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Axial 3D gradient-echo imaging for improved multiple sclerosis lesion detection in the cervical spinal cord at 3T

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Abstract

Introduction—In multiple sclerosis (MS), spinal cord imaging can help in diagnosis and follow-up evaluation. However, spinal cord magnetic resonance imaging (MRI) is technically challenging, and image quality, particularly in the axial plane, is typically poor compared to brain MRI. Because gradient-recalled echo (GRE) images might offer improved contrast resolution within the spinal cord at high magnetic field strength, both without and with a magnetization transfer prepulse, we compared them to T2-weighted fast-spin-echo (T2-FSE) images for the detection of MS lesions in the cervical cord at 3T.

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Conflict of interest We declare that we have no conflict of interest.

Methods—On a clinical 3T MRI scanner, we studied 62 MS cases and 19 healthy volunteers. Axial 3D GRE sequences were performed without and with off-resonance radiofrequency irradiation. To mimic clinical practice, all images were evaluated in conjunction with linked images from a sagittal short tau inversion recovery scan, which is considered the gold standard for lesion detection in MS. Two experienced observers recorded image quality, location and size of focal lesions, atrophy, swelling, and diffuse signal abnormality independently at first and then in consensus.

Results—The number and volume of lesions detected with high confidence was more than three times as high on both GRE sequences compared to T2-FSE ($p<0.0001$). Approximately 5 % of GRE scans were affected by artifacts that interfered with image interpretation, not significantly different from T2W-FSE.

Conclusions—Axial 3D GRE sequences are useful for MS lesion detection when compared to 2D T2-FSE sequences in the cervical spinal cord at 3T and should be considered when examining intramedullary spinal cord lesions.

Keywords

Multiple sclerosis; Diagnostic imaging; Magnetic resonance imaging; Spinal cord; Magnetization transfer contrast imaging

Introduction

In multiple sclerosis (MS)—a common, chronic, inflammatory disease of the central nervous system that mainly presents in young adults—the diagnosis requires the presence of typical clinical findings. However, additional tests, particularly magnetic resonance imaging (MRI), are helpful for confirming the diagnosis [1], and MRI scanning has contributed greatly to an improved understanding of the effects of MS on the brain and spinal cord. Nevertheless, MRI remains only partially sensitive to the structural changes caused by MS [2]. Thus, there is a need to improve the quality of routine scanning in clinical studies, particularly in the spinal cord [3, 4].

About 50–90 % of MS patients have lesions that are observable with conventional spinal cord imaging; of these, approximately 60 % occur in the cervical region [5–7]. The presence of at least one spinal cord lesion forms part of the 2010 McDonald criteria for dissemination in space, a key component of the MS diagnosis [1]. This is a key point, as prior work has suggested that spinal cord lesions do not develop as a consequence of age-related diseases such as small-vessel ischemia; such lesions are quite common in the brain [8]. In progressive MS, particularly the primary-progressive subtype, studies have suggested that there may be more spinal cord (relative to brain) involvement [9, 10]. Uncommonly, patients with normal brain MRI may have spinal cord lesions that corroborate the clinical findings and ultimately establish the diagnosis [11, 12]. Finally, spinal cord damage may have a profound impact on physical disability [13].

Visually, spinal cord abnormalities in MS have been reported to take two forms: focal and diffuse signal abnormalities [14, 15]. Focal lesions can sometimes be detected on fast-spin-echo (FSE) proton-density- and T2-weighted MRI [16], and diffuse abnormalities are typically observed on proton-density-weighted MRI as areas of increased signal intensity [9]. However, although axial proton-density-weighted imaging has been recommended as part of the standard MS spinal cord imaging protocol [17], it is not commonly acquired in practice.

