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Simultaneous Diffusion and T1 Weighted Contrast Imaging for Human Brain Mapping

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ABSTRACT

Introduction: Diffusion tensor imaging (DTI) is typically obtained by echo-planar imaging (EPI) to map the human brain. However, EPI is sensitive to susceptibility effects, requiring elaborate image post-processing. Besides, DTI alone is limited in assessing gray and white matter boundaries of the brain, which has important implications for obtaining accurate images from brain atrophy. This study aimed to design and evaluate simultaneous diffusion and T1 weighting high-resolution imaging for human brain mapping.

Material and Methods: The method of T1 weighted three-dimensional Magnetization-prepared rapid gradient-echo (T1w 3D MPRAGE), which is conventionally used for structural brain mapping of gray and white matter, was extended to incorporate diffusion encoding using simulation and experiment to develop high-resolution DTI and T1-weighted human brain data.

Results: Theoretical simulations, as well as experimental results from in-vivo human brain studies at 4 Tesla magnetic field strength, showed that the DTI contrast, including fractional anisotropy (FA) and mean diffusivity (MD), incorporated into T1w 3D MPRAGE improves the contrast between gray and white matter sub-structural boundaries. Moreover, diffusion encoding into 3D MPRAGE avoids the inherent image distortions typically seen in EPI-based DTI.

Conclusion: This study suggests the capability and effectiveness of the combined DTI weighted 3D MPRAGE and T1 weighted for improving the detection of gray/white matter boundaries in human brain imaging.

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Introduction

Detection of brain tissue boundaries, including cortical thickness using magnetic resonance imaging (MRI), has been widely used to study neurodegenerative diseases such as Alzheimer's disease [1-3]. High-resolution T1 weighted three-dimensional Magnetization-prepared rapid gradient-echo (T1w 3D MPRAGE) is the preferred method for structural mapping of gray and white matter in brain imaging. However, the sole application of T1 weighting may not be sufficient to obtain a high contrast between tissue boundaries.

Diffusion tensor imaging (DTI), a variant of MRI, provides significant microstructural information of tissues in the brain [4-8], which in combination with high-resolution T1 weighted (T1w) contrast can improve the delineation of tissue boundaries. However, gaining contrast from separate acquisitions of 3D MPRAGE and DTI is challenging, not at least due to the need to fuse (register) images from these two techniques and their typically different spatial resolutions [9,10].

Previously, 3D MPRAGE has been combined with diffusion encoding [11-13] to achieve DTI without susceptibility distortions, which is inherent to the standard echo-planar imaging (EPI) acquisitions of DTI [14- 17]. According to the best knowledge of the authors, this is the first study that used diffusion contrast in 3D MPRAGE on the human brain *in vivo*. In particular, simultaneous T1- and diffusion weighting in brain imaging should enhance gray and white matter contrast, which in turn translates into the improved delineation of brain structures.

The main goal of this study was to increase the contrast of high-resolution MRI sequences. According to the findings, combined use of DTI information, such as fractional anisotropy (FA) and mean diffusivity (MD), and T1w 3D MPRAGE with simultaneous diffusion weighting improved gray and white matter contrast compared to the sole T1-weighting. The findings are derived using computer simulation as well as experimental brain imaging data from human volunteers obtained at 4Tesla (4T) magnetic field strength. The simulations were performed based on analytical equations to evaluate the longitudinal spin magnetization as described in [18].

A further consideration for 3D MPRAGE data acquisition is the choice of phase encoding order to sample spatial information, also known as *k-space*

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sampling. In general, phase encoding with a centric order, in which the lower spatial frequencies are sampled first before the higher ones, has been shown to improve image contrast over the more conventional linear order (i.e. sampling from the most negative to the most positive frequencies in k-space) [19- 21]. However, centric ordering induces non-uniform *k*-space weighting that may result in degradation of T1 contrast [19, 20]. Centric phase encoding with alternating polarity as gradients increase (0, -1, +1, -2, +2, ...) is the method of choose to decrease this potential effect [21]. Some studies of 3D MPRAGE with diffusion weighting on rats have used the centric ordered phase encoding to reduce the T1w effect from the data [11- 13]. Therefore, the current study aimed to extend a similar approach to 3D MPRAGE with diffusion weighting to human brain imaging.

