Does focal remyelination in white matter influence myelin-weighted network properties in patients with Multiple Sclerosis?

Background

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system that leads to demyelination, axonal damage and neurodegeneration 1 .

Structural connectivity investigates white matter tracts through diffusion MRI (dMRI)2-3. Recent studies have shown that focal repair activity can be measured in MS patients, which varies widely among individuals 4-6. Myelination Streamline Decomposition (MySD), a quantitative tractography method 7 adapted to focal lesions can be applied to reconstruct myelinated brain networks 8 .

Aim: To investigate the relationship between (i) the presence of remyelinated lesions along fiber tracts and (ii) brain network properties in patients with Multiple Sclerosis (pwMS).

Methods

All pwMS (n=129) underwent 3T MRI, with a 64-channel head and neck coil including FLAIR (TR/TE/TI=5000/1800/1200) 1mm isotropic; MP2RAGE (TR/TE/TI =5000/700/2500ms) 1mm isotropic; multi-shell dMRI (TR=4.5s/75ms) 1.8mm isotropic with b=0/700/1000/2000/3000/mm² and 12/6/20/45/65 measurements, respectively, with additional 12 b=0 in reversed phase encoding; MT-weighted (TR/TE=25/4.92 ms, alpha=5, Gaussian MT pulse Delta F=2.2KHz).

The myelin volume fraction (MVF) map was estimated as MVF = c×MTsat, with calibration constant c=0.2161. Quantitative susceptibility maps were derived from Echo-Planar Imaging (EPI) using MED 9. Lesion masks were automatically generated 10 and manually corrected on FLAIR. QSM lesion classification and identification of remyelinated lesions (hypo- and isointense on QSM) were performed manually by two experienced readers 11. The QSM map was registered to diffusion image space and then lesions were mapped to the reconstructed tractogram.

Using FreeSurfer (https://surfer.nmr.mgh.harvard.edu), MP2RAGE images were segmented into 85 gray matter regions. dMRI were pre-processed, and 3M of streamlines were reconstructed using anatomically constrained tractography algorithm of MTrix3 12.

We used MySD accounting for lesions to weight the connectomes. In the extended model both the intracellular compartment and lesion compartment were integrated to evaluate the contribution of the streamlines and the contribution of axonal damage concerning the estimated signal in the MVF map. To account for sensitivity to axonal damage, the model utilizes the estimated contribution of axonal damage to adjust the weights of streamlines accordingly. Specifically, it assigns the lowest value found along the streamlines crossing the lesions, adhering to the principle that ‘a chain is only as strong as its weakest link’ 13.

From each connectome, whole-brain network measures quantifying the average (mean strength), network segregation (modularity, clustering coefficient) and integration (efficiency) were extracted.

We assessed linear robust models to explore the effect of network metrics (dependent variable) on the remyelinated patient group (independent variable) accounting for Age, Age², density, gender as covariable.

Results

MS patients were divided into two groups considering patients with remyelination load along the white matter tracts based on the 50th percentile.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Low remyelination load</th>
<th>Group 2: High remyelination load</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age/sex</td>
<td></td>
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<tr>
<td>Age [years]: mean (sd)</td>
<td>39.0 ±13.1</td>
<td>51.2 ±13.1</td>
<td>p=0.001</td>
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<tr>
<td>MS-Phenotype</td>
<td></td>
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<td>EISD- median (Q3)</td>
<td>3 (1-5.0)</td>
<td>5 (0-9.0)</td>
<td>p=0.05</td>
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<tr>
<td>Disease-duration: mean (sd)</td>
<td>4.1±5.0</td>
<td>14.4±13.0</td>
<td>p&lt;0.001</td>
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<tr>
<td>Remyelinated lesion number: mean (sd)</td>
<td>2.1±1.6</td>
<td>14.8±13.4</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Remyelinated lesion volume: mean (sd)</td>
<td>1283±519</td>
<td>931±312</td>
<td>p&lt;0.001</td>
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<tr>
<td>Total count lesions: mean (sd)</td>
<td>36.7±143.9</td>
<td>74.2±147.8</td>
<td>p&lt;0.001</td>
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<tr>
<td>Total lesion volume: mean (sd)</td>
<td>3760±4710</td>
<td>10786±9193</td>
<td>p&lt;0.001</td>
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</table>

Patients with higher volume of remyelinated lesions along the tracts showed decreased efficiency, clustering coefficient and increased modularity (p<0.01, adj. R²=0.37) and a tendency towards a decreased mean strength (p=0.055, adj. R²=0.31).

Patients with higher number of remyelinated lesions along the tracts showed more segregated and less efficient brain networks than patients with lesser remyelinated lesions (p<0.05, adj. R²>0.35).

Discussion & Conclusion

The overall number or volume of remyelinated lesions along the tracts constituting the brain connectomes of pwMS did not compensate for network properties deficits.

In patients with higher remyelinated lesion load, efficiency was lower and modularity was higher in patients with low remyelinated lesion load constituting the connectomes. Interestingly, the second group was older and had longer disease duration, which might explain the accumulation of irreversible damage that could not be compensated.

The presence of focal remyelination along the tracts constituting brain connectomes in pwMS is not associated with compensatory changes in myelin-weighted network properties. Future work will extend these findings to larger populations of MS patients and consider the imbalance between damage and repair along the tracts.

References