Resolution-Dependent Estimates of Multiple Sclerosis Lesion Loads

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ABSTRACT: *Background:* Changes in brain lesion loads assessed with magnetic resonance imaging obtained at 1.5 Telsa (T) are used as a measure of disease evolution in natural history studies and treatment trials of multiple sclerosis. *Methods:* A comparison was made between the total lesion volume and individual lesions observed on 1.5 T images and on high-resolution 4 T images. Lesions were quantified using a computer-assisted segmentation tool. *Results:* There was a 46% increase in the total number of lesions detected with 4 T versus 1.5 T imaging (p<0.005). The 4 T also showed a 60% increase in total lesion volume when compared with the 1.5 T (p<0.005). In several instances, the 1.5 T scans showed individual lesions that coalesced into larger areas of abnormality in the 4 T scans. The relationship between individual lesion volumes was linear (slope 1.231) showing that the lesion volume observed at 4 T increased with the size of the lesion detected at 1.5 T. The 4 T voxels were less than one quarter the size of those used at 1.5 T and there were no consistent differences between their signal-to-noise ratios. *Conclusions:* The increase in signal strength that accompanied the increase in field strength compensated for the loss in signal amplitude produced by the use of smaller voxels. This enabled the acquisition of images with improved resolution, resulting in increased lesion detection at 4 T and larger lesion volumes.

RÉSUMÉ: Estimation du fardeau lésionnel par l'imagerie en fonction de la résolution dans la sclérose en plaques. *Introduction:* Les changements du fardeau lésionnel cérébral évalués par imagerie par résonance magnétique obtenue à 1,5 Telsa (T) sont utilisés comme mesure de l'évolution de la maladie dans les études sur l'histoire naturelle de la maladie et au cours des essais thérapeutiques dans la sclérose en plaques. *Méthodes:* Le volume total des lésions et les lésions individuelles observées sur des images 1,5 T ont été comparés aux données obtenues sur des images 4 T à haute résolution. Un outil de segmentation assistée par ordinateur a été utilisé pour quantifier les lésions. *Résultat:* L'imagerie 4 T détectait 46% plus de lésions que l'imagerie 1,5 T (p < 0,005) et un volume total de lésions 60% plus élevé (p < 0,005). Dans plusieurs cas, les scans 1,5 T montraient des lésions individuelles qui se fusionnaient en zones anormales plus vastes sur les scans 4 T. La relation entre le volume individuel des lésions était linéaire (pente de 1,231) démontrant que le volume des lésions observées sur l'imagerie 4 T augmentait selon la taille de la lésion détectée à l'imagerie 1,5 T. Les voxels 4 T étaient moins que le quart de la taille de ceux utilisés à 1,5 T et il n'y avait pas de différence constante entre leur rapport signal-bruit. *Conclusions:* L'augmentation de la force du signal qui accompagnait l'augmentation de la force du champ magnétique compensait pour la perte d'amplitude du signal produit par l'utilisation de voxels plus petits, ce qui permettait l'acquisition d'images dont la résolution était meilleure et donc une meilleure détection des lésions et une meilleure appréciation de leur volume par l'imagerie 4 T.

Multiple sclerosis (MS) is a chronic debilitating disease of the central nervous system (CNS) characterized by multifocal demyelinated areas throughout the white matter.[1] During the course of MS, the integrity of the blood brain barrier is compromised, inflammatory cells enter the CNS and demyelination ensues. It is hypothesized that in genetically susceptible individuals, an autoimmune response against myelin antigens is initiated by exposure to an environmental factor.[1-3] The severity of clinical symptoms is more often related to the location of the damage than to the degree and extent of the pathological process.[4] The disease course, both within and between subjects, is highly variable.[2]

Magnetic resonance imaging (MRI) provides an objective and direct assessment of the evolving pathology in MS.

Inflammation and demyelination produce increased water content in MS lesions, making them relatively easy to discern from other neuroanatomical structures.[5] As MRI technology advances, it is likely that MR techniques will continue to play an important role in investigating the natural history of the disease

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and monitoring treatment efficacy.[6] MRI systems that exceed 3 Tesla (T) are able to produce higher resolution images within a similar time frame to conventional clinical systems (1.5 T). The higher resolution images may be more accurate in detecting MS lesions, which could result in earlier diagnosis of clinically definite MS, a better understanding of the underlying pathological process of the disease and more precise monitoring of treatment effects. While the potential benefits of higher field MRI systems include higher signal-to-noise ratio (SNR), high speed of acquisition, increased resolution, and the capability for MR spectroscopy and functional imaging, there is a definite cost advantage to employing middle-field-strength units. Although there is a consensus that magnets with higher field strengths produce images that are subjectively better than lower field systems, this has not been proven to result in increased accuracy in the detection of pathology.[7,8]

The objective of this research was to determine if the number of lesions, lesion volume, and total lesion load detected within the MS brain would be different on images acquired at 4 T versus 1.5 T. It was hypothesized that high resolution 4 T MRI images would result in an increased detectable lesion load when compared with standard clinical MRI exams performed at 1.5 T.

