Measurement of iron concentration in human brain using Quantitative Susceptibility Mapping (QSM): correlation with age

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Introduction: Excessive iron deposition is often associated with neurodegenerative disorders, such as Parkinson's disease (PD), Alzheimer's disease and Huntington's Chorea [1]. Quantitative measurement of regional iron deposition in the brain may help with diagnosis and assessment of disease progression. In order to use iron deposition as a new biomarker to stratify the stages of diseases, it is necessary to establish a baseline of iron deposition from normal volunteers.

In the past, post-mortem studies have shown increasing iron deposition with increasing age, most noticeably in the striatum [2]. Similar conclusions were made from *in vivo* studies of healthy volunteers. In MRI, Field Dependent R2 Relaxation Increase (FDRI) [3] and corrected phase images [4] have demonstrated a correlation between phase shift or R2 relaxation increases with age in putamen. However, it would be better to measure the exact amount of iron from MRI as has been done in postmortem investigations.

If we assume that the major paramagnetic substance in brain is Fe^{3+}, then at body temperature, 310°K, susceptibility has a linear relationship with iron χ = 117ppmL/mol×(iron concentration) [5-6] . In this study, we used MR Quantitative Susceptibility Mapping (QSM) to measure the mean susceptibility values in putamen from 100 healthy volunteers. A strong linear correlation between the measured mean susceptibility and age was observed. Our results indicate that the Fe^{3+} concentration increases 0.57mg/100g fresh weight per decade, and iron concentrations in senior volunteers are 3.3±1.1mg/100g, which agreed well with post-mortem measurements [8].

Materials and Methods:

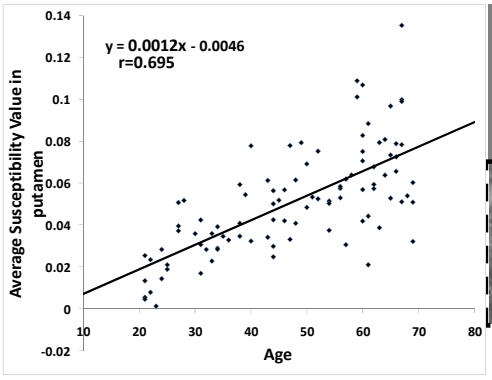
Subjects: 100 adult volunteers without history of trauma, neurological or psychiatric disease were recruited. Informed consent was obtained from all subjects. The sample consisted of 100 healthy adults ranging in age from 20 to 79 years (mean=47, SD=15, M=49, F=51).

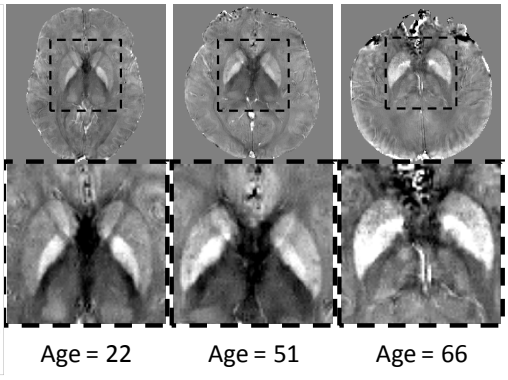
Data acquisition: Experiments were conducted at 1.5T (GE Signa EXCITE 14.0) using a 3D spoiled gradient echo sequence with flow compensation. Axial slices were acquired with FOV=24cm, matrix was down sampled to 256×256×40 from 512×512×40, slice thickness= 3mm, bandwidth=31.25×2kHz, flip angle=30˚, TR=53ms and TE=40ms. Both magnitude and phase images were saved for off-line processing. Additional axial T1 and T2 weighted images were also acquired to screen for space-occupying lesions and cerebrovascular diseases.

Data processing: Quantitative Susceptibility Maps (QSM) of the entire brain were generated using a weighted gradient regularization method, which calculates the arbitrary susceptibility distributions from the local magnetic fields measured from MR phase images. The original ill-posed field to source inverse problem was solved by taking advantage of the magnitude images, where uniform regions were favored to have uniform susceptibilities. This regularized QSM [7] was successfully applied to all cases. Computational time for each case averaged 21min using MATLAB codes on a Pentium-4 3.2 GHz PC.

ROI identification: The mean susceptibility values of putamen were measured on the QSM. A radiologist, blinded to the subject's information, was asked to 1) choose the slice optimally depicting putamen and then 2) delineate putamen boundary. An automatic eroding algorithm was applied to erode the boundary by 2 pixels to avoid partial volume effects. The area after erosion was defined as the ROI. Average susceptibility values were subsequently measured within this ROI.

Results: A strong linear correlation was obtained between the average susceptibility value in putamen and age ($r=0.695$, $p<0.001$). Susceptibility increased 0.012ppm per decade, which corresponded to 0.57mg/100g/decade if we attribute the susceptibility to Fe^{3+}. Average susceptibility value in putamen of senior volunteers (Age>60) is 0.069±0.024ppm, corresponding to 3.3±1.1mg/100g. Four representative reconstructed susceptibility maps from different ages were shown.





Discussion and conclusion: These results demonstrate that Fe^{3+} deposition measured in putamen using MR QSM increases with age similar to what has been observed in post-mortem studies. The quantification of Fe^{3+} in older volunteers is in excellent agreement with a post mortem study of control brains (3.1±0.56mg/100g) [8]. Although Fe^{3+} is one contributor to the total non-haemin iron deposition (13.32mg/100g) [6], it might be more closely related to PD [8]. Our regularized QSM technique robustly processed 100 cases. A complete study requires a more thorough analysis of other brain regions.

Ref: [1]Zecca et al. Nat Rev Neurosci:5(11):863-73; [2] Hallgren. J Neurochem:3:41-51; [3] Pfefferbaum et al. J Neurochem:47:493-500; [4] Xu et al. Neuroimage:40:35-42; [5] Kahn. Molecular magnetism. [6] Liu et al. MRM:61:196-204; [7] de Rochefort et al. MRM: *in press*; [8] Riederer et al. J Nuerochem:52:515-520.