The relationship between brain NAWM and GM damage is localised to specific clinically relevant regions in early PPMS

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Introduction

Diffuse MRI abnormalities have been demonstrated both in the normal appearing white matter (NAWM) and grey matter (GM) of patients with primary progressive multiple sclerosis (PPMS) even in the early stages [1-3], and have been shown to be clinically relevant. The questions that remain unanswered are whether, where and to what extent the NAWM damage correlates with the connected abnormal GM. To date, MRI studies have limited this investigation to the correlation between WM lesions and GM damage [3], without yielding a definite answer. We combined two recently introduced techniques: tract-based spatial statistics (TBSS) [4] and voxel-based morphometry (VBM) [5] in order to clarify the relationship between grey and white matter damage in vivo in the early phase of PPMS.

Methods

We studied 35 patients (15 females, 20 males, mean age 45.3 years, SD 11.32) with definite or probable PPMS within 5 years of symptom onset. All patients were assessed on the day of the scanning with the Expanded Disability Status Scale (EDSS) [6] and the Multiple Sclerosis Functional Composite (MSFC) subtests [7]. All MR imaging was obtained at 1.5T, and consisted of a) a dual-echo FSE sequence (TEs=17/92 ms; TR=2000 ms); B) a 3D inversion recovery fast SPGR (TI=450 ms, TE=4.2 ms, TR=13.3 ms); C) a cardiac gated diffusion tensor (DT) EPI (TE=95 ms, maximum *b* factor=1000 smm-2, 25 diffusion directions). Two separate groups of controls were used for the TBSS (18 subjects, 8 females and 10 males, age 41.5 years, SD 12.63), and for the VBM analysis (23 subjects, 12 females, 11 males, mean age 35.1 years, SD 7.9). Lesions were delineated on the dual-echo scans of all patients. Binary lesion masks were created and normalised to standard space. Fractional anisotropy (FA) maps were created for all subjects using *dtifit* (http://www.fmrib.ox.ac.uk/fsl/), and they were fed into TBSS to obtain a projection of all subjects' FA data onto a mean FA tract skeleton. The average lesion mask was subtracted from the skeleton to produce a skeleton of the NAWM only, and voxel-wise statistics was carried out to identify areas of reduced FA in patients. The SPGR volumes were processed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/), according to the optimised VBM protocol [8], modified to account for the presence of white matter lesions. Data were smoothed using a 12-mm FWHM Gaussian kernel. We compared patients and controls using an analysis of covariance (ANCOVA), adjusting for age and for GM total volume. Statistical maps were thresholded at $p<0.05$ corrected for multiple comparisons. Areas of anatomical correspondence between reduced GM volume and lower FA in patients were identified by overlaying the results of the two different analysis on the same anatomical image. Then we extracted the mean FA value of the NAWM, and the mean GM volume to assess the presence of a quantitative association using the Spearman's correlation coefficient. For each region where a quantitative relationship between grey and white matter was found, the association between clinical scores and GM and NAWM changes was assessed using either multiple linear or ordinal logistic regression.

Results

Patients showed significantly lower FA in the NAWM along the bilateral cortico-spinal tract, in NAWM adjacent to the bilateral premotor cortex, in the whole corpus callosum, in the thalamic radiations, in the optic radiations, in the fornix, in the fasciculus arcuatus, in the inferior longitudinal fasciculus, and in the white matter of the temporal and frontal lobes. Patients showed significantly reduced GM volume in the bilateral sensory-motor cortex, in the right middle and bilateral inferior frontal gyrus, in the right superior and left middle temporal gyrus, in the GM around the sylvian fissure, in the left precuneus, in the left cerebellar hemisphere, in the right angular and cingulate gyrus, in both thalami and insulae. Anatomical correspondence (Fig 1) between reduced FA and reduced GM volume was found in 11 areas (sensory-motor areas, the left inferior frontal gyrus, the right superior temporal gyrus, the left middle temporal gyrus, around the left sylvian fissure, the left precuneus, the right angular gyrus, both thalami, the left insula). Only in 4 of these areas there was also a quantitative correlation: (i) the right sensory-motor region with the adjacent cortico-spinal tract; (ii) the left and right thalamus with the corresponding thalamic radiations; (iii) the left insula with the immediately adjacent white matter). All the four areas with quantitative correlation between NAWM and GM damage showed a significant association with clinical disability.

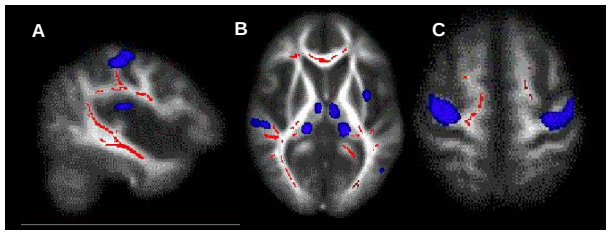

Fig 1. *Examples of regions where anatomical (A and B) or anatomical and quantitative correlations (C) between NAWM damaged tracts (voxels in red) and GM atrophy. (areas in blue) have been found in patients.*

Discussion

Considering all these results together, our interpretation is that the relationship between NAWM damage and GM atrophy in early PPMS varies amongst different brain regions. In many of the abnormal areas, the NAWM and GM pathologies seem to be independent, but in four regions they are highly correlated. However, we cannot exclude the fact that the quantitative relationship between the two abnormal compartments simply reflects the concomitant and independent pathologic processes affecting NAWM and GM in the early phase of PPMS, without a cause- effect relationship. Importantly, all the four areas of visually evident and quantitatively confirmed correlation between NAWM damage and GM atrophy were clinically eloquent, and in each area we observed an independent and selective contribution of the two compartments to disability.

References

[1] Sastre-Garriga J, et al. Neuroimage 2005; 22: 353-9.
[2] Pirko I, et al.,Neurology 2007 ; 68: 634-42.
[3] De Stefano N, et al. Neurology 2003; 60: 1157-62
[4] Ashburner J and Friston K. Neuroimage 2001;14: 1238-43.
[5] Smith S, et al. Neuroimage 2006; 31: 1487-505..
[6] Kurtzke JF. . Neurology 1983 ; 33: 1444-52..
[7] Cutter GR, et al." Brain 1999 ; 122: 871-82.
[8] Good CD et al. Neuroimage 2001;14: 21-36.