REGIONAL VARIATION IN THE METHYL 1H SIGNAL INTENSITY OF ETHANOL IN THE NON-HUMAN PRIMATE BRAIN.

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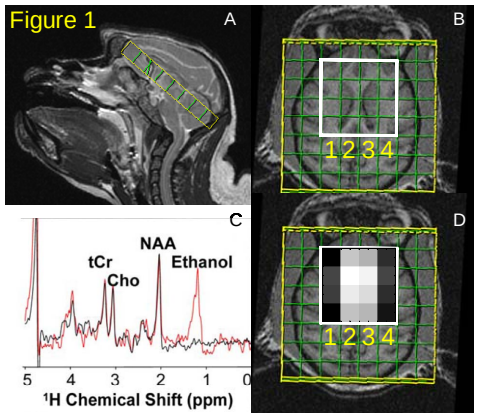
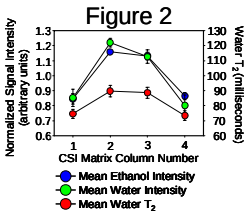
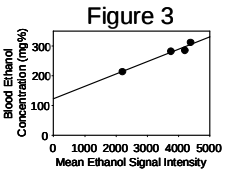
Introduction Studies examining the neurotoxic effects of ethanol on the human brain frequently report conflicting results. Such disparate results are likely due, in large part, to methodological challenges inherent in human subjects research. Less variation is seen in animal studies where brain structures can be examined before and after the controlled administration of known quantities of ethanol. Yet, in spite of this greater level of control over the conditions of ethanol exposure, individual differences among subjects remain. The source of this variability is not known, however, NMR spectroscopy allows for the examination of the possibility that differences in the pattern of brain damage following chronic ethanol exposure parallels individual differences in the distribution of ethanol in the brain, as well as differences in the manner in which ethanol interacts with the local molecular environment (reflected in brain region specific changes in ethanol T2).

Methods Four female cynomolgus monkeys served as subjects. Using a Siemens 3T trio MRI system, a T2-weighted scout image was first obtained in the sagittal plane. This image was then used to orient a transverse 3D-MPRAGE image in an ACPC frame of reference. A similarly oriented single transverse baseline CSI (TE/TR = 150 ms/1770 ms, isotropic 8-mm-sided voxels) was then obtained and an intravenous infusion of 1.5 g/kg of ethanol was given over the course of 15 minutes. Subsequent CSIs were obtained every two minutes for one hour. Every other CSI was obtained without water suppression and at randomly determined echo times (ranging from 20-500 ms) to quantify the regional variation in water signal intensity and T2. The ethanol MR signal was quantified as the integrated intensity of the pre/post infusion difference spectrum from 1 to 1.5 ppm. Blood samples were obtained by venipuncture for the determination of blood ethanol concentration 10 and 60 minutes following the ethanol infusion.

Results and Discussion The approach used to quantify brain ethanol MR signal intensity is shown in Fig. 1. The CSI plane is overlaid on anatomical images for one monkey in Figs. 1a and 1b. The methyl ^{1}H resonance intensity is determined from difference spectra recorded prior to (black, Fig. 1c) and following (red, Fig. 1c) ethanol administration. Fig. 1d shows the average intensity map obtained from three animals, each measured in duplicate over a period of 4 days, relative to the anatomy for one of the animals.







Intra-animal variability A regional pattern in ethanol signal intensity is observed using an echo time of 150 ms, in which medial voxel positions exhibit approximately 30% greater intensity than lateral positions. A similar pattern is observed for H_2O signal intensity in spectra obtained using a TE of 150 ms, and in the H_2O T_2 value (Fig. 2). These findings suggest that ethanol signal intensity is strongly correlated with the voxel volume fraction of CSF, and are consistent with their being an MRS-invisible pool of motionally-restricted ethanol in the brain (Meyerhoff et al., 1996). The CSF contribution to the total ethanol MR signal intensity is expected to increase with TE, and therefore be of importance in the interpretation of MRS studies of human brain ethanol.

Inter-animal variability The MRS signal intensity per concentration of ethanol infused was observed to vary as much as two-fold between animals. This variability is reflected in venous BEC (Fig. 3), however BEC and MRS measurements are not proportional (i.e. they cannot be represented as a line in Fig. 3 through the origin). Experiments are underway to investigate the potential role of variability in ethanol T_2 values as a source of BEC/MRS mismatch.

References Meyerhoff DJ, Rooney WD, Tokumitsu T, Weiner MW (1996) Evidence of multiple ethanol pools in the brain: an in vivo proton magnetization transfer study. Alcohol Clin Exp Res 20: 1283-8