# Directional Independence of Water Diffusion Heterogeneity in the Human Brain

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**Introduction:** Signal decay with diffusion-weighted imaging (DWI) is non-exponential (1,2), and can be described with the stretched-exponential function $S/S_0 = \exp\{-(b \times DDC)^{\alpha}\}$, plotted with respect to b (3). The signal attenuation $S/S_0$ is the magnitude S of signal using diffusion-weighting b, divided by the magnitude of the signal $S_0$ (b = 0). The b-value is determined by the magnitude and duration of applied magnetic field gradients in a Stejskal-Tanner pulse-sequence. The stretched-exponential is useful for measuring non-exponential decay when the number of contributing water pools is unknown, and has a known relationship to the underlying distribution of water diffusion rates. The distributed diffusion coefficient (DDC) and heterogeneity index $\alpha$ are obtained in fits of the model to signal attenuation data. The parameter $\alpha$ tracks the number of discrete decay components when the average decay rate is constant (Fig 1). Bennett et al. applied diffusion gradients in a single direction to avoid artificially adding heterogeneity to the decay in studies of rat brain. It was suggested that $\alpha$ was insensitive to tissue anisotropy, though the concept was not studied. The goal of the present work was to study $\alpha$ and DDC in images of the human brain. It was discovered that $\alpha$ is relatively insensitive to the direction of the applied magnetic field gradients, as measured by relative anisotropy. This suggests a tensor model of DDC is feasible for clinical use to track intra-voxel heterogeneity changes associated with disease.

**Methods:** Three healthy human volunteers were imaged using a GE 1.5T Horizon scanner, with a combined exciter/receiver, 11 cm inner diameter local head quadrature gradient coil of 41.0 cm length. A $64 \times 64$ matrix, a FOV of 27 cm, five axial slices of thickness 5.0 mm, and a TE of 80 to 140 ms were used. A Stejskal-Tanner spin-echo DWI sequence was used, with EPI acquisition. The b-values were 500, 1000, 3000, 5000 and 7000 s/mm$^2$. Imaging was performed with a CSF-nulling FLAIR pulse (TI = 2200 ms). The signal attenuation curves corresponding to DWI with x-, y-, and z-gradient directions were fitted separately to the stretched-exponential function using Matlab. Relative anisotropy (RA) was calculated for each of the parameters as: $RA = \sqrt{\{_1(V_x\text{-}Vy)^2 + (Vx\text{-}Vz)^2 + (Vy\text{-}Vz)^2\}}/\{Vx+Vy+Vz\}$, for parameter V in x-, y- and z-directions. White- and gray-matter (WM and GM) ROIs were defined by visual inspection of the diffusion-weighted image. The RA of the mono-exponential apparent diffusion coefficient (ADC) for b = 1000 s/mm$^2$ was calculated for comparison.

**Results and Conclusions**: A map of $\alpha$ is shown in Fig 1b. As reported in (3), WM and GM could be visually identified by $\alpha$ values. White-matter tracts could be identified using the $\alpha$ maps, and penetrated into GM near the surface of the brain. Figure 2 shows the RA calculated for $\alpha$ and DDC in gray- and white- matter. The RA of $\alpha$ and DDC were both low in GM, but only $RA_{DDC}$ was increased in WM. CSF nulling increased the difference in $RA_{DDC}$ between gray- and white-matter, but not in $RA_{\alpha}$. The RA of ADC was similar to that of DDC (data not shown). It was concluded that the heterogeneity index is relatively insensitive to the direction of applied magnetic field gradients in DWI of the human brain. The result was repeatable, as indicated by comparisons of the RA values of Table 1 in each subject. A measurement of $\alpha$ in a single direction therefore gives reliable information about intra-voxel heterogeneity, and permits a comparison of heterogeneity across voxels. A tensor model of DDC could also be created using four extra parameters rather than the expected six. This method may be practical for tracking changes in intra-voxel heterogeneity with disease progression.

