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# The Effect of Section Thickness on MR Lesion Detection and Quantification in Multiple Sclerosis

Paul D. Molyneux, Niall Tubridy, Geoff J. M. Parker, Gareth J. Barker, David G. MacManus, Paul S. Tofts, Ivan F. Moseley, and David H. Miller

**BACKGROUND AND PURPOSE:** The purpose of our study was to investigate the effect of section thickness on MR detection of brain lesion volume and measurement precision in patients with multiple sclerosis (MS).

**METHODS:** Eight subjects with known MS were studied on a 1.5-T MR system. We used a 3D fast fluid-attenuated inversion-recovery sequence to obtain contiguous axial brain images at section thicknesses of 5 mm, 3 mm, and 1 mm. Two sets of images were acquired at each section thickness during two sessions, between which the patient was removed from the scanner. Lesion volumes were measured at each section thickness using a semiautomated local thresholding technique.

**RESULTS:** We found that progressive reduction in section thickness led to detection of smaller lesions, resulting in a significant (8%) increase in lesion volume on MR images as section thickness was reduced from 5 mm to 3 mm. However, despite a further increase in lesion detection at a section thickness of 1 mm, this did not result in an increase in total lesion volume. This finding indicates that the relationship between section thickness and lesion volume on MR images is not linear. Scan-rescan reproducibility was improved by reducing section thickness, at the cost of increased analysis time.

**CONCLUSION:** This study shows that acquisition of very thin sections increases the sensitivity and precision of MS lesion measurement. Serial studies assessing lesion changes over time are needed to define the impact of this increase on sample size requirements for MS treatment trials.

Serial quantification of brain lesion volume in multiple sclerosis (MS) can be used to assess disease evolution, encouraging its use as an outcome measure in MS treatment trials (1–4). However, it has become clear that a substantial proportion of white matter disease is not detectable on standard 2D conventional spin-echo (CSE) sequences with 5-mm-thick sections (5–8) and that this undetected lesion load might be important in functional terms (9).

One approach to increasing lesion detection is to increase spatial resolution in the section-select direc-

tion by reducing the section thickness (6, 10). Where a lesion occupies only part of a voxel, the contrast relative to background tissue is dependent on both the signal from the lesion and the proportion of the voxel that it occupies (11). With a standard section thickness of 5 mm, small low-contrast lesions occupying only part of a voxel can go undetected. A further effect of this volume averaging is blurring of the apparent border of a lesion, if its surface is not along the section-select direction, even if a biologically sharp boundary exists (6, 12). This loss of edge definition leads to difficulty in defining lesion boundaries in a reproducible manner.

Reducing the section thickness from 5 mm to 3 mm has been shown to increase the MR-visible lesion volume by about 9% with a standard CSE sequence (6), and it may increase the precision of volume measurement (13). However, it has not yet been possible to obtain adequate 2D CSE images down to very thin sections, since the necessary scan time becomes prohibitive and the poor signal-to-noise ratio (SNR) unacceptable. Three-dimensional MR sequences allow

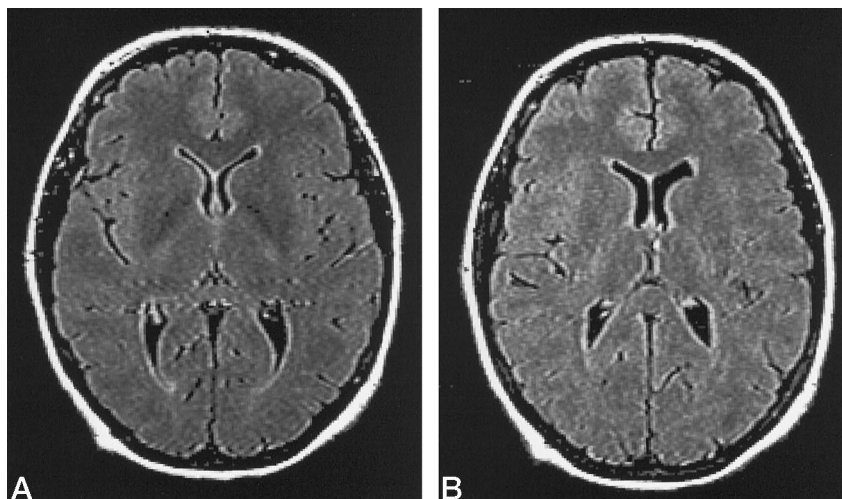
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FIG 1. A and B, Normal findings with the 3D fast-FLAIR sequence (TR/TE, 4600/140; inversion time, 1740; echo train length, 24; section thickness, 1.5 mm) from two healthy subjects. Note the increased signal around the occipital horns of the lateral ventricles (A), the thin rim of high signal around the rest of the ventricle, and the areas of increased signal at the frontal poles of the lateral ventricles (B).



acquisition of thinner sections with acceptable acquisition times and SNR. When such a sequence was applied to the detection of contrast-enhancing lesions, detection rates were shown to be 12% higher at a 1-mm section thickness than at a 3-mm thickness (14).

