

Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI



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ABSTRACT

Background: Different double inversion recovery (DIR) sequences are currently used in multiple sclerosis (MS) research centers to visualize cortical lesions, making it difficult to compare published data. This study aimed to formulate consensus recommendations for scoring cortical lesions in patients with MS, using DIR images acquired in 6 European centers according to local protocols.

Methods: Consensus recommendations were formulated and tested in a multinational meeting.

Results: Cortical lesions were defined as focal abnormalities on DIR, hyperintense compared to adjacent normal-appearing gray matter, and were not scored unless ≥ 3 pixels in size, based on at least 1.0 mm² in-plane resolution. Besides these 2 obligatory criteria, additional, supportive recommendations concerned a priori artifact definition on DIR, use of additional MRI contrasts to verify suspected lesions, and a constant level of displayed image contrast. Robustness of the recommendations was tested in a small dataset of available, heterogeneous DIR images, provided by the different participating centers. An overall moderate agreement was reached when using the proposed recommendations: more than half of the readers agreed on slightly more than half (54%) of the cortical lesions scored, whereas complete agreement was reached in 19.4% of the lesions (usually larger, mixed white matter/gray matter lesions).

Conclusions: Although not designed as a formal interobserver study, the current study suggests that comparing available literature data on cortical lesions may be problematic, and increased consistency in acquisition protocols may improve scoring agreement. Sensitivity and specificity of the proposed recommendations should now be studied in a more formal, prospective, multi-center setting using similar DIR protocols. *Neurology*® 2011;76:418-424

GLOSSARY

DIR = double inversion recovery; **EDSS** = Expanded Disability Status Scale; **GM** = gray matter; **MS** = multiple sclerosis; **WM** = white matter.

Histopathology studies have shown that demyelination of the gray matter (GM) is extensive in multiple sclerosis (MS).¹⁻⁴ However, visualization of cortical lesions in MS with standard MRI techniques remains difficult.⁵ More advanced MRI techniques, like double inversion recovery (DIR), enabled substantial improvement of cortical lesion detection,⁶⁻⁸ and showed that cortical lesions are associated with clinicocognitive impairment.⁹⁻¹¹

In healthy brain, DIR visualizes GM, while suppressing the signals from white matter (WM) and CSF.^{6,12} Unfortunately, this double suppression scheme creates an image with low signal-to-noise, which, combined with the influence of a nonuniform magnetic field in the cortex and

Editorial, page 412

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flow artifacts, has sparked debate as to whether all signal hyperintensities on DIR should be considered actual cortical lesions. Subsequently, high-field¹³⁻¹⁵ and (combinations of) T1-based and phase-sensitive inversion-recovery techniques¹⁶⁻¹⁹ were shown to improve visualization of cortical lesions.¹⁹ A recent study using advanced multicontrast 3-dimensional imaging confirmed the potential of DIR imaging, by showing that DIR permits the highest detection of cortical lesions when compared with other sequences.²⁰

Postmortem verification of cortical hyperintensities on DIR is ongoing, but is hampered by several challenges posed by optimization of DIR for postmortem tissue imaging. Therefore, a true gold standard is currently unavailable. With this in mind, a multinational meeting was organized to reach consensus and propose recommendations for scoring cortical MS lesions on available *in vivo* DIR images. The results of this consensus meeting, and the first application of the recommendations to a DIR dataset, are presented here.

METHODS Participating centers. Twelve researchers with various degrees of experience in identifying MS lesions on conventional scans, from 6 specialized European MS centers (University College of London, UK; University Hospital Basel, Switzerland; University Hospital Vall d'Hebron, Barcelona, Spain; University Hospital San Raffaele, Milan, Italy; Multiple Sclerosis Center of Veneto Region, Padova, Italy; and VU University Medical Center, Amsterdam, the Netherlands) convened for a 2-day consensus meeting in Amsterdam. Before the meeting, representative DIR images from healthy controls and patients with MS were acquired in the different centers according to their local protocols, and were discussed digitally by the researchers, so that they had the

opportunity to become acquainted with the different sequences before the meeting.

