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Improved in vivo detection of cortical lesions in multiple sclerosis using double inversion recovery MR imaging at 3 Tesla

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Abstract *Objective:* To investigate the impact of a higher magnetic field strength of 3 Tesla (T) on the detection rate of cortical lesions in multiple sclerosis (MS) patients, in particular using a dedicated double inversion recovery (DIR) pulse sequence. *Methods:* Thirty-four patients with clinically isolated syndromes or definite MS were included. All patients underwent magnetic resonance imaging (MRI) at 1.5 T and 3 T, including T2-weighted turbo spin echo (TSE), fluid-attenuated inversion recovery (FLAIR) and DIR sequences. All images were analysed for focal lesions categorised according to their anatomical location. *Results:* The total number of detected lesions was higher at 3 T across all pulse sequences. We observed significantly higher numbers of lesions involving the cortex at 3 T using a DIR sequence. DIR at 3 T showed 192% more pure intracortical ($p<0.001$) and 30% more mixed grey matter-white matter lesions ($p=0.008$). No significant increase in cortical lesions could be detected on the FLAIR and T2-weighted images. Using the T2-weighted and FLAIR sequences, significantly more lesions could be detected at 3 T in the infratentorial, periventricular and juxtacortical white matter. *Conclusion:* DIR brain MR imaging at 3 T substantially improves the sensitivity of the detection of cortical lesions compared with the standard magnetic field strength of 1.5 T.

Keywords Multiple sclerosis ·
Magnetic resonance imaging ·
Double inversion recovery ·
Cortical lesions · Pulse sequences

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS) in young adults and is characterised by the presence of multifocal inflammatory demyelinating lesions disseminated in space and in time [1, 2]. Although MS has been considered a disease primarily affecting the white matter, it has been conclusively shown that MS lesions occur abundantly in the grey matter as well [2, 3].

Magnetic resonance imaging (MRI) is the most sensitive paraclinical method in the detection of focal and diffuse abnormalities in the brain of MS patients. Using conventional MRI techniques, MS lesions are frequently and

typically detected in certain anatomical regions, such as the periventricular, juxtacortical and infratentorial white matter, which is reflected by current MRI and clinical diagnostic criteria [1, 2, 4–7]. However, despite the histopathological abundance of cortical lesions in MS patients, the sensitivity of MRI in the detection of cortical lesions remains rather low [3, 8].

Because of the substantial increase in the signal-to-noise ratio (SNR), high-field MRI beyond 1.5 Tesla (T) offers several advantages and new possibilities especially in the field of neuroimaging [9]. In patients with suspected and/or definite MS, high-field MRI provides higher lesion load measurements of acute and chronic white matter lesions. This higher sensitivity becomes specifically obvious in anatomical regions that are important for the diagnosis and prognosis of MS [10]. However, whether higher magnetic field strengths also provide an improved in vivo detection of cortical abnormalities has not been investigated and remains questionable.

The aim of our study was to investigate the impact of a higher magnetic field strength of 3 T on the detection rate of cortical lesions in MS patients, in particular using a dedicated double inversion recovery (DIR) pulse sequence.

Materials and methods

Study design

This study was designed as an intraindividual comparative study in patients with a clinically isolated syndrome (CIS) suggestive of MS or patients with definite MS. The study protocol was approved by the local institutional review board and written informed consent was obtained from all participants. Inclusion criteria were: CIS of the central nervous system (CNS) suggestive of MS or definite MS as defined by the International Panel on MS diagnosis [2]; exclusion criteria were: any vascular, malignant and other immunological CNS diseases in the present and/or past medical history.

Patients and healthy controls

Thirty-four patients (26 female; median age at the time of MR examination 38 years, range 22–52 years) and nine healthy controls (three male, six female; median age at the time of MR examination 34 years, range 24–61.5 years) were included in this study. Two patients presented with a CIS and 32 patients had a relapsing-remitting course of MS (RR-MS) according to the revised International Panel criteria on MS diagnosis [2]. None of the patients received any treatment with corticosteroids in the month before the MR examination. All patients with RR-MS were under immune-modifying treatment at the time of the MR examination. The median disease duration (estimated from the first clinical event) of the CIS patients was 6.5 months (patient 1, 3 months; patient 2, 10 months), and 8 years (range 2 months to 26.3 years) for the RR-MS group. The median disability score of the patients according to the Expanded Disability Status Scale [11] at the time of the MRI examination was 1.6 (range 0–4), indicating mild disability.