In this study, firstly, a comparison of 3D MPRAGE with sole T1w contrast is carried out and, secondly, it is compared with a combination of diffusion weighting, using both computer simulations and *in-vivo* brain images of human volunteers. Written informed consent was obtained from all participants. In addition, the study is approved by the Committee of Human Research at the University of California in San Francisco (UCSF).

Materials and Methods

Simulations

The evolution of longitudinal spin magnetization in MPRAGE was programmed in Matlab 7.0.4 (The MatWorks Inc. Natic, MA) using the following equation:

$$M_z(t) = M_{eq}(1-\exp(-TI/T1)) + C(\alpha,\tau,n,T1) \quad (1)$$

where $M_z(t)$ is the longitudinal magnetization as a function of time t. M_{eq} is the equilibrium magnetization of the tissue and $C(\alpha, \tau, n, T1)$ is related to the strategy of MPRAGE data sampling and is a function of the flip angle, α, the RF pulse duration, τ, and the number of the pulses, n, of the MPRAGE sampling block (see Figure1a). T1 is the inversion time in MPRAGE and a function of the longitudinal spin relaxation time of the specific tissue type, i,e, gray matter. Incorporating diffusion weighting into the MPRAGE, as sketched in Figure 1b, leads to:

$$M_z(t)=M_{eq}\exp(-TE_{diff}/T2)\exp(-b.ADC)+C(\alpha,\tau,n,T1) \quad (2)$$

where, TE_{diff} is the diffusion encoding time before the start of MPRAGE sampling block, $b=\gamma^2g^2\delta^2(\Delta-\delta/3)$ is the degree of diffusion weighting and is a function of the diffusion encoding gradient amplitude (g_i) in each spatial direction i, gradient duration (δ) and mixing time (Δ) between the diffusion gradients (Figure 1b). ADC is the apparent diffusion coefficient of the specific tissue type [21-23]. The radiofrequency (RF) pulse train (90^o_{+x}-180^o_{+y}-90^o_{-x}) in presence of diffusion sensitization gradients is used to achieve the diffusion weighting in MPRAGE. T2 is the relaxation time of the transverse spin magnetization.

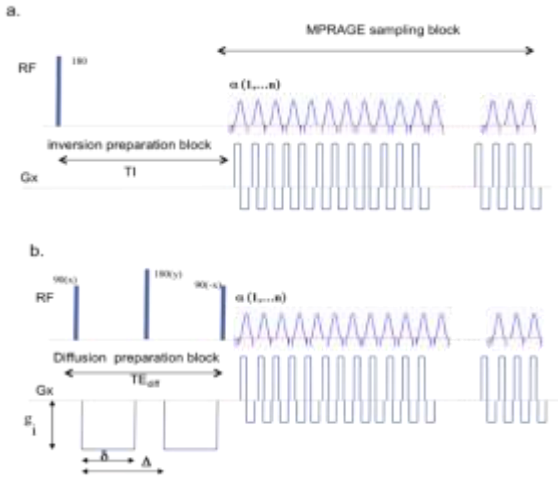

Figure 1. a) The T1w MPRAGE pulse sequence with TI inversion time using n number of α RF pulses and appropriate gradients. b) The diffusion encoding MPRAGE with gradients with duration of δ, amplitude of g_i in one direction and Δ as mixing time used in simulation.

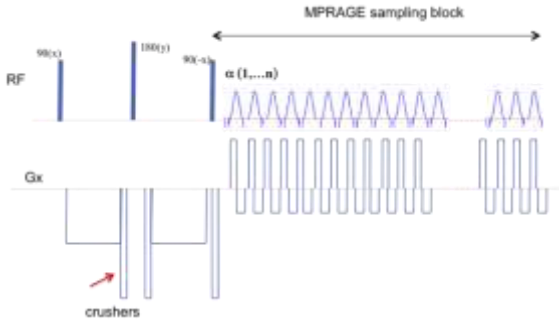

Figure 2. DTI- 3D MPRAGE pulse sequence. The diffusion gradients are applied in 6 directions for DTI in this study, where the figure shows just one. Crushers are indicated with red arrows for B1 field inhomogeneity correction.

The weighting from T2, which generally leads to image blurring, can be practically ignored as long as TE_{diff} is relatively short compared to T2.

The following tissue relaxation parameters were used to carry out simulations (to obtain an estimation from the human brain tissue model at 4T): T_1=1724 ms and T_2=70 ms for gray matter, and T_1=1043 ms and T_2=65 ms for white matter. For diffusion contrast simulations, the apparent diffusion coefficients of ADC=0.00079 mm^2/s and ADC=0.00056 mm^2/s were used, respectively, for gray and white matter, based on the values reported in the literature [8].

