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Deep repetitive transcranial magnetic stimulation with H-coil on lower limb motor function after stroke: a pilot study

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Running head: Lower limb H-coil rTMS in chronic stroke

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Conflicts of interest

A. Zangen is a key inventor of deep TMS H-coils and has financial interst in Brainsway Ltd. The other authors declare no conflicts of interest related to the present study.

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Deep repetitive transcranial magnetic stimulation with H-coil on lower limb motor function after stroke: a pilot study

Abstract

Objectives: To assess the efficacy of high frequency (20 Hz) brain stimulation on lower limb motor function in subjects with chronic (> 6 months) subcortical stroke in a double-blind, placebo-controlled crossover study.

Design: double-blind, placebo controlled, crossover study

Setting: University hospital.

Participants: ten right-handed subjects affected by a first-ever subcortical stroke in the territory of the middle cerebral artery were included in this study.

Interventions: rTMS was delivered with the H-coil, specifically designed to target deeper and larger brains regions. Each subject received both real and sham rTMS in a random sequence. The two rTMS cycles (real or sham) were composed of 11 sessions each, administered over 3 weeks and separated by a 4-week wash-out period.

Main Outcome Measures: lower limb functions were assessed by the lower limb Fugl-Meyer (FM) scale, the 10 meters walking test (10MT) and the six minutes walking test (6MWT), before and 1 day after the end of each treatment period, as well as at a 4-week follow-up.

Results: real rTMS treatment was associated with a significant improvement in lower limb. This effect persisted over time (follow-up) and was significantly greater than that observed with sham stimulation. A significant increase in walking speed was also found after real rTMS but this effect did not reach statistical significance in comparison with the sham stimulation.

Conclusions: these data demonstrated that 3 weeks of high-frequency deep rTMS could induce long-term improvements in lower limb functions in the chronic post-stroke period, lasting at least 1 month after the end of the treatment.

Keywords: stroke, lower limbs, rehabilitation, rTMS, H-coil.

List of abbreviations

rTMS: repetitive transcranial magnetic stimulation; FM: Fugl-Meyer scale; 10MT: 10 meters walk test; 6MWT: 6 minutes walk test.

Stroke is a leading cause of long term disability and non invasive brain stimulation techniques have been recognized as a promising intervention for the treatment of post-stroke motor deficits [1-3]. Although the ability to walk is impaired in more than 80% of post-stroke subjects [4], the pathophysiological reorganization of lower limb motor areas after stroke is still unclear as relatively fewer data are available compared with the upper extremity. A study performed with Near-infrared Spectroscopic Imaging System in stroke subjects during walking showed that, similarly to upper limb, the cortical activation patterns of motor, premotor and supplementary lower limb motor cortex was greater for the unaffected hemisphere rather than for the affected hemisphere [5]. The latter data suggest that the concept of interhemispheric competition, proposed for homologues upper limb motor areas [6], might be applied even in the case of lower extremity post-stroke recovery. Consistently, improvements of gait parameters of the paretic lower limb have been found associated with a reduction of the interhemispheric asymmetry of the primary sensori-motor cortical activations

[7]. Wang and colleagues [8] first evaluated in a placebo controlled study, the therapeutic effect of task-oriented training associated with 1Hz repetitive transcranial magnetic stimulation (rTMS) (with the figure-of-eight coil) performed to inhibit the unaffected lower limb motor cortex in chronic stroke subjects. The authors found that inhibitory rTMS enhanced the effect of task-oriented training on walking performance and motor control ability, leading to a more symmetric gait pattern. Recovery of motor deficits was associated with a reduction of the interhemispheric asymmetry of the leg motor excitability.

However, in the chronic phase after stroke, the interhemispheric competition, at least in the upper limb, has been found less pronounced than in the subacute period, and it is commonly observed that the transcallosal asymmetry slows down with time [9]. Moreover, as bi-hemispheric control of foot movements in healthy subjects have been proposed [10] one could hypothesize a positive, rather than detrimental role of the unaffected lower extremity motor system in recovery mechanisms occurring after stroke. Moreover, in a more recent placebo controlled cross-over study, a single session of high-frequency rTMS, over the leg motor area bilaterally using a double-cone coil, has been reported to significantly improve walking performance for 20 minutes after stimulation in comparison with sham stimulation in a group of chronic post-stroke subjects [11].

