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Research Article

Intensity Inhomogeneity Correction for Magnetic Resonance Imaging of Human Brain at 7T

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Running Title: Inhomogeneity Correction in 7T MRI

Abstract (228 words)

Purpose: To evaluate the performance and efficacy for intensity inhomogeneity correction of various sequences of the human brain in 7T MRI using the extended version of the unified segmentation algorithm.

Materials and Methods: Ten healthy volunteers were scanned with 4 different sequences (2D spin echo [SE], 3D fast SE, 2D fast spoiled gradient echo, and 3D time-of-flight) by using a 7T MRI system. Intensity inhomogeneity correction was performed using the "New Segment" module in SPM8 with 4 different values (120, 90, 60, and 30 mm) of full width at half maximum (FWHM) in Gaussian smoothness. The uniformity in signals in the entire white matter was evaluated using the coefficient of variation (CV); mean signal intensities between the subcortical and deep white matter were compared, and contrast between subcortical white matter and gray matter was measured. The length of the lenticulostriate (LSA) was measured on maximum intensity projection (MIP) images in the original and corrected images.

Results: In all sequences, the CV decreased as the FWHM value decreased. The differences of mean signal intensities between subcortical and deep white matter also decreased with smaller FWHM values. The contrast between white and gray matter was maintained at all FWHM values. LSA length was significantly greater in corrected MIP than in the original MIP images.

Conclusion: Intensity inhomogeneity in 7T MRI can be successfully corrected using SPM8

for various scan sequences.

Key Words: 7T; MRI; intensity inhomogeneity correction

Introduction

Recent advancement of ultra-high field MR systems has enabled the use of 7T MRI for clinical research, and these systems are steadily increasing in number. Ultra-high field MRI offers several advantages over conventional clinical MRI (3.0T or below), such as higher signal-to-noise ratio, higher spatial resolution, better image contrast, prolonged T1 relaxation time, and increased susceptibility effects [1, 2]. However, intensity variation or inhomogeneity are remarkable at 7T because of main magnetic field (B_0) and radio frequency (RF) field (B_1) inhomogeneity [1, 3, 4], susceptibility effects [1, 4-6], and use of a multi-channel surface coil [1, 4, 7]. Among these factors, B_1 inhomogeneity is of particular importance in 7T brain imaging [8], in which RF wavelength becomes similar to the diameter of the human head [9, 10]. These intensity inhomogeneities may cause under-representation of lesions and must be minimized in clinical imaging [11].

Bias correction of intensity inhomogeneity is categorized into prospective and retrospective approaches (see [12] and [13] for details). Prospective approaches aim to acquire more uniform signal distribution by improving the imaging device, such as the development of special sequence designs or parallel transmission with B_1 shimming [14, 15] or a modified RF pulse [16, 17]. These prospective developments are more difficult to apply than retrospective methods, because intensity uniformity varies among sequence types as well as among tissues and subjects. In contrast, retrospective approaches are post-processing techniques applied to

the acquired images. These approaches are independent of special hardware or sequence designs, and are used for correcting intensity nonuniformity in the acquired images. Previous reports have reviewed the techniques proposed to correct intensity inhomogeneity [12, 13], e.g., nonparametric nonuniform intensity normalization (N3) [18], BrainSuite [19, 20], and statistical parametric mapping (SPM) (SPM99 [21] of old version, SPM2 [22], SPM5 [23] and SPM8 [23, 24] of newer version). A quantitative comparison of these methods [25-29] has also been performed for human brain imaging at 3.0T or below. For 7T, however, the performance of retrospective correction approaches has not been investigated in human brain imaging, although studies have been performed that validated the approaches by using phantom data [30] or that introduced the results when the approaches were applied to human brain images [31].

The purpose of this study was to evaluate the performance and efficacy of a post-processing technique using the extended version of the unified segmentation algorithm available with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) [23, 24] for intensity inhomogeneity correction of various sequences of the human brain in 7T MRI.

Methods

Subjects

Ten healthy volunteers (6 men [mean age, 29.5 years; age range, 24–39 years] and 4 women [mean age, 31.8 years; age range, 28–34 years]) were included in the study, which was conducted between June 13 and July 12, 2012. These volunteers were confirmed to have no past history or symptom of brain disorders. All experiments were carried out after obtaining the approval of the institutional review board and written informed consent from all subjects.

7T MRI

We used a 7T MRI scanner (Discovery MR950; GE Healthcare, Milwaukee, WI) with quadrature transmission and 32-channel receive head coils. The examination consisted of 4 different sequences: 2D spin echo (2D-SE), 3D fast SE (3D-FSE), 2D fast spoiled gradient echo (2D-FSPGR), and 3D time-of-flight (3D-TOF) (Table 1).

