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Focal Cortical Lesion Detection in Multiple Sclerosis: 3T DIR versus 7T FLASH-T2*

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Abstract

Purpose—To evaluate the inter-rater agreement of cortical lesion detection using 7T FLASH-T2* and 3T DIR sequences.

Materials and Methods—Twenty-six patients with multiple sclerosis were scanned on a human 7T (Sidemen’s) and 3T MRI (TIM Trio, Sidemen’s) to acquire 3T DIR/MEMPR and 7T FLASH-T2* sequences. Four independent reviewers scored and categorized cortical lesions in the bilateral pre-central gyri (motor strips) as leukocortical, intracortical, or subpial. Inter-rater agreement was assessed according to lesion category using the kappa statistic. The sensitivity of recent MAGNIMS consensus guidelines for cortical lesion detection using 3T DIR was assessed with 7T FLASH-T2* as the reference gold standard.

Results—Inter-rater agreement at 7T was excellent compared to 3T (k=0.97 vs. 0.12). FLASH-T2* at 7T detected subpial lesions while 3T DIR did not. The predicted sensitivity of 3T DIR sequence for cortical lesions in vivo is modest (range of 13.6 to 18.3%).

Conclusion—7T FLASH-T2* detects more cortical—particularly subpial—lesions compared to 3T DIR. In the absence of DIR/post-mortem data, 7T FLASH-T2* is a suitable gold-standard instrument and should be incorporated into future consensus guidelines.

Keywords

multiple sclerosis; magnetic resonance imaging; Ultra-high field; cerebral cortex; demyelination; MAGNIMS consensus guidelines

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INTRODUCTION

Advances in immunohistochemistry have recently refocused the attention of multiple sclerosis (MS) research from a pathophysiologic paradigm of white matter (WM) disease to the neocortical grey matter (GM). Pathology studies in MS attribute a substantial proportion of total disease burden to neocortical lesions. (1–5) Among this body of literature, neocortical demyelination, (6) neuronal and axonal damage, (4, 5) and remyelination have been described. (7) Cortical lesion (CL) morphology is most commonly classified by three main types: 1) type I (leukocortical) that span the GM/WM boundary; 2) type II (intracortical) that do not involve the pial surface or GM/WM boundary; 3) type III/IV (subpial) that extend from the pial surface to various depths of the cortex but do not involve the WM. (4, 5) Clinical manifestations of cortical involvement in MS include rare seizures and more commonly experienced cognitive dysfunction. (8, 9)

Limitations of conventional MRI at standard field strength results in poor sensitivity (~5%) of intracortical lesion detection compared with post mortem histology. (10) Technical challenges of imaging the cortex likely reflects differences between WM and GM tissue: 1) low myelin density in the GM resulting in inherently longer relaxation times and reduced contrast between CL and adjacent normal appearing GM; 2) partial volume effects due to weighted averaging of signal from adjacent cerebrospinal fluid and GM; 3) relatively sparse inflammation in the GM resulting in low magnitude alterations in MR signal. (4) Novel pulse sequences, such as double inversion recovery (DIR), which nulls the cerebrospinal fluid and normal appearing white matter signal, appears to improve intracortical lesion detection, but only increasing the predictive sensitivity over fluid attenuated inversion recovery (FLAIR) sequences to 12.5%.(11) DIR has been criticized for its limitations including low signal-to-noise ratio (SNR), partial volume averaging that obscures the WM/GM boundary, flow artifacts, and regional GM inhomogeneity. (12) Use of three dimensional (3D) magnetization-prepared rapid acquisition with gradient echo (MPRAGE) at 3T field strength has demonstrated improved classification of one-quarter of the CLs detected on DIR—suggesting that the addition of this sequence may lead to better accuracy of CL classification. (12)

Ultra-high Field (7T) MRI combined with multichannel radiofrequency (RF) technology may add 4 to 9-fold increase in signal-to-noise ratio with the greatest gains within the cortex when compared to conventional 3T MRI scanners (13–15)—potentially resulting in improved rater confidence of cortical lesion detection. Recently, Mainero et al (13) showed that FLASH-T2* sequences exhibit a superior contrast-to-noise ratio when compared with TSE T2-weighted, T1-weighted, and Phase sequences in detecting focal cortical pathology at 7T field strength. The FLASH-T2* sequence disclosed focal cortical lesions by pathological type at a distribution similar to that reported in the histopathology literature. (4, 5, 13) We propose a study that evaluates the frequency and inter-rater agreement of focal cortical lesion detection in an MS cohort using FLASH-T2* at 7T and DIR with MEMPR sequences at 3T. Specifically, we focus on individual CLs by pathologic type through the use of the kappa statistical test.