Methods

Subjects

Written informed consent was obtained with the approval of the University of Western Ontario's Review Board for Health Sciences Research Involving Human Subjects. Eight outpatients with clinically definite secondary progressive MS were recruited from the London Health Sciences Centre Multiple Sclerosis Clinic, Ontario, Canada. The subjects mean age was 42.8 years; mean duration of disease was 9.1 years; with an average Expanded Disability Status Scale score of 4.0. The eight subjects underwent 4 T MR imaging just prior to, or immediately following a regularly scheduled 1.5 T imaging. In some cases the two examinations occurred on separate days, however, the 4 T exams were always completed within 48 hours of imaging at 1.5 T.

MR Imaging

1.5 Tesla imaging was performed with a transmit-receive quadrature head RF coil on GE Signa™ scanners (GE Medical Systems, Milwaukee, WI) by technicians in the department of diagnostic radiology and nuclear medicine, University Campus-London Health Sciences Centre, either as part of the subjects' ongoing care or as part of a concomitant, through unrelated, clinical trial. Axial images through the brain were obtained in the oblique plane with the corpus callosum as an internal landmark, with slices angled along the inferior aspect of the genu and splenium of the corpus callosum. The exam consisted of the acquisition of T2-weighted (T2W) and proton density weighted images using a dual echo spin echo sequence and T1-weighted (T1W) conventional spin echo sequence. The 4 T imaging was performed using a custom-made 27 cm diameter quadrature birdcage RF head coil on a ᵁᴺᴵᵀʸINOVA™ MR scanner (Varian Associates, Palo Alto, CA and Siemens Medical Systems, Erlangen, Germany) with the axial images acquired in a -similar manner to the 1.5 T imaging. A three-dimensional

magnetization-prepared fast low-angle shot (mpFLASH3d) sequence was used to obtain the T1W images at 4 T and conventional spin echo sequence was used for the T2W images.[9] The T2W sequence parameters of the two field strengths (2000 ms at 1.5T and 4000 ms at 4 T) were selected from previous *in vivo* research of the guinea pig brain obtained from the same scanners.[5] Imaging parameters are summarized in the Table.

Imaging Techniques and Analysis

All 1.5 T and 4 T images were digitized and transferred to a Sun SPARC 4 workstation (Sun Microsystems, Mountain View, CA) for processing. Three-dimensional image sets were created from each exam by stacking the T1W and T2W (or proton density weighted and T2W) images, respectively.[10] Since a greater number of T1W images were acquired compared to the T2W images at 4 T, the excess T1W slices were not included in the 3D image sets. The 1.5 T and 4 T image sets were then analysed with the aid of the computer-assisted, semi-automated image segmentation program, Segtool, employing an algorithm based on multispectral analysis and *k*-nearest-neighbour clustering.[10] This method used a computer to outline lesions from an operator selected starting point, followed by manual editing. The program employed an algorithm based on multispectral analysis that provided interactive assistance to a knowledgeable operator and acted locally upon individual lesions. A *k*-nearest-neighbour cluster classification was applied

Table: Summary of Imaging Parameters

Parameters	1.5 T	4 T
MR scanner	GE Signa LX MR scanner	ᵁᴺᴵᵀʸINOVA™ MR scanner
T2-/PD-weighted	Dual echo spin echo pulse	Conventional spin echo
	TR 2000 ms	TR 4000 ms
	TE 30/80 ms	TE 70 ms
T1-weighted	Conventional spin echo	mpFLASH3d
	TR 550 ms	TR 11.8 ms
	TE 13 ms	TE 6 ms
		11° flip angle
Number of Slices	30	T2-/PD-weighted 39
		T1-weighted 64
Slice thickness	Contiguous 5 mm	Contiguous 2.2 mm
Field of View (FOV)	22 cm x 16 cm	22 cm x 22 cm
Matrix	256 x 192	512 x 256
Number of excitations	T2-/PD-weighted 1	T2-/PD-weighted 2 (average)
(NEX)	T1-weighted 2 (average)	T1-weighted 1
Voxel	3.58 mm³	0.812 mm³
Duration of scan	T2-/PD-weighted 11 min	T2-/PD-weighted 34 min
	T1-weighted 6 min	T1-weighted 5 min
	Total 17 min	Total 39 min

TR = repetition time; TE= echo

to differentiate the intensity characteristics of a single lesion from that of surrounding tissue. The lesion voxels were then identified by the computer and edited.[10] A lesion was outlined when it appeared on both the T1W and T2W images on the image set. The SNRs of the lesions, white matter, gray matter and cerebrospinal fluid (CSF) of each MR contrast were calculated at both field strengths by dividing mean signal intensity of the tissue by the standard deviation of the air. Contrast-to-noise ratios (CNRs) were also calculated between white matter and lesion, grey matter and lesion, and CSF and lesion by taking the difference the signal intensity difference between the two tissues (e.g. white matter and lesion) and dividing it by the standard deviation of air.