Intensity inhomogeneity correction using SPM8

Intensity inhomogeneity correction was performed using the "New Segment" module in SPM8, which is the extended version of the unified segmentation algorithm implemented in SPM8 [23, 24] adopting an extended set of tissue probability maps and improved registration

model. The algorithm implements segmentation, bias correction, and spatial normalization in one step, and the underlying generative model includes a correction for intensity non-uniformity and is estimated for a maximum a posteriori solution. For the parameter of full width at half maximum (FWHM) in Gaussian smoothness, the operator can select values from 30 to 150 mm (with an interval of 10 mm) on the graphical user interface, although any other value can be set by modifying the script file. If the acquired MR image has conspicuous inhomogeneous intensities, the operator can select a smaller FWHM value (default value in SPM8 is 60 mm). We used 4 different FWHM values (120, 90, 60, and 30 mm) and default parameters including bias regularization of 0.0001, warping regularization of 4, and sampling distance of 3; in addition, the number of Gaussians used to represent the intensity distribution for each tissue class was 2 for grey matter, 2 for white matter, 2 for CSF, 3 for bone, 4 for other soft tissues, and 2 for air (background).

Table 1 MRI parameters used in this study

	2D-SE	3D-FSE	2D-FSPGR	3D-TOF
Repetition time (ms)	3,000	3,000	800	14
Echo time (ms)	60	60	15	2.9
Excitation flip angle (°)	90	90	20	12
Refocusing flip angle (°)	140	variable	n/a	n/a
Receive bandwidth (kHz)	62.5	83.33	62.5	35.7
Number of excitations	0.5	1	1	1
Scan time	5 min 48 s	7 min 12 s	2 min 40 s	8 min 7 s
Field of view (mm)	256	256	256	256
Slice thickness (mm)	4	1	4	1
Acquisition matrix	512 × 256	512 × 256	512 × 256	512 × 256
Reconstruction matrix	512 × 512	512 × 512	512 × 512	512 × 512
Reconstruction voxel (mm)	0.5 × 0.5 × 4	0.5 × 0.5 × 0.5	0.5 × 0.5 × 4	0.5 × 0.5 × 0.5

2D-SE, 2D spin echo; 3D-FSE, 3D fast spin echo; 2D-FSPGR, 2D fast spoiled gradient echo; 3D-TOF, 3D time-of-flight

Data analysis

Eight sections, the middle of which was at the level of the centrum semiovale, were chosen for ROI measurements (every 2 and 16 sections for 2D and 3D sequences, respectively, as the sections were thicker in 2D). Using ITK-SNAP (www.itksnap.org) [32], one of the authors (IU) manually drew 8 spherical ROIs with a diameter of 2.5 mm on each section, in the subcortical and deep white-matter areas, respectively (total 16 ROIs × 8 sections). ROIs with the same size were also placed in the gray-matter areas near the ROIs of subcortical white matter (total 8 ROIs × 8 sections). All ROIs were carefully placed in the white matter having uniform intensity while avoiding areas with intensity variation such as the optic radiation, perivascular space, and small arteries. Because 3D-FSE images were taken as

sagittal sections, the ROI measurements for 3D-FSE images were performed on the reformatted axial sections (slice thickness of 0.5 mm).

For the evaluation of signal uniformity in the entire white matter, we calculated the coefficient of variation (CV) [33], defined as the ratio of the standard deviation and the mean signal intensity for all ROIs (both subcortical and deep white matter). A smaller CV represented more uniform signals in the entire white matter. The Steel–Dwass test was used for nonparametric multiple comparisons between CV values of the original and corrected images using 4 different FWHM values ($p < 0.01$). For the evaluation of the signal variation between the subcortical and deep white-matter images, mean signal intensities of ROIs were compared between the subcortical and deep white-matter images with the Wilcoxon matched-pairs signed-ranks test ($p < 0.01$). If the difference of mean signal intensities between both white matters was smaller values, it represented more improvement of signal drop in the center of the brain. Moreover, for evaluation of the impact of inhomogeneity correction on the contrast between different tissues, we calculated the contrast ratio between the subcortical white matter and gray matter. The Wilcoxon matched-pairs signed-ranks test with Bonferroni adjustment was used for multiple comparisons between contrast ratios of the original and corrected images using 4 different FWHM values ($p < 0.01$ after Bonferroni adjustment).

The efficacy of intensity correction on the maximum intensity projection (MIP)

image in MR angiography (MRA) was also evaluated. Coronal MIP images (thickness of 70 mm), including anterior and middle cerebral arteries, lenticulostriate arteries (LSA), and basal ganglia, were reconstructed from 3D-TOF original and corrected images with the best FWHM value decided by two evaluations (CVs and signal intensities in the subcortical and deep white matter). Basilar and posterior cerebral arteries were excluded because the posterior cerebral artery mimics the LSA on coronal MIP images. MIP reconstructions were performed by one of the authors (IU) using a commercially available workstation (Advantage Workstation 4.5; GE Medical Systems, Milwaukee, WI).