Collection of MRI. Prior to the consensus meeting, each center was asked to send to the meeting organizers whole-brain DIR scans of 3 patients with MS and one healthy control. This resulted in imaging data from a total of 18 patients with MS (mean age: 42 years \pm 9 years; 10 women; mean disease duration: 129 \pm 103 months; median Expanded Disability Status Scale (EDSS) score: 3.0 [range 1.0–6.5]) and 6 healthy controls (mean age: 35 \pm 6 years; 4 women). Since these DIR images were acquired for previous studies using local protocols, the final imaging dataset was heterogeneous. In particular, 1.5 T scanners were used in 3 centers, 3 T scanners in 2 centers, and both 1.5 T and 3 T scanners in one center. In addition, 4 centers acquired 3-dimensional images, while 2 centers acquired 2-dimensional images. Sequences featured different slice thicknesses (mean 1.4 mm; range 1.3–3.0 mm), spatial resolution (mean 1.21 mm²; range 0.98–1.3 mm²), and number of slices (mean 124; range 44–256). For an illustration of the collected DIR images from the different centers, and differences in parameters, see the table and figure 1.

Definition of recommendations. The consensus meeting was conducted in 2 parts. During the first day, the 12 meeting participants discussed the definition of formal criteria for international cortical lesion scoring, based on DIR imaging. The discussion was supported by 2 practice sessions, during which readers applied interim recommendations to a test set of DIR images (of both patients and healthy controls, selected from existing databases from Padova, Amsterdam, and Milan). This allowed them to share experiences concerning the feasibility of interim recommendations, upon which suggestions for modification and refinement were discussed. At the end of the first day, final scoring recommendations were formulated and agreed upon. It was decided to score cortical lesions, which had to be entirely or partly located in the cortical GM, but that subpial demyelination² and lesions located in WM directly adjacent to the cortex (i.e., not entering the cortical GM) would not be scored.

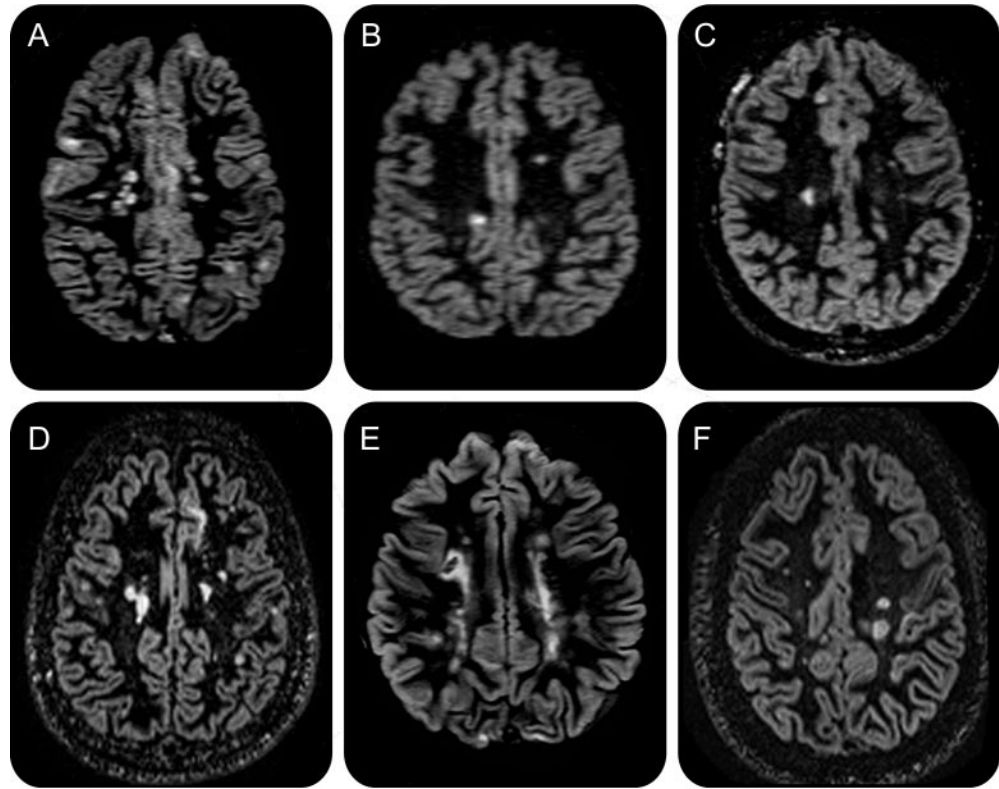
Application of the recommendations using the collected data. On the second day of the meeting and after a brief recapitulation of the defined scoring recommendations, 5 teams, consisting of 2 or 3 readers each, scored the collected DIR images (axial representation) of the 18 patients with MS and 6 healthy controls (described above). The use of images from hu-

