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Thumbs up: Imagined hand movements counteract the adverse effects of post-surgical hand immobilization. Clinical, behavioral, and fMRI longitudinal observations

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ABSTRACT

Motor imagery (M.I.) training has been widely used to enhance motor behavior. To characterize the neural foundations of its rehabilitative effects in a pathological population we studied twenty-two patients with rhizarthrosis, a chronic degenerative articular disease in which thumb-to-fingers opposition becomes difficult due to increasing pain while the brain is typically intact. Before and after surgery, patients underwent behavioral tests to measure pain and motor performance and fMRI measurements of brain motor activity.

After surgery, the affected hand was immobilized, and patients were enrolled in a M.I. training. The sample was split in those who had a high compliance with the program of scheduled exercises (T+, average compliance: 84%) and those with low compliance (T−, average compliance: 20%; cut-off point: 55%). We found that more intense M.I. training counteracts the adverse effects of immobilization reducing pain and expediting motor recovery. fMRI data from the post-surgery session showed that T+ patients had decreased brain activation in the premotor cortex and the supplementary motor area (SMA); meanwhile, for the same movements, the T− patients exhibited a reversed pattern. Furthermore, in the post-surgery fMRI session, pain intensity was correlated with activity in the ipsilateral precentral gyrus and, notably, in the insular cortex, a node of the pain matrix.

These findings indicate that the motor simulations of M.I. have a facilitative effect on recovery by cortical plasticity mechanisms and optimization of motor control, thereby establishing the rationale for incorporating the systematic use of M.I. into standard rehabilitation for the management of post-immobilization syndromes characteristic of hand surgery.

1. Introduction

What could we possibly do without our thumbs? They are a crucial part of our biological make-up, and the ability to efficiently oppose them to the other fingers tells us apart from any other species (Napier, 1993; Napier and Napier, 1985). Their movement repertoire can be disrupted by several causes (e.g., the damage of the pyramidal tract), rhizarthrosis being a major cause of orthopedic origin (Patel et al., 2013).

In this study, we tested the hypothesis that motor imagery (M.I.) training can mitigate the consequences of hand immobilization following surgical treatment for rhizarthrosis and that this improvement is accompanied by meaningful changes of brain activity instructive on principles of brain plasticity. We reasoned that if the two were mutually supportive, we would provide a strong argument in favor of the systematic use of mental training as a complementary form of rehabilitation in orthopedic patients.

The form of mental training adopted here was explicit M.I., that is the mental rehearsal of hand movements without their overt execution (Jeannerod, 1995; Jeannerod and Decety, 1995). The psychophysical/

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physiological (Decety and Jeannerod, 1995; Fusi et al., 2005; Parsons, 1994) and neural similarities (Jeannerod and Decety, 1995; Kosslyn et al., 2006) between imagined and executed movements have set the rationale for using training based on M.I. to enhance motor behavior in healthy subjects such as athletes or musicians or as a rehabilitative tool in different conditions (Feltz and Landers, 1983; Feltz et al., 1988; Malouin and Richards, 2010). In healthy subjects, M.I. training can induce improvement in motor performance (Driskell et al., 1994; Nyberg et al., 2006; Olsson et al., 2008b; Ranganathan et al., 2004; Zhang et al., 2011), and also it potentiates the efficacy of physical training (Feltz and Landers, 1983; Olsson et al., 2008b) even though, if used alone, it appears less effective than the physical practice (Lacourse et al., 2004; Nyberg et al., 2006; Olsson et al., 2008b). In patients, M.I. training has been extensively used for the rehabilitation of disorders like stroke (Dijkerman et al., 2004; Liu et al., 2004; Malouin et al., 2009a; Malouin et al., 2009b; Page et al., 2007; Riccio et al., 2010), spinal cord injury (Jackson et al., 2001), Parkinson's disease (Tamir et al., 2007), tetraplegia or paraplegia (Cramer et al., 2007), and hand burn (Guillot et al., 2009). More recently, M.I. has been also used in patients with orthopedic disease caused by injury with contrasting results (Christakou and Zervas, 2007; Christakou et al., 2007; Cupal and Brewer, 2001; Gassner et al., 2007; Hoyek et al., 2014; Lebon et al., 2012; Maddison et al., 2012; Mayer et al., 2005; Stenekes et al., 2009). Interestingly, M.I. training also reduces pain in patients with complex regional pain syndrome (Moseley, 2004, 2005), phantom limb pain (MacIver et al., 2008), and different kinds of orthopedic injuries (Christakou et al., 2007; Hoyek et al., 2014).

The neural underpinnings of these behavioral and clinical effects remain to be fully understood. There are contrasting results depending on the technique used, whether M.I. was used alone or in combination with “true” motor practice (i.e., physical training), the nature of the populations involved (healthy subjects or pathological subjects), or whether M.I. was used after immobilization or after chronic reduced use (Jackson et al., 2003; Lacourse et al., 2004; Nyberg et al., 2006; Olsson et al., 2008a,b; Zhang et al., 2011).

To explore the brain mechanisms whereby M.I. may help motor rehabilitation, in this paper we take the orthopedic disease rhizarthrosis as a case study, evaluating patients before and after hand surgery. Rhizarthrosis is a disorder that induces chronic hand disuse because of a chronic degeneration of the trapeziometacarpal (TM) joint that limits the thumb-to-other fingers opposition movements[1] with considerable arthritic pain. Because the brain of these patients is substantially intact, rhizarthrosis represents an ideal model to assess maladaptive brain plasticity induced by hand disuse (Gandola et al., 2017) during post-surgical immobilization and the expected plasticity effects triggered by M.I. performed after surgery, before cast removal (our case study here).

In what follows, we briefly discuss the evidence of experimental models and data that are relevant to the main topic of our investigation: (i) the effects of M.I. when used as a performance booster in healthy subjects; (ii) the effects of experimental or post-traumatic immobilization on somatosensory and motor brain networks; (iii) the motor representations in orthopedic patients with chronic rhizarthrosis before surgery, an issue addressed in our previous paper on the subject (Gandola et al., 2017). Discussion of these sources of evidence will permit the formulation of predictions regarding the outcomes of our investigation on the brain correlates of mental practice through motor imagery after surgery and before cast removal in patients with rhizarthrosis.

1.1. M.I. as a training strategy in healthy subjects

Studies with Transcranial Magnetic Stimulation (TMS) have shown that M.I. produces changes in cortical excitability by inducing enlargement of the cortical representation of muscles on the contralateral primary motor cortex map (see for example: Abbruzzese et al., 1999; Fadiga et al., 1999; Hashimoto and Rothwell, 1999; Pascual-Leone et al., 1995; Rossini et al., 1999).

By contrast, neuroimaging evidence concerning the impact of mental imagery training on brain organization is controversial. Jackson and colleagues (Jackson et al., 2003), using Positron Emission Tomography (PET), found increased activations in the contralateral medial OrbitoFrontal Cortex (OFC) and reduced ipsilateral cerebellum activations after an intensive M.I. training consisting in learning a new sequence of foot-movements (Jackson et al., 2003). On the contrary, Lacourse and coworkers (Lacourse et al., 2004) described an increased activation in the contralateral cerebellum that was only present in the motor imagery-based mental practice group, suggesting that this activation is related explicitly to motor imagery training (Lacourse et al., 2004).[2] Other more recent studies, found that while physical practice is associated with increased activation in premotor regions and cerebellum (e.g., SMA and cerebellum in Nyberg et al., 2006; ventral premotor cortex, BA 6/44 in Olsson et al., 2008b) or decreased activation of the posterior parietal cortex (Olsson et al., 2008a), M.I. training of motor sequences is associated with a specific increased activity in the parietal cortex (Lebon et al., 2018) or in the visual occipital cortex (BA 18 in Nyberg et al., 2006; fusiform gyrus, BA 19, in Olsson et al., 2008b). Increased activity in the fusiform gyrus was also found by Zhang and coworkers in both motor execution and motor imagery tasks after a 2-week of motor imagery training (Zhang et al., 2011). Conversely, combined motor and mental training may induce an increased activation of both motor and visual regions (Olsson et al., 2008b). These activations of the visual cortex have been linked by the authors with the generation, through mental training, of visual memories of the motor task.

To summarize, these findings let one anticipate M.I. training-related changes in motor cortical and cerebellar responses. By contrast, a prediction on the direction of such changes is more problematic.

1.2. Motor representations after experimental or post-traumatic immobilization

Immobilization in healthy subjects or patients with orthopedic diseases has been used as an experimental model to study short-term brain plasticity. In these studies, immobilization has been either induced experimentally in healthy subjects using constraint devices (Facchini et al., 2002), soft bandages (Avanzino et al., 2011), a volar cast (Weibull et al., 2011) or it was the result of a medical treatment for physical limitation of acquired origin, such as joint traumatisms (Liepert et al., 1995; Zanette et al., 1997, 2004).

TMS studies demonstrated changes in the excitability of the sensorimotor cortex after immobilization, even if the results are controversial (decrease of excitability of motor areas in Avanzino et al., 2011; Facchini et al., 2002; Huber et al., 2006; Liepert et al., 1995; volumetric increase of motor maps in Zanette et al. (1997, 2004).

fMRI studies on immobilization confirm the observations of reduced activation in the sensorimotor cortex (Lissek et al., 2009; Weibull et al., 2011) and significant modifications at the structural level (Granert et al., 2011; Langer et al., 2012). Interestingly, these cortical changes seemed to be reversible and disappeared two weeks after cast removal

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[1] The human trapeziometacarpal (TMC) joint has a crucial functional importance as it permits the rotation and opposition of the thumb to the other fingers (i.e., the pulp-to-pulp contact). The resulting precision grip is considered one main evolutionary factor, because it permits handling small objects, tools grasping, and manipulation (Napier and Napier, 1985; Napier, 1993).

[2] Lacourse et al. (2004) used conjunction analyses with uncorrected thresholds and compared the number of supra-threshold voxels across conditions in predefined ROIs: this approach is now considered below current analytical standards.

(Lissek et al., 2009; Weibull et al., 2011). Burianova et al. (2014) found a significant decrease in neural activity in the primary motor (M1) and somatosensory cortex (SI) and the premotor cortex (BA6) after a short-term immobilization of the dominant hand.

Taken together this previous evidence allows one to predict that patients with a transitory immobilization due to traumatism of orthopedic surgery of some kind should display reversible maladaptive changes of somatosensory cortical responses. The evidence on M.I. training discussed before would suggest that M.I. could boost recovery.

However, it remains to be seen whether these principles apply to patient populations with chronic disorders. As much as acute short-term immobilization represents a different scenario compared to long-term adaptations to a chronic disorder, age is also a variable of interest for our case as most studies on immobilization or M.I. training were performed in young subjects.

Here was where our investigation started, i.e., by assessing motor representation of hand movements in rhizarthrosis before any surgery (Gandola et al., 2017) with the long-term goal of studying the effects of M.I. training on these patients following reparative surgery.

1.3. *Motor representations in chronic hand disuse in rhizarthrosis*

In our recent study (Gandola et al., 2017), using fMRI, we evaluated the brain correlates of explicit motor performance and M.I. for a finger opposition task in patients with rhizarthrosis. In particular, we tested whether the chronic reduction of hand motoric repertoire of rhizarthrosis, in the absence of any neurological impairment, was sufficient to induce maladaptive neurofunctional patterns in the cortical representation of hand movements. In comparison with the brain patterns of age-matched healthy controls, we found reduced activations in the left premotor cortex (BA6) and the right primary motor cortex (BA4) for explicit movements of the hands. This BOLD (Blood Oxygen Level Dependent) reduction was task-specific, being only present for the motor execution and more prominent for the more affected hand. However, the fMRI data and the behavioral data did point towards a marginally deficient, yet still possible, M.I. for our patients suggesting that M.I. could still be a viable complementary rehabilitation strategy for the post-surgical time of immobilization in this case (Gandola et al., 2017).

