EVALUATION OF GLUTAMATERGIC METABOLISM AND ITS ROLE IN NEUROVASCULAR COUPLING BY COMBINED PROTON MAGNETIC RESONANCE SPECTROSCOPY AND PSEUDO-CONTINUOUS ARTERIAL SPIN LABELING IN AGING

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Target audience: Clinical scientists and clinicians who are interested in proton magnetic resonance spectroscopy in Alzheimer's disease and aging

Purpose: Glutamate (Glu) is the major excitatory neurotransmitter in the brain and thought to be involved in functions such as motor behaviour, cognition and emotion, which alter with age. In this study, we investigated the relationship between absolute Glu and glutamine (Gln) concentrations in anterior cingulate cortex (ACC) during normal aging in a local Chinese cohort using quantitative proton magnetic resonance spectroscopy. Moreover, since changes in glutamatergic metabolism might indicate altered brain functions, which could lead to changes in cerebral blood flow (CBF) via neurovascular coupling [2]. We also measured CBF in our cohort using pseudo-continuous arterial spin labeling (PCASL), and explored the relationship between glutamatergic metabolism and CBF.

Methods: 33 cognitively normal (Montreal Cognitive Assessment≥28) subjects (mean=48.67±15.08 years, age range 26-82 years) underwent MR scan using 3.0T scanner (Achieva, Philips Healthcare). STEAM (TE/TR/TM=80/2000/8.7ms) was used as volume selection method with single voxel of 2x2x2cm^3 placed in ACC. Glu and Gln were measured and quantified with cerebrospinal fluid normalization using internal water as reference by QUEST in jMRUI (4.0) (Figure 1). Imaging parameters for PCASL were similar to a prior study [3] with 29 slices, bottom slice at 60mm below the AC-PC line, slice thickness=5mm, no gap, 30 pairs of labeled and control images. CBF maps were calculated using in-house MATLAB scripts following [4]. Global CBF and ACC-regional CBF were obtained for each subject. Bivariate linear and logistic regressions in SPSS version 20.0 were used for statistical analysis and level of significance was set at 0.05.

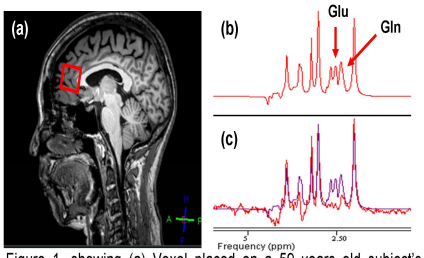

Figure 1. showing (a) Voxel placed on a 59 years old subject's anterior cingulate cortex, (b) simulated spectrum using the parameter QUEST in jMRUI, and (c) spectrum obtained from the subject (red) was superimposed on the estimated spectrum (blue) from QUEST.

Results: Gln showed a significant positive correlation with age [6.29±1.66mmolkg^{-1}; Pearson correlation coefficient (r)=0.346; p=0.048] (Fig. 2a). However, Glu did not show a significant age-dependence (Fig. 2b). Global CBF [mean=63.00±11.49ml/100g/min; r=-0.419; p=0.021] and regional CBF [mean=85.54±20.04ml/100g/min; r=-0.564; p=0.001] both revealed significant negative correlation with age (Figure 3). When comparing the glutamatergic metabolism with CBF, no significant correlation was found between {Glu, Gln} and {global CBF, regional CBF} in ACC. Regression analysis showed that the Gln increase with age effect is not strengthened by adding CBF as a covariate.

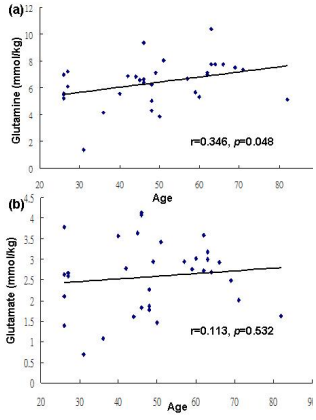

Figure 2 shows scatter plots between age and the concentrations of Gln and Glu.

Discussion: This increase of Gln with age could be due to conversion of excess Glu to prevent excitotoxicity associated with aging. We did not find age-related decrease in Glu concentration as showed by a recent study [5], which could be due to different population and sample size. Consistent with previous literature [6], we also found a significant age-effect on CBF, and ACC CBF was found to decline at a faster rate than global CBF. We found no direct relationship between CBF and glutamatergic synaptic activity in aging, suggesting that the alteration of glutamatergic metabolism in aging might not play a major role in age-related CBF changes.

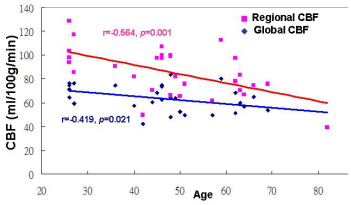

Figure 3 shows the relationship between age and CBF.

Conclusion: Age-related alteration in glutamatergic metabolism might not directly affect CBF.

[1] G. Segovia et al, 2001. Mechanisms of Ageing and De6elopment 122: 1–29; [2] Sibson, 1998. Proc. Natl. Acad Sci. 95:316-321; [3] Liu et al., 2012. NMR in Biomed. 25:779-786; [4] Alsop et al, 2014. MRM, doi: 10.1002/mrm.25197; [5] Hadel et al., 2013. JMRI 38:1480; [6] Lu et al. 2011. Cereb Cortex. 21:1426-1434.