Once the initial lesions were identified on both sets of images from each patient, a lesion-to-lesion comparison began. Images acquired at 4 T and 1.5 T were displayed simultaneously on the computer monitor and lesions that appeared on both image sets were identified. The 3D connected-component labeling feature of Segtool made it possible to identify a lesion that extended through multiple slices. The volume of each lesion was calculated by multiplying the lesion area by the slice thickness. Therefore, from each image set, the number and volume of individual lesion volumes were recorded and total lesion load (summation of all lesion volumes throughout the brain) was calculated.

Due to the obvious differences in the in-plane and out-of-plane resolution of the images, the operator was not blinded to the field strength used to acquire the images. Thus, to ensure minimal intra-observer variability, the 1.5 T and 4 T image sets of each patient were analysed at least one week apart and reviewed 24 hours following the completion of the initial identification process. The intra-observer reliability exceeded 94% throughout the study.

The identification of individual lesions was complicated when focal lesions appeared to merge resulting in areas of confluent abnormality. In such cases it was necessary for the operator to make subjective judgments as to the identification of a lesion as distinct or part of a diffuse abnormality. Only lesions that were identified with certainty by the operator were further analyzed. An expert observer (SJK) further verified the identification and volume from randomly selected image sets. The inter-rater reliability exceeded 95%.

One subject was excluded from the lesion number and volume comparisons due to the diffuse nature of the identified lesions. A second subject was also excluded in the analysis of lesion volume due to a small difference in the imaging plane at 4 T versus 1.5 T. These factors (diffuse lesions and angle incompatibility) made the positive identification and accurate quantification of the corresponding lesions difficult and unreliable.

Statistical Analysis

Product-moment correlation analysis was used to investigate the relationship between the number of lesions detected, the total lesion load, and the individual lesion volumes. A one-way analysis of variance was employed to examine differences between image SNR and CNR. *Post hoc* comparisons were performed using Dunnett's test. In all cases, a 95% confidence limit was used to determine significance.

RESULTS

Signal-to-Noise and Contrast-to-Noise Ratios

There was a higher mean CSF and lesion SNR on T1W images acquired at 1.5 T compared to T1W images at 4 T (p < 0.05). No significant differences were found between the mean SNR of white matter or gray matter on the T1W images obtained at 1.5 and 4 T (Figure 1). The CNR, however, for white matter-lesion and gray matter-lesion were higher on the T1W images at 4 T, and the CNR for CSF-lesion was significantly lower on the T1W images at 4 T compared to 1.5 T images (p < 0.05) (Figure 2). The SNRs of white matter, gray matter and lesions on the T2W images were all significantly higher at 1.5 T when compared to 4 T (p < 0.05) (Figure 3). There were no significant difference between CNRs (white matter and lesion, gray matter and lesion, and CSF and lesion) on the T2W images obtained at 1.5 T and 4 T (Figure 4).

Total Lesion Number

A 46% increase in the total number of lesions was detected with 4 T imaging as compared to 1.5 T. This linear relationship (slope = 2.146, r = 0.905, p < 0.005, DF = 6) suggests that the total number of lesions detected with 4 T imaging tend to increase with the total number of lesions detected at 1.5 T (Figure 5). Figure 6 depicts the breakdown of the total lesions detected with 4 T imaging with each subject. The number of lesions not detected at 1.5 T ranged from 6% to 62%. Eleven percent of lesions identified at 1.5 T were not viewed on the corresponding 4 T images.

Lesion Volume

Individual lesion volumes were significantly increased with 4 T imaging when compared to 1.5 T. The relationship between lesion volumes at the two field strengths was linear with a correlation coefficient of 0.943 (p < 0.001, DF = 135), and a slope of 1.231 (Figure 7). Overall, there was a 60% increase in the mean lesion volume measured at 4 T. The lesions that were seen only with 4 T imaging had a mean volume ± SE of 0.060 ± 0.010 cm^3 (range, 0.004 – 0.470 cm^3) (Figure 8). The lesions identified only on 1.5 T images have a mean volume of 0.075 ± 0.020 cm^3 (range, 0.009 – 0.320 cm^3). Fourteen percent of the lesions identified on both 4 T and 1.5 T image sets had measured volumes that were higher at 1.5 T than at 4 T.

