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Fluid and White Matter Suppression

New Sensitive 3 T Magnetic Resonance Imaging Contrasts for Cortical Lesion Detection in Multiple Sclerosis

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Objective: Cortical lesions are common in multiple sclerosis (MS), but their visualization is challenging on conventional magnetic resonance imaging. The uniform image derived from magnetization prepared 2 rapid acquisition gradient echoes ($MP2RAGE_{uni}$) detects cortical lesions with a similar rate as the criterion standard sequence, double inversion recovery. Fluid and white matter suppression (FLAWS) provides multiple reconstructed contrasts acquired during a single acquisition. These contrasts include FLAWS minimum image ($FLAWS_{min}$), which provides an exquisite sensitivity to the gray matter signal and therefore may facilitate cortical lesion identification, as well as high contrast FLAWS ($FLAWS_{hco}$), which gives a contrast that is similar to one of $MP2RAGE_{uni}$. In this study, we compared the manual detection rate of cortical lesions on $MP2RAGE_{uni}$, $FLAWS_{min}$, and $FLAWS_{hco}$ in MS patients. Furthermore, we assessed whether the combined detection rate on $FLAWS_{min}$ and $FLAWS_{hco}$ was superior to $MP2RAGE_{uni}$ for cortical lesions identification. Last, we compared quantitative T1 maps (qT1) provided by both MP2RAGE and FLAWS in MS lesions.

Materials and Methods: We included 30 relapsing-remitting MS patients who underwent MP2RAGE and FLAWS magnetic resonance imaging with isotropic spatial resolution of 1 mm at 3 T. Cortical lesions were manually segmented by consensus of 3 trained raters and classified as intracortical or leukocortical lesions on (1) MP2RAGE uniform/flat images, (2) $FLAWS_{min}$, and (3) $FLAWS_{hco}$. In addition, segmented lesions on $FLAWS_{min}$ and $FLAWS_{hco}$ were merged to produce a union lesion map ($FLAWS_{min\ +\ hco}$). Number and volume of all cortical, intracortical, and leukocortical lesions were compared among $MP2RAGE_{uni}$, $FLAWS_{min}$, and $FLAWS_{hco}$ using Friedman test and between $MP2RAGE_{uni}$ and $FLAWS_{min\ +\ hco}$ using Wilcoxon signed rank test. The FLAWS T1 maps were then compared with the reference MP2RAGE T1 maps using relative differences in percentage. In an exploratory analysis, individual cortical lesion counts of the 3 raters were compared, and interrater variability was quantified using Fleiss $\varkappa$.

Results: In total, 633 segmentations were made on the 3 contrasts, corresponding to 355 cortical lesions. The median number and volume of single cortical, intracortical, and leukocortical lesions were comparable among $MP2RAGE_{uni}$, $FLAWS_{min}$, and $FLAWS_{hco}$. In patients with cortical lesions (22/30), median cumulative lesion volume was larger on $FLAWS_{min}$ (587 μL; IQR, 1405 μL) than on $MP2RAGE_{uni}$ (490 μL; IQR, 990 μL; $P = 0.04$), whereas there was no difference between $FLAWS_{min}$ and $FLAWS_{hco}$, or $FLAWS_{hco}$ and $MP2RAGE_{uni}$. $FLAWS_{min\ +\ hco}$ showed significantly greater numbers of cortical (median, 4.5; IQR, 15) and leukocortical (median, 3.5; IQR, 12) lesions than $MP2RAGE_{uni}$ (median, 3; IQR, 10; median, 2.5; IQR, 7; both $P < 0.001$). Interrater agreement was moderate on $MP2RAGE_{uni}$ ($\varkappa = 0.582$) and $FLAWS_{hco}$ ($\varkappa = 0.584$), but substantial on $FLAWS_{min}$ ($\varkappa = 0.614$). qT1 in lesions was similar between MP2RAGE and FLAWS.

Conclusions: Cortical lesions identification in $FLAWS_{min}$ and $FLAWS_{hco}$ was comparable to $MP2RAGE_{uni}$. The combination of $FLAWS_{min}$ and $FLAWS_{hco}$ allowed to identify a higher number of cortical lesions than $MP2RAGE_{uni}$, whereas qT1 maps did not differ between the 2 acquisition schemes.

Key Words: cortical lesions, FLAWS, $FLAWS_{hco}$, $FLAWS_{min}$, multiple sclerosis, MRI, MP2RAGE, T1 mapping, 3 T

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that leads to substantial disability.[1] In patients with MS, cortical lesions are frequent,[2,3] and baseline cortical lesion number and formation over time predict disability worsening and cognitive decline.[4] In patients with clinically isolated syndrome, the presence of a single cortical lesion identifies patients that are at high risk of developing a clinically definite MS in the following years.[5] As cortical lesions have not been found on magnetic resonance imaging (MRI) in many diseases mimicking MS, they may help to distinguish MS from neurologic conditions such as migraine or neuromyelitis optica.[6] Because of this, cortical lesions have become an integral part of the current MS diagnostic criteria.[7]

Although MS white matter (WM) lesions are classically seen as periventricular, juxtacortical, infratentorial, or spinal T2 hyperintensities,[8] gray matter (GM) lesions are barely visible on conventional 1.5 or 3.0 T MRI sequences.

Increasing the field strength improves the cortical lesion detection rate,[9,10] but even on 7 T MR images, only a small proportion of lesions can be identified compared with histological postmortem specimen.[11,12]

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Advanced 3 T MRI techniques such as double inversion recovery (DIR)[13] or phase-sensitive inversion recovery (PSIR)[14] have shown better results than conventional 3 T MRI to detect cortical lesions, with a higher pathological specificity, but still a poor overall maximum sensitivity of 23% and 24%, respectively.[15] Furthermore, DIR was shown to be prone to flow-related artifacts[13] and provided a low interrater accordance so that complete agreement between raters was only achieved in 19% of cortical lesions.[16] To date, both PSIR and DIR are considered as criterion standard confirmatory sequences for cortical lesion detection in a clinical setting.[6,17] Magnetization prepared 2 rapid acquisition gradient echo (MP2RAGE), a self bias-field corrected sequence for improved segmentation and T1 mapping, has shown equal[18] or superior[19] performance when compared with DIR.

MP2RAGE is a variant of the MPRAGE sequence where, after the inversion of the longitudinal magnetization, 2 images with 2 different inversion times TI1 and TI2 are acquired using rapid gradient echo readout trains.[20] By optimizing the sequence parameters, a combination image is produced ($MP2RAGE_{uni}$), which is free of proton density, T2* contrast, and reception bias-field. Recently, a different optimization of the MP2RAGE pulse sequence known as fluid and white matter suppression (FLAWS) has been proposed,[21] which applies a different parameters optimization. The FLAWS sequence provides both WM- and cerebrospinal fluid (CSF)–suppressed 3D high spatial resolution contrasts simultaneously (FLAWS1, acquired at TI1, WM-suppressed; and FLAWS2, acquired at TI2, CSF-suppressed). Given that the 2 contrasts derive from the same acquisition, they naturally offer a near-perfect alignment. Hence, the signal intensities of FLAWS1 and FLAWS2 can be combined in a voxel-based manner to reconstruct multiple contrasts.

