EFFECTS OF ACTION OBSERVATION THERAPY ON REHABILITATION OF MOTOR DEFICITS OF THE DOMINANT RIGHT UPPER LIMB IN MS PATIENTS: AN EXPLORATORY STUDY WITH STRUCTURAL AND FUNCTIONAL MRI

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INTRODUCTION and PURPOSE

Motor disability has a high prevalence and dramatic effects on daily life activity of MS patients. Several rehabilitative strategies are currently available to treat these patients, but often their efficacy is suboptimal and their benefits are generally not long-lasting. In patients with chronic stroke, action observation therapy (AOT) has been proposed as an effective rehabilitative intervention for regaining motor function [1,2]. AOT is based on visual stimulation and it is thought to act through the function of the mirror neuron system (MNS), an observation-execution matching system [3-6].

In MS, MRI techniques provide objective measures to monitor disease evolution and treatment effects and might increase our understanding of the mechanisms responsible for a favourable clinical outcome following rehabilitation.

In this study, we applied AOT in right (R)-handed MS patients with motor impairment of their R hand to assess:

1) whether this strategy may lead to a clinical improvement of motor deficits;
2) the variation of brain gray matter (GM) volumes following AOT;
3) the modifications of recruitment of the motor network and MNS following AOT;
4) the correlations between MRI changes and improvement at functional motor scales.

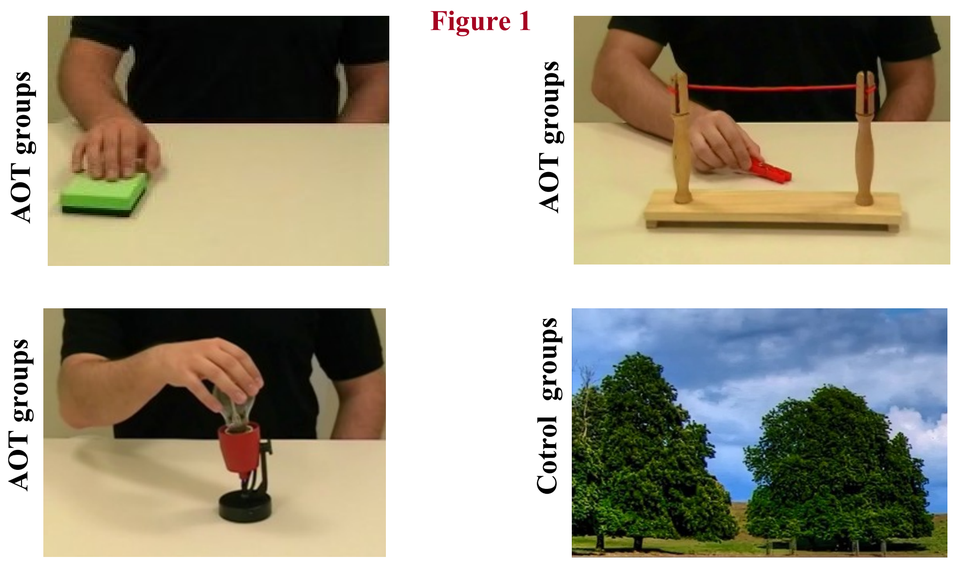
METHODS

Subjects: 25 R-handed MS patients with motor impairment in their R hand and 46 sex- and age-matched R-handed healthy controls (HC).

Behavioural assessment: Nine-hole peg test (9HPT), finger tapping (FT), Jamar and Pinch dynamometers scores, MSFC, EDSS, PASAT test and FIM were measured before (T0) and after two weeks (W2) of motor training.

Motor training: Subjects were randomized into 4 groups: 2 experimental groups (HC-AOT, n=23 and MS-AOT, n=12) and 2 control groups (HC-C, n=23 and MS-C, n=13). The rehabilitative training consisted of 40 minutes daily sessions, five time per week, for 2 weeks. The 10 sessions were composed by 10 minutes of passive mobilization of the R upper limb, vision of 3 videos lasting 5 minutes and execution, with the R hand, of three daily-life actions. AOT-groups watched videos representing daily-life actions, while C-groups watched videos of different landscapes (**Figure 1**).

