Functional activity during working memory processing correlates with the effect of computer-assisted cognitive rehabilitation

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Background

Cognitive impairment is highly prevalent in Multiple Sclerosis (MS) patients. To date, cognitive rehabilitation strategies have provided some interesting results, in particular on attention[1] and information processing speed performances. Few studies have also included functional MRI (fMRI) as an outcome of the cognitive training.

Objectives

To evaluate:

- the effect of a home-based computerized program for retraining attention dysfunction on behavioral performances
- the relationship between fMRI functional activity during working memory (WM) at baseline and cognitive outcomes at the end of training.

Methods

Inclusion criteria:

Relapsing-remitting (RR) MS patients, aged 18-55 years, with an EDSS score ≤5.5, who failed ≥ 2 tests of attention on an extensive neuropsychological evaluation (NP).

Random allocation to:

- **Specific computerized training (ST):** based on the ***Attention Processing Training (APT)*** program, a group of hierarchically organized tasks that exercise different components of attention (sustained, selective, divided, alternating attention);
- **Non specific training (nST):** non-specific computerize exercises (e.g. text and newspaper's articles reading and comprehension).

Both performed at home, in one-hour sessions, twice a week for three months.

Outcome measures:

NP performed before and after the completion of the cognitive training.
The Cognitive Impairment Index (CII) as a measure of global cognitive function was calculated for each patient.
At baseline, all the patients underwent a task-related fMRI while performing the N-Back (NB) tasks.

Researchers involved in the acquisition and analysis of fMRI data were blind to the treatment allocation.

Statistical analysis:

A repeated measures ANOVA was used to evaluate changes in the CII and as a function of the computerized training. SPM multiple regression analysis was performed to investigate if CII improvement as a function of cognitive training was predicted by brain activity during WM.

Results

Fifty RRMS patients were randomized, 26 were assigned to the ST group, 24 to the nST. Demographic and clinical characteristics (**Table 1**) and baseline neuropsychological performances were not significantly different between the 2 groups. ST exposed patients reported a significant improvement in verbal memory (SRT LTS/CTLR/D), attention and information processing speed performances (SDMT, PASAT 3 and 2), whereas those exposed to the nST slightly improved in verbal memory (SRT CTLR/D), visuo-spatial memory (SPART) and information processing speed performances (PASAT 3 and 2) (**Table 2**).

Table 1. Baseline demographic and clinical characteristics

Variable	Specific Training	Non Specific Training
Sex (F/M), n	17/9	16/8
Age, years, Mean (SD)	37.2 (7.98)	37.0 (8.36)
Disease Duration, years Mean (SD)	11.28 (6.98)	12.43 (7.86)
Disease modifying therapy, n		
Interferon beta	14	8
Glatiramer Acetate	0	3
Natalizumab	7	4
Fingolimod	3	9
Dimethyl fumarate	2	0
Annualized Relapse Rate, Mean (SD)	0.12 (0.33)	0.25 (0.44)
EDSS, Median (min - max)	2.5 (1.0 - 5.0)	3.0 (1.0 - 5.0)
School Education, years, Mean (SD)	12.92 (3.24)	11.46 (2.95)

All the comparison were not statistical significant

Table 2. Pre-training vs post-training comparison

Cognitive Test	Specific Training			Non Specific Training		
	Pre	Post	P - value	Pre	Post	P - value
SRT LTS	**31.7 (7.4)**	**36.1 (6.9)**	**0.02**	32.8 (6.5)	33.6 (5.5)	0.5
SRT CLTR	**25.8 (6.9)**	**29.8 (6.6)**	**0.01**	**25.3 (6.9**	**28.5 (5.7)**	**0.03**
SPART	22.7 (4.7)	23.1 (3.3)	0.7	**21.7 (3.7)**	**23.4 (4.0)**	**0.01**
SDMT	**31.6 (8.6)**	**42.7 (10.3)**	**<0.0001**	34.7 (10.6)	39.0 (9.3)	0.1
Pasat 3	**10.8 (8.9)**	**26.4 (14.0)**	**<0.0001**	**12.0 (10.0)**	**20.5 (12.9)**	**0.002**
Pasat 2	**7.6 (10.8)**	**23.4 (13.8)**	**<0.0001**	**9.0 (11.1)**	**18.2 (12.9)**	**0.005**
TMT A	47.7 (21.6)	48.5 (14.0)	0.9	46.3 (17.4)	47.2 (14.6)	0.8
TMT B	79.5 (35.1)	84.5 (41.5)	0.6	83.6 (24.8)	96.0 (42.4)	0.2
SRT D	**6.2 (1.2)**	**7 (1.0)**	**0.001**	**6.2 (1.7)**	**6.9 (1.3)**	**0.04**
SPART D	7.2 (3.7)	7.0 (1.1)	0.9	6.5 (1.6)	6.8 (1.2)	0.4
WLG	21.3 (5.6)	21.6 (3.9)	0.7	20.1 (4.3)	21.5 (4.1)	0.1
Stroop	67.3 (19.5)	65.2 (11.4)	0.7	64.8 (8.6)	62.6 (6.5)	0.2
CII	**17.2 (3.1)**	**11.4 (4.8)**	**<0.0001**	**16.6 (2.7)**	**14.8 (3.2)**	**0.016**