In this study, we used 2 reconstructed FLAWS contrasts: (1) $FLAWS_{min}$, which suppresses both CSF and WM signal and yields a GM-specific contrast[22] that may facilitate cortical lesion identification; and (2) $FLAWS_{hco}$, which obtains a CSF-suppressed, MPRAGE-like, T1-weighted contrast[23,24] that could be used similarly as one of the current criterion standards for cortical lesion detection, MPRAGE. The objective of this study was to compare the manual detection rate of cortical lesions when using $MP2RAGE_{uni}$, $FLAWS_{min}$, and/or $FLAWS_{hco}$. Furthermore, we compared T1 relaxation times in cortical lesions and other brain regions of interest (ROIs) between MP2RAGE and FLAWS at 3 T, because both approaches provide the option to quantify tissue microstructural integrity.

MATERIALS AND METHODS

Study Design and Participants

This study was designed as a comparison of manual cortical lesion detection rate on 3 MRI contrasts ($MP2RAGE_{uni}$ and 2 reconstructed sets of FLAWS: $FLAWS_{min}$ and $FLAWS_{hco}$; see Fig. 1) in patients with diagnosis of definite MS. The number and volume (cumulative lesion load per patient as well as lesion sizes) of cortical lesions served as primary outcomes. The null hypothesis was that there is no numerical difference in manual cortical lesion number and volume between MP2RAGE and FLAWS contrasts. Furthermore, T1 relaxation times of cortical lesions and specific normal-appearing ROIs (see below) as well as contrast-to-noise ratios (CNRs) were compared between MP2RAGE and FLAWS.

Inclusion criteria were (1) relapsing remitting MS according to the McDonald criteria 2017,[7] (2) 18 years of age or older, and (3) ability to give informed consent. Individuals with neurologic comorbidities, contraindications for MRI, and pregnant women were excluded. Images were acquired between November 2018 and December 2020. The study protocol was approved by the local ethics committee. All subjects gave written informed consent.

Magnetic Resonance Imaging Acquisition, Reconstruction, and Processing

All MRI scans were performed on a 3.0 T whole-body MR system (Magnetom Prisma; Siemens Healthineers, Erlangen, Germany) using a 64-channel head and neck RF coil for reception. All patients underwent MRI including (1) MP2RAGE uniform/flat images and (2) FLAWS alongside the conventional MRI protocol in 1 session. Acquisition time was 8:20 minutes for MP2RAGE and FLAWS each. No contrast agent was administered.

Both MP2RAGE and FLAWS used an isotropic 1 mm voxel size, anteroposterior phase encoding, and a symmetrical echo. Magnetic resonance imaging acquisition parameters of the sequences of interest are specified in Table 1. For each subject, a $B1$ map was obtained using the unbalanced steady-state free precession-based B1-TRAP approach[25] (in-plane resolution, 4×4 mm; 15 slices of 5 mm thickness; slice gap, 5 mm; acquisition time, 2:09 minutes). $MP2RAGE_{uni}$ images were acquired based on 2 inversion times (see Table 1). Bloch equations were used to optimize the CNR and to minimize the effect of $B1+$ variations through space. The FLAWS used a TI1 of 449 milliseconds and a TI2 of 1270 milliseconds, resulting in 2 sets of images: FLAWS1 (acquired at TI1, WM-suppressed) and FLAWS2 (acquired at TI2, CSF-suppressed).[26]

For the reconstruction of the FLAWS contrasts and computation of FLAWS T1 maps, the FLAWS-Tools open-source software was used (https://github.com/jerbeaumont/FLAWS-Tools).[27] By using this tool, the total processing time, that is, the time to reconstruct 6 different FLAWS contrasts (including $FLAWS_{hco}$ and $FLAWS_{min}$) and perform the T1 mapping with a $B1+$ correction, was 1:09 minutes on average (run on a Intel Core i7-67000K computer). $MP2RAGE_{uni}$ was processed and provided automatically by the scanner. $FLAWS_{min}$ (GM-specific) was reconstructed in a voxel-wise manner[23] by applying the equation

$$S_{min} = \min(S1, S2),$$

where $S1$ and $S2$ reflects the magnitude of the FLAWS1 and FLAWS2 signal, respectively. Similarly, $FLAWS_{hco}$ (CSF-suppressed with low $B1$ sensitivity) was computed[23] by applying the equation

$$S_{hco} = -S_{hc} = \frac{S2-S1}{S1+S2}$$

.The T1 maps of the MP2RAGE sequence were corrected for inhomogeneities as proposed by Marques and Gruetter.[28] T1 maps of FLAWS were computed as described by Beaumont et al.[27]

Cortical Lesions Identification and Processing

Cortical lesions were segmented manually by 3 experienced raters (J.M., C.T., R.R.; 5, 6, and 5 years of experience in MS imaging, respectively) on $MP2RAGE_{uni}$, $FLAWS_{min}$, and $FLAWS_{hco}$ (Fig. 2) using ITK-SNAP.[29] In a first step, raters segmented the cortical lesions individually on $MP2RAGE_{uni}$ images of every single patient, without consideration of any other MRI sequence. In a second step, a consensus for $MP2RAGE_{uni}$ was reached among the 3 raters. Subsequently, the same procedure was applied for $FLAWS_{min}$ and $FLAWS_{hco}$ (see Supplementary Fig. 1, http://links.lww.com/RLI/A688). Time between consensus reading sessions was >4 weeks. Consensus segmentation maps were used for the assessment of cortical lesion numbers and volumes, whereas individual segmentation maps of the raters were used for the analysis of interrater agreement. Raters were blinded to the clinical status of the patients at all times.

Cortical lesions were defined as focal hypointensities relative to the adjacent normal-appearing GM, occupying at least 3 voxels[13] on at least 2 orthogonal planes. Lesions that were entirely located within the cortical GM were subclassified as intracortical lesions; lesions that involved both the cortex and juxtacortical WM were scored as leukocortical lesions. On $FLAWS_{min}$, the hyperintense "halo" around the lesion (see Discussion) was not included to the lesions segmentation.