MRI

The MR examination was performed on 1.5-T and 3-T whole-body MRI (Achieva, Philips Medical Systems, Best, the Netherlands). The examinations at both field strengths

Table 1 Sequence parameters used at 1.5 T and 3T (*TR* repetition time, *TE* echo time, *IR* inversion recovery, *SENSE* sensitivity encoding, *NSA* numbers of signals averaged)

System Parameter Orientation	1.5 T FLAIR Transverse	3 T Transverse	1.5 T T2 TSE Transverse	3 T Transverse	1.5 T DIR Transverse	3 T Transverse
Number of sections	40	40	40	40	40	40
Slice thickness/gap (mm)	3/0	3/0	3/0	3/0	3/0	3/0
Measured voxel size (mm)	1/1/3	1/1/3	1/1/3	1/1/3	1/1/3	1/1/3
Echo train	21	38	18	40	16	13
TR (ms)	6,000	12,000	4,100	5,100	13,092	11,000
TE (ms)	140	140	100	100	25	25
IR delay (ms)	2,000	2,850	–	–	3,400/325[a]	3,400/325[a]
SENSE factor	1.9	1.35	1	1	–	2
NSA	2	1	2	1	2	2
Imaging time (min:s)	5:12	4:00	3:41	1:42	8:17	6:36

[a] The long inversion time TI_1 (3,400 ms) is defined as the interval between the *first* 180° inversion pulse and the 90° excitation pulse. The short inversion time TI_2 (325 ms) is defined as the interval between the *second* 180° inversion pulse and the 90° excitation pulse

were performed in a randomised order within a time interval of 12 h. Both MRIs were equipped with standard gradients (a maximum slew rate of 150 mT/m/ms and a maximum strength of 30 mT/m). For the examinations at both MRI systems, an eight-element phased array sensitivity encoding (SENSE) head-coil (Philips Medical Systems, Best, the Netherlands) was used.

The imaging protocol at both field strengths included 40 contiguous sections in two-dimensional (2D) transverse orientation of the following pulse sequences: T2-weighted turbo spin echo (TSE), fluid-attenuated inversion recovery (FLAIR) and DIR. The MR sequence parameters were separately optimised for 1.5 T and 3 T. The parameters are given in detail in Table 1. The same repositioning was used for all pulse sequences across both 1.5-T and 3-T MRIs according to the Consortium of MS Centers consensus guidelines [12].

Image analysis

The image analysis was performed by two radiologists in consensus, each with experience of at least 5 years in neuroradiology and with special expertise in the field of inflammatory demyelinating diseases such as MS. The images were analysed at a digital workstation (Centricity Radiology RA 600 version 6.1, General Electrics Medical Systems, USA) and the order of analysis randomised for the different pulse sequences of the MR examinations. Both readers were blinded to the clinical presentation and paraclinical tests (visual evoked potentials, CSF analysis, blood tests). The images of healthy controls were evaluated in terms of artefacts that might impair the diagnostic quality and lead to false-positive or -negative results. All images obtained from the patient group were analysed for focal lesions, which were categorised according to their anatomical location in: pure cortical, mixed white matter-grey matter, deep grey matter, juxtacortical, deep white matter, periventricular white matter and infratentorial lesions. Regarding the white matter lesions, we considered focal high signal intensity lesions with a size of ≥3 mm. The classification in terms of different anatomical locations was performed according to published criteria [4, 5]. Intracortical lesions and mixed white matter-grey matter lesions were defined as focal lesions with higher signal intensity than the normal appearing grey matter. Intracortical lesions were further defined as lesions purely located in the cortex not involving the white matter. Abnormalities only involving the subpial layer of the cortex suggesting subpial demyelination were not considered. White matter-grey matter lesions were defined as lesions partially located in the white matter as well as in the cortical grey matter. The criteria for the identification and classification of cortical lesions were adapted from recently published studies [3, 8, 13, 14]. In order to avoid false positive results due to artefacts (in particular on the DIR), we discriminated

between lesions and artefacts by considering images obtained from healthy control subjects.

