BRAIN TISSUE RESPONSE TO CHRONICALLY IMPLANTED NMR MICROCOILS

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Introduction: The feasibility to use a new generation of microcoils was proposed in a recent study [1]. It demonstrated having potential opportunities in terms of increased signal-to-noise ratio (SNR), spatial resolution, and limits of detection (LOD) [2] compared to the surface-coil [3]. Their use for localized spectroscopic studies of NMR observable cerebral metabolites into 2mm^3 region of interest (ROI), aims to push limits of *in vivo* detection. Available evidence suggests that detected metabolites variation comes from studied ROI without influence of the brain tissue reaction against these implantable microcoils, making biocompatibility and period of cicatrization a primary concern before spectroscopic investigations on animal models. The presented research is focused on evaluation of vasogenic edema and blood-brain barrier (BBB) disruption following microantenna implantation, longitudinally with MRI and to assess the macrophage response using immunohistology at Day 14 post-implantation.

Materials and methods: For in vivo implantation, two cohorts of 5 healthy rats Wistar (230-300g), 3 implanted and 2 control rats were used. The animal handling was carried out according to recommendations of the local ethics committee. MRI experiments were performed using a 4.7T-Bruker Biospec System. The microcoil, "needle" part only (micro surface coil, with 4 concentric loops, L= 9mm, l= 400µm [1]) was introduced into the brain by stereotaxy [4]. In vivo MRI acquisitions (stereotaxic coordinates of ROI (LDT) checked) were carried out using a Rapid-Biomed birdcage coil (6.9cm diameter).

T2-weighted images were acquired using RARE sequence (TR/TE = 3000 / 75 ms Nav= 4, Mx=256*256 FOV=4*4 cm), T1-weighted images were acquired using FLASH sequence (TR/TE=350/5.4 ms Nav=4, Mx=256*256) pre and post Gd injection. During the MRI experiments, anesthesia was maintained using isofluorane (1.5% in oxygen/nitrous oxide 1:2). An integrated heating system was used to maintain the body temperature at 37°C, and a pressure probe was used to monitor the respiration. The MR images were acquired from each animal at the 2nd day of implantation (D2) as well as on the 5th (D5), 7th (D7) and 13th (D13) days. Fig.1 shows axial MRI slices, from control and implanted animals at D5.

On the 14th day, after implantation and MRI investigations, rats were perfused transcardially with PBS followed by 4% praformaldehyde in PBS. The brain was removed and conserved in solution containing 40% sucrose at 4°C. Axial (10 µm thick tissue) sections were processed with a particular antigen using immunohistochemical methods, ED-1 (1:100, mouse IgGl) was used to identify macrophage/microglia.

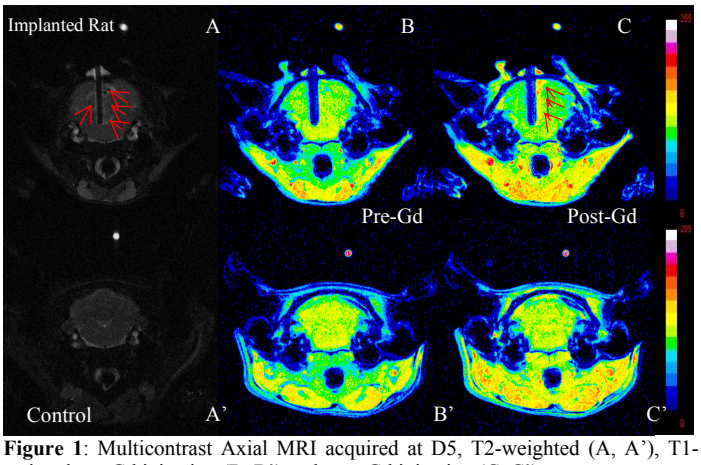

Figure 1: Multicontrast Axial MRI acquired at D5, T2-weighted (A, A'), T1-weigted pre-Gd injection (B, B') and post-Gd injection (C, C').

