Role of functional brain changes in primary progressive multiple sclerosis

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Introduction: Functional MRI (fMRI) studies (1,2) have suggested that functional brain reorganization in patients with multiple sclerosis (MS) might have an adaptive role, e.g. contribute to maintaining clinical function. However, these studies mainly employed active hand movement. Our aim was to investigate functional reorganization in patients with Primary Progressive (PP) MS using not only active but also passive movement of the foot. The advantage of using passive movements is that they do not depend on voluntary planning or ability to execute the task. To understand the role of functional changes in patients, the relationships between the strength of the fMRI responses to active and passive movements and measures of disability, brain lesion load and spinal cord atrophy were assessed.

Methods: *Subjects.* Thirteen patients with PP MS [mean age 46 (SD 11.5), 9 men and 4 women, median EDSS 4.0 (range 3-6.5), mean 25foot Timed Walked Test (TWT) 7.42 sec (SD 3.44), mean 9hole Peg Test (9HPT) 24.99 sec (SD 5.03) of right hand and 26.55 sec (SD 6.33) of left hand, median Ashworth score for spasticity 2 (range 0-3) for right leg and 1 (range 0-3) for left leg] and 16 healthy controls [mean age 36.22 (SD 11.7), 12 men and 6 women] were studied. All subjects were right-foot dominant. *Paradigm*. A pseudo-randomly interleaved block design comprising 20 sec periods of active or passive movement interleaved with 20 sec rest periods. One fMRI experiment for each foot was performed. The motor task was dorsi- plantar-flexion of the foot. Subjects were studied supine with their knees flexed and their thighs supported. Each foot was strapped into a custom made wooden manipulandum. The active task was auditory-cued by a metronome at 1.5Hz, and the same rate was followed by the operator who elicited the passive movement. All subjects underwent a training session prior to fMRI that involved recording of surface EMG from tibialis anterior and soleus. The EMG-percentage of the maximum contraction was calculated during active movements. During the fMRI, the movement amplitude of the foot dorsi- and plantar-flexion was obtained. To assess differences in EMG-percentage and movement amplitude between patients and controls, a Mann-Whitney U test was used. *fMRI protocol and analysis*. All imaging was performed at 1.5 T. The fMRI protocol consisted of 27 interleaved ascending slices covering the whole brain using a single shot gradient echo EPI [slice thickness 4.6 mm, slice gap 0.4 mm, in-plane resolution 3×3 mm, TR 4 seconds, matrix 128×64, 220 scans acquired over 14 min and 40 sec]. The analysis was performed using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK). The images were realigned to the first image of each experiment and a mean image was obtained and reoriented. The reorientation parameters were applied to all the images, which were then normalized into a standardized space (as defined by the Montreal Neurological Institute (MNI)) and smoothed using a Gaussian filter of 8 mm. For each subject, a fixed effect approach was adopted where the smoothed images were entered into a design matrix, in which the realignment parameters were included as covariates of no interest. For each foot, the contrasts of parameter estimates for active and passive were generated. To investigate differences in fMRI response between patients and controls, a single-subject conditions and covariates model was performed using subject's specific contrasts; patient and control groups were considered as conditions and movement amplitude as covariate. Two contrasts, e.g. patients greater than controls and controls greater than patients, were estimated separately for active and passive movement. Statistical SPM(T) images were thresholded at $p < 0.05$ corrected at voxel level for multiple comparisons within regions of interest (ROIs) which were chosen *a priori*, and reported in previous publications. *Structural MRI*. All patients also underwent: 1) dual echo FSE imaging of the brain, which was used to calculate lesion load [mean 10.7 ml (range 0.2-31.9)]; 2) volume-acquired, inversion-prepared, FSPG echo sequence of the spinal cord, which was used to obtain cervical cord area [mean 64.08 mm^2 (SD 9.68)]. *Correlations.* In patients, to investigate whether clinical and MRI measures had an effect on the fMRI response, a linear regression analysis was performed separately for each measure. Statistical inferences were performed by using a p value < 0.01 corrected at voxel level for multiple comparisons within ROIs.

