Functional Spectroscopy of Pain at 4T

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Background

Brain activity measured with fMRI is thought to reflect hemodynamic changes associated with increase in energy demand due to neuronal activation. Specifically, the energy demand increase is thought to reflect enhanced glutamate neurotransmission, and Glutamate – Glutamine cycling [1, 2]. Proton MR spectroscopy (^{1}H-MRS) is a non-invasive technique that allows the measurement of metabolites such as N-acetyl aspartate (NAA), glutamate (Glu) and glutamine (Gln) in-vivo. Changes in Glu and Gln concentrations can be well resolved in humans with a 4T MR scanner [3]. Painful stimuli has been shown to activate the Anterior Cingulate gyrus (ACg) in previous neuroimaging studies [4]. This activation may reflect an increase in Glu neurotransmission, yielding an increase in Gln through glial uptake and conversion of Glu [2, 5]. The primary goal of this study was to investigate the effects of adverse stimuli (pain) on glutamatergic activity in the ACg as assessed with proton spectroscopy (^{1}H-MRS).

Methods

Five subjects (3 F/ 2 M 20 – 28 yrs) participated in the study. Two scanning sessions a week apart were performed on a 4T Varian whole body scanner equipped with a TEM quadrature head coil. The paradigm consisted of ten minutes of rest, followed by either ten minutes of pain stimulus or ten minutes of sham stimulus (randomized), and ending with two ten minute rest periods. Single voxel STEAM (Voxel size 20 x 20 x 20 mm^3, TR =2000 ms, TE = 20 ms, TM = 30 ms) MRS was acquired from the ACg during scans. Spectra were acquired as 16 blocks of 16 averages, blocks were phase corrected and added together. A modified cold pressor test (frozen compress placed on the base of the subject's foot for ten minutes) was used to induce pain. In the sham condition a room temperature compress was used. Subjects rated pain levels while in the scanner using a customized response device on a scale of 0 – 10. Spectra were analyzed using curve-fitting software developed at the University of Western Ontario[6]. Metabolite concentrations were calculated for NAA, Glu, Gln, Choline, and Creatine, using an internal water reference. Changes from baseline in the metabolite concentrations were analyzed within and between conditions (sham vs. painful-stimuli) with paired t-tests.

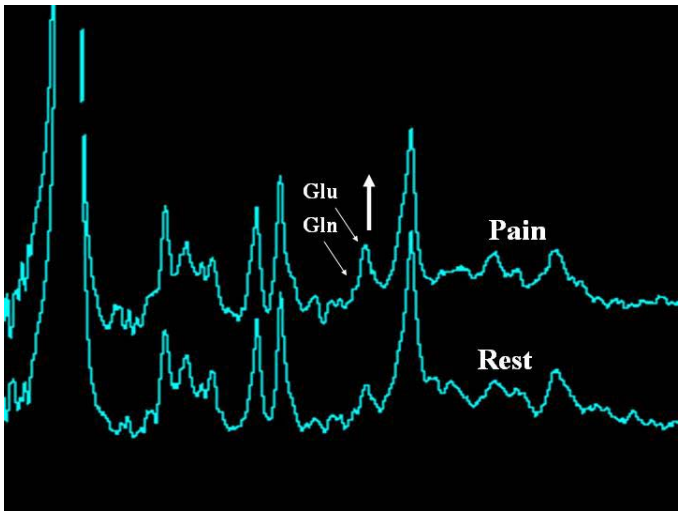

Figure 1. Representative spectra acquired from rest and pain periods. The Glu + Gln peak is seen to increase during pain.

Results

Five subjects participated in this study. A representative spectrum from the ACg at rest and during pain is displayed in figure 1. Average pain levels reported during the pain condition was 5, and during the sham condition was 0. Absolute concentrations for NAA, Cho, Cre, Glu, and Gln were measured, and changes from baseline during and after painful administration calculated. During the painful stimuli administration Glu and Gln alone changed significantly from baseline measures (Table 1. Glu average increase = 9.9% $p<0.05$, and Gln =20.3% $p< 0.05$). This response was significantly different from that seen with sham administration ($p< 0.05$, one tailed t-tests). No other metabolites changed significantly from baseline.

Table 1. Percentage change from Baseline concentrations for NAA, and Glx compounds (* = different from sham p<0.05, ** = significantly different from sham p<0.01)

	Pain	Sham	Effect size
NAA	**-0.79**	**-3.67**	**0.13**
Glu	**9.90 ****	**-5.78**	**0.71**
Gln	**20.30***	**-2.87**	**0.48**

Discussion

To our knowledge this is the first study to demonstrate an increase of brain Glu and Gln concentration using ^{1}H-MRS due to an external painful stimulus. The increases in Gln may indirectly reflect increased glutamate neurotransmission, also reflected by increased Glu concentration. These results, highlighting the non-invasive measurement of Glu and Gln changes, and hence Glu neurotransmision, introduces a new and unique tool for studying brain activation *in vivo*. Combining dynamic spectroscopic imaging and fMRI in future studies will allow the regional specificity and time course of metabolic changes to be determined, and could prove to be a useful tool in the study of pharmacologic intervention in pain.

References

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