In evaluations of MIP images, we compared the length of the LSA in 3D-TOF original and corrected MIP images, because the LSA located in the center of the brain is most severely affected by the signal drop in the center of the 3D-TOF image in particular. Then, 2 radiologists (KK and TH with 17 and 4 years of experience, respectively) independently measured the length of the longest LSA (right and left, respectively) on MIP images by using commercially available software (VOX-BASE II; J-MAC SYSTEM, Sapporo, Japan). The inter-observer variability of LSA measurements was assessed using the intra-class correlation coefficient (ICC). The Wilcoxon matched-pairs signed-ranks test was used to evaluate differences of mean length of the LSA between the original MIP and SPM8-corrected MIP images.

Results

The signals in the central part of the brain in the original axial images were weaker than those in the peripheral part (Fig. 1), which was most noticeable in 3D-TOF images. In addition, signals were stronger in the lower left part than in the other parts in SE sequences (2D-SE and 3D-FSE images). The caudal part in sagittal 3D-FSE images also had weaker signals. All of these intensity inhomogeneities were successfully corrected using SPM8 with decreasing FWHM values.

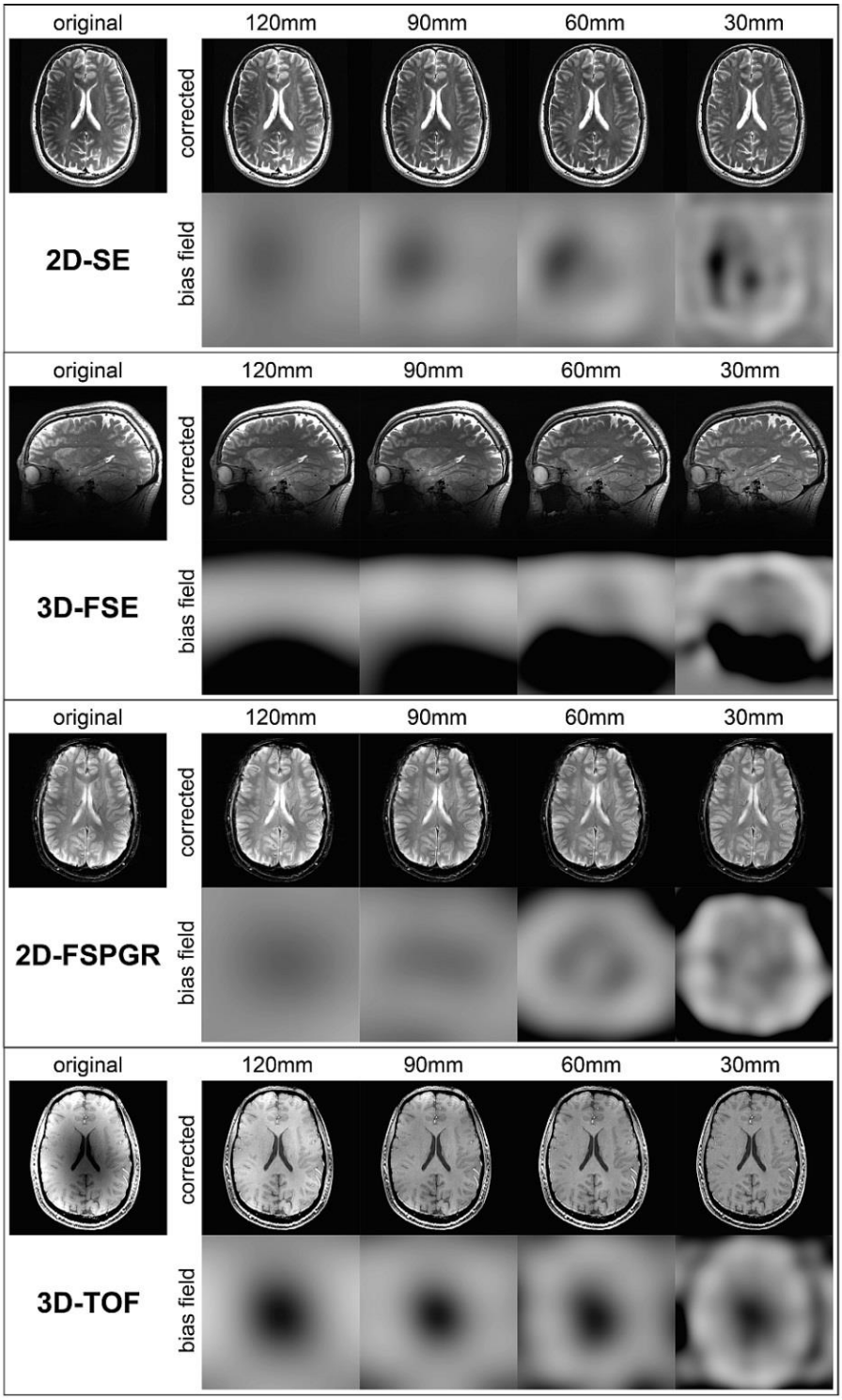

