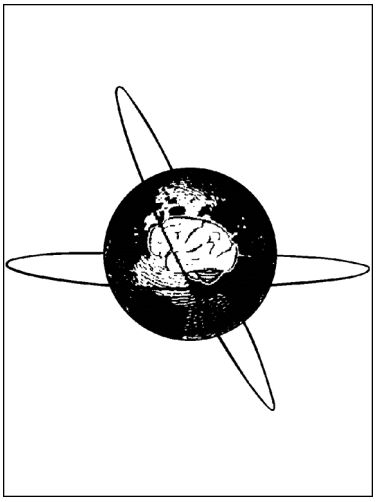

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REPETITIVE PERIPHERAL MAGNETIC NEUROSTIMULATION OF MULTIFIDUS MUSCLES COMBINED WITH MOTOR TRAINING INFLUENCES SPINE MOTOR CONTROL AND CHRONIC LOW BACK PAIN

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HIGHLIGHTS

- Combining repetitive peripheral magnetic neurostimulation and motor training immediately decreased chronic low back pain.
- This intervention helped normalize the control of spine one week after study onset.
- These motor and pain changes were paralleled by an increase of intracortical motor facilitation.

ABSTRACT

OBJECTIVE. The study tested whether combining repetitive peripheral magnetic neurostimulation (RPMS) and motor training of the superficial multifidus muscle (MF) better improved the corticomotor control of spine than training alone in chronic low back pain (CLBP).

METHODS Twenty-one participants with CLBP were randomly allocated to [RPMS+training] and [Sham+training] groups for three sessions (S1-S3) over a week where MF was stimulated before training (volitional contraction). Training was also home-practiced twice a day. Changes were tested at S1 and S3 for anticipatory postural adjustments (APAs) of MF and semi-tendinosus (ST), MF EMG activation, cortical motor plasticity (transcranial magnetic stimulation) and pain/disability.

RESULTS The RPMS group showed immediate decrease of pain at S1, then improvement of MF activation, ST APA, M1 facilitation, and pain/disability at S3. Changes were larger when brain excitability was lower at baseline. Disability index remained improved one month later.

CONCLUSIONS Combining RPMS with training of MF in CLBP impacted motor planning, MF and lumbopelvic spine motor control and pain/disability one week after the onset of protocol. Brain plasticity might have favoured motor learning and improved daily lumbopelvic spine control without pain generation.

SIGNIFICANCE Clinically, RPMS impacted the function by improving the gains beyond those reached by training alone in CLBP.

KEYWORDS: magnetic neurostimulation; paravertebral muscles; motor training; APA; M1 excitability; chronic low back pain.

1. INTRODUCTION

Chronic low back pain (CLBP) alters the sensorimotor control of the lumbopelvic spine. Patients with CLBP present with impaired activation of lumbopelvic muscle during anticipatory postural adjustments (APA) (Hodges et al., 1996b, Massé-Alarie et al., 2015), as well as during functional activities, such as forward bending (Shirado et al., 1995, Alschuler et al., 2009) and gait (Arendt-Nielsen et al., 1996). Our research group also showed that the activation of remote muscles such as semitendinosus could be delayed during ballistic movement of upper limbs thus reflecting a broad alteration of motor planning that might spread out the painful area (Massé-Alarie et al., 2015). Over-activation of superficial paravertebral muscle (erector spinae and/or multifidus - MF) has also been reported in these patients, even during periods of pain remission (van Dieen et al., 2003, Macdonald et al., 2011). These motor changes are accompanied by sensory changes in the lower back, such as a decrease in tactile acuity (Luomajoki et al., 2011), alterations in the integration of vibratory and proprioceptive stimuli (Brumagne et al., 1999, Claeys et al., 2011), increased pressure pain threshold (Peters et al., 1989, Puta et al., 2013) and impaired position sense (O'Sullivan et al., 2003). Neuroplastic changes in brain, such as a map shift in the primary motor cortex (M1) of the transversus abdominis muscle (TrA) (Tsao et al., 2008), missing inhibitory mechanisms of M1 (Massé-Alarie et al., 2012, Massé-Alarie et al., 2016b) and reorganization in the primary sensory cortex (Flor et al., 1997) (Baliki et al., 2012) have been reported in parallel to or in correlation with APA delay in CLBP. Also, white matter disorders in the

cerebellum of patients with CLBP were associated with the alteration of responses to vibratory stimuli, thus reflecting impairment of proprioceptive integration (Pijnenburg et al., 2014).

These extensive neuroplastic changes represent potential targets of treatments to improving pain and disability, particularly in people with minimal benefit after conventional approaches (Hayden et al., 2010, Rubinstein et al., 2011). It is acknowledged that motor training triggers neuroplastic changes in brain (Jensen et al., 2005), in likely relation to the high-level of attention and cognitive demand required to properly perform exercises following therapists' instructions. For example, it was shown that exercises involving the maintenance of isometric activation of the deep trunk muscles contributed to normalize M1 maps (Tsao et al., 2010b), and reactivated M1 inhibition mechanisms in association with pain decrease in individuals with CLBP (Massé-Alarie et al., 2016a). Motor training may also improve spine motor control by decreasing the paravertebral muscles overactivation (Tsao et al., 2010a) and reducing latencies of MF and TrA APA (Tsao et al., 2010a, Tsao et al., 2010b, Massé-Alarie et al., 2016a). Clinically, motor training was shown to improve pain and disability in CLBP (for a systematic review see (Macedo et al., 2009)), but residual pain and disability can persist one year after the intervention (Macedo et al., 2012, Macedo et al., 2014).

Novel technologies of neurostimulation that drives similar neuroplastic changes as those driven by motor training may have the potential to increase the effects of motor training if used in combination (Massé-Alarie et al., 2011, Schabrun et al., 2012a). Repetitive peripheral magnetic stimulation (RPMS) noninvasively

applied over a muscle or spinal nerve roots seems to not activate the cutaneous and nociceptive afferents (Zhu et al., 1991, Kunesch et al., 1993) and rather generates massive flows of pure proprioceptive inputs to the brain without nociceptive components (Struppler et al., 2003, Beaulieu et al., 2015c). This differs from electrical stimulation that strongly recruits superficial cutaneous receptors (Zhu et al., 1991) and might generate noisy and meaningless information for the sensorimotor control of movement (Refshauge et al., 2003, Struppler et al., 2003, Struppler et al., 2007b, Beaulieu et al., 2015b, c). These proprioceptive inputs generated by RPMS can influence the excitability of fronto-parietal areas in brain (Struppler et al., 2007a), of the corticospinal tract, and of the intracortical circuits of M1 inhibition and facilitation (Krause et al., 2005, Krause et al., 2008), and has also shown a potential for the treatment of pain (for review (Beaulieu et al., 2015c)). Our first study on the combination of RPMS with the practice of physical exercises reported that one RPMS session was sufficient to influence the corticomotor control and APA of deep abdominal muscles in people with CLBP (Massé-Alarie et al., 2013). The longer-term impact of this combined treatment, and its influence on different markers of corticomotor control and pain, however, have yet to be determined.

The present study aimed at testing whether the combination of RPMS with motor training (namely, practice of physical exercises engaging MF) could increase the benefits of training alone in CLBP. The influence on brain plasticity was assessed by M1 excitability and function, as tested with transcranial magnetic stimulation (TMS). The influence on motor planning was assessed by APA of MF and remote

muscles in different postural tasks and by MF activation during forward bending. It was further questioned whether M1 markers of brain plasticity could discriminate between the better and the lesser responders to the intervention. The hypothesis was that, due to a similar influence of RPMS and motor training on mechanisms of brain plasticity, their combination should potentiate the after-effects on brain function, spine motor control, pain and disability.

2. METHODS

2.1. Participants

Twenty-one individuals with CLBP were recruited with the following inclusion criteria: to be over than 18 years old, to be living with a pain having affected daily activities for more than 3 months. The sample size is beyond the effect size calculated by means of G*Power software (Faul et al., 2009) with previous published data on the APA and corticomotor changes related to deep abdominal muscles and following the combination of RPMS with motor training in CLBP (Massé-Alarie et al., 2013). The exclusion criteria were: non-mechanical LBP (e.g., fracture, malignancy, infection), more than 2 radicular signs, lumbar infiltration in the last 6 months, facet denervation, lumbar surgery, other chronic pain pathology, litigation, specific training of multfidus muscles, any major circulatory, respiratory, neurological or cardiac disease, severe orthopaedic troubles (e.g., scoliosis with gibbosity > 8mm), cognitive deficit, or recent/current pregnancy. Exclusion criteria related to TMS testing are reported elsewhere

(Rossi et al., 2009) and mainly concerned brain surgery, lesion or injury, any history of seizure or concussion, pacemaker/pump holder, change of medication in the 2 weeks preceding enrollment, medication affecting cortical excitability, metallic implants in skull or jaw. The local research ethics boards approved the protocol and the participants' informed written consent, in accordance with the Declaration of the World Medical Association (www.wma.net).

Participants were randomly allocated to two groups, [RPMS+training] (n=11) and [Sham+training] (n=10), using statistical software (see Table 1 for group characteristics). The group allocation was in a sealed envelope (one per participant) which was opened at the onset of protocol by a person not involved in the study. Procedures were taken to ensure proper blinding of experimenters (see Data reduction and statistical analyses).

(Insert Table 1 near here)

2.2. Study design

The study was conducted over one week (see Fig. 1) during which the participants had to perform twice daily at home the exercise (motor training taught in laboratory) and to fulfill an exercise log so that compliance could be assessed (see Table 1). They came three times to the laboratory during the week to receive the intervention, i.e. RPMS or sham (depending on the randomization) before performing the exercise under supervision. Outcomes (APA, muscles activation, M1 function, pain) were collected at the first session (S1) and the third session 1 week later (S3 – follow-up). No measure was done at the second

session. At the first session, the pre-intervention measures corresponded to the baseline. The order of outcome testing between pre- and post-intervention was randomised.

(Insert Fig. 1 near here)

2.3. Motor training

Each participant was provided detailed information on the low back anatomy and the rationale for paravertebral muscle exercises in the management of LBP. Both groups performed an exercice based on isometric contraction of the lumbar MF, with particular attention to contracting the deep MF with minimal activation of the superficial MF and adjacent erector spinae (ES) (Richardson et al., 2004). The participants were asked to perform a symmetrical contraction (same strength and duration for both MF). For instance, if an asymmetrical contraction was denoted (delayed or lower activation on one side), the physical therapist applied different strategies to facilitate the target contraction on the affected side and ensure its quality and symmetry with the other side: real-time ultrasound imaging (Terason t3200 MSK series15L4, Burlington, MA, USA), palpation, verbal cues and virtual motor imagery (e.g., tensing a rope between the thorax and pelvis, bringing together two points on each side of the lumbar spine, palpation with instruction to progressively harden the palpated muscles, etc.). Each muscle contraction was held for 10s, without holding breath. At each session (S1 to S3), one-on-one supervision was given for 3 sets of 10 repetitions. At home, participants were asked to perform 3 sets of 10 repetitions, twice a day.

The specific isometric contraction training of multifides was chosen given its impact on M1 plasticity and motor control (Tsao et al., 2010b, Massé-Alarie et al., 2016a). Also, combination with neurostimulation promised enlargement of training after-effects given the common mechanisms of synaptic plasticity shared with peripheral magnetic stimulation (Massé-Alarie et al., 2011, Massé-Alarie et al., 2012, Beaulieu et al., 2015a, Beaulieu et al., 2015c).

2.4. Repetitive peripheral magnetic stimulation (RPMS)

RPMS was delivered over lumbar MF at L4-L5 level using an air film cooled figure-of-8 coil (7 cm outer diameter each wing) connected to 2 rapid-rate magnetic stimulators (Rapid2; The Magstim Company Limited), with the CLBP patients positioned in prone lying. The RPMS group received 20 Hz-RPMS for 20 minutes, i.e. 30 contractions of 10s with 30s off between contractions for a total of 6000 stimulations. The intensity was set between 35 and 40% of maximal stimulator output, i.e. at an intensity eliciting MF contraction that was palpable and with visual detection of a slight lumbar spine extension.

The stimulation parameters were used to replicate the parameters of physical exercise, i.e. 30 cyclic contractions/relaxations of the muscle, with a contraction time of 10 s. Moreover, pain seems to be reduced by high-frequency RPMS as reported in a recent systematic review (Beaulieu et al., 2015c). The parameters of the exercise, in turn, were designed to match the postural function of MF (Richardson et al., 2004).

The stimulated side was chosen following a clinical evaluation of isometric voluntary contraction capacity of the MF at L4-L5 level while prone lying. RPMS was thus applied on the side that presented, under manual assessment, an asymmetry of MF contraction (decrease/delay) when the participant was asked to activate MF bilaterally and isometrically (Richardson et al., 2004). In case of a symmetrical MF activation, the right MF was stimulated, because study design excluded both sides stimulation, and previous data showed that the left hemisphere (contralateral to right MF) was predominantly affected by pain (Massé-Alarie et al., 2016b).w

Sham was applied with same parameters as RPMS but with the stimulating coil upside-down. The participants heard the RPMS noise (clicks) and felt the coil on their back, but received no stimulation of MF (Beaulieu et al., 2015c). At the end of the study, the participants were asked to guess their group of allocation, actual stimulation or Sham group (see Blinding item in Table 1).

2.5. Surface electromyography (EMG)

Parallel-bar surface EMG sensors were positioned bilaterally to record the activity of superficial MF, semitendinosus (ST), and anterior deltoid (AD) muscles (16-Channel Bagnoli EMG System, Delsys Inc., Boston, MA). Electrodes were placed following SENIAM recommendations (Hermens et al., 2000), after careful skin preparation. A common ground electrode was positioned over the C7-T1 spinous processes. EMG signals were bandpass-filtered (10Hz–450Hz), amplified before digitization (2 kHz), and stored for online display and offline

analysis (PowerLab acquisition system, LabChart-ADInstruments, Colorado Springs, CO).

2.6. Focal movement tasks

Two rapid focal movement tasks were used to study APA latency.

The bilateral shoulder flexion task began in quiet standing, holding a rigid stick in front of the thighs with the hands at shoulder width. The participants were instructed to flex the shoulders (raise the stick) to 90° as fast as possible in response to an auditory tone. Ten trials were recorded with rest breaks, and the onsets of MF and ST activation were assessed relative to AD onset (primum movens).

The unilateral hip extension task was performed in prone lying, beginning with the hips at ~10° of flexion (pillow under pelvis). The participants were instructed to extend one hip to the neutral position, as fast as possible, in response to an auditory tone. Five trials were recorded on each side (for more details (Massé-Alarie et al., 2015)) with rest breaks, and the onset of MF activation was assessed relative to ST onset (primum movens).

2.7. Trunk Movement Task

Participants began in quiet standing (QS), with the feet at hip width. Following the experimenter's count, the participants bent forward (slow and controlled flexion) to reach maximal trunk flexion, with minimal knee flexion, and maintained the position. The participants then returned to the upright posture. Following practice

trials, the sequence was repeated 5 times with rest breaks, each phase of the movement lasting 3s.

2.8. TMS testing of MF muscle

TMS testing of MF is challenging at rest (Ferbert et al., 1992), and M1 function is best tested with tonic activity of the muscle in order to increase M1 excitability and stabilize motoneuronal excitability and spinal cord output (Darling et al., 2006). Thus, the participants were seated in a chair without arm support, with their feet flat on the floor (O'Connell et al., 2007, Tsao et al., 2011a, Tsao et al., 2011b), and were asked to lean the trunk forward and maintain the lumbar spine in lordosis. The mean rectified MF EMG corresponding to 10% of maximum voluntary contraction (MVC - measured for resisted back extension in prone) was displayed as a line on an oscilloscope screen, and the participants had to match this target line with the real-time visual feedback of their MF activation (2 Hz low-pass filtered). Trials in which EMG fell outside the acceptance window (± 3.5%) were rejected online.

TMS of M1 was applied over the hemisphere contralateral to the stimulated MF. Magnetic stimuli were applied using a double-cone coil (7-cm outer diameter each wing; Magstim Company Limited, Whitland, UK) optimal for the activation of MF M1 cells (Nowicky et al., 2001, Davey et al., 2002, Tsao et al., 2011a). The TMS coil was positioned over the MF area, first approximated at 2 cm lateral to the vertex using a 10-20 EEG system (Tsao et al., 2011a). The position then was adjusted to determine the ‘hot spot’; the location eliciting the largest amplitudes

of MF MEP at a given intensity. Scalp locations were marked using a surgical marker to ensure reliable positioning and orientation of the coil. The active motor threshold (AMT) was defined as the TMS intensity eliciting at least 5 measurable MEP in the pre-activated MF, out of 10 trials.

Double TMS paradigms (coil connected to two Magstim 200² monophasic stimulators via a BiStim unit) were used to test the function of the intracortical circuits of M1. The short-interval intracortical inhibition (SICI) was probed by the combination of a subthreshold conditioning TMS (70% AMT) and a suprathreshold test TMS at 120% AMT; two inter-stimulus intervals (ISI) were tested (2ms, 3ms), i.e. with the conditioning TMS delivered 2 ms then 3 ms before the test (Kujirai et al., 1993). The short-interval intracortical facilitation (SICF) was probed by a subthreshold conditioning TMS (90% AMT) delivered 1 ms after a test TMS at 100% AMT (Tokimura et al., 1996, Ilic et al., 2002). In each paradigm, eight unconditioned (test) MEP and 8 conditioned MEP were elicited. Inhibition or facilitation (as appropriate per paradigm) corresponded to the decrease or increase, respectively, of the conditioned MEP amplitude as compared to its test MEP. The amplitudes of the conditioned MEP were then expressed in percent of the mean test MEP amplitude. For each participant, the amplitude of the test MEP was matched between pre-intervention at the first session (S1) and all other time points (adjustment of test TMS intensity) to ensure valid comparisons of conditioned MEP amplitudes. Rest periods were allowed between TMS trials to avoid fatigue and pain.

2.9. Questionnaires (pain, function, kinesiophobia)

The Global Physical Activity Questionaire (GPAQ) was used to rate the level of physical activity at baseline, i.e. pre-intervention at the first session (S1). At S1 and S3 (i.e. 1 week apart), the Visual Analogue Scale (VAS) (Price et al., 1983) was used to assess the intensity of LBP in a sitting position at the time of testing (spontaneous pain) and the intensity of the average pain over the last 2 days (average pain); the Oswestry disability index (ODI) (Fairbank et al., 1980) and the Patient-Specific Functional Scale (PSFS) (Stratford et al., 1995) were used to assess the functional disability of the participants; the Tampa Scale of Kinesiophobia (TSK) (Vlaeyen et al., 1995) was used to measure the fear of movement or of (re)injury. Only spontaneous pain was also assessed using the VAS at post-intervention in each session (S1, S3). In addition, the ODI and TSK were administrated at 2 follow-ups (2 weeks and 1 month after the last S3 session). The psychometric properties of these scales and questionnaires in CLBP, such as validity, test-retest reliability and responsiveness are reported elsewhere (Chapman et al., 2011).

2.10. Data reduction and statistical analysis

The investigator responsible for data collection and extraction / analysis was not present during RPMS application and all data collected were codified so that he remained blinded to individual, group of allocation and time points until completion of analysis.

2.10.1. APA outcomes in focal movement task

The onset of activation for each muscle was determined by visual inspection. If this onset was difficult to identify, the first point at which EMG levels rose above background levels, by one standard deviation, and for at least 50 ms, was used. The average and standard deviation of EMG background levels was measured during the 500-ms epoch preceding the auditory tone (Hodges et al., 1996a).

Precisely, for the bilateral shoulder flexion task, the onsets of MF and ST activation (APAs) were both expressed relative to AD onset. ST APA was tested because previous studies described delayed activation in this muscle (Massé-Alarie et al., 2015), and because any improvement in a non-stimulated muscle could reflect changes in cerebral areas implied in the cognitive aspects of motor function. A multiple analysis of variance, with repeated measures ($ANOVA_{RM}$) using a mixed design and factors Group (RPMS vs. Sham) X Time (S1 vs. S3) X Period (Pre vs. Post) and Side (Right MF vs. Left MF) was applied on MF and ST APAs.

For the prone hip extension task, MF onset (APA) was expressed relative to ST onset. An $ANOVA_{RM}$ with factors Group X Time X Period X Side of effect (contralateral vs ipsilateral to hip extension) was then applied on MF APA.

2.10.2. Activation outcomes in forward bending task

MF EMG activity was extracted for three different phases of the trunk flexion/extension task: Flexion (FLX: mean of 200-ms epoch of maximal activation), Full Flexion (Full FLX: mean of 3-s activation) and extension (EXT: mean of 200-ms epoch with maximal activation). $ANOVA_{RM}$ using a mixed design

and factors Group (RPMS vs. Sham) X Time (S1 vs. S3) X Period (Pre vs. Post) and Side (Right MF vs. Left MF) was applied on the ratios EXT/Full FLX and FLX/Full FLX, both of which having previously been reported as decreased in CLBP (Alschuler et al., 2009). These ratios are also used to differentiate between pain-free people and people with CLBP (Alschuler et al., 2009, Neblett et al., 2013).

For the RPMS group only, a three-way $ANOVA_{RM}$ using a mixed design with factors Time (S1 vs. S3) X Period (Pre vs. Post) and Side stimulated (Stimulated vs. Non-stimulated) was additionally applied on APAs and MF activation outcomes to determine the influence of the side of stimulation.

2.10.3. TMS outcomes

Six TMS outcomes associated with MF were acquired for each participant: the AMT (% maximum stimulator outcome, MSO) reflecting the basic M1 excitability during tonic MF activity; the peak-to-peak amplitude of test MEP (μV) reflecing the volume of M1 cells synchronized by TMS and the synchronicity of descending volleys onto motoneurons; the amplitudes of the two different conditioned MEP (% test MEP) informing on the levels of SICI (ISI: 2 and 3 ms) and SICF; the duration of the EMG silent period (% test MEP amplitude) (Orth et al., 2004). The relative (% of test MEP) and the raw amplitude of the conditioned MEP of SICF was also tested since the validity and reliability of the relative conditioned MEP could have been contaminated by the high variability denoted

for this test MEP (elicited at 100% AMT). A three-way $ANOVA_{RM}$ with factors Group X Time X Period was applied on all TMS outcomes.

2.10.4. Questionnaire outcomes

A three-way $ANOVA_{RM}$ with factors Group X Time X Period was applied on the spontaneous pain. A two-way $ANOVA_{RM}$ with factor Group X Time (S1 vs. S3) was applied on spontaneous and mean pain, ODI, PSFS and TSK scores. An additional two-way $ANOVA_{RM}$ had to be done on spontaneous pain due to missing data for 3 people at post-S1. An ANOVA with factor Group X Time (S1, 2 weeks follow-up, 1 month follow-up) was also applied to ODI and TSK scores.

Contrast analyses of ANOVA (planned comparisons) tested where differences did lie. Pearson's correlation coefficients probed the link between changes of APAs, forward bending task, M1 function and pain, and initial values of outcomes, i.e. the existence of possible predictive factors of success of the intervention.

Significance level was set at $p<0.05$ for all tests. However, running multiple analyses increased the possibilities of type I error (false positive) and results close to significance should be interpreted with caution.

3. RESULTS

Characteristics were comparable at baseline (at pre-intervention for the first session) between RPMS and Sham groups (Table 1). Two participants, one in

each group, dropped out due to availability (Fig. 1). Thus, 19 participants completed the protocol (10 in RPMS group and 9 in Sham group). Due to technological issues in TMS testing, data from one participant was withdrawn (n=9 for TMS outcomes analysis in RPMS group) and SICI data were not properly collected thus were not analyzed. No adverse effects were reported.

3.1. Focal movement tasks

3.1.2. Earlier MF onset in Sham group at 1 week follow-up

In the bilateral shoulder flexion task, the $ANOVA_{RM}$ applied on MF APA detected a main effect of Time ($F_{(1, 17)}$ = 7.53; p=0.01; Fig. 2A) with significance only in Sham group presenting an earlier APA at S3 (1.4 ± 10.2 ms) compared to S1 (5.3 ± 12.4 ms; $F_{(1, 17)}$ = 9.041; p=0.008) and no change in RPMS group (S1: -1.3 ± 14.1 ms; S3: -2.7 ± 14.2 ms; Fig 2A).

3.1.2. Earlier ST onset in RPMS group at 1 week follow-up

$ANOVA_{RM}$ applied on ST APA detected a Time X Group interaction ($F_{(1, 17)}$ = 5.22; p=0.03), with earlier ST APA at S3 (7.6 ± 24.5 ms) than at S1 (16.3 ± 22.3 ms) for the RPMS group only ($F_{(1, 17)}$ = 8.53; p=0.009; Fig. 2B). A Period X Group interaction was also detected for ST APA ($F_{(1, 17)}$ = 4.55; p=0.048; Fig. 2B) with ST APA systematically and close-to-significantly earlier at post-intervention (9.0 ± 25.0 ms) than at pre-intervention (14.8 ± 21.5 ms) for RPMS group only ($F_{(1, 17)}$ =

4.01; p=0.055). No other effects were detected. No effect was detected for MF APA in the unilateral hip extension task.

(Insert Fig. 2 near here)

3.2. Forward bending task

3.2.1. Increase of MF ratio (FLX / Full FLX) in RPMS group at 1 week follow-up

The $ANOVA_{RM}$ detected a main effect of Time for the FLX / Full FLX ratio ($F_{(1, 17)}$ = 5.64; p=0.03). Fig. 3A shows however that, in RPMS group only, the ratio was increased at S3 (857.2 ± 689.8 %) compared to S1 (623.9 ± 526.1 %; $F_{(1, 17)}$ = 5.26; p=0.03). The ratio was higher at pre-intervention in S3 (801.1 ± 550.3 %) than at pre-intervention in S1 (585.0 ± 461.1 %; $F_{(1, 17)}$ = 5.78; p=0.03) and the increase was close to significance at post-intervention in S3 (913.2 ± 876.9 %) as compared to post-intervention in S1 (662.9 ± 646.8 %; $F_{(1, 17)}$ = 4.41; p=0.051).

3.2.2. Increase of MF ratio (EXT / Full FLX) in RPMS group at 1 week follow-up

Also, the $ANOVA_{RM}$ detected a main effect of Time for the EXT / Full FLX ratio ($F_{(1, 17)}$ = 6.67; p=0.02). Fig. 3B shows however that, in RPMS group only, the ratio was increased at S3 (1706.9 ± 1384.2 %) compared to S1 (1297.8 ± 1214.8 %; $F_{(1, 17)}$ = 7.01; p=0.02). The ratio was higher at pre-intervention in S3 (1620.0 ± 1226.3 %) than at pre-intervention in S1 (1280.1 ± 1202.8%; ($F_{(1, 17)}$ = 6.46; p=0.02). It was higher at post-intervention in S3 (1793.8 ± 1595.1 %) than at post-intervention in S1 (1315.5 ± 1283.6 %; $F_{(1, 17)}$ = 6.70; p=0.02). No other effects were detected in RPMS group. Sham yielded no effect (p>0.05).

3.2.3. Increase MF ratio (EXT / Full FLX) on the stimulated side in RPMS group at 1 week follow-up

Fig. 3C shows the $ANOVA_{RM}$ results for the comparison between the stimulated and non-stimulated sides in RPMS group. A main effect of Time ($F_{(1, 9)}$ = 6.74; p=0.03) and a Time X Side interaction ($F_{(1, 9)}$ = 5.68; p=0.04) were detected for the EXT / Full FLX ratio. Planned comparisons showed that the ratio was increased on the stimulated side at S3 (1790.6 ± 1435.4 %) compared to S1 (1246.2 ± 1151.6 %; $F_{(1, 9)}$ = 7.10; p=0.03) and on the non-stimulated side at S3 (1623.2 ± 1354.6 %) compared to S1 (1349.4 ± 1285.9 %; $F_{(1, 9)}$ = 5.22; p=0.048).

For the stimulated side only, the ratio was higher at pre-intervention in S3 (1802.7 ± 1423.0 %) than at pre-intervention in S1 (1252.2 ± 1152.2 %; $F_{(1, 9)}$ = 5.57; p=0.043) and higher at post-intervention in S3 (1778.6 ± 1457.6 %) than at post-intervention in S1 (1240.2 ± 1182.8 %; $F_{(1, 9)}$ = 8.30; p=0.02). No other effects were detected for the EXT / Full FLX ratio, and none were found for the FLX / Full FLX ratio.

(Insert Fig. 3 near here)

3.3. TMS outcomes

3.3.1. Increase of SICF in RPMS group at 1 week follow-up

The three-way $ANOVA_{RM}$ detected a Time X Group interaction for the raw conditioned MEP amplitude of SICF paradigm ($F_{(1, 15)}$ = 5.21; p=0.04; Fig. 4).

Planned comparisons showed a close-to-significance increase of MEP amplitude at S3 (70.9 ± 43.4 µV) compared to S1 (49.1 ± 19.7 µV) in RPMS group only ($F_{(1, 15)}$ = 4.41; p=0.053). The three-way $ANOVA_{RM}$ applied on AMT showed a main effect of Period with a decrease of AMT from pre- to post-intervention when both groups were pooled ($F_{(1, 16)}$ = 7.21; p=0.02). No other effects were detected in TMS outcomes (Table 2).

(Insert Fig. 4 and Table 2 near here)

3.4. Questionnaires

Table 2 presents the questionnaires' scores at specific time points.

3.4.1 Acute and long-term decrease of spontaneous pain in RPMS group

The three-way $ANOVA_{RM}$ detected a close-to-significant Time X Group X Period interaction ($F_{(1, 14)}$ = 4.48; p=0.053) with a decrease of spontaneous pain in the RPMS group at post-intervention in S1 ($F_{(1, 14)}$ = 4.96; p=0.04) and pre-intervention in S3 ($F_{(1, 14)}$ = 8.27; p=0.01), as compared to pre-intervention in S1. In support, the two-way $ANOVA_{RM}$ detected a significant Time X Group interaction ($F_{(1, 17)}$ = 7.63; p=0.01) with a decrease of spontaneous pain level at pre-intervention in S3 (11.6 ± 10.1) as compared to pre-intervention in S1 (27.9 ± 20.6) in RPMS group only ($F_{(1, 17)}$: 10.98; p=0.004; Fig. 5A). Sham yielded no effect.

3.4.2. Decrease of average pain in RPMS group at 1 week follow-up

The two-way $ANOVA_{RM}$ detected a main effect of Time ($F_{(1, 17)}$ = 10.41; p=0.005) with a decrease of average pain from S1 to S3 which was significant in RPMS group ($F_{(1, 17)}$ = 6.11; p=0.02) and close-to-significance in Sham group ($F_{(1, 17)}$ = 4.41; p=0.051).

3.4.2. Decrease of disability (ODI and PSFS) in RPMS group

The two-way $ANOVA_{RM}$ detected a main effect of Time ($F_{(1, 17)}$ = 19.63; p=0.0004) but with ODI scores decreased only in RPMS group between S1 and S3 ($F_{(1, 17)}$ = 20.86; p=0.0003; Fig. 5C). $ANOVA_{RM}$ also detected a main effect of Time at two weeks follow-up ($F_{(1, 15)}$ = 8.00; p=0.01) and one month follow-up ($F_{(1, 17)}$ = 5.99; p=0.03), both compared to S1, but with ODI scores significantly decreased in RPMS group only between S1 and one month ($F_{(1, 17)}$ = 6.30; p=0.02; Table 3). Of note, one Sham-group participant washed-out the effect of exercise and had an increase of +20 points for ODI score at one month follow-up.

The two-way ANOVA detected a main effect of Time ($F_{(1, 17)}$ = 8.14; p=0.01) with an increase of PSFS score in RPMS group only ($F_{(1, 17)}$ = 11.06; p=0.004; Fig. 5D). PSFS scores were higher in RPMS group than in Sham at S3 ($F_{(1, 17)}$ = 11.06; p=0.004) and not different at S1 (p>0.05).

No effect was detected for TSK score.

(Insert Fig. 5 and Table 3 near here)

3.5. Correlations between outcomes

In RMPS group only, Pearson's correlation found that the S1-to-S3 changes of the average pain (r= -0.86; p=0.003) and PSFS scores (r=0.86; p=0.003; Fig. 6A-B) were both correlated with the AMT measured at baseline (i.e. at pre-intervention in S1). These correlations suggest that the participants with higher AMT at pre-intervention in S1 (i.e. lower M1 excitability) had larger decrease of average pain and larger increase of functional capacity scores following the combination of RPMS with motor training. In the sham group, the variations of clinical outcomes from S1 to S3 were not correlated with AMT.

(Insert Fig. 6 near here)

4. DISCUSSION

This original study tested how the combination of RPMS with motor training of MF muscle in CLBP influenced M1 function, spine motor control and pain as compared to the combination of sham stimulation with motor training. The findings support the initial hypothesis that RPMS combination with motor training ought to provide more benefits than motor training alone (sham combination). Earlier onset of ST muscle after one week of training were detected in the RPMS group for the bilateral shoulder flexion task, along with MF activation during forward bending, up-regulation of M1 circuits of corticospinal facilitation, and decrease of pain and of disability that persisted one month later. Potential mechanisms related to pain processing and functional plasticity are addressed to better understand the improvement obtained in RPMS group.

4.1. Reduction of pain and disability

The after-effects of RPMS administration in CLBP is not well known and only two studies in literature reported some changes after one RPMS session in CLBP (Lo et al., 2011, Massé-Alarie et al., 2013). Our present results showed a significant decrease of pain at post-intervention in the first session and persistence over one week while Sham did not yield any influence. These effects are stronger than in the study of Lo et al. (2011), where pain, even still decreased 4 days after the stimulation, had returned closer to baseline (Lo et al., 2011). Thus, the present study on pain reduction (VAS score) and function improvement (ODI & PSFS scores) over one week provides ancillary evidence that multiple RPMS sessions (at least 3 sessions) combined with motor training can contribute to maintain the acute reduction of pain (obtained at the first session) across several days. The fact that these effects were not observed in the Sham group with however the same motor training, suggests that the combination of RPMS with training could (1) potentiate practice-dependent plasticity mechanisms, (2) boost the effect with multiple sessions and/or (3) influence the endogenous pain system. This may explain the larger functional gains obtained in the RPMS group. It can be hypothesized that the increased number of proprioceptive stimuli (RPMS) and the combined influence of RPMS and training on brain plasticity and motor learning (Massé-Alarie et al., 2013) may have contributed to reduce pain and ease motor learning during training. This is in line with recent studies reporting the impact on pain and brain reorganization of the combination of two interventions that influenced M1 plasticity (Boggio et al., 2009, Schabrun et al.,

2014). Thus, how RPMS combination with motor training drove M1 plasticity in our study should be addressed.

4.2. Influence on M1 plasticity

Only the TMS outcome of SICF was influenced by the combination of RPMS and training at 1 week follow-up. However, due to the use of raw peak-to-peak amplitudes of the conditioned MEP (to avoid variability of SICF expression relative to test MEP elicited at 100% AMT, see Methods), the interpretation of this result should be taken with caution and changes of MF SICF under RPMS and training should be replicated in future studies. The rationale for using RPMS as an adjunct in motor training is that RPMS can influence synaptic plasticity in M1 circuits and frontal-parietal areas to favour motor learning and promote motor control (Struppler et al., 2007a, Massé-Alarie et al., 2011, Massé-Alarie et al., 2013). In RPMS group, the increase of SICF at S3 could reflect the up-regulation of synaptic mechanisms involved in M1 facilitation. Indeed, the SICF mechanisms of synaptic facilitation are regulated in M1 circuits by inhibitory connections from GABAergic circuits (Peurala et al., 2008, Shirota et al., 2010). Thus, an increase of SICF suggests a decrease of M1 inhibition. In support, it was shown that RPMS combined with skilled motor practice for TrA/IO training released M1 from local inhibition (Massé-Alarie et al., 2012). Also, it is acknowledged that such M1 disinhibition favours the induction of plasticity by unmasking of synapses and increase of synaptic strength (Jacobs et al., 1991, Hess et al., 1994, Liepert, 2006). Thus, the increase of SICF, potentially

paralleled by M1 disinhibition, could reflect plastic mechanisms that may have contributed to motor learning and may have enhanced MF motor control.

Unexpectedly, no change of TMS outcomes was detected immediately after the intervention in the first session of RPMS-training (RPMS group). A first assumption could be that the combination of two interventions that influence brain plasticity can cancel the immediate (but not long-term) neuroplastic influence that each intervention could have, owing to the mechanisms of homeostatic metaplasticity where increase of excitability in brain due to a first stimulation can reverse the influence of a second stimulation (Gamboa et al., 2010, Schabrun et al., 2013a). Also, acute changes of TMS outcomes may have been missed given that we tested MEP amplitude at 120% AMT (mean of 59.8 ± 6.3% MSO) whereas it was shown that higher stimulation intensities (80-90% MSO) were required to detect modulation of M1 excitability for the paravertebral muscles (Tsao et al., 2011c). Furthermore, the optimal timing to influence M1 excitability and corticospinal function during one week of training is not known and other changes could have occurred after the first session and returned to baseline within a few days of practice. The possibility that RPMS did not influence M1 but other structures in brain and spinal circuits must also be considered. Therefore, further studies are warranted to determine more precisely the mechanisms (and their timing) of the combined influence of RPMS and training on plasticity related to MF M1 area. Also, to validate that the combination of RPMS with motor training potentiated the gains beyond those likely obtained in

each intervention alone, future studies are warranted to investigate the influence of RPMS alone on M1 plasticity and motor control of multifides in CLBP.

4.3. Improvement of motor control

The pain decrease still present at one week was likely the result of the combined influence of RPMS and motor training, i.e. an intertwined action on motor control and pain modulation. For example, the increase of MF activation ratios during forward bending reflects a higher MF activation during the concentric and eccentric phases of the task and a better relaxation in full flexion. These ratios are decreased in CLBP (Alschuler et al., 2009) and their increase could reflect a better motor control of spine during functional activities, in likely relation to the up-regulation of the circuits of M1 facilitation (SICF). Therefore, the improvement of spine motor control may have efficiently protected spine from microtraumas in day-to-day tasks, thus maintaining pain level at a decreased level over the week of the training at home.

RPMS on its own could have improved motor control by activating central areas involved in motor planning. A previous study from our group reported a delay in the onset of ST APA in CLBP (Massé-Alarie et al., 2015) and surprisingly, APA was fastened by RPMS administration in the present study, i.e. with no obvious relation to the practice of MF activation. Of note, ST onset was not delayed at baseline (at pre-intervention in S1) in our participants (both groups) as compared to pain-free participants enrolled in a recent study (Massé-Alarie et al., 2015). It is thus still unclear whether earliness of ST onset in bilateral flexion task after

one week in the RPMS group actually represents an improvement of APA programming. For instance, like mechanical tendon vibration of triceps surae (Fujiwara et al., 2003), RPMS could have changed the perception of body in space (e.g. forward leaning) thus modifying the posture and requiring postural adaptation (earlier ST) to avoid forward fall. Nevertheless, RPMS after-effects are deemed to be related to an influence on the central processing of sensory inputs (Struppler et al., 2007a). For example, it was shown that RPMS over wrist extensors generated a massive flow of proprioceptive inputs that activated the frontal-parietal pathways involved in perception and sensorimotor planning (Struppler et al., 2007a). It follows that, in our study, an increased availability of proprioceptive inputs (usually decreased in CLBP) could have contributed to the selection of more appropriate strategies of motor control and APA in postural tasks. Interestingly, only the sham group presented with earlier MF onset at 1 week of follow-up. This result in the sham group is consistent with previous studies that showed APA improvement with voluntary and isometric contraction of MF muscle (Tsao et al., 2007, Massé-Alarie et al., 2016a). Why RPMS has not influenced MF APA could be due to the earlier APA at baseline (-1.6 ± 11.8 ms) as compared to the sham group (5.9 ± 15.2 ms; Fig. 2A), i.e. a likely result of randomization that may have precluded any improvement in RPMS group. Thus, it seems that APA can be influenced differently owing to the type of physical exercises (training) or neurostimulation techniques (to influence neuroplasticity) and this will have to be considered in the development of future guidelines in

rehabilitation (Tsao et al., 2007, Tsao et al., 2010a, Tsao et al., 2010b, Chipchase et al., 2011, Massé-Alarie et al., 2016a).

4.4. Possible influence of RPMS on the mechanisms of pain modulation

Altogether, the present findings suggest that RPMS combination with training induced an acute and persistent decrease of pain that likely eased physical practice at home over the week and lead to long-term improvements of motor control and functional capacity, and reduction of disability. However, it is noteworthy that pain reduction in RPMS group at post-intervention in the first session and at 1 week follow-up could result from different mechanisms. For example, given the absence of MF motor changes at post-intervention in S1, the acute pain reduction could have been related to the immediate activation of descending anti-nociceptive pathways and spinal inhibition mechanisms, rather than a change of corticomotor control of spine. The likely peripheral mechanisms of RPMS action should thus be tested in the future along with central processing.

One striking result is however the association between baseline AMT and improvement of pain and disability in RPMS group. Participants with CLBP presenting with higher AMT at baseline, i.e. lower excitability within M1 circuits at pre-intervention in S1, did self-report larger improvement of pain and of functional capacity than participants with higher M1 excitability at baseline. It is possible that people with CLBP who will benefit more from RPMS-induced proprioceptive inputs to the sensorimotor cortex are those with impairments of proprioceptive and multisensory integration following reorganization of cortical sensory maps

(Flor et al., 1997), thus those with lower M1 excitability given the intertwined excitability between sensory and motor maps (Schabrun et al., 2012b, Schabrun et al., 2013b). This hypothesis has to be tested in future studies.

4.5. Methodological considerations

The change of ODI score at S3 in RPMS group (+ 6 points) is considered a minimum difference with clinical significance (Fritz et al., 2001). Thus, our results suggest that RPMS combination with training can induce changes of clinical importance, even if the study was not specifically designed to detect pain/disability differences. Although surface electrodes were carefully positioned over MF muscle at L4-L5 level, cross-talk from adjacent paravertebral muscles could have been recorded, especially in MF response to TMS (Tsao et al., 2011a). Therefore, studies using fine-wire electrodes are warranted to delineate whether changes of TMS outcomes in RMPS group are specific to MF muscles. The use of the raw conditioned MEP amplitudes to interpret SICF data was justified in SICF by the fact that the high variability of the test MEP elicited at 100% AMT (very small amplitudes in MF muscle) could have substantially impacted the SICF ratio (conditioned MEP amplitudes expressed in % of the test MEP). Therefore, a test TMS at 100% AMT for probing SICF mechanisms of the MF muscle could be replaced in future studies by a test TMS at 120% AMT or by monitoring a specific MEP amplitude by a stringent window of acceptance (e.g., 100 µV) (Ziemann et al., 1998). Of note, 9 out of the 10 participants in RPMS

group guessed their group of allocation, whereas only 4 out of 9 in Sham group (Table 1). The difficulty to blind RPMS group is thus a concern owing to the strong contractions elicited and cutaneous tingling sensation. Finally, our sample of participants was not homogeneous, i.e. was not recruited according to a specific motor dysfunction. This decision was based on the evidence that even heterogeneous groups of CLBP present with MF atrophy, APA delays and abnormal motor patterns during trunk movement (MacDonald et al., 2009, Beneck et al., 2012). Nonetheless, most participants (16 out of 21) presented with asymmetric MF activation (in term of spatial and temporal contraction), thus received RPMS over a muscle whose motor control might have been impaired.

4.6. Conclusion

This study showed the benefits of RPMS combination with motor training on pain, disability, function and lumbopelvic spine motor control one week after the onset of protocol, as compared to motor training alone and in relation to M1 excitability and plasticity. Clinically, RPMS seems a promising adjuvant in CLBP to potentiate the gains of physical practice on lumbopelvic spine control and pain that are intertwined in any daily life activity; therefore, more evidence-based data should be collected. Also, the influence of RPMS alone (i.e. without motor training) on pain and sensorimotor systems should be more thoroughly tested for identifying the neural mechanisms underlying the improvements observed.

Conflict of Interest Statement

None.

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FIGURE LEGENDS

Fig. 1. Flowchart of the study design. CLBP: chronic low back pain; RPMS: Repetitive peripheral magnetic stimulation combined with motor training (multifide muscles); Sham: Sham stimulation combined with motor training; data acquisition at pre- and post-intervention: corticomotor outcomes and anticipatory postural activation of multifide muscles.

Fig. 2. Anticipatory postural adjustments. Mean onset (± SD) of (**A**) MF and (**B**) ST muscles activation relative to AD onset in bilateral shoulder flexion task in RPMS and Sham groups at pre- and post-intervention for the first session (S1: upper part of each graph) and the third session (S3 i.e. 1 week follow-up: lower part). MF: multifidus; ST: semi-tendinosus; RPMS: Repetitive peripheral magnetic stimulation combined with training; Sham: sham stimulation with training. * $p<0.05$

Fig. 3. Ratios of MF EMG (± SD) activity during forward bending. (**A**) FLX / Full FLX and (**B**) EXT / Full FLX in both RPMS and Sham groups; (**C**) EXT / Full FLX in RPMS group only on the stimulated and non-stimulated sides. FLX / Full FLX: ratio during the flexion on full flexion; EXT / Full FLX: ratio during the extension on full flexion; RPMS: Repetitive peripheral magnetic stimulation combined with training; Sham: sham stimulation with training; S1: first session; S3: third session, i.e. 1 week follow-up; pre, post: before, after intervention. * $p<0.05$

Fig. 4. Short-interval intracortical facilitation (SICF). Means of conditioned MEP amplitude (± SD) at pre- and post-intervention for the first session (S1) and the

third session (S3, i.e. 1 week follow-up) in both RPMS and Sham groups. MEP: motor evoked potential; RPMS: Repetitive peripheral magnetic stimulation combined with training; Sham: sham stimulation with training; S1: first session; S3: third session i.e. 1 week follow-up; pre, post: before, after intervention.

Fig. 5. Clinical scores at sessions 1 and 3 in both RPMS and Sham groups for (**A**) Mean spontaneous pain intensity (± SD) reported at onset of assessment; **(B**) Mean average pain intensity (± SD) in the two days preceding the assessment; (**C**) Mean Oswestry disability index (ODI, ± SD); (**D**) Mean Patient-specific functional score (PSFS, ± SD). RPMS: Repetitive peripheral magnetic stimulation combined with training; Sham: sham stimulation with training; S1: first session; S3: third session i.e. 1 week follow-up; pre, post: before, after intervervention. * $p<0.05$; ** $p<0.01$; ***$p<0.0001$

Fig. 6. Correlations between the value of AMT at baseline (at pre-intervention for the first session) and changes (△ : from first to third session) of (**A**) mean average pain and of (**B**) mean PSFS score in the RPMS group. Note that in Fig. 6A TMS data from one participant was withdrawn (n=9 points); in Fig. 6B, three participants had superimposed coordinates (AMT=51, PFSF=3; n=7 points visible). AMT: active motor threshold; PSFS: Patient-specific functional score; MSO: maximal stimulator output; RPMS: Repetitive peripheral magnetic stimulation combined with training

Table 1. Characteristics of participants and groups (mean ± SD)

Groups	RPMS	Sham	*p*
Participants (n)	11	10	-
Gender (M:F)	6 :5	5 : 5	1.00[a]
Age (years)	33.2 ± 10.8	42.1 ± 17.2	0.18
Handedness (Right : Left)	9 : 2	9 : 1	1.00 [a]
Height (cm)	164.4 ± 10.6	167.9 ± 5.5.	0.35
Weight (kg)	73.7 ± 19.8	68.6 ± 11.7	0.48
BMI (kg/m²)	26.9 ± 5.4	24.3 ± 3.6	0.20
GPAQ (METS)	4047.3 ± 2844.4	2638.0 ± 1860.9	0.19
Sedentarity (h)	7.9 ± 3.3	9.9 ± 3.6	0.20
Pain duration (months)	56.7 ± 29.3	130.8 ± 126.2	0.10
Voluntary contraction (Asymmetric : Symmetric)	8 : 3	8 : 2	1.00[a]
Stimulated side (Right : Left)	7 : 4	5 : 5	0.67[a]
Exercise adherence (%)	91.4	84.7	0.29
Blinding (matched : unmatched)	9 : 1	4 : 5	0.14[a]

BMI; Body mass index; GPAQ: Global Physical Activity Questionnaire; ODI: Oswestry disability index; PSFS: Patient specific functional scale; TSK: Tampa Kinesiophobia Scale; mo: months; METS; metabolic equivalent.
p : Bilateral unpaired t-test;
[a] *Bilateral Fisher's exact test.*

Table 2. TMS outcomes

RPMS group	Pre-S1	Post-S1	Pre-S3	Post-S3
AMT (%MSO)	50.7 ± 5.8	49.8 ± 6.0	49.7 ± 7.5	48.7 ± 6.9
MEP amplitude (μV)	61.3 ± 25.3	63.1 ± 28.9	70.6 ± 50.8	74.4 ± 49.3
SP/MEP (%)	92.5 ± 59.1	90.6 ± 49.1	87.5 ± 40.0	90.8 ± 50.8
SICF (% test MEP)	175.7 ± 73.9	145.5 ± 57.7	183.5 ± 59.6	206.6 ± 87.8
SICF (μV)	56.0 ± 23.5	47.4 ± 20.7	73.0 ± 43.5	67.5 ± 38.9
Sham group	Pre-S1	Post-S1	Pre-S3	Post-S3
AMT (%MSO)	49.9 ± 6.3	49.1 ± 6.0	50.7 ± 8.1	49.3 ± 6.7
MEP amplitude (μV)	65.6 ± 42.8	64.7 ± 45.6	56.2 ± 28.0	61.5 ± 31.0
SP/MEP (%)	152.2 ± 100.6	127.9 ± 95.2	137.5 ± 59.5	143.9 ± 87.5
SICF (% test MEP)	174.1 ± 49.7	187.6 ± 73.2	181.4 ± 72.6	201.8 ± 92.2
SICF (μV)	55.9 ± 38.3	55.2 ± 36.1	48.4 ± 27.2	50.9 ± 26.5

AMT: active motor threshold; MEP: motor evoked potential; SP: silent period; SICF: short-interval intracortical facilitation; S1: first session; S3: third session; pre, post: before, after training; GLOB: global exercise; ISOM: isometric exercise.

Table 3. Changes in questionnaire over time

RPMS	S1	S3	2 w post-S3	1 mo post-S3
Spontaneous pain[a] (/10)	27.9 ± 20.6	11.6 ± 10.1*		
Average pain (/10)	36.6 ± 18.5	19.6 ± 14.0*		
ODI (%)	17.6 ± 8.4	11.6 ± 9.8*	14.5 ± 14.7	10.0 ± 8.2 ˣ
PSFS (/30)	15.8 ± 5.1	21.2 ± 3.9*		
TSK (/68)	40.0 ± 8.4	38.1 ± 9.4	39.1 ± 10.9	37.7 ± 9.6
Sham	**S1**	**S3**	**2 w post-S3**	**1 mo post-S3**
Spontaneous pain[a] (/10)	16.6 ± 9.8	20.0 ± 15.9		
Average pain[b] (/10)	34.4 ± 19.8	19.2 ± 10.5		
ODI (%)	21.1 ± 7.4	18.7 ± 9.0	17.0 ± 10.3	18.0 ± 14.4
PSFS (/30)	15.2 ± 4.2	16.6 ± 4.1		
TSK (/68)	36.3 ± 4.7	37.3 ± 6.0	38.3 ± 9.4	35.4 ± 8.6

ODI: Oswestry disability index; PSFS: Patient specific functional scale; TSK: Tampa Scale of Kinesiophobia; w: week; mo: month.

[a] *Measured in sitting (S1 refer to pre-S1; S3 refer to pre-S3)*

[b] *Mean pain level of the last 2 days.*

* Significant difference between S1 and S3;

ˣ Significant difference between S1 and 1 month post-S3

Figure 1

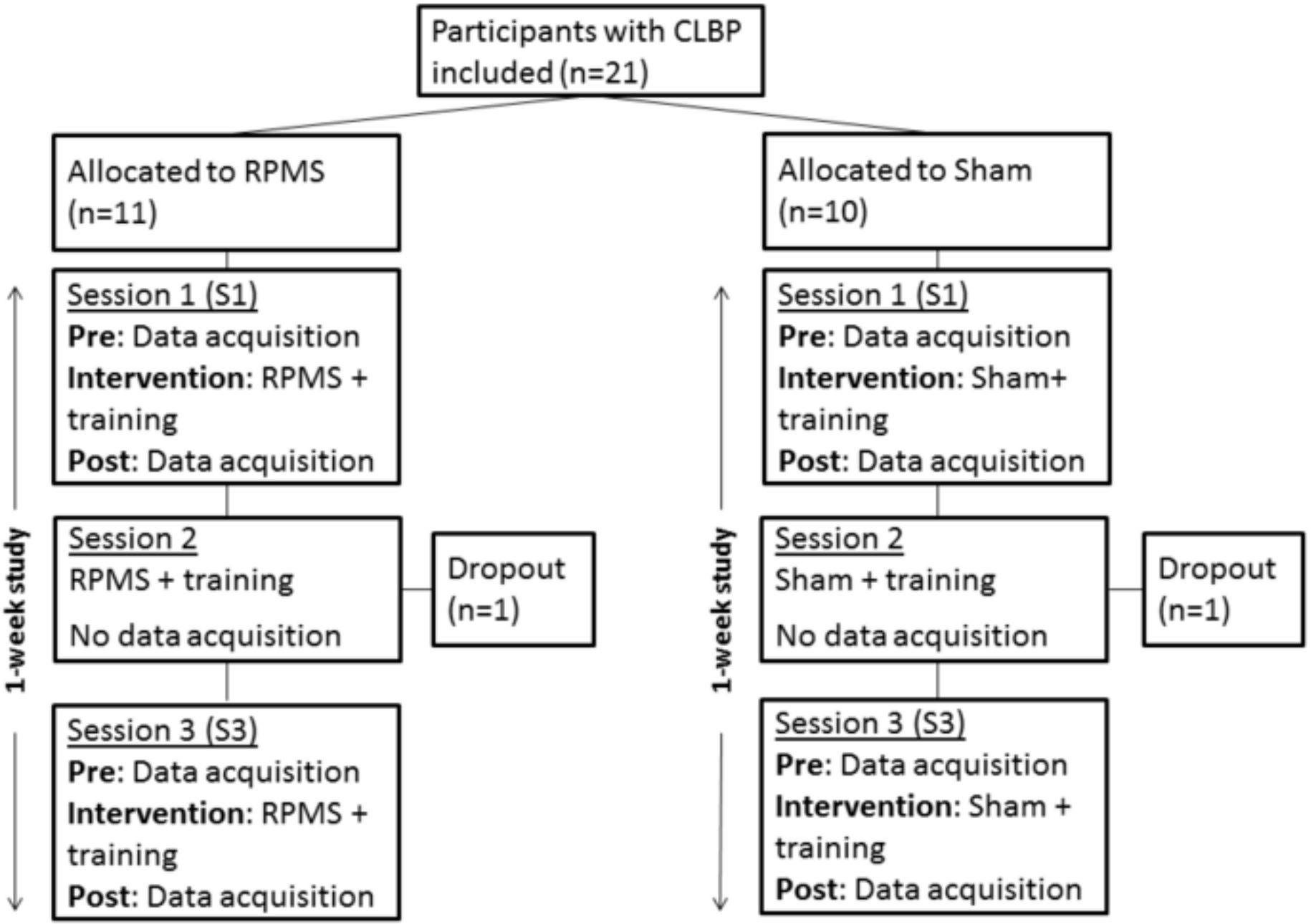
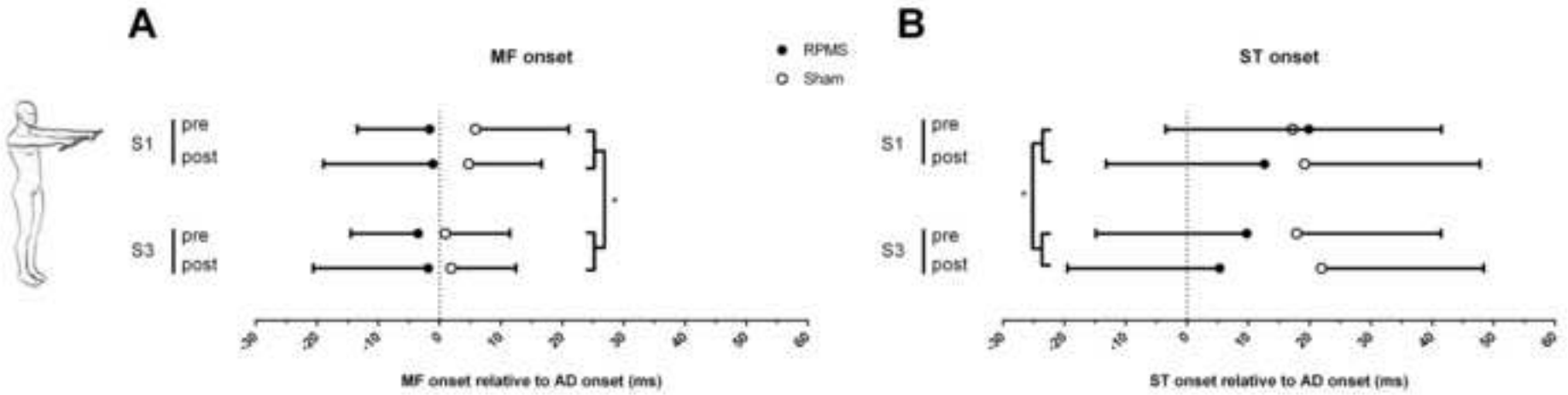


Figure 2



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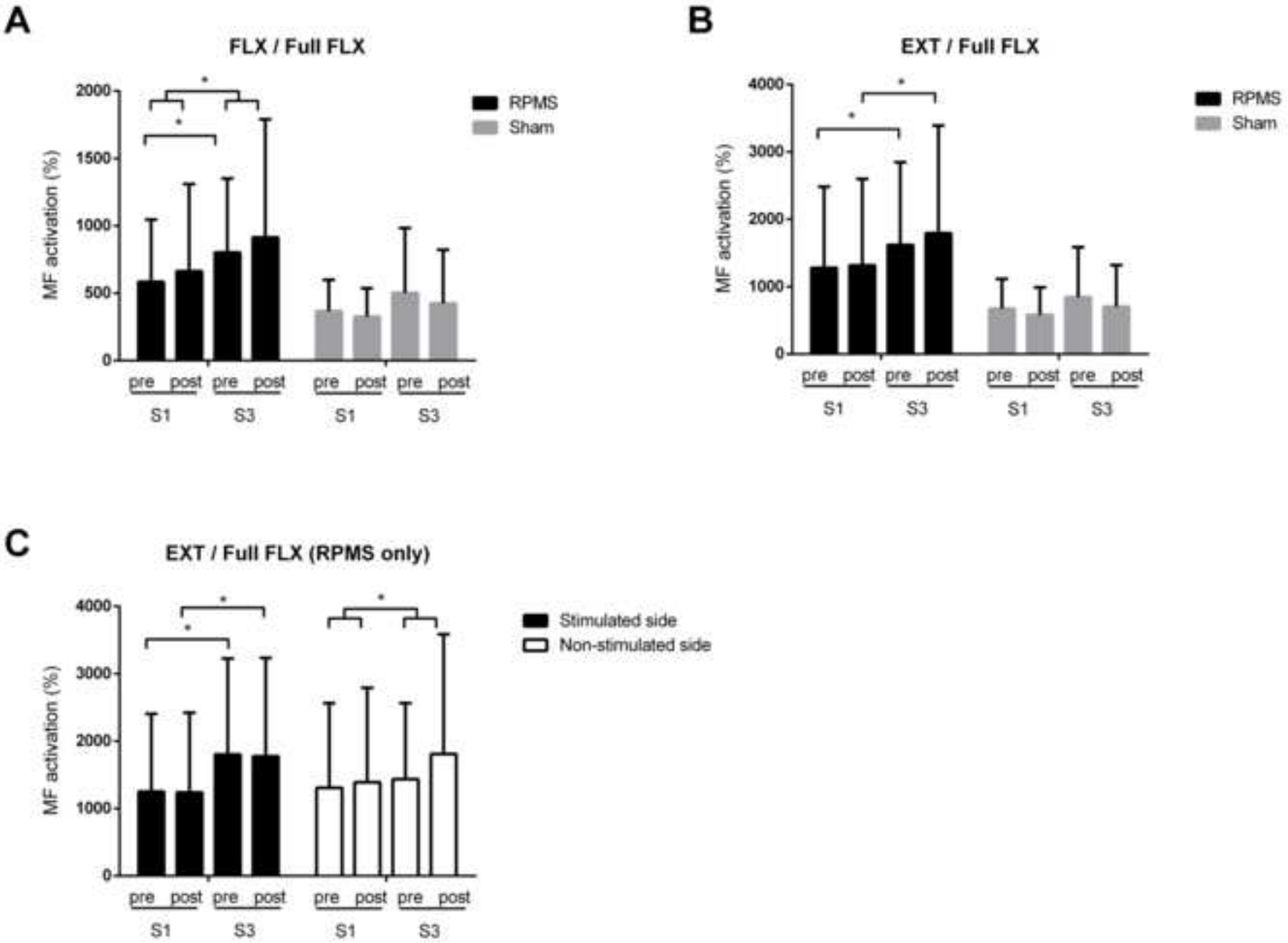

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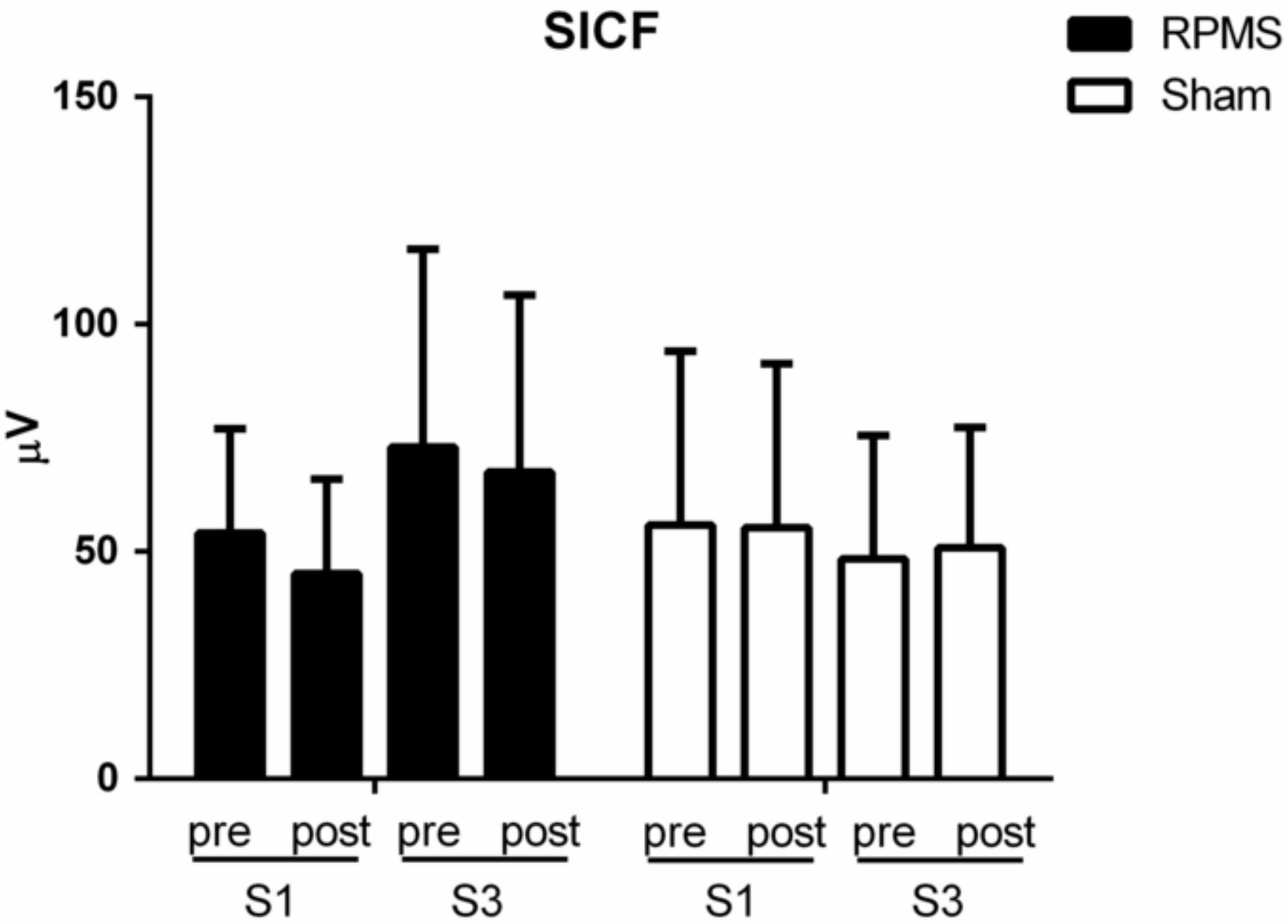

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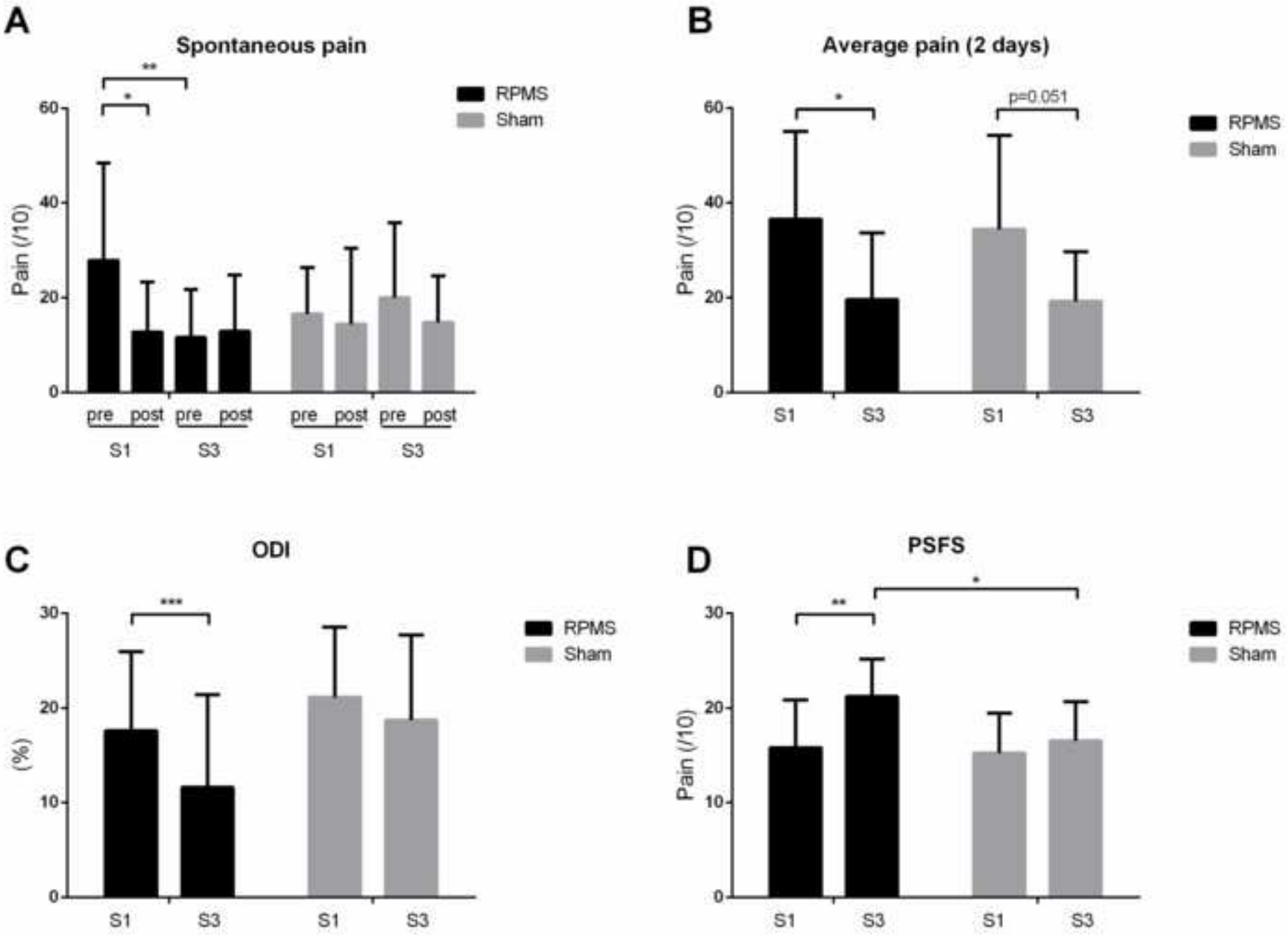

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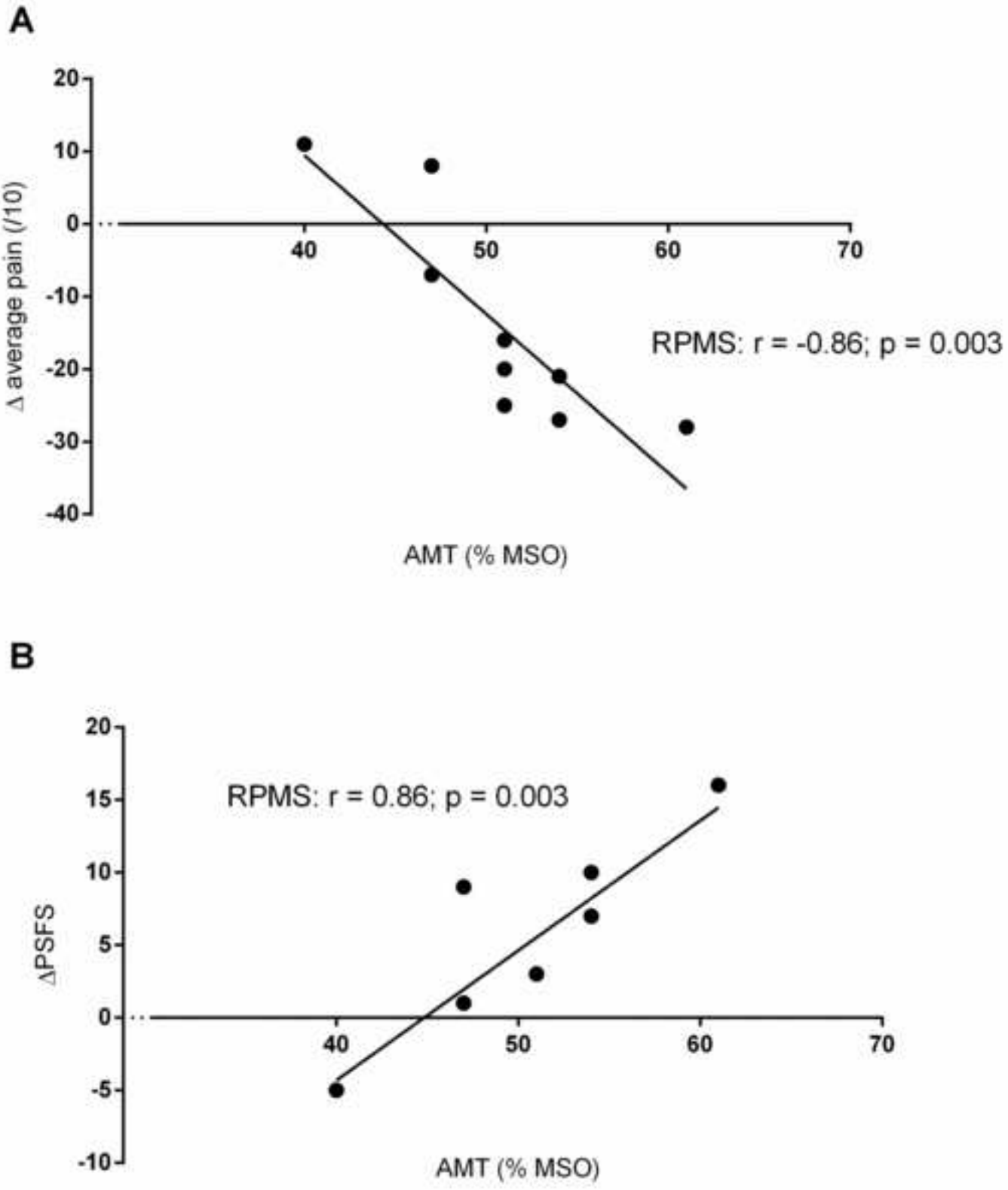

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Effects of Repetitive Peripheral Magnetic Stimulation on Patients With Acute Low Back Pain: A Pilot Study

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Objective To investigate the effects of real repetitive peripheral magnetic stimulation (rPMS) treatment compared to sham rPMS treatment on pain reduction and functional recovery of patients with acute low back pain.

