Brain sodium accumulation correlates with electrical abnormalities in drug-resistant epilepsy: a 23Na MRI and intracranial EEG recording study

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Purpose: Patients suffering from pharmacoresistant partial epilepsy are potential candidates for epilepsy surgery consisting of removal of the epileptogenic zone (EZ). The localization of the EZ during presurgical assessment is a crucial issue and often requires invasive intracranial EEG recordings. Therefore, developments of new non-invasive localizing methods are of particular interest in this context.
Concurrently, in animal models of epilepsy, sodium channels have been found to be altered, inducing sodium accumulation in regions involved by seizures[1]. Brain sodium MRI can provide a non-invasive mapping of abnormal sodium accumulations and has been used in other neurological pathologies as a marker of neuronal suffering/degeneration[2-5].
In order to assess if brain sodium MRI can be a surrogate marker of the epileptogenic area in drug-resistant epilepsy, we assessed for the first time in this study the potential correlation between the abnormal quantitative sodium maps and the electrical alterations evaluated by intracranial recordings representing the current gold standard[6].
Methods: 8 patients with drug-resistant epilepsy were explored by MRI on a 3T system (Verio, Siemens, Erlangen, Germany) and 48h later by intra-cerebral electroencephalography (iEEG) recordings. Fifteen healthy controls were explored by MRI only.
^{23}Na MRI was acquired using a double-tuned ^{23}Na-^{1}H volume head coil (Rapid Biomedical, Rimpar, Germany) and a density-adapted three-dimensional radial projection reconstruction pulse sequence[7] (TE=200µs, TR=120ms, 17000 projections, acquisition time=34 min, nominal spatial resolution of 3.6x3.6x3.6mm^3, with two external references filled with 50 mM of sodium and placed very close to the head for quantification). High-resolution **^{1}H MRI** was obtained with a 3D-MPRAGE sequence (TR=2300ms, TE=3ms, TI=900ms, FOV=256x256mm^2, matrix=256x256, 160 slices, 1x1x1mm^3 of resolution) using a 32-element ^{1}H head coil (Siemens).
iEEG was performed 48h after the MRI exploration using multiple contact depth electrodes (10–15 contacts, length: 2 mm, diameter: 0.8 mm, spaced 1.5 mm apart) positioned according to Talairach's stereotactic method[8]. After implantation of the intracranial electrodes, a MPRAGE sequence was performed. iEEG signals were recorded on a 128 channels system (DeltamedTMH, France) during interictal periods and allowed to assess the number of spikes and the epileptogenic index (EI).
The **MR post-processing** pipeline included *(1)* offline reconstruction of the quantitative 3D radial sodium images (q^{23}Na MRI) (home-made procedure developed on Matlab[7]); *(2)* coregistration of the q^{23}Na MRI with the high-resolved ^{1}H 3D-MPRAGE (before and after intracranial electrodes implantation); *(3)* normalization of the coregistered q^{23}Na MRI and ^{1}H-MPRAGE (without electrodes) and *(4)* Creation of q^{23}Na MRI of the whole brain as well as the grey matter (GM). First, statistical mapping analyses of the whole brain q^{23}Na maps were performed to locate the potential sodium accumulations in the patients' brain compared to the healthy controls. Second, sodium concentrations were extracted from the GM q^{23}Na using spherical ROI of 10mm of diameter corresponding to the region characterized electrophysiologically by each iEEG depth electrode contacts to assess the correlations between sodium concentration and the number of spikes or the EI (Spearman rank correlations).
Results: By using a statistical threshold of p<0.005 for which no significant cluster survived when comparing any individual control with the whole population of controls (two-sample t-test, SPM8), we observed significant sodium accumulation in all patients with the abnormal TSC increases always located in the side of the epileptogenic zone (Fig1). We also found in regions both explored by ^{23}Na MRI and iEEG a significant positive correlation between the sodium concentrations in GM and the numbers of spikes (p=0.003 and rho=0.169) and a trend for a positive correlation between the sodium concentrations in GM and the EI (p=0.066 and rho=0.114) (Fig 2).
Conclusion: These results demonstrate for the first time that abnormal accumulation of sodium concentrations succeeded to lateralize epilepsy and that the sodium concentrations in the GM of patients suffering from drug-resistant epilepsy are correlated with the interictal electrical abnormalities in the regions that are the most prone to be part of the epileptogenic zone. Brain sodium MRI appears as a promising non-invasive presurgical tool in drug-resistant epilepsy.
References: (1) Wang et al, Epilepsia 1996; (2) Thulborn et al, Neuroimaging Clin N Am 2005; (3) Zaaraoui et al, Radiology 2012; (4) Inglese et al, Brain 2010; (5) Reetz et al, Neuroimage 2012; (6) Bartolomei, et al, Brain 2008; (7) Nagel et al, Magn Reson Med 2009; (8) Talairach J et al, Neurochirurgie 1974.

Fig 1: Typical statistical maps of abnormal increases in brain sodium concentrations from 2 patients with drug-resistant epilepsy relative to control subjects (SPM8, p<0.005, k=10; at this threshold none of the controls showed significant clusters compared to the the whole population of controls)

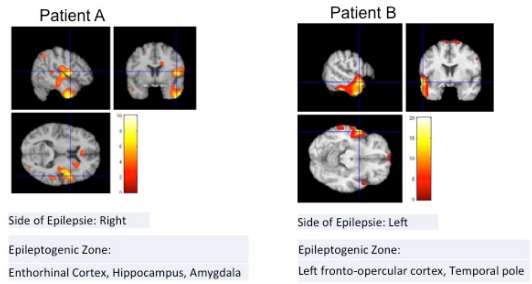

Fig 2: Sodium accumulation in regions (red) involved by electrical abnormalities (yellow and copper) beyond the sole atrophy (blue) in a patient suffering from drug-resistant epilepsy