Table DIR sequence parameters from the different sites

Sequence parameters	London	Basel	Barcelona	Milan	Milan	Padova	Amsterdam
Field strength	3.0 T	1.5 T	1.5 T	1.5 T	3.0 T	1.5 T	1.5 T
TR, ms	10,000	7,500	2,350	11,000	11,000	15,631	6,500
TE, ms	83	311	356	25	25	25	355
Tl _{1,2} , ms	510, 3,000	500, 3,000	350, 2,350	325, 3,400	325, 3,400	325, 3,400	350, 2,350
Slice thickness, mm	1.3	1.5	1.3	3.0	5.0	3.0	1.2
No. of slices	120	128	120	44	24	50	256
In-plane resolution, mm \times mm	1.2 \times 1.2	1.3 \times 1.3	1.3 \times 1.3	1.0 \times 1.1	0.9 \times 1.2	1.9 \times 0.8	1.2 \times 1.3
2D/3D	3D	3D	3D	2D	2D	2D	3D
Acquisition time, min:sec	15:00	08:02	09:45	06:03	08:00	05:31	09:50

Abbreviations: DIR = double inversion recovery; TE = echo time; Tl = inversion time; TR = repetition time.

Figure 1 Double inversion recovery (DIR) sequences from the different sites collaborating in this study



(A) DIR from Padua (1.5 T), (B) Barcelona (1.5 T), (C) Amsterdam (1.5 T), (D) Basel (1.5 T), (E) Milan (3.0 T), and (F) London (3.0 T).

man subjects for this study was approved by the local Institutional Review Board, and written informed consent was obtained from all participants. Data were fully anonymized, i.e., no patient, site, or sequence information was visible on the images. Teams of readers, instead of single raters, were chosen to stimulate discussion between participants about the application of the newly proposed scoring recommendations. DIR hyperintensities were marked as lesions if consensus was reached between the members of a given team.

All scorings were analyzed after the meeting and a comparison of lesion ratings between teams was made. Agreement between rating teams on the level of individual lesions was assessed, by noting whether ≥ 3 , ≥ 4 , or all 5 teams had scored the same lesion. Similarly, agreement was investigated on the patient level, i.e., the total cortical lesion number per patient, by calculating a coefficient of variation.

RESULTS Recommendations for cortical lesion scoring in patients with MS. The meeting resulted in the definition of a set of to-the-point recommendations for cortical lesion scoring.

It was deemed obligatory that:

1. Cortical lesions are hyperintense on DIR images, compared to surrounding normal-appearing GM.
2. Moreover, cortical hyperintensities should occupy at least 3 pixels (based on minimally 1 mm² in-plane resolution).