Results: All subjects were able to relax completely during passive movements. Although patients and controls showed similar values of EMG-percentage, patients had smaller left movement amplitude than controls. Patients activated more than controls during active movement in a pattern of regions, which included the contralateral cerebellum and precuneus. This pattern extended to the ipsilateral postcentral gyrus and ipsilateral SMA when trends were also considered. Further, patients demonstrated greater fMRI response in several other specific regions depending on which foot was considered (Fig 1). Patients activated more than controls during passive movement in the ipsilateral striatum (e.g. putamen for the right foot and caudate for the left foot) (Fig 1). Controls demonstrated greater fMRI response than patients only during right passive movement in the inferior vermis. *Correlations*. The strength of the fMRI responses to active and passive movements showed several positive and inverse correlations with clinical and structural MRI measures depending not only on the measure considered, but also on the brain region. For example, the activation in the ipsilateral inferior frontal gyrus and in the contralateral cerebellum was greater in patients who had lower EDSS, lower brain T2 lesion load, and performed better on the TWT. In contrast, the activation in the ipsilateral superior temporal gyrus was greater in patients with higher brain T2 lesion load. Activation in the contralateral postcentral gyrus was greater in patients with higher 9HPT of the left hand. Higher leg spasticity was associated with greater activation during left passive movement in the contralateral SMA, but with a smaller activation in the ipsilateral caudate. Spinal cord atrophy had a positive effect on the fMRI response to passive movement in either foot in the contralateral postcentral gyrus.

Discussion: Patients with PP MS showed functional brain reorganization during active and passive movements compared with controls. Activation changes, which occurred during passive movement, might represent a true functional reorganization of the motor pathways. Disability and brain lesion load had positive and negative effects on the fMRI response to passive and active movements. Therefore, we suggest that some of these changes might have an adaptive role in limiting the impact of brain damage on the level of mobility, and others do not. Longitudinal fMRI studies are needed to elucidate whether the adaptive or non-adaptive role of some brain regions may change over time.

References: (1)Filippi M, Rocca MA, Falini A *et al*. Correlations between structural CNS damage and functional MRI changes in primary progressive MS. *Neuroimage 2002*, 15:537-46 (2)Reddy H, Narayanan S, Woolrich M *et al*. Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability. *Brain 2002*, 125:2646-57. **Acknowledgements:** O Ciccarelli is supported by TEVA Pharmaceuticals Ltd. The NMR Research Unit is funded by the MS Society of Great Britain and Northern Ireland.

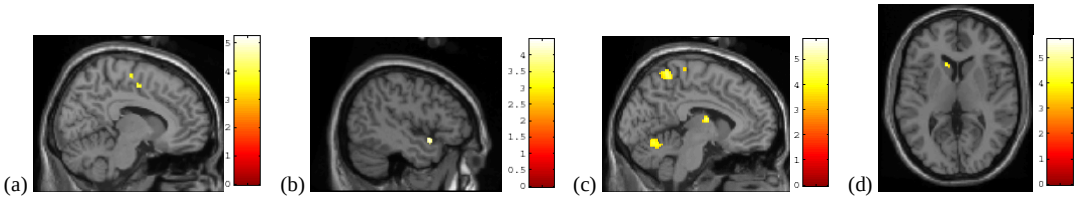

Fig 1. Patients activated more than controls (a) in the right SMA and cingulate cortex during right active movement (MNI x=10, y=-6, z=50), (b) in the left superior temporal gyrus during right passive movement (x=-44, y=8, z=-10), (c) in the left precuneus, left SI-MI, superior vermis and left thalamus during left active movement (x=-6, y=-31, z=70), (d) in the left caudate during left passive movement (x=-10, y=20, z=6). Results are overlaid onto T1-weighted template and corrected for multiple comparisons. The colour scale indicates the T score.