ANATOMICAL BRAIN CONNECTIVITY TO ASSESS COGNITIVE DYSFUNCTION IN MS

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Background and Objective.

Anatomical disconnection between important processing regions by damage to the interconnecting white matter (WM) provides a potential mechanism for the accrual of disability in multiple sclerosis (MS)[1]. So far, structural disconnection in MS brains has been estimated by measuring lesion loads (LL) or microscopic indexes of WM integrity, such as mean diffusivity and fractional anisotropy (FA) as derived by diffusion-weighted (DW)-MRI. However, these quantities reflect only a local measure of damage, but do not quantify the actual loss of "brain connectivity". Aim of this study was to apply to relapsing-remitting (RR)-MS a recently developed method[2] based on DW-MRI tractography to assess the patterns of anatomical brain disconnection and its impact on the observed cognitive disabilities.

Subjects and Methods.

Twenty-five RRMS patients [F/M=19/6; mean age ± SD = 34.3 ± 8.2 years; median EDSS = 2 (range 0-4.5); mean disease duration ± SD = 8 ± 4.2 years] were recruited together with 25 sex- and age-matched healthy controls.

After recruitment, all MS patients were assessed by the Multiple Sclerosis Functional Composite score, in which Paced Auditory Serial Addition Test (PASAT) is the cognitive test[3].All subjects underwent MRI at 3T, including dual-echo, FLAIR, T1-w volumes, and DW-MRI scans.

WM lesions were outlined on the proton-density weighted maps to compute T2-LL.

Volumetric scans were coregistered to FA maps and segmented into WM, grey matter (GM), and cerebrospinal fluid. A parenchymal map was obtained by combining WM and GM segments. Probabilistic tractography, based on Q-ball and on the probabilistic index of connectivity[4], was initiated from all voxels in the parenchymal mask. ACM maps were

Fig 1. Anatomical Connectivity Mapping: scheme of data analysis.

obtained by counting the total number of tractography streamlines passing through each voxel, and normalising it by the total number of streamlines initiated. ACM maps were transformed into standard space (Fig.1). Voxel-wise statistics was carried out using SPM8 (www.fil.ion.ucl.ac.uk/spm) to assess: 1) the presence of between-group ACM differences; 2) the correlation between ACM and performance obtained by patients at the PASAT. In both analyses age, gender and number of voxels in the parenchymal mask were entered as covariates of no interest. T2-LL was entered as additional covariate in the correlation analysis performed in the patient group. In both analyses, statistical threshold was set to p-FWE-corrected<0.05 at cluster level.

Results.

The 96% of MS patients performed poorly at the PASAT. The average T2-LL volume in MS patients was 7.85 mL (SD=8.3).

When comparing groups, RRMS patients had reduced ACM in the corpus callosum, in the left prefrontal lobe, and in the head of the caudate nucleus (bilaterally) (Fig.2). No regions of increased in ACM were observed in MS patients Correlation analysis between patients' ACM and performance at the PASAT (number of correct responses), showed areas of direct association in the anterior cingulate gyrus and in the anterior thalamic radiation bilaterally (Fig.3). The inverse correlation did not produce any significant result.

Conclusions.

These results support on an "anatomical connectivity" basis the role of disconnection as a major mechanism for accumulation of disability in RRMS. The pattern of reduced ACM we observed in MS patients might account for both, deficits in the higher level control of motor abilities (midbody of the corpus callosum; caudate nuclei) and cognitive dysfunctions (isthmus of the corpus callosum; caudate nuclei; left prefrontal lobe).

Interestingly, our correlation analysis between ACM and patients' performance at the PASAT revealed a well defined pattern of associations, including the anterior cingulate and the anterior thalamic radiations. These regions are known to be part of the attentional and working-memory network (anterior cingulte), and of the information-processing network (anterior thalamic radiation).

In conclusion, ACM opens a new perspective for clarifying in a more direct way the contribution of anatomical disconnection to clinical and cognitive disabilities in MS.
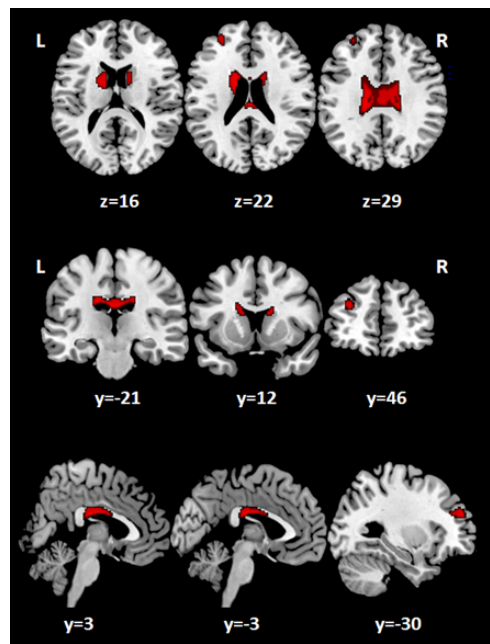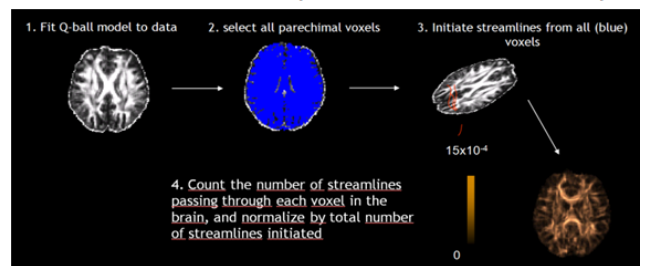

Fig 3. Voxel-wise comparison of ACM values between MS patients and HS. Reductions of structural connectivity in patients are shown in red. Statistical threshold set to p-FWE-corr.<0.05 at cluster level.
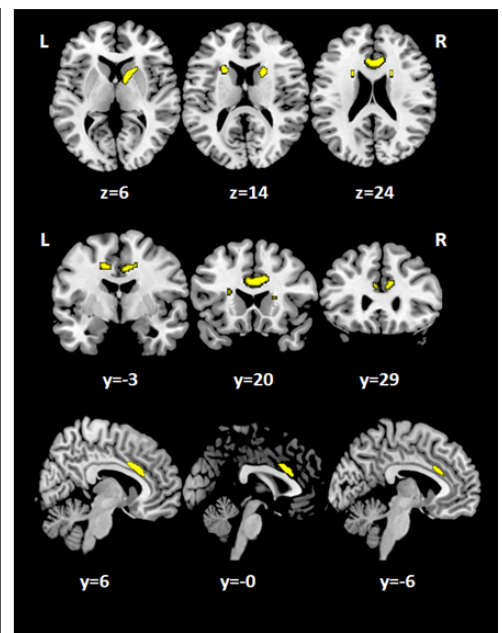

Fig 3. Direct associations (yellow areas) between ACM values and scores obtained by MS patients at the PASAT. Statistical threshold set to p-FWE-corr.<0.05 at cluster level

References

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