Multivariate combination of quantitative $T_2^*$ and $T_1$ at 7T MRI detects in vivo subpial demyelination in the early stages of MS.

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Backgrounds and goals

Subpial demyelination occurs early in the course of multiple sclerosis (MS), but in vivo detection with MRI is challenging due to low contrast at conventional field strengths. Quantitative mapping of $T_2^*$ and $T_1$ relaxation rates at 7T MRI was shown to be sensitive to cortical myelin content [1-2], and to cortical MS demyelination associated with clinical measures [3]. Given that several confounds hamper the specificity of both metrics, we used multivariate statistics to combine cortical $T_1$ and $T_2^*$ maps to gain specificity to subpial demyelination in early MS. This approach has shown improved sensitivity to cortical myelin content in healthy subjects [4].

Methods

Acquisition: In 5 healthy controls (HC, 34±12 years, 3 females) and 10 early MS patients (37±9 years, 8 females; disease duration≤3 years, median $T_1$ range Expanded Disability Status Scale score = 0.3) we obtained 7T high resolution quantitative $T_2^*$ ($0.5 \times 0.5 \times 0.5 \text{ mm}^3$) and $T_1$ ($0.75 \times 0.75 \times 0.75 \text{ mm}^3$) maps. For each subject, $T_1$ and $T_2^*$ were sampled at 25%, 50% and 75% depth from the pial surface. Scan parameters were: TR/T1=3680/3.12+3.32[1..6]ms for $T_2^*$ and MP2RAGE sequence, double inversion gradient echo. TR/T1/TE=5000/2.93[900 3200]ms for $T_1$. Raw images are shown in figure 1A.

Processing: For each subject, $T_1$ and $T_2^*$ were sampled at 25%, 50% and 75% depth along the cortex ($Paiol = 0\%$; $WM = 100\%),$ figure 1A. Then, we applied a first-order correction for partial volume effect to both metrics and a spatial Independent Component Analysis was used to extract the shared myelin related signal in $T_1$ and $T_2^*$ maps (figure 1B) thus creating the Combined Myelin Estimation (CME), a new metric more specific to myelin than $T_1$ or $T_2^*$ separately, as previously done in [4].

Statistics: A General Linear Model (GLM), including age and gender as adjustment factors, was used to compare $T_1$, $T_2^*$ and CME in MS patients vs healthy controls in whole cortex and in selected Brodmann areas (BA).

Results

Figure 2 shows the myelin estimated maps averaged across HC and MS groups. We can visually observe a qualitative loss of myelin around the motor, visual and auditory cortices. Quantitatively, in the whole cortex, CME was decreased while $T_1$ and $T_2^*$ were increased in MS vs HC. CME=47±0.8% vs $49\pm1.3\%$; $T_1=1727\pm56\text{ ms}$ vs $1654\pm70\text{ ms};$ $T_2^*=34.0\pm1.2\text{ ms}$ vs $33.0\pm1.1\text{ ms}.$ A statistical analysis showed a significant decrease of CME, reflecting a loss of myelin ($p<0.05$, whole cortex GLM), whereas variations of $T_2^*$ and $T_1$ alone were not significant. Within Brodmann areas, the GLM of CME showed significant loss of myelin in sensory, motor (BA1, BA4, BA6) and prefrontal (BA10) areas ($p<0.05,$ Figure 3). A significantly higher $T_1$ was observed in frontal cortex (BA45, $p<0.05$). No regions were significantly different using $T_2^*$.

Discussion

CME, a multivariate statistical framework combining quantitative $T_1$ and $T_2^*$, provides improved resolution 7T scans. It shows increased specificity to detect changes in early MS compared to $T_1$ and $T_2^*$ separately. Furthermore, it supports subpial demyelination as an early event in MS, even in the presence of mild neurological disability.