Quantitative 7T Detection of Gadoteridol in the Ventricles of the Aging Human Brain

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Introduction: Decreased cerebrospinal fluid (CSF) turnover and expansion of cerebrospinal spaces are hallmark features of the aging brain.[1,2] In humans, ultrastructural abnormalities of the ventricular cytoskeleton, ependyma, astroglia, and subventricular zone cells that form the lining of the ventricles are also known to increase with age.[3] Longitudinal water proton (^1H_2O) relaxation rate constants (R_1) are strongly associated with macromolecular volume fraction[4] and are a potentially powerful probe of CSF dynamics and blood cerebrospinal fluid barrier (BCSFB) function. The aim of this study was to investigate the effect of aging on the permeability of the BCSFB using a low molecular weight gadolinium contrast reagent (CR).

Methods: 34 healthy older subjects (13 M, 69 ± 6 yrs; 21 F, 68 ± 6 yrs) provided informed consent and were enrolled. MR data were acquired on a 7T Siemens MAGNETOM instrument with 8-channel RF transmit/receive head coil. Full volume axial IR-MPRAGE acquisitions (TR/TE= 3500/2.4 ms; FA= 6°; 1 mm^2 in-plane resolution; 2 mm slice thickness) centered on the lateral ventricles were sampled at different inversion times (TI= 300, 1800, 3200 ms; and no inversion pulse). IR datasets were collected prior to and 12, 31, 45 min post CR (gadoteridol) injection (0.11 mmol/kg; 2 mL/s). Parametric maps were prepared after co-registration of all images (using FIRST, a tool in FMRIB's Software Library, FSL)[5] and voxelwise evaluation of the Bloch equation for each variable TI dataset accounting for all RF pulses and delays with the constraint that each voxel exhibit monoexponential IR recovery.[6] IR-MPRAGE structural images were also acquired (TR/TE/TI 2300/2.8/1050 ms; FA 6°; 0.8 mm^3 resolution) and used for determination of total CSF and intracranial volume (FSL, SIENAX).

A bilateral ROI was defined in the superior lateral ventricles by a binary CSF mask prepared by 3-class segmentation (FSL, FAST) of the TI1800 MPRAGE image. Erosion (1 mm) of the mask prior to application to the R_1 maps ensured minimal partial volume averaging by the ventricular lining. Visual inspection of source files confirmed the ROI was superior to the fornix and free from any visual choroid plexus in all subjects. Mean ROI volume was 1.02 ± 0.53 mL. Statistical analyses were performed using Stata (College Station, TX).

Results and Discussion: ^1H_2O R_1 values pre-CR (≡ R_{10}) are inversely correlated with CSF volume in the elderly brain (**Figure 1**, top). Together with the age-related increase in ventricular volume observed here (Fig 1, bottom) and by others,[7] this result suggests that ventricular expansion, a hallmark of the aging brain, is associated with an increased CSF water:macromolecule ratio. Since CSF protein concentrations vary little with age,[8] this finding may reflect changes in overall water flux with ventricular dilatation. The time course of ^1H_2O R_1 values after CR injection is shown in **Figure 2** (top). These data confirm, for the first time, that administration of CR increases ^1H_2O R_1 in the ventricles of the human brain (P= 0.006). In the context of a relatively intact blood-brain barrier, the temporal changes in R_1 observed here may reflect CR leakage across the BCSFB (ca. 2 μM hr^{-1}), the clearance of which is likely to decrease with age.[9] As shown in Fig 2 (bottom), the rate of R_1 change after CR administration (ΔR_1) varies significantly with gender. Since no gender-dependent differences are observed in blood ΔR_1 values, as measured at the sagittal sinus (P= 0.83; data not shown), concentration dependent effects on ventricular ΔR_1 differences are likely small. Thus, the difference in the temporal changes in ^1H_2O R_1 values after CR administration may reflect alterations of BCSFB function and/or disturbances in CSF dynamics in elderly females, leading to accumulation of CR in the ventricles. Increased temporal resolution (both in the early and long-times post CR) and additional subject numbers will be necessary to substantiate these results.