The purpose of our study was to assess the safety and efficacy of bilateral excitatory, high frequency rTMS over the lower limb cortical motor representation in chronic subcortical stroke. To reach the lower limb cortical motor areas, deeply located in the mesial cortical surface of the hemispheres, we delivered rTMS was delivered using the H-coil, designed to effectively stimulate at about a depth of 3-5 cm below the skull [12, 13]. Compared with the standard figure-of-eight coil, the H-coil has been reported to require lower intensities to obtain lower limb motor responses[14] and larger volumes of the induced electric field [14, 15]. The H-coil rTMS has been reported effective in the treatment of psychiatric disorders such

as major depressive disorder or bipolar depression [13, 16, 17]. Recently, analgesic effects in subjects with painful diabetic neuropathy were obtained using deep rTMS with H-coil targeting the leg motor cortex [15].

We hypothesized that high-frequency rTMS delivered with the same H-coil type over the lower limb motor cortical areas could improve the paretic lower limb function in chronic post-stroke subjects.

Methods

Subjects

Ten right-handed subjects affected by a first-ever stroke in the territory of the middle cerebral artery were included in this study. The inclusion criteria for participants were: evidence of acute brain lesion on computerized tomography-CT or magnetic resonance-MR scans at symptoms onset; time between the stroke event and the enrolment in the protocol ranging from 6 months to 3 years (chronic phase); age at admission between 25 and 80 years; ability to walk independently for at least 10 meters, even with assistive devices (cane, ankle-foot orthoses etc.). Exclusion criteria were: history of other neurological disorders, lesions involving the cortical lower limb motor representation, use of drugs acting on central nervous system; presence of contraindications to undergo rTMS such as pregnancy, cochlear implants, neurostimulator, metal in the brain or skull, cardiac pacemaker, history of epilepsy or head trauma diagnosed as a concussion[18].

Subjects' age at admission ranged between 49 and 74 years (mean 62.2 years). All subjects suffered from sub-cortical stroke, the affected hemisphere was the right in 6 subjects, while the other 4 subjects had a lesion in the left hemisphere. Subjects' data and lesion localization are reported in Table 1.

All subjects gave their signed written informed consent to participate in the study that was approved by our local ethics committee (DO/MS/ER protocol number: 111/11).

Procedures

We performed a double blind, placebo controlled crossover study. Each subject received both real and sham rTMS treatment cycles separated by a four week washout period in a random sequence (sham-real or real-sham). After full randomization, performed through administrative personnel not involved in the protocol, each participant was assigned two blank-coded magnetic cards (A and B), to be used respectively in the first and second cycle. Each card pair contained opposite types of treatments (sham and real). Consecutive subjects were randomized with a global 1:1 ratio, so that 5 participants performed the real-sham and 5 the sham-real treatment sequence. Active or sham modes were determined by a switch controlled through the assigned magnetic card. This procedure ensured blindness of subjects, examiners and treating personnel. Each treatment cycle lasted 3 weeks for a total of 11 high-frequency rTMS sessions (5 in the first week and 3 in the second and third weeks) (Figure 1). No specific motor task involving the lower limb was associated to the rTMS treatment.

Deep rTMS

A Magstim Rapid^2 stimulator (Magstim Company Ltd, Whitland, Dyfed, UK) was coupled with an H-coil (Brainsway Ltd, Jerusalem, Israel) to deliver rTMS. The H-coil, designed for effective activation of hand or leg motor cortex, contained 14 windings. Three medial groups conduce current along a postero-anterior axis, and two other groups return currents in the opposite (anterior-posterior) direction [15]. Resting motor threshold was measured after positioning the H-coil over the vertex on the optimal location for obtaining lower limb motor responses. Resting motor threshold was defined as the minimal intensity evoking visible movements on either lower limb or electromyographic motor evoked

potentials on tibialis anterior muscle that were monitored bilaterally, with amplitude of 50 μV or higher in 5 out of 10 stimuli, using 1% increments of stimulator output. Then, the H-coil was tightly fixed on the same position with a belt and the sham or real rTMS treatments were delivered (90% of resting motor threshold or up to 84% maximal stimulation output; 30 trains at 20 Hz, 60 sec inter-train interval; total number of pulses 1500). Sham stimulation was performed by activating a sham coil placed in the same stimulation helmet designed to mimic a similar acoustic artifact and some scalp sensation but without inducing an effective field inside the brain. The sham stimulation is, indeed, non tangentially orientated on the scalp, with components cancelling the electric field, which is rapidly reduced as a function of distance[12]. Each rTMS session lasted about 30 minutes.