The MPRAGE sequence parameters used in the simulations are as follows: the number of RF pulses (n=168); and flip angle (8 degrees) i. For diffusion, b=1000 s/mm^2 was used and the TE_{diff} ranged from 30 to 100 ms to investigate the effect of diffusion on tissue

boundary contrasts (the results are ranked from the shortest to the longest diffusion times only).

In-vivo Experiments

3D MPRAGE with diffusion weighting was programmed in the Sequence Development Environment of Siemens and implemented on a 4T MR scanner (Bruker). The RF pulses of (90^{o}_{+x}-180^{o}_{+y}-90^{o}_{-x}) along with diffusion sensitizing gradients in six different directions were applied to attain the diffusion weighting in MPRAGE. This makes diffusion information be encoded in the longitudinal spin magnetization before the magnetization is read out using the conventional train of RF pulses with a small flip angle of MPRAGE. It is worth noting that the interference of the remainder transverse spin magnetization with the MPRAGE signal during diffusion weighting, which results in image artifacts, should be minimized, which can be accomplished by either applying crusher gradients or using RF pulses with uniform flipping. In addition, we used crushers along each diffusion gradient direction immediately before and after the 180^{o} RF refocusing pulse, as indicated in Figure 2. Representative brain images with and without an effective suppression of transverse magnetization by crushers are shown in Figure 3. As can be seen, any residual transverse spin magnetization leads to B1 inhomogeneity artifacts in the images (Figure 3).

Of note, no artifact from magnetic susceptibility distortions, which typically hamper diffusion images based on EPI acquisition, is detectable in diffusion-weighted MPRAGE.

The experiments were performed on four healthy subjects (24 to 40 years old) using a 4T whole-body magnet. Diffusion encoding was performed along six spatial directions for each subject to obtain DTI information. The parameters for DTI were; b-value= 1000 s/mm^2 with the gradient strength g=15 mT/m and a gradient duration δ=30 ms as the shortest available time for diffusion encoding on the 4T scanner and TE_{diff}= 70 ms. A single RF transmit, and 8-channel receiver head coil were used. The parameters for MPRAGE were as follows: TR/TE=1700/1.6 ms, flip angle=8 degrees, the isotropic spatial resolution of 2x2x2 mm^3 with 128x128 matrix size, 32 number of slices, and readout bandwidth of 480 Hz/pixel. The number of averages used in DTI was one (NEX=1). Maps of MD and FA were computed using DTI-studio software [24, 25]. All other image post-processing and analysis were performed using Medical Image Processing and Visualization (MIPAV 5.1.0) software.

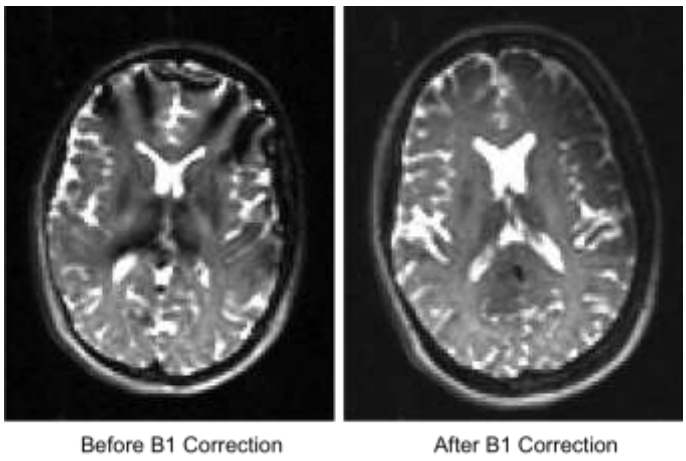

Figure 3. The individual b_0 image of the human brain using DTI 3D-MPRAGE before and after B1 inhomogeneity correction by crusher gradients in XY directions.