An alternative approach to increasing lesion detection is to increase lesion-to-background contrast at a given section thickness. The 2D fast fluid-attenuated inversion recovery (fast-FLAIR) sequence produces higher contrast and therefore greater conspicuity of cortical and subcortical lesions than does a standard CSE sequence (7, 15, 16), albeit with a reduced sensitivity to lesions in the posterior fossa (7), and may yield a higher overall brain lesion volume than a standard CSE sequence at the same 5-mm section thickness (7). The reproducibility of lesion volume quantification with fast-FLAIR is as good as (16) or better than (13, 15) with CSE, probably owing to increased lesion-background contrast and better edge definition.

We initially experimented with a 3D fast spin-echo (FSE) sequence but found the results unsatisfactory because of high CSF signal and increased signal at CSF-tissue interfaces. We found that the 2-mm 2D fast-FLAIR sequence enabled us to detect more brain lesions than the 1.5-mm 3D FSE sequence (17). With 2D fast-FLAIR, sections thinner than 2 mm were not possible owing to unacceptable SNR and acquisition time. We therefore developed a 3D fast-FLAIR sequence for this study, combining the greater lesion conspicuity of the FLAIR sequence with the higher spatial resolution and SNR per unit time possible with 3D imaging (18). This provided an opportunity to study the impact of increasing resolution down to a section thickness of 1 mm on MR-derived lesion volumes. We acquired 3D fast-FLAIR images at three section thicknesses (5 mm, 3 mm, and 1 mm). Our aim was to study the impact of decreasing section thickness on both the MR-visible lesion volume and the reproducibility of volume measurement.

## Methods

### Patients

We studied eight patients (four men and four women) with clinically definite MS (19). Their mean age was 45 years (range, 31 to 56 years), mean disease duration was 16 years (range, 8 to 26 years), and mean Expanded Disability Status Scale (EDSS) score (20) was 4.9 (range, 1.0 to 8.5). Three patients had relapsing-remitting MS and five had secondary-progressive MS. Written informed consent was obtained before entry into the study.

### MR Imaging

Patients were imaged during a single visit, in two sessions separated by an interval of 5 minutes. A 1.5-T imager was used to acquire the images with contiguous interleaved slabs/sections in the axial plane. During the first session, an oblique axial dual-echo CSE sequence was used with contiguous 5-mm-thick sections and the following parameters: TR/TE, 2000/34,90; matrix,  $256 \times 256$ ; and field of view (FOV), 25 cm. The 3D fast-FLAIR images were then obtained with axial sections in order of decreasing section thickness (5 mm, 3 mm, and 1 mm). To allow meaningful comparison between the 3D fast-FLAIR sequences, the following parameters were used at all section thicknesses: TR/TE, 4600/140; inversion time (TI), 1740; echo train length, 24; FOV, 25 cm; and matrix size,  $256 \times 192$ . For the 5-mm and 3-mm sequences, acquisition time was 12 minutes, and 48 sections were acquired. The 1-mm sequence required 18 minutes and produced 144 sections.

Next, the patient was removed from the imager for 5 minutes and then, during a second session, a further set of 3D fast-FLAIR images was obtained at each section thickness. Repositioning for the second session was performed according to a standardized protocol developed by this unit (21).

