Analysis of the Local Susceptibility Effects in Diffusion Tensor Imaging (DTI) on Alzheimer's disease

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Introduction: In diffusion tensor imaging (DTI), magnetic field gradients induced by local susceptibility variations in the brain may be superimposed on external diffusion-sensitizing gradients, leading to gradient cross-terms that may limit accuracy of DTI. However, the extent of distortions from cross-terms in diffusion measurement remains controversial (1;2;3;4) and there were no previous studies investigating cross-term effects on DTI in the human brain. Our goals were therefore 1) to investigate the effect of locally induced magnetic field gradients on diffusion tensor measurements and 2) to explore if gradient cross-terms lead to a systematic distortion pattern for DTI in brain studies, especially in Alzheimer's disease (AD) which may exhibit large variations of tissue susceptibility because of increased deposition of brain iron.

Theory: In DTI experiments the signal intensity as a function of external diffusion gradient is given by **Eq. [1]**. Here, the diffusion-weighted factor b_e is proportional to the square of the magnitude of external diffusion gradients. $\mathbf{g}_e$ is a vector for the directionally dependent encoding of the external diffusion gradients and $\boldsymbol{D}$ is the rank 2 diffusion tensor. In presence of an additional magnetic field gradient (background gradient) due to local susceptibility and for external diffusion gradients with either positive (p) or negative (n) polarities, the signal intensities, S_p and S_n, are modified according to **Eq [2]**. Here, $\mathbf{g}_i$ is the directionally dependent encoding of the local internal background gradient and $b_{p/n} = b_e + b_i \pm b_{cross}$ where b_e is proportional to the square magnitude of either positive or negative external diffusion gradients. b_i is proportional to the square magnitude of the background gradient and b_{cross} is proportional to the cross-term $G_e{*}G_i$. Since b_p, b_n, and $\mathbf{g}_i$ are *unknown*, $\boldsymbol{D}$ cannot directly be obtained from Eq. [2]. Assuming that $\mathbf{g}_i$ is *rotationally symmetric* (but magnitude may differ) and $G_i << G_e$, a mean diffusion weighting factor $b = (b_p + b_n)/2 = b_e + b_i \approx b_e$ can be computed and Eq. [2] rewritten to obtain $\boldsymbol{D}$, according to Eq. [3]. Here, $\mathbf{D'}_p=(1+b_{cross}/b)\,\mathbf{D}$ and $\mathbf{D'}_n=(1-b_{cross}/b)\,\mathbf{D}$ (where $b_{cross} = (b_p - b_n)/2$) are simply scalar transformation of **D**. Thus, sclar tensor metrics such as mean diffusivity **MD**, surface area **SA**, magnitude **NORM**, and volume **VOL** of diffusion tensor are scaled too. However, directional tensor metrics such as fractional anisotropy **FA** and relative anisotropy **RA** are *not affected*.

Methods: *Data Acquisitions*: Fourteen AD patients were studied using a 1.5T MRI system (Siemens, Magnetom Vision). DTI measurements were performed using a single shot EPI sequence with inversion-prepared magnetization to suppress CSF (5). A double refocusing spin-echo acquisition and bipolar external diffusion gradients (6) were employed to minimize artifacts due to eddy-currents without sacrificing SNR. Six optimally selected encoding directions (7) were used and five *b*-values of 0, 160, 360, 640, and 1000 sec/mm^2 were acquired to determine the ADC and diffusion tensor matrix for each voxel. Furthermore, two DTI data sets were acquired with alternating polarities of the external diffusion-sensitizing gradients (8). Imaging parameters were TR/TE/TI=5000ms/100ms/3000ms with 2.4x2.4mm^2 in-plane resolution and 19 slices with 5mm slice thickness without gap. In addition to the DTI scan, 3D-MPRAGE sequence, a multi-slice double spin-echo (DSE) sequence, and T_2-weighted spin-echo EPI images (referred to below as reference EPI images) were acquired for tissue segmentation and image registration to brain template. *Post-Processing*: D_p and D_n, were separately DTI measurements according to Eq. [3] and MD, FA, and other DTI measures were calculated for the positive and the negative polarities of external diffusion gradient. Post-processing for image coregistration and spatial normalization was performed using the SPM2 software (Wellcome Department of Cognitive Neurology, England, UK). *Statistical Analyses*: To determine if background gradients induced systematic effects for DTI, spatially normalized and smoothed DTI quantities from positive and negative diffusion gradients were compared across subjects on a voxel-to-voxel basis using paired T tests in SPM2. Significance level was p=0.05 with correcting multiple comparison.

Results: The effects of local background gradients on the DTI quantities MD (first row), SA (second row), NORM (third row), and VOL (fourth row) from 14 AD patients are shown in the **Fig. 1**. The statistical T-map depicted significant systematic regional variations, most prominently in the occipital, parietal, and temporal lobes of the brain involving white matter, while frontal regions where less involved, suggesting a regional heterogeneity for microscopic susceptibility effects in the brain. Shaded regions in Fig. 1 indicate that DTI data were not acquired from these regions. As expected, no systematic effects from background gradients were detected for maps of FA and RA. **Fig. 2** shows regions, where effects from background gradients were most significant on all four DTI measures (MD, SA, NORM, and VOL). The locations were the right fronto-parietal white matter junction (top left, p=0.004 and T-score=10.24), the diencephalon (top right, p=0.004 and T-score=11.22), and the right white matter of corona radiate (bottom left, p=0.008 and T-score=9.41).

Conclusion: Presence of local background gradients can introduce errors in DTI by scaling scalar tensor measures such as MD, SA, NORM, VOL. Systematic background gradients, impacting DTI maps of the brain, were detected in AD patients, presumably reflecting systematic variations of local tissue susceptibility due to increased deposition of brain iron. Therefore, cross-term effects must be considered for accurate DTI measurements in the brain.

References: 1. Does MD, et. al. MRM 41, 1999; 2. Trudeau JD, et.al. JMR(B), 108, 1995; 3. Beaulieu C, Allen PS. MRM 36, 1996; 4. Clark CA, et.al. JMR 141, 1999; 5. Hirsch JG, et. al. MRI 17, 1999; 6. Reese TG, et.al. MRM 49, 2003; 7. Jones DK, et.al. MRM 42, 1999; 8. Neeman M, et.al. MRM 21, 1991.

$$\ln\left(\frac{S}{S_0}\right) = -b_e\left(\mathbf{g}_e^{\mathrm{T}} \cdot \mathbf{D} \cdot \mathbf{g}_e\right) \qquad [1]$$

$$\ln\left(\frac{S_{p/n}}{S_0}\right) = -b_{p/n}\left\{(\mathbf{g}_e + \mathbf{g}_i)^T \cdot \mathbf{D} \cdot (\mathbf{g}_e + \mathbf{g}_i)\right\} \qquad [2]$$

$$\ln\left(\frac{S_{p/n}}{S_0}\right) = -b\left\{\mathbf{g}_e^T \cdot \mathbf{D}'_{p/n} \cdot \mathbf{g}_e\right\} \qquad [3]$$

Fig.2. Three brain regions showing the most significant different effects of internal gradients shown in Fig.1.

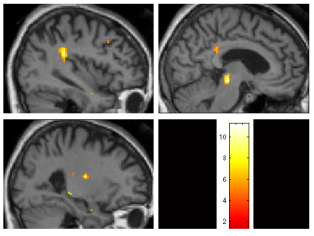

Fig.1.Significant T-statistics of MD, SA, NORM, and VOL.