1.3.1. *Research questions and aims of the study*

To the best of our knowledge, the functional effects of mental practice used for the rehabilitation of hand arthrosis have not yet been investigated. Rhizarthrosis is usually treated by surgery followed by a period of hand immobilization, and thus it represents an ideal model to indirectly test motor cortex plasticity mechanisms and their eventual modulation through M.I. training because, as mentioned, the patients' brains should be macroscopically intact.[3] In our previous study (Gandola et al., 2017), we reported differences between patients with rhizarthrosis (only studied before surgery) and normal age/gender-matched controls for the behavioral and fMRI data taken from M.E. and M.I. tasks of movement performed with the right or the left hand. The novelty of the present study is that we performed a longitudinal study only in patients with rhizarthrosis where we looked at the effect of a two-week motor mental training program on the clinical response and fMRI patterns measured before and after surgery.

At the time of study design, we had several questions in mind: on the one hand, we were curious to learn whether a M.I. based mental training program could improve the clinical outcome of rhizarthrosis patients tested after the removal of the immobilizing soft cast. In particular, we were interested in learning whether any amelioration would occur in the motor performance domain, if symptoms such as pain would show improvement, and whether or not it would still be possible to see results in these patients who were older than subjects described in studies on experimental immobilization.

According to the evidence reviewed in the introduction, we hypothesized that M.I. training could accelerate the recovery of patients after immobilization and prevent or reduce transient negative effects on central brain organization induced by the surgery and the ensuing immobilization.

As students of brain physiology, we wanted to learn whether any specific clinical effect of the motor imagery treatment was accompanied by meaningful changes in brain activation that may correlate with changes in the clinical picture.

We reasoned that if any clinical effect could be demonstrated that was also associated with meaningful brain correlates, the two sources of evidence combined would represent a stronger case in favor of the use of M.I. in the rehabilitation of these orthopedic patients.

For this purpose, we studied a sample of 22 patients with rhizarthrosis (a selection of the patients included in our previous study: see Gandola et al., 2017) divided into two groups on the basis of the examination of the training records: patients who complied with the treatment scheme for more than the 55% (the group training mean) were included in the high-training group (T+) while those below such threshold were included in the low-training group (T−). This represented a blocking classifying factor for further analyses on the effects of the treatment.

2. Materials and methods

2.1. *Study design*

The study involved a longitudinal observation of clinical (motor performance, spontaneous and evoked pain) and fMRI data of a cohort of 22 patients with rhizarthrosis who underwent surgical treatment for their condition. For the clinical data, there were multiple observations: before and immediately after surgery, during motor imagery rehabilitation, and after cast removal. fMRI data during motor execution of finger movements were collected before surgery and after cast removal. Also, before any other procedure, all subjects had a short neuropsychological assessment to exclude cases with hidden mental deterioration (see Fig. 1 for an illustration of the experimental design).

2.2. *Clinical information*

2.2.1. *Participants*

Of thirty-five patients originally studied in Gandola et al. (2017) for a cross-sectional comparison with age-matched controls, twenty-two patients with rhizarthrosis (16 female and 6 males; mean age: 62.4 ± 9.5 years; mean education: 10 ± 3.6 years) participated in this longitudinal study. The subjects had no history of neurological, psychiatric or cognitive disorders. All participants were right-handed as assessed by using the Edinburgh Handedness Inventory (Oldfield, 1971). Clinical data are reported in Table 1.

All subjects gave their written informed consent, and the study was approved by the Local Ethical Committee of the ASL of Milan. The experiment was performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964), and later amendments (World Medical Association, 2013).

Patients were selected for surgery by an experienced orthopedic surgeon (MB). All the patients had rhizarthrosis, which was more symptomatic for pain and functional limitation in one hand: the right hand in 15 cases, the left one in 7 cases. The patients had suffered pain in the affected hand for an average of 34.9 months (SD = 29.7) before contacting an orthopedic surgeon. Four patients (P4, P18, P25, P28) had already undergone a hand surgery for the treatment of rhizarthrosis in the other hand, two patients (P17 and P19) for the treatment of the carpal tunnel syndrome, and one patient (P26) for the treatment of the stenosing tenosynovitis of finger ("trigger finger"). Fifteen patients out

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[3] In our study this was the case also by design, as we did not recruit subjects with a medical history of neurological disorders.

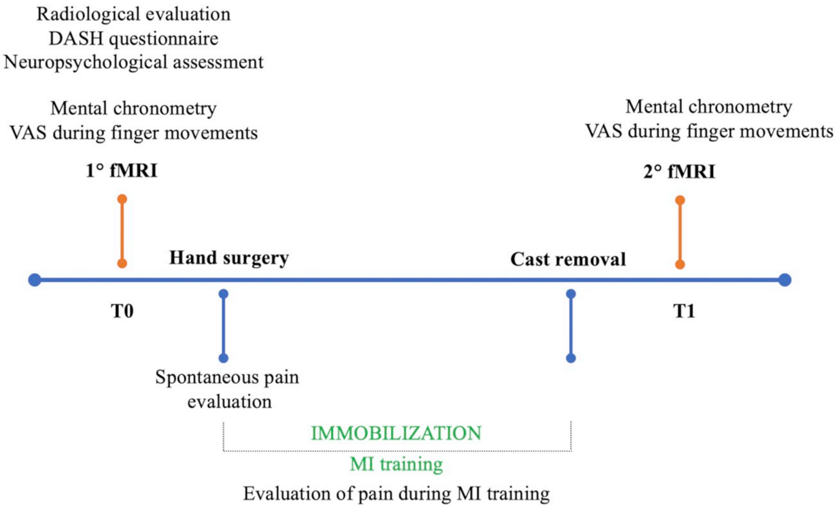

Fig. 1. Illustration of the experimental design. Patients underwent two fMRI sessions, one before (T0, 1° fMRI) and one after elective surgery and cast removal (T1, 2° fMRI)). DASH = Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire; VAS = Visual Analogue Scale; MI = mental imagery.

Table 1
Patient's clinical data.

Patient	Sex	Side	Duration months	Eaton-Littler classification		DASH	Group	Training %
				RH	LH			
P2	F	RH	12	—	—	75,00	T−	0,0
P3	F	RH	36	II	II	65,83	T−	26,9
P4[a]	F	LH	18	—	—	51,00	T−	39,3
P6	M	RH	36	II	III	53,33	T−	47,8
P7	F	RH	12	II	—	63,33	T+	85,7
P10	M	LH	96	—	—	37,50	T−	23,9
P11	F	RH	12	II	—	58,33	T+	100,0
P16	F	LH	12	III	III	40,83	T+	96,4
P17[b]	F	LH	24	—	—	49,17	T+	92,9
P18[a]	F	RH	36	—	—	75,83	T+	58,0
P19[b]	F	RH	4	II	—	55,00	T−	2,6
P22	F	RH	24	—	—	76,67	T−	0,0
P23	M	LH	12	—	III	31,67	T−	27,5
P24	F	LH	48	—	—	53,33	T+	58,6
P25[a]	M	LH	24	—	—	18,33	T+	100,0
P26[c]	M	RH	18	—	—	8,33	T+	75,9
P27	F	RH	120	III	II	69,83	T−	0,0
P28[a]	F	RH	60	III	—	25,00	T−	33,1
P29	F	RH	48	IV	III	56,90	T+	71,4
P30	F	RH	36	III	III	35,00	T+	71,4
P32	F	RH	72	—	—	57,50	T+	97,9
P33	M	RH	8	I	II	30,00	T+	100,0

LH: left hand; RH: right hand; F = female; M = male; Dash scores: 0 score is no disability and 100 score is complete disability.
— = X-ray not available. Data of the same patients studied in the pre-operative phase were included in a previous paper [see Supplementary Table S1 in Gandola et al., 2017].

[a] Patients had already undergone a hand surgery for the treatment of rhizarthrosis.

[b] Patients had already undergone a hand surgery for the treatment of the carpal tunnel syndrome.

[c] Patient had already undergone a hand surgery for the treatment of the stenosing tendosynovitis of fingers ("trigger finger").

of 22 had some pain also on the other hand, in line with the bilateral nature of this orthopedic condition.

2.2.2. *Radiological evaluation of the hand X-ray examinations*

The stage of rhizarthrosis was defined by a senior hand surgeon (VS) using the Eaton-Littler radiographic classification. This classification system includes four stages of carpometacarpal (CMC) joint arthritis. ***Stage I*** shows normal cartilage with joint space widening due to synovitis, effusion or laxity of the joint. ***Stage II*** features narrowing of the joint space with osteophytes or loose bodies smaller than 2 mm in diameter and at least 1/3 subluxation of the metacarpal. ***Stage III*** exhibits more severe joint narrowing with > 1/3 subluxation of the joint and osteophytes exceeding 2 mm in diameter. Finally, ***stage IV*** shows arthritic changes in the CMC joint as in Stage III with the involvement of the scaphotrapezial joint (Eaton and Glickel, 1987; Eaton et al., 1984; Eaton and Littler, 1973). The radiographic films were available for 12 of the 22 patients. The classification of the stage of rhizarthrosis is reported in Table 1.

2.2.3. *Impact of the disease on daily life activity*

We evaluated the impact of rhizarthrosis on daily functioning with the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (Hudak et al., 1996) in its Italian edition (Padua et al., 2003). The subscale related to sports and musical activities was not considered, as a limited number of patients practiced sports or played music (47.3%). In the main part of the questionnaire (DASH-FS) the patients are asked to judge on a 5 point Likert scale his/her difficulty in performing different daily activities (21 items; items 1–21), his/her level of pain, activity-related pain, tingling, weakness and stiffness (5 items; items 24–28) and the impact of the upper limb disability on social activities, work, sleep and self-image (4 items; items 22, 23, 29, 30). The raw score was converted into a 0–100 scale (see Table 1).

2.2.4. *Neuropsychological assessment*

All participants performed a neuropsychological screening to exclude subjects with age-related cognitive deficits. The neuropsychological battery included: The Mini-Mental State Examination (Folstein et al., 1975), short story recall (Novelli et al., 1986), delayed recall of the complex Rey's figure (Carlesimo et al., 2002) and the Frontal Assessment Battery (FAB: Dubois et al., 2000). None of the subjects had pathological performances on any test of this battery.

2.2.5. *Surgical procedure*

The surgical intervention was performed by an experienced orthopedic surgeon (MB) and consisted in a complete trapeziectomy and suspension arthroplasty of the first metacarpal bone using the abductor pollicis longus and the tendon of the flexor carpi radialis. By means of this surgery it was possible to obtain stabilization of the metacarpal base, the reconstruction of the pinch between first and second metacarpal bones and the opposition of the first digital radius. After surgery, the affected hand was immobilized using a bulky dressing for two weeks to maintain the correct position and impede the thumb-to-other finger opposition movement.

2.2.6. Clinical and behavioral experimental tests

Patients were tested before (baseline, T0) and two weeks after hand surgery (T1, Fig. 1). Patients were enrolled in a M.I. training program focused on imagined hand movements for the time of their immobilization. The training involved two motor imagery sessions per day (a morning and an afternoon session, of about 30′ each depending on the subject's speed). In both the pre-surgery and the post-surgery session they underwent fMRI examination during the execution of a simple explicit motor execution task (thumb to finger sequential opposition). They also were submitted to behavioral tests for the evaluation of motor execution and motor imagery speed, pain and impact of the disease in the everyday life (DASH questionnaire; Padua et al., 2003).