Figure 1



MRI acquisition (3.0 T scanner):
At T0 and W2, the following brain sequences were acquired: DE TSE, 3D T1-weighted FFE and functional MRI (fMRI) (T2*-weighted single-shot EPI sequence), during object manipulation with the R hand.

Structural MRI analysis: Assessment of brain T2 and T1 lesion load (Jim 6.0).

Mapping modifications of GM volumes:

• Voxel-Based Morphometry (VBM) (T0) (SMP8, DARTEL): Transformation of GM maps to MNI space, non-linear deformation of GM maps to match the final customized template, modulation to keep original volume unchanged, and smoothing (8 mm gaussian kernel) [7] after T1-hypointense lesion refilling.

• Tensor-Based Morphometry (TBM) (longitudinal changes) (SPM8, High Dimensional Warping + DARTEL): Warping of follow up to baseline scan, calculation of volume changes, and normalization to atlas using the transformation from VBM analysis [8].

Mapping modifications of fMRI activations:

• Estimation of task-related single subject activations (SPM8).

Statistical analysis:

• Comparison of demographic, behavioural and MRI data between study groups (SPSS);
• VBM and TBM (SPM8) (p<0.001 uncorrected): one sample and two sample t test, using age and sex as covariates;
• fMRI analysis (SPM8): one-sample t test, paired t test and ANOVA 2x2 factorial design (p<0.05 FWE and p<0.001 uncorrected, cluster extent=10 voxels).

RESULTS

Demographic and behavioural data:
At T0, no significant differences were found in the comparison between the AOT and the respective control groups in both HC and MS. **Table 1** shows clinical characteristics of the two MS groups at T0.

	Median EDSS (range)	Disease duration (range) [years]	Median T2 lesion load (range) [ml]
MS-AOT	6.0 (4-7.5)	21.6 (7-44)	8 (1-41)
MS-C	6.0 (5.0-6.0)	16.1(5-31)	5 (2-19)
P	n.s.	n.s.	n.s.

Table 1.

Table 2 shows modification of behavioral measures at W2 compared to T0 in the four study groups. Data are expressed as mean values (*p<0.05).

	HC-AOT		HC-C		MS-AOT		MS-C	
	t0	w2	t0	w2	T0	W2	T0	W2
PASAT	49.2	53.2*	46.8	52.2*	38.0	44.8*	38.8	46.1*
MSFC	0.2	0.4*	-0.2	0.1*	-0.0	0.3*	0.0	0.2
FIM	42.0	42.0	42.0	42.0	31.2	32.5*	36.4	37.0*
FT R (/sec)	137.3	139.7	125.1	126.2	44.8	55.3*	50.1	56.9
9HPT R (sec)	17.5	17.1	18.5	18.1	75.6	68.1	54.4	61.4
PINCH R (Kg)	8.9	9.5*	7.8	7.5	4.0	5.1*	4.2	4.9
JAMAR R (Kg)	41.1	41.4	34.5	34.2	14.4	17.1*	14.2	14.9

Table 2.

VBM analysis (t0): Compared to HC, MS patients showed a distributed atrophy involving several deep GM nuclei and many cortical regions in the fronto-parieto-temporal lobes. No GM volume difference was detected between patients' subgroups as well as between HCs' subgroups.

TBM (within-group analysis): **Figure 2** shows regions with GM volume changes in the different study groups at W2 *vs* T0 (p<0.001 uncorrected).

