A High-Resolution Quantitative Method for the Study of the Post Mortem Brain

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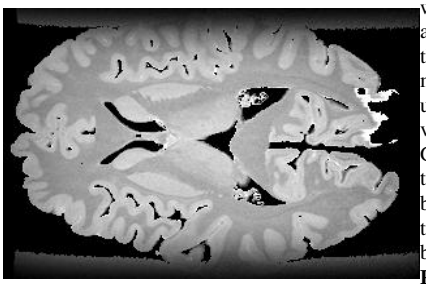
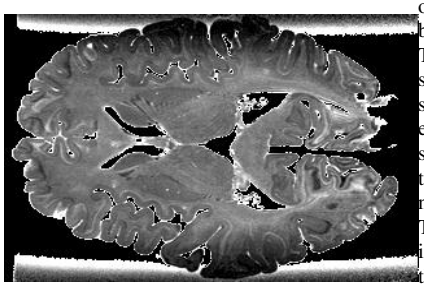
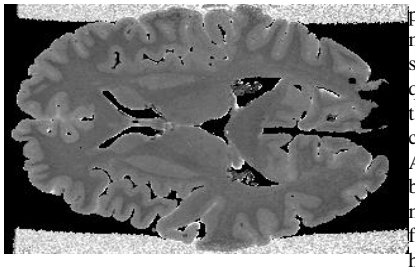
Introduction MRI-based investigations of the post mortem brain are relevant to brain mapping endeavours [1] as well as to a better understanding of brain pathology (e.g. Alzheimer's and Huntington disease [2]). Both research directions, but in particular the latter, would benefit from the availability of quantitative data to characterise post mortem tissue. Amongst other reasons, quantitative data could serve to provide a better description of brain iron, which can be directly compared to quantification by invasive methods. The same holds for demyelination diseases and a variety of brain lesions. From the NMR point-of-view, quantitative parameters determined on post mortem tissue can be related to the microscopic properties of the tissue in terms of cell density, cell size, myelin distribution and distribution of various chemical elements. This study aims to quantitatively characterise the whole post mortem brain using a 3D method which provides proton density, longitudinal and relaxation times maps.

Methods Measurements were performed using a whole-body 3T scanner (Siemens Tim-Trio), equipped with a gradient coil with maximum field strengths of 40mT/m on each axis. An RF body coil with a homogeneous B_1-field distribution over the head was used for RF transmit and a 12-element, phased-array head coil was used for signal detection. A post mortem brain from a 73-year old female with no previous history of neurological disease at the time of death was obtained from the brain donor programme of the University of Duesseldorf. The brain had been kept in 4% formaldehyde solution for more than 2 years prior to the MR measurements.

A two-point method for high-resolution, 3D mapping of proton density, T1 and T2* was developed. It consists of two 3D multiple-echo gradient echo scans with different TR and/or flip angle, two 2D scans for transmit B1 calibration and, in the case of separate transmit and receive coils, an additional 2D scan for receiver B1 calibration. The acquisition parameters for the 3D scans included: TR1=50ms, TR2=50ms, flip1=35deg, flip2=17deg, slab selective pulses, matrix size 320x260x224, voxel size (0.56x0.56x0.64)mm^3, 3 averages, acquisition time of 2hrs:26min. Eight gradient echoes were acquired with TE ranging between 3.4 and 32.5 ms and the 3D images were reconstructed for each echo. Transmit inhomogeneity mapping was performed using two sets of 2D multiple-echo gradient echo acquisitions with very long repetition time TR=8000ms and additional parameters: flip1=45deg, flip2=90deg, matrix 128x104, voxel size (1.41x1.41x2)mm^3, 70 interleaved slices, acquisition time 14min. The 2D scan with flip=90deg was repeated using the body coil for RF receive, in addition to RF transmit. A reference probe consisting of water doped with Gd-DTPA was placed in the field-of-view and allows for the conversion of proton density maps to water content. The data were processed using an in-house tool based on Matlab (www.mathworks.com) scripts. Briefly, the T1 and M0 values were calculated based on the Ernst equation [3] and the signal intensity measured with the two parameter sets. Since SNR is a determining factor for the 2-point method, all eight echoes were averaged and the resulting high-SNR data used for M0 and T1 determination. The water content is obtained by extrapolating the signal intensity to TE=0, based on T2* fit, and normalising to the value obtained from the reference probe. We mention that the method is similar to the one reported in [4]. The precision and accuracy of the method were verified using simulations and phantom results. The T1 results obtained with the two-point method were compared with the values obtained with an inversion-prepared spin echo sequence (IR-SE) on a phantom with different concentrations of Gd DTPA. The simulations were based on the signal equation for 3D GRE (Ernst equation) [3] and white noise added to the real and imaginary parts of the signal. For a range of T1 values, the experimental parameters which deliver the best results for T1 and M0 quantification were determined, with the constraint imposed by the available measurement time that TR should not exceed 50ms. A T1 relaxation range of 200-300ms was expected for the post mortem brain, based on previous results at 1.5T [5] and thus the measurement parameters were optimised correspondingly.