MATERIALS AND METHODS

Subjects

Twenty-six patients with a diagnosis of clinically isolated syndrome (CIS) (16) or MS (17)—categorized as early MS, relapsing-remitting MS (RRMS), and secondary-progressive MS (SPMS)--were recruited from our academic MS center case load. Clinical and demographic characteristics of this cohort include: 20 (77%) women and 6 (23%) men, mean age±SD of 45.5±7.6 years, mean EDSS (18) ± SD—an ordinal scale of physical disability ranging from zero (no disability) to ten (death)—of 3.1±1.7, and mean disease duration±SD of 11.4±8.9 years. Among our cohort were 4 CIS/early MS, 13 RRMS, and 9 SPMS patients. Project approval was granted through our institutions' research ethics review board, and participating subjects provided informed consent.

Data Acquisition

Subjects were scanned on two separate occasions: 1) on a 7T MRI (Sidemen's Medical Solutions) and 2) on a 3T MRI (TIM Trio, Sidemen's Medical Solutions). Less than two weeks separated the two scans for 16 of the 26 patients, six individuals were scanned within two and four weeks, while time elapsed between scans for the remaining four patients ranged from one to six months. For the 7T scanner an in-house single channel volume coil was used for RF transmission, while RF reception utilized an in-house 32-channel phased array coil. On the 3T scanner we used a body coil for RF excitation and a commercially available 32-channel coil (19) for signal reception.

Sequences

At the beginning of each 7T session we performed manual B_0 shimming to minimize susceptibility effects. We acquired $T2^*$-weighted 2D Fast Low Angle Shot (FLASH) spoiled gradient-echo images (TR/TE=1000/22ms, 2–3 slabs to cover the supratentorial brain, $0.33\times0.33\times1mm^3$ resolution, 0.25 mm gap between slices, time of acquisition (TA) for each slab= ~7 min). Our 3T scanning protocol included 2D double inversion recovery (DIR) sequence (TR/TE/TI1, TI2=10580/30/325,3400 ms, echo train length (ETL)=16, flip angle=129°, 3 slabs to cover the supratentorial brain, $0.8\times0.8\times3mm^3$ resolution, 3 mm gap between slices, TA for each slab=~7 min) and a high- structural 3D scan with a magnetization-prepared rapid acquisition with multiple gradient echoes (MEMPR) (20) sequence (resolution=$0.9\times0.9\times0.9$ mm^3, TI/TR=1200/2530ms, flip angle=7°, TE=[1.7; 3.6; 5.4; 7.3] ms, FoV=230mm, bandwidth=651Hz/px). For image positioning and acquisition across participants and across scans we used the "Auto- Align" software. (21)

Data Analysis

Four independent and experienced reviewers scored the bilateral precentral gyri (motor strips) using either 7T FLASH-$T2^*$ or 3T DIR with MEMPR on all 26 subjects. Reviewers were blinded to patient demographic and clinical information. 3T DIR cortical lesions were identified according to recently proposed MAGNIMS consensus recommendations (22)—1) lesions are hyperintense compared to surrounding normal-appearing GM, and 2) lesions occupy at least 3 pixels (based on a minimum of 1 mm^2 in-plane resolution). The 3T

MEMPR sequence was used to aid in artifact identification (ie, vessels) and classification of cortical lesion type observed on 3T DIR sequences. Cortical lesions identified on 7T FLASH-T2* scans were defined as focal cortical hyperintensities and classified by previously described neuropathologic type. (13) Reviewers were required to mark each lesion identified and assign a neuropathologic-defined lesion category: type I, II, or III/IV. Lesions that spanned more than one axial slice were only counted once.

Statistical Methods

To investigate the hypothesis that 7T FLASH-T2* detects more cortical lesions than 3T DIR with MEMPR, descriptive statistics are presented. Due to differences in slice thickness between DIR and 7T images, slices that were not common between both sequences were excluded from the analysis. (23) For these analyses, only lesions identified by both independent raters were considered. To determine the relative level of agreement for all individual focal cortical lesions and common identified lesions between raters (3T vs. 3T and 7T vs. 7T), the kappa statistic was calculated (range 1.0 to −1.0, where higher values indicate agreement greater than that expected by chance, zero indicates no agreement, and negative values indicating a level of agreement less than chance). To investigate the relative level of agreement between raters according to focal cortical lesion type, the Kappa test was utilized. (24) Summary statistics were used to identify the sensitivity of cortical lesion detection using 3T DIR with MEMPR and the new consensus criteria (22) while using 7T FLASH-T2* as a reference gold standard. All statistical analyses were performed using the statistical package SAS®, version 9.2.

