detailed account of the topography of cortical plaques. Cortical lesions were classified into seven subtypes depending on their spatial relationship to superficial and principal cortical veins (Kidd et al., 1999). Later, the stratification of cortical lesion types was adjusted and lesions were grouped into three currently accepted types: type I lesions are leukocortical, affecting juxta-cortical U-fibers and the deeper layers of the cortex; type II lesions are entirely intracortical; type III lesions are ribbon-shaped subpial lesions extending into the cortex in variable depths without reaching the cortical/white matter boundary (Peterson et al., 2001). A *trans*-cortical lesion type (type IV) spanning the entire cortex has also been described (Bo et al., 2003a; Trapp et al., 2018). However, this lesion type may be seen as a variant of type III lesions.

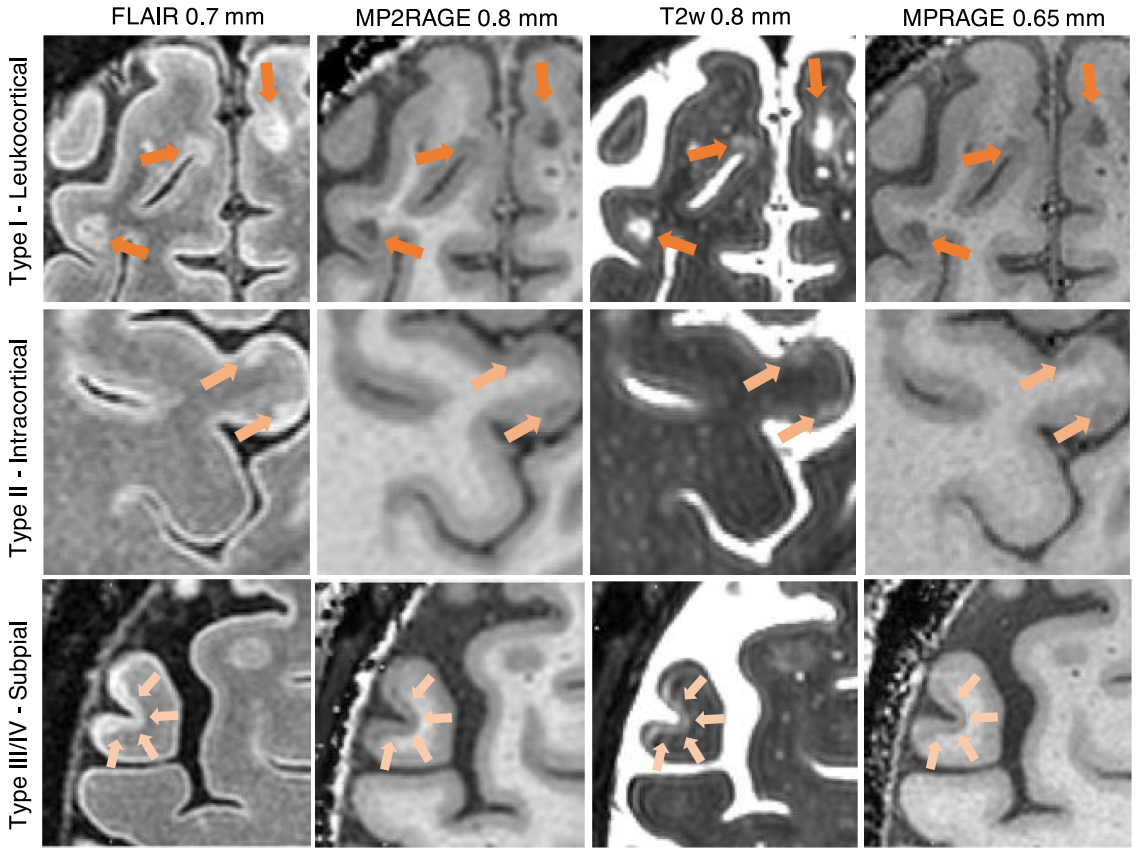

Fig. 1. Examples of different cortical lesion types depicted on different 7 T MRI sequences. Images are from a single relapsing remitting multiple sclerosis patient (male, 42 years, EDSS = 1.5, disease duration = 14 years). Images were acquired in-house and are unpublished. Abbreviations: fluid attenuated inversion recovery, MPRAGE: magnetization prepared rapid gradient echo, T2w: T2-weighted.

Fig. 1 shows the different lesion types as they can appear on different 7 T MRI sequences. All three cortical plaque types can be found already at RRMS onset, with type I being the most frequent at this stage (Lucchinetti et al., 2011). Histopathological studies from long standing disease samples suggest that the majority of lesions are subpial (type III/IV), about 55%. (Bo et al., 2003a; Pitt et al., 2010; Peterson et al., 2001; Kilsdonk et al., 2016; Jonkman et al., 2015; Geurts, Bo, et al., 2005; Seewann et al., 2011; Schmierer, Parkes, et al., 2010). Type II intracortical lesions amount to roughly 20% and type I, i.e. leukocortical lesions, to about 25%.

1.1.1. Recent views on the possible pathogenesis of cortical plaques

Early histological studies on cortical lesions found that they contained fewer lymphocytes, had a less permeable blood brain barrier and showed only narrow rims of activated microglia compared to white matter lesions (Peterson et al., 2001; Bo et al., 2003b). In particular, perivascular infiltrates were uncommon and CD3-positive lymphocyte and CD68-positive microglia/macrophage densities were only a fraction of respective cell densities in white matter lesions (Peterson et al., 2001). Additionally, the presence of transected neurites and reduced neuronal density (Vercellino et al., 2005) led to the notion that neurodegenerative mechanisms might contribute independently to the formation of cortical lesions (Peterson et al., 2001; Bo et al., 2003b; Trapp et al., 2018). Yet, several lines of recent research challenge this notion: (i) Complement markers of classic, alternative and membrane attack complex activation are increased in cortical plaques and associated with neuronal injury (Watkins et al., 2016). (ii) Biopsies taken from early RRMS patients show signs of active demyelination in ~ 65% of type I, ~ 25% of type II and ~ 20% of type III cortical plaques (Lucchinetti et al., 2011). (iii) Contrast enhancing type I lesions are found in early RRMS patients, suggestive of acute blood brain barrier disruption and a peripherally driven inflammatory response (Maranzano et al., 2017). (iv) A cortical model of experimental autoimmune encephalomyelitis (EAE) described rapid type III-like subpial plaque formation associated with intracortical perivascular lymphocytic infiltrates and complement deposition (Merkler et al., 2006). (v) Finally, it was shown that meningeal follicle-like lymphocytic infiltrates coincide with subpial cortical lesion formation (Choi et al., 2012; Howell et al., 2011; Magliozzi et al., 2007). Taken together, these data are consistent with an adaptive immune response driving inflammatory demyelination in both the cortex and white matter. The factors inducing cortical myelin injury and phagocytosis remain unresolved.

1.2. MRI of cortical lesions at clinical field strength

Despite the detailed insights gained from histopathology, the *in vivo* implications of cortical lesions are difficult to evaluate with current clinical MRI techniques. Consequently, many efforts have been undertaken to improve cortical lesion detection with MRI. Double inversion recovery (DIR) utilizes two inversion pulses to cancel signal from both cerebrospinal fluid (CSF) and white matter (Geurts, Pouwels, et al., 2005). By cancellation of the white matter signal, DIR improves the detection of cortical lesions compared to fluid attenuated inversion recovery (FLAIR) (Geurts et al., 2011). However, DIR images suffer from a low signal to noise ratio and their specificity can be compromised by flow artifacts, among other limitations (Nelson et al., 2007; Geurts et al., 2011; Saranathan et al., 2017). Phase sensitive inversion recovery (PSIR) imaging uses phase-sensitive reconstruction along with a T1-weighted sequence to increase the range of signal intensities, which seems to improve detection of cortical lesions at 3 T compared to DIR imaging (Sethi et al., 2013; Sethi et al., 2012). However, superiority of PSIR over DIR was not confirmed in recent *post-mortem* work using immunohistochemical stains (Bouman et al., 2020). Very recently, a susceptibility-weighted image contrast that utilizes signal inversion (IR-SWIET) has been proposed as another promising avenue for cortical lesion visualization at 3 T (Beck et al., 2020).

Despite these efforts, prospective sensitivity remains poor at 3 T (18–23% for DIR in *post-mortem* studies including histological validation (Seewann et al., 2012; Bouman et al., 2020)). Using multiple sequences for lesion segmentation increases lesion detection rates (Nelson et al., 2008; Maranzano et al., 2016), but further improvements for the *in vivo* depiction of cortical lesions are still warranted in order to accelerate correct diagnosis and management of the MS spectrum.

