# $^{17}O$ $T_1/T_2$* tissue-relaxation rates with anatomical contrast in the rat brain at 16.4 T

**H. M. Wiesner[1], D. Z. Balla[1], R. Pohmann[1], W. Chen[2], K. Ugurbil[2], and K. Uludag[1]**

[1]High-Field Magnetic Resonance Center, Max Planck Institute for Biological Cybernetics, Tübingen, Germany, [2]Radiology, Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, MN, United States

**Introduction** The measurement of cerebral metabolic rate of oxygen ($CMRO_2$) via direct NMR detection of the stable oxygen isotope $^{17}O$ is a promising tool to study neuroenergetics, brain activity and pathology [1]. Due to the low natural abundance of $H_2{}^{17}O$ (0.037%) and fast relaxation rates of the $^{17}O$ nucleus [2-4], sequences with short acquisition delays and optimized acquisition parameters are crucial for $^{17}O$ imaging of metabolically produced cerebral water. It has been demonstrated that signal-to-noise ratio (SNR) of $^{17}O$ NMR increases almost quadratically with $B_0$ due to its field-independent quadrupolar relaxation properties [2, 3]. Thus, in comparison to studies at lower field strengths, the increased SNR available for MRS imaging (MRSI) at 16.4 T allows enhanced spatial resolution. Therefore, the aim of this study was the tissue-specific determination of $^{17}O$ relaxation times and the anatomical imaging of $^{17}O$ contrast in the rat brain.

**Methods** A 3-D chemical shift imaging sequence was chosen to minimize acquisition delays (here: 456 µs) for in-vitro & in-vivo $^{17}O$ MRSI [5]. All acquisitions were performed on a 16.4 Tesla magnet (Magnex/Varian Inc.) with a 26 cm bore diameter, maximal gradient-strength 1 T/m (Resonance Research Inc.) interfaced to an Avance III - Paravision 5.0 (Bruker BioSpin) console. Samples were excited by custom-built silver wire surface-coils (diameter 1 & 2 cm) tuned at $\omega_0$=94.63 MHz with a 50-µs RF hard pulse adjusted to a nominal flip angle of 90° for each sample and the inversion pulse was achieved by doubling the 90° pulse width. Spectral bandwidth was 9369 Hz (~100 ppm) throughout all scans.

Samples In-vitro: 25 g water-phantom with enriched 10% $H_2{}^{17}O$ in a glass cylinder. Ex-vivo: 1 male Wistar rat (550 g).

In-vivo study 4 self-breathing isoflurane anesthetized male Wistar rats (470±50 g) with head fixated in a stereotaxic frame were studied. Exhaled gases were continuously monitored and body temperature was maintained at rectally measured 37±0.3 °C with an electric heat blanket. $T_1$ and $T_2$* methodologies were validated on the enriched $H_2{}^{17}O$ phantom in terms of distance from the coil and flip-angles.

Parameters for $^{17}O$ $T_1$ measurements (ex-vivo/in-vivo at natural abundance $H_2{}^{17}O$ concentration): An 8-step inversion recovery method (TI 1.5 - 50 ms) with repetition times TR>5$T_1$ was used. Other parameters are: FOV 3.5×3.5×2.5 cm³; matrix 15×15×7; TR 65 ms, spectral acquisition points 94; total acquired FIDs 51200 (max. 339 averages in the center of k-space) with an overall duration of 55 min per 3D $^{17}O$ MRSI volume.

Parameters for $^{17}O$ $T_2$* measurements (ex-vivo/in-vivo): FOV 3.62×3.62×2.5 cm³; matrix 51×51×7 (voxel-volume: 1.8 µl); TR 5.08 ms with an acquisition duration of 3.91 ms with 37 spectral points; total acquired FIDs 409600 (max. 205 averages in the center of k-space) with an overall duration of 34 min per 3D $^{17}O$ MRSI volume. Additional FLASH images, although at lower SNR due to longer acquisition delays, were used for qualitative verification of $T_2$*-contrast and tissue separation obtained by 3D-CSI.