Furthermore, the following points were suggested as supportive recommendations:

1. Readers should become acquainted with common artifacts (i.e., unwanted changes in signal intensity) on DIR. Several areas in the brain seem to be especially artifact-prone on DIR (for an illustration of common [sites of] artifacts on DIR, see figure 2). Readers should be familiarized with these artifacts using healthy control DIR images acquired with the same imaging parameters as those used for the MS patient scans to be scored.
2. Near-constant image contrast settings should be maintained while scoring, to avoid confusion resulting from inherent inhomogeneous signal abnormalities (subtle and diffuse hyperintensities) in the cortex.
3. Multiple slices may need to be viewed when determining whether or not a DIR signal hyperintensity should be scored as a cortical lesion; in this way, lesions can be distinguished from (round, traceable) cortical vessels (see figure 2). A slightly irregular shape (as opposed to neatly rounded vessels) of a hyperintensity may also be a supporting feature of demyelination.
4. Other MRI contrasts, notably T1-based and T2 or fluid-attenuated inversion recovery images (preferably 3-dimensional isotropic volumes to allow reformatting and optimal matching with

Figure 2 Common (sites of) artifacts on double inversion recovery (DIR) images (healthy control subject)



Left panel: Areas of high signal in the archicortex and paleocortex, such as the insula (arrows). Right panel: Cortical vessels may be a nuisance factor when examining DIR images; arrows indicate hyperintense vessels which may on occasion be mistaken for cortical lesions, and the box (right panel) and inset (top panel) illustrates that the cortex may appear "grainy" as a result of vessel hyperintensities.

DIR), may be used to verify suspected lesions and to distinguish them from artifacts.

Cortical lesion scoring using the recommendations. A total of 537 cortical lesions were scored by the 5 teams, with a range of 4 to 142 lesions per patient (for examples of lesions scored by only one or by multiple rating teams, see figure 3). Using the proposed scoring recommendations, complete agreement (i.e., all 5 teams scoring the same lesion) was reached in 104 out of 537 lesions (19.4%), whereas 4 or more teams agreed about 212 lesions (39.5%) and 3 or more teams out of 5 agreed on 290 lesions (54.0%). Full agreement was generally reached more easily when lesions contained a WM part (mixed WM/GM lesions), while agreement was low in the case of smaller intracortical lesions and lesions affecting the cerebellar cortex (figure 3). Also, hyperintensities in the insula or any of the other archicortical and paleocortical regions (inherently higher signal intensity on DIR sequences) were rarely scored by all 5 teams (6 out of 47 lesions). The DIR sequences acquired in Padova, Amsterdam, and Basel (see table) generated the highest average agreement (2.58, 2.48, and 2.63 teams out of 5 agreeing per lesion, respectively).