**References**: 1. Sehy JV et al. Magn Reson Med 2002; **48**:76. 2 Mulkern et al. NMR Biomed 1999; **12**:51.3.Bennett KM et al. Magn Reson Med, 2003;**50**:727.

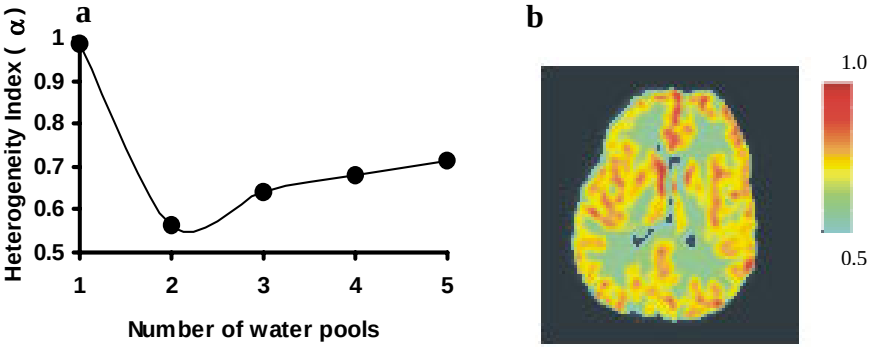


Figure 1: (a) The modulation of intra-voxel heterogeneity in diffusion with the number and distribution of contributing water diffusion rates. In each case, the average diffusion rate is held constant. The heterogeneity index $\alpha$ is obtained by fitting the signal attenuation curves with a stretched-exponential model. (b) A map of $\alpha$ resulting from stretched-exponential fit in each voxel in images of a human subject.

Table 1: Values and relative anisotropy (RA) of $\alpha$ and DDC in white-matter (WM) and gray-matter (GM), for each subject. The inter- voxel average ± 1 SD is reported.

| Subject | $RA_{\alpha}$, GM | $RA_{\alpha}$, WM | $RA_{DDC}$, GM | $RA_{DDC}$, WM |
|---|---|---|---|---|
| 1 | 0.14 ±0.07 | 0.19± 0.12 | 0.19± 0.11 | 0.48± 0.33 |
| 2 | 0.17± 0.09 | 0.21± 0.12 | 0.19± 0.12 | 0.40± 0.25 |
| 3 | 0.18± 0.09 | 0.12± 0.11 | 0.22± 0.12 | 0.35± 0.21 |

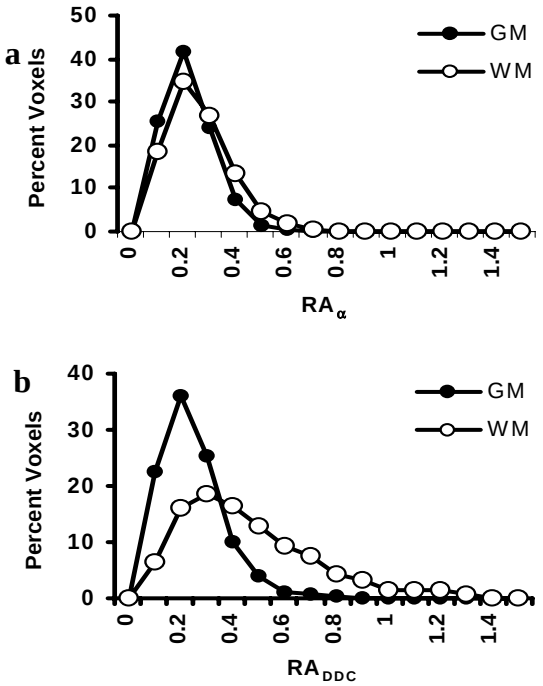


Figure 2: Histograms of the relative anisotropy (RA) for (a) heterogeneity index $\alpha$ and (b) distributed diffusion coefficient (DDC) in a representative slice in the brain of a human subject. The distribution of values in both gray-matter (GM) and white-matter (WM) voxels are shown.