Figure 1 Original and SPM8-corrected images. In the original images, the signals in the central parts of the axial images (2D-SE, 2D-FSPGR, and 3D-TOF) and caudal parts of the sagittal 3D-FSE image are weaker than those in the other parts. These intensity inhomogeneities are reduced as the FWHM values decrease in all sequences. The estimated bias field, which represents the distribution map of intensity inhomogeneity that was calculated by SPM8 with each FWHM value, is shown at the bottom. Decreased FWHM value tends to strengthen the signal variations of estimated bias field images.

The CV constantly decreased as the FWHM value decreased for all imaging sequences (Fig. 2), indicating that signal intensities in the white matter became homogeneous. In 3D-TOF images, the differences were statistically significant for all pairs of FWHM values ($p < 0.01$ for all pairs). In the 2D-SE, 2D-FSPGR, and 3D-FSE images, most of the pairs showed statistically significant differences, with a few exceptions.

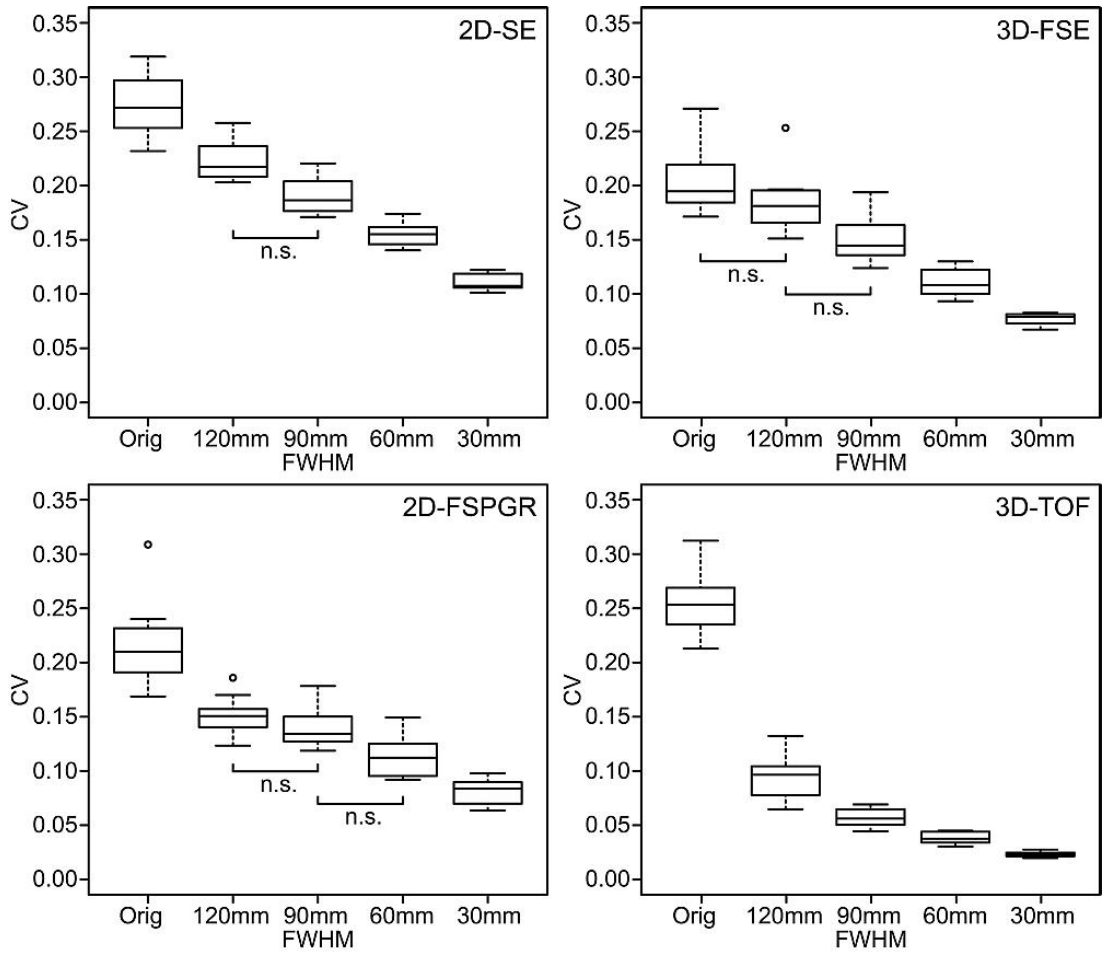

Figure 2 Coefficient of variation (CV) for the original and SPM8-corrected images. In all sequences, the CV decreases as the FWHM value decreases, indicating that the white-matter signals become homogeneous. In the 3D-TOF, the differences are statistically significant for all pairs of FWHM values (Steel–Dwass test, $p < 0.01$ for all pairs). In the 2D-SE, 2D-FSPGR, and 3D-FSE, most of the pairs show statistically significant differences, although there are a few exceptions. n.s. indicates no significant difference.