Methods A total of 26 patients with acute low back pain were randomly allocated to the real rPMS group and the sham rPMS group. Subjects were then administered a total of 10 treatment sessions. Visual analogue scale (VAS) was assessed before and after each session. Oswestry Disability Index (ODI) and Roland-Morris Disability Questionnaire (RMDQ) were employed to assess functional recovery at baseline and after sessions 5 and 10.

Results Real rPMS treatment showed significant pain reduction immediately after each session. Sustained and significant pain relief was observed after administering only one session in the real rPMS group. Significant functional improvement was observed in the real rPMS group compared to that in the sham rPMS group after sessions 5 and 10 based on ODI and after session 5 based on RMDQ.

Conclusion Real rPMS treatment has immediate effect on pain reduction and sustained effect on pain relief for patients with acute low back pain compared to sham rPMS.

Keywords Acute low back pain, Repetitive peripheral magnetic stimulation, Pain reduction, Functional recovery

INTRODUCTION

Low back pain, one of the major causes of disability worldwide, is a very common reason for seeking medical care [1]. Low back pain can be classified based on duration as follows: (1) acute back pain that lasts less than 6 weeks; (2) sub-acute back pain lasting from 6 to 12 weeks; and (3) chronic back pain that persists for more

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than 12 weeks. Among these three types, acute low back pain (ALBP) generally demonstrates favorable prognosis with recovery rate ranging from 39% up to 90% within 6 weeks [2,3]. However, ALBP patients who seek medical care show an upper margin of moderate level of pain (i.e., average visual analogue scale [VAS] of 6.25) which causes disability (i.e., average Roland-Morris Disability Questionnaire [RMDQ] score of 13.04) [4]. Accordingly, appropriate pain control is required for ALBP patients. As a way to improve the pain and disability that ALBP patients experience, staying active is advised while bed rest is discouraged [5]. However, such advice can be hard to follow when one is in pain. Up to date, options that have shown proven effects for pain reduction with minimal adverse effects in ALBP patients are limited [2,6-10].

Repetitive peripheral magnetic stimulation (rPMS) is a non-invasive treatment method that can penetrate to deeper conductive structure with relatively painless stimulation. Of various studies conducted since 1995, no study has observed any adverse effects with the exception of certain participants reporting tight feelings within a tolearble range. Thus, rPMS can be considered as a treatment method with a high level of tolerance and safety. It has been demonstrated that rPMS has therapeutic effects on musculoskeletal pain [11]. However, no established guideline exists. Thus, further study is required.

Based on literature search, rPMS has been applied to chronic low back pain (CLBP) patients in four studies [12-15]. However, no study has observed its effects on ALBP patients. Therefore, the objective of this pilot study was to investigate clinical effects of rPMS on pain reduction and functional recovery in ALBP patients with a randomized controlled design.

MATERIALS AND METHODS

Subjects

Patients with ALBP occurring within the last 6 weeks who reported pain with VAS of 3 or higher were recruited. Magnetic resonance imaging study was performed if there was any possibility of a diagnosis other than acute lumbar sprain based on patient's symptoms, physical examination, and a lumber X-ray. Patients with age of 19 years or more who possessed linguistic and cognitive capabilities to explain the degree of pain were selected. Exclusion criteria were: (1) weakness in lower extremities due to lumbar radiculopathy or myelopathy, (2) lumbar fracture, (3) non-mechanical low back pain due to neoplasia, inflammatory arthritis, or infection, (4) pacemaker, (5) history of seizure, pregnancy, malignancy, or (6) history of lumbar surgery. None of participants in this study had any form of magnetic stimulation treatment previously. This study was approved by the Institutional Review Board of Hallym University Chuncheon Sacred Heart Hospital (No. 2017-12).

Methods

A total of 26 subjects were randomly allocated into real rPMS group and sham rPMS group using a block randomization program. Subjects were blinded to which group they would be allocated into. The purpose of this study was explained to subjects to determine how to perform rPMS treatment more effectively. Patients in the two groups had general physical therapy modality and medication concurrently with the intervention introduced through this study. Neuro MSL magnetic stimulator (MR Inc., Seoul, Korea) was used in this study. It is known that a round coil is more advantageous than a figure-8 coil for stimulating structures in a deep layer such as spinal roots and covering a larger area such as a paraspinal muscle group [11]. Thus, round coil suitable for treating low back pain was employed in this study. Stimulation site was determined based on patient's most tender point prior to the start of each treatment session. For patients in the real rPMS group, the coil was placed at a flat tangential orientation targeting the most painful lumbar region in prone position. This is the orientation that enables the coil to be positioned parallel to the body surface, thereby maximizing effects of magnetic stimulation applied to the target area. For patients in the sham rPMS group, the coil was applied at a transverse orientation to the most painful lumbar region in prone position. This is the orientation which positions the coil at a 90° angle to the body surface, thereby minimizing effects of magnetic stimulation applied to the target area [16].

Both groups underwent 10 sessions over a span of 2 weeks. Each session lasted 20 minutes and entailed an intermittent stimulation protocol consisting of 5 seconds of stimulation at a frequency of 20 Hz followed by 25 seconds of resting. The total number of stimuli over 20 minutes amounted to 4,000 times. The stimulus intensity level for the real rPMS group commenced at 20% of the

maximal stimulator output. It was gradually raised by 5%. The final stimulation intensity was determined at the maximum intensity level which induced sufficient contraction of the paraspinal muscle while still falling within tolerable range of the patient [11,17,18]. For the sham rPMS group, the stimulus intensity level was set at 5% of the maximal stimulator output to minimize magnetic stimulation. Both groups were exposed to identical clicking sound generated during each session. As in the real rPMS group, the coil directly touched the skin of patients in the sham rPMS group, thereby exposing them to similar sensation [3]. The application of rPMS coil to both groups of patients was conducted by experienced physical therapists with sufficient preliminary training on the application of rPMS before the study. Physical therapists applying the magnetic stimulation could not be blinded. Thus, their conversion with patients was limited for both groups in order to minimize their effects on patients. Authors were blinded to group allocation of patients.

Assessments

For the evaluation of back pain, VAS was used as the primary endpoint. Oswestry Disability Index (ODI) and RMDQ were employed as secondary endpoints. ODI is a tool that can evaluate functional impairment of a low back pain patient. It has a value of 0% to 100%, with higher value indicating higher level of disability. The validity of ODI has long been proven and its ability to discern levels of functional disability has been extensively documented [19]. RMDQ evaluates limitations in activities of daily living due to low back pain with 24 questions, with higher number of positive answers indicating more severe functional disability. The reliability and validity of RMDQ have been confirmed [20]. Each assessment was conducted via subjects completing questionnaires with assistance from an independent researcher who was blinded as to group allocation. VAS was evaluated before and after every session whereas ODI and RMDQ were assessed at the baseline and after sessions 5 and 10.

Statistical analysis

In normal distribution evaluation using Kolmogorov-Smirnov test and Shapiro-Wilk test, normality of either group was satisfied. Accordingly, statistical analysis was performed using the nonparametric method. Mann-Whitney U-test was used to compare the two groups for each session evaluated. Wilcoxon signed-rank test was employed to compare differences between pre-manipulation and post-manipulation. Courses of pain relief and functional recovery were analyzed by repeated-measures analysis of variance (ANOVA). Post-hoc analyses were undertaken using Bonferroni correction. Pearson correlation test was performed to assess changes in pain and disability. A p-value <0.05 was considered statistically significant. SPSS version 21.0 (IBM SPSS, Armonk, NY, USA) was used for all statistical analyses.

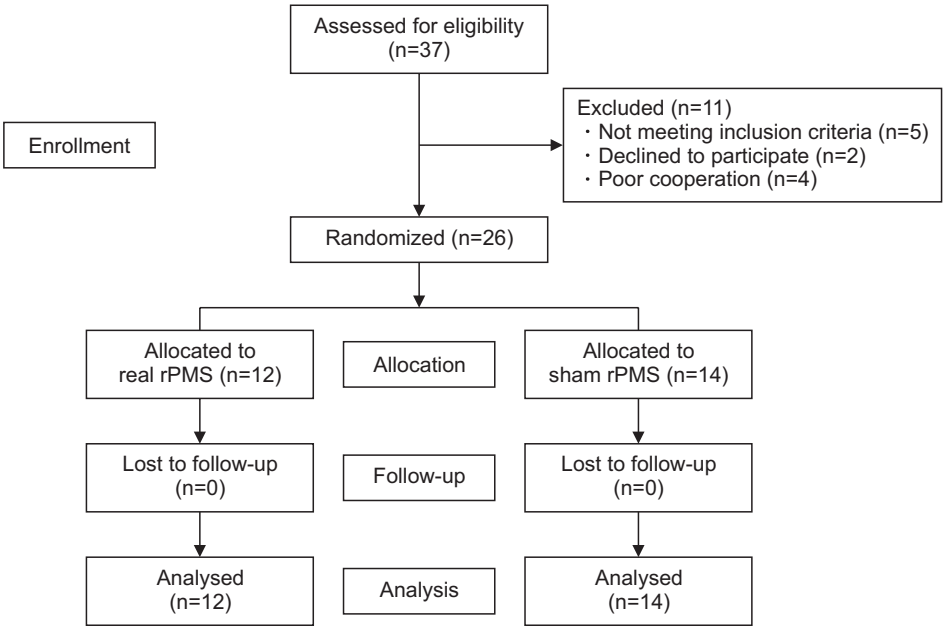

Fig. 1. Consort chart of the study design. rPMS, repetitive peripheral magnetic stimulation.

RESULTS

Baseline characteristics of subjects

In the present study, a total of 26 ALBP patients were enrolled, including 18 patients diagnosed with lumbar sprain and 8 patients diagnosed with lumbar herniated nucleus pulposus. Lumbar herniated nucleus pulposus was identified through magnetic resonance imaging study. Only those patients without any motor weakness were included in this study. Twelve and 14 patients were randomly allocated to the real rPMS group and the sham rPMS group, respectively. All subjects completed a total of 10 treatment sessions (Fig. 1). Baseline characteristics of subjects in the two groups are summarized in Table 1. There were no significant differences in baseline characteristics between the two groups.

Immediate effects of rPMS on ALBP

According to VAS results, significant pain reduction was observed after each session compared to VAS evaluated before each session in the real rPMS group, with average VAS gap (VAS after session – VAS before session) of -12.42±8.71. By contrast, subjects in the sham rPMS group showed marginal changes, with average VAS gap of -1.00±4.67. There was no significant change in VAS gap in any session for this group (Fig. 2). Mann-Whitney U-test was used to compare VAS gaps of each session between the two groups. Pain relief in the real rPMS group was found to be significantly greater than in the sham rPMS group for all sessions except session 9.

Persistent effects of rPMS on ALBP

Repeated-measures ANOVA showed significant VAS differences over the passage of time in both the real rPMS group and the sham rPMS group (baseline, after session

Table 1. Baseline characteristics of subjects

	Real rPMS group (n=12)	Sham rPMS group (n=14)	p-value
Age (yr)	52.50±21.45	51.21±17.98	0.869
Sex (male:female)	6:6	6:8	0.512
Height (m)	1.64±0.11	1.62±0.10	0.519
Body weight (kg)	67.06±15.24	63.31±11.64	0.485
BMI (kg/m^2)	24.5±4.23	23.94±3.17	0.705
Diagnosis (LS:LHNP)	8:4	10:4	0.563
VAS	63.75±14.64	66.07±12.28	0.705
ODI	50.98±10.70	51.87±8.86	0.899
RMDQ	13.67±3.82	13.79±3.09	0.860

Values are presented as mean±standard deviation.
rPMS, repetitive peripheral magnetic stimulation; BMI, body mass index; LS, lumbar sprain; LHNP, lumbar herniated nucleus pulposus; VAS, visual analogue scale; RMDQ, Korean version of Roland-Morris Disability Questionnaire; ODI, Korean version of Oswestry Disability Index.

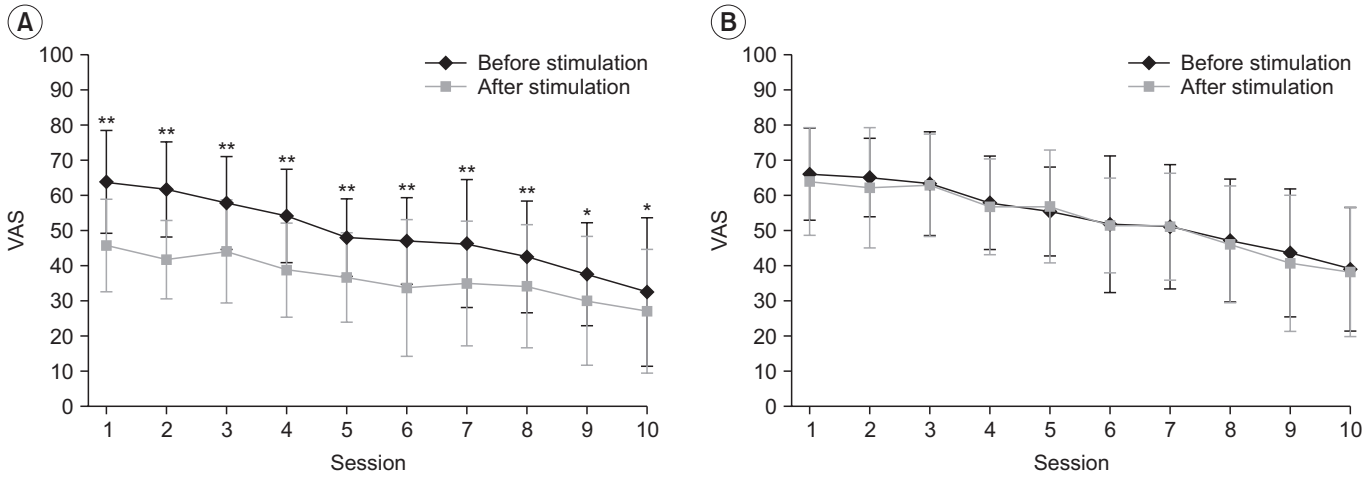

Fig. 2. Changes in VAS before and after each session observed in the real rPMS group (A) and the sham rPMS group (B). In the real rPMS group, VAS was reduced after every session compared to VAS measured before such session. The sham rPMS group showed no significant VAS change in any session. VAS, visual analogue scale; rPMS, repetitive peripheral magnetic stimulation. *p<0.05, **p<0.01.

5, and after session 10: $F_{(2,48)}$=86.07, p<0.001). There were also significant VAS differences between the two groups ($F_{(1,24)}$=4.35, p=0.048). Difference in the change of VAS between the two groups over time was also significant (baseline, after session 5, and after session 10: ($F_{(2,48)}$=6.51, p=0.003) (Fig. 3A). Bonferroni post-hoc tests showed that the VAS of the real rPMS group was significantly decreased both after session 5 (36.67±12.67, p<0.001) and after session 10 (27.08±17.64, p<0.001) compared to that at baseline (63.75±14.64). On the other hand, the VAS of the sham rPMS group was only significantly decreased after session 10 (38.21±18.25, p<0.001). VAS was not significantly decreased after session 5 (56.79±16.01, p=0.377) compared to that at baseline (66.07±12.28) in this group. Mann-Whitney U-test was used to compare the VAS after each session between the two groups. Results showed that the real rPMS group demonstrated significant more pain relief compared to the sham rPMS group until session 7. In sessions 8 to 10, the VAS of the real rPMS group was lower than that of sham rPMS group by an average of 11.25±7.06. However, the difference between the two groups was not statistically significant (Fig. 4A). We also compared baseline VAS and VAS before each session to confirm the persistence of pain relief under conditions that excluded the effect of immediate pain reduction (right after rPMS treatment). The real rPMS group showed significant improvement is VAS evaluated before session 2 and sessions thereafter compared to baseline

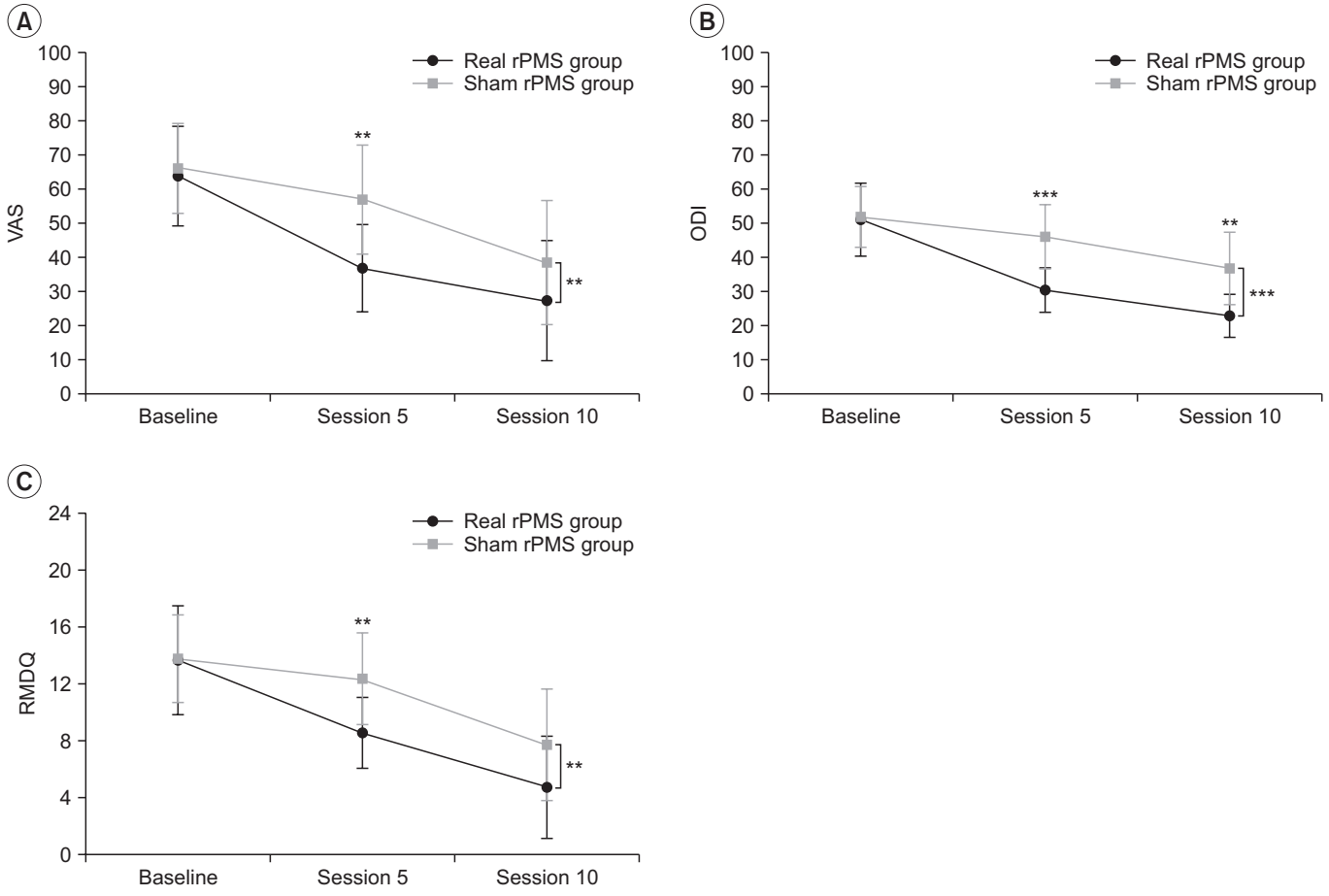

Fig. 3. Changes in VAS (A), ODI (B), and RMDQ (C) of the real rPMS group and sham rPMS group according to passage of time. Differences in changes of the VAS, ODI, and RMDQ over the course of time between the two groups were significant (p=0.003, p<0.001, and p=0.006, respectively). In comparing the two groups, there was a significant difference in VAS at session 5, but not at session 10; ODI showed a significant difference at sessions 5 and 10; and there was a significant difference in RMDQ at session 5 but not at session 10. VAS, visual analogue scale; ODI, Korean version of Oswestry Disability Index; RMDQ, Korean version of Roland-Morris Disability Questionnaire; rPMS, repetitive peripheral magnetic stimulation. *p<0.05, **p<0.01, ***p<0.001.

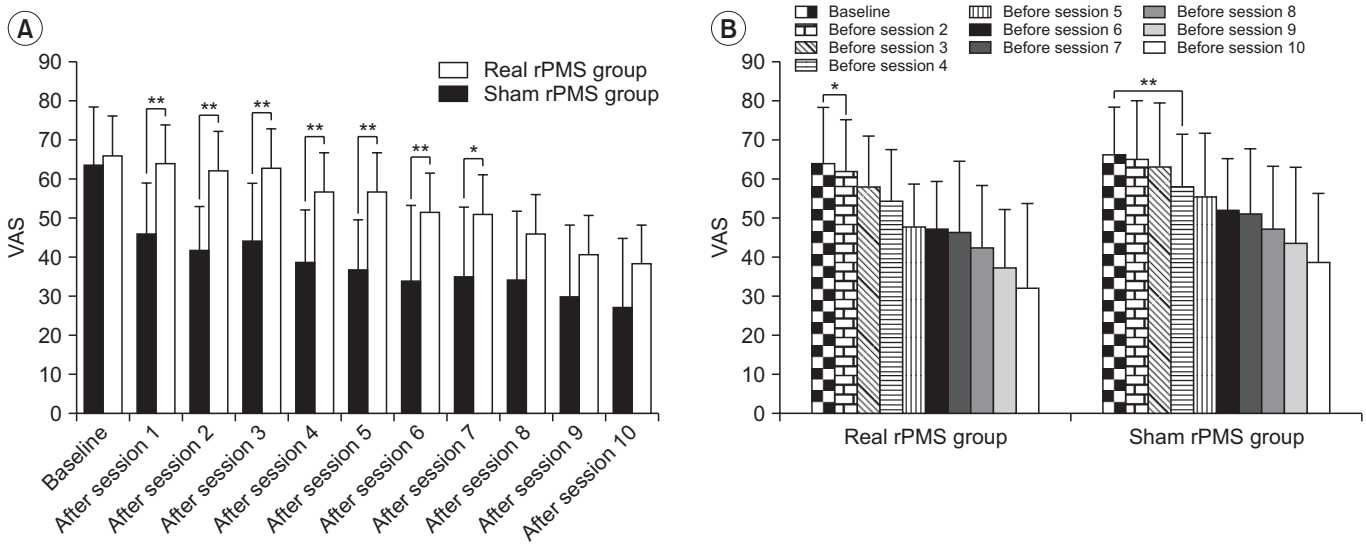

Fig. 4. Comparison of VAS between the real rPMS group and the sham rPMS group after each session. (A) From sessions 1 to 7, the VAS of the real rPMS group evaluated after each session was significantly lower than that of the sham rPMS group. Changes in VAS evaluated before each session of the real rPMS group and sham rPMS group. (B) Compared to baseline VAS, the real rPMS group showed significant VAS reduction starting from session 2 (p=0.025) whereas the sham rPMS group showed significant VAS reduction starting from session 4 (p=0.003). VAS, visual analogue scale; rPMS, repetitive peripheral magnetic stimulation. *p<0.05, **p<0.01.

VAS (the first comparison), confirming 'sustained' pain relief effect of rPMS. On the other hand, the sham rPMS group showed significant improvement in VAS evaluated before session 4 and sessions thereafter compared to baseline VAS (Fig. 4B).

Functional recovery

Results of repeated-measures ANOVA showed significant differences in ODI ($F_{(2,48)}$=86.07, p<0.001) and RMDQ ($F_{(2,48)}$=86.07, p<0.001) over the passage of time (baseline, after session 5, and after session 10) in both the real rPMS group and the sham rPMS group. There was a significant difference in ODI between the two groups ($F_{(1,24)}$=11.19, p=0.003). However, the difference in RMDQ was only marginally insignificant ($F_{(1,24)}$=3.83, p=0.062). Difference in changes of ODI ($F_{(2,48)}$=12.84, p<0.001) and RMDQ ($F_{(2,48)}$=5.76, p=0.006) over the course of time were significant between the two groups (Fig. 3B, 3C). Bonferroni post hoc tests showed that the ODI of the real rPMS group was significantly decreased both after session 5 (30.39±6.53, p<0.001) and after session 10 (22.74±6.29, p<0.001) compared to baseline ODI (50.98±10.70). On the other hand, the ODI of the sham rPMS group was only significantly decreased after session 10 (36.70±10.74, p=0.001) without showing significant decrease after session 5 (45.97±9.45, p=0.348) compared to baseline ODI (51.87±8.86). The RMDQ of the real RPMS group was also significantly decreased both after session 5 (8.58±2.50, p=0.002) and session 10 (4.75±3.60, p<0.001) compared to baseline RMDQ (13.67±3.82). The RMDQ of the sham rPMS group was only decreased significantly after session 10 (7.71±3.93, p<0.001) compared to baseline RMDQ (13.79±3.09) without showing significant decrease after session 5 (12.36±3.23, p=0.834). Results of Mann-Whitney U-test showed that, after session 5 (p<0.001) and session 10 (p=0.002), the real rPMS group showed significant functional superiority compared to the sham rPMS group based on ODI (Fig. 3B). The real rPMS group also showed significant functional improvement in terms of RMDQ compare to the sham rPMS group when they were evaluated after session 5 (p=0.004). However, there was no significant difference in functional improvement between the two groups after session 10 (p=0.095) (Fig. 3C). Pearson correlation coefficient analysis indicated that decrease of VAS in the real rPMS group was strongly correlated with decrease of ODI (r=0.680, p=0.015) and RMDQ (r=0.934, p<0.001). Pearson correlation coefficient analysis also showed that that the decrease of VAS in the sham rPMS group was significantly correlated with decrease of ODI (r=0.650, p=0.012) and RMDQ (r=0.879,

p<0.001).

DISCUSSION

The purpose of this study was to determine the effects of real rPMS on pain relief and functional recovery in ALBP patients compared to sham rPMS. As we postulated, real rPMS showed effects of immediate pain reduction and sustained pain relief, leading to early functional recovery. In three of four studies conducted previously, effects of immediate pain relief through rPMS were confirmed in patients with CLBP [13-15]. The remaining one was evaluated 8 hours after rPMS was administered. Accordingly, it was difficult to assess the effects accurately [12]. In this study on ALBP patients, immediate and significant pain improvement was also confirmed after each session in the real rPMS group. The mechanism of such effects has not yet been sufficiently studied or discussed. One possible explanation is based on the gate control theory. The electrical field formed by magnetic stimulation dominantly might depolarize large diameter myelinated Aβ afferent fibers due to their high conduction velocity, thereby inhibiting the depolarization of relatively small diameter Aδ nerve fibers and C nerve fibers which in turn can block pain signals from traveling to the brain [21]. However, the gate control theory alone cannot fully explain the immediate effects in relieving the pain by magnetic stimulation given that magnetic stimulation is relatively ineffective in recruiting cutaneous sensory afferents. This is because magnetic stimulation bypasses the cutaneous layer with minimal resistance to penetrate to deeper layers such as muscles and spinal roots. It directly recruits proprioceptive afferents (types Ia, Ib, II). Another possibility involves the immediate activation of a descending inhibitory pathway. However, there is no evidence or study supporting that rPMS activates the brain stem area such as rostral ventral medulla (RVM) and periaqueductal gray (PAG) that constitute this pathway. Furthermore, intensities of magnetic stimulation applied in this study were not robust enough to generate nociceptive signals.

The immediate effect of pain reduction of rPMS is not limited to low back pain patients. Previous studies have shown significant pain relief right after application of rPMS in various types of musculoskeletal pain including myofascial pain syndrome. This suggests that rPMS can initiate immediate pain modulatory mechanisms in general. However, no clear explanation has been provided yet. Accordingly, further research on this subject is warranted.

Through this study, the persistence of pain relief since session 1 in the real rPMS group was observed. To confirm whether the effect from the first session persisted, we compared VAS before the second session to baseline VAS and observed that the real rPMS group showed significant improvement in pain relief. Following each session, the VAS before such session was compared to baseline VAS, through which we confirmed that there was significant improvement. However, in the sham rPMS group, we began to see significant improvement only starting from session 4. As reviewed in the introduction section, most cases of ALBP show rapid improvement within weeks. Therefore, the improvement observed in the sham rPMS group can be attributable to the natural course of the disease. These effects are consistent with those found in studies conducted on CLBP patients. They have been described as 'residual', 'persistent', 'maintained', or 'long-term' relief of pain [13-15]. The most likely explanation for this is improvement in motor control by rPMS-induced brain plasticity.

CLBP patients typically undergo changes in motor coordination of abdominal and paravertebral muscles, resulting in decrease in spine control. Persistence of low back pain may be due to microtrauma caused by motor control impairment of these adjacent trunk muscles supporting the spine [22-24]. There is an increasing amount of evidence suggesting that such alterations in motor control are caused by plastic changes in the sensorimotor cortex that is responsible for planning movements [25]. For example, changes in M1 excitability have been observed in CLBP patients through motor evoked potential (MEP) studies [26,27]. Substantial reorganization of the primary somatosensory cortex (S1) and impairment of connectivity with the M1 cortex have been confirmed by magnetic source imaging [28].

Once rPMS activates muscles, proprioceptive afferents are generated through two pathways: indirect activation of mechanoreceptors on fibers (type Ia, Ib, II), and direct activation of sensorimotor nerve fibers [29]. This proprioceptive influx into the brain is believed to cause cortical plasticity [25,30-32]. Studies using MEP recruitment curves have confirmed that corticospinal excitability is

maintained for up to 60 minutes if rPMS is conducted at a frequency of 25 Hz [31]. The duration of corticospinal excitability cannot be 60 minutes in all cases since there may be differences in the duration of cortical activation depending on the frequency of the rPMS applied. However, the fact that pain relief persisted long after the excited period suggests the possibility of long-term potentiation due to brain plasticity. In fact, activation of the premotor cortex and the posterior parietal cortex, both of which are closely related to motor control, has been confirmed on functional magnetic resonance imaging (fMRI) after rPMS treatment [30]. Improvement in the motor control of subjects is also confirmed [30]. In addition, it has been confirmed that the real rPMS group shows more distinct difference in activation of the precentral area (M1) and the postcentral area (S1) compared to the sham rPMS group through fMRI [31]. Increased excitability of these sensorimotor cortexes involved in motor planning and control may potentiate motor control improvement. This could lead to efficient protection of the spine from microtraumas in daily activities, thus enabling persistence of pain reduction. However, this effect is known to be further enhanced when rPMS is combined with motor training [14,15,25]. One limitation of this study was that we did not create a group of ALBP patients who carried out lumbar exercise.

In this study involving ALBP patients as in the rPMS study of CLBP patients, the pain relief effect did not remain transient. Based on knowledge gained from past researches, we postulate that this is because magnetic stimulation might have activated a modulatory mechanism which maintains pain relief at brain level in ALBP patients. Although ALBP patients are less extensively documented than CLBP patients, they also show changes in trunk muscle activities. One study with experimentally induced acute back pain patients has suggested that changes in immediate motor control are caused by acute pain. Although there is variability depending on muscles, electromyographic studies and researches using MEP have shown that muscles such as abdominal external oblique and lumbar erector spinae in the superficial layer are activated in experimentally-induced acute back pain patients. This might have the effect of splinting the trunk to protect further injury. As a result, the mobility of the spine is reduced. On the other hand, decreased activities and delayed recruitment have been observed for transversus abdominis located relatively in a deeper layer [33,34]. This may reduce the stability of the spine itself. As a result, physiologic motion of the spine does not occur in daily life. Once the stability of the spine is reduced, it may become vulnerable to microtraumas. This might interfere with pain relief in patients with ALBP. In a previous MEP study on induced acute back pain subjects, the difference in cortical excitability according to the type of trunk muscles [34] suggests possible occurrence of corticomotor plasticity in ALBP patients as in CLBP patients. In addition, the neuromodulatory effect of an rPMS therapy might be achieved at the brain level in ALBP patients. However, advanced studies addressing topics such as which area of the brain undergo changes in ALBP patients are lacking. Further study is needed to obtain a more convincing explanation. In this study, the persistence of pain relief due to real rPMS treatment was confirmed. It is noteworthy that significant pain relief can be expected in patients with ALBP who receive rPMS treatment compared to patients who do not, at least for the first 9 days (i.e., 7 sessions).

Another important effect of rPMS identified in this study is early functional recovery. It seems that improvement in disability can be attributable to decrease of pain in the first place. Correlation coefficient analysis showed a significantly positive correlation of the VAS with ODI and RMDQ. In addition, deducing from studies conducted on CLBP patients, improvement in motor control might have contributed to functional recovery. According to studies performed so far, differential muscle activation identified in induced acute back pain subjects seems to be related to changes at brain level that might inhibit functional movement of the spine [33,34]. As with CLBP patients, if rPMS is shown to reverse brain plasticity caused by acute pain, we might be able to provide a clear explanation on functional recovery based on rPMS treatments. To this end, further study is needed to determine whether motor control is improved and how the sensorimotor cortex is reorganized when rPMS is applied to ALBP patients.

In conclusion, rPMS treatment appears to have effects of immediate pain reduction as well as sustained pain relief. It can also induce early functional recovery for patients with ALBP. Therefore, rPMS treatment could be used as an effective option for patients with ALBP seeking medical care.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Noninvasive neurostimulation in chronic stroke: a double-blind randomized sham-controlled testing of clinical and corticomotor effects

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Background: Repetitive peripheral magnetic stimulation (RPMS) is a painless and noninvasive method to produce afferents via the depolarization of the peripheral nervous system. A few studies tested RPMS after-effects on cerebral plasticity and motor recovery in stroke individuals, but evidences remain limited.
Objectives: This study aimed to explore whether RPMS could mediate improvements in corticomotor and clinical outcomes associated with ankle impairments in chronic stroke.
Methods: Eighteen subjects with chronic stroke were randomly allocated to RPMS or sham group and compared to 14 healthy subjects. Stimulation was applied over the paretic tibialis anterior (TA). Ankle impairments on the paretic side and ipsilesional TA cortical motor representation were tested clinically and by transcranial magnetic stimulation (TMS), respectively.
Results: In the RPMS group, ankle dorsiflexion mobility and maximal isometric strength increased and resistance to plantar flexor stretch decreased. The magnitude of change seemed to be related to cortical and corticospinal integrity. Sham stimulation yielded no effect. Changes in TMS outcome and their relationships with clinical improvements were limited.
Conclusions: RPMS improved ankle impairments in chronic stroke likely by a dynamic influence of sensory inputs on synaptic plasticity. The neurophysiological mechanisms potentially underlying the clinical effects are unclear. More studies are warranted to test the spinal and hemispheric changes responsible for the clinical improvements with emphasis on circuits spared by the lesion.

Keywords: Peripheral neurostimulation, Primary motor cortex, Transcranial magnetic stimulation, Cortical motor function, Ankle impairments, Chronic stroke

Introduction

Subjects having sustained a stroke often present with sensorimotor deficits contralateral to the side of the lesion,[1,2] such as muscle spasticity (velocity-dependent increase in muscle tone and resistance to stretch resulting from spinal hyperexcitability),[3,4] paresis (muscle weakness) and loss of dexterity that persist at the chronic stage.[3,5,6] To guide post-stroke recovery and improve motor function rehabilitative therapies apply principles of motor learning[7] and minimize the negative consequences of immobilization and learned non-use.[8] However, people with severe and persistent sensorimotor impairments are often unable to perform intense and repeated therapies oriented to the task, thus experiencing maladaptive changes (negative plasticity) in sensorimotor networks.[5,9,10] The use of noninvasive external devices that induce repetitive muscle contractions and joint movements to promote neural plasticity and motor recovery after stroke are under study as a means of avoiding limb immobilization and learned non-use.[11–13] The influence of muscle stimulation on cortical motor activation and joint movement suggests that cerebral plasticity responsible for motor improvement depends in part on proprioceptive afferents[14–16] that have both direct and indirect connections to the motor cortex.[2,17,18]

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Repetitive peripheral magnetic stimulation (RPMS) provides noninvasive and painless high-frequency stimulation of muscles, nerves or spinal roots capable of producing muscle contraction and has the advantage over electrical stimulation of activating sensory afferents with negligible recruitment of cutaneous and nociceptive receptors.[19–23] In healthy subjects, it was shown by means of transcranial magnetic stimulation (TMS) applied over the primary motor cortex (M1) that RPMS of spinal roots increased the corticospinal excitability and the level of inhibition of M1 circuits in the hemisphere contralateral to the side stimulated.[24,25] The authors suggested that RPMS could influence the cortical plasticity by up-regulating M1 transsynaptic efficacy, thus increasing the excitability of both excitatory and inhibitory circuits involved in motor planning. In subjects at a chronic stage post-stroke, positron emission tomography was used to test how RPMS of the paretic finger/hand extensor muscles could influence the patterns of cerebral activation during a finger extension task.[23] It was shown that RPMS increased the regional blood flow in fronto-parietal regions of the contralateral (lesioned) hemisphere and this was paralleled by an increase in movement amplitude and velocity during the task. The authors suggested that the massive sensory inputs generated by RPMS activated the fronto-parietal areas involved in motor learning thus explaining the improvements of finger/hand function observed.[23] Others reported a significant decrease in muscle spasticity after RPMS, most likely related to lower excitability of spinal circuits, but it remains unclear whether these changes originated from plasticity at the spinal and/or cortical level.[26]

Despite this interesting observation, literature is scant and inconsistent and only a few studies with experimental designs tested the underlying neural mechanisms of RPMS after-effects.[26] Furthermore, most authors investigated the stimulation of spinal roots or upper extremity muscles and only one focused on lower limb muscle stimulation in healthy individuals.[26] The after-effects of RPMS of lower limb muscles in chronic stroke remain unknown and its utility in enhancing function has not been reported. For example, paretic foot drop observed during walking and known to relate to plantar flexor spasticity and dorsiflexor paresis[27] could be alleviated following RPMS due to its after-effects on ankle motor impairments, which, in turn, may improve gait performance.[28]

The present study was a first step to understand the immediate clinical and corticomotor effects of RPMS applied over the paretic tibialis anterior muscle (TA, ankle dorsiflexors) on the ankle's function in people with chronic stroke. Transcranial magnetic stimulation of the lesioned M1 and clinical testing of the paretic leg were conducted pre- and post-RPMS administration and comparisons were made with sham stimulation and with values obtained from healthy counterparts. Relationships between clinical and corticomotor changes and predictive indicators of success were examined. We hypothesized that RPMS of TA would reduce ankle muscle paresis and spasticity and dynamically influence the motor systems controlling ankle function in chronic stroke.

Methods

Participants and study design

Eighteen persons with chronic unilateral, first-ever stroke more than 12 months prior to the study were randomly allocated to RPMS group ($N=9$, 51 ± 15 years) or sham group ($N=9$, 55 ± 11 years) and were compared pre- and post-intervention to a group of healthy subjects involved in baseline testing only ($N=14$, 50 ± 7 years, Table 1). Participants with stroke presented with paretic ankle muscles with spasticity (medical records), had a CT or MRI scan taken within the last 5 years, and were able to walk independently (i.e. no physical assistance) more than 10 m with or without an assistive device. Exclusion criteria included the use of anti-spastic medication, past vertebral surgery, major circulatory, respiratory or cardiac disease, neurological disease/deficit other than stroke, severe lower limb orthopedic conditions, or cognitive disorder. All participants were screened to ensure they had no contraindications for TMS.[29] Medical evaluation by a physician before and after the study ensured compliance with all selection criteria and monitored any adverse effects. All subjects provided informed written consent and protocols had been approved by the local ethics committees. A double-blind, randomized sham-controlled design was adopted such that the experimenter not involved in pre- and post-intervention measures and analysis applied the intervention (RPMS or sham) to subjects with stroke who were naïve to what they were receiving. The experimenters performing the pre- and post-intervention measures and analysis had to leave the room during the intervention and they remained blind to group allocation during the experiments and also to time of measures during analysis (i.e. pre- or post-intervention) until completion of the analyses. All testing was completed in a single session lasting 2–3 hours including rest breaks. Figure 1 presents

Table 1 General characteristics of participants and details related to the lesions

General characteristics	RPMS group	Sham group	Healthy counterparts
Participants (*N*)	9	9	14
Age (years): mean ± SD	51 ± 15	55 ± 11	50 ± 7
Gender (*N*: males/females)	4/5	3/6	6/8
Height (cm)	167 ± 7	165 ± 7	168 ± 15
Footedness (*N*: right/left)*	9/0	9/0	14/0
Lesion details			
Location (*N*: cortical/subcortical/mixed)	3/0/6	3/3/3	–
Nature (*N*: ischemic/hemorrhagic)	8/1	8/1	–
Hemisphere (*N*: right/left)	4/5	5/4	–
Time elapsed (months): mean ± SD	52.9 ± 36.7	82.7 ± 101.2	–
Range	16–132	22–365	–
Age at lesion (years): mean ± SD	44.4 ± 13.8	49.1 ± 14.3	–

Note: *before lesion for participants with stroke, *N*=number.

the order of testing for the paretic leg in stroke: clinical assessment (see clinical testing below), TMS measures (see TMS testing below), intervention (RPMS or sham), TMS measures 10 minutes later, clinical assessment. The healthy counterparts had their dominant leg tested first for clinical outcomes then for TMS outcomes. Dominance was determined as the foot used to kick a ball or to write one's name in the sand. Based on TMS safety guidelines, each subject was contacted by phone 2, 10 and 30 days after the experiment to document any adverse effects.[29]

EMG recordings

EMG recordings of background activity during the clinical assessment and responses to TMS were performed using adhesive surface Ag–AgCl electrodes (Kendall MediTrace 200 Series, MyWellCare, Concord, ON, Canada) in a bipolar configuration over the belly of TA and soleus muscles.[30] A common ground electrode was positioned on the patella. Signals were bandpass-filtered (20–450 Hz) and amplified (× 1500) before digitization (2 kHz; Biometrics-NexGen amplifiers, Gwent, UK). Signals were displayed in real-time and stored for offline analysis (PowerLab acquisition system, LabChart-ADInstruments, Colorado Springs, CO, USA).

Clinical testing

Three trials were averaged per outcome and up to two supplementary trials were performed in cases when variation exceeded 2SD from the mean. The participants adopted a standardized supine position on a therapeutic table with full-extended knee.

Range of motion (ROM)

The ankle's range of dorsiflexion (DF) for active motion (volitional upward movement with verbal encouragement) and passive motion (manually imposed, no stretch reflex at slow speed, silent EMG monitored) were measured using an extendable-hinged goniometer (*Lafayette-Instrument*) aligned with the rotational axis.[31,32] Skin markers were used to position the goniometer and measure the angle formed by the fibular head, the lateral malleolus and the fifth metatarsal head to enable reliable repositioning of the goniometer. Of note, this underestimated the true DF angle due to the natural angle formed by the fifth metatarsal and fibular head subtended by the external malleolus. A value of 0° corresponded to a goniometer reading of 90°, negative or positive values referring to plantar or dorsal flexion, respectively.

Isometric muscle strength

A hand-held dynamometer (*Châtillon-Instrument*) was used to measure maximal isometric strength of the ankle dorsiflexors when placed perpendicular to the metatarsal heads on the dorsal surface of the foot. The participants were instructed to push as hard as possible against the dynamometer (gradual increase to maximal strength) and were given verbal encouragement. The experimenter matched the strength of the maximal isometric voluntary contraction (MVC) without "breaking" it (the "make" test).[33–35]

Resistance of plantar flexors to stretch

The dynamometer was placed perpendicular to the metatarsal heads on the plantar surface of the foot to measure the resistance force in response to

Figure 1 Diagram of experimental setup in stroke.

high-speed passive plantar flexor stretch.[36] Stretch was initiated from the ankle's resting position and stopped 5 deg before the participant's maximal passive DF end range of motion (measured in previous step). This procedure was adopted to minimize the contribution of the soft tissue viscoelastic properties associated with plantar flexor stretch to the resistance measured by the dynamometer. EMG traces monitored the initial relaxation of soleus muscle and stretch reflexes were recorded.

TMS testing

Participants were comfortably seated in a reclining chair with legs and arms supported. Their knees were flexed 20° from full extension and the test foot firmly strapped in an ankle-foot orthosis to ensure standardized positioning across subjects. Participants were first instructed to dorsiflex the ankle three times eliciting an MVC against the strap. Fifteen percents of the mean rectified TA EMG activity associated with the MVC was calculated and displayed as a target line on a screen. During TMS testing, real-time EMG activity of TA was low-pass filtered at 2-Hz and displayed online as visual feedback on the same screen. Participants activated their TA to superimpose their EMG output on the target line representing 15% MVC. This served to stabilize motoneuronal excitability and spinal cord output.[37] Trials in which the EMG fell outside the acceptance window (15% MVC $\pm$5%) were rejected. Magnetic stimuli were applied using a double-cone coil (7-cm outer diameter each wing; Magstim Company Limited, Whitland, UK) optimal for activating TA M1 cells.[38] The TMS coil was positioned over M1 for the TA area that was first approximated at 0.5–2cm lateral to the vertex[39,40] using 10–20 EEG system[41–44] and with the long axis of the two-wing intersection pointing antero-posteriorly.[37,39,45] Once a motor evoked potential (MEP, i.e. TA response to TMS of TA M1 area) could be detected in EMG recordings, the position was adjusted slightly to determine the "hot spot." The hot spot was defined as the coil's location where MEPs of the largest amplitudes could be elicited at the lowest TMS intensity, as compared to other coil positions.[37,38,45] Scalp locations were marked using a surgical marker to ensure reliable positioning and orientation of the coil. The active motor threshold (AMT) was determined as the stimulus intensity required to elicit at least five TA MEPs out of 10 trials with amplitudes $\geq$100 μV.[37] Test TMS was set at 120% AMT to elicit MEPs in the preactivated TA and test the corticospinal excitability. Paired-pulse TMS paradigms (coil connected to two Magstim 200^2 monophasic stimulators) were used to test short-interval intracortical motor inhibition and facilitation (SICI, SICF). In SICI, a subthreshold conditioning TMS (70% AMT) was delivered 2 ms before introducing a test TMS at 120% AMT. In SICF, a subthreshold conditioning TMS (90% AMT) was delivered 1 ms after a test TMS at 100% AMT. For both SICI and SICF, the amplitude of the conditioned MEP was expressed relative to the amplitude of the corresponding test MEP. This provided measures of pure $GABA_A$ inhibition (SICI, i.e. conditioned MEP $<$ 100% amplitude of test MEP elicited at 120% AMT) and glutamate facilitation (SICF, i.e. conditioned MEP $>$ 100% amplitude of test MEP elicited at 100% AMT) of M1 circuits under preactivated conditions.[46] For each participant, eight to 10 test MEPs and eight to 10 conditioned MEPs were elicited within each paired-pulse TMS protocol (SICI, SICF).[47] The test TMS intensity was adjusted post-intervention to match the amplitudes of test MEPs obtained at pre-intervention. This procedure ensured valid comparisons of conditioned MEPs amplitudes at the two time points.

Peripheral neurostimulation

Participants remained relaxed in the same position as for TMS testing. RPMS was applied using an air film cooled figure-of-eight coil (7 cm outer diameter, each wing) known to limit the co-activation of surrounding conductive structures as compared to other coil conformations.[48] The coil was held tangentially on the skin overlying the paretic TA muscle belly with the long axis of the coil junction perpendicular to the orientation of muscle fibers.[48–50] Repetitive magnetic stimuli (biphasic waveform, 400-μs pulse width, rapid-rate magnetic stimulator Rapid^2 Magstim) were delivered at a theta-burst frequency, i.e. 5-Hz bursts of three 50-Hz pulses each.[51] This specific pattern of peripheral stimulation applied in chronic stroke has been successfully tested by our research group in other populations.[52,53] Intermittent theta-burst stimulation of 2 s ON 8 s OFF (600 pulses) was applied for 190 s: this avoided saturation of spinal circuits or muscle fatigue and cyclical activation/relaxation of muscle fibers likely recruited proprioceptive afferents that best activated fronto-parietal mechanisms of neuroplasticity.[23,54] The RPMS intensity was set at 42% of the maximal stimulator output, which was the highest intensity that our theta-burst pattern of stimulation could produce without causing overheating of the coil. This intensity was sufficient to produce palpable TA contraction with visible DF movements. Sham stimulation was applied using the same parameters but at a very low intensity (5% of maximal stimulator output)

with the coil positioned directly above the metatarsals (dorsal surface of foot) to avoid the recruitment of proprioceptive afferents from ankle muscles. To ensure blinding, all participants were informed at enrolment that they could receive either real RPMS or sham stimulation over the paretic lower limb but they were not provided with information about the coil's location or sensations induced by the stimulation. Our sham technique had the advantage of producing a clicking noise and a tingling sensation, which would be expected if they were in receipt of RPMS, but proprioceptive afferents from ankle muscles were recruited only in the RPMS group.

Data reduction and statistical analysis

Five clinical outcomes were measured pre- and post-intervention: maximum active and passive ankle DF ROM (deg); strength of isometric DF; plantar flexor resistance to high-speed stretch and the associated soleus stretch reflex. Six TMS outcomes associated with TA were acquired pre- and post-intervention: AMT reflected the basic M1 excitability; mean MEP latency reflected conduction time and indirectly, the synchronous arrival of descending volleys to depolarize spinal motoneurons; mean peak-to-peak amplitude of the test MEP (elicited at 120% AMT) reflected the volume of M1 cells activated by TMS (i.e. the corticospinal cells and associated interneurons);[55] duration of the EMG silent period following the MEP superimposed on isometric contraction was referred to as the cortical silent period since it potentially indicated the activation of M1 $GABA_B$ inhibitory interneurons;[56] mean amplitude of the conditioned MEPs testing SICI and expressed as a percentage of the mean amplitude of the test MEP elicited at 120% AMT; mean amplitude of the conditioned MEPs testing SICF and expressed as a percentage of the mean amplitude of the test MEP elicited at 100% AMT. Analyses of variance (ANOVA) were applied to all variables with a factor of intervention (RPMS, Sham) and time (Pre-intervention, Post-intervention). Planned comparisons (two-sided) were used to detect where differences lay. A one-way ANOVA was used to compare RPMS and sham groups to the healthy counterparts at pre- and post-intervention. Pearson's correlation matrices were produced to examine the associations between clinical and TMS changes (change=[(post-intervention–pre-intervention)/pre-intervention]*100) and the relationship between change and pre-intervention value. The two-sided *t*-test enabled comparisons of age and height between groups of subjects with stroke and healthy participants and of lesion characteristics between RPMS and sham groups (time since stroke, age at lesion). The post-hoc statistical power of change measures for all outcomes was tested using G*Power software,[57] which also provided information about sample size. Significance level was set at $P<0.05$.

Results

RPMS and sham groups presented with similar lesion characteristics ($P>0.05$ for time since lesion and age at lesion) and similar age and height to healthy counterparts ($P>0.05$). All subjects with stroke completed the protocol. Statistical power reached 80–85% for the significant changes.

RPMS after-effects

Clinical outcomes

A significant group × time interaction was detected for plantar flexor resistance to stretch ($F=5.71$; $P=0.03$) and a trend only for active DF ROM ($F=3.92$; $P=0.065$). Planned comparisons determined that after RPMS plantar flexor resistance to stretch was reduced (mean decrease of 2.4 ± 2.0 kg; $P=0.0007$; Fig. 2A) with concomitant increases in active DF ROM (mean increase of $7.8\pm7.3°$; $P=0.0005$; Fig. 2B), passive DF ROM (mean increase of $2.2\pm1.9°$; $P=0.03$; Fig. 2C) and DF strength (mean increase of 1.32 ± 1.25 kg; $P=0.05$; Fig. 2D). The decrease in plantar flexor resistance was not accompanied by any change in the soleus stretch reflex. Comparison of the RPMS group with the healthy counterparts showed differences for the pre-RPMS plantar flexor resistance ($P=0.04$), active DF ROM ($P=0.002$) and DF strength ($P=0.0001$). After RPMS, only DF strength remained below the values obtained from healthy counterparts ($P=0.0006$). Sham yielded no effect and its contrasts with the healthy counterparts remained unchanged at both pre- and post-sham for active DF ROM ($P<0.01$), passive DF ROM ($P<0.01$), and DF strength ($P<0.0001$).

TMS outcomes

TA MEPs following TMS of the lesioned M1 were absent in two participants at pre- and post-intervention (one in RPMS group, one in sham), thus the analyses of TMS data resulted in RPMS and sham group sizes of 8. ANOVAs did not detect any effect of either RPMS or sham on TMS outcomes. Table 2 however denotes lower TA AMT after RPMS than after sham and longer MEP latency after sham than found in the healthy counterparts.

Correlations between clinical and TMS outcomes

In the RPMS group, changes in DF strength were correlated with the duration of the cortical silent

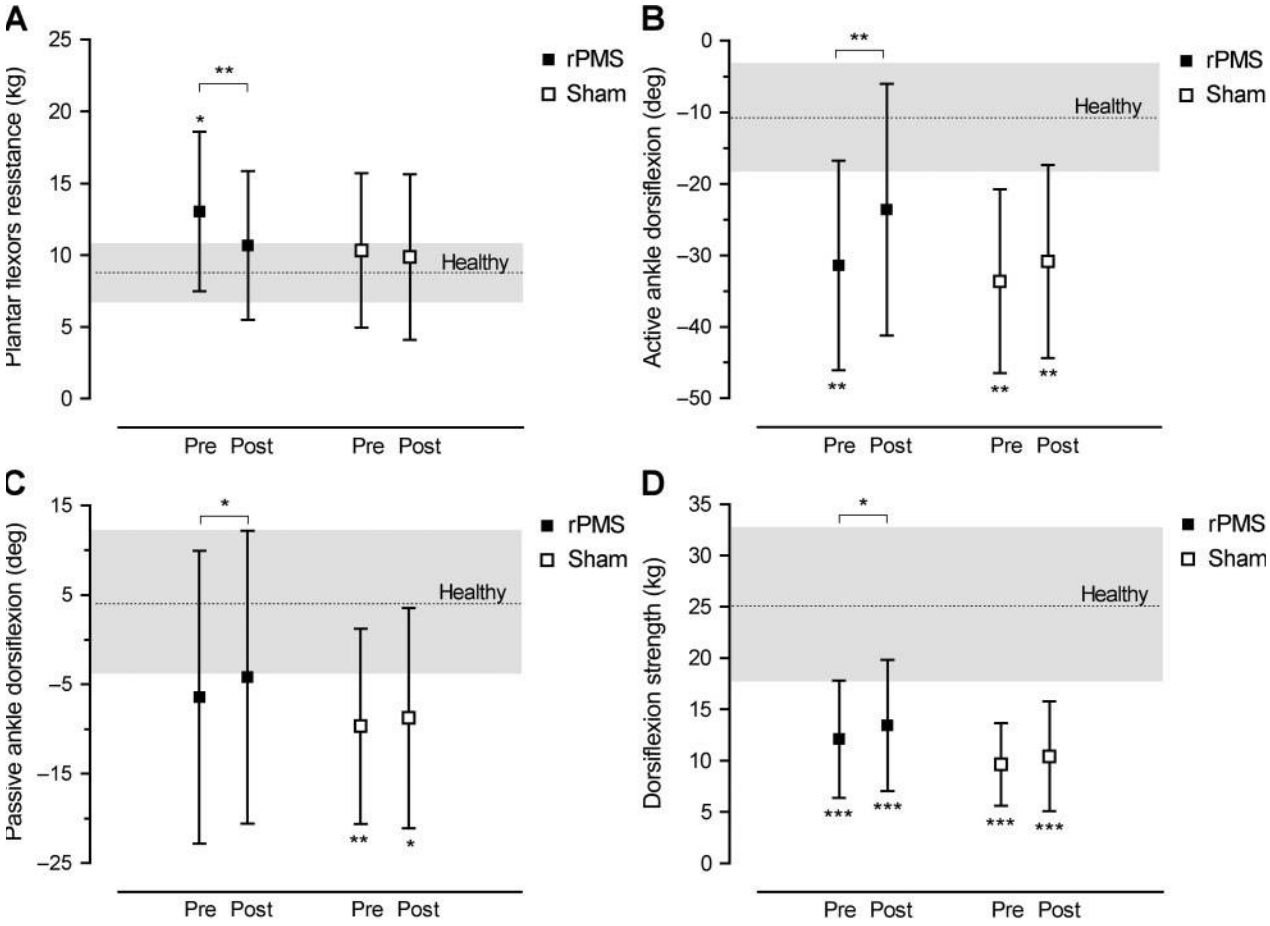

Figure 2 Clinical outcomes. RPMS and sham influence (means ± SD) on plantar flexors resistance to high-speed stretch (A), active and passive ankle dorsiflexion (B, C) and on dorsiflexion strength (D). The dashed area represents the healthy counterparts' mean ± SD. Stars below/above symbols indicate significant differences with healthy counterparts. *$P<0.05$; **$P<0.01$; ***$P<0.0001$.

period measured pre-intervention ($r=0.81$, $P=0.016$; Fig. 3A) denoting that participants with a longer TA cortical silent period pre-intervention demonstrated a larger increase in DF strength after RPMS. DF strength changes were also correlated with AMT changes ($r=0.94$, $P=0.0006$; Fig. 3B). Interestingly, Fig. 3B suggests a distinction between two subgroups of participants responding differently to RPMS intervention. A secondary analysis showed that the four participants with the lesser increase in DF strength ($1.6 \pm 4.4\%$) presented a higher AMT at pre-RPMS that decreased after RPMS (57.5 ± 9.9 versus $53.2 \pm 9.0\%$ of the maximal stimulator output (MSO)) whereas in the four participants with the

Table 2 TMS outcomes

	RPMS group		Sham group		Healthy counterparts
	Mean(SD)		Mean(SD)		Mean(SD)
	Pre	Post	Pre	Post	
AMT (%MSO)	51.5(9.4)	50.0(7.2)[a]	62.5(11.9)[b]	61.9(11.8)[b]	49.8(9.1)
Unconditioned MEP (mV)	0.98(0.78)	0.97(0.81)	0.81(0.56)	0.77(0.54)	1.27(0.53)
Latency (ms)	38.4(5.3)	38.1(5.6)	41.4(7.7)	42.6(8.0)[b]	35.1(2.5)
Silent period (ms)	85.7(54.4)	100.6(46.8)	63.9(30.3)	66.1(33.9)	73.8(45.5)
SICI (%MEP 120% AMT)	61.6(22.6)	70.8(38.9)	65.5(30.4)	64.0(31.1)	54.0(30.3)
SICF (%MEP 100% AMT)	265.1(194.5)	243.3(95.9)	183.5(143.7)	256.2(211.1)	285.7(140.7)

Note: TMS=transcranial magnetic stimulation; AMT=active motor threshold; MSO=maximal stimulator output; MEP=unconditioned motor evoked potential elicited at 120% AMT; SICI=short-interval intracortical inhibition; SICF=short-interval intracortical facilitation. [a] significant difference with sham value. [b] significant difference with healthy counterparts.