Safety

Vital signs were recorded before and after each rTMS session. Participants were asked to report every possible adverse event; especially the most frequently reported side effects such as headache, or dizziness. We also performed continuous visual monitoring of participants throughout all treatment sessions, excluding the occurrence of involuntary movements suggesting stimulation above motor threshold or seizures.

Clinical evaluation

Clinical evaluation was performed before and one day after the end of the treatment period, as well as at a four-week follow-up (which served as baseline for the second treatment cycle) (Figure 1). The residual neurological deficit (National Institutes of Health Stroke Scale-NIHSS) and the degree of disability (Barthel Index and modified Rankin Scale) were quantified at enrollment.

The primary outcome was the Fugl-Meyer (FM) assessed for the affected lower limb. The motor score ranges from 0 (hemiplegia) to a maximum of 34 points (normal motor performance). It includes items measuring synergic and simple movements, coordination, and reflex at the hip, knee, and ankle levels [19]. As exploratory measures (secondary outcome) we used:

- 10 meter walk test (10MT): the subject was asked to walk as quickly as possible, back and forth, along a 10-meter path marked by a starting and arriving line on the floor. Assistive devices were allowed except the walker. The task was administered twice in a row. The best time of the two trials was considered for our data analysis.
- 6 minute walk test (6MWT) (secondary outcome): this test measured the distance walked in a period of 6 minutes [20].

Statistical analysis

Given the exploratory nature of this pilot trial, no sample size determination was performed. Statistical analysis was performed using the SPSS software (version 13.0, SPSS Inc., USA). After verifying the normal distribution with the Kolmogorov-Smirnov Test, parametric tests were used. When appropriate, the Geisser-Greenhouse procedure was applied to correct degrees of freedom. The significance level was set at $p \leq 0.05$ for all analyses.

Changes over time in clinical outcomes after real or sham (9 subjects) treatment were first evaluated. Absolute clinical measures (lower limb FM, 10MT and 6MWT) underwent two separate one-way ANOVA for repeated measures for the real and the sham group respectively, with Time as within subject factor (baseline, end of treatment and follow-up).

To directly compare the effects of real and sham treatment on clinical outcomes we calculated the percent change to the relative baseline of clinical scores obtained immediately after sham or real treatment (end of treatment) and after 1-month follow-up as follows:

% end of treatment = [(end of treatment – baseline) / baseline] x 100;

% follow-up = [(follow-up – baseline) / baseline] x 100

Then, a two-way ANOVA for repeated measures was performed using "treatment" (real and sham) and "time" (end of treatment and follow-up) as within subject factors. If a significant main effect was found, post-hoc comparisons were performed using paired Student's T-tests. Differences in the two baseline measurements (before real and sham treatment) were evaluated with paired T-tests.

Results

Of the 10 participants, results will be presented for 9 since one left the study because of a cardiac disease and was therefore not included in the statistical analysis (patient 6-Table 1). Lower limb motor responses, at rest or with facilitation through voluntary contraction, were obtained in all subjects.

Safety

No subject reported any adverse effects related to rTMS, including seizures. No significant changes in blood pressure levels were observed throughout the protocol periods. Finally, the applied stimulation parameters were well tolerated by all subjects.

Clinical outcomes

The two treatment baselines (T_1vs T_3; n=9, paired T-test) of the clinical measures were not significantly different (lower limb FM p=0.1; 10MT p=0.5; 6MWT p=0.4).

