Magnetic susceptibility of the ageing brain is correlated with motor function decline

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INTRODUCTION: Recent studies have shown that magnetic susceptibility of brain tissues reflects myelin concentration in the white matter (1) and iron deposits in the deep nuclei (2, 3, 4). Maintaining proper levels of myelin and iron is essential for normal brain development and aging. For example, iron deficiency anemia among infants has been shown to predict performance in cognitive test at later developmental periods. Iron content of the brain increases with age, and iron has been shown to accumulate in senile plaques and neurofibrillary tangles. Increased levels of iron have also been found in the brains inflicted with Parkinson's disease. Given that magnetic susceptibility increases with increased iron deposit, it is likely that magnetic susceptibility is correlated with cognitive performance. In this retrospective study of a group of 126 healthy subjects, we found that quantitative magnetic susceptibility values of the brain nuclei are highly correlated with a number of cognitive test scores. For instance, increased susceptibility value is shown to be associated with deteriorated motor skill which is particularly relevant to Parkinson's disease. If the results are further validated in diseased populations, magnetic susceptibility could be proven to be a potential useful quantitative biomarker for certain neurological diseases and cognitive impairment.

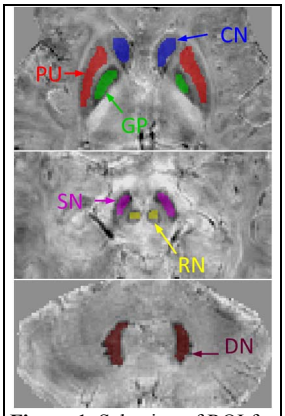

Figure 1. Selection of ROI for susceptibility and labels.

METHODS: A group of 126 healthy adult volunteers ranging from age 40-83 y/o (64±11 y/o) was included in this study. Each subject went through a set of MRI scans on a 3T scanner with a 12-channel receive array coil. A 3D multi-echo gradient-echo sequence was used with the scan parameters: FOV = 23.0 x 16.6 cm^2, matrix = 256 x 208, BW = 320 Hz/px, slice thickness = 4 mm, TE of first echo = 4.92 ms, echo spacing = 4.92 ms, TR = 60 ms, and number of echoes = 6. Phase images were extracted from the complex 3D images. Phase wraps were removed with a Laplacian based algorithm. Background phases that were generated by magnetic sources outside the brain were eliminated by a spherical-mean-value (SMV) based algorithm. Removing the background phase is critical for obtaining the phase generated by the brain tissue itself. Quantitative susceptibility values were calculated based on an LSQR algorithm which resulted in high-quality susceptibility maps with few artifacts.

Each volunteer also completed a series of tests for cognitive functions. A brief 30-point questionnaire test – the mini mental score (MMSE) – was used to screen for cognitive impairment. All volunteers have a score higher than 25 and thus considered normal. The test scores from Trail Making Test B, Digit Span Test, Purdue-Pegboard-Test, Wisconsin Card Sorting Test and Word Fluency Test were recorded. The scores were first correlated with age and magnetic susceptibility of selected regions of interest separately with a linear regression model that gives regression coefficients and statistics. A general linear model was then used to determine the relative significance of age and susceptibility and their interference. ROI for susceptibility were drawn in the red nucleus (RN), the substantia nigra (SN), the globus pallidus (GP), the putamen (PU), the caudate nucleus (CN) ad the dentate nucleus (DN) (Fig. 1).

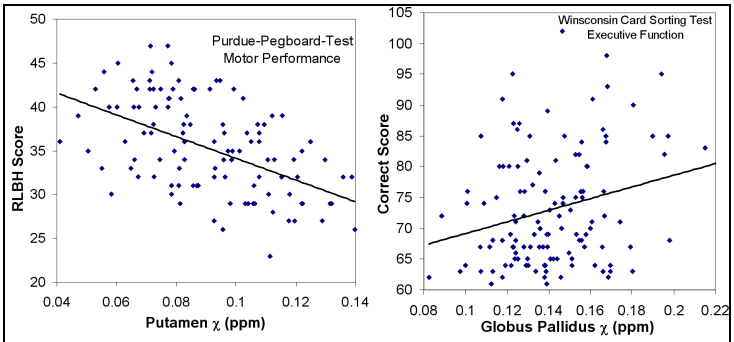

Figure 2. Examples of the correlation between cognitive test score and brain magnetic susceptibility. Left: Purdue-Pegboard test score is negatively correlated with the susceptibility of the putanen. Right: Wisconsin test is positively correlated with the susceptibility of the globus pallidus.