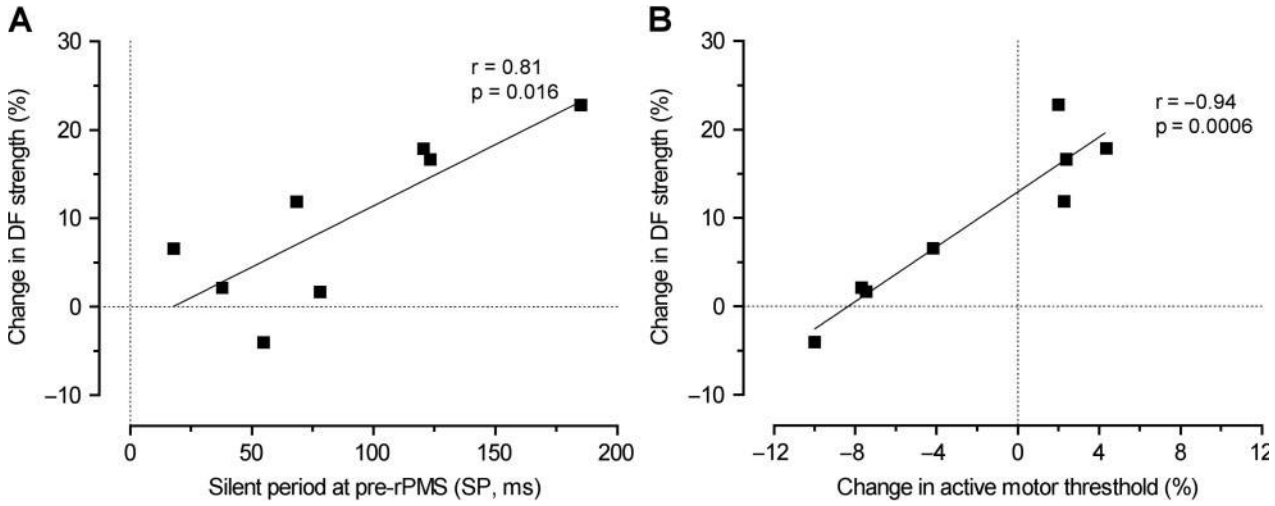

Figure 3 Correlations of clinical and TMS outcomes. Correlations of post-RPMS changes in dorsiflexion (DF) strength with the cortical silent period of TA measured at pre-RPMS (A), and with the post-RPMS changes of TA active motor threshold (B).

larger increase of DF strength (17.4 ± 4.5%) AMT was lower at pre-RPMS and did not change after RPMS (45.5 ± 3.4 versus 46.8 ± 3.5% MSO). Also, those with lesser increase in DF strength had a shorter silent period pre-RPMS (47.2 ± 25.6 ms) than subjects with larger DF strength increase (124.3 ± 47.7 ms). No other relationship was detected.

Discussion

Our study tested the immediate influence of TA RPMS on clinical impairments and TMS outcomes of the ankle in chronic stroke. RPMS (not sham) improved most clinical outcomes. These dynamic changes are potentially related to the integrity of corticospinal and intracortical pathways. Identification of the underlying mechanisms of action is limited by the relative absence of changes detected in TMS outcomes.

Dynamic changes of impairments and benefits to motor function in stroke

It is acknowledged that the manipulation of somatosensory inputs to the human brain drives M1 plasticity in healthy persons and could be associated with improvement of motor function in people with stroke.[14–16,58] Plastic mechanisms of M1 are attributed in healthy people to rapid homeostatic metaplasticity,[59] i.e. the ability of M1 circuits to balance between inhibition and facilitation in order to modulate cortical excitability during simple or complex volitional tasks.[46,60] Stroke can severely affect these intra- and inter-hemispheric mechanisms to balance activity[61] and any intervention supplying brain with sensory information could help promote neuroplasticity beneficial for function.[58]

Our study provides new evidence of immediate effects of RPMS on ankle function. RPMS systematically improved ankle joint mobility, strength and reduced plantar flexor resistance to high-speed stretch. Of note, the mean increase of passive DF ROM (2.2 ± 1.9°) was within the intra-observer variability reported for hinged goniometry.[62] This change, tough statistically significant, may be of limited clinical value given the small magnitude. Comparison with healthy participants showed that most outcomes suggestive of impairment pre-RPMS no longer distinguished between groups after RPMS, except DF strength which improved but remained lower than was observed in healthy counterparts. Nevertheless, after a single session of RPMS, the clinical outcomes did not overlap with those of the similarly-aged healthy group and therefore, may still limit mobility. The lack of effect in the sham group indicates the ineffectiveness of sham and suggests that the outcome measures were stable over the course of the protocol. Following RPMS, the concomitant decrease in plantar flexor resistance to stretch and increase in active DF ROM suggest that joint mobility may have been enhanced by a decrease in spasticity as proposed for the upper limb by protocols testing an index finger extension task.[23,63,64] Changes in dorsiflexor paresis and plantar flexor spasticity have a functional impact on foot drop and gait symmetry.[27,28] Although not tested in the present study, it follows that RPMS-related reduction of these impairments may influence walking performance. Future studies using RPMS should include measures of walking performance to determine the impact on gait function and mobility.

Potential mechanisms underlying the RPMS-induced improvements

Our TMS findings in chronic stroke offer limited insight with respect to the possible changes in M1 that could explain the significant clinical effects of RPMS. The undetected TMS changes observed in

the current study despite significant improvement of ankle impairments warrants explanation. The heterogeneity of lesions in our sample (see Table 1) may have masked the detection of a RPMS effect on TMS measures of M1 function. Indeed, in the upper limb the mechanisms underlying functional improvements in different individuals with stroke vary with the severity of the lesion or the level of impairment.[65,66] The stroke-related structural involvement in our RPMS sample varied owing to M1 cell death alone (i.e. pure cortical lesion) or with Wallerian degeneration of corticospinal tracts or thalamo-cortical pathways (i.e. mixed cortical–subcortical lesion). The presence or not of a subcortical component of the lesion may have mediated different mechanisms of plasticity following RPMS administration thus masking any group effect on M1 function. RPMS over the paretic TA could have induced changes in the contralesional hemisphere via transcallosal routes which could explain the significant improvement of sensorimotor impairments. Interhemispheric inhibition imbalance is well documented in stroke in the form of excessive inhibition from the contralesional M1 to the ipsilesional M1[65,67,68] and decreasing the contralesional overactivity improved upper limb motor recovery.[69–71] It follows that downregulation of the contralesional M1 after RPMS (not tested in our study) may have contributed to the significant clinical improvements. The influence of RPMS on spinal excitability evidenced by a depression of the soleus H-reflex has been reported though studies remain inconclusive (see Beaulieu and Schneider (2013)[26] for review). We did not test spinal excitability but recordings of soleus EMG during high-speed plantar flexor stretch did not reveal any change in burst although resistance to plantar flexor stretch decreased after RPMS.

However, an interesting finding was that the magnitude of DF strength increases following RPMS delineated two subgroups of subjects with stroke in relation to the TA cortical silent period and AMT measured pre-RPMS (see Fig. 3). Larger increases in DF strength were observed in subjects with pre-RPMS silent periods greater than 100 ms and corresponding to normal post-MEP inhibition of pure cortical origin (potentially from $GABA_B$ inhibition in TA M1 area).[55,65] In subjects with lesser increases in DF strength, pre-RPMS silent periods less than 50 ms matched the duration of the post-MEP spinal motoneuron refractory period,[72,73] suggesting that TMS might have been unable to recruit M1 $GABA_B$ interneurons. The contribution of the silent period in stroke recovery remains unclear. It was reported however with respect to the upper limb, that a better motor improvement occurred when the initially prolonged silent period was shortened to normal values.[65] We propose that the length of the silent period at baseline may be a predictive factor for RPMS-induced improvement of ankle impairments. Compatible with this view is that in chronic stroke, the integrity of corticospinal and intracortical inhibitory motor pathways was proposed as a predictor of hand function recovery.[74–77] The relationship between higher M1 excitability (lower pre-RPMS AMT) and greater increases in DF strength after RPMS may be an extension of a similar phenomenon, that is, a more efficient homeostasis between intracortical inhibition and facilitation at the basis of larger RPMS-induced effects. It is noteworthy that this relationship was tested on small sample groups (Fig. 3) and thus requires replication in larger samples.

Conclusions

TMS and clinical testing provided novel findings demonstrating immediate improvements of ankle joint impairments following RPMS in chronic stroke though the underlying mechanisms of M1 plasticity remain unclear. RPMS-induced proprioceptive inputs to the lesioned hemisphere may have influenced M1 homeostasis, a mechanism potentially at the origin of recovery though the small sample size and the heterogeneity of lesions limited the ability to detect significance. To identify the mechanisms of RPMS action that underlie clinical changes requires testing of larger samples of persons with chronic stroke over several RPMS sessions, and contrasting the effects in those with cortical and subcortical lesions. Further, testing both hemispheres and spinal circuits would provide important insight.

Disclaimer Statements

Contributors

All authors contributed equally.

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Conflicts of interest

None

Ethics approval

All subjects provided informed written consent and protocols had been approved by the local ethics

committees in conformation to the Helsinki Declaration of 1975, as revised in 2000.

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REVIEW/MISE AU POINT

Repetitive peripheral magnetic stimulation to reduce pain or improve sensorimotor impairments: A literature review on parameters of application and afferents recruitment

Stimulations magnétiques répétitives périphériques pour réduire la douleur ou améliorer les désordres sensorimoteurs : une revue de la littérature sur les paramètres d'application et le recrutement des afférences

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KEYWORDS
Repetitive peripheral magnetic stimulation;
Stimulation parameters;
Proprioceptive afferents;
Neurological disorders;
Musculoskeletal pain

Summary
Introduction. — Repetitive peripheral magnetic stimulation (rPMS over spinal root, nerve or muscle belly) is a promising technology in physiopathology research. As compared to electrical stimulation, rPMS is deemed to activate deep conductive structures and produce strong muscle contractions and massive proprioceptive afferents with minimal cutaneous recruitment. RPMS may thus act differently on neural plasticity involved in pain reduction and motor recovery in musculoskeletal or neurological conditions. However, literature is very scant and still controversial concerning afferents recruited by rPMS, thus no consensus is reached yet for its clinical use.
Study aim. — This review dealt with stimulation parameters reported in any scientific research that applied rPMS as an intervention to improve somatosensory or motor disorders with a view of proposing recommendations for future applications. Also, controversy on afferents recruitment was discussed.

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Results. — The literature search resulted in 24 studies. Literature is scant on the topic but our review presents the rationale and the experimental data that may underlie the selection of parameters in future studies using rPMS as an intervention. Although controversy remains, the review presents that the specific recruitment of sensory afferents by magnetic stimulation may offer advantages and disadvantages depending on the pathology.
Conclusions. — The review proposed recommendations to improve rPMS application in clinical research. However, the development of guidelines still requires methodological and clinical studies enrolling larger samples and with randomized sham-controlled designs.

MOTS CLÉS
Stimulation magnétique périphérique répétitive ;
Paramètres de stimulation ;
Afférences proprioceptives ;
Problèmes neurologiques ;
Douleur musculosquelettique

Résumé
Introduction. — La stimulation magnétique périphérique répétitive (rPMS de racine spinale, nerf ou muscle) est une technologie prometteuse en recherche clinique. Comparée à la stimulation électrique, la rPMS produirait de fortes contractions musculaires avec recrutement massif des afférences proprioceptives et recrutement minimal des fibres cutanées. La rPMS pourrait ainsi agir différemment sur la plasticité neuronale à l'origine de la baisse de douleur et de la récupération motrice après lésion ou maladie affectant le système musculosquelettique ou nerveux. La littérature est cependant limitée et toujours controversée quant aux afférences recrutées. Aucune recommandation n'existe quant à l'utilisation de la rPMS en recherche clinique.
But de l'article. — La revue s'est intéressée aux paramètres de stimulation rapportés dans toutes les études scientifiques utilisant la rPMS pour améliorer les désordres somatosensoriels et moteurs et propose des recommandations pour applications futures. Aussi, la controverse concernant les afférences recrutées a été discutée.
Résultats. — La recherche littéraire a permis d'obtenir 24 articles. Malgré un manque d'évidences scientifiques, les données expérimentales et le rationnel présentés dans la revue pourraient aider à la sélection de paramètres appropriés dans les études futures, utilisant la rPMS comme une intervention. Quoique certaines controverses persistent, la spécificité de recrutement des afférences par la stimulation magnétique semble offrir des avantages et inconvénients, dépendant de la pathologie.
Conclusions. — La revue propose des recommandations pour améliorer l'application de la rPMS en recherche clinique. Cependant, le développement de guides de pratique requiert plus d'études méthodologiques et cliniques sur un plus grand nombre de participants et présentant un plan d'analyse randomisé contrôlé avec placebo.

Introduction

Non-invasive peripheral stimulation refers to the use of an external device that can produce muscle contractions and sensory afferents via the depolarisation of conductive structures within the peripheral nervous system. For example, transcutaneous electrical stimulation (TES) and peripheral magnetic stimulation (PMS) create voltage differences and ion flows, thus activating conductive structures beneath the stimulated region [5]. Repetitive trains of TES and PMS stimuli are used in clinical research, with varying parameters, for reducing pain or promoting sensorimotor recovery [7,12,15,62,63,65]. The mechanisms potentially involved include local changes of muscle and nerve function, synaptic strengthening in the ventral horn of spinal cord [13], and also remote changes in fronto-parietal activation between sensory and motor cortices and in corticospinal and intracortical motor excitability regulation [13,33,61,68]. These mechanisms of action were discussed in our last review, especially for the after-effects of PMS (named repetitive peripheral magnetic stimulation, rPMS), a novel easy-to-administer approach in neurological conditions affecting sensorimotor control [7] and in pain conditions affecting the musculoskeletal system [55,65]. Conversely to TES, rPMS is considered a painless method deemed to preferentially recruit proprioceptive afferents with minimal activation of cutaneous fibers [67,68]. However, rPMS popularity and applicability are limited owing to missing evidence and recommendations on parameters of application, conversely to TES whose guidelines are already published [15,62]. Furthermore, the preferential recruitment of cutaneous vs. proprioceptive afferents by rPMS over nerves and muscles and whether this preferential activation is beneficial in pathological conditions are still controversial topics [38,77,78]. The present work included all papers using rPMS as an intervention to improve somatosensory or motor disorders with limitations of musculoskeletal function. The primary objective was to review some selected parameters to refine rPMS application in future protocols. The work also discusses which afferents are preferentially recruited by rPMS and whether this basic knowledge has a potential clinical impact.

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RPMS parameters

Methods

The literature search was undertaken in 3 databases (Pubmed, CINAHL and SPORTDiscus) with no time restriction using the following search strategy: (peripheral magnetic stimulation) OR (spinal magnetic stimulation) AND (repetitive OR Hz OR Hertz) NOT ''repetitive transcranial magnetic stimulation'' NOT ''transcranial direct current stimulation''. Additional relevant studies were also hand-searched in the references list of the papers selected for the review. Articles that met the following selection criteria were retained for full-length examination: full-text original papers written in English, which used rPMS as an intervention to improve somatosensory or motor disorders that limit the musculoskeletal function.

Results

The literature search was ended in March 2015 and included 24 papers (Fig. 1). Sixteen studies had administrated rPMS in order to improve sensorimotor impairments caused by several neurological pathologies: multiple sclerosis [34,49—51], spinal cord injury [32], stroke [8,22,23,29,37,66,68], traumatic brain injury [37,66], cerebral palsy [19,20], traumatic brachial plexopathy [30] and Parkinson's disease [4]; eight studies used rPMS to reduce pain caused by various pathological conditions: musculoskeletal injuries [55], myofacial pain syndrome [64,65], complex regional pain syndrome [35], lumbosacral spondylotic pain [40] chronic low back pain [46], neuroma/nerve entrapment [39] and pudendal neuralgia/sciatica [60]. RPMS parameters were retrieved along with authors' justifications in each study, including coil design and location, coil orientation and current direction, duty cycle, duration, frequency and intensity (Table 1). Furthermore, because rPMS was used for two main purposes across the included studies (i.e. sensorimotor improvements or pain), a secondary analysis was performed to verify whether parameters differed between these therapy goals. Also, details concerning the use of sham stimulation in the included studies were reported.

Coil design and location

The information regarding the type of coil was provided in 22 of the 24 papers. The round coil (RC) and the figure-of-eight coil (Fof8) were respectively used in 7 and 12 studies. The three remaining studies used both Fof8 and RC, alternatively. The effects of coil design or location of stimulation were addressed in a few studies. Krause et al. [32,34,35] selected RC to stimulate lumbar and cervical spinal roots with higher magnetic strength, whereas Struppler's group [66,68] used Fof8 to selectively stimulate the superficial paretic muscles. Smania et al. [64,65] used Fof8 and RC over the superior trapezius muscle in alternation due to coils overheating, but they acknowledged that each coil presented specific advantages: Fof8 was better for accurate targeting of painful trigger points whereas RC enabled stimulation of deeper and larger painful muscle areas. In that vein, out of the 12 studies that used Fof8, 11 intended to stimulate superficial muscles or nerves and out of the 7 studies that used RC, 7 intended to reach deeper conductive structures such as spinal roots. Table 1 shows that this dichotomous use of Fof8 vs. RC was true either in studies focusing on sensorimotor improvements and in studies tackling pain reduction. The choice made by the authors on whether which coil to use relay on the impact of the between-coil differences of focality and depth of penetration on their objectives. The electric field induced in the tissue by RC and Fof8 can be visually inspected for focality in Figure 8 of [52] and for depth of penetration in Figure 7 of [44] and Figure 14 of [28]. RC is the less focal with a stimulated area equivalent to its diameter because electrical currents are produced along the whole winding [5]. Currents are in opposite directions in the two windings of Fof8, thus passing the coil's center in the same direction and the periphery in opposite directions. The resulting magnetic field is thus weaker at the periphery and 2—3 times stronger at the center [5] with a focus (called virtual cathode) that is relatively accurate (2.5—3.0 cm from coil's center to handle, Table 2) [52,58]. Fof8 thus enables the selective stimulation of nerves without co-activation of surrounding structures that often occurred with RC [53]. Nevertheless, RC focality can be significantly improved by tilting the coil 45° from the skin surface (see section ''Coil orientation and current direction'') [42] or by using smaller diameters [18], e.g. 7 cm diameter instead of 14 cm. Manufacturers must however respect a minimal size of coils to avoid unsafe heat dissipation produced by the large current flows [17]. Fof8 is therefore a better choice to selectively stimulate a specific muscle or a distal nerve, at least at weak intensities of stimulation [28]. Small peaks of half the amplitude of the center peak can be produced on either side of the windings and could depolarize conductive structures at greater intensities [28].

A recording probe in restricted and unrestricted volume conductors was used to study depth of penetration and it showed that fall-off of magnetic field with distance was faster with Fof8 than with RC [44], thus indicating that RC should be preferentially used to stimulate deeper structures. Indeed, a large-diameter RC was shown to be more suitable to depolarize deep structures such as spinal nerve roots at weaker intensities, especially if the edge of the coil coincides with the neuro-foramina [43]. For example, Chokroverty et al. [14] stimulated the L5/S1 nerve roots with RC and from the latencies of the direct motor response (direct recruitment of alpha-motor neurons) and spinal reflex loops (recruitment of 1a-fibers) recorded in the soleus muscle, they calculated that both afferent and efferent fibers were depolarized near the spine exit at the intervertebral foramina (20 cm from the anterior horn cells). In line with this, the laws of physics teach that the magnetic field, even if bypassing bones, will follow the path of less resistance, i.e. the electric current generated by magnetic stimulation concentrates at the entrance of the narrow channel formed by high-resistance structures of bones (foramina) [72].

Recommendations. Evidence suggests that RC is more efficient for stimulating the deep conductive structures. However, due to large diameter of action, if co-activation of other nerve roots is unwanted, a meticulous EMG monitoring of multiple muscles is recommended to adjust coil position for the specificity of stimulation. This procedure was already

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Table 1 Parameters of rPMS application.

Reference	Population	Coil type	Coil location	Coil orientation/Current direction	ON/OFF (s)	Duration (min)	Number of pulse	Frequency (Hz)	Intensity (T)
Sensorimotor impairments									
Nielsen et al., 1995	MS, $n = 12$	RC	Caudal part of the coil at T8	NM/NM	8/22	30	5760	12	0.95—1.2, above SMT
Nielsen et al., 1996	MS, $n = 38$	RC	Caudal part of the coil at T8	NM/NM	8/22	25	10,000	25	1.05—1.26, above SMT
Nielsen and Sinkjaer, 1997	MS, $n = 11$	RC	Caudal part of the	NM/NM	NA	NM	1	NA	1.26, above SMT
	HS, $n = 9$	RC	coil at T8, C7 and L3		Continuous	NM	16	25	1.26, above SMT
		RC			5/5	5	3750	25	1.26, above SMT
Heldmann et al., 2000	SK, $n = 14$ HS, $n = 7$	Fof8	Finger and hand extensors	NM/NM	NM	NM	NM	NM	Above MCT
Havel and Struppler, 2001	SK, $n = 1$	Fof8	Extensor indices proprius	NM/NM	1.5/NM[a]	NM	~2100	20	Above MCT
Kerkhoff et al., 2001	SK, $n = 14$ HS, $n = 7$	NM	Hand's dorsal palm	NM/NM	NM	20	NM	NM	NM
Struppler et al., 2003	SK, $n = 47$ TBI, $n = 5$	Fof8	Extensor indices proprius	NM/NM	1.5/4	~15	4500	20	Above MCT
Krause et al., 2004	VSP, $n = 15$ HS, $n = 16$	RC	2 cm paravertebral between L3 and L4	TE/NM	10/40	~8.3	2000	20	20% above SMT
Krause and Straube, 2005	SCI, $n = 1$	NM	Over lumbar nerve roots	NM/NM	10/NM	~20	2000	20	20% above SMT
					10/NM	~30	2000	15	20% above SMT
					10/NM	~40	2000	10	20% above SMT
Struppler et al., 2007	SK, $n = 8$	Fof8	Finger/hand extensors	Adjusted/NM	1.5/4	~15.3	5000	20	1.2, above MCT
Khedr et al., 2012[b]	TBP, $n = 34$	Fof8	Superior trapezius	NM/NM	10/20	~3.5	1050	15	Below MCT
					10/30	~33.3	1500	3	1.54, above MCT
Flamand et al., 2012	CP, $n = 5$	Fof8	Tibial nerve	FL/NM	Continuous	1	900	TB (15)	Above MCT
			Common peroneal nerve		2/8	5	900	TB (15)	
Arii et al., 2014	PD, $n = 37$	RC	Over thoraco-lumbar vertebras[c]	ST/NM	1/10	~1.3	40	5	1.0, above SMT

Table 1 (*Continued*)

Reference	Population	Coil type	Coil location	Coil orientation/Current direction	ON/OFF (s)	Duration (min)	Number of pulse	Frequency (Hz)	Intensity (T)
Flamand and Schneider, 2014	CP, $n=1$	Fof8	Sciatic nerve Tibial nerve Common peroneal nerve	FL/NM	Continuous Continuous 2/8	3 1 5	2700 900 900	TB (15)	Above MCT
Krewer et al., 2014	SK, $n=60$ TBI, $n=3$	Fof8	Arm muscles[d]	NM/NM	1/2	~10	5000	25	10% above MCT
Beaulieu et al., 2015	SK, $n=18$	Fof8	Tibialis anterior	FT/NM	2/8	3.33	600	TB (15)	1.47, above MCT
Pain conditions									
Pujol et al., 1998	MKI, $n=30$	Fof8 RC	Various painful musculoskeletal structures	NM/NM	5/25	40	8000	20	Below MCT
Sato and Nagai, 2002	PN, $n=4$ Sciatica, $n=1$	RC	Over S2—S3	TE/NM	Continuous	1—2	30—50	< 0.5	1.5, above MCT
Smania et al., 2003	MPS, $n=18$	Fof8 RC	Most painful superior trapezius trigger point	NM/NM	5/25	20	4000	20	Below MCT
Smania et al., 2005	MPS, $n=53$	Fof8 RC	Most painful superior trapezius trigger point	NM/NM	5/25	20	4000	20	Below MCT
Krause et al., 2005	CRPS, $n=12$ HS, $n=10$	RC	Over C7—C8	NM/NM	10/NM	~10	NM	20	20% above SMT
Lo et al., 2011	LSD, $n=20$	Fof8	Over cauda equina (T12—L1)	FL/NM	0.5/4.5	~16.7	1000	10	Below MCT
Massé-Alarie et al., 2013	CLBP, $n=13$ HS, $n=9$	Fof8	Transversus abdominis/obliquus internus	NM/NM	2/8	10	1800	TB (15)	1.16, above MCT
Leung et al., 2014	N/NE, $n=5$	Fof8	Over the site of N/NE	NM/NM	Continuous	~13.33	400	0.5	NM

ON: phase of active stimulations; OFF: phase of rest (no stimulation); T: Tesla; MS: multiple sclerosis; RC: round coil; C7—C8—T8—T12—L1—L3—L4—S2—S3: refer to either cervical (C) — thoracic (T) — lumbar (L) or sacral (S) vertebrae; NM: not mentioned; SMT: spinal motor threshold; HS: healthy subject; NA: not applicable; SK: stroke; Fof8: figure-of-eight; MCT: muscle contraction threshold; TBI: traumatic brain injury; VSP: various spinal disorders; TE: flat tangential edge; SCI: spinal cord injury; TBP: traumatic brachial plexopathy; CP: cerebral palsy; TB: theta-burst frequency; FL: flat longitudinal; PD: Parkinson disease; ST: symmetrical-tangential; FT: flat transverse; MKI: various musculoskeletal injuries; PN: pudendal neuralgia; MPS: myofacial pain syndrome; CRPS: complex regional pain syndrome; LSD: lumbosacral spondylotic pain; CLBP: chronic low back pain; N/NE: neuroma/nerve entrapment.

[a] The authors applied approximately 70 cycles of 1.5 sec each.

[b] Two different rPMS interventions were separated by a 10-min resting period.

[c] Adaptation of coil placement helped target the largest spinal anteflexion in standing posture for each participant (photograph or spinal X-ray films).

[d] Stimuli were distributed among arm/forearm extensor and flexor muscles.

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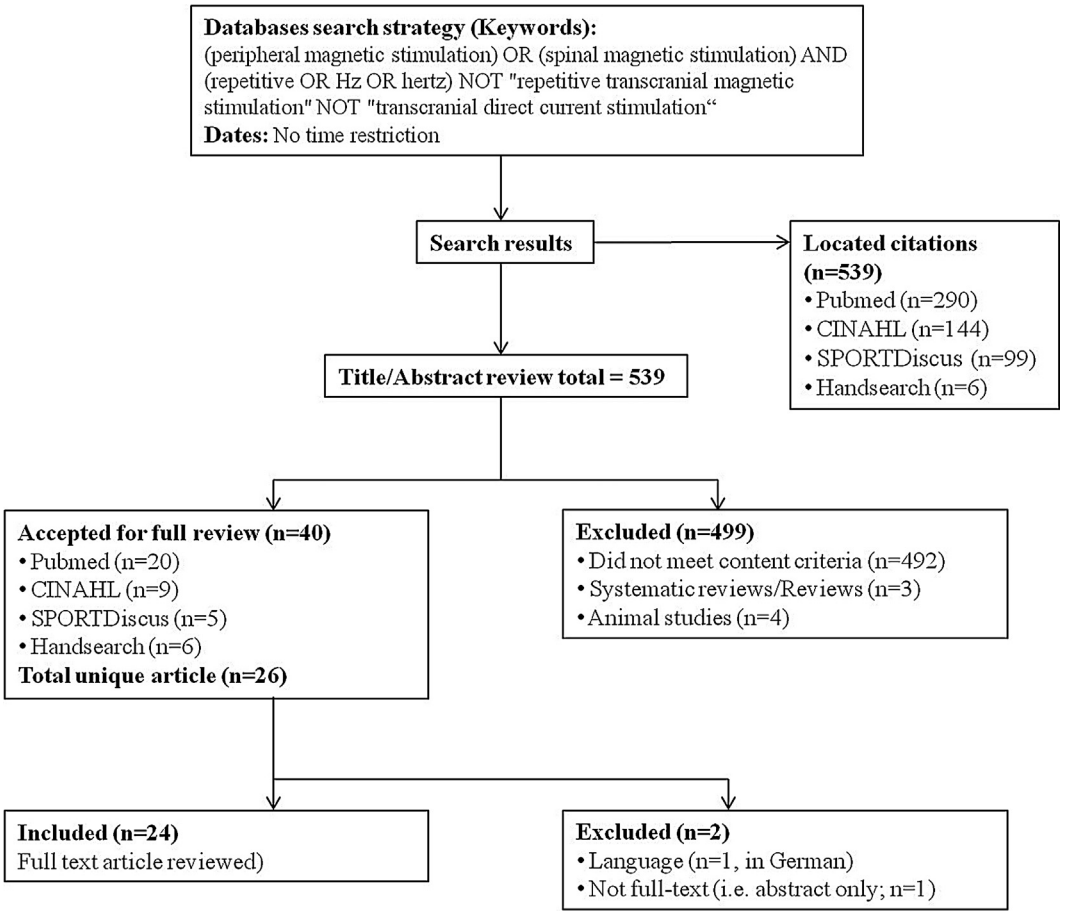

Figure 1 Flow chart of the review's research strategy. CINAHL: cumulative index to nursing and allied health literature.

Table 2 Pros and cons of magnetic stimulation applied at the periphery.

Advantages	Disadvantages
Painless[a] [3,5,6,10,14,16,17,21,26,36,41,54,56,71,73,77]	Locus of stimulation not well-defined[a] [3,5,6,11,17,38,42,56,73]
Non-invasive [3,5,6,10,14,16,17,41,54,56,73,77]	Slowed by overheating of the coil[a] [5,6,10,11,38,42,56]
Deeper penetration[a] [3,5,6,14,16,17,41]	Larger area stimulated with increased intensity [3,6,17,52,56,74]
Easy administration [3,5,6]	Bulky and expensive equipment[a] [5,6]
Induces higher muscle torque[a] [21,26,36]	Muscle contractions uncomfortable at higher intensities [11,17]
Useful in children stimulation [3]	Time-consuming for positioning because site of stimulation and orientation more critical[a] [11]
Separate stimulation of a variety of different muscles[a] [77]	Coil often displaced by muscle contractions [11]
Induces better torque output, smoothness, and symmetry of pedaling movement on a cycling ergometer in patients with stroke, SCI or MS and with partially or completely preserved sensitivity[a] [70,71]	Induces lesser torque output and power of pedaling movements on a cycling ergometer in patients with complete SCI[a] [70]

M-responses: muscle contraction evoked by the direct depolarisation of the α-motor neuron axons in the stimulated nerve; H-responses: Hoffmann reflexes; SCI: spinal cord injury; MS: multiple sclerosis.
[a] As compared to electrical stimulation.

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followed to target a nerve root [34,35,45]. Conversely, Fof8 is appropriate for selective recruitment of superficial structures, such as muscles and nerves, without co-activation of surrounding tissues. Future studies will have to compare the effectiveness and selectivity of different coil designs at different sites of stimulation.

Coil orientation and current direction

Seven studies provided sufficient details on the specific orientation of the coil relative to the target structure but none informed on current direction within the coil (Table 1). Four studies used basic data to support coil orientation over spinal roots [34], nerve trunks [19,20] and muscle [8]. Another study performed pilot testing to determine the optimal coil position/orientation over spinal roots [4]. The two last studies did not justify their coil orientation [40,60]. Interestingly, one study reported that coil orientation was adapted per participant to induce the strongest contraction/movement [68]. The following paragraphs depict the basic knowledge underlying the selection of coil's orientation and current direction for rPMS application.

In the late 1980s, basic studies tested how different orientations of coil and direction of electrical current in the coil impacted on the effectiveness of magnetic stimulation to depolarize peripheral conductive structures. Maccabee et al. [42,44] reported six RC orientations relative to the longitudinal axis of a conductive structure, as follows, from the most to the lesser effective to induce large amplitudes of electrical current: flat tangential edge (0° to horizontal/0° to axis); tilted (45° to horizontal/0° to axis); orthogonal-longitudinal (90° to horizontal/0° to axis); orthogonal-rotated (90° to horizontal/45° to axis); symmetrical-tangential (0° to horizontal/90° to axis); transverse (90° to horizontal/90° to axis) (see Figure 3 in [42] and Figure 9 in [44]). The three former orientations produced strong muscle contractions but the tilted and orthogonal-longitudinal were more accurate with minimal loss of effectiveness [17,42,44]. Two orientations were tested for Fof8 coil with the flat longitudinal (0° to horizontal/0° to axis) more effective than the flat transverse (0° to horizontal/90° to axis) (see Figure 5 in [44]). Higher effectiveness was explained in all cases by the optimal location of virtual cathode and anode along the course of the conductive structure [44].

It was also questioned whether reversing the current direction, i.e. interchanging the cathode/anode virtual position along the nerve without changing coil orientation, could influence the effectiveness of stimulation [1,17,42,48,76]. Over cervical spinal roots, motor latencies are relatively unaffected by current direction because the depolarization site remains similar at the low threshold region near neuro-foramina [72,76]. Over a nerve, when the virtual cathode is proximal (further from muscle) and the anode distal (closer to muscle), the current is directed toward the muscle (see Figure 6 in [42]). In this case, given that fibers are depolarized under the cathode, muscle response latencies are slightly longer and amplitudes slightly lower [1] or unaffected [42,48] as compared to a current directed toward the spine (distal cathode, proximal anode) and for which stronger muscle contractions are induced at lower intensities [76]. In order to explain why muscle action potentials were smaller when the cathode was located proximally, Tuday et al. [75] used EMG recordings (muscle action potentials) and electroencephalography (sensory evoked potentials) and showed that the cathodal depolarization triggered bidirectional action potentials along the nerve and that propagation to the anode was blocked or attenuated by local hyperpolarization (anodal block). Finally, the impact of coil orientation and current direction on muscle belly stimulation has not yet been thoroughly studied. Theoretically, nerve endings roughly follow muscle fiber orientation, especially for long parallel and fusiform muscle shapes; thus this may be a starting point for selection of coil orientation/current direction. However, recent evidence with the Fof8 coil suggested that even a flat transverse orientation relative to the tibialis anterior muscle axis is effective in inducing contractions and movements [8]. Also, it was impossible to predict which orientation/current direction would be more effective to activate a peripheral structure with no longitudinal axis (for example, the trigger point of painful trapezius muscle [64,65]).

Recommendations. Basic knowledge is sufficient to select a coil orientation that will efficiently stimulate a nerve trunk or spinal root. However, there is limited evidence for other peripheral conductive structures (such as muscles) where fibers orientation varies between individuals. Also, the choice of the most efficient coil current direction remains hypothetical (anodal block). Thus, care should be taken at the onset of future rPMS studies for testing the combination of coil orientation and current direction that will best respond to the objectives of the intervention. Researchers should be aware of the fact that different combinations may be required to induce either stronger muscle contractions [68] or better-tolerated sensations when stimulating injured musculoskeletal structures [55,75].

Duty cycle

Seventeen papers used intermittent stimulation and provided details on the duration of ON (active stimulation) and OFF periods (pause) of rPMS application, two studies used continuous stimulation (i.e. no OFF), two studies combined intermittent and continuous stimulation, one study used only ON periods and the information was missing in two studies (Table 1). In intermittent protocols, OFF periods were overall 4.4 ± 2.2 times longer than ON periods. More specifically, OFF periods were longer in studies using rPMS to reduce pain (mean ratio OFF/ON: $5.7 \pm 1.8\%$) than in studies focusing on sensorimotor impairments (mean ratio: $3.9 \pm 2.2\%$). However, no rationale supported between-study differences thus this result might be fortuitous. Anecdotally, it was mentioned that pilot testing in myofacial pain syndrome (four participants) helped determine that 5 s ON duration had better therapeutic effects than 1 s or 3 s [64]. Also, the specific duty cycle of theta-burst frequency protocol (2 s ON/8 s OFF) was used in four studies but no rationale was proposed to support this choice [8,19,20,46]. The choice of longer OFF periods was however related in several studies to coil overheating which is a major problem in repetitive magnetic stimulation protocols (see Table 2) especially in former rPMS studies [50,51]. Most authors used a coil-implemented cooling device while others prevented overheating by using two coils in alternation

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[32,34,55,64,65]. However, despite the advent of improved devices for rapid-rate stimulation, repetitive magnetic stimulation cannot yet be conducted for long durations without a parallel adjustment of intensity, frequency or OFF duration. Seven studies postulated that intermittent ON/OFF periods of rPMS above muscle contraction threshold (rather than continuous) produced physiological contraction/relaxation of muscles and generated massive proprioceptive inflows to sensorimotor networks by ascending pathways, thus influencing neuroplastic mechanisms [8,19,20,46,66,68] and avoiding unnecessary fatigue of paretic muscles [8]. They did not however justify the ON and OFF durations chosen. Specifically, Flamand et al. [19,20] applied intermittent ON/OFF rPMS over the common peroneal nerve to mimic contraction/relaxation of the paretic ankle dorsiflexors in cerebral palsy just after the application of continuous stimulation (no OFF) over the tibial nerve [19,20] and the sciatic nerve [19] to reduce the reflex hyperactivity of the triceps surae and hamstrings circuits. They hypothesized that continuous rPMS could best induce transient saturation (i.e. inhibition) of hyperactive spinal circuits of spastic muscles.

Recommendations. The selection of a specific ON duration seems arbitrary whereas applying longer OFF periods depends on technological limitations related to magnetic stimulators. Although the choice of protocols relies on interesting hypotheses, no study has yet evaluated the specific after-effects of continuous (ON with no OFF) versus intermittent rPMS protocols (ON/OFF) in physiopathology. Two pilot studies [19,20] proposed a rationale for each protocol (intermittent to improve motor control of the paretic muscles; continuous to down-regulate spinal circuits of spastic muscles), but applied them in combination, thus challenging the detection of a specific influence. When repetitive magnetic stimulation is applied over the skull, intermittent protocols may help minimize the risk of tissue heating, magnetic field exposure and side effects: this safety issue was recently dealt by the International Federation of Clinical Neurophysiology [57]. Although this knowledge cannot be directly transferred to rPMS application (at the periphery), the question remains whether longer continuous protocols could increase the risk of adverse events. Table 3 shows that rPMS side effects are not often reported and insights on rPMS safety remain insufficient. Future studies should thus test the after-effects of ON vs. ON/OFF protocols and report any side effect. If rPMS are to be administrated over a long period of time or with short OFF periods, then a minimal safety measure should be the use of a coil-implemented cooling device.

Duration/total number of stimuli

Twenty-two studies reported on the total duration of rPMS application or gave sufficient details on frequency, ON/OFF repetitions, number of stimuli, etc., to infer the information. Twenty-one studies reported on the total number of stimuli. Given inconsistent length of OFF periods across studies, the total number of magnetic pulses appeared to be a more relevant parameter and more readily comparable between studies. This parameter is also considered a determining factor of effectiveness in brain stimulation studies [57]. Results from rPMS duration and number of stimuli are discussed together because they were not different between studies on sensorimotor impairments (mean $\pm$ SD = 13.5 ± 9.5 min and 2979 ± 2527 stimuli) and studies on pain reduction (13.1 ± 7.5 min and 2749 ± 2814 stimuli).

Overall, duration of stimulation and number of stimuli are highly variable across studies (13.4 ± 8.8 min and 2914 ± 2552 stimuli). Their choice missed rationale, although some authors relay on evidences from previous studies with rPMS [45,64] or protocols published for repetitive transcranial magnetic stimulation [8,19,20,46]. One study tested three different rPMS frequencies (20, 15 and 10 Hz) and durations (20, 30 and 40 min) but with always the same number of stimuli [32] thus did not investigate the effect of changing rPMS duration/number of pulses per se. Another study tested how different numbers of rPMS stimuli above thoraco-lumbar spinal roots, thus with different durations and always the same frequency (25 Hz), influenced the soleus spinal excitability measured by H-reflex (electrical analogue of stretch reflex) [49]. It was reported that increasing the number of stimuli decreased more H-reflex and for a longer time, especially in multiple sclerosis where 5-min rPMS (3750 stimuli) down-regulated H-reflex during 28 min [49]. Also, spasticity of lower limbs (assessed by ordinal scale) decreased more in multiple sclerosis when the total number of stimuli was almost twice higher (i.e. from 5760 [51] to 10,000 [50] pulses). However, although the two previous studies used the same coil type, location and duty cycle, the latter used higher frequency and intensity of rPMS thus mitigating the interpretation of results. Recent works with theta-burst frequency showed that short rPMS durations (3—10 min) applied on lower limb muscles in stroke [8] and cerebral palsy [19,20] and over deep abdominal muscles in combination with manual therapy in chronic low back pain [46] improved spasticity, corticomotor control and pain. The total number of stimuli in a theta-burst session was similar to longer classic repetitive protocols, i.e. between 600—4500 pulses. Interestingly, two studies reported that a single rPMS session with a total of only 30—50 magnetic pulses induced significant long lasting pain reduction in pudendal neuralgia or sciatica [60] and improvement of postural abnormality in Parkinson's disease [4].

Recommendations. The scarce data available tend to show that longer rPMS durations or larger numbers of stimuli may better impact on sensorimotor systems. However, this is not yet clear because significant and long lasting improvements could have been obtained recently after short lasting application of rPMS with either a small number of pulses or instead, a high number of stimuli (available in complex stimulation patterns such as theta-burst stimulation). Clinical studies are warranted to test the efficiency of such protocols in terms of time-consumption, persistence of effects, improvement of function and quality of life, before any knowledge transfer.

Frequency

Eleven studies applied rPMS at a frequency of 20—25 Hz (Table 1), six studies used 15 Hz or less, one study used different frequencies, four studies used theta-burst stimulation (5 Hz trains of three pulses elicited at 50 Hz, see Figure 1a in [24]) and the information was missing in two papers. Very low frequencies (≤ 0.5 Hz) were used only in

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Table 3 Side effects of magnetic stimulation applied at the periphery.

Reference	Side effects
Sensorimotor impairments	
Nielsen et al., 1995	No major side effects. All reported a ''tight feeling as if wearing a narrow ring around the midthoracic level during stimulation''. One participant had a single episode of brief dizziness
Nielsen et al., 1996	Two participants complained of irregular heartbeats 2 hours after stimulation, but showed a normal rhythm on electrocardiogram. One participant complained of low cost-benefit ratio, mostly because of long transportation time. All reported a ''tight feeling as if wearing a narrow ring around the midthoracic level during stimulation''. Two episodes of brief dizziness were reported immediately after rPMS
Nielsen and Sinkjaer, 1997	All reported a ''tight feeling as if wearing a narrow ring around the midthoracic level during stimulation''. This feeling was well tolerated, except for one who refused to participate to the final study part applying a longer stimulation duration
Heldmann et al., 2000	NM
Havel and Struppler, 2001	NM
Kerkhoff et al., 2001	NM
Struppler et al., 2003	Two participants developed a slight rigidity in the stimulated arm
Krause et al., 2004	NM
Krause and Straube, 2005	NM
Struppler et al., 2007	NM
Khedr et al., 2012	RPMS was well tolerated by all participants, without any adverse effects
Flamand et al., 2012	No side effects reported. The children ''demonstrated curiosity and enjoyment from one session to another, laughing with their parents when the foot on the stimulated side was moving on its own''
Arii et al., 2014	No major safety issues. No participant reported pain during rPMS, but two reported mild discomfort 1–3 hours after rPMS that disappeared by the next day
Flamand and Schneider, 2014	NM
Krewer et al., 2014	RPMS and sham were well tolerated by all participants. None reported pain or uncomfortable feeling during or after the treatments
Beaulieu et al., 2015	NM
Pain conditions	
Pujol et al., 1998	RPMS was well tolerated by all participants. None reported excessive discomfort or pain during and immediately after the treatments
Sato and Nagai, 2002	RPMS was well tolerated by all participants without any adverse effects
Smania et al., 2003	NM
Smania et al., 2005	High intensity rPMS did not cause any significant discomfort
Krause et al., 2005	NM
Lo et al., 2011	RPMS was well tolerated by all participants without any adverse effects
Massé-Alarie et al., 2013	No adverse effect reported after rPMS
Leung et al., 2014	NM

RPMS: repetitive peripheral magnetic stimulation; NM: not mentioned.

studies focusing on pain reduction [39,60], thus results from sensorimotor impairments and pain conditions are discussed separately.

Sensorimotor impairments. Three studies [8,19,20] applied the theta-burst frequency without providing a sound rationale. Two studies compared the effectiveness of different frequencies, and their results questioned whether rPMS frequency influenced the outcomes. They showed that frequency used for paravertebral rPMS did not actually impact on the reduction of spinal excitability (assessed by soleus H-reflex in three healthy subjects) [49] or of muscle tone (assessed by the Modified Ashworth Scale and the Wartenburg's Pendulum Test in a case of spinal cord injury) [32]. Precisely, Nielsen and Sinkjaer [49] showed that the only difference was a more pronounced H-reflex inhibition at 10 and 25 Hz than at 1 Hz but Krause and Straube [32] did not reproduce any difference between 10, 15, and 20 Hz. A sixth study [66] reported longer lasting improvements of spasticity and motor control with 20 Hz rPMS. This result differed from the authors' previous German-written study (not included in the review) where better improvements were obtained with 40 Hz in about half of their participants with various spastic disorders. They proposed that rPMS after-effects might depend on the spastic paresis pathogenesis.

Pain conditions. As for duration/number of stimuli, some authors justified the frequency used on the basis of previous rPMS studies [64] or on results from repetitive transcranial magnetic stimulation (rTMS) literature [39,46]. Frequency below 1 Hz could have been used to reduce pain because low frequency rTMS of the motor cortex induces a transient inhibition of cortico-cortical connections [39]. It was

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hypothesized that low-frequency rPMS over the site of neuroma/nerve entrapment could inhibit neural hypersensitivity and thus reduce pain. In the same vein, a former study by Sato and Nagai used frequencies below 0.5 Hz in cases of painful nerve hypersensitivity caused by pudendal neuralgia or sciatica [60]. However, all other studies used frequencies higher than 10 Hz and significantly reduced pain [35,40,46,55,64,65]. This discrepancy (low vs. high frequency to reduce pain) may be related to the existence of different origins of the pain conditions, those studies with higher frequencies having not included nerve irritation/hypersensitivity. One study [46] used theta-burst frequency and refereed to Huang et al. [24] seminal work on brain stimulation but no rationale was provided to select this specific stimulation pattern at the periphery.

Recommendations. No evidence yet allows determination of whether rPMS frequency is a factor of influence for the outcomes tested. Although appealing, the rationale for using very low frequency in order to reduce pain caused by nerve hypersensitivity comes from insights on motor cortex inhibition by transcranial stimulation. No neurophysiological data can yet confirm whether this hypothesis is true with rPMS administration. Also, H-reflex hyperexcitability was best inhibited when using higher rather than lower rPMS frequencies over spinal roots. However, this knowledge is based on too small-sampled studies for any clear conclusion to be drawn. Future studies ought to test larger samples with different frequencies over the same locations. Also, no evidence tackled the impact of using lower versus higher frequencies in terms of quality of muscle contractions. Evidence from rPMS at sufficient intensity to produce muscle contractions denote that lower frequencies (for example 5 Hz and less [4]) and theta-burst frequency [8] induced muscle twitching whereas higher frequencies (for example above 10 Hz) produced sustained muscle contractions due to temporal summation of motor units recruitment [26]. When compared to sustained contraction, muscle twitching gave rise to more but weaker contractions and smaller joint movements. For example, 5 Hz rPMS-induced 5 weak contractions or small movements per second while 20 Hz induce one strong contraction or larger movement during the whole ON period. It would be of interest to address, for example, whether frequencies producing sustained contractions or muscle tetanus impact differently from those producing muscle twitching. Sustained contraction may be chosen to strengthen muscles [21,26] and muscle twitching would be a better choice to improve movement by mimicking contractions/relaxations [7] and triggering massive proprioceptive inflow towards fronto-parietal areas [68].

Intensity

Nine papers provided rPMS intensity in Tesla or in percentage of the maximal stimulator output (%MSO then transformed in Tesla if MSO value available). However, the magnetic field strength at the depth of the targeted structures cannot be estimated because it depends on the type of coil, the depth of tissue stimulated and the geometry of the area beneath the coil [28]. A solution could be the expression of rPMS intensity in percentage of muscle contraction threshold. However, accurate surface EMG determination of this threshold can be contaminated by rPMS artifacts when the coil is placed near the recording electrodes [11]. Also, visual detection of slight contractions is challenging, especially when the coil is positioned directly above the muscle. Alternatively, movement threshold and spinal motor threshold correspond to the lowest rPMS intensity eliciting respectively a joint movement detected visually and the minimal intensity to depolarize a nerve root and evoke contraction of innervated muscles. Some authors thus expressed rPMS intensity in percentage of movement threshold [37] or spinal motor threshold [32,34,35]. The present review details such information on threshold when available in papers and if not, it refers to supra-threshold versus sub-threshold stimulation when reported, i.e. intensity eliciting muscle contraction or not. Almost all papers set supra-threshold rPMS (i.e. 17 studies, Table 1), four used sub-threshold intensities, one used both supra- and sub-threshold protocols and the information was missing in two studies. Of note, all studies using sub-threshold intensities focused on pain reduction. The study with both protocols [30] was in traumatic brachial plexopathy participants: sub-threshold rPMS was used to reduce shoulder pain and rPMS inducing strong muscle contractions was used to strengthen the trapezius muscle affected. Therefore, rPMS studies aiming at improving sensorimotor impairments vs. decreasing pain are discussed separately.

Sensorimotor impairments. The rationale available in studies supports that muscle contraction and joint movement produce massive ascending flows of proprioceptive afferents thus influencing the plasticity of residual sensorimotor circuits available for recovery after lesion or disease of central or peripheral nervous system [20,23,30,68] (see Beaulieu and Schneider, 2013 [7] for a review). Two papers specifically tested how changing rPMS intensity could influence the outcomes. Nielsen and Sinkjaer [49] showed in three healthy subjects that soleus H-reflex was more depressed when rPMS intensity over spinal roots was increased from 30% MSO (minor contractions) to 45% MSO (moderate contractions) and 45—60% MSO (strong contractions), thus suggesting that the magnitude of after-effects could be intensity-dependent. In line, Krause et al. [32] compared the influence of supra-threshold (120% MSO) and 'sham' rPMS consisting of sub-threshold stimulation (50% MSO) of spinal roots in a spinal cord injury case and reported that supra-threshold rPMS reduced lower limb spasticity whereas sub-threshold did not influence.

Pain conditions. Most studies [40,55,64,65] referred to evidence from the electrical stimulation literature where intensity of pure sensory stimulation (i.e. transcutaneous electrical stimulation insufficient to induce muscle contraction) was effective to reduce pain in various disorders. However, two rPMS studies [35,60] that used supra-threshold intensities to reach deep spinal roots still observed a significant reduction of pain. The last study was on chronic low back pain [46]: the authors refereed to the influence of rPMS-induced proprioceptive afferents on cortical sensorimotor plasticity and used supra-threshold rPMS over the transversus abdominis muscle to improve lumbar spine motor control and reduce pain.

Recommendations. Intensity seems to be a determining factor for rPMS after-effects. The choice depends on the depth of the targeted structure and on the afferents recruited, thus a different rationale is used to influence sensorimotor impairments or to reduce pain. However,

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the section ''Preferential afferents recruitment'' of this review deals with the capacity of rPMS to strongly activate cutaneous fibers as compared to electrical stimulation and thus questions the potential of sub-threshold intensity in rPMS protocols. The expression of intensity relative to a specific threshold should help standardize the procedures and compare results between studies. Methodological studies are warranted to circumvent or reduce surface EMG recordings contamination by rPMS artifacts and enable motor threshold determination. Importantly, the use of high intensities reduce the magnetic coil's focality [1] thus a compromise between intensity and focality should help selectively recruit a muscle whose spinal and corticospinal excitability have to be influenced without co-activation of surrounding structures.

Sham stimulation

Sham-controlled protocols contribute to evidence especially for demonstrating the effectiveness of a new approach, such as rPMS. A very limited number of rPMS studies used a placebo [7] and this section details the methods they used.

Plastic or air isolation. Nielsen et al. [50] used real rPMS but with a 15-cm plastic tube inserted between the coil and the skin. A recent study rather maintained the coil away from the participant, i.e. without skin contact [30]. These two studies shared the advantage of producing the same clicking noise associated with repeated magnetic stimulation and the former [50] also ensured a same skin contact between rPMS and sham stimulation.

Coil position/orientation and stimulation parameters. Two studies tilted the round coil vertically (i.e. orthogonally relative to muscle or nerve fibers) and either reduced stimulation intensity and frequency [55], or kept the same parameters as for real rPMS [40]. Significant differences were detected between groups treated with rPMS (improvements) and sham (no effects or slight improvements). However, the orthogonal orientation of a round coil relative to fibers can reduce muscle contraction by only 25% [42] and a 45- to 90-degree orientation can even improve stimulation focality with minimal loss of magnetic strength [3,17,44,58], thus mitigating the choice of orthogonal orientation for sham stimulation. Transverse placement of the coil relative to the fibers could be less effective thus preferred for sham (see Figure 3 in Maccabee et al. [42]). The situation is relatively similar for the figure-of-eight coil whose small peripheral peaks produced around the windings are about half the amplitude of the central peak [28]. Two studies used the same position/orientation of coil between rPMS and sham series but reduced intensity in sham [32,46] in order to avoid muscle [46] or spinal root activation [32]. A recent study in stroke to improve ankle motor control [8] also used a very low intensity but with the coil positioned over the metatarsals to ensure that no muscle was beneath the sham stimulation. The tingling sensation produced by magnetic stimulation over the skin presents the advantage of more easily blinding participants but differences in sensory coding between higher (rPMS) and lower magnetic strength (sham) are unknown. Therefore, convenient orientations/parameters of rPMS coil for sham stimulation may combine a transverse and orthogonal tilting with the use of lower intensity away from nerve trunks or muscles (like in [55]).

Inactive intervention. Two studies applied an ultrasound device that was turned off [64,65]. The obvious disadvantage of using turned-off devices is the risk of nocebo effect when the participant is aware that he/she may receive a sham or a real intervention [27]. Therefore, the use of a sham coil where strength and frequency of the clicking noise was similar to rPMS but with no magnetic stimulation or other methods homogenizing sham and rPMS devices is preferred. For example, two coils could be used and hidden from the participants, one inactive positioned over the skin and one active and triggered away from the participants [2,37]. Earplugs could also be used to reduce possibilities for the participant to distinguish between rPMS and sham stimulation [9].

Recommendations. Various techniques are described for sham stimulation and it appears that the obvious sensations elicited by rPMS (i.e. tingling, muscle contractions) challenge the effectiveness of any placebo tested. It is therefore important to recruit participants with no previous experience of magnetic stimulation and who are naïve to what they receive (rPMS or sham). Amongst all techniques reported, the sham coil is preferred, as it shares the same skin contact and noise patterns with real rPMS. However, less expensive alternatives were described with minimal disadvantages and successful blinding of participants.

Preferential afferents recruitment

Understanding how peripheral magnetic stimulation recruits fibers is crucial to better tackle the pros and cons of magnetic stimulation compared to electrical stimulation, as denoted in Table 2, and to point out the potential impact in clinical research and physiopathology when administrated with a repetitive pattern (rPMS). This section on the magnetic stimulation principles of action essentially concerns the preferential recruitment of fibers as compared to electrical stimulation, even if intensities between both methods cannot be directly compared due to a distinct mode of energy transfer (magnetic vs. electrical).

Preferential recruitment over a nerve trunk

Preferential fibers recruitment when varying stimulation intensity differs between magnetic and electrical stimulation of a nerve trunk. Low intensities of electrical stimulation selectively recruit the large-diameter 1a-fibers (giving rise to H-response of the muscle via the mono- or disynaptic reflex loops between 1a-fibers and alpha-motor neurons) whereas higher intensities are required to recruit the motor neuron axons (giving rise to short-latency M-response of the muscle) [25]. Hence, at maximal electrical stimulation that gives rise to M-plateau almost all 1a-fibers are recruited too [25]. The same was not observed for magnetic stimulation, with M-response easily produced at low intensities and H-reflex being recorded at same or greater stimulus strength [41,77] or even not obtained [17]. A difference in pulse conformation and duration could underlie the different order of fiber recruitment between magnetic stimulation (0.05 ms spike) and electrical (longer square-wave,

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0.2—1 ms). Indeed, M-response and H-reflex thresholds can be similar if electrical pulse is shortened to a pulse duration similar to magnetic, as already reported by Zhu and Starr [77]. Also, electrical stimulation transfers electrons to the skin and produces superficial ion flows with some ions passing through nearby axons; the resulting density of current is thus limited to the skin and efficacy of recruitment depends more on the depth and impedance of tissues beneath the coil. Conversely, the time-varying magnetic field bypasses skin without any resistance and induces a voltage difference between two virtual points thus resulting in a secondary ion flow in the tissues [31]. Theoretically, magnetic stimulation triggers an electric field in any volume (even in air or free space) but electrical current will flow only in a conductive volume, such as a nerve [5]. This illustrates why motor fibers are magnetically recruited at the same threshold as sensory fibers, which is not the case with electrical stimulation.

Given its negligible attenuation by skin impedance and depth, magnetic stimulation can activate the dorsal spinal roots with tolerable intensities (Table 2). This was confirmed by electroencephalography recordings of somatosensory evoked potentials (SEPs) in sensory areas of brain with latencies shorter for magnetic than for electrical stimulation [73,74], thus reflecting the recruitment of large-diameter proprioceptive afferents. The authors suggested that magnetic stimulation could directly activate roots whereas electrical stimulation, at tolerable intensities in their protocol, most likely depolarized the cutaneous branch of the dorsal primary ramus of spinal nerves [73,74].

Preferential recruitment over a muscle

Magnetic stimulation over a muscle belly can trigger muscle contractions at relatively low intensities with minimal cutaneous sensations. Conversely, with electrical stimulation, muscle contraction threshold can be higher than depolarization threshold of cutaneous and nociceptive receptors. In line, SEPs evoked in brain by electrical stimulation of the vastus lateralis muscle, even at high intensity, could be completely suppressed by a procaine nerve block of the lateral femoral cutaneous nerve whereas the same injection during magnetic stimulation had no effect on the early SEPs components and only modified the late components [77]. Furthermore, compared to electrical stimulation of digital nerves (using ring electrodes), magnetic stimulation over the finger pads (with no underlying motor fibers) failed to produce synchronized SEPs, even at high intensity [38]. These studies strongly suggested that magnetic stimulation, in contrast to electrical stimulation, could not depolarize the thin superficial cutaneous nerves. Therefore, SEPs induced by rPMS over a muscle may be less contaminated by cutaneous inflows [77] and depend more on muscular proprioceptive afferents [68]. However, it remains unclear whether magnetic stimulation over a muscle produces SEP via the direct activation of 1a-afferents from the spindles, or indirectly via muscle contraction and joint movement that stretch spindles or excite Golgi organs. For example, SEP latencies were compared in 14 healthy individuals between magnetic stimulation of gastrocnemius muscle and electrical stimulation of the posterior tibial nerve at the ankle and it was shown that SEPs were of similar sequential components (P40, N50, P60, N70, and P100) but peaked 0.2 to 8.9 ms earlier for electrical stimulation, even if the stimulation was elicited more distally [77]. The authors thus suggested that SEPs, induced by magnetic stimulation over the muscle belly, did not result from a direct recruitment of sensory fibers (such as 1a-afferents). These longer latencies of SEPs elicited by magnetic stimulation could alternatively be explained by the indirect recruitment of 1a-afferents from the contracting muscle, from its joint antagonist stretched by the induced movement or from the activation of 1b-afferents subsequent to fiber shortening in the contracting muscle. Kunesh et al. [38] conversely found that SEPs latencies of electrical and magnetic stimulation at the wrist were similar, thus suggesting that proprioceptive fibers were directly activated by both types of stimulations. These authors however nuanced that indirect activation of proprioceptive afferents was more likely to occur for the coil over a muscle belly far from nerve trunks, which was the case for gastrocnemius's experiment of Zhu and Starr [77] but not for wrist joint [38]. A few years later, Zhu et al. [78] replicated their earlier study on muscle paralysis but instead of local drug injection in muscle, they used intravenous administration of succinylcholine (curare) in three patients undergoing general anaesthesia for cancer surgery. They showed that SEPs, evoked by magnetic stimulation over the gastrocnemius and with electrical stimulation over the tibial nerve, were still present during paralysis. They eliminated the hypothesis of an indirect activation of muscle spindles with contractions, and rather proposed that 1a-afferents terminals can be directly activated in the muscle. However, the use of a large round coil (12-cm diameter) compared to earlier study (pointed coil of 4.1-cm diameter [77]) cannot exclude a possible recruitment of the tibial nerve near the popliteal fossae. Also, the small sample size and the specific context of the experiment (general anaesthesia, total muscle paralysis) limit the strength of this demonstration.

Recommendations for rPMS application based on preferential recruitment of afferents

The previous sections described the basic differences between magnetic and electrical stimulation owing to their preferential recruitment of afferents over nerves and muscles. Although evidence remains controversial, it is clear that the main difference between each technique is cutaneous inflow (including afferents to lemniscal and spino-thalamic pathways), being more easily and strongly recruited with electrical stimulation. The relative inability of rPMS to recruit skin afferents may share advantages and disadvantages when applied in physiopathology. For example, if the aim is to reduce pain with intensities below muscle contraction threshold in order to target the analgesic gating system [47], electrical stimulation would be a better choice [59]. However, rPMS should be preferred if the objective is rather to generate proprioceptive inflow (directly via 1a-afferents recruitment or indirectly via muscle contraction and joint movement) or to target deeper conductive structures such as spinal roots or profound muscles [7,68,73,74]. Also, when the aim is to favour brain

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plasticity and motor recovery via the repetitive production of muscle contractions/joint movements, then the use of electrical stimulation may be limited in the presence of painful disorders, such as post-stroke spasticity or incomplete spinal cord injury [70,71]. Indeed, painless magnetic stimulation enables the production of greater joint movements when compared to electrical stimulation [21,26,36,69].

Conclusions

This work overviewed current knowledge on use of rPMS in various pathological disorders. Literature remains very scant and no consensus yet proposes guidelines on the best parameters of rPMS application. Future rPMS studies should however rely on experimental data, rationale and hypotheses reported in the review and in relation to health problem (e.g., reducing pain with sub-threshold intensity and low frequency, improving sensorimotor disorder with supra-threshold intensity and intermittent protocols, increasing muscle strength with continuous high frequency) or in relation to the basic after-effects targeted (depth and focality of the stimulation depending on coil design, orientation, current direction). Future studies should propose more structured designs in larger samples and with the contribution of different imaging technologies to investigate whether magnetic stimulation actually generates pure proprioceptive flows (no cutaneous recruitment) and if such specificity has a real advantage to favor sensorimotor plasticity. This question is of basic clinical importance to recommend the use of magnetic stimulation in pain conditions and sensorimotor impairments for the control of musculoskeletal function.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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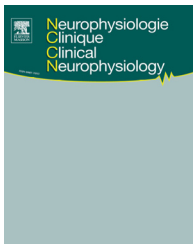

ORIGINAL ARTICLE/ARTICLE ORIGINAL

After-effects of peripheral neurostimulation on brain plasticity and ankle function in chronic stroke: The role of afferents recruited

Effets de la neurostimulation périphérique sur la plasticité cérébrale et la fonction de la cheville en AVC chronique : le rôle des afférences recrutées

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KEYWORDS
Repetitive peripheral magnetic stimulation;
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Muscle tendon vibration;
Brain plasticity;
Neurorehabilitation;
Sensorimotor impairments

Summary
Aims of the study. — This study tested the after-effects of neuromuscular electrical stimulation (NMES), repetitive peripheral magnetic stimulation (rPMS) and muscle tendon vibration (VIB) on brain plasticity and sensorimotor impairments in chronic stroke to investigate whether different results could depend on the nature of afferents recruited by each technique.
Materials and methods. — Fifteen people with chronic stroke participated in five sessions (one per week). Baseline measures were collected in session one, then, each participant received 4 randomly ordered interventions (NMES, rPMS, VIB and a 'control' intervention of exercises). Interventions were applied to the paretic ankle muscles and parameters of application were matched as closely as possible. Standardized clinical measures of the ankle function on the paretic side and transcranial magnetic stimulation (TMS) outcomes of both primary motor cortices (M1) were collected at pre- and post-application of each intervention.