RESULTS

Both raters of 7T FLASH-T2* sequences identified a total of 97 and 94 focal cortical hyperintense lesions respectively. Between the two raters, 103 unique CLs were marked in the bilateral precentral gyri of the cohort. Among these lesions, 88 (85.4%) were identified by both raters as lesions while 15 (14.6%) were scored by one rater but not the other. Conversely, raters of the 3T DIR with MEMPR sequences detected a total of 47 and 38 focal cortical hyperintensities respectively. Sixty-seven unique CLs were identified among these gyri at 3T with only 18 (26.9%) of them recognized by both raters as CLs and 49 (73.1%) hyperintensities identified by one but not the other rater.

Distribution of CL type differed between FLASH-T2* and DIR/MEMPR sequences. Scoring between raters at 7T disclosed a frequency of type I, II, and III/IV CLs at 29 (29.9%) vs. 30 (31.9%), 1 (1%) vs. 0 (0%), and 67 (69.1%) and 64 (68.1%), respectively. While type III/IV CLs were the most frequently identified lesions at 7T, none were detected on 3T DIR/MEMPR sequences. Conversely, both raters of 3T sequences scored 40 (85.1%) vs. 30 (78.9%) type I and 7 (14.9%) vs. 8 (21.1%) type II CLs.

Inter-rater agreement was poor (below that expected by chance, k= −0.36) between both raters of 3T images when considering all CLs detected, and improved to a modest level of agreement when comparing only those hyperintensities that were considered lesions by both raters independently (k= 0.12, table 1). The modest agreement was driven by a higher frequency of type I lesions scored the same by both raters (n=12), while there was

disagreement in detecting type II lesions at 3T (of 6 potential type II lesions, only one was agreed upon by both raters, while the remaining 5 were scored as a type I by the other rater). Comparing inter-rater agreement by lesion type demonstrated a modest level of agreement for type I and II CLs, while no type III/IV lesions were detected on 3T DIR (table 1).

By contrast, 7T FLASH-T2* sequence demonstrated strong inter-rater agreement (k=0.69, table 1) when considering all CLs detected. When considering hyperintensities that both raters independently identified as a CL, the inter-rater agreement by CL type was excellent (k=0.97, table 1). The excellent agreement was a reflection of only 1 disagreement of CL type assignment between raters (of 88 consensus lesions, one lesion was scored as a type III/IV and type I by the independent raters respectively). At 7T, type I and III/IV CLs demonstrated excellent inter-rater agreement; however, type II lesions were rare and could not be assessed for inter-rater agreement in this cohort.

Retrospective analysis of type I lesions detected on 7T or 3T and scored by one set of raters but not the other (n=14) resulted in the recognition of three overlooked lesions (two lesions on 3T DIR and one on 7T FLASH-T2* were re-classified as type I)—in each case, the lesion was prospectively identified as juxtacortical in location (figure 1). Of the remaining 11 lesions, 7T FLASH-T2* disclosed type I lesions (n=4), a juxtacortical lesion (n=1), normal cortex (n=4), or in-flow pulse artifact from a neighboring vessel (n=2). Two of these 11 type I lesions were noted on 3T DIR completed over one month after the 7T scan.

Using 7T FLASH-T2* as a provisional gold standard in CL detection in vivo, the sensitivity of 3T DIR using recent MAGNIMS consensus guidelines complemented by MEMPR for subjects scanned within 2 weeks (n=16) is 18.3% (11/60), 4 weeks (n=22) is 15% (12/80), and all subjects (n=26) is 13.6% (12/88). Subpial CLs represent the greatest proportion of CL subtype not detected on 3T sequences while detected on 7T. The frequency and proportion (%) of total undetected CLs on 3T that were disclosed as subpial CLs on 7T stratified by inter-scan interval of 2, 4, and all weeks: n=43 (87.8%), 62 (89.9%), and 69 (89.6%), respectively.

