Rapid Brain Glutamate Mapping in Central and Peripheral Gray Matter at 3 and 4 Tesla using short TE Proton-Echo-Planar-Spectroscopic-Imaging (PEPSI)

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Introduction: Glutamatergic excitotoxicity has been hypothesized to be a common mechanism across several neuro-psychiatric diseases [1]. Consequently, mapping glutamate and glutamine in human brain, which are tightly coupled to energy metabolism and excitatory synaptic neurotransmission [2], is of great interest. In this study we assess the reliability of mapping glutamate and other multiplet resonances at 3 and 4 Tesla across a whole brain slice that includes peripheral gray matter using the Proton-Echo-Planar-Spectroscopic-Imaging (PEPSI) method [3].

Methods: Measurements were performed in more than 30 healthy subjects at 3 sites at 3 Tesla (Siemens Trio) and at one site at 4 Tesla (Bruker MedSpec). PEPSI data were acquired from axial slices parallel to AC-PC above the lateral ventricles and through the anterior cingulate (AC) using TR = 2s, 32x32 spatial matrix, FOV = 256 mm, slice thickness = 15 mm, voxel size 0.75 cc. Outer volume suppression was applied using 8 slices positioned on the periphery of cortical tissue to reduce peripheral lipid signals. Single average non-water suppressed data were obtained for phase and frequency shift correction. Two different echo times (TE = 30ms, 15ms) were examined at different acquisition times (from 2 minutes to 24 minutes), using different number of averages. Metabolite maps from the inferior slice were computed by combining two data sets obtained with region-optimized higher order shim settings: (a) whole slice (b) 5x5 cm^2 VOI across the AC. Spectral fitting was performed with LCModel [4], and mean Cramer-Rao lower bounds (mCRLB) were used to assess the quality of the fit for ten metabolites (Ala, Cho, Cre, Gln, Glu, Glu+Gln, Ins, macromolecules (MM), NAA, NAA+NAAG – Note: same labels are used in the figures) across the entire spectroscopic slice (over 100 voxels).

Results: Consistent spectral quality and lipid suppression was obtained across the entire slice, including peripheral gray matter areas (**Fig.1**), at both 3 and 4 T in measurement times as short as 2 min. Metabolite concentrations were within the ranges of previously published studies. Mean CRLBs for Ino and Glu in supra-ventricular slices at 8.5 min were 7 and 8 %, respectively (**Fig.2**). Glutamate maps displayed approx. two-fold concentration differences between white matter and central and peripheral gray matter areas (**Fig.3**). Smaller, but consistent gray /white matter differences were also seen in Cr maps. Mean CRLBs in slices through AC were similar to those in supra-ventricular slices for singlet resonances and approx. 50 % larger for Ino and Glu (**Fig.4**). For all metabolites studied, the mCRLB's were significantly smaller at TE = 15 than at TE = 30 ($p < 0.05$, except Ala, **Fig.5**). The reduction was strongest for Gln (30 %, ; $p < 0.033$), Glu (70 %, ; $p < 0.002$), and Ins (60 %, ; $p < 0.007$). For all metabolites, maximum improvement in mCRLB's was achieved with 8 averages (8.5 min acquisition), beyond which mCRLBs decreased only asymptotically. Mean CRLBs at 4 T in supra-ventricular slices were significantly smaller than those at 3 T ($p < 0.05$, except Ala and Gln) (**Fig.6**).

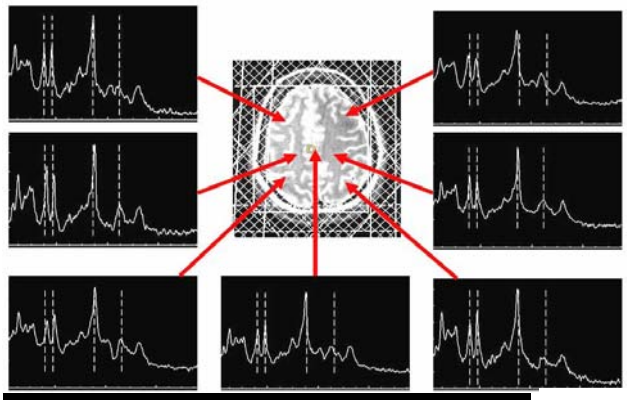


Fig.1: Selected spectra at 4 T acquired in 8.5 min.

