Dissociation of anterior cingulate Glutamate and induced theta EEG activity in schizophrenia.

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Introduction: Schizophrenia is a common and debilitating chronic psychiatric illness which affects 1% of the population. The pathophysiology is still unknown with several lines of evidence pointing to a crucial role of hypofunction of NMDA receptors and resulting prefrontal glutamatergic dysfunction. This so called glutamate hypothesis stimulated over the last two decades several MRS studies to research alterations of glutamate levels in schizophrenia. Findings to date are highly controversial and do not allow to conclude whether differences between studies are due to technical challenges in estimating glutamate levels or effects from disease heterogeneity, duration or medication (1-5). On the other hand, there is accumulating evidence for abnormal cortico-limbic functional connectivity in schizophrenia that is reflected in abnormal theta EEG activity. Recently, a positive relationship between hippocampal Glu and theta was established in healthy volunteers (6). Here, we used a combined EEG/MRS protocol to investigate whether prefrontal glutamate levels are altered in patients with early schizophrenia and whether there is an interrelation between glutamate and theta activity in schizophrenia.

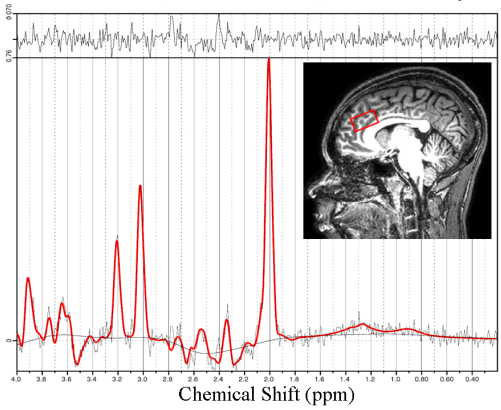

Fig 1: Example of spectrum from ACC (TE=80 ms). T1 Weighted MPRAGE Image (inset)

Methods: The study was approved by the local ethic committee and all subjects, 20 early stage shizophrenic patients and 23 age and education matched controls, gave written informed consent. EEG was recorded in all subjects prior to MRI with a 128 electrode cap while subjects were performing a visual go/no-go task. A 3T Philips Achieva scanner was used and the protocol consisted of anatomical MPRAGE, 32 directions DTI and Glu optimised PRESS TE =80 ms (7) (voxel size =30x15x15mm^3, TR=2000ms, 128 averages) localized on the ACC (Anterior Cingulate Cortex). MRS was processed with LcModel software. SPM was used for image segmentation to compute the water content and the CSF fraction of two shifted voxels to account for the chemical shift displacement. The data was tested for normal distribution through Lilliefors test. The T-test and Pearson test for correlation was performed using the Matlab statistic toolbox. The EEG data were artefact corrected, referenced to the joint mastoids and event-related induced theta activity (4-8 Hz) in response to correctly rejected Go stimuli was extracted for each subject at frontal electrode Fz.

Results: Most of the data showed a linewidth of 0.030 ppm and the fitting produced accurate quantification of all major metabolites including Glu (averaged CRLB<12%). Glutamate in the ACC were unchanged while NAA was significantly reduced in patients (10%, $p<0.002$, Fig.2). A strong correlation was found between glutamate and induced theta in the frontal cortex of healthy volunteers ($r=0.65$ $p<0.002$, Fig 3). In contrast, this correlation was lost in patients ($r = -0.09$, p= ns). No evidence of correlation between NAA and theta activity was found in patients and controls.

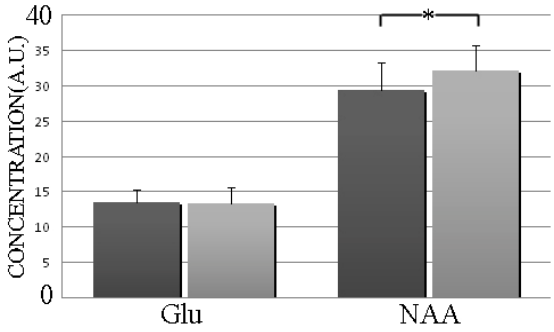

Fig 2: Differences in concentration for patients (left) and controls (right) for glutamate and NAA.

Discussions: Our study showed that glutamate levels in the ACC predict induced frontal theta activity in healthy subjects, which is partly consistent with a previous study in healthy volunteers showing correlation between frontal theta activity and hippocampal Glu levels (7). Remarkably, this interrelation between ACC Glu and induced theta activity was lost in patients with schizophrenia. Although our findings have to be considered preliminary they provide first evidence that prefrontal glutamatergic activity modulates oscillatory theta activity and that this modulation is defunct in patients with schizophrenia. This dissociation may explain the cognitive deficits seen in schizophrenia despite unchanged glutamate pools. Cerebral glutamate is divided into two different pools, the neurotransmission and metabolic pool. The majority of the Glu that is MRS visible is in fact associated with glucose metabolism precluding inference on neurotransmitter activity changes between patients and controls and its associations with theta activity. Nevertheless, a direct link between cingulate glucose metabolism and theta activity has been established in healthy volunteers using FDG-PET(8). This lends further support to the notion that MRS visible Glu mainly reflects the metabolic pool that is however linked with neuronal activity.

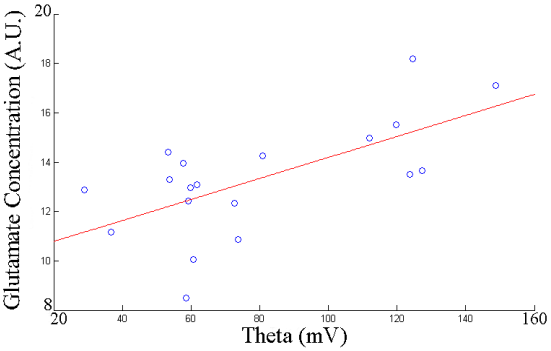

Fig.3: Correlation between Theta activity and Glutamate concentrations in healthy controls.

Conclusion: Association between prefrontal glutamate levels and theta activity is lost in schizophrenia. This finding in combination with unchanged concentrations suggests glutamatergic dysfunction despite preserved glutamate metabolism.

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