2.3. Behavioral tasks: assessments

2.3.1. Mental chronometry

The participants executed (motor execution: M.E.) and imagined (motor imagery: M.I.) three different movements involving the upper hand/limb, varying in complexity: (i) a thumb-to-finger sequential opposition task, which involved four taps (from thumb-to-index, to thumb-to-little finger) with the forearm lying in a supinated position, (ii) a pronosupination of the forearm and (iii) a fist-making movement (hand open and closed).

Each type of movements was tested with trials of different lengths (t2, t3, t4, t5) made of changing the number of repetitions of the same movement (2, 3, 4 or 5 cycles[4]). Each trial (for example: "t2 for the thumb-to-finger opposition task") was repeated twice so that there were eight trials overall for each limb for each movement. To reduce task requests predictability, the order of the trials was randomized across lengths and type of movement (e.g., "t4-thumb-to-finger", followed by "t3-pronosupination", followed by "t5–fist making", etc.). The entire protocol was performed separately for the right and the left hand. We first tested one hand, and then we moved to the other hand: the starting hand was counterbalanced across participants. For all conditions (M.E. right hand; M.I. right hand; M.E. left hand; M.I. left hand), the subjects sat comfortably in front of an examination desk.

For the motor imagery task, the subjects were invited to imagine the movement using a kinesthetic first-person imagery modality while keeping their eyes shut.

Motor execution and motor imagery durations were timed by a manual stopwatch, which measured the interval between the examiner's "go-signal" and the "stop-signal" shouted out loud by the participant at the end of each trial of M.E. and M.I. All subjects were first trained with the task to reach the required speed (approximately 1 Hz; see also Gandola et al., 2017; Zapparoli et al., 2013). During the motor imagery task, one experimenter (MG) carefully monitored the participants during the task to control for the presence of movements. If a movement was observed the subjects were invited not to move and the trial was repeated.[5]

2.3.2. Evaluation of pain associated with finger movements: VAS scale

To evaluate hand pain intensity, we used the same Visual Analogue Scale (VAS) described in Gandola et al. (2017). Patients were asked to execute three different movements involving the affected hand, which are known to be particularly painful for patients whit this degenerative pathology: **single unimanual thumb-to-finger opposition movements**, verbally cued by the examiner in a random order (thumb-index finger; thumb-middle finger, etc.), **thumb flexion** (the patient was asked to place his/her forearm and hand perpendicular to the table surface with the affected thumb extended and to move his/her thumb to reach the palm), and **thumb circumduction**. Each of the single thumb-opposition movements was repeated five times (20 trials), while thumb flexion and circumduction were repeated ten times, for a total of 40 trials. After the execution of each movement, the patient was requested to mark the intensity of his/her pain on a 100 mm long VAS scale marked at the extreme left as "no pain" and at the extreme right as "highest intensity of pain". For each trial, the distance between the participant's mark and the origin of the line was measured.

Patients were also asked to report the intensity and duration of the spontaneous pain felt immediately after surgery using an 11-point numerical rating scale ranging (NRS) from 0 ("no pain") to 10 ("highest intensity of pain"). Moreover, we also took records of the medications taken by the patients after surgery to trait pain.

2.4. Behavioral intervention

2.4.1. Post-surgery motor imagery training

The M.I. training, or mental motor practice, was carried out for two weeks (14 consecutive days) during the immobilization period that followed hand surgery. For each day, the participants were asked to perform two training sessions, one in the morning and one in the afternoon at home. In each training session, the patients were instructed to imagine specific movements with the immobilized hand. Before surgery, patients received a training diary containing the list of the requested exercises and a manual stopwatch. The patients were trained to imagine the movement, use the stopwatch to time it, write on the booklet the duration of the imagined movement[6] and indicate if any pain was present during the movement using a numerical rating scale (0 = no pain, 10 = highest intensity of pain). Participants reported in the diary the time duration of each trial and the global time of each session of imagination by recording the time when each session started and finished. This information was used to control the effective execution of the training.

Participants were instructed to imagine each movement in a first-person imagery perspective ("feel" as if they were performing the movement - kinesthetic motor imagery). During the training patients imagined four different types of movement, illustrated by a picture on the first page of the training diary:

(1) Thumb-to-finger sequential opposition task in which (i) the direction of the movement (*forward* - thumb-to-index, thumb-to-middle finger, thumb-to-ring finger, and thumb-to-little finger and *backwards* - thumb-to-little finger, etc.), (ii) the starting finger and (iii) the number of cycles varied (from 2 to 5);
(2) Thumb flexion task (the patient was asked to imagine his/her forearm and hand perpendicular to the table surface with the affected thumb extended and to move his/her thumb to reach the palm) in which (i) the starting position of the thumb (flexion or extension) and (2) the number of cycles varied (from 2 to 5);
(3) Circumduction of the thumb task in which (i) the direction of the rotation (clockwise or counterclockwise) and (ii) the number of circumductions varied (from 2 to 5);
(4) Guided-tapping task. In this task, patients were asked to imagine a specific thumb-finger opposition movement (i.e., thumb-to-index) and subsequently imagine performing a variable number of thumb-opposition movements (i.e., three movements). Finally, he/she was

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[4] For example, two cycles of the thumb-to-finger opposition movement (2 cycles) implied 8 taps, 4 taps for each cycle, whereas five cycles of the thumb-to-finger opposition movement (5 cycles) implied 20 taps.

[5] Even the visual monitoring of the experimenter during the task do not exclude the possibility that minimal movements might have occurred during the M.I. task, we do not believe that the lack of an EMG recording represents a major issue for this study (see also Zapparoli et al., 2013, footnote 5, page 535).

[6] The participants were instructed to press the chronometer when they began to imagine and when it was over.

asked to indicate the name of the last finger touched (i.e., thumb-to-little finger).

The training consisted of a total of 2968 trails (212 per day, 106 in the morning and 106 in the afternoon).

2.4.2. Analysis of the behavioral data

Statistical analyses of the behavioral data were performed using the SPSS software (Statistical Package for the Social Sciences, IBM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp) and the Statistical Analysis Software *SAS* 9.4 (SAS Institute, Cary NC) for the Generalized Linear Mixed Models (GLMMs). See the results section for further details.

2.4.3. fMRI experiment: motor execution task cued finger opposition

The fMRI experiment involved a M.E. task. During the M.E. task, the participants were asked to perform movements of the right, and left hand alternated with periods of rest. The movements, performed at a frequency of approximately 1 Hz,[7] involved thumb-to-finger sequential opposition (finger-tapping task): thumb to index finger, thumb to middle finger, etc. Subjects practiced the finger opposition task before scanning. The task was self-paced, but the subjects' performances were loosely cued in that they were reminded to perform the task by verbal instructions once every 6″ ("move the right hand" or "move the left hand"). The auditory cues were delivered using Presentation® software (www.neurobs.com) via fMRI-compatible headphones. These conditions were alternated with resting state scans according to a block design. During the rest baseline control conditions, subjects were instructed to relax and to think of nothing. As before, subjects were loosely cued and reminded to remain in resting by a verbal instruction once every 6″ ("Rest"). Each block was 30″ long (10 scans in each epoch). The experiment consisted in 3 blocks of right-hand motion (RH), three blocks of left-hand motion (LH) and three rest blocks for each hand in a counterbalanced order (rest-RH–rest-LH–rest-LH–rest-RH–rest–RH–rest-LH). By the end of each motor or rest fMRI block, subjects were asked whether they did or did not move their fingers. Subjects responded by pressing a button on a keypad with their right hand. Each block was 9 s long (3 scans in each epoch). These events have been excluded from the fMRI analysis. One experimenter (MG) was in the scanner room to monitor that patients performed the task at the desired rate. All subjects performed this exceedingly simple task as requested. The task was performed with eyes closed to avoid any possible confounding effect due to visual information.

2.4.4. fMRI data acquisition and analysis

2.4.4.1. Data acquisition. Functional MRI scans were performed at the IRCCS *Galeazzi* using a 1.5 Tesla Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, echo time (TE) = 60 ms, repetition time (TR) = 3000 ms, field of view (FOV) = 280 × 210 mm and matrix size = 96 × 64). The slice thickness was 5 mm. We collected 158 complete brain volumes. The first ten volumes of each sequence, corresponding to the task instructions, were discarded from the fMRI analyses.

2.4.4.2. Preprocessing. After image reconstruction, the raw-data visualization and conversion from DICOM to the NIFTI format were performed using the program DCM2NII implemented in the software MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron/). All of the subsequent data analysis was performed in MATLAB version 8.1 (Math Works, Natick, MA, USA) using the Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). The fMRI scans were first realigned to account for any movement during the experiment and then were stereotactically normalized into the symmetrical MNI-EPI fMRI template space to permit group analyses of the data (Ashburner and Friston, 1999; Friston et al., 1995). At this stage, the data matrix was interpolated to produce voxels of dimensions 2 × 2 × 2 mm. The stereotactically normalized scans were smoothed through a Gaussian filter of 10 × 10 × 10 mm to improve the signal-to-noise ratio. This level of smoothing is considered ideal for the application of Gaussian field theory for cluster level corrections for multiple comparisons (Flandin and Friston, 2017).

2.4.4.3. fMRI statistical analysis. After the pre-processing, the BOLD signal associated with each experimental condition was analyzed by a convolution with a canonical hemodynamic response function (Worsley and Friston, 1995). The global differences in fMRI signals were removed by using proportional scaling for all of the voxels on the global counts. High-pass filtering was used to remove artifactual contributions to the fMRI signal, such as physiological noise from cardiac and respiratory cycles. The realignment parameters were also entered into the design matrix to further remove artifactual contributions to the signal due to movement.

First, a fixed-effect block analysis was performed in each subject to characterize the BOLD response associated with each task as opposed to its baseline condition; second, we entered the relevant contrast images into a second-level full factorial random effect ANOVAs which permits a generalization of the statistical inferences to a population level (Holmes and Friston, 1988; Penny and Holmes, 2004).

A Full factorial repeated-measures ANOVA was performed with two within-subjects factors [*Session* (Pre-immobilization, Post-immobilization) and *Hand* (Right hand, Left hand)] and one between subjects factor *Group* (T+, T−), as implemented in SPM8. F-contrasts were obtained for main effects and interactions. We then performed post-hoc analyses to examine the direction of the effects using appropriate linear t-contrasts.

For all analyses, the statistical threshold was set at 0.05 corrected for multiple comparisons (Family-Wise Error Rate, FWER) at the cluster level, after a voxelwise threshold of 0.001 (uncorrected). Contrary to the suggestions of Eklund et al. (2016), as remarked by Flandin and Friston (2017), the preliminary spatial smoothing of 10x10x10 mm combined with a voxel-level preliminary threshold $p < 0.001$, makes cluster level correction valid under the Gaussian fields theory framework, the number of false positives being within acceptable family-wise error rates.