$MP2RAGE_{uni}$ images were patient-wise coregistered to the FLAWS space using advanced normalization tools.[30] Subsequently, manually created lesion maps were aligned to the same space. Lesion

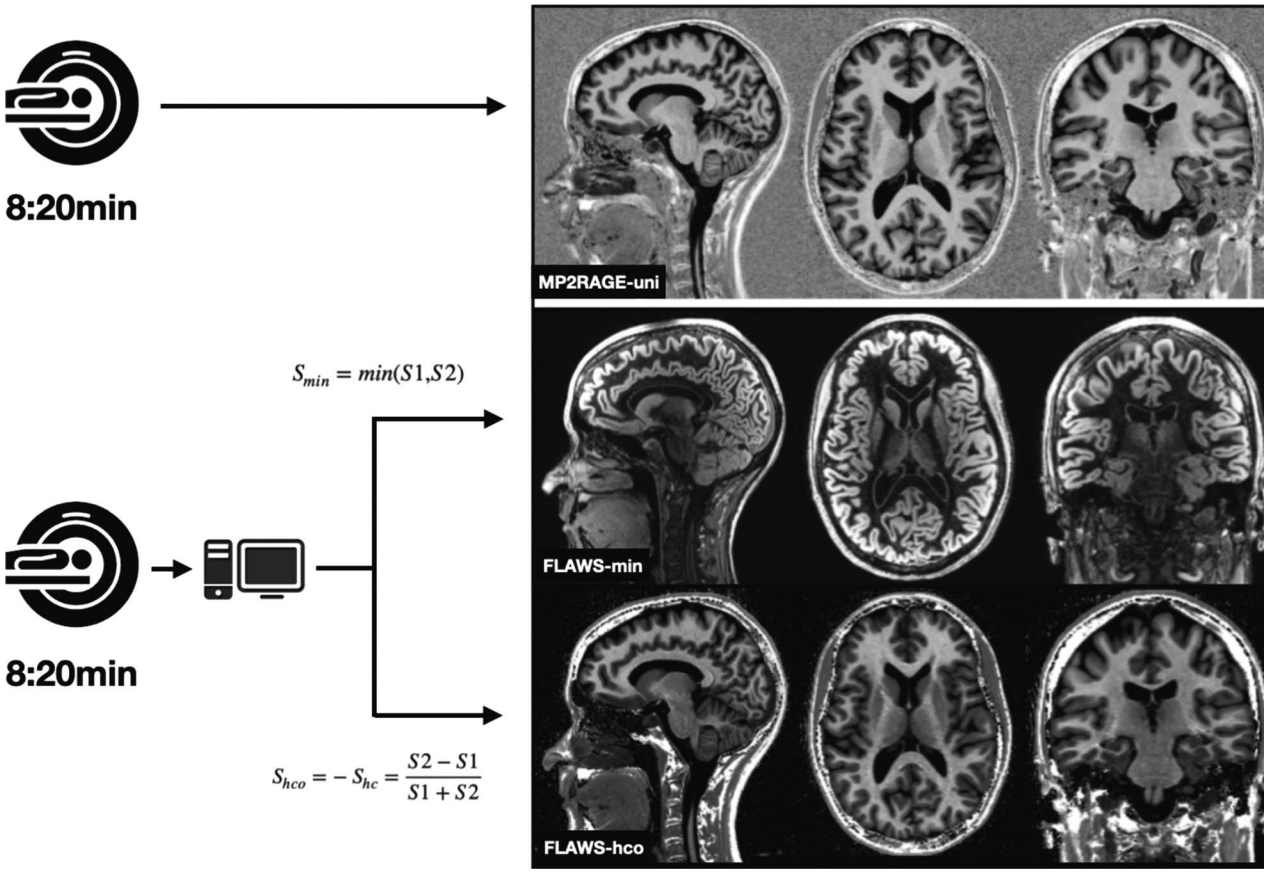

FIGURE 1. Acquisition procedure and final contrasts of $MP2RAGE_{uni}$ (top row), $FLAWS_{min}$ (mid row), and $FLAWS_{hco}$ (bottom row). Sagittal (left column), axial (mid column), and coronal (right column) view in an MS patient without cortical lesions. FLAWS indicates fluid and white matter suppression; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo.

counts and volumes were extracted from the lesion maps obtained by each reader and from the consensus union map using Python scripts. To assess the overlapping of lesions on different contrasts, segmentations were subsequently dilated by 3 voxels to mitigate residual coregistration imperfection between $MP2RAGE_{uni}$ and FLAWS. Lesions that overlapped by at least 3 voxels on all contrasts were defined as common cortical lesions. Lesions that were only segmented on 1 contrast ($MP2RAGE_{uni\ only}$, $FLAWS_{min\ only}$, or $FLAWS_{hco\ only}$) were retrospectively assessed on the other contrasts and defined as retrospectively identified cortical lesion, if visible at the given locality.

To assess the combined detection rate of $FLAWS_{min}$ and $FLAWS_{hco}$ ($FLAWS_{min\ +\ hco}$) versus $MP2RAGE_{uni}$, a union lesion mask of $FLAWS_{min}$ and $FLAWS_{hco}$ was produced by unifying lesions of consensus lesion maps on $FLAWS_{min}$ and $FLAWS_{hco}$. Lesions that overlapped by at least 3 voxels on $FLAWS_{min}$ and $FLAWS_{hco}$ were counted as 1 lesion. For lesion volumes of $FLAWS_{min\ +\ hco}$, the sum of the lesion volumes of $FLAWS_{min}$ and $FLAWS_{hco}$ was used, by counting overlapping voxels only once.

TABLE 1. Magnetic Resonance Imaging Sequence Parameters

	MP2RAGE	FLAWS
Resolution, voxel size, mm^3	1.0 × 1.0 × 1.0	1.0 × 1.0 × 1.0
Orientation	Sagittal	Sagittal
Phase encoding	Anteroposterior	Anteroposterior
FoV, mm^3	256 × 240 × 176	256 × 240 × 192
TR/TE, ms	5000/2.98	5000/2.19
TI 1, ms	700	449
TI 2, ms	2500	1270
Flip angle 1, degrees	4	5
Flip angle 2, degrees	5	6

FLAWS, fluid and white matter suppression; FoV, field of view; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo; TE, echo time; TI, 1 inversion time 1; TI, 2 inversion time 2; TR, repetition time.

Comparison of T1 Relaxation Times

T1 relaxation times (milliseconds) were assessed on MP2RAGE T1 and FLAWS T1 maps, in ROIs of healthy tissue and in cortical lesions. Normal-appearing WM, cortical GM, putamen, and caudate nucleus served as ROIs, as previously described.[31] Regions of interest were manually segmented on the MP2RAGE and FLAWS T1 maps. For T1 values of cortical lesions, manual segmentation maps were rigidly coregistered to the according T1 maps ($MP2RAGE_{uni}$ lesion maps on MP2RAGE T1 map). For FLAWS T1 maps, the lesion map of $FLAWS_{hco}$ was considered. For comparison of T1 values between MP2RAGE and FLAWS, the median T1 value of the ROI/lesion was used.

