Origin of B0 orientation dependent R2* (=1/T2*) in white matter: magic angle effect vs. magnetic susceptibility

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Introduction: In a certain tissue with anisotropic microstructures, relaxation rates (R_2 and R_2^*) are modulated by the orientation of the anisotropic microstructures relative to B_0. One of these phenomena is a magic angle effect, which is observed at tendons, ligaments, and menisci [1,2]. The effect exhibits a decrease in R_2 when the anisotropic microstructure is orientated at specific angles ($R_2(\theta) = R_{2,\text{orient indep}} + (3\cos^2\theta - 1)^2$ (Eq. 1)) relative to B_0 (Fig. 1A). Another mechanism is the magnetic susceptibility, which affects R_2^* [3]. In white matter of the brain, axons and myelin sheaths form cylindrical structures and magnetic susceptibility difference exists between myelin and surrounding water [4,5]. This angular dependency has been shown to change as follows: $R_2^*(\theta) = R^*_{2,\text{orient indep}} + c_{iso} \cdot \cos 2\theta + c_{ansio} \cdot \cos 4\theta$, (Eq. 2; Fig. 1C) [6]. The second term is from isotropic susceptibility (Fig. 1B) whereas the last term is from anisotropic susceptibility, which was suggested to originate from myelin [7]. The same orientation dependency as in Eq. 2 can be generated by the combination of isotropic susceptibility and magic angle effects (Fig. 1D). Hence, in R_2^* measurement, it is difficult to confirm whether the magic angle effect (with isotropic susceptibility) or the susceptibility effect (with susceptibility anisotropy) is the primary contributor of R_2^* orientation dependency (Figs. 1C and 1D). On the other hand in R_2 measurement using SE, magnetic susceptibility effect is minimized while the magic angle effect is sustained in the same magnitude. In order to identify the origin of R_2^* orientation dependency, we have performed an experiment on fixed human brain specimens to estimate the contribution of the magic angle and susceptibility effects. Both white matter (corpus callosum) and deep gray matter (basal ganglia) was investigated.

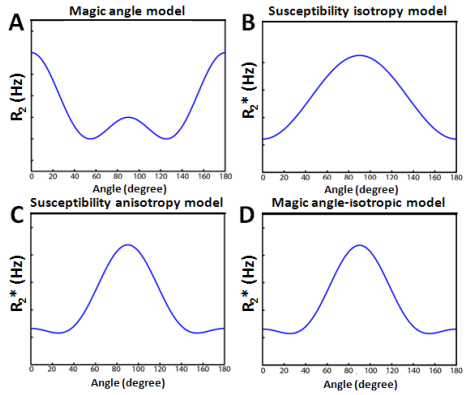

Fig.1: **Orientation dependence of magic angle (A); isotropic susceptibility (B); susceptibility anisotropy model (C); and magic angle-isotropic susceptibility model (D).**

Methods: Two coronal slabs of formalin-fixed human brain specimens were used for the experiments. One of the slabs was used for the orientation dependent R_2 and R_2^* measurements in corpus callosum (Fig. 2A) and the other for the orientation dependent R_2^* measurements in basal ganglia (Fig. 3A). To measure the orientation dependence, the specimen was scanned at 12 different orientations, each rotated approximately by 15°. For R_2 estimation, a 2D SE sequence with a single echo was used. The scan parameters were: resolution = 0.75 x 0.75 x 1 mm^3, matrix size = 128 x 128 x 20, and TR = 2.5 s. The single echo acquisition was repeated 7 times with different TEs (= 9:5:39 ms). For R_2^* estimation, a 3D multi-echo GRE sequence was used. The same resolution and matrix size were used as in the SE sequence. Other parameters were: TR = 100 ms, flip angle = 15° and TE = 4:5:39 ms (8 echoes). After acquisition, both SE and GRE, were aligned to the first orientation image of the SE data. The voxel-wise R_2 and R_2^* values were estimated by a weighted least-square fit. For each angle, the averaged R_2 and R_2^* values and its standard deviation within a ROI were calculated to generate orientation dependent curves. These curves were then fitted to the suscep-aniso model ($M_{suscep-aniso}(\theta) = R^*_{2,\text{orient indep}} + c_{iso} \cdot \cos 2\theta + c_{ansio} \cdot \cos 4\theta$) and the magic-iso model ($M_{magic-iso}(\theta) = R^*_{2,\text{orient indep}} + c_m \cdot (3\cos^2\theta - 1)^2 + c_{iso} \cdot \cos 2\theta$) to calculate the goodness of fit of each model. In the magic-iso model, the contribution of orientation dependent R_2 from the magic angle effect was expected to stay the same in the R_2^* measurement since R_2^* is sum of R_2 and R_2'. As a result, the regression result of the magic angle regressor obtained from the R_2^* measurement was removed from the R_2 curve of the magic-iso model. After that, an adjusted R^2 values were calculated to estimate goodness of fit in each model. For basal ganglia specimen, only R_2^* was measured as it did not show any orientation dependency (Fig.3B).

