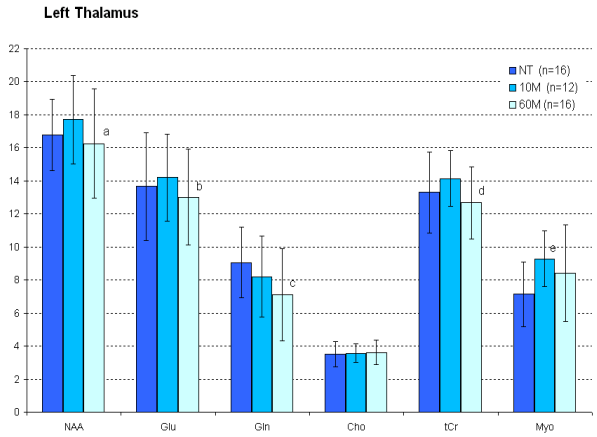
Glutamatergic Changes in First Episode Schizophrenia after Long Term Assessment

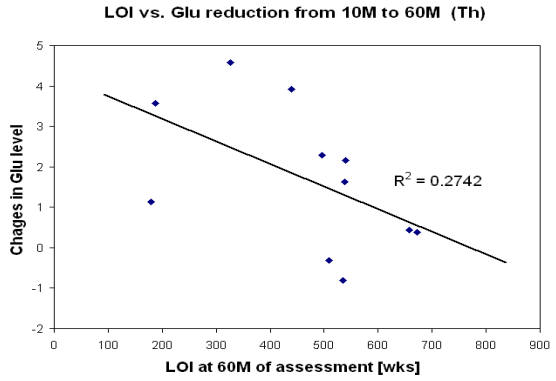
N. Aoyama[1,2], J. Theberge[1,3], D. J. Drost[1,3], R. W. Neufeld[4,5], R. Manchanda[4], M. Densmore[2,3], B. Schaefer[4], and P. C. Williamson[1,4]

[1]Medical Biophysics, University of Western Ontario, London, Ontario, Canada, [2]Lawson Health Research Institute, London, Ontario, Canada, [3]Diagnostic Imaging, St. Joseph's Health Care, London, Ontario, Canada, [4]Psychiatry, University of Western Ontario, London, Ontario, Canada, [5]Psychology, University of Western Ontario, London, Ontario, Canada

Introduction: 1 in 100 people in the world suffer from schizophrenia. Psychotic symptoms such as hallucinations (positive symptoms) are stabilized effectively by medication. Negative symptoms, such as lack of motivation, are not treated effectively and affect patients for their whole life. The cause or even the mechanism for schizophrenia is still unknown. However, one possible explanation is the glutamate hypothesis, which suggests that decreased NMDA glutamate receptor activity results in a paradoxical increase in glutamatergic activity which may eventually lead neuronal degeneration. Basal ganglia-thalamocortical neuronal circuits implicated in schizophrenia are interconnected by glutamatergic neurons. We have previously reported that glutamine level in the thalamus had significantly decreased in the schizophrenic patients 30 months after diagnosis (1). This study will present the long-term follow up with data measured 60 months after the initial examination.

Methods: 16 patients experiencing first episode schizophrenia participated in this study. All but two patients were never treated (NT) before their initial assessment. These two patients had taken medication to stabilize their symptoms 7 to10 days prior to their first scan. All patients were scanned 10 months (10M) and 60 months (60M) after their initial scan. MRI and MRS data were collected on a Varian/Siemens Unity INOVA 4 Tesla whole body scanner. T1 weighted transverse images (3D MPRAGE sequence, TI=500ms, TE=6.2 ms, TR=11.4ms, α=11°, 0.78mm x 0.78mm x 2.75mm, 256 x 256 matrix, 64 slices) were acquired from each subject. Water suppressed proton spectra were collected with single voxel STEAM (TE=20ms, TM=30ms, TR=2000ms, dwell time=500µs, 256 averages) from 15mm x 10mm x 10mm voxel in the anterior cingulate (AC) and the left thalamus (Th). Eddy current correction and line shape correction were done with the unsuppressed water acquisition (16 averages) (2). After this pre-processing, water suppressed spectra were fit by Levenberg-Marquardt minimization algorithm in the time domain using in-vitro priori knowledge from twelve metabolites with in house software (3). Metabolite concentration levels were normalized with the amplitude of the unsuppressed water signal and corrected for the fraction of gray matter, white matter and CSF in each voxel. Univariate ANOVA was performed on the individual metabolites in the anterior cingulate and the thalamus.





Results: No significant change was found in any metabolites on the univariate tests in the anterior cingulate. In the thalamus, glutamine levels of the 60M group were relatively lower than that of NT group (p=0.073, a). Significantly decreased levels of NAA, glutamate and creatine were found in the thalamus in the 60M group compared to those in 10M group as well (p<0.05, bcd). Myo-Inositol levels in the 10M group were significantly higher than in the NT patients group (p<0.05, e). We also found that the changes in NAA between 10M and 60M correlated inversely with the length of illness at the last assessment (r=-0.550, p=0.040, one-tailed, df=11) as well as the changes in glutamate (r=-0.523, p=0.049, one-tailed, df=11) in the thalamus. NAA and glutamate mainly decreased in the first years of disease.

Discussion: Decreased glutamine level in the thalamus after 60 months of assessment may indicate the process of neuronal degeneration in schizophrenic patients over the first years of illness. Significantly decreased NAA level in 60M compared with 10M could also suggest neuronal loss as NAA is often considered as a marker of neuronal density. A correlation between NAA as well as glutamate reduction from 10M to 60M and the length of illness may show that neuronal degeneration happens in the early stage of schizophrenia.

Reference:

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Acknowledgements:

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