A Three-Field Study of Cerebral Transverse Relaxation Rates *in vivo*: Implications for Brain Iron Measurements

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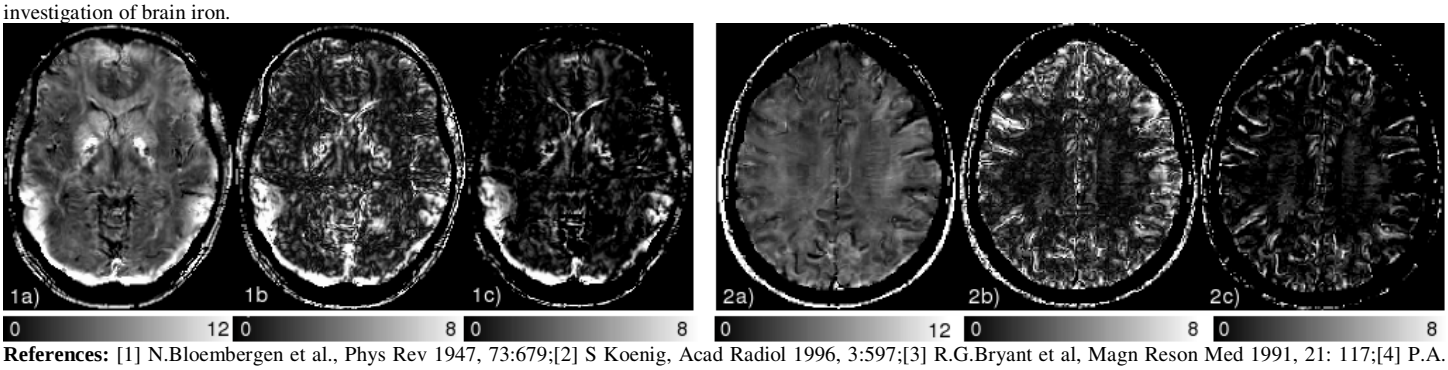
Introduction The field dependence of the relaxation times of pure water is well predicted by the Bloembergen-Purcell-Pound theory [1] and is negligible for the range of frequencies currently used in MRI. In tissue, however, the proton relaxation times are different from those of pure water and they also show a pronounced field dependence. Several factors related to the microscopic structure of the tissue are known to influence the relaxation times: the protein content of the tissue as a source of dipolar relaxation [2,3,4], the cytoarchitecture of the tissue e.g. through effects of diffusion in internal field gradients [5], local deposits of paramagnetic elements (for example Mn) and ferritin [6,7,8]. It is, however, usually difficult to separate a single contribution and quantify it through relaxation time mapping. An important exception seems to be ferritin which induces a contribution to the transverse relaxation rate of protons that depends *linearly* on field strength. This property has been investigated quite extensively over the years with the aim of providing a measure of the iron deposits in the living brain (Bartzokis et al [6], Vymazal et al [7]; see Haacke et al. [8] for a recent review) and this unique linear field dependence has been recently explained [9]. The Field Dependent Transverse Relaxation Rate Increase (FDRI)-based iron quantification [6] works well for specific iron-rich regions (globus pallidus, putamen, substantia nigra, red nuclei) and is particularly useful for the detection of diseases such as Alzheimer's or Huntington disease [10]. However, information regarding the field dependence of the transverse relaxation rates in the whole brain and its relevance to iron content outside of the few specific regions is still scarce. Here, we report on a 3-field study of transverse relaxation times *in vivo*. The study was performed with the aim of providing quantitative information about transverse relaxation in a clinically relevant as well as a high-field relevant field range of 1.5T-4T [11]. We discriminate between the linear and quadratic dependence of the relaxation rates on field strength and we investigate the correlation between the rate increase in regions with clear a linear dependence and their estimated iron content [12].