Total Lesion Load

There was a 51% increase in the total lesion load of the MS brains measured using 4 T imaging compared to 1.5 T imaging. The relationship between the lesion load measurements was linear with a correlation coefficient of 0.954 (p = 0.003, DF = 5) and a slope of 1.065 (Figure 9). Each subject had an increased lesion load at 4 T compared to 1.5 T that ranged from 28% to 282%. On average 96% of the increase in total lesion load as measured at 4 T came from an increase in the volume of individual lesions compared to 1.5 T. The remaining 4% increase was attributed to the volume of lesions identified at 4 T that were not seen at 1.5 T. When analyzed on a subject-by-subject basis, the percent contribution of increased lesion volume to the increase in total lesion load was present in all but one subject (Figure 10a). One subject (S3) had a decreased mean volume of lesions at 4 T than at 1.5 T resulting in a negative contribution to
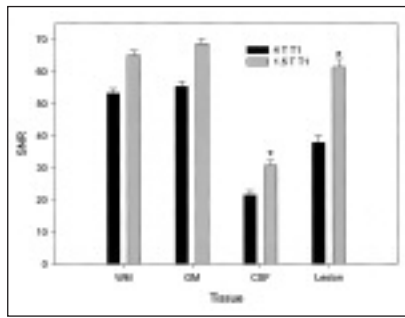
Figure 1: *Mean T1W image SNR ± standard deviation at 1.5 T and 4 T*
No significant differences were found between the mean SNRs of WM (white matter) or GM (gray matter) on the T1W images obtained at 1.5 T and 4 T. However, the greater mean CSF and lesion SNRs on the 1.5 T T1W images did reach statistical significance when compared to the 4 T T1W images. (p<0.05, Dunnett's test)*
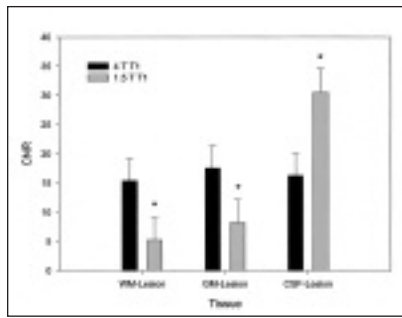

Figure 2: *Mean T1W image CNR ± standard deviation at 1.5 T and 4 T*
The CNR for white matter-lesion and gray matter-lesion was significantly higher on the 4 T T1W images than on the 1.5 T images. Conversely, the CSF-lesion CNR was higher on the 1.5 T images than it was on the 4 T images. (p<0.05, Dunnett's test)*
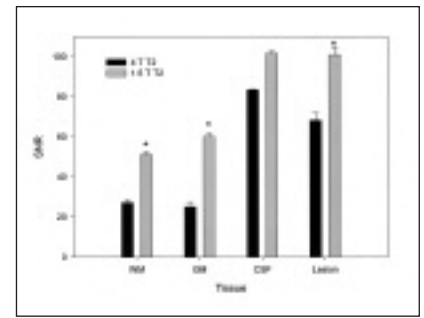

Figure 3: *Mean T2W image SNR ± standard deviation at 1.5 T and 4 T*
No significant difference was found between the mean SNR of CSF on T2W images at 1.5 T and 4 T. T2W 1.5 T images did have larger SNRs for WM (white matter), GM (gray matter), and lesion, which reached statistical significance when compared to the 4 T T2W images. (p<0.05, Dunnett's test)*
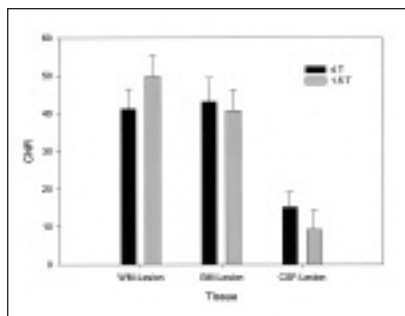

Figure 4: *Mean T2W image CNR ± standard deviation at 1.5 T and 4 T*
No significant differences were found between the CNR for white matter-lesion, gray matter-lesion, and CSF-lesion on T2W images obtained at 4 T versus those obtained at 1.5 T.
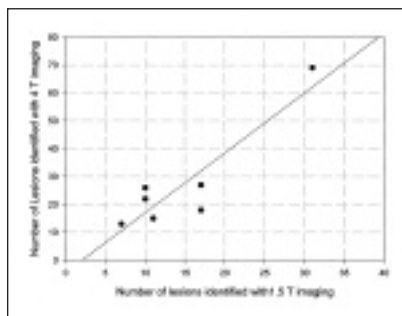

Figure 5: *Number of lesions detected using 4T versus 1.5 T imaging*
The number of lesions detected in each subject, using 1.5 T imaging, was plotted against the number seen using 4 T. When all seven subjects were compared there was a 46% increase in the number of lesions detected using 4 T versus 1.5 T. As demonstrated by the correlation line, the relationship between individual lesion volumes was linear (r = 0.905, p = 0.005, DF = 6), with a slope of 2.146 showing that the number of lesions detected using 4 T imaging increases with the number of lesions detected using lower fields.
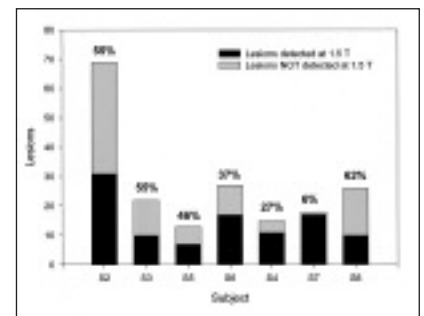

