

# Functional connectivity in multiple sclerosis after robotic rehabilitative treatment

## A case report

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### Abstract

**Rationale:** Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system and it is associated with an impaired motor function status. The efficacy of rehabilitation in promoting functional recovery and increasing quality of life in MS patients has been demonstrated.

**Patient concerns:** A 47-year-old woman was diagnosed with relapsing-remitting multiple sclerosis (RRMS) in November 2014 because of left upper limb hypoesthesia and weakness with difficulty in hand manipulation skills (there was a 1-point Expanded Disability Status Scale (EDSS) progression, i.e., 2.5 vs 1.5). Magnetic resonance image (MRI) showed a new frontal right cortical high-signal-intensity lesion.

**Diagnosis:** Neurological and MRI examination were suggestive of MS diagnosis.

**Interventions:** Patient was treated with robotic rehabilitation and evaluated by a Glove Analyzer for fMRI system (GAF). Functional MRI (fMRI) was acquired before and at the end of rehabilitative treatment performed with robotic device (Armeo-power).

**Outcomes:** At the end of the rehabilitation program, most of the behavioral parameters, GAF and fMRI evaluation, showed a significant improvement. Moreover, fMRI showed a significantly increased functional activation within the sensory-motor network in the active, motor task.

**Lessons:** Our findings suggest a possible restorative effect of robotics on brain networks. Moreover, we may argue that GAF may be a valuable tool in assessing functional recovery after upper limb rehabilitation, especially of associated to fMRI examination.

**Abbreviations:** BA = Broca area, fMRI = functional MRI, FMRIB = functional magnetic resonance imaging of the brain, FSL = FMRIB's Software Library, GAF = Glove Analyzer for fMRI system, ITI= inter-tapping interval, MRI = magnetic resonance imaging, MS = multiple sclerosis, RCI = reliable change index, TD = touch duration.

**Keywords:** activation, Armeo-power, case report, functional magnetic resonance, Glove analyzer, multiple sclerosis, rehabilitation

## 1. Introduction

Sensorimotor impairments of lower limbs are reported in 75% of multiple sclerosis (MS) patients, whereas dysfunctions of upper limbs occur in 66% of MS.<sup>1,2</sup> The level of arm and hand

disabilities is strictly correlated to the ability to perform daily living activities like eating, dressing, and grooming.<sup>3</sup> Consequently, upper limb dysfunction could potential interfere with patient's quality of life. For this reason, the possibility to recovery patient motor activity is very important. To date, however, few studies about the effectiveness of physiotherapy on upper limb functions in MS have been performed.

Despite some differences about neuropsychological and clinical outcome, task-related fMRI and RS-fMRI findings are quite consistent, pointing out the role of some specific brain regions such as cingulated cortex, precuneus, and cerebellum.<sup>4-6</sup> The cingulated cortex is known to cover emotion formation and processing, learning, and memory.<sup>7</sup> The precuneus is involved in episodic memory and visuospatial imagery and it has been suggested to be a specific target for visual mirror therapy and virtual reality-based rehabilitation.<sup>8</sup> Being connected with many association networks, the cerebellum has been now recognized to be not only involved in motor planning and learning, but also in different cognitive domains, including attention, memory, and learning, executive control, language, and visuospatial function.<sup>9</sup>

Preliminary magnetic resonance imaging (MRI) studies showed that robotic rehabilitation in MS has a positive effect on neural plasticity. Nonetheless, few studies have addressed the application of robot-based treatment of upper limbs in MS,<sup>10-14</sup> demonstrating a posttreatment improvement in the execution of

Editor: N/A.

Funding Statement: None.

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Medicine (2019) 98:17(e15047)

Received: 26 October 2018 / Received in final form: 14 February 2019 / Accepted: 5 March 2019

<http://dx.doi.org/10.1097/MD.00000000000015047>

functional tasks of proximal and distal movements. Functional MRI represents a powerful tool to detect task-related cortical activations and their changes potentially related to brain reorganization following MS damage,<sup>[15]</sup> and to study the connectivity between specific regions and brain networks.

