Magnetic susceptibilities of iron rich gray matter nuclei are negatively correlated with various brain functions in healthy adults

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AUDIENCE: Researchers interested in quantitative susceptibility mapping (QSM), brain iron, and normal aging.

INTRODUCTION: In the human brain, several deep gray matter structures, including putamen, globus pallidus, substantia nigra, and etc, have much higher iron contents than surrounding tissues. Iron is essential for normal brain functioning. However, excessive iron can stimulate oxidative damage through free radical generation, which is believed to be associated with neurodegeneration in e.g. Parkinson's disease, Huntington's disease, and aging. In this study, we correlated the magnetic susceptibility – a surrogate marker of brain iron – of these gray matter structures with several clinical measures of brain function in 135 healthy adults aged 40~83 years, to explore the potential impact of high brain iron on various brain functions during normal aging.

MATERIALS and METHODS Human brain imaging**: A** total of 135 participants were included in this study. The age of study participants was between 40 and 83 years with a mean age of 65±10 years. There were 80 (59%) women and 55 (41%) men. Each participant was scanned on a 3T scanner using a spoiled 3D multi-echo gradient-echo sequence. The scan parameters were: in-plane resolution = 0.9 x 0.9 mm², matrix = 256 x 208, flip angle = 20°, TE of first echo = 4.92 ms, echo spacing = 4.92 ms, and number of echoes = 6. The slice thickness was either 4 mm or 2 mm with TR = 68 ms and TR = 35 ms, respectively. T1-weighted images of the same participants were acquired using a 3D MPRAGE sequence with the following parameters: data matrix = 224x256x176, 1 mm isotropic resolution, flip angle = 9°, TI = 900 ms, TE = 2.19 ms and TR = 1900 ms.
Image analysis: Brain tissue magnetic susceptibility was obtained as described previously (1, 2). The susceptibility maps were nonlinearly registered to the standard template in FSL (MNI152_T1_1mm) using the corresponding T1 images. An atlas containing the putamen (PU), globus pallidus (GP), caudate nuclei (CD), red nuclei (RN), substantia nigra (SN) and dentate nuclei (DN), was created from the mean susceptibility maps. This atlas was then transformed back to the subject space. The ROIs of each subject was visually examined and minor refinement of the ROIs was made when necessary. The susceptibility values of the selected ROIs were averaged and directly used for correlation with clinical test scores.
Brain function tests and multiple linear regression: A series of tests target in selected cognitive functions, were performed within one month of MRI scan, including Purdue-Pegboard-Test (motor function), Walking speed test, Trail Making Test B (visual search, scanning, speed of processing, mental flexibility and executive functions), Wisconsin Card Sorting Test (WCST, executive functions), Digit Span Test (transit memory) and Word fluency test. We correlated the clinical scores of brain functions (y), with magnetic susceptibility of the gray matter nuclei (χ) and participant age using the following multiple linear regression model: $\mathbf{y = \beta1 \bullet \chi + \beta2 \bullet age + \beta3}$. The same regression analysis were performed for all subjects (All), male (M) and female (F) groups, respectively. $P<0.05$ is considered statistically significant.

RESULTS and DISUSSION: Fig. 1A, B shows the two representative correlations between clinical scores and susceptibility of DN and GP. The decreased clinical cores with susceptibility can be seen in Fig. 1B. From Fig. 1C-D, the significant negative correlation between the Purdue Pegboard test with susceptibility of GP and RN were apparent. This correlation is independent to the age, since the age is also included in the correlation. Table 1 summarized all the significant correlations between the clinical scores and the magnetic susceptibility of the gray matter structures. Strikingly, all but one significant correlation are negative.
These results suggest that magnetic susceptibility of iron rich gray matter nuclei is a potentially valuable indicator of functional decline, even in participants without clinical signs of neurodegeneration.

Table 1. Summary of the statistically significant correlations between magnetic susceptibility of brain structures with clinical functional test scores

	CN	PU	GP	SN	RN	DN
Purdue Pegboard Test		M, F	F		All, M, F	
Walking speed	M				All, M	M
Trail making test B			All			
Digit span		F	M	All, M		
Word fluency			All			
WCST		F	F		F	All

Note: All correlations are negative except the positive correlation between the assembly score of Purdue Pegboard Test and susceptibility of PU in male participants as highlighted with underline.

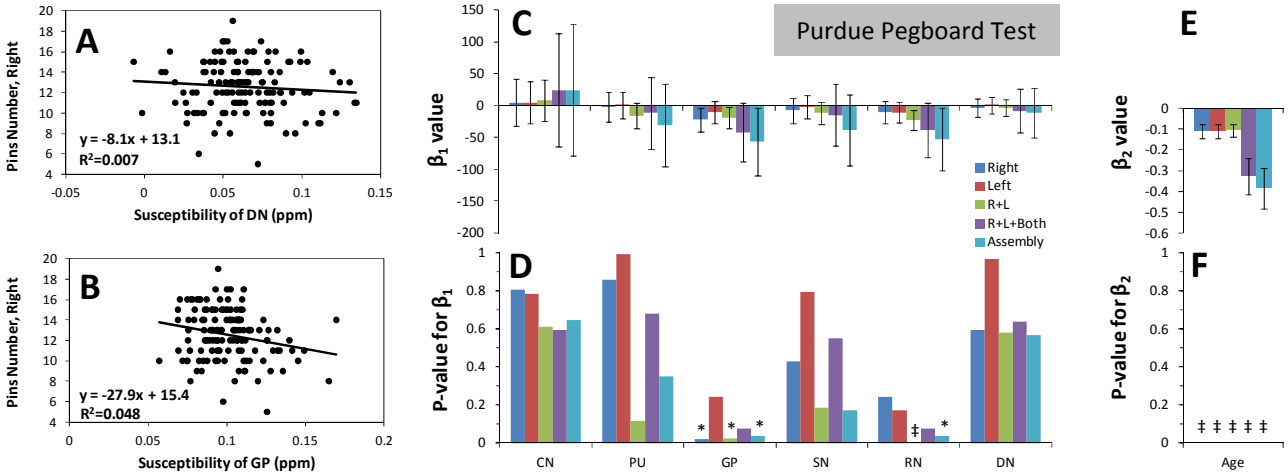

Fig. 1. The correlation of the number of pins by the right hand in the Purdue Pegboard test with the magnetic susceptibility of DN (A) and GP (B); Correlation between motor function as assessed by Purdue Pegboard test and tissue magnetic susceptibility. The upper panels (C, E) show the coefficients from the multiple linear regression model and the lower panels (D and F) show its corresponding significance level.

REFERENCES: [1] Li et al. NeuroImage. 2011; 15; 55:1645. [2] Li et al, Human brain mapping, doi: 10.1002/hbm.22360.