2. Methods

2.1. Systematic literature search of cortical lesions imaged at ultra-high field

To retrieve all relevant publications, we combined the search terms "Multiple Sclerosis" OR "MS" AND "7T" OR "7 T" OR "7Tesla" OR "7 Tesla" OR "7.0-T*" OR "ultra-high field" AND "cortical" AND "lesion*" in PubMed. The time-period covered in the search included all peer-reviewed publications up until September 1st, 2020. Identification, screening, eligibility and inclusion procedures followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 flow diagram (Moher et al., 2009). Two readers (MAJM and VW) independently screened the abstracts of all identified publications. Studies that fulfilled the following criteria were included in the qualitative analysis: 1) peer-reviewed, original articles written in English; 2) a study population including human patients diagnosed with MS; 3) investigation of cortical lesions using structural, UHF MRI. Review articles and commentaries were excluded prior to full-text assessment.

For the quantitative analysis, included manuscripts were assessed with regards to four points of interest: i) comparison of cortical lesion counts between 7 T and 3 T MRI, both *in vivo* and *post-mortem*; ii) *in vivo* MRI studies of adult-onset MS patients reporting total, mean or median and range counts of cortical lesions from whole- or supratentorial brain scans; iii) comparisons of cortical lesion counts between one or more 7 T MRI sequences both *in vivo* and *post-mortem* and iv) the sensitivity of *post-mortem* cortical lesion detection by UHF MRI, before and after knowledge of subsequent histopathology of the same tissue blocks. Duplicate data were identified either in text or through contact with the corresponding author(s) and included based on whether studies reported mean cortical lesion count, and secondarily based on the largest cohort. Any disagreement between the two readers regarding the inclusion of potential duplicate studies was followed up by HRS. A final decision was made in consensus between all researchers based on apparent demographic overlap between studies.

2.2. Outcome variables

Data extraction was done by MAJM under supervision of VW and HRS. Outcome variables included cortical lesion count for the entire MS population and for the separate MS phenotypes, where available. In line with the stratification that has been used in the included articles (Granberg et al., 2017; Harrison, Oh, et al., 2015), MS phenotypes were grouped into three groups: *early MS (eRRMS)*, including patients with clinically isolated syndrome (CIS) and RRMS patients < 5 years from diagnosis, *RRMS* ≥ 5 years from diagnosis, and *progressive MS (PMS)*, i.e. including both SPMS and PPMS patients. Additionally, lesion counts for individual cortical lesion types were extracted and lesion type ratios calculated, where applicable. Studies often collapsed type III and IV into a subpial category, or used a cruder classification pattern of intracortical (type II-IV) and leukocortical (type I) lesions (Treaba et al., 2019). Thus, to allow for between study comparisons, we analyzed data using both methods.

If a study only reported pooled total cortical lesion counts from its entire MS population, the group mean was calculated by dividing the count by the number of patients. If only the median and range of cortical lesion counts were reported, the group mean was estimated using the method by (Luo et al., 2018), which uses the median and range together

with the sample size to estimate the sample mean. Differences in field strength performance were computed as the ratio of total cortical lesion counts between each reported sequence at 7 T and the most sensitive 3 T sequence within each study. This analysis was also done for lesion subtypes, where available. Sequence performance at 7 T was evaluated by computing ratios of mean total cortical lesion counts and lesion subtype ratios relative to the best performing sequence within each study. For histological examinations, retrospective and/or prospective sensitivity of cortical lesion counts, and lesion type ratios were extracted.

3. Results

Fig. 2 depicts the PRISMA flow chart and screening procedures for study inclusion. A total of 144 articles were screened by title and abstract. Of these, 84 articles, which did not fulfill our inclusion criteria, were excluded. Another six publications were excluded after full-text screening because they did not investigate cortical lesions. The remaining 54 articles were included in the qualitative analysis. For quantitative data extraction, 20 of these 54 studies were excluded for reasons described in Fig. 2. 34 articles remained for the quantitative analysis. Of these, 25 were included in the *in vivo* lesion count analysis. Eight articles were included in the field strength comparison (one *post-mortem*, seven *in vivo*), eight publications in the sequence comparison (three *post-mortem*, five *in vivo*) and five articles that validated UHF MRI data against histology. An overview of all included studies and relevant study parameters is provided in supplementary Table 1. Among the 25 *in vivo* studies, sample size ranged from 8 to 90 patients, mean age from 36 to 54 years and female proportion from 33 to 81%. Median expanded disability status scale (EDSS) was between 1.5 and 5 and mean disease duration ranged from 2.5 to 24 years. All *in vivo* studies were carried out at 7 T.

3.1. Detection and segmentation of cortical lesions at 7 T

The MRI sequences and contrasts used for detection and segmentation of cortical lesions varied considerably across studies. Most commonly, T2*weighted (w) images were used (n = 17), followed by

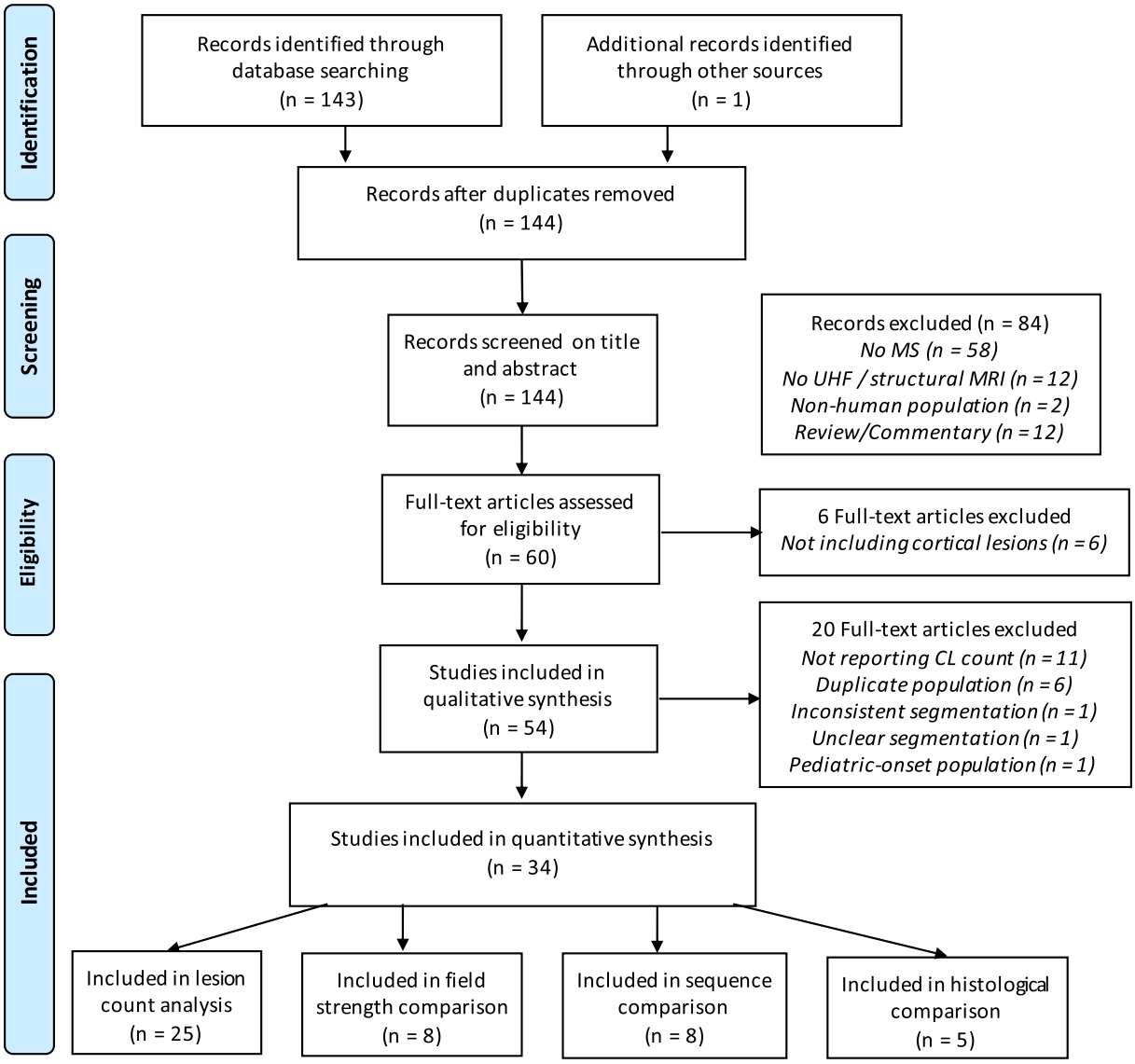

Fig. 2. Prisma reporting chart. Initial screening excluded all reviews and commentaries and all publications that did not include MS, structural MRI at 7 T or above, or included only non-human populations. Further articles were excluded if they did not assess cortical lesions. All remaining studies were included in the qualitative synthesis. Further quantitative analysis was performed by four synthesis points. Note that publications may be included in more than one of the quantitative synthesis points, shown in the bottom row.