We describe the case of a female MS patient with left upper limb motor impairment, treated with robotic rehabilitation and evaluated by means of a Glove Analyzer for fMRI system (GAF).

## 2. Case report

A 47-year-old woman was diagnosed with relapsing-remitting multiple sclerosis (RRMS) in November 2014. She was treated by interferon beta (Rebif 44), with a suboptimal response. In August 2015, she developed a sudden onset of tingling and motor impairment on left upper limb. Neurological examination showed left upper limb hypoesthesia and weakness with difficulty in hand manipulation skills (there was a 1-point EDSS progression, i.e., 2.5 vs 1.5). A brain MRI detected a new frontal right cortical high-signal-intensity lesion on T2-weighted MR images (T1-weighted Gadolinium-enhanced lesion). The patient was prescribed a 3-day i.v. solumedrol protocol, with an improvement of hypoesthesia after 1-month. As the motor impairment persisted, the patient was submitted to a rehabilitative treatment with robotic device Armeo-power. After 1 month of robotic training, she showed an improvement of clinical symptoms. Before and after rehabilitative treatment, we tested the hand dexterity with a finger-thumb opposition task by using an MRI compatible sensor-engineered glove after Nine Hole Peg Test for hand dexterity then, we assessed brain connectivity by fMRI examination. The study protocol was approved by the Local Ethics Committee according to Declaration of Helsinki (39/2013). Informed written consent was obtained from the patient for publication of this case report and accompanying images.

AP (Hocoma AG, Volketswil, Switzerland) is a rehabilitative exoskeleton used as early treatment of motor abilities. It provides an intelligent arm support in a large 3D workspace. The suspension system is an exoskeleton that supports the subject's arm from proximal to distal region and improves any residual active movement of paretic arm in a 3D space. Virtual reality settings are designed to provide different difficulty levels. The system is able to calibrate the working space according to patient's active mobility, and provides information about specific movement parameters. In addition, it permits an adjustment of level of difficulty for each patient during the entire training.

Our patient underwent a total of 40 1-hour training sessions (i.e., 5 times a week for 8 consecutive weeks). During the first session, the device was adjusted for patient's arm size and angle of suspension. Once the UL was fitted to the system, the working space and the exercises were selected. The working sessions were supervised by a skilled physiotherapist, who modified the exercise programs according to patient's progress.

We used GAF,<sup>[16]</sup> to analyze the kinematics of finger opposition movement sequences in uni-manual or bimanual motor tasks in fMRI environment.<sup>[17,18]</sup> The subject wore a sensor-engineered glove<sup>[19]</sup> on own hand. Data were acquired at 1 kHz (National Instrument Board 800008B-01). The subject performed repetitive finger opposition movements (thumb to index-middle-ring-little) with her right and left hand respectively for 180 consecutive seconds (60 active movements–60 resting state) at self-paced tone. In addition she performed a bimanual task paced her movements with the tone of a metronome fixed at

2 Hz. The following parameters were taken into account: touch duration (TD), that is, the contact duration between thumb and finger during the sequence, measured in ms; inter-tapping interval (ITI), that is, the time occurring between the end of a thumb-finger contact and the beginning of following one (in ms); the % correct sequences (%SEQCORR) and mean rate (MR), that account for touches frequency, in Hz (see Fig. 1) before (T0) and after (T1) the rehabilitative upper limb training.