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Results. — The ankle muscle strength was significantly improved by rPMS and VIB ($P \leq 0.02$). rPMS influenced M1 excitability (increase in the contralesional hemisphere, $P = 0.03$) and inhibition (decrease in both hemispheres, $P \leq 0.04$). The group mean of a few clinical outcomes improved across sessions, i.e. independently of the order of interventions. Some TMS outcomes at baseline could predict the responsiveness to rPMS and VIB.
Conclusion. — This original study suggests that rPMS and VIB were efficient to drive M1 plasticity and sensorimotor improvements, likely via massive inflows of 'pure' proprioceptive information generated. Usefulness of some TMS outcomes to predict which intervention a patient could be more responsive to should be further tested in future studies.

MOTS CLÉS
Stimulation magnétique périphérique répétitive ;
Stimulation électrique neuromusculaire ;
Vibration musculo-tendineuse ;
Plasticité cérébrale ;
Neuroréadaptation ;
Déficiences sensorimotrices

Résumé
Objectifs de l'étude. — Tester si les effets de la stimulation électrique neuromusculaire (NMES), la stimulation magnétique périphérique répétitive (rPMS) et la vibration musculo-tendineuse (VIB) sur la plasticité cérébrale et les déficiences sensorimotrices en AVC chronique dépendent des afférences recrutées par chaque intervention.
Matériels et méthodes. — Quinze personnes avec AVC chronique ont participé à cinq sessions (une par semaine). La première servait de ligne de base, et les interventions (NMES, rPMS, VIB et une intervention « contrôle » d'exercices) ont été réalisées dans les quatre sessions suivantes, dans un ordre aléatoire entre participants. Chaque intervention visait les muscles parétiques de la cheville, leurs paramètres étant le plus possible semblables. Différentes mesures cliniques et neurophysiologiques [stimulation magnétique transcrânienne (TMS) du cortex moteur primaire (M1)] ont été mesurées avant et après chaque intervention.
Résultats. — rPMS et VIB ont amélioré la force des muscles de la cheville ($p \leq 0{,}02$), mais seule rPMS a influencé l'excitabilité du M1 (augmentation dans l'hémisphère contra-lésionnel, $p = 0{,}03$) et l'inhibition intracorticale (levée d'inhibition dans les deux hémisphères, $p \leq 0{,}04$). Quelques mesures cliniques ont démontré des améliorations progressives entre les sessions, et certaines mesures TMS étaient prédictives du succès clinique des interventions.
Conclusion. — Cette étude exploratoire supporte que rPMS et VIB seraient plus efficaces que NMES pour induire des changements plastiques dans M1 et des améliorations sensorimotrices, probablement étant donné leur activation minimale des afférences cutanées permettant un recrutement « pure » des afférences proprioceptives. Ces résultats, incluant l'utilité pronostique de certaines mesures TMS, devront être approfondis dans des études futures.

Introduction

Non-invasive peripheral stimulation (NIPS) consists of applying an external stimulating device over a nerve, muscle or spinal root to depolarize the conductive structures within the peripheral nervous system [9]. NIPS use in research and in clinical settings has increased in recent years for a myriad of pathological conditions [5,9,47,58,90]. In particular, peripheral stimulation alone or in combination with rehabilitation regimens to induce muscle contractions and joint movements have been studied in patients with post-stroke spastic hemiparesis [5,8,47,90]. These studies reported improvements of sensorimotor deficits and functional independence, in parallel with plastic changes of the sensorimotor cortices, as tested by brain imaging and transcranial magnetic stimulation (TMS). It was proposed that the massive recruitment of sensory afferents by NIPS could activate the lemniscal and extra-lemniscal pathways and influence the excitability of spinal and cerebral networks (intra- and interhemispheric) and the corticospinal tract, thus contributing to promote sensorimotor function on the affected side [5,9,20,74].

Neuromuscular electrical stimulation (NMES) and repetitive peripheral magnetic stimulation (rPMS) are two NIPS devices that have shown promising results in populations with pathological affections [14,51,90,95], but some specific pros and cons may impact their use in routine stroke rehabilitation (for a review see [9]). Briefly, the rPMS equipment is bulky (generator, coil of stimulation) and expensive, but this stimulation is painless and less affected by the depth and impedance of the structures beneath the coil, as compared to NMES [9]. Also, when applied at intensities above the contraction threshold, rPMS and NMES seem to recruit proprioceptive afferents the same way, i.e. directly by the depolarization of sensory fibers terminals and indirectly via the induction of repeated contractions and joint movements [5,9]. However, NMES recruits cutaneous receptors, whereas rPMS seems to generate almost pure proprioceptive information during muscle contraction and joint movement (i.e. with limited recruitment of cutaneous

afferents) [9]. This difference is important given the belief that proprioceptive feedbacks induced by repeated movements/contractions preferentially influence brain plasticity and sensorimotor improvements, while the recruitment of superficial cutaneous receptors could generate noisy and meaningless signals for the sensorimotor system [93—95] or might even inhibit the primary motor cortex (M1) [19]. Given the link between proprioceptive information, brain plasticity and motor recovery in stroke [21,23,69,85,96], it seems that rPMS could be more efficient than NMES in stroke rehabilitation. This said, however, the improvements related to rPMS should be substantially greater than those related to NMES to overcome the aforementioned limitations of rPMS (cost, bulkiness). This question is important though, as yet unanswered by the literature.

Another question is whether specific afferents recruited by NIPS might play a key role in post-stroke motor improvement. Precisely, Ib-afferents (Golgi tendon organ) contribute to the sensory coding of repeated contractions/relaxations and Ia- and II-afferents (spindles) of the muscle stretched contribute to the sensory coding of bidirectional joint movements [11,27,76,77,79], as well as skin receptors stretched by the movements [1,2]. Thus, the sole comparison of rPMS and NMES will not discriminate between these different afferents, i.e. will not inform on whether joint movements in addition to muscle contractions are required to influence brain plasticity underlying functional improvement. Therefore, rPMS and NMES should be compared with another approach that recruits specifically one type of afferents. This is the case for muscle tendon vibration (VIB) applied to an accessible tendon at an optimal and fixed joint angle, at high frequencies (i.e. 80—100 Hz) and low amplitudes (0.25—2 mm) [78]. Studies using microneurographic recordings of sensory afferents demonstrated that the Ia-afferents from muscle spindles were most sensitive to VIB as compared to II-afferents (less responsive) and Ib-afferents (not responsive) [78]. Furthermore, the activation of muscle spindles and subsequent recruitment of Ia-afferents by VIB are so strong that, in the absence of any other sensory feedback (i.e. vision, cutaneous cues), VIB induces an illusion of movement whose direction corresponds to a movement that would have normally stretched the muscle vibrated [3,80]. In healthy individuals, illusion is reliable and direction-specific [11,79], and it is accompanied by a strong activation of the parieto-frontal areas involved in the control of the vibrated muscle [63—66,81]. Our recent pilot study denoted that individuals with chronic stroke could perceive these illusions of movement on the paretic side, but at lower strength and clearness than healthy counterparts [7]. It thus seems feasible to match the illusory sensations produced by VIB with the real movements induced by rPMS and NMES.

The present study proposed to compare for the first time in chronic stroke the after-effects of one session of VIB with one session of rPMS and one session of NMES, using parameters matched as closely as possible so that the main difference between interventions would be the nature of afferents recruited. Comparison was also made with one session of volitional exercises. Each participant received the four interventions in a randomized order, with a one-week washout period between each session. The interventions were applied to the paretic ankle muscles given their importance in post-stroke functional impairment [6,8]. Ankle function and brain plasticity were tested before and after each intervention to determine whether the nature of afferents recruited was a factor of importance and whether the non-invasive devices improved the outcomes more than the volitional exercises. As supported by the abovementioned evidence, we hypothesized that post-rPMS improvements would be larger than post-NMES and that the after-effects of VIB-related illusions would depend on the intensity and quality of the illusions in chronic stroke. Correlations between brain plasticity and sensorimotor changes and the existence of neurophysiological predictive factors (TMS outcome measures) of responsiveness to the interventions were studied for each intervention [8].

Table 1 General characteristics of participants with chronic stroke.

General characteristics	
Participants (*n*)	15
Age (years)	
Mean ± SD	51.1 ± 15.9
Range	20—69
Gender (*n*: males/females)	9/4
Footedness (*n*: right/left)[a]	13/2[a]
CMSA — Stage of foot	
Median score (on the 0—7 ordinal scale)	4
Range	2—7
Lesion details	
Location (*n*: cortical/subcortical/mixed)	2/0/13
Nature (*n*: ischemic/haemorrhagic)	15/0
Hemisphere (*n*: right/left)	8/7
Time since stroke (months)	
Mean ± SD	59.3 ± 24
Range	22—115

n: number; CMSA: Chedoke McMaster Stroke Assessment [a measure of motor recovery level, from complete paralysis (0) to full recovery (7)].
[a] Before lesion.

Material and methods

Participants and study design

Fifteen chronic stroke individuals were recruited after providing informed written consent approved by local ethics committees and the declaration of Helsinki (Table 1). The inclusion criteria were: age ≥ 18 years old; first unilateral stroke resulting in ankle paresis more than 12 months prior to enrolment in the study; a recent CT or MRI scan (≤ 5 years) for the description of the lesion (Table 1); and the capacity to slightly dorsiflex the paretic ankle on request (Chedoke McMaster Stroke Assessment [CMSA] [28] — Stage of foot ≥ 2). The exclusion criteria were: any administration of anti-spastic medication in the last 6 months or central nervous system (CNS) active drugs (for example lowering the seizure threshold); vertebral surgery; any other medical condition including (but not limited to) major circulatory, respiratory or cardiac disease, neurological disease/deficit other than stroke, severe lower limb orthopedic condition,

or cognitive disorder. Exclusion criteria related to TMS further included a history of seizure, cardiac pacemaker and intracranial metallic implants [82]. Also, it is known that TMS outcomes are sensitive to the cortical vs. subcortical level of the lesion [6,99] and recruitment of patients with pure subcortical stroke was more difficult in our previous studies [6,8]. Thus, to improve the homogeneity of our sample and facilitate recruitment, patients with pure subcortical strokes were excluded so that all participants had cortical damage (see Table 1). Footedness was determined by the foot used before stroke to kick a ball or to write in the sand. Participants were instructed not to change their medication intake and other lifestyle habits throughout the study.

The study design consisted of five sessions, each lasting 2.5—3 h, conducted at one week apart and at the same period of the day for a given participant. The after-effects of a single session of peripheral neurostimulation are unlikely to last more than 48 h [46,50,94] thus a one-week washout period seemed reasonable between sessions for extinction of effects. The first session was used to collect the baseline measures. The four other sessions (S1, S2, S3, S4) served to conduct the interventions, i.e. rPMS, NMES, VIB and the 'control' intervention of volitional exercises. Each intervention had been randomly allocated to one of the four sessions (S1, S2, S3 and S4) by means of a random number generator (random rank of each intervention for each participant). Baseline measures included the CMSA (stage of foot) and, on both the non-paretic and the paretic sides, clinical testing of ankle function and TMS outcomes related to the tibialis anterior muscle (see next sections). In S1 to S4, all measures were systematically collected pre- and post-intervention, on both hemispheres for TMS outcomes, but only on the paretic side for clinical outcomes. TMS and clinical testing were randomly ordered for each participant at pre- and at post-intervention by means of the random number generator. The experimenters conducting data acquisition were not blinded to the interventions. However, all data was codified post-hoc (participant, session, pre- and post-intervention) until completion of analyses. Also, participants were blinded to the study's specific objectives and hypotheses and were all naïve to the interventions. Based on TMS safety guidelines, each participant was contacted by phone 2 days after the first session, then 10 and 30 days after the last session to document any adverse effects [82].

Surface EMG recordings

After standard skin preparation (i.e. cleaning the skin with alcohol and shaving whenever necessary) [34], the parallel-bar EMG sensors with adhesive skin interfaces were installed on each participant (fixed 1 cm distance between electrodes; 16-channel Bagnoli EMG System, Delsys Inc., Boston, MA). EMG sensors were placed bilaterally on the tibialis anterior (TA) muscles (foot invertor and ankle dorsiflexor), soleus (SOL, ankle plantar flexor) and fibularis longus (FL, foot evertor and synergist during ankle plantar flexion), strictly following SENIAM guidelines and using anatomical landmarks [34]. The position of each electrode relative to these landmarks was recorded for each subject at baseline. To ensure consistency between sessions, each electrode position was marked with a surgical pen on the skin and subjects were instructed to avoid scrubbing the area. A common ground electrode was positioned on the patella of the tested limb. EMG signals were bandpass-filtered (20—450 Hz), amplified before digitization (2 kHz), and computer-stored for online display and offline analysis (PowerLab acquisition system; LabChart-ADInstruments, Colorado Springs, CO).

TMS testing of tibialis anterior M1 area

TMS procedures were strictly replicated for each hemisphere pre- and post-intervention, following the guidelines from the International Federation of Clinical Neurophysiology [31,82,83]. Position of participants was the same as for clinical testing and the tested foot was firmly strapped in an ankle-foot orthosis to ease the isometric volitional contraction of TA. The participant was first instructed to dorsiflex the ankle three times at maximal isometric contraction (MVC) against the orthosis: elastic straps and manual stabilization helped avoid any hip and knee movement. Also, constancy of MVC for the 3 trials was monitored online by visual inspection of the signals recorded and instantaneous calculation of the coefficient of variation (SD/mean). The 15% MVC was then calculated from the mean TA EMG activity and displayed as a target line on a scaled screen in front of the participant. During TMS testing, a copy of the real-time raw EMG activity of TA was provided as a visual feedback for the participant (and not recorded): it was sent for rectification and low-pass filtering (2 Hz) to an external device via a parallel cable and displayed on the scaled screen. The participant had to superimpose this real-time EMG line on the 15% MVC target line. All TMS trials (acquired with 20—450 Hz bandpass filters and 2 kHz sampling rate) falling outside a stringent window of EMG acceptance ($15 \pm 5\%$ MVC, implemented in our software) were rejected online and acquired de novo. These conditions of 15% MVC TA preactivation contributed to stabilize motoneuronal excitability and motor output during TMS testing [87] and facilitated TA responses to TMS by the increase of the corticospinal excitability associated with TA M1 area in the lesioned hemisphere [6,8,83]. Resting breaks were given on request and after each series of 8—10 TMS trials.

Magnetic stimuli were applied on the scalp over M1 representation of the TA with a double-cone coil (7 cm outer diameter each wing; monophasic pulse, Magstim Company Limited, Whitland, UK), which is optimal for activating lower limb M1 cells [31]. More precisely, the TMS coil was positioned first at 1.5—2 cm lateral from the vertex using 10—20 EEG system (TA M1 area) [45], with the long axis of the two-wing intersection pointing antero-posteriorly and inducing an electrical current of posterio-anterior direction in M1 [83]. The position was then adjusted slightly to determine the 'hotspot', namely the location eliciting the largest TA motor evoked potentials (MEPs) using the lowest TMS intensity. This approach provided the most selective activation of M1 foot area cells at the lowest threshold to elicit MEP in the contralateral ankle muscles [18,31]. Visual inspection of FL and SOL EMG recordings (absence of MEP) ensured the selective recruitment of TA M1 area and visual inspection of EMG recordings from the other leg monitored the complete relaxation of the limb ipsilateral to the stimulated hemisphere.

Scalp locations were marked using a surgical pen to ensure reliable positioning and orientation of the TMS coil across times of testing. Thereafter, the following seven TMS outcomes associated with TA M1 representation were acquired on both sides.

Active motor threshold (AMT)

The AMT, expressed in % of maximal stimulator output and reflecting M1 excitability [83,109] was determined as the stimulus intensity required to elicit at least 5 TA MEPs out of 10 trials with amplitudes $\geq$ 100 μV [83].

MEP amplitude, latency and silent period

A suprathreshold unconditioned (test) TMS, with intensity fixed at 120% AMT, enabled recording and measurement of the MEP amplitude, latency and of the duration of the EMG silent period following the MEP in pre-activated conditions [31,83,105]. Mean MEP latency, reflecting conduction time and indirectly the synchronous arrival of descending volleys to depolarize spinal motoneurons [31,48] was measured from stimulation time to MEP onset. MEP amplitude, reflecting the volume of M1 cells activated by TMS and the excitability of the corticospinal pathway [48,83] was measured peak-to-peak. Duration of the EMG silent period (SP), indicating in part M1, $GABA_B$ inhibition [71] was measured from MEP offset to the return of EMG activity and expressed in ms (raw data) and also as the ratio (SP/MEP amplitude) $\times$ 100 to reduce inter-individual variability [70].

SICI and SICF

Paired-pulse TMS (coil connected to two Magstim 2002 monophasic stimulators) was used to test the short-interval intracortical inhibition and facilitation (SICI and SICF, respectively) [38,52]. In SICI, a subthreshold conditioning TMS (70% AMT eliciting no MEP on its own) was delivered 2 ms before the unconditioned TMS at 120% AMT [6,52]. The conditioned MEP was expressed post-hoc relative to the amplitude of the unconditioned MEP at 120% AMT, which is acknowledged as probing the function of $GABA_A$ interneurons within M1 [83,109]. In SICF, two stimulus were delivered 1 ms apart, the first TMS at 100% AMT and the second at 90% AMT. MEP amplitude was then expressed relative to the amplitude of test MEP at 100% AMT, which likely reflects I-waves summation following the depolarisation of M1 interneurons by TMS [6,38,83,109]. For both SICI and SICIF paradigms, 8—10 unconditioned MEPs and 8—10 conditioned MEPs were elicited in each case at a rate of about 0.2—0.3 Hz.

Clinical testing

These outcomes were collected on both sides at baseline and only on the paretic side from S1 to S4. Each participant was comfortably seated in a reclining chair with legs and arms supported, and with the knees flexed 20° from full extension. An experimenter manually stabilised the leg against the chair, whenever necessary. Three trials were averaged per clinical outcome and up to 2 supplementary trials were performed if variation exceeded 2 standard deviations from the mean.

Range of motion (ROM)

The ankle ranges of dorsiflexion were measured under two conditions: voluntary active motion (volitional upward movement with verbal encouragements from the experimenters) and passive motion (manually driven at slow speed, absence of stretch reflex monitored with online EMG signals). An extendable-hinged goniometer (Lafayette-Instrument) was aligned with skin markers positioned at the fibular head, the lateral malleolus (rotational axis) and the fifth metatarsal head [6,8,25]. Thus, values higher or lower than 90° (right angle) referred to plantar or dorsal flexion, respectively. In addition, the maximal eversion ROM reached during active dorsiflexion were obtained using a 17 cm flexible goniometer (Jamar® E-Z Read). Skin markers were drawn distally on the tibial crest, the ankle rotation axis (halfway between the lateral and medial malleoli) and on the second metatarsal on the foot's dorsal surface. Values lower (negative) or higher (positive) than 0° (neutral position) referred to inversion or eversion, respectively.

Isometric muscle strength

A hand-held dynamometer (Châtillon-Instrument) was used to measure the maximal voluntary isometric strength of the ankle dorsiflexors and of the foot evertors under manual stabilisation of the knee. The participant was instructed to push as hard as possible against the dynamometer during 5—10 s and was given verbal encouragements [4,59] as well as feedbacks on the performance to ensure maximal possible strength. The experimenter matched the strength without 'breaking' it (the 'make' test) [92]. For ankle dorsiflexors, the dynamometer was placed perpendicular to the metatarsal heads on the dorsal surface of the foot. For the foot evertors, the dynamometer was placed on the lateral surface of the foot, approximately over the fifth metatarsal head. These procedures are valid and reliable in healthy people and in populations with neurological disorders [53,73,89]. Both the dorsiflexion and eversion strength were measured with the ankle joint at its natural resting angle. This angle measured at baseline was strictly replicated per participant at each time point of strength measurement.

Stretch reflex of plantar flexors

The soleus stretch reflex was used to probe the after-effect of each intervention on the spinal excitability related to the spastic plantar flexor muscles, given that the modulation of plantar flexors resistance to stretch in chronic stroke might influence the ankle function [8]. The experimenter counted mentally one second to dorsiflex the ankle at a high-speed from the resting position [53]. This provided a high-speed stretch reflex of plantar flexors whose amplitude was analyzed post-hoc on SOL EMG traces [103]. A few practice trials were performed to ensure reliability of the technique [53]. The Tardieu scale (ordinal variable) was rated by the experimenter after each stretch [33]. SOL relaxation at the resting position was monitored by visual inspection of EMG traces, and a 10-s post-stretch period was recorded to measure any clonus in response to high-speed stretch (alternate reflex contractions/relaxations between dorsal and plantar flexors) [29,67]. The integral of the SOL stretch reflex was calculated post-hoc from the rectified SOL EMG

signals (from onset to offset determined visually) [103]. If no clonus occurred after the stretch reflex, a value of zero was attributed for the clonus measure. In the case of a clonus, the first burst corresponding to the stretch reflex was measured alone and the integrals of each successive burst were then summed together. The count of clonus bursts was also used as a simple ordinal scale outcome [101]. To enable reliable comparisons throughout all times of measurement, SOL EMG measures at pre- and post-intervention were normalized relative to its maximal voluntary contraction (MVC) obtained at pre-intervention of the same session. The MVC of SOL muscle corresponded to the mean EMG activity associated with three trials of isometric plantar flexion against an ankle-foot orthosis (see TMS section). For each MVC, the integral was calculated from the rectified EMG signal over a 3-s period.

Interventions

Procedures and parameters matched between interventions

The participant remained comfortably seated in the reclining chair. rPMS and NMES were similarly applied at a frequency of 20 Hz with 40 repetitions of 3 s ON/19 s OFF (duty cycle chosen to avoid overheating of the rPMS coil) and a biphasic waveform of 400 μs pulse width (no up/down ramping of intensity, to match magnetic stimulation characteristics). The stimulation intensity could not be directly compared between rPMS (in Tesla) and NMES (in ampere). As recommended previously, a meaningful comparison may rather rely on physiological feedbacks [9], such as the amplitude of joint movements induced by each intervention or the expression of stimulation strength relative to contraction threshold. Therefore, the intensity and position of the coil (in rPMS intervention) or of skin electrodes (in NMES intervention) inducing the maximal amplitudes of dorsiflexion/eversion were first determined before the intervention. Then, for each intervention, the amplitudes of dorsiflexion and associated inversion/eversion were collected in the first 10 repetitions of duty cycle and the last 10 repetitions with a view of between intervention comparison. The intervention of volitional ankle exercises was matched in terms of duty cycle (3 s ON/19 s OFF), number of repetitions (40), and participants were asked to dorsiflex/evert the ankle as far as possible (the amplitudes of joint movements were also measured for the first and the last 10 repetitions). In VIB intervention, the number of repetitions and the total duration were also matched (40 illusions of ankle dorsiflexion/eversion), but illusions of movement required additional specific parameters (see next section).

After each intervention, the participant rated on a visual analogue scale (VAS, 0—100) the level of pain and effort perceived during the intervention.

Procedures and parameters specific to each intervention

rPMS was applied using an air film cooled figure-of-eight coil (7 cm outer diameter per wing; Rapid^2 Magstim, Magstim Company, England) held tangentially on the skin overlying the paretic dorsiflexor and evertor muscle bellies. NMES was applied with the BioStim® NMS^2 stimulator over the paretic dorsiflexor and evertor muscle bellies by means of two disposable pre-wired self-adhesive 2 × 2 inches electrodes. The exercises consisted of performing the maximal possible synergistic movements of dorsiflexion/eversion, and feedbacks were frequently given to ensure that the participant remained focused on the task and reproduced the desired movements at the best of its capacity. Practice trials were allowed before the onset of the intervention.

In VIB, the participant was comfortably installed on the reclining chair, with the paretic ankle and foot free from any cutaneous contact, and with hips and knee joints flexed respectively at 20° and 50°. The VB115 VIBRASENS© vibrator (Techno Concept, France) was positioned on the Achilles's tendon on the paretic side and firmly stabilized with elastic straps around the ankle. With eyes close and no cutaneous feedback, VIB of Achilles's tendon induces an illusion of ankle dorsiflexion [26,77]. A soft elastic band was strapped around the metatarsal heads, so that the experimenter could touch the foot (see below) with limited cutaneous feedbacks. In order to monitor a stable ankle position throughout the VIB intervention, a light plastic goniometer (Jamar® E-Z Read) was fixed (double-side taped) over the same anatomical landmarks used for the measure of ankle dorsiflexion ROM [6]. VIB was applied at 80 Hz frequency, at 1 mm amplitude and during 10 s [77,78]. One practice trial with eyes open helped the participant to familiarize with the vibration and to ensure that the setup was comfortable. The participant was instructed on which sensation he/she will have to concentrate on (i.e. a perception of ankle movement and not skin perception of vibration). Then, eyes were closed for a few VIB trials under complete relaxation (EMG monitoring) and at different dorsiflexion angles in order to determine the optimal angular position per participant for eliciting the best illusions of dorsiflexion/eversion [26,77]. The participant had to rate the clearness and precision of the illusion using a 3-levels ordinal scale (3 = perfectly clear and precise, like a real movement; 2 = moderately clear and precise; 1 = vague and not precise) [102]. The angle of the optimal position was maintained during the intervention. Of note, if a participant did not perceive any illusion with this standardized technique, a small and slow stretch of plantar flexors was attempted (5° dorsiflexion imposed by the experimenter during the first two seconds of VIB), as previously done to increase the strength and clearness of illusion [7,22]. The intervention consisted of 40 repetitions of 10 s ON/15 s OFF VIB to induce ankle dorsiflexion/eversion illusions. A 10 s VIB is ideal in healthy people for the illusion to build up and be reliably perceived [16,17,26,77]. Obviously, the amount of angular ankle movement perceived during each VIB trial could not be reliably measured and compared with the other interventions. Instead, participants had to rate the clearness and precision of ankle movement illusion after each of the 40 repetitions, during the 15-s rest breaks.

Statistical analysis

Assumption of normality was validated using the Shapiro—Wilk test. When a data set was not normally distributed, a natural logarithmic transformation was performed and normality was re-tested. Between-side differences at baseline were tested with the paired Student's

t-test (two-sided) for the continuous variables and with the Wilcoxon signed ranks test for the ordinal variables.

An analysis of variance with repeated measures was applied to all TMS outcomes with the factors 'Intervention' (rPMS, NMES, exercises, VIB), 'Pre/Post' (pre-intervention, post-intervention) and 'Side' (paretic, non-paretic). Factors 'Intervention' and 'Pre/Post' were applied to the clinical outcomes on the paretic side. A one-way ANOVA compared the outcomes between baseline and pre-intervention in each session to test extinction of effects between interventions. Planned comparisons (two-sided post-hoc tests) were used to detect where differences lay if between factor interactions or main effects were detected by ANOVAs. Concerning ordinal-scaled outcomes (Tardieu score, number of clonus bursts), the Friedman test was used to test effects' extinction between interventions; the Wilcoxon signed ranks test was used to detect where differences lay and the acute after-effects in each intervention.

One-way ANOVAs were used to test whether dorsiflexion and eversion ROMs reached during rPMS, NMES and exercises were similar, and to compare the pain and fatigue perceived after each intervention. Matrices of Pearson's and Spearman's rank correlations (continuous and ordinal variables, respectively) were produced to examine the associations between clinical and TMS outcome measures having significantly changed for a specific intervention and the existence of a link between a significant clinical change and a specific TMS outcome value measured at pre-intervention. The latter correlation was used to assess whether TMS outcome measures could predict the success of an intervention, as previously reported [8,91]. Significance level was set at $P < 0.05$.

Results

All procedures were well tolerated by the participants and no adverse effect was reported during the study (5 sessions) or during the one-month follow-up by phone. Clinical outcomes from the paretic side and TMS outcomes from the non-paretic side were analyzed in all the 15 participants. Due to the absence of MEP in two participants, TMS outcomes were analyzed in 13 participants on the paretic side. The SICI paired-pulse artefact contaminated SICI data in some participants for whom very high intensities of TMS were required to elicit a response (given high motor thresholds), thus bringing to 8 the number of participants with SICI analyzed on the paretic side and 13 on the non-paretic side. The amplitude of TA MEP on the paretic and non-paretic sides had to be log-transformed (LN_MEP) before analysis because of non-normal distributions.

Baseline differences between the paretic and non-paretic sides

Group means ± SD of baseline measures on the paretic and non-paretic sides and the between-side comparisons (*P*-values) are presented in Table 2 (TMS and clinical outcomes). TMS outcomes revealed longer MEP latency, smaller LN_MEP amplitude and longer SP/MEP ratio on the paretic side as compared to the non-paretic. Also, all clinical outcomes were impaired on the paretic side, confirming muscle paresis, spasticity (i.e. higher resistance of plantar flexors to rapid stretch, higher stretch reflex and clonus) and loss of joint flexibility.

Ankle movement, pain and fatigue

The one-way ANOVA applied on the maximal dorsiflexion ROM reached during rPMS, NMES and exercises was significant ($F_{(2,13)} = 8.35$; $P = 0.001$). Planned comparisons showed that dorsiflexion ROM driven by stimulation was similar between rPMS (128.5 ± 10.6°) and NMES (126.3 ± 14.3°; $P = 0.60$), but dorsiflexion was higher during the volitional exercises (111.4 ± 15.6°; $P \leq 0.02$ for comparisons with rPMS and NMES). No difference was detected for eversion ROM ($F_{(2,13)} = 0.46$; $P = 0.63$). All participants perceived reliable illusions of dorsiflexion/eversion during VIB intervention, but more frequently rated them as vague and not precise ($n = 7$ participants) or moderately clear and precise ($n = 6$) rather than perfectly clear and precise ($n = 2$). The one-way ANOVA was significant for pain ($F_{(3,12)} = 9.51$; $P < 0.0005$), i.e. more pain was felt during NMES (28.8 ± 25.8% of VAS) as compared to rPMS (0.4 ± 1.1%, $P = 0.001$), exercises (5.1 ± 14.1%, $P = 0.012$) and to VIB (5.0 ± 13.2%, $P = 0.002$). Also, more fatigue was reported after the exercises (18.8 ± 24.5%) and VIB (12.5 ± 21.8%) than after rPMS (4.5 ± 13.0%) and NMES (4.5 ± 7.0%) but without reaching significance ($F_{(3,12)} = 2.31$; $P = 0.090$).

Acute after-effects in each intervention

TMS outcomes

The three-way ANOVA applied on AMT detected a main Pre/Post effect ($F_{(1,12)} = 5.38$; $P = 0.039$). Planned comparisons showed that a pre-post effect was significant only for rPMS. Precisely, AMT on the non-paretic side was lower after rPMS (46.6 ± 10.3% of maximal stimulator output [MSO]) as compared to pre-rPMS (47.7 ± 10.7% MSO; $P = 0.029$, Fig. 1A). On the paretic side, the AMT reduction after rPMS (49.4 ± 8.4% MSO) as compared to pre-rPMS (50.4 ± 8.2% MSO) was close to significance ($P = 0.072$). The ANOVA applied on the amplitude of the SICI-related conditioned MEP detected close to significance interactions for factors Intervention × Pre/Post ($F_{(3,21)} = 3.00$; $P = 0.058$) and Intervention × Pre/Post × Side ($F_{(3,21)} = 2.73$; $P = 0.074$). Planned comparisons revealed a significant increase of the conditioned MEP amplitude (decrease of SICI) on the paretic side after rPMS (56.1 ± 18.3%) as compared to pre-rPMS (46.0 ± 13.8%; $P = 0.036$; Fig. 1B) and on the non-paretic side (67.4 ± 20.0%) as compared to pre-rPMS (57.5 ± 21.8%; $P = 0.040$; Fig. 1B). Fig. 1B also suggests an increase of the conditioned MEP amplitude after VIB but this effect was due to one participant with no group significance ($P = 0.39$). The ANOVA applied on MEP latency detected a Pre/Post × Side interaction ($F_{(1,12)} = 10.07$; $P = 0.009$). Planned comparisons showed that a pre-post effect was significant only for the non-paretic side after the exercises, with MEP latency longer post-exercises (36.5 ± 5.8 ms) than pre-exercises (34.3 ± 4.1 ms; $P = 0.017$, Fig. 1C). No other acute effect was detected for TMS outcomes.

Table 2 TMS and clinical outcomes at baseline.

TMS measures	Mean ± SD Ipsilesional hemisphere	Mean ± SD Contralesional hemisphere	*P* value
AMT (%MSO)	51 ± 9	51 ± 9	0.70
Latency (ms)	38.13 ± 4.98	34.80 ± 4.55	**0.01**
MEP amplitude (μV)	222.94 ± 261.13	303.68 ± 205.80	NA
LN_ MEP amplitude	4.97 ± 0.93	5.49 ± 0.71	**0.01**
SP duration (ms)	81.93 ± 33.61	63.79 ± 34.27	0.15
SP/MEP (%)	77.69 ± 67.48	27.74 ± 14.30	**0.02**
SICI (% MEP amplitude)	48.92 ± 13.94	56.52 ± 26.58	0.89
SICF (% MEP amplitude)	249.16 ± 95.32	208.69 ± 63.37	0.25
Clinical measures	**Paretic side**	**Non-paretic side**	***P* value**
Active DF (°)	111.7 ± 12.8	92.4 ± 5.3	**< 0.001**
Passive DF (°)	89.0 ± 9.9	78.8 ± 6.7	**< 0.001**
Active EV (°)	16.6 ± 14.2	33.2 ± 6.8	**< 0.001**
Passive EV (°)	43.7 ± 6.7	52.6 ± 6.7	**< 0.001**
Maximal EV during active DF (deg)	−2.8 ± 13.6	11.2 ± 10.8	**< 0.001**
DF strength (kg)	15.5 ± 6.8	19.8 ± 3.9	**< 0.001**
EV strength (kg)	6.5 ± 6.2	13.5 ± 4.3	**< 0.001**
Tardieu (ordinal)	2.5 ± 0.8	0.9 ± 1.0	**0.001***
Clonus (nb of beatings)	3.9 ± 3.2	1.1 ± 0.9	**0.001***
Clonus (% MVC SOL)	13.5 ± 15.7	0.4 ± 1.2	**0.001**
SOL stretch reflex (% MVC SOL)	7.7 ± 8.2	1.9 ± 3.1	**0.001**

AMT: active motor threshold; MSO: maximal stimulator output; MEP: motor evoke potentials obtained with a test stimulus at 120% AMT; LN: data transformed with a natural logarithm; SP: silent period; SICI and SICF: short-interval intracortical inhibition and facilitation as expressed relative to their respective unconditioned MEP amplitude (i.e. 120% AMT for SICI and 100%AMT for SICF); DF: dorsiflexion; EV: eversion; SOL: soleus muscle; MVC: maximal voluntary contraction. Numbers in bold represent significant statistical differences ($P < 0.05$) between the paretic and non-paretic sides.

* Tested with the Wilcoxon signed ranks test.

Clinical outcomes on the paretic side

The two-way ANOVA applied on isometric eversion strength detected a main Pre/Post effect ($F_{(1,14)} = 9,09$; $P = 0.009$). Planned comparisons revealed a significantly higher strength after rPMS (8.1 ± 7.6 kg) than pre-rPMS (7.6 ± 7.5 kg; $P = 0.016$, Fig. 2) and after VIB (7.9 ± 6.7 kg) than pre-VIB (7.1 ± 6.6 kg; $P = 0.0078$; Fig. 2). No other acute effect was detected for clinical outcomes.

Cumulative effects

TMS outcomes

The one-way ANOVA run to compare baseline and the pre-intervention measures at each session did not detect any cumulative after-effect for any TMS outcome.

Clinical outcomes on the paretic side

The one-way ANOVA applied on maximal eversion ROM reached during active dorsiflexion detected a progressive increase across sessions ($F_{(4,56)} = 4.06$; $P = 0.006$, Fig. 3A). Eversion ROM was higher at pre-S3 (3.4 ± 12.8°) than pre-S1 (−3.1 ± 14.3°; $P = 0.049$) and baseline (−2.8 ± 13.6°; $P = 0.018$), as well as higher at pre-S4 (4.5 ± 14.4°) than pre-S1 ($P = 0.026$) and baseline ($P = 0.019$). Also, the isometric dorsiflexion strength increased across sessions ($F_{(4,56)} = 5.52$; $P = 0.0008$; Fig. 3B), with higher strength than baseline (15.5 ± 6.8 kg) at pre-S2 (17.7 ± 7.6 kg; $P = 0.006$), pre-S3 (17.0 ± 7.1 kg; $P = 0.028$) and pre-S4 (17.4 ± 7.0 kg; $P = 0.007$). Similarly, the isometric eversion strength increased over time ($F_{(4,56)} = 4.51$; $P = 0.003$, Fig. 3C), being higher than baseline (6.5 ± 6.2 kg) at pre-S2 (7.3 ± 7.0 kg; $P = 0.026$), pre-S3 (7.7 ± 7.4 kg; $P = 0.011$) and pre-S4 (7.5 ± 6.7 kg; $P = 0.002$). The one-way ANOVA detected that clonus at pre-intervention decreased across sessions ($F_{(4,56)} = 2.87$; $P = 0.031$, Fig. 4). Precisely, a close to significance decrease of clonus was present between baseline (13.5 ± 15.7% of SOL MVC) and pre-S1 (8.2 ± 11.0%; $P = 0.06$), i.e. with no intervention, then decrease became significant at pre-S2 (7.1 ± 8.0%; $P = 0.05$) and significance was maintained at pre-S3 (7.8 ± 9.0%; $P = 0.04$) but not at pre-S4 ($P > 0.05$).

Correlations

The increase of isometric EV strength after rPMS was negatively correlated between participants with pre-rPMS measures of MEP latency on the non-paretic side ($r = -0.61$; $P = 0.015$, Fig. 5A). The increase of isometric EV strength after VIB was correlated with pre-VIB measures of SICF on the paretic side ($r = 0.80$; $P = 0.001$, Fig. 5B) and with duration of SP on both the paretic ($r = 0.56$; $P = 0.04$, Fig. 5C) and

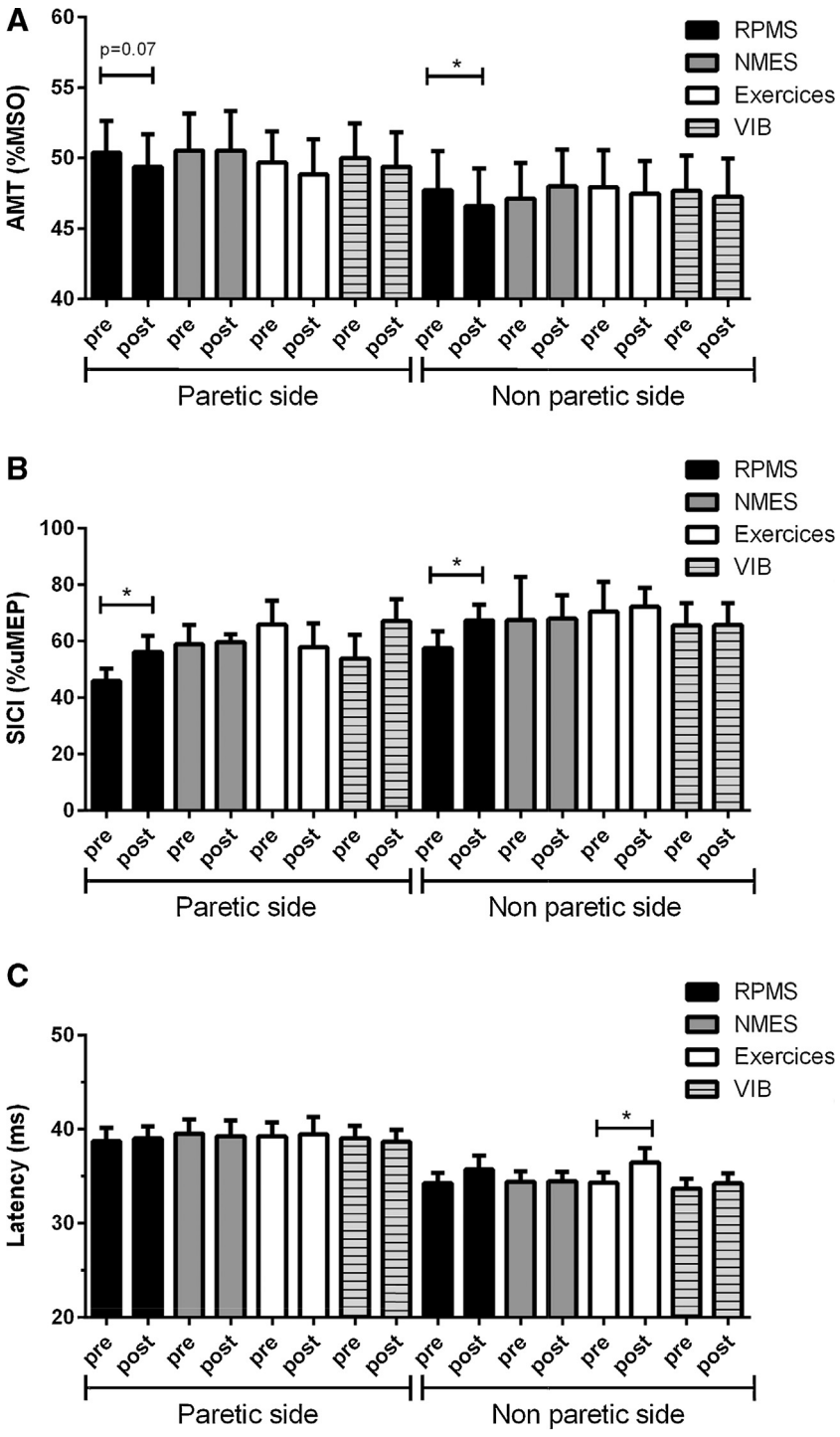

Figure 1 Acute pre/post changes of TMS outcomes in the lesioned hemisphere (paretic side) and the non-lesioned hemisphere (non-paretic side) for each intervention. A. Active motor threshold (AMT) expressed in % of the maximal stimulator output (MSO). B. Short-interval intracortical inhibition (SICI), i.e. the amplitude of the conditioned motor evoked potential (MEP) obtained with double TMS paradigm and expressed in % of the amplitude of the unconditioned MEP (uMEP). C. Latency of uMEP in milliseconds (ms). Each histogram represents the group mean and one standard deviation. RPMS: repetitive peripheral magnetic stimulation; NMES: neuromuscular electrical stimulation; exercises: volitional mobilization of the paretic ankle; VIB: muscle tendon vibration; pre/post: before/directly after the intervention. $^{*}P < 0.05$.

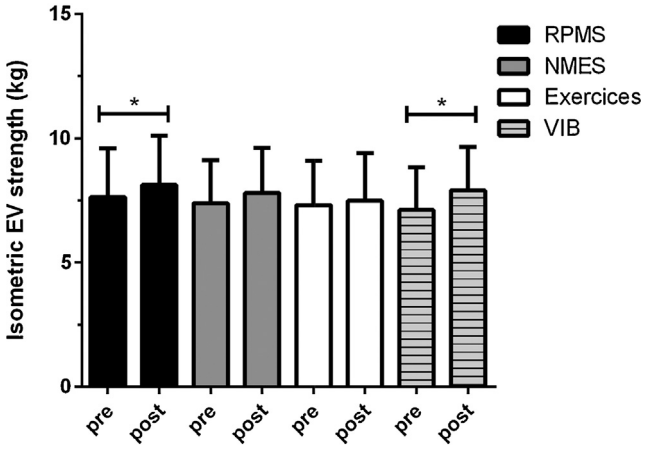

Figure 2 Acute pre/post changes of isometric eversion (EV) strength on the paretic side after each intervention. Each histogram represents the group mean and one standard deviation. RPMS: repetitive peripheral magnetic stimulation; NMES: neuromuscular electrical stimulation; exercises: volitional mobilization of the paretic ankle; VIB: muscle tendon vibration; pre/post: before/directly after the intervention. $^{*}P < 0.05$.

non-paretic sides ($r = 0.87$; $P < 0.0001$, Fig. 5D). No correlation was detected between changes per intervention.

Discussion

This study aimed at testing whether NIPS devices (rPMS, NMES, VIB), recruiting sensory afferents of different natures, had a specific impact in chronic stroke on brain plasticity and sensorimotor deficits. Results showed that small but significant improvements of ankle function were induced by rPMS and VIB, the two interventions that preferentially recruited muscle proprioceptive afferents. Furthermore, brain plastic changes were observed only after rPMS. Unexpectedly, cumulative improvements of clinical outcomes were also obtained from one intervention to one another (whatever the order of interventions between participants). The correlations found between TMS measures at pre-intervention and clinical changes suggest a link between the state of motor systems related to the control of ankle muscles in chronic stroke and the responsiveness to NIPS for improvement of ankle/foot function on the paretic side. The role of afferents in the after-effects, the efficacy of one or combined NIPS to improve the function and the potential underlying mechanisms of brain plasticity are discussed below along with methodological considerations.

Acute after-effects in each intervention

The role of recruited afferents in NIPS after-effects

The improvement of isometric eversion strength only after rPMS and VIB suggests that the massive flows of relatively pure proprioceptive information they generated influenced motor planning and corticospinal drive required for isometric contraction. In particular, spindles of plantar flexors that are activated during rPMS-induced dorsiflexion and recruited directly by VIB may play a key role in clinical

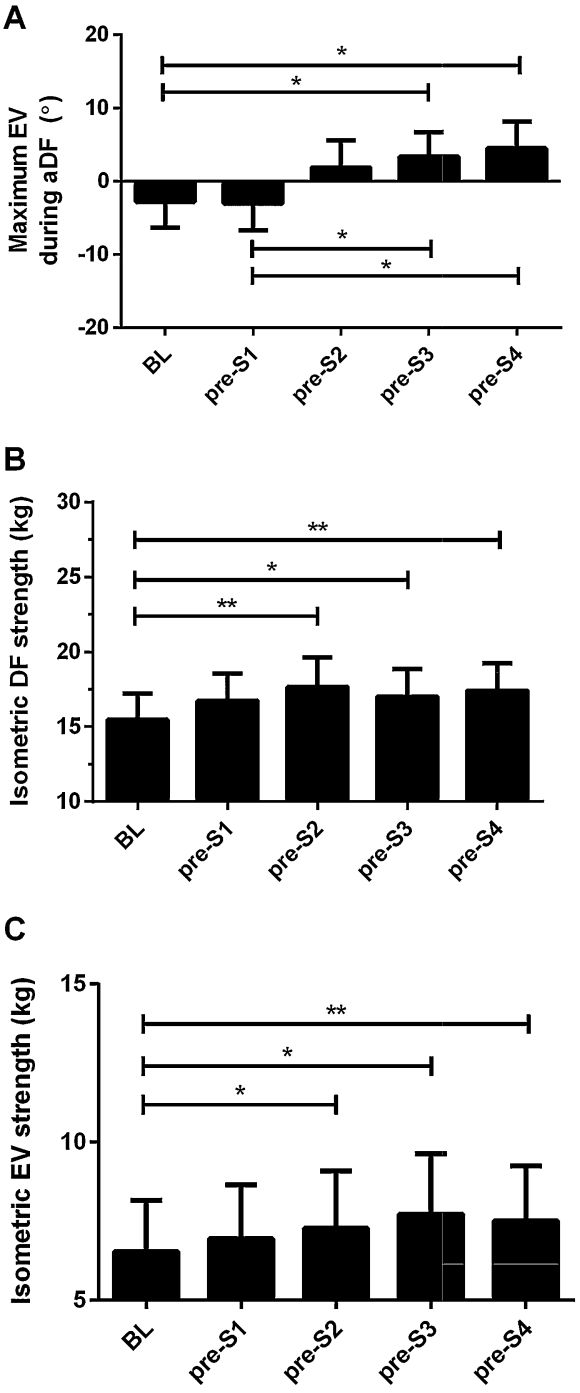

Figure 3 Cumulative effects across the five sessions in all participants for (A) the maximal eversion (EV) strength developed during the active dorsiflexion testing (aDF); (B) the isometric strength developed during aDF testing; (C) the isometric strength developed during EV testing. Each histogram represents the group mean and one standard deviation. The order of intervention did not influence (randomized between participants). BL: at baseline; S: session; pre: before the intervention at the session. $^{*}P < 0.05$; $^{**}P < 0.01$.

improvement. The fact that NMES yielded no after-effect, although matched as closely as possible with rPMS (parameters, movements), supports the idea that cutaneous afferents might have brought non-physiological noises

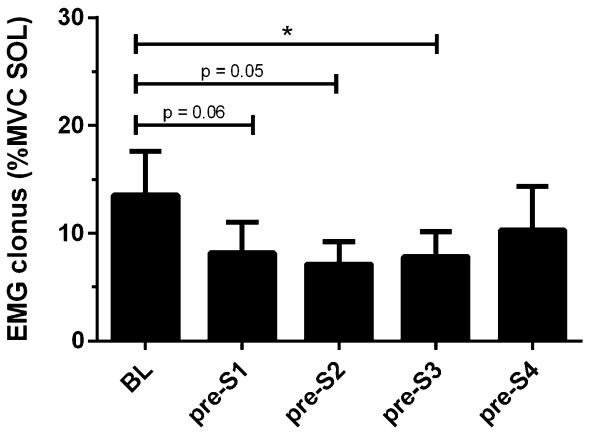

Figure 4 Cumulative decrease of clonus detected by EMG of the soleus muscle across the five sessions and expressed in percent of the maximal voluntary contraction (MVC) of soleus. Each histogram represents the group mean and one standard deviation. The order of intervention did not influence (randomized between participants). BL: at baseline; S: session; pre: before the intervention at the session. $^{*}P < 0.05$.

competing with the meaningful proprioceptive information. This competitive influence has already been shown in fundamental studies that used electrical stimulation of skin areas adjacent to or far from a moving joint, similarly to our NMES intervention [60,75,104]. For example, Refshauge et al., [75] showed that detection of finger movements (proprioceptive task) was hindered by electrical stimulation applied above the perceptual threshold at the tips of the adjacent digits, an effect that was not due to attentional distraction. Participants of our study found NMES more painful than rPMS, as already reported in the literature [9,98]. Given that painful stimulations can inhibit M1 excitability [19,54,86,97], the slight recruitment of nociceptors during NMES application may have further competed with (and hindered) the plastic phenomena at the origin of clinical improvement.

It was not surprising that eversion strength improved after VIB and rPMS because these interventions had been settled to induce maximal ankle DF and eversion movements (or perception of movements). However, no change was observed for DF strength. This may be related to the fact that participants had recovered more DF strength than

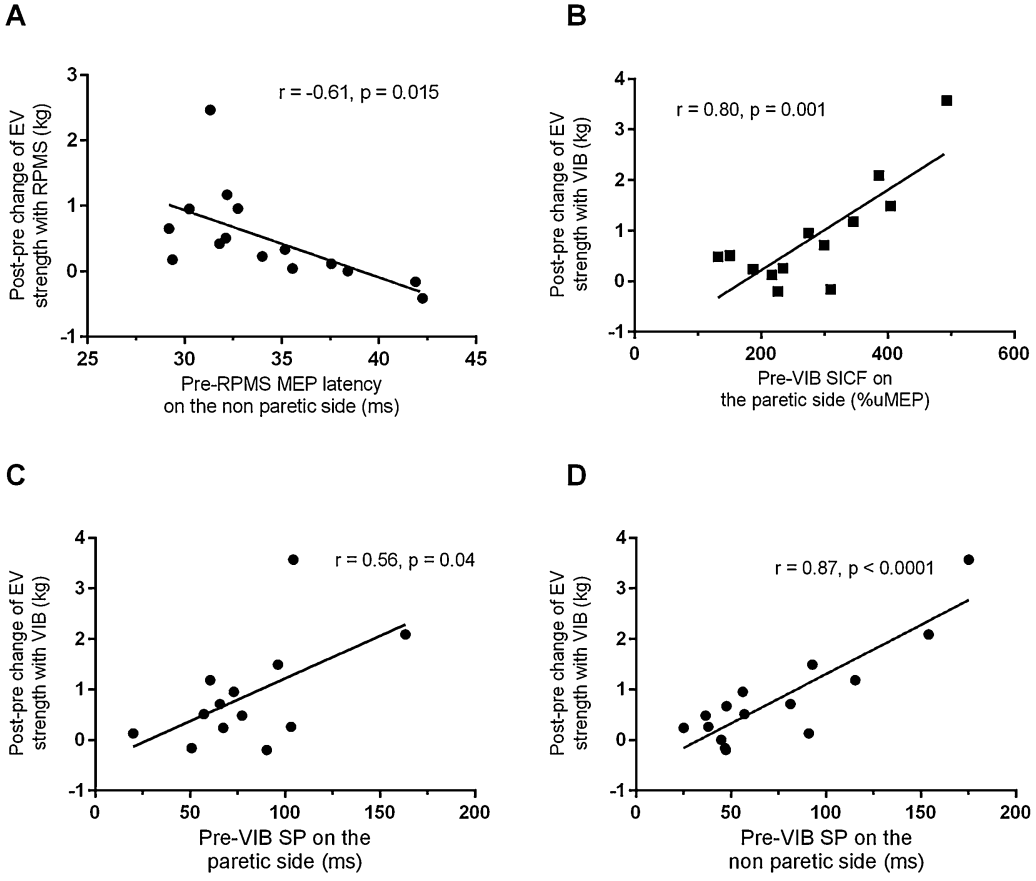

Figure 5 Group correlations between improvements of ankle muscles isometric strength and TMS outcomes measured at baseline. A. Decreasing relation between the improvement of eversion (EV) strength after RPMS and baseline measure (pre-RPMS) of uMEP latency for the non-lesioned hemisphere (non-paretic side). B—D. Increasing relations between the improvement of EV strength after VIB and baseline measures (pre-VIB) of (B) the level of short-interval intracortical facilitation (SICF) for the lesioned hemisphere (paretic side), and the duration of the post-MEP silent period (SP) for (C) the lesioned hemisphere (paretic side) and (D) the non-lesioned hemisphere (non-paretic side). Each point represents a participant. RPMS: repetitive peripheral magnetic stimulation; VIB: muscle tendon vibration; uMEP: unconditioned motor potential evoked by TMS of M1.

expected before enrolment (see Table 2), hence reducing the room for immediate improvements. In support, our previous study with rPMS of the paretic dorsiflexors in patients with weaker DF strength levels at enrolment (i.e. 4.7 kg less than the present sample) did report a significant increase of DF strength immediately after rPMS administration [8]. Although this between-study comparison is limited by the use of different rPMS paradigms, it motivates the conduction of rPMS and VIB studies in samples with more severe ankle paresis.

Interestingly, in parallel with eversion strength improvement, only rPMS (not VIB) induced TMS changes, i.e. an increase of M1 transsynaptic excitability (as suggested by AMT decrease [109]) in the contralesional hemisphere and the decrease of SICI in both hemispheres. This likely reflected dynamic mechanisms of brain plasticity in sensorimotor networks following the generation of proprioceptive information in coherence with actual contractions and joint movements. The mechanisms underlying the decrease of SICI and AMT after rPMS may have likely involved unmasking of latent synapses [39,84] and modification of synaptic strength [36], which are known to preferentially occur when GABAergic inhibition is reduced [35,39,55] (and as discussed owing to sensory interventions in [12]). Furthermore, SICI is known to regulate the plastic adaptations of M1 circuits [43]. For example, an increase in $GABA_A$-related inhibition disrupts M1 use-dependent plasticity, as shown by $GABA_A$ agonist administration in healthy subjects [15]. Conversely, brain plasticity is enhanced by M1 disinhibition, as shown with $GABA_A$ antagonist administration [108]. Thus, our results on SICI decrease in M1 circuits of both hemispheres could reveal a specific plastic adaptation leading to the increase of eversion strength. Literature in stroke clearly supports that the recruitment of sensory afferents activates these adaptive plastic mechanisms, not only in M1 circuits, but also within distributed sensorimotor networks. More precisely, one potential mechanism underlying the bilateral disinhibition after rPMS could be the activation, by rPMS-induced proprioceptive inflows, of specific fronto-parietal networks in the lesioned hemisphere [95], then an influence on the contralesional side via transcallosal or subcortical interhemispheric facilitation pathways (or lacking interhemispheric inhibition) [40]. Such mechanisms have been already reported in cortical or cortico-subcortical stroke [13,88] and in animal models of stroke [107]. Another possibility could have been parallel processing by both M1s of the proprioceptive afferents from the stimulated side, given that spared sensory areas in both the ipsilesional and contralesional hemispheres may contribute to a better recovery of sensorimotor functions (for reviews see [30,107]). However, whatever the underlying mechanisms, our data support that rPMS might have favoured the involvement of the contralesional M1 in the sensorimotor control of the paretic side. It is acknowledged that, during the first weeks after stroke, the contralesional hemisphere may compensate for lost functions of the ipsilesional hemisphere [30,107]. For example, the strength of ipsilateral connectivity (i.e. between the contralesional M1 and the lower limb paretic muscles) has already been correlated with the level of walking impairments [41]. However, persistence of such compensation at more chronic stages has been related to lesser recovery of sensorimotor function [30,62,106]. Therefore, it is questionable whether the bilateral facilitation detected after rPMS represent a desirable goal in terms of longer-term after-effects (e.g., transfer to functional recovery). This point deserves further consideration in future studies, especially for lower limb muscles.

The mechanisms explaining the absence of cortical changes post-VIB, despite similar improvement of eversion strength as after rPMS, remain speculative to date. Beyond the fact that stimulation parameters could not have been perfectly matched between rPMS and VIB interventions owing to their respective requirements and limitations, it may be proposed that the proprioceptive signals elicited by VIB intervention could have been inefficient to significantly influence our TMS outcome measures. Indeed, kinaesthetic illusions were inaccurate in most participants and did not induce any ankle joint movement whereas rPMS triggered strong muscle contractions and fast joint movements. In other words, coding and integration of VIB-induced proprioceptive signals in the sensorimotor networks could have been impaired in our stroke sample and less efficient for sensorimotor transduction at the origin of M1 changes after VIB. In support of this notion, it was shown that VIB could activate M1 only in the presence of a clear illusion of movement [81]. That said, VIB directly and preferentially recruits Ia-fibers of only one muscle group (plantar flexors), conversely to rPMS that indirectly recruits all proprioceptive receptors via the repeated ankle movements and muscle contractions/relaxations. Thus, VIB might not have sufficiently activated TA M1 area but rather M1 areas of plantar flexors or evertors likely engaged in the clinical improvements observed. It should be also noticed that visual inspection of Fig. 1B reveals a potential decrease of SICI after VIB only in the ipsilesional hemisphere (paretic side) and no change in the contralesional (non-paretic side), conversely to rPMS which induced a parallel change in both hemispheres. Although not statistically significant ($P = 0.20$), this change specific to the ipsilesional side after VIB warrants further investigations. Indeed, increasing the ipsilesional hemisphere excitability and decreasing (or avoiding) the involvement of the contralesional is currently tested post-stroke to induce longer-term improvements of the ankle motor control and transfer to functional tasks such as walking. Also, the idea of different mechanisms of action is fostered by the correlations (Fig. 5) suggesting that rPMS and VIB clinical after-effects did depend on the integrity of different components of the motor systems: post-rPMS after-effects were greater in participants with better corticospinal integrity (shorter MEP latency: better synchronicity and conduction time of descending volleys onto spinal motoneurons [48]) whereas post-VIB after-effects were greater in participants with better M1 function (higher SICF: upregulation of glutamatergic circuits of M1 [32,38]; longer SP: upregulation of $GABA_B$ inhibitory circuits of M1 [71]). Nevertheless, the present results cannot establish a direct causal relationship between these variables and future studies should confirm the existence of a link between TMS markers and the success of rPMS and VIB to promote the ankle function in chronic stroke. This may be critical for improving a patient-oriented (individualized) approach to rehabilitation. M1 plasticity related to other muscles involved in the clinical improvements post-VIB should also

be studied with other TMS outcomes (recruitment curve, interhemispheric inhibition or facilitation, etc.).

Are NMES and exercises inefficient?

Our study was not designed to test whether NMES and exercises are efficient and useful interventions in stroke, but rather highlighted that the nature of afferents is important for the activation of brain plastic mechanisms. Matching parameters of application between NMES and rPMS had to respect rPMS technology limitation of coil overheating (even with a cooling system), thus impeding the interventions intensity, duty cycle and repetitions. NMES has virtually no such limitations and could have been more intensive in terms of duty cycle and repetitions, which are basic principles for the induction of neural plasticity after a brain lesion [44]. Also, the present findings solely apply to similar NMES devices and parameters and do not question the relevance of other approaches, such as tactile stimulations considered as key components of rehabilitation in clinical practice.

It is acknowledged that the volitional aspect of training during exercises is important for motor learning and recovery post-stroke [14,56,57]. However, a one session practice may not induce detectable brain plasticity and clinical improvements [58,72], thus explaining the lack of acute effects after the exercise session. Also, more exertion was reported after the repeated exercises despite resting periods (i.e. a duty cycle of a 3 s ON and 19 s OFF). In rPMS, conversely, the movement was triggered without any exertion from the participants. Fatigue is commonly acknowledged as having an inhibitory influence on M1 excitability [100]. Thus, plasticity and clinical improvement may have been masked by peripheral and central motor fatigue related to the practice of skill-focused movements (volitional dorsiflexion/eversion, especially with spastic paretic muscles). It is also known that fatigue lengthens MEP latency [24] and this is precisely what we observed in our participants: M1 cells desynchronization or decrease of synchronicity of descending volleys onto alpha-motoneurons could have negatively impacted motor control. Detection of MEP latency lengthening on the contralesional side further suggests that the contralesional hemisphere was substantially involved in the sensorimotor control of the paretic ankle.

Cumulative after-effects between sessions

Ankle dorsiflexion (ROM and strength) and eversion (strength) improved over sessions and clonus decreased. These non-specific improvements, independently of the order of intervention, were not expected because NIPS after-effects of a single session are typically short lasting [46,50,94]. However, each intervention was designed to generate some 40 repetitions of dorsiflexion/eversion movements, which are the most difficult to recover after a stroke [28]. It is thus possible that this favoured long-term potentiation of circuits involved in the ankle motor control, hence leading to motor learning [49]. However, this was not detected by TMS outcomes. One explanation could be that plastic changes in M1 circuits can return to baseline over time between training sessions [42]. Also, decrease of clonus could suggest a spinal effect reinforced by motor training. That being said, cumulative changes might have masked the detection of other acute after-effects per intervention. Further studies are thus warranted to compare TMS and clinical changes following repeated sessions of rPMS, NMES, VIB or exercises, separately. Also, spinal after-effects should be further explored with the use of more robust and reliable procedures than the one applied in the present work (mentally counting one second for inducing stretch reflexes and clonus), such as the H reflex procedures [37,103], the use of isokinetic devices [53] or some other versions of the Tardieu scale with different speeds of stretching and ROM measurements [33,61].

Methodological considerations

Although TMS testing was conducted in pre-activated conditions to reduce variations of spinal excitability [87], changes could have occurred indeed at the neuromuscular junction and in spinal cord under the influence of NIPS and thus could have contributed to the TMS changes detected [10,68,83,109] and to the clinical improvements. Future NIPS studies in chronic stroke should test this point. This however does not concern data acquired with the paired-pulse SICI paradigm that typically investigates intracortical inhibitory mechanisms [71,109]. Also, the design of the study required that the experimenter applying the interventions also collected data and was not blinded to objectives and hypotheses. Thus, to avoid any bias, all pre/post-intervention measures were strictly replicated in each session and all data were codified until completion of analyses. It is noteworthy that participants were positioned with the knees flexed at 20°, thus stretching the biarticular gastrocnemius muscle. It is thus possible that contractures of the spastic gastrocnemius muscle might have limited the active ankle dorsiflexion ROM before the plantar flexors spasticity did. Future studies should consider testing ankle ROMs at different knee positions. In addition, the amplitudes of ankle eversion were unusually large (see Table 2). A plausible error of measure could have come from the soft goniometer used or from the procedure (e.g., incorrect skin markers, insufficient stabilisation of other joints than the ankle or incorrect reading of the goniometer). However, the small standard deviations reflect that the problem was systematic, thus likely having a negligible impact on the statistical analyses. Also, we did not perform a thorough characterization of sensory deficits, which may have provided interesting responses. For example, could patients with severe vs. mild sensory deficits have responded differently to each NIPS intervention? On the other hand, could sensory inflows induced by the NIPS interventions have influenced these deficits? Futures studies are warranted to investigate these important questions. The small sample and effect sizes may have affected the strength of the results obtained, especially for TMS outcomes with missing data. Also, no statistical correction for multiple comparisons has been used and post-hoc tests have been applied in the absence of significant interaction between factors: this less conventional statistical approach was used to minimize the risk of type II errors (missing of significant changes) because ANOVA ability to detect interactions could have been affected by the fact that (a priori hypothesis) two

out of the four interventions could have induced the largest changes (i.e. rPMS and VIB with preferential recruitment of proprioceptive afferents). It follows that studies on larger samples and more powerful study designs are warranted to replicate our results with more conventional statistical approach.