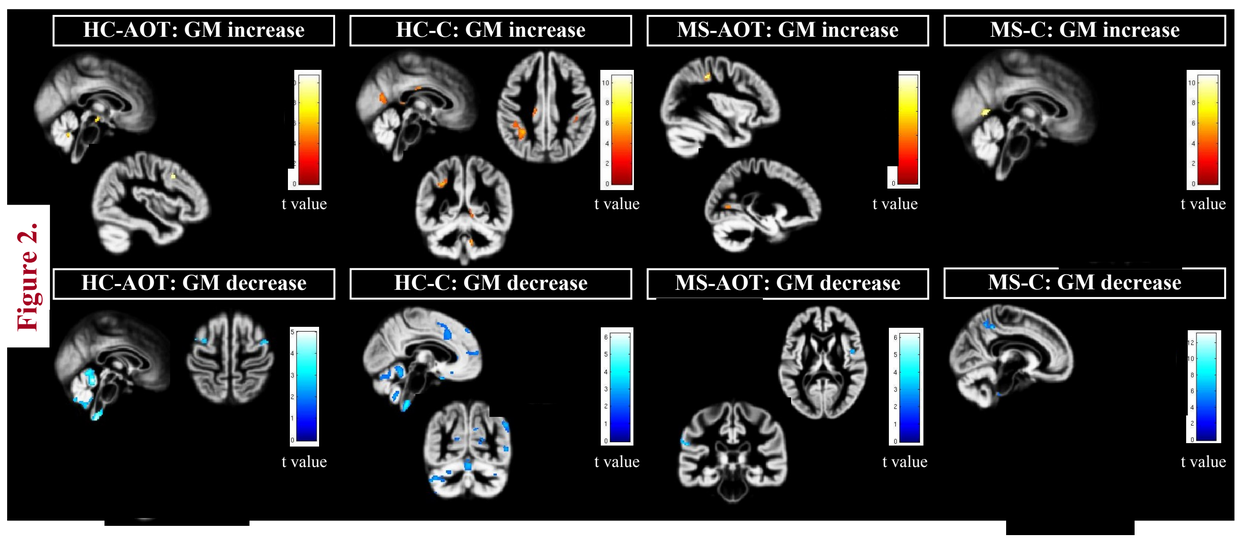


Figure 2.

TBM (between-group analysis): **Figure 3** shows regions with GM volume differences at W2 between study groups (p<0.001 uncorrected).

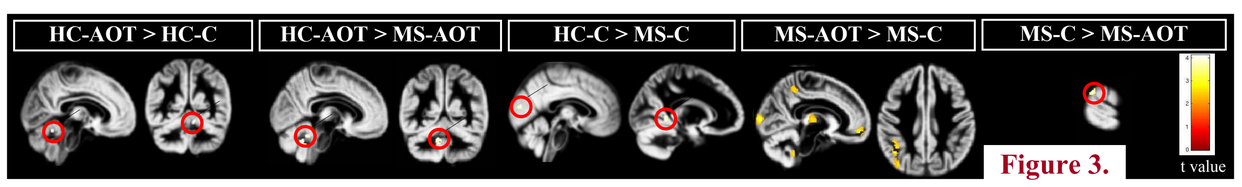


Figure 3.

fMRI analysis (T0): **Figure 4** shows differences of activation during R-hand manipulation between MS patients and HC at T0 (p<0.001 uncorrected).

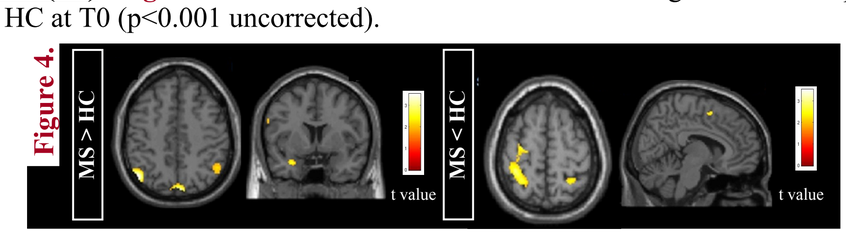


Figure 4.

Figure 5 shows modifications of activations during R-hand manipulation at W2 compared to T0 in the four study groups (p<0.001 uncorrected).