### Image Analysis

The images obtained at each section thickness for each patient were first assessed in isolation, in randomized order, and with a delay of at least 1 week between assessing any set of images of the same patient. Lesions were identified and marked on a hard copy using a consensus approach by two of the authors over a 3-month period. Prior to this study, 10 healthy control subjects had been imaged with the 3D fast-FLAIR sequence using a section thickness of 1.5 mm to identify areas of hyperintensity that could be confused with lesions in the patient group. The normal findings (Fig 1) were 1)

increased signal around the occipital poles of the lateral ventricles; 2) small areas of increased signal around the temporal horns; 3) a thin rim of high signal around the remainder of the third and lateral ventricles; 4) areas of high signal at the frontal poles of the lateral ventricles; 5) symmetrical areas of increased signal in the posterior limbs of the internal capsules; and 6) slightly increased signal in the posterior centrum semiovale. When identifying lesions on the 3D fast-FLAIR images, such "normal" areas of higher signal were excluded unless they were particularly prominent and asymmetrical. The aim of this conservative approach in these regions was to minimize the potential for tissue misclassification. Lesion volumes were quantified by a single experienced observer using a semiautomated local thresholding technique incorporating a contour-based algorithm (22, 23). The time taken to perform the quantitative analysis at each section thickness was recorded. Only lesions marked on the hard copy were included in the analysis. Lesion volume was calculated automatically as the total lesion area in the imaging plane multiplied by the section thickness.

The 3D fast-FLAIR images of each patient obtained during the first session were then reviewed side by side by the same two observers. The images with 5-mm section thickness were compared with those with 3-mm thickness, and all lesions marked on just one image were identified. The same procedure was adopted for comparison of the 3-mm and 1-mm images. The volume of these "missed" lesions was quantified from measurements previously obtained using the semiautomated segmentation technique.

Finally, 32 lesions more than 1 cm in diameter were randomly selected to provide an estimate of both contrast-to-noise ratio (CNR) and contrast ratio (CR) at each section thickness. The CNR was calculated according to the following formula:  $CNR = (SI_{\text{lesion}} - SI_{\text{NAWM}})/\text{noise}$ , where SI represents signal intensity and NAWM indicates an area of normal-appearing white matter adjacent to the lesion. Noise was estimated from a region of the FOV not containing tissue and not contaminated by phase-encoding artifacts. The CR was calculated as a measure of lesion conspicuity according to the following formula:  $CR = (SI_{\text{lesion}} - SI_{\text{NAWM}})/SI_{\text{NAWM}}$ .

#### Statistical Analysis

The mean of the two lesion volumes at each section thickness was used to compare the effects of section thickness, as this approach should reduce the impact of random measurement error. Friedman two-way analysis of variance (ANOVA) was used to assess the significance of differences in lesion volume between the images. Post hoc comparisons were performed using the Wilcoxon signed rank test. The same statistical approach was used to assess differences in time taken to quantify lesion volumes at each section thickness. Scan-rescan reproducibility was assessed as the percentage of agreement between the lesion volumes obtained from the first and second sessions (13).

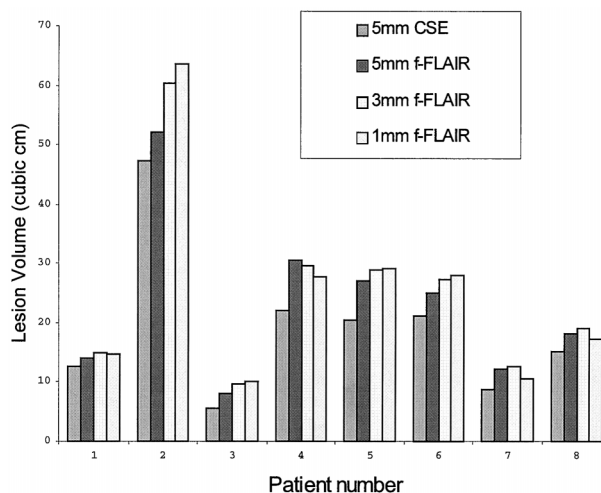
### Results

The lesion volumes obtained with the different images (Table 1 and Fig 2) were significantly different ( $P < .001$ ). The mean lesion volumes obtained with the 5-mm 3D fast-FLAIR sequence were 22% greater (range, 10% to 48%) than those identified for the corresponding 5-mm CSE sequence ( $P = .01$ ). Reducing the section thickness from 5 mm to 3 mm increased derived lesion volumes for all but one patient by an average of 8.1% (range, -2.9% to 19.2%). This difference was statistically significant ( $P < .05$ ). In contrast, reducing the section thickness further from, 3 mm to 1 mm, did not yield an additional

**TABLE 1: Lesion volumes (cm<sup>3</sup>) obtained with the each sequence/section thickness**

Sequence/Section Thickness	Mean	Median	Range
5-mm CSE	19.2	17.8	5.5–47.3
5-mm fast-FLAIR	23.4	21.7	8.1–52.2
3-mm fast-FLAIR	25.3	22.6	9.7–60.4
1-mm fast-FLAIR	25.1	22.6	10.1–63.6

Note.—CSE indicates conventional spin echo; FLAIR, fluid-attenuated inversion-recovery sequence. For the fast-FLAIR sequences, the above values represent the mean of the measurements obtained at the two imaging sessions.