There are anatomical and technical considerations that render spinal cord imaging challenging. The spinal cord is small and mobile, and it is affected by ghosting artifacts from the heart and large vessels as well as by flow-related and Gibbs/truncation artifacts—all of which reduce the ability to detect cord lesions [18–23]. Improvements in imaging techniques such as cardiac gating [23], spatial presaturation slabs, and fast imaging sequences, as well as spinal phased-array coils [24], have partially addressed some of these problems. However, excellent image quality remains challenging to achieve, and the detection sensitivity is often poor, particularly for small, subtle lesions. This makes analysis of change over time a difficult endeavor [17].

High-field (3T) scanners can provide increased signal-to-noise, allowing faster acquisition, higher spatial resolution, and improved quantification, and they are therefore gradually becoming the clinical standard. However, artifacts can be exacerbated at 3T, although this presents less of a problem in the cervical cord than in the thoracic cord. As such, the advantages of scanning at 3T are not as clear for spinal cord imaging as for brain imaging.

In an effort to improve spinal cord imaging at 3T and to facilitate future development of standard protocols [25], we compared three axial MRI acquisition methods with respect to their ability to detect MS lesions in the cervical cord. Specifically, we compared axial 2D T2-weighted fast-spin-echo (T2-FSE), the clinical standard acquisition, with two T2*-weighted gradient-recalled-echo (GRE) acquisitions, performed with and without a magnetization transfer (MT-GRE) prepulse. In our clinical experience, the GRE data improve contrast within the spinal cord parenchyma. We hypothesized that the MT-GRE sequence would provide the best contrast for lesions due to suppression of normally myelinated white matter [26]. To mimic clinical practice, and because biplanar imaging improves the reliability of lesion detection [7] and lessens the chance that artifacts will interfere with study interpretability, we analyzed the images by juxtaposing each of these axial image sets to linked sagittal short tau inversion recovery (STIR) images.

Materials and methods

Participants

The study group consisted of 62 MS cases (39 women, 25–67 years old, age [mean $\pm$ standard deviation] 46 ± 10 , disease duration 11 ± 9 years) and 19 healthy volunteers (11 women, 22–65 years old, mean age 39 ± 12). Of the MS cases, 27 were classified by the referring physician as relapsing remitting, 24 as secondary progressive, and 11 as primary progressive. The median expanded disability status scale score [27] was 4 (range: 0–8). MS cases were recruited from the university clinic and healthy volunteers from the community. The diagnosis of MS was made by the treating physician, and prospective participants were excluded if they had additional diagnoses that could confound MRI interpretation. Written informed consent was obtained from all participants. The research protocol was approved by the institutional review board.

MRI

Scans were performed on a 3T scanner (Achieva; Philips Medical Systems, Best, The Netherlands). Axial T2-FSE, GRE, MT-GRE, and sagittal STIR images were obtained in all participants, with pulse sequence parameters presented in Table 1. No cardiac or respiratory gating was performed. The first 57 scans were acquired using a 2-element phased-array surface coil, and the remaining 24 using a 16-channel phased-array neurovascular coil covering the head and neck (10 of these channels were used for spinal cord imaging). Note that two MS cases, whose data were acquired at the beginning of the study, were scanned with slightly different parameters for the T2-FSE and GRE sequences.

Lesion evaluation

Cord lesions seen on images obtained with each sequence were evaluated by two neuroradiologists with 15 and 5 years of experience. Sequence parameters and diagnosis were not provided with the images at the time of evaluation. Presentation order of the MRI studies to the observers was randomized across sequence type and participant. To mimic clinical practice, each axial series was displayed adjacent to the sagittal STIR series for the same subject, since STIR images often show excellent contrast for lesions, and the presence of signal abnormality in the same location on two separately acquired scans increases confidence in lesion identification. Linking lines were used to allow correspondence between the sagittal and axial image sets. STIR images were not evaluated in isolation. Each observer initially viewed the images on his/her own, and subsequently the two observers came to an agreement about the presence and location of lesions.

