Dynamic Glu+Gln alterations in a FOS patient investigated by ^{1}H-fMRS and CSI

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INTRODUCTION Magnetic resonance spectroscopy (MRS) is a noninvasive methodology that can detect concentrations of some of the most important brain metabolites; among these, the sum of glutamate (Glu) and glutamine (Gln). The study of this metabolite complex may be a fruitful choice in epilepsy research, as it is one of the principal mediators of excitatory synaptic transmission.

Fixation-off sensitivity (FOS) is a rare phenomenon in which epileptic activity is induced by elimination of central vision and fixation (i.e. in darkness, staring at a blank screen, etc.) and was first reported by Panayiotopoulos in 1981. FOS is a convenient human model for the study of epilepsy for its high level of reproducibility and absence of associated movement. Since FOS is a rare syndrome with a difficult diagnosis, not many other cases of FOS epilepsy are available in literature

Previous EEG/fMRI studies performed with the FOS patient who volunteered to participate in this study showed a significant activation area in the right temporo-occipital regions, closely related to epileptiform abnormalities in the eyes-closed condition [Iannetti2002]. The reproducibility of this fMRI activation was confirmed over time [DiBonaventura2005].

In a previous experiment it was observed that during FOS activation in this patient, Glu+Gln concentration linearly increased with time [Giove2006].

In the present study, single-voxel functional MRS and multi-voxel MRS were performed on this FOS epileptic patient in order to confirm previous results and evaluate regional Glu+Gln concentration variations.

METHODS The MRS acquisition was preceded by an EEG monitoring session performed in order to choose a stimulation paradigm that optimizes the intensity and stability of the FOS phenomenon. For this purpose, brief eye-openings were used to refresh paroxysmal activity.

The stimulation was thus designed in 88 s blocks, each consisting in 72 s of eyes-closed condition followed by 16 s of eyes-open. During eyes-open, the screen displayed three circular targets with a color pattern that changed at random every 2 s, to guarantee continuous visual fixation and attention (Cogent 2000 v125, presented to the patient using back-projection and an overhead mirror). With the eye-closure command (via NMR-compatible headphones), the screen went black.

1.Single-voxel MRS The magnetic resonance spectroscopy experiment was performed at 3.0 T on a Siemens Magnetom Allegra head scanner (Siemens Medical Solutions, Erlangen, Germany) using a birdcage transceiver head coil. A PRESS (Point RESolved Spectroscopy) sequence (TR/TE/FA=2000 ms/30 ms/80°, 2048 temporal sampling points, 2 kHz bandwidth) with a 4-step EXOR phase cycle, preceded by a 35 Hz bandwidth CHESS water suppression module, was used for acquisition. The voxel was chosen to have size 18×18×18 mm^3 and to be placed obliquely in the axial plane [fig.1]. The MRS acquisition was performed during 13 stimulation blocks (FOS-activated state) and a resting state (eyes always open). Finally, the unsuppressed water with TR=6000 ms was acquired.

After a preliminary quality check which discarded about 7% of the measurements, spectra of each block were averaged, but only those corresponding to eyes closed (72 s each block) were considered. The measurements acquired during the final resting state, were averaged in 4 groups.

The resulting averages were quantified in the frequency domain using LCModel Version 6.1-0, with the built-in tailored basis set. Eddy-current correction and water scaling by means of the unsuppressed water spectrum were applied. A tissutal water content of 41.7 mol/kg was assumed. The quantifications with Cramér-Rao Lower Bounds (CRLB) above 40% were discarded. Consequently, a time course of 17 points corresponding to about 25 minutes was obtained for Glu+Gln and creatine [fig.1]. The temporal resolution was 88 s during the stimulation and 96 s during the final resting state.

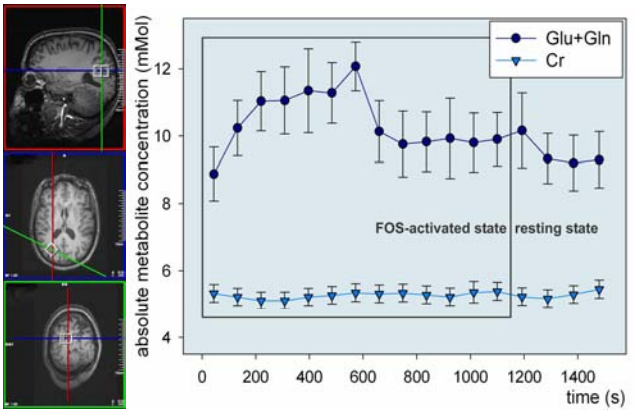

fig.1 *Time course for Glu+Gln and Cr concentrations in the voxel.*

2.Multi-voxel MRS The multi-voxel MRS (i.e. CSI, Chemical Shift Imaging) experiment was performed with parameters TR/TE/FA=2000ms/30ms/90°, 2048 points with 2 kHz bandwidth, no phase cycling, and CHESS water saturation with 45 Hz bandwidth. To reduce acquisition time, weighted k-space sampling with NEX=4 was applied. The field of view (FOV) was placed in the coronal plane with a 25° rotation towards the sagittal plane as to cover the FOS area as well as part of the primary visual cortex. The FOV was 160×160 mm^2 with 10 mm thickness, divided into 256 1 ml voxels, of which the volume of interest (VOI) comprised the central 64 voxels. Outer volume suppression was performed with six presaturation bands.

CSI data were also quantified with LCModel. Data was corrected for partial volume effects and absolute metabolite quantitation was performed with the reciprocity principle and the external replacement phantom method. Two-dimensional concentration maps were obtained for the most prominent metabolites [fig.2]. Quantifications with CRLW > 40% were discarded.

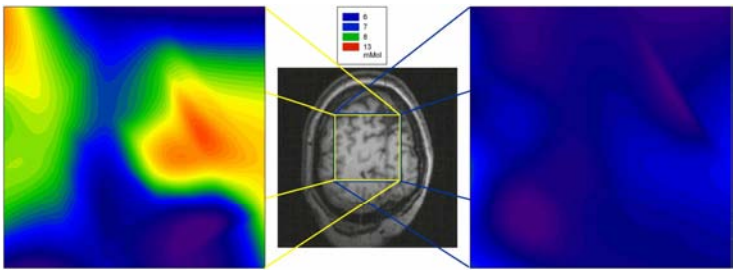

fig.2 *Concentration maps for Glu+Gln (left) and Cr (right).*

RESULTS AND DISCUSSION Functional single voxel MRS confirmed previous findings of an increase in Glu+Gln concentration in the putative FOS region during the first ten minutes of paroxysmal activity. In addition, after ten minutes of FOS activity, concentration returned to baseline, which was maintained also in resting state. CSI shows that Glu+Gln is not uniformly distributed but is localized especially in proximity to the supposed FOS region and primary visual cortex. Creatine, on the other hand, remains constant in concentration and uniformly distributed. These results suggest that paroxysmal neuronal firing rapidly alters glutamate and/or glutamine metabolism and possibly that chronic epileptic activity determines regional metabolic alterations.

References

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