Contrast-to-Noise Ratio

To objectively compare the contrast of $MP2RAGE_{uni}$ and FLAWS, means and standard deviation of signal intensities were measured in ROIs of WM (splenium of the corpus callosum), GM (head of the caudate nucleus), and CSF (lateral ventricles). The CNR was calculated for

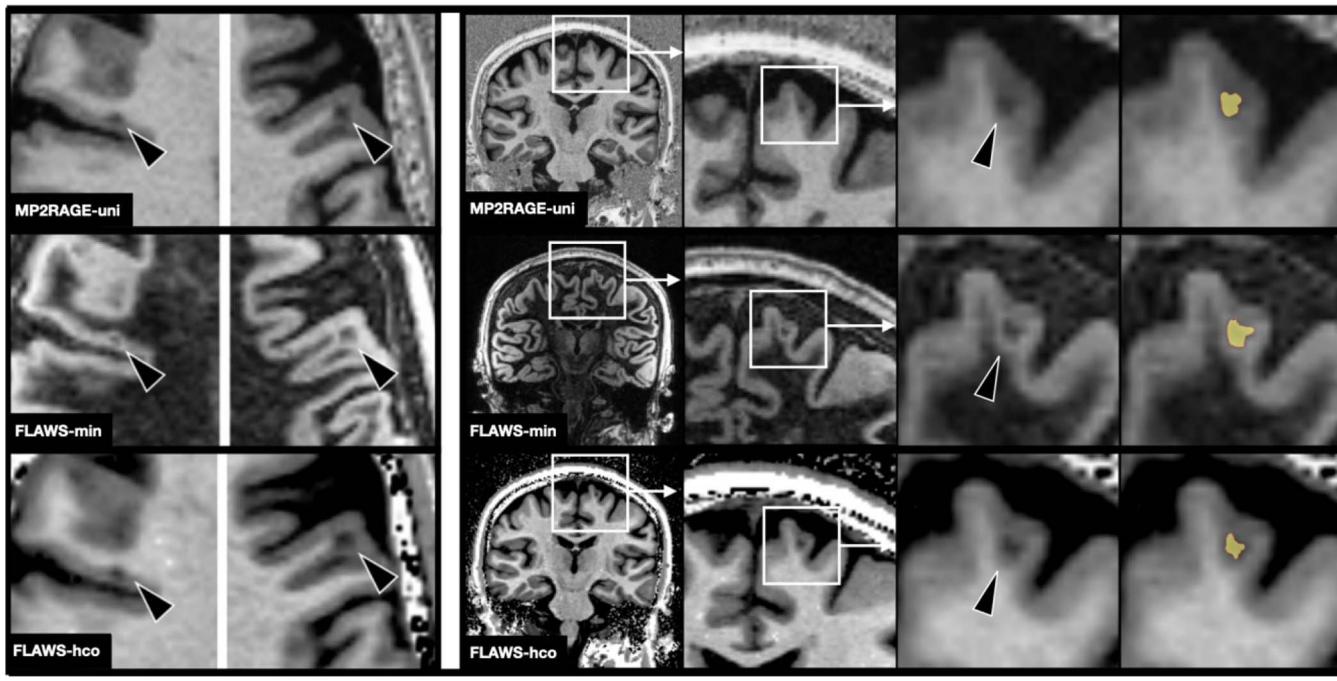

FIGURE 2. A, Example of 2 cortical lesions (arrowheads) on $MP2RAGE_{uni}$ (top row), $FLAWS_{min}$ (mid row), and $FLAWS_{hco}$ (bottom row). B, "Zoom in" on a cortical lesion on $MP2RAGE_{uni}$ (top row), $FLAWS_{min}$ (mid row), and $FLAWS_{hco}$ (bottom row) and its segmentation (in yellow). Note that the clear delineation on $FLAWS_{min}$ allows a slightly larger segmentation of the cortical lesion. FLAWS indicates fluid and white matter suppression; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo.

WM/GM, WM/CFS, and GM/CSF as previously described[21,23,27] on $MP2RAGE_{uni}$ and $FLAWS_{hco}$, before the $B1+$ correction.

Statistical Analysis

Continuous data are given as mean ± one standard deviation (SD) if normally distributed and median and interquartile range (IQR) if nonnormally distributed. Categorical data are summarized using cross tables providing counts and percentages. Data sets without any detected cortical lesions (n = 32/90) were included for analyses regarding the cortical lesion detection rate (lesion numbers), but excluded from the analyses comparing lesion volumes and T1 values.

Comparisons of lesion numbers and volumes of cortical lesions were performed using Friedman test. A Wilcoxon signed rank test was conducted to compare lesion counts and volumes on $MP2RAGE_{uni}$ and $FLAWS_{min + hco}$, and to assess CNR on MP2RAGE and $FLAWS_{hco}$. In case of significance, a post hoc Dunnett-Bonferroni test was used to correct for the comparisons of multiple groups. After that, a 2-tailed $P < 0.05$ was regarded as statistically significant.

The comparison of T1 relaxation times between MP2RAGE and FLAWS was described using relative differences in percentage.

In an exploratory analysis, individual cortical lesion counts of the 3 raters were compared, and interrater variability was quantified using Fleiss $\varkappa$. Statistical analysis was conducted using IBM SPSS Statistics (version 25; IBM, Armonk, NY).

TABLE 2. Clinical Characteristics of MS Patients

Females, n (Proportion)	**23/30 (76.7)**
Disease course	
RRMS, n (proportion)	23/30 (76.7)
SPMS, n (proportion)	1/30 (3.3)
PPMS, n (proportion)	6/30 (20)
Age, mean ± SD, y	43.4 ± 13.6
EDSS, median (range)	2.0 (1.0–7.0)
Disease duration, median (interquartile range), y	4.8 (14.0)

EDSS, expanded disability status scale; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

RESULTS

Patients characteristics are reported in Table 2.

Cortical Lesions Numbers

Lesion counts deriving from consensus lesion maps on $MP2RAGE_{uni}$, $FLAWS_{min}$, and $FLAWS_{hco}$ are summarized in Table 3. Cortical lesions were identified in 20/30 patients on MP2RAGE, 19/30 patients on $FLAWS_{min}$, and 19/30 patients on $FLAWS_{hco}$. In total, 633 segmentations were made on the 3 contrasts (109 intracortical, 524 leukocortical lesions), corresponding to 355 cortical lesions. Of the segmentations, 207 were made on MP2RAGE, 182 on $FLAWS_{min}$, and 244 on $FLAWS_{hco}$. The number of detected cortical lesions per patient was comparable among the 3 sequences (median $MP2RAGE_{uni}$, 3.0; IQR, 10.0; $FLAWS_{min}$, 3.5; IQR, 9.0; $FLAWS_{hco}$, 3.0; IQR, 11.0; $P > 0.05$). The same was true for the subclasses of cortical lesions (leukocortical and intracortical lesions).