Methods Measurements were performed using three nearly identical whole-body scanners, operating at field strengths of 1.5T (Siemens Avanto), 3T (Siemens Trio) and 4T (Siemens/Bruker MedSpec). The scanners have identical software platforms except for different SYNGO version numbers and very similar hardware. All three gradient coils had maximum field strengths of 40mT/m on each axis. At 1.5T and 3T, an RF body coil with a very homogeneous B_1-field distribution over the head was used for RF transmit and 12-element, phased-array head coils for signal detection. At 4T, a composite transmit/receive head coil was used; this consisted of a birdcage coil for transmit and an 8-element phased-array coil for signal detection. Twelve healthy volunteers (8 males, 4 females, average age 34 (SD 9) years, ranging from 23 to 54 years) were scanned at all three fields over a period of one month. The average interval during which the three scans were performed on any given volunteer amounted to 17 (SD 10) days. T_2* mapping was performed with a multi-slice, multi-echo, gradient echo sequence in a variant named QUTE [13]. Separate k-spaces were acquired for 32 echoes, and images corresponding to each echo time were reconstructed. A multi-slice, multi-echo spin-echo sequence provided by the anufacturer was used for T2 mapping with 20 time points. Details concerning the acquisition parameters are provided in [11]. Near whole brain coverage was obtained for the T_2* maps (two sets of interleaved 27+28=55 slices) and around half of the brain volume (two sets of interleaved 14+13=27 slices) was investigated regarding its T_2 properties. A rather high in-plane resolution for a quantitative method, of 1mm x 1mm was achieved, but due to time constraints and the wish to cover as large a volume as possible, the slice thickness was set to 2mm. The AutoAlign facility of the SYNGO software was used in order to acquire slices in close to identical positions at all three fields. The alignment was good between 1.5T and 3T but not better than manual repositioning at 4T, due to differences in the software versions. Volumes were constructed from the acquired slices for each method. The T2 data were aligned to the T2* data at each field, and the T2* data acquired at 1.5T and 4T were aligned to the data acquired at 3T using FSL [www.fmrib.ox.ac.uk/fsl] routines. Maps of the coefficients characterising the field dependence of the relaxation rates were constructed following either a linear or a quadratic fit on a pixel-by-pixel basis. The $\chi^2$of the linear fit was calculated. A two-field (1.5T and 3T) based linear fit was calculated for comparison.

Results and Discussion With increasing field, a global shortening and an increased heterogeneity in the T2 and T2* of both white and grey matter is observed [11]. The maps of the leading-order coefficient of the linear and quadratic fit to R2* vs B0 are compared in Fig. 1a and 1c, respectively, for a selected slice through the basal ganglia of a representative volunteer. Fig. 1b shows the map of χ^2 of the linear fit. The coregistration of the T2* data across fields was very good, as also reflected in the high level of anatomical detail seen in the maps. The regions in the selected slice showing the strongest field dependence correspond to globus pallidus (~16 Hz/T), known to have high iron content [6,7,12], and some cortical regions of high global field inhomogeneity. A pronounced field dependence is also observed for the substantia nigra and red nuclei. The nucleus caudate, putamen, as well as the corpus callosum, all depicted in Fig. 1, have a rather strong (5-8 Hz/T) and linear field dependence. The errors of the linear fit are usually small for the aforementioned regions, and the quadratic fit often produces a negative (and unphysical) coefficient of the quadratic term (the scale of the figure has been chosen such that the regions of unphysical fit results are shown as black). Fig. 2 shows the comparison of the same coefficients for a different slice. Fibre-like structures seem to follow more of a linear dependence, while homogeneous appearing white matter regions can be described better with a quadratic fit. Dephasing due to diffusion in field gradients is the mechanism expected to affect most the relaxation rates in both cases and leads to a quadratic field dependence [5]. The interplay between enhanced diffusion and the rather weak inhomogeneities within fibre bundles, both reducing the importance of the quadratic contribution to the relaxation rate, might explain the observation of a linear field dependence in this case. The coefficients of the linear variation with field for R2, R2* and R2' of selected regions (data not shown) show a good correlation with the calculated iron content using the formulae provided by [12], and change little in comparison to the fit using only the lower fields (1.5T and 3T). In conclusion, the addition of a third point to the investigation of the field-dependent changes of the transverse relaxation rates, whist keeping the quantifying power of the two-field approach [6,10], allows for discrimination between regions where a linear dependence is the appropriate description and regions which are better described by a quadratic approach. Complementing the R2 and R2* information with quantitative diffusion data will help to provide a better understanding of the apparently linear change of these relaxation rates in fibre bundles. The number of centres where more than one, and even more than two magnetic fields are used for MRI is steadily increasing, making possible the use of the field dependence of the relaxation rates for the investigation of brain iron.



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