# Sub-Millimeter Imaging of Brain-Free Water for Rapid Volume Assessment in Atrophic Brains

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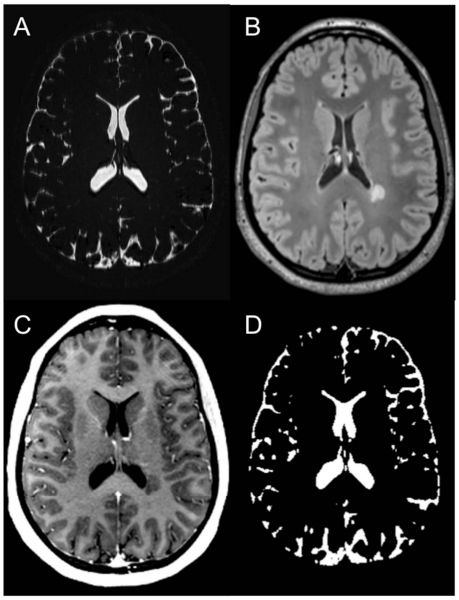
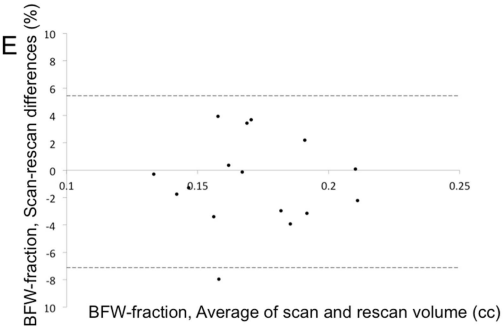
**Target Audience:** Researchers and clinicians studying cerebral atrophy in neurological disorders and aging.

**Purpose:** Cerebral atrophy, a common feature of neurological disorders as well as normal aging, is well known to contribute to clinical disability. Previous imaging measurements of brain atrophy are based on tissue segmentation and classification techniques, which may require multiple imaging contrasts for computation of brain tissue volumes. Here we describe brain-free water (BFW) volume, derived from intensity-thresholding a heavily T2-weighted sub-millimeter resolution scan, as a surrogate for imaging the loss of cerebral tissue volume.

**Methods:** Seven healthy volunteers and 83 MS cases were imaged with a heavy T2-weighted scan (3D TSE, TR/TE=4800/752 ms, FA=100°, GRAPPA=2, fat-sat, 0.65 mm isotropic resolution, and acquisition time=4:43 min), as well as T2-FLAIR (3D SPACE, TR/TE/TI=4800/354/1800 ms, 1 mm isotropic resolution, TA=7:02 min) and post-contrast T1-weighted (3D GRE, TR/TE=7.8/3 ms, FA=18°, 1mm isotropic resolution, TA=3:30 min) sequences on a 3T Siemens Skyra scanner. Sixteen MS cases were rescanned within 2 months to assess reproducibility of the technique. Images were registered to a standard atlas, eyes and sinuses masked, and intensity-thresholded at a fraction of 98$^{th}$-percentile intensity to derive the BFW-volume and BFW-volume normalized to the intracranial volume (BFW-fraction). The results were compared with CSF-volume and CSF volume normalized to the intracranial volume calculated using Lesion-TOADS, a tissue classification algorithm designed for MS brains. MS cases were clinically assessed on Expanded Disability Status Scale (EDSS), Scripps Neurological Rating Scale (SNRS), Paced Auditory Serial Addition Test (PASAT-3), 9-Hole Peg Test (9HP), written Symbol Digit Modalities Test (SDMT), and 25-Foot Walk. The atrophy measures from BFW method and Lesion-TOADS were correlated with clinical measures of disability upon adjusting for age and sex.

**Results:** Heavily T2-weighted images (Fig A), FLAIR (Fig B), T1-weighted (Fig C), and thresholded BFW image (Fig D) from a representative case (25 y.o. woman) are shown. BFW-volume and BFW-fraction were highly reproducible, with rescan COV of 1.4% and 1.8% (Fig E, Bland-Altman plot), respectively. Atrophy measures from BFW techniques consistently showed stronger correlations with clinical measures of disability, than those derived from Lesion-TOADS (Fig F). These stronger correlations accounted for 8-19% more variance in clinical measures after adjusting for age and sex. Among the clinical measures tested, modality-specific measures of disability such as SDMT and 9HPT were more strongly associated with BFW-fraction than composite measures such as EDSS and SNRS.




| F | Volume | | Fraction | |
|---|---|---|---|---|
| | BFW | Lesion-TOADS | BFW | Lesion-TOADS |
| EDSS | 0.15 | 0.12 | 0.25* | 0.14 |
| SNRS | -0.15 | -0.04 | -0.27* | -0.17 |
| SDMT | -0.30** | -0.25* | -0.52** | -0.43** |
| PASAT | -0.23* | -0.09 | -0.38** | -0.34** |
| 9HPT | 0.42** | 0.08 | 0.39** | 0.26* |
| 25' walk | 0.05 | 0.08 | 0.15 | 0.03 |

* p<0.05; **p<0.005, adjusted for age and gender

**Discussion:** Stronger correlations seen in the BFW-based atrophy measures with clinical scores were primarily attributed to errors in skull stripping and tissue classification that plague traditional T1-based segmentation techniques. In BFW-imaging, skull and fat are hypo-intense, circumventing the need for skull stripping, and segmentation is achieved by a simple intensity thresholding. Furthermore, sub-millimeter resolution of the BFW-imaging captures CSF in the sulcal spaces, improving the accuracy of the calculated BFW-volume.

**Conclusion:** BFW-fraction is a fast, robust, and reliable measure of cerebral atrophy, providing better correlation with clinical measures of disability than conventional T1-based segmentation. It holds great promise as a surrogate end point in clinical trials of cerebral atrophy.