Cortical Lesions Volumes

In patients with cortical lesions (22/30), median cumulative lesion volume per patient was larger on $FLAWS_{min}$ (587 μL; IQR, 1405 μL) than on $MP2RAGE_{uni}$ (490 μL; IQR, 990 μL; $P = 0.04$), whereas there was no difference between $FLAWS_{min}$ and $FLAWS_{hco}$ (611 μL; IQR,

TABLE 3. Cortical Lesion Number and Volumes Deriving From Consensus Segmentation Maps on the 3 Contrasts (MP2RAGE, $FLAWS_{min}$, $FLAWS_{hco}$) and the Merged Map ($FLAWS_{min + hco}$)

	$MP2RAGE_{uni}$	$FLAWS_{min}$	$FLAWS_{hco}$	*P* ($MP2RAGE$ vs $FLAWS_{min}$ vs $FLAWS_{hco}$)	$FLAWS_{min + hco}$	*P* ($FLAWS_{min + hco}$ vs MP2RAGE)
No. CL, median (IQR), n	3 (10)	3.5 (9)	3 (11)	0.082	4.5 (15)	**<0.001**
No. intracortical lesion, median (IQR)	0 (2)	0.5 (2)	0 (1)	0.241	1 (3)	0.068
No. leukocortical lesions, median (IQR)	2.5 (7)	2.0 (7)	2.0 (9)	0.011*	3.5 (12)	**<0.001**
Total cortical lesion volume, median (IQR), µL	490 (990)	587 (1405)	611 (844)	**0.039**†	612 (1446)	**<0.001**
Total intracortical lesion volume, median (IQR), µL	58 (81)	109 (151)	52 (79)	0.565	51 (133)	**0.037**
Total leukocortical lesion volume, median (IQR), µL	471 (1012)	433 (1365)	593 (830)	0.185	610 (922)	**<0.001**
Volume per cortical lesion, median (IQR), µL	47.7 (40)	54.91 (42)	53.4 (38)	0.057	53.8 (40)	**0.027**
Volume per intracortical lesion, median (IQR), µL	14.3 (8)	22.1 (30)	24.0 (14)	0.565	18.5 (13)	0.110
Volume per leukocortical lesion, median (IQR), µL	62.1 (56)	77.8 (86)	64.6 (52)	0.05‡	71.5 (31)	**0.048**

A *P* value less than 0.05 (typically ≤ 0.05) is statistically significant (boldface).

*After post hoc test of Dunnett-Bonferroni to correct for comparisons of multiple groups: MP2RAGE vs $FLAWS_{min}$, $P = 1.0$; MP2RAGE vs $FLAWS_{hco}$, $P = 0.364$; $FLAWS_{min}$ vs $FLAWS_{hco}$, $P = 0.099$.

†After post hoc test of Dunnett-Bonferroni to correct for comparisons of multiple groups: MP2RAGE vs $FLAWS_{min}$, $P = 0.04$; MP2RAGE vs $FLAWS_{hco}$, $P = 0.231$; $FLAWS_{min}$ vs $FLAWS_{hco}$, $P = 1.0$.

‡After post hoc test of Dunnett-Bonferroni to correct for comparisons of multiple groups: MP2RAGE vs $FLAWS_{min}$, $P = 0.102$; MP2RAGE vs $FLAWS_{hco}$, $P = 1.0$; $FLAWS_{min}$ vs $FLAWS_{hco}$, $P = 0.102$.

CL, cortical lesion; FLAWS, fluid and white matter suppression; IQR, interquartile range; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo.

844 µL), or $FLAWS_{hco}$ and $MP2RAGE_{uni}$. Cumulative lesion volume was comparable among the 3 contrasts when comparing leukocortical and intracortical lesions.

For the median volume per single cortical lesions, $MP2RAGE_{uni}$ (47.7 µL; IQR, 40 µL), $FLAWS_{min}$ (54.9 µL; IQR, 41.8 µL), and $FLAWS_{hco}$ (53.4 µL; IQR, 37.6 µL) showed similar results ($P > 0.05$). The same was true for the median volume of single intracortical lesions. Leukocortical lesions were numerically larger on $FLAWS_{min}$ (median, 77.8 µL; IQR, 86.3 µL) than on $MP2RAGE_{uni}$ (62.1 µL; IQR, 56.4 µL) and $FLAWS_{hco}$ (64.6 µL; IQR, 52.0 µL; $P = 0.05$), but this finding did not survive the correction for comparisons of multiple groups.

Cortical Lesions in $MP2RAGE_{uni\ only}$, $FLAWS_{min\ only}$, $FLAWS_{hco\ only}$, and Retrospectively Identified Cortical Lesion

Of 355 identified single cortical lesions, 100 were segmented on all sequences (common cortical lesions, 28.2%). A total of 175 lesions (49%) were segmented on 1 sequence only, hereof 43 (26%)

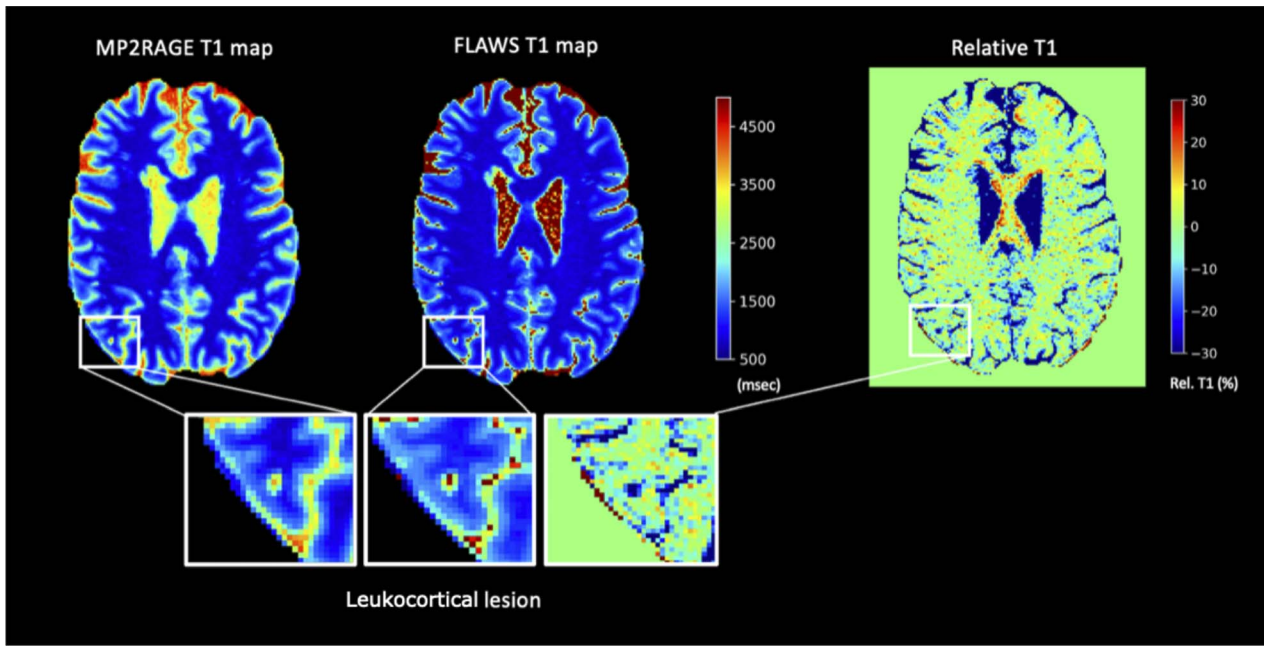

FIGURE 3. From left to right, MP2RAGE T1 map, FLAWS T1 map, and their relative difference in percentage. The "zoom in" shows a leukocortical lesion. FLAWS indicates fluid and white matter suppression; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo.