Data were reconstructed and further processed using MATLAB (Matworks): 1. Zero-filling and line-broadening were used for anatomical visualization of muscle, cortex and deeper (sub-cortical) brain tissue in images of the spectral integral (Fig. 1a). 2. Relaxometry was performed on raw-data: $T_1$ estimation was based on fitting of spectral peak intensity at different inversion times according to a mono-exponential function. Estimation of $T_2$* was based on the decay rate of FIDs transformed into image space (Figs. 1b and 1c). All voxels selected for relaxometry were masked to have at least a spectral SNR > 12 and were less than 1 cm distant from the coil (Fig. 1c).

**Results**

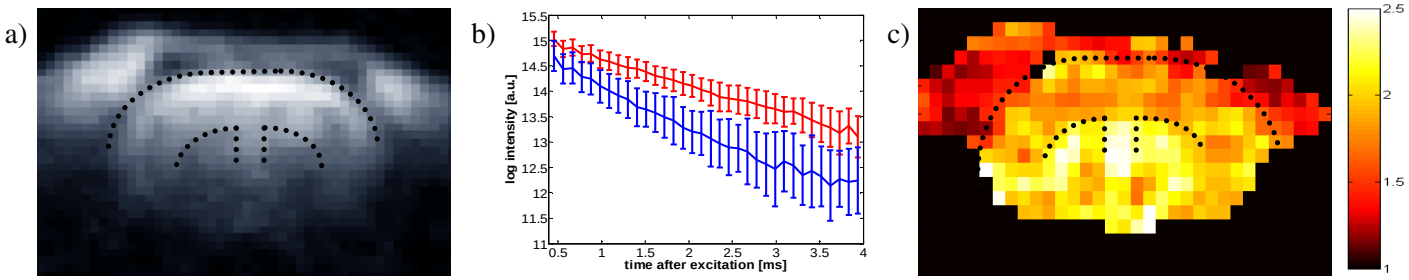


Figure 1 (a) In-vivo CSI of natural abundance $H_2{}^{17}O$ in a coronal slice of a rat head with inner brain-structures (highlighted by dotted lines for outlining cortical and deep sub-cortical brain regions). (b) log-scaled decays (in image-space) of muscle (blue) and brain tissue (red) of an in-vivo rat. (c) $T_2$* map of the same slice as in (a) with structures of distinct $T_2$* relaxation (scale in ms).

| Phantom | $T_1$: 6.24±0.37 (ms) | $T_2$*: 2.24±0.09 (ms) | |
|---|---|---|---|
| Ex-vivo rat | $T_1$: 4.09±0.05 (226 µl brain tissue) | $T_2$* muscle tissue: 2.31±0.47 (86 µl) | $T_2$* cortex: 2.48±0.51 (118 µl) |
| In-vivo rats | $T_1$: 6.87±0.46 (155 µl brain tissue) | $T_2$* muscle tissue: 1.50±0.20 (442 µl) | $T_2$* cortex: 2.02±0.24 (597 µl) |

Relaxation rates in ms (mean± std) and volume of selected voxels in brackets. Signal decay was mono-exponential.

**Conclusions** We have shown, for the first time, natural abundance $^{17}O$ brain images with anatomical contrast at 16.4 T. Significant difference in $T_2$* of muscle tissue in comparison to cortex tissue was determined (Fig. 1b and Table). Fast $T_2$* relaxation rate of muscle tissue might be beneficial for reducing partial-volume contaminations if read-out and TR is optimized for cortex $H_2{}^{17}O$. Furthermore, intra-cortical differences in intensity and $T_2$*-relaxation were observed (e.g. cortex vs. deep sub-cortical areas in Figs. 1a and 1c), but their assignment needs $^1H$-MRI anatomical overlay. The $T_1/T_2$* values determined can be used to tune sequence parameters (e.g. Ernst angle, read-out duration, TR) to maximize SNR per unit time [6, 7], as required in functional $CMRO_2$ measurements by short inhalations of $^{17}O_2$ gas [1].

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**References**: [1] Zhu et. al. PNAS (2002), [2] Thelwall et. al. Proc. ISMRM (2003), [3] Zhu et. al. MRM (2001), [4] de Graaf et. al. JMR (2008), [5] Brown et. al. PNAS (1982), [6] Ernst et. al. Rev. Sci. Inst. (1966), [7] Pohmann et.al. JMR (1997).