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Commentary: T1 Mapping from routine 3D T1-weighted inversion recovery sequences in clinical practice: comparison against reference inversion recovery fast field echo T1 scans and feasibility in multiple sclerosis

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ABSTRACT

MRI has long been a critical tool for diagnosing and monitoring Multiple Sclerosis (MS). Conventional MRI employed in clinical practice is non-parametric, which disallows quantitative measures of tissue damage. This creates an unmet need to develop a post-acquisition image processing algorithm that can convert a qualitative image into a corresponding quantitative map. We present a methodology that can convert a clinically routine T1-weighted MPRAGE image into a parametric T1 map with high accuracy and precision in relation to a commonly used T1 mapping reference standard. We evaluate the methodology's performance in Multiple Sclerosis for the purpose of quantifying tissue damage primarily in lesions and secondarily in white matter and gray matter regions.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the CNS characterized by focal lesions in the white and gray matter[1]. These focal lesions are regions of inflammation, degeneration of myelin, and neuronal loss[2], and are associated with clinical sequela of physical and cognitive disability[3,4]. Magnetic Resonance Imaging (MRI) is an indispensable tool for examining tissue injury in MS. However, conventional MRI sequences are non-parametric, which does not allow quantitative assessment of lesion and non-lesional tissue damage. There is an unmet need to develop a post-acquisition image processing algorithm that can convert qualitative images into corresponding quantitative maps. We successfully developed a methodology that converts MPRAGE scans into parametric T1 maps with high accuracy and precision and compared them to a commonly used T1 mapping reference standard.

T1 mapping is one of several advanced MRI sequences that establishes a quantitative index of the severity of tissue injury in MS lesions. T1 is reflective of the water, iron, and myelination content in tissues[5,6]. T1 mapping can examine disease pathology in MS, with changes in T1 correlating with lesion evolution, clinical disability, and disease progression[7-9]. Higher lesional T1s (>2000ms) and increasing T1 over time show a significant correlation with clinical disability[10-12].

Despite enthusiasm for adding T1 mapping to imaging protocols, e.g. MP2RAGE, synthetic MRI, MR fingerprinting[13-15], it has not been widely adopted in clinical settings as it requires additional scanning time, local expertise for complicated protocols and post-processing,

and greater dependence on MRI software and hardware upgrades. Different T1 mapping sequences also yield different T1s[16,17]. T1-REQUIRE was developed as a T1 mapping technique that retrospectively calculates T1 maps from any T1w images to avoid additional scan time and variations due to MRI sequences. T1-REQUIRE calculates T1 maps via iterative, analytic mathematical solutions to MRI signal equations that incorporate image acquisition parameters, internal tissue references, and normative T1s. T1-REQUIRE values were shown to be within 10% of the reference inversion recovery (IR) T1s in phantoms and healthy controls[18].

In the study titled "T1 Mapping from routine 3D T1-weighted inversion recovery sequences in clinical practice: comparison against reference inversion recovery fast field echo T1 scans and feasibility in multiple sclerosis", we applied the T1-REQUIRE technique to MS[19]. MS is a disease state with a diverse range of lesion pathology in the same individual, with each lesion unique to its time of occurrence, severity of injury, and remyelination. We hypothesized that retrospective T1 maps calculated from high spatial resolution MPRAGE images would preserve lesion heterogeneity with high fidelity to input images. We also hypothesized that lesions, non-lesional white matter (WM), and various gray matter (GM) regions would have T1s within 10% of the reference IR-FFE T1 maps. The results of the study could provide a practical tool for examining microstructural changes via T1 mapping, allowing for quantitative assessment of disease activity and progression.

T1 Retrospective Quantification Using Internal References (T1-REQUIRE)

MPRAGE was selected as the input T1w acquisition as it is commonly used for structural brain imaging for its high spatial resolution and contrast, whole brain coverage, short scan time, and capture of lesion heterogeneity[20]. We were primarily interested in examining the intrinsic tissue properties of MS lesions and WM, and GM regions secondarily.

T1-REQUIRE integrates into the clinical workflow as a post-acquisition step. Post clinical imaging in which an MPRAGE was acquired, T1-REQUIRE processes DICOM images via MATLAB and the SPM toolbox to measure key sequence parameters, correct bias field inhomogeneities, and segment tissue into GM, WM, and cerebrospinal fluid (CSF). An analytical solution using the MRI signal equation is constructed, which uses the key sequence parameter measured earlier. The equilibrium magnetization (M0) is estimated iteratively by minimizing the root mean square error between the average signal intensities of GM, WM, and CSF and the calculated signal intensities using the analytical solution and M0 estimate. A lookup table is calculated to convert between image signal intensity and T1s from 100-4000ms.