**FIG 2.** The effect of sequence/section thickness on total lesion volume. For each patient, the mean volume of the two measurements (scan and rescan) is shown for each section thickness of the fast-FLAIR sequence to reduce the impact of random measurement error.

**TABLE 2: The effects of progressive reduction in section thickness for the 3D fast-FLAIR sequences**

	No. of Extra Lesions*	Total Volume Contribution (cm <sup>3</sup> ) of Extra Lesions, mean (range)†	Individual Lesion Volume of Extra Lesions (cm <sup>3</sup> ), mean (range)‡
5 mm vs 3 mm	170	2.2 (0.6–6.2)	0.13 (0.012–0.31)
3 mm vs 1 mm	185	0.6 (0.2–1.4)	0.027 (0.006–0.085)

\* The number of additional lesions identified by progressive reduction in section thickness. Eleven lesions were marked on the 5-mm sequence and not on the 3-mm sequence, and a further 11 lesions were marked at 3 mm and not at 1 mm.

† The volume contribution of these additional lesions to total lesion volume per patient.

‡ The individual lesion volume of these additional lesions.

increase in total lesion volume ( $P = .9$ ). The mean volume obtained with the 1-mm 3D fast-FLAIR sequence was on average 31% higher ( $P = .01$ ) and the 3-mm 3D fast-FLAIR sequence 32% higher ( $P = .01$ ) than with the standard 5-mm CSE sequence.

The effects of progressive reduction in section thickness on lesion detection are shown in Table 2. Comparing the 5-mm and 3-mm images side by side, we identified 170 lesions on only the 3-mm images, whereas just 11 lesions were marked exclusively on



**TABLE 3: Contrast to noise (CNR) and contrast ratios (CR) for each sequence**

	CNR, mean (SD)	CR, mean (SD)
5-mm CSE	13.8 (2.6)	0.27 (0.05)
5-mm fast-FLAIR	30.2 (7.5)	0.83 (0.19)
3-mm fast-FLAIR	20.4 (3.3)	0.86 (0.15)
1-mm fast-FLAIR	7.4 (3.3)	0.81 (0.15)

Note.—CSE indicates conventional spin echo; FLAIR, fluid-attenuated inversion-recovery sequence. Differences between 3D fast-FLAIR CNR at different section thicknesses were significant ( $P < .001$ ); differences between CR at different section thicknesses were not significant ( $P = .4$ ).

the 5-mm images. When only lesions seen at both 5 mm and 3 mm section thicknesses were included in the lesion volume, thereby excluding the additional contribution of lesions identified only at 3 mm, the mean lesion volumes at 5 mm and 3 mm were 23.0 cm<sup>3</sup> and 23.1 cm<sup>3</sup>, respectively ( $P = .7$ ). A similar side-by-side comparison of the 3-mm and 1-mm images revealed that 185 lesions were seen on only the 1-mm sequence, whereas just 11 lesions were identified exclusively on the 3-mm sequence. Considering only those lesions identified on both 3-mm and 1-mm sequences, lesion volumes were 25.3 cm<sup>3</sup> and 24.7 cm<sup>3</sup>, respectively; a difference that approached statistical significance ( $P = .07$ ).

The values for CNR and CR are given in Table 3. The 3D fast-FLAIR sequence showed significantly higher CR than the 2D 5-mm CSE sequence at each section thickness ( $P < .001$ ). There was no significant difference in CR at different section thicknesses on fast-FLAIR images ( $P = .4$ ). However, the CNR became progressively worse as section thickness was reduced ( $P < .001$ ), being approximately proportional to section thickness, as would be expected.

The mean operator times required to perform the quantification on the 3D fast-FLAIR images at 5 mm, 3 mm, and 1 mm were 31 minutes (SD, 9.9), 58 minutes (SD, 16.2), and 154 minutes (SD, 30.9), respectively. These differences were significant overall ( $P < .001$ ) as well as for each decrement in section thickness ( $P < .05$ ).