In all sequences, mean signal intensities had significantly higher values in the subcortical white matter than in the deep white matter in the original images (Fig. 3). After correction of intensity inhomogeneity, the difference of signal intensities between subcortical and deep white matter decreased; however, there were still significant differences between FWHM values of 120 and 90 mm in all sequences. With an FWHM value of 60 mm, the differences in the white-matter signals became nonsignificant in all sequences, while the differences became significant again with an FWHM value of 30 mm for the 2 gradient echo (GRE) sequences (2D-FSPGR and 3D-TOF).

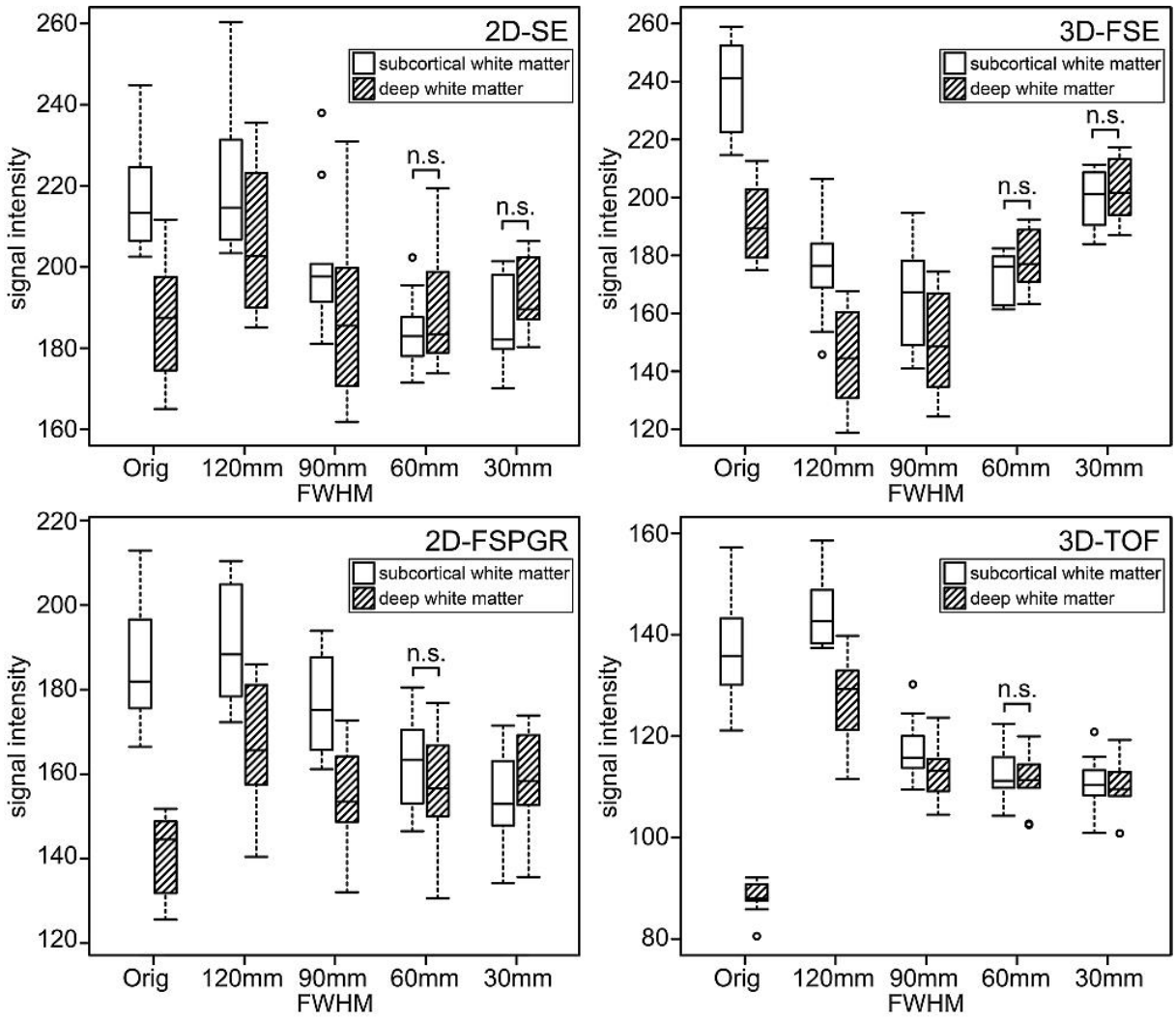

Figure 3 Mean signal intensities of subcortical and deep white matter. In the original images of all sequences, mean signal intensities in the subcortical white matter have significantly higher values than in the deep white matter. After correction of intensity inhomogeneity, the difference of signal intensities between subcortical and deep white matter decreases; however, there are still significant differences between FWHM values of 120 and 90 mm in all sequences (Wilcoxon matched-pairs signed-ranks test, $p < 0.01$). With an FWHM value of 60 mm in all sequences, the differences of signal intensities between subcortical and deep white matter are nonsignificant; however, the differences are significant again with an FWHM value of 30 mm for the 2 GRE sequences (2D-FSPGR and 3D-TOF). n.s. indicates no significant difference.

