Associations of glutamate, membrane phospholipid and high energy metabolism – a combined ^{1}H- and ^{31}P-MR spectroscopic imaging study

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Target audience: Psychiatric research and MR spectroscopy community.

Purpose

As reported in recent studies, several psychiatric disorders like schizophrenia are often associated with local changes in brain morphology [1, 2]. These processes may be related to the excitotoxic cellular damage that occurs as a result of deregulated glutamatergic activity, which in turn leads to an altered cell membrane turnover associated with changes in phospholipid and energy metabolism. The neurochemical mechanisms behind these changes can be investigated *in vivo* by combining proton (^{1}H) and phosphorous (^{31}P) MR spectroscopy (MRS) to quantify glutamate, compounds of phospholipids (PDE and PME) and the metabolite phosphocreatine (PCr), which is related to energy demand. We applied this combined approach in a large cohort of healthy volunteers to analyse the metabolic associations under normal physiological conditions.

Methods

58 healthy controls participated in this study (31 males and 27 females, age: 25±6 years). All MR measurements were performed with a whole-body 3 T MR scanner (Magnetom Trio, Siemens) and a double tuned (^{1}H/^{31}P) head coil (Biomedical Rapid GmbH). The protocol (TA ≈ 1.5 h) included a whole-head 3D MRI scan (MP-RAGE) with isotropic spatial resolution (1 mm^3) as well as identically oriented 2D ^{1}H-PRESS-CSI (TE/TR = 30/2000 ms, matrix: 16×16, FoV = 240×240 mm²) and 3D ^{31}P-CSI (TR = 3 s, interpolated matrix: 16×16×16, FoV = 240×240×240 mm³). Due to low B_0 homogeneity in the occipital part of the CSI slices, only spectra of 22 voxels located in the frontal central brain regions were analysed (blue marked RoI in Fig. 1b). Intensities of ^{1}H and ^{31}P compounds were quantified with LCModel [3] and jMRUI [4], respectively. Absolute concentrations of ^{1}H metabolites were estimated by using the water intensity as internal reference [5]. ^{31}P compounds are presented in arbitrary units that represent intensities normalized to the total phosphorus amount in the spectra. Associations between glutamate and membrane lipid and energy turnover were analysed by means of Pearson correlation analysis.

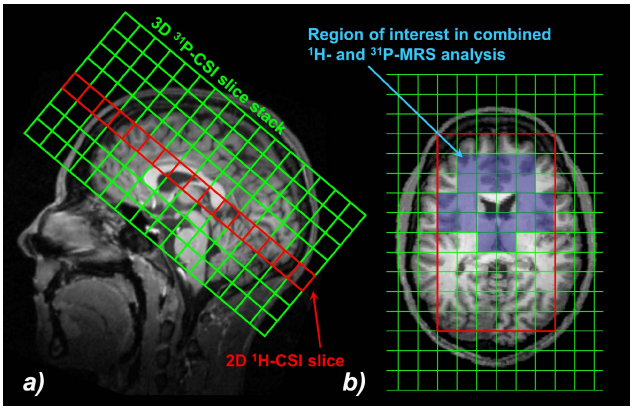

Fig. 1 Position of CSI volumes in sagittal (a) and transverse (b) planes of MP-RAGE data. For improved illustration, only 8 slices of the ^{31}P-CSI volume (green) are displayed in (a). The blue box in (b) shows the CSI voxels that were evaluated in this study.

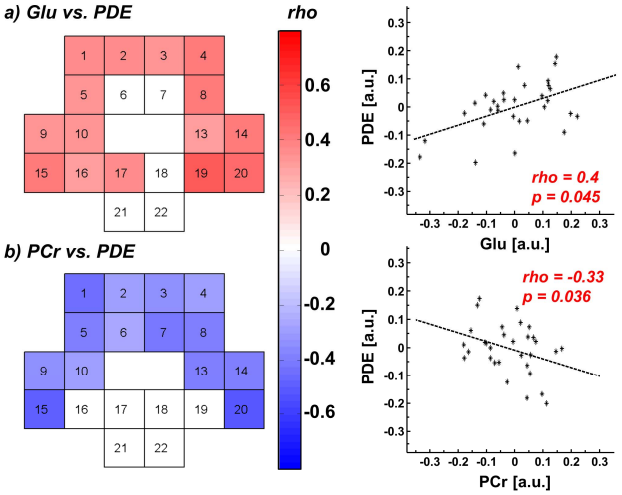

Fig. 2 Distributions of Pearson coefficients (rho) for the association between Glu and PDE (a) as well as between PCr and PDE (b) within the CSI RoI (only correlations with $p < 0.1$ are highlighted). Right subplots show the trend lines obtained for these associations in the anterior cingulate cortex (voxel 3).

Results

The PDE revealed significant positive correlations with glutamate in almost all voxels of the selected region of interest (rho range between 0.30 and 0.50, $p < 0.1$; Fig. 2a). At the same time PCr decreased significantly with increasing PDE in voxels covering the outer areas of the region of interest (rho range between -0.50 and -0.25, $p < 0.1$; Fig. 2b). Few local PME increases were seen with increasing glutamate (rho range: 0.28 and 0.55) as well as with decreasing PCr (rho range: -0.39 and -0.30) (not shown).

Discussion and Conclusion

The current study underlines the advantage of using combined ^{1}H- and ^{31}P-MR spectroscopy to directly analyse associations between glutamatergic tone and several phosphorous metabolites. The observed positive correlations between glutamate and PDE suggest that, under healthy conditions, the glutamatergic tone modulates the turnover of membrane phospholipid breakdown. Simultaneously, the negative associations between phospholipids and intracellular phosphate buffer PCr may be interpreted as an activation of glycolytic energy pathways due to the elevated energy demand for maintaining the membrane structure. Our currently ongoing study is focused on applying this approach to patients with psychiatric diseases to explore the short and long term effects of glutamatergic deregulation on cell membrane impairments. In addition, combined analysis of spectroscopic and morphological data may help to identify associations between neurochemical dysfunctions and brain tissue changes and, thus, to specify disease phenotypes.

References

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