For simplicity, the hemispheres controlling the more affected hand were all placed on the left half of a neurologically oriented stereotactic space. This implied a rotation along the antero-posterior axis of the data from patients with a dominant pathology affecting the left hand. This is a standard procedure when handling data from a mixed cohort of patients with either right or left sided motor deficits (Ward et al., 2006)

3. Results

3.1. Clinical and behavioral results

3.1.1. Compliance with the motor imagery treatment

Exploration of the data showed that patients had variable compliance to the treatment whereby some patients performed up to the 100% of the treatment while other patients were much less compliant, with three cases of no compliance at all. To compare the effect of the training, we decided to split the sample and classify the patients with compliance below the mean (< 54.97%) as T− (n = 10) and those with compliance above that threshold (n = 12) were classified as T+. More specifically, the T− group had average compliance of 20% (range: 0%–48%), with three cases of zero compliance; the T+ group had average compliance of 84% (range 58%–100%) with three cases of 100% compliance. Importantly, the T− group was not dominated by

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[7] Subjects practiced the tapping task briefly until the desired 1 Hz pace was reached.

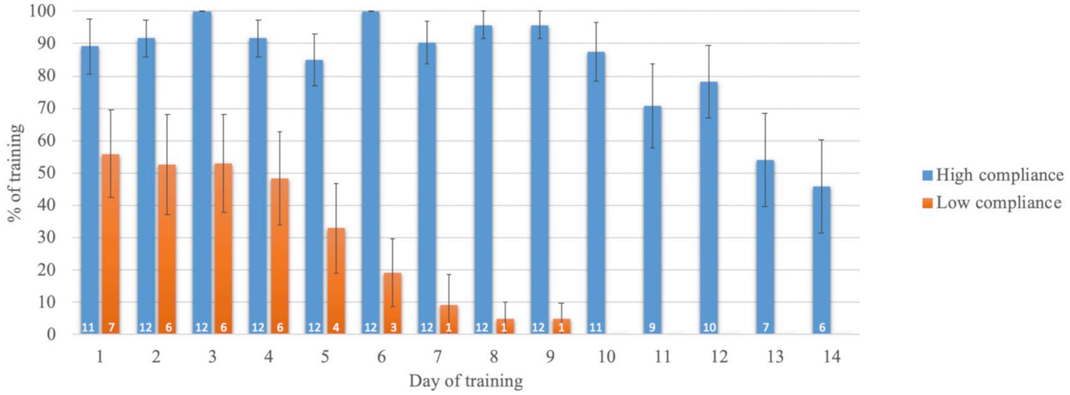

Fig. 2. Mean of the percentage of training performed (i.e., compliance) in each day of the training period in the high compliance (T+, n = 12, blue bars) and low-compliance groups of patients (T−, n = 10, orange bars). The numbers inserted in each bar represent the number of patients in each group that were involved in the training in the day considered. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

subjects with zero compliance to the treatment, nor the T+ group was represented only by subjects with 100% compliance. Accordingly, the label T− does not indicate the lack of any instruction, nor zero-training. Given the average compliance to the training program, the T− group resembles, loosely, to a "low dosage" training group that provides a control for (1) the fact of having had instructions to adopt our mental training program and (2) some varying degree training below a cut-off threshold (here 55%, corresponding to the grand mean of the entire patient sample).

In Fig. 2, we report the percentage of training (i.e., compliance) in each day of the practice in the high compliance (T+, n = 12, blue bars) and low-compliance groups of patients (T−, n = 10, orange bars). The compliance for training is higher at the start than at the end of the immobilization period. This is evident in particular for the low-compliance group. The graph illustrates that the two groups differ not only for the quantity of training but also for the persistence along the two weeks.

The two groups (T+ and T−) were comparable for age ($t_{(20)} = 0.560$; $p = 0.581$), gender distribution [Chi-square, χ^2 (1):0.069; p = 0.79] and education ($t_{(20)} = 0.177$; $p = 0.861$).

3.1.2. DASH questionnaire

The DASH questionnaire average score for the disability/symptom score was 49.4 (standard deviation: 19, range: 8.3–76.7). All subjects but seven were above the score 40 (see Table 1) to indicate that for most subjects the presence of rhizarthrosis had important consequences on the ability to perform daily activities with the affected hand (the mean score for the upper limb function in the general population is 10.1 with a standard deviation of 14.68 (see page 211 in Hunsaker et al., 2002). The two groups were comparable for the degree of impairment in the DASH test [$t_{(20)} = -1.047$; $p = 0.308$; mean T+ = 45.6, SD = 19.6; mean T− = 54.1, SD = 18.2)].

3.2. Pain

The feeling of pain was evaluated at different time-points and in different conditions: before and after surgery during the explicit movement tasks; during the immobilization period while performing the mental training tasks; in its spontaneous manifestation immediately after surgery to have a further reference measure to evaluate the effect of mental training. The pre-surgery pain related to movement is described in paragraph 3.2.3, as these measures were analyzed together with the post-surgery ones using Generalized Linear Mixed Models.

3.2.1. Intensity of spontaneous pain immediately after surgery

After surgery, when the effect of the sedation disappeared, patients presented a variable degree of pain in the operated hand and, when present, the pain sensation lasted, on average, for 5.2 days. Importantly, there were no differences in the intensity of spontaneous pain (Mann-Whitney test, U = 38.5; p = 0.262) between trained (median = 4.50) and untrained patients (median = 8.00). Also, the duration of spontaneous pain after surgery was comparable (Mann-Whitney test, U = 31.5; p = 0.645) between groups (median T+ = 4 days; median T− = 2 days). Overall 17 patients reported spontaneous pain immediately after surgery that was treated with analgesic: 5 patients were treated with paracetamol, 2 with tramadol, 3 with nimesulide and one with ketoprofen. Six patients did not take medications. There were no differences in the two groups concerning the number of medicated and not medicated patients (Chi-square, χ^2 (1): 0.064; p = 0.801).

3.2.2. Pain during the motor imagery training sessions

During training, patients were asked to report whether pain was present during the imagined movement using an 11-point numerical rating scale ranging from 0 (no pain) to 10 (highest intensity of pain). All the patients[8] but one reported pain feelings during mental imagery of the movements (mean = 2.74; SD = 2.55). The pain during practice was more intense on the first (median = 2.70) than on the last day of the training (median = 1.15; Wilcoxon test (n = 19): Z = −2.430, p = 0.015). There were no differences between T+ (mean = 2.40; SD = 2.58) and T− (mean = 3.33; SD = 2.59) in the intensity of imagined pain (N = 19; $t_{(17)} = -0.760$; $p = 0.458$).

We also determined whether there were between groups differences in the level of pain experienced during the first and the last session before quitting the treatment. In the first session, the median pain score for T+ (3.25) and T− (2.33) was not statistically significant different (Mann-Whitney *U* test: U = 38; z = −0.338, p = 0.735). Also, in the last session before leaving the treatment there were no differences between T+ (median score = 1.11) and T− (median score = 3.86; Mann-Whitney *U* test: U = 32; z = −0.853, p = 0.394). This finding suggests that a greater pain during the training was not a major reason to quit the training program.

3.2.3. Pain associated with finger movements

In what follows with the terminology post-surgery or post-immobilization we refer to the post-surgery testing that occurred immediately after the soft-cast removal (two weeks after surgery).

This analysis incorporated the data collected during the execution of specific movements before surgery and after cast removal. We used Generalized Linear Mixed Models (GLMMs) to compare pain levels in the two groups, concerning the experimental conditions. The VAS score

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[8] The three cases with no compliance at all to the treatment (percentage of training = 0) were excluded from this analysis.

Table 2
Generalized linear mixed models behavioral analysis results.

Effect	DF	F-value	P-value
A) Pain: VAS scores			
Group	1–20	2.68	0.1170
Session	1–1726	28.28	< **0.0001**
Movement	2–1726	89.04	< **0.0001**
Group*Session	1–1726	36.68	< **0.0001**
Group*Movement*Session	6–1726	15.41	< **0.0001**
B) Motor Execution			
Group	1–20	0.00	0.9719
Session	1–2052	24.75	< **0.0001**
Movement	2–2052	490.24	< **0.0001**
Hand	1–2052	67.07	< **0.0001**
Hand*Group*Session	3–2052	8.80	< **0.0001**
Group*Session	1–2052	0.11	0.7351
Group*Movement*Session	6–2052	2.39	**0.0264**
C) Motor Imagery			
Group	1–20	2.50	0.1294
Session	1–2076	4.51	**0.0339**
Movement	2–2076	445.39	< **0.0001**
Hand	1–2076	30.04	< **0.0001**
Hand*Group*Session	3–2076	2.25	0.0807
Group*Session	1–2076	1.02	0.3134
Group*Movement*Session	6–2076	1.27	0.2662
D) Motor Imagery Quality Index			
Group	1–20	0.01	0.911
Session	1–2028	8.34	**0.003**
Movement	2–2028	1.95	0.142
Hand	1–2028	6.86	**0.009**
Hand*Group*Session	3–2028	1.91	0.126
Group*Session	1–2028	1.65	0.199
Group*Movement*Session	6–2028	0.48	0.826

F and P-value of main effect and interactions are reported for each analysis. Statistically significant p-values ($p < 0.05$) are indicated in bold. DF = degree of freedom.

was modeled as the dependent variable. Group (T+, T−), Session (Pre, Post) and Movement type (Thumb-to-finger opposition, Thumb flexion, Thumb circumduction) were modeled as fixed factors. For what concerns the random effect structure of the model, a by-subjects random intercept was included to account for participant-specific variability; moreover, a random effect nested structure was preferred in order to take into account also the effect of the group.

We first explored the data distribution of the dependent variable (i.e., VAS scores) separately in the two groups. For both T+ and T− this was positively skewed (Skewness T+: 0.827) and slightly platykurtic (Kurtosis: −0.678) with a significant departure from normality (Shapiro-Wilk test: $S\text{-}W_{(960)} = 0.850$, $p < 0.001$). Therefore, in this analysis, we adopted a Beta distribution (particularly suited for positively skewed data) with a Logit function.

We discuss here only the significant effects, while all the main effects and interactions are formally reported in Table 2A. Since the Session by Movement type by Group interaction was significant [$F_{(6,1726)} = 15.41$, $p < 0.0001$] we performed a separate analysis for each type of movement.

3.2.3.1. *Pain: thumb-to-finger opposition.*

We found a highly significant main effect of the factor Session [$F_{(1,855)} = 55.37$, $p < 0.0001$]: the feeling of pain was greater after immobilization in both trained and untrained patients. The interaction Session by Group was not significant [$F_{(1,855)} = 0.17$, $p = 0.68$, Fig. 3A]. In particular, there were no differences between T+ and T− in the pre-surgery session ($t_{(855)} = -1.16$, $p > 0.99$).

3.2.3.2. *Pain: thumb flexion.*

We found again a main effect of the factor Session [$F_{(1,416)} = 29.86$, $p < 0.0001$] and a Group by Session interaction [$F_{(1,416)} = 9.18$, $p = 0.0026$]. Bonferroni adjusted pairwise comparisons showed that in T− patients the feeling of pain in the post-immobilization session was higher (mean = 6.37; SD = 2.98) compared with the pre-surgery session (mean = 5.12; SD = 4: $t_{(416)} = 5.6$, $p < 0.0001$). By contrast, in T+ patients the feeling of pain did not change between the two sessions (mean VAS scores post-surgery session = 3.51; SD = 2.90; mean VAS scores pre-surgery session = 3.12; SD = 3.49: $t_{(416)} = 1.87$, $p = 0.37$; Fig. 3B). Furthermore, there were no differences between T+ and T− in the pre-surgery session ($t_{(416)} = -1.43$, $p = 0.92$).