We reported a cohort of 24 subjects, 14 with relapsing-remitting MS (RRMS) and 10 health controls. From these, 159 T1w hypointense MS lesions and 288 GM regions were examined. All MS patients were imaged with MPRAGE, FLAIR, and IR-FFE with 5 inversion times on a Philips 3T Achieva scanner (Philips Medical Systems, Best, The Netherlands). Healthy controls were imaged with the same MPRAGE and IR-FFE scans on a 3T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). T1 maps were calculated from MPRAGE images using T1-REQUIRE; reference T1 maps were calculated from IR-FFE images using 3-parameter fit with Look-Locker correction. T1s for MS lesions showed a Pearson's correlation of r=0.81 ($p<0.000$) and bias=4.18%. Non-lesional WM showed r=0.82 ($r<0.000$) and bias=8.78%. Pooled analysis of all GM structures in MS showed r=0.93 ($p<0.001$) and bias=2.22%. This study showed that T1-REQUIRE can convert MPRAGE images into high spatial resolution quantitative T1 maps while preserving distinct lesion features. Overall, the bias between T1-REQUIRE and reference standard T1 was <10% in lesions, WM, thalamus, and cortical GM of MS patients. These regions have a high predictive value in correlation with disability[21,22].

Our results showed T1-REQUIRE is best suited for examining white matter lesions, particularly T1 hypointense lesions. After an acute inflammatory stage, 40-50% of the MS lesions enter a chronic inflammatory stage in which inflammation persists leading to progression of tissue injury[23]. MS lesions that slowly expand over time are called slowly expanding lesions (SELs), which represent approximately 27% of all lesions[24]. On T1w images, the most degenerative of these lesions appear hypointense and are called "black holes," which represent about 10% of all lesions[24,25]. Preventing lesions from evolving into SELs and black holes is an important therapeutic target given SELs are the most destructive and have the highest correlation with MS disability. T1-REQUIRE offers a standardized and effective method for monitoring T1w SEL and it provides a specific biomarker for disease activity and response to treatment as it stratifies MS lesions based on the severity of tissue damage. Finally, T1-REQUIRE's retrospective nature gives it strong potential to be applied to several of the neuroimaging databases for quantitative analysis. Given its retrospective nature and use of internal tissue references and normative T1s, T1-REQUIRE has the potential to harmonize data cross-scanner, and potentially cross-vendor[18].

A limitation of this study is the lack of T2* correction of MPRAGE images. T2* effect is due to iron content of tissues, with high iron content corresponding to lower T1s. Our technique focuses on lesions and brain structures relevant to MS that are low in iron content and therefore

do not require much T2* correction. In areas with high iron content such as the globus pallidus, T2* correction could affect T1. Nonetheless, our estimated T1s do capture the iron heterogeneity seen in subdivisions of the basal ganglia, with T1s in the globus pallidus < putamen < caudate, corresponding to previously reported iron concentrations in these regions, with globus pallidus as the highest[26]. Preliminary follow-up to this study shows that in healthy controls, T2* correction has the most influence in the globus pallidus but minimal impact in the WM, GM, thalamus, caudate, and putamen. We believe when using T1-REQUIE to examine SELs, T2* correction is needed when there is uniformly a high deposition of iron in regions of interest, especially in brain structures such as the globus pallidus and deep cerebellar nuclei. Minor iron deposition in MS lesions compared to the total lesion area or volume is expected to have a very little effect on the mean lesion T1s. Of note, only 10% of MS lesions are paramagnetic rim lesions (PRLs)[24,25]. Of the SELs, only 7% are PRLs[24,25] so their contribution to overall lesion analysis is minor. PRLs are seen in susceptibility weighted scans, which are not routinely done nor were available for our study. Future studies could address this limitation by acquiring a susceptibility-weighted image to subtract the iron rim component of the lesions.

Conclusion

T1 mapping provides a valuable index of tissue injury and longitudinal monitoring of disease activity. T1-REQUIRE was developed to retrospectively calculate T1 maps from T1w images to examine the intrinsic properties of brain tissue, and was applied to MS to interrogate the severity of tissue damage in MS lesions. T1-REQUIRE T1s showed high correlation with reference IR-FFE T1s.

T1-REQUIRE has the greatest applicability to existing neuroimaging databases. The retrospective nature of T1-REQUIRE makes it ideal for application to databases with MPRAGE scans (e.g. ADNI, PPMI) from which T1 maps can be calculated to quantify the severity of tissue injury in each disease, especially longitudinally. This will allow for development of biomarkers predictive of disease worsening. For prospective imaging studies, only an MPRAGE acquisition is necessary for T1-REQUIRE. For diseases that introduce a T2* effect such as bleeding or iron deposition, acquisition of a T2* map may be necessary to calculate accurate T1 in areas with large T2* effect. Work is ongoing for applying T1-REQUIRE to the ADNI database and to validate T1-REQUIRE in the presence of brain hemorrhages. Ultimately, T1-REQUIRE could be broadly implemented in clinical practice or research trials to quantify tissue injury in the white matter of the brain, and it has a strong potential for application to neuroimaging databases for estimation of T1 maps from existent images for outcome research.

Competing Interests

The authors report no conflict of interest related to the work presented.

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