**In vivo investigation of metabolic changes in the first episode schizophrenia with combined $^{31}$P/$^{1}$H MR spectroscopy**

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**Purpose:** As reported in recent studies, first episode schizophrenic patients (FEP) reveal local neurodegenerative changes in the brain, which correlate with the symptomatology and after during the disease progress [1,2,3]. These processes may be related to the excitotoxic cellular damage occurring due to deregulated glutamatergic activity, which again leads to an altered cell membrane turnover associated with changes in phospholipid and energy metabolism. This hypothesis can be investigated in vivo by phosphorus MR spectroscopy ($^{31}$P-MRS), which allows detecting the phospholipids compounds phosphomonoesters (PME) and phosphodiesters (PDE) as well as energy demand related metabolites phosphocreatine (PCr) and adenosine triphosphate (ATP). Additionally, proton MRS ($^{1}$H-MRS) enables direct investigation of glutamatergic neurotransmission by detecting glutamate (Glu) and glutamine (Gln) as well as analysis of the cell integrity by evaluating concentrations of the cell density markers N-acetyl aspartate (NAA). In the present work, combined $^{1}$H/$^{31}$P chemical shift imaging (CSI) as well as structural brain MR imaging was performed in brains of FEPs and healthy controls (HC) to evaluate local metabolic and morphological changes occurring during the first manifestation of schizophrenia.

**Material and methods:** 6 non-medicated first episode schizophrenic patients (3 males / 3 females) and 18 age matched healthy controls (12 males/6 females) participated in this study (age: 24±5). All MR measurements were performed with a whole-body 3 T MR Scanner (Magnetom Trio TIM, Siemens, Germany) and a double tuned ($^{1}$H/$^{31}$P) transmit/receive volume head coil (Biomedical Rapid GmbH, Germany). The measurement protocol (TA = 2.5 h) included a whole-head 3D MRI scan (MP-RAGE; TR/TE/TI = 2300/3.03/900 ms; α: 9°; 192 sagittal 1 mm thick slices, FOV$_{ax}$ = 256×256 mm$^2$) as well as 2D $^{1}$H-CSI (PRESS, TE/TR = 30/2000 ms, matrix: 16×16, FoV = 240×240 mm$^2$, with and without water suppression) and 3D $^{31}$P-CSI data acquisitions (FID sequence, TR = 3 s, interpolated matrix: 16×16×16, FoV = 240×240×240 mm$^3$). The $^{1}$H- and $^{31}$P-CSI volumes were acquired with identical positions and orientations to obtain voxel alignment between both scans (see Fig. 1a). Due to a low B$_0$ homogeneity in the occipital part of the CSI slice, only spectra from the frontal part were analysed in this preliminary study (see the red marked region in Fig. 1b). Data post-processing comprised the quantitation of $^{1}$H and $^{31}$P compound intensities with the LCModel [4] and jMRUI [5]. Further, tissue segmented MP-RAGE brain data were co-registered with the CSI volumes to determine the volume fractions of brain’s grey and white matter (GM, WM) and CSF in the CSI voxels. Absolute concentrations of $^{1}$H metabolites were estimated by using the water intensity as internal reference and by considering tissue composition in spectroscopic voxels [6]. $^{31}$P compound intensities were presented as standard values in arbitrary units which represent quantitated metabolite intensities normalized to the total phosphorus amount in spectra. In all included CSI voxels, metabolic values as well as CSF corrected WM and GM volume fractions (V$_W$ = V$_W$[1-V$_{CSF}$]) were compared between FEP and HC by using the Wilcoxon-Mann-Whitney-test.

**Results:** Patients revealed significantly decreased WM volume fractions in frontal brain regions (up to -10%, p < 0.08). Neither significant GM volume fraction differences nor substantial changes of absolute $^{1}$H metabolite concentrations and $^{31}$P compound intensities were observed between FEP and HC. Additional group comparisons were performed with metabolic values, which were normalised to the WM content in spectroscopic voxels (I$_{WM}$ = I$_{WM}$/V$_{WM}$), to take into account the detected WM differences between both person groups. Fig. 2 shows CSI voxels with significant (p < 0.08, see the voxel marked by cyan box) and apparent (p < 0.2, non marked voxels) differences of normalised metabolic levels between FEPs and HCs. Patients revealed significantly increased Glu, NAA, Cr, choline (tCho), PCr and PDE levels (up to 30%) in the right anterior cingular cortex indicating for an elevated glutamatergic activity as well as an increased energy demand and phospholipids breakdown. Apparent but not significant increases of WM normalised PDE and PCr intensities were also observed in parietal white matter of patients bilaterally and in the right hemisphere, respectively. Finally, NAA and tCho concentrations were decreased in the left thalamus of patients although without reaching statistical significance.

**Conclusion:** By detecting $^{1}$H and $^{31}$P metabolic levels from multiple brain regions within a single examination, the proposed study design allows to investigate different metabolic processes, which may underlie the neurodegenerative changes during the manifestation of schizophrenia. In addition, metabolic information can be related to morphological properties accessed by volume fractions of brain tissue compartments. The increase increases of metabolic values in the anterior cingular cortex of FEP’s may be ascribed to the elevated neurotransmission, membrane turnover and energy demand, which underlie the disease related neurodegenerative processes. However, further investigations with an larger patient and control samples are necessary to prove these assumptions and specify the results in other brain regions.