Results

Patients exposed to the ST experienced a more pronounced reduction of the CII in comparison to patients trained with the nST (ST: 17.2±3.1 vs 11.4±4.8; nST: 16.6±2.7 vs 14.8±3.2; F= 12.342; p=0.001). (**Figure 1**) The analysis of fMRI data revealed a significant BOLD response involving the fronto-parietal network during the working memory processing. SPM multiple regression analysis indicated an interaction between Δ CII and treatment group on superior and middle frontal gyrus activity (Broadman Areas 6, 8, 9 – x: 31, y: 19, z: 62; z = 4.86, p = 0.011 FWE corrected at pick level). **(Figure 2**). Patients with lower functional activity in superior and middle frontal gyrus (Broadman Areas 6, 8, 9) while performing the N-Back had greater improvement after the cognitive training (p<0.05 FWE whole brain corrected). (**Figure 3**).

Figure 1. The effect of cognitive training on the CII

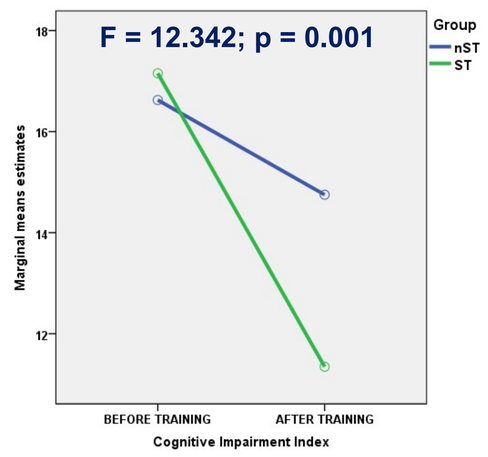
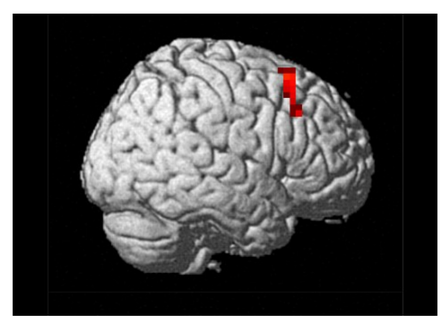
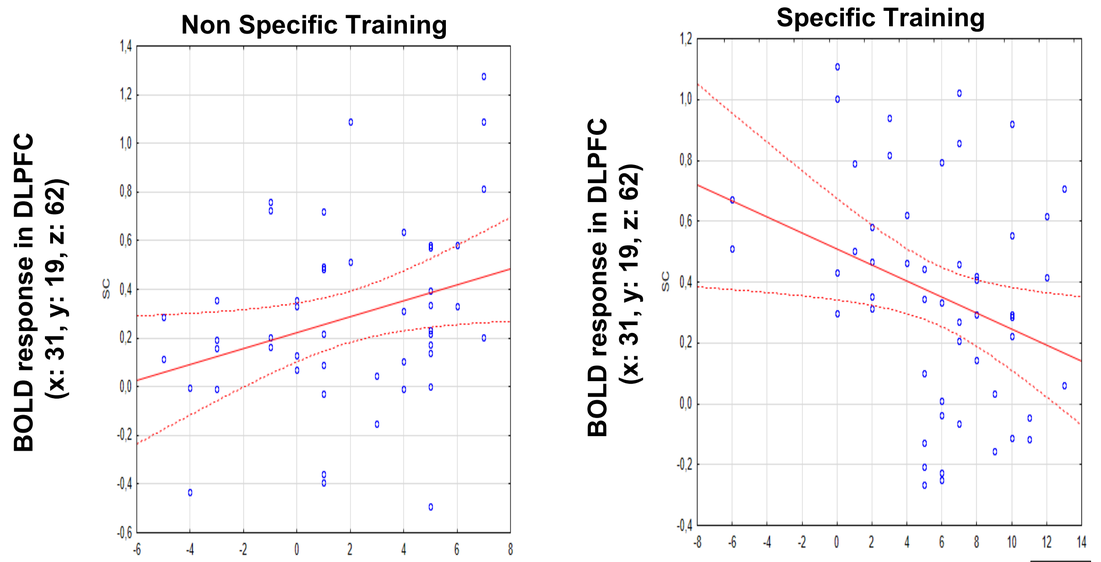


Figure 2. Baseline fMRI & 1-2-back condition



Sagittal sections (whole brain corrected) of the BOLD response of the multiple regression of Δ CII x group condition x 1-2 Back on superior and middle frontal gyrus (Broadman Areas 6, 8, 9) activity (x: 31, y: 19, z: 62).

Figure 3. Baseline fMRI & 1-2-back condition II



Scatterplots show a positive regression between Δ CII and BA 6, 8, 9 activity in control group and a negative regression between Δ CII and BA9 activity in experimental group.

Conclusions

Our results indicate that an Attention Specific Training improves the global cognitive functions as measured by the reduction of the CII in RRMS patients.
In this study we have observed that the positive impact of a computerized training for attention correlates with FC measures obtained during WM processing. Moreover, in our sample the cognitive training has been more efficacious in patients who have showed a lower FC during baseline WM processing. In conclusion, our results suggest that task-related fMRI could be a useful tool to select patients who, at the end of the training, would benefit from cognitive rehabilitation.

References
1. Amato, M. P., B. Goretti, et al. (2014). "Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial." Mult Scler **20**(1): 91-98.

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