Elevated glutamate levels in the visual cortex of patients with Migraine detected at 7 Tesla
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Introduction:
Migraine is a neurovascular disorder that affects up to 15% of the general population. The glutamatergic system is implicated in the pathophysiology of migraine. Glutamine (stored in glial cells) is the source for glutamate synthesis (in neurons). Glutamate is the main excitatory neurotransmitter of the CNS. Elevated glutamate levels are linked to cortical spreading depression, trigeminovascular activation, and central sensitization, processes that are highly important in migraine aura and headache symptoms.

In this 7T MRS study we compared the interictal (between attacks) glutamate levels between migraine patients and healthy controls.

Methods:
Migraine patients without aura (n=20, MO) and age and sex matched controls without headache (n=20, CO) participated, after giving informed consent. All patients were examined interictally (no headache +/- 3 days around the MRS exam). Participants retained from food and drinks from midnight until the examination. A 7T MR system (Phillips, Cleveland, USA), with a 32 channel receive and quadrature transmit coil (Nova Medical, Wilmington, MA), acquired MRS with semi-LASER sequences (TE=30ms, 70ms, 100ms and 120ms, TR=5s, NSA=32) and a VAPOR water suppression, using optimized 2nd-order shim gradients. Voxel location (3x2x2cm) was planned in the visual cortex on a 3DT1 series (Fig. 1).

Data analysis:
Data were corrected for the receive sensitivity of the coil and for eddy currents. MR spectra were analyzed with LCModel, using 22 simulated metabolites and a measured macromolecular profile (Fig. 1). Based on the T1 images, the fraction of gray matter (GM), white matter and CSF within the voxel was calculated. The LCModel-data were then corrected for water fraction, water T1 and T2 relaxation and metabolite T1 and T2 relaxation, using relaxation values from literature.

Figure 1: Example of MR spectrum at TE 30ms, showing individual fits of Glu (red) and Gin (blue).

Metabolite T2 relaxation was calculated using a linear fit of the logarithmic values of the metabolite levels at 4 different echo times.

Statistical analysis:
Correlation analysis was performed on metabolite levels and GM fraction. T-tests were performed on T2 values between the MO and CO groups. Linear regression of between subject effects was performed on the glutamate concentration with the fraction of gray matter (GM) in the voxel as covariate.

Results and Discussion:
All metabolite levels correlated significantly with the GM-fraction in the voxel, which was therefore taken as covariate in the group comparison. In migraine patients, the interictal glutamate concentration was higher compared to controls (p=0.049, GM-fraction corrected; Fig. 2). There were no differences between the T2 relaxation values of migraine patients and controls (Fig. 3).

Conclusions: Interictal glutamate levels in patients with migraine without aura are higher compared to controls. This supports the concept that the glutamatergic systems plays a key role in migraine pathophysiology. This study further demonstrates that glutamate can be robustly detected at ultra-high field and opens opportunities for future studies in migraine.