No absolute significant changes over time in any clinical measure were found after sham treatment (repeated measures ANOVA: lower limb FM: F=0.8, p=0.4; 10MT F=0.7, p=0.4; 6MWT F=0.7, p=0.4). A significant effect of "time" factor on lower limb FM and

10MT (F= 17.1, p<0.001 and F=3,7, p=0.05 respectively) but not on 6MWT (F=0.2, p=0.1) was found in the real group. The post-hoc analysis revealed a significant improvement of lower limb FM score between baseline and both end of treatment evaluations (baseline *vs* end of treatment: p=0.009; baseline *vs* follow-up p=0.001) as well as a persisting improvement in the follow-up period (end of treatment *vs* follow-up p=0.05). The improvement at follow-up *vs* baseline suggests a carry-over effect up to the second baseline measurements for the real treatment (Figure 2). We also found a significant amelioration in 10MT performance at the end of the real treatment in comparison with baseline (baseline vs end of treatment p=0.04). The persistent improvement after 1 month follow-up did not reach significance (baseline vs follow-up p=0.07) (Table 2).

Comparing the effects of real and sham stimulation, the ANOVA analysis showed a significant effect of "treatment" factor (F=12, p=0.008) as well as a significant interaction between "time" and "treatment" factors (F=11.3, p=0.01) only on lower limb FM score (6MWT and 10MT: n.s.). The percentage improvement of lower limb FM resulted significantly greater for real *vs* sham stimulation at the end of treatment and even more at 1-month follow-up (p=0.01 and p=0.006 respectively). Moreover, clinical gains with real stimulation significantly progressed between end of treatment and follow-up evaluations (end of treatment vs follow-up: p=0.04) (Figure 3).

Discussion

The deep representation of lower limb muscles in the human brain makes it difficult to approach with standard non-invasive stimulation techniques. So far, few studies have been published about potential therapeutic rTMS application on post-stroke walking deficits. A recent open study showed that a protocol consisting in 20 sessions of high-frequency rTMS delivered with double cone coil associated with mobility training is safe and can improve

walking function after stroke [21]. To our knowledge, this is the first placebo controlled study evaluating the safety and the therapeutic effect of deep non invasive brain stimulation delivered with H-coil over the lower limb motor cortex bilaterally in post-stroke gait disturbance. For this pilot study we enrolled participants with stroke in the territory of the middle cerebral artery and excluded those with stroke in the territory of the anterior cerebral artery, in order to avoid cortical lesions of the target lower limb representation, mainly for safety reasons (i.e. to avoid epileptic activation). Moreover, subjects with lesions involving the motor cortex have been reported as less likely to benefit from rTMS treatment[22]. Our results suggest an effective role of deep high-frequency rTMS in ameliorating lower limb motor function, especially regarding the Fugl-Meyer lower limb scores. Evaluating the duration of such effect over time, participants not only maintained the benefits of the H-coil treatment at one month follow-up, but they continued to ameliorate after the end of the treatment, showing better scores at the follow-up compared to the post-rTMS evaluation. This could be explained by the long-lasting modulatory effects of non-invasive brain stimulation techniques [23, 24], probably potentiated by the daily use of the paretic lower limb. Consistently with this finding, the differences between real and placebo effects were mainly seen at the 4-week follow up. Although our data might be limited by a relatively short wash-out period, the crossover design of our study helped to point out the presence of a considerable long lasting effect of deep rTMS (Figure 2). Sham stimulation showed a weak effect on Fugl-Meyer lower limb score scale immediately after the end of treatment that faded away with time. Participants improved by 10.6 % on average after real rTMSvs 0.6 % after sham stimulation. An amelioration of about 30% of FM lower limb score in the experimental group has been obtained following 1 Hz rTMS over the unaffected lower limb motor area [23]. However, it is important to note that in the latter study rTMS was combined with task-oriented training, which is, by itself, beneficial for motor recovery [25]. Indeed, an improvement of about 20% in

lower limb FM scale was found in the control group undergoing motor training associated with sham rTMS. In our study, walking speed evaluated by the 10MT test significantly increased only after real and not sham rTMS, but this effect did not reach statistical significance in comparison with sham stimulation. Improvement after sham treatment on 10MT measurement was indeed greater than on FM lower limb scales, suggesting that pure motor ability of the paretic limb, compared with walking speed, is less likely to improve after sham stimulation. On the other hand, walking speed does not necessarily take into account the quality of movement itself. Indeed, the 10MT test cannot allow to discriminate between movement speed of the paretic and unaffected limbs. Moreover, all subjects included were all autonomous in walking and therefore they might have had a limited margin for improvement.