The mean scan-rescan agreement for derived lesion volumes was 91% (range, 87% to 97%) at the 5-mm section thickness, 95% (range, 92% to 98%) at 3 mm, and 98% (range, 93% to 100%) at 1 mm.

## Discussion

Several previous studies have addressed the impact of section thickness on both the sensitivity and precision of MS lesion volume quantification (6, 10, 13). Progressive reduction in section thickness from 15 mm to 3 mm on T2-weighted images has been shown to increase the number of detected lesions and lesion volume (6). In one study, a gain in derived lesion volume of 9% was produced by reducing the section thickness from 5 mm to 3 mm (6), and the authors of that study postulated a linear relationship between section thickness and MR-visible lesion volume, esti-

imating that a further reduction in section thickness might produce up to a 20% increase in MR-detectable lesion volume.

Our results are similar, with an increase in detected lesion volume of 8% with a reduction in section thickness from 5 mm to 3 mm. We found that this increase was a consequence of the greater sensitivity of the 3-mm sequence to small, generally low-contrast lesions obscured by volume averaging at a 5-mm section thickness. Comparing the images obtained with 3-mm and 1-mm section thicknesses, we found a further similar increase in the number of detectable lesions. However, the mean individual volume of lesions detected by going from 5 mm to 3 mm was more than four times that observed when decreasing from 3 mm to 1 mm (Table 2); thus, the extra contribution of the small lesions detected at 1 mm to total lesion volume was extremely small. It is therefore not surprising that reducing the section thickness from 3 mm to 1 mm did not increase the overall lesion volume. Indeed, further analysis of our data shows that when considering only those lesions identified at both 3 mm and 1 mm section thicknesses, the derived lesion volumes at the 1-mm thickness were generally smaller.

Several possible factors may have contributed to these findings. First, the lower SNR and CNR at the lesser section thickness may have altered the observers' perception of lesion boundaries. A previous study has suggested that as lesion contrast is reduced, the reported volume decreases (12). Second, differences in volume averaging may be important. For a lesion of similar diameter to the section thickness, volume averaging will tend to cause an overestimation of volume (6), while at lesser thicknesses this effect would diminish. The impact of this will depend on the size distribution of lesions for an individual patient, but this averaging may have been more apparent with the 3-mm acquisitions. Third, we found that with the increased spatial resolution at 1 mm, several lesions that appeared as confluent areas of high signal at 3 mm were, at a section thickness of 1 mm, in fact seen to comprise several smaller, discrete lesions (Fig 3). This effect would result in smaller volumes being measured for such regions at very small section thicknesses. Because such confluent regions can make a substantial contribution to total lesion volume, even if this change in perception of lesion boundaries at a 1-mm section thickness occurred only rarely, it might be sufficient to produce an apparent difference in total measured lesion volume.

It might be concluded from our results that lesion volumes derived at 3 mm and 1 mm are not substantially different and that therefore no advantage in terms of sensitivity is conferred by reducing the section thickness beyond 3 mm. However, although total lesion volumes were not different, several small, low-contrast lesions were identified only on the thinnest section acquisitions. Such small lesions might be important in functional terms: it is conceivable that gradual accumulation of a large number of these small lesions in a strategic pathway could result in a slow progression in disability (9). A particular advan-