Conclusion

Our study provided promising findings in chronic stroke on the nature of afferents recruited by NIPS, which activate rapid plastic mechanisms of brain to acutely promote ankle sensorimotor function. The relatively 'pure' proprioceptive inflows induced by rPMS and VIB were more efficient than NMES (proprioceptive afferents mixed with cutaneous) and volitional exercises (inducing fatigue). These results support the potential of peripheral interventions targeting repetition of joint synergies to promote the function, still years after stroke, and underline that the preferential recruitment of proprioceptive afferents is worth being considered in physical therapy. Further larger sampled studies should test the extent to which the TMS outcomes probing at baseline the motor systems integrity can predict the best intervention per patient, thus contributing to an individualized approach, and potentiating the mechanisms of motor recovery.

Ethical approval

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure of interest

The authors declare that they have no competing interest.

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Review

Underlying Signaling Pathways and Therapeutic Applications of Pulsed Electromagnetic Fields in Bone Repair

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Pulsed electromagnetic fields • Signaling pathways • Therapeutic applications • Bone repair • Bone tissue engineering

Abstract
Pulsed electromagnetic field (PEMF) stimulation, as a prospective, noninvasive, and safe physical therapy strategy to accelerate bone repair has received tremendous attention in recent decades. Physical PEMF stimulation initiates the signaling cascades, which effectively promote osteogenesis and angiogenesis in an orchestrated spatiotemporal manner and ultimately enhance the self-repair capability of bone tissues. Considerable research progresses have been made in exploring the underlying cellular and subcellular mechanisms of PEMF promotion effect in bone repair. Moreover, the promotion effect has shown strikingly positive benefits in the treatment of various skeletal diseases. However, many preclinical and clinical efficacy evaluation studies are still needed to make PEMFs more effective and extensive in clinical application. In this review, we briefly introduce the basic knowledge of PEMFs on bone repair, systematically elaborate several key signaling pathways involved in PEMFs-induced bone repair, and then discuss the therapeutic applications of PEMFs alone or in combination with other available therapies in bone repair, and evaluate the treatment effect by analyzing and summarizing recent literature.

Introduction

Bone loss and defective repair mechanisms brought by trauma, osteonecrosis, osteoporosis, arthritis, tumors, and other diseases affecting bone cause severe pain, dyskinesia, psychological agony, and economic burden to patients [1, 2]. Therefore, effective treatment strategy for promoting bone growth and remodeling is needed. Pulsed electromagnetic fields (PEMFs) have been recently employed as a effective method to enhance bone repair because of their non-invasiveness, safety, lack of side effects, convenience, and superior treatment prospects in several refractory bone diseases, such as non-unions and delayed healings of

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fractures [3-5], osteoporosis [6, 7] and osteonecrosis of the femoral head (ONFH) [8, 9]. In this review, we analyze and summarize the latest research progress on the underlying signaling pathways of PEMFs-induced bone repair and its therapeutic application.

Basic knowledge of PEMFs for bone repair

In 1892, Wolf indicated that mechanical stress determines bone growth and remodeling [10]. In 1953, Yasuda revealed that bending the long tubular bone is related with the development of electric currents and this instance is defined as piezoelectric phenomenon [11]. Since then, the theory that electrical stimulation is the path for bone formation in response to applied load has been gradually recognized, and various devices have been developed to produce electrical stimulation for promoting the healing of bone fracture. In 1978, Bassett first applied noninvasive PEMFs to treat delayed union or non-union fractures and have achieved good clinical effect [12]. Shortly thereafter, PEMFs were approved as a safe and effective method for treating delayed union or non-union fractures by the US Food and Drug Administration [13, 14]. Inductive coupling is the rationale for the application of PEMFs [15]. PEMFs consist of a wire coil wherein a current passes and a pulsed magnetic field is generated. The pulsed magnetic field, in turn, induces a time-varying secondary electrical field within the bone. The secondary electrical field is dependent on the characteristics of the applied pulsed magnetic field and the tissue properties. Magnetic fields of 0.1–20 G are usually applied to produce electrical fields, ranging from 1 mV/cm to 100 mV/cm in the bone [16]. Through the PEMF device, a time-varying electrical field is produced to simulate the normal response of bone cells physiologically to the applied mechanical stress [17], and the subsequent enhanced growth and remodeling bioeffects on the bone are initiated by the time-varying electrical field.

Underlying signaling pathways

Recently, considerable research progresses have been made in exploring the underlying cellular and subcellular mechanisms of PEMF promotion effect in bone repair. Several key signaling pathways during the osteogenesis and angiogenesis which are two essential aspects for bone repair, were revealed by various studies when the bone was exposed to PEMFs. In this section, we will elaborate the roles of some of these pathways, including Ca^{2+}, Wnt/β-catenin, mitogen-activated protein kinase (MAPK), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β/ bone morphogenetic proteins (BMP), insulin-like growth factor(IGF), Notch, and cAMP/protein kinase A (PKA), in PEMF-induced bone repair.

Ca^{2+} signaling

The therapeutic effect of non-thermal bioeffects of PEMFs on bone disorders is yet to be elucidated because these photons are insufficiently energetic to directly influence the chemistry of cells. Intracellular Ca^{2+} is generally considered as one of the main actors to translate the PEMF signal into a biological signal [18]. Many studies revealed that PEMF signal passes through the cell membrane to set up a time-varying electrical field within the cytosol; this electrical field subsequently induces the release of intracellular Ca^{2+}, leading to increases in cytosolic calcium and activated calmodulin and the enhancement of bone cell viability [17, 19, 20]. Voltage-gated Ca channels (VGCCs), especially the L type, play a pivotal role in intracellular Ca^{2+} release. PEMF exposure significantly elevated the expression levels of VGCCs in MSCs during osteogenesis [21, 22]. PEMF-initiated Ca^{2+} signaling strikingly accelerates the osteogenic differentiation of MSCs as represented by the upregulated osteogenic markers, such as collagen I and ALP, and the increased deposition of extracellular calcium [21]. Accumulated studies indicated that increased intracellular Ca^{2+} caused by PEMF

stimulation leads to increased nitric oxide levels, which in turn increases the synthesis level of cGMP and the subsequent activation of protein kinase G. Through the Ca^{2+}/nitric oxide/cGMP/protein kinase G pathway, PEMFs promote osteoblast differentiation and maturation, exert their therapeutic effect on bone repair, and remarkably reduce the pain of patients by modulating the release of inflammatory cytokines, such as interleukin-1 beta (IL-1β) [20, 23-27]. Moreover, the activated Ca^{2+}/nitric oxide/cGMP cascade is also closely related to the increased expression of FGF-2 and VEGF, two key regulators of angiogenesis [27]. In addition, the crosstalk between Ca^{2+}, ERK, PKA, and PKG signaling under PEMF stimulation was also reported [19, 22]. All these findings show the prominent role of Ca^{2+} signaling in PEMFs-induced bone repair.

Wnt/β-catenin signaling pathway

Extracellular Wnt ligands bind to their seven-pass transmembrane Frizzled receptors simultaneously with a co-receptor of the arrow/Lrp family (e.g., LRP5 and LRP6), thus stabilizes β-catenin in the cytoplasm and initiates the canonical Wnt/β-catenin signaling pathway [28].This signaling pathway is conserved throughout metazoans and is essential for cell proliferation, differentiation, development, self-renewal, and cell fate determination [29, 30]. Much evidence has suggested that the Wnt/β-catenin signaling pathway acts as a key regulator in PEMF-induced osteogenic differentiation of mesenchymal progenitor cells, bone formation and repair. For instance, *in vitro* assay studies, gene and protein expressions of canonical Wnt/β-catenin signaling pathway, including Wnt1, LRP6, and β-catenin, were all significantly enhanced after PEMF exposure at both proliferation and differentiation stages of osteoblast-like MC3T3-E1 cells [31]. In addition, except the upregulation of mRNA expressions of Wnt1, Wnt3a, LRP5 and β-catenin in tissue derived mesenchymal stem cells (ADSCs), PEMFs intervention could also reduce the expression of dickkopf1 (DKK1) which usually acts as an inhibitor of Wnt signaling pathway [32]. Furthermore, the enhanced Wnt/β-catenin signaling induced by PEMFs notably elevated the expression of proliferation phase related target genes, Ccnd 1 and Ccne 1, and differentiation phase related genes, ALP, OCN, COL1, and Runx2, in osteoblast cells, which accelerated the osteoblasts proliferation, differentiation, and mineralization, three pivotal processes of bone formation [31, 32]. On the other hand, according to *in vivo* assay studies, PEMFs effectively reversed the bone mass loss and deterioration of bone microarchitecture analyzed by microCT and attenuated biomechanical strength deterioration evaluated by three-point bending test in hind limb-suspended ovariectomized rats through the Wnt/Lrp5/β-catenin signal pathway [33, 34], indicating that activating this pathway by PEMF exposure is beneficial for bone disorders.

MAPK pathway

The MAPK pathway is important in the transduction of extracellular signals to various cellular compartments and is involved in cell proliferation, differentiation, migration, and death [35]. Conventional MAPKs include Erk1/2, JNK, and p38. The MAPK pathway plays a critical role in PEMF-induced osteogenic differentiation and osteoblasts' viability and function. For example, extremely low-frequency pulsed electromagnetic field (ELF-PEMF) treatment could significantly increase the total protein content, mitochondrial activity, and ALP activity and enhance the formation of mineralized matrix of human osteoblasts with a poor initial osteoblast function through triggering the ERK1/2 signaling pathway. When the cells were treated with U0126, an inhibitor of the ERK1/2 signaling cascade, the positive effects of the ELF-PEMF treatment on osteoblast function were abolished [36]. Other studies also revealed that the MEK/ERK signaling pathway regulated the promoting effects of PEMF on bone marrow mesenchymal stem cell (BMSC) proliferation, expression of osteogenic genes (RUNX2, BSP, OPN), ALP activity, and calcium deposition [22, 32, 37, 38]. Additionally, one study reported that the p38 MAPK pathway is involved in the increased production of collagen synthesis in osteoblast-like cells stimulated by ELF-EMF exposure [39]. Interestingly, a recent research suggested that a 45 Hz EMF promoted the osteogenic differentiation of adipose-derived stem cells, whereas a 7.5 Hz EMF directly augmented the

expression of osteoclastogenic markers and regulated the osteoclast differentiation through ERK and p38 MAPK activation [40]. This finding indicated that PEMFs can simultaneously influence osteoblastic and osteoclastic activities under defined electromagnetic conditions.

FGF and VEGF pathways

Osteogenesis and angiogenesis, including cell–cell communication between blood vessel cells and bone cells, are essential for bone repair. Many studies suggested that PEMFs play a promotion effect not only in osteogenesis but also in angiogenesis [41-44]. PEMFs may facilitate bone repair by augmenting the interaction between osteogenesis and blood vessel growth. During this complex process, FGF and VEGF, two key angiogenesis-related cytokines, may play critical regulatory roles. The FGF signaling pathway has been demonstrated to contribute in the regulation of proliferation and differentiation of osteoblasts and in angiogenesis [45] and the VEGF signaling pathway has also been reported to be involved in a reciprocal, functional, and regulatory relationship between osteoblasts and endothelial cells during osteogenesis [46-48]. A study indicated that a 150% increase in FGF-2 mRNA and a fivefold elevation of FGF-2 proteins in human umbilical vein endothelial cells (HUVECs) exposed to PEMF were monitored and the release of functional FGF-2 from PEMF-stimulated HUVECs specially increased endothelial cell proliferation and tubulization, processes that are important for vessel formation [49]. KDR/Flk-1, a tyrosine kinase receptor of VEGF, is autophosphorylated in response to VEGF stimulation and is capable of transducing VEGF signals. One research has revealed that PEMF stimulation significantly increased the expression and phosphorylated levels of KDR/Flk-1 and promoted proliferation, migration, and tube formation of HUVECs [43]. The proangiogenesis effect through the FGF and VEGF signaling pathways of PEMFs provide another explanation for the therapeutic function of PEMFs in bone repair. Many studies are still required to further clarify the efficacy of FGF and VEGF in PEMF-induced bone repair.

TGF-β/BMP pathway

TGF-βs and BMPs, as multifunctional growth factors, belong to the TGF-β super family. The interaction of TGF-βs/BMPs with TGF-β specific type 1 and type 2 or BMP serine/threonine kinase receptors initiates the signaling cascade via canonical (or Smad-dependent pathways) and non-canonical pathways (or Smad-independent signaling pathways) [50]. The TGF-β/BMP signaling pathway plays an important regulatory role in bone repair [51-56]. It is also confirmed to be involved in PEMF-induced osteogenesis. Several studies demonstrated that PEMF stimulation could significantly increase the expression of TGF-β in both osteoblast-like cells and cells from atrophic or hypertrophic non-unions [17, 57-60]. Moreover, a recent research suggested that PEMFs activated the TGF-β signaling via Smad2 in differentiated and mineralizing osteoblasts and augmented the expression of osteoblast differentiation marker genes, such as ALP and type I collagen, andexerted its osteogenesis promotional function [3]. The expression of BMPs in osteogenesis was also enhanced by PEMFs according to *in vitro* and clinical studies [5, 61, 62]. Furthermore, another recent study revealed that PEMFs stimulate osteogenic differentiation and maturation of osteoblasts by primary cilium-mediated upregulated expression of BMPRII, one of the receptors of BMPs, and subsequently activation of BMP–Smad1/5/8 signaling [63]. Given the separate promotional effects

Table 1. Signaling pathways involved in PEMF-induced bone repair

Signaling pathway	Role of PEMF stimulation	References
Ca^{2+}	Activate	17,19,20
Wnt/β-catenin	Activate	31,32,33
MAPK	Activate	22,36,39
FGF	Activate	45,49
VEGF	Activate	43,46
TGF-β/BMP	Activate	3,63
IGF	Activate	70,71
Notch	Activate	73
cAMP/PKA	Activate	38,74

on the differentiation and maturation of osteoblasts of BMPs and PEMFs, many studies found that combined BMP and PEMF stimulation would augment bone formation to a greater degree than treatment with either stimulus [64-67].

Other pathways

IGF signaling pathway is also an important signaling implicating in osteoblast differentiation and bone formation [68, 69]. It was reported that PEMFs significantly increase the level of mRNA expression of IGF-1 and promote bone formation in rat femoral tissues *in vitro* [70]. In addition, IGF-1 in combination with PEMFs augmented cartilage explant anabolic activities, increased PG synthesis, restricted the catabolic effect of IL-1b, and showed a synergistic chondroprotective effect on human articular cartilage [71]. Another study showed that dexamethasone combined with PEMF upregulated the mRNA expression of IGF-1 and improved dexamethasone-induced bone loss and osteoporosis [72]. Notch signaling is a highly conserved pathway that regulates cell fate decisions and skeletal development. A recent research advocated that the expression levels of Notch receptor (Notch4) and its ligand DLL4 and nuclear target genes (Hey1, Hes1, and Hes5) were upregulated during the PEMF-induced ostogenic differentiation of hMSCs. Moreover, the Notch pathway inhibitors effectively inhibited the expression of osteogenic markers, including Runx2, Dlx5, Osterix, as well as Hes1 and Hes5, indicating that the Notch signaling plays an important regulatory role in PEMF-induced osteogenic differentiation of hMSCs [73]. The cAMP/PKA signaling pathway is another signaling involved in the PEMF-induced bone repair. Recent studies have demonstrated that PEMFs notably increased the cAMP level and PKA activity and accelerated the osteogenic differentiation of MSCs [32, 38, 74]. (Table 1.)

Therapeutic applications of PEMFs in bone repair

The promotional effects of PEMFs on osteogenesis and angiogenesis in bone repair have been well established in either vitro or *in vivo* animal studies. Several key signaling pathways involved in PEMF-induced bone repair were elaborate above. Moreover, several decades of PEMF applications in the treatment of skeletal diseases have clearly proved its potential benefit in augmenting bone repair. This part of review will tackle the recent therapeutic applications of PEMFs in bone repair and evaluate their clinical treatment effect.

Fractures, delayed unions, and non-unions

Fractures, particularly those that had developed into delayed unions or even non-unions, have a substantial clinical, economic, and quality of life impact [75]. Apart from traditional surgical management and rigid fixation (either internal or external), noninvasive PEMFs have already been used effectively in clinics as physical therapy to accelerate and finalize the healing process of a fresh fracture and reactivate the healing process of delayed unions and non-unions for nearly forty years since they were first approved by the US Food and Drug Administration [13, 14]. A recent systematic review and meta-analysis of randomized controlled trials showed that PEMFs significantly shortened the time to radiological union for acute fractures undergoing non-operative treatment and acute fractures of the upper limb and accelerated the time to clinical union for acute diaphyseal fractures [76]. Moreover, a prospective study that evaluated the treatment effect of PEMFs on 64 patients undergoing hindfoot arthrodesis (144 joints) revealed that the adjunctive use of a PEMF in elective hindfoot arthrodesis may increase the rate and speed of radiographic union of these joints [77]. Despite the relative scarcity of well-organized randomized controlled trials, many studies highlight the practice usefulness of PEMFs in treating tibial delayed unions or non-unions, with efficacy up to 87% [13, 15, 78, 79]. Furthermore, in a broad literature review comparing PEMF treatment of non-unions with surgical therapy, Gossling noted that 81% of reported cases healed with PEMF versus 82% with surgery. Obvious therapeutic advantages of PEMFs were showed compared with surgery in treatment for infected non-unions (81%

versus 69%) and closed injury caused non-unions (85% versus 79%) [80]. In addition, a recent double-blind randomized study advocated that the adjunctive use of PEMF for fifth metatarsal fracture non-unions significantly shortened the average time to complete radiographic union from 14.7 weeks to 8.9 weeks compared with the control group without PEMF exposure; the elevated expression levels of PIGF, BMP-5, and BMP-7, key regulators of angiogenesis and osteogenesis, were first detected in the non-union environment before and after the application of PEMFs [5]. These studies strikingly support PEMFs as an optional and effective method to accelerate fracture healing.

Osteonecrosis of the femoral head

ONFH is the endpoint of a disease process that results from insufficient blood flow and bone tissue necrosis, leading to joint instability, collapse of the femoral head, and joint arthritis that necessitates total hip arthroplasty in many patients [81]. As the mean age of the patients is only approximately 40 years, long-term results of total hip arthroplasty in these young patients are not always satisfactory. PEMFs have been regarded as a prospective noninvasive treatment strategy for ONFH because of their positive effects on osteogenesis and chondroprotective effect of articular cartilage. To date, six clinical studies have investigated and evaluated the therapeutic effect of PEMFs on ONFH [82]. Three studies have used PEMFs as a single management to treat ONFH [83-85] and have revealed that PEMFs can prevent the progression of the disease and significantly preserve majority of femoral heads (80.2% by Massari [83], 88.57% by Cebrian [84], 83.9% by Bassett [85]) in the first stages of avascular necrosis of the femoral head at Ficat 0, I, and II or Steinberg II and III. Moreover, according to two of these studies, PEMFs have also been shown to reverse disease progression. Bassett found that 9 hips showed improvement, and they were all in Steinberg stages II to III, demonstrating a 60% improvement rate. Of these 9 hips, 3 of these even returning to normal [85], whereas Massari showed improvements in Ficat stages [83]. Additionally, PEMFs were also effective in improving osteonecrosis symptoms, including relieving joint pain and alleviating subchondral bone marrow edema [83]. However, for Ficat stage III patients, PEMFs may be beneficial only for younger patients and show no beneficial effect to patients whose hip has already collapsed or is biomechanically compromised. The effect of PEMF therapy as an adjunct to other treatments, such as core decompression and bone grafting, was also assessed in other three studies [8, 16, 86, 87]. By combining PEMFs with core decompression and autologous bone grafts, 81% of patients with Steinberg II scores showed good results radiographically and clinically and had no pain or limp [8]. Moreover, 68% patients treated with PEMFs alone achieved the clinical success determined as marginal pain with retention of the femoral head, while only 44% of those treated with core decompression alone [87]. In sum, all these studies showed the non-invasive therapeutic effect of PEMFs on ONFH, either alone or in combination with other treatments.

Osteoporosis

Osteoporosis is a worldwide health problem with high morbidity, especially in postmenopausal women [88-90]. It is generally defined as a systemic skeletal disease characterized by low bone mineral density (BMD) and compromised bone strength, leading to enhanced bone fragility, increased fracture risk, and resultant disability, which strikingly affects patients' quality of life [91, 92]. As PEMFs were verified to be equally effective with mechanical stimulation in maintaining or improving bone mass according to experiments of NASA between 1976 and 1979, many clinical studies have gradually achieved positive therapeutic effects for osteoporosis by PEMF exposure [93-99]. Chronic pain is a common symptom of people with osteoporosis [100]. Many randomized controlled trials indicated that PEMF exposure could relieve chronic pain caused by osteoporosis [97, 98]. Moreover, in a study of 126 patients with primary osteoporosis, PEMF provided a faster and significant effect in relieving pain for patients with type I osteoporosis than those with type II [99]. BMD is the gold standard for diagnosing osteoporosis and the best quantitative indicator for forecasting the risk of osteoporotic fracture, monitoring the natural course of osteoporosis,

and evaluating the effect of osteoporosis. Tabrah indicated that BMD of the treated radii was elevated notably in the sixth week in a clinical study of 20 women with PMOP treated with PEMFs [94]. In Garland's research, which evaluated the effect of PEMFs on knee osteoporosis in individuals with spinal cord injury, BMD was also elevated. At three months, BMD was increased by 5.1% in the stimulated knees but declined to 6.6% in the control knees. PEMFs as a noninvasive physical therapy method avoids the defects of pharmacotherapy for osteoporosis, including the multiple side effects, the more cost and the low persistence. More importantly, a randomized, active-controlled clinical trial on postmenopausal osteoporosis (PMO) in Southwest China revealed that PEMFs had the same effect as alendronate, which is, currently, the most commonly prescribed medication for treating PMO within 24 weeks [101]. Furthermore, the hemorheological safety of PEMFs for treating osteoporosis was also observed by a randomized, placebo-controlled clinical study [102]. All these results support the efficiency and safety of PEMFs for osteoporosis treatment and as an advantageous treatment strategy in the future.

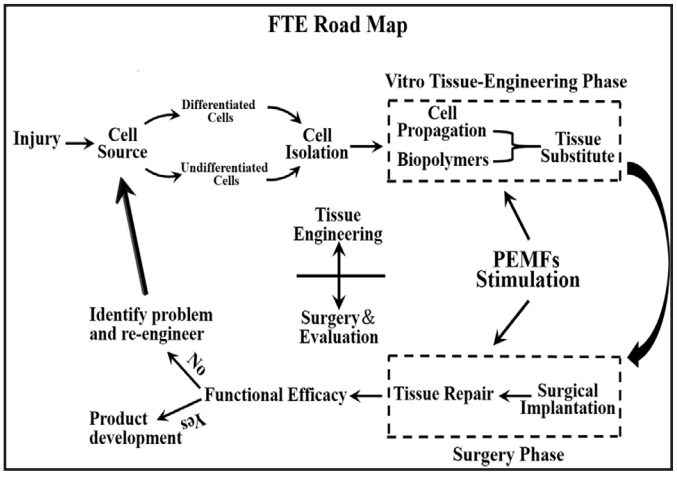

Fig. 1. Functional Tissue Engineering (FTE) Road Map. This road map was adapted from Ref. 113 and described the combination of PEMFs and tissue engineering to obtain effective tissue substitutes.

Bone tissue engineering

Although the bone has a large self-healing capacity, in some complex clinical conditions, such as large bone defects created by trauma, infection, tumor resection, and skeletal abnormalities, or in cases where bone repair failed, a large quantity of bone regeneration are required [103]. In this case, bone tissue engineering has emerged as a promising alternative to augment insufficient bone repair. Bone tissue engineering generally starts with the *in vitro* culturing of BMSC cells with high osteogenic differentiation potential alone or in the presence of scaffold carriers to develop and manipulate a tissue-engineered construct followed by implanting into the defected site to augment bone repair [104]. Despite bone tissue engineering possess the advantages that the same mechanical and functional properties and superior integration to the host bone tissue and has already acquired some better satisfactions in the clinical treatment of bone defect [105-108], the extended clinical application is hampered by major limitations, such as the poor availability and the time required to differentiate up to a stage suitable for implantation of the BMSCs, the inflammatory environment of implanted site triggered by the bone defect itself and the surgical procedure and the further new bone tissue and surrounding host tissue degeneration after construct implantation [21, 109, 110]. Therefore, the improvement of the present available technologies is still needed to acquire more satisfactory clinical outcomes in bone defect repair. PEMFs, as described above, have a marked function to accelerate the proliferation, osteogenic differentiation, and mutation of BMSCs by activating a series of signaling pathways [7, 21, 25, 31, 38, 73]. Moreover, the expressions of many osteogenesis- and angiogenesis-promoting cytokines, including TGF-β, BMPs, IGFs, FGFs, and VEGFs, in BMSCs are strikingly elevated by PEMF exposure. In addition, the anti-inflammatory effect of PEMFs was also verified by studies [27, 111, 112]. PEMFs could upregulate the expression of A_{2A} AR, which is linked to G proteins and stimulates the activity of adenylate cyclase, mediating an increase in cAMP accumulation [111]. The

presence of cAMP mediates a number of anti-inflammatory pathways, resulting in the inhibition of TNF-α and IL-1β [111, 112].Altogether, these data display the potential positive functions of PEMFs in bone tissue engineering on the vitro construct culture, in favoring the anabolic activities of the implanted cells, and in protecting the construct from the catabolic effects of inflammation after vivo implantation. An functional tissue engineering (FTE) roadmap to describe the combination of PEMFs and tissue engineering was drawn based on the benefits of combining PEMFs with bone tissue engineering to obtain effective tissue substitutes to realize the structural and functional repair of bone defects and its feasibility of this paradigm was also evaluated (Fig.1) [104, 113]. In spite of these encouraging results, additional studies are needed to promote this therapeutic strategy for bone defect repair in clinics in the future.

Conclusion

In recent decades, PEMF stimulation has received tremendous attention as a prospective, noninvasive, and safe physical strategy to accelerate bone repair. Physical PEMF stimulation initiates the signaling cascades, which effectively promote osteogenesis and angiogenesis in an orchestrated spatiotemporal manner, ultimately enhancing the self-repair capability of bone tissue. Although the bone repair promotion potential of PEMF stimulation has showed positive benefits in the treatment of various skeletal diseases, many studies about PEMFs in experimental biology and clinical therapy are still needed to make them more effective and extend their clinical applications.

In this review, we elaborated the involvement of various key molecular signaling pathways in PEMF-induced bone repair. Targeting the molecular signaling pathways described above may be a prospective strategy to further enhance the bone repair promotion effect of PEMFs via increasing the number of osteoblasts and their maturation and elevating endothelial cell proliferation and tubulization, processes important for osteogenesis and angiogenesis. For instance, a small molecule inhibitor termed 603281-31-8 could impair the activity of GSK3b, which plays a negative regulatory role in the Wnt signal transduction pathway, and result in considerable increase in bone mass [114]. Inhibiting DKK1 activity or using anti-sclerostin antibody in mice increased bone formation and bone mass [115]. Combining PEMF exposure with these indirect Wnt/β-catenin signaling pathway activators may further activate this pivotal signaling pathway and enhance the biological response of bone tissue to PEMF stimulation, leading to more effective bone repair. However, risk of cancer, osteoarthritis symptoms and osteophytes are some the evils of the long-term activation of the Wnt/β-catenin signaling pathway. Additionally to the Wnt signaling pathway, many studies have showed that combining PEMF stimulation with BMPs or IGFs could also augment bone formation [65, 70]. We also discussed the recent clinical therapeutic application of bone repair promotion potential of PEMFs in the treatment of skeletal diseases, such as fractures, delayed unions and non-unions, ONFH, and osteoporosis. The clinical latent benefits of the incorporation of PEMFs and bone tissue engineering for large bone defect repair were also evaluated. Despite positive effects of PEMF stimulation for bone repair alone or as an adjunct to other treatments were definite in clinics, sometime, the effectiveness is discrepant for the same disease in different studies [6, 15]. This is mainly because of the lack of a standardized intensity, frequency, and therapeutic course and time of PEMFs. In this regard, more studies need to be conducted to determine unitive and high-efficiency parameters. In summary, as PEMF stimulation offers noninvasive, effective, safe, and convenient effects, it opens up a new avenue for bone repair. However, much work remains to be done to extend its clinical application in the future.

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Disclosure Statement

No conflict of interest exists.

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REVIEW

Repetitive Magnetic Stimulation for the Management of Peripheral Neuropathic Pain: A Systematic Review

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ABSTRACT

Introduction: Repetitive magnetic stimulation (rMS) is a safe and well-tolerated intervention. Transcranial magnetic stimulation (TMS) is used for the treatment of depression and for the treatment and prevention of migraine. Over the last few years, several reports and randomised controlled studies of the use of rMS for the treatment of pain have been published. The aim of this systematic review was to identify the available literature regarding the use of rMS in the treatment of peripheral neuropathic pain.
Methods: After a systematic Medline search we identified 12 papers eligible to be included in this review.
Results: The majority of the studies were on patients with phantom limb pain, followed by radiculopathy, plexopathy, post-traumatic pain and peripheral neuropathy. The treatment protocols vary significantly from study to study and, therefore, pooling the results together is currently difficult. However, rMS has a definite immediate effect in pain relief which, in the majority of studies, is maintained for a few weeks.
Conclusion: rMS seems to be a promising intervention in the treatment of peripheral neuropathic pain. Further research is in the field is needed. Use of neuronavigation might increase the precision of stimulation and subsequently its effectiveness.

Keywords: Neuropathic pain; Peripheral; Repetitive magnetic stimulation; TMS

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Key Summary Points

Both peripheral and central repetitive magnetic stimulation have been employed for the treatment of peripheral neuropathic pain.

Repetitive magnetic stimulation has potential in the treatment of peripheral neuropathic pain.

Use of neuronavigation might increase the precision of stimulation and subsequently the effectiveness of repetitive magnetic stimulation.

Assessment of brain networks might be the way forward to developing an objective means of studying the effect of repetitive magnetic. stimulation.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique based on the principle of electromagnetic induction of an electric field in the brain [1]. Anthony T. Barker was the first to explore the use of magnetic fields to alter electrical signalling within the brain, in Sheffield, and the first stable TMS devices were developed in 1985 [2].

The therapeutic utility of repetitive TMS (rTMS) has been demonstrated in a variety of neurological [3] and psychiatric conditions [4] and has already been approved as a treatment for depression and migraine in many countries. TMS is a safe and well-tolerated intervention whilst serious adverse events during TMS are rare [5].

Neuropathic pain is a common presenting complaint of patients with peripheral neuropathy (PN) and is considered one of the most detrimental aspects of the condition with regards to patients' quality of life [6–13]. It is therefore imperative for robust pain therapeutic interventions to be innovated, improved and implemented.

Over the years, increasing reports of the clinical utility of magnetic stimulation (MS) in the management of peripheral neuropathic pain and in particular rMS delivered either through a peripheral or transcranial route have been attempted with promising results.

The aim of this work was to systematically review the current literature regarding the use of rMS for the management of peripheral neuropathic pain. We aimed to describe the different treatment protocols that have been used and their efficacy in order to establish the therapeutic utility of rMS in the management of peripheral neuropathic pain.

METHODS

Search Strategy

A systematic computer-based literature search was conducted on 12 June 2019 using the PubMed database. We evaluated all articles published between the dates of 1 January 1999 and 12 June 2019. For the search, we used three Medical Subject Heading (MeSH) terms that had to be present in the title or the abstract. Term A was "neuropathy" or "phantom limb" or "polyneuropathy" or "peripheral" or "neuronopathy" or "radiculopathy" or "polyradiculopathy" or "dorsal" or "low back". Term B was "magnetic stimulation" or "magnetic therapy" or "electromagnetic". Term C was "pain" or "painful". No filters were applied to our search.

Inclusion and Exclusion Criteria

In order to be included in this review articles were required to meet the following criteria: (1) be original articles; (2) involve study of human subjects; (3) be written in the English language; (4) refer to transcranial magnetic stimulation or peripheral magnetic stimulation; (5) refer to pain because of peripheral nervous system involvement. The exclusion criteria for the articles were as follows: (1) book chapters, reviews, meta-analyses, systematic reviews,

letters to the editor and editorials not providing new data and study protocols; (2) articles which did not discuss magnetic or electromagnetic stimulation as a management option; (3) articles with a lack of individual results for the management of painful peripheral neuropathies, even if those subjects were included in the study; (4) articles not referring to patients with painful peripheral neuropathies.

Synthesis of Results

The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [6]. Where studies did not provide raw values in graphically displayed results, an open-source programme was used to extract raw data (Engauge Digitizer, http://markummitchell.github.io/engauge-digitizer). A database was developed using the Statistical Package for Social Sciences, version 24 for Mac. Pooled frequencies and descriptive characteristics of demographic parameters were extracted.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Our literature search strategy identified 332 articles. Of these, 12 met the inclusion criteria and were included and analysed in this review. Of them five were randomised controlled trials (RCTs), two were small case series and five single case reports. The majority of the papers (50%) tested the use of rMS in phantom limb pain, followed by radiculopathy (17%), brachial plexopathy (17%), post-traumatic pain (8%) and peripheral neuropathy (8%).

The PRISMA chart displays the process of article selection (Fig. 1). Table 1 summarizes the characteristics of the papers included and gives a detailed summary of the treatment protocols and outcomes.

PHANTOM LIMB PAIN

Phantom limb pain (PLP) is difficult to treat and often responds poorly to conventional pain management [15, 16]. Phantom limb sensations can be experienced following amputation. Phantom limb-like sensations can also be seen in patients with spinal cord injury, nerve avulsions and with congenital limb aplasia [17]. In PLP, maladaptive plasticity and reduced connectivity in interhemispherical and sensorimotor networks play a major role in pain. rTMS has been tested in PLP as a tool for blocking maladaptive plasticity in the sensorimotor cortex and has shown analgesic effects when used on the motor cortex, through modulating cortical reorganisation [18]. One particular study has shown that amputees with PLP have a significantly greater activation in the primary motor cortex and supplementary motor cortex of the affected hemisphere compared to those without pain, likely due to increased excitability after limb amputation [19].

Malavera et al. studied the effects of rTMS in the treatment of PLP in a randomised double-blinded placebo-controlled study [16]. Fifty-four patients underwent real or sham rTMS of the primary motor area contralateral to the amputated limb. The analgesic effect of the treatment was significant for the first 15 days; however, it was not after 30 days. The analgesic effect found in this study can possibly be explained by the effect of rTMS over the central pathophysiological mechanisms relating to PLP. After a traumatic amputation, maladaptive reorganisation of the sensorimotor cortex involves a reduction in intracortical inhibition mechanisms, an imbalance between γ-aminobutyric acid (GABA) and glutamate and an increase in excitability of corticospinal neurons. High frequency rTMS over the motor cortex enhances its excitability leading to the indirect activation of inhibitory projections towards the thalamus, resulting in the modulation of pain signalling pathways [16].

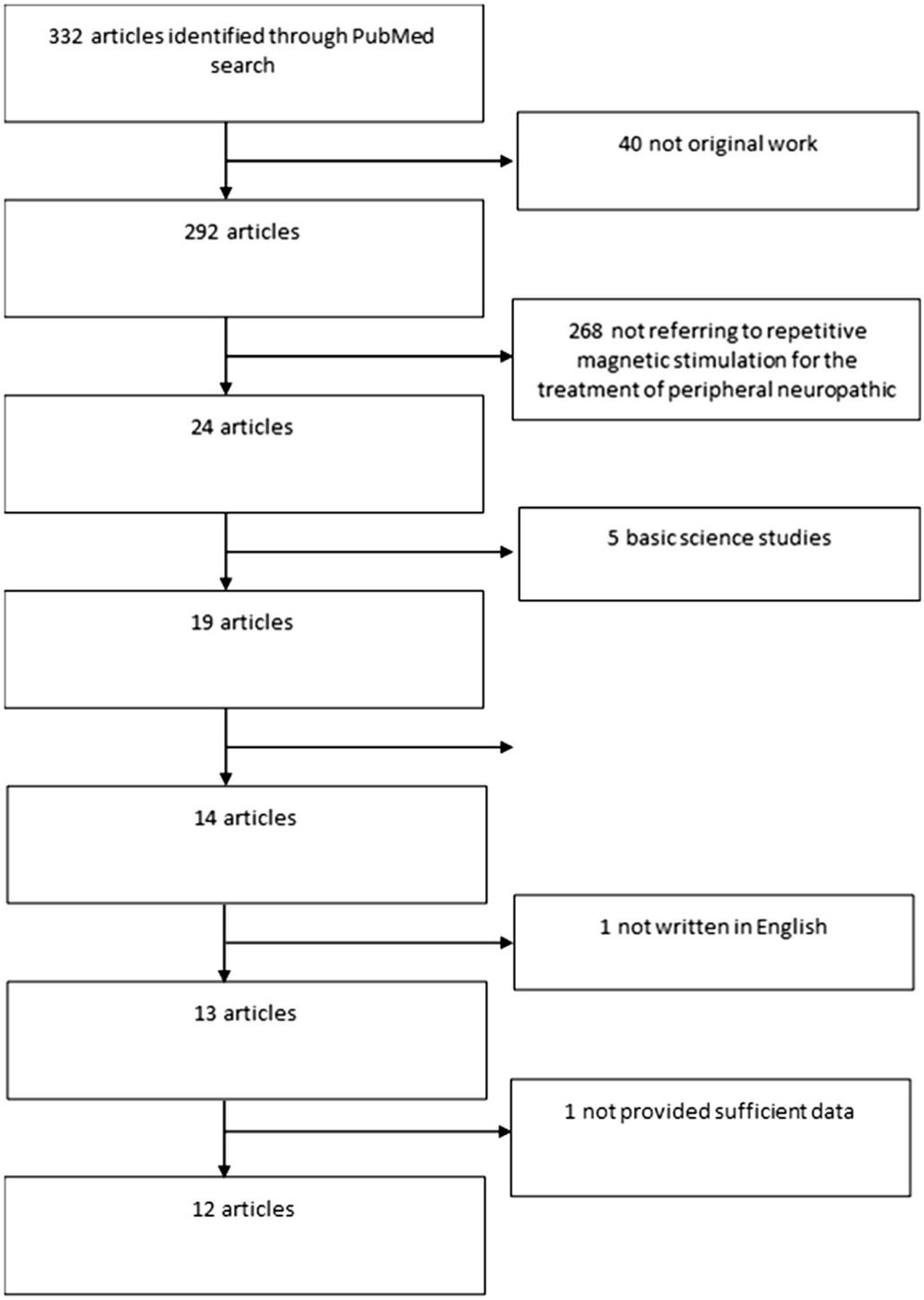

Fig. 1 PRISMA chart

In contrast to the RCT conducted by Malavera et al., a study by Ahmed et al. showed a significant and prolonged reduction of pain in patients with PLP receiving real rTMS versus sham. The authors randomised patients to receive either real rTMS (n = 17) or sham rTMS

Table 1 Description of protocols and outcomes reported in the studies included in this review

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Malavera (2016)	RCT	Phantom limb pain	54	Brain: hemisphere contralateral to the pain	Magstim Rapid 2 (Magstim, Whitland, UK)	No	Double	10 daily sessions over 2 weeks Primary motor area was stimulated at 10 Hz, with an intensity of 90% of the resting motor threshold. Each session had 20 bursts. Each burst consisted of 60 pulses (6 s). Interval between bursts was 54 s. In total, 1200 pulses were delivered in each session	70% of patients had a clinically significant pain reduction (> 30%) in the active group compared to 41% in the sham group 15 days after completion of treatment. This effect was not significant 30 days after treatment
Ahmed (2011)	RCT	Phantom limb pain	27	Brain: hemisphere contralateral to the pain	Mag-Lite r25 stimulator (Dantec Medical, Skovelund, Denmark	No	Double (90 mm)	Five consecutive daily sessions Primary motor area was stimulated at 20 Hz, with an intensity of 80% of the resting motor threshold. Each session had 10 bursts. Each burst consisted of 200 pulses (10 s). Interval between bursts was 50 s. In total, 2000 pulses were delivered in each session	Significant pain reduction in the active rTMS group compared to sham; 55% pain reduction at completion of treatment which remained reduced by 52% at 1 month after completion of treatment and reduced by 39% at 2 months after completion of treatment
Scibilia (2018)	Case report	Phantom limb pain	1	Brain: hemisphere contralateral to the pain	Nexstim NBS system 4.3 (Nexstim Oy, Finland)	Yes	Not specified	30 consecutive daily sessions Primary motor area and dorsolateral prefrontal cortex were stimulated at 10 Hz, with an intensity of 120% of the resting motor threshold. Each session had 75 bursts. Each burst consisted of 40 pulses (4 s). Interval between bursts was 26 s. In total, 3000 pulses were delivered in each session Primary sensory area was stimulated at 1 Hz, with an intensity of 100% of the resting motor threshold. Each session had 77 bursts. Each burst consisted of 26 pulses (26 s). Interval between bursts was 4 s. In total, 2002 pulses were delivered in each session	55% pain reduction at 1 month after completion of treatment and remained at 6 months

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Grammer (2015)	Case report	Phantom limb pain	1	Brain: hemisphere contralateral to the pain	Not specified	No	Double	2 rounds over 6 weeks (in total 28 daily sessions) First round: primary sensory area (five sessions) was stimulated at 1 Hz, with an intensity of 100% of the resting motor threshold. Each burst consisted of 26 pulses (26 s). Interval between bursts was 4 s. In total, 2000 pulses were delivered in each session Second round: alternating pattern between sessions as per round 1 and stimulation of the dorsolateral prefrontal cortex as follows Dorsolateral prefrontal cortex was stimulated at 10 Hz, with an intensity of 120% of the resting motor threshold. Each burst consisted of four pulses (4 s). Interval between bursts was 26 s. In total, 3000 pulses were delivered in each session Supplementary motor complex (2nd to 6th rounds) was stimulated at 1 Hz for 800 s, with an intensity of 85% of the resting motor threshold. In total, 800 pulses were delivered in each session	60% pain reduction after three low frequency sessions stimulating the primary sensory area and 90% pain reduction after completion of all 28 sessions

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Lee (2015)	Case report	Phantom limb pain	1	Brain: hemisphere contralateral to the pain	Magstim Rapid 2 (Magstim, Whitland, UK)	Yes	Double (70 mm)	Six rounds, each consisting of 10 daily sessions over 2 weeks (varying intraround interval) Primary motor area (1st round) was stimulated at 1 Hz for 800 s, with an intensity of 85% of the resting motor threshold. In total, 800 pulses were delivered in each session Supplementary motor complex (2nd to 6th rounds) was stimulated at 1 Hz for 800 s, with an intensity of 85% of the resting motor threshold. In total, 800 pulses were delivered in each session	Significant pain relief was reported after using low frequency rTMS over the supplementary motor complex, but not over the primary motor area
Di Rollo (2011)	Case report	Phantom limb pain	1	Brain: hemisphere ipsilateral to the pain	Magstim Rapid (Magstim, Whitland, UK)	No	Double (70 mm)	15 daily sessions over 3 weeks Primary motor area was stimulated at 1 Hz, with an intensity of 80% of the resting motor threshold. Each session had 30 bursts. Each burst consisted of 20 pulses (20 s). Interval between bursts was 10 s. In total, 600 pulses were delivered in each session	33% pain reduction at completion of treatment and remained reduced by 25% at the end of week 1 after completion of treatment and 17% at the end of week 3 after completion of treatment
Attal (2016)	RCT	Radiculopathy	36	Brain: hemisphere contralateral to the pain	MagPro X100 (Magventure, Farum, Denmark)	No	Double	Three consecutive daily sessions Primary motor area was stimulated at 10 Hz, with an intensity of 80% of the resting motor threshold. Each session had 30 bursts. Each burst consisted of 100 pulses (10 s). Interval between bursts was 20 s. In total, 3000 pulses were delivered in each session	43% of patients had a clinically significant pain reduction (> 30%) in the active repetitive transcranial magnetic stimulation (rTMS) group compared to 22% in the active transcranial direct current stimulation (tDCS) and 17% in the sham group. The superiority of rTMS was demonstrated for at least 5 days after treatment

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Töpper (2003)	Case series	Radiculopathy	2	Brain: hemisphere contralateral to the pain	Magstim Rapid (Magstim, Whitland, UK)	No	Double (90 mm)	Two rounds. Each round consisted of 15 daily sessions over 3 weeks (in total 28 daily sessions). The two rounds were separated by 4–6 weeks First round: Parietal cortex was stimulated at 10 Hz, with an intensity of 110% of the resting motor threshold. Each session had 20 bursts. Each burst consisted of 20 pulses (2 s). Interval between bursts was 1 min. In total, 400 pulses were delivered in each session Second round: Parietal cortex was stimulated at 1 Hz, with an intensity of 110% of the resting motor threshold. Each session a single burst lasting for 12 min. In total, 720 pulses were delivered in each session	Pain reduction only lasted for 10 min after the end of treatment
Leung (2014)	Case series	Post-traumatic pain	5	Peripheral: over the site of trauma, where neuroma developed	Not specified	No	Double	3–4 daily sessions over 2 months Stimulation frequency was 0.5 Hz. In total, 400 pulses were delivered in each session	85% pain reduction after 3–4 sessions Limitation due to lack of information about intensity of each treatment

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Khedr (2012)	RCT	Brachial Plexopathy	34	Peripheral: over the superior trapezius muscle	Magstim model 200 (Magstim, Whitland, UK)	No	Double (70 mm)	10 daily sessions over 2 weeks. Two protocols were applied (10 min apart) For pain relief: stimulation at 15 Hz, with an intensity of 100% of the resting motor threshold was applied. Each session had seven bursts. Each burst consisted of 150 pulses (10 s). Interval between bursts was 20 s. In total, 1050 pulses were delivered in each session For strength increase: stimulation at 3 Hz, with an intensity of 70% of the resting motor threshold was applied. Each session had 50 bursts. Each burst consisted of 30 pulses (10 s). Interval between bursts was 30 s. In total, 1500 pulses were delivered in each session	Real rMS led to a significant reduction of the VAS compared to sham rMS, which lasted for at least 1 month after completion of treatment
Lefaucheur (2004)	Case report	Brachial Plexopathy	1	Brain: hemisphere contralateral to the pain	Super-Rapid Magstim (Magstim, Whitland, UK)	No	Double (70 mm)	One session per month Primary motor area was stimulated at 10 Hz, with an intensity of 80% of the resting motor threshold. Each session had 20 bursts. Each burst consisted of 100 pulses (5 s). Interval between bursts was 55 s. In total, 2000 pulses were delivered in each session	Satisfactory reduction of pain (mean VAS score reduction of more than 5/10) was achieved with active rTMS. The effect lasted for at least 1 week and faded away at 4 weeks
Onesti (2013)	RCT	Peripheral Neuropathy	25	Brain	Magstim Rapid 2 (Magstim, Whitland, UK)	No	H-coil	5 consecutive daily sessions Primary leg motor areas were stimulated at 20 Hz, with an intensity of 100% of the resting motor threshold. Each session had 30 bursts. Each burst consisted of 50 pulses. Interval between bursts was 30 s. In total, 1500 pulses were delivered in each session	Real rTMS led to a significant reduction of the VAS compared to sham rTMS, which lasted for up to 3 weeks after completion of treatment

(n = 10). Sham rTMS involved elevating and angling the magnetic coil away from the cortex. The authors found a 55% reduction in pain in the treatment group immediately following the fifth session. This effect was still seen at 2 months follow-up [20]. Interestingly the percentage of pain reduction was higher in patients with upper limb phantom pain compared to patients with lower limb phantom pain. Whilst the results reported are positive, there are multiple drawbacks in the methodology within this study including non-standard randomisation criteria, small sample size and unequal group allocation. Additionally, the study recruited a heterogenous population of patients affected by PLP, in both upper (n = 11) and lower limbs (n = 16).

Navigated TMS employs conventional TMS combined with sophisticated neuronavigational software providing precise anatomical information necessary for anatomically controlled cortical stimulation. It can be used to stimulate highly selected areas in the brain in PLP. It promotes the modulation of brain connectivity to induce its rearrangement in chronic pain syndromes. In a patient with PLP, Scibilia et al. used high frequency stimulation (10 Hz) of the primary motor area and the dorsolateral frontal cortex contralateral to the pain, and low frequency (1 Hz) stimulation of the primary somatosensory area contralateral to the pain, using navigated TMS [21]. Using resting state functional magnetic resonance, they showed that rTMS promoted cortical and subcortical plasticity, which led to an associated pain reduction. After treatment, the patient experienced a significant reduction of 5 points on the visual analogue scale (VAS) in terms of pain. This suggests that high frequency stimulation of the motor cortex contralateral to site of PLP can induce an analgesic effect. As this was a single case report, larger cohort studies are warranted to validate these findings.

In cases such as motor function recovery post stroke, stimulation with low frequency rTMS in the unaffected hemisphere has shown beneficial results [22]. Di Rollo et al. reported the effect of stimulating the hemisphere ipsilateral to the PLP in a single patient [15]. The patient showed a 33% reduction in pain at the end of the third week of treatment and a decrease of 17% at the follow-up visit which was 3 weeks after the last session.

Lee et al. described a case report of PLP treated with rTMS of the supplementary motor cortex and the primary motor cortex, using neuronavigation. Magnetic therapy dramatically reduced the pain intensity when directed over the supplementary motor cortex; however, there was no reduction in pain with therapy directed over the primary motor cortex [23]. The authors postulate that this is due to a reported greater activation of the supplementary motor cortex in amputees with PLP than those without [24]. These results, however, are to be taken with caution, owing to the patient receiving one round of treatment to the primary motor cortex, versus five rounds to the supplementary motor cortex.

Grammer et al. reported a patient with upper extremity PLP. Over 6 weeks they delivered 28 sessions of rTMS to the dorsolateral prefrontal cortex and primary sensory area contralateral to the side of pain. The sessions were of low frequency (1 Hz) for the first five sessions, thereafter alternating between low frequency (1 Hz) and high frequency (10 Hz). This protocol led to an 80% decrease in pain as rated on the VAS [25].

RADICULOPATHY

Attal et al. studied the efficacy of rTMS in patients suffering from neuropathic pain secondary to unilateral lower lumbar radiculopathy in an RCT. In tandem with this they compared the efficacy of rTMS to transcranial direct current stimulation (tDCS), which applies low intensity electrical currents directly, rather than the magnetic field employed in rTMS [26]. In an altered crossover methodology, they randomised 36 patients to receive either active rTMS and tDCS or sham rTMS and tDCS, with a 3-week period between either modality. Results showed that rTMS was more effective than tDCS and sham (tDCS and rTMS), after the third and final stimulation session. Repetitive magnetic stimulation maintained its efficacy over sham when pain was measured 5 days after the final

session, but not in comparison to tDCS. The study was limited by its relatively short treatment and follow-up period.

Töpper et al. evaluated the use of rTMS in two patients with PLP-like syndrome who had suffered cervical nerve root (C7 and C8) injuries secondary to road traffic collisions [27]. The authors investigated two separate protocols of rTMS directed over the posterior parietal cortex contralateral to the symptomatic side. The first included high frequency stimulation (10 Hz) and the second low frequency (1 Hz). The two protocols were separated by at least 4 weeks. Whilst the authors reported a significant reduction in pain measured with VAS during the rTMS treatment, this effect was seen only for up to 15 min after therapy. The study is, however, limited by its small number of participants.

Brachial Plexopathy

In an RCT of 34 patients with traumatic brachial plexopathy, Khedr et al. evaluated the efficacy of rTMS as an adjuvant intervention to physical therapy, consisting of electrical stimulation, ultrasound, heat therapy and therapeutic/active exercises [28]. Magnetic stimulation was directed over the superior trapezius muscle, using stimulation at both 3 Hz (aiming to increase strength) and 15 Hz (aiming to relieve pain). The authors reported a significant reduction in the VAS score in patients receiving real therapy compared to sham therapy. This effect was seen both at the end of the therapy and at 1-month follow-up. The study is limited by the fact that the sham protocol was substandard as the authors used an active coil that was elevated away from the muscle, rather than a sham coil applied directly over the muscle [29].

In a case report of a 37-year-old patient with brachial plexopathy, Lefaucheur et al. assessed the efficacy of high frequency rTMS targeting the precentral gyrus [30]. Over a treatment period of 16 months, they found that rTMS provided a statistically significant reduction in VAS scores. Whilst the study provides evidence of long-term use of rTMS, it is limited by being a single patient report with no matched control.

POST-TRAUMATIC NEUROPATHIC PAIN

Peripheral nerve injury can lead to the formation of a neuroma which results from abnormal nerve regeneration, which is often refractory to medications and invasive interventions. In a small case series reported by Leung et al., five patients tolerated well low frequency TMS over the site of the neuroma formation and showed long-term pain relief [31]. This is in line with other studies demonstrating that low frequency rTMS provides an inhibitory effect on neuronal activities. However, this study is limited by its small sample size, lack of control and unclear frequency of treatment sessions.

PERIPHERAL NEUROPATHY

Peripheral neuropathy is common amongst the diabetic population [32]. In a cross-over RCT Onesti et al. were the first to investigate the effect of deep rTMS, achieved by using the H-coil in 25 patients with diabetic neuropathic pain. The H-coil allows safe access to deep cortical areas which otherwise could not be accessed [33] and has been proven to be effective in the management of major depressive disorder, bipolar disorder and focal dystonias [34–36]. In this study the authors used deep real or sham rTMS of the lower limb motor cortex. The authors reported that real rTMS at 20 Hz reduces chronic drug-resistant distal diabetic neuropathic pain for 3 weeks.

CONCLUSIONS

Chronic pain perception has been found to propagate through central brain sensitisation, particularly involving the prefrontal cortex and the thalamus, in comparison to acute pain scenarios primarily recruiting the spinothalamic pathways [37]. This presents an opportunity to identify therapeutic interventions that are able to target this central processing of pain. Magnetic stimulation exerts its effect by the magnetic field generated inducing a subsequent electrical field that is able to depolarise axons

and therefore modulate active neural networks within the cortex [38]. This effect may differ depending on factors such as the magnetic pulse waveform, the intensity, frequency and pattern of stimulation [38]. There is consensus in the literature that low frequency stimulation (< 1 Hz) and high frequency stimulation (> 5 Hz) are responsible for suppression and facilitation of corticospinal excitability, respectively [39]. There is some consensus that high frequency rather than low frequency stimulation is able to illicit an analgesic effect in neuropathic pain [38]. Indeed, a similar conclusion may be drawn from the studies that have been included in this review.

On a molecular level, rTMS has been reported to induce endogenous opioid release, with one study demonstrating a reduction of the analgesic effect when stimulating the primary motor cortex in subjects administered naloxone. The authors did not find this to be the case when rTMS was applied to the dorsolateral prefrontal cortex [40]. It is important to note, however, that naloxone is known to play a role in reducing the perceived analgesic effect derived through placebo [41]. Various other neurochemicals have been reported to be implicated during rTMS therapy, including GABA, glutamate and dopamine. Glutamate *N*-methyl-D-aspartate (NMDA) receptors are known to be responsible for synaptic plasticity and have been reported to be associated with the long-term analgesic effect of rTMS [42]. In the context of PLP in particular, high frequency rTMS may indirectly activate inhibitory thalamic projections, thereby modulating ascending nociceptive pathways [43]. Neuropathic pain of diverse aetiologies has been shown to be associated with decreased intracortical inhibition (ICI) and interestingly rTMS therapy has been correlated with increased ICI in tandem with pain relief, particularly in patients with drug-resistant neuropathic pain [44]. Functional magnetic resonance imaging has revealed that rTMS of the motor cortex results in subsequent activity within the ipsilateral thalamus and putamen, structures known to be linked to the sensorimotor cortex, implicated in the centralisation of pain [45].

This review identified five RCTs, highlighting a paucity in the literature of well-designed placebo-controlled trials evaluating rMS for relief of peripheral neuropathic pain. Although the majority of the studies included in this review show that rMS has potential for the treatment of peripheral neuropathic pain, there is a need for further studies in the field. Whilst its efficacy is still debated, rMS has been demonstrated to be a safe and tolerated intervention, with no serious adverse effects noted in the studies included in this review. Furthermore, there is a need to create consensus regarding optimum stimulation protocols and procedures [46]. The use of neuronavigation might increase the precision of stimulation and subsequently its effectiveness; however, this requires further robust assessment as current evidence is lacking. Finally, assessment of brain network function, with techniques such as functional magnetic resonance or appropriate TMS-compatible EEG recordings, with various quantitative EEG metrics, might be the way forward to developing an objective means of studying the effect of rMS on widely distributed brain network constituents involved in the generation and persistence of neuropathic pain.

Limitations

- As in all studies measuring pain with the VAS, a self-reported questionnaire, there is potential for an inherent response bias when reporting the nature and extent of the pain.
- The variations in treatment protocols between studies and the limited number of studies eligible for inclusion make it impossible to use a meta-analytic approach.
- A more comprehensive search using databases other than PubMed alone might have identified a greater number of articles suitable for analysis.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Bioelectromagnetics 32:200–208 (2011)

Pulsed Magnetic Fields Enhance the Rate of Recovery of Damaged Nerve Excitability

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Pulsed magnetic fields (PMFs) have well-known beneficial effects on nerve regeneration. However, little research has examined the nerve conduction characteristics of regenerating peripheral nerves under PMF. The main goal of this study was to examine the conduction characteristics of regenerating peripheral nerves under PMFs. The sucrose-gap recording technique was used to examine the conduction properties of injured sciatic nerves of rats exposed to PMF. Following the injury, peripheral nerves were very sensitive to repetitive stimulation. When the stimulation frequency was increased, the amplitude of the compound action potential (CAP) decreased more at 15 days post-crush injury (dpc) than at 38 dpc. PMF treatment for 38 days after injury caused significant differences in the conduction of CAPs. Moreover, application of PMF ameliorated the abnormal electrophysiological activities of nerves such as hyperpolarizing afterpotentials and delayed depolarizations that were revealed by 4-aminopyridine (4-AP). Consequently, characteristic findings in impulse conduction of recovered nerves under PMF indicate that the observed abnormalities in signaling or aberrant ion channel functions following injury may be restored by PMF application. Bioelectromagnetics 32:200–208, 2011. © 2010 Wiley-Liss, Inc.

Key words: pulsed magnetic field; nerve conduction; action potential; injury; rat sciatic nerve

INTRODUCTION

Application of a magnetic field is one of the most important alternative therapies for clinical conditions. Previous studies using magnetic field applications have reported profound effects of magnetic fields on a large number of biological processes and have suggested that non-invasive magnetic fields can be effective and practical for clinical applications [Shupak, 2003; Markov, 2007a,b].

The response of peripheral nerves to injury has been extensively studied to elucidate the possible mechanisms and evaluate the potential therapeutic interventions in demyelinating problems. Regeneration or functional recovery of peripheral nerves following injury depends on the combined effects of several neuronal and non-neuronal factors [Schafer et al., 2006]. There are a large number of in vitro experimental studies that have suggested that after injury, incomplete functional peripheral nerve regeneration causes several electrophysiological abnormalities [Gordon et al., 1991; Mert et al., 2004; Mert, 2007]. Disturbed axonal excitability results in the inability to maintain conduction of a meaningful impulse train in the damaged nerve bundle [Mert, 2006, 2007]. It is well known that voltage-dependent ion channels are normally responsible for generation and propagation of action potentials along nerve fibers. As a result of injury/damage to myelinated nerve fibers, the distribution of voltage-dependent channels located along the axon is altered and thus the conduction of nerve action potentials is reduced or blocked [Rasband and Trimmer, 2001; Mert et al., 2004].

Animal nerve injury models provide excellent opportunities for introducing and subsequently assessing the effects of pulsed magnetic fields (PMFs) on peripheral nerve regeneration. PMFs have been extensively used in investigations [Shupak, 2003; Markov, 2007a]. A great number of studies have reported that PMFs can stimulate nerve growth, regeneration, and functional recovery of peripheral nerves in both in vitro and in vivo studies [Sisken et al., 1989, 1993; Walker et al., 1994; Macias et al., 2000; Mert et al., 2006]. However, little research has examined the nerve conduction characteristics of regenerating peripheral

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nerves under PMFs. Examination of nerve conduction properties at various discharge frequencies is very important because nerves repetitively discharge in vivo. Even a small amount of damage could limit the nerve discharge frequency. In this study, we therefore aimed to provide electrophysiological evidence of the curative effects of PMF application on the abnormal impulse activities of regenerating peripheral nerves after crush injury.

MATERIALS AND METHODS

Animals

Animals used in this study were adult female Wistar rats (230–250 g) obtained from the Medical Sciences Research Centre of Cukurova University. The rats were maintained in a climate-controlled room under a 12-h light/dark cycle (6:00 am–6:00 pm), and food and water were available ad libitum. This study adhered to the ethical guidelines of the International Association for the Study of Pain, and the experimental protocols were reviewed and approved by the Institutional Animal Care and Use Committee of Cukurova University.

Surgical Procedure

All surgical procedures were performed under deep anesthesia with a premixed solution containing ketamine (80 mg/kg) plus xylazine (2.5 mg/kg). Crush injury was performed as previously described [Mert et al., 2004]. Briefly, the left lateral thigh was shaved and prepped with Betadine solution. The sciatic nerve was identified by dissecting the plane separating at the mid-thigh level between the gluteal musculature. At the ischial tuberosity, the nerve was crushed with fine surgical forceps on the second lock for 30 s. In sham crush surgery, the sciatic nerve of the right hind limb was exposed under the same surgical conditions, but no crush was made. After the wound was closed with 4-0 silk sutures, the animals were allowed to recover for 15–38 days. These time frames were based on our previous studies [Mert et al., 2004, 2006] and were chosen with the expectation that, at these post-surgical delays, possible PMF-induced changes on nerve regeneration could be determined. All surgical procedures were performed by the same researcher and conducted under sterile conditions using protocols approved by the animal care and use committee of our institution.

Pulsed Magnetic Field Treatment

PMF application to rats was performed as previously described [Mert et al., 2006, 2010]. Before the PMF treatment, all rats were acclimated to their environment for 1 week. Habituation to the treatment conditions was accomplished by placing the rats in the restrainer at least three times for 30 min.

PMF application was performed by using Helmholtz coils 60 cm in diameter, placed 30 cm apart (Fig. 1B). When connected to a signal generator (ILFA Electronic, Adana, Turkey), these coils produced a magnetic field peak amplitude of 1.5 mT (1.49–1.51 mT). The peak value of the magnetic field was measured using a gauss meter with a Hall-effect probe (F.W. Bell Model 6010, Sypris, Orlando, FL). The time-varying magnetic field consisted of a quasitriangular waveform, with a rise time of 0.5 ms and a fall time of 9.5 ms (Fig. 1C).

The waveform of the induced electric field was measured using a search coil probe (50 turns of 30 gauge copper wire with an internal diameter of 50 mm) that was placed in the midcenter axis of the Helmholtz coils. Probe leads were connected to an oscilloscope (Hitachi, Tokyo, Japan) and the induced voltage was read directly. The corresponding induced electric field was a unipolar rectangular waveform having peak electric fields of 0.6 V/m (0.59–0.61 V/m) in the restrainer located between the coils (Fig. 1B). The maximum induced electrical field between the coils was calculated using Faraday's law. The current ($I = 5.2$ A) in the circuit was also monitored on an oscilloscope via a resistor (0.1 Ω) connected in series between the output of the power amplifier and coil.

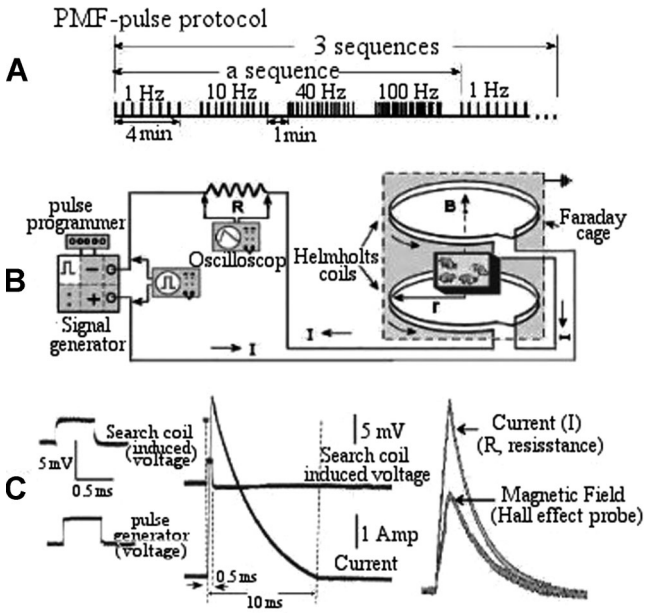

Fig. 1. **A**: Schematized pulsed magnetic field (PMF) application protocol. **B**: Schematic of PMF exposure system. **C**: Description of the waveforms.