TABLE 4. T1 Relaxation Times (Milliseconds) for the FLAWS and MP2RAGE T1 Maps Considering Areas of Healthy Tissue

	WM	Putamen	Caudate	Cortical GM
MP2RAGE (n = 20)	867 ± 31	1243 ± 39	1320 ± 34	1527 ± 28
FLAWS (n = 20)	823 ± 28	1245 ± 49	1315 ± 30	1543 ± 29
Relative difference	5.1%	0.2%	0.4%	1.0%

ROIs were manually segmented in the MP2RAGE T1 maps and FLAWS T1 maps separately.

FLAWS, fluid and white matter suppression; GM, gray matter; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo; ROI, region of interest; WM, white matter.

$MP2RAGE_{uni\ only}$, 75 (43%) $FLAWS_{min\ only}$, and 54 (31%) $FLAWS_{hco\ only}$. Of the 43 lesions that were seen on $MP2RAGE_{uni\ only}$, 27 (62%) were retrospectively also visible on $FLAWS_{hco}$, and 23 (53%) also on $FLAWS_{min}$. Of the 75 lesions that were segmented on $FLAWS_{min}$ only, 57 (76%) were retrospectively also detected on $MP2RAGE_{uni}$ and 51 (68%) also on $FLAWS_{hco}$. From the 54 lesions that were seen on $FLAWS_{hco\ only}$, 33 (61%) were also visible on $MP2RAGE_{uni}$, and 31 (57%) also on $FLAWS_{min}$.

The number of lesions segmented both on $MP2RAGE_{uni}$ and $FLAWS_{hco}$ (n = 54) was higher than the lesions seen on $MP2RAGE_{uni}$ and $FLAWS_{min}$ (n = 10) or $FLAWS_{min}$ and $FLAWS_{hco}$ (n = 16).

Assessment of Combined $FLAWS_{min\ +\ hco}$ Versus MP2RAGE

The merged map of $FLAWS_{min}$ and $FLAWS_{hco}$ ($FLAWS_{min\ +\ hco}$) yielded cortical lesions in 21/30 patients. Using this image contrast, 305 single lesions were identified, 243 leukocortical and 62 intracortical lesions. $FLAWS_{min\ +\ hco}$ (median, 4.5; IQR, 15) showed significantly more cortical lesions per patient than $MP2RAGE_{uni}$ (median, 3.0; IQR, 10; $P < 0.001$). $FLAWS_{min\ +\ hco}$ detected more leukocortical lesions per patient (median, 3.5; IQR, 12) than $MP2RAGE_{uni}$ (median, 2.5; IQR, 7; $P < 0.001$), whereas there was no difference regarding intracortical lesions.

$FLAWS_{min\ +\ hco}$ showed larger cumulative volumes per patient than $MP2RAGE_{uni}$ (median, 612 μL; IQR, 1446 μL vs 490 μL; IQR, 990 μL; $P < 0.001$). This was also true for the 2 subdivisions of cortical lesions (leukocortical lesions: median, 610 μL; IQR, 922 μL vs 471 μL; IQR, 1012 μL; $P < 0.001$; intracortical lesions: median, 110 μL; IQR, 124 μL vs 58 μL; IQR, 81 μL; $P = 0.037$).

The median volume of single cortical lesions was larger on $FLAWS_{min\ +\ hco}$ than on $MP2RAGE_{uni}$ (53.8 μL; IQR, 40 μL vs 47.7 μL; IQR, 40 μL; $P = 0.027$). The same was true for the subdivision of leukocortical lesions (71.5 μL; IQR, 31 μL vs 62.1 μL; IQR, 56 μL; $P = 0.048$), whereas there was no difference regarding median volume of intracortical lesions.

Interrater Variability

Interrater agreement of lesion counts was moderate for cortical lesions on $MP2RAGE_{uni}$ ($\varkappa = 0.582$) and on $FLAWS_{hco}$ ($\varkappa = 0.584$) but substantial on $FLAWS_{min}$ ($\varkappa = 0.614$). For intracortical lesions, interrater agreement was moderate for $MP2RAGE_{uni}$ ($\varkappa = 0.541$) but substantial for $FLAWS_{min}$ ($\varkappa = 0.676$) and $FLAWS_{hco}$ ($\varkappa = 0.774$). For leukocortical lesions, interrater agreement was moderate for all sequences ($MP2RAGE_{uni}$ $\varkappa = 0.518$, $FLAWS_{min}$ $\varkappa = 0.560$, $FLAWS_{hco}$ $\varkappa = 0.565$).

T1 Mapping Analysis

Exemplary T1 maps from MP2RAGE and FLAWS and their relative difference in percentage are shown in Figure 3. In ROIs of healthy tissues (normal-appearing WM, cortical GM, putamen, and caudate nucleus), relative differences of T1 values between MP2RAGE and FLAWS were close to or below 5% for all ROIs (Table 4). The median T1 relaxation values in cortical lesions were approximately 1700 milliseconds on both MP2RAGE and FLAWS (Fig. 4). The same was true for the 2 subdivisions of leukocortical and intracortical lesions.

Contrast-to-Noise Ratio

$FLAWS_{hco}$ showed a significantly higher WM/GM contrast than $MP2RAGE_{uni}$ ($P < 0.005$). Contrast-to-noise ratio for GM/CSF was comparable between the 2 contrasts (see Supplementary Table 1, http://links.lww.com/RLI/A688).

DISCUSSION

Cortical lesion detection in MS is challenging, and various sequences and contrasts have been suggested to improve the cortical lesion detection rate such as DIR, PSIR, MP2RAGE, and high-spatial resolution MPRAGE.[9,13,14,18] In this study, we used first FLAWS—a sequence that provides multiple 3D high-resolution contrasts in a single acquisition[21,23,24]—and demonstrated that $FLAWS_{min}$ and $FLAWS_{hco}$ are both equally effective as MP2RAGE to manually detect cortical lesions in MS patients. Moreover, our study provides evidence that the combination of these 2 FLAWS contrasts yields the highest number and the largest volumes of cortical lesions.

