Feasibility and reproducibility of neurochemical profile quantification in the human hippocampus at 3T

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Introduction: The hippocampus, a brain structure located deep in the temporal lobe, plays an essential role in learning and memory formation [1] and is thought to play a role in regulation of stress[2]. Hippocampus dysfunction is thought to be involved in several neurological, psychological and metabolic diseases, including Alzheimer's disease[3], temporal lobe epilepsy[4], schizophrenia[5], stress- and trauma-related disorders[6] and diabetes[7]. Therefore there is great interest in studying the hippocampus using ^{1}H MRS to identify how these diseases alter its neurochemistry. However, prior ^{1}H MRS studies reported hippocampal concentrations of 3-5 neurochemicals only[3, 8], even at 3T, and demonstrated substantial challenges with obtaining high quality spectra from this structure (small size, susceptibility effects leading to broad linewidths)[9]. Here we investigated the feasibility of obtaining high quality hippocampal spectra that allow quantification of a neurochemical profile using standard hardware (clinical 3T scanner & coil) with an in-house implemented single-voxel, short-echo semi-LASER sequence and optimized parameters. We further investigated the intersession reproducibility of neurochemical concentrations in hippocampus, a critical consideration when planning longitudinal clinical studies.

Methods: Six healthy volunteers (2 males, 4 females, age 33±7 years) were enrolled in the study. ^{1}H MR spectra were measured from a 13 x 26 x 12 mm³ hippocampus voxel (Fig. 1) at 3 T (Siemens Tim Trio) with body coil excitation and 32 channel receive array in two sessions performed 34±30 days (±SD) apart. A modified semi-LASER sequence[10] (TE = 28 ms, TR = 5 s, NEX = 64) was used for localization. Single-shot data were frequency and phase corrected prior to summation. First- and second-order shims were adjusted using FASTMAP[11]. Metabolites were quantified with LCModel[12] using the unsuppressed water signal as reference. A spectrum of fast-relaxing macromolecules measured on the same magnet was included in the basis set. Only those metabolites measured with Cramér-Rao lower bounds (CRLB) < 50% in at least 50% of the spectra are reported. If the cross-correlation coefficients between 2 metabolites was consistently < -0.5, their sum was reported. Coefficients of variance (CV) reflecting intersession reproducibility of metabolite concentrations were calculated for each subject and the between-subject mean CV were reported. Gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) content of each voxel was derived using SPM8 and an in-house written MATLAB script for brain segmentation.

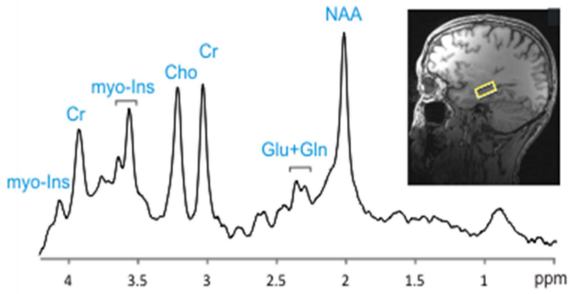

Fig.1.Representative spectrum acquired in hippocampal voxel (semi-LASER, TR=5s, TE=28ms, 64 transients). Gaussian smoothing was applied for display purposes (gaussian factor was 0.15).

Results: Spectral quality (SNR, resolution, water and unwanted coherence suppression) and the LCModel fitting (CRLB, spline baseline and residuals) were highly reproducible between the spectra of the 6 volunteers (sample spectrum in Fig. 1). FASTMAP shimming resulted in water linewidths of ~8 Hz. The spectral quality allowed quantification of 6 metabolites with mean CRLB ≤ 10%. Four other metabolites with low concentrations had CRLB ≤ 30% (Fig. 2). Mean intersession CV was below 10% for 8 metabolites. Brain tissue segmentation identified intra-voxel CSF content of 5.5±1.8% and hippocampal gray matter content of 68.8±6.4% (mean±SD). The segmentation results were very consistent between sessions and therefore the correction of concentrations for intra-voxel CSF content had minimal impact on the mean CV values. Mean intersession CV of the intravoxel CSF content was 8.3%.

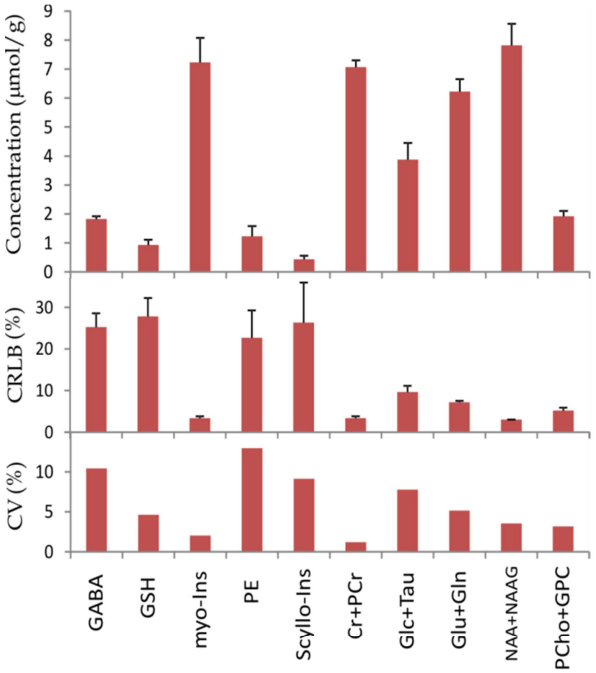

Fig.2. Mean metabolite concentrations and CRBLs for hippocampus are shown. Error bars represent intersubject variability (SD). Mean test-retest coefficients of variance (CV) express intersession variability of concentrations.

Conclusions: High spectral quality can be obtained reproducibly from a ~4mL hippocampal voxel with minimal partial voluming using standard 3T hardware, an in-house implemented short echo, single voxel pulse sequence and 5 min data averaging. These spectra allow the reliable quantification of a neurochemical profile from this challenging volume-of-interest. The pattern of neurochemical concentrations was in agreement with prior studies[9]. Namely, a lower NAA+NAAG and a higher *myo*-inositol concentration relative to cortical areas were consistent with a lower neuronal density and higher glial density than in neocortical tissues[9]. This methodology will allow investigations of neurochemistry in many common clinical conditions using widely available hardware.

References: **1.** Squire & Zola-Morgan, *Science* (1991) 253:1380; **2.** Jacobson & Sapolsky, *Endocrine Rev* (1991) 12:118; **3.** Dixon et al, *Brain* (2002) 125:2332; **4.** Chang & Lowenstein, *N Engl J Med* (2003) 349:1257; **5.** Shenton et al, *N Engl J Med* (1992) 327:604; **6.** Karl et al, *Neurosci Biobehav Rev* (2006) 30: 1004; **7.** den Heijer et al, *Diabetologia* (2003) 46:1604; **8.** Reyngoudt et al, *Eur J Radiol* (2012) 81:e223, Shiino et al, *JCBFM* (2012) 32:805; Watanabe et al, *Neurobiol Learning&Memory* (2012) 97:289; **9.** Choi & Frahm, *MRM* (1999) 41:204, Geurts et al, *JMRI* (2004) 20:366; **10.** Oz & Tkac, *MRM* (2011) 65:901; **11.** Gruetter & Tkac *MRM* (2000) 43:319; **12.** Provencher, *NMR Biomed* (2001) 14:260.

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