Figure 6: *Per subject increase in the number of lesions identified at 4 T*
The number of lesions detected at 4 T and the percentage of those lesions that were not seen at 1.5 T. The light gray area of each bar represents the number of lesions not detected at 1.5 T, while the lower portions of the bars represent lesion detected at 1.5 T. An increase in the number of lesions identified at 4 T as compared to 1.5 T is variably present in all subjects.
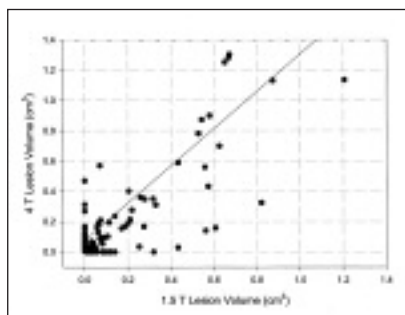

Figure 7: *Individual lesion volumes using 4 T versus 1.5 T imaging.*
Individual lesion volumes as measured at 1.5 T are plotted against volumes measured from a 4 T exam. When individual lesions were directly compared (n=136), 47% of those seen at 4 T were not detected at 1.5 T. These lesions were small with an average mean volume ± SE of 0.060 ± 0.010 cm^3 (range, 0.004 – 0.470 cm^3). As demonstrated by the correlation line, the relationship between individual lesion volumes was linear (r=0.943 (p < 0.001, DF = 135), with a slope of 1.231 showing that the lesion volume detected at 4 T tend to increase with that detected at lower field. However, 14% of the lesions measured were larger at 1.5 T than at 4 T, and 11% of the lesions seen at 1.5 T were missed at 4 T. Like their 4 T counterparts, these undetected lesions were small (mean volume ± SE of 0.075 ± 0.020 cm^3; range, 0.009 – 0.320 cm^3).
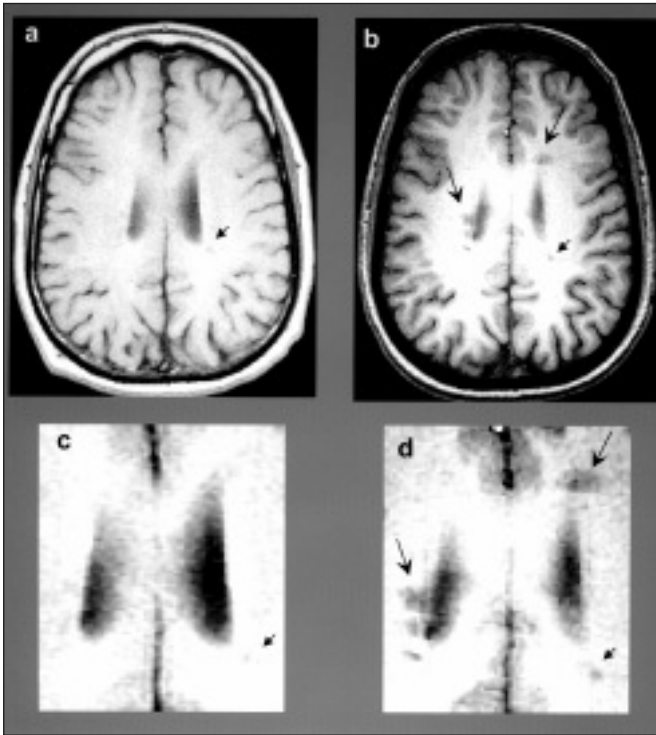
Figure 8: *4 T Lesions that are not seen at 1.5 T and a lesion that appears smaller and more focal at 4 T.*
T1-weighted images (a and b) and enlarged regions of interest (c and d) acquired at 1.5 T (left) and 4 T (right). These images reveal four lesions that can be identified at 4 T but not at 1.5 T (large arrows). Also visible is a lesion that appears smaller and more focal at 4 T than at 1.5 T. (small arrows).

the increase in 4 T lesion load (Figure 10b). This negative contribution was offset in subject S3 by the large positive contribution of volume from lesions identified at 4 T that were not identified at 1.5 T, producing a net increase in 4 T lesion load. Figures 10b and c represent subjects who both had lesions identified on the 4 T images and not at 1.5 T.