The axial and sagittal images were scored for overall image quality as uninterpretable, poor, and good. Artifacts were scored as absent, present but not affecting image interpretation, and present and interfering with image interpretation. The confidence level for lesion identification was judged as high if the lesion clearly appeared on both axial and sagittal sequences, moderate if the lesion was present in the best judgment of the observers, and low if the observers were unsure. Lesion size was also evaluated semiquantitatively as a percentage of the cross-sectional area of the cord: <25 % of spinal cord cross-sectional area; 25–50 %; 50–75 %; and >75 %. Lesions identified with high confidence were counted between the C2 and C5 vertebral body levels, and approximate lesion burden was estimated by multiplying the fractional cross-sectional area of each lesion by the number of slices on which that lesion appeared by the slice thickness; this measure has units of mm. The presence of atrophy, swelling, and diffuse signal abnormality—in the best judgment of the observer—was also recorded.

Statistics

Since pathologic confirmation was unavailable, we used a radiologic reference-standard: consensus between the two neuroradiologists. Statistical calculations were performed in Stata 9.0 (Stata LP, College Station, TX); specific tests are referenced in Results. A threshold significance level of $p = 0.05$ was adopted, without adjustment for multiple comparisons.

Results

Imaging

GRE and MT-GRE images demonstrated good contrast between white and gray matter structures in the cervical spinal cord (Fig. 1) and between MS lesions and adjacent normal-appearing tissue (Fig. 2). Visualized MS lesions were hyperintense compared to normal white matter on all three pulse sequences (Fig. 2) but were generally easier to detect on the GRE and MT-GRE sequences (as demonstrated quantitatively below).

Scan quality

A few (~5 %) of the GRE and MT-GRE scans were marred by artifacts that interfered with image interpretation (Table 2). Overall, however, scan quality was similar across sequences, with no significant differences in terms of the presence or absence of imaging artifacts as judged by the two observers, regardless of whether the subject had MS or not (ANOVA, $p = 0.7$). In the GRE sequences, most artifacts arose from subject motion as well as blurring between adjacent slices; the latter results from the slice oversampling technique used in the acquisition. Only scans without artifacts, or in which artifacts did not affect interpretation, were further analyzed.

Diffuse abnormalities

Gross cervical cord atrophy was detected in less than 10 % of MS cases, regardless of sequence type (Fig. 3 and Table 2). Diffuse signal abnormality was present in less than 5 % of cases, again without a clear effect of sequence type on its detection. No healthy volunteer was judged to have either atrophy or diffuse signal abnormality on any of the sequences.

Lesions

For all sequence types, median estimated lesion count and burden was 0 in the healthy volunteers (Fig. 4). In a few cases, more commonly on the GRE-based sequences, spurious lesions, not confirmed later by consensus evaluation, were detected. In MS cases, the GRE-based sequences each identified three times as many lesions as the T2-FSE (repeated measures ANOVA, $p < 0.0001$). The estimated lesion burden was also approximately three times higher in the GRE sequences: 4.9 ± 1.0 mm (mean $\pm$ standard error) for T2-FSE, 17.4 ± 2.6 mm for GRE, and 13.5 ± 2.0 mm for MT-GRE ($p < 0.0001$).

In GRE images, lesion burden was higher in progressive MS (23.5 ± 4.1 mm) vs. relapsing–remitting MS (10.1 ± 2.3 mm; $p = 0.02$, Wilcoxon rank-sum test). There was no difference in lesion burden in primary-progressive MS (15.0 ± 5.7 mm) vs. combined relapsing–remitting and secondary-progressive MS (17.9 ± 2.9 mm; $p = 0.6$). In MS cases, lesion count was correlated across sequence types (Spearman's correlation coefficient for T2-FSE vs. GRE: $r = 0.52$; T2-FSE vs. MT-GRE: $r = 0.56$; GRE vs. MT-GRE: $r = 0.49$; $p < 0.0001$ in all cases).

Discussion

We demonstrate here that axial 3D GRE sequences, with or without an MT-prepulse, are useful for MS lesion detection in the cervical spinal cord at 3T, especially in comparison to conventional 2D T2-FSE sequences. To mimic clinical practice and strengthen the relevance of this study, we compared each set of axial images with a linked set of sagittal STIR images.