T1w images (n = 7), T2w images (n = 6) or multiple sequences together (n = 9). Only one study investigated the potential of 7 T MRI for automated cortical lesion detection (Fartaria et al., 2019). With a sensitivity of 58% and a false-positive rate of 40%, automated segmentation of cortical lesions was still far from a performance level that would be clinically acceptable. In all other studies, cortical lesions were manually segmented. The specific segmentation procedure was only disclosed in 32 of 54 studies. Of these, the majority of studies used two or more trained readers (n = 16), who scored lesions by consensus or segmented images independently, reaching consensus thereafter (n = 13). 11 studies did not report the number of readers.

Cortical lesions were mostly defined as being clearly demarked on the MR image and to span at least three adjacent voxels in plane, in either one (n = 8) or two consecutive slices (n = 11). Five studies used a contrast threshold of 15% compared to adjacent grey matter. Seven studies reported that hyper-/hypointensities should not be classified as cortical lesions if they appeared linear or tubular, to avoid segmentation of blood vessels (Fartaria et al., 2019; Datta et al., 2017). Five studies used the DIR consensus guidelines that were proposed for 1.5 and 3 T MRI (Geurts et al., 2011). Segmentation was most often carried out in a designated MRI viewer (e.g. MIPAV, ImageJ, Slicer, Display). In two studies, it was proposed that images should be viewed in the axial plane and that lesions should be visible in the two orthogonal planes.

3.2. Comparison of cortical lesion detection at 7 T with clinical field strengths

Eight studies performed a quantitative analysis to compare detection performance of 7 T and 3 T MRI, using various image contrasts. The 7 T sequences detected on average 52% more cortical lesions (95% CI [26–77%]) than the best performing 3 T sequence. Considering only the best performing 7 T sequence for each study, cortical lesion detection improved on average by 73% (95% CI [30–117%]) compared to the best performing 3 T method (Fig. 3). DIR was the best performing 3 T sequence in four studies, using multiple image contrasts in two studies, and T2w and magnetization prepared 2 rapid gradient echo (MP2RAGE) each performed best in one study (Fig. 3).

All studies reported cortical lesion subtype counts from both 3 T and 7 T. The increase in lesion detection at 7 T MRI was particularly prominent for type II-IV intracortical lesions (166% increase in detection performance, 95% CI [39–294%]), whereas the increase in detection rate was modest for leukocortical type I lesions with an average increase in cortical lesion detection of 26% (95% CI [-13–65%]).

3.3. Extent and distribution of cortical lesions detected with 7 T MRI

Three studies investigated the topographical cortical lesion distribution with 7 T MRI. In line with *post-mortem* histopathological data (Kutzelnigg et al., 2005; Haider et al., 2016), these studies described a predilection for sulci and deep parts of the gyri as opposed to more superficial parts of the gyri close to the hemispheric surface. Only a slight regional preponderance in temporal, frontal motor and parietal sensory areas was reported (Treaba et al., 2019; Mainero et al., 2009; Louapre et al., 2015). Only a single 7 T MRI study investigated development of cortical lesions over time (Treaba et al., 2019). That study showed that 81% of patients developed new cortical lesions after 1.5 years, with a yearly rate of 1.1 new cortical lesions in RRMS and 3.6 cortical lesions in SPMS patients (Treaba et al., 2019).

Twenty-five studies reported supratentorial or whole brain cortical lesion counts. Cortical lesions were frequently evident on 7 T MRI, with the majority of studies reporting cortical lesions in at least 90% of patients (Mehndiratta et al., 2020; Ighani et al., 2020; Harrison, Roy, et al., 2015; Granberg et al., 2017). Mean lesion counts per patient varied substantially across 7 T MRI studies, ranging from a mean of 2.5 to 78.5 cortical lesions per patient (Fig. 4A). The average cortical lesion number/patient across all studies was 17 (95% CI [11–24]). Variability in 7 T

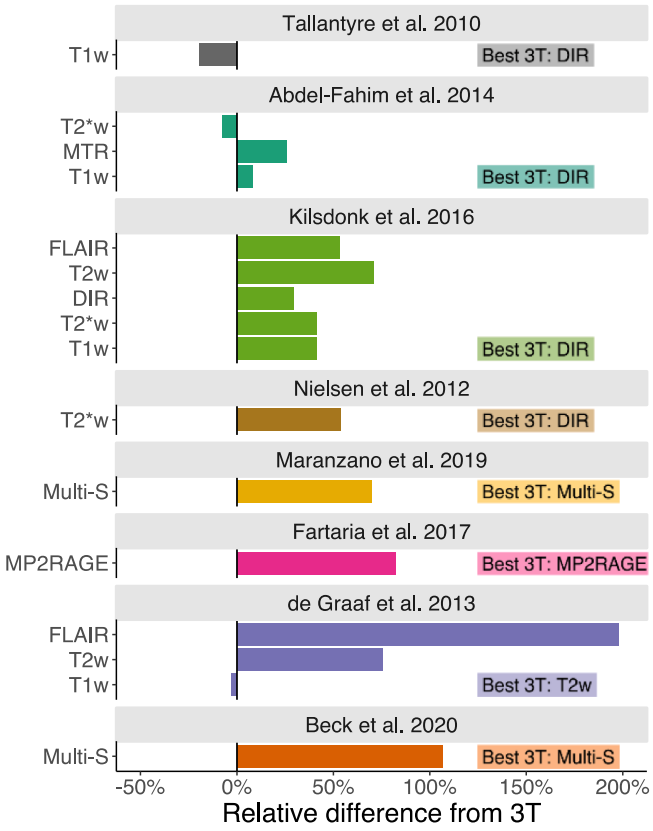

Fig. 3. Overview of studies directly comparing cortical lesion detection counts between 3 T and 7 T MRI. Data shown reflect the percent difference in lesion counts relative to the 3 T sequence that detected the highest number of cortical lesions within each study. Abbreviations: T1w = T1-weighted, T2*w = T2*-weighted, MTR = Magnetization Transfer Ratio, FLAIR = Fluid attenuated inversion recovery, T2w = T2-weighted, DIR = Double inversion recovery, Multi-S = Multiple sequences (Fartaria et al., 2017).

MRI lesion counts can at least in part be attributed to differences in the imaging sequences (see section 3.5) and differences in the clinical characteristics of the studied populations.

14 studies reported counts of cortical lesions from one or more phenotypes. PMS patients showed consistently higher cortical lesion load than RRMS patients (Cocozza et al., 2020; Harrison, Oh, et al., 2015; Harrison, Roy, et al., 2015; Mainero et al., 2009; Mainero et al., 2015; Maranzano, Dadar, et al., 2019). Across all applied sequences, the mean lesion count was approximately four times higher in PMS (PPMS/SPMS) (41, 95% CI [27–55], n = 9) compared to eRRMS (10, 95% CI [6–15], n = 3) and RRMS (11, 95% CI [7–15], n = 13) (Fig. 4B). This difference is unlikely explained by disease duration alone since cortical lesion load was found not to correlate with disease duration in individual studies (Abdel-Fahim et al., 2014; Datta et al., 2017; Mainero et al., 2009; Maranzano, Dadar, et al., 2019). Taken together, 7 T MRI data seem to be in line with *post-mortem* observations, i.e. showing a marked increase in cortical lesion loads and counts in cohorts that have entered the progressive stages of MS.

