Brain Magnetic Susceptibility is Increased with Cognitive Impairment in a Community Population

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TARGET AUDIENCE: This research is targeted to magnetic resonance (MR) scientists and clinicians interested in diagnosis and management of diseases involving cognitive decline, such as Alzheimer's disease and amnestic mild cognitive impairment. Also MR scientists and technologists who are involved in the design and application of quantitative susceptibility mapping (QSM) may benefit from this study.

PURPOSE: The ability to measure changes in regional iron concentration *in-vivo* may provide insights to understand sequence of events that leads to cognitive impairment and may offer a biomarker for early detection of cognitive impairment. We hypothesize that susceptibility in selected regions of the brain is lower in normal compared to cognitively impaired but otherwise healthy subjects, after controlling for age-related changes.

METHODS: Forty-nine presumed normal individuals (22 male; 51 ± 15 yr, mean ± standard deviation) were imaged on a 3-T MR scanner (Discovery 750; General Electric Healthcare, Wauksesha, WI). Exclusion criteria were: 1) history of neurological disorders, 2) MR incompatibility, and 3) claustrophobia. A pre-scan Montreal cognitive assessment (MoCA) test was used to divide the group into normal (MoCA ≥ 26; $n = 40$) and cognitively impaired (MoCA < 26; $n = 9$) groups.[1] QSM images were generated using a custom program, Cerebra QSM (Calgary Image Processing and Analysis Centre, Alberta, Canada).[2] Image processing for QSM included: skull stripping, 3D phase unwrapping [3] RESHARP background field removal [4] and regularized deconvolution.[5] Cerebrospinal fluid was used as the background susceptibility reference.[6] The external and internal globus pallidus (eGP and iGP), putamen (P), caudate nucleus (CN), red nucleus (RN) and thalamus (T) were identified on the International Consortium of Brain Mapping (ICBM) brain atlas. Regional masks were registered to susceptibility maps using symmetric diffeomorphic image registration.[7] Kolmogorov-Smirnov normality, Mann-Whitney rank sum, analysis of covariance (ANCOVA) and Spearman correlation tests were used for statistical analysis. A p-value <0.01 was considered statistically significant to control for multiple region comparisons.

RESULTS: Regional susceptibility was normally distributed in the P, iGP, eGP, RN, and T ($p > 0.20$) but not in the CN ($p = 0.037$). The median (inter-quartile range) susceptibility for each region across all subjects is reported in Table 1. Susceptibility was significantly higher in the cognitively impaired group than the normal group in four regions (P, iGP, eGP and CN, all $p < 0.001$) and trended toward significance in T ($p = 0.077$). After controlling for age, susceptibility remained significantly higher in P, iGP, eGP and CN (Table 1 third column and Figure 1A). Significant correlation between regional magnetic susceptibility and MoCA score was found in P, iGP and eGP (Table 1 fourth column and Figure 1B).

DISCUSSION: This study provides initial evidence for the potential value of MR-derived susceptibility as a biomarker for differentiating early cognitive decline from normal aging after controlling for age. Despite a relatively small sample size, significant differences were found between normal and cognitively impaired groups drawn from an otherwise healthy population. These regional differences were located in areas of known iron concentration change in aging [8,9] and neurodegenerative diseases that involve cognitive decline such as Alzheimer's disease.[10,11] While the applied threshold for normal cognition in MoCA is well established,[1] significant negative correlations between susceptibility and MoCA score ensures that the observed pattern is not dependent on the choice of MoCA dichotomization threshold. Our finding highlights the potential value of susceptibility imaging as a biomarker in identifying early cognitive decline in presumed normal subjects. The methodology and findings also suggest that the QSM technique is ready for larger-scale and potentially clinical analysis.

CONCLUSION: Quantitative susceptibility mapping distinguished in multiple important brain regions (after controlling for age) subjects who achieved a MoCA score < 26 drawn from a presumed normal population.

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Table 1. Summary of results indicating the distribution of susceptibility across all patients, ANCOVA comparison between normal and cognitively impaired groups, and correlation of regional susceptibility with MoCA.

Region	Susceptibility in ppm Median (interquartile)	ANCOVA *p-value*	Correlation with MoCA coefficient (*p-value*)
P	0.130 (0.083 – 0.181)	**0.001**	**-0.345 (0.008)**
iGP	0.346 (0.294 - 0.403)	**0.007**	**-0.494 (<0.001)**
eGP	0.369 (0.315 - 0.416)	**0.009**	**-0.613 (<0.001)**
CN	0.076 (0.058 - 0.102)	**<0.001**	-0.266 (0.033)
RN	0.142 (0.093 - 0.185)	0.961	-0.235 (0.104)
T	0.063 (0.037 - 0.093)	0.161	-0.058 (0.692)

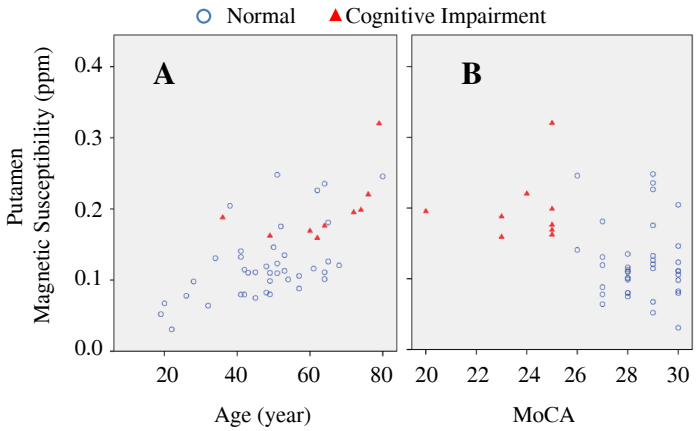

Figure 1. Scatter plots of magnetic susceptibility versus age (A) and MoCA (B) for putamen as an example region.