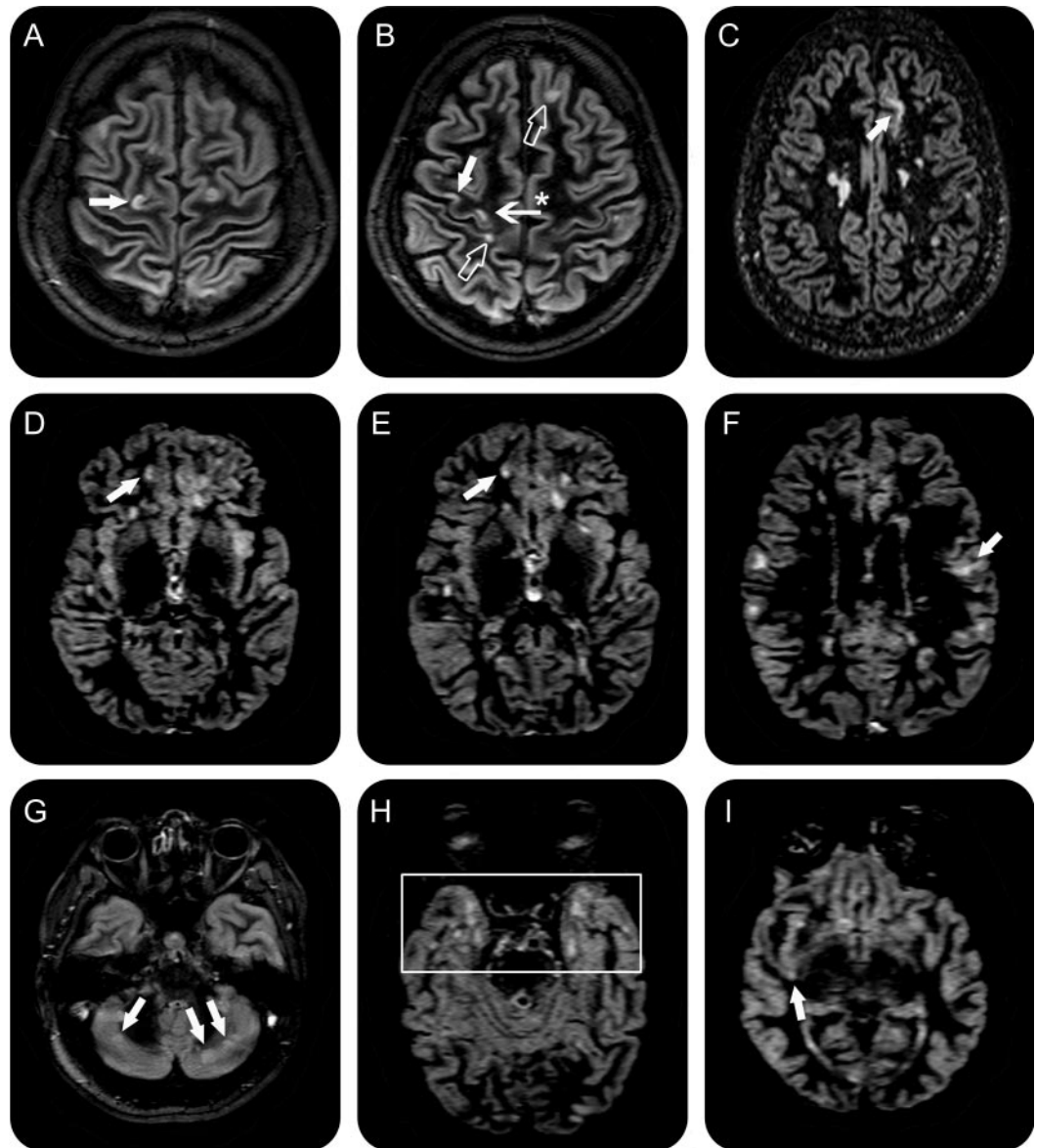
On the patient level, i.e., concerning agreement on the total number of cortical lesions per patient,

the teams scored with a coefficient of variation of 42%.

DISCUSSION Cortical MS lesions are difficult to visualize in vivo when using standard MRI techniques,⁵ and the introduction of DIR has led to a major improvement in the detection of these lesions.⁶ Realizing the potential of this technique, several research groups have started implementing DIR on their scanner systems and, at different sites, DIR has been used to visualize cortical lesions in patients with MS and to relate cortical lesion numbers and volumes to clinical, especially cognitive, deficits.^{9,11,21} Furthermore, DIR has been used to study the relation between cortical lesions and other MRI characteristics of patients with MS, such as cortical atrophy and WM damage.^{10,11} However, different DIR sequence parameters are currently being applied worldwide, and images are acquired at different field strengths, which makes it difficult to compare available cortical lesion data from the different groups. The aim of the consensus meeting reported here was to assess the existing DIR imaging data from different European centers, and formulate internationally useful recommendations for scoring of cortical lesions in MS. The usefulness of these recommendations was provisionally explored by determining agreement of cortical lesion scorings between different reader teams, and it was found that, when using this inherently heterogeneous set of images, more than half of the readers (≥ 3 out of 5 teams) agreed on slightly more than half (54%) of the cortical lesions scored. On a patient-by-patient level, a coefficient of variation of 42% was found. These findings indicate that it is possible to reach agreement, albeit moderate, concerning cortical lesion scoring in MS with ratings being based on available DIR data. In particular, confidence in scoring of a lesion (inter-team agreement) increased in cases of large and mixed GM/WM lesions, suggesting that a comparison between available literature data on cortical lesions may become problematic if lesion characteristics depart from these features.