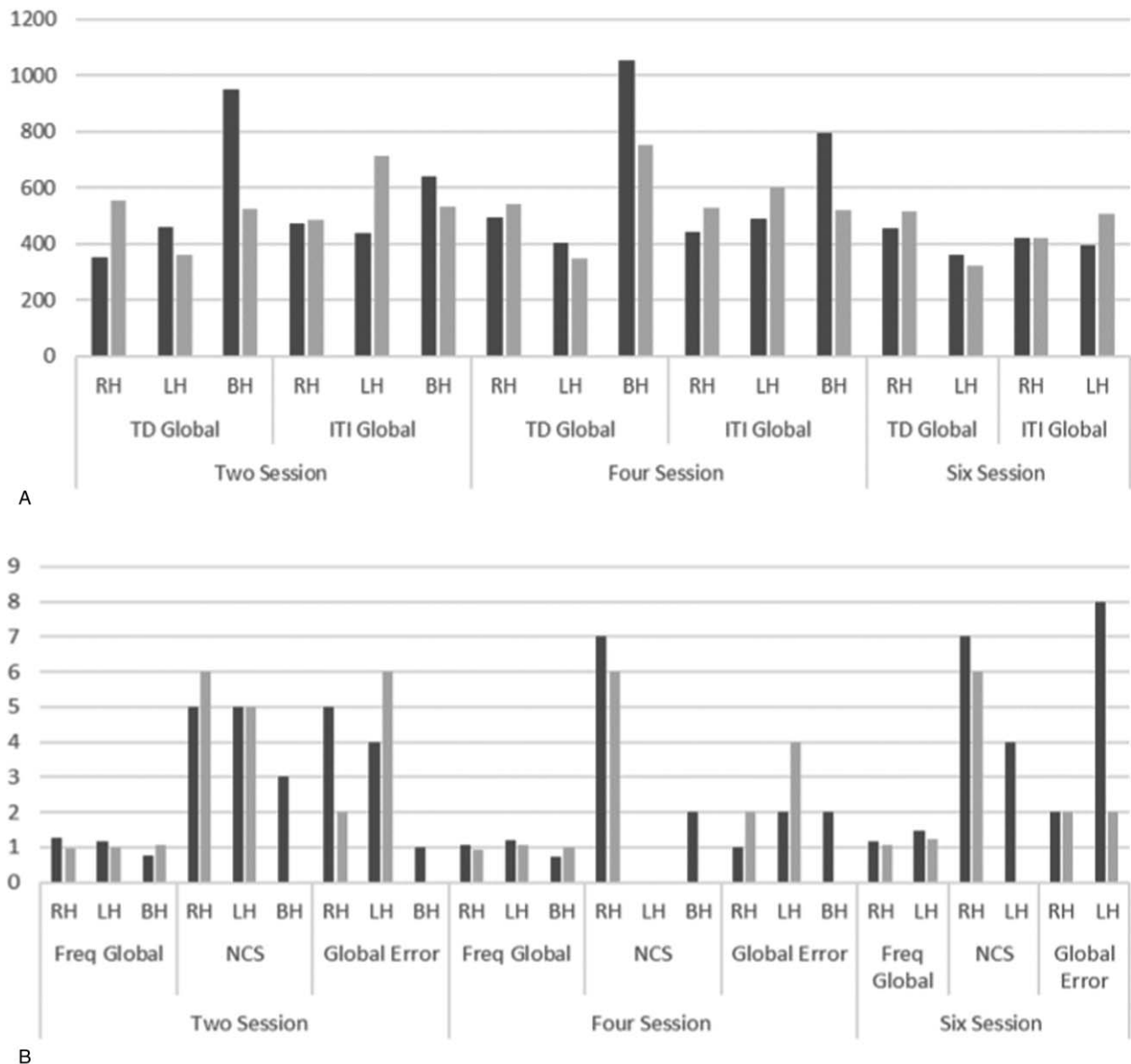
The patient underwent a MRI examination with MRI scanner operating at 3.0T (Achieva, Philips Healthcare, Best, The Netherlands), by using a 32-channel SENSE head coil. The MRI protocol included: T1-weighted (repetition time [TR]=8 ms, echo time [TE]=4 ms, slice thickness/gap=1/0 mm, number of slices=173, field of view 240 mm) used as structural reference for fMRI acquisition. fMRI-sequences were build on block paradigm of 60 volumes (number of slice=35, slice thickness=5 mm; TR=3000 ms; TE=30 ms; field-of-view=224 × 240 mm; matrix=2 × 2 mm, duration=3.09 minutes).