3.4. Cortical lesion type classification at 7 T

In vivo cortical lesion type distributions, by 7 T MRI sequence and disease phenotype, are displayed in Figs. 5 and 6. Corresponding lesion-type distributions from *post-mortem* studies are shown in Fig. 6B. 24 studies, included in the *in vivo* mean cortical lesion count analysis, reported counts of cortical lesion subtypes at 7 T. On average, 63% of detected cortical lesions were classified as type I (95% CI [57%-70%]) and 37% as type II-IV lesions (95% CI [31–43%]) (Fig. 5A). 12 studies

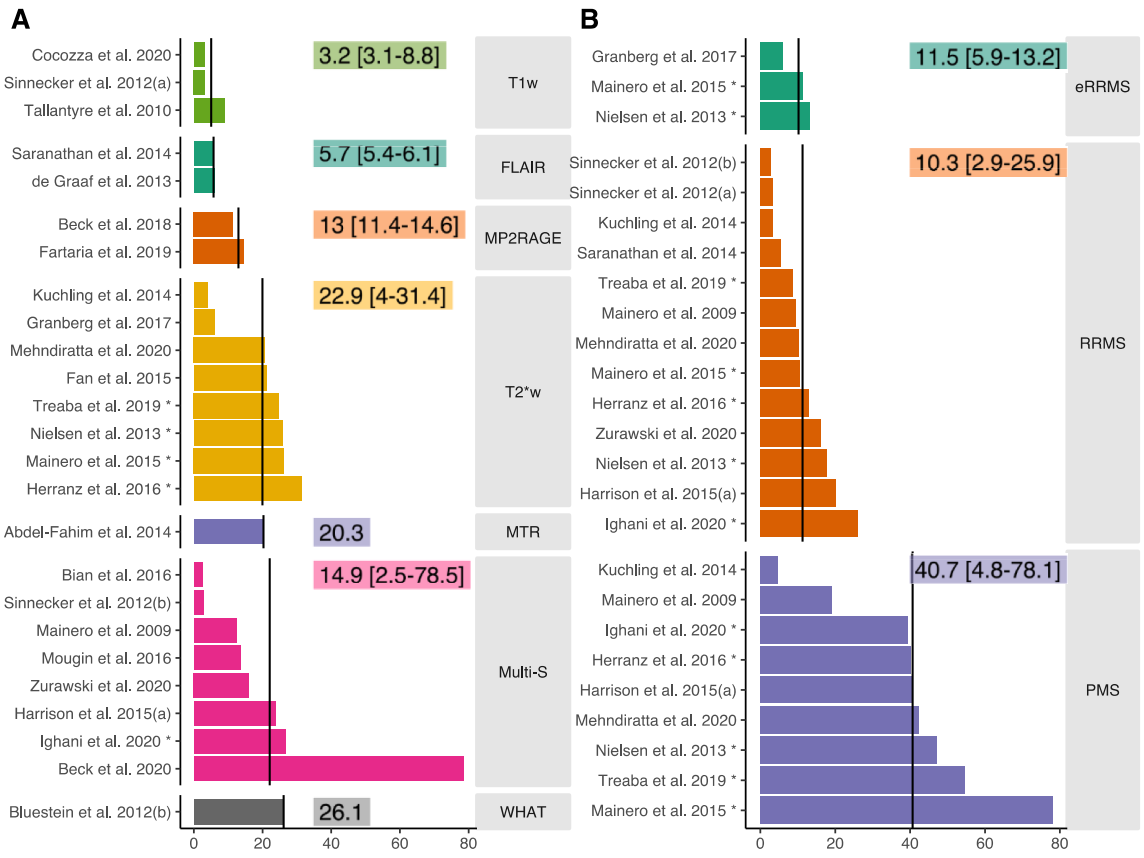

Fig. 4. Mean cortical lesion counts per patient. A) 7 T cortical lesion counts of the best performing sequence reported by each study, sorted by sequence. **B)** 7 T cortical lesion counts per phenotype. Black vertical lines denote the mean cortical lesion count per sequence, numbers denote median and range. * = mean was estimated based on median calculations as proposed by Luo et al., (2018). Abbreviations: T1w = T1-weighted, T2*w = T2*-weighted, MTR = magnetization transfer ratio, FLAIR = fluid attenuated inversion recovery, Multi-S = multiple sequences, MP2RAGE = magnetization prepared 2-rapid gradient echo, WHAT = white matter signal attenuation, RRMS = relapsing remitting multiple sclerosis, eRRMS = early RRMS, PMS = progressive multiple sclerosis (Bian et al., 2016; Herranz et al., 2016; Kuchling et al., 2014; Sinnecker et al., 2012b; Zurawski et al., 2020).

reported separate counts for type II and type III/IV lesions. In these studies, 54% (95% CI [46–62%]) of lesions were type I, 11% (95% CI [7–14%]) type II and 35% (95% CI [25–46%]) type III/IV (Fig. 5B & 6C-E). Interestingly, we did not find any differences in lesion type ratios between RRMS and PMS groups (46% type II-IV both), while the eRRMS group had 69% type II-IV lesions (Fig. 5C). However, only results from three studies were included in the eRRMS group.

Lesion type distributions differed depending on the 7 T images used for lesion segmentation and classification. FLAIR, T2w and MPRAGE/MP2RAGE (n = 11) identified 77% (95% CI [71–83%]) of lesions as leukocortical (de Graaf et al., 2013; Kilsdonk et al., 2013; Tallantyre et al., 2010; Cocozza et al., 2020). T2*w images have been suggested to be more sensitive to intracortical and subpial lesions, reporting lesion type distributions similar to histopathology (Mainero et al., 2009). From studies using either a T2*w sequence alone for lesion segmentation and classification or in combination with other MRI sequences (n = 16), we found that 54% (95% CI [44–64%]) were type I and 46% (95% CI [36–55%]) were type II-IV lesions.

3.5. Cortical lesion detection by different MRI sequences at 7 T

In one of the first studies comparing multiple sequences at 7 T, de Graaf et al., (2012) found no difference in cortical lesion detection between 7 T FLAIR and 7 T DIR, although the DIR sequence has been shown to be superior at 3 T (Bouman et al., 2020; Nelson et al., 2007). However, in an expanded cohort, FLAIR detected 89% more (primarily type I) cortical lesions than DIR at 7 T (Kilsdonk et al., 2013). In both studies, FLAIR and DIR detected more cortical lesions than either 2D T2w or 3D T1w, possibly due to better contrast to noise ratios between lesions and normal appearing gray matter (NAGM). Another popular sequence for cortical lesion detection is a 2D fast low-angle shot (FLASH) T2*w sequence with a high in-plane resolution (typically 0.33x0.33x1mm^3) (Mainero et al., 2009). The T2*w magnitude image provides good gray matter/white matter contrast and a better lesion/NAGM contrast than T2w, T1w and the phase image from the FLASH sequence (Mainero et al., 2009). Because T2*w also provides excellent interrater agreement, it has been suggested as the new 'gold standard' for cortical lesion detection at 7 T (Nielsen et al., 2012). However, 7 T *post-mortem* verification studies have not confirmed superiority of T2*w, but have conversely shown either superior or similar prospective detection rates of T2w and FLAIR compared with T2*w (Jonkman et al., 2015). In addition, drawbacks of this T2*w sequence are the need to acquire 2–3 slabs, a long total scan time of almost 20 min to cover the supratentorial brain (Mainero et al., 2009), and the 2D nature of the acquisition, which may hamper accurate co-registration to other image contrasts (Moraal et al., 2008). By decreasing the spatial resolution to 0.7 mm in-plane, scan time can be reduced to approximately 9 min, although this might influence sensitivity (Cocozza et al., 2020). We found no *in vivo* studies that directly compared lesion detection performance of FLAIR with T2*w sequences at 7 T. Only one study compared MP2RAGE with T2*w, and found T2*w performance to be inferior, revealing only half as many cortical lesions as MP2RAGE (Beck et al., 2018). Another study compared a 3D T2*w sequence at 0.5 mm isotropic resolution with an MPRAGE sequence and magnetization transfer ratio (MTR) imaging at 7 T. Again the T2*w sequence performed the worst out of the three (Abdel-Fahim et al., 2014).