From a theoretical point of view, even in more homogeneous datasets than the one used for the current study, agreement on what is and what is not a cortical lesion may be challenging. Owing to 2 subsequent inversion pulses that together suppress the signal from CSF and WM, an image with a relatively low signal-to-noise is produced.^{6,12,20} This, in combination with a certain proneness to artifacts, such as flow and slice profile inhomogeneities (i.e., nonuniform signal in multislab imaging volumes), has already prompted researchers to replace multislab⁶ versions of DIR by single-slab versions.^{12,20} However,

Figure 3 Examples of cortical lesions on double inversion recovery using 3 T (A, B, G) and 1.5 T (C, D, E, F, H, I)



In all panels (A–I), scored intracortical lesions are indicated by closed arrows, and scored mixed white matter/gray matter lesions are indicated by open arrows. Lesions marked by all rating teams are shown in panels (A) to (C), with the exception of the juxtacortical lesion indicated by the arrow marked with an asterisk in (B), where raters disagreed about the localization of the lesion. The lesion indicated by the arrow in (D) and (E) was viewed over 2 consecutive slices to ensure its localization. Lesions scored by only 1 or 2 out of the 5 rating teams are shown in panels (G) to (I); these lesions often occur in the cerebellar gray matter (G), the medial temporal lobes (H) (indicated by the box), and the insular cortex (I). Please see text for more details.

variation of T1 properties of different cortical areas, which is generally appreciated on DIR images (figure 2), may still get in the way of reliable lesion scoring, which has led to debate about whether all hyperintensities scored on DIR images are, in fact, cortical lesions. With a postmortem verification of DIR findings still lacking at this point, and given the ongoing use of DIR images to identify GM lesions, the consensus recommendations presented here sought to establish a unified set of practical rules for GM lesion scoring, applicable to currently available multicenter

DIR data. It is anticipated that, with further improved imaging techniques, and future information from postmortem work, these recommendations will be revised. However, in their present form they may provide a useful baseline against which subsequent ones can be compared.

The recommendations recommend that areas identified as GM lesions be clearly hyperintense on DIR, and cover at least 3 pixels (based on a minimal in-plane resolution of 1.0 mm^2). These criteria were proposed to account for the relatively low signal-to-

noise of DIR images at 1.5 T and 3 T (compared with, for example, conventional 2-dimensional T2-weighted images). Furthermore, the recommendations take into account that DIR images at 1.5 T and 3 T are relatively noisy and inhomogeneous in terms of T1, and that cortical vessels may be a nuisance factor when scoring cortical lesions. The supportive recommendations take this further, suggesting that image readers become acquainted with signal intensities in archicortical and paleocortical areas, such as the hippocampus and insula, which may be inherently higher on DIR compared to those of neocortical areas (figure 2). Also, following suspected lesions over several slices and using other MRI contrasts like T1-weighted or phase-sensitive or fluid-attenuated inversion recovery to consider the morphologic features of observed DIR hyperintensities may further convince the reader on whether or not to score hyperintensities as cortical lesions. It should be noted that different techniques may visualize different subpopulations of cortical lesions,¹⁷ and that the absence of a signal abnormality on T1 or fluid-attenuated inversion recovery does not necessarily imply that a signal hyperintensity on DIR should be artifactual. However, one may choose to be prudent in individual cases where lesions do not match on different image contrasts. For the time being, the consortium gathered for this meeting decided against scoring subpial demyelination on DIR, as it is known from comparative MRI–histopathology studies that these lesions create extremely low contrast on MRI.^{5,22} Scoring of demyelination within the upper layers of the cortex may therefore a priori be expected to generate high numbers of false-positive results, and generally poor agreement between readers. In the future, visualization of these lesions may be facilitated by the use of higher field strengths,^{13,14} and hence be considered as part of updated scoring recommendations.

