Semiautomatic Segmentation and Quantification of Volume, T2 Relaxation time and Mean Diffusivity of the Human Brain CSF Compartments across the Lifespan

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Introduction: Due to its close interplay with the vasculature, cerebrospinal fluid (CSF) serves as a chemical conduit in intracranial pressure regulation and chemical function **(1).** Whole brain, sulcal and ventricular CSF volumes have been used as a marker of normal brain development and aging **(2,3)** and atrophy in a host of pathologies, including closed traumatic brain injuries **(4)**. In addition CSF chemical and metabolic content serves as a robust biomarker of neural degeneration **(5).** A comprehensive analysis of normative CSF compartmental volumetry, relaxometry and diffusimetry has not been described previously using quantitative magnetic resonance imaging (qMRI). In this report, we applied novel and validated atlas-based segmentation methods **(6,7)** for a detailed investigation of age dependent qMRI changes in the CSF compartments in both men and women.

Methods: The participants included 130 healthy age-matched males and females (p=0.2; age range =18-69 years). The cohort consisted of 61 males (age mean ± S.D = 35.6 ± 11.7 years), and 69 females (38.3 ± 12.4 years). All MRI studies were performed on a 3T Philips Intera scanner. The MRI protocol included fast dual-echo ($TE_1/TE_2/TR$= 9/90/6800) for T2 relaxation mapping and a high resolution (voxel size 0.94 mm) 3D T1-weighted spoiled gradient sequences. The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence, b=1000 sec mm^{-2}, T_R/T_E = 6100/84 msec **(4)**. The slice thickness was 3.0 mm with 44 contiguous axial slices covering the entire brain; FOV=240x240 mm^2 and matching the dual echo sequence:***CSF segmentation and Quantification***: Whole brain CSF (wbCSF) was segmented into ventricular (vCSF) and non-ventricular or sulcal CSF (sCSF). Ventricular CSF included the lateral ventricles body and anterior horns (LV), inferior lateral ventricles (iLV), third ventricle (anterior and posterior) in addition to the 4th ventricle. The ventricles were semi-automatically segmented using an extended and CSF-customized version of a DTI-atlas based approach **(4)** that utilized the superior contrast between CSF and brain parenchyma on the mean diffusivity maps **(4).** Residual CSF-parenchyma partial-averaging was avoided by the application of an erosion mask to the segmented CSF ventricular zones. Systematic validation of these methods was also conduced using serial data, manual delineation, and automated methods that included popular packages such as FreeSurfer **(3)** and FSL **(8).** CSF volume, corresponding average_T2 relaxation time and mean diffusivity average values were computed for each of the CSF compartments. We also applied these methods to the DTI data pooled from different 3T MRI centers utilizing same vendor clicial scanner to assure stability and reliability. The approach provides the volume and corresponding mean diffusivity. Regional and global CSF volumes were normalized to the intracranial volume obtained from each subject to minimize the effects due to skull size variability between subjects (4). **Statistical Analyses**: Comparisons of qMRI(CSF) values between males and females were conducted using analysis-of-variance and generalized linear regression models were used to analysis the age vs. qMRI scatter.

Results: ventricular and sulcal CSF volumes increased with age (**Fig. 1A**); the rates were comparable between men and women in sulcal CSF, but were greater in men than women in vetricular CSF. T2 Relaxation time exhibited strong regional spatial heterogeneity and variability. T2 values were greater in ventricular CSF compared to sulcal CSF and were significantly longer in men compared to women (**Fig. 1B**) Mean diffusivity was greater in vCSF compared to sCSF (**Fig. 1C**). Mean diffusivity was larger in men than in women and increased with age at comparable rates in men and women (**Fig. 1D**).

Discussion: To the best of our knowledge, this is the first cross-sectional report on the combined volumetry, relaxometry and diffusimetry of human brain CSF compartments on a large cohort of healthy men and women. Our results on the age and gender dependence of CSF ventricular and sulcal volumetry are consistent with previous reports using manual delineation (4) and automatic methods (**3, 6**) and show the utility of the global and regional CSF to indirectly monitor tissue brain atrophy. Spatial heterogeneity of T2 values (**9**) and changes in T2 with age may be related to alteration in CSF-dissolved oxygen content as has been shown using T1 relaxometry (**10**). The increase in CSF diffusivity with age may relate to reduced macromolecular or protein content with age due to alteration in blood-CSF barrier and accumulation of proteins in the brain extracellular space **(1).** The spatial heterogeneity of CSF mean diffusivity and T2 values highlight the complex interplay between brain and CSF. Our work paves the way to studies that explore the optimization and use CSF-derived MRI metrics as markers of pathology.

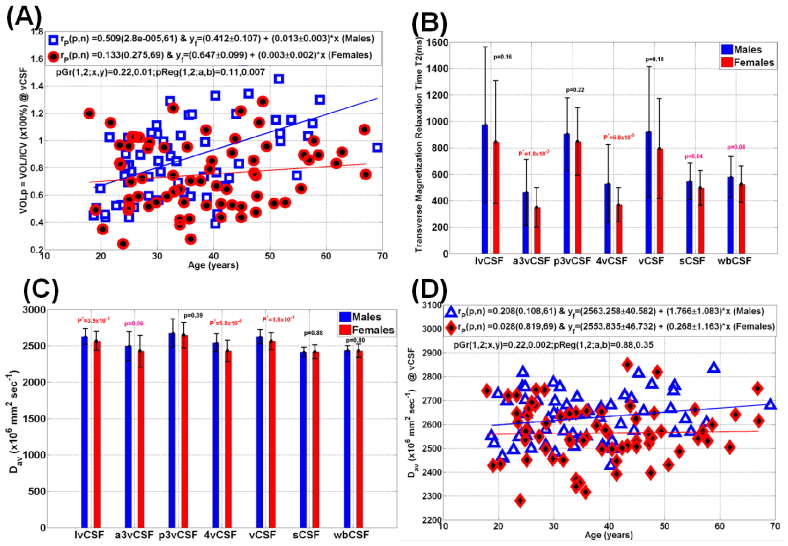

Figure 1. Representative scatter and bar plots of regional heterogeneity age and gender dependence in CSF compartmental **(A)** volumetry, **(B)** T2 and mean diffusivity **(C, D).**

References

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