Manganese-enhanced MRI (MEMRI) for investigating a genetic rat epilepsy model

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Target audience: Preclinical Neuroscientists interested in potential MRI parameters

Purpose:

Absence seizures are non-convulsive, frequently occurring, brief periods of unconsciousness which are accompanied by large-amplitude synchronized spike-and wave discharges (SWD). Electrophysiology studies in patients and animal models indicate that the thalamocortical network is involved in seizure genesis and distribution. The exact localisation of epileptogenic areas within this network is not fully understood. MEMRI has the potential to identify functional components of neuronal networks with high spatial resolution. Here we investigated whether local accumulation after systemic, fractionated administration of manganese assessed by T1 weighted (T1w) imaging and T1 mapping may help to identify epileptogenic brain areas in a rat model for human absence epilepsy, the Genetic Absence Epilepsy rats from Strasbourg (GAERS).

Methods:

Adult GAERS and NEC (non-epileptic control) rats (n=5, each) were i.p. dosed with 100 µmol/ kg $MnCl_2 \times 4H_2O$ at 5 consecutive days. One day after the last injection 2D and 3D T1w images, and T1 maps were acquired at 9.4 T (Bruker Biospec) with a rat brain surface coil. Imaging parameters were as follows: T1w 2D MSME, axial, fat suppression (fs), TR/TE 350/10.5 ms, slice thickness 0.75 mm, FOV 2.6 x 2.6, matrix 256^2, in plane resolution 102 µm², T1w 3D FLASH, fs, TR/TE/FA 17/2.6/20°, FOV 1.6 x 2.4 x 2.6, matrix 160 x 256 x 64, resolution 100 x 97 x 406 µm; RARE T1map, TR/TE 550, 3000, 1500, 800, 400, 200 / 10 ms, FOV 2.6 x 1.8 cm, matrix 256 x 128, in plane resolution 102 x 141 µm, slice thickness 1 mm. For bilateral EEG recordings, four silver electrodes were positioned on the dura of frontal and parietal cortices of an additional GAERS rat.

Results:

All rats tolerated systemic, fractionated manganese administration well. Generally, T1w images of GAERS and NEC rats revealed high signal intensity due to manganese accumulation in the hippocampus, especially the dentate gyrus, and the granular cell layers of the olfactory bulb (cf. fig. 1). Comparison of signal pattern in T1w images between animals was impaired by surface coil related inhomogeneities. ROI analysis was therefore performed on T1maps (cf. fig. 1c). We found slight, but significantly reduced T1 relaxation times within the somatosensory cortex of GAERS rat, but no significant differences within thalamus or striatum, when compared to NEC rats (cf. fig. 2).

Figure 1: Representative images of a T1w 2D multislice data set. (a) Cell layers of the olfactory bulb, (b) hippocampus and especially the dentate gyrus appear with high signal intensity. OV=olfactory ventricle, GrO=granular cell layer, G1=glomerular layer, ON= olfactory nerve layer, HC=hippocampus, DG=dentate gyrus, cc= corpus callosum. **Figure 2:** (a) Representative T1map of a NEC rat with ROIs (only shown unilateral) in the somatosensory cortex, thalamus, striatum, and hippocampus. (b) Bar graph of bilateral ROI analysis.

Discussion:

The reduction in T1 relaxation rate in the somatosensory cortex and the slightly lower T1 values in the thalamus indicate preferred accumulation of manganese in these brain areas. MR findings agree with electrophysiological recordings performed in our lab (cf. fig.3): GAERS rats generate frequent and bilaterally synchronized spike-wave-discharges with mean frequencies of 7-8 Hz under control conditions. However, more prominent effects had been expected. The blood brain barrier effectively impairs manganese penetration into the brain. The low T1 relaxation time reducing effects may be due to the limited amount of manganese that could reach the thalamocortical target region.

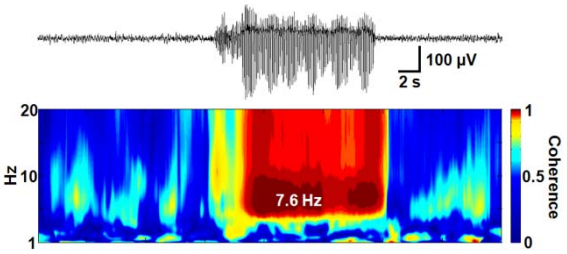

Figure 3: Surface EEG trace recorded from the left somatosensory cortex (upper panel) and color-coded power spectrum of the trace (lower panel).

Conclusions:

Systemic administration of manganese is not sufficient and intracranial application has to be performed in future studies.

References:

Budde T, Pape H-C et al. 2006, "Thalamic, thalamo-cortical and cortico-cortical models of epilepsy with an emphasis on absence seizures" in: Models of Seizures and Epilepsy, A. Pitkänen, P. A. Schwartzkroin and S. L. Moshé (Eds.). Oxford, Elsevier