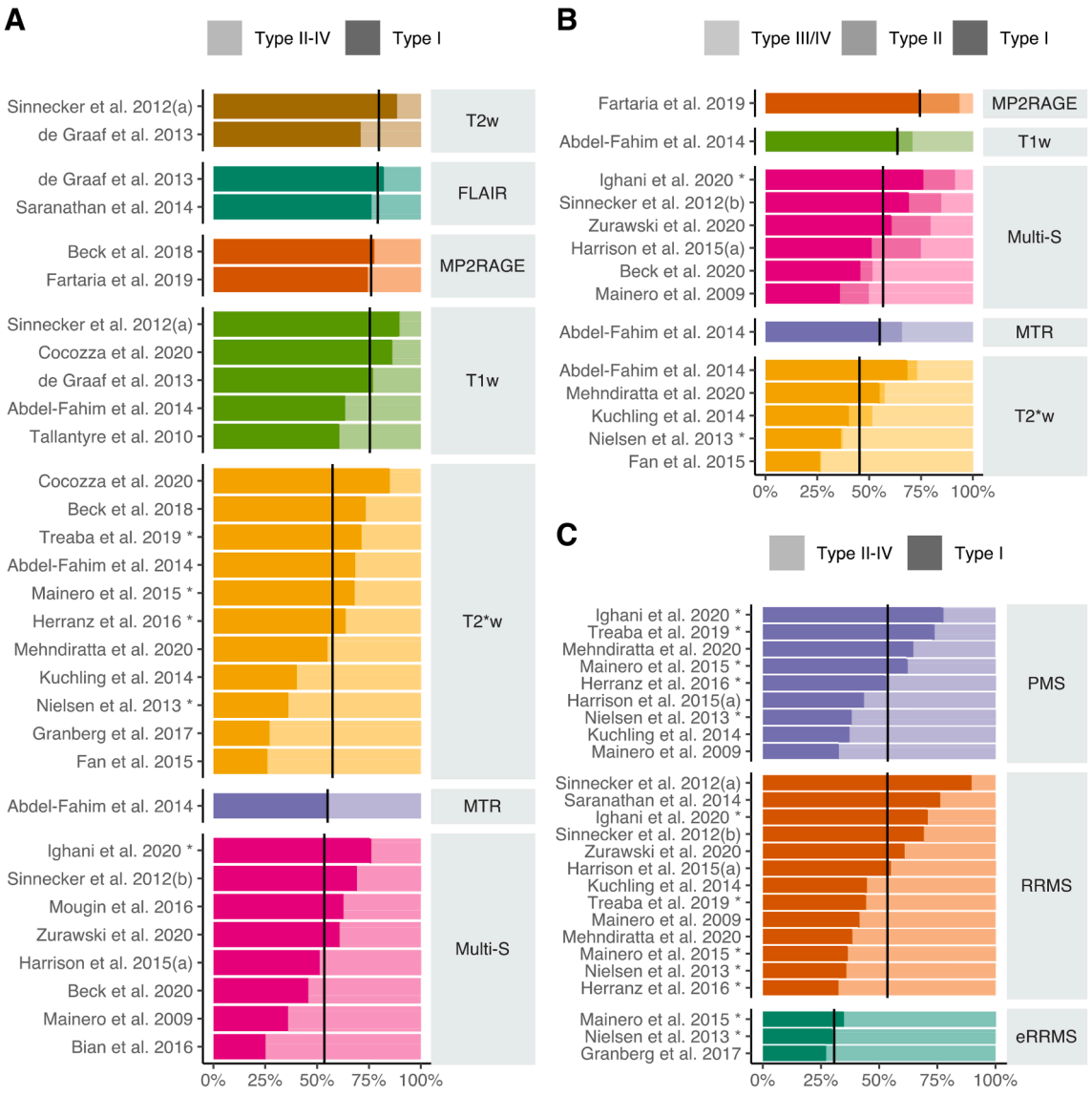

Fig. 5. Lesion type distributions detected with 7 T MRI. A) Lesion type ratio between type I, leukocortical, and type II-IV, intracortical lesions, for each study sorted by sequence. High opacity denotes type I lesions. **B)** Lesion type ratio between type I, type II and type III/IV for each study reporting separate type II and type III/IV lesion counts. High opacity denotes type I lesions, medium opacity denotes type II and low opacity type III/IV. **C)** Lesion type ratios for the three MS phenotypes. Denotation is the same as in A. Abbreviations: T1w = T1-weighted, T2*w = T2*-weighted, MTR = magnetization transfer ratio, FLAIR = fluid attenuated inversion recovery, T2w = T2-weighted, Multi-S: Multiple sequences, MP2RAGE: Magnetization prepared 2-rapid gradient echo, PMS: progressive multiple sclerosis, RRMS: relapsing remitting multiple sclerosis, eRRMS: early RRMS.

From the eight studies performing head-to-head sequence comparisons, FLAIR, MTR and MP2RAGE seem to outperform other sequences at 7 T (Tables 1 and 2). Since the number of studies comparing similar sequences is small, no definitive conclusions can be drawn from the existing data. The highest mean number of cortical lesions was found in studies using either T2*w, white matter attenuation (WHAT), MTR or multiple sequences (Fig. 4A). These results are, however, also highly confounded by the low number of studies, differences in study populations and lesion identification methods.

3.6. *Post-mortem validation of cortical lesion detection at 7 T and 9.4 T*

Four *post-mortem* studies investigated the prospective sensitivity of 7 T MRI and five studies reported retrospective sensitivity at 7 T (n = 4) or 9.4 T (n = 1) MRI, verified by immunohistological myelin staining. An early study reported a prospective sensitivity of 46% using a 3D T2*w sequence at a resolution of 0.15x0.15x0.3 mm^3 (Pitt et al., 2010). Later, Kilsdonk et al., (2016) reported a prospective sensitivity of only 29% with T2*w, at 0.18 mm isotropic resolution. Another study from the same group found a sensitivity of just 16% for the 3D T2*w and 28% for a 2D T2w sequence (Jonkman et al., 2015). In all three studies, sensitivity was highest for type I and type IV cortical lesions. Notably, scan times in these studies often exceeded two hours, far beyond clinical feasibility. In another study, 3D T2*w prospective sensitivity was found to be 46% at more clinically feasible scan-times (~20 min whole cerebral coverage) and 0.21 mm isotropic resolution (Yao et al., 2014). It should be noted that acquisition parameters often differ between *post-mortem* and *in vivo* sequences, potentially hampering the comparability between the two (Boon et al., 2019). Overall, mean prospective sensitivity calculated from four 7 T studies across ten sequences was 33% (95% CI [27–39%]). Following retrospective assessment, including knowledge of lesion location from histology, sensitivity increased to 71% (95% CI [61–81%], five studies, 11 sequences). At very high resolution, retrospective sensitivity may be even as high as 80–90%