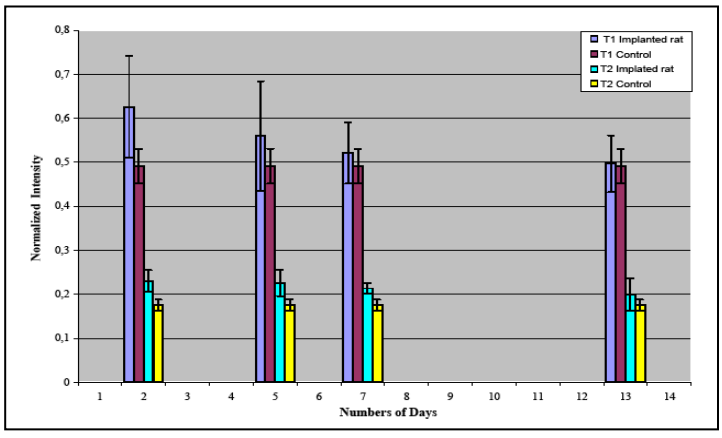

Figure 2: Plots of measured intensity at the lesion edge, from T2 and T1 weighted images of implanted rats and controls.

Results: The implantable microcoil appears as a dark trace on all images which allowed the measurement of the dimension of the induced lesion, compared then with the microcoil size and to stereotaxic coordinates determined thanks to the rat brain anatomy atlas [4]. These results demonstrate that microcoil positioning in intra-cerebral structure is well reproducible under stereotaxic conditions. Fig.1C (arrows) shows T1 enhancement at the lesion edge indicative of BBB disruption. This longitudinal study highlights 2 stages: inflammatory one from D2 to D5 (Fig.1 A) depicted by an hypersignal (arrows) and cicatricial one after D7. An artificial marker (reference Gd/NaCl 1:1600) used in MR images appears to be a bright disk at upper in the centre. From the T2 and T1weighted images, the local tissue intensities (Fig.2) at the lesion edge were normalized using the reference signal intensity. The ROIs used to calculate the normalized intensity in each case were carefully chosen to be the same sizes for all animals. As shown in Fig. 2, the edge lesion signal decreases and becomes identical to the control thus corroborating cicatrization and brain restructuration around the implantable microcoil. Histopathological sections immunostainned by ED1 antibody were analyzed at 14th day (D14), it confirms the vasogenic edema resorption (Fig.3).

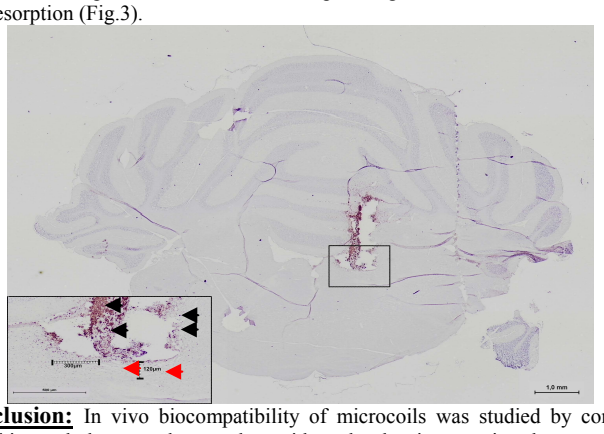

Figure 3: ED1 immunohistochemistry of tissue slice from implanted brain at 14th day shows cicatricial area with gliale and necrotic cells local and limited presence (insert, black and red heads arrows). Cells found at the boundary of the lesion had the typical round shaped morphology of phagocytic macrophages.

Discussion/Conclusion: In vivo biocompatibility of microcoils was studied by comparing immunohistochemistry and MRI images of control and implanted animals. MRI and histopathology results correlate with each other in assessing the presence of inflammation until 5 days after implantation and its decrease after 7th day. Our results demonstrate the limited brain tissue reaction that exists in the chronic implants showing that the tissue was able to recover from any initial damage related to implantation. The present study shows that a cicatrization period (> 15 days) is necessary. In no cases, we observe evidence of infection at the fixation point or along the implant, so the localized spectroscopic investigations can be performed. With chronic implantation, the rats survived up to 4 months. These results are important since the proposed "needle-coil" concept implies a breakthrough in biomedical research based on NMR micro-detector for brain exploration, early diagnosis and treatment follow up. To the best of our knowledge, no in vivo study has been already reported with such sensors. Reinforced by acquisition and signal processing methodology [5,6], it aims at pushing the limits of in vivo spectroscopic detection.

References: [1] Baxan et al, C.R.Chim.2007; [2] Lacey et al, Chem.Rev.1999; [3] Kadjo , et al, ESMRMB, Valencia, 2008; [4] Paxinos and Walton, Academic Press.1998; [5] http://www.mrui.uab.es; [6] Stefan et al, Meas. Sci. Technol, 2009.