Statistical methods

The relative comparison of numbers of lesions seen on 3 T versus 1.5 T for each type of sequence and separated for different anatomical locations was expressed as a percentage of the lesion number seen on 1.5-T MRI. A positive relative comparison indicates an increase in lesions identified at 3 T (higher sensitivity), whereas a negative relative comparison indicates a decrease in the number of detected lesions at 3 T (lower sensitivity).

The statistical evaluation of the patient-based analysis in terms of lesion load measurements (number of lesions) on 3 T and 1.5 T, respectively, was performed with the Wilcoxon test for matched pairs. In order to account for clustering (repeated measurement) a negative binomial regression model with robust sandwich estimators was performed. In the case of a significant interaction between method (different pulse sequences: T2-weighted TSE, FLAIR, DIR) and technique (different magnetic field strengths: 1.5 T, 3 T) the differences between the techniques were tested and adjusted for multiple comparisons (Bonferroni p values).

P values <0.05 were considered statistically significant. The data were analysed using SPSS version 17.0 (SPSS, Chicago, Ill., USA) and Stata version 10.0 (Stata, College Station, Tex., USA) for the negative binominal model.

Results

Healthy control subjects

Focal lesions, artefacts

The MR examinations of the eight healthy controls at both field strengths showed 13, 17 and nine lesions on the T2-weighted TSE, FLAIR and DIR respectively. Most of the lesions were located in the deep white matter [11 (85%) on T2-weighted TSE, ten (59%) on FLAIR, six (67%) on DIR]. The remaining lesions were located in the periventricular white matter. Cortical lesions could not be identified on any of the used pulse sequences in any control subject.

DIR sequences of the healthy control subjects at 1.5 T and 3 T showed comparably high signal changes of certain cortical areas particularly involving the archicortex and palaeocortex as previously described [13, 15]. Moreover, artefacts due to vessel and CSF pulsation could be observed more frequently and prominently on DIR sequences at both field strengths compared with FLAIR and T2-weighted TSE. These artefacts were particularly located in the posterior fossa close to the fourth ventricle, around the

mesencephalic aqueduct and close to the choroid plexus (Fig. 1).

MS and CIS patients

All included patients (CIS and MS) showed focal lesions on MRI. The numbers of detected lesions at both field strengths separated according to their anatomical locations are listed in Table 2. The data of a patient-based analysis are presented in Table 3. The total number of lesions detected was higher at 3 T compared with 1.5 T across all pulse sequences. Separated by different anatomical locations, the lesion load at 3 T was significantly higher in the periventricular ($p=0.016$) and deep white matter regions ($p=0.002$) for the T2 weighted TSE, and in the infratentorial ($p=0.012$), periventricular ($p=0.027$), juxtacortical ($p=0.005$) and deep white matter regions ($p<0.001$) for the FLAIR sequence. For the DIR sequence, the higher lesion count at 3 T reached statistical significance for the infratentorial ($p<0.001$), juxtacortical ($p=0.001$) and deep white matter region ($p<0.001$), but also regarding the pure intracortical ($p<0.001$) and mixed grey matter-white matter lesions ($p=0.008$) (Figs. 1, 2, 3 and 4).