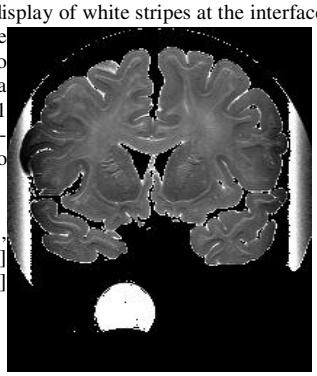






Results and Discussion The relation between the T1 values obtained with the 2-point method and the T1 values obtained with IR-SE is linear, with slope of 1.03(2). The M0 map of the phantom was found to show little variation between tubes, consistent with the very small deviations from the 100% H2O content of each tube. In Fig. 1, the M0, T1 and T2* maps of the brain (from top to bottom) are shown in axial orientation. The images were acquired in sagittal orientation and the darkening at the edges of the resliced images is due to the imperfect profile of the slab selective pulse. A spatially-selective pulse is required for high-resolution, 3D imaging to keep the number of slab encoding steps reasonable. Furthermore, since B1 mapping is performed with a 2D method, the pulses in the two sequences (slab- and slice- selective) need to be the same. The region of accurate quantification for M0 and T1 is therefore limited to the central part of the slab, where the slab selective pulse is homogeneous. This restriction does not apply to T2* maps and only effects of the reduced SNR are visible at the edges of the slab.

The bulk of T1 values are contained in the interval 150-300ms and the vast majority of the T2* values can be found in the range of 20-40ms. It is therefore quite surprising that the T2* contrast is so clear, indicating a homogeneity of the GM and WM properties which is not met *in vivo*. The magnetisation density shows the highest contrast and the proton density in the GM is found to be approximately equal or even 10% higher than that of the reference probe. This might be due to the effect of formalin fixation, which creates links between proteins and a medium with a higher surface-to-volume ratio than *in vivo* tissue. Materials such as agarose or zeolites are known to absorb a much larger quantity of water than contained in a drop of the same apparent volume. A striking feature seen in the axial T1 map is the good visualisation of the stria of Gennari, despite the fact that the voxel size is comparable to the thickness of this cortical layer. Portions of the stria can be seen in the other two maps, especially M0, but not with the same clarity. Another striking feature of the T1 map, better seen in the coronal reslice, is the display of white stripes at the interface between the grey and the white matter, with the same T1 properties as the myelinated layer of the stria of Gennari. These stripes might well correspond to fibres, but this hypothesis must be verified with diffusion data. In conclusion, a high-resolution, 3D method was developed to allow the quantification of M0, T1 and T2* in the post mortem brain. Several interesting features of fixed tissue were identified which are not apparent in higher-resolution images with mixed contrast [5-7]. It is to be expected that the method will provide new and quantitative insights into brain pathologies, especially upon comparison with histology.



References: [1] K. Amunts and K. Zilles, Neuroimaging Clin N Am 2001, 11: 151; [2] Chen et al., Am J Neuroradiol 1993, 14:273; [3] RR Ernst and W.A. Anderson, Rev Sci Instrum 1966, 37: 93; [4] G. Helms et al, Magn Reson Med 2008, 59: 667; [5] A.M. Oros et al., Proceedings of Human Brain Mapping 2003, p760; [6] F. Kruggel et al., Medical Image Analysis 2003, 7:251;[7] G.M. Fatterpekar et al, Am J Neuroradiol 2002, 23:1313.