GRE-based sequences are not routinely included in MS spinal cord imaging protocols [17], but our own experience and the results reported here demonstrate their value for clinical assessment. A few recent studies have evaluated other axial GRE-based sequences for MS lesion detection, deriving similar results [28, 29]. It should be noted that scan times for our 3D GRE and MT-GRE sequences are comparable to conventional T2-FSE and therefore do not impose large scan-time inflation. Since we did not observe stark differences in lesion conspicuity or artifacts comparing the GRE and MT-GRE images, scan time for this sequence can be halved by acquiring the GRE alone.

In past imaging studies of cord involvement in MS, the technique that revealed the greatest number of lesions has been considered to be optimal [30], as the detection of more lesions is thought to increase diagnostic accuracy. A better standard would be comparison with pathology, but this is of course difficult to achieve in more than a handful of individuals [31]. Note that in this study, we used, in addition to lesion count, a semiquantitative assessment of lesion volume based on identification of lesions in each axial slice and estimation of the fractional cross-sectional area of each lesion on each slice. We adopted this approach over manual delineation, which we felt might be unreliable in the spinal cord.

Importance of spinal cord imaging in the clinical work-up

The presence or absence of focal spinal cord lesions contributes to the current consensus criteria for the diagnosis of MS [1]. However, in routine imaging follow-up of MS patients and even at the time of diagnosis, spinal cord MRI is not performed as frequently as brain

MRI, mainly owing to technical difficulties, long acquisition time, and the relative insensitivity of axial T2-FSE sequences to cord lesions. Nevertheless, because MS involves the whole central nervous system, imaging of the complete neuraxis may help elucidate the substrates of disability, much of which arises from spinal cord damage [6]. The MT-GRE scan can be quantified using a normalization approach, either to the cerebrospinal fluid or to the GRE scan (the so-called magnetization transfer ratio); results based on these normalized data have been linked to disability in MS [32, 33].

High-field MR imaging in the MS spinal cord

Advantages of 3T scanning include better image quality, specifically spatial contrast resolution and signal-to-noise ratios, in similar scan times [34, 35]. Although these advantages should directly translate into improved evaluation of the spinal cord, particularly for patients whose disability makes them less able to cooperate with longer scanning times, success has been limited to date [36]. This is partially due to increased susceptibility (T_2') effects at high field [37], which can result in loss of signal intensity and distortions. Parallel imaging techniques, in conjunction with phased-array coils, allow more rapid imaging of the spinal cord with shorter echo times and fewer susceptibility-related artifacts, yielding higher sensitivity for MS pathology [30, 38, 39, 40]. Indeed, as demonstrated here and in several recent studies, high-field MRI with the appropriate sequence optimization can be quite useful in the imaging evaluation of MS patients [3, 29].

Pulse sequences in spinal cord imaging

Prior work has led to conflicting recommendations about the best pulse sequence for detecting spinal cord lesions when MS is suspected. For imaging MS lesions in the sagittal plane, cardiac-triggered, dual-echo, spin-echo images of the spinal cord may offer benefits with regard to artifact interpretation and lesion detection over FSE, STIR, T2-weighted fluid-attenuated inversion recovery (FLAIR), and GRE sequences [40]. Such images can also assist in the detection of diffuse MS abnormalities and lesion location within the cord. In the sagittal plane, FSE techniques are shorter than their conventional single-echo, spin-echo counterparts [38], and feature improved lesion detection [41]. Sagittal STIR images are superior to conventional spin echo, T2-FSE, and T2-FLAIR images [30]. Note that standard T2-FLAIR sequences are particularly poor with respect to detection of spinal MS [30, 42, 43]. In the work described here, we used sagittal STIR images to guide interpretation of the axial images.