The negative binomial regression model showed no significant interaction between the magnetic field strength and pulse sequences regarding the total number of lesions ($p=0.067$). Considering the subgroup analysis for different anatomical locations, a positive interaction between the magnetic field strength and pulse sequence was significant for intracortical ($p=0.004$) and infratentorial lesions ($p<0.0001$). Separated by the different pulse sequences, it became obvious that this interaction was driven by a significantly increased detection rate for FLAIR ($p=0.0026$; adjusted for multiple comparisons, $p=0.0078$) and DIR ($p<0.0001$; adjusted for multiple comparisons, $p<0.0001$) but not for T2 TSE ($p=1$) regarding infratentorial lesions. Concerning intracortical lesions this effect was only significant for the DIR ($p<0.0001$; adjusted for multiple comparisons, $p<0.0001$) but not for the FLAIR ($p=0.40$; adjusted for multiple comparisons, $p=1$) and T2 TSE sequences ($p=0.49$; adjusted for multiple comparisons, $p=1$).

Discussion

Since gaining the approval of the American Food and Drug Administration (FDA) in 2002, the advantages and challenges of brain imaging using clinical high-field MRI at 3 T have been extensively investigated. In patients with CIS suggestive of MS and definite MS, it has been conclusively shown that imaging at higher magnetic field strengths leads to significantly higher lesion load measurements [16–18]. This is particularly obvious in anatomical regions that are highly important for the diagnosis of MS in the context of diagnostic criteria and prognostic purposes such as the juxtacortical, periventricular and infratentorial white matter [10, 16–18]. Contrary to these studies, which were performed with a rather low spatial resolution using a slice thickness of 5 mm, we used a higher spatial resolution
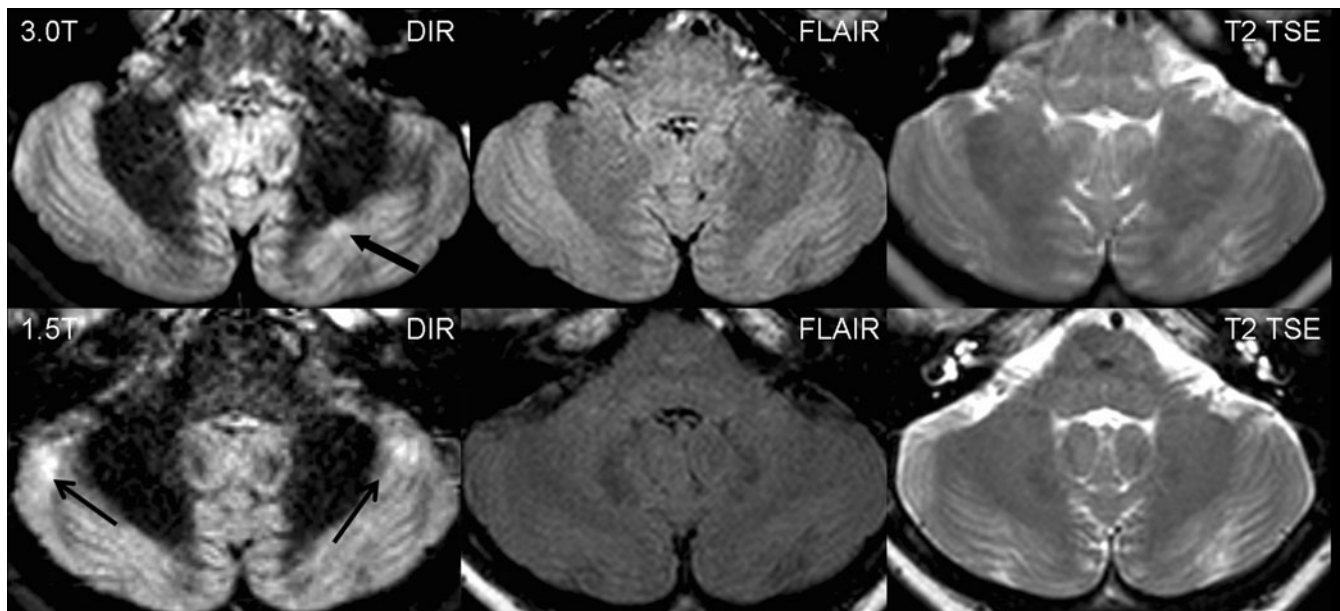