At T0 and T1, we acquired 3 fMRI run based on a block paradigm alternating 3 30 seconds task periods with 3 30 seconds rest periods. The 3 fMRI sequences consisted of a finger opposition task one with right hand, a finger opposition task with left hand, and a bimanual task. During the rest periods, the patient was instructed to stay at rest without movement. A red light was projected on the monitor to indicate the stop. The motor task consisted in the repetition of a finger-to-thumb with the right hand (index, medium, ring, and little fingers), with left hand (second run) and finally with both hands (3 runs). For both hands, the finger motor sequence was paced by a metronome set at 2 Hz.

fMRI-analysis was performed with FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-processing procedure was applied: employing different modules of the FSL-software package, motion correction using MCFLIRT,<sup>[20]</sup> non-brain removal using BET,<sup>[21]</sup> spatial smoothing using a Gaussian kernel of FWHM=6 mm, mean-based intensity normalization of all volumes by the same factor, and highpass temporal filtering (sigma=30 seconds). Registration of functional images to high resolution structural images was performed with FLIRT.<sup>[20,22]</sup> For the analysis of the functional data, we used the time course of motor task as the main explanatory variable (EV1) convolved with a Double-Gamma hemodynamic response function. It is a mixture of 2 Gamma functions—a standard positive function and a small delayed, inverted Gamma to model the late undershoot. The resulting activation maps were normalized via non-linear registration of the MPAGE to the Montreal Neurological Institute (MNI) coordinate system 2-mm brain template and applying a cluster significance threshold of  $Z > 2.3$  and a (corrected) cluster significance threshold of  $P < 0.05$ .

To examine whether the parameter registered by GAF pre and post robot-based treatment improved significantly, reliable change index (RCI) was calculated. The RCI is considered to have a normal distribution with mean=0 and standard deviation (SD)=1. Based on  $\alpha=0.05$  (2-tailed significance testing) or based on  $\alpha=0.025$  (1-tailed significance testing), a RCI  $> 1.96$  or  $< -1.96$  indicates statistical significance, suggesting real change. We used significance testing with RCI  $> 1.96$ , based on  $\alpha=0.025$  (1-tailed significance testing).

During a finger to thumb opposition task with right hand (at T0), we revealed a more distributed activation pattern in left primary sensory cortex BA1, BA2, BA3b ( $Z=11.6$ ;  $P < .05$ ), in the left inferior parietal lobule (Pft), right Broca area BA9 ( $Z=5.68$ ,  $P < .001$ ) and right cerebellum ( $Z=7.29$ ,  $P < .001$ )



**Figure 1.** Representation of some parameters at T0 and T1. BH=bimanual hands, ITI=inter-tapping interval, LH=left hand, NCS=number of correct sequences, RH=right hand, TD=touch duration.

(Table 1). At T1, we found activations in right cerebellum ( $Z=7.29, P<.001$ ); in left premotor cortex BA6, primary motor cortex BA4a ( $Z=7.33, P<.001$ ); secondary somatosensory cortex/parietal operculum OP1, OP4, Heschl gyrus (includes H1 and H2); in right supramarginal gyrus (BA40) ( $Z=6.07, P=.04$ ) and left middle temporal gyrus, temporo-occipital part, lateral occipital cortex, inferior temporal gyrus ( $Z=3.97, P=.04$ ) (Table 1).

At T0, we found a more distributed activation pattern in right precentral gyrus, postcentral gyrus, and, in particular, in premotor cortex BA6, primary motor cortex BA4a, primary somatosensory cortex BA3b, BA1 ( $P<.05$ ). Moreover, we highlighted left middle temporal gyrus, angular gyrus, lateral occipital cortex ( $Z=6.37, P=.001$ ), left putamen and left caudate ( $Z=4.35, P=.04$ ) activations (Table 1). At T1, we

found cortical activation in right primary motor cortex BA1, BA4a, BA3b, premotor cortex BA6, primary motor cortex BA4a ( $Z=9.87, P<.05$ ); right frontal pole, right middle frontal gyrus ( $Z=4.03, P=.04$ ), inferior frontal gyrus with Broca area BA45 (Table 1).