In the contrast ratio between white and gray matter, there were no statistically significant differences in all sequences (Table 2), indicating that inhomogeneity correction in SPM8 maintained the contrast between white and gray matter ($p > 0.05$ for all pairs).

Table 2 Contrast ratio between subcortical white matter and gray matter (subcortical white matter ROI/gray matter ROI)

	FWHM				
	Original	120 mm	90 mm	60 mm	30 mm
2D-SE	0.80 ± 0.07	0.80 ± 0.06	0.80 ± 0.06	0.80 ± 0.06	0.81 ± 0.05
3D-FSE	0.79 ± 0.03	0.79 ± 0.03	0.79 ± 0.03	0.80 ± 0.03	0.81 ± 0.03
2D-FSPGR	0.78 ± 0.03	0.79 ± 0.03	0.79 ± 0.03	0.80 ± 0.03	0.80 ± 0.03
3D-TOF	1.07 ± 0.02	1.09 ± 0.02	1.08 ± 0.02	1.08 ± 0.02	1.08 ± 0.02

2D-SE, 2D spin echo; 3D-FSE, 3D fast spin echo; 2D-FSPGR, 2D fast spoiled gradient echo; 3D-TOF, 3D time-of-flight

In MIP images, the corrected MIP image was created from the corrected 3D-TOF image with an FWHM value of 30 mm, which was decided by two evaluations of CVs (Fig. 2) and signal intensities in the subcortical and deep white matter (Fig. 3). The LSAs and distal arteries were better seen in the corrected MIP image compared with the original MIP image, in which the central part of the brain was darker than the peripheral part (Fig. 4). The measured LSA length was significantly greater in the corrected than original MIP images (Fig. 5). The ICC of inter-observer variability for LSA measurements was 0.86.

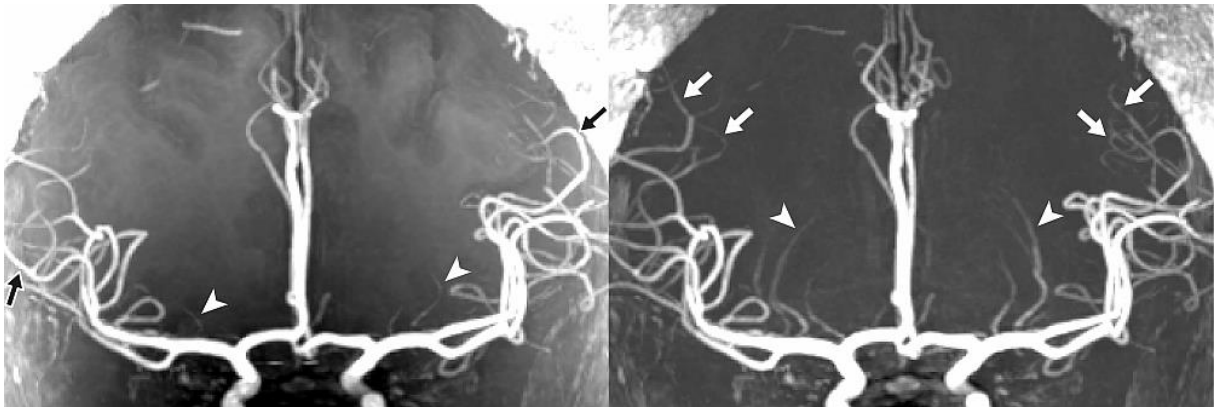

Figure 4 Original and corrected MIP images in 3D-TOF. Maximum intensity projection (MIP) images of 70-mm slabs, showing the horizontal portion of the middle cerebral artery, have been created from the original 3D-TOF image (left) and SPM8-corrected image with an FWHM value of 30 mm (right). As the mean signal intensities were changed by the correction of the inhomogeneity at each FWHM value (see Fig. 3), both MIP images were normalized with an optimal window level and width. ROI measurements of the M1 segment of the middle cerebral artery were completed, and the maximum value of the ROI was used for determination of the window level and width (maximum value × 0.4 for window level, and maximum value × 0.5 for window width). The lenticulostriate arteries (arrowheads) are seen more clearly in the corrected MIP image than in the original MIP image. Although some distal branches of the middle cerebral artery (MCA) are thicker and/or brighter in the original image (black arrows) than in the corrected MIP image, most peripheral MCA branches are seen more clearly in the corrected MIP image (white arrows). Note that brain parenchyma is visible in the original MIP image and that the central part of the brain is darker than the peripheral part.