Fig. 1 Transverse sections of the infratentorial brain at 3 T (*top row*) and 1.5 T (*bottom row*) obtained from a 50-year-old woman with relapsing-remitting MS. The DIR sequence (*left column*) is able to detect more infratentorial lesions at 3 T compared with 1.5 T and other pulse sequences such as FLAIR (*middle column*) and T2 TSE (*right column*). Those lesions can also affect the cortex (*closed arrowhead*). Please note the higher propensity of DIR to vessel and CSF pulsation artefacts particularly in the posterior fossa (*open arrowhead*)

Table 2 Numbers of lesions detected at 1.5 T and 3 T categorised according to different anatomical regions (*GM* grey matter, *WM* white matter)

Region	T2			FLAIR			DIR		
	1.5 T	3 T	Relative comparison[a]	1.5 T	3 T	Relative comparison[a]	1.5 T	3 T	Relative comparison[a]
Intracortical	7	5	− 29	10	13	+30	26	76	+192
Mixed GM-WM	44	50	+14	70	84	+20	76	99	+30
Deep GM	3	4	+33	3	4	+33	5	5	0
Juxtacortical	350	389	+11	381	449	+18	286	354	+24
Deep WM	448	513	+15	516	609	+18	408	518	+27
Periventricular	342	392	+15	424	468	+10	434	464	+7
Infratentorial	64	64	0	46	75	+63	77	121	+57
Total	1,258	1,417	+13	1,450	1,702	+19	1,312	1,637	+25

[a] Data represent relative differences in the numbers of lesions detected at 3 T vs 1.5 T expressed as percentages

with a slice thickness according to current imaging guidelines and obtained concordant results. Using 3-T MRI, we were able to identify significantly more lesions than at 1.5 T in the periventricular white matter on the T2 TSE and additionally in the juxtacortical and infratentorial white matter on the FLAIR sequence. The DIR provided the highest lesion load measurement within the posterior fossa at both field strengths. Beside diagnostic imaging criteria, this finding is of special prognostic interest, as it has been shown that the number of infratentorial lesions at baseline plays an important prognostic role in the prediction of long-term disability in patients presenting with CIS suggestive of MS [19].

MS has been traditionally considered as a chronic inflammatory disease predominantly affecting the white matter of the CNS, which is somehow reflected by the high sensitivity of MRI in the detection of focal and diffuse white matter abnormalities in MS patients. However,

pathological studies have convincingly shown that cortical grey matter lesions occur abundantly in MS across all different disease courses and are linked to certain clinical manifestations such as physical disability, cognitive impairment and epilepsy [3, 20, 21]. From the radiological point of view, grey matter manifestations in MS have been disregarded for a long time because of the low sensitivity of conventional MRI techniques in the detection of cortical lesions. As it has been shown that DIR sequences, simultaneously suppressing CSF and the white matter, are able to increase the detectability of grey matter lesions in MS significantly [13], the possible role of MRI in detecting grey matter changes in MS has become a major focus of interest. Currently, DIR applications at 1.5 T are increasingly being used to detect and quantify cortical lesion load in MS patients as well as to correlate these measures with the clinical course, outcome measures and symptom manifestations [14, 22–23]. Compared with

Table 3 Patient-based analysis. Data represent the number of patients with more lesions detected at 1.5 T or 3 T respectively categorised according to different anatomical regions

Region	T2			FLAIR			DIR		
	More lesions at 1.5 T	More lesions at 3 T	p value[a]	More lesions at 1.5 T	More lesions at 3 T	p value[a]	More lesions at 1.5 T	More lesions at 3 T	p value[a]
Intracortical	4	1	0.750	3	5	0.563	0	26	<0.001
Mixed GM-WM	6	8	0.540	6	14	0.483	2	14	0.008
Deep GM	2	3	1.000	3	3	1.000	2	2	1.000
Juxtacortical	10	16	0.136	6	21	0.005	5	20	0.001
Deep WM	6	21	0.002	5	23	<0.001	3	24	<0.001
Periventricular	9	17	0.016	8	18	0.027	9	17	0.060
Infratentorial	9	7	0.993	3	11	0.012	1	20	<0.001
Total	9	20	0.002	5	27	<0.001	3	30	<0.001