3.2.3.3. *Pain: thumb circumduction.*

The Group by Session interaction was highly significant [$F_{(1,415)} = 75.89$, $p < 0.0001$]. Bonferroni adjusted pairwise comparisons showed that for the trained T+ patients the feeling of pain in the post-immobilization session was lower (mean = 3.17; SD = 2.83) compared to the pre-surgery session (mean = 5.50; SD = 4.15: $t_{(415)} = -7.21$, $p < 0.0001$). On the contrary, in the untrained T− patients the level of pain was significantly higher in the post-immobilization session (mean = 7.24; SD = 3.24) compared to the pre-surgery session (mean = 5.59; SD = 4.14; $t_{(415)}$: 5.53 $p < 0.0001$). Moreover, we found a difference between T+ and T− patients in the post-surgery phase [$t_{(415)}$: 3.36, $p = 0.005$, see Fig. 3C]. On the other hand, there were no differences between T+ and T− in the pre-surgery session ($t_{(415)} = 0.06$, $p > 0.99$).

To summarize, there were session effects for all movements but, importantly, for the more demanding movements of the thumb (i.e., thumb circumduction), the two groups diverged in that the T+ group had less pain after cast removal in comparison with the T− group, and in comparison with their pre-surgical pain.

3.3. *Motor behavior*

3.3.1. *Motor execution*

We used Generalized Linear Mixed Models (GLMM) to study patterns of M.E. changes in relation to the experimental conditions. The movement times were considered as dependent variable. Group (T+, T−), Session (Pre, Post), Movement type (Thumb-to-finger opposition, Pronosupination, Fist-making movement), and Hand (Affected, Unaffected) were modeled as fixed factors. Again, for what concerns the random effect structure of the model, a by-subjects random intercept was included to account for participant-specific variability; moreover, a random effect nested structure was preferred in order to take into account also the effect of the group.

We first explored the data distribution of the dependent variable (i.e., M.E. times) separately in the two groups: all dependent variables showed a significant departure from normality (Shapiro-Wilk test: $p < 0.001$). M.E. score was modeled as the target variable, and random intercept was modeled on Subjects (i.e., Group). After having graphically examined the distribution of these data, we selected the gamma distribution with a Logit function as reference. Main effects and interactions are formally reported in Table 2B. Since we found a 3-way **Session by Group by Hand interaction** [$F_{(3,2025)} = 8.80$, $p < 0.0001$] we performed separate analyses for the affected and unaffected hand. Thus, we performed two separate GLMMs to study patterns of M.E. changes for each hand in relation to the experimental conditions. The movement times were considered as dependent variable. Group (T+, T−), Session (Pre, Post), and Movement type (Thumb-to-finger opposition, Pronosupination, Fist-making movement) were modeled as fixed factors. Again, for what concerns the random effect structure of the model, a by-subjects random intercept was included to account for participant-specific variability; moreover, a random effect nested structure was preferred in order to take into account also the effect of the group.

3.3.1.1. *Motor execution: affected hand.*

We found a main effect of the factor Session [$F_{(1,1000)} = 20.36$, $p < 0.0001$] and the factor

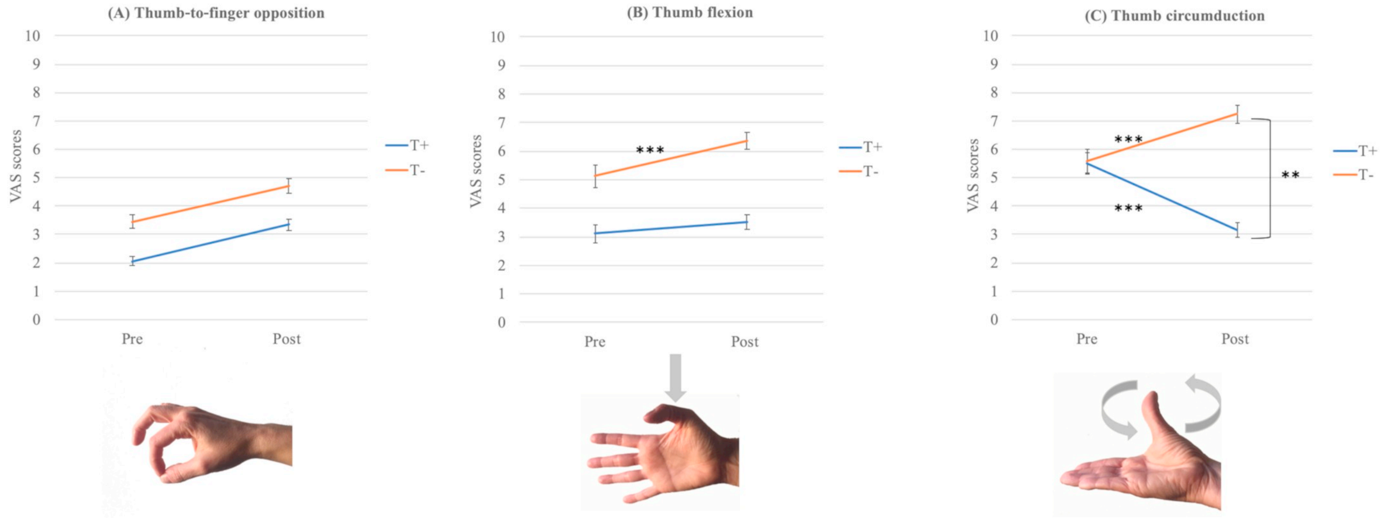

Fig. 3. Mean VAS score for the executed movement: (a) thumb-to-finger opposition, (b) thumb flexion and (c) thumb circumduction. T+ = trained group, T− = untrained group, Pre = pre-surgery session; Post = post-surgery session. Asterisks indicate significance: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. The error bars refer to the standard error of the mean (SEM).

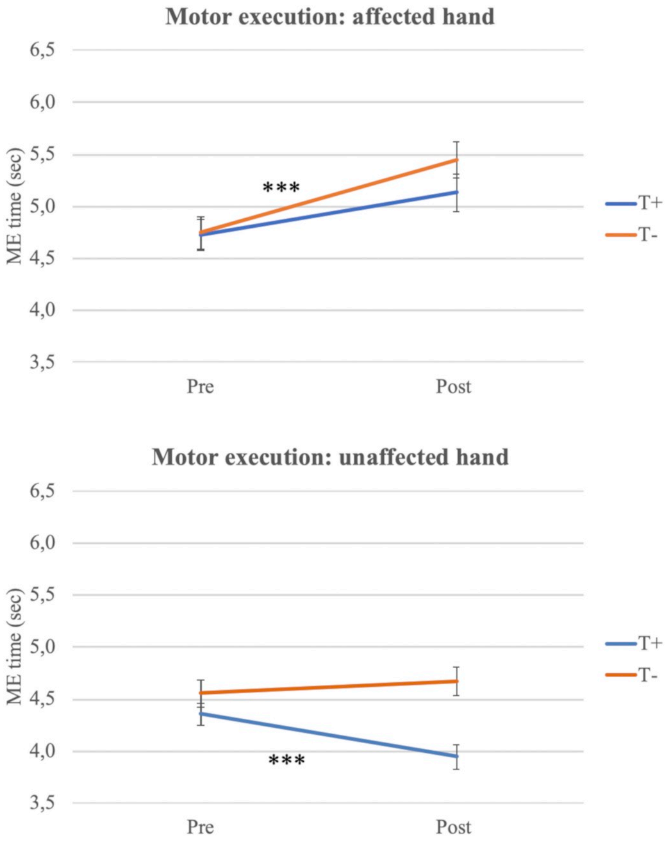

Fig. 4. Distribution of the motor execution durations (seconds). Pre = pre-surgery session; Post = post-surgery session; T+ = trained group, T− = untrained group. Asterisks indicate significance: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Movement type [$F_{(2,1000)} = 236.11$, $p < 0.0001$] with the more complex movements (i.e., thumb-to-finger opposition) requiring more time and a Group by Session interaction [$F_{(1,1000)} = 4.37$, $p = 0.037$]. Bonferroni adjusted pairwise comparisons showed that the untrained T− patients were slower after cast-removal (pre-surgery session: mean = 4.75″, SD = 2.3; post-surgery session: mean = 5.45″; SD = 2.68, $t_{(1000)} = 4.37$, $p < 0.0001$; Fig. 4, upper graph). Conversely, no differences were found in movement time between the pre (mean = 4.72″; SD = 2.50) and post-surgery session (mean = 5.13″; SD = 3.02; $t_{(1000)} = 1.85$, $p = 0.39$) in the trained T+ patients (Fig. 4, upper graph). Conversely, the main effect of the factor Group [$F_{(1,20)} = 0.28$, $p = 0.6025$] and the interaction Group by Movement type by Session were not significant [$F_{(6,1000)} = 1.90$, $p = 0.0777$].

3.3.1.2. Motor execution: unaffected hand. The same analysis was performed for the unaffected hand. Results showed a main effect of the factor Session [$F_{(1,1024)} = 4.90$, $p = 0.0271$] and the factor Movement type [$F_{(2,1024} = 270.80$, $p < 0.0001$] and a Session by Group interaction [$F_{(1,1024)} = 10.70$, $p = 0.0011$]. Bonferroni adjusted pairwise comparisons showed a difference between pre (mean = 4.35″; SD = 1.88) and post-surgery (mean = 3.94″; SD = 1.98) movement time in T+ patients ($t_{(1024)} = -4.07$, $p = 0.0003$; see Fig. 4, lower graph). Conversely, no differences were found in movement time between the pre (mean = 4.55″; SD = 2.05) and post-surgery session (mean = 4.67″; SD = 2.17) in the untrained patients ($t_{(1024)} = 0.72$, $p > 0.99$; see Fig. 4, lower graph). Conversely, the main effect of the factor Group [$F_{(1,20)} = 2.38$, $p = 0.1389$] and the interaction Group by Movement type by Session were not significant [$F_{(6,1024)} = 0.91$, $p = 0.4885$].

3.3.2. *Motor imagery*

For the motor imagery task, we used the same analysis performed for the motor execution task. Main effects and interactions are formally reported in Table 2C. Since there were differences in motor imagery durations for the affected and unaffected hand ($F_{(1,2076)} = 30.04$, $p < 0.0001$), we performed a separate analysis for each hand. Thus, we performed two separate GLMM to study patterns of M.I. changes for each hand in relation to the experimental conditions. The movement times were considered as dependent variable. Group (T+, T−), Session (Pre, Post), Movement type (Thumb-to-finger opposition, Pronosupination, Fist-making movement) were modeled as fixed factors. Again, for what concerns the random effect structure of the model, a by-subjects random intercept was included to account for participant-specific variability; moreover, a random effect nested structure was preferred in order to take into account also the effect of the group.

3.3.2.1. Motor imagery: affected hand. The data were analyzed as for the motor execution task. We found a main effect of Movement type

[$F_{(2,1024)} = 224.80$, $p < 0.0001$] with the more complex movements (i.e., thumb-to-finger opposition) requiring more time to be imagined. Conversely, no main effect were found for the factors Group [$F_{(1,20)} = 3.51$, $p = 0.0758$] and Session [$F_{(1,1024)} = 1.25$, $p = 0.2635$] and the interactions Group by Session [$F_{(1,1024)} = 3.30$, $p = 0.0696$] and Group by Movement type by Session [$F_{(6,1024)} = 0.67$, $p = 0.6776$] were not significant.

3.3.2.2. Motor imagery: unaffected hand. We performed the same analysis for the unaffected hand, and we found a main effect of Session [$F_{(1,1024)} = 6.52$, $p = 0.0108$] and Movement type [$F_{(2,1024)} = 230.40$, $p < 0.0001$]. No other main effects or interactions were observed. Indeed, the main effect of Group [$F_{(1,20)} = 4.31$, $p = 0.0509$], and the interactions Group by Session [$F_{(1,1024)} = 0.35$, $p = 0.5515$] and Group by Movement by Session [$F_{(6,1024)} = 0.82$, $p = 0.5515$] were all not significant.