The application of inhibitory rTMS over the contra-lesional motor cortex is based on the model of interhemispheric competition after stroke established for the upper limb extremity [6]. In fact, early hyperexcitability and increased interhemispheric inhibition of the contralesional motor cortex have been demonstrated to the upper limb using TMS after unilateral stroke [26, 27]. However, in the post-stroke chronic phase the interhemispheric competition is less pronounced than in the sub-acute period, as it is commonly observed that the transcallosal asymmetry decreases with time [9]. Moreover, contralesional premotor and motor cortex interference by TMS after chronic unilateral stroke worsens motor performance during complex movement of the paretic hand. This finding has been interpreted as suggesting a beneficial role of contra-lesional motor areas in effectively recovered complex motor behavior after subcortical stroke [28]. However, the mutual inhibition between homologous motor areas can be modulated under physiological conditions. For example, during movement preparation of the non-dominant hand the dominant hemisphere is facilitated [29, 30]. Moreover, studies on normal subjects suggest a bi-hemispheric control of foot movements in healthy subjects. In particular, a more lateralized pattern of activation at

functional MRI has been found to finger movements versus lower limb joints, with increased lateralization from proximal to distal lower joints [31] implicating a different functional specialization. Moreover, after training of the right lower limb an increased strength of the homologous, with increased excitability of the corresponding motor cortex, has been reported [30]. The latter findings implicate changes in functional interhemispheric connections between the two motor cortices [32]. These findings could have important clinical implications for subjects with reduced limb mobility after a stroke. Accordingly, our data suggest that bilateral high frequency rTMS over the lower limb motor cortical representation may have a beneficial role in motor recovery of the paretic limb. Further studies are needed to better understand the mechanisms underlying this effect, in particular the role of plastic changes over the motor cortex controlling the two lower limbs.

Study limitations

The small sample size is the major limitation of this study. Another limitation is the crossover design of the study with a relatively short washout period with a carry-over effect up to the second baseline measurements for the real treatment. Some feelings (e.g. scalp sensations) may have differed in the placebo and real conditions. Therefore, the future use of a questionnaire for study participants and evaluating physicians would be recommended to help verifying that blinding is maintained throughout the conduction of the study.

Conclusions

Despite the limits of our studyour main results suggests a potential beneficial role of high-frequency rTMS delivered with the H-coil in improving lower limb motor function. These findings represent the first evidence about a relevant but greatly unexplored field of therapeutic application of non invasiveneuromodulation.

Suppliers

a. Magstim Rapid^2 stimulator (Magstim Company Ltd, Whitland, Dyfed, UK)

b. H-coil (Brainsway Ltd, Jerusalem, Israel)

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384 **Legends**

385 **Figure 1**: Study design: double-blind placebo-controlled crossover study

386 For both real and sham treatment, 11 rTMS sessions (grey vertical bars) were performed

387 within a 3-week period (5 in the first week and 3 in the second and third weeks), separated by

388 a 4-week wash-out. W: week; T: time of clinical evaluations.

389 **Figure 2:** lower limb FM (Fugl-Meyer) scores grouped according to treatment sequence.

390 Black circles: real-sham sequence (4 subjects) and grey squares: sham-real sequence (5

391 subjects). Continuous lines: rTMS period; dashed lines: wash-out period. In both groups,

392 after real stimulation performance grows even after the end of treatment, while placebo effect

393 fades away.

394 **Figure 3:** (A) lower limb FM (Fugl-Meyer) score: real vs sham comparison (9 *vs* 9 patients)

395 revealed a significant improvement at the end of treatment (p=0.01) as well as at follow-up (p

396 =0.006). Amelioration was greater after 4 weeks from the end of real treatment as confirmed

397 by a significant difference in baseline percent change at the end of treatment *vs* follow-up (p=

398 0.04).

Table 1 Demographic data, clinical features and treatment sequence of each patient are reported.