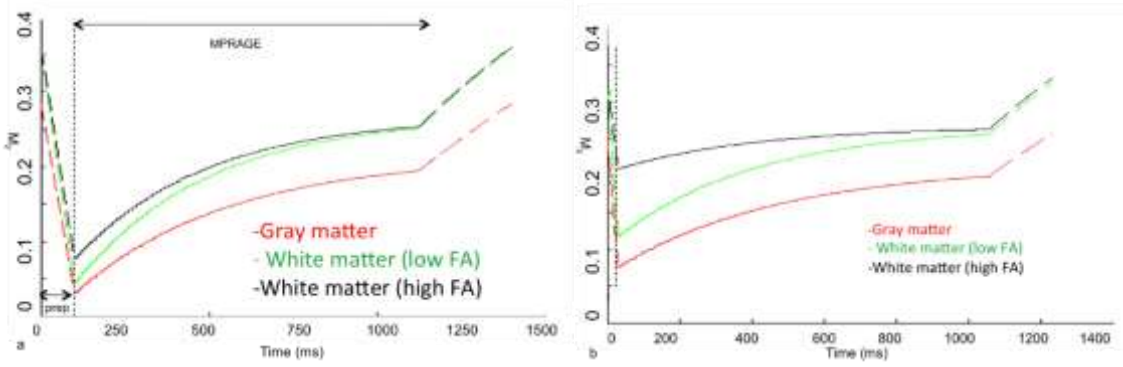

Figure 4. Evolution of longitudinal magnetization using simulated diffusion 3D-MPRAGE with diffusion encoding preparation time of TE_{diff}=100 ms (a) compared with TE_{diff}=30 ms(b).

Data on all types of brain tissues were analyzed separately. The total image contrast of the tissue boundaries was calculated and averaged over the brain images of four volunteers, separately based on T1w alone as well as on MD or FA computed maps from diffusion-weighted MPRAGE.

Results

The simulated evolution of the longitudinal spin magnetization in MPRAGE affected by diffusion weighting is provided in Fig. 4. The sequential order of phase encoding was used in simulations. The white matter with high (black) and low (green) diffusion directionality, i.e. FA, is shown in Fig. 4a and 4b, respectively, for the magnetization in MPRAGE affected by diffusion weighting is provided in Fig. 4. The sequential order of phase encoding was used in simulations. The white matter with high (black) and low (green) diffusion directionality, i.e. FA, is shown in Fig. 4a and 4b, respectively, for the shortest and the longest diffusion encoding times, indicating the range of diffusion contrast in MPRAGE.

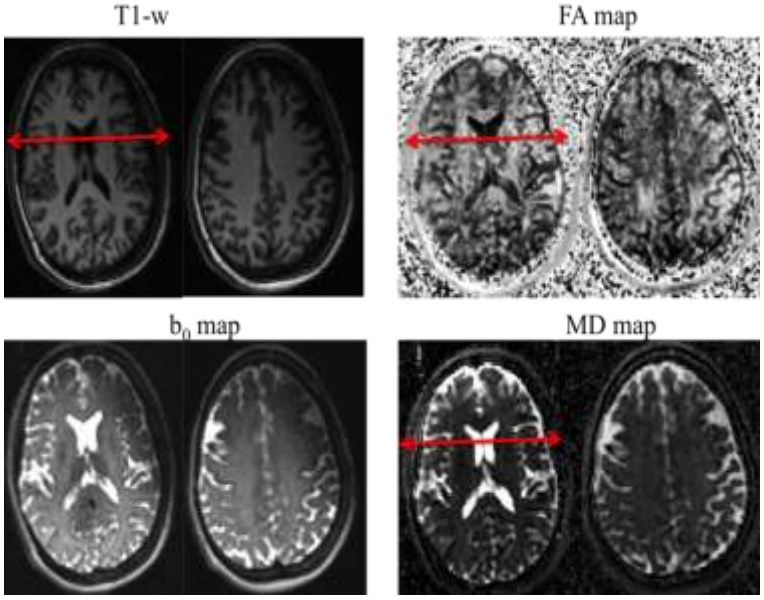

Figure 5. Representative T1w, b0, FA and MD maps of an individual healthy human brain scanned using T1w and DTI 3D MPRAGE. The red line is line of interest to analyze the intensity profile along tissue boundaries of gray and white matter.

