PHOSPHOLIPID AND HIGH-ENERGY PHOSPHATE LEVELS IN MULTIPLE BRAIN REGIONS IN ALZHEIMER'S DISEASE: A 3D ^{31}P-MRSI STUDY

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Target audience: Researchers and clinicians interested in brain metabolism in Alzheimer's disease (AD).

Background. Alterations in membrane phospholipid metabolism and energy metabolism in the brain have previously been reported in Alzheimer's disease (AD) [1]. Whereas phospholipids are the main components of cell membranes, and thereby involved in structural integrity, high-energy phosphates are necessary for providing energy to the cell [2]. Furthermore phospholipid metabolism is important for the formation of new and maintenance of existing synapses. In AD, synaptic loss and neurodegeneration follow a distinctive regional pattern during the course of the disease, starting in the hippocampus and progressing to mediotemporal, posterior cingulate and frontal regions. In addition, resting metabolism in the retrosplenial cortex (RSC) as measured by FDG-PET is consistently found to be reduced in AD. **Purpose.** To assess whether phospholipid and energy metabolism shows regional variation in AD we performed 3D phosphorus Magnetic Resonance Spectroscopic imaging (^{31}P-MRSI) in AD patients.

Methods. ^{31}P MRSI was performed in 17 drug-naïve mild (MMSE >20) AD patients, aged 60-86 years. ^{31}P-MRSI spectra were acquired of the whole brain on a Siemens Magnetom Trio 3T scanner with a dual-tuned ^{1}H / ^{31}P volume head coil (RAPID) and a 3D pulse-acquire sequence with the following parameter values: TR=2000 ms, TE=0.10 ms, 40° flip-angle, NA=4, WALTZ4 proton decoupling, nominal voxel size=16x16x16mm). Additional T1-weighted images were segmented into gray matter (GM), white matter (WM) and cerebral spinal fluid (CSF). Resonances in spectra from four regions of interest (ROI; left and right hippocampus, HL and HR; anterior cingulate cortex, ACC; and retrosplenial cortex, RSC) were fitted (Figure 1), resulting in metabolite levels of the phosphomonoesters phosphocholine (PCho) and phosphoethanolamine (PEtn), the phosphodiesters glycerophosphocholine (GPCho) and glycerophosphoethanolamine (GPEtn), inorganic phosphate, phosphocreatine, nicotinamide adenine dinucleotide and ATP. For all metabolites the ratio to the total phosphorus signal was calculated. In addition we calculated pH and ratios for phosphomonoesters to phosphodiesters (PME/PDE), PC to GPC, PE to GPE, and PCr to Pi. Multilevel linear mixed models and planned comparisons were used to test for differences in metabolite peak areas among brain regions. This analysis method was chosen because it can model effects in correlated data. This correlation arises from the multiple brain regions within participants that are being analyzed.

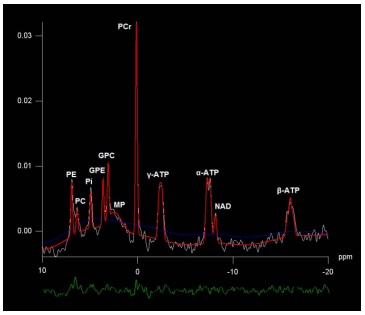

Fig. 1 ^{31}P spectrum from a voxel (16x16x16 mm) in the retrosplenial cortex. Spectral fitting was performed with Metabolite Report (Siemens). The raw spectrum (white), the modelled fit (red), the baseline (blue) and the residual (green) are shown.

Results. PME/PDE, PC/GPC and PE/GPE ratios were significantly predicted by the type of ratio, by ROI and by gray matter fraction {GM/(GM+WM+CSF)}. PCr/Pi ratio was significantly predicted by ROI and by gray matter fraction.