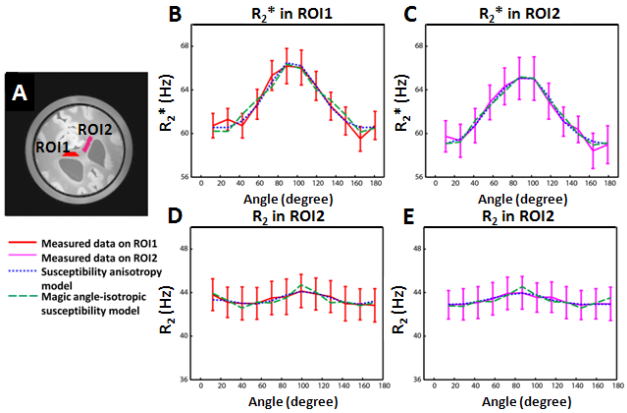

Fig.2: (A) ROIs, (B and C) R_2^* measurements and model-fitted curves, (D and E) R_2 measurements and model-fitted curves

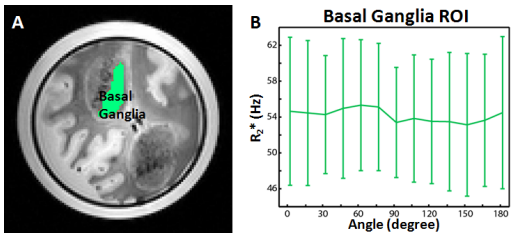

Fig.3: (A) ROI, (B) R_2^* curves in basal ganglia

Results: ***Corpus callsom***: The R_2^* curves (Figs. 2B and 2C) clearly demonstrate B_0 orientation dependence. They show much larger signal variations than the R_2 curves in Figs. 2D and 2E suggesting the susceptibility effect is the primary origin of the contrast. The maximum R_2^* measurements were observed when the fibers were perpendicular to B_0 (66.9 ± 1.8 Hz at 85° in ROI1; 64.8 ± 2.1 Hz at 93° in ROI2) whereas much lower R_2^* values were observed when the fiber orientations were parallel to B_0 (58.8 ± 1.2 Hz at 160° in ROI1; 57.6 ± 1.8 Hz at 162° in ROI2). When the two models, the suscep-aniso model and the magic-iso model, were fitted to the R_2^* curves, the adjusted R^2 showed the same results (R^2 = 0.96 in ROI1 and 0.97 in ROI2). On the other hand, when the two models were fitted to the R_2 curves, much reduced adjusted R^2 values were found in the magic-iso model (0.42 in ROI1 and 0.42 in ROI2) as compared to the suscep-aniso model (0.77 in ROI1 and 0.91 in ROI2) (Figs. 2D and 2E). These results suggest that the suscep-aniso model better explains the orientation dependent R_2^* and R_2 than the magic-iso model. ***Basal ganglia***: Basal ganglia showed no orientation dependency that can be explained by the models (R^2 = 0.0).

Discussion and Conclusion: In this study, we investigated the effects of magic angle and susceptibility on R_2^* and R_2. The relative orientation between white matter fibers and B_0 predominately affects R_2^* as compared to R_2, suggesting that the primary origin of the contrast is magnetic susceptibility. The orientation dependency in R_2 was better explained by the susceptibility anisotropy model. The R_2^* values in basal ganglia show there is no orientation dependence in deep gray matter. These results indicate that myelin is a primary source for R_2^* contrast because of its highly oriented structure and large susceptibility value.

References: [1] Chappell, AJNR,2004 [2] Fullerton, Radiology,1985 [3] Yablonskiy, MRM, 1994 [4] Liu, NeuroImage, 2011 [5] Lee, NeuroImage, 2012 [6] Lee, Neuroimage,2011 [7] Li, Neuroimage,2012