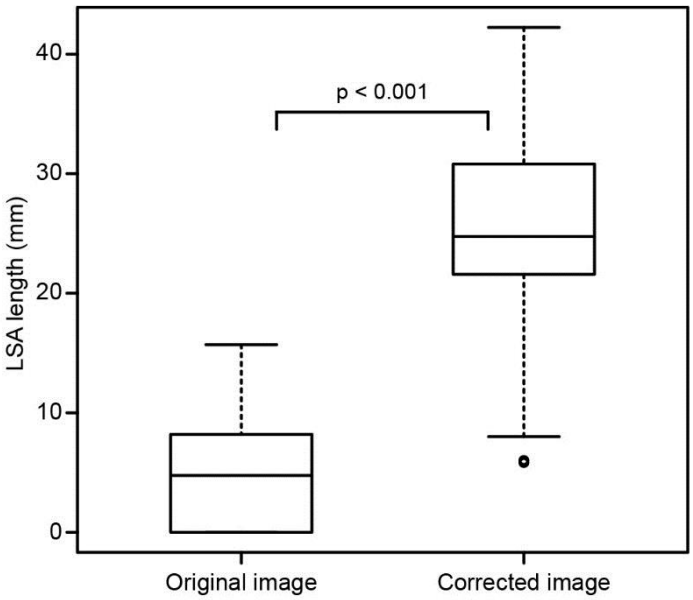

Figure 5 Comparison of LSA length in the original and corrected MIP images. LSA length measured in the corrected MIP image is significantly greater than that in the original MIP image (Wilcoxon matched-pairs signed-ranks test, $p < 0.001$).

Discussion

In this study, we tested the performance of intensity inhomogeneity correction using SPM8 for various scan sequences of the human brain at 7T, and evaluated the efficacy of the correction with various FWHM values in Gaussian smoothness. We found that inhomogeneity correction in the 7T MR images was more effective with smaller FWHM values. The RF wavelength decreases with increasing field strength, and when it is shorter than the dimensions of the human head, constructive interferences of standing waves occur [9, 10]. This produces a very inhomogeneous RF distribution and, consequently, inhomogeneous signal variation is seen across the image. The standing wave effects at 7T lead to more pronounced B_1 inhomogeneities compared with 3T and below. Although this intensity inhomogeneity is low frequency compared with anatomical brain structures, the inhomogeneity with greater field strength may modulate to a higher frequency or increase low-frequency bandwidth; therefore, inhomogeneity correction using SPM8 may require lower FWHM (smoothness constants of the bias field) values to obtain uniform image intensity at 7T. Any FWHM parameter in SPM8 can be chosen by modifying the script file used to run the New Segment module; however, the smallest FWHM value on the graphical user interface is 30 mm, so we used FWHM values of 30 to 120 mm. In our study, the best FWHM value was considered 30 mm. Weiskopf et al.[24], who introduced New Segment in SPM8, reported that the optimal FWHM value at 3T was 60 mm for R1 (longitudinal relaxation rate) brain maps using dual

angle FLASH imaging (testing range, 30–150 mm). In addition, our study revealed that New Segment in SPM8 for 7T can also correct intensity inhomogeneities better with smaller FWHM values than the default value of 60 mm (which was determined for 3T or below on conventional clinical MRI). Therefore, the optimal FWHM value tends to decrease with increasing magnetic field strength. In the 2 GRE sequences, however, the difference of signal intensity between the subcortical and deep white matter was statistically significant with an FWHM value of 30 mm, although there were no significant differences at 60 mm. This was probably due to over-correction of intensity inhomogeneity, and the best FWHM value for GRE sequences might be between 60 and 30 mm. However, further evaluation is needed to clarify this issue (see limitations below).

There are concerns that inhomogeneity correction with retrospective methods may have undesirable effects such as reduction of the contrast between different tissue types. We found that the contrast between white and gray matter was maintained after inhomogeneity correction at four FWHM values in SPM8. Tissue probability maps in the unified segmentation implemented in SPM may have the favorable effect of maintaining contrasts between different tissue types. However, the contrast between different tissues may be reduced at FWHM values of less than 30 mm because of over-correction of intensity inhomogeneity (see limitations below).