[a] P value obtained by Wilcoxon's test for matched pairs. P values < 0.05 are considered statistically significant

Fig. 2 Transverse sections of the supratentorial brain of a 31-year-old man with relapsing-remitting MS. *Upper row images* were obtained at 3 T, *bottom row images* were obtained at 1.5 T. *Left column* DIR images, *middle column* FLAIR images, *right column* T2 TSE images. The 3-T images offer better image quality allowing better delineation of focal inflammatory lesions, regardless of the specific anatomical location. At both field strengths, the DIR sequence allows a better classification of lesions close to the cortex or in the cortex itself as juxtacortical lesions (*closed-head arrows*) or cortical lesions and mixed white matter-grey matter lesions (*open-head arrows*), respectively. In particular, the DIR at 3 T shows more lesions purely located in the grey matter and lesions partially located in the grey and white matter
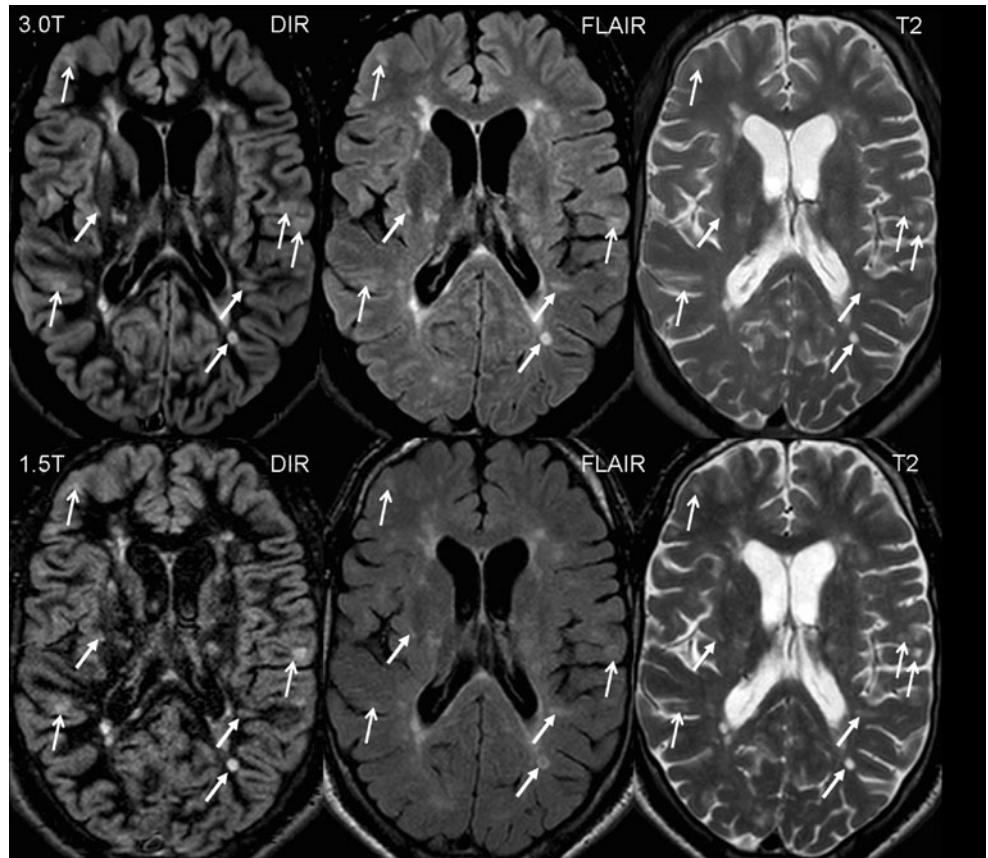
standard pulse sequences such as FLAIR and T2 TSE, substantial drawbacks of DIR applications at 1.5 T are the higher propensity to produce artefacts (in particular because of vessel and CSF flow) but also the relatively low SNR due to the application of two consecutive inversion pulses. These factors can substantially impair the image quality and diagnostic accuracy in many disease entities [24–26]. Because of the higher SNR, imaging at higher magnetic field strengths is, therefore, a promising application of DIR imaging, allowing a further characterisation of cortical structures even with a high spatial resolution [27].