DISCUSSION

This study demonstrated that when compared to standard clinical imaging at 1.5 T, 4 T imaging can detect a greater number of lesions and an increased lesion volume. Within a somewhat longer time frame, higher resolution images can be obtained at 4 T to detect smaller lesions and increased volume within individual lesions. These two factors ultimately lead to an increased lesion load seen on 4 T images. The white matter within MS brains viewed during MRI has long been considered to be abnormal and is commonly referred to as "normal appearing" white matter (NAWM).[11-13] Several studies have examined NAWM and have suggested the "invisible" lesion load would provide a clearer picture as to what is occurring within the MS brain. In the current study, the use of 0.8 mm^3 voxel at 4 T resulted in a 46% increase in the total number of lesions detected, a 60% increase in the mean lesion volume measured, and a 51% increase in total lesion load when compared to the standard 5.3 mm^3 voxel size used at 1.5 T imaging. Volume

averaging can cause small lesions or small portions of lesions divided between voxels to go undetected, while the same lesion or part of a lesion located in the middle of a voxel may be easily identified. The increased number of lesions observed in this study was not isolated to a specific anatomical location, but rather was evident throughout the white matter. It would appear that smaller lesions located within the NAWM could be detected with higher resolution images.

Analysis of the increased 4 T lesion load revealed that 96% of the increase can be attributed to the larger 4 T volumes of lesions that were identified at both 4 T and 1.5 T. The lesions detected on the higher resolution 4 T images had a more defined lesion edge resulting in a more accurate volume measurement. Only a small fraction (4%) of the total increase in 4 T lesion load resulted from the added volume from the newly detected lesions not seen on the lower resolution images. The lesions detected only on the 4 T images were small in size (mean volume of 0.060 ± 0.010 cm^3). In order to contribute to the lesion load, a large number of these new lesions would have to be present. That is not to say their detection is trivial. The anatomical location of these small lesions may be more beneficial in understanding the functional impairment of the individual or how the disease progresses.

Some of the lesions (11%) detected at 1.5 T were not visible on the 4 T images. Previous MR studies conducted at 4 T and 4.7 T examined the central nervous system of an animal model of MS.[14-15] Both studies reported an increased signal intensity on T1W images that were associated with lesions that contained edema, inflammation and demyelination. These results suggest that T1W images acquired at the higher field strengths have some T2-weighting. Therefore, the contrast on those images may be altered resulting in undetectable lesions.

When the subjects were examined individually, the increase in the number of lesions seen at 4 T ranged from 6% to 62% and the total lesion load ranged from 28% to 282%. The range seen
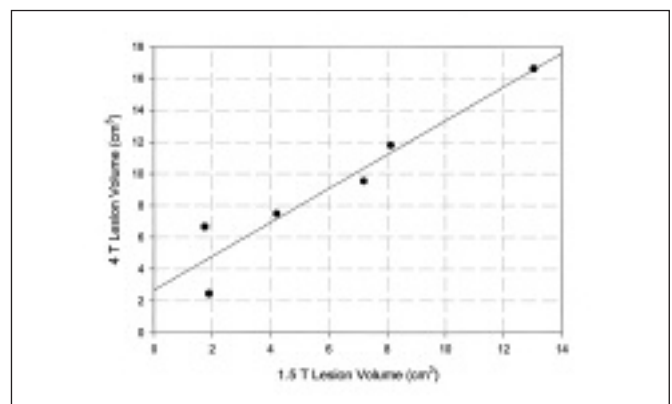

Figure 9: *Total lesion load using 4 T versus 1.5 T imaging*
The total lesion load detected in each subject using 1.5 T imaging is plotted against the total lesion load measured at 4 T. When all six subjects were compared there was a 51% increase in the total lesion load detected using 4 T versus 1.5 T imaging. As demonstrated by the correlation line, the relationship between the lesion loads was linear (r=0.954, p = 0.003, DF = 5), with a slope of 1.065, showing that the total lesion load detected at 4 T tends to increase with increasing 1.5 T lesion load.
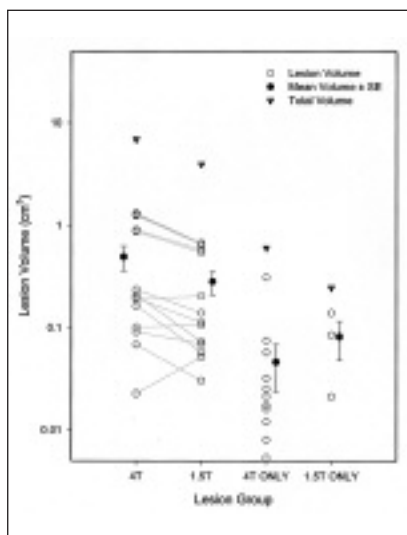
Figure 10a: Individual lesion volumes at 4 T and 1.5 T as measured in subject S6 Comparison of the 4 T volumes and 1.5 T volumes of 14 lesions seen at both field strengths in subject S6, as well as of the volumes of the lesions seen only at 4 T and the volumes of the lesions seen only at 1.5 T. Although the volume of some individual lesions decreased when measured at 4 T as compared to 1.5 T, there was a 74% increase in both the mean volume (0.492 ± 0.135 cm³ vs. 0.283 ± 0.072 cm³) and total volume (6.890 cm3 vs. 3.961 cm³) of lesions measured at 4 T. A total of 13 lesions, with a mean volume of 0.046 ± 0.023 cm³ and a total volume of 0.604 cm³, were detected at 4 T and missed at 1.5 T. Three lesions, with a mean volume of 0.082 ± 0.034 cm³ and a total volume of 0.247 cm³ were not identified at 4 T and seen only at 1.5 T.
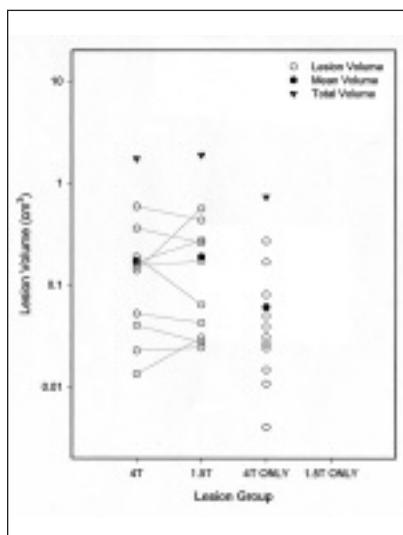