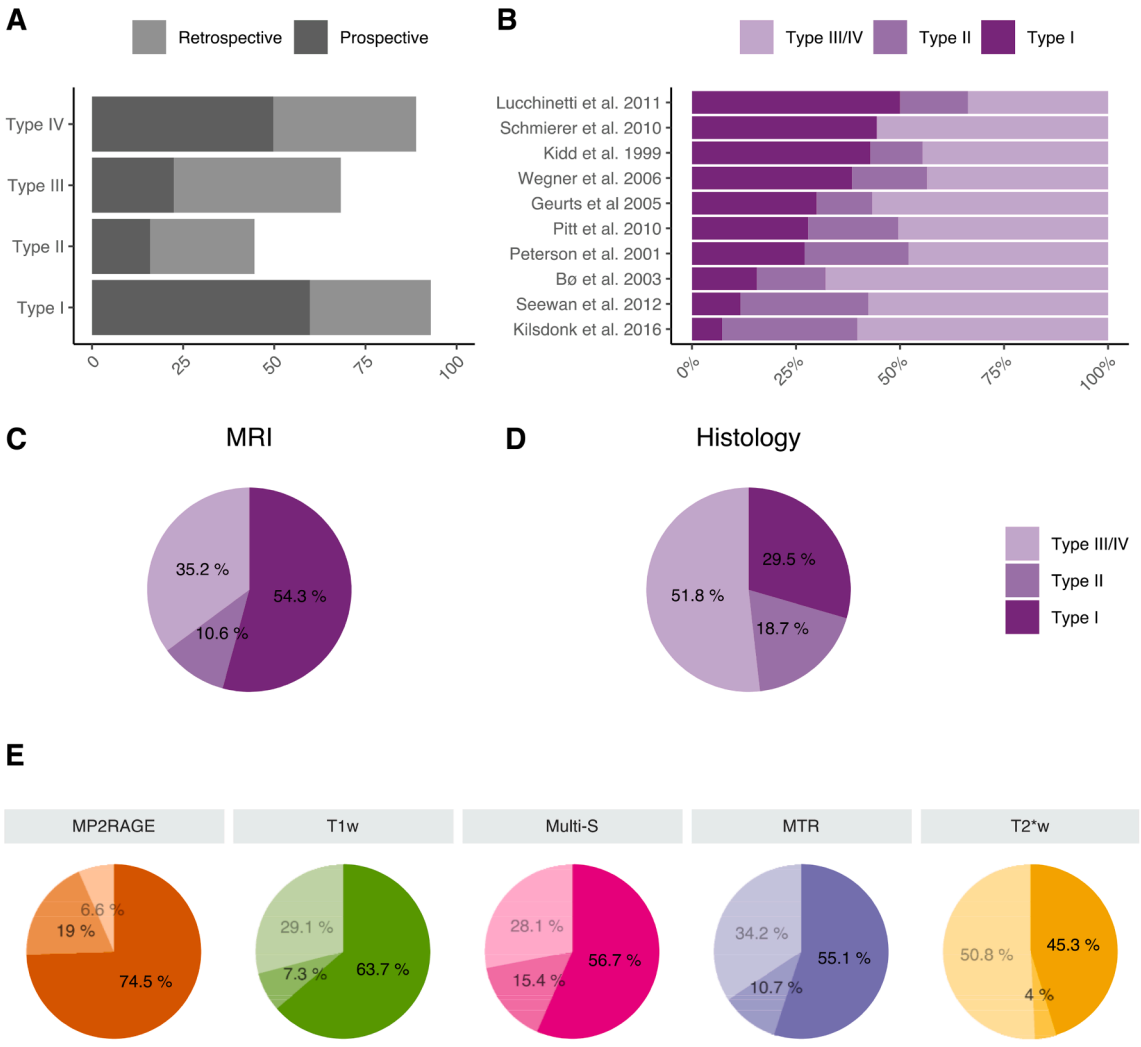

Fig. 6. Lesion type distributions from 7 T MRI and selected histological studies. A) Mean prospective and retrospective sensitivity of cortical lesion detection with ultra-high field MRI compared to histological staining. **B)** Cortical lesion type distributions from selected *post-mortem* studies. **C)** Mean cortical lesion type distribution from included 7 T MRI studies and **D)** selected *post-mortem* studies. **E)** Mean lesion type distribution for different 7 T sequences. Abbreviations: T1w = T1-weighted, T2*w = T2*-weighted, MTR = magnetization transfer ratio, FLAIR = fluid attenuated inversion recovery, T2w = T2-weighted, Multi-S: Multiple sequences, MP2RAGE: Magnetization prepared 2-rapid gradient echo, DIR = double inversion recovery, WHAT = white matter signal attenuation.

(Jonkman et al., 2015, Pitt et al., 2010). The highest retrospective sensitivity of 96 % was reported using 9.4 T (Schmierer, Parkes, et al., 2010). Both prospective and retrospective sensitivity differed between lesion types. Sensitivity was highest for type I lesions (60% and 93%, respectively) followed by type IV (50% and 89%, respectively) and type III lesions (22% and 68%, respectively). Type II lesions were most difficult to identify on MRI (16% and 45%, respectively) (Fig. 6A).

3.7. Clinical implications of cortical lesions

Eight studies reported relationships between cortical lesions detected at 7 T and cognitive or motor dysfunction, using specific tests, or general disease-related impairments using the EDSS disability score.

3.7.1. Relationship between cortical lesion load, cognitive and motor impairment

Five studies investigated 7 T cortical lesions in relation to cognitive performance. Of these, four studies demonstrated negative correlations between cortical lesion count or volume and one or more metrics of cognition (Louapre et al., 2018; Cocozza et al., 2020; Harrison, Roy, et al., 2015; Nielsen et al., 2013) with correlation coefficients ranging from 0.33 to 0.7. Using a large battery of cognitive tests in visuospatial, learning/memory, processing speed and semantic domains, Nielsen et al., (2013) found that the number of type I lesions was most frequently associated with poor cognitive performance, followed by subpial lesions. This observation was replicated in another study of 36 patients, in which a natural log increase in total cortical lesion volume was associated with an odds ratio of 3.4 for being cognitively impaired. The odds ratio was 9.7 when analyzing type I lesion volume alone (Harrison, Roy, et al., 2015). Leukocortical lesions together with age have also been shown to be the best predictor of cognitive performance in both the symbol digit modalities test (SDMT) and the revised brief visuospatial memory test (BVMT) (Cocozza et al., 2020). Using multivariate regression models, three studies showed that associations with cognitive performance were independent of white matter lesion volume and other global markers of disease severity (Harrison, Roy, et al., 2015; Cocozza et al., 2020; Louapre et al., 2018). In summary, cortical MS lesions, and leukocortical lesions in particular, seem to contribute to cognitive decline in MS, although another recent study found no association between cortical lesion volume and SDMT performance (Mehndiratta et al., 2020).

Only two studies have investigated cortical lesions detected at 7 T in relation to fine motor impairment (Harrison, Roy, et al., 2015; Cocozza et al., 2020). In both studies, cortical lesion load correlated negatively with performance on the 9-hole peg test, with correlation coefficients

Table 1
Overview of studies directly comparing cortical lesion counts for different 7 T sequences. Values for lesion types and absolute lesion count are means of the absolute supratentorial lesion count. The relative lesion count is calculated as the proportion of cortical lesions detected by each sequence compared to the best performing sequence within each study. Abbreviations: T1w = T1-weighted, T2*w = T2*-weighted, MTR = magnetization transfer ratio, FLAIR = fluid attenuated inversion recovery, T2w = T2-weighted, Multi-S: Multiple sequences, MP2RAGE: Magnetization prepared 2-rapid gradient echo, DIR = double inversion recovery, WHAT = white matter signal attenuation.

Author	Sequence	Type I	Type II	Type III/IV	Total lesion count	Relative lesion count [%]
		Mean	*Mean*	*Mean*	*Mean*	*Mean*
Abdel-Fahim et al., 2014	T2*w	8.8	0.6	3.4	12.8	63.3
	T1w	10.2	1.2	4.7	16.1	79.2
	MTR	11.2	2.2	6.9	20.3	100.0
Beck et al., 2018	T2*w	3.7	1.3	–	5.0	43.6
	MP2RAGE	8.8	2.5	–	11.4	100.0
Cocozza et al., 2020	T2*w	2.6	0.4	–	3.0	96.8
	T1w	2.7	0.4	–	3.1	100.0
Jonkman et al., 2015	T2*w	2.0	5.0	9.0	16.0	59.3
	T2w	8.0	3.0	16.0	27.0	100.0
Kilsdonk et al., 2013	T1w	1.4	0.4	–	1.8	30.5
	DIR	1.9	1.2	–	3.1	52.5
	FLAIR	4.8	1.1	–	5.9	100.0
	T2w	2.2	0.9	–	3.1	52.5
Kilsdonk et al., 2016	T2*w	3.0	0.0	21.0	24.0	82.8
	T1w	4.0	2.0	18.0	24.0	82.8
	DIR	5.0	1.0	16.0	22.0	75.9
	FLAIR	4.0	3.0	19.0	26.0	89.7
	T2w	6.0	3.0	20.0	29.0	100.0
Pitt et al., 2010	T2*w	23.0	8.3	18.0	49.3	100.0
	WHAT	21.3	4.3	10.3	36.0	73.0

Table 2
Summary statistics of the relative and absolute cortical lesion counts across studies that directly compared cortical lesion detection between different 7 T sequences. The relative lesion count was calculated as the proportion of cortical lesions detected relative to the best performing sequence. Abbreviations: T1w = T1-weighted, T2*w = T2*-weighted, MTR = magnetization transfer ratio, FLAIR = fluid attenuated inversion recovery, T2w = T2-weighted, Multi-S: Multiple sequences, MP2RAGE: Magnetization prepared 2-rapid gradient echo, DIR = double inversion recovery, WHAT = white matter signal attenuation.

Sequence	Relative lesion count [%]	Total lesion count	Type I	Type II-IV	
	Mean	Mean	Mean	Mean	N
DIR	64.2	12.6	3.5	9.1	2
T2*w	69.9	16.4	6.7	9.8	7
WHAT	73.0	36.0	21.3	14.7	1
T2w	74.3	15.1	4.4	10.8	4
T1w	78.5	9.6	4.2	5.4	5
FLAIR	94.8	15.9	4.4	11.6	2
MTR	100.0	20.3	11.2	9.1	1
MP2RAGE	100.0	11.4	8.8	2.5	1

ranging from 0.4 to 0.56. This association was strongest for type I lesions, but not shown to be independent of other global MRI metrics.

3.7.2. Relationships between cortical lesion load and EDSS

Eight studies investigated the relationship between cortical lesion load and the EDSS (Kurtzke 1983). Of these, six studies reported that cortical lesion load was positively correlated with EDSS (Louapre et al., 2018; Harrison, Roy, et al., 2015; Mehndiratta et al., 2020; Nielsen et al., 2013; Mainero et al., 2009; Treaba et al., 2019) with correlation coefficients ranging from 0.59 to 0.7. Cortical lesion subtype data were available from five of these six studies: In three studies, the association was primarily driven by subpial type III/IV lesions (Mainero et al., 2009; Mehndiratta et al., 2020; Nielsen et al., 2013), while leukocortical type I lesions were driving the relationship between cortical lesion load and the individual EDSS score in the remaining two studies (Harrison, Roy, et al., 2015; Treaba et al., 2019). One study that did not find any relationship between cortical lesions and EDSS was limited by a small sample size (n = 18) (Abdel-Fahim et al., 2014). In the other one, the relationship lost significance after correction for age and disease duration (Cocozza et al., 2020).