PMF application was presented in three sequences. Each sequence included four different consecutive pulse trains (1, 10, 40, and 100 Hz). The duration of each pulse train was 4 min, and the interval between each pulse trains was 1 min (Fig. 1A). A digital timing device controlled the timing. The waveforms of magnetic field were determined using a search coil probe. There were no clear differences in the shape and magnitude of these waveforms. In this PMF administration, both the frequency and sequencing of pulses can be modulated. Therefore, the excitatory/stimulatory actions of PMF treatment can be increased and the probable accommodation of the animals to a single frequency can be prevented.

Animals were placed in an all-plastic restrainer located between the coils. Whole-body exposure to PMF began the first day after crush injury and was applied for 1 h each day. Daily PMF exposure continued for 15 days (PMF-treated 15 days post-crush (dpc)) or 38 days (PMF-treated 38 dpc). The distribution of the magnetic density was measured using a gauss meter. The density was homogeneous within 5% in the exposure area (restrainer: 30 cm long, 20 cm wide, and 15 cm high). It has been previously reported that rats are subject to the circadian cycle [Cain et al., 2004] and that light can be a source of an aversive stimulus [Stern and Laties, 1998]. All PMF treatments were carried out at the same time period each day (9:00 am–10:00 am) and kept throughout the experimental period under the same light conditions in a separate laboratory. The temperature (23–25°C) and humidity (40–60%) were monitored continuously throughout the treatments. Sham exposure to animals was performed under the same environmental conditions, using another apparatus in a Faraday cage outfitted with only the Helmholtz coils.

Electrophysiological Examinations

In preparation for sucrose-gap recordings [Mert et al., 2004, 2006] the animals were killed by cervical dislocation and their sciatic nerves were resected from the posterior thigh, desheathed (removal of circumferential sheath), and placed in oxygenated Krebs solution.

The desheathed sciatic nerves were superfused with an oxygenated Krebs solution to achieve a stable baseline and to record reproducible compound action potentials (CAPs). Following a period of equilibration (30 min), individual nerves (the nerve segment with the crush lesion was positioned in the test pool) were placed in a sucrose-gap apparatus partitioned into pools by a Vaseline–silicon oil mixture and superfused with the appropriate solution at a flow rate of 1–2 ml/min. There were four pools: (a) stimulating pool containing a pair of platinum electrodes and filled with Krebs solution (in mM, 124.0 NaCl, 3.0 KCl, 1.3 NaH_2PO_4, 2.0 $MgCl_2$, 2.0 $CaCl_2$, 26.0 $NaHCO_3$, and 10.0 dextrose); (b) test pool containing Krebs or test solution; (c) iso-sucrose pool containing 320 mM isotonic sucrose; and (d) iso-KCl pool containing an isotonic KCl solution (in mM, 120.0 KCl, 7.0 NaCl, 1.3 NaH_2PO_4, 2.0 $MgCl_2$, 2.0 $CaCl_2$, 26.0 $NaHCO_3$, and 10.0 dextrose). Test solutions were made by adding appropriate concentrations to the Krebs solution, and were bubbled continuously with a 95% O_2 and 5% CO_2 gas mixture during the experiments.

Agar-bridged Ag/AgCl recording electrodes positioned in the test and iso-KCl pool of the apparatus were connected to the inputs of a high impedance amplifier (P-16, Grass Instruments, West Warwick, RI). During recordings, amplification was set to 100–1000 and frequencies filters were set to DC and 40 kHz. The nerve was stimulated with a stimulator (S-48, Grass Instruments) and a stimulus isolation unit (SIU5, Grass Instruments) with short (0.05 ms) depolarizing pulses. To obtain complete stimulation of all fibers, a nerve was stimulated with voltages two times the threshold stimulus required to achieve maximum amplitude of the initial CAP.

The nerves were stimulated with a single stimulus every minute for 30 min at the lowest stimulation rate. To examine the stimulation frequency, we used three consecutive frequencies (10, 40, and 100 Hz). Each frequency train was composed of 20 impulses and the interval between each train was 30 s. Stimulation pulses were delivered through an isolation unit and a digital timing device that controlled the timing of the pulses. The changes in CAP, delayed depolarization (Del-Dep), and hyperpolarizing afterpotential (HAP) were recorded (Fig. 2), and all records were transferred to a computer to be evaluated later. In the experiments, after the initial 30 min equilibration period, all nerves were exposed to 2 mM 4-aminopyridine (4-AP) in Krebs solution. This concentration was also used in our previous studies and was chosen because it permits the evaluation of activities of 4-AP-sensitive K^+ channels located in the internodal segment. Following nerve injury, the incomplete regrowth of the myelin sheath causes an increase in K^+ currents through these channels [Gordon et al., 1991; Rasband et al., 1998; Mert, 2007].

Sucrose-gap recordings were carried out at 23–25 °C. Deionized and bi-distilled water were used for the solutions, and the pH of the solutions was adjusted to 7.4 with NaOH or HCl. All chemicals used in electrophysiological studies were purchased from Sigma (Taufkirchen, Germany).

Experimental groups were determined in accordance with our previous studies [Mert et al., 2004, 2006,

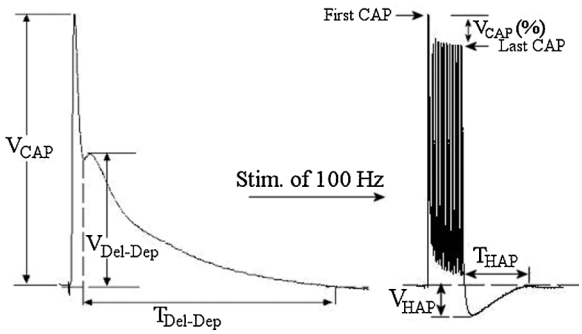

Fig. 2. Analysis of the compound action potential (CAP), delayed depolarization (Del-Dep), and a frequency-dependent stimulation pattern. A series of CAPs recorded from an injured sciatic nerve before and after frequency-dependent stimulation of 100 Hz. The peak to peak amplitude of the CAP is represented by V_{CAP} $V_{Del-Dep}$ reflects the amplitude of Del-Dep. The duration of Del-Dep ($T_{Del-Dep}$) was measured from the end of the CAP to the baseline value. When V_{CAP} was calculated as a percentage, the amplitude of the last CAP was proportional to the amplitude of the first CAP. The amplitude of the hyperpolarizing afterpotential (V_{HAP}) was measured as maximum negative deflection.

2010] and several pilot studies. In this study we used two sham crush surgery groups (sham PMF (SPMF)-treated 15 dpc ($n = 6$) and SPMF-treated 38 dpc ($n = 6$)). The data from the two sham surgery groups and intact animals were pooled together as the SPMF-treated intact groups, since they did not differ statistically. Accordingly, experimental groups were designed as below.

Following the crush injury, animals were divided into two main groups: SPMF and PMF. Each group was separated into two subgroups: SPMF-treated 15 dpc ($n = 8$) and 38 dpc ($n = 8$), and PMF-treated 15 dpc ($n = 8$) and 38 dpc ($n = 8$). In addition, there were two groups of intact (unoperated) rats: SPMF-treated intact (for 15 days ($n = 14$) and 38 days ($n = 14$)) and PMF-treated intact (for 15 days ($n = 8$) and 38 days ($n = 8$)). Furthermore, two crush groups (no PMF/SPMF 15 dpc ($n = 8$) and 38 dpc ($n = 8$)) were used as control.

Statistical Analysis

All the data given here are reported as mean $\pm$ standard error of the mean (SEM). For statistical analyses, all data were evaluated with one-way ANOVA and post hoc Tukey's honestly significant difference test for multiple comparisons, and Mann–Whitney *U*-tests when variables were not normally distributed, using SPSS 11.0 statistical software (SPSS, Chicago, IL). *P* values <0.05 were considered significant.

RESULTS

Effects of PMF on Signals of Regenerating Nerves in the Absence of 4-AP

Before the application of 4-AP, the CAPs (control) that were recorded from 15 dpc, 38 dpc, and intact sciatic nerves in response to a single stimulus exhibited significant differences between their amplitudes or time parameters ($P < 0.05$; Table 1). After nerve crush injury, development of the regeneration was accompanied by an increase in amplitude of the CAPs and a decrease in time to peak of the CAPs. PMF treatment for 15 or 38 days following the crush injury did not cause any differentiation in these parameters of CAPs.

When the nerve stimulation frequency was progressively increased, amplitudes of the CAP decreased more in the 15-dpc group than the 38-dpc and intact groups (Fig. 3A). At the highest stimulation frequency, 100 Hz, the amplitudes were decreased by 18.6 $\pm$ 1.1,

TABLE 1. Effects of Pulsed Magnetic Field Treatment on Compound Action Potentials

	CAP parameters—control		CAP parameters in 4-AP	
Exposure groups	V_{CAP} (mV)	Time to peak (ms)	Amplitude (mV)	Time to peak (ms)
SPMF				
15 dpc	7.8 $\pm$ 0.8$^{\&}$	2.18 $\pm$ 0.04$^{\&}$	14.4 $\pm$ 0.7$^{\#}$	4.12 $\pm$ 0.10$^{\#}$
38 dpc	41.0 $\pm$ 1.7$^{\&}$	0.82 $\pm$ 0.03$^{\&}$	39.8 $\pm$ 1.1	0.86 $\pm$ 0.05
Intact	78.2 $\pm$ 0.9	0.61 $\pm$ 0.01	75.5 $\pm$ 1.2	0.63 $\pm$ 0.01
PMF				
15 dpc	8.5 $\pm$ 0.1$^{\&}$	2.08 $\pm$ 0.07$^{\&}$	15.1 $\pm$ 1.0$^{\#}$	3.99 $\pm$ 0.09$^{\#}$
38 dpc	43.6 $\pm$ 2.1$^{\&}$	0.88 $\pm$ 0.05$^{\&}$	50.8 $\pm$ 1.2*	0.90 $\pm$ 0.07
Intact	74.1 $\pm$ 1.3	0.62 $\pm$ 0.01	73.1 $\pm$ 1.1	0.60 $\pm$ 0.01

V_{CAP}, amplitude of compound action potential (CAP); PMF, pulsed magnetic field treatment; SPMF, Sham PMF treatment; 4-AP, 4-aminopyridine.
$^{\&}P < 0.05$ compared to intact in the SPMF- and PMF-treated groups.
$^{\#}P < 0.05$ compared to CAP controls in the SPMF- and PMF-treated 15-dpc groups.
$^{*}P < 0.05$ compared to the SPMF-treated 38-dpc group.

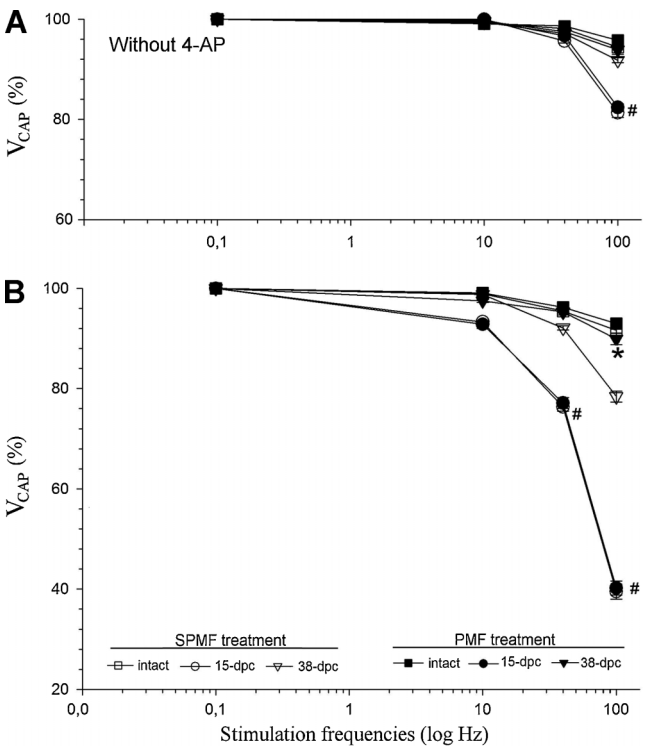

Fig. 3. Effects of pulsed magnetic field (PMF) on the compound action potential (CAP) amplitude (V_{CAP}) of the regenerating and intact nerves stimulated with different frequencies. **A**: In the absence of 4-aminopyridine (4-AP), PMF did not cause any significant change. **B**: In the presence of 4-AP, a decrease in the amplitude by 100 Hz in the 38 days post-crush (38 dpc) group (▽) was significantly different from the PMF-treated 38 dpc (▼) and intact groups (■). Ordinate: When V_{CAP} was calculated as a percentage, the amplitude of the last CAP was proportional to the amplitude of the first CAP. Abscissa: Stimulating frequency (Hz) in log scale. Each point represents the mean value of 8 nerves and the vertical bars indicate the mean ± SEM. $^*P < 0.05$ compared to SPMF-treated 38-dpc group.

9.1 ± 0.8, and 5.2 ± 0.4% in the 15 dpc, 38 dpc, and intact groups, respectively ($P < 0.05$).

Furthermore, when 40 and 100 Hz nerve stimulation were applied, HAPs were observed in all experimental groups. However, HAPs did not occur at the stimulation of 10 Hz. Previous studies have also reported that pronounced HAPs can appear in whole nerve recordings after the nerve crush injury [Poulter et al., 1995; Mcintyre et al., 2002; Mert et al., 2004]. We observed large HAPs following the crush injury (Table 2). Increasing the nerve stimulation frequency enhanced the amplitudes of the HAPs, but not their duration. No statistically significant difference was observed for frequency-dependent effects between the PMF-treated and untreated groups ($P > 0.05$; Table 2).

4-AP-Induced Changes in Signals of Regenerating Nerves Under PMF

After nerve crush injury and damage to the myelin sheath, juxtaparanodal K^+ channels (4-AP-sensitive K^+ channels proteins; Kv1 channels) are reorganized [Rasband et al., 1998; Mert, 2007]. When activated, these channels briefly hyperpolarize the membrane. Inhibition of these channels restores the signaling in damaged axons and provokes reexcitation and repetitive firing [Waxman and Ritchie, 1993; Vabnick et al., 1999; Mert, 2006]. Therefore, determination of the changes in activities of 4-AP-sensitive K^+ channels is important for the evaluation of nerve regeneration processes.

There was an enhanced sensitivity to 4-AP in crushed nerves compared to intact nerves. Following the administration of 4-AP, while both amplitude and time to peak of the CAP was enhanced by about twofold at 15 dpc, these CAP parameters did not significantly change in the 38 dpc and intact groups (Table 1 and Fig. 4). After crush injury, PMF treatment for 15 or 38 days only significantly changed the amplitude of the CAP in the 38 dpc group compared to the SPMF-treated 38-dpc group (Table 1).

After 4-AP application to the nerves, Del-Dep was observed as another waveform following the CAP in the 38 dpc and intact groups (Table 3 and Fig. 4). We noted significant differences in amplitude and duration of Del-Dep between the 38 dpc and PMF-treated 38 dpc groups ($P < 0.05$). Application of PMF for 38 days after injury significantly reduced the amplitude and prolonged the duration of Del-Dep compared to the SPMF-treated 38-dpc group ($P < 0.0$; Table 3). Both the amplitude and duration of the Del-Dep in the PMF-treated group approached that of the intact group (Fig. 5).

In the presence of 4-AP (Fig. 3B), when stimulation frequency was increased, amplitude of the CAPs significantly decreased in all experimental groups compared to the control (in the absence of 4-AP, see Fig. 3A). This influence of stimulation frequency can reflect the use-dependent block of 4-AP on Kv1 channels [Russell et al., 1994]. At the highest stimulation frequency, 100 Hz, the amplitudes were decreased by 60.5 ± 1.4, 22.8 ± 1.1, and 8.4 ± 0.4% in the 15 dpc, 38 dpc, and intact groups, respectively ($P < 0.05$). At the 100 Hz frequency, treatment with PMF for 38 dpc significantly reduced the influence of 4-AP on the CAP amplitude when compared to the SPMF-treated group (10.1 ± 1.1% and 22.8 ± 1.1%, respectively; $P < 0.05$; Fig. 3B).

Application of 4-AP markedly increased the amplitude and duration of the HAPs at both stimulation

TABLE 2. Hyperpolarizing Afterpotentials at 40 and 100 Hz Stimulation Frequencies

	Stimulation of 40 Hz		Stimulation of 100 Hz	
Exposure groups	V_{HAP} (mV)	T_{HAP} (ms)	V_{HAP} (mV)	T_{HAP} (ms)
SPMF				
Control				
15 dpc	0.7 ± 0.03	300.0 ± 3.5	1.2 ± 0.04	290.0 ± 4.6
38 dpc	1.3 ± 0.02	250.0 ± 2.8	2.4 ± 0.06	200.0 ± 3.7
Intact	0.4 ± 0.02	200.0 ± 6.2	0.8 ± 0.02	235.0 ± 8.4
In 4-AP				
15 dpc	1.3 ± 0.05$^{\#}$	356.0 ± 3.5$^{\#}$	1.8 ± 0.05$^{\#}$	357.0 ± 5.3$^{\#}$
38 dpc	2.4 ± 0.20$^{\#}$	335.0 ± 6.2$^{\#}$	3.9 ± 0.10$^{\#}$	345.0 ± 7.1$^{\#}$
Intact	1.3 ± 0.06$^{\#}$	380.0 ± 7.3$^{\#}$	1.7 ± 0.10$^{\#}$	363.0 ± 8.1$^{\#}$
PMF				
Control				
15 dpc	0.7 ± 0.01	265.0 ± 5.5	1.4 ± 0.09	260.0 ± 5.0
38 dpc	1.4 ± 0.06	215.0 ± 4.7	2.6 ± 0.06	188.0 ± 3.7
Intact	0.4 ± 0.02	195.0 ± 6.0	0.7 ± 0.04	240.0 ± 8.1
In 4-AP				
15 dpc	1.2 ± 0.10$^{\#}$	365.0 ± 4.5$^{\#}$	1.6 ± 0.10$^{\#}$	360.0 ± 3.0$^{\#}$
38 dpc	2.1 ± 0.20$^{\#}$	365.0 ± 9.2$^{\#}$	2.5 ± 0.30$^{\#,*}$	355.0 ± 8.1$^{\#}$
Intact	1.3 ± 0.20$^{\#}$	390.0 ± 6.6$^{\#}$	1.9 ± 0.20$^{\#}$	340.0 ± 7.2$^{\#}$

V_{HAP}, amplitude of hyperpolarizing afterpotential (HAP); T_{HAP}, duration of HAP; PMF, pulsed magnetic field treatment; SPMF, Sham PMF treatment; 4-AP, 4-aminopyridine.
$^{\#}P < 0.05$ compared to HAP controls in the SPMF- and PMF-treated groups.
$^{*}P < 0.05$ compared to the SPMF-treated 38-dpc group.

frequencies (Table 2 and Fig. 6). PMF treatment did not significantly change the HAP parameters in the 15 dpc and intact groups. In the 100 Hz condition, the HAP amplitude of the PMF-treated 38-dpc group was significantly decreased relative to the untreated 38-dpc recordings. HAP durations were not altered by PMF treatment (Table 2 and Fig. 6).

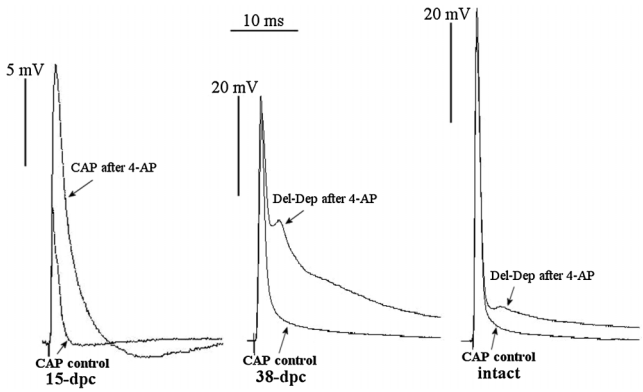

Fig. 4. Effects of 4-aminopyridine (4-AP) on regenerating and intact nerves. At 15 days post-crush (15 dpc), 4-AP enhanced the amplitude and time to peak of the CAP. However, after the 4-AP application, delayed depolarizations (Del-Dep) occurred following the CAP in the 38-dpc and intact groups. The time calibration at the top pertains to all figures.

DISCUSSION

Previous ultrastructural examinations have reported that crush injury results in axon and myelin degradation (at 15 dpc) and moderate to severe myelin sheath degeneration and disruption (at 38 dpc) [Mert et al., 2006]. In addition, it has been suggested that PMF application can accelerate the formation of the myelin sheath [Mert et al., 2006]. Examination of the conduction characteristics of peripheral nerves can provide evidence of the beneficial actions of PMF on peripheral nerve regeneration. PMF has been used as an alternative therapeutic agent [Sisken et al., 1993; Shupak, 2003]. It has been suggested that PMF exposure can enhance nerve regeneration to approximately the same degree as growth factors, hormones and other treatments [Henderson, 1996; Gordon et al., 2003; Markov, 2007a].

A great number of studies have reported the changes in ultrastructure and electrophysiological properties of regenerating peripheral nerves [Gordon et al., 1991; Ide, 1996; Johnson et al., 2005]. Also, electrophysiological characteristics of crushed and intact peripheral nerves after low and high frequency stimulations have been presented in our previous studies [Mert et al., 2004].

In accordance with data reported previously [Mert et al., 2004], the results presented in this study may also

TABLE 3. Effects of Pulsed Magnetic Field on Amplitude and Duration of 4-AP-Induced Delayed Depolarization

	SPMF		PMF	
Exposure groups	$V_{\text{Del-Dep}}$ (mV)	$T_{\text{Del-Dep}}$ (ms)	$V_{\text{Del-Dep}}$ (mV)	$T_{\text{Del-Dep}}$ (ms)
Intact	9.6 ± 0.5	92 ± 5.1	10.8 ± 0.8	100 ± 5.5
38 dpc	22.6 ± 1.2$^{\#}$	58 ± 3.6$^{\#}$	14.4 ± 1.3$^{\#,*}$	88 ± 6.3*

$V_{\text{Del-Dep}}$, amplitude of delayed depolarization (Del-Dep); $T_{\text{Del-Dep}}$, duration of Del-Dep; PMF, pulsed magnetic field treatment; SPMF, Sham PMF treatment; 4-AP, 4-aminopyridine.
$^{\#}P < 0.05$ compared to the intact group.
$^{*}P < 0.05$ compared to the SPMF-treated 38-dpc group.

suggest that injured nerves in the 15-dpc group are more susceptible to high repetitive stimulation than nerves in the 38-dpc group because of the insufficient formation of myelin, or axon–myelin interactions and Na^+ channel-poor membranes [Rasband and Trimmer, 2001]. As myelin formation develops, and the number of Na^+ channels increases at later stages of recovery (38 dpc), the propagating impulse may successfully pass through the damaged segments.

Alterations in ultrastructures following the injury result in abnormal electrophysiological characteristics in nerves due to the reorganization of ion channels at both internodes and nodes [Schafer et al., 2006; Mert, 2007]. Na^+ and K^+ channels provide the generation and propagation of the nerve action potentials [Hille, 1992; Catterall, 2000; Fedida and Hesketh, 2001; Lai and Jan, 2006]. Experiments with blocking drugs and genetic deletion have shown that the Kv1 channels (Kv1.1 and Kv1.2; juxtaparanodal K^+ channels) may serve important functions during remyelination and regeneration stages [Rasband et al., 1998; Vabnick et al., 1999]. Several studies have reported that 4-AP can specifically block these juxtaparanodal Kv channels (4-AP-sensitive K^+ channels) [Waxman and Ritchie, 1993; Rasband et al., 1998; Vabnick et al., 1999]. From a electrophysiological point of view, changes in activities of 4-AP-sensitive K^+ channels have been used as a probe for the evaluation of myelin sheath formation, since K^+ channels sensitive to 4-AP are located in the internodal axon membrane and are masked by the overlying myelin sheath [Gordon et al., 1991; Waxman, 1995; Rasband and Trimmer, 2001; Mert, 2006, 2007]. These channels may serve important functions during remyelination and regeneration.

Application of 4-AP markedly increased the amplitude and time to peak of CAPs in all four of the 15-dpc groups. By 38 dpc, only one of the CAP indices was still significant. These findings also show that activation of 4-AP-sensitive K^+ channels can

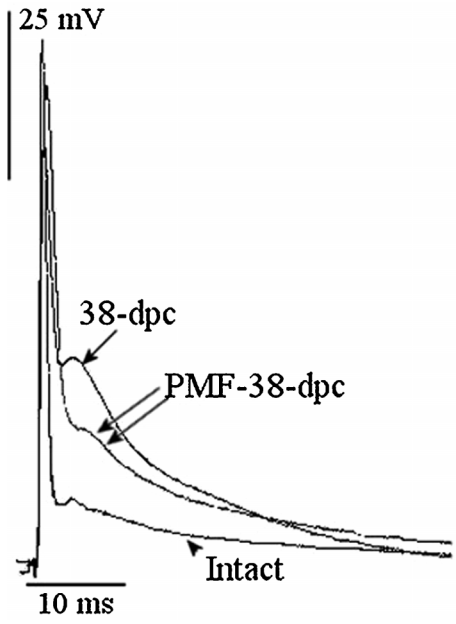

Fig. 5. Effects of pulsed magnetic field (PMF) treatment on compound action potentials (CAPs) with delayed depolarizations (Del-Dep). 4-Aminopyridine (4-AP) application caused Del-Dep in intact nerves (arrowhead) and injured nerves at 38 days post-crush (38 dpc; single arrow). In the PMF-treated 38-dpc group (double arrow), the amplitude of Del-Dep decreased and the value approached that of the intact group.

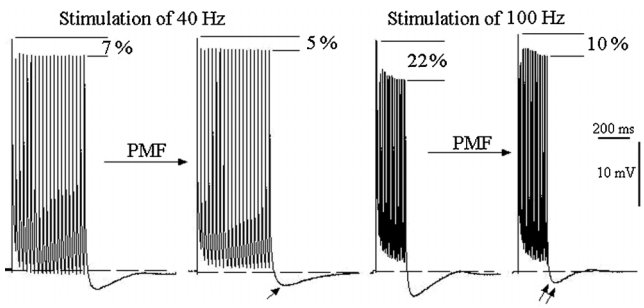

Fig. 6. Hyperpolarizing afterpotentials (HAP) produced by stimulation of 40 and 100 Hz in the presence of 4-aminopyridine (4-AP) at 38 dpc. Pulsed magnetic field (PMF) treatment caused a significant decrease in the amplitude of HAP at the 100 Hz test frequency (double arrow) but not at the 40 Hz test frequency (single arrow). PMF treatment significantly rescued the decrease in the compound action potential (CAP) amplitude observed in the 100 Hz condition.

increase after the myelin sheath damage and can gradually decrease due to myelin sheath regeneration, consistent with other previous papers [Gordon et al., 1991; Rasband and Trimmer, 2001; Mert, 2006]. Furthermore, 4-AP application to the injured nerves in the 38 dpc and intact groups resulted in an occurrence of Del-Deps following the CAP. After nerve crush injury, the amplitude of Del-Dep significantly shifted in the 38-dpc group when compared to the intact group. Del-Dep results from the inhibition of juxtaparanodal K^+ currents by 4-AP [Mert, 2007]. These results may also indirectly support the fact that during the regeneration process, there is a decrease in the pharmacological sensitivity of nerve fibers to 4-AP due to the myelination.

This present paper demonstrated that PMF application for 15 or 38 days to injured animals did not cause any significant changes in the electrophysiological properties of nerves. However, in the presence of 4-AP, significant electrophysiological differences were noted only in PMF-treated 38-dpc group. PMF caused a significant decrease in the frequency-dependent inhibition of the CAP amplitude at only the highest stimulation frequency, 100 Hz, but not at 40 or 10 Hz. It has been previously shown that increasing the repetitive stimulation can enhance Na^+ channel inactivation [Hille, 1992] and application of 4-AP to nerves can increase the number of inactivated Na^+ channels due to Del-Dep and HAP [Mert et al., 2004]. As a result of the decrease in the number of Na^+ channels, the CAP amplitude gets smaller with an increased stimulation frequency. Reducing the activation of 4-AP-sensitive K^+ channels by PMF-induced myelin sheath regeneration may increase the number of resting Na^+ channels. Furthermore, PMF treatment for 38 days after injury also significantly reduced the Del-Dep that appeared after 4-AP application. Taken together, these results suggested that application of PMF for 38 days may provoke the process of myelin compaction, or may decrease the breaks in the myelin sheath and prevent the appearance of abnormal impulse patterns.

Examinations of HAPs are important because of the substantial changes in nerve excitability during regeneration. HAP activities have been discussed in our previous papers [Mert et al., 2004]. Briefly, HAP occurs with increasing K^+ conductance and is generated by an outwardly oriented K^+ current due to the K^+ electrochemical gradient. HAPs elicited by repetitive stimulation is an adaptation of the nerve to high frequency stimulation. Increasing the amplitude of the HAP by 4-AP may be explained by the increase in outward K^+ currents in response to elevated intracellular Na^+ concentration during the high stimulation frequency [Poulter et al., 1995; Mcintyre et al., 2002]. The other distinctive difference due to PMF application on the frequency-dependent activities of injured nerves appeared on the HAP recorded from 38-dpc and PMF-treated 38-dpc nerves in the presence of 4-AP. This can also demonstrate the restorative effects of PMF on damaged myelin sheaths.

Previous investigations performed with PMF applications have demonstrated that PMF can promote peripheral nerve regeneration [Sisken et al., 1989; Kanje et al., 1993; Walker et al., 1994; Shupak, 2003; Markov, 2007a]. Electrophysiological findings presented in this paper can support these studies. A number of studies have shown that PMF influences growth factor activity and levels in injured nerves [Sisken et al., 1993; Longo et al., 1999; Macias et al., 2000]. Growth factor actions may be considered as important effects for both regenerative and corrective mechanisms of PMF on injured peripheral nerves.

Determination of nerve activities at various nerve conduction frequencies is very important because nerves are stimulated by repeated impulses in vivo. High frequency conduction of action potentials depends on excellent myelin integrity over the axon, and thus any damage to the myelin sheath limits the nerve conduction frequency. Characteristic findings in impulse conduction in recovered nerves under PMF treatment indicate that the observed abnormal impulse patterns or aberrant ion channel functions following injury may be partially restored by PMF application. Present findings, taken together with those of previous reports, suggest that PMF treatment may reduce the time required for healing and rehabilitation in peripheral nerve injury.

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Repetitive peripheral magnetic stimulation alleviates tactile extinction

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Despite its frequency in right brain damaged patients crucial mechanisms of tactile extinction are still obscure and treatments are unavailable. Recent PET observations suggest a hypometabolism in the primary and secondary somatosensory cortex of the lesioned hemisphere in patients with tactile extinction. Functional and morphological investigations have shown that the sensorimotor cortex has a remarkable capability of reorganization when the sensory inflow is changed. Repetitive peripheral magnetic stimulation (RPMS) applied in patients suffering from central paresis alleviates sensorimotor as well as cognitive deficits by the induction of proprioceptive inflow, thereby activating plasticity in the CNS. Based on the observation of reduced metabolic activity in patients suffering from tactile extinction we applied RPMS to explore the effects of peripheral sensory stimulation on tactile extinction. Fourteen right-hemisphere lesioned patients with tactile extinction were randomly allocated to an experimental and a control group. The experimental group received one single RPMS treatment of the left forearm as well as a condition of attentional cueing known to improve visual extinction. The control group, with comparable tactile extinction scores, neither received RPMS nor verbal cueing, but was tested twice to evaluate possible learning or test repetition effects. In the experimental group RPMS led to a significant reduction of left-sided extinctions in the recognition of different tactual surfaces, but had no effect on ipsilesional errors. In contrast, attentional cueing had no significant effect on left-sided extinction errors but unexpectedly increased right-hand extinction errors slightly but significantly. The control group showed stable extinction scores of the left- and right-hand stimulus across two measurements, thus ruling out learning or test repetition effects. These results show that sensory inflow is an important modulatory factor in tactile extinction. Furthermore, multiple RPMS may prove a promising way for the rehabilitation of patients with this disorder. *NeuroReport* 11:3193–3198 © 2000 Lippincott Williams & Wilkins.

INTRODUCTION

Extinction of sensory stimuli is defined as the inability to process or attend to the more contralesionally located stimulus when two stimuli are simultaneously presented. By definition the processing of a single stimulus should be only marginally impaired, thereby ruling out gross elementary sensory deficits, i.e. hemianopia or hemianaesthesia. Extinction may occur in the visual [1], auditory [2–4], olfactory [5] or tactile modality [6,7]. The disorder is particularly frequent in right-hemisphere lesioned patients of whom 70% show left-sided tactile extinction [7]. Extinction is often found in patients with parietal or basal ganglia lesions [8], but occurs after frontal [2] and temporal [3] lesions as well. It is probably a rather persistent deficit since it can be found a long time after lesion onset [9].

Two main explanations of extinction have been proposed: sensory [6] and attentional theories [8]. While the prior explain extinction as the result of a weakened sensory integration process [6] the latter hold that elementary sensory abilities may be completely intact, and yet extinction occurs. In favour of the latter account several studies have shown that early sensory or preattentive processes are often reasonably intact in patients with visual extinction. Thus, extinction is reduced when the two stimuli perceptually grouped into a coherent 'Gestalt' [10], show a similar visual orientation in paracentral field areas [11], when both stimuli form one perceptual object [12], or when both stimuli are perceptually very different [13,14]. Obviously, sensory information regarding the extinguished stimulus is covertly processed up to higher cortical integration areas which renders pure sensory explanations of extinction unlikely [15].

Despite the increasing knowledge concerning the mechanisms guiding visual extinction much less is known about the genesis of tactile extinction, and even less how to rehabilitate it. Tactile extinction is usually tested with light touches of the patient's left and right back of the hand [6], or more quantitatively with same or different tactual surfaces delivered to both hands [7]. Here, the patient has to verbally identify both tactile surfaces beyond the mere detection of a touch, thus increasing task difficulty and reducing guessing errors. As in visual extinction, covert

processing of information regarding the extinguished stimulus has been found in tactile extinction [16]. This residual information is significantly modulated by spatial factors, i.e. the position of the hands to each other (crossed or uncrossed, cf. [17]), or their position in the patient's contra- or ipsilesional hemispace [18]. A recent PET study [19] suggests that tactile extinction is associated with a reduced metabolic activity in primary (SI) and secondary somatosensory cortex (SII) during bilateral vibration stimulation of the hands. Consequently, maneuvers suitable to increase neural and/or metabolic activity in cortical somatosensory areas might reduce tactile extinction of the contralateral hand. Similarly, visual stimulation with drifting patterns towards the contralesional hemispace and transcutaneous electroneural stimulation (TENS) of the left body side transiently reduce left-sided tactile extinction [20].

During developments of a stimulation method for the rehabilitation of central paresis of arm and hand it could be shown [21,22] that repetitive magnetic stimulation above the innervation zone of arm and hand muscles could alleviate voluntary motor performances such as precision grip, finger extension and tactile exploration. The concept implies the activation of proprioceptive inflow to the associative areas involved in goal directed movements of forearm and hand in order to activate modulatory effects (plasticity) in the CNS. Repetitive peripheral magnetic stimulation (RPMS) applied to the innervation zone elicits proprioceptive inflow to the CNS adequately via induced muscle contractions as well as directly via stimulation of afferent proprioceptive nerve fibers.

In order to explore further modulatory factors on tactile extinction that might also be suitable for rehabilitation we evaluated in the present study the effectiveness of two experimental manipulations on tactile extinction. First, RPMS of the contralesional hand was studied in seven patients (experimental group), with severe tactile extinction of left-sided stimuli, to increase inflow of afferent somatosensory information to the lesioned right hemisphere. As outlined above, RPMS leads to significant improvements in sensorimotor performances in patients suffering from central paresis [21,22] and activates fronto-parietal systems in the lesioned hemisphere which are involved in control of sensorimotor as well as cognitive–spatial functions. This activation might have a modulating effect on tactile extinction.

As a second manipulation, verbal cueing of the patient's attention towards the contralesional stimulus is known to reduce extinction of left-sided stimuli in the visual domain [9].This maneuver was used as a second manipulation to explore the effect of attentional modulation on tactile extinction. As mentioned in the introduction extinction is viewed as an attentional disorder by some theories [10–12]. According to these accounts the simultaneous processing of two sensory stimuli is limited due to reduced attentional resources and/or inhibition between the two inputs. Consequently, the cueing of attention to the left-sided, probably extinguished stimulus might enhance performance on this side. An interesting by-effect of this manipulation is to look for possible cost effects on the performance of the right, ipsilesional side when attention is cued to the left-side. Since tactile extinction is also influenced by fatigue, repeated testing or learning [3,23] we tested a second comparable group of patients, all with severe left-sided, tactile extinction, and tested them twice in the same extinction test to estimate possible learning or test repetition effects. This control group received neither RPMS nor verbal cueing.

MATERIALS AND METHODS

Patients and normal subjects: Fourteen patients with left-sided, tactile extinction following unilateral, right-hemispheric brain lesions were included in the study (Table 1). Seven were allocated randomly to the experimental group and were selected for RPMS and the verbal cueing experiment while the remaining seven patients served as a patient control group. Seven age-matched normal subjects (four female, three male, aged 22–67 years) served as normal controls in the extinction test. All patients had normal or nearly normal ($>90\%$ correct identifications) of *single* tactile stimulations of the left and right hand using the same tactual surfaces as in the bilateral tests.

Quality extinction test (QET): An assortment of materials differing in tactile qualities, such as silk, sandpaper, foam rubber, jute and fleece, were fixed on wooden boards (15×10 cm). The patient was told that his sensory functions were examined with a tactile test. He/she was blindfolded for the duration of the test and was given all items of the QET sequentially. Subjects were instructed to handle and identify each material with either hand so that they could recognize and name them when tested later in the experiment. Tactile stimulation occurred on the back of each hand because some patients were not able to open their hand completely due to their paresis. First, we investigated each hand alone to find out whether the hand has the sensitivity to identify the different materials. If the patient repeatedly was not able to name a material when it was presented to one single hand (unilateral trials) he was excluded from the study. The patient then was instructed to hold both hands parallel in front of his body on a table. The examiner presented simultaneously one material to each hand by pushing it with a velocity of $\sim$5 cm/s over the back of the hand from distal to proximal. The patient was not told whether the stimulation included identical or different materials applied to the two hands. He was instructed to name the material he recognized on each hand. Each naming response was reinforced by the examiner, but the patient was not informed about his performance. There were 18 trials with the same material on each hand (each material was presented three times simultaneously) and 18 trials with different materials on each hand. Every material was presented with the same frequency to each hand; every combination of materials occurred twice during the test. An extinction response was scored when the subject could identify in a trial with two different materials only one of the materials. The raw score and percentage of left- and right-sided extinctions during bilateral stimulation trials with different materials were computed for every subject.

Repetitive peripheral magnetic stimulation (RPMS): To activate patterns to the CNS similar to the propriceptive inflow of physiological movements, we induced controlled

Table 1. Summary of clinical and demographic data of 14 right-hemisphere lesioned patients with tactile extinction in the experimental (RBD-experimental group) and control group (RBD-control group).

Patient code	Age, sex	Etiology, months since lesion	Lesion side, localization	Hemianopia Field sparing	Motor deficit left arm	Sensory deficit left arm	Left spatial neglect
RBD-experimental group							
1-JD	29, m	ICB, 12	R, T-P	Left, 3°	+	+	+
2-VC	67,m	PCA, 4	R, T-P, Thalamus	Left, 2°	+ +	+ +	+
3-MO	57, f	MCA, 14	R, P	Left, 2°	+ +	+ +	+
4-WI	45, m	MCA, 15	R, P-T-O	Normal	+	+	+
5-TAU	47, f	ICB, 5	R, P	Normal	+ +	(+)	+
6-KAP	49, m	MCA, 4	R, P	Normal	+ +	(+)	+
7-BAL	63, m	MCA, 12	R, T-P	Normal	+ +	+	+
RBD-control group							
1-SCHN	63, m	MCA, 10	R, BG	Normal	+ +	+ +	+
2-VIE	51, f	MCA, 20	R, BG, T	Left, 5°	+ +	+ +	+
3-GRA	69, m	ICB, 13	R, BG	Normal	+ +	+	+
4-KEL	52, m	ICB, 5	R, Thalamus	Normal	Normal	Normal	+
5-IBR	49, f	MCA, 7	R, F-P	Normal	+ +	+	+
6-TAB	47, f	ICB, 5	R, BG	Left, 2°	(+)	+ +	Normal
7-SAC	53, f	ICB, 7	R, BG	Normal	+	+	+

MCA: middle cerebral artery infarction; ICB: intracerebral bleeding. The field sparing in the hemianopic subjects is given for the horizontal meridian lying within the scotoma. L/R: left/right; f/m: female/male; F/T/P/BG: frontal, temporal, parietal, basal ganglia. Motor and sensory functions as well as left-sided visuospatial neglect were rated as marginal (+), slight +, moderate ++ or severe +++, according to the patient's performance in the physical examinations and the results in number cancellation, line bisection and figure copying tasks.

muscle contractions by RPMS [24]. RPMS activates predominantly thick, myelinated nerve fibres lying in well-conducting tissue. Due to this fact pain can not be elicited by this stimulation technique, in contrast to transcutaneous electrical stimulation. RPMS applied to the innervation zone elicits proprioceptive inflow to the CNS adequately via induced muscle contractions as well as directly via stimulation of afferent fibres. We developed a new high power magnetic stimulator, which can be computer-controlled in instantaneous intensity (maximum 1500 J) and rate (maximum $40/s^{-1}$; [25]). By placing the center of a figure-of-eight coil (Fig. 1) over the innervation zone, we can generate movements even of single fingers. In order to generate stimulation patterns similar to physiological patterns, we use a closed-loop control, which generates position-controlled movement of the forearm and fingers. The effects of magnetic stimulation on tactile extinction were evaluated by comparing the prestimulation (first baseline) results with those obtained 30 min after RPMS.

Verbal cueing of attention: Here, the patient was encouraged to report the quality of the contralesional stimulus before that of the ipsilesional stimulus. Subjects were instructed immediately before every bilateral stimulation trial to report first the tactual surface on his/her left dorsal palm, and then the stimulus felt on the right dorsal palm. Due to longer lasting improvements in the extinction tests after RPMS in a pilot study it was necessary to establish a second baseline 2–3 weeks after the RPMS experiment. The effects of attentional cueing on tactile extinction are compared with this second baseline data.

Statistics: Due to the small samples nonparametric tests were used for within-group comparisons (Wilcoxon tests, two-tailed, $\alpha = 0.05$) and between-group comparisons (Mann-Whitney-tests, two-tailed, $\alpha = 0.05$).

RESULTS

Normal subjects: Normal subjects showed a mean of 4.7% (range 0–11%) left-hand errors in the extinction test, and 2.4% (range 0–5.5%) right-hand errors. Although left-hand errors were numerically more frequent, the performance between the left and right hand was not significantly different ($z = -1.134$, n.s.).

Right brain-damaged experimental group: Figure 2 summarizes the results of the experimental group. In the first baseline test all experimental patients showed moderate to severe extinction scores on their left (contralesional) hand (mean 90.4%, range 77–100%, Fig. 2, upper plot). They also showed some errors on their right hand (mean 18.2%, range 0–27%; Fig. 2, lower plot). Following one single session of RPMS the percentage of left-sided extinctions was reduced significantly in the experimental group by 25% (mean extinction ratio 64.2%, range 39–83%), and remained relatively unchanged for the right hand (mean 24.5%, range 16–44%). Non-parametric statistics confirmed that the number of left-sided extinctions was significantly reduced after RPMS ($z = -2.384$, $p < 0.017$), but not the number of right-sided errors ($z = -1.069$, n.s.).

In the condition of left-sided attentional cueing the experimental group showed 77% (range 55–100%) extinc-

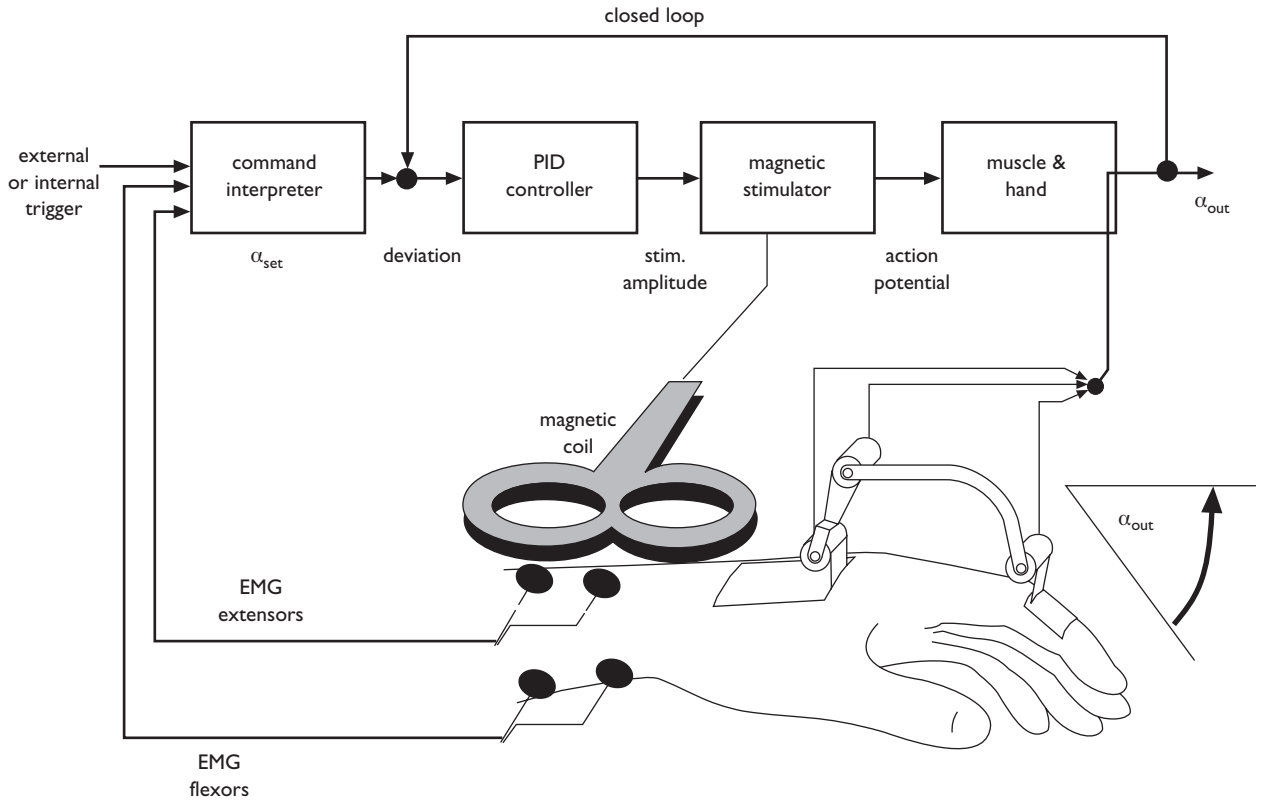

Fig. 1. Schematic layout of the setup for RPMS of the left finger. The stimulation is triggered either by pressing a button with the unaffected hand or by the EMG of the extensors of the affected finger. The closed loop PID controller sets the stimulation intensities in order to induce a smooth movement to the position set by the command interpreter. The position of the affected finger is measured by a light goniometer.

tions on their left hand, and 29.3% (range 16–38%) on their right hand. The result of their left-hand performance was not significantly different from that of the second baseline (mean 81.6%, range 66–100%; $z = -0.962$, n.s.), while the number of right-hand errors was slightly but significantly higher in the attentional cueing condition (see above) than that in the second baseline (mean 16.6%, range 0–22.7%; $z = -2.214$, $p < 0.027$; Fig. 2).

To summarize, RPMS improved selectively the contralesional tactile extinctions in the experimental group without affecting ipsilesional tactile performance significantly. In contrast, left-sided attentional cueing had no effect on contralesional extinctions, but increased the number of ipsilesional errors significantly.

Right brain-damaged control group and normal subjects: The seven right brain-damaged control patients who did not receive RPMS or cueing had comparable extinction scores on bilateral different trials in the first baseline measurement with the QET (mean 87.3% on the left hand, range 55–100%; mean 19.9% on the right hand, range: 0–38.8%; Fig. 3). Mann-Whitney tests did not reveal any significant difference between the two right brain-lesioned groups (experimental *vs* control patient group) regarding age, months since lesion, motor, sensory and neglect status (largest U 24.5, smallest p-value 0.508, n.s.). Furthermore, left-hand errors ($z = 0.0$, n.s.) and right-hand extinction errors ($z = -0.662$, $p > 0.05$) did not differ significantly between the two patient groups in the first baseline test, thus ruling out group differences as a possible explanation for the differential results in the extinction test.

The results of the control patient group in the second baseline test were quite similar to those of the first baseline test (left hand: mean 84.2%, range 55–100%; right hand: mean 24%, range 11.1–38.8%; Fig. 3). Wilcoxon tests did not reveal any significant difference between the first and second baseline in the seven control patients (left hand: $z = -0.272$, $p > 0.05$; right hand: $z = -1.89$, $p > 0.05$). Hence, the right brain damaged control group was comparable to the right brain-lesioned experimental group but showed no learning or test repetition effects in the same extinction test as used in the experimental group.

DISCUSSION

The present study shows clearly that peripheral magnetic stimulation of the contralesional, extinguishing hand reduces tactile extinction significantly in this hand, without any negative cost effect in the ipsilesional hand. Moreover, this effect was found within a time period of some 30 min post-stimulation, thus clearly demonstrating beneficial effects outlasting the stimulation. In contrast the attentional cueing technique used here was ineffective in reducing contralesional extinctions although it led to a small but

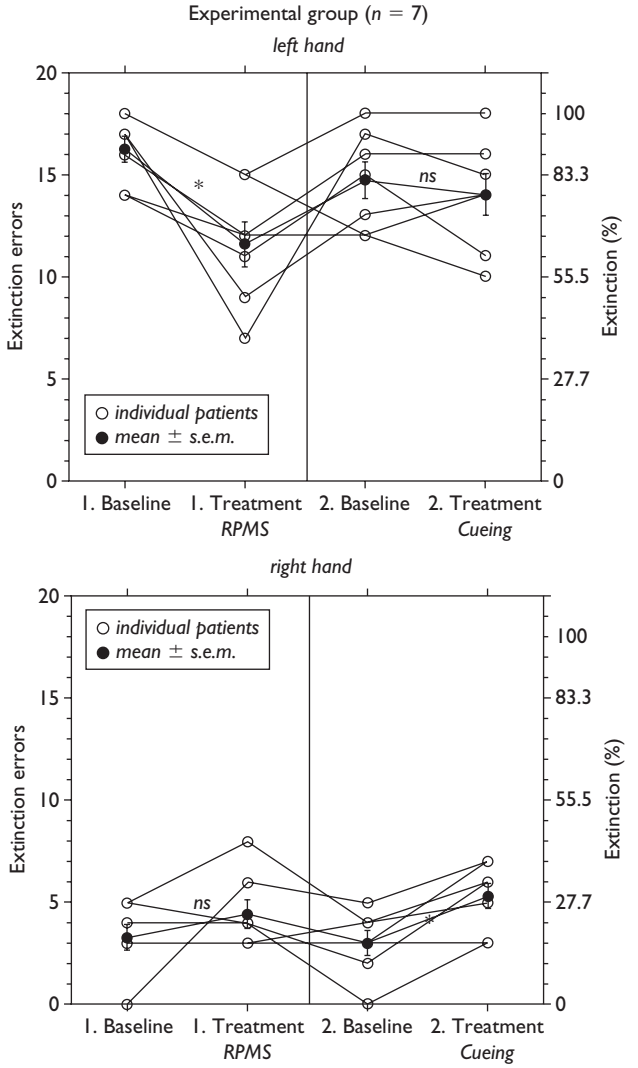

Fig. 2. Tactile extinction errors (%) in the seven patients with right hemisphere lesions (experimental group) 30 min before and 30 min after repetitive peripheral magnetic stimulation of the left dorsal palm (RPMS, 1. treatment). The upper figure shows the performance of the left hand, the lower figure the results of the right hand. Thin lines represent individual data of the seven patients, the bold lines represent the mean ± s.e.m. group data. The second treatment included verbal cueing of attention before each trial to report the left-hand stimulus before the right-hand stimulus (Cueing). Note the significant reduction of left-hand extinction errors after magnetic stimulation, whereas no change is seen for the ipsilesional right hand. In contrast, left-sided verbal cueing had no significant effect on left-sided extinction errors but raised significantly rightsided (ipsilesional) extinction errors. ns: non-significant with $p > 0.05$, two-tailed; *significant with $p < 0.05$.

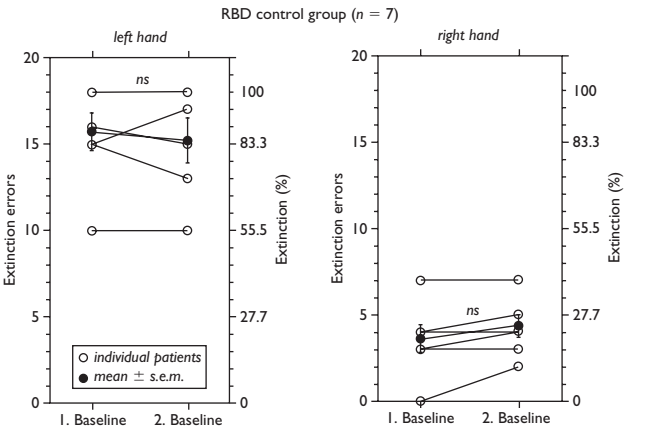

Fig. 3. Performance of the seven right brain-damaged patients (RBD-control group) in the extinction test across two baseline measurements (without RPMS and without attentional cueing), separated by 30 min. The left part of the graphs reflect the contralesional (left hand), the right part the ipsilesional (right hand) extinction errors. No significant change in contra- or ipsilesional tactile performance was seen across the two measurements, thus ruling out learning or test repetition effects in the tactile extinction test. ns: non-significant with $p > 0.05$, two-tailed; *significant with $p < 0.05$.

significant increase in ipsilesional errors. This latter cost effect indicates that the patients somehow tried to employ the cueing technique they had been instructed to use but still were unable to discriminate the left tactual surface during bilateral stimulation. This finding is quite the opposite of what has been found with a similar cueing technique in visual extinction [9] or line bisection judgments (summarized in [16]). Perhaps this cost effect of contralesional cueing on ipsilesional performance results from the relatively demanding tactile extinction test we used (discrimination instead of detection). If this hypothesis is true, positive attentional cueing effects might be obtained with less demanding tactile detection tasks.

Our results obtained with the non-invasive and non-painful peripheral magnetic stimulation technique show that repetitive sensory inflow is an important modulatory factor in tactile extinction that deserves further exploration. Our observations are compatible with the findings of reduced metabolic activity in SI and SII in patients with tactile extinction [19]. Since RPMS activates parieto-frontal circuits [21,22] it is conceivable that this sensory inflow increases neural and metabolic activity in primary and secondary somatosensory cortices, thereby enhancing performance in bilateral tactile discrimination tasks. In contrast to most of the other sensory stimulations or behavioural manipulations evaluated in tactile extinction (summarized in [16]) that produce short-lived effects which disappear immediately after cessation of the modulation [20], RPMS seems to induce longer lasting behavioural and possibly physiological effects. This makes it a promising candidate for the treatment of tactile extinction. Furthermore, other disorders frequently associated with spatial neglect and extinction [16], i.e. the disturbed position sense, impaired pain sensitivity or avoidance of contralateral limb use as well as astereognosis ([19], see [16] for review) might be also modulated by RPMS. Still greater and enduring effects might be reached by combining peripheral magnetic stimulation with a behavioural tactile discrimination training since clinical [24,26] as well as animal studies [27] show a significant potential for perceptual learning in the tactile modality following repetitive training which is based on cortical plasticity and reorganization.

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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Therapeutic effects of peripheral magnetic stimulation on traumatic brachial plexopathy: Clinical and neurophysiological study

Étude clinique et neurophysiologique des effets thérapeutiques de la stimulation magnétique périphérique en cas de plexopathie brachiale traumatique

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KEYWORDS
Therapeutic magnetic stimulation;
Brachial plexopathy;
Pain

Summary
Objective. — To evaluate the therapeutic effects of peripheral repetitive magnetic stimulation (rMS) on recovery of traumatic brachial plexopathy.
Patients and methods. — Thirty-four patients with traumatic brachial plexopathy were studied. Strength of different muscles of upper limbs was evaluated neurologically. Nerve conduction studies (NCS), upper limb F-waves and visual analogue scales (VAS) for shoulder pain were obtained for all patients. These were randomly assigned into two groups with a ratio of 2:1; each patient received conventional physical therapy modalities and active exercises as well as real or sham rMS applied over the superior trapezius muscle of the affected limb daily for 10 sessions. Patients were reassessed with the same parameters after the 5th and the 10th session, and 1 month after rMS treatment.
Results. — No significant between-group differences were recorded at baseline assessment. Significant improvement was observed (time X groups) after real rMS in comparison to the sham group ($P = 0.0001$ for muscle strength and 0.01 for VAS of shoulder pain). These improvements were still present at 1 month after the end of treatment. In accordance with the clinical improvement, a significant improvement was recorded in the neurophysiological parameters in the real vs the sham group.

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Conclusions. — We demonstrate that peripheral rMS for 10 sessions may have positive therapeutic effects on motor recovery and pain relief in patients with traumatic brachial plexopathy. Therefore, it is a useful adjuvant in the therapy of these patients.

MOTS CLÉS
Stimulation magnétique thérapeutique ;
Plexopathie brachiale ;
Douleur

Résumé
But de l'étude. — Évaluer les effets de la stimulation magnétique répétitive (SMR) périphérique sur la récupération d'une plexopathie brachiale traumatique.
Patients et méthodes. — L'étude porte sur 34 patients atteints de plexopathie brachiale traumatique. La force de différents muscles des membres inférieurs a été mesurée cliniquement. Nous avons obtenu, chez tous les patients, une mesure des conductions nerveuses incluant celle des ondes F des membres supérieurs ainsi qu'une échelle visuelle analogique (EVA) des scapulalgies. Les patients ont été aléatoirement distribués en deux groupes selon une proportion 2:1; chaque patient a bénéficié d'une prise en charge physiothérapeutique conventionnelle incluant des exercices de mobilisation active et a suivi dix sessions au cours desquels une SMR réelle ou fantôme était appliquée sur le muscle trapèze du membre atteint. Les mêmes paramètres ont été évalués chez les patients après la cinquième et la dixième session et un mois après la SMR.
Résultats. — La ligne de base ne différait pas entre les deux groupes. Une amélioration significative fut observée après la SMR réelle par comparaison à la SMR fantôme ($p = 0{,}0001$ pour la force musculaire et 0,01 pour l'EVA). Cette amélioration était toujours manifeste un mois après le traitement. Parallèlement à l'amélioration clinique, une amélioration significative des paramètres neurophysiologiques fut observé après SMR réelle par opposition à la SMR fantôme.
Conclusions. — Dix sessions de SMR périphérique peuvent avoir un effet favorable sur la récupération motrice et l'atténuation de la douleur en cas de plexopathie brachiale traumatique. La SMR périphérique peut, dès lors, constituer une thérapie adjuvante utile chez ces patients.

Introduction

Brachial plexopathy is a common complication of traffic accidents. It is characterized by brachial neuralgia and upper limb weakness. One approach to treatment of the peripheral pain consists of repetitive electrical stimulation of peripheral nerve; however, deep structures are difficult to activate due to local discomfort at the site of stimulation. Single and repetitive pulse magnetic coil stimulation (rMS) can activate deeper neural structures without causing irritation and has been successfully applied to reduce musculoskeletal pain for several days [14]. The mechanism of action is unclear, although it may be similar to transcutaneous electrical nerve stimulation (TENS) with actions at both peripheral and/or central levels of the nervous system. For example, it has been proposed that TENS could cause slowing of conduction in both small and large afferent nerve fibers [19,23]. Kaelin-Lang et al. [6] concluded that TENS elicits focal increase of cortico-motorneuronal excitability outlasting the stimulation period and probably occurring at cortical sites.

Struppler et al. [21,22] found that rMS could reduce spasticity and improve perception of joint position in stroke patients. Heldmann et al. [5] found that prolonged peripheral rMS could modulate the response of primary and secondary somatosensory cortices to afferent input. Recent studies on healthy subjects demonstrated that somatosensory input produced by peripheral nerve stimulation or muscle stretch can produce a lasting increase in cortico-motorneuronal excitability of the stimulated body parts [15]. Thus, peripheral mixed nerve stimulation may evoke conjoint activity of somatosensory afferents and intrinsic motor cortical circuits. Such combination seems particularly effective in modulating motor output, as shown by the fact that median nerve stimulation paired with transcranial magnetic stimulation can lead to lasting changes in excitability of motor cortex [20].

The aim of this study was to evaluate the therapeutic effects of peripheral rMS on pain relief and motor recovery as an adjuvant therapy in patients with traumatic brachial plexopathy.

Patients and methods

Neurophysiological measurements

Ulnar and median nerve motor conduction velocities, distal latencies and compound muscle action potentials (CMAP) amplitudes were measured with standard surface stimulating and recording electrodes in both affected and unaffected arms. For the axillary and suprascapular nerves, the technique described by Gassel [4] was used for measuring motor nerve conduction time (latency) to the deltoid and suprascapular muscles, respectively, using a concentric needle as the recording electrode. A concentric needle electrode was placed in the middle of the biceps, deltoid, and supraspinatus muscles.

The brachial plexus was stimulated with bipolar surface electrodes at Erb's point (a few centimeters above the clavicle in the angle between the posterior border of the sternomastoid muscle and the clavicle at the level of the 6th cervical vertebra). Latency values obtained with anodal and cathodal stimulation were averaged to calculate the

final value. The normal limits of motor conduction velocities, distal latencies and conduction times were set at +2 SD from the mean values of the healthy arm of the same group of patients. The CMAP was considered abnormal if the peak-to-peak amplitude was below the lowest value found in the healthy arm.

F-waves from both upper limbs were recorded to median and ulnar nerves supramaximal stimulation at the wrist using surface electrode at thenar and hypothenar eminences, respectively. The ground electrode was placed at the forearm. Twenty trials for each nerve were recorded; the mean F-wave latency was measured. A 1.5-ms F-wave latency difference between both arms was considered abnormal.

Skin temperature was controlled. Recordings were performed with a Nihon Kohden equipment (model 7102), with the following parameters: sweep time 8 ms/D, sensitivity 0.5 mV/D, low frequency 2 Hz, high frequency 10 Hz, stimulation duration 0.1 ms, stimulation frequency 1 Hz.

Magnetic stimulation

Resting motor threshold of the 1st dorsal interosseous muscle (FDI) of the unaffected limb was measured for each patient using a Magstim Super Rapid (Magstim, Whitland, UK) stimulator connected to a 90-mm outer diameter figure-of-eight coil. First, we determined the optimal scalp location by moving the figure-of-eight coil systematically in 1-cm steps in order to determine the scalp position from which transcranial magnetic stimulation (TMS) (constant suprathreshold intensity) evoked motor potentials of maximum peak-to-peak amplitude in the target muscle. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at a 45° angle from the mid-sagittal line. Single-pulse TMS was then delivered to the optimal location, starting at suprathreshold intensity and decreasing in steps of 2% of the stimulator output. Relaxation and EMG signals were monitored for 20 ms prior to stimulation. Resting motor thresholds was defined as the minimum output of the stimulator that induced reliable MEPs (amplitude of 50 μV and 200 μV at rest or during weak voluntary contraction, respectively) in at least five of 10 consecutive trials in the FDI muscle.

Patients

We conducted this study in the Department of Neurology in collaboration with the Department of Rheumatology and Rehabilitation at Assiut University Hospital, Assiut, Egypt. The study included 40 consecutive patients (28 males) with traumatic weakness of one upper limb. These were recruited from the outpatient clinics of Rehabilitation and Orthopedic, during the period from March 2005 to December 2010. The mean age was 37.2 ± 14.1 years (range: 16 to 59 years). All patients had been treated after trauma with conventional physical therapy, muscle strengthening exercises and medications, including anticonvulsants, narcotic or non-narcotic analgesics, without any satisfactory pain control or improvement in muscle strength for at least one and half month. Exclusion criteria were: patients with open injury, fractures, dislocation, head trauma, tendon tears of shoulder joint, severe limb paralysis and wasting of the muscles, in which no evoked potential could be recorded. Four cases were excluded due to the presence of associated tendon tear and fracture in the shoulder (Fig. 1; flow chart). Out of the remaining 36 patients, 20 presented with right and 16 with left brachial plexopathies. Traffic accident (16 patients) was the most common cause followed by lifting heavy objects on the shoulder (10 patients), direct trauma, object striking shoulder or falling from a height (six patients), and postoperative arm traction during general anesthesia (four patients). Mean illness duration was 7.8 ± 2.1 weeks (range: 6 to 12 weeks). This study was approved by the local ethical committee of Assiut University Hospital. Written informed consent was obtained from all of the subjects.