Achievement of higher cortical lesion detection rates using combinations of multiple MRI contrasts has previously been reported[32,33] and is partly ascribed to the repetitive assessment of multiple MRIs of the same patient. However, compared with previous investigations, the present study suggests 2 major advantages of FLAWS. First, the approach of reconstructing multiple contrasts deriving from 1 session conserves acquisition time. Second, based on its reconstruction properties,

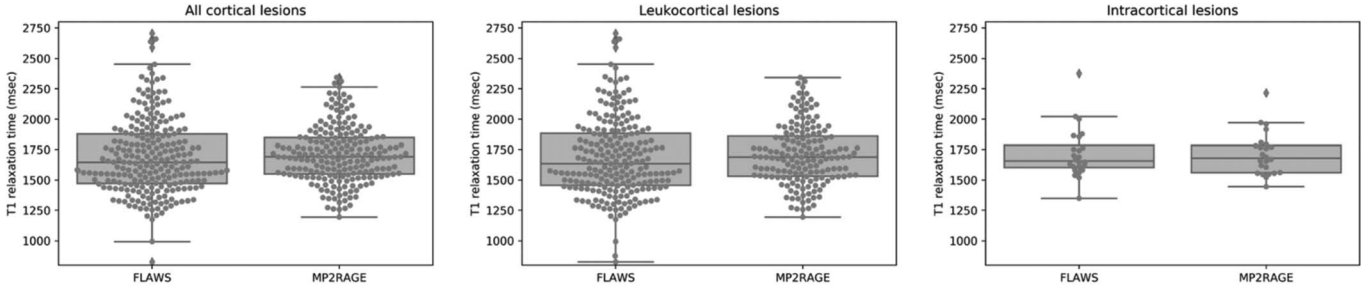

FIGURE 4. T1 relaxation times (milliseconds) for cortical lesions in the FLAWS T1 and MP2RAGE T1 maps. For the FLAWS T1 map, the cortical lesions segmented on $FLAWS_{hco}$ were considered. FLAWS indicates fluid and white matter suppression; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo.

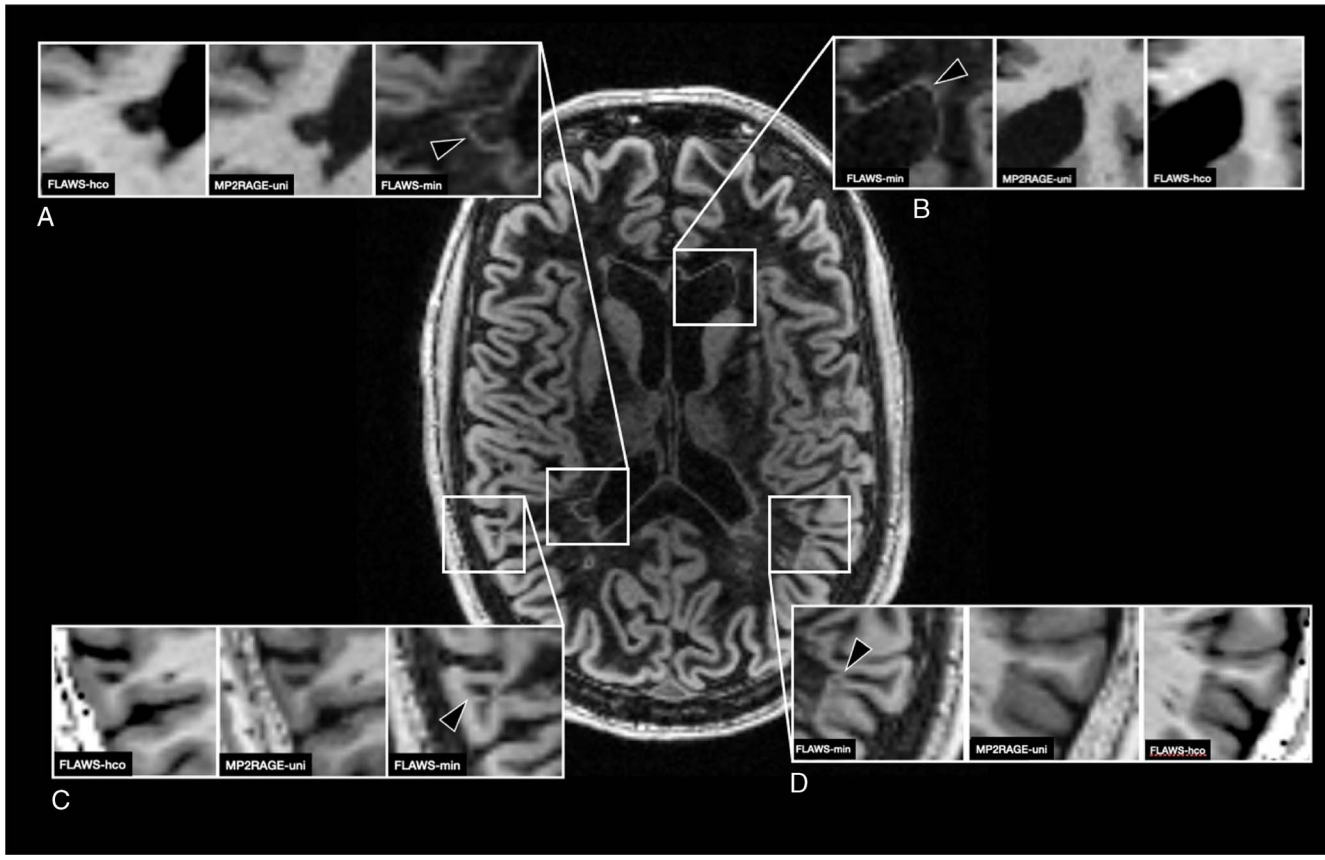

FIGURE 5. $FLAWS_{min}$ of a patient with MS demonstrating the "halo" appearance. Partial volume effects at the border of tissues with high divergence of signal intensities lead to a hyperintense band at the respective border. $MP2RAGE_{uni}$ and $FLAWS_{hco}$ are shown for reference. A, Hyperintense band (arrowhead) around a periventricular white matter lesion (not systematically assessed in this study). B, Hyperintense band (arrowhead) at the normal-appearing border between CSF and brain tissue. C, Hyperintense band (arrowhead "halo") around a leukocortical lesion. D, Hyperintense band (arrowhead, "halo") around an intracortical lesion. FLAWS indicates fluid and white matter suppression; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo.

FLAWS naturally provides a near-perfect alignment of the 2 contrasts, which is generally known to be favorable when analyzing small brain structures such as cortical lesions. The present study shows that FLAWS has similar characteristics to $MP2RAGE_{uni}$ (clinically compatible acquisition time, T1-weighted images with high WM-GM contrast, eg, $FLAWS_{hco}$, and T1 maps) but also the advantage to provide many more contrasts ($FLAWS_{min}$ and $FLAWS_{hco}$, FLAWS1, FLAWS2, $FLAWS_{uni}$, $FLAWS_{hco}$). Future studies should assess whether those contrasts may reveal specific properties of cortical and WM MS lesions.

