ACTION OBSERVATION THERAPY MODIFIES BRAIN FUNCTIONAL REORGANIZATION IN MS PATIENTS WITH RIGHT UPPER LIMB MOTOR DEFICITS

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INTRODUCTION

Motor disability has a high prevalence and dramatic effects on daily life activity of patients with multiple sclerosis (MS). Several rehabilitative strategies are currently available to treat these patients, but often their efficacy is suboptimal and their benefits are generally not long-lasting. Brain plasticity is likely to play an important role in promoting a positive clinical outcome following rehabilitation. In patients with chronic stroke, action observation therapy (AOT) has been proposed as an effective rehabilitative intervention for regaining motor function in combination with conventional approaches [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].

OBJECTIVES

We applied AOT in right (R)-handed MS patients with motor impairment of their R hand to assess:

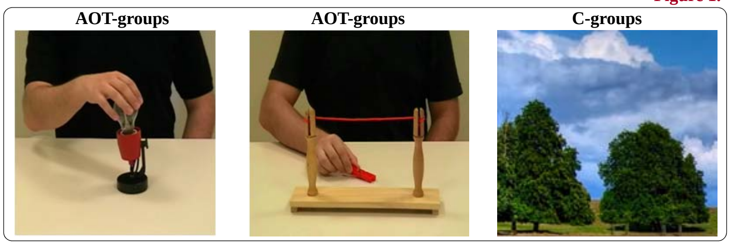
1. Whether this strategy may lead to a clinical improvement of motor deficits;
2. The modifications of recruitment of the motor network and MNS following standard rehabilitative treatment and AOT;
3. The correlations between the detected functional MRI changes and improvement at clinical scales.

METHODS

Subjects: 46 R-handed healthy controls (HC) [19 men and 27 women; mean age=42.5 years, SD=15.9 years] and 41 R-handed MS patients [15 men and 26 women; mean age=50.3 years, SD=8.7 years; median Expanded Disability Status Scale (EDSS)=6.0, range=2.0-7.5; median disease duration (DD)=15, range=2-44 years] with motor impairment of their R hand were randomized into 4 groups: 2 experimental groups (AOT-HC n=23; AOT-MS n=20) and 2 control groups (C-HC n=23; C-MS n=21).

Motor training: The training consisted of 10 sessions of 45 minutes for 2 weeks. During each training session, after 10 minutes of passive mobilization of the R upper limb, AOT-groups watched 3 videos (5 minutes each) of daily-life actions alternated by their execution with the R hand; C-groups performed the same tasks, but watched landscape videos (Figure 1).

Figure 1.



Behavioral and clinical assessment: Nine-hole peg test (9HPT), finger tapping (FT), Jamar dynamometer and Pinch dynamometer scores, PASAT test and functional independence measure (FIM) were measures at baseline (before motor training) (T0) and at the end of motor training (after two weeks ±1 day) (W2). For MS patients, EDSS score was also rated.

MRI assessment:

- Dual-echo TSE: quantification of T2 lesions volume (LV) and new T2 lesions.
- Active fMRI (T2*-weighted single-shot EPI sequence): object manipulation task (R hand). Subjects were asked to manipulate six different complex common objects alternated to a neutral one (a sphere) [2].

Statistical analysis:

- Demographic and behavioral data: comparison at T0, changes over time and group x time interactions assessed with hierarchic linear models, adjusted for age and sex (p<0.05).
- Active fMRI analysis (SPM12 software): ANOVA 2x2 factorial design (two factors, group and time, consisting of two categories, adjusted for age and sex) to assess within-group activation, within-group changes over time, between-group differences and group x time interactions (p<0.001 uncorrected).
- Correlations between behavioral and clinical measures and fMRI changes: linear regression analysis (p<0.001 uncorrected).

RESULTS

Behavioral and clinical assessment: HC and MS patients groups did not differ for demographic, behavioral and clinical data. Tables 1 and 2 summarize changes of behavioral and clinical data of the four study groups after the training.

Table 1.

Variables Median (range)	AOT-HC		p	C-HC		p	AOT-MS		p	C-MS		p
	T0	W2		T0	W2		T0	W2		T0	W2	
FIM	-	-	-	-	-	-	33 (12-42)	34.5 (14-42)	0.02	36 (23-42)	36 (23-42)	0.1
Jamar R*	37 (22-58)	38 (24.6-62)	0.6	30 (23.3-56)	30 (21.3-54)	0.7	15.9 (2-44.7)	19.2 (2-47.3)	0.0002	15.3 (1-32)	13 (0.3-38)	0.3
Jamar L	36 (20.3-54)	36 (23-60)	0.8	28 (22.3-51.6)	30 (20-61)	0.4	19.6 (0-43.7)	20.7 (0-49)	0.03	23.3 (1-48)	24 (0-56)	0.1
Pinch R**	8 (3.8-14)	9 (6.2-12)	0.01	7 (3.8-11.5)	7 (2.66-12)	0.3	4.9 (0.5-10)	5.2 (1-12.7)	0.0001	4.6 (0.4-11.3)	4.2 (0.4-13.3)	0.004
Pinch L	8 (3.8-12.5)	9 (4.5-12)	0.4	7 (3.8-11)	6.6 (2.5-12)	0.1	5.3 (0-13.3)	6.7 (0-13.3)	0.09	6.5 (0.3-12.3)	6.6 (0-13.3)	0.7
FT R	4.7 (2.5-5.6)	4.6 (2.5-6.1)	0.3	4 (2.9-5.6)	4.3 (3.3-5.6)	0.7	1.7 (0-4.3)	2 (0-4.4)	0.02	1.6 (0-3.5)	1.7 (0-3.3)	0.01
FT L	4.3 (2.3-5)	4.4 (2.9-5.1)	0.1	3.9 (2.5-4.8)	4 (2.1-5.5)	0.2	2.5 (0-5.3)	2.6 (0-5)	0.5	2.6 (0.9-3.9)	3 (0-4.1)	0.1