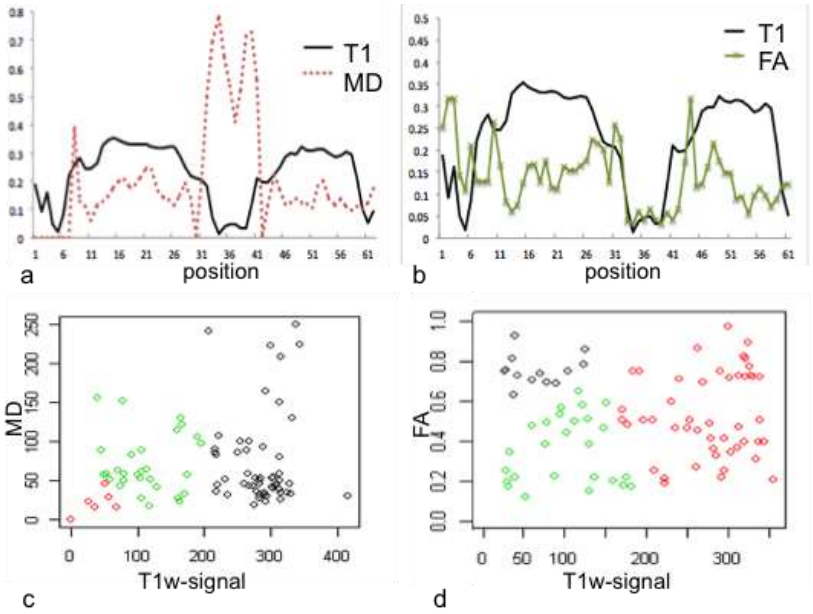

Figure 6. The intensity profile of T1w map superimposed on MD (a) and FA(b) maps in the line of interest shown in fig.5. The Y axis is the normalized signal intensity to 1.

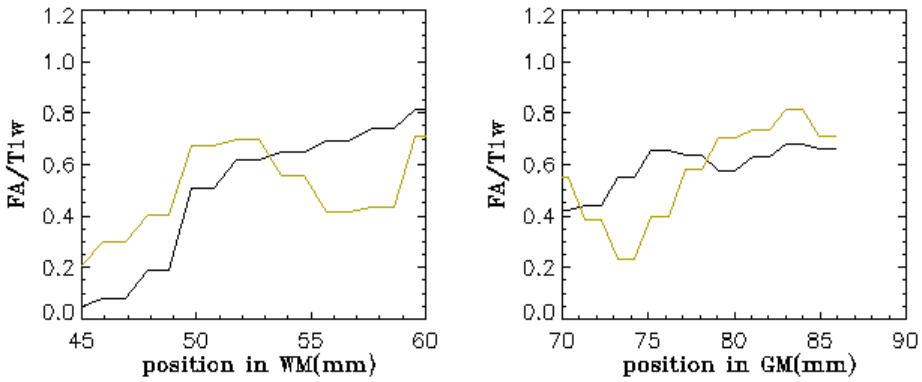

Figure 7. The intensity profile of the line of interest shown in fig.5 between T1(black line) and FA (green line) in white matter(a) and in gray matter(b) regions.

The three intensity clusters in c and d present the correlation between T1w and MD and T1w and FA maps respectively. The gray matter is highlighted using the red color. The progression of the spin magnetization back towards equilibrium is conducted by a combination of the RF train with small flip angles and the T1 relaxation of tissue [12]. Comparing the two diffusion encoding preparation times (TE_{diff}=30 and 100 ms) revealed that the lower the diffusion time (30 ms), the higher the contrast of sub tissue of white matter with low and high FA during the evolution of magnetization approaching the steady-state (see Fig. 4b) compared to that of obtained by administering a long diffusion preparation time (100 ms), which is presented in Figure 4a.

The simulations also show a considerable diffusion contrast between white matter in high and low FA values. The contrast exists over a reasonably long inversion time period (about 400ms) of MPRAGE before its disappearance simultaneous with the progress of the longitudinal spin magnetization towards its steady-state, as seen in Figure 4b.

Representative experimental MPRAGE brain images with T1w, as well as computed maps of b0, MD, and FA from an individual subject, are displayed in Fig. 5. In general, T1w and the diffusion-based FA and MD maps show high contrast between gray and white matter. However, the FA and MD maps provide additional information that is not available with T1w alone.

Table 1. The normalized average contrast over four healthy human subjects in gray/white matter region of interest along the cross section (Fig. 5) of the brain maps of MD and FA compared with T1w alone using MPRAGE.