Because of the way signal intensities are calculated in $FLAWS_{min}$ (minimum signal intensity of FLAWS1 and FLAWS2 is used for each voxel), partial volume effects at interfaces between brain tissues with a high signal divergence (eg, brain vs CSF border; lesion vs nonlesion tissue) lead to hyperintense voxel signals at the respective border (Fig. 5). In cortical lesions, this generally results in a hyperintense "halo" around the lesions. We do not believe that this "halo" has any structural correlate and is rather caused by the aforementioned partial volume effect, only (it is therefore also not to confuse with so-called paramagnetic rim lesions[34]). However, this hyperintense "halo" considerably facilitates the delineation of the lesion against the surrounding cortex and/or WM (the same holds true for WM lesions, although those were not assessed in this study). The easier depiction of cortical lesions on $FLAWS_{min}$ was shared by the subjective judgment of the raters and reflected in the higher interrater agreement between the raters on $FLAWS_{min}$ compared with $MP2RAGE_{uni}$ and $FLAWS_{hco}$. In this study, we did not include the "halo" itself in the lesions segmentation. Still, the easier delineation may partly explain why leukocortical lesions were found to be larger on $FLAWS_{min}$ than on $MP2RAGE_{uni}$ (Fig. 2B). In addition, the "halo" appearance with clear demarcation of lesion tissue against the cortical GM might help to distinguish cortical from juxtacortical lesions (see Supplementary Fig. 2, http://links.lww.com/RLI/A688).

The clear border between lesion and nonlesion tissue might also be from interest for future analyses of automated lesion detection, where a clear delineation may be particularly desirable. In fact, manually annotating cortical lesions in both $FLAWS_{min}$ and $FLAWS_{hco}$, or analyzing both contrasts simultaneously, is more time-consuming compared with the evaluation of a single sequence such as the $MP2RAGE_{uni}$. The characteristics of MS lesions in $FLAWS_{min}$ and $FLAWS_{hco}$ could therefore improve the sensitivity of recently proposed automated methods for cortical lesions detection/segmentation[35] without any acquisition time increase.

The fact that only 28.2% of the lesions overlapped on all 3 contrasts and that a high proportion of the noncommon lesions were retrospectively also visible on the other contrasts (between 57% and 76%, depending on the contrasts combination) suggests a generally low sensitivity of manual cortical lesion detection, even when performed by 3 trained raters. Previous studies have also demonstrated a low sensitivity of MRI for cortical lesion detection compared with postmortem identification.[11,15,36] This has been ascribed to their small size, the lack of inflammation compared with WM lesions, or partial volume effects from adjacent CSF and WM.[2,11,36] Another factor that might have

contributed to the low detection rate is that we purposely abstained from an additional consideration of cortical lesions on a T2-weighted image (eg, DIR), to render clearer the comparison between $MP2RAGE_{uni}$ and FLAWS.

T1 relaxation times may be exploited to characterize lesions microstructural characteristics,[37] and recent works have shown that those characteristics are related to patients clinical impairment[38,39] and to specific histopathological MS lesion types.[40] At 7 T, it has been shown that quantitative T1 mapping using MP2RAGE can be obtained with high spatial resolution.[28] Recently, T1 mapping deriving from FLAWS at 7 T was shown to be similarly reliable.[27]

To date, only one study compared T1 values of MP2RAGE and FLAWS at 3 T in healthy individuals, showing remarkable consistency.[26] In this work, we assessed T1 relaxation times provided by FLAWS and MP2RAGE in cortical lesions and ROIs of normal-appearing brain tissue of MS patients. Confirming the previous report in healthy subjects,[26] we found very small differences between the maps provided by those sequences in normal-appearing brain tissue in MS patients (≤5%, Table 4). On the other hand, in cortical lesions, we showed first that MP2RAGE and FLAWS measured very similar T1 relaxation (mean qT1 ~ 1700 milliseconds, Fig. 5). This average value is slightly higher than the one previously described using MP2RAGE in cortical lesions in a small and homogeneous group of very early relapsing-remitting MS patients,[18] possibly due to the more destructive characteristics of cortical lesions in the heterogeneous cohort of patients (including secondary and primary progressive patients) as the ones studied in this work. Also, these results should be interpreted with caution, given the challenges that arise when quantitatively assessing such small brain structures as cortical lesions.

In our study, the WM/GM contrast was higher on $FLAWS_{hco}$ than $MP2RAGE_{uni}$, which is in line with a previous study comparing the 3 contrasts (among others) at 7 T.[27]

This study has some limitations. We did not compare the results obtained with FLAWS to cortical lesion detection performed with DIR, PSIR, and MPRAGE, which are recommended as criterion standard confirmatory sequences in recent guidelines.[6,17] However, we chose a comparator such as $MP2RAGE_{uni}$, which has shown to identify a similar[18] or higher[19] number of cortical lesions as one of DIRs. $MP2RAGE_{uni}$ has the advantage not be susceptible to flow-related artifacts as DIR[13] and PSIR.[14] Also, 1-mm isotropic MP2RAGE may be acquired in shorter time (8:20 seconds) compared with DIR (12:02 minutes),[18] which might render this sequence more applicable in daily clinical practice. Furthermore, compared with MPRAGE, MP2RAGE provides a contrast that is free of proton density, T2* contrast, and reception bias-field, which was shown to improve the identification of MS-related WM lesions.[18] Still, it may be of interest to compare the performance of FLAWS to the current criterion standard sequences in future studies.

In this study, we decided not to acquire an additional T2-weighted contrast (eg, DIR) to enhance the sensitivity to cortical lesion detection, because this combination would not be realistic in clinical practice and because we aimed at gaining knowledge about the sensitivity of FLAWS alone. Another limitation of this study was the lack of postmortem validation of the cortical lesions detected by both FLAWS and $MP2RAGE_{uni}$, hence we provided only a comparison of the sensitivity of those 2 acquisition methods to the number and volume of focal pathological cortical changes in MS patients in vivo. Future MRI histopathology studies should assess whether the additional lesions identified using the combined $FLAWS_{min\ +\ hco}$ images are real or false-positive findings. In this study, we did not evaluate the correlation between cortical lesion number and clinical patient characteristics. Nevertheless, we provided first evidence that the contrasts provided by FLAWS deliver additional information compared with $MP2RAGE_{uni}$, which significantly facilitates the detection and the quantification of the area of focal damage. Furthermore, we have supported with data that show that qT1 as provided by FLAWS and MP2RAGE yields similar results in lesions, hereby suggesting that both methods may be well used to quantify microstructural damage in lesioned cortical areas. Future work will aim at validating the specificity of FLAWS in a postmortem MRI setting and at assessing the utility of $FLAWS_{hco}$ and $FLAWS_{min}$ in comparison to other sequences such as DIR or PSIR, and in combination with T2-based sequences such as DIR or FLAIR.

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