DISCUSSION

Ultra-high field (7T) MRI utilizing FLASH-T2* sequence detected more CLs than 3T DIR operating under recent consensus guidelines. (22) Our optimized FLASH-T2* sequence at 7T detected 489% more consensus CLs than 3T DIR (n=88 vs. 18). The improved SNR and spatial resolution at 7T and/or the FLASH-T2* sequence allows for more confident CL detection and categorization—particularly the type III/IV subpial lesion not detected using 3T DIR in our cohort. Our data suggests that 3T DIR informed by the MEMPR sequence is best for type I lesion detection but appears to be insensitive to the common subpial lesions identified in our 7T FLASH-T2* analysis and previously reported in post-mortem studies. (4, 5) While DIR proffers a conspicuous GM/WM boundary, the lack of subpial lesion detection using 3T DIR in our cohort may be due to poor spatial resolution and partial volume effects at the pial surface/CSF interface (the location common to all subpial lesions) in addition to the inherently low contrast between subpial lesions and normal cortex—particularly in the sparsely myelinated region of the superficial cortex. Previously, the

MAGNIMS consensus group published reservations regarding use of the DIR sequence for subpial lesion detection due to the low contrast of these lesions within the upper layers of the cortex and the possibility of a high false positive rate and poor inter-rater agreement. Moreover, the consensus statement acknowledges that visualization of subpial lesions may be facilitated by use of Ultra-high field MRI, and if demonstrated, may be considered for future consensus guidelines. (22)

Consensus guidelines (22) for the detection of cortical lesions in MS may be overly conservative in requiring cortical hyperintensities on DIR sequences to be a minimum 3 pixels. These criteria may decrease the artifact misclassification rate and increase rater confidence in lesion detection but at the expense of its negative predictive value. Testing this hypothesis is problematic as a post-mortem evaluation of the consensus criteria would be unable to evaluate flow artifact that is influential in CL detection in-vivo. Unlike a previously published Ultra-high field (7T)/post-mortem investigation demonstrating excellent CL sensitivity (93%),(26) to date, no DIR/post-mortem validation study has been reported.

Our optimized FLASH-T2* sequence at 7T enables very small voxel volumes (13)—approximately 0.1 mm^3—providing improved spatial resolution with reduced partial volume effects and the ability to confidently resolve focal hyperintensities in the cortical ribbon beyond the conventional MRI 3 pixel volumes afforded by the consensus criteria. Indeed, our data demonstrate strong inter-rater agreement using FLASH-T2* while 3T DIR was modest. Improved rater confidence and agreement should be a desirable feature for future single or multisite research when Ultra-high field MRI becomes more widely available. Our data demonstrate that 3T DIR using the consensus guidelines has a modest detection rate (13.6% – 18.3%) for CLs when compared to 7T FLASH-T2*.

Limitations of the present study include multi-slab acquisition of 3T DIR images. Multiple slabs increase scanning time and may increase the sensitivity to in-flow “venetian blind” artifacts. (27) Our experience scoring the 3T DIR sequence was hampered by significant regional RF inhomogeneity (producing variable hyperintense cortex making prospective CL detection difficult). In addition, discriminating juxtacortical from type I (leukocortical) CLs using 3T DIR was difficult in rare instances potentially as a result of poor resolution of the GM/WM boundary due to partial volume effects and/or regional RF inhomogeneity. While we found that the 3T MEMPR sequence aided in more confident categorization of these lesions, we cannot exclude the possibility that the T_1-weighted sequence may have a differential sensitivity for detecting demyelination within the sparsely myelinated cortex compared to the adjacent densely myelinated subcortical white matter. Such uncertainty confounds discrimination between juxtacortical and type I lesions at 3T in rare instances where the cortical component of the leukocortical lesion is minor (figure 1). In addition, the time elapsed between 7T and 3T scans was variable and for some subjects was long. We cannot exclude the possibility that cortical lesions developed, or alternatively disappeared, within this time frame which would affect the sensitivity analysis; however, our stratified results by time elapsed between scans demonstrates a sensitivity range between 13.6% and 18.3%. The modest sensitivity of CL detection using 3T DIR in our cohort is consistent with

previous estimates of predicted CL sensitivity using 3T DIR by Tallantyre et al (~12.5%). (25)

While we cannot assert that FLASH-T2* at 7T detects all CLs present in these subjects, or that all lesions visible on 7T FLASH-T2* are lesions in terms of histopathology, our optimized sequence has previously demonstrated the ability to detect all lesion types defined in the pathology literature with similar frequency (13). Moreover, Ultra-high field MRI has demonstrated the ability to disclose all pathologically defined CL types ex vivo (28) while Pitt et al (26) demonstrated that T2*GRE 3D sequence at 7T retrospectively detects 93% of post-mortem cortical lesions, including subpial lesions. In the absence of post-mortem validation of CLs detection using DIR, our FLASH-T2* sequence at 7T is a reasonable reference gold standard instrument.