The strength of different upper limb muscles was neurologically assessed in each patient using the Medical Research Council Scale [12] and each patient was asked to score shoulder pain using a visual analogue scale (VAS) [13].

The patients were randomly classified into one of the two groups with a 2:1 ratio, using closed envelopes. The first group (24 patients) received both physical therapy (electrical stimulation, ultrasound, heat therapy and therapeutic as well as active exercises) and real rMS. Physical therapy aimed at alleviating pain, maintaining range of motion (ROM), and optimizing motor-function recovery at the time of muscle reinervation. Therapeutic exercises gradually progressed from passive to active ROM, as tolerated. The second group (12 patients) received the same physical therapy with sham rMS.

Two types of real rMS were used. The first one (''7 Trains'') was designed to relieve shoulder pain: stimulation at motor threshold, 15 Hz, 10 seconds per train with an 20-second inter-train interval for a total of 1050 pulses. The second one (''50 Trains'') was designed to increase strength: stimulation at 70% of the motor output, sufficient to give rise to arm contraction, 3 Hz, 10 seconds per train with a 30-second inter-train interval, for a total of 1500 pulses. A 10-minute rest period was observed between both types of stimulation. Both were daily applied over the superior trapezius muscle (10 sessions, five sessions/week). The same parameters were used for sham rMS and real rMS but the coil was elevated away from the trapezius muscle (not touching the patient). The magnetic stimulator (Magstim model 200; Magstim, Whitland, UK) was connected to a 70-mm outer diameter figure-of-eight coil, which resulted in a maximal output of 2.2 Tesla. Two patients in the real group were lost to follow-up, so that 34 patients completed the study (Fig. 1).

Patients were evaluated before rMS, after the 5th session and the 10th session, and at 1 month, using VAS for assessment of shoulder pain and rating scale for strength of power. Neurophysiological assessment was performed both before and after the series of sessions. Patients were not aware of the type of stimulation. The investigator who was responsible for clinical and neurophysiological follow-up was blind to the type of treatment. However, the investigator who assessed muscle strength was aware of the type of stimulation.

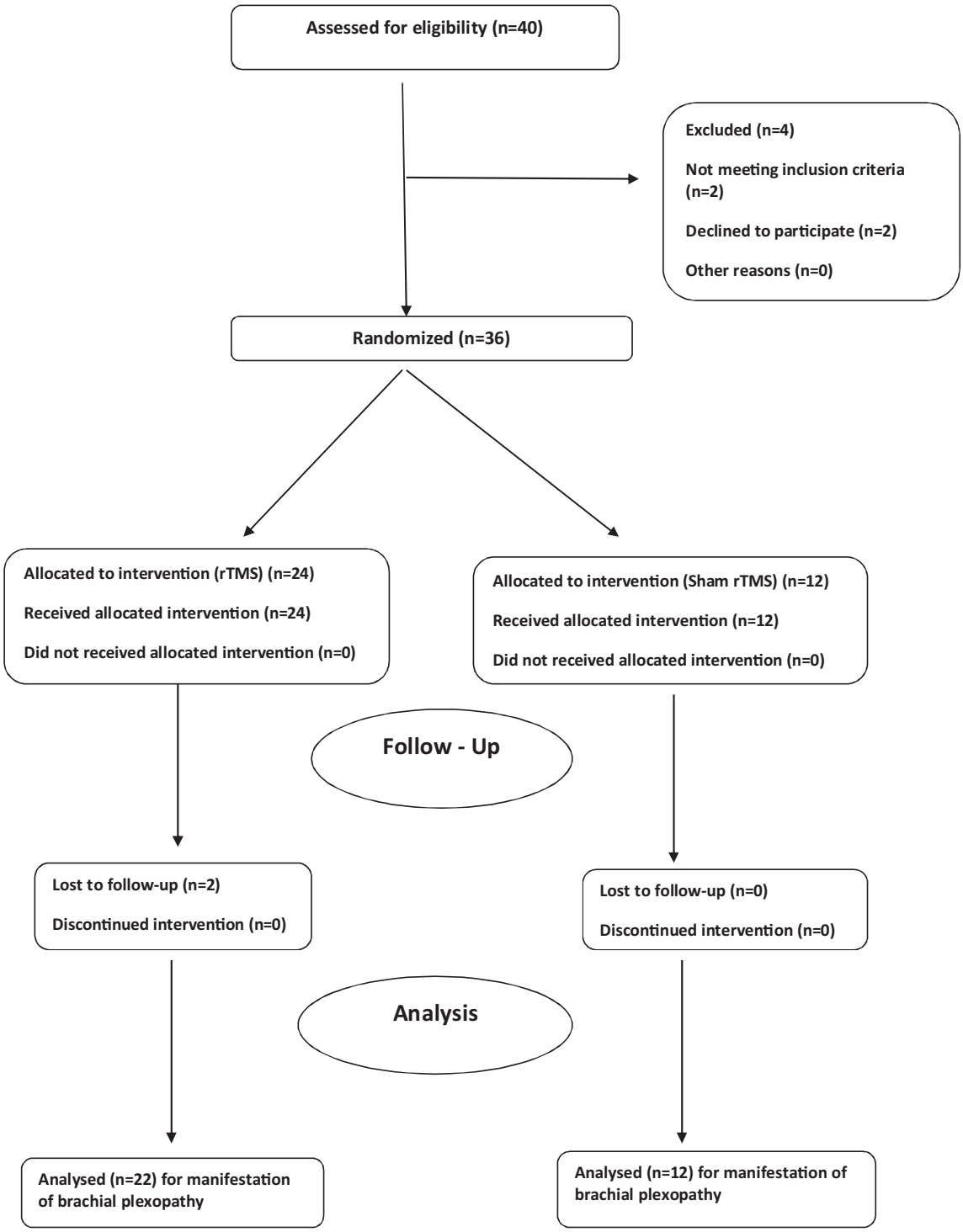

Figure 1 Study flow chart. Two patients in the real group were lost to follow-up, so that 34 patients completed the study.

Data analysis

Pain level and muscle strength at baseline, 5th, 10th and after 1 month were evaluated using a 2-factor analysis of variance (Anova) (''time factor'' as the main factor pre, 5th, 10th, 1 month) and ''session type'' (real vs sham), for both rating scores (muscle strength and VAS). Paired *t* test was used to evaluate the pre- vs post-changes in neurophysiological parameters. The Greenhouse—Geisser correction of degrees of freedom was used whenever necessary to correct non-sphericity. Spearman's correlation between the degree of improvement in muscle strength and VAS (pre-rMS—1 month after) were calculated for the different muscles.

Results

Table 1 shows the demographic and clinical data of the patients at admission. Weakness was more pronounced in

Table 1 Demographic and clinical data of the studied patients (that complete the follow-up) at baseline assessment.

Variable	Real group $n=22$	Sham group $n=12$	*P* value
Age mean (SD) (years)	33.9 (11.1)	30.9 (11.70)	0.197
Sex (Male/Female)	18/4	10/2	NS
Duration of illness (weeks) mean (SD)	7.8 (2.2)	8.4 (2.5)	0.611
Affected arm (Right/Left)	12/10	6/6	NS
Causes			
Motor car accident	10	6	
Lifting heavy objects	5	3	NS
Postoperative traction to the limb	3	1	
Direct trauma	4	2	
Strength of the muscles mean (SD)			
Hand grip strength	3.9 (0.9)	3.6 (1.2)	NS
Elbow flexor (biceps muscle)	3.6 (0.9)	3.9 (0.9)	NS
Elbow extensor (triceps muscle)	3.9 (0.9)	3.8 (1.0)	NS
Deltoid muscle	2.5 (1.4)	2.3 (1.1)	NS
Supraspinatus muscle	2.6 (1.3)	2.3 (1.1)	NS

NS: non-significant.

Table 2 Neurophysiological data of the studied patients (34 patients) at base line assessment.

	Normal arm (34 arms)	Affected arm	Affected arm	*P* value
		Real group (22 arms)	Sham group (12 arms)	Between both groups
Median nerve (mean ± SD)				
Distal latency (ms)	3.7 ± 0.5	3.7 ± 0.6	3.6 ± 0.5	0.93
NCV (m/s)	56.5 ± 6.8	53.1 ± 6.2	56.4 ± 5.8	0.95
CMAP amplitude (μV)	10.1 ± 4.3	6.8 ± 4.6	6.1 ± 3.1	0.23
F-wave latency (ms)	27.5 ± 2.9	29.6 ± 3.7	28.7 ± 2.6	0.36
Ulnar nerve (mean ± SD)				
Distal latency (ms)	2.6 ± 0.6	2.9 ± 0.6	2.5 ± 0.4	0.2
NCV (m/s)	56 ± 6.6	54.8 ± 9.3	54.8 ± 13.5	0.27
CMAP amplitude (μV)	8.9 ± 3.7	6.8 ± 3.7	8.7 ± 8.2	0.09
F-wave latency (ms)	28.8 ± 2.7	29.8 ± 3.0	34.5 ± 12.8	0.53
Axillary nerve (mean ± SD)				
Conduction time (ms)	3.5 ± 0.7	5.5 ± 2.9	5.9 ± 3.4	0.3
CMAP amplitude (μV)	8.3 ± 6.1	2.5 ± 3.6	2.4 ± 4.4	0.4
Musculocutaneous nerve (mean ± SD)				
Conduction time (ms)	4.1 ± 0.8	6.1 ± 2.8	5.1 ± 1.8	0.4
CMAP amplitude (μV)	8.2 ± 5.3	3.9 ± 5.1	3.3 ± 3.2	0.1
Suprascapular nerve (mean ± SD)				
Conduction time (ms)	2.7 ± 0.5	4.7 ± 0.8	4.7 ± 1.5	0.74
CMAP amplitude (μV)	6.9 ± 4.9	2.1 ± 4.6	2.9 ± 1.9	0.1

muscles supplied by the upper trunk of the brachial plexus (deltoid, supraspinatus and biceps muscles) followed by triceps and hand grip muscles. Table 2 confirms that the neurophysiological abnormalities were more severe in axillary, suprascapular and musculocutaneous nerves (upper trunk of brachial plexus) followed by median nerve and the ulnar nerve as the least affected one.

Peripheral rMS was well-tolerated by all patients, without any adverse effects.

Effect of treatments on muscle strength

The mean rating score of muscle strength increased over the four times of assessment in the real rMS group, for all

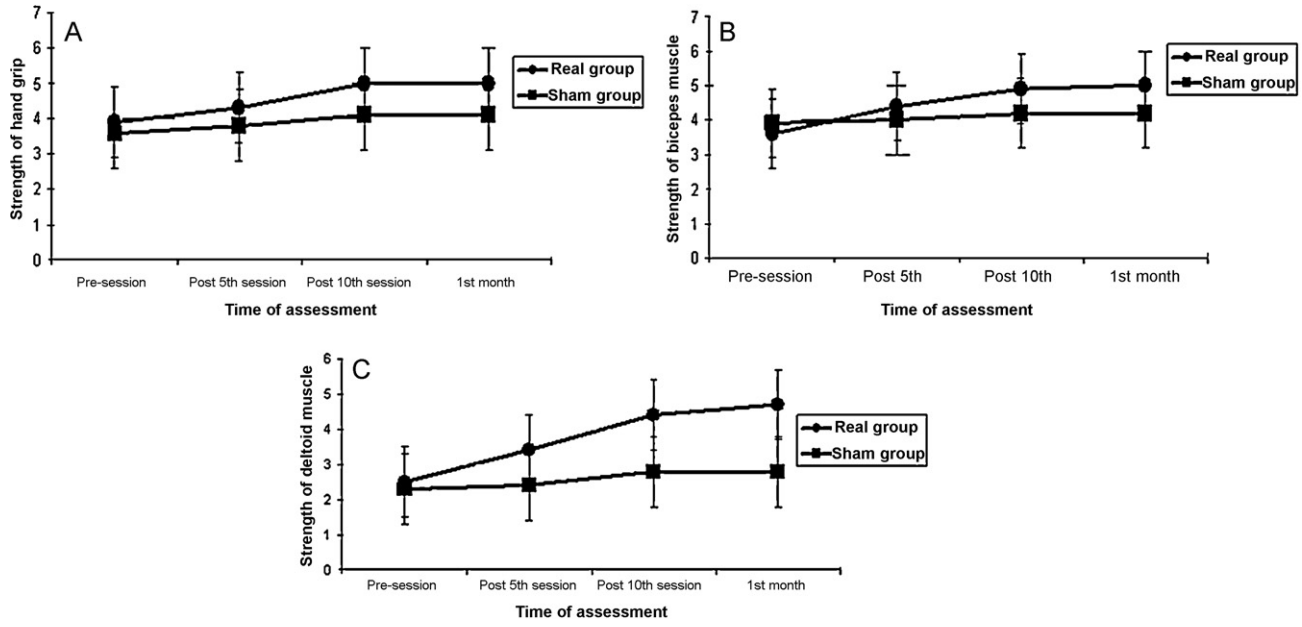

Figure 2 Changes in mean power rating scores of hand grip (A), elbow flexion (B), and deltoid (C) at the four assessment points (pre, 5th, 10th, 1 month). The first assessment was performed immediately prior to a 10-session repetitive magnetic stimulation (rMS) treatment, the 2nd and 3rd assessments immediately after the 5th and 10th sessions of transcranial magnetic stimulation of the brain (rTMS), respectively, and the last assessment one month after the end of sessions. There were no significant between-group differences in muscle strength at baseline assessment, while a significant improvement was observed over the course of the real repetitive magnetic stimulation (rMS) treatment as compared to the sham group ($P = 0.03$, for hand grip, and 0.0001, for elbow flexor and deltoid muscles).

Table 3 Neurophysiological parameters (pre- and post-sessions) of nine cases of real and six cases of sham groups.

	Real group (nine cases)			Sham group (six cases)		
	Pre-sessions	Post-sessions	*P* value	Pre-sessions	Post-sessions	Paired *t* test
Median nerve (mean ± SD)						
Distal latency (ms)	3.5 ± 0.33	2.85 ± 0.01	0.002	3.6 ± 0.5	3.65 ± 0.01	0.85
NCV (m/s)	59.5 ± 5.5	57.3 ± 2.8	0.13	53.8 ± 4.9	54.3 ± 3.3	0.83
CMAP amplitude (μV)	7.2 ± 3.0	14.5 ± 2.5	0.04	6.6 ± 3.7	6.56 ± 3.3	0.92
F-wave latency (ms)	27.3 ± 0.8	25.4 ± 1.6	0.006	29.7 ± 0.8	29.0 ± 2.1	0.21
Ulnar nerve (mean ± SD)						
Distal latency (ms)	2.6 ± 0.34	2.2 ± 1.8	0.08	2.5 ± 0.5	2.5 ± 1.8	0.63
NCV (m/s)	56.9 ± 9.4	58.2 ± 9.3	0.109	56.9 ± 9.4	58.2 ± 9.3	0.08
CMAP amplitude (μV)	13.4 ± 8.6	15.5 ± 8.9	0.123	5.3 ± 2.6	5.2 ± 2.7	0.64
F-wave latency	29.4 ± 4.2	26.2 ± 2.8	0.58	30.7 ± 3.6	29.9 ± 3.2	0.03
Axillary nerve (mean ± SD)						
Conduction time (ms)	7.98 ± 4.1	4.1 ± 0.78	0.028	6.1 ± 3.8	6.3 ± 4.5	0.51
CMAP amplitude (μV)	0.48 ± 0.11	1.6 ± 0.88	0.009	0.5 ± 0.12	1.1 ± 0.85	0.06
Musculocutaneous nerve (mean ± SD)						
Conduction time (ms)	5.2 ± 1.6	3.8 ± 0.4	0.04	5.6 ± 1.6	5.4 ± 1.6	0.29
CMAP amplitude (μV)	4.08 ± 3.5	4.9 ± 0.95	0.16	4.08 ± 3.5	4.9 ± 0.95	0.88

CMAP: compound muscle action potentials; NCV: nerve conduction velocity.

muscles. This was evident for the deltoid: $P < 0.0001$, F = 91, df = 1.6 (33), supraspinatus, $P < 0.0001$, F = 102, df = 2.1 (44), elbow flexors $P < 0.0001$, F = 45, df = 1.5 (31), elbow extensors $P < 0.0001$, F = 39, df = 1.3 (27.7), and hand grip muscles $P < 0.0001$, F = 44.1, df = 1.3 (27.6). In the sham group, there was a significant improvement in hand grip only, while the other muscles showed a non-significant improvement: $P < 0.01$, F = 5.8, df = 1.5 (18) for hand grip, $P = 0.10$, 0.51, 0.06 and 0.6 for elbow flexor, extensor, deltoid, and supraspinatus muscles respectively. Fig. 2A, B and C

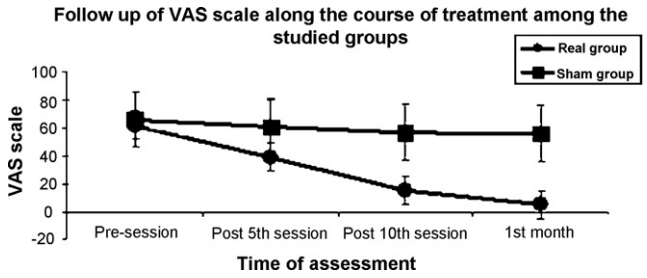

Figure 3 Changes in mean pain rating scores (Visual Analogue Scale [VAS]) over the course of the treatment. The Visual Analogue Scale improvement is significantly more marked in the real vs sham repetitive magnetic stimulation (rMS) group ($P = 0.0001$).

illustrate changes in the mean scores of hand grip, elbow flexion, and deltoid muscles at each assessment time (pre, 5th, 10th, 1 month).

Improvements were statistically significant at the second and third assessment points (pre vs 5th and 5th vs 10th) $P = 0.001$, and 0.0001 respectively for all muscles except the elbow extensor ($P = 0.15$ 5th vs 10th). At 1 month, the improvements were stationary with no significant changes (10th vs 1 month) in any muscle except the deltoid muscle ($P = 0.04$).

Effect of treatment on neurophysiological parameters

Nine cases in the real group and six cases in the sham group were neurophysiologically re-evaluated after the last session. Paired *t* test showed that the mean value of the neurophysiological parameters in each nerve was significantly improved after real rMS especially for the axillary, median and musclucutaneous nerves. No similar changes were recorded in the sham group except for a small improvement in ulnar nerve parameters. Details are provided in Table 3.

Pain assessment

A significant improvement in VAS was noticed during the course of treatment: $P < 0.0001$, $F = 27$ and $df = 1$ (21) for both the real and the sham group: $P < 0.01$, $F = 6.1$ and $df = 1.6$ (24). However, a two-way Anova time X groups showed that the improvement was significantly greater in the real group in comparison to the sham group: $P < 0.0001$, $F = 25.9$ and $df = 2.1$ (66). This improvement also persisted until 1 month (Fig. 3). There was a significant correlation between the degree of improvement in muscle strength and VAS (pre-rMS—1 month after) ($P = 0.001$ for all muscles) in the real group.

Discussion

This preliminary study demonstrates that 2 weeks of real rMS combined with conventional physical therapy can improve pain and muscle strength in cases of brachial plexopathy. Noteworthy, these changes started during the peripheral rMS therapy and improvement continued during the following month. Pain improvement paralleled the progressive increase in muscle strength.

The advantage of rMS over conventional therapeutic electrical stimulation lies in its ability to stimulate deep structures without the local discomfort that is produced by high intensities of electric stimulation [1]. That is to say that brachial plexus activation was readily obtained in all patients.

The mechanisms of the response to rMS are still uncertain, and, objective effects could occur at both spinal and supraspinal levels. There could be a direct effect on pain, with a secondary increase in muscle strength as patients start to increase their use of the affected limb. Conversely, there could be a direct effect on strength with a secondary effect on pain. Finally, there could even be a direct effect of rMS on both pain and strength.

Muscle strength

In this study, we applied a mixture of sub-motor threshold stimulation, in order to activate only sensory afferents, together with supra-motor threshold stimulation, in order to evoke clear muscle contraction through stimulation of the efferent nerve. As noted by Struppler et al. [21], the latter will activate sensory afferent fibers by direct depolarization as well as indirectly via the muscular contractions evoked by stimulation of efferent motor fibers. This will produce a large input to the CNS and a strong sensation of contraction and movement. Pain could be influenced by activation of large diameter afferent fibers that may excite inhibitory neurons in the spinal dorsal horn and suppress the neurons in laminae I, II, and V, which ordinarily fire in response to noxious stimuli [8]. They also may activate supraspinal inhibitory systems acting on nociceptive spinal neurons [18].

Several factors could explain the improvement in muscle strength. However, it is important to note that even though rMS induces muscle contraction, it is unlikely that the increase in muscle strength observed was due to a direct effect on the muscle. Indeed, a direct effect would take several weeks to occur, whereas the increase in strength was evident after the first 5 days of stimulation. Therefore, it is likely to be due to increased volitional drive to the remaining peripheral connections. Reduced pain could be one factor that would increase volitional output. In addition, Ridding et al. [15] noted that prolonged peripheral input can increase corticospinal excitability, which would also tend to increase voluntary strength. Both hypotheses are consistent with a PET study of stroke patients by Spiegel et al. [18] who found that rMS of the upper extremity increased activation of fronto-parietal circuits.

Another possibility is that magnetic stimulation of the nerve trunk of the brachial plexus increases the number of the endoneurial vessels, thereby improving the ischemic state of damaged nerve and promoting axonal regeneration. Such effects might contribute to the gradual increases in strength that are observed after cessation of treatment. This is in keeping with the significant improvement in neurophysiological parameters that was recorded in this study. An additional mechanism might be that rMS enhances the effect of physiotherapy at some central site.

Pain

Although several previous studies underlined the usefulness of transcranial magnetic stimulation of the brain (rTMS) to treat pain syndromes [2,3,7,9—11], only a few studies dealt with the effects of peripheral magnetic stimulation. In keeping with the studies of Smania et al. [16,17] on myofascial pain syndromes and Pujol et al. [14] on musculoskeletal pain, our study indicates that rMS might be an effective tool to reduce peripheral pain.

Despite some of its limitations (small sample size, short follow-up, incomplete blinding), this preliminary study should encourage further research aimed at establishing the clinical usefulness of this new procedure in the treatment of brachial plexopathies.

Conclusion and recommendations

Even if the mechanisms of improvement need further investigations, peripheral rMS for 10 sessions might enhance motor recovery and pain relief in patients with traumatic brachial plexopathy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgement

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ORIGINAL RESEARCH

Difference in Pain and Discomfort of Comparable Wrist Movements Induced by Magnetic or Electrical Stimulation for Peripheral Nerves in the Dorsal Forearm

This article was published in the following Dove Press journal:
Medical Devices: Evidence and Research

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Purpose: Both repetitive peripheral magnetic stimulation (rPMS) and transcutaneous electrical current stimulation (TES) could elicit the limb movements; it is still unclear how subjective sensation is changed according to the amount of limb movements. We investigated the pain and discomfort induced by newly developed rPMS and TES of peripheral nerves in the dorsal forearm.

Methods: The subjects were 12 healthy adults. The stimulus site was the right dorsal forearm; thus, when stimulated, wrist dorsiflexion was induced. The rPMS was delivered by the new stimulator, Pathleader at 10 stimulus intensity levels, and TES intensity was in 1-mA increments. The duration of each stimulation was 2 s. The analysis parameters were subjective pain and discomfort, measured by a numerical rating scale. The rating scale at corresponding levels of integrated range of movement (iROM) induced by rPMS or TES was compared. The subjective values were analyzed by two-way repeated measures ANOVA with the stimulus conditions (rPMS, TES) and the seven levels of iROM (20–140 °s).

Results: In the rPMS experiments, stimuli were administered to all subjects at all stimulus intensities. In the TES experiments, none of the subjects dropped out between 1 and 16 mA, but there were dropouts at each of the intensities as follows: 1 subject at 17 mA, 20 mA, 22 mA, 23 mA, 27 mA, 29 mA and 2 subjects at 21 mA, 24 mA, 26 mA. The main effects of the stimulus conditions and iROM were significant for pain and discomfort. Post hoc analysis demonstrated that pain and discomfort in rPMS were significantly lower compared to TES when the iROM was above 60 °s and 80 °s, respectively.

Conclusion: New rPMS stimulator, Pathleader, caused less pain and discomfort than TES, but this was only evident when comparatively large joint movements occurred.

Keywords: peripheral magnetic stimulation, peripheral electrical stimulation, pain, discomfort, integrated range of wrist movement

Introduction

Transcutaneous electrical current stimulation (TES) of peripheral nerves is widely used in rehabilitation medicine. Its objective is to restore motor function in patients with central nervous system diseases or orthopedic disorders.[1–4] When TES is used to restore finger motor function in stroke patients, it is usually administered on the dorsal side of the forearm. This is because wrist and finger extension movements are often more difficult to reacquire compared to flexion movements after a stroke.

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However, a problem with TES is that a strong stimulus is required to induce joint movement by contracting the paralyzed muscles, thus making it a painful process.[5]

Repetitive peripheral magnetic stimulation (rPMS) is a non-invasive, nearly painless, clinically promising method of bringing about neural modifications.[6–10] The difference between the amount of pain caused by rPMS and that caused by TES can be explained by understanding that the Aδ and C nociceptive fibers that run through the superficial layers have fine axons with higher excitation thresholds. In contrast, α motor neuron axons run at a deeper level, are thicker, and have a low excitation threshold.[11,12] To excite deeply located α motor neuron axons with TES requires a strong electric current that is more likely to excite superficial nociceptive neurons and result in pain. In rPMS, motor axons are stimulated by pulsed currents that cancel out the magnetic field by repeatedly passing a transient electric current through a stimulus coil. Because the magnetic flux density is not affected by skin resistance, the induced current is able to stimulate motor axons in the deep tissues. These neurons have low excitation thresholds and do not excite nociceptive neurons in the superficial layer and therefore it is less painful.

Although previous literature reported that rPMS produced less pain compared to TES, quantitative studies that compared pain induced by magnetic versus electric stimulation are limited.[6,8–10,13–15] Han et al reported that when rPMS or TES was administered to the anterior surface of the distal thigh, rPMS was significantly less painful than TES at the same amount of knee extension torque.[10] Ito et al compared hip flexion torque when rPMS and TES were administered to the anterior surface of the hip. The stimulation intensities were adjusted to the maximal tolerance of each participant. They found that hip flexion torque was significantly greater for rPMS than for TES.[9] Thus, rPMS produced less pain at a given level of stimulus-induced muscle contraction and a greater joint torque at the intensity of maximum tolerance.

No study has compared pain between magnetic and electrical stimuli over a wide range of stimulation intensities except Szecsi's study. This study demonstrated the relationship between knee extension torque and pain when applying magnetic and electrical stimulation over the quadriceps muscle in subjects with paresis and preserved sensation. Szecsi et al established that pain reached maximum tolerance earlier for electrical stimulation than for magnetic stimulation using a saddle-shaped coil with increasing torque. Stimulus intensities were increased from zero to the maximum tolerable level.[15]

Pain induced by magnetic stimulation can be affected by the coil shape and the stimulation site. Mori et al developed a compact U-shaped coil for contracting suprahyoid muscles in order to reduce stimulation of the inferior alveolar nerve, which can be excited using the usual round coil.[16] Kagaya et al revealed this U-shaped coil could induce hyoid bone movement with minimal pain. It is essential to examine the pain-stimulus intensity relationship for both individual target body sites and the type of device used when applying rPMS.[17] The purpose of the present study was to investigate the relationship between rPMS-induced movement and pain when stimulating the dorsal forearm using a newly developed magnetic stimulator and a conventional electrical stimulator. In addition, we evaluated discomfort as secondary outcome. Our working hypothesis was that magnetic stimulation might excite motor axons with low excitation thresholds in the deep tissue while generating only limited excitation of nociceptive neurons in the superficial layers. Thus, rPMS should result in less pain and discomfort than TES for the same amount of induced movement.

Materials and Methods

Subjects

The subjects were 12 healthy adults with no neurological abnormalities of the arms. The group was comprised of 7 men and 5 women with a mean age of 23.0 ± 5.0 years (all data are presented as means ± standard deviations). All subjects were right-handed according to the Edinburgh inventory of handedness[18] (mean score 92.86 ± 10.57).

Measurement Procedures

Stimulus Devices

Two types of stimulus devices were used. Magnetic stimuli were administered using a peripheral magnetic stimulator (Pathleader, IFG, Sendai, Japan). The main unit measures 340 mm wide × 265 mm deep × 175 mm high, it weighs approximately 15 kg, and the coil weighs 1.5 kg. The coil is a circular coil with a magnetic core and the outer-diameter is 70 mm. This is different from the one used in previous studies (diameter 160 mm, round coil in Han's study;[10] outer diameter 130 mm, annular round coil in Szecsi's study;[15] diameter 200 mm, round coil in Matsumoto's study[19]). The stimulus intensity (with maximum stimulus intensity defined as 100%) was adjusted by

changing the charging voltage applied to the condenser (Figure 1 left). Our previous study has confirmed the linear relationship between stimulus intensity and pulsed magnetic field intensity adjacent to the coil, what stimulus frequency can be adjusted in 2.5 Hz increments to any value within the range of 10–50 Hz.[20–22]

Electrical stimulation was delivered using a transcutaneous electrical current stimulator (Espurge, Ito CO., Ltd, Saitama, Japan) and a 50 × 50 mm electrode band (PALS Platinum, Axelgaard Manufacturing, Fallbrook, CA, USA). The main unit measured 151 mm high × 84 mm wide × 23.5 mm deep and weighed approximately 230 g. The maximum output current was 31 mA ± 20% (effective value), maximum output voltage was 40 V ± 20% (peak value, 500-Ω load), and maximum output frequency was 400 Hz ± 10% (Figure 1 right).

Parameters Measured

The main parameters measured were the angle of wrist movement and subjective pain and discomfort. The angle of wrist movement was measured using an electrogoniometer (SG65, Biometrics Ltd, UK) at a sampling frequency of 100 Hz. This was converted to digital data using the PowerLab 16/35 (AD Instruments, Inc., Charlotte, NC, USA), and recorded on a personal computer. Lab Chart 7 software (AD Instruments, Inc.) was used for the data collection and analysis. The electrogoniometer was attached along the line of the second metacarpal bone from the distal radius. The output signals from both stimulus devices were imported into the PowerLab and synchronized with the electrogoniometer to identify the trigger outputs.

Subjective pain and discomfort were measured by using an 11-point numerical rating scale (NRS), which is a standard measuring method.[23] We selected NRS as it could be answered verbally, instead of a visual analog scale (VAS), because it was assumed the subjects could not use their dominant hands when performing the test.

Pain was scored from 0 (no pain) to 10 (unbearable pain). Discomfort was scored from 0 (no discomfort) to 10 (unbearable discomfort). The investigator asked the subjects about their pain and discomfort levels and recorded them on the record sheet.

Experimental Conditions

The stimulus intensity was adjusted under the experimental conditions shown in Table 1. For rPMS, the stimulus intensity was adjusted on the Pathleader to 10 different levels, ranging from 10% to 100% in 10% increments. The Espurge was used for TES. Following preliminary screening, the maximum stimulus intensity was set at either (1) 1 mA below the intensity reported by the participant to cause unbearable pain or discomfort, or (2) 3 mA higher than the stimulus intensity that triggered an electrical current-induced wrist movement equivalent to the angle of the maximum possible voluntary movement. The stimulus intensity was then adjusted between the minimum and maximum values in 1 mA increments.

As for the stimulus placement of TES, the anode and cathode electrodes were placed side-by-side in parallel with the extensor carpi radialis (ECR) muscle fibers over the ECR muscle belly.

For both devices, the stimulus frequency was set at 30 Hz.[20,24] The stimuli were administered a total of 4 times at each intensity for a duration of 2 s each, with intervening 8 s breaks. Although the nature of the devices did not permit the use of an identical pulse width, the pulse widths were set as close to equivalent as possible, 350 μs for rPMS and 300 μs for TES.

Figure 1 Stimulus instruments.
Notes: Left is rPMS and right is TES. Both instruments were portable and easy to use.
Abbreviations: rPMS, repetitive peripheral magnetic stimulation; TES, transcutaneous electrical current stimulation.

Table 1 Experimental Conditions

	Conditions	
	TES	**rPMS**
Stimulation intensity	From 1 mA to endurable value: 1) 1 mA lower than the intensity associated with a pain or discomfort score of 10 or 2) 3 mA greater than the intensity reaching the angle of maximum voluntary movement of the wrist	10 levels from 10% to 100% of the maximum stimulus intensity
Stimulation frequency	30 Hz	30 Hz
Pulse width	300 μs	350 μs
Stimulation and pause time	2 sec, 8 sec	2 sec, 8 sec
Stimulus count	4 times	4 times

Notes: Stimulus parameters (frequency, pulse width, stimulation and pause time, stimulus count) were set as same as possible.
Abbreviations: rPMS, repetitive peripheral magnetic stimulation; TES, transcutaneous electrical current stimulation.

Stimulation Site

The stimuli were administered to the ECR muscle in the right dorsal forearm. For rPMS, the Pathleader coil was placed on the right dorsal forearm with visual monitoring of the wrist movements during stimulation. The coil's position was adjusted by moving it to a site where a lower-intensity stimulus induced a larger wrist extension movement. For the TES, the electrode band was attached to the right dorsal forearm and its position was adjusted using the same procedure as that used for the rPMS.

Experimental Procedure

Subjects were seated in a comfortable chair with the forearm in pronation and the wrist extended from the edge of the table in order to allow for a wide range of wrist extension. All subjects underwent both types of stimulation on the same day. They sat stationary in a chair with their shoulders and elbows slightly flexed and the forearms pronated. The right forearm was placed on a table so that the hand distal to the wrist projected beyond the edge of the table and was allowed to drop. Because the wrist angle changed, if the forearm was moved backward or forward, indicator stickers were placed on the table. The forearm and wrist positions were matched before each stimulus to ensure that the forearm was consistently in the same position. An electrogoniometer was attached to the subject's right wrist before the start of the experiment. The voltages during maximum voluntary extension and flexion of the wrist were recorded. These goniometer voltages were converted to angles based on measurements using an analog goniometer and angle corrections were performed. The angles of maximum voluntary extension and flexion of the wrist were recorded.

For the rPMS, the stimuli were administered at 10–100% of the maximum stimulus intensity and wrist angles were measured. Subjects were asked about their pain and discomfort after administration of the stimulus.

For the TES, after a preliminary investigation of the maximum intensity of electrical stimulation, stimuli were administered at levels ranging from 1 mA to the maximum tolerable stimulus intensity and wrist angles were measured. Subjects were asked about their pain and discomfort after administration of the stimuli.

To prevent an order effect, stimuli were administered in the following order: rPMS → TES in 6 subjects and TES → rPMS in the other 6. Subjects were given a 10-min break between the two procedures to recover from fatigue. The order of stimulus intensities was randomized using a random number table. A break of approximately 1 min was provided between the different stimulus intensities to allow the subjects to relax their wrists and ensure that the starting angles were consistent.

Analysis Methods

Because rPMS and TES are based on different design principles, it was not possible to ensure that the stimulus conditions in this study were completely consistent. We attempted to compare the two types of stimuli by analyzing a kinematic parameter induced by both devices. The procedures used were as follows:

1. Definitions of the parameters analyzed.

Figure 2 shows the definitions of the parameters analyzed. The period between the start (0 sec) and end (2 sec) of the stimulus was defined as the analysis section (AS). The integrated value of the angle data during the AS was defined as the integrated range of movement (iROM).

2. Nonlinear regression analysis using a sigmoid function.

A nonlinear regression analysis of stimulus intensity and the iROM was carried out using a sigmoid function. In this

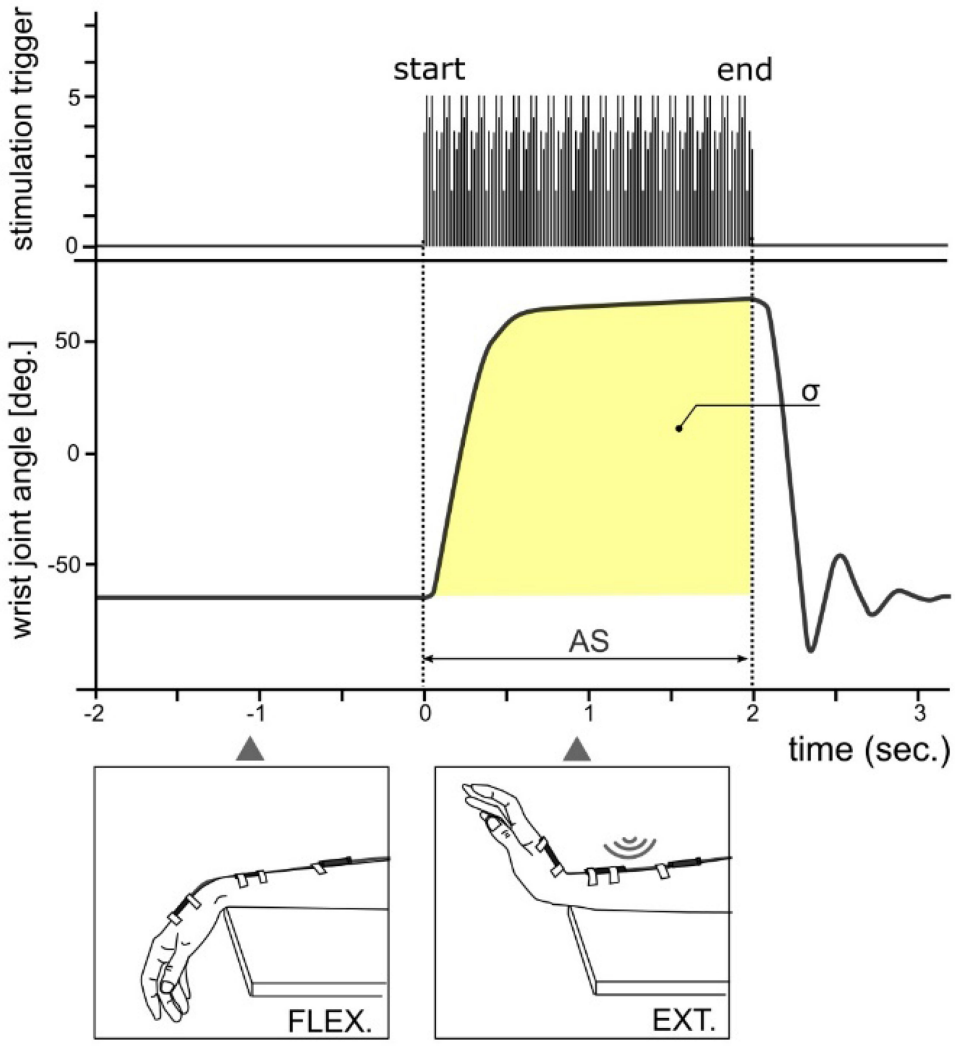

Figure 2 Definitions of the analytical parameters.
Abbreviations: AS, analysis section from 0 to 2 seconds; σ, integral value of wrist joint angle during; deg, degree.

study, we used the Rodbard function to express the four-parameter general form of a logistic function or sigmoidal curve.[25]

$$Y = d + (a - d)/1 + (X/c)^b$$

In this formula, Y represents the iROM and X represents the stimulus intensity. Regression formulae were produced with the constants a, b, c, and d calculated for each individual subject. The coefficient of determination for each subject was also calculated to assess the accuracy of fit between the measured and predicted values of iROM.

The range of iROM values collected from all subjects were examined and the values were divided into seven categories in 20ºs increments from 20ºs to 140ºs. The different categories of iROM (20ºs, 40ºs, 60ºs, 80ºs, 100ºs, 120ºs, and 140ºs) were then substituted into the regression formula and the stimulus intensity X was inversely estimated. These nonlinear regression analyses were carried out using Image J ver.1.51 software (NIH, Atlanta, GA, USA).

3. Selection of subjective evaluations

The actual measured values that most closely approximated stimulus intensity X (one of 10%, 20%, 30%, … 100% for magnetic stimuli, and one of 1 mA, 2 mA, 3 mA, … for electrical stimuli) were examined. The subjective assessments (pain or discomfort) corresponding to these values were selected.

Statistical Analysis

In the statistical analyses, the subjective evaluations of pain and discomfort were analyzed in a two-factor repeated

measures analysis of variance (ANOVA) with the two stimulus devices (rPMS, TES) and seven levels of iROM (20°s, 40°s, 60°s, 80°s, 100°s, 120°s, and 140°s) as factors. If a main effect was found, Bonferroni correction was used in a post hoc test. Statistical analysis was carried out using SPSS for Windows ver. 23 (IBM Corp., Armonk, NY, USA), with $p < 0.05$ regarded as significant.

Ethical Considerations

This study was approved by the Tohoku University Hospital Clinical Research Ethics Committee (approval number: 2017-2-113-1) and was conducted in compliance with the ethical standards of the Helsinki Declaration. Written informed consent was obtained from all subjects after a full written and oral explanation of the purpose and methods of the study was provided. Also, this trial was registered at the UMIN Clinical Trials Registry as UMIN000022632 [http://www.umin.ac.jp/ct-r/index.htm]

Results

Stimulus Intensity and iROM in rPMS and TES Modalities

There were no adverse events during or after the experiments. In the rPMS experiments, stimuli were administered to all subjects at all stimulus intensities. In the TES experiments, none of the subjects dropped out between 1–16 mA, but there were dropouts at each of the intensities as follows: 1 at 17 mA, 1 at 20 mA, 2 at 21 mA, 1 at 22 mA, 1 at 23 mA, 2 at 24 mA, 2 at 26 mA, 1 at 27 mA, and 1 at 29 mA.

Figure 3A and B shows an example of a subject's regression curve using the sigmoid function in rPMS and TES, respectively. The other results are shown in Appendix Figure 1. As for the regression curve for the sigmoid function related to stimulus intensity and wrist iROM, the mean values (ranges) of the coefficients of determination for the observed and predicted values of iROM were $R^2 = 0.988$ (0.916–0.999) for rPMS and $R^2 = 0.980$ (0.911–0.999) for TES. The actual stimulus intensities closest to the stimulus intensities that were inversely estimated from the iROM values according to the regression formula are shown in Appendix Table 1.

Pain

The ANOVA results for pain revealed significant main effects with respect to both the types of stimulus devices and the iROM (stimulus device: F 1, 11 = 8.261, p = 0.015; iROM: F 6, 66 = 5.459, $p < 0.001$). No interactions were observed (F 6, 154 = 0.345, p = 0.911). Post hoc test revealed significant differences between the stimulus devices when the iROM were at 80°s, 100°s, 120°s, or 140°s (80°s: p = 0.007; 100°s: p = 0.009; 120°s: p = 0.001; 140°s: p = 0.028). The pain was significantly lower during rPMS compared to TES at these levels of iROM. While the pain at 140°s was significantly greater than it at 20°s (p = 0.044) in the TES, the pain was not significantly different between any pair of iROM levels in rPMS (Figure 4).

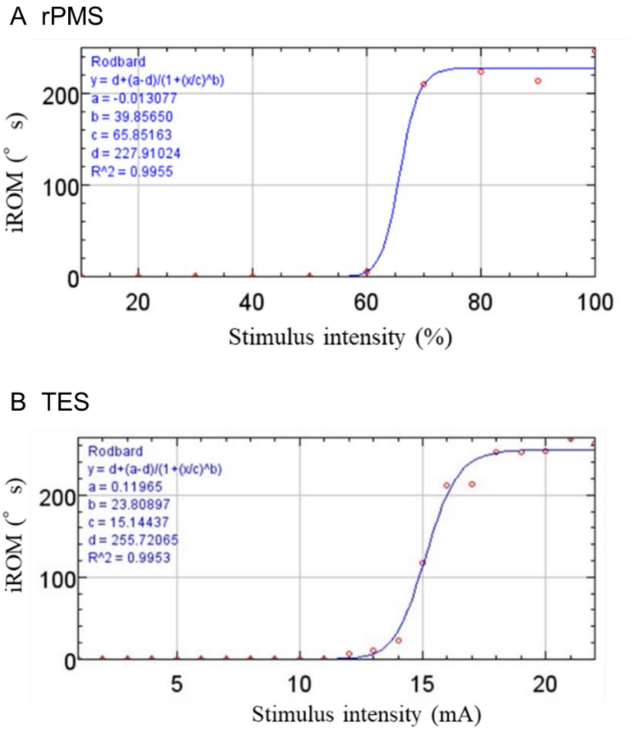

Figure 3 An example of a subject's regression curve using the sigmoid function.
Notes: (**A**) is rPMS and (**B**) is TES. X-axis shows stimulus intensity, which the unit of rPMS is "%" and it of TES is "mA". Y-axis shows iROM, which the units are "°s". Both rPMS and TES condition, stimulus intensity and iROM were strongly correlated using by regression curve of sigmoid function.
Abbreviations: rPMS, repetitive peripheral magnetic stimulation; TES, transcutaneous electrical current stimulation; iROM (°s), integrated range of movement (degree multiplied by second).

Discomfort

The results regarding discomfort revealed significant main effects in both the type of stimulus device and iROM (stimulus device: F 1, 11 = 7.051, p = 0.022; iROM: F 6, 66 = 4.668, p = 0.001). No interactions were observed (F 14, 154 = 0.856, p = 0.532). A post hoc test revealed significant differences between rPMS and TES when the iROM were 60°s, 80°s, 100°s, 120°s, or 140°s (60°s: p = 0.046; 80°s: p = 0.013; 100°s: p = 0.006; 120°s: p = 0.004; 140°s: p = 0.035). The discomfort was lower with rPMS

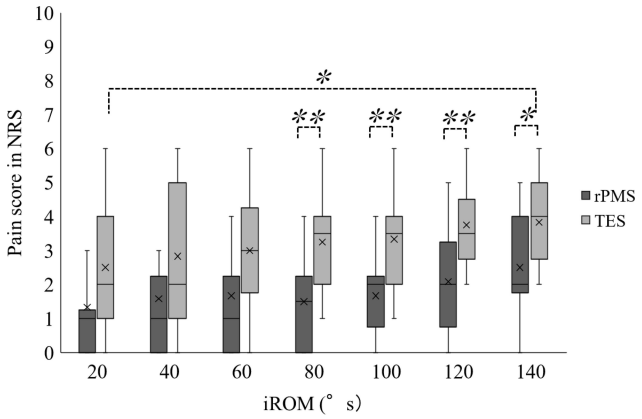

Figure 4 Pain caused by the differences in the integral value of the wrist movements and the stimulus conditions.
Notes: The two-factor repeated measures analysis of variance (ANOVA) revealed significant main effects with respect to both the types of stimulus devices and the iROM. ×, mean value; -, median value; *p < 0.05; **p < 0.01.
Abbreviations: NRS, numerical rating scale; iROM (°s), integrated range of movement (degree multiplied by second); rPMS, repetitive peripheral magnetic stimulation; TES, transcutaneous electrical current stimulation.

compared to TES at these levels of iROM. However, there was no significant difference among different levels of iROM for the two stimulus conditions (Figure 5).

Discussion

In this study, we applied rPMS and TES under a wide range of stimulus intensities on peripheral nerves in the dorsal forearm. We investigated the resulting changes in wrist iROM and the resulting pain and discomfort. We compared subjective pain and discomfort using an NRS at the corresponding iROM induced by the individual stimulation modalities. Although previous studies compared pain between rPMS and TES at a given amount of knee extension[10,15] and hip flexion torque,[9] there is no comparative study of pain induced by rPMS and TES under a wide range of stimulus intensity except for Szecsi's study. Furthermore, there is no paper comparing pain or discomfort in the upper limbs.

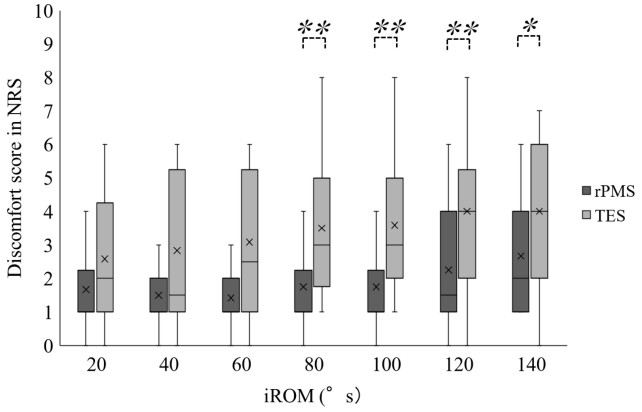

Figure 5 Discomfort caused by the differences in the integral value of the wrist movements and the stimulus conditions.
Notes: The two-factor repeated measures analysis of variance (ANOVA) revealed significant main effects with respect to both the types of stimulus devices and the iROM. ×, mean value; -, median value; *p < 0.05; **p < 0.01.
Abbreviations: NRS, numerical rating scale; iROM (°s), integrated range of movement (degree multiplied by second); rPMS, repetitive peripheral magnetic stimulation; TES, transcutaneous electrical current stimulation.

Pain

The pain was overall low (1.76 ±1.63) in rPMS, which was not significantly different between each level of iROM. The pain was significantly lower in rPMS compared to TES when the iROM was from 80º s to 140º s. This is a similar result that was found in previous studies that reported less pain with rPMS.[9,10,15] Our results demonstrated that rPMS induced less pain compared to TES when the value of iROM was relatively large (80ºs to 140ºs). In addition to the reasons mentioned in introduction section, this may have reflected a difference in the motor units recruited, which derives from variations in the two stimulation modalities, ie, differences in the characteristics of induced-electrical current by rPMS and the electric current generated by TES. For TES, wrist dorsiflexion movements may be generated by mobilizing the motor units of the ECR or extensor carpi ulnaris (ECU) which are superficially located on the surface. In addition to mobilizing ECR and ECU muscles, more deeply located muscles such as extensor indicis would be also mobilized in rPMS. Thus, TES induces intense muscle contractions due to a summation of the electrical stimulus. This may have induced painful wrist movements.

Discomfort

The discomfort was also low overall (1.86 ±1.57) with rPMS and was not significantly different between each level of iROM. The discomfort was significantly lower in rPMS compared to TES when the iROM ranged from 60ºs to 140ºs. These results suggest that rPMS can induce a relatively large joint movement while minimizing discomfort.

We measured the subjective discomfort and pain separately, because subjective sensation was evaluated by discomfort as well as pain in Han's study.[10] Moreover, Takahashi's study suggested that the dull sensation, which is characteristic of muscular pain, is related to processing of emotion-related brain region by fMRI study.[26] Considering previous studies and our findings, discomfort does not represent the same perception as pain, however may be an emotional response related to muscular pain.

The present findings support the working hypothesis that rPMS would result in less pain and discomfort than TES at the same level of induced movement.

Limitation

This study had limitations. First, our findings are limited to experimental conditions. rPMS may induce movements with pain and discomfort at strong stimulus intensities, when iROM is above 140º's, because of no interaction between the stimulus device and iROM. Second, we were unable to administer rPMS and TES stimuli at exactly the same site. The stimulation site was determined to be the site where a weaker stimulus induced a larger wrist dorsiflexion movement. However, this could have been a result of the investigator's observations and technique. In particular, the setting of rPMS may have affected the induced movements with even a slight repositioning of the coil or a slightly different tilt angle. Furthermore, the forearm contains several wrist extensor muscles that are in close proximity to each other. The thickness of fat and other subcutaneous tissue is inconsistent. As such, it is debatable whether the stimulation site used in this study was the most appropriate location for inducing wrist dorsiflexion movements. Because of the difficulty of directly observing the nature of subcutaneous tissue and its response to stimulation, future measurements will require optimization of the coil position and its angle of inclination by using markers to identify stimulation site categories, and by using a clinometer. Third, subjective evaluations could be affected by the subject's expectations. The physiological mechanism of both stimulus devices was not explained to the subjects in advance to reduce preconception. However, there are possibilities that preparations affected subjective evaluations, such as attaching electrode pads before electrical stimulation.

Conclusion

rPMS of peripheral nerves in the forearm resulted in less pain and discomfort than TES. However, the difference between the amount of pain and discomfort induced by rPMS and that of TES was only significant when joint movements were comparatively large. When the stimulated joint movements were small, there was no significant difference between the two methods.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, GA, upon reasonable request.

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Author Contributions

GA, HO, ZL and AA conceived the study. GA, HO, ZL, KH, and KY performed the experiments and collected and analyzed the data. GA, HO, KH and KY established the instrumental settings. GA, HO and SI wrote the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Kenji Yashima is an employee of IFG Corporation. Shin-Ichi Izumi owns shares/stock of IFG Corporation, Ltd. and reports a patent issued: MEDICAL SUCCESSIVE MAGNETIC PULSE GENERATION DEVICE (US 10,173,071 B2). IFG Corporation developed the repetitive peripheral magnetic stimulation which is used in our study. The authors report no other potential conflicts of interest for this work.

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SHORT COMMUNICATION

Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study

Fred R. Nelson · Raimond Zvirbulis · Arthur A. Pilla

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Abstract This study examined whether a non-thermal, non-invasive, pulsed electromagnetic field (PEMF), known to modulate the calmodulin (CaM)-dependent nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling pathway, could reduce pain in early knee OA. This randomized, placebo-controlled, double-blind pilot clinical study enrolled 34 patients. Patient selection required initial VAS ≥4, 2 h of standing activity per day, and no recent interventions such as cortisone injections or surgery. Results showed VAS pain score decreased in the active cohort by 50 ± 11 % versus baseline starting at day 1 and persisting to day 42 ($P < 0.001$). There was no significant decrease in VAS versus baseline at any time point in the sham cohort ($P = 0.227$). The overall decrease in mean VAS score for the active cohort was nearly threefold that of the sham cohort ($P < 0.001$). The results suggest that non-thermal, non-invasive PEMF therapy can have a significant and rapid impact on pain from early knee OA and that larger clinical trials are warranted.

Keywords Knee OA · PEMF · Calmodulin · NO signaling

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Introduction

PEMF have been employed for the conservative treatment of knee OA with varied success [1]. A recent meta-analysis concluded PEMF improved clinical scores and function in patients with osteoarthritis of the knee and should be considered as adjuvant therapies in their management [2]. It has recently been suggested that PEMF signals can act as first messengers in the CaM-dependent signaling pathways that orchestrate the release of cytokines and growth factors in cellular responses to injury [3]. This has enabled PEMF signals to be successfully configured a priori to modulate such tissue repair pathways [4–13]. A therapeutic target for the relief of knee OA pain is the CaM-dependent nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) cascade [14], which can modulate blood, as well as lymph flow [15]. This same pathway also modulates the release of inflammatory cytokines, such as interleukin-1beta (IL-1β) [16] and growth factors such as basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) [17].

PEMF signals have been shown to modulate the CaM-dependent NO signaling cascades in articular chondrocytes [9] and other cells [3] using CaM antagonists, and NO and downstream inhibitors. These signals have also been reported to accelerate cutaneous wound repair by 59 % and Achilles' tendon repair by 69 % at 21 days in rat models; angiogenesis as quickly as 7 days in a thermal myocardial necrosis rat model, wherein L-NAME, a nitric oxide synthase inhibitor, blocked the PEMF effect [5]; and rapidly decrease post-operative pain concomitant with an equally rapid reduction of IL-1β in the wound bed in a double-blind, randomized, human clinical trial [10]. This study was, thus, designed to determine whether PEMF, configured to modulate the CaM/NO/cGMP signaling pathway, would reduce pain in early knee osteoarthritis.

Materials and methods

This double-blind, placebo-controlled, randomized pilot study was approved by the Institutional Review Board at Henry Ford Hospital and all enrolled patients gave informed consent. The primary outcome measure was VAS pain score on a 0–10 cm scale with respect to baseline in each cohort. Although consensus guidelines suggest a 20 % decrease in VAS as the minimum clinically relevant difference in knee OA pain [18], a 40 % difference was chosen as the clinically desirable outcome. Thus, prior to the start of this study, a sample size analysis, assuming a 40 % (±35 % SD) decrease in pain scores from PEMF treatment, suggested a minimum of 14 patients per group were needed. Patient selection required that subjects have knee pain for at least 3 months with an imaging study that confirmed articular cartilage loss, an initial VAS score ≥4, and at least 2 h of daily standing activity in a physical occupation. Patients with rheumatoid arthritis, gout, and pregnancy were excluded. Patients with cortisone injections, surgery, or an effective viscosupplementation series within the past 6 months were excluded. Patients with implanted electronic devices were excluded. Patients on disability or with third party claims were excluded. Since all patients were actively employed, NSAID use was unrestricted. PEMF therapy was the only addition to the current standard of care.

A PEMF signal consisting of a 7 ms burst of 6.8 MHz sinusoidal waves repeating at 1 burst/s delivering a peak induced electric field of 34 ± 8 V/m in the knee from the portable battery operated device shown in Fig. 1 (Palermo, Ivivi Health Sciences, LLC, San Francisco, CA), was used for 15 min twice daily. Each device had an inaccessible counter which recorded the total number of treatments for each patient. The device was light weight and patients could easily position the coil directly over the knee, even over clothing. Once manually activated, treatment was automatically applied for 15 min. Manual activation was required for each treatment.

Randomization was performed by the blinded assignment of devices according to their serial numbers. Device randomization was performed by the manufacturer (Ivivi Health Sciences, LLC) and all devices with the randomization code were sent to the Epidemiology Dept at Henry Ford Hospital, from which assignment to patients was controlled. Sham devices were activated with a switch, just as active devices, and both sham and active units had blinking indicator lights. The PEMF signal from these devices does not produce heat or cause any other sensation in tissue. The average in situ magnetic field induced by the PEMF signal employed in this study is at least 1,000-fold below the ambient magnetic field and cannot be detected using standard Gauss meters. Therefore, only measurements with specialized laboratory equipment, not readily available to the patient or health care practitioner, could determine whether a device was active. General unblinding occurred after all data were collected.

Fig. 1 The non-thermal pulsed radio frequency PEMF device used in this randomized, double-blind clinical study on knee OA pain. The device consists of a single loop wire coil with integrated amplifier (Palermo, Ivivi Health Sciences, San Francisco, CA) that delivers a PRF signal configured to modulate the CaM/NO/cGMP signaling pathway, which consisted of a 7-ms burst of a 6.8 MHz sinusoidal carrier repeating at 2 bursts/s, delivering a peak induced electric field amplitude of 34 ± 8 V/m in the knee. The device is portable and easily positioned by the patient over the knee with the Velcro™ strap. The *number* displayed is the number of PEMF treatments

PEMF signal parameters were verified for each device by a third party, who had no contact with patients, at the beginning and end of treatment, with a calibrated field probe (model FCC-301-1-MR1, Fischer Custom Communications, Torrance, CA) connected to a calibrated 100-MHz oscilloscope (model 2358, Tektronix, Beaverton, OR).

Patients were required to self-report maximum daily VAS pain scores on an unmarked horizontal 10 cm line (0 is no pain and 10 is worst possible pain) at baseline (day 0), daily for the first 14 days, then daily from day 29 to day 42. The 2-week gap in VAS data collection was designed to assess for possible accommodation to PEMF therapy. By not reporting VAS scores for 2 weeks, patients would be more likely not to remember their last score. Results were analyzed using the Student's *t* test or one-way repeated measures ANOVA with Holm–Sidek post hoc analysis, as appropriate (Sigmastat 3.0, SPSS). Intent-to-treat analysis using last data carried forward [19] was employed for patients who did not complete the study. Significance was accepted at $P \leq 0.05$. Data are displayed ± SEM.

Results

The portable PEMF devices were well tolerated. No adverse events were reported. Device verification for each patient at the end of treatment revealed all devices to be functioning as randomized. No signal variations or deteriorations were noted in the active devices. The mean ± SD of the total number of treatments delivered by all devices in this study was 80 ± 9 compared with the expected 84, suggesting that devices were used as prescribed by all patients. There were no significant baseline differences in mean age, body mass index (BMI), or Kellgren–Lawrence (K-L) radiographic scores, between active and sham cohorts, as shown in Table 1.

Thirty four patients started treatment. Of these, 19 (14F, 5M) were shams, and 15 (10F, 5M) were actives. The imbalance in treatment groups was due to initial drop outs (entered patients not starting treatment), the total number of available randomized devices, and the sequential distribution of devices over time. Given there were no significant differences in baseline parameters between the cohorts, the imbalance was not a factor. All enrolled patients received PEMF treatment to day 14. Thereafter, 3 active and 7 sham patients dropped out of the study by day 42, citing lack of perceived benefit as the reason, confirmed by VAS scores. Patient flow is outlined in Fig. 2.

Table 1 Baseline patient demographics

Index	Active	Sham	*P* value
Age	55.5 ± 2.5	58.4 ± 2.5	0.434
BMI	33.5 ± 1.9	34.7 ± 1.7	0.644
K-L	2.7 ± 0.33	2.9 ± 0.25	0.532

The results for all enrolled patients show the PEMF signal caused 50 ± 11 % decrease in mean maximum VAS versus mean baseline VAS for the treated group starting on day 1, persisting to day 42 ($P < 0.001$). There was no significant decrease in mean maximum VAS compared with mean start VAS at any time point in the sham group ($P = 0.227$). The overall decrease in VAS scores from baseline was 2.7 ± 0.57 ($P < 0.001$) for the active group versus 1.5 ± 0.41 ($P = 0.168$) for the sham group. There was no significant difference in mean start VAS between the active and sham groups (Active = 6.8 ± 0.31, Sham = 7.1 ± 0.34, $P = 0.430$). A summary of mean intra-cohort VAS scores from baseline to day 42 for all patients is shown in Fig. 3. Inter-cohort VAS scores are compared in Table 2. As may be seen, the overall pain decrease in the active cohort was approximately 60 % by

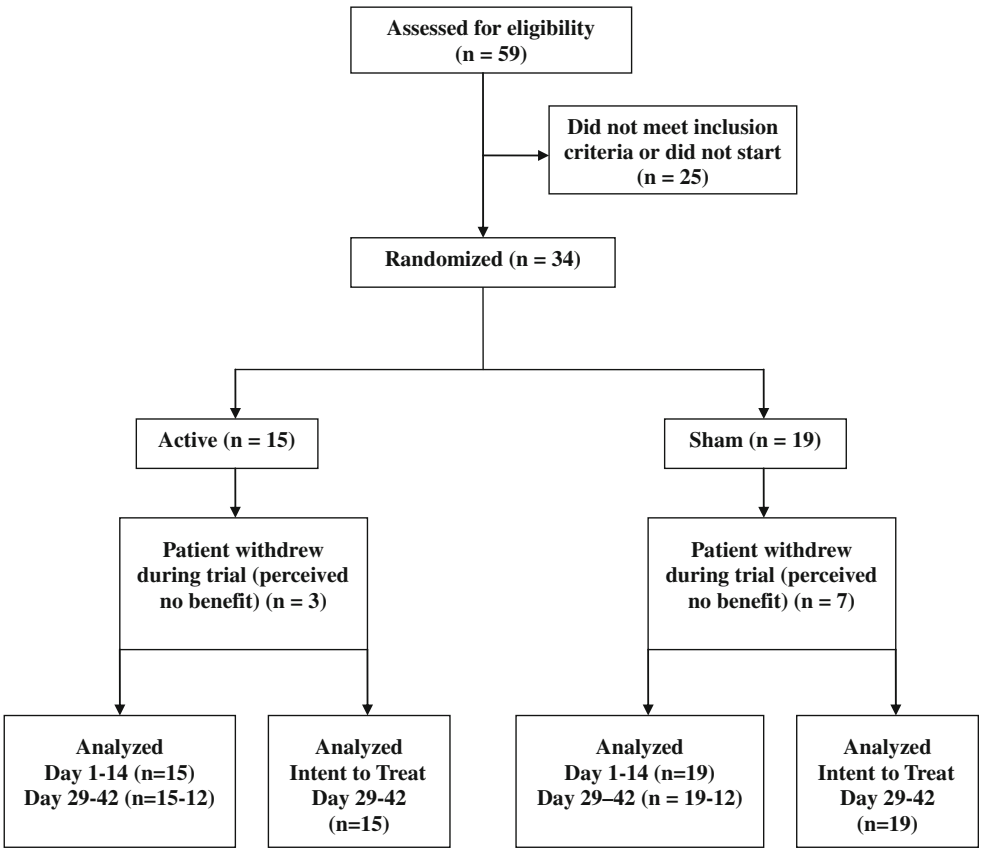

Fig. 2 Randomized pilot clinical trial on PEMF effect on knee OA pain: patient flow chart

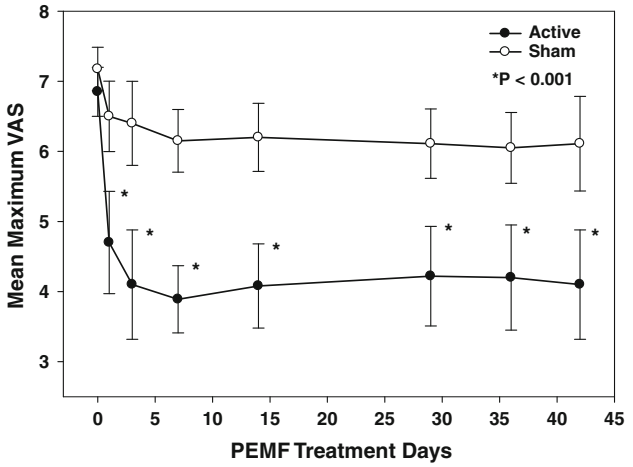

Fig. 3 Effect of a radio frequency PEMF signal, configured, a priori, to target the CaM/NO/cGMP signaling pathway, on pain from early stage knee OA. This is a repeated measures intra-cohort comparison which shows this signal caused a nearly 60 % reduction in mean VAS pain scores within the first 3 days for the active cohort, which persisted to day 42 for all enrolled active patients. There was no significant difference in mean VAS scores for the sham cohort at any time point, or in mean baseline VAS scores for the active and sham cohorts

Table 2 Mean VAS pain scores: inter-cohort comparisons

Day	Mean VAS active	Mean VAS sham	*P* value
Baseline	6.85 ± 0.33	7.18 ± 0.31	0.481
3	4.13 ± 0.48	6.84 ± 0.43	0.008*
14	4.08 ± 0.60	6.21 ± 0.50	0.011*
29	4.22 ± 0.66	6.11 ± 0.52	0.041*,[a]
42	4.19 ± 0.71	6.11 ± 0.54	0.036*,[a]

* Significantly different

[a] Intent-to-treat

day 42 ($P < 0.001$), whereas in the sham cohort pain decrease was only 18 % ($P = 0.206$). Thus, even assuming a placebo effect, pain decrease was approximately three-fold greater in the active cohort, within the first 3 days of PEMF treatment.

