Iron quantification in normal aging brain accessed by the MR signal decay in the static spin dephasing regime of spherical perturbations

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Introduction: Quantification of iron deposits in the brain has great potential for the diagnosis of diseases related to pathological iron deposition, such as Alzheimer's disease or Parkinson's disease. In vivo iron quantification may help to better understand the pathogenesis and progression of these diseases and to monitor treatment response **(1)**. It has been successfully demonstrated that MRI is able to quantitatively detect iron deposition by changes in transverse relaxation rates (R2*=R2+R2') and signal phase **(2)**. Recently, quantitative susceptibility mapping (QSM) was used to further extract the underlying magnetic susceptibility $\Delta\chi$ from the MR signal phase information which allows to draw direct conclusions on the relationship between the true iron content (IC) and $\Delta\chi$ (Fig. 1) **(3)**. The purpose of this study was to demonstrate that true IC can be derived from the transverse relaxation rates by using the analytical model of the static spin dephasing regimen of spherical perturbations **(4)**. The established control values of IC in the normal aging brain will serve as control for future clinical studies of neurodegenerative diseases at our institution.

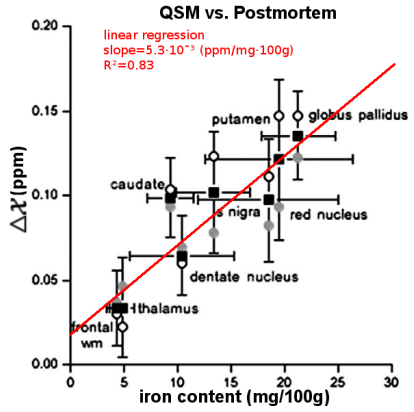

Fig. 1*: Calibration curve of $\Delta\chi$ with iron content of wet weight tissue. Linear regression obtained $\Delta\chi = 5.3 \cdot 10^{-3}$ ppm/mg·100g. Figure modified from* ***(3)****.*

Materials and Methods: 64 healthy volunteers (34f, 29m, mean age 39y, 18y-75y) were scanned using a 3T whole body MRI and a 20 channel receive only head coil. Quantitative R2 and R2* data were acquired with multi echo turbo spin echo (mTSE) and multi echo gradient recalled echo (mGRE) sequences, respectively. Sequence parameters were: mTSE: TEs = 12, 86, 160 ms, TR = 5580 ms, tubo factor 5, mGRE: TEs = 3.6, 8.4, 13, 18, 23 ms, TR = 748 ms, mTSE/mGRE: FOV = 240 x 240mm^2, matrix = 128 x 128, slice thickness = 5 mm, 27 slices. Individual R2 and R2* maps were calculated by non-linear fitting of mono-exponential decay curves to the multi echo data, but R2* maps were corrected for macroscopic B_0 field inhomogeneities by an additional *sinc* term **(5)**. B_0 field maps were derived from phase images of the mGRE data. R2' maps were calculated by subtracting R2 maps from realigned R2* maps (FSL FLIRT tool). ROIs were automatically segmented from anatomical MPRAGE data (FreeSurfer) and realigned to R2' maps. Median values of the ROIs were extracted by masking R2' maps with segmented ROIs using MatLab. IC was calculated from R2' values using equation 11 of Yablonskiy's and Haacke's work on NMR signal behavior in magnetically inhomogeneous tissue **(4)**. Solving this equation for the volume fraction which is assumed to equal IC in our case, we obtain:

$$IC = 9 \cdot \sqrt{3} \cdot R2' \cdot (2\pi \cdot \gamma \cdot \Delta\chi \cdot B_0)^{-1}. \qquad [1]$$

γ is the gyromagnetic ratio ($2.675 \cdot 10^8$ rad·s^{-1}·T^{-1}), $\Delta\chi$ the magnetic susceptibility difference of the iron deposits.

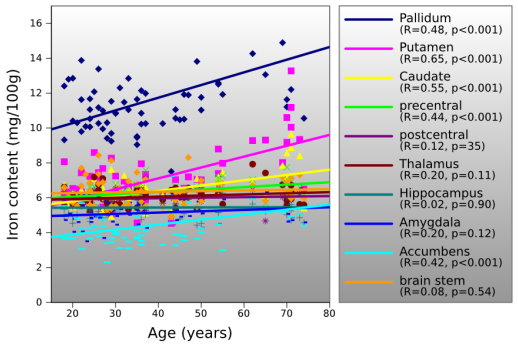

Fig. 2*: Iron content of wet weight tissue (Eq. 1) over age. Person's correlation coefficients and p-values are given in the figure legend.*

Table 1*: Slopes and intercepts with 95% confidence intervall (CI) of linear regression of iron content over age.*

Region	Slope (95%CI) (10^{-3}mg/100g/y)	Intercept (95%CI) (mg/100g)
Precentral	13.87 (6.67-21.07)	5.78 (5.48-6.08)
Postcentral	3.12 (-3.51-9.76)	5.85 (5.57-6.13)
Thalamus	6.36 (-1.57-14.29)	5.81 (5.48-6.15)
Caudate	30.39 (18.63-42.15)	5.18 (4.69-5.68)
Putamen	62.32 (43.63-81.01)	4.62 (3.84-5.41)
Pallidum	72.65 (39.36-105.93)	8.83 (7.44-10.23)
Hippocampus	0.58 (-8.32-9.49)	5.42 (5.04-5.79)
Amygdala	7.73 (-2.08-17.55)	4.84 (4.43-5.26)
Accumbens	28.63 (12.89-44.38)	3.32 (2.66-3.98)
Brain Stem	3.64 (-8.17-15.45)	6.20 (5.71-6.70)

Results: The magnetic susceptibility difference of the iron deposits $\Delta\chi$ was found to be $5.3 \cdot 10^{-3}$ ppm/mg iron in 100g tissue by linear regression between $\Delta\chi$ and IC measurements (Fig. 1). Figure 2 shows the obtained IC by age. The highest IC was found in the pallidum (10-15mg/100g), the lowest in the nucleus accumbens (2.5-5mg/100g). Strong correlation of the IC with age was identified in pallidum, putamen, caudate, precentral cortex and accumbens ($p<0.001$), weak correlation was found in the postcentral cortex, thalamus, hippocampus, amygdala and brainstem ($p>0.1$). Results of linear regression of IC over age, as shown in Table 1, are the basis for normal values of IC of certain age groups.

Discussion/Conclusion: We were able to demonstrate that the analytical framework of Yablonskiy and Haacke **(4)** allows to derive quantitative IC values from R2' data using previous results from QSM **(3)**. Data for IC values are in agreement with those previously reported **(2)**. However, different IC values may be derived with different $\Delta\chi$ calibrations. Therefore, future clinical studies on R2' derived IC values should consistently apply the same $\Delta\chi$ value to be comparable between each other and to the normal values presented here. We propose using a $\Delta\chi$ of $5.3 \cdot 10^{-3}$ ppm/mg·100g.

References: **(1)** Hider RC et al. 2011Metallomics 3:239-49. **(2)** Haake EM et al. 2005MRI 23:1-25. **(3)** Bilgic B et al. 2011 NeuroImage Sep 8 [Epub]. **(4)** Yablonskiy DA et al. 1994 MRM 32:749-63. **(5)** Fernández-Seara MA et al. 2000 MRM 44:358-66.