Iron-related Microstructural Alterations in Deep Gray Matter: Correlations from Diffusional Kurtosis Imaging and Quantitative Susceptibility Mapping

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Target audience: Those who study DKI, QSM or brain gray matter.

Purpose: Age-related iron depositions in subcortical gray matter such as globus pallidus (GP) and putamen (Pu) have already been widely reported in studies that quantified R2* or phase information[1]. The increase in iron content with the increase of age has also been suspected to contribute to microstructural alterations in deep gray matter[2]. However, in spite of indirect evidence implying such changes, no study has investigated this problem using both of the newly introduced quantitative susceptibility mapping (QSM)[3] and diffusional kurtosis imaging (DKI) methods[4], which were most suitable for measuring iron content and detecting microstructural changes in gray matter, respectively.

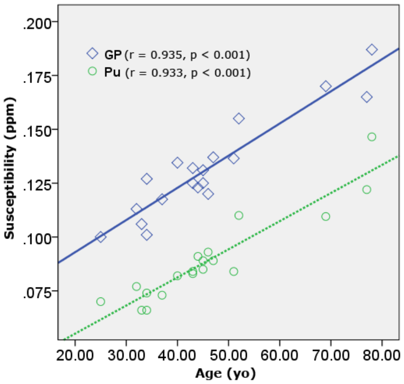

Fig 1. Correlations between susceptibility and age.

Methods: Nineteen normal subject (age, 25~78 yo) were recruited with IRB approval and written informed consent. Both DKI and QSM data were acquired from each single subject using 3T Philips Achieva scanner with 8-channel head coil. DKI data were acquired using a single shot EPI sequence with 32 gradient directions and two nonzero b values (1000 and 2000 s/mm^2). Other imaging parameters were: TR/TE = 2000/69 ms, reconstruction resolution = 2×2×3 mm^3, 33 axial slices with no interslice gap to cover the brain. The diffusion-weighted images were first corrected of eddy-current distortion and heads' motion using FSL, and then Gaussian smoothed. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (D axial), radial diffusivity (D radial), mean kurtosis (MK), axial kurtosis (K axial) and radial kurtosis (K radial) were derived from DKI data[5]. Using 3D GRE sequence, phase images were acquired with TE = 23ms, resolution = 0.45×0.45×1 mm^3, TR=28ms, α=15. Phase images were unwrapped using a Laplacian-based method[6], then divided by 2π*TE to obtain a raw frequency map. Background field frequency was removed using dipole fitting[7] and later converted to susceptibility map with the L$_1$ norm minimization method[8]. All processes were conducted using in-house MATLAB program.

Results: To detect age-related iron deposition, Pearson's correlations between age and susceptibility were tested. Significant positive correlations with age were observed for susceptibilities in GP (r = 0.935, p < 0.001) and Pu (r = 0.933, p < 0.001) (Fig. 1). To detect iron-related microstructural change, Pearson's correlations between DKI parameters and susceptibility were tested. In GP, weak correlation with susceptibility was observed for FA (r = 0472, p = 0.041), while no significant correlations was detected for MD, D axial and D radial (Fig. 2). In Pu, more substantial correlation between FA and susceptibility (r = 0.913, p < 0.001) was observed. Besides, significant negative correlations with susceptibility were also found for MD (r = -0.576, p = 0.010) and D radial (r = -0.844, p < 0.001) (Fig. 2). All the correlations for kurtosis parameters were not significant. To find out microstructural differences between GP and Pu, DKI parameters were compared using Mann-Whitney test. Significant but small differences were observed for D axial and D radial between GP and Pu. Difference in MD was not significant. In sharp contrast, MK, K axial and K radial in GP were much larger than, reaching nearly 1.5 times their corresponding values in Pu.

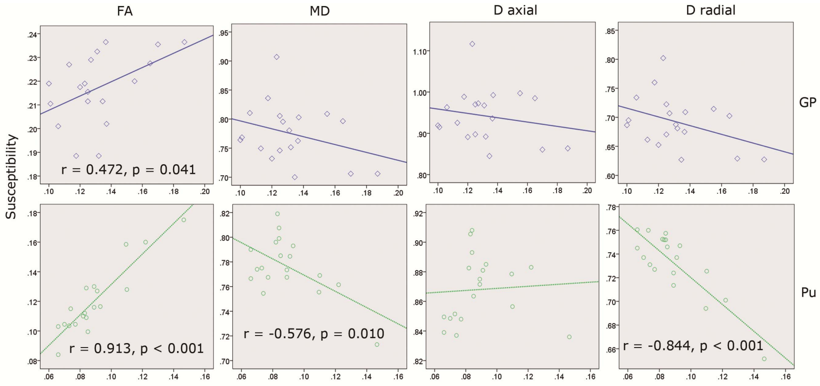

Fig 2. Correlations between DKI parameters and susceptibility.

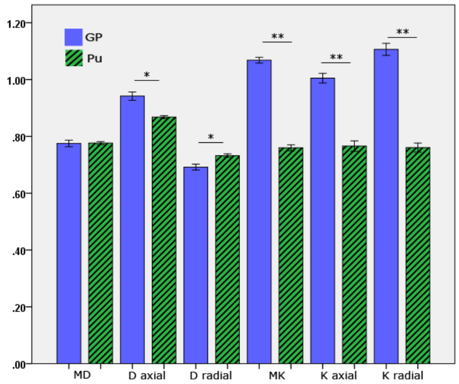

Fig 3. Bar charts of regional DKI parameters. *:p<0.05, **:p<0.001

Discussion: From 25 yo to 78 yo, evident age-related iron depositions were observed for both GP and Pu, which agreed with previous histological study[9]. In Pu, such raise in iron content resulted in significant decrease in D radial and MD, increase in FA and no change in D axial. Based on this observation, we speculate that iron accumulation altered the tissue structure and increased the degree of tissue compaction. Unlike Pu, GP was traversed by myelinated axons[10]. Although water diffusivity in GP was similar as that in Pu, the original microstructure in GP was far more complex, which was reflected by the significantly larger kurtosis values. Therefore, later structural modification induced by iron deposition was not as prominent as in Pu.

Conclusion: In deep gray matter such as GP and Pu, iron content increased substantially with aging. In Pu, such age-related iron deposition deterred water diffusion along radial direction and increased diffusional directionality. In GP, however, iron accumulation had nearly no effect on absolute diffusivity and merely small effect on diffusional directionality. The differences of iron-related microstructural changes in GP and Pu were caused by their distinct degrees of complexity in microstructure. The original tissue structure of GP was far more complex than that of Pu, therefore, iron-related effect was more prominent in the latter while nearly unnoticeable in the former.

References: [1] Bilgic, et al. Neuroimage. 2012;59(3):2625-35. [2] Pfefferbaum, et al. Neurobiol Aging. 2010;31(3):482-93. [3] de Rochefort, et al. Magn Reson Med. 2010;63(1):194-206. [4] Jensen, et al. Magn Reson Med. 2005;53(6):1432-40. [5] Lu, et al. NMR Biomed. 2006;19(2):236-47. [6] Li, et al. Neuroimage. 2011;55(4):1645-56. [7] Liu, et al. NMR Biomed. 2011;24(9):1129-36. [8] Liu, et al. Neuroimage. 2012;59(3):2560-8. [9] Haacke, et al. Magn Reson Imaging. 2005;23(1):1-25. [10] Sato, et al. J Comp Neurol. 2000;417(1):17-31.