3.3.3. Motor imagery quality index

We calculated an index of the quality of M.I. (Motor Imagery Quality Index – MIQI, differences between M.I. and M.E.) for each pair of M.E. and M.I. trials,[9] according to the following formula:

$$|(\mathrm{M.\ I.}\ time - \mathrm{M.\ E.}\ time)|/[(\mathrm{M.\ I.}\ time + \mathrm{M.\ E.}\ time)/2]$$

The same index was called respectively “delta time” in Beauchet et al. (2010) and “chronometry ability” in Allali et al. (2014). The closer to zero is the MIQI score, the smaller is the difference between executed and imagined movement times, the better the M.I. abilities. We used Generalized Linear Mixed Model (GLMM) to study patterns of MIQI changes in relation to the experimental conditions. The MIQI score was modeled as dependent variable.

Session (Pre, Post), Movement type (Thumb-to-finger opposition, Thumb flexion, Thumb circumduction), Hand (Affected, Unaffected) and Group (T+, T−) were modeled as fixed factors.

For what concerns the random effect structure of the model, a by-subjects random intercept was included to account for participant-specific variability; moreover, a random effect nested structure was preferred in order to take into account also the effect of the group.

We first explored the data distribution of the dependent variable separately in the two groups. For both T+ and T− this was positively skewed (Skewness T+: 1.510; T−: 1.190) and leptokurtic (Kurtosis T+:4.255; T−:1.618) with a significant departure from normality (Shapiro-Wilk test T+: $S\text{-}W_{(1152)} = 0.884$, $p < 0.001$; Shapiro-Wilk test T−: $S\text{-}W_{(1152)} = 0.904$, $p < 0.001$). After having graphically examined the distribution of these data, we selected the exponential distribution as a reference, with a Logit function.

All the main effects and interactions are formally reported in Table 2D, while here we discuss only the significant effects. Since there were differences in the MIQI index for the affected and unaffected hand ($F(1,2028) = 6.86$, $p = 0.0089$), we performed two separate analyses for the two hands.

3.3.3.1. MIQI: affected hand. The analysis confirmed a main effect of Session [$F_{(1,1000} = 10.92$, $p = 0.0010$] and a Session by Group interaction [$F_{(1,1000)} = 8.47$, $p = 0.0037$]. Bonferroni adjusted pairwise comparisons showed a difference between the MIQI scores in the pre and post- surgery session only in trained patients. This result indicates as expected that these patients had greater motor imagery skills after training (mean = 0.153; SD = 0.134) than before surgery (mean = 0.216; SD = 0.163), their MIQI scores being closer to zero ($t_{(1000)} = -4.73$, $p < 0.0001$; Fig. 5, left graph). By contrast, no differences were found in the MIQI score between the pre (mean = 0.209; SD = 0,171) and post-surgery session (mean = 0.197; SD = 0.160) in the untrained patients ($t_{(1000)} = -0.26$, $p > 0.99$; Fig. 5, left graph).

3.3.3.2. MIQI: unaffected hand. We performed the same analysis for the unaffected hand, and we found a Session by Group interaction [$F_{(1,1000)} = 4.91$, $p = 0.0270$]. Bonferroni adjusted pairwise comparisons showed that there were not differences in the trained group in the MIQI score before (mean = 0.221; SD = 0.181) and after training (mean = 0.172; SD = 0.145; $t_{(1000)} = -2.03$, $p = 0.2566$; Fig. 5, right graph). Moreover, there were no differences in the untrained group in the MIQI score before (mean: 0.230; SD = 0.191) and after training (mean:0.256; SD = 0.205: $t_{(1000)} = 1.17$, $p > 0.99$).

3.4. fMRI results

All the fMRI analyses were performed on the entire brain volume (i.e., whole brain analysis).

3.4.1. Within-group effects

The within group activation patterns for the M.E. were consistent with what previously found in the literature (see Supplementary Material, Fig. S1) and a recent example in Zapparoli et al. (2013) or in Gandola et al. (2017) with the activation of a vast fronto-parietal motor networks.

3.4.2. Between-group comparisons

3.4.2.1. Interaction Group by Session [(Pre > Post) T+ > (Pre > Post) T−)]. The T+ patients had a comparatively larger session effect in the form of decreased activations (i.e., hypoactivation) in the precentral gyrus (premotor cortex, BA6) bilaterally, in the right supplementary motor area (SMA, BA6), and in the left paracentral lobule (see Fig. 6 and Table 3). Only clusters that survived to $p < 0.05$ FWER correction for multiple comparisons are reported.

3.4.2.2. Interaction Group by Session by Hand [(Post > Pre)(RH > LH) T+ > (Post > Pre)(RH > LH) T−]. The T+ patients in the post-surgery session showed a greater activation during the movement of the affected hand in the right cerebellum. This effect was significant at $p = 0.034$ FWER - corrected for cluster size - after voxel thresholding at $p < 0.001$ (cluster size (k) = 314; MNI coordinates: x = 30; y = −66; z = −44 and x = 42; y = −62; z = −38, Table 3b).

3.4.3. Correlations between brain activations and VAS scores

Here we tested the hypothesis that changes of the pain felt by our patients could predict the changes in the patterns of brain activation measured with fMRI during the finger opposition task. In the analysis, the dependent variables were the post-surgery > pre-surgery differences of the activations for the affected hand in each voxel of the brain, as represented by specific differential contrast images; the predicting variable contained the individual post minus pre differences of the VAS pain scores (positive scores indicate that the pain was more intense in the post-session than in the pre-session, i.e., increase of pain, negative scores indicate that the pain was less intense in the post-session than in the pre-session, i.e., decrease of pain) for the circumduction of the thumb (the most painful movement for our patients). This measure was collected outside the scanner making the linear regression analysis with the fMRI data less prone to circularity biases. We found a positive correlation between the two variables in the right precentral/post-central gyrus (BA6), and in the inferior parietal gyrus (see Table 4, Fig. 8). Substantial uncorrected trends were seen in the insula (x = 42; y = −12; z = 12; Z score = 3.46; p = 0.0003) and in the thalamus (x = 12; y = −26; z = 16; Z score = 3.37; p = 0.00016). These correlations indicate that the larger was, comparatively, the pain in the second session the stronger was the brain activity in the regions mentioned above.

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[9] Each motor execution trial (e.g., thumb to finger five times) was followed by the same trial in motor imagery modality representing a pair of trials of the same movement.

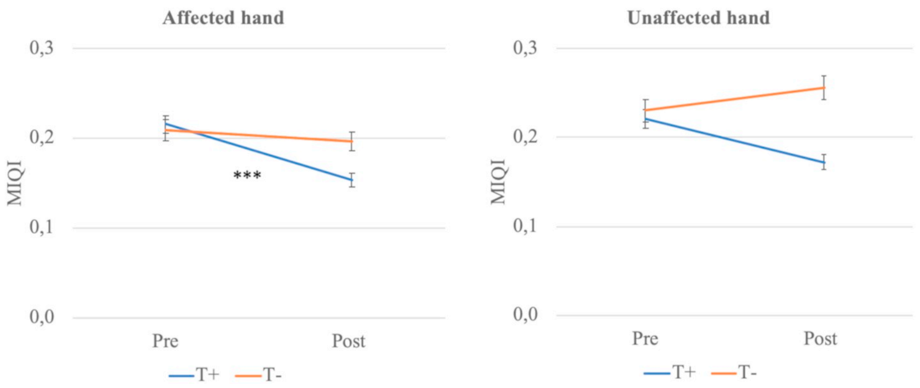

Fig. 5. Motor Imagery Quality Index – MIQI. The figure shows the mean MIQI - [|(M.I. − M.E.)/[(M.I. + M.E.)/2] - for the affected (left graph) and unaffected hand (right graph). T+: trained group; T−: untrained group. Asterisks indicate significance: $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

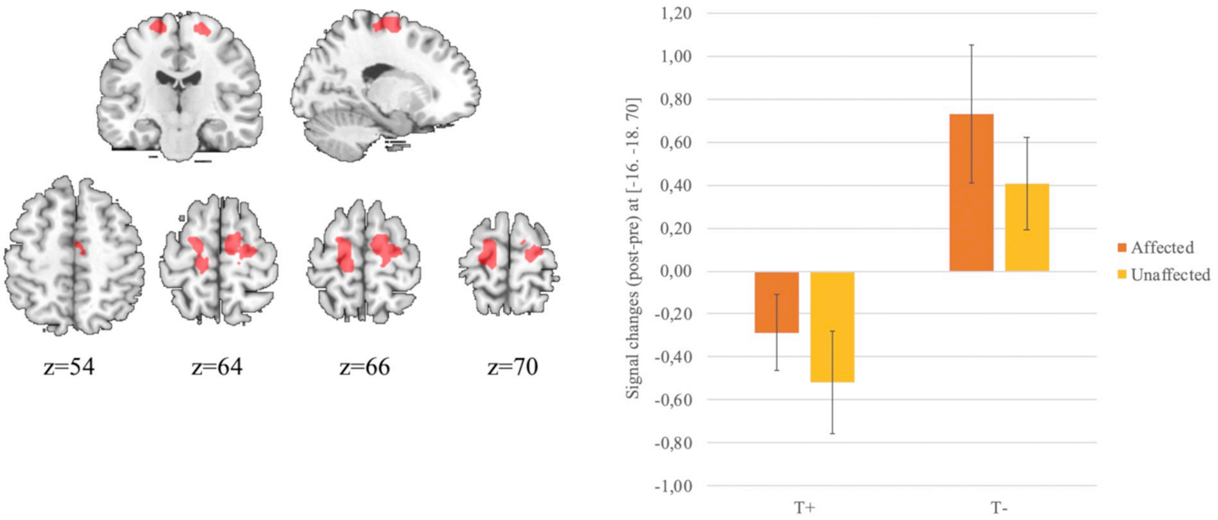

Fig. 6. Motor execution task: fMRI results. Interaction Group by Session: $[(\text{Pre} > \text{Post T}+) > (\text{Pre} > \text{Post T}-)]$. Brain activations are visualized on a standard MNI template (Montreal Neurological Institute, MNI). Only clusters that survived to $p < 0.05$ FWER cluster-level correction for multiple comparisons are visualized, after a voxel-wise threshold of $p < 0.001$ uncorrected.

4. Discussion

To date, only a few studies have investigated the effects of rehabilitative training based on kinesthetic mental imagery in patients with orthopedic diseases of traumatic origin (Christakou and Zervas, 2007; Christakou et al., 2007; Cupal and Brewer, 2001; Gassner et al., 2007; Hoyek et al., 2014; Lebon et al., 2012; Maddison et al., 2012; Mayer et al., 2005; Stenekes et al., 2009). However, to our knowledge, there are no studies that investigated both the behavioral and functional consequences of mental practice on motor execution tasks in orthopedic patients. In particular, our study enabled us to simultaneously investigate the effects of two different processes that take place after hand surgery, namely the consequences of hand immobilization that were present in both trained and less trained patients and the effects on brain organization of a period of motor imagery training on any maladaptive plasticity induced by immobilization.

The idea underlying this approach is that M.I. training, activating sensorimotor networks even in the absence of explicit motor outputs (Zapparoli et al., 2013), could be used as a rehabilitative treatment also for categories of patients for which movement is temporarily not possible.

