

Normalization of White Matter Intensity on T1-weighted Images of Patients with Acquired Central Nervous System Demyelination

Rezwan Ghassemi¹, Robert Brown¹, Brenda Banwell^{2,3}, Sridar Narayanan¹, Kunio Nakamura¹, and Douglas Arnold¹

¹Montreal Neurological Institute, McGill University, Montreal, QC, Canada, ²The Children's Hospital of Philadelphia, Philadelphia, PA, United States, ³Neurology, The Hospital for Sick Children, Toronto, ON, Canada

Background: A major challenge in multicenter magnetic resonance imaging (MRI) studies of brain diseases is comparison of the intensity of pathological tissue on images from different subjects, acquired over time, on different scanners and/or with different sequences. Most intensity normalization techniques are based on histogram matching or depend on the intensity of white matter (WM), and consequently can be sensitive to the effects of WM pathology. We propose a novel intensity normalization method independent of WM.

Objective: (1) To develop a T1-weighted (T1w) intensity normalization method independent of WM, (2) assess the performance in terms of improvements to inter-protocol and inter-scanner variance, as well as statistical power, and (3) compare this with a commonly used histogram-based method proposed by Nyul *et. al.* (1).

Methods and Subjects: Images were evaluated for adequate signal-to-noise ratio, freedom from significant motion or other artifacts, consistency of the sequence parameters, and corrected for spatial intensity non-uniformity. Subsequently, masks of grey matter and intraconal orbital fat, free of partial volume effect, were generated as shown in **Figure 1**, and the median intensity in each mask on T1w images was calculated. Using these two reference tissue intensities we calculated a linear normalization function and applied this to the T1w images to produce normalized T1w (NT1) images. These were compared with unnormalized images and Nyul. Datasets used for validation tests included: (1) 25 patients with multiple sclerosis (MS) scanned on each of two different types of Siemens scanners using different parameters, used to test inter-scanner normalization, (2) a group of MS patients scanned with two different T1w imaging protocols on one of four scanners from different manufacturers (General Electric, 22; Marconi, 19; Philips, 8; Siemens, 11), to test inter-protocol normalization, (3) 10 MS patients with three scans, one year apart, to test longitudinal normalization. The different normalization methods produce images with different intensity ranges so we used a normalized mean absolute difference (nMAD) metric, analogous to the coefficient of variation, for comparison: the mean absolute difference between an image pair was divided by the median whole-brain intensity. For each subject in each dataset, the nMAD between that subject's images was calculated. These were compared using general linear models. Required sample size for an example study was calculated using G*Power software (2) and dataset 3.

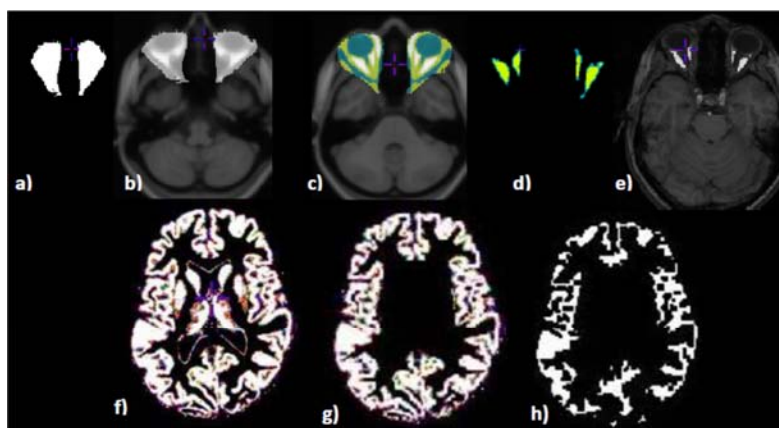


Figure 1: Top row shows intraconal orbital fat segmentation based on: a) the eye structure mask of the International Consortium for Brain Mapping (ICBM) model, b) the ICBM eye mask superimposed on the T1w image non-linearly transformed to ICBM space, c) classification of structures within the eye mask, d) orbital fat mask with erosion, e) inverse transformation of intraconal orbital fat mask to T1w image in native space. Bottom row shows GM segmentation: f) GM probability map obtained from our automatic tissue classifier, g) GM probability map after removal of deep GM, h) mask of cortical GM voxels with 90% or greater GM class probability.

Results: Joint histograms of the scans acquired with different protocols suggested that the intensity differences between T1w images acquired by these protocols are close to linear (**Figure 2**). Statistical modeling showed marked decreases in T1w intensity differences after normalization in both datasets 1 and 2 ($p < 0.0001$). Both Nyul and NT1 normalization also improved longitudinal measurements. Sample size calculations for assessing T1 change within T2w lesions in MS patients suggested 366 subjects would be needed to detect a 50% treatment effect in lesion T1 recovery using unnormalized data, 60 subjects using Nyul normalization and 13 with NT1.

Conclusions: We developed a novel intensity normalization technique independent of WM intensity. Our validation tests showed it outperformed Nyul's method in reducing inter-protocol and inter-scanner differences and in improving the sensitivity of longitudinal change measurements. We suggest that this technique can be applied in longitudinal multicenter MRI clinical studies of brain diseases for assessment of the recovery or progress of disease affecting WM.

References

1. Nyul LG, Udupa JK. On standardizing the MR image intensity scale. *Magn Reson Med* 1999;42:1072-1081.
2. Erdfelder E, Faul, F., & Buchner, A. GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers* 1996;28, 21-11.

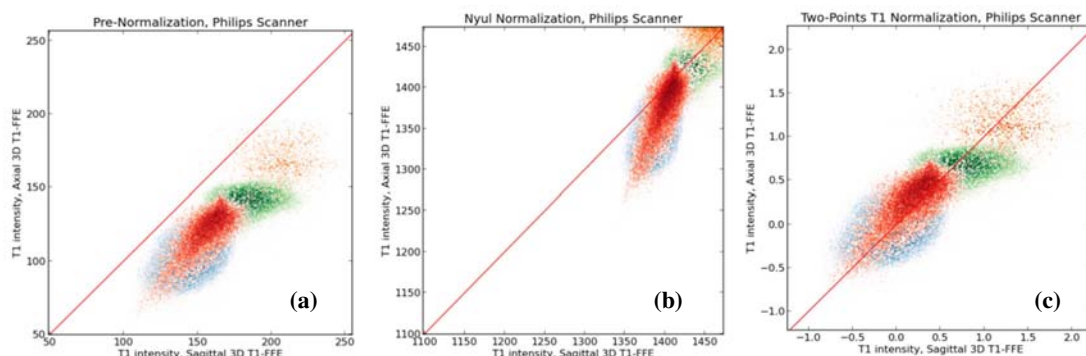


Figure 2: Joint histogram of intensity of two T1w images of the same MS patient acquired with different protocols on the same scanner (a) pre-normalization, (b) post-normalization using Nyul and (c) post-normalization using NT1.