Without intensity correction, signal intensities of clinical images at 7T are

inhomogeneous and may negatively affect clinical diagnosis on visual inspection. For example, it has been discussed that subpial lesions in multiple sclerosis may not be detected because of intensity nonuniformity [11]. Therefore, intensity inhomogeneities should be reduced or minimized by applying intensity inhomogeneity correction. Inhomogeneity correction has also been reported to improve accuracy and reliability of various computational analysis techniques such as anatomical tissue classification and cortical segmentation and registration [29, 34]. MR angiography at 7T has enabled imaging of microvasculature including smaller peripheral vessels [35, 36]; however, as shown in the results of our experiments (Fig. 4 and Fig. 5), small perforating arteries in the middle of the brain, such as the LSA, could not be well visualized on MIP images without intensity correction because the center of the brain has low signal intensity in the original image at 7T. Reduction of intensity inhomogeneity in MR angiography provided clear anatomic delineation of the microvasculature and is, therefore, likely to play an important role in clinical assessment of microvasculature imaging.

There are 2 types of correction methods for intensity inhomogeneities, prospective and retrospective procedures. The retrospective, post-processing methods, such as SPM8 used in this study, are able to simply correct intensity inhomogeneity without any special hardware or sequence designs; however, the areas of severe signal loss cannot be recovered or corrected because the corrupted source signal cannot be regenerated. On the other hand, the prospective methods can minimize signal error during the MR image-acquisition process by applying (1)

RF shimming, where the channels of the transmitting coil are driven with tunable global RF phase and amplitude to optimize homogeneity of the resulting B_1 field [14, 15], (2) parallel transmission techniques, which use multiple excitation coils driven by independent RF pulses [37], or (3) special imaging sequences [38]. Although these methods are still under development in the ultra-high field over 7T, it is expected that these procedures or hardware will be incorporated into commercial MRI in the near future.

In the original images, signal drop in the center of the brain was more remarkable in GRE sequences (2D-FSPGR and 3D-TOF) than in SE and FSE images. This may be explained by the GRE sequence having a smaller flip angle, single excitation RF pulse (i.e., no refocusing RF pulse), and shorter repetition time (TR) [39]. Hence, GRE sequence images are less affected by B_1 inhomogeneity and more strongly influenced by inhomogeneous coil sensitivity. As a result, the signal drop is more remarkable in the area distant to the surface coils. In contrast, the SE sequence has 2 RF pulses with a larger flip angle of excitation together with refocusing, and a longer TR. Therefore, SE is more susceptible to B_1 inhomogeneity than inhomogeneous coil sensitivity [3, 10, 40]. Both types of inhomogeneities have similar low-frequency components in MR signal intensity; therefore, SPM8 used as a post-processing method in our study successfully corrected intensity inhomogeneities of B_1 fields and coil sensitivity at 7T.

This study has several limitations. First, CV was used for the evaluation of correction

performance of intensity inhomogeneity correction. CV has been commonly used to evaluate correction performance in conventional MRI at 3.0T or below, and it assumes that the signals in the entire white matter are uniform. However, white matter signals are not necessarily uniform because white-matter structures including different fibers and microvasculature have intensity variation. Therefore, smaller CV values may not necessarily reflect the best correction results. However, because ROIs in our experiments were located avoiding white-matter structures with intensity variation, such as fibers and microvasculature, CV was considered appropriate for correction performance in our study. Second, the best FWHM value for inhomogeneous signal correction in 7T images was considered 30 mm; however, we did not test FWHM values below 30 mm because this is the smallest value that can be selected on the graphical user interface of New Segment in SPM8. However, FWHM values less than 30 mm may cause erroneous correction as a result of reduced contrast between white matter and gray matter due to over-fitting to the model [23, 33]. Moreover, further study might be needed to evaluate the correction performance in FWHM values between 60 and 30 mm, because the best FWHM value for GRE sequences might be between 60 and 30 mm. Third, although the best FWHM value in our tests was 30 mm, further studies are needed, such as visual inspection by expert radiologists, to confirm that smaller FWHM values result in better clinical performance in lesion detection and diagnosis. Fourth, our study modified only FWHM value among all tunable parameters in the New Segment module. Further study is

needed to evaluate correction performances at 7T with various combinations of parameters. Fifth, although our study used SPM8 as a technique for correcting nonuniformity in 7T MR images, there are several other techniques and software such as N3 [18], BrainSuite [19, 20], and BrainVoyager (http://www.brainvoyager.com; Brain Innovation, Maastricht, Netherlands). Further study is needed to evaluate correction performances at 7T of these approaches. Sixth, we examined images from healthy volunteers only. Further studies are needed to evaluate performance in signal correction by SPM8 in patient groups with various brain disorders, in which SPM8 may produce incorrect results such as less contrast between the lesion and surrounding normal tissue, or over-correction.

In conclusion, the intensity inhomogeneities caused by both inhomogeneous B_1 field and coil sensitivity in 7T MRI were successfully corrected using SPM8 for various clinical sequences. In Gaussian smoothness, smaller FWHM values yielded better results in correction of intensity inhomogeneity, and the best FWHM value was considered 30 mm for the sequences evaluated in this study.

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Conflict of Interest

We declare that we have no conflict of interest.

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