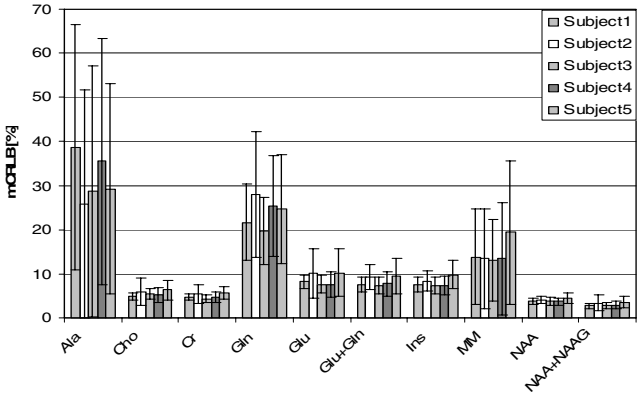


Fig.2: Means and standard deviations of metabolite CRLBs at 4 T averaged across whole supra-ventricular slices in 5 subjects

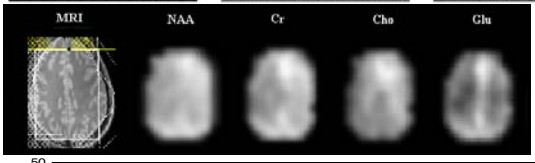
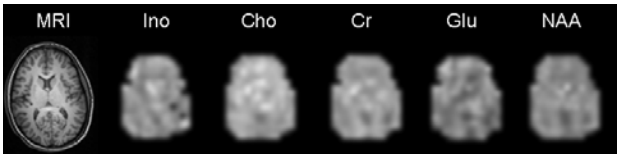


Fig.3: GM/WM contrast in supra-ventricular slice at 4 T at TE 15 msec.

Fig.4: Metabolite maps at 4 T in slice through anterior cingulate at TE 15 msec



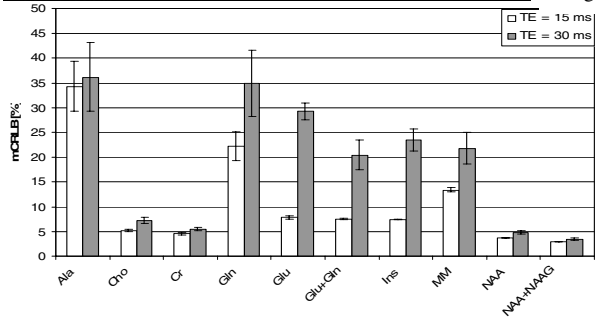
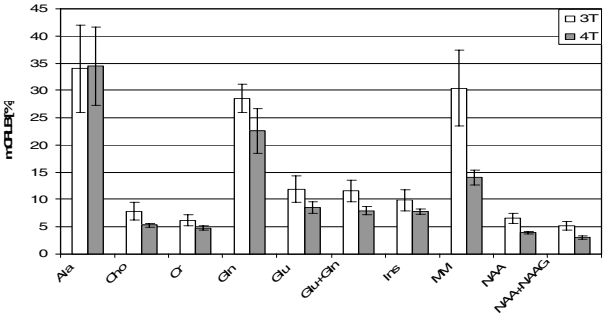


Fig.5: Mean CRLBs at TE 15 ms (white bars) versus 30 msec (gray bars).

Fig.6: Mean CRLBs at 3 T (white bars) and 4 T (gray bars).



Discussion: This PEPSI methodology enables tissue type specific quantification of multiplet resonances in whole brain slices. Spectral quantification was consistent across multiple research centers and benefits of increased field strength were shown. In vivo mapping of glutamate in clinically feasible acquisition times may have important diagnostic applications [5]. This methodology is applicable to identifying metabolic biomarkers in a wide range of neurological and psychiatric disorders.

Literature: (1) Coyle JT, et al. Curr Drug Targets CNS Neurol Disord. 1:183, 2002. (2) Shulman RG, et al. Trends Neurosci. 27:489, 2004. (3) Posse, S., Magn Reson Med, 33, 34, 1995 (4) Provencher, S., Magn Reson Med 30:672, 1993. (5) Sanacora G, et al. Arch Gen Psychiatry 61:705, 2004. *Supported by NIDA 1 R01 DA14178-0, NIH RR008079, P41 008079, the MIND Institute and the Keck Foundation. We thank Ranee Barrows, Robert Moseley and Diana South for technical support.*