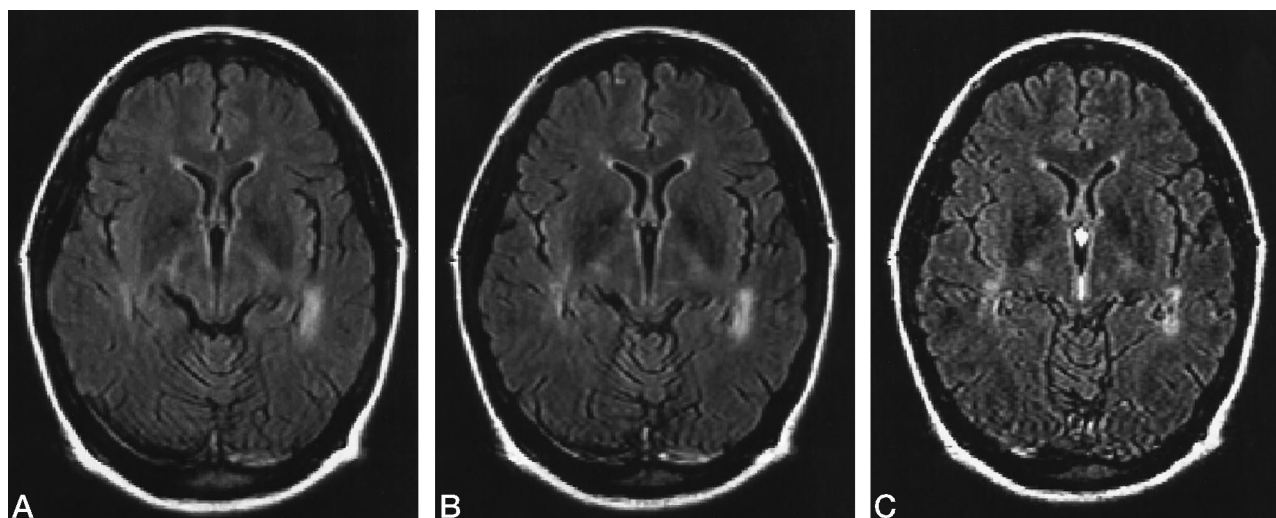


FIG 3. A–C, 3D fast-FLAIR images (TR/TE, 4600/140; inversion time, 1740; echo train length, 24) of a patient at section thicknesses of 5 mm (A), 3 mm (B), and 1 mm (C). The SNR can be seen to deteriorate as section thickness is reduced. However, despite this, there is an increase in resolution of periventricular lesions with decreasing section thickness. Lesions that look confluent at 5 mm appear as smaller, discrete areas of high signal at 1 mm.

tage of increased section resolution may be the ability to identify and localize smaller lesions in pathologically eloquent areas, such as the pyramidal tracts. This may yield stronger correlations between MR measures and functional systems scales. Furthermore, it is conceivable, if unlikely, that new treatments may predominantly alter the development of lesions of a particular size or contrast. If a putative drug were to preferentially inhibit the development of small, low-contrast lesions, such a treatment effect might only be seen at high section resolution.

We also found that despite the decreasing CNR as section thickness decreased, the scan-rescan reproducibility improved. Several sources of error contribute to scan-rescan variability (4, 24, 25); notably, differences in the extent of motion and flow artifacts, inconsistent patient positioning that causes variable volume averaging (26–28), and observer inconsistency in application of the quantitative technique (measure-remeasure variability) (13, 23, 28, 29). Scan-rescan reproducibility is a more meaningful reflection of the variability that might be found in a longitudinal study than assessment of measurement error on a single scan alone. As section thickness decreases, the impact of suboptimal patient repositioning on lesion volume measurements should become less important, since the reduction in volume averaging should allow more consistent identification of lesion boundaries.

Against the increased detection of small lesions and greater reproducibility achieved by reducing section thickness must be weighed the increase in both acquisition time and loss of SNR (Fig 3). Furthermore, there is a substantial increase in operator time needed to perform the quantification at very thin sections with the semiautomated technique used in this study. The exact relationship between sensitivity, reproducibility, and sample size requirements for treatment trials is not yet known. It may be possible to

reduce the number of patients and examinations necessary to show a significant treatment effect with MR imaging by increasing the sensitivity and reproducibility of quantification with very thin sections. Therefore, the increasing analysis time with thin section thickness acquisition could be at least partially offset by the requirement for fewer patients. This issue will only be resolved when the interaction between measurement error and sample size is better defined. However, the quantitative technique used in this study required a mean analysis time of more than 150 minutes per data set at a section thickness of 1 mm. For serial studies involving large numbers of patients, this time requirement will almost certainly preclude the routine incorporation of such a protocol. The much more feasible analysis times for 3-mm-thick sections suggest that this section resolution is more appropriate for studies in which a semiautomated segmentation technique such as this is used. However, several automated techniques are now being developed with the potential for minimal operator intervention (30–33). Once such methods are validated in the context of treatment trials, they offer the potential for application to images with 1-mm-thick sections, with the benefits of better sensitivity and less susceptibility to repositioning errors.

### Conclusion

This study shows that reducing section thickness increases detection of small lesions and increases reproducibility, at the expense of increasing operator time. It also shows that the relationship between section thickness and MS lesion volume is not linear at very small section thicknesses. More work is needed to define the impact of these improvements on both MR/clinical correlations and sample size requirements for MS treatment trials. If the very small gains in sensitivity and precision do not achieve these goals,

the continuation of 3-mm-thick sections as the standard of reference will be confirmed.

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