True MR microscopy on a clinical 7 tesla scanner: application to plaque detection in ex vivo HCHWA-D samples

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Introduction. Characteristic of Alzheimer's and related neurodegenerative diseases is the accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles. Although high resolution in vivo studies have been performed in mouse models (1), in which distinct plaques or collections of plaques have been visualized, this has not yet been reliably performed in humans. Much work in characterizing plaques has, therefore, been performed on ex vivo samples (2). Previous studies have been performed on either relatively large sections of brain at coarse spatial resolution, or much smaller sections at high resolution, followed by histology. In these cases, it has proved challenging to relate different parts of the brain across the size scales. In this work we have developed a simple RF setup which has been used to image a large brain section for initial screening, combined with a much smaller flexible surface coil which can be positioned over a ROI for much higher resolution imaging. Using a clinical 7 tesla system, the sensitivity is sufficiently high so that true MR microscopy can be performed, highlighting individual plaques ~50 µm in size.

Methods. Studies were performed on samples from deceased patients who had hereditary cerebral haemorrhage with amyloidosis-Dutch type (HCHWA-D). Previous results have shown that the vascular amyloid deposits are related to the beta-protein associated with Alzheimer disease (3). Brain samples were approximately 8-10 cm in diameter and 1-2 cm thick. In order to acquire images over the entire brain specimen, a specialized histological coil was constructed, as shown in Figure 1(a). This consisted of a single wide-band loop resonator, segmented capacitively eight times, and with eight shielding pads placed under each capacitor. Balanced impedance matching capacitors were used. Images were acquired at an isotropic spatial resolution of 200 x 200 x 200 µm. Based upon these initial images, a region of interest was chosen, and the small integrated surface coil positioned directly on top of this region. Images were then acquired at 100 x 100 x 100 µm and 40 x 50 x 100 µm resolutions. In MR microscopy, the ultimate limit in spatial resolution is determined by the effects of molecular diffusion, with the full-width-half-maximum values (Δx) for frequency and phase encoding, given, respectively, by:

$$\Delta x_{freq} = 2.6\left(\frac{D}{\gamma G}\right)^{\frac{1}{3}}, \qquad \Delta x_{phase} = 1.92\sqrt{Dt_{enc}}$$

where D is the diffusion coefficient, G the gradient strength, and t_{enc} the phase encoding time. With a gradient strength of 21 mT/m and encoding time of 6 ms, the diffusive contribution to the spatial resolution is an order of magnitude less than the digital resolution.

Results. Figure 1 shows images obtained at three different spatial resolutions. Figure 1(b) already represents voxel sizes 3-4 times smaller than reported previously (2), with figures 1(d) and 1(e) representing further reductions by factors of eight and forty, respectively. It should be noted that the 100 µm resolution in the third dimension is currently a software rather than hardware or signal-to-noise limitation.

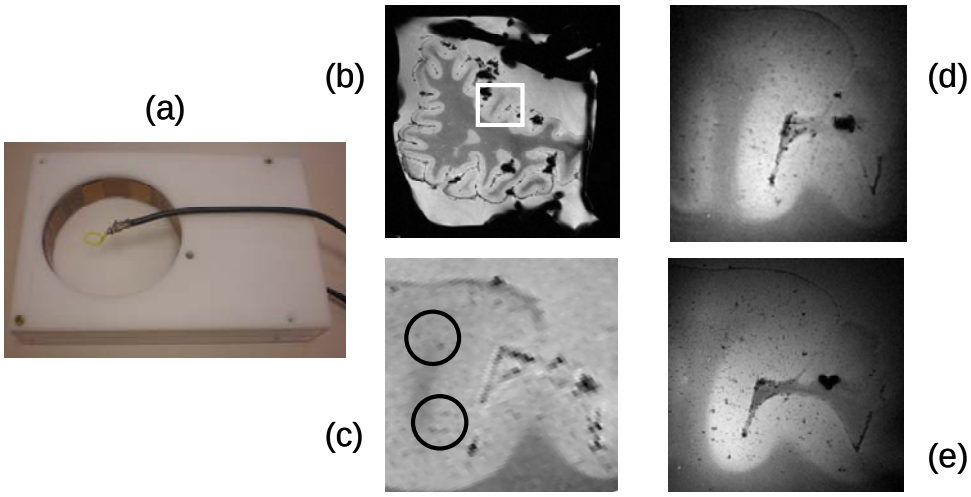

Figure 1. (a) Photograph of the RF probe combination used for microscopy. The outer coil is used to acquire images at a resolution of 200 x 200 x 200 µm, and the flexible smaller coil is then positioned over an ROI for high resolution imaging. (b) 3D gradient echo image: TR/TE 39/17 ms, 9 x 9 x 1.1 cm fov, 450 x 450 x 56 data matrix, data acquisition time 1.5 hours, (c) 3D GE image: TR/TE 73/17 ms, spatial resolution 100 x 100 x 100 µm, data acquisition time 3 hours. (d) 3D GE image: TR/TE 73/17 ms, spatial resolution 40 x 50 x 100 µm, data acquisition time 12 hours.

Discussion. Although not conventionally used for MR microscopy, clinical systems have sufficient gradient strength (20 – 40 mT/m for whole body gradients) to be able to obtain spatial resolutions on the order of 50 µm, with echo times ~10-20 ms, if specialized RF coils can be constructed and interfaced. In this example, images of ex vivo human brain with a severe neurological disease have been obtained with voxels more than 50 times smaller than reported previously. This enables the visualization of individual plaques, which form large signal voids at lower spatial resolution.

References. 1. Wengenack TM et al. Eur J Nucl Med Mol Imaging, 2008, 35, S82-8. 2. van Rooden et al. Proc ISMRM, Toronto, 2008, p 3535. 3. van Duinen S.G. et al. P.N.A.S. 1987, 84: 5991.