In agreement with recent studies at 1.5 T and 3 T, our study showed that DIR is of greater benefit in the detection of pure intracortical and mixed white matter-grey matter lesions compared with FLAIR or conventional T2-weighted TSE sequences at both field strengths. This finding is mainly based on two different observations: on a better contrast between lesions and the surrounding normal-appearing grey matter due to a slight attenuation of the cortex itself on DIR [13], and also because of a better distinction between pure cortical, mixed white matter-grey matter and juxtacortical lesions on DIR images [13, 28]. Many of these lesions are scored as juxtacortical on conventional T2-weighted FLAIR images leading to a high amount of juxtacortical lesions and rather low numbers of

cortical lesions [29]. This explains the relatively lower numbers of juxtacortical lesions on DIR images (regardless of the field strength used) because many of these lesions were classified as pure cortical or mixed white matter-grey matter lesions.
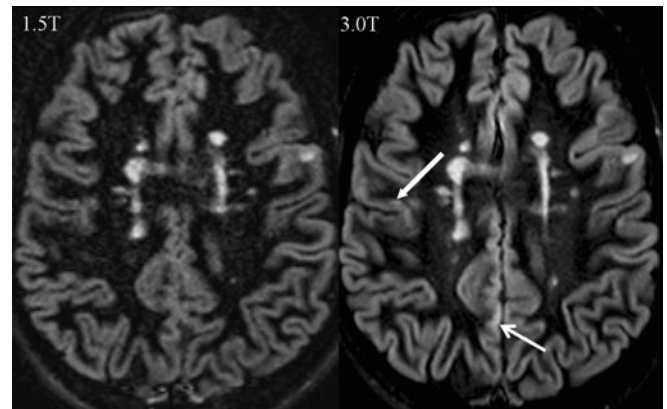

Fig. 3 Transversal sections of a DIR sequence at 1.5 T (*left*) and 3 T (*right*) from a 44-year-old woman with relapsing-remitting MS. Please note the higher conspicuity and improved detection of a lesion purely located in the cortex (*closed-head arrow*). Please note also the diffuse high signal changes in the parasagittal cingulate cortex which can also be frequently observed in healthy control subjects and have to be considered artefacts (*open-head arrow*)
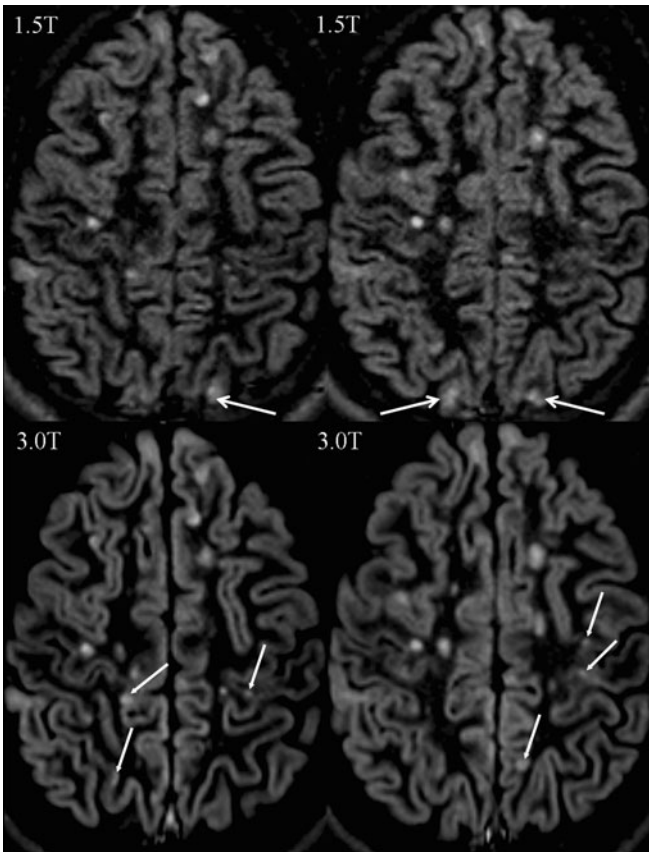
Fig. 4 Two consecutive DIR sections of the supratentorial brain of a 31-year-old man with relapsing-remitting MS obtained at 1.5 T (*top row*) and 3 T (*bottom row*). The DIR sequence benefits from the higher signal at 3 T leading to better delineation of the cortex and inflammatory lesions affecting the cortex (*close-headed arrows*). Please note also diffuse symmetric high signal changes in the occipital cortex (*open-head arrows*) which do not represent real cortical abnormalities and have to be considered artefacts