*** Significant differential effect in time between AOT-MS and C-MS, p=0.04**
**** Significant differential effect in time between AOT-HC and C-HC, p=0.01**

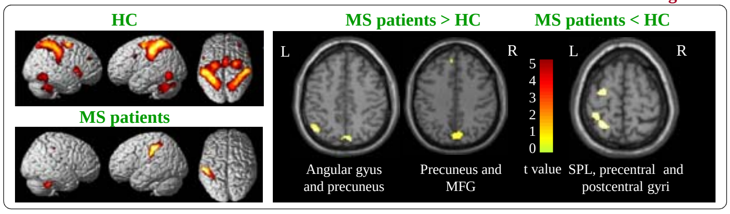
Table 2. Significant changes of behavioral and clinical data of the four study groups after the training.

Variables Mean±SD	AOT-HC		p	C-HC		p	AOT-MS		p	C-MS		p
	T0	W2		T0	W2		T0	W2		T0	W2	
z9HPT	0.27 ±1.08	0.49 ±1.17	0.05	-0.27 ±0.85	-0.08 ±0.95	0.09	-4.11 ±1.44	-3.86 ±1.60	0.06	-3.47 ±1.26	-3.14 ±1.52	0.01
z9HPT R	0.23 ±1.14	0.34 ±0.97	0.5	-0.23 ±0.79	-0.05 ±0.92	0.2	-4.41 ±1.43	-4.13 ±1.57	0.09	-4.15 ±1.48	-3.72 ±1.70	0.009
z9HPT L	0.29 ±1.02	0.62 ±1.39	0.02	-0.29 ±0.90	-0.10 ±1.00	0.2	-3.32 ±1.62	-3.13 ±1.78	0.2	-2.31 ±1.41	-2.12 ±1.54	0.2
zPASAT	0.11 ±0.85	0.49 ±1.05	0.006	-0.21 ±1.02	0.33 ±0.75	0.0002	-0.85 ±1.58	-0.21 ±1.65	0.001	-0.68 ±1.41	0.06 ±1.35	0.0001

MRI analysis: At T0, T2 LV did not differ between the two groups of MS patients (p=0.9).

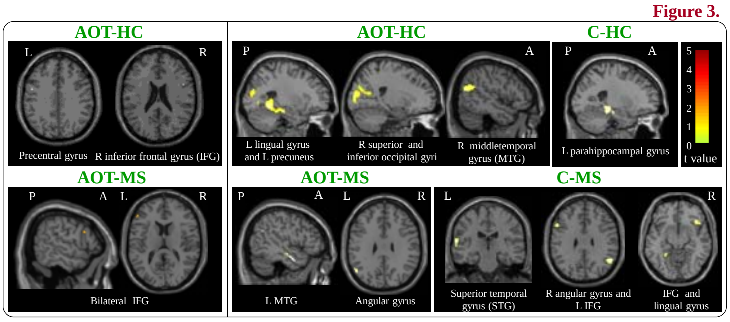
fMRI analysis at T0: Figure 2 shows differences of activation during R-hand manipulation between MS patients and HC (p<0.001 uncorrected).

Figure 2.



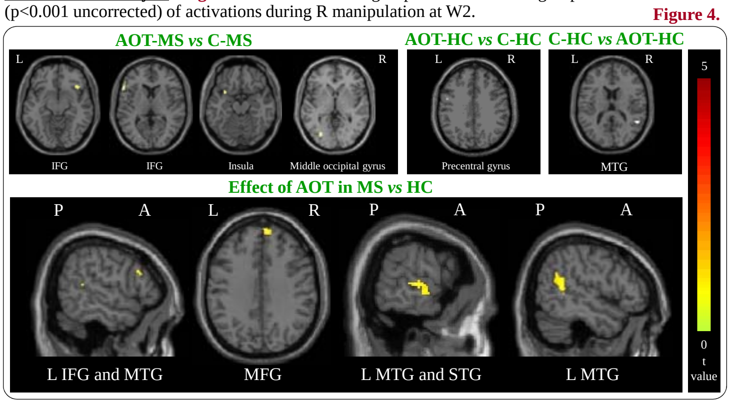
Active fMRI analysis: Figure 3 shows areas of increased (L panel) and decreased (R panel) activation during R-hand manipulation at W2 in the four study groups (p<0.001 uncorrected).

Figure 3.



Active fMRI analysis: Figure 4 shows between-group differences and group x time interactions (p<0.001 uncorrected) of activations during R manipulation at W2.

Figure 4.



Correlations: significant positive correlations (p<0.001) between increased fMRI activity and better performances at functional scales were found only in AOT-MS, between the following:

- Increased activation of the R and L IFG and increased scores at PASAT (r=0.62 and 0.44), R Jamar dynamometer (r=0.53 and 0.50), R Pinch dynamometer (r=0.57 and 0.51) and R FT (r=0.42 and 0.57);
- Increased activation of the L insula and a better score at the R Jamar (r=0.63);

In AOT-MS, negative correlations (p<0.001) between reduced activation of the L angular gyrus and L MTG and better score at the R Jamar dynamometer were found.

CONCLUSIONS

- AOT acts on both the motor and the MNS in healthy subjects and in patients with MS, modulating their pattern of activations.
- Compared to standard rehabilitation, AOT yielded better performances at some functional scales, which were significantly correlated with modifications of the patterns of brain activations.
- The application of AOT, combined with standard rehabilitation, might be a valid rehabilitative approach for MS patients with motor impairment of their upper limbs.

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