4. Discussion

Our systematic review on 7 T MRI of cortical lesions in MS confirms the notion that 7 T MRI detects more cortical lesions than 3 T MRI, capturing on average 52% more cortical lesions than the best performing MRI sequence at 3 T. Although 7 T MRI improved lesion detection compared to 3 T, *post-mortem* 7 T MRI only performed modestly compared to histopathology. However, our data suggest that *in vivo* 7 T MRI may still prove sufficiently representative of cortical MS pathology since i) *in vivo* 7 T MRI revealed cortical lesions in the vast majority of patients and across clinical phenotypes, ii) the relative improvement in lesion detection with 7 T MRI was most prominent for type II-IV lesions, and iii) 7 T MRI showed a four-fold increase in cortical lesions in progressive compared to relapsing MS, reflecting the extensive increase in cortical lesion number associated with a progressive phenotype, in line with observations from histopathology.

4.1. 3 T MRI vs 7 T MRI of cortical lesions in MS

Increases in the magnetic field strength provide a supra-linear increase in the signal to noise ratio for MRI (Pohmann, Speck, and Scheffler 2016) and amplify the susceptibility weighting in T2*w sequences. This offers higher spatial resolution, reduces partial volume effects, while increasing contrast, all of which are pivotal for the detection of cortical MS lesions (Pitt et al., 2010; Seewann et al., 2012). Our systematic review indicates that the detection of subpial and intracortical lesions improved more from 7 T vs 3 T MRI than detection of leukocortical type I lesions. Some studies have reported that cortical lesion detection more than doubles when comparing similar sequences at 7 T and 3 T (Kilsdonk et al., 2016; de Graaf et al., 2013). However, the gain from 7 T was not as dramatic when we compared with the best 3 T sequence in each study (52% overall and 73% considering the best 7 T sequence). It should be noted that performance at different field strengths is difficult to compare as sequence parameters vary and scanning time at 7 T is typically longer than at 3 T (Kilsdonk et al., 2016, de Graaf et al., 2013' Abdel-Fahim et al., 2014; Maranzano et al., 2019a). Decreasing scanning time will be of essence before 7 T MRI technology can mature into clinical routine.

4.2. Extent and distribution of cortical lesions at 7 T

Our review shows that cortical lesions detected with 7 T MRI are prevalent and abundant in all MS stages. On average, we found 17 cortical lesions per patient. But, multiple studies found a skewed distribution in cortical lesion numbers, with some patients displaying very high cortical lesion loads, including one study that reported patients with more than 200 lesions (Beck et al., 2020). It has been suggested that patients with extensive cortical lesion load may belong to a different "myelo-cortical" phenotype of MS, where patients present with extensive cortical and spinal demyelination but few or no cerebral white matter lesions (Trapp et al., 2018). Our summarized data indicate that the variability in cortical involvement may be partly explained by differences in MS phenotypes among studies: Patients with PPMS or SPMS had considerably more cortical lesions than those with longstanding or early RRMS (Datta et al., 2017; Maranzano, Till, et al., 2019; Nielsen

et al., 2013; Mainero et al., 2015; Maranzano et al., 2017). This is an important finding since cortical lesion burden at disease onset is associated with a higher risk of conversion to SPMS (Pisani et al., 2021; Scalfari et al., 2018). Longitudinal studies of clinically feasible 7 T sequences are needed to help identify patients at risk for conversion from RRMS to SPMS.

With respect to the spatial distribution of cortical lesions, a slight preponderance of cortical lesion presence in prefrontal, parietal, temporal and cingulate areas was noted at 7 T. This corroborates findings from earlier work at 3 T, showing an accentuated cortical involvement of motor and cingulate areas (Calabrese et al., 2010). In good agreement with histopathology, 7 T MRI showed that lesions are more commonly found in the sulci and deeply situated gyri as opposed to gyri located superficially in the cerebral convexities (Louapre et al., 2015; Mainero et al., 2009; Treaba et al., 2019; Kutzelnigg et al., 2005; Haider et al., 2016). This notion is further supported by a reported increase in T2* relaxation time as a measure of diffuse demyelination that was primarily located in the sulci (Mainero et al., 2015). Deeply located cortical regions may be more prone to demyelination, because they are putatively exposed to low CSF flow. This explanation would be consistent with the notion that cortical demyelination originates from perivascular meningeal infiltrates (Haider et al., 2016). It should be noted that 7 T MRI has greater B_0 and B_1 field inhomogeneities than 3 T MRI. This results in regional differences in terms of sensitivity to cortical lesions and may introduce systematic spatial biases in cortical lesion detection.

4.3. Cortical lesion morphology

Low spatial resolution has rendered it difficult to distinguish between the different lesion subtypes proposed by Bo et al., (2003a) when using 3 T MRI (Maranzano, Dadar, et al., 2019). The improved grey/white matter contrast and higher spatial resolution at 7 T allows to divide cortical lesions more easily into the different subtypes. Despite improved detection of intracortical and subpial lesions compared to 3 T, and the relatively high sensitivity towards type IV lesions, the distribution of cortical lesion types revealed by 7 T MRI still differed from that seen in histopathological studies (Fig. 6B-D). This discrepancy between radiological and histological findings can possibly be attributed to a misclassification of juxtacortical lesions as leukocortical lesions but also to insufficient sensitivity to subpial lesions on 7 T MRI (Kilsdonk et al., 2016). Low subpial sensitivity may be due to lower myelin densities in the superficial cortical layers (Braitenberg 1962) resulting in lower lesion/cortex contrast, but partial volume effects and artifacts are also still present at 7 T. Estimating whether *in vivo* MRI may reflect subpial type III/IV pathology is of clinical importance since subpial demyelination is an MS-specific pathology and a potential hallmark of a progressive disease course. The limited sensitivity described by *post-mortem* 7 T MRI does not preclude further exploration of subpial demyelination and cortical lesions *in vivo*, since i) tissue fixation alters MRI contrasts (Schmierer, Thavarajah, et al., 2010) ii) *post-mortem* cohorts are typically biased toward longstanding and severe disease and iii) tissue sample bias may skew histological (and radiological) assessments toward more severely affected tissue. For instance, biopsy samples taken from early RRMS patients suggest that type I lesions are most preponderant earlier in the disease (Lucchinetti et al., 2011). Although this has recently been disputed (Bevan et al., 2018), longitudinal 7 T MRI studies of older populations seem warranted to gain knowledge of cortical lesion morphology over time. Nevertheless, our data support the notion that 7 T MRI has the potential to visualize cortical changes associated with conversion from RRMS to SPMS and to some extent represent all cortical lesion types. Thus, subpial cortical lesion detection is no longer exclusive to histopathology, but can be reliably performed using 7 T MRI, although sensitivity towards type III lesions is still low.

4.4. Which MRI sequences at 7 T are most suited for cortical lesion detection?

Recommending an optimal 7 T MRI sequence, or combination of sequences, for detection of cortical lesions in MS remains difficult. Formal head-to-head comparisons remain sparse and we found high variability in mean cortical lesion counts between studies, even for comparable MRI sequences. Our analysis of existing head-to-head comparisons suggested either 7 T FLAIR, MTR or MP2RAGE as good candidate sequences for cortical lesion detection. However, mean whole brain cortical lesion counts for both FLAIR and MP2RAGE were low, and only one study utilitized MTR for cortical lesion detection (Fig. 4A).

T2*w and multiple sequence approaches showed the highest mean whole brain cortical lesion counts. However, T2*w generally performed poor in head-to-head comparisons (Table 2), which may be due to lower sensitivity towards leukocortical lesions (Maranzano, Dadar, et al., 2019). Nevertheless, the T2*w sequence may be the best current sequence for detection of subpial type III/VI lesions. Timely identification of subpial lesions could prove to accelerate the stratification of RRMS patients at risk for conversion to SPMS. By including additional sequences in the segmentation process (Figs. 4 & 5), or by acquiring multiple signal averages to improve SNR sensitivity towards leukocortical lesions may be improved, albeit at increased scan times.

Parallel to improving existing 7 T sequences, novel sequences are being developed to improve contrast for cortical lesions, including for instance WHAT T1w (Bluestein et al., 2012b; Saranathan et al., 2015), and PSIR, which has been adapted to 7 T by including a *null point image* (NPI) into the MP2RAGE sequence (Mougin et al., 2016). Overall, head-to-head comparisons of both new and existing sequences at 7 T are missing in order to establish their value.