Patient	age	lesion	onset (months)	NIHSS	BI	mRS	Sequence
1	50	right capsulo-lenticular ischemia	20	3	90	2	real-sham
2	74	right internal capsular ischemia	21	2	100	1	real-sham
3	65	left capsulo-lenticular hemorrhagia	8	5	100	2	sham-real
4	49	right capsulo-lenticular hemorrhagia	21	5	100	2	real-sham
5	65	right capsular hemorrhagia	10	4	85	2	sham-real
6*	71	right capsular hemorrhagia	30	3	60	3	real-sham
7	74	left capsular ischemia	24	4	95	2	sham-real
8	69	left capsulo-lenticular hemorrhagia	30	6	85	2	real-sham
9	50	left capsulo-lenticular ischemia	21	3	100	1	sham-real
10	55	right capsular ischemia	25	2	100	1	sham-real

* = drop out; M= male; F= female; NIHSS= National Institutes of Health Stroke Scale; BI= Barthel Index; mRS= modified Rankin Scale

Table 2 Performance scores grouped according to treatment type (n=9).

	FM-LL					10 MT					6 MWT				
	baseline	post	FU	Post vs baseline	FU vs baseline	baseline	post	FU	Post vs baseline	FU vs baseline	baseline	post	FU	Post vs baseline	FU vs baselin
Real rTMS	24,7±1,4	26,8±1,5	27,7±1,5	p=0.009	p=0.001	9,4±1,1	8,5±0,9	8,7±0,9	p=0.04	p=0.07	320,6±29,7	338,9±24,9	345,1±30,9	ns	ns
Sham rTMS	26,2±1,4	26,7±1,4	25,9±1,1	ns	ns	9,2±1,0	9,0±1,1	8,8±0,9	ns	ns	307,4±34,9	325,7±25,2	309,4±27,5	ns	ns

Values are expressed as mean ± squared error.

FU= follow up, ns= not significant.