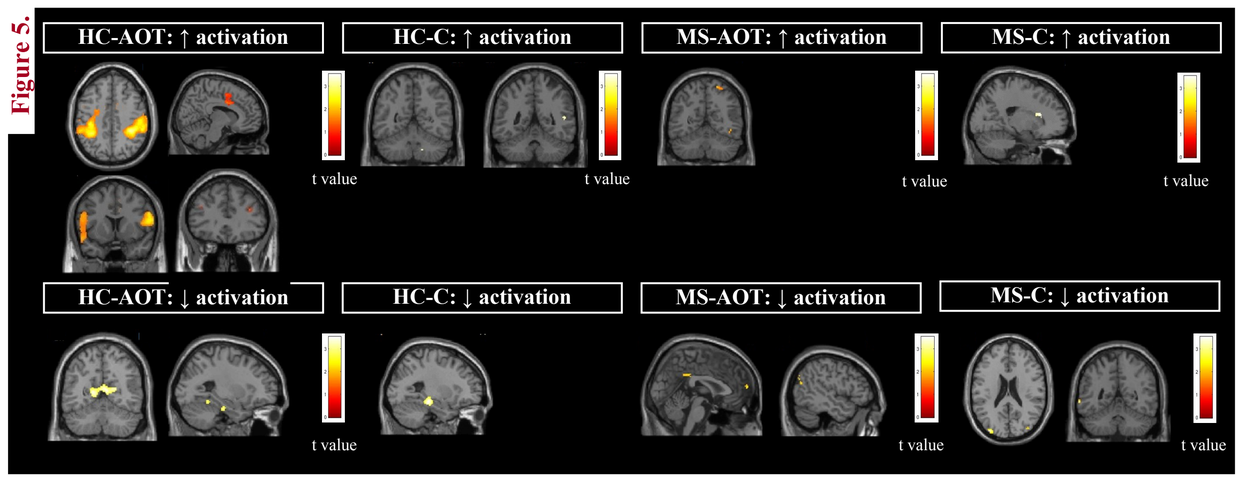


Figure 5.

Figure 6 shows differences of activation between study groups at W2 (p<0.001 uncorrected).

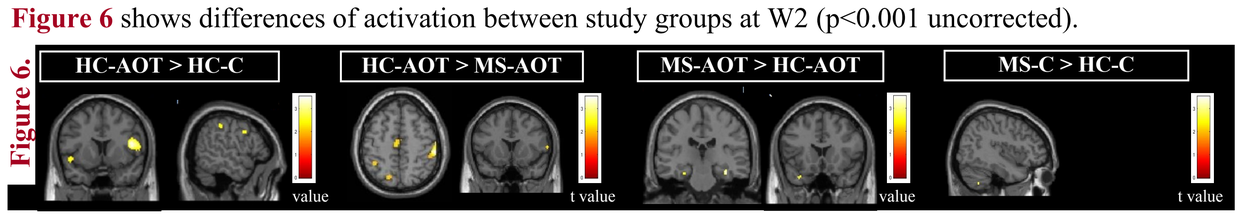


Figure 6.

Analysis of correlations: In all study groups, significant correlations (p<0.001) were found between modifications of GM volume of several brain regions and modifications of the brain pattern of cortical activations during the manipulation task *vs* improvement of motor performance at 9HPT, FT, Jamar and Pinch performed with the R hand.

CONCLUSIONS

• Modifications of structure and function of the motor network and the MNS occur in HC and MS patients after a motor training, which correlate with motor performance improvements.
• A 10-day manual dexterity training with AOT influences structural reorganization of GM and activity variation of the motor network and the MNS, suggesting that it might facilitate motor skill improvement promoting structural and functional brain plasticity.
•These findings suggest that AOT might be a valid rehabilitative approach for MS patients with motor impairment of their upper limbs.

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DISCLOSURES

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G. Comi has received compensation for consulting services and/or speaking activities from Novartis, Teva Pharmaceutical Ind., Sanofi-Aventis Pharmaceuticals, Genzyme, Merck Serono, Biogen-Dompè, Bayer Shering, Actelion, Serono Symposia International Foundation, Almirall, Chugai and Receptos.

M. Filippi serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

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