Grant Support: NIH (AG 033638, AG 08017, EB 007258), the Oregon Partnership for Alzheimer's Research, and the Oregon Opportunity. **References: 1.** Fjell and Walhovd, *Rev Neurosci* 21, 187-221 (2010) **2.** Redzic, et al., *Curr Top Dev Biol* 71, 1-52, (2005) **3.** Del Bigio *Acta Neuropathol* 119, 55-73 (2010) **4.** Rooney, et al., *Magn Reson Med* 57, 308-18 (2007) **5.** Smith, et al., *Neuroimage* 17, 479-89 (2002) **6.** Deichmann and Haase, *J Magn Reson* 96, 608-12 (1992) **7.** Schwartz, et al., *Ann Neurol* 17, 146-57 (1985) **8**. May, et al., *Neurology* 40, 500-03 (1990) **9.** Silverberg, et al., *Lancet Neurol* 2, 506-511 (2003).

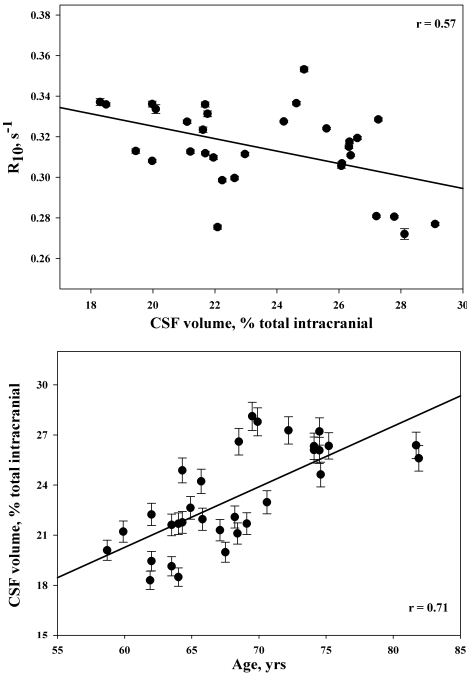

Figure 1. Linear regression fits of CSF volume to (top) ^1H_2O R_1 values (P= 0.007), and (bottom) age (P< 0.001). Values are ± SE. Data from 2 subjects excluded as outliers.

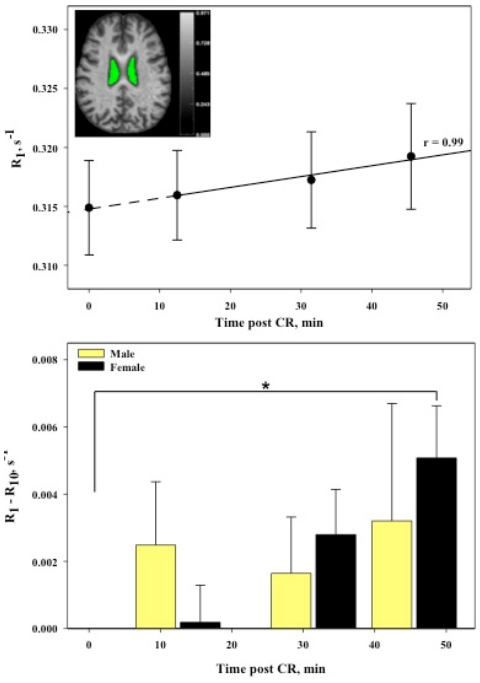

Figure 2. (top) Mean (± SE) ^1H_2O R_1 values vs. time after CR administration. A representative pre-CR R_1 map from a 74 year old female is also shown. (bottom) Mean ^1H_2O R_1 values (± SE) in males and females. Temporal changes are significantly different in females and males (P= 0.02; repeated measures anova).