Figure 1

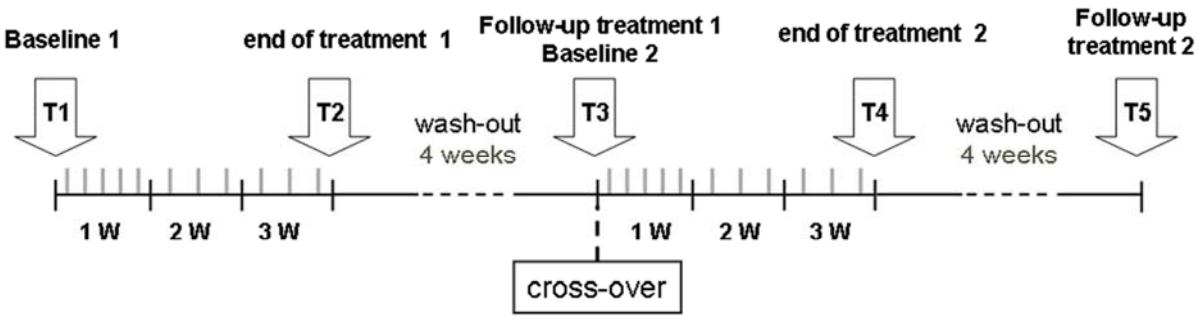


Figure 2

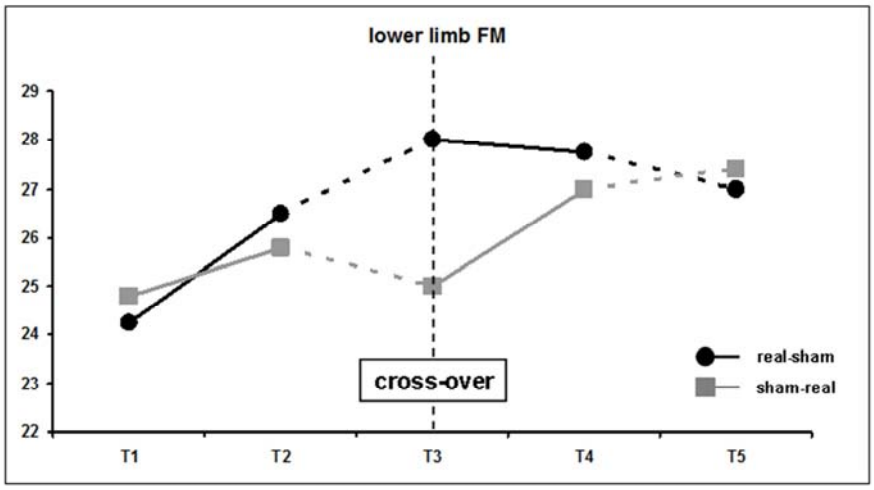
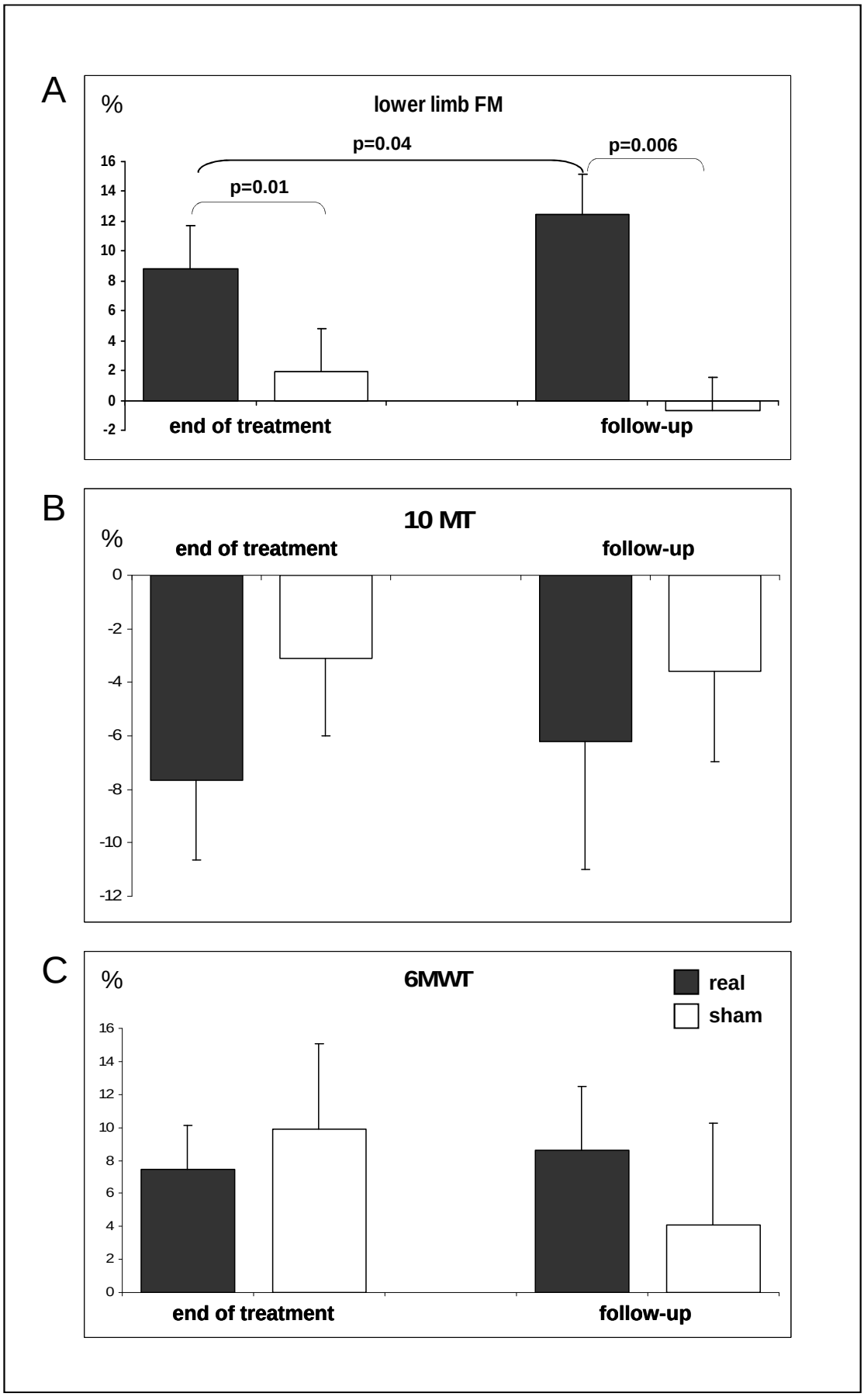


Figure 3


A
%
lower limb FM
p=0.04
p=0.006
p=0.01
16
14
12
10
8
6
4
2
0
-2
end of treatment
follow-up
B
10 MT
%
end of treatment
follow-up
0
-2
-4
-6
-8
-10
-12
C
%
6MWT
real
sham
16
14
12
10
8
6
4
2
0
end of treatment
follow-up