4.5. Segmentation and classification of cortical lesions

Standardized identification and segmentation of cortical lesions is of pivotal importance in studies assessing the value of cortical lesions in diagnosis and monitoring of MS. Whereas guidelines for segmentation and scoring of cortical lesions have been established for 1.5 T and 3 T DIR (Geurts et al., 2011), few recommendations exist for 7 T. Our synthesis showed that DIR guidelines sometimes are applied to 7 T MRI data (de Graaf et al., 2013; Kilsdonk et al., 2013; Saranathan et al., 2014). However, given the higher resolution of anatomical scans at 7 T, adhering to these guidelines may lead to segmentation of smaller lesions and potentially increase the false-positive detection rate. Different sequence- or field-strength related artifacts, including B_0 and B_1 inhomogeneities, could complicate application across field strengths even further. Moreover, we found that the procedure and criteria for cortical lesion segmentation were only reported in 32 and 28 studies, respectively. This complicates study replication and impairs the training of less experienced readers. It is very likely that the large variability observed in cortical lesion counts between studies (see Fig. 4) is in part due to differences in segmentation procedures. Thus, there is a pressing need for the development of guidelines directed at segmentation and scoring of cortical lesions at 7 T.

4.6. Clinical impact of cortical lesions

At 1.5 T and 3 T, cortical lesions have been related to both clinical severity and disease progression (Calabrese et al., 2012; Scalfari et al., 2018; Nelson et al., 2011; Mike et al., 2011; Forslin et al., 2018). However, numerous studies have also failed to show correlations between cortical lesions detected 1.5 or 3 T and cognitive function or EDSS (Catalaa et al., 1999; Lazeron et al., 2000; Rovaris et al., 2000; Yousuf et al., 2016), and correlation coefficients are generally lower than those observed using 7 T, especially when considering EDSS (Mike et al., 2011; Papadopoulou et al., 2013; Dolezal et al., 2007). As cortical lesion detection depends on lesion size and myelin density in the surrounding

tissue, MRI at 3 T and 1.5 T preferentially detects leukocortical type I lesions (Forslin et al., 2018; Mike et al., 2011). Consequently, results from 3 T and 1.5 T MRI studies might underestimate how clinical severity is influenced by cortical lesions, and subpial lesions in particular.

This review supports the notion that cortical lesions are a highly relevant marker of clinical severity, relating to EDSS, cognitive and motor function. Associations between specific cortical lesion types and disability measures were less clear, and might be biased by the MRI sequence used. Episodes of cognitive worsening have been documented in relation to cortical lesion development at 3 T, supporting a notion of "cortical" relapses due to newly developing cortical lesions (Puthenparampil et al., 2016). Rather than focusing on whole brain lesion counts and overall clinical impairment, future studies should address the structure–function relations between the manifestation of individual cortical lesions, in terms of location, lesion-type, and impairment within specific functional domains, such as motor, sensory, cognitive impairment or fatigue. Mental fatigue is one of the most frequent and disabling symptoms in MS. Clinicians and patients are frequently frustrated by this symptom, which cannot be accounted for by white matter lesions alone (Sepulcre et al., 2009). An impact of cortical lesions on fatigue is plausible, since neurons in cortical MS lesions show signs of mitochondrial injury and respiratory chain dysfunction (Campbell, Worrall, and Mahad 2014). However, assessment of the independent contribution of cortical lesions to impairment of specific domains is complicated by confounding factors, including e.g. atrophy and spinal cord involvement. Future study designs should account or correct for these factors by patient selection in longitudinal studies or by advanced statistical procedures in cross-sectional designs.

4.7. Moving ultra-high field MRI of cortical lesions into the clinical setting

Despite the well-documented advantages of 7 T MRI in MS, it has not yet been implemented as a clinical tool. Fortunately, the recent certifications of some 7 T MRI systems by the Food and Drug Administration (FDA) and the Conformité Européenne (CE), may facilitate clinical use of 7 T MRI in MS. Using the MAGNIMS recommended protocol for clinical workup (T1w, T2w and FLAIR images) (Rovira et al., 2015), 7 T images acquired in ~ 30 min improved cortical lesion detection by all three sequences compared to corresponding 3 T sequences without compromising sensitivity for white matter lesions (de Graaf et al., 2013). In a clinically feasible protocol, including T2*w at a total scan time of ~ 22 min, all cortical lesion types were captured with high inter-rater agreement in patients with RRMS and PMS (Cocozza et al., 2020). One study comparing 7 T with 3 T MRI in a clinical setting described increased confidence in MS diagnosis with 7 T MRI, which related partly to improved cortical lesion detection (Springer et al., 2016). Additionally, histopathological data indicated that 7 T MRI of cortical lesions may accelerate differential diagnosis of primary demyelinating diseases such as MS and rare acute syndromes associated with IgG antibodies against myelin oligodendrocyte glycoprotein as opposed to other diseases with features of demyelination such as neuromyelitis optica spectrum disorder, hereditary leukodystrophies and neuro-infections (Sinnecker et al., 2012a; Behrens et al., 2018; Junker et al., 2020; Fischer et al., 2013). However, the potential of cortical lesions for improved differential diagnosis needs confirmation by systematic comparative studies at 7 T. A thorough review on the diagnostic potential of 7 T MRI in MS can be found elsewhere (Sati 2018). There are, however, also technical challenges with 7 T MRI, including higher B_1 and B_0 field inhomogeneities, potentially greater impact of subject motion and specific absorption rate limitations that need to be addressed before 7 T can become a useful clinical tool (Sati 2018). In addition, stricter safety precautions may exclude more patients from 7 T as compared to 3 T MRI.

4.8. Limitations

The conversion from median and range of cortical lesion counts to means from some studies limits the interpretation of our results. Cortical lesion counts often have a skewed distribution, biasing the estimation of group means, although the method used in this study provides a better protection against this bias than previous ones (Luo et al., 2018). We did not perform any statistical testing due to the low number of studies included in the sub-analyses. Therefore, the numbers are not corrected for variations in population demographics, which might limit the interpretability of our results. Because many studies only reported combined intracortical lesion counts, we also pooled cortical lesion type II and III/IV into one category, although histopathology proposes that the two lesion types have different origins (Peterson et al., 2001; Kidd et al., 1999). Pooling may be justified in so far as type II-IV lesions are all drained by strictly intracortical venules as opposed to type I lesions, which are associated with principal cortical veins that are transcortical and drain into the juxta-cortical white matter (Duvernoy, Delon, and Vannson 1981; Kidd et al., 1999). However, compared to type II and type I lesions, type III/IV subpial lesions may be more specific for MS or MOG-AD.

5. Conclusion and outlook

7 T MRI improves cortical lesion detection in MS compared to clinical field strengths, especially for subpial demyelination which is of high diagnostic and prognostic relevance. However, our review emphasizes the need for standardization in both acquisition and processing (i.e. segmenting) of 7 T MRI data. Nonetheless, based on the combined findings from 7 T MRI studies, is seems that the MAGNIMS protocol at 7 T is clinically feasible and improves detection and monitoring of cortical lesions. Adding a sequence more sensitive to subpial lesions, like T2*w, would most likely be beneficial, although further histopathological validation is warranted. Importantly, improved cortical lesion visualization at 7 T can be achieved without compromising the sensitivity for white matter lesions. By providing a clearer view of cortical pathology, 7 T will improve the management of demyelinating diseases by accelerating differential diagnosis of encephalopathies affecting myelin and phenotyping within the MS-spectrum. Alleviating the difficulty in MS phenotyping is of immense clinical concern since emerging therapies are licensed and accessible only to patients of specific MS phenotypes.

Funding and competing interests:

M.A.J.M., V.W. and J.R.C. have nothing to declare.

H.R.S. has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark, Lophora, Denmark, and Lundbeck AS, Denmark, and as editor-in-chief (NeuroImage: Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark.

V.W. receives research support from the Danish Multiple Sclerosis Society and the Lundbeck Foundation.

F.S. has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, H. Lundbeck A/S, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme.

S.B. received one speaking honorary from Biogen Idec (Denmark) and reimbursement for congress participation from Biogen, Roche, Merck and Sanofi Genzyme.

This work was supported by the Danish Multiple Sclerosis Society [Grant numbers: A33409, A35202, A38506] and the Independent Research Fund Denmark [Grant number: 9039-00330A].

H.R.S. holds a 5-year professorship in precision medicine at the Faculty of Health Sciences and Medicine, University of Copenhagen which is sponsored by the Lundbeck Foundation [Grant Nr. R186-2015–2138].

CRediT authorship contribution statement

Mads A.J. Madsen: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Vanessa Wiggermann:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Stephan Bramow:** Investigation, Writing – original draft. **Jeppe Romme Christensen:** Writing - review & editing. **Finn Sellebjerg:** Writing - review & editing. **Hartwig R. Siebner:** Conceptualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102847.

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