Relationship between structural brain damage and functional cortical reorganisation in patients with Benign Multiple Sclerosis

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Introduction

Benign Multiple Sclerosis (B-MS) is characterised by a favourable clinical status several years after disease onset, despite overtly visible brain tissue damage. It has been hypothesised that this might be due to the presence of a more efficient functional cortical reorganisation in patients with a non-disabling disease evolution, although no imaging evidence is available at present. The aim of this study was to assess the relationship between magnetic resonance imaging (MRI) measures of structural brain damage and movement-associated functional cortical reorganisation in patients with B-MS.

Materials and Methods

Twenty-five right-handed (Edinburg Handedness Inventory=96.5±7.5) patients (3 males, 22 females, mean age=47±6.3 years) with B-MS (defined as having Expanded Disability Status Scale [EDSS] <3 and disease duration >15 years) were studied. Right hand motor functional assessment was performed on the same day of MRI acquisition, using the nine-hole peg test (9-HPT; mean values=24.6±4.2) and maximum finger-tapping rate within 10 seconds (mean values= 27.9±5.4). All patients underwent conventional brain MRI and magnetisation transfer (MT) imaging at baseline and after a mean of 1.31±0.18 years. Functional MRI (FMRI) was also acquired at follow-up in patients and in a group of 10 right-handed normal controls (NC) (6 males, 4 females, mean age=29.6±4.1 years). FMRI paradigm consisted of 6 x 30 second 1Hz visually cued (red flashing light placed at subject's feet) even right-hand tapping and intercalated 30-second rest period (approx. 6 minutes) ("block design"). This sequence was repeated 4 times in each scanning session. To minimise learning effects during scanning, hand tapping was practised twice for 30 seconds before scanning. FMRI sequence (120 volumes) was a gradient-echo planar imaging (EPI) sequence (TE=60ms, TR=3000ms, FOV= 240x240 mm), with 21 contiguous 6mm-thick axial slices covering the whole brain. FMRI data processing was performed using tools from FSL (FMIB Software Library, www.fmrib.ox.ac.uk/fsl). For first-level (within-sequence) analysis we used motion correction with MCFLIRT, non-brain removal with BET, spatial smoothing with a Gaussian kernel of FWHM 6mm, grand-mean intensity normalisation of the whole 4D dataset by a single multiplicative factor, high-pass temporal filtering (sigma=75 seconds). Independent Component Analysis (ICA)-based exploratory analysis was carried out using MELODIC, in order to investigate the possible presence of unexpected artefacts or activation ("data denoising"). Time-series statistical analysis was carried out using a General Linear Model (GLM) method called FILM with local autocorrelation correction. Registration of FMRI to high-resolution structural T1-weighted images and standard space was carried out using FLIRT. Registration from high-resolution structural T1-weighted image to standard space was then further refined using FNIRT nonlinear registration. In second-level (within-subject) analysis the four analysed sequences were combined for each subject, yielding an average activation map for each subject using a fixed-effect model in FLAME. In third-level (group) analysis, images were thresholded using clusters determined by Z>2.3 and a corrected cluster significance threshold of p=0.05. Voxel-wise GLM models for mean activation (one-sample t-test), unpaired t-tests and correlation analyses were used. Age was used as a covariate of no interest in the statistical models. T2-weighted lesion volume (LV) and their changes, Normalised Brain Volume (NBV) and Percent Brain Volume Change (PBVC) were measured. A fully automated procedure was used to compute MT ratio (MTr) in lesions and normal-appearing brain tissue (NABT).

Results

Comparison between Benign Multiple Sclerosis patients and normal controls

In B-MS patients, movement-related activations (Fig. 1) were found bilaterally in brain regions including the precentral, inferior frontal, anterior cingulate and superior temporal gyri, frontal pole, supplementary motor cortex, basal ganglia, insula and cerebellum. B-MS patients showed a trend towards greater activation than NC in clusters (Fig. 2, where crosshairs point at local maxima for each cluster) located in the posterior cingulated gyrus (A), left and right frontal pole (B and C), right supramarginal gyrus (D) and left precentral gyrus (E).

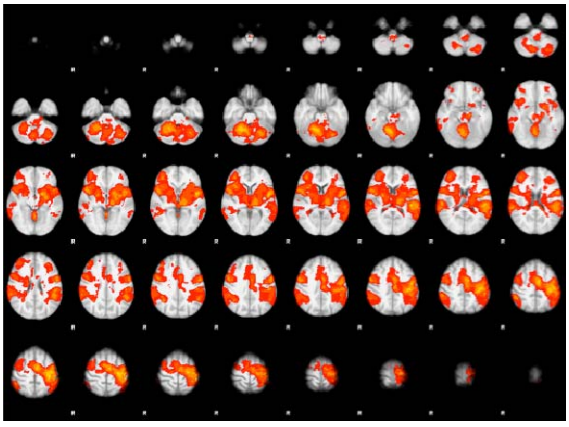
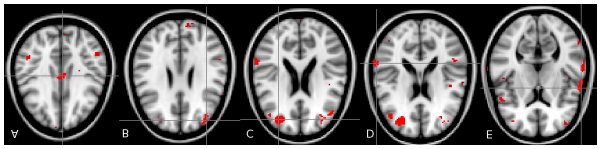


Figure 1

Figure 2



Correlations between FMRI and brain structural measures in Benign Multiple Sclerosis patients

In B-MS patients, significantly greater activations in different cortical regions were found with increasing NABT-MTr (not shown), T2-LV change (Fig. 3), and with decreasing lesion-MTRr (Fig. 4) and annualised PBVC (Fig. 5).

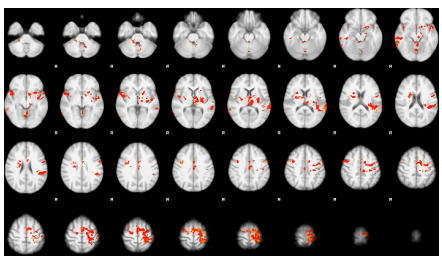


Figure 3

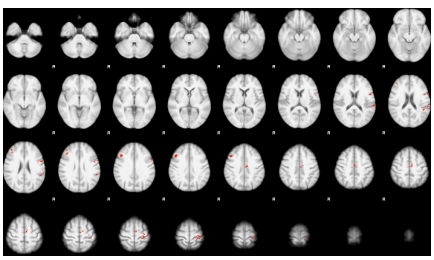


Figure 4

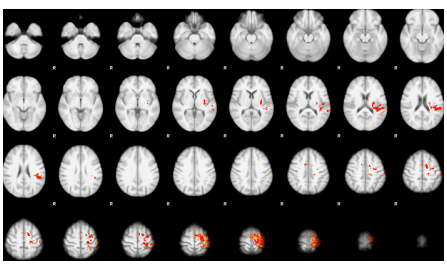


Figure 5

Conclusions

Different bilateral cortical areas, not only those devoted to motor tasks, are recruited during a simple motor task in patients with Benign Multiple Sclerosis. This movement-related activation is more widespread compared to normal controls and seems to represent a functional cortical reorganization directly related to the integrity of normal appearing brain tissues and inversely associated with focal WM pathology and progressive brain volume loss. Such a complex process might contribute to explain the favourable clinical expression of the disease in patients with Benign Multiple Sclerosis.