The behavioral results revealed that in patients with rhizarthrosis, a two-week motor imagery training was sufficient to counteract the negative effect of hand immobilization after surgery, speeding up motor recovery, reducing the magnitude of pain, and improving the quality of mental imagery. We start by discussing the effects of M.I. training on motor performance. Next, we consider the behavioral and functional effects of M.I. training on pain and finally, we discuss what the fMRI results tell us about the mechanisms behind the effects of M.I. training.

4.1. Effects of M.I. training on motor performance

The behavioral data showed that motor performance deteriorated after a two-week immobilization in the less trained group for the affected hand as the movement execution time was significantly longer. It was not so for the T+ group who had only a marginal motor speed reduction after immobilization (the Group by Session by Hand interaction was highly significant).

Interestingly, the effects of the M.I. training generalized also to the unaffected hand with faster movements. This surprising finding is open to discussion: the unaffected hand had not been operated nor was it immobilized nor was it directly mentally trained; one possible reason might be that in eminently bi-manual people as we are, the bilateral patterns of premotor activity associated with unimanual motor imagery (Zapparoli et al., 2013) inevitably “train” both hands.

Much as expected, M.I. training ameliorated the quality of motor imagery expressed as the difference between motor execution and motor imagery times (MIQI index): in T+ patients, the index became closer to zero (zero represents a perfect temporal match between execution and imagery), indicating a training-induced improvement of motor imagery abilities. By contrast, the speed of M.I. was not affected by training a finding that is consistent with the increased quality of M.I. that, by definition, implies a tight coupling of imagination and explicit execution rather than speed per se. Overall, these results are in

Table 3
Interaction group by session [(Pre > Post T+) > (Pre > Post T−)] and group by session by hand.

Brain region	Cluster			Peak			
	K	P-value (FWE corr)	P-value (unc)	Z-score	MNI coordinates		
					x	y	z
Motor execution task							
(a) Interaction Group × Session							
Cluster 1	**353**	**0.022**	**0.003**				
L Precentral gyrus (6)				4.07	−16	−18	70
L Paracentral lobule				3.92	−14	−26	66
Cluster 2	**401**	**0.013**	**0.002**				
R SMA (6)				4.04	12	−6	64
				3.28	6	−12	54
R Precentral gyrus (6)				3.85	24	−14	66
(b) Interaction Group × Session × Hand							
Cluster 1	**314**	**0.034**	**0.005**				
R Cerebellum lobule VIII				4.73	30	−66	−44
R Cerebellum Crus 1				3.96	42	−62	−38

Brain region (R = right hemisphere; L = left hemisphere), cluster size (k = number of voxels), FWE-corrected p-value and uncorrected p-value, peak *Z*-score and Montreal Neurological Institute (MNI) coordinate are reported. $p < 0.05$ FWER corrected at cluster-level after a voxel-wise threshold of $p < 0.001$ uncorrected. SMA = Supplementary Motor Area; corr = corrected; unc = uncorrected. The significant clusters, the cluster size (k), and corrected (FWE-corrected) and uncorrected p-value are reported in bold.

agreement with previous studies suggesting the efficacy of mental practice on motor performance both in healthy subjects and in patients with different diseases (Driskell et al., 1994; Liu et al., 2004; Riccio et al., 2010).

4.2. Behavioral and functional effects of M.I. training on pain

Our results also show that M.I. is effective in reducing pain in patients with rhizarthrosis. While in less trained patients (T−) the level of pain increased after surgery, in T+ patients the intensity of pain remained stable or even decreased in the case of the most sensitive thumb circumduction task. Importantly, the level of pain immediately after surgery was matched across groups. These observations expand the findings of previous studies which demonstrated the efficacy of different techniques based on motor imagery, mainly the mirror therapy, for the treatment of chronic pain in patients with complex regional pain syndrome type 1 initiated by limb fractures (Moseley, 2004, 2005, 2006), chronic back pain (Wand et al., 2011), stroke (Cacchio et al., 2009a,b), in patients with acute or chronic phantom limb pain (Chan et al., 2007; Foell et al., 2014) and in patients with orthopedic diseases (Christakou and Zervas, 2007; Hoyek et al., 2014). Mosley (2004, 2005, 2006), for example, used a graded motor imagery (GMI) procedure, namely a three stages treatment that includes implicit motor imagery (Hand Laterality Task, HLT), explicit motor imagery (imagined hand movements) and the mirror therapy. Mosley proposes that the order of the type of motor imagery intervention might be crucial and an unordered program might achieve less improvement (Moseley, 2005). By contrast, when used alone, explicit M.I. was found to induce an increased pain in patients with chronic regional pain syndrome (Moseley et al., 2008), in patients with stroke (Cacchio et al., 2009b) and patients with phantom limb pain (Chan et al., 2007).

Without questioning the empirical facts described in this literature, it has to be said that the rationale for the progression from implicit motor imagery, to its explicit form, to mirror therapy appears to us in search of confirmation, at best. For example, the assumption that the primary motor cortex is involved in explicit motor imagery but not in the implicit imagery condition (i.e., HLT task) is not confirmed by recent meta-analytical reviews (Hetu et al., 2013; Zapparoli et al., 2014) nor in our experience with these very tasks (Zapparoli et al., 2014, 2016).

It also has to be mentioned that the conditions in which the graded motor imagery program has been tried are very different from the one assessed in present study, with extreme modifications either at the central end, as in stroke patients (Cacchio et al., 2009a; Cacchio et al., 2009b), or at both ends, the brain and the periphery, as in amputees (Chan et al., 2007).

In our experiment, we instead studied the effect of motor imagery on the consequences of short-term hand immobilization due to surgery. The specificity of the effects of our treatment is out of the question as the pain felt immediately after surgery was the same in the T+ and T− groups as much as the duration of spontaneous pain. It is also worth noting that the T+ and T− groups had the same level of pain during specific actions before surgery for the most painful movement of thumb circumduction: the pain felt changed in the two groups after release from immobilization following a different degree of training.

To summarize, our study shows that explicit M.I. is sufficient *per se* to achieve a protective effect on the consequences of a two-week immobilization in patients with rhizarthrosis.

4.3. fMRI results

A longitudinal fMRI exploration of the effects of a 14 days motor imagery training gave us the opportunity to study how post-surgery immobilization affects the brain and whether motor imagery could counterbalance the observed effects. The task explored was a simple explicit finger opposition task. The enhancement of motor performance observed at the behavioral level was mirrored by a specific group by session interaction, a *reduction* of brain activations for the trained patients in the premotor cortex bilaterally and supplementary motor area (SMA). This pattern is highly reminiscent of what seen in motor learning in normal conditions (Debarnot et al., 2014). Both the SMA and the premotor cortex (BA6) are normally activated both during

Table 4
Correlation of the differences between post and pre-surgery VAS scores (post minus pre-session) for the circumduction of the thumb and BOLD response (post > pre affected hand contrast).

Brain region	Cluster			Peak	MNI coordinates		
	k	P-value (FWE corr)	P-value (unc)	Z-score	x	y	z
Cluster 1	474	0.001	< 0.001				
R Precentral gyrus (6)				4.73	32	−26	62
R Precentral gyrus (6)				4.10	22	−28	68
R Inf. parietal gyrus (2)				4.13	40	−36	52

Only clusters that survived to $p < 0.05$ FWER correction for multiple comparisons are reported. Brain region (R = ipsilateral hemisphere; L = contralateral hemisphere), cluster size (k = number of voxels), FWER-corrected p-value and uncorrected p-value, peak Z-score and Montreal Neurological Institute (MNI) coordinates are reported. corr = corrected; unc = uncorrected.

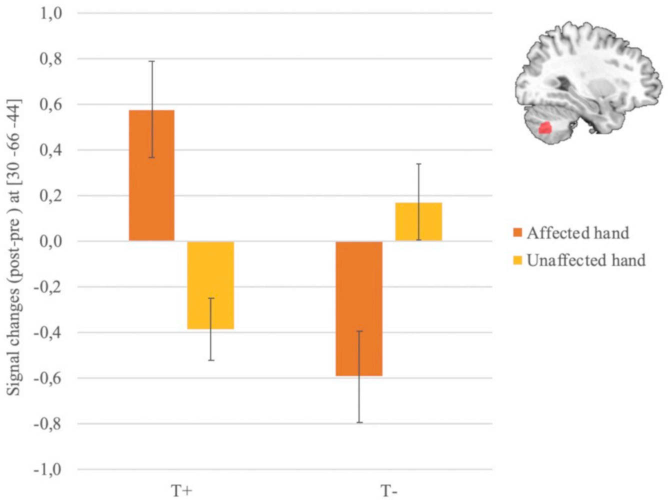

Fig. 7. Motor execution task. Interaction group by session by hand: [(Post > Pre)(RH > LH) T+ > (Post > Pre)(RH > LH) T−]. Brain activations are visualized on a standard MNI template (Montreal Neurological Institute, MNI). RH = right hand, LH = left hand. Only clusters that survived to $p < 0.05$ FWER cluster-level correction for multiple comparisons are visualized, after a voxel-wise threshold of $p < 0.001$ uncorrected.

motor execution and motor imagery (Roland, 1984; Roland et al., 1980; Stephan et al., 1995). Premotor cortex is involved in different stages of movement preparation, motor planning and control. Moreover, this region has a crucial role during the early phases of motor sequence learning (see review in Guillot et al., 2014).

There was another group by session interaction, this time in the form of an increased activation of the ipsilateral cerebellum that was specific for the movement of the affected hand (Fig. 7, Table 3b). This activation was localized in the region of Crus 1, lobule VIIb, and VIII. In particular, the anterior lobule VIII is known to be part of the sensorimotor cerebellum, it contains a somatotopic representation of the body, and it is active during both movement and tactile stimulation of the hand (Stoodley and Schmahmann, 2009). The increased activation observed in the ipsilateral cerebellum may reflect an expansion or a strengthening of the motor representation trained during motor imagery exercises that become evident when the action is actually executed after mental training. Furthermore, in stereotactic coordinates substantially identical to our own, an increased cerebellar activation has been seen in learning for a serial reaction time task (Rieckmann et al., 2010; Van Der Graaf et al., 2004).

Another finding connects the fMRI data with the clinical changes observed in our patients: we found that the more intense was the change of the feeling of pain in the post-surgery post-immobilization session, the higher the change of activity was in the ipsilateral motor/premotor and somatosensory cortex during the execution of movement with the affected hand. In other words, there was more ipsilateral activity associated with a less favorable outcome of the pain symptoms after surgery. The ipsilateral involvement of motor/premotor cortex for unimanual motor tasks is broadly seen as a sign of compensation for movement that are felt as more difficult, as during recovery from a brain insult (Ward et al., 2003). We imply that the more cumbersome were the movements of the operated hand for our patients, the greater was the need of cortical resources, including those of the same hemisphere.

There are some differences between our findings, and previous reports (see for example: Lacourse et al., 2004; Nyberg et al., 2006; Zhang et al., 2011): these differences may be caused by the nature of the training used, its timing and the underlying pathology. These are all factors that may justify different outcomes. The more remarkable such discrepancy is the lack of differences between trained and untrained patients in the visual association cortex (Nyberg et al., 2006). This difference might depend on the fact that, in our study, patients were explicitly instructed during motor training to use an internal kinesthetic first-person motor imagery perspective. By contrast, some of the previous studies used an external, mainly visual imagery approach (i.e., visualization of the movement; Nyberg et al., 2006) that may induce different effects on both motor skills and brain activations. Moreover, in those studies the participants were normal controls. By contrast, in our study, we investigated the impact of M.I. training on the consequence of immobilization, which is an entirely different model of experience related brain re-organization.

