Age Related Differences in Brain Iron Detected In Vivo at 3T With Quantitative MRI: Comparison of R2, R2' and R2*

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Introduction

Brain iron concentrations increase as part of the normal aging process, with levels typically reaching a plateau at approximately 50 years of age [1]. In disease, elevated iron levels compared to healthy controls (HCs) of the same age, have been reported in Multiple Sclerosis, Alzheimer's Parkinson's Disease (PD) and others [2]. Differences of approximately 65 ng/mg wet weight (ww) of ferritin have reported between PD patients and age-matched HCs in the substantia nigra (SN) [3]. A similar sized difference in iron levels in the SN would be expected between HCs aged approximately 25 and 50 [4]. Therefore detecting differences in iron levels between these two age groups may indicate the sensitivity to detecting iron-related pathology in patient studies. In white matter, iron levels are lower than in the SN at all ages, with differences of less than 5 ng/mg ww expected between the age groups above [1]. Several different MR measures have been proposed to quantify brain iron including transverse relaxation rates R_2, R_2' and R_2^* ($=R_2+R_2'$). By measuring multiple points on a signal curve from a pulse sequence including both spin-echo (SE) and gradient echo (GE) elements, R_2 and R_2' can be estimated, with several variants proposed [5][6]. GESE (Gradient-Echo Spin-Echo) [7] samples the echo signal before, at and after the spin-echo and the resulting signal intensity is given by: $S(t) = S(0)exp-(tR_2+|t-\tau|R_2')$ [8], where τ is time between the first and spin echo. The aim of this work was to compare the ability of transverse relaxation rates, R_2, R_2' and R_2^*, (measured with the GESE sequence) to detect expected differences in iron levels with age.

Methods

Subjects: Two groups of subjects, one with a mean age of 25.1 s.d=1.6 yrs, n=6, (the "younger" group), and the other of 52.5 s.d=6.3 yrs, n=6, (the "older" group) were scanned after giving informed consent according to local ethics procedures. Imaging: The GESE sequence was implemented on a Signa HDx 3T MRI (General Electric, Milwaukee, WI) scanner. Imaging parameters were: #gradient echoes=32, echo spacing, $\Delta\tau$=1.2ms, spin-echo TE=54ms, TR=3000ms, matrix=128x128, FoV=23.4x23.4cm, #slices=32, slice thickness/gap=2.4/0.0mm, scan time=6:33''. Processing: Magnitude images for each gradient echo were reconstructed offline (Viewit, NCSA, Champaign, IL). R_2, R_2' and R_2^* were fitted for in separate steps; R_2 was estimated from the ratio of signal intensities either side of the spin echo by performing a linear fit of $ln(S(TE-i\Delta\tau)/S(TE+i\Delta\tau))$ vs. $2i\Delta\tau$ [9]. Measured signal intensities were then corrected for T_2 decay [7] using this estimate of R_2. The T_2 corrected signal intensities (Y) for echoes before (Y_b) and after (Y_a) the SE can be written as $ln(Y_b(t))=-R_2'(\tau - t) + ln(Y(\tau))$ and $ln(Y_a(t))=-R_2'(t-\tau) + ln(Y(\tau))$ allowing R_2' to be estimated from the complete data set, fitting $ln(Y_b)$ and $ln(Y_a)$ vs. $(\tau - t)$ and $(t - \tau)$ respectively. Data points for the R_2' fit were weighted by the reciprocal of the T_2 correction factor to account for changes to the signal (and therefore noise estimates) by applying the correction. R_2^* was found using the measured signal intensity after the spin echo by fitting $ln(S_a)$ vs. $t - \tau$. Analysis: The spin-echo volume was used to draw regions of interest (ROI) in the substantia nigra (SN) and in the centrum semiovale region (to be consistent with sections sampled for iron in the reference work [1]) for the white matter (WM) ROI. The mean of R_2, R_2' and R_2^*, in the two age groups was compared with a one-tailed, unpaired t-test in each ROI.