As confirmed here, spinal cord lesions can indeed sometimes be well seen on axial T2-FSE, even at 3T. However, artifacts due to partial volume averaging and cerebrospinal fluid flow often interfere [41], as do the relatively long examination times compared to gradient-echo images. FSE imaging can shorten the examination [44] at the expense of additional confounding factors contributing to the signal, including echo-train length and echo spacing [45]. However, FSE at high field strength is also challenging due to transmit-field (B_1) inhomogeneity, which can result in stimulated echoes and intrusion of some T1 weighting.

T2*-weighted GRE sequences can overcome these disadvantages using small flip angles and shorter repetition and echo times, resulting in overall shorter acquisition times. Two potential problems for GRE imaging, especially with respect to intraparenchymal lesion detection, include lower contrast-to-noise ratio due to the small flip angle as well as increased sensitivity to magnetic susceptibility due to the absence of a 180° refocusing pulse. High signal intensity from cerebrospinal fluid can also cause artifacts [39]. For these reasons, it has been suggested that GRE-based sequences might actually be less sensitive to intrinsic cord lesions than their multislice T2-FSE counterparts [39, 46]. Nevertheless, 2D (multislice) T2*-weighted sequences, particularly those in which the signal is combined

over multiple echo times, have now been shown to be useful in detection of cervical cord MS lesions at both 1.5T [28] and 3T [29], with results consistent with those reported here.

In this study, we adopted a 3D GRE approach. In 3D scans, where data are acquired simultaneously over a large imaging slab, motion occurring at any point during data acquisition affects all slices, although the degree to which this is perceptible depends on the portion of k-space that is being filled when the motion occurs. An important advantage of 3D GRE imaging is its lower sensitivity to flow artifacts [46], which may mitigate some of the motion-induced drawbacks.

Magnetization transfer imaging of the spinal cord

MT imaging can increase tissue contrast on MR images, particularly between gray and white matter structures. It involves saturation of the bound proton pool, resulting in a decrease in signal intensity that particularly affects highly organized tissue with many bound protons, such as healthy white matter. In the spinal cord, the application of an MT pulse results in a significant increase in the contrast-to-noise ratio, which in prior studies has been shown to improve delineation of intrinsic cord lesions [47, 48]. However, under the imaging conditions adopted in this study, the MT preparation did not improve lesion detection relative to the GRE scan, which appeared to be excellent on its own.

Limitations

The most important limitation of our study is the absence of pathologic confirmation, requiring us to use a radiologic reference standard and an assumption that the technique that depicts the largest number of lesions is best. For clinical evaluation, accurate assessment of spinal cord lesion volume is probably not necessary, so we used a semiquantitative approach rather than attempting to delineate each lesion. This approach is also imperfect; for example, even if overall scan quality was good, as it was in most cases, individual slices could have included artifacts, which might have interfered with judgment of lesion presence or absence. Indeed, the finding that a few spurious lesions were detected in the GRE sequences underlines the importance of acquiring data in multiple planes, and with several pulse sequence types, in order to assure reliable interpretation. An additional, important limitation is that we did not perform scan–rescan experiments and cross-observer analysis to assess the reliability and reproducibility of the GRE-based techniques; such work is ongoing.

Conclusions

Improving MS lesion detection in the spinal cord on MR images may help improve diagnostic accuracy. Our results demonstrate that axial GRE sequences are useful for MS lesion detection, especially in comparison to T2-FSE sequences, in the cervical spinal cord at 3T. Thus, we advocate their routine use in clinical evaluation of the cervical spinal cord in MS.

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Fig. 1.

Axial T2-weighted fast-spin-echo (**a**), gradient-echo (**b**), and magnetization transfer-prepared gradient-echo (**c**) images at the C4 vertebral body level in a 23-year-old healthy woman. Note the excellent contrast between the gray and white matter on the gradient-echo images, particularly on the magnetization transfer-prepared image. Typical flow artifacts within the CSF are apparent on the T2-weighted image

Fig. 2. Sagittal short tau inversion recovery (a), axial T2-weighted fast-spin-echo (b), axial gradient-echo (c), and axial magnetization transfer-prepared gradient-echo (d) images of the spinal cord of a 25-year-old man with relapsing–remitting multiple sclerosis. Note bilateral cord lesions within the lateral columns at the C4 vertebral body level. No focal swelling or atrophy is present

