Quantitative Susceptibility Mapping in Human Brain with Normal Aging

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INTRODUCTION: Magnetic susceptibility changes due to iron deposition in deep brain nuclei are an important characteristic of aging.[1] Iron is deposited in the brain via a number of mechanisms including leakage of blood from the vascular system. Iron deposition is expected in both neurodegeneration [2] and normal aging.[3] The spatial and temporal variation of iron deposits can be identified and measured using quantitative susceptibility mapping (QSM).[2] In this study, we use QSM to quantify susceptibility changes in the external and internal globus pallidus (GP), putamen, caudate nucleus (CN) and red nucleus (RN); five regions that have been previously suggested to have iron changes due to aging.[3] Specifically, we compare quantitative susceptibility values between groups of young and elderly, cognitively normal subjects.

METHODS: Forty-seven, normal, individuals (age = 51 years ± 15 years, mean ± standard deviation, SD) were imaged on a 3-T MR scanner (Discovery 750; General Electric Healthcare; Waukesha, WI) and divided based on median age into young (<51 years, n = 23) and elderly (≥51 years, n = 24) groups. Exclusion criteria included: a) history of neurological disorders, b) MR incompatibility, c) claustrophobia, and d) mild cognitive impairment (Montreal Cognitive Assessment (MoCA) score < 27). Image acquisition parameters were multi-echo gradient-recalled sequence: TE1 =2.1 ms; 8 echoes at ΔTE = 2.4 ms; TR = 22 ms; voxel size = 1 mm^3; and acquisition matrix = 256×256×128. Data underwent skull stripping,[6] 3D phase unwrapping [7] and dipole fitting.[4] The magnetic field was calculated using phase data and the background field was removed using the RESHARP technique.[8] A regularized deconvolution method was utilized to generate QSM data. The International Consortium of Brain Mapping (ICBM) brain atlas was registered to the subject native space using symmetric diffeomorphic image registration [9] and used to anatomically segment the QSM data into regions. Two-tailed student's t and Mann-Whitney tests were used to compare young and elderly groups and female (n = 25) and male (n = 22) groups. A Kruskal-Wallis test was used to compare regions of interest (external and internal GP, putamen, CN and RN). Differences with a p-value < 0.05 were considered to be statistically significant. Regional susceptibility data were analyzed versus age using dichotomization based on median age, linear regression and Spearman's rank correlation tests. Results are reported as mean ± SD in units of parts per billion (ppb).

RESULTS: Susceptibility was significantly different for all regions of interest across all patients (p < 0.01). External GP showed the highest susceptibility (270 ppb ± 79 ppb), followed by RN (268 ppb ± 105 ppb), internal GP (200 ppb ± 82 ppb), putamen (144 ppb ± 53 ppb), and CN (143 ppb ± 40 ppb). Comparison between young and elderly groups showed that the elderly group had a higher average susceptibility in the internal GP (32.5% larger, p = 0.023), putamen (23.5%, p = 0.048), and external GP (23.8%, p = 0.011). A trend towards significance with aging was seen in the RN (20.1%, p = 0.133) and no significant changes were found in the CN (1.0%, p =0.895). Linear regression of susceptibility against age showed positive slopes in internal GP (2.62 ppb/year, p = 0.006), putamen (1.60 ppb/year, p = 0.001), external GP (2.45 ppb/year, p = 0.002), RN (2.99 ppb/year, p = 0.133) and CN (0.14 ppb/year, p = 0.730, see Figure 1). Age was significantly correlated with susceptibility changes in the internal GP (ρ = 0.376, p = 0.014, Spearman test), putamen (ρ = 0.515, p < 0.001), external GP (ρ = 0.453, p = 0.002), and RN (ρ = 0.427, p = 0.006). The correlation between age and susceptibility in CN was not significant (ρ = -0.014, p = 0.925). No significant differences in susceptibility were found between female and male subjects in any of the regions: internal GP (p = 0.558), putamen (p = 0.314), external GP (p = 0.377), CN (p = 0.742), and RN (p = 0.590).

DISCUSSION AND CONCLUSIONS: QSM highlighted spatial susceptibility differences in multiple deep grey matter regions due to iron deposition associated with the normal aging processes. Regional susceptibility changes in the human brain have been previously investigated in young and elderly groups [5] and over the lifespan.[1] This study addresses some of the limitations of previous studies. Specifically, the current study a) performed MoCA test to all subjects and applying a stringent threshold to ensure exclusion of any subject with below normal cognition; b) used an atlas-based approach to objectively study regional changes; and c) included subjects with over a wide age range. We found a significant and monotonic increase in susceptibility throughout lifetime in most regions. These increases are consistent with previous work [1,5] in iron-rich deep grey matter nuclei. The putamen and the internal and external GP susceptibilities were found to be particularly sensitive to age. In the RN, a positive correlation was found between susceptibility and age, but the regression results were not significant. While a previous study [1] found difference between male and female subjects, we found no significant gender effects, even after age matching. Quantification and location of susceptibility variation characterizes iron deposition in deep nuclei with age may improve understanding of healthy and disease-related functional changes associated with cognitive decline. Quantifying susceptibility changes with normal aging will allow for distinguishing the pattern of iron-related susceptibility changes in neurodegenerative diseases of aging from healthy aging.

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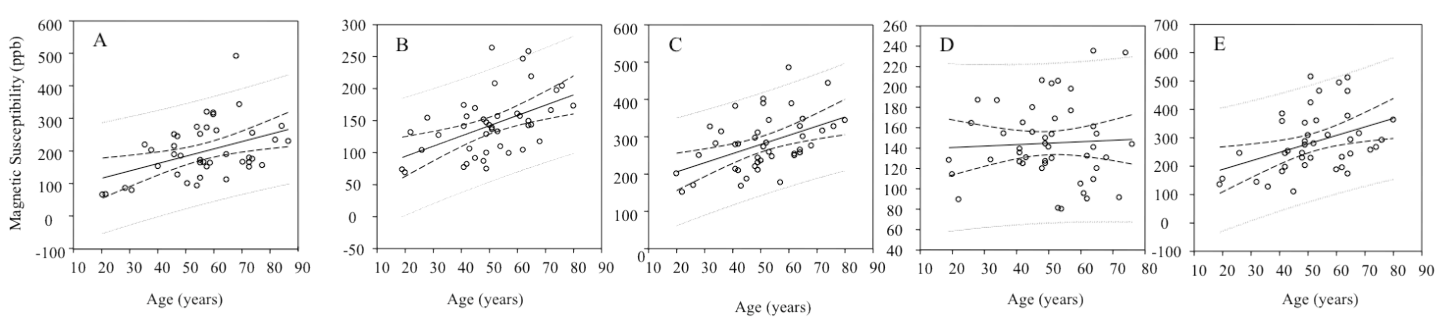

Figure 1. Magnetic susceptibility significantly increased with age in the internal GP (A), putamen (B), external GP (C) but did not reach significance in the CN (D) and RN (E). The dashed and dotted lines represent 95% confidence and prediction intervals, respectively.