Results

Figure 1 shows representative R_2^* maps for a younger and older subject at the level of the SN. Measured values of R_2, R_2', and R_2^* for all subjects are shown in figure 2 and are consistent with previous studies [8][10]. Significant differences ($p < 0.05$) with age were detected in the SN for both R_2' and R_2^*, but not R_2. No significant differences in any of the measures were seen in the WM ROI.

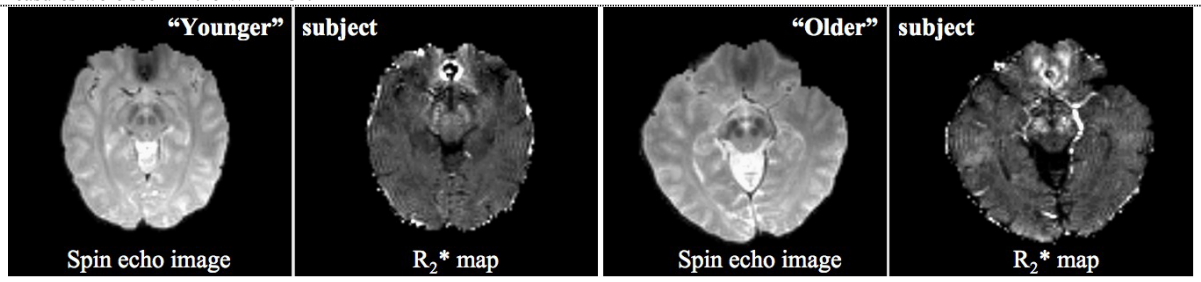

Figure 1. Example spin-echo images and R_2^* maps for a "younger" (left) and "older" subject (right). R_2^* maps shown with same windowing.

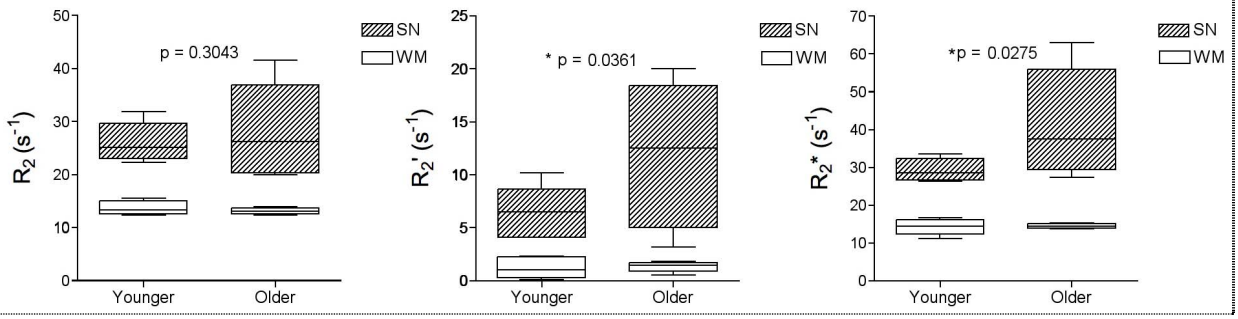

Figure 2. Stem and leaf plot showing measured values of R_2 (left), R_2' (centre) and R_2^* (right) in the SN and WM ROI for both age groups.

Discussion and Conclusion

Detection of age-related changes in brain iron are of interest in studying normal physiology, and here also of interest as a proxy for differences in iron levels expected in pathology, to inform clinical studies. This result adds to reports by others [11][12] that R_2^* may be more sensitive to iron than R_2, suggesting that iron contrast is contributed to by macroscopic field inhomogeneities, producing reversible de-phasing (characterised by R_2') in a spin-echo acquisition. This work appears to show that of the three possible transverse relaxation rates, R_2' (and hence also R_2^*) are more sensitive to differences in putative iron concentrations than R_2. However not all changes in transverse relaxation rates can be attributed to iron; therefore phase data suitable for susceptibility mapping and also a symmetric and asymmetric spin-echo for data for magnetic field correlation mapping have been collected on this group of subjects (but is beyond on the scope of this abstract).

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