

Assessment of hippocampal activation and resting state glutamate concentration by using functional MRI and ^1H MR spectroscopic imaging

Alexander Gussew¹, Gerd Wagner², Andreas Deistung¹, Reinhard Rzanny¹, Patrick Hiepe¹, Marianne Cleve¹, Karl-Jürgen Bär³, and Jürgen R. Reichenbach¹

¹Medical Physics Group, Department of Diagnostic and Interventional Radiology I, Jena University Hospital, Jena, Thuringia, Germany, ²Centre for Neuroimaging, Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Thuringia, Germany, ³Pain & Autonomics group, Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Thuringia, Germany

Target audience: psychiatric research, functional imaging and MR spectroscopy community

Purpose: Recent studies have shown that substantial memory impairments in late adulthood as well as in different psychiatric diseases are associated with structural and functional changes in the hippocampus [1, 2]. These changes can be evaluated by means of morphological high resolution MR imaging and functional MRI (fMRI) with dedicated paradigms. In addition, proton MR spectroscopy (^1H -MRS) allows detection of several brain metabolites *in vivo*, such as neuronal integrity marker N-acetyl aspartate or neurotransmitter glutamate, thus allowing assessment of the neurochemical background of these functional and structural alterations [3]. In the present work, combined fMRI and proton chemical shift imaging (^1H -CSI) were performed in healthy volunteers to investigate the relationship between BOLD contrast changes and resting state concentrations of the excitatory neurotransmitter glutamate in different hippocampal areas.

Methods: Eight male, right handed healthy volunteers participated in this study (age: 25 ± 2). All measurements were performed with a whole-body 3 T MR scanner (Magnetom Trio TIM, Siemens, Germany) and a 12 channel head matrix coil. The measurement protocol (TA \approx 1.3 h) included a functional whole-brain T_2^* -weighted EPI scan with an appropriate paradigm (TR/TE: 2700/30 ms; α : 90° , 48 parallel 2.7 mm thick slices; FOV: 192×192 mm²; matrix 72×72 voxels), a structural whole-head 3D T_1 -weighted MRI scan (MP-RAGE; TR/TE/TI: 2300/3.03/900 ms; α : 9° ; 192 sagittal 1 mm thick slices, FOV_{APxRH}: 256×256 mm²; matrix: 256×256 voxels) as well as a resting state 2D ^1H -CSI scan (PRESS, TR/TE = 2000/30 ms, slice thickness: 12 mm; FoV = 240×240 mm²; matrix: 16×16 voxels; NAS = 16). The EPI volume was first oriented parallel to the AC-PC line and then clockwise rotated by 20° around the left-right axis. The CSI slice was oriented parallel to the hippocampus plane (see Fig. 1). The fMRI paradigm, which provides specific activations in the hippocampus, targeted on the association between words and pictures and consisted of two randomly presented conditions. During the first condition subjects had to indicate which of the two presented words was associated with the picture, which the subjects had learned outside the scanner. In the second condition subjects had to recognize whether the presented word-picture association was new or old. Functional image analyses were performed by using SPM8 [4]. A linear regression model with two linearly independent coefficients (β_1, β_2 , range [-1, 1]) was used to assess the BOLD contrast changes associated with both fMRI paradigm conditions. MR spectra were post-processed and analyzed with the LCModel [5]. Absolute concentrations of glutamate and other brain metabolites (N-acetyl aspartate, creatine, total choline and *myo*Inositol) were estimated by using the water intensity as internal reference and accounting for the tissue composition in spectroscopic voxels [6]. Two regions of interests representing the left and right anterior and posterior hippocampal areas, were defined within the CSI matrix (see blue and yellow boxes in Fig. 1). The β values were extracted from the same areas within the EPI volumes and related to the determined metabolic concentrations.

Results: The main fMRI finding was that predominantly the posterior hippocampus was specifically activated above fixation baseline when subjects had to recognize the word-picture association (first condition, $p < .001$, see Fig. 2). In the second condition, which tests the old/new status of the presented association, significant bilateral deactivation was observed in the posterior hippocampus relative to the fixation baseline ($p < .001$). Positive correlations were observed between glutamate concentration and BOLD activation in the left and right posterior hippocampus for the first condition of the fMRI paradigm (see Fig. 3). No correlations were identified between the glutamate concentration and BOLD deactivation in the posterior hippocampus during the second paradigm condition. Finally, no associations were observed between functional changes and concentrations of NAA, Cr, tCho and mI in all investigated regions of interest.

Conclusion: The proposed study design allows a spatially resolved investigation of glutamatergic neurotransmission that underlie neuronal activity changes during functional tasks. This may improve the understanding of neurotransmitter regulation of neuron firing and may also provide an explanation of inter-individual variations of observed activations. Of note is the absence of a correlation between glutamate concentrations and hippocampus deactivation that may be ascribed to an elevated inhibitory neurotransmitter turnover. However, since the applied spectroscopic method does not provide reliable quantitation of GABA, this assumption has to be proved in further studies with application of dedicated methods (e.g. spectral editing technique).

Ref.: [1] Raz N et al., Cereb Cortex 2005, 15:1676-89; [2] Aleman A et al., Am J Psychiatry 1999, 156:1358-66.; [3] Hutcheson NL et al., Schiz Res 2012, 140:136-42; [4] <http://www.fil.ion.ucl.ac.uk/spm/>; [5] Provencher SW, Magn Reson Med 1993, 30:672-9; [6] Gussew A et al., MAGMA 2012, 25(5):321-33.

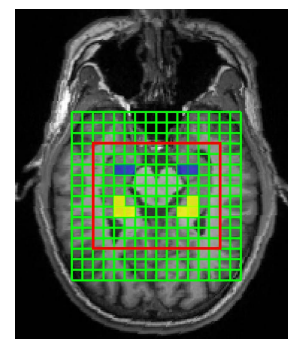


Fig. 1 CSI grid with a PRESS volume (red box) on a T_1 -weighted image (parallel to hippocampus plane). Blue and yellow boxes mark the voxels in the anterior and posterior hippocampus regions, respectively.

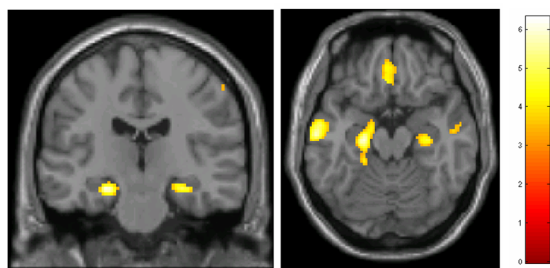


Fig. 2 Bilateral activations in the posterior hippocampus (group comparison) associated with the first condition of the fMRI experiment.

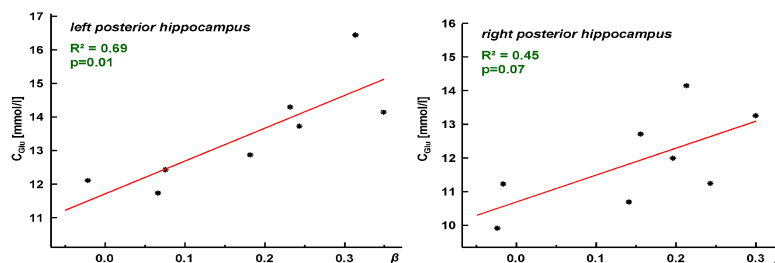


Fig. 3 Correlation between resting state glutamate concentrations (C_{Glu} in mmol/l) and corresponding regression coefficients (β_1), estimated in the left and right posterior hippocampus for the first condition of the fMRI paradigm.