Moving to higher magnetic field strengths, the results of our studies have shown that 3-T MRI allows a significantly higher in vivo lesion load measurement of cortical lesions in MS patients compared with 1.5 T. However, this higher sensitivity in the detection of cortical lesions using 3 T instead of 1.5 T was only present on DIR and was not significant for the T2-weighted or FLAIR sequences. DIR was the only sequence for which 3 T showed a significant increase in both pure cortical and mixed white matter-grey matter lesions. Keeping in mind that cortical lesions correlate strongly with clinical outcome measures such as cognitive impairment and physical disability [14, 20], the clinical relevance of higher in vivo cortical lesion load measurement using clinical high-field MRI operating at 3 T becomes even more obvious.

The higher cortical lesion load at 3-T MRI using DIR is probably based on a higher SNR and on the re-classifica-

tion of juxtacortical lesions into pure cortical or mixed white matter-grey matter lesions. This can, of course, have substantial consequences in terms of classification of patients (particularly CIS patients) according to MRI criteria [5–7]. As 3-T MRI systems are increasingly being used in a clinical routine setting and multi-centre treatment trials, this higher lesion load of cortical lesions at 3 T and the substantial clinical relevance of cortical lesions are good arguments when considering cortical lesions for future imaging and diagnostic criteria.

However, compared with histopathological studies showing up to nearly 60% of the lesion load in MS patients to be located in cortical areas, we have to be aware that the sensitivity of MRI using DIR even at 3 T remains relatively rather low. Only 10% of all detected lesions on DIR at 3 T were (at least partially) located in the cortex.

The next step might be to investigate whether the next generation of whole-body high-field MRI operating at 7 T can further increase the in vivo detection of cortical lesions. First results are promising but also challenging in particular with regard to the implementation of DIR imaging techniques [30–33].

A limitation of our study is that our image analysis of cortical lesions was limited to the classification of pure cortical and combined (mixed) grey matter-white matter lesions. Although we applied a spatial resolution according to current MS imaging guidelines, we did not try to further classify cortical lesions according to histopathological cortical lesion-type classification. In particular, subpial demyelination, which is the most frequent type of lesion manifestation in the cortex, cannot be reliably visualised on MRI even using ultra-high-field MRI because of a lack of myelin in the superficial cortical layers and a lack of inflammation [34, 35]. Moreover, our study is based on two-dimensional (2D) pulse sequences. The implementation of 3D sequences allowing the acquisition of high-resolution imaging with isotropic voxels and reducing flow artefacts might further increase the lesion count of cortical lesions [13, 36–37]. Additionally, we have to be aware that the readers might not have been sufficiently blinded to the images in terms of the magnetic field strength. Although the readers were formally blinded to the magnetic field strengths, they might have been able identify the 3-T and 1.5-T image by analysing the better image quality and lesion conspicuity on 3 T. This could have resulted in a certain reading bias, which cannot be avoided, however, and is a limitation for all intra-individual magnetic field strength comparisons.

In conclusion, the combination of 3-T MRI and a dedicated DIR pulse sequence leads to a significantly higher sensitivity for the detection of cortical lesions in MS patients, which might lead to considerable consequences for future imaging studies dealing with clinical outcome measures and diagnostic criteria.

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