In conclusion, Ultra-high field (7T) MRI using an optimized FLASH-T2* sequence demonstrated impressive inter-rater reliability for focal CL detection in our MS cohort while 3T DIR/MEMPR sequences using new consensus guidelines was modest. (22) In the absence of post-mortem DIR imaging studies, 7T FLASH-T2* is a suitable gold-standard instrument for the detection of MS cortical pathology in vivo. In order to determine the contribution of cortical pathology to MS disability and pathophysiology, it is imperative to accurately, reliably, and precisely identify and measure in vivo CLs. (11) Our data suggests that FLASH-T2* sequences at Ultra-high field MRI should be incorporated into future consensus guidelines.

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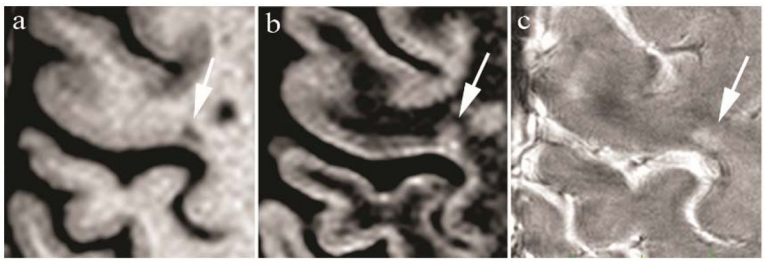

Figure 1.

Prospective scoring on 3T MEMPR (a) and DIR (b) disclosed a juxtacortical lesion (arrow). Prospectively, 7T FLASH-T2* (c) confirmed the lesion as a type I (arrow). Retrospective analysis re-categorized the juxtacortical lesion (a, b) as a type I CL. Time between scans is 6 days.

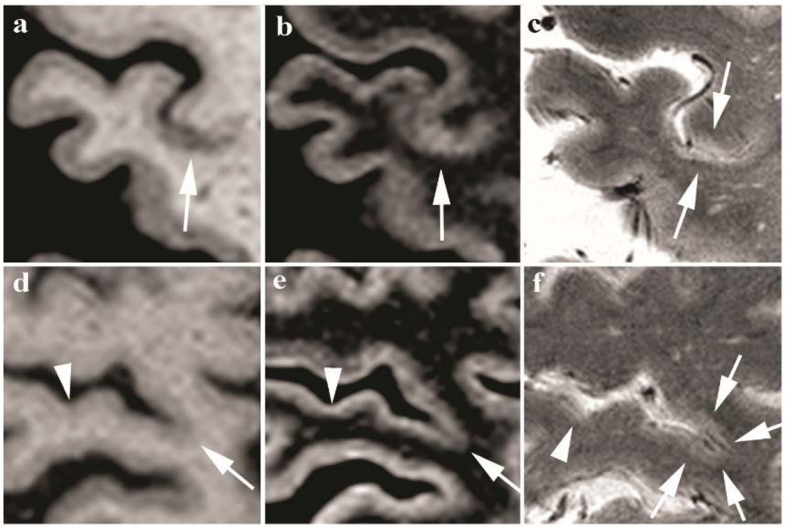

Figure 2.

Two patients (a–c and d–f). 3T MEMPR (a, d), DIR (b, e) and 7T FLASH-T2* (c, f) sequences. Arrows and arrowheads identify the same area/lesions within each patient respectively. Raters at 3T MEMPR and DIR did not detect the presence of lesions (arrows/arrowheads). 3T DIR sequences do not clearly demonstrate hyperintense signal in contrast to adjacent normal grey matter. Complementary 3T MEMPR sequences demonstrate subtle and patchy hypointense signal in the cortex (arrows) but not at the arrowhead. 7T FLASH-T2* demonstrates two subpial (type III/IV) lesions in each patient—upper row disclosed dual lesions on opposite side of the sulcus, and the bottom row demonstrates a round (arrowhead) and a longer lesion wrapping around the base of the sulcus (arrows). Elapsed time between scans is 8 days (a, b versus c) and 6 days (d, e versus f).

Table 1

Kappa (K) Level of Agreement

	All Cortical Lesions		Consensus Cortical Lesions†	
	K	**95% CI**	**K**	**95% CI**
3T vs. 3T	−0.36	−0.52, −0.21	0.12	−0.39, 0.62
Type I	—	—	0.12	−0.39, 0.62
Type II	—	—	0.12	−0.39, 0.62
Type III/IV	—	—	—	—
7T vs. 7T	0.69	0.57, 0.82	0.97	0.92, 1.0
Type I	—	—	0.97	0.92, 1.0
Type II	—	—	—	—
Type III/I	—	—	0.97	0.92, 1.0

Inter-rater agreement of CL detection by type (I, II, III/IV) using 7T FLASH-T2* and 3T DIR with MEMPR sequences. CI = confidence interval for kappa (K).

†Hyperintensities identified by both independent reviewers as a cortical lesion.