4.4. Mechanisms of the effects of M.I. on post-surgical recovery after hand surgery

The mechanisms of the effects of M.I. on overt motor performance appear evident given the mental motor rehearsal implied by explicit M.I. in which kinesthetic first-person aspects of imagery are emphasized. This is what we would have predicted, for example, from the literature on the effects of mental motor training in athletes (Feltz and Landers, 1983).

On the other hand, the beneficial effect of M.I. on pain was pleasantly surprising and yet it remains in need of a mechanistic explanation. Several mechanisms have been invoked. Some of these remain not tested by our study or appear unlikely. For example, in a recent review about the effects of M.I. on the complex regional pain syndrome (CRPS) (de Souza et al., 2015) the authors hypothesized three different processes: (i) the release of encephalin and meta-encephalin in analogy with physical exercise, (ii) the modulation of pain perception at spinal (dorsal horn) or (iii) cerebral neuromodulatory process leading to the inhibition of the pain pathway. None of these mechanisms were tested by us.

It has also been proposed that M.I. training might be effective by promoting sustained attention towards the painful body part (Moseley, 2005). While this cannot be easily dismissed, it seems a non-specific explanation because, for the same reason, any form of pain should become less intense for its ability to attract attention to the painful body part.

One other hypothesis, grounded on the data also emerging from studies on patients with phantom limb pain and CRPS, is that the reduction of pain depends on the sequential activation of cortical premotor and motor regions through M.I., without pain evocation (Moseley, 2005). This contrasts with our data as the act of motor imagery was associated with some pain (see the records of pain level during the M.I. training period) and indeed some adaptation of motor imagery associated with pain may contribute to make the motor experience less painful after the training.

Finally, as hypothesized for patients with phantom limb pain, M.I. may represent a mechanism that is capable of reversing maladaptive neuroplastic cortical changes (de Souza et al., 2015). For patients with painful phantoms limb, the level of pain has been correlated with the degree of cortical disorganization since the reduction of such disorganization leads to a reduction of pain (Flor et al., 1995).

This latter mechanism seems to fare well in explaining our results. Indeed, our clinical and the fMRI findings, combined, suggest that the analgesic effect of M.I. training on pain was mediated by processes of cortical plasticity induced by repetitive motor simulation and rehearsal. We found important changes within the motor system in the form of a session specific reduced activation of the premotor cortex and SMA after training and augmented cerebellar activation.

A relationship between pain and the physiology of M.I. is also supported by studies that looked at this relationship from a reversed perspective: it has been shown that pain can cause a deficit in mental rotation affecting high-level motor representations (Coslett et al., 2010; Schwoebel et al., 2001). Using the HLT task, it has been found that patients with CRPS of the upper limb were slower to respond to pictures

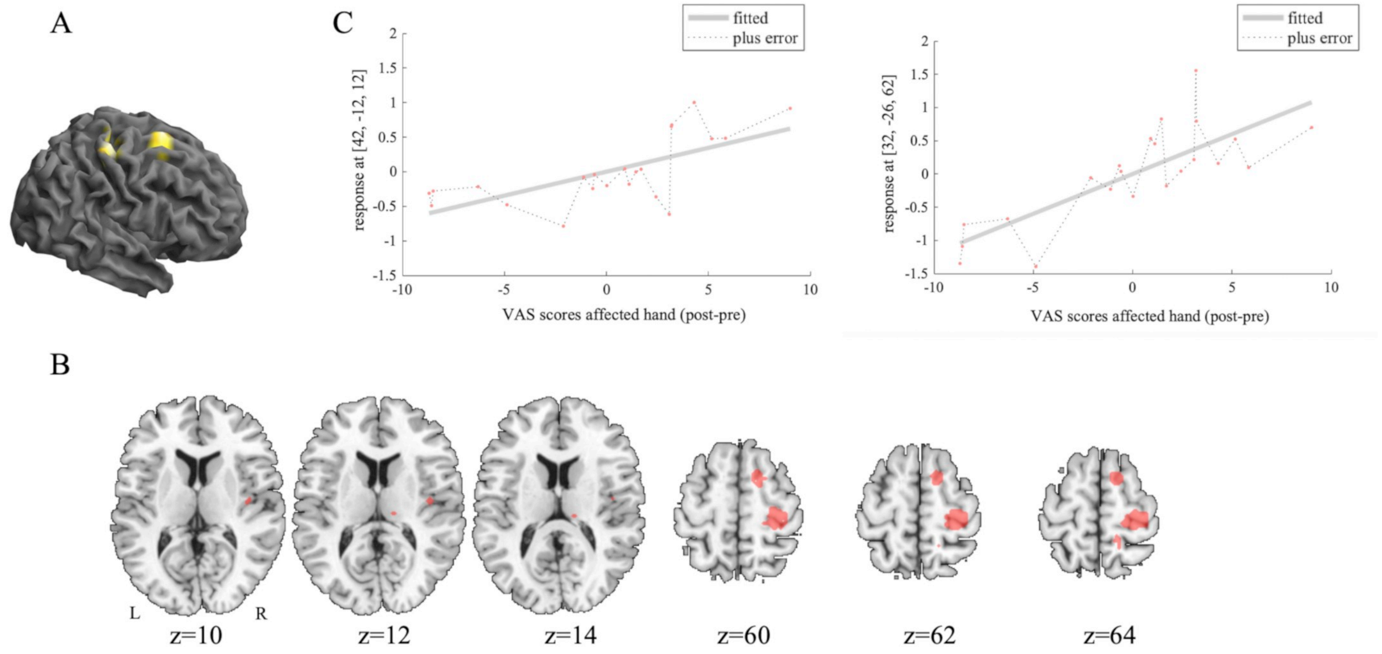

Fig. 8. (A and B) Correlation of the differences between post and pre-surgery VAS scores (post-scores minus pre-scores) for the circumduction of the thumb and BOLD response (post > pre M.E., affected hand contrast). (C) Plots of the linear regression in the insula (MNI: $x = 42$; $y = -12$; $z = 12$) and in the right precentral/postcentral gyrus (MNI: $x = 32$; $y = -26$; $z = 62$). Brain activations are visualized on a standard MNI template (Montreal Neurological Institute, MNI), thresholded at $p < 0.001$ uncorrected.

of the painful hand and that this difference was eliminated after treatment that reduced the subjects' pain (Schwoebel et al., 2001). Moreover, there was a correlation between RTs and the rating of pain (Coslett et al., 2010) and the performance was best predicted by the degree of pain that subjects believed would be provoked by putting their hand in the depicted position (Moseley, 2004).

Our data confirm an interplay between motor control and pain, as the greater was the post-immobilization pain the greater was the need of larger ipsilateral sensory-motor activations in the same hemisphere of the affected hand. We interpret this as an adaptive compensatory activity needed to cope with the motor demands that followed the release from immobilization. As the level of pain for the most demanding thumb movement correlated with the degree of compliance with the training program, we can imply a connection between pain and motor imagery here. This evidence confirms the presence of a (mal)adaptive two-way traffic between pain and motor control.

Finally, it is possible that at a peripheral level the mental simulation of actions during training was accompanied by some minimal movements of the affected hand: these may induce a residual activation of the primary somatosensory areas. Indeed, even if patients wore a bulky dressing for all the immobilization period, which impeded the execution of thumb-to-finger opposition movement, a minimal contraction of finger muscles was still possible. It is conceivable that this residual activity on the somatosensory network might have modulated the activity of the cortico-thalamic loop and descending projections involved in pain suppression.

5. *Thumbs up*: clinical implications of the study

Very briefly, we conclude that our findings have some promising clinical implications. Motor imagery during the immobilization period after hand surgery could, or perhaps should, be added to conventional preventive measures in the clinical management of the pathology considered here. The benefits, at least at the time of release from immobilization, are advantages concerning motor speed and pain to the affected hand that are reflected by brain physiology. Whether this may apply to more dramatic hand surgery scenarios remains a question open for future research. It also remains to be established whether a different form of mental motor training could achieve a better compliance: our program implied explicit, first person perspective, motor imagery. Other, implicit, forms of motor imagery, like the hand laterality task or a grip selection task (Zapparoli et al., 2014, 2019), for example, may be found more entertaining particularly if transformed into a videogame. It remains to be seen in further research whether adopting such a training format could result in a better compliance to the training while preserving the same effects.

6. Limitations of the study

6.1. Statistical approach

As reported on paragraph 3.1.1, in this study we decided to split the sample into two groups using the mean score of the percentage of training (mean = 54.97% of compliance) having in mind a conceptually simple 50% of treatment boundary as an indication for the discussion of the practical implications of our approach. For this reason, patients with compliance below the mean (< 54.97%) were classified as T− (n = 10), and those with compliance above that threshold (n = 12) were classified as T+. We could have used a linear regression analysis or a non-parametric variant of it, avoiding to split of the sample in two groups using the level of compliance to treatment; however, our data do not permit to test linear relationship between the percentage of training and behavioral and fMRI response, primarily because of the non-normal distribution of the independent variable. Of course, we could have opted for non-parametric techniques, but these analyses have well-known limitations in power, nor they do permit to capitalize on all behavioral observations as generalized mixed-models used here do.

While we acknowledge this potential limitation, we believe that, our study permits to tell that the adoption of our mental training program over 50% of the time recommended, is associated with less pain and better motor recovery at the time of cast removal. It is possible that one important factor might be not only the overall amount of training but also its duration and persistence over the two weeks (see Fig. 2). For the time being we are unable to say whether a more limited training yet spread consistently across the two weeks would be as good as the one originally recommended and performed by the T+ group.

6.2. Causes of poor compliance to the treatment among the T− patients as an explanation of the present findings

In the line of principle, there could have been many reasons that could have led to the poor compliance of the T− group patients: for example, differences in motor and motor imagery abilities between patients in the pre-surgery phase, variations in the intensity and duration of spontaneous pain after surgery, or motivational factors. However, we have evidence that this was not the case here. First, in the pre-surgical sessions (baseline), the two groups were comparable for motor execution and imagery speed and matching between motor imagery and motor execution. More relevant, as pointed out on paragraph 3.2.1, there were no differences in the intensity of spontaneous pain measured immediately after surgery between trained and untrained patients, nor in pain during the M.I. training sessions at the time of quitting for T− patients (paragraph 3.2.2). Also, the duration of spontaneous pain after surgery was comparable.

Most importantly, the endpoints of the efficacy of our training program were very basic behaviors or symptoms such as motor and motor imagery speed and congruity and level of pain before and post-surgery. Again, these were matched before treatment, the main difference being in how they changed after more intensive mental motor training.

The only possible confound that would remain is that the if the T− subjects had engaged as much as T+ subjects in any other training, they would have had the same benefits. This possibility cannot be addressed in our study. However, since the average training in the T− group was 20% and not zero, the T− group resemble to a low-dose/duration therapy group rather than to a zero-therapy group.

Further, the greater improvement in the T+ group in the matching between motor execution and motor imagery (an indirect index of the quality of motor imagery) strongly suggests that the effects of motor mental training were specific and hardly related to a generic difference in terms of motivational factors. Indeed, it is unlikely that motivation alone may affect such ratio: it may affect absolute speed, perhaps, but not the ratio.

Finally, the fMRI differences between-groups (i.e., the Session by Group interaction effects) were primarily in the form of greater attenuation in motor cortices for the T+ group, a sign of motor learning at the cortical level: again, it looks implausible that this effect during the fMRI scans could be associated with a greater motivation for training in such group. A more motivated group of subjects may express more force, perhaps, but this would translate in stronger activations of motor cortices (Dettmers et al., 1995).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101838.

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