Brain Adaptive Changes Following Tissue Damage in PPMS: A Multiparametric Study using fMRI, MTI and DTI

Introduction
The factors responsible for the accumulation of irreversible disability in multiple sclerosis (MS) are poorly understood. Although the extent of macroscopic lesions, their intrinsic nature and location as well as the extent and nature of microscopic changes in the normal-appearing white matter (NAWM) are all relevant factors (1), the strength of the correlation between the level of disability and magnetic resonance imaging (MRI) findings are only moderate, at best. The paucity of such a correlation might be, at least partially, explained by the presence of reparative mechanisms, which can limit the functional impact of MS-related tissue damage and, as a consequence, the relationship between MRI measures of pathology and clinical measures of disability. In this respect, primary progressive MS (PPMS) is an intriguing condition. Patients with PPMS typically have progressive clinical symptomatology affecting a specific functional system as well as few and small lesions on T2-weighted MRI scans of the brain and cord (2). In this study, we evaluated the influence of brain and cord macroscopic and microscopic damage on the pattern of cortical activity in PPMS patients, in order to better clarify the mechanisms responsible of disability in these patients.

Methods
We studied 30 right-handed patients with PPMS (mean age=50.4 years, median disease duration=10 years, median Expanded Disability Status Scale (EDSS) score=5.5) and isolated pyramidal deficits, diagnosed following the criteria of Thompson et al. (2). None of the patients had motor symptoms at the level of the right upper limb. Fifteen sex- and age-matched right-handed healthy volunteers served as controls. For the brain, the following scans were acquired: a) dual-echo turbo spin echo (TR/TE/NEX=3300/16-98/1, 24 axial slices, 5 mm thick), b) 2D gradient-echo (GE) (TR/TE=640/12, 24 axial slices, 5 mm thick) with and without an off-resonance radio-frequency saturation pulse (offset frequency=1.5 kHz, Gaussian envelope duration=7.68, flip angle=500°), c) pulsed-gradient spin-echo echo-planar (EPI) pulsed sequence (inter-echo spacing=0.8, TE=123, 10 axial slices, 5 mm thick) with diffusion gradients applied in 8 non-collinear directions. For the cervical cord, the following sequences were acquired: a) sagittal fast short-tau inversion recovery (fast-STIR) (TR/TE/TI=2288/60/10, number of signal averages=4, 8 sagittal slices, 3 mm thick); b) axial 2D GE, with the same parameters used for the brain (20 axial slices). Lesions on brain and cord scans were identified and measured using a semiautomated technique based on local thresholding (3). Magnetization transfer imaging (MTI), DW and fractional anisotropy (FA) normalized histograms were created as previously described (1).

Functional MR images (fMRI) were acquired using a T2*-weighted EPI sequence (TR/TE=96/66, matrix size=128x128, interscan interval=5.5 s, 24 axial slices, 5 mm thickness). The fMRI paradigm was a motor task (repetitive flexion-extension of the last four fingers of the right hand). FMRI data were analyzed using statistical parametric mapping (SPM99) (4). To assess the intergroup differences in task performance a random-effect analysis was performed. From the patients' group analysis we could identify several areas involved in task execution. Correlations between percentage signal changes at the level of single subject motor areas and clinical and MR metrics were assessed by Spearman Rank Correlation Coefficient.

Results
We found significant differences during hand movement between the two groups studied at the level of the right cerebellum (more active in controls), the basal ganglia (more active in controls), the right middle frontal gyrus (more active in patients), the left insula (more active in patients), the left ascending limb of sylvian fissure (SII) (more active in patients) and the right cingulate motor cortex (CMA) (more active in patients). In patients' group analysis we could identify several areas: the left primary somatomotor cortex (SMC), the left supplementary motor area (SMA), SII, the left superior temporal gyrus (STG) and the right cerebellum. We found significant correlations between EDSS and the activity in the STG (r=0.7, p=0.02), disease duration and the activity in the SMC (r=0.3, p=0.04) and STG (r=0.8, p=0.01), age and the activity in the cerebellum (r=-0.4, p=0.01), dual-echo lesion load and the activity in SII (r=0.3, p=0.04). Considering DW histograms metrics, significant correlations were found between histogram peak location and the activity in STG (r=0.3, p=0.04), histogram peak height and the activity in SII (r=0.5, p=0.007) and histogram mean values and the activity in the cerebellum (r=0.3, p=0.05). The activity in this latter region was also correlated with all FA histogram derived metrics (r ranging from 0.3 to -0.5, p ranging from 0.05 to 0.002). Considering brain MTR histograms metrics, significant correlations were found between the activity in the cerebellum, SMC and SMA and histograms mean MTR and peak location (r=0.4, p ranging from 0.02 to 0.02). Finally, considering spinal cord MR metrics, significant correlations between MTR histogram peak height and the activity at the level of SMA (r=-0.4, p=0.01), SMC (r=-0.5, p=0.002) and SII (r=-0.4, p=0.009) were found. The activity of this latter region was also correlated with the number and extension of lesions detected in the spine (r=-0.4, p=0.009).

Discussion
Our study shows that in PPMS patients there are significant correlations between the brain pattern of cortical activity and macro- and micro-sopic disease burden. Interestingly, the regions that better correlated with MR derived and clinical metrics were represented by areas that are usually involved in the execution of motor complex tasks and are usually considered "secondary" motor areas (SII, STG). The activation of these areas could be related to unmasking or dishinibition of latent motor pathways to limit functional impairment following MS tissue damage.

References