At T0, we found activation in right postcentral gyrus, supramarginal gyrus, precentral gyrus, primary somatosensory cortex BA2, BA3b, BA3a, BA1 ( $Z=8.45, P=.04$ ), primary motor cortex BA4p, inferior parietal lobule (PFt), anterior intra-parietal sulcus (hIP2), superior parietal lobule (7PC) ( $P<.05$ ); left cerebellum ( $Z=6.26, P<.001$ ), right frontal pole, right middle frontal gyrus ( $Z=5.15, P=.008$ ) (Table 1). At T1, we highlighted activation ( $Z=8.92, P<.001$ ) in left primary somatosensory cortex BA1, BA2, inferior parietal lobule PF, PFt, and right cerebellum ( $Z=6.8, P<.001$ ) (Table 1).

**Table 1**  
fMRI cortical activation during finger-to-thumb task in MS patient at T0 and T1.

Finger to thumb	Anatomical region	Side	MNI-coordinates*			Conventional model (Z-value)
			X	Y	Z	
Rhand	Primary sensory cortex (BA1)	L	-52.8	-23.6	57.8	11.6
	Middle frontal gyrus (BA9)	R	39.9	42.3	25.7	5.68
	Cerebellum	R	8.84	-74	-50.5	7.29
Lhand	Premotor cortex (BA6)	R	38.9	-17.9	67.2	12.1
	Middle temporal gyrus	L	-61.5	-61.9	6.53	6.37
	Caudate	L	-18.1	15.6	0	4.35
Bhand	Primary sensory cortex (BA1)	R	39.1	-24.6	46.3	8.45
	Cerebellum	L	-13.3	-82.8	-54.6	6.26
	Middle frontal gyrus (BA9)	R	39.8	39.7	33.9	5.15
Rhand	Cerebellum	R	8.84	-74	-50.5	7.29
	Premotor cortex (BA6)	L	-36.7	-20.8	70.2	7.33
	Supramarginal gyrus (BA40)	R	56.9	-17.5	15.8	6.07
Lhand	Middle temporal gyrus	L	-54.7	-64	-24	3.97
	Primary motor cortex (BA4)	R	44.7	-17.7	60.2	9.87
	Middle frontal gyrus (BA9)	R	39.6	35.6	24.2	4.03
Bhand	Primary sensory cortex (BA1)	L	-47.1	-32.3	58.4	8.92
	Cerebellum	R	14.1	-74.4	-49.8	6.8

BA = Brodmann area, L = left, R = right.

\* Coordinates are given for peak activation according to the conventional model.

Local maxim are given in MNI standard brain coordinates at voxel-level  $P < .05$ .



**Figure 2.** fMRI analysis during a finger motor sequence repetition with the right, left, and bimanual hand at T0 and T1 ( $Z$ -score activation map;  $3.5 \leq Z \leq 12$ ). Axial images of MNI-152 standard anatomical image. The left side of the brain corresponds to the right hemisphere and vice versa.  $Z$ -coordinates of each slice in the MNI-152 standard space are given. fMRI = functional MRI.



**Table 2**  
**Reliable change index (RCI) results for self-report of relapsing-remitting multiple sclerosis patient.**

Session	Scale	Hand	Pretest score	Posttest score	SD normative sample	RCI
Two	TD global	R	351.5	553.14	162.91	2.43
	ITI global	L	436.63	713.24	86.20	6.29
	TD global	B	948.42	523.42	102.71	8.12
	ITI global	B	641.33	533.33	74.18	2.86
Four	ITI global	L	490.13	602	99.82	2.2
	TD global	B	151.50	752.88	96.53	12.22
	ITI global	B	793.63	520.71	68.80	7.78
	ITI global	L	393.67	506.67	107.24	2.07
Six	ITI global	L	393.67	506.67	107.24	2.07
	Global error	L	8	2	4.01	2.93

$P < .05$ .