Fig. 3. Sagittal short tau inversion recovery (a), axial T2-weighted fast-spin-echo (b), axial gradient-echo (c), and axial magnetization transfer-prepared gradient-echo (d) images of the spinal cord of a 55-year-old woman with secondary-progressive multiple sclerosis. There are bilateral lesions within the lateral columns, as well as a dorsal column lesion, at the C4-5 intervertebral disk level. Both raters judged this spinal cord to be diffusely atrophic

Fig. 4.

Estimated cervical spinal cord lesion count (**a**) and lesion burden (**b**; see “Materials and methods” for details), as detected on T2-weighted fast-spin-echo (*T2-FSE*, *left*), gradient-echo (*GRE*, *center*), and magnetization transfer-prepared gradient-echo (*MT-GRE*, *right*) sequences. *HV*, healthy volunteers; *RRMS*, relapsing-remitting MS; *SPMS*, secondary-progressive MS; *PPMS*, primary-progressive MS. For lesion count, *orange lines* represent the median for each group; for lesion burden, *orange lines* and *error bars* represent the mean and its standard error

Table 1

Pulse sequence parameters

Sequence	Short tau inversion recovery (STIR)	T2-weighted fast-spin-echo (T2-FSE)	T2*-weighted gradient-recalled echo (GRE) and magnetization transfer-prepared GRE (MT-GRE)
Imaging plane	sagittal	axial	axial
Imaging mode	2D (multislice)	2D (multislice)	3D (slab)
Repetition time (TR, ms)	2948	3825	110
Echo time (TE, ms)	70	120	12.5
Inversion time (TI, ms)	200	N/A	N/A
Flip angle (deg)	90	90	9
Parallel imaging factor	2	2	2
Echo-train length	20	39	N/A
Echo-planar-imaging (EPI) factor	N/A	N/A	3
# Averages	1	2	2
Nominal in-plane resolution (mm)	0.8×1.1 (<i>n</i> =55)/0.9 × 1.3 (<i>n</i> =24)	0.9×1.2	0.6×0.6
Reconstructed in-plane resolution (mm)	0.5×0.5	0.4×0.4	0.4×0.4
Slice thickness (mm)	3 (0.3 mm gap) (<i>n</i> =55)/2 (0.2 mm gap) (<i>n</i> =24)	2 (<i>n</i> = 55)/3 (<i>n</i> = 24)	4.5, reconstructed to 2.25 (<i>n</i> = 55)/6, reconstructed to 3 (<i>n</i> = 24)
Acquisition time (min:s)	4:18 (<i>n</i> =55)/3:06 (<i>n</i> =24)	4:35 (<i>n</i> = 55)/3:04 (<i>n</i> = 24)	4:30 (<i>n</i> = 55)/3:04 (<i>n</i> = 24)
Magnetization transfer pulse	N/A	N/A	For MT-GRE: 24 ms duration, 8.5 3T amplitude, sinc-shaped pulse at 1.5 kHz off-resonance with respect to water

Table 2**Results**

		Axial T2-FSE	Axial GRE	Axial MT-GRE	Sagittal STIR
Artifacts	Interfering with image interpretation	0	5 (6 %)	4 (5 %)	2 (2 %)
	Not interfering with image interpretation	33 (41 %)	29 (36 %)	28 (35 %)	22 (27 %)
Atrophy	Absent	48 (59 %)	47 (58 %)	49 (60 %)	57 (71 %)
	MS	4 (6 %)	4 (7 %)	6 (10 %)	
	HV	0	0	0	
Diffuse signal abnormality	MS	2 (3 %)	3 (5 %)	1 (2 %)	
	HV	0	0	0	
Median lesion burden, mm (IQR)	MS	19 (40)	42 (42)	44 (44)	
	HV	0 (0)	0 (6)	0 (4.5)	