Detecting diffuse white matter alterations in healthy volunteers using Tissue Specific Imaging: Potential implications for cognitive function

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Introduction

Diffuse changes in white matter (WM), usually seen in MRI as distributed non-specific WM hyperintensities in T_2 weighted images, are a common finding in neurologically healthy people. Although uncertainty still remains regarding their etiology, loss of myelinated axons, gliosis and vascular ecstasia [1,2] have been suggested as potential causes. No clinical significance has been attributed to them.

In the current study, we operate on the hypothesis that diffuse WM changes can also affect T_1 of WM. Indeed, subtle T_1 changes in normal WM have been reported in pathological conditions like multiple sclerosis [3]; however, conventional T_1 weighted imaging techniques are not sensitive enough to depict slight changes in the range of normal WM T_1, i.e. around 800-950 ms for 3T.

Double inversion recovery (DIR) [4] offers excellent contrast in the normal WM range, but quantifying affected white matter from it remains subjective and affected by intensity variations due to field inhomogeneity. Thus, for this study we used Tissue Specific Imaging (TSI) [5] to characterize WM as "hyperintense" and obtain masks of affected WM. The methodology presented takes advantage of the three TSI images and a B_1 map in order to normalize intensity and thereby overcome the problems of field and intensity inhomogeneity, offering a semi-quantitative technique to assess WM integrity, thus augmenting the diagnostic value of a DIR technique.

Methods

Twenty six healthy volunteers (44.9±10.6 years old, 19 females, 7 males) participated in the study. All subjects had a clinical evaluation inclusive of a 1.5T clinical MRI read as normal for their age by a radiologist. They all had a 3T MRI (GE Signa Excite) exam, including conventional T_1 and T_2 weighted imaging, TSI (1.5mm isotropic resolution) and B_1 mapping. They all underwent the complete Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery. All cognitive assessments were performed in the AM of the same day.

TSI images were corrected for transmit B_1 inhomogeneity as described in [5]. Subsequently, they were normalized to a zero-contrast reference image [5]. Normalization calculates the contribution of each of the three TSI images to the reference, and removes intensity variations due to B_1 receive inhomogeneity, but also T_2^* and proton density weighting. The resulting three images are largely T_1 weighted maps with values in the range of 0-1, which can serve as likelihood maps for membership to three classes defined as "WM", "gray matter" (GM) and "cerebrospinal fluid" (CSF).

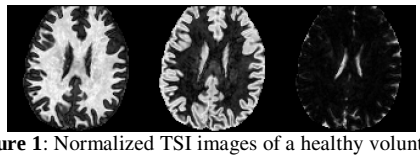

Figure 1: Normalized TSI images of a healthy volunteer

Voxels having WM likelihood values between 0.45 and 0.65 (corresponding approximately to T_1 values between 930 and 1050 ms) were selected as normal appearing WM (NAWM). Thresholds were selected based on T_1 measurements for that region of the brain and minimization of misclassification of the basal ganglia. Erosion with a 2x2 pixel mask, followed by dilation by the same mask was applied to discard isolated voxels at the edge between WM and GM structures, included due to partial volume effects at the transition region. The volume of NAWM masks was measured in a 39 mm thick slab ranging from 8.25 mm below to 30.75 mm above the base of the lateral ventricle (identified manually), and normalized to the total intracranial volume in the slab, obtained by thresholding the reference image.

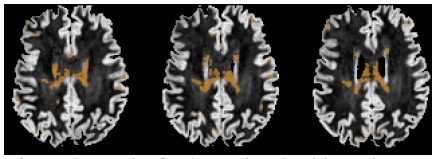

Figure 2: Mask of NAWM in a healthy volunteer

In order to assess the significance of our results, Spearman correlation was used to test for relationships between the NAWM volume fractions obtained and the results of the cognitive tests of the volunteers. A p-value≤0.05 was set as a cut-off through the statistical analysis.

Results

Five volunteers were excluded from the analysis due to image artifacts. For the remaining 21, NAWM volume fraction ranged from 0.8% to 4.2% of the intracranial volume. Those voxels appeared as hyperintense in the GM TSI image. Correlation of NAWM volume fraction with age did not reach significant levels in this study cohort. NAWM volume fraction correlated significantly with the results of the MACFIMS Paced Auditory Serial Addition Test (PASAT) (r=-0.57, p-value=0.007), the MACFIMS Symbol Digit Modalities Test (SDMT) (r=-0.55, p-value=0.01) and the MACFIMS Delis-Kaplin Executive Function Scale Sorting subtest (DKEFS) (r=-0.47, p-value=0.032). A trend towards correlation with the MACFIMS Judgment of Line Orientation Test (JLO) did not reach significance levels (r=-0.42, p-value=0.064). No correlation was seen between the NAWM volume fraction and the MACFIMS Brief Visuospatial Memory Test learning score or the MACFIMS California Verbal Learning Test score.

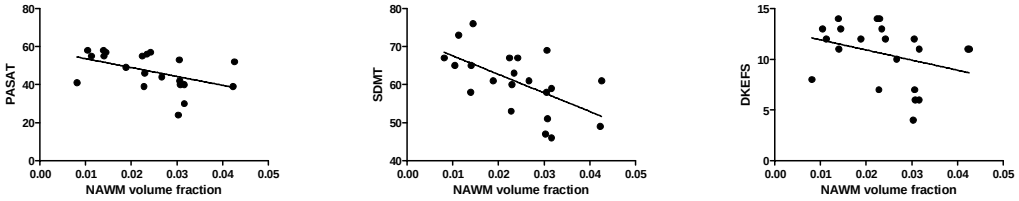

Figure 3: Correlation of NAWM fraction with cognitive scores (PASAT, SDMT and DKEFS)

Discussion

We have presented a novel, semi-automated technique that can be used to give the volume fraction of NAWM. This technique overcomes the lack of sensitivity of conventional T_1 weighted methods for subtle T_1 changes in normal WM, combining the diagnostic value of a DIR technique with a semi-quantitative WM assessment. The resulting volumes appear to be T_1 weighted, and are thus different, albeit related to, diffuse T_2 hyperintensities encountered in neurologically healthy subjects.

In our cohort of neurologically healthy volunteers, a significant volume fraction (0.8-4.2%) appeared to be affected. A portion of it may still be due to partial volume effects, although the net effect on the results is likely minimal. NAWM volume fraction explained decreased function in cognitive tests reflecting subcortical activity, such as processing speed (PASAT, SDMT) and executive functions (DKEFS).

References

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