3DMPRAE	T1w	MD+T1w	FA+T1w
CR	0.941	0.970	1.000
±SD	0.033	0.042	0.026

In detail, the intensity profiles of T1w, FA, and MD maps along cross-sections through the images (red lines of interest in Fig. 5) are shown with superimpositions of T1 and MD signals (Fig. 6a) and T1 and FA signals (Figure 6b), which indicates a systematic difference between T1w and MD compared to that of T1w with FA along with the tissue substructures, which can be attributed to the improved delineation of brain structures. The figures show a great number of up and down peaks of signal intensity of T1w, FA, and MD, indicating the contrast along the regions. As noticed in the profiles, FA and MD may provide more contrasts along the regions than T1w alone. In addition, Fig. 6c and Fig. 6d show the correlation between T1w and MD maps and between T1w and FA maps, respectively.

The three clusters of Fig. 6c show the linear correlation between MD and T1w in low signals (red cluster), which indicate a similar contrast across the regions. On the other hand, data dispersion in medium and high signals (green and black clusters) indicates more regional contrast in the MD compared to the T1.

Also, the three clusters in Fig. 6d show the linear correlation between FA and T1w across low to high signals (red and green clusters). Nevertheless, some data dispersions in low T1w signals (black cluster) indicate more regional contrast in FA than T1.

In particular, T1w and FA intensity profiles of both gray and white matter are plotted (see Fig. 7a, b). These profiles differ substantially in the regions, implying additional contrast information from simultaneous diffusion and T1 weighted MPRAGE.

The total image contrast, calculated using the average of the four volunteers, along with the cross-sections in T1w, MD, and FA maps is provided in Fig. 5. As indicated in the figure, the contrast of the obtained average is substantially higher than that of the sole T1w. The averaged contrast (CR) and standard deviation (SD) of data of four volunteers ($CR \pm SD$) are given in Table 1. For data of T1w alone, MD and FA data were superimposed with T1w, i.e. (MD+T1w) and (FA+T1w).

Discussion

This study demonstrates that incorporating diffusion weighting into 3D MPRAGE yields diffusion images that are large deploys of the typical artifacts in conventional EPI-based DTI, such as N/2 (Nyquist) ghosting and magnetic susceptibility distortions [14].

Image artifacts from residual transverse spin magnetization caused by RF field inhomogeneities, which can induce susceptibility distortions, were effectively removed by applying gradient crushers. Eventually and on visual inspection, brain images without major spatial distortions were obtained using the imaging sequence presented in this study.

The findings also show that information of diffusion and T1-weighting can be simultaneously obtained in a modified 3D MPRAGE sequence for human brain imaging, which in turn translated into increased tissue contrast. The gain in contrast should be helpful in better delineating brain tissue boundaries and structures. Previous studies showed the feasibility of DTI 3D MPRAGE on rats [11- 13]. Here, we demonstrated that the DTI 3D MPRAGE is feasible for human brain imaging *in-vivo*. This would benefit the assessment of gray and white matter boundaries with additional and higher contrast resolution, while T1w contributes to DTI 3D MPRAGE. For this reason, the standard sequential order of phase encoding was chosen for *k-space* sampling; where centric order has been used in other studies [13] to reduce T1 relaxation effects [19].

The intensity profiles of combined T1w with DTI scalar data, such as MD and FA, in comparison with that of T1w alone, show the additional contrast in sub tissue structures of gray or white matter across the region of interest of the brain maps. The detail is also extended for FA intensity profile for an individual healthy subject compared with T1w alone in Fig. 7(a-b).

The results obtained from repeated experiments on four subjects, presenting the average total contrast in Table 1, show that our sequence of DTI combined with T1w MPRAGE reliably could improve the evaluation of gray and white matter boundaries, particularly when utilizing FA information.

It is necessary to mention some limitations and biases of our study, including the 2 mm spatial resolution, which was limited, due to not losing signal-to-noise ratios (SNR). To achieve a higher resolution, the SNR can be increased by shortening the diffusion time (TE_{diff}), which in turn causes increased tissue contrast, as suggested by the simulations. In addition, SNR can be boosted by more efficient signal averaging schemes, i.e. utilizing parallel imaging [15- 17]. Another limitation was a technical limit for applying dense *k-space* sampling concerning the diffusion signal decay, which can improve the DTI contrast. This requires substantial technical developments and future works.

Conclusion

This study demonstrates that simultaneous diffusion and T1 weighting in 3D MPRAGE is feasible for human brain imaging without image artifacts from conventional EPI-based diffusion mapping. The combination improves image contrast and is also expected to benefit the evaluation of gray and white matter boundaries.

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