Histological correlation with diffusion MRI to monitor transient and permanent cell permeabilization in the brain

Faisal Mahmood[1], Rasmus H. Hansen[2], Birgit Agerholm-Larsen[3], Hanne Gissel[4], Per Ibsen[5], and Julie Gehl[1]

[1]Department of Oncology, Copenhagen University Hospital, Herlev, Denmark, [2]Herlev Hospital, Herlev, Denmark, [3]Glostrup Hospital, Glostrup, Denmark, [4]Aarhus University, Aarhus, Denmark, [5]Hvidovre Hospital, Hvidovre, Denmark

Target audience: Basic scientists and medical scientists.

Purpose: To evaluate diffusion weighted MRI (DW-MRI) as a non-invasive technique to monitor permeabilized zones in the brain, in particular to differentiate between transiently and permanently permeabilized brain tissue.

Methods: Electroporation (EP) was applied in the rat brain *in vivo* (n=48) (Fig. 1) to induce cell permeabilization ranging from transient to permanent (Fig. 2). DW-MRI (human 3T MRI system) was acquired 5min, 2h, 24h and 48h after EP. The DWIBS sequence (b-values: 50,100,150,600,800,1000 s/mm^2) was applied. ADC and kurtosis were derived by polynomial fitting to the series expansion of the Stejskal-Tanner expression.[1] Electric field calculations were based on the finite element method.

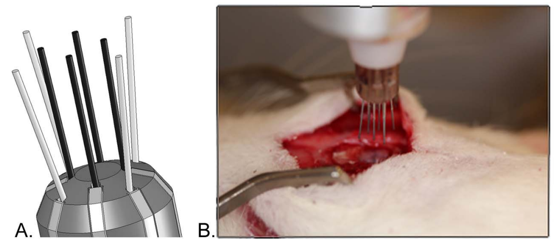

Fig. 1 A. The rat brain electrode device: eight electrodes, 0.2 mm in diameter and 5 mm in length. **B.** The electrode device was applied trough a 5 mm burr hole in the skull using a stereotactic setup.

Results: ADC was significantly increased in the transiently permeabilized brain tissue (pooled: P<0.01, 2h: p<0.04), and in the more severely permeabilized brain tissue (24h: p<0.03) (Fig. 3). ADC increase in the permanently permeabilized tissue was delayed. Kurtosis was increased in both the transiently and permanently permeabilized brain tissue (pooled: P<0.01, P<0.02, P<0.00003). Histology showed correlation to the ADC and kurtosis changes. Overlay of calculated electric field contour on histology samples (Fig. 2) confirmed transient permeabilization (oedema at 300-600 V/cm) and permanent permeabilization (lysis and necrosis at 1000-1200 V/cm).

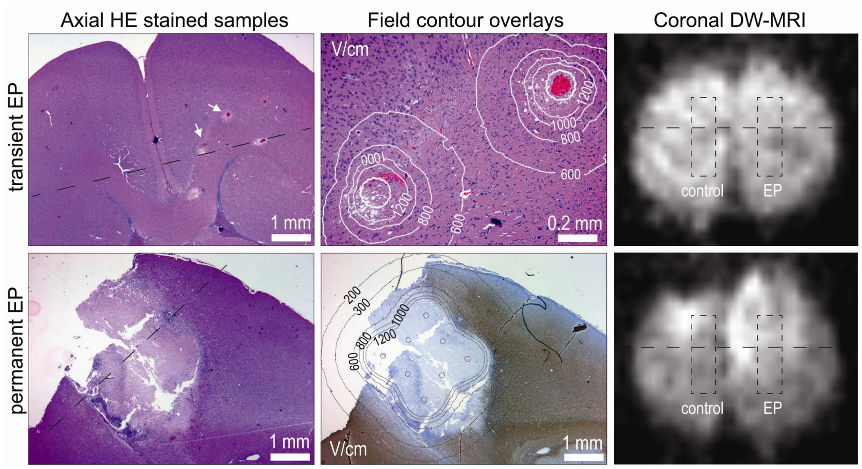

Fig. 2 Representative histological samples and DW-MRI images (right column) of both transiently (24h) and permanently permeabilized (48h) zones in the brain. The dashed lines show the correspondence between the planes. The dashed boxes show the selected regions of interest (ROI).

Discussion: The results should be interpreted carefully since EP did not distinctly induce either transient or permanent permeabilization, due to field inhomogeneities. The combined use of ADC and kurtosis seems to increase sensitivity and specificity of DW-MRI for monitoring permeabilized states.

Conclusion: Results indicate that DW-MRI is capable of defining permeabilized zones in the rat brain, and specifically to differentiate between transiently and permanently permeabilized tissues. DW-MRI may potentially be used for verification of membrane permeabilizing treatments such as radiation therapy [2] and gene electrotransfer.

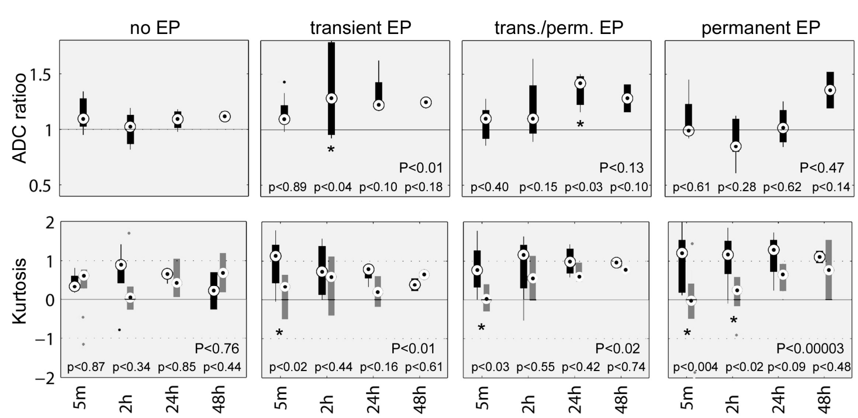

Fig. 3 Upper panel: ADC ratio is the ratio of ADC in EP ROI and the ADC of the control ROI. **Lower panel:** Black and grey bars correspond to the kurtosis of the EP ROI and kurtosis of the control ROI, respectively. The columns correspond to different degrees of permeabilization.

References: 1. Jensen JH, Helpern JA. MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed. 2010;23(7):698-710. 2. Hannig J, Lee RC. Structural changes in cell membranes after ionising electromagnetic field exposure. IEEE Trans Plas Sci. 2000;28(1):97-101.