ITI=inter-tapping interval, L=left, R=right, RCI=reliable change index, SD=standard deviation, TD=touch duration.

fMRI showed an increased of activation between T0 and T1 and, in addition, an improvement of parameters recorded by the treatment (Figs. 1 and 2). The RCI was calculated to indicate the improvement of recorded pre- and post-treatment for real change. To calculate the RCI, we used test/retest reliability = 0.87. Some score with RCI >1.96, indicate that robot-based treatment had significantly improved the clinical status of patient. Indeed, behavioral parameters (evaluated by means of GAF) showed that left unilateral and right TD and ITI increased after robotic treatment, whereas number of errors diminished. On the other hand when the task was performed bilaterally ITI decreased (Table 2).

### 3. Discussion

Upper limb impairment in MS is a common symptom which is under-recognized and adversely affects the ability to perform common daily activities. Brain plasticity represents the substrate to assess functional recovery, by means of neural restoration or compensation.<sup>[23]</sup> Many studies showed the MRI-based evidence that functional or structural plasticity occurred following motor or cognitive rehabilitation in MS patients. In addition, some studies also showed relevant relationship between clinical improvement and MRI-detected brain changes.<sup>[4,5]</sup>

Our findings showed clusters of concordance in regions commonly associated with motor performances, including primary sensorimotor cortex (SM1), supplementary motor area (SMA), basal ganglia (BG), and cerebellum. The primary sensorimotor cortex has traditionally been considered the main executive locus for simple voluntary movements; however, recent studies have implicated this region in the processing of complex sequential tapping task as well as the processing of bimanual movements.<sup>[24]</sup> In our case, we found a cluster definition dedicated to hand movement (at T1). In particular, we showed an increase of activation of dedicated areas for right hand and bimanual hands. For left hand we highlighted an activation in both hemispheres. This is due to the fact that the patient has a greater difficulty to perform finger tapping with her left hand producing an increase in fatigue during execution. The inability of MS patients to respond to the fatigue challenge by increasing activation may represent the effects of central fatigue that have been previously observed in TMS studies.<sup>[25,26]</sup>

Studies on motor rehabilitation support the notion that brain plasticity is enhanced by task-dependent and target-selected training. Improved microstructural properties of corpus callosum

were found following high-intensity, repetitive training of motor functions involving at improving upper limb functions.<sup>[16–27]</sup>

Nonetheless, few studies have addressed the application of robot-based treatment of upper limb in MS,<sup>[10–13]</sup> demonstrating a post-treatment improvement in the execution of functional tasks that implies proximal and distal movements. In particular, Carpinella et al<sup>[12]</sup> showed an improve in manual dexterity as measured by Nine Hole Peg Test (NHPT) after 8 robot sessions in 22 patients with MS, while Squeri et al<sup>[10]</sup> in a pilot study, showed that after training arm movements became faster, smoother, and with a more symmetric speed profile. In our study the functional improvement was confirmed by using the GAF; indeed, the bilateral decrease in ITI demonstrates that the rehabilitative training may have boosted neural plasticity at sensorimotor area leading to a better bilateral manual dexterity. To this end, the Armeo-Power offers a considerable amount of sensory input, given that primary motor cortex and supplementary motor area are activated during a sensory stimulation using passive cyclical joint movements.<sup>[28]</sup> In conclusion, although the results from this case report are highly encouraging, additional studies are needed to confirm our findings. Larger samples of MS patients, with different MS subtype, with different pharmacological treatment and with different EDSS scores, should be studied, to evaluate and identify fMRI findings as potential predictors of rehabilitative outcome.

### Author contributions

**Data curation:** Margherita Russo, Rocco Salvatore Calabrò.

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