Figure 10b: Individual lesion volumes at 4 T and 1.5 T as measured in subject S3 Comparison of the 4 T volumes and 1.5 T volumes of 10 lesions seen at both field strengths in subject S3, as well as of the volumes of the lesions seen only at 4 T. There was an 8% decrease in both the mean volume (0.173 ± 0.057 cm³ vs. 0.189 ± 0.060 cm³) and total volume (1.730 cm³ vs. 1.889 cm³) of lesions measured at 4 T than at 1.5 T, resulting in a negative contribution to the increase in 4 T lesion load. This negative contribution was more than offset by the large positive contribution of volume from 12 lesions identified at 4 T that were not identified at 1.5 T (Mean volume of 0.061 ± 0.025 cm³ and total volume of 0.729 cm³), producing a net increase in 4 T lesion load. No lesions were seen only at 1.5 T.
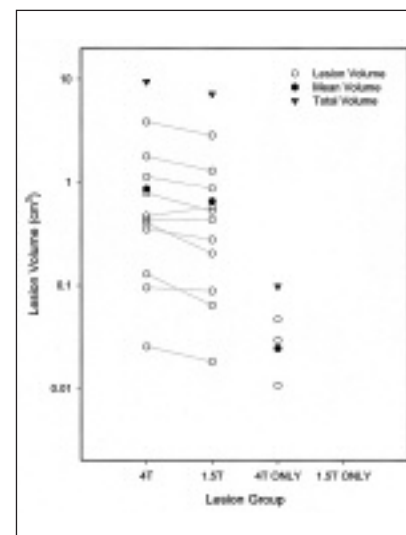

Figure 10c: Individual lesion volumes at 4 T and 1.5 T as measured in subject S4 Comparison of the 4 T volumes and 1.5 T volumes of 11 lesions seen at both field strengths in subject S4, as well as of the volumes of the lesions seen only at 4 T. Although the volume of some individual lesions decreased when measured at 4 T as compared to 1.5 T, there was a 31% increase in both the mean volume (0.859 ± 0.337 cm³ vs. 0.654 ± 0.248 cm³) and total volume (9.447 cm³ vs. 7.193 cm³) of lesions measured at 4 T. A total of 4 lesions, with a mean volume of 0.025 ± 0.009 cm³ and a total volume of 0.098 cm³, were detected at 4 T and missed at 1.5 T. No lesions were seen only at 1.5 T.

in these measurements is not too surprising since the clinical and pathological manifestations of MS are highly variable from one individual to another. All subjects in this study were diagnosed with the secondary-progressive form of MS, but the duration of which the subjects displayed this phenotype ranged from two to 20 years. Biological heterogeneity may the reason for this range in intersubject variability.

When the lesion-to-lesion comparison was analyzed, 14% of the lesions identified on the 1.5 T image sets had larger volume measurements than on the 4 T images. Filippi and colleagues[16] used an idealized spherical lesion model to investigate the effects of reducing slice thickness on partial volume effects, and noted that lesion volumes tend to be overestimated when lesion dimensions are of the order of the slice thickness. A subject with a large number of convex lesions with dimensions similar to the slice thickness would demonstrate a marked decrease in lesion load.[16] Thinner slice thickness used to acquire the 4 T images may have been beneficial in detecting more lesions, but if a lesion's dimension was similar to its slice thickness, the volume of that lesion could have been underestimated.