RESULTS: Of the six anatomical regions analyzed, the globus pallidus and the putamen demonstrated the most significant correlation with the cognitive test scores. Putamen is most highly correlated with the Purdue-Pegboard Test for motor function with a negative correlation coefficient. An example scatter plot of the RLBH score of the Purdue Test vs. the susceptibility of the putamen is shown in Fig. 2. The globus pallidus, on the other hand, is more associated with Wisconsin Test score. Higher susceptibility in the GP appears to be positively correlated with executive function (Fig. 2). The substantia nigra and the dentate nucleus are mostly uncorrelated or weakly correlated in limited cases with all the test scores. The red nucleus only shows significant correlation with the Word Fluency Test ($p = 0.04$). This seems to support previous belief that the red nucleus may participate in language functions (5).

Table 1 summarizes the statistics of regression between the selected nuclei and various motor skill test scores. It is striking that nearly all correlation coefficients are negative with one exception of RN vs. left-hand score at 0.729. The statistical significance of the correlation varies with the highest significance observed for the putatmen.

Statistics		Purdue-Pegboard-Test (Motor)				
		RH	LH	BH	RLBH	Assembly
RN	coefficient	-3.044	0.729	-6.138	-5.881	-15.945
	p-value	0.652	0.911	0.328	0.740	0.435
SN	coefficient	-1.083	-4.294	-5.977	-4.763	-14.178
	p-value	0.888	0.563	0.403	0.813	0.542
GP	coefficient	-13.718	-10.983	-13.632	-35.603	-37.152
	p-value	0.061	0.122	0.045	0.064	0.094
PU	coefficient	-27.794	-23.923	-26.123	-76.978	-80.270
	p-value	1.5E-04	8.0E-04	1.3E-04	6.0E-05	3.0E-04
CN	coefficient	-16.906	-17.899	-16.507	-48.299	-44.956
	p-value	0.126	0.094	0.108	0.095	0.179
DN	coefficient	-4.871	-1.085	-3.034	-11.403	-4.557
	p-value	0.394	0.845	0.569	0.448	0.792

Table 1. Susceptibilities of all six nuclei are negative correlated with motor function. PU shows the highest statistical significance (red p-values). RH: right hand; LH: left hand; BH: both hands; RLBH: right + left + both hands.

DISCUSSIONS AND CONCLUSIONS: In the normal brain, iron is believed to be most abundant in ferritin within oligodendrocytes and microglia. It is also present in neurons, particularly in the substantia nigra and globus pallidus. Abnormal iron concentration has been implicated in several major neurological diseases including Alzheimer's disease, Parkinson's disease, Huntingon's disease and multiple sclerosis. In addition, iron deficiency during development can result in irreversible life-long cognitive and motor impairment. Assessing brain iron level thus has significant clinical implication. Previous studies have suggested magnetic susceptibility as a quantitative measure for iron deposit in the brain. Our study further revealed a strong correlation between magnetic susceptibility and certain cognitive functions in healthy adults. Magnetic susceptibility of the globus pallidus and putamen appear to be associated with executive function of the frontal lobe as measured by the Wisconsin Test. In healthy adults, changes in magnetic susceptibility are primarily driven by ageing as demonstrated by the analysis based on the general linear model. In patients with certain neurological diseases, our data would predict that increased magnetic susceptibility in the deep nuclei could provide important information of severity of the symptoms. For example, in Parkinson's disease, elevated magnetic susceptibility values in the substantia nigra, the putamen and the globus pallidus would be negatively correlated with motor function. Therefore, understanding the temporal evolution of iron imbalance in relation to neuronal loss and cognitive impairment would provide important information on disease pathogenesis. To conclude, our study raised the possibility of using magnetic susceptibility as a marker for disease progression and cognitive decline.

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