The final set of recommendations presented in the current article were created through discussion between MRI experts from 6 different MS centers in Europe, and were fine-tuned during image review sessions and verification of interim recommendations. The ultimate set of obligatory and supportive recommendations presented in the current article was used by the experts for the first, provisional scoring of a small selected dataset of DIR images from both patients with MS and healthy controls. Although agreement was calculated based on these ratings, the current study was not designed as a formal interrater study, and hence did not specifically aim to validate the formulated recommendations, nor to determine their sensitivity, specificity, or predictive value. Rather, these results, based on the defined scoring recommendations, should be seen as a first

and tentative exploration, showing that it is possible to reach moderate consensus about roughly half of the observed cortical hyperintensities on DIR, when using currently available and heterogeneous data. Although these recommendations may enable a more integrated interpretation of DIR hyperintensities, they still leave readers divided as to the nature of almost half of the hyperintensities identified by at least one group. This suggests that increased consistency in acquisition protocols may improve future scoring agreement. The DIR sequences acquired in Padova, Amsterdam, and Basel elicited the highest average agreement per lesion, but it is difficult to recommend any of these sequences for clinical or therapeutic applications at this point, as this would require a study specifically designed for this purpose. Lesion type, size, and location, as well as field strength, image quality measures, and sequence type, are likely to have an effect on scoring agreement, even though these factors did not reach statistical significance in the current, restricted sample. The recommendations proposed here should now be studied within a more formal, prospective setting, using multicenter DIR data with similar sequence parameters and field strengths, in order to determine their practical value, and to further adapt them to improve the reliability of cortical lesion number and volume comparisons between different studies and raters in future MS studies. When sufficient reliability regarding cortical lesion assessment is reached, they might be incorporated in updated MS diagnostic criteria and an optimal DIR sequence for the clinical setting should be proposed.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. J.J.G. Geurts and Dr. B.M.J. Uitdehaag.

COINVESTIGATORS

The current work was conducted on behalf of the MAGNIMS Study Group. The following Contributors provided patient data and discussed the contents and interpretation of the study: F. Barkhof, MD (Department of Radiology, VU University Medical Centre, Amsterdam, the Netherlands); X. Montalban, MD (Clinical Neuroimmunology Unit, Multiple Sclerosis Centre of Catalonia, Hospital Vall d'Hebron, Barcelona, Spain); N. de Stefano, MD (Department of Neurological and Behavioral Sciences, University of Siena, Siena, Italy); F. Fazekas, MD (Department of Neurology, Medical University Graz, Graz, Austria); M. Filippi, MD (Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University, Ospedale San Raffaele, Milan, Italy); J. Frederiksen, MD (MS Clinic, Department of Neurology, University of Copenhagen, Glostrup Hospital, Denmark); L. Kappos, MD (Department of Neurology, University Hospital, Kantonsspital, Basel, Switzerland); D. Miller, MD (NMR Research Unit, Institute of Neurology, University College London, London, UK); J. Palace, MD (Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK); C.H. Polman, MD (Department of Neurology, VU University Medical Centre, Amsterdam, the Netherlands); M. Rovaris, MD (U.O. Sclerosi Multipla, IRCCS S. Maria Nascente, Fondazione Don Gnocchi, Milan, Italy); M. Rocca, MD (Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University, Ospedale San Raffaele,

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DISCLOSURE

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