While quantitative measurement of lesion load in MS is a widely used marker of disease progression, it has been difficult to measure lesion load with a high degree of reproducibility. It has already been shown that several factors markedly influence lesion volume estimates in MS, including intrasubject biological variations,[17] the use of multiple MR scanners,[18,19] different pulse sequences,[20-24] acquisition parameters,[16,19,23] T2 natural lesion oscillation,[17] segmentation techniques,[24-27] relatively thin slices,[6,19,27-29] quality assurance checks,[19,27] operator training,[27,30] and accuracy of subject repositioning.[19,26,27,31,32] Because the magnitude of the variability introduced by all of these factors make it difficult to reliably detect lesion load change, several strategies to reduce the effect of these sources have been developed.[4,19,27,32-34] Imaging the MS brain at different field strengths in this study dictated the use of different scanners, pulse sequences, and acquisition parameters, thereby contravening many of the strategies developed to reduce the inherent variability of lesion load estimates. Sources of variation in lesion load estimates include the scanners, pulse sequences, subjects, techniques, and operators used in the study. These

factors influence the quality (i.e. SNR, contrast and spatial resolution) of the resultant images and the results of quantification. Accurate repositioning was complicated by the deficiencies in the 4 T planning tools despite following the repositioning technique recommended by the *ad hoc* European Community Committee.[34]

Improvements in image SNR, arising from the use of 3D acquisition, increased voxel size or MR sequences can make a lesion more conspicuous resulting in its detection.[20,21,35] In this current study, if the magnetic field strength and voxel size were the only parameters that differed between the images, the mean SNR of the 4 T images would be expected to be 0.59 times as great as 1.5 T. However, different pulse sequences and acquisition parameters such as repetition time, echo time, and receiver gain also differed between the two sets of images. The SNR of white matter, gray matter, CSF, and lesions were measured in order to determine if a higher signal contributed to the lesion volume and detection. When the ratios of 4 T SNR to 1.5 T SNR from white matter, gray matter, CSF, and lesion on both the T2W and T1W images were averaged, the mean 4 T image SNR was found to be 0.69 times that of the 1.5 T image SNR indicating the use of different imaging hardware and pulse sequences had only a minor impact on mean image SNR. As expected, the 1.5 T T1W and T2W images had increased SNRs in more than one tissue type compared to the 4 T images. The signal intensity differences between the different tissues, expressed as CNRs, indicated the difference between white matter-lesion and gray matter-lesion were both higher and the difference between CSF-lesion was lower on the T1W images acquired at 4 T. Since MS brain lesions are found within the white matter and typically have a periventricular or juxtacortical location, the increased CNR between gray matter-lesion would not expect to have a substantial outcome on the identification of lesions. The increased contrast between the white matter and lesions may have attributed to the detection of some lesions. However, if individual image slices from either 1.5 T or 4 T were viewed, it was difficult to identify which images were acquired at which field strength. The measurable differences in SNR and CNR did not produce a discernable qualitative difference. It is unlikely these factors had a major influence in lesion volume or detection in this study. Therefore, the increase in 4 T lesion load can be primarily attributed to the increased resolution of the 4 T images.

Image analysis methods are time consuming and prone to operator-induced errors as ambiguities often arise in identifying lesions and evaluating their size and extent.[36-37] These difficulties arise from the fact that MS lesions are inherently fuzzy with "soft" rather than "hard" boundaries and small in size. A previous comparison of techniques found the semi-automated local thresholding techniques to be more reliable resulting in an intra-observer lesion load variability of 6% compared to 12-33% variability for the manual outlining technique.[36] Although the intra-observer variability in lesion volume estimates is relatively low when a semi-automated segmentation tool such as Segtool is used,[10] the degree of vacillation will depend on operator experience and characteristics of the image sets under analysis. Since all images in this study were analyzed using Segtool and reviewed by a single operator over a relatively short period of time, intra-observer variability was kept to a minimum (less than 6%).

High-resolution MR imaging of MS subjects at 4 T results in dramatically improved lesion detection, which may have important implications for the study of MS and the design and monitoring of treatment trials. The increase in intrinsic SNR afforded by the use of a 4 T magnetic field permits the acquisition of images with increased resolution in times comparable to those used in current clinical settings at 1.5 T. This improvement resolution resulted in a large increase in both the number and volume of MR-visible lesions, with a subsequent increase in total lesion load detected. In the current study, the use of 0.8 mm^3 voxels at 4 T, as compared to voxel volumes ranging from 5.3 mm^3 at 1.5 T, resulted in a 46% increase in the total number of lesions detected, a 60% increase in the mean lesion volume measured, and a 51% increase in total lesion load. The detection of large numbers of these small lesions, which in the current study represented 47% of all the lesions identified at 4 T (but only accounted for 4% of the total lesion volume), may also help to explain the discrepancies observed in studies of NAWM and the poor correlation that has been found between lesion load and clinical disability to date. The lesion load within individual subjects depends on the number, size distribution and location of lesions, the decrease in partial volume effects that accompanies the use of high-resolution images should reduce the variations in lesion load estimates. Thus, high-resolution 4 T imaging has the potential to substantially increase the accuracy of large-scale multicenter clinical trials and serial studies of MS.

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