Correlation of change in phase and R2* with putative iron content in deep gray matter of healthy adults

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Introduction: Iron has long been recognized to play a key role in brain function such as in oxygen transport, neurotransmitter synthesis, electron transfer and myelin production (1). Despite the positive implications of iron, in its free ferrous form, iron is known to be toxic and lead to free radical production. Recently, there has been a renewed interest in the role of iron in neurodegenerative diseases such as aging, multiple sclerosis, Parkinson's disease, and other diseases. Developing and improving magnetic resonance imaging (MRI) has been an important task for decades, trying to establish a correlation between its signal and iron concentration. A variety of methods have been employed, including T2, T2* and T2' as well as Field Dependent R2 Increase and Susceptibility Weighted Imaging (SWI). Deep gray matter structures accumulate ferritin at different rates throughout different ages. It is believed and often quoted (2) that iron increases quickly with age and then levels off or increases more slowly. Further, it has been shown that there are major iron deposits in the form of ferritin associated with the basal ganglia (3). Among these MR methods for detecting iron content, T2' is more robust and better for large amounts of iron content but not as good as phase for small amounts of iron. SWI is a method that can combine the two types of information from the local magnetic field. To data, people analyze the entire structure of interest which may reduce the sensitivity to more subtle changes in iron content when the region containing the iron is a small fraction of the total area. In this project we applied a two region analysis to avoid this problem and to study not only iron increases but the overall area of iron content as a function of age.

Materials and methods: One hundred **(**100) healthy adults (20-69 yr.; mean = 43 yr) were evaluated for this study. A fully flow-compensated, three dimensional, high in-plane resolution, gradient-echo susceptibility weighted imaging (SWI) sequence was used. All data including magnitude and phase images were acquired on a GE 1.5T scanner with a resolution of 0.60 mm × 0.75mm × 3mm, TE = of 40ms, TR = 53ms, FA = 20°, BW = 31.25 Hz/pixel, and matrix size = 384 × 320. The original magnitude and high pass filtered (64×64) phase data were evaluated as proxy variables for iron content in the substantia nigra, red nucleus, globus pallidus, putamen, caudate nucleus, thalamus and pulvinar thalamus. They were all measured bilaterally. Each structure was broken into two parts, a low iron content region (RI) and a high iron content region (RII). These regions were separated using thresholds set from the data in ref. 4. Linear regression was performed for the iron measurements as a function of age.

Results: Both magnitude and phase data in both RI and RII showed an increase in iron content with age (Figures 1, 2, 3). However, the high iron content region revealed two new pieces of information: both the average iron content per pixel and the area (Figure 4) of RII increased with age. Further, the rate of increase in iron appeared to increase after the age of 40, a new finding in this field of iron quantification (Figure 3).

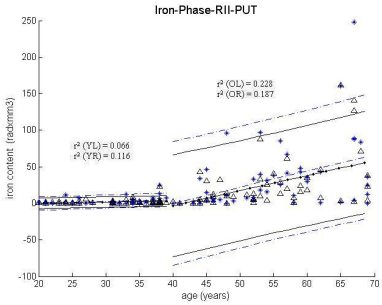

Fig 1. Iron content measured in phase in RII as a function of age divided into two intervals in putamen.

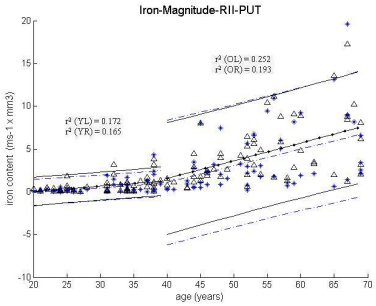

Fig 2. Iron content measured in magnitude in RII as a function of age divided into two intervals in putamen.

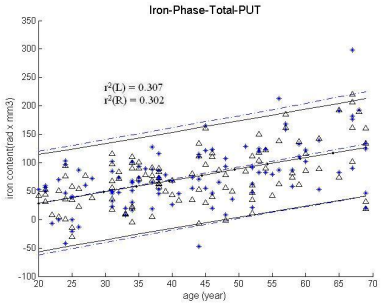

Fig 3. The total iron content in putamen measured in phase in RII as a function of age.

Discussion and Conclusion: Phase aliasing could lead to an underestimate of the total area of RII but overall we found this not to be a problem. A multi-echo SWI approach would be the best way to handle this problem in the future. In conclusion, we have introduced a two-region of interest analysis for iron quantification which appears to be a much more sensitive means to evaluate iron content changes over time. Contrary to current belief, iron content increases do not level off with age but rather continue growing.

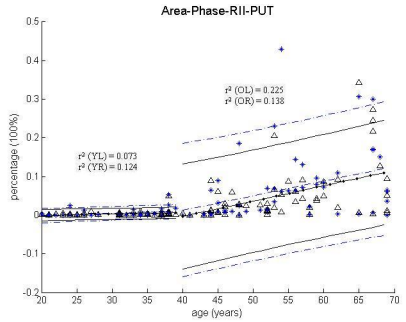

Fig 4. Percentage area of RII in phase as a function of age divided into two intervals in putamen.

References: 1) Stankiewicz J et al. Neurotherapeutics 2007;4:371-386. 2) Hallgren B, Sourander P. J Neurochem 1958;3(1):41-51. 3) Morris CM et al. 1994;3(4):267-275 and 4) Haacke EM et al. J Magn Reson Imaging 2007;26(2):256-264