Quantitative Magnetic Resonance Imaging of Multiple Sclerosis

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Introduction: Multiple sclerosis (MS) is an autoimmune disease affecting the nervous system and causing various neurological complications mainly due to demyelination and axonal loss. Although there are different types of MS lesions, most appear as areas of demyelination in the brain's white matter (WM). MRI has played an important role and emerged as a powerful non-invasive technique to assist in the diagnosis and monitoring of multiple sclerosis. The use of MRI in MS has been increasing in the field of research in recent years. Standard MRI techniques for MS now include central nervous system atrophy, T1 and T2 weighted imaging and gadolinium enhancement. These measures provide a better understanding to the underlying mechanisms of MS disease and have uncovered remarkable information about MS in recent years. However, the contribution of MRI conventional measures to MS is only at the macroscopic level. They lack the specificity required to understand the MS disease process and have thus failed to provide a complete picture of the underlying pathology which leads to a so called clinico-radiological paradox. In other words, the clinical status of MS patient does not correlate well with MRI findings. Advanced quantitative MRI measures are capable of revealing a range of changes that occur in the normal appearing brain tissue (NABT) which cannot be detected on standard MR images. These advanced quantitative MRI measures include magnetization transfer (MT), T1 and T1 relaxometry, magnetic susceptibility mapping, diffusion imaging and magnetic resonance spectroscopy (MRS). The increased signal to noise ratio (SNR) and spatial resolution available at ultra high field MRI also improves specificity as well as sensitivity to MS lesions and diffuse changes in the central nervous system (CNS). A reduction in scanning time is of importance for most MS patients especially those who are debilitated and thus cannot stay still in the scanner for long time. The main aim of this work was to study the diffuse occult disease outside the macroscopic lesions in the NABT (including the deep grey matter structures) in patients at presentation with clinically isolated syndromes suggestive of MS (CIS) as well as in relapsing-remitting MS (RRMS) patients using advanced quantitative imaging techniques at 7 Tesla MRI mentioned above.

Methods: Twenty two patients with CIS and twenty patients with RRMS were recruited from Nottingham University Hospital, UK. Twenty age and sex matched healthy volunteers were also recruited. All groups were consented according to local ethics approval. Scanning was performed on a 7T Philips Achieva MR system, equipped with a 16-channel receive coil and head-only, volume transmit coil. MT weighted images were acquired using a 3D magnetization Transfer Prepared-Turbo Field Echo (MT-TFE) sequence with 0.86×0.86×1.5 mm voxel size; TE = 5.7 ms; TR = 9.8 ms; 20 slice. Three acquisitions were made, one with no presaturation, one with presaturation -1.05 kHz off resonance to water (sensitive to Magnetization Transfer and NOE), and one with presaturation +1.05 kHz off resonance to give sensitivity primarily to MT (total scan time = 8:22 min for the three acquisitions). The pulsed saturation was applied as a train of 20 off-resonance pulses (13.5 µT Gaussian-windowed, sinc pulses with a bandwidth of 300 Hz and off-resonance by ±1.05 kHz (3.5 ppm), with 55 ms between each pulse). T1 maps were created from 3D invert recovery - Turbo Field Echo (IR-TFE) images (also known as MPRAGE images (8) acquired at 7 different inversion times (150, 300, 500, 800, 1200, 1800, 2500 ms). The acquisition parameters were TE = 3.2 ms; TR=6.9 ms; flip angle of the TFE readout pulse = 8o; TFE factor per inversion = 240; shot-to-shot interval = 8 s; spatial resolution = 1.25×1.25×1.25 mm; Field of View = 200×200×72.5 mm; reconstruction matrix = 160×160×58; scan time per TI = 2 min. The scanning protocol included a B1 map using the two TR method (10) to correct the MT images for the effect of B1 inhomogeneity and to calculate the readout flip angles for T1 mapping. A 3-dimensional, T2*-weighted gradient echo sequence was acquired with the following settings: TR = 150 ms, TE = 20 ms, flip angle = 14o, SENSitivity Encoding (SENSE) factor = 2, Echo Planar Imaging (EPI) factor = 3, number of excitations = 1 and imaging time = 8.5 minutes. We acquired 200 transverse slices parallel to the Anterior Commissure -Posterior Commissure (AC-PC) line, in four interleaved stacks (with 5 mm overlap between each adjacent stack), to achieve a whole-head coverage with a relatively long TR. The spatial coverage was $192 \times 164 \times 25$ mm per stack, with 0.5 mm isotropic voxel size. T1 maps were calculated from the IR-TFE images using Neuroi software. The MT images acquired at positive and negative frequency offset were co-registered to the reference scan acquired with no saturation pulse using rigid body registration with 6 degrees of freedom in FSL (FMRIB, Oxford UK). MTR maps were then calculated on voxel by voxel basis using [MTR=(S_{mt}-So)/So]. The NAWM for each of MTR and T1 maps was then segmented and used in Matlab for further analysis. For the magnetic susceptibility maps, phase images were unwrapped, filtered and converted into susceptibility maps on which twelve different ROI were drawn to cover the deep grey matter structures. Different statistical parameters were derived from all these three maps and analyzed for any significant statistical differences.

Results: The results showed a significant difference ($p<0.05$) in the median peak position, full width at half maximum, the 25th percentile of the MTR histograms and the 75th of the T1 histograms. The magnetic susceptibility mapping technique showed an increase in iron deposition in the caudate nucleus, putamen, globus pallidus structure in CIS and RRMS when compared to those in healthy controls.

Conclusion: Conventionally, MRI scanning does not detect changes in MS outside macroscopic lesions and generally fails to provide information about the full extent of macroscopic lesions. Quantitative MRI techniques were able to explore the underlying 'diffuse' changes in NAWM and correlate with clinical status of MS patients. T1 relaxation time of the NAWM varies and depends on the MS type and its course. Furthermore, MTR values tend to decrease in NAWM of CIS and RRMS patients when compared with healthy controls suggesting white matter demyelination. Magnetic susceptibility values measured in deep grey matter structures of CIS and RRMS patients showed a significant increase indicating an increase in iron deposition in these structures following some degenerative processes.
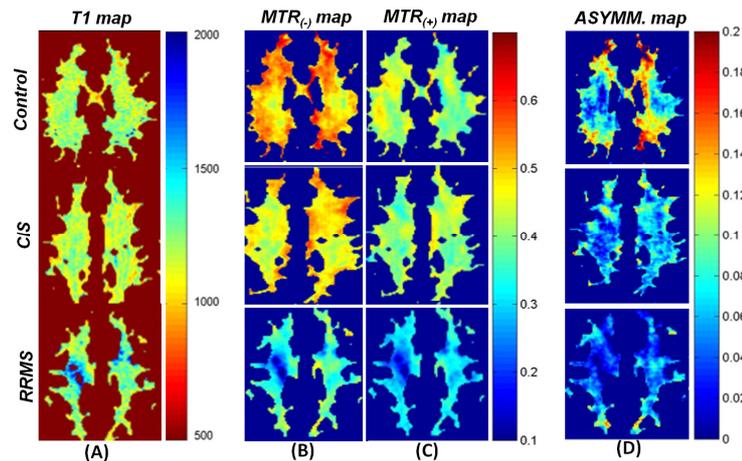
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