Results for the planned comparisons are shown in Figure 2 (phospholipids) and Figure 3 (high energy phosphates). Metabolite peak areas were significantly (P<.01) higher in the ACC compared to the RSC for PC, PE and NAD. Metabolite peak areas were significantly lower in the ACC compared to the RSC for PCr. Significant lower metabolite peak areas in the RSC compared to both hippocampi were observed for PC, α-ATP, β-ATP, γ-ATP and NAD. Comparing the ACC to both hippocampi showed significant lower metabolite peak areas in the ACC for PCr, α-ATP, β-ATP, γ-ATP and higher metabolite peak areas in the ACC for PE and Pi. No significant differences in metabolite peak areas between HL and HR were observed for any of the metabolites. MP was not analysed, since 45% of its values were of low quality (CRLB > 30%). There were no significant differences for the metabolites GPE and GPC. The ratios of PME/PDE, PC/GPC and PE/GPE were significantly (P<.01) higher in the ACC compared to the RSC and the hippocampi. The PCr/Pi ratio was significantly (P<0.01) lower in the ACC compared to the RSC and the hippocampi. Mean pH over the whole brain was 7.02 ± 0.03. No significant pH differences between brain regions were observed.

Discussion and Conclusion. The pattern of high energy phosphates in the RSC (high PCr, low ATP, Pi and NAD) is in agreement with the expected pattern in AD, whereas the pattern of high-energy phosphates in the ACC (high Pi and NAD, low PCr and ATP) fits the pattern we expect in normal aging. The ACC is a brain region especially vulnerable to age-related hypometabolism, with no evidence of an enhanced decline in AD [3,4]. The observed variations in the phosphomonoesters, combined with literature findings of increased PME compared to healthy elderly in the frontal cortex, and decreased PME compared to healthy young people in the hippocampus [2,5,6], suggest a compensatory mechanism to restore membrane phospholipids, which is more pronounced in the ACC compared to the hippocampi and the RSC. These data indicate regional differences of phosphorus metabolites in the mild AD brain.

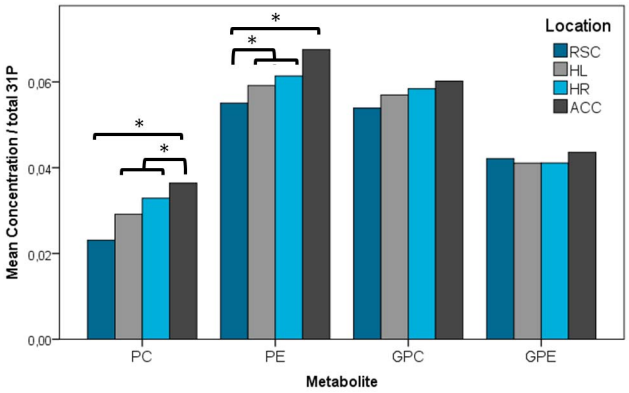

Fig. 2 Metabolite concentrations of PE, PC, GPE and GPE in the four investigated brain regions. * p<.01.

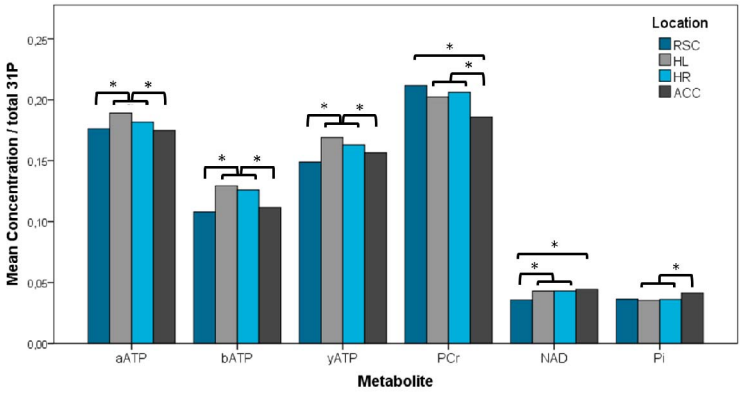

Fig. 3 Metabolite concentrations of the ATPs, PCr, NAD, and Pi in the four investigated brain regions. * p<.01.

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