Discussion

The results from this randomized, double-blind, placebo-controlled study demonstrate that non-thermal, non-invasive PEMF, when configured to dose CaM-dependent NO/cGMP signaling, has a significant and rapid impact on pain from early knee OA. The intervention is novel since the patient population treated did not have end stage disease and were required to be on their feet at least 2 h a day. The PEMF treatment time is short (15 min), and use of the device did not interfere with work or off-work activities. Review of patient notes reveals that the majority of patients in the active group were convinced the PEMF treatment had a functionally significant impact on their pain. It is noted that more than twice as many sham versus active patients opted out of the study after the initial 14-day phase.

In persons with knee OA, bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears are all causes of knee pain [20]. Effusion (edema) is one manifestation of the inflammatory response to bone injury attributable to knee OA. The rapid onset response in the active group is remarkably similar to that reported for a similarly configured PEMF signal, which produced approximately 2.5-fold reduction in pain from breast reduction surgery within 5 h post-op [10]. That study also showed IL-1β, a master inflammatory cytokine, was concomitantly reduced by approximately 2.5-fold in the wound bed. Certainly, there are no data from this study, which directly support a PEMF effect on CaM-dependent NO signaling. However, it is reasonable to speculate that the effect of PEMF on knee OA pain reported here could involve modulation of CaM-dependent NO signaling which is known to rapidly reduce edema (effusion) [15]. This is consistent with the rapid effects of similar PEMF signals reported on edema from ankle sprains in randomized studies [21, 22] and could explain the rapidity of the PEMF effect in this patient population.

The persistence of pain reduction in active patients to day 42 suggests daily use of PEMF produced a sustained anti-inflammatory effect, perhaps via down-regulation of IL-1β, which may slow the progression of knee OA. Obviously, this pilot study was not designed to assess the effect of this PEMF treatment on OA per se in this patient population. However, it is useful to consider evidence suggesting that PEMF could attenuate the effects of the prolonged inflammation caused by IL-1β. Thus, weak electric fields partially reversed the decrease in the production of extracellular matrix caused by exogenous IL-1β in full-thickness articular cartilage explants from osteoarthritic adult human knee joints [23]. Similar studies showed the decreased production of proteoglycans caused by exogenous IL-1β was reversed by PEMF in bovine articular cartilage explants [24]. There are also reports that PEMF can increase proliferation in chondrocyte cultures [9, 25]. Finally, there are reports which suggest that PEMF can affect the progression of OA [26] and heal cartilage defects in animal models [27, 28].

The rapid and substantial effect of non-thermal, non-invasive PEMF therapy on knee OA pain in this double-blind, randomized, placebo-controlled pilot clinical study are promising enough to warrant further larger studies designed to confirm the PEMF effect on pain, in which

standard clinical measures of function, as well as effusion and inflammatory markers are included. Once confirmed, use of this PEMF therapy may provide an important simple and economical adjunct for the non-invasive, non-pharmacological treatment of OA.

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Conflict of interest FN and RZ have no association with Ivivi Health Sciences. AAP is a basic science consultant to Ivivi Health Sciences and had no contact with patients in this study.

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RESEARCH ARTICLES

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Modulatory effect of repetitive peripheral magnetic stimulation on skeletal muscle tone in healthy subjects: stabilization of the elbow joint

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Abstract To investigate the role of repetitive peripheral magnetic stimulation (RPMS) on the postural component of motor performances, the long-lasting modulatory effect of RPMS on the stabilization of the elbow joint was examined in 13 healthy subjects. The resistance against very slow passive movements in the relaxed state was recorded simultaneously with the electromyogram (EMG) of the forearm extensor and flexor muscles. The experiments show that RPMS performed on the forearm flexor muscles increased the degree of stabilization of the elbow joint, whereas RPMS on the forearm extensor muscles caused a decrease in stabilization. This leads to the assumption that the postural component of motor tasks depends on the motor task itself: motor tasks like manipulation, pointing or grasping which are fine skilled movements require an increase in stabilization while goal-directed movements require a decrease in stabilization. Therefore RPMS is involved in sensorimotor integration and may modulate the motor program at the cortical level.

Keywords Sensorimotor control · Repetitive peripheral magnetic stimulation · Neuromodulation · Postural component of motor tasks · Joint stabilization · Muscle spindle

Introduction

Recent studies in healthy subjects have demonstrated that somatosensory input in the form of peripheral nerve stimulation or muscle stretching results in functional changes in corticomotor excitability: 300 passively induced wrist extension and flexion movements elicited by a torque motor showed a higher activation (fMRI) of contralateral primary motor cortex (cM1), even though this effect of motor performance improvement is significantly lower than the improvement caused by voluntary (active) movements (Lotze et al. 2003).

Ridding et al. (2000) showed that a prolonged period of peripheral nerve stimulation can induce a lasting increase in corticomotoneuronal excitability to stimulated body parts. The importance of the conjoint activity of somatosensory afferents and intrinsic cortical motor circuits was shown by Stefan et al. (2000) by using low frequency median nerve stimulation paired with transcranial magnetic stimulation (TMS). The motor evoked potentials (MEP) were increased if the somatosensory input of these stimulations was synchronous at the level of the motor cortex. Kaelin-Lang et al. (2002) concluded that electrical ulnar nerve stimulation elicited a focal increase in corticomotoneuronal excitability which outlasted the stimulation period and probably occurred at cortical sites.

Repetitive peripheral magnetic stimulation (RPMS) in the area of the muscle supplying terminal branches represents an alternative method to transcutaneous electrical stimulation (TES). In contrast to TES, the biologically effective electrical field is considerably lower. This avoids activation of cutaneous receptors like nociceptors as well as the activation of mechanoreceptor afferents from the skin and fiber groups III and IV. The spatial field distributions are also different in terms of spreading. The magnetic field depends upon the ion environment and penetrates deeper regions of the muscle, whereas the current caused by the electrical field will take the path of lowest resistance, thus being fairly limited spatially on the surface.

RPMS in the area of the muscle supplying terminal branches elicits a proprioceptive input to the central nervous system (CNS) in two different ways:

– Adequate activation (indirectly due to stimulation) of mechanoreceptors (fiber groups Ia, Ib, II) during the rhythmic contraction and relaxation as well as vibration of the muscles.

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– Inadequate activation (directly due to stimulation) of sensorimotor nerve fibers with orthodromic and antidromic conduction.

This afferent input leads to sensations such as movement and vibration and is conveyed simultaneously at higher CNS levels. Earlier studies have shown that RPMS elicits improving effects at various levels of the sensorimotor and the cognitive systems (Struppler et al. 2003; Struppler and Havel 2001).

RPMS caused a dramatic decrease in spasticity in a clinical experimental investigation of spastic paresis of finger and hand extensors as well as spastic paraplegia (Struppler et al. 2003). In a PET study investigating the different cerebral activation during a simple motor task, after RPMS the activation was focused on a frontoparietal circuit (Spiegel et al. 2000).

To investigate the influence of RPMS on a pure cognition ability, the effect of RPMS on local tactile extinction in patients after right-sided brain lesions was examined in a study of cognitive functions showing a significant reduction of cognition errors after RPMS (Heldmann et al. 2000). To consider the modifying effect of RPMS on spatial cognition, the position sense under static as well as the position sense during goal-directed pointing tasks with the index finger has been investigated. This also shows a remarkable improvement following RPMS.

Clinical observations show that the regularity of disturbed goal-directed motor performances such as reaching and grasping can be improved. These findings strongly indicate that not only transient spinal mechanisms are responsible for the improvement of voluntary movements but also cortical neuroplasticity.

The aim of the experimental investigations presented in this paper was to give a greater insight into the underlying modulatory mechanisms of RPMS. We attempted to clarify whether RPMS modifies muscle intrinsic factors such as viscoelasticity or if it works at a central, i.e., cortical level.

Materials and methods

Subjects

The investigations were performed on 13 healthy subjects aged from 25 to 80 years with an average age of 35 years.

Methods

To evaluate the resistance against very slow alternating movements, a torque motor (TM) was used. This TM was controlled by a closed-loop position control to impose the movements on the subject's forearm. The schematic mechanical arrangement for this purpose is depicted in Fig. 1. The reference of the TM is equivalent to an almost relaxed position, which is around 115° at the elbow joint.

The alternating movements applied to the subject's elbow joint can be seen in Fig. 2, where the desired angle of the TM is depicted over time. The velocity of the movements is shown to be really slow (2.5°/s); hence the inertia of the forearm and the lever of the TM can be neglected.

In order to exclude the role of the preceding movements, two different movement schemes were used: "cycle a" and "cycle b."

Cycle a

From the starting position at 0° the lever was moved to 25° (flexion) at a velocity of 2.5°/s. After a break of 8 s in this

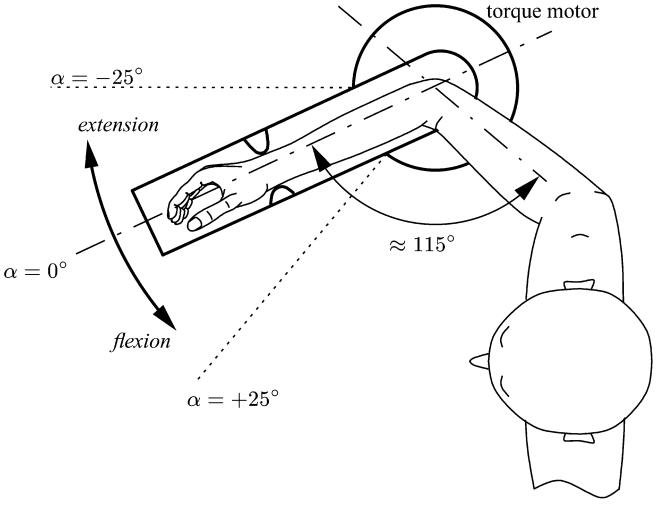

Fig. 1 Mechanical arrangement and definition of the reference for the position α of the TM; the figure shows the subject in a comfortable and relaxed sitting position; the forearm is fixed at the lever of the TM

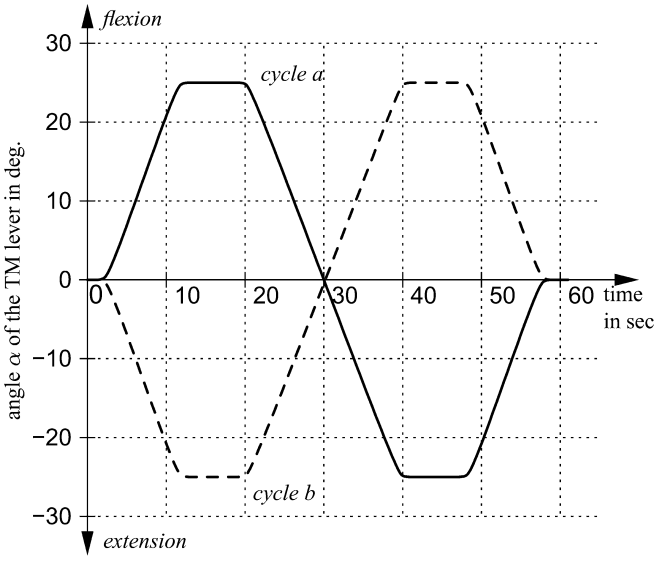

Fig. 2 Desired angle α of the TM over time for the different movement schemes cycles a and b

Table 1 Definition of the three different subject groups including the reference group

	Pre-registration sequence	Conditioning RPMS	Postregistration sequence
Group A (seven subjects)	Measurement of the mechanical and EMG parameters (pre-RPMS)	Stimulation of the m. triceps brachii	Measurement of the mechanical and EMG parameters (post-RPMS)
Group B (nine subjects)	Measurement of the mechanical and EMG parameters (pre-RPMS)	Stimulation of the m. biceps brachii	Measurement of the mechanical and EMG parameters (post-RPMS)
Group C (seven subjects)	Measurement of the mechanical and EMG parameters	No stimulation	Measurement of the mechanical and EMG parameters

position, an extension of 50° at the same velocity followed. After another break of 8 s, the system returned to the starting position by a flexion of 25°.

Cycle b

The movement pattern described by cycle b is the inverse pattern of cycle a as depicted in Fig. 2 (dotted line). For evaluation purposes the angle α of the TM as well as the torque T of the forearm against the lever were measured (Given et al. 1995; Struppler and Jakob 1995). The resistance against slow alternating movements (measured torque) is based on the simultaneous lengthening and shortening reactions of the involved synergistic and antagonistic muscle groups, respectively.

Hence the EMG of the agonistic and antagonistic muscles was recorded simultaneously with the mechanical parameters. The muscles recorded were m. biceps brachii (caput longum), m. biceps brachii (caput breve) and m. triceps brachii. To measure the EMG, skin-surface electrodes and a sample rate of 2,080 samples/s were used. The angle α of the TM and the torque T were sampled with $^{20804}/_{4}$=520 samples/s.

RPMS was transcutaneously performed on the area of muscle supplying the terminal branches by a conventional stimulation coil (Magstim double 70-mm coil). For every application of RPMS, 5,000 single magnetic field impulses at an average amplitude of 1.2 T[1] were applied. The field impulses were generated by a self-built stimulator (Schmid 1992) and repeated at a physiologically orientated frequency of 20 Hz.

After every 30 impulses a break of 3 s was left to induce repetitive contractions and relaxations to the target muscles. This stimulation elicited mainly a proprioceptive inflow to the CNS together with the sensation of movement and vibration.

Experimental protocol

To investigate the influence of RPMS on the stabilization of the elbow joint, the mechanical and EMG parameters from the synergistic and antagonistic muscles were measured before and after the conditioning RPMS.

[1] 1.2 T=12,000 G

To obtain more accurate results during one recording sequence, the movement cycles a and b were applied four times to each subject. With these 2×4 cycles one average cycle a and one average cycle b was calculated for the evaluation process.

During the measurement session the subject was advised to relax the shoulder (clinically controlled) and the forearm (no burst activity in the raw EMG data). This sequence was followed by the RPMS conditioning either of the biceps or of the triceps. Approximately 30 min after the RPMS, the mechanical and EMG parameters were measured again. This was done although it could be shown that the maximum effects of RPMS developed after 2–4 h (Struppler et al. 1996, 2003).

Subject group definition

To investigate whether the RPMS of forearm flexor muscles causes effects other than the RPMS of forearm extensor muscles, different subject groups were defined (see Table 1):

A. RPMS of the forearm extensor muscles
B. RPMS of the forearm flexor muscles

Each subject was assigned to one of these groups. However, it was possible to stimulate and examine the same person, after an adequate period of time (at least 4 weeks), under the conditions of the other group.To exclude any time-dependent factor during the experiment (e.g. fatigue-induced effects), a third group was defined. In this group the mechanical and EMG parameters were also measured twice. In contrast to groups A and B, instead of the conditioning RPMS a break of approximately 15 min was left between the two recording sequences. This led to a reference subject group:

C. Pause of 15 min (control group)

Results

For the evaluation of the conditioning effect of RPMS on the stabilization of the elbow joint (resistance against extension and flexion), the average results for the different subject groups had to be compared. For this purpose the measured torque T_C of group C was taken as the baseline to evaluate the changes in the measured torque T_A and T_B.

This is represented by the following equation:

$$\delta T_{A/B} = T_{A/B} - T_C \tag{1}$$

In order to analyze the change of the measured torque $\Delta T_{A,B}$ related to the conditioning RPMS, the difference in the measured torque before and after the RPMS has to be considered. This leads to the equation:

$$\begin{aligned} \Delta t_{A/B} &= \delta T_{A/B,\text{post}} - \Delta T_{A/B,\text{pre}} = \\ &= \left(T_{A/B.\text{post}} - T_{C.\text{post}}\right) - \\ &= \left(T_{A/B.\text{pre}} - T_{C.\text{pre}}\right) = \\ &= \left(T_{A/B.\text{post}} - T_{A/B.\text{pre}}\right) - \\ &= \left(T_{C.\text{post}} - T_{C.\text{pre}}\right) \end{aligned} \tag{2}$$

This equation is used for statistical evaluation. However, Figs. 3 and 4 show the absolute values $T_{A/B,\text{pre,post}}$.

The data presented in Figs. 3 and 4 are the average of all subjects in the corresponding group. Hence significant changes can only be seen in some areas of the applied movements, which are marked by thick lines. Due to measurement noise the significant areas are additionally reduced.

Results for group A

In group A RPMS applied on the triceps muscle tended to result in a *decrease* (p<0.1) of the stabilization of the elbow joint, as can be seen in Fig. 3.

Results for group B

In group B RPMS applied on the biceps muscle tended to result in an *increase* (p<0.1) of the stabilization of the elbow joint, as can be seen in Fig. 4. Concerning the only

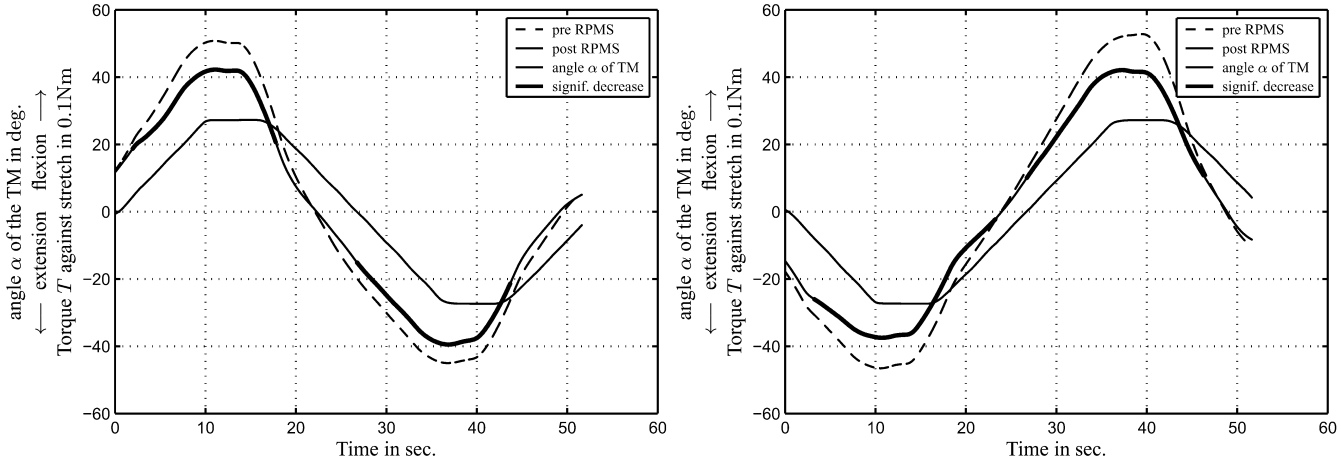

Fig. 3 Decrease (p<0.1) in the stabilization of the elbow joint for group A vs group C (triceps RPMS vs no RPMS; *left* cycle a, *right* cycle b); the *dashed line* represents the torque before the RPMS application whereas the *medium solid line* represents the torque 30 min after RPMS; the *thick line* depicts the area of statistically relevant decrease in comparison to the reference group; the *fine solid line* describes the position of the forearm

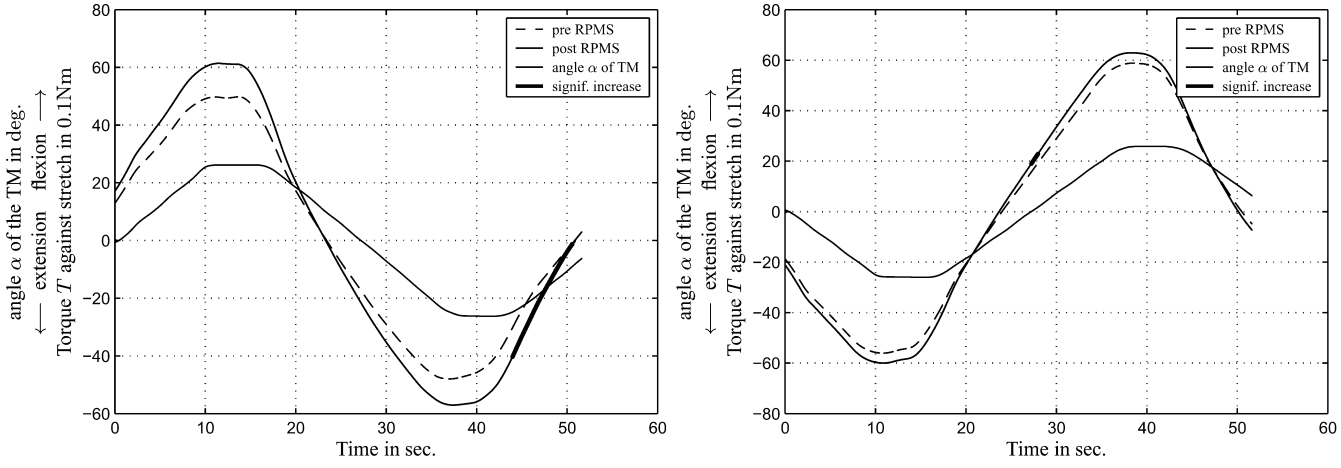

Fig. 4 Increase (p<0.1) in the stabilization of the elbow joint for group B vs group C (biceps RPMS vs no RPMS; *left* cycle a, *right* cycle b); the *dashed line* represents the torque before the RPMS application whereas the *medium solid line* represents the torque 30 min after RPMS; the *thick line* depicts the area of statistically relevant increase in comparison to the reference group; the *fine solid line* describes the position of the forearm

obvious small difference between the control group and the conditioned group, the different muscle masses and the completely different representation in motor tasks between biceps and triceps have to be considered.

Comparison of groups A and B

However, if the conditioned groups are directly compared, the difference between biceps and triceps results in a broad area of a significant ($p<0.05$) decrease of resistance against slow movements, which is depicted in Fig. 5. *This means that the stabilization of the elbow joint is significantly lower after the conditioning RPMS is applied to the triceps than to the biceps.* All statistical proofs were done by the Institute of Statistics in Medicine and Epidemiology (TUM). The analysis was performed using a general linear model with repeated measurements and a between-subjects factor. An interaction term was included.

Electromyogram

In Fig. 6 the ratio of the mean EMG before and after the conditioning stimulation can be seen together with the standard deviation. For an assessment of this figure it

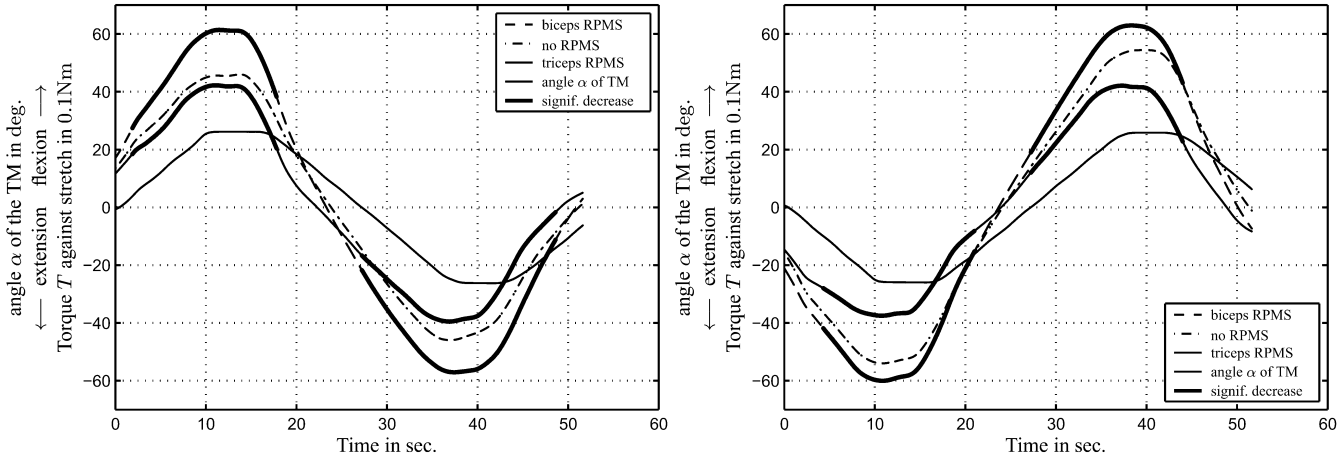

Fig. 5 Significant decrease ($p<0.05$) in the stabilization of the elbow joint after RPMS performed on the triceps in comparison to the stabilization of the elbow joint after RPMS performed to the biceps; *left* cycle a, *right* cycle b; the *dashed line* represents the torque 30 min after RPMS on the biceps whereas the *medium solid line* represents the torque 30 min after RPMS on the triceps; the *thick line* depicts the area of significant decrease; the *fine solid line* describes the position of the forearm; the *dashed-dotted line* corresponds to the reference group with no RPMS intervention

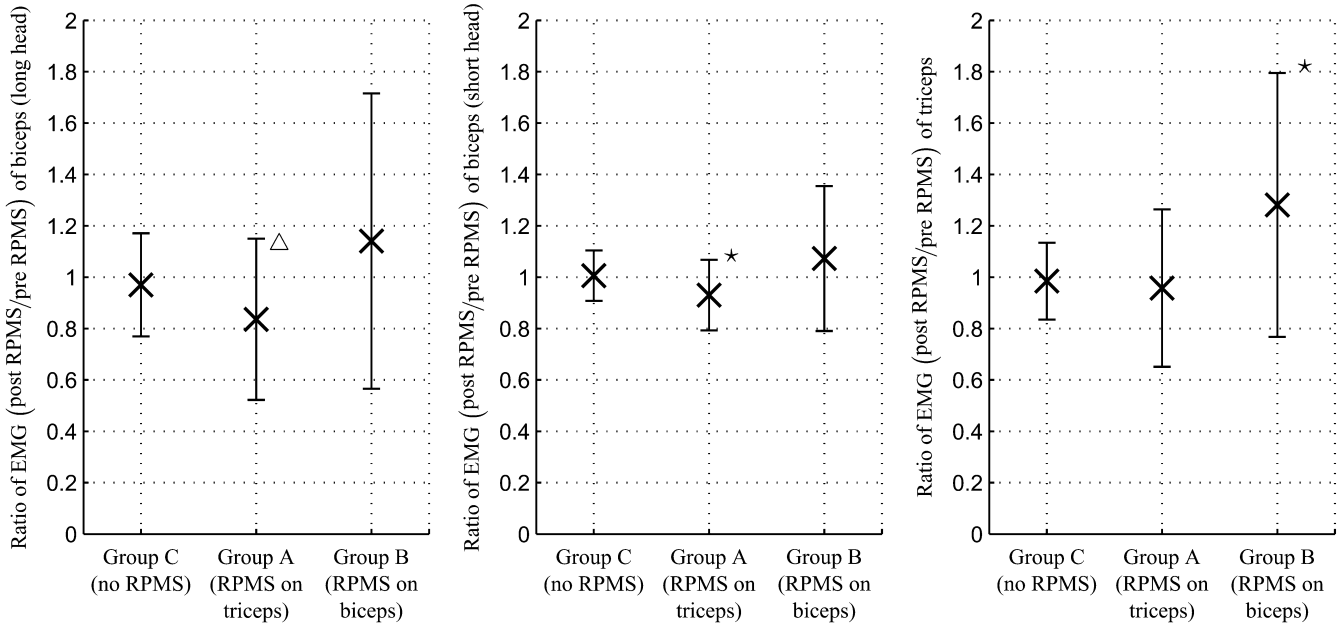

Fig. 6 Ratio of the EMG between pre-RPMS and post-RPMS (*1* no change, *>1* increase, *<1* decrease); together with the standard deviation; the significant ($p<0.05$) changes between groups A and B in comparison to the reference group are marked with an *asterisk,* whereas tendencies ($p<0.1$) are marked with a *triangle;* the comparison between groups A and B always shows a significant ($p<0.05$) decrease in the EMG after RPMS applied to the triceps in contrast to RPMS applied to the biceps

needs to be considered that the EMG under relaxation is really low, since only a few small motor units are activated and only the superficial ones are recorded. To obtain more accurate results, the movement schemes cycle a and b are put together and the EMG activity is averaged over the complete movement cycle. Hence the results of the EMG are only complementary to the torque and should satisfy that the changes in the torque are based on neuronal activity.

The results of the EMG correspond with the measured torque since an increase in the stiffness after RPMS performed on the biceps (group B) shows a higher activity in the biceps and triceps muscles in comparison to the control group (group C). This means that the balance in the elbow joint is raised to a higher level on stiffness, which increases the torque against extension and flexion but leaves the relaxed position unchanged. On the other hand, RPMS performed on the triceps (group A) shows a lower activity in the biceps and triceps together with a decrease in stiffness around the elbow joint.

Discussion

The role of RPMS on skeletal muscle tone regarding stiffness and tonic activity around the elbow joint has been investigated during slow alternating passive movements under relaxed state conditions in 13 healthy subjects. RPMS performed on the biceps (flexor muscles) increased the stiffness and EMG in comparison to the control group, whereas RPMS applied to the triceps (extensor muscles) caused a decrease in comparison to the control group. Depending on the location of the conditioning RPMS, the muscle tone changed in the same way in the agonists and the antagonists. This influence of the conditioning RPMS outlasted the displacement at least 8 s. These 8 s correspond to the break during the movement cycles as can be seen in Fig. 2. This means that there is no reciprocal effect as under dynamic passive or active movements.

To interpret these results it has to be considered that the imposed passive alternating movements around the elbow joint were performed very slowly (2.5°/s) and in an almost relaxed state. To gain a more detailed insight into the modulatory mechanism of RPMS, different effects dependent on RPMS need to be distinguished: *Skeletal muscle intrinsic factors* (like viscosity and elasticity) can be modified directly via induced repetitive contraction and relaxation of the underlying skeletal muscle fibers. Due to the opposite conditioning effect, muscle intrinsic factors are not capable of explaining such behavior since muscle intrinsic factors for the biceps and the triceps are influenced in the same way by RPMS. Therefore the stiffness can be excluded from the stabilization of the elbow joint (resistance against very slow movements) while the effects which depend on neuronal activity (skeletal muscle tone) must be taken into account. This is also shown by the EMG since the changes in activity of the biceps and triceps muscles are in the same direction.

It is assumed that under optimal voluntary relaxation there is just a small tonic activity of S-units (Petit et al. 1990). However, the EMG recordings cannot be distinguished between the three basic types of muscle units in mammalian limb muscles. The basic types are fast twitch fatigable (FF) units, fast twitch fatigue resistant (FR) units and slow (S) units which are resistant to fatigue (Burke 1999).

On a receptor level the repetitive induced movements might modify the thixotropic behavior of receptor-bearing intrafusal muscle fibers due to aftereffects of repetitive stretch and/or contractions (Hagbarth et al. 1995; Jahnke et al. 1989). Since the conditioning effect is long lasting and independent of intermediate movements, it seems that neuromodulation on a CNS (intraneuronal) level must be involved.

Since direct effects on the underlying muscle seem to be excluded by the data, effects on neural commands should be considered: The proprioceptive inflow has modifying effects on spinal, supraspinal and cortical level as described in the "Introduction." Due to the mechanism of action of the RPMS, it is assumed that the proprioceptive inflow originates in the fiber groups Ia, Ib and II and not in the receptors lying in the skin.

The group Ia fibers with their dynamic and static components take the well-known reciprocal facilitatory and inhibitory effect in antagonistic muscles on a spinal level. Hence the Ia fibers are not capable of explaining the non-reciprocal modulatory effect in the antagonistic muscles.

It seems unlikely that the Ib afferents play a role with their negative feedback (control of muscle tension via the homonymous and synergistic motoneurons due to inhibitory Ib interneurons). Their activation via descending tracts follows a greater development of muscle tension. Furthermore, the inhibitory effect of group Ib afferents will be activated by a descending drive when the muscle tension increases (Ib: Interneuronal System; Jankowska and Lundberg 1981). In addition, the antidrome activation of the Renshaw feedback under relaxation is not likely, because this negative feedback is only effective under the activation via descending tracts, as in group Ib.

Recently there has been increasing attention on the function of the group II afferents in sensorimotor integration. Prochazka has shown that group II afferents follow muscle length changes even more clearly than Ia afferents especially during imposed movements (Prochazka and Gorassini 1998; Prochazka et al. 2002).

Furthermore muscle spindle secondaries provide strong input to γ-motoneurons (γ-MN) in the lower extremity. Gladden and Jankowska (1998) show that group II afferents of one muscle can excite γ-MN of the same muscle, which means a positive feedback loop. Experiments using natural stimuli (muscle stretch and vibration) to excite γ-MN indicate that secondary afferents are the main source of input for these neurons. The positive feedback between muscle spindle secondaries and γ-MN can be modulated directly and indirectly via intermediate zone interneurons (Jankowska and Gladden 1999).

Supposing that these findings in the lower extremity are also valid for the upper extremity, it can be assumed that the positive feedback between group II muscle spindle afferents and γ-MN could act as an enhancement of effects of the RPMS at the spinal level.

The positive feedback between secondary endings and homonymous γ-MN would increase muscle tone by increasing the feedback from primary and secondary endings directly to α-motoneurons, and indirectly through group II interneurons.

However, the modulatory effect need not be confined to the spinal pathways—the conditioning RPMS may have changed the descending control of the interneurons from supraspinal and/or cortical level. The presented data suggest that agonistic and antagonistic muscular afferent inputs may evoke facilitation of both muscles or inhibition of both muscles at the cortical level.

To investigate whether the long-latency component of the human stretch reflex (LLSR) corresponds to the increase in motor cortical activity, the time course of the cortical excitability state following muscle stretch during isometric activity (deep finger flexor muscles) was tested using TMS. When the magnetic cortical stimulus was timed to produce an EMG response in the period of the later part of the long-latency stretch reflex, the response was larger than if it was timed to produce a response in the period of the short-latency spinal reflex or when superimposed on the tonic muscle activity used to resist the standing torque of the motor. When the intensity of magnetic cortical stimulation was reduced so that it was just below threshold to produce an EMG response in the short-latency reflex period or in the background tonic EMG activity, it was still capable of producing a response when superimposed on the long-latency stretch reflex. This suggests that inputs from muscle receptors of the stretched muscle contribute to the effect since neuronal afferents from skin, joint and muscle receptors of the hand could be excluded by nerve block (Day et al. 1988). However, if transcortical electrical stimulation (TES) is used, no significant facilitatory effect on the long-latency stretch reflex can be found (Day et al. 1991).

Cheney and Fetz (1984) observe in the monkey that corticospinal cell couples are activated by stretching of the wrist muscles in both the extension and flexion direction and that (transcortical) reflex bursts were seen in both agonistic and antagonistic muscles. They suggested that this could be of importance for the regulation of the stiffness across the ankle joint by eliciting co-contraction of the antagonistic muscles.

To clarify whether muscle afferents influence the excitability of corticospinal projections to antagonist muscles, the excitability of the right forearm muscles at rest was tested by TMS and electrical brain stimulation by Bertolasi et al. (1998). After nerve stimulation (median and radial nerve) the corticomotoneuronal connections to the right forearm at rest were tested. These authors propose that activation of median nerve muscle afferents can suppress the excitability of cortical areas controlling the antagonist forearm extensor muscles acting on the hand (Bertolasi et al. 1998). The inhibitory effect occurs at short latency and might assist spinal pathways mediating reciprocal inhibition by contrasting the coactivation of antagonistic pools of corticospinal cells.

The aim of the study by Lewis and Byblow (2001) was to investigate modulations in corticomotor excitability during passive rhythmic movement, in order to elaborate the level of the neuroaxis at which such changes are mediated. TMS is delivered to cortical areas representing the flexor carpi radialis muscle during different phases of passive rhythmic flexion/extension movements of the contralateral wrist joint. The results of the static trials provide evidence that corticomotoneuronal excitability of the flexor carpi radialis muscle is altered by changes in the wrist joint angle. When the wrist is in a flexioned posture, the response amplitude is higher than if the wrist joint is in extended postures. This may reflect a reduction in static spindle receptor output at the shortened muscle lengths (Carson et al. 2000).

The aim of the experiments presented by Stinear and Byblow (2002) was to examine the regulation of inhibitory mechanism in human primary motor cortex during different patterns of rhythmical bimanual movements. Flexor carpi radialis and extensor carpi radialis corticomotor pathway as well as spinal pathway excitability were examined during synchronous and asynchronous bimanual wrist flexion/extension under active and passive conditions. The results of these experiments indicate that modulation of inhibitory activity takes place at the cortical level.

Aimonetti and Nielsen (2001) investigated how the transcortical reflexes are integrated into the central motor commands at a cortical level during contraction of either the wrist extensor or flexor muscles. The effects of homonymous and antagonist nerve stimulation on the intracortical inhibition and facilitation in the cortical areas that control the wrist extensor and flexor radialis muscles were tested by double pulse TMS.

It is suggested that the observed effects do not reflect activation of a simple reflex system, where the sensory input is relatively closely linked to the output. In both flexor and extensor muscles, antagonist nerve stimulation 40 ms before the test double pulse TMS decreased intracortical inhibition and increased intracortical facilitation. In contrast, homonymous nerve stimulation has no effect on intracortical inhibition and increased intracortical facilitation.

Conclusion

Concerning the functional relevance of the elbow joint stabilization, it has to be considered that forearm flexor and extensor muscles are facilitated or inhibited concomitantly depending on the location of the conditioning RPMS. This means that RPMS modulates the stabilization of the elbow joint most likely at a cortical level, corresponding adequately to the planned motor tasks:

– Preceding motor tasks such as manipulation, pointing, grasping (postural component in forearm and shoulder), a stabilization of the elbow joint is necessary.
– Preceding goal-directed movements (kinetic component), the stabilization of the joint has to be decreased in order to facilitate the movements.

Increased stabilization may also ameliorate the spatial cognition of the limb due to increased proprioceptive afferent inflow especially from the group II afferents, which are responsible for the tonic component.

Future work

To investigate whether the modulatory effect (facilitation or inhibition respectively) takes place at a cortical level, the conditioning influence of RPMS on the MEP elicited by double pulse TMS needs to be examined.

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A fronto-parietal network is mediating improvement of motor function related to repetitive peripheral magnetic stimulation: A PET-H_2O^{15} study

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Repetitive peripheral magnetic stimulation (RPMS) is a focused and painless stimulation method, in which muscle contractions are elicited by depolarization of the terminal motor branches. Clinical–experimental investigations on different disorders of sensorimotor integration in the last decade have shown that RPMS can be used for the rehabilitation of motor functions after stroke. It is supposed that this therapeutic effect is based on the RPMS-induced proprioceptive inflow to the CNS. To analyze the conditioning effects of RPMS on reorganization of the motor system on cortical level positron emission tomography (PET) is used. Regional cerebral blood flow (rCBF) has been measured using H_2O^{15}-PET in eight patients with arm paresis following focal cerebral ischemic infarction before and after treatment using RPMS on upper arm flexor muscles. Behavioral measures showed a significant improvement of kinematics of finger movements and a reduction of spasticity in the affected arm following RPMS treatment. The recovery was associated with significant increase of neural activation within the superior posterior parietal lobe and the premotor cortex (PM) areas. The increase of activation of the parieto-premotor network following RPMS treatment indicates a significant conditioning effect of RPMS on the cortical level. These results emphasize the positive therapeutic effect of RPMS and describe the physiological bases of its function on the central level.

Introduction

In central paresis morphological and functional investigations revealed that even in adults the sensorimotor cortex retains a great capability to adapt to altered afferent input (Merzenich et al., 1983; Sanes et al., 1990; Brasil-Neto et al., 1992; Sadato et al., 1995; Ziemann et al., 1998a,b). The cortical representations of the limbs are not static or fixed in structure, but are subject to a permanent, dynamic balance in an extended, redundant and overlapping network of neuronal circuits (Liepert and Weiller, 1999; Cramer and Basting, 2000). Even the mature brain is capable of considerable, partly also structural modifications (Bütefisch et al., 2003; Johansen-Berg et al., 2002; Pineiro et al., 2002; Carey et al., 2002; Stefan et al., 2000; Weiller and Rijntjes, 1999; Dettmers et al., 1996).

Cortical reorganization probably forms one of the bases for relearning lost motor functions after brain injury. The deficit in proprioceptive input has a negative effect on the motor recovery after stroke (Fries et al., 1993; Binkofski et al., 1996). Therefore one of the crucial mechanisms for the induction of a beneficial reorganization seems to be the compensation of the lost (reduced) proprioceptive input (Binkofski et al., 1996). There is increasing evidence for the importance of the afferent especially the proprioceptive somatosensory inflow for the somatosensory control. Peripheral afferents due to passive movements or electrostimulation elicit a conditioning effect on the excitability of the primary motor cortex (tested by MEP evaluation). This is shown for single stimuli (Chen et al., 1999) and for continuous stimulation over 2 h (Ridding et al., 2000, 2001; Conforto et al., 2002; Kaelin-Lang et al., 2002; Khaslavskaia et al., 2002).

Apart from these electrophysiological results the regional cerebral blood flow (rCBF) has also been investigated during long lasting passive wrist movements which elicit a higher activation of the contralateral primary motor cortex, although the increase in activation was significantly higher when the movements were performed voluntarily (active) (Lotze et al., 2003). Also, the cortical representation of the activated proprioceptive afferents was

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analyzed by neuroimaging methods. For example, the different cortical representation of active and passive finger movements (Mima et al., 1999), the activation of different subareas of the primary sensory cortex (S1) by different sensory stimuli (Bodegård et al., 2000), central effect of vibratory stimulation (Cordo et al., 1995; Naito et al., 1999) and the different central representation of proprioceptive and cutaneous cortical inflow (Narici et al., 1989; Rausch et al., 1998) have been demonstrated. All these studies show that the activation of the primary somatosensory cortex can be substantially activated by proprioceptive afferents. In the recent years a new focused and painless method of repetitive peripheral magnetic stimulation (RPMS) has been developed for treatment of motor deficits after stroke (Struppler et al., 1996). Hereby the muscle contractions are elicited by depolarization of the terminal motor branches. Since RPMS is activating mostly proprioceptive afferents, the primary effects of RPMS at the central level should be caused by the representation of this proprioceptive inflow to the CNS. We hypothesize that one major effect of RPMS in the treatment of motor deficits is the reorganization of central motor representations of movements that is brought about by the massive proprioceptive input provided by this new technique.

Currently, some physiotherapy schemes aim to achieve positive therapeutic effects through externally applied passive movements (Bobath, 1990). When the lost movements are induced by muscle stimulation, the associated proprioceptive input is much higher and corresponds closer to the lost voluntary action patterns. In this context the functional electrical stimulation (fES) is a well-known method to induce movements by muscle stimulation (e.g. Crago et al., 1991; Gollee et al., 2001). However, the fES not only activates somatosensory nerve fibers, also cutaneous receptors are activated. The generalized activation of the fiber spectrum caused by fES is an essential drawback of this approach. This is reflected in a critical discussion of the fES in context with the rehabilitation of skilled hand and finger movements (see e.g. Barreca et al., 2003; Platz, 2003; Hesse et al., 2004). In contrast to transcutaneous electrical stimulation, the biologically effective electrical field in RPMS is considerably lower. This avoids activation of cutaneous receptors, like nociceptors. The spatial field distributions are also different in terms of spreading. Since the magnetic field is marginally influenced by human tissue and the induced current depends upon the ion environment deeper regions of the muscle are penetrated. In contrast, the current caused by electrical stimulation will take the way of lowest resistance, thus being largely limited to the surface (Angerer, 2006). RPMS in the area of the muscle supplying terminal branches elicits a proprioceptive input to the CNS in two different ways:

- Adequate (indirect) activation of mechanoreceptors (fiber groups Ia, Ib, II) during the rhythmic contraction and relaxation as well as vibration of the muscles.
- Inadequate (direct) activation of sensorimotor nerve fibers with an orthodromic and antidromic conduction.

Clinically, this afferent input leads to sensations like movement and vibration, while fibers of the groups III and IV, like nociceptors, as well as mechanoreceptor afferents from the skin may not be activated by RPMS. Our studies performed under normal and pathological conditions showed that the proprioceptive inflow induced by RPMS elicits conditioning effects on various levels of the sensorimotor and cognitive systems: RPMS can effectively SUPPRESS SPASTICITY (Struppler et al., 1996, 2003), has a modulatory effect on POSTURAL COMPONENT OF MOTOR PERFORMANCES like stabilization of the elbow joint under relaxed state (Struppler et al., 2004) and can improve HIGHER SENSORY (INTEGRATIVE) FUNCTIONS like spatial cognition in patients (Kerkhoff et al., 2001; Kerkhoff, 2003). Also, recognition errors of different tactile stimuli could be clearly reduced after RPMS (Heldmann et al., 2000).

The aim of the present study is the investigation of the central reorganization mechanisms involved in the improvement of repetitive finger movements under the treatment with RPMS using positron emission tomography (PET). According to our hypothesis, we expected an increase of activation in the higher motor areas related to reorganization of the central representations of movements following RPMS treatment.

Patients and methods

Patients

Eight right-handed patients (3 women, 5 men; age range 38–70 years; mean 55 years; see Table 1) with spastic paresis (Ashworth scale 3–4) of the upper extremity as a result of cerebral ischemic infarction were chosen for detailed investigation. Additionally, the patients' state allowed for a 4 h lasting PET investigation. All patients had no other antecedent neurological or significant general medical history. Four patients had lesion on the left side and four patients on the right side of the brain (see Table 1).

Table 1
Patient list of the experimental investigation and PET study—demographic data of the eight patients; LS=left side; RS=right side

No.	Patient sex/ age in years	Lesion and time since lesion in month		Symptom Ashworth scale		Somatosensory deficit
1	f/70	Traumatic brain stem lesion (LS)	54	Spastic tetra paresis dominant in RS	4	Yes
2	m/58	Striolenticular ischemic lesion (LS)	6	Hemiparesis (RS) dom. on brachio facial	3	No
3	m/75	Ischemic brain stem lesion pontomedular (LS)	4	Spastic hemiparesis (RS), dom. on lower extremity	4	Yes
4	m/64	Lacunar pons infarction (LS)	3	Spastic hemiparesis (RS), dom. on lower extremity	3	None
5	m/59	Striolenticular ischemic lesion (RS)	5	Spastic hemiparesis (LS)	3	None
6	f/60	Striolenticular ischemic lesion (RS)	12	Spastic hemiparesis (LS) dom. on upper extremity	3	None
7	m/75	Ischemic lesion of dorsal capsula interna (RS)	3	Incomplete hemiparesis (LS), dom. on upper extremity	3	None
8	m/55	Multilacunar (RS)	12	Progradient spastic tetra paresis, dom. on LS	3	Yes

In accordance with the declaration of Helsinki all patients gave their informed written consent to participate in the study after the experimental procedure and radiation effects had been explained. The experiment had the approval of the Ethics Committee of the Faculty of Medicine of the University of Technology Munich and the radiation protection authorities.

Conditioning stimulation—RPMS

In between the PET scanning sessions RPMS was transcutaneously applied to the area of muscle supplying terminal nerve branches of the finger and hand extensor muscles by a conventional stimulation coil (magstim double 70 mm coil) and a self built stimulation device (Schmid et al., 1993). In Fig. 1 the principal stimulation coil position and orientation for the stimulation of the finger and hand extensor muscles are depicted. The best position and orientation of the stimulation coil are adjusted clinically for each patient.

For every conditioning RPMS 5000 single magnetic field impulses at an amplitude of 1.2 T (=12,000 G) and a repetition frequency of 20 Hz were applied (Struppler et al., 2003). After every 30 impulses a break of 4 s was made to induce repetitive contractions and relaxations simultaneously with the sensation of movement and vibration.

Experimental task

To investigate the conditioning effect of the RPMS a simple and reproducible motor task is used. This task consisted of an acoustically triggered goal directed selective index finger extension. Patients are asked to extend the index finger as quickly and as extensively as possible and to hold the index finger in a constant length for a given time (3 s). Because the degree of spasticity (see Table 1) the voluntary intended extension is relatively small although the patients are asked for maximum voluntary extension. After this extension the patients are asked to relax for approximately 3 s. Since the eyes are closed, the finger position is only under proprioceptive control. Hence the motor task includes motivation, attention, planning, programming, intention, execution and proprioceptive control. This paradigm is a modification of a motor task described in previous studies (Bartenstein et al., 1997; Colebatch et al., 1991). This experimental task and the conditioning RPMS are used in a physiological evaluation study and in the presented PET study. The participants (see Table 1) and the basic conditions on both studies are identical. The subdivision is done to keep the duration for each study in a reasonable dimension.

Physiological evaluation

Before and 45 min after the conditioning RPMS each patient executes the experimental task three times with a break of 3 s between the repetitions. During each experimental task the displacement and the velocity of the finger extension are measured with a goniometer. The motor activity is electromyographically recorded. Each three measurements are averaged to get more accurate results. These experiments are described in detail by Struppler et al. (2003).

PET paradigm design

In order to compare the results of the physiological evaluation with the results of the PET study, almost the same experimental protocol is used for the PET study. Therefore twelve PET scans were performed in each patient: six before and six 45 min after the RPMS. During the active scans subjects were asked to perform the experimental task, triggered by a metronome at a pace of 0.3 Hz (B). Each active condition was preceded by a rest condition (A). The sequence of scans in each subject was ABABAB–RPMS–ABABAB. The sound of the metronome could be heard equally during the active and the baseline conditions. Scans were performed with the subjects eyes open in dimmed ambient light.

Three repetitions of each condition (A+B) are necessary in order to achieve robust activation levels. However, because the safety limit of applied radioisotopes was reached by those twelve scans, we could only measure the main effect of stimulation and had no space for a control group (no stimulation or shammed stimulation). This could be done since the preceding clinical evaluation shows no significant changes of kinematics in the control group (Struppler et al., 2003).

PET scanning and image reconstruction

PET measurements were performed using a Siemens 951 R/31 PET scanner (CTI Knoxville/TN, USA) with an axial field of view

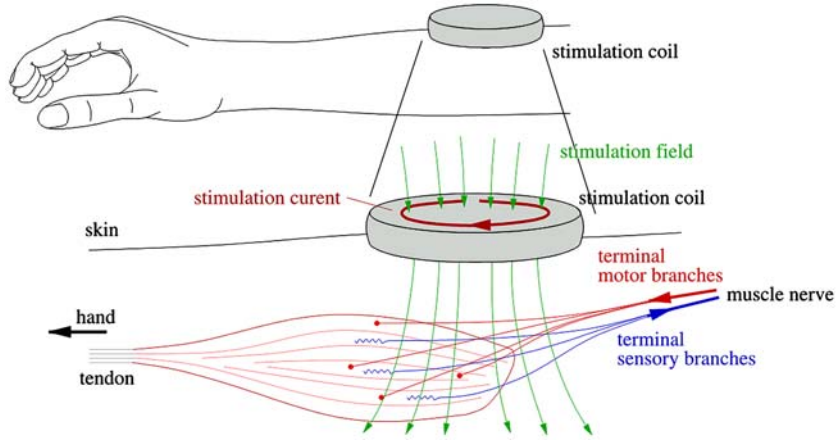

Fig. 1. Principal scheme for the application of the conditioning RPMS (finger and hand extensor muscles).

of 1.5 cm and no interplane dead space under standard resting conditions (eyes open in dimmed ambient light). Attenuation was corrected using a transmission scan with an external 68Ge/68Ga ring source obtained prior to the tracer injection.

A semibolus injection of 7.5 mCi H_2O^{15} was administered intravenously over 35 s using an infusion pump. A dynamic acquisition protocol was performed starting with the infusion followed by a sequence of 8 short-duration frames: first one 15 s frame and second seven 10 s frames, covering a total scan time of 85 s. The motor task started with the beginning of the scan. Following corrections for random, dead time and scatter, images were reconstructed by filtered back-projection with a Hanning filter (cut-off frequency 0.4 cycles/projection element), resulting in 31 slices with a 128×128 pixel matrix (pixel size 2.0 mm) and interplane separation of 3.375 mm. Since time–activity curves of the whole brain showed initial tracer appearance during scan 4 and its maximum between scans 4 and 8 in all subjects, frames 4–8 were added to a single frame consisting of 50 s for further analysis.

Statistical analysis

Determination of areas showing rCBF increase during activation before and after application of RPMS: In the first step a group analysis summarizing the data of all patients in one group was performed (Spiegel et al., 2000). For statistical reasons all lesions of our patients were assigned to the left side. Therefore, scans of patients with lesions on the right side were flipped from right to left. After this procedure all contralesional hemispheres were scattered on the left side (Weiller et al., 1992). Tracer counts were proportionally normalized to the global cerebral activity, which was arbitrarily set to 1000, in order to perform analysis on relative tissue rCBF activity (Fox and Raichle, 1984). An automated program (NEUROSTAT; University of Michigan; SPM-Mich.) was used to coregister, reslice and transform the image arrays into the stereotactic space of Talariach and Tournoux (1988), as described in Minoshima et al. (1993, 1994). To eliminate individual differences in gyral anatomy, these images were further smoothed with a three-dimensional Gaussian filter to give an effective resolution of 18 mm (full width half maximum). Repeated control and activation images were averaged within each subject. Differences between control and activation images were then averaged across subjects and were expressed as voxel-by-voxel *t*-statistic values using a pooled variance estimated from the whole brain gray matter (Worsley et al., 1992). Since the resulting *t*-statistic map, by the method described above, is known to be a good approximation for a standard Gaussian distribution, we described those values as *Z*-scores. In order to determine a threshold for significant activation on resulting *Z*-map, we calculated the image smoothness (Friston et al., 1991) and estimated a statistical threshold at a one-tail (positive) probability of $p=0.05$ using a statistical model which adjusts multiple comparisons and the inherent correlation of neighboring voxels (Montreal threshold). This subtraction analysis between rest and activation condition was performed independently for the scans before and after application of RPMS.

Comparison of rCBF changes before and after RPMS

Additionally, neural activity after and before application of RPMS was compared in order to identify increases or decreases of activation related to RPMS treatment. The comparison of rCBF changes between task and rest after and before RPMS was calculated as follows: the differences of the adjusted error variance were estimated for each group and its mean value was used to compute the *t*-statistics. A one-tailed *t*-test was used and a significance level of 0.01 without correction for multiple comparisons was allowed (Kew et al., 1993). To exclude the detection of small differences in areas where no relevant or only inconsistent activation had occurred, this analysis was restricted to voxels where rCBF increases during activation either before or after application of RPMS achieved a *Z*-score above 1.64 ($p=0.05$, one tail) (Wenzel et al., 1996). To estimate the change in normalized rCBF, the voxel showing maximally different motor task activation was used.

Analysis of rCBF in the single patients

Visual analysis

In order to reduce confounds resulting from the lesion size on the general rCBF an individual analysis of patients scans was performed without stereotactic normalization. For this analysis again tracer counts were proportionally normalized to the global cerebral activity. Coregistration was done using an automated program (NEUROSTAT), but no stereotactic normalization or inversion about the midsagittal plane was performed. Repeated rest and activation images were averaged within each subject. Differences between control and activation images were calculated by a voxel-by-voxel subtraction analysis. The results were visualized creating an MR-overlay for each patient using the individual MRIs.

Quantification of rCBF increases/decreases in the single subjects

To quantify the differences of activation in the single subjects we made an additional region of interest (ROI) analysis using the stereotactically normalized images of each subject. For this automated analysis three-dimensional templates were derived from the significantly activated areas in the first step of the study. So the templates covered those areas where either before or after application of RPMS significant activation occurred. Significance level of 0.001 (not corrected) was used as a cut-off threshold. To estimate the change in normalized rCBF of a single subject, the average of counts within a predetermined area was calculated and the rCBF increase respectively decrease between rest and activation condition was expressed in percent. For statistical analysis we inverted the data of the four patients with the lesion on the right side again and performed a paired *t*-test using data of all patients.

Results

Results of the physiological evaluation

Initially the voluntary finger extension is very disturbed by flexor spasticity and extensor paresis. After one stimulation session the movement amplitude (displacement) and velocity are highly improved, spastic activity (EMG) of the flexors is significantly reduced (Wilcoxon test: $p>0.026$) and the motor task could be performed with less activity in the extensors as can be seen in Fig. 2. These results are described an discussed in detail by Struppler et al. (2003). Because of these physiological results it seems possible that despite the spasticity also the central drive may be modulated

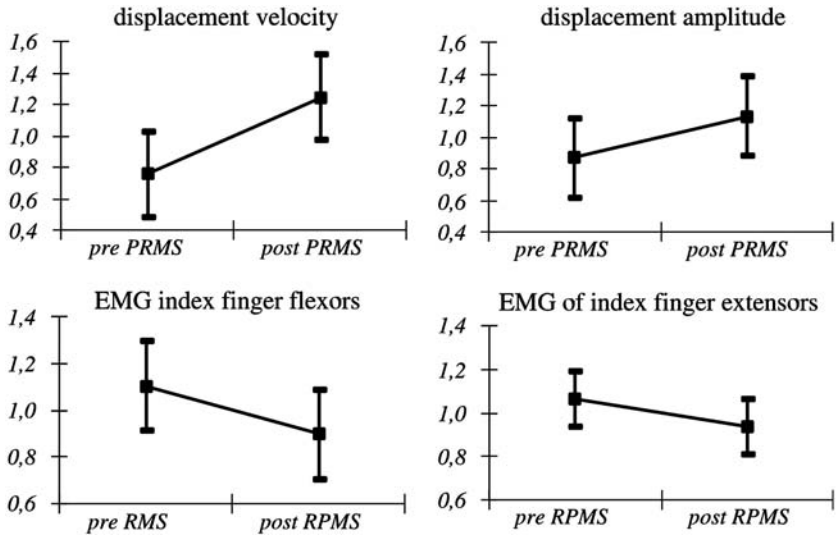

Fig. 2. Conditioning effect measured by means of active finger extensions: mean values and standard deviation of standardized parameter values of 8 patients before (pre) and after (post) conditioning using RPMS (mod. from Struppler et al., 2003).

by the RPMS. To clarify the conditioning effect of the RPMS on cortical level the same patients and the same experimental task are investigated in the presented PET study (see Fig. 2).

PET results

Neural activity due to the specific motor task

The neural activation during the voluntary extension movements of the spastic-paretic index finger (specific motor task) before the application of RPMS was compared to the activation at rest. This comparison shows significant increases of rCBF ($p \leq 0.05$, corrected for multiple comparisons) correlated to the experimental task bilaterally in the primary sensorimotor cortex, in the premotor cortex, in the supplementary motor area (SMA) with adjacent parts of the cingulate gyrus, in the neostriatum, in the cerebellum and in the contralateral parietal cortex, as can be seen in Fig. 3. The areas where the increases reached a *Z*-score above the estimated threshold of 4.64 for $p \leq 0.05$ considering multiple comparisons and the inherent correlation of neighboring voxels are summarized in Table 2.

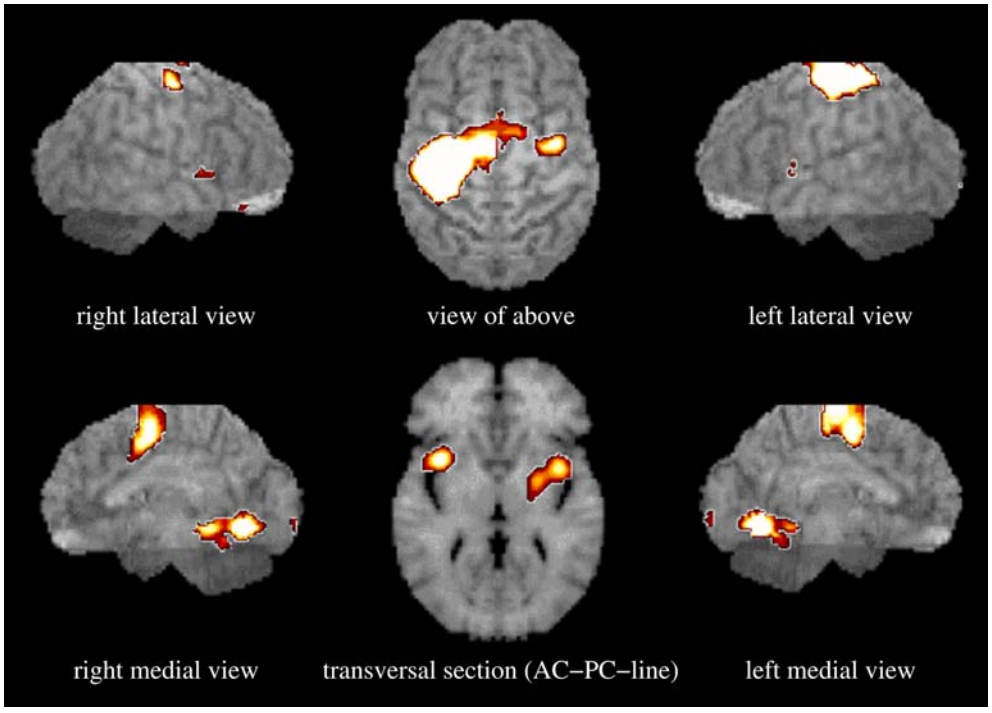

Fig. 3. Neural activation compared to rest *before* the application of RPMS.

Table 2
Areas with significant rCBF increases during the motor task before (upper part) and after (lower part) RPMS

	Area (Brodmann area)	Talairach coordinates			Z-score
		x	y	z	
Increase before RPMS	Left motor cortex (BA 4)	33	−22	54	11.5
	Vermis	1	−62	−7	6.8
	SMA (BA 6)	3	−1	50	6.0
	Right neostriatum/insula	−37	8	2	5.6
	Left premotor cortex (BA 6)	12	−10	63	5.2
	Left neostriatum (insula)	35	5	9	5.2
	Right premotor cortex (BA 6)	−37	8	52	5.1
	Right primary sensorimotor cortex	−53	26	34	3.75
Increase after RPMS	Left motor cortex (BA 4)	30	−22	56	12.5
	Left SMA (BA 6)	6	−8	50	7.3
	Right premotor cortex (BA 6)	−30	−15	54	5.8
	Left primary sensorimotor cortex	44	−24	29	4.2

A Z-score above the estimated threshold of 4.64 for $p \leq 0.05$ considering multiple comparisons and the inherent correlation of neighboring voxels is reached.

When the patients performed the motor task after the application of RPMS (again compared to rest) the primary sensorimotor cortex was activated to the same extent as before RPMS. Also a significant activation of the PM, of the contralateral parietal cortex and of the supplementary motor area with adjacent parts of the cingulate gyrus could be found (see Fig. 4). Table 2 summarizes the areas where the increases reached a Z-score above the estimated threshold of 4.62 for $p \leq 0.05$ considering multiple comparisons and the inherent correlation of neighboring voxels. The difference between the activation patterns before and after RPMS is the lack of significant activation in the neostriatum and in the cerebellum.

Differences in neural activation due to RPMS

As described above there are various areas where an increase of activation due to the performed motor task can be seen independent of the RPMS. Therefore it has to be considered that there is always an increase of activation in the examined areas. To analyze the impact of the conditioning RPMS the difference of the increase before and the increase after the RPMS is evaluated. Hence the general rCBF increase caused by the experimental task can be higher or lower correlated to the conditioning RPMS. This means that in combination with the RPMS only the change of the increase before and after the RPMS can be discussed. This change can be a higher or a lower increase. The comparison of the neural activation before and after the application of RPMS shows a significant higher increase of rCBF in the contralateral premotor cortex, in the contralateral parietal cortex and in the posterior part of the anterior cingulate (motor cingulate). These results are shown in Fig. 5 and summarized in Table 3 together with the corresponding statistical data. A significant lower increase related to RPMS could be found in the contralateral neostriatum, in the thalamus and in the ipsilateral insula as shown in Fig. 6 and described together with the statistical data in Table 3.

Single subject analysis

Visual analysis

The analysis of the individual activation patterns after the coregistration with the individual high resolution structural MRIs showed that after application of RPMS a general shift of activation from subcortical to cortical structures could be found in all eight patients as described in Tables 4 and 5.

For illustrative purposes two examples of single patients are shown in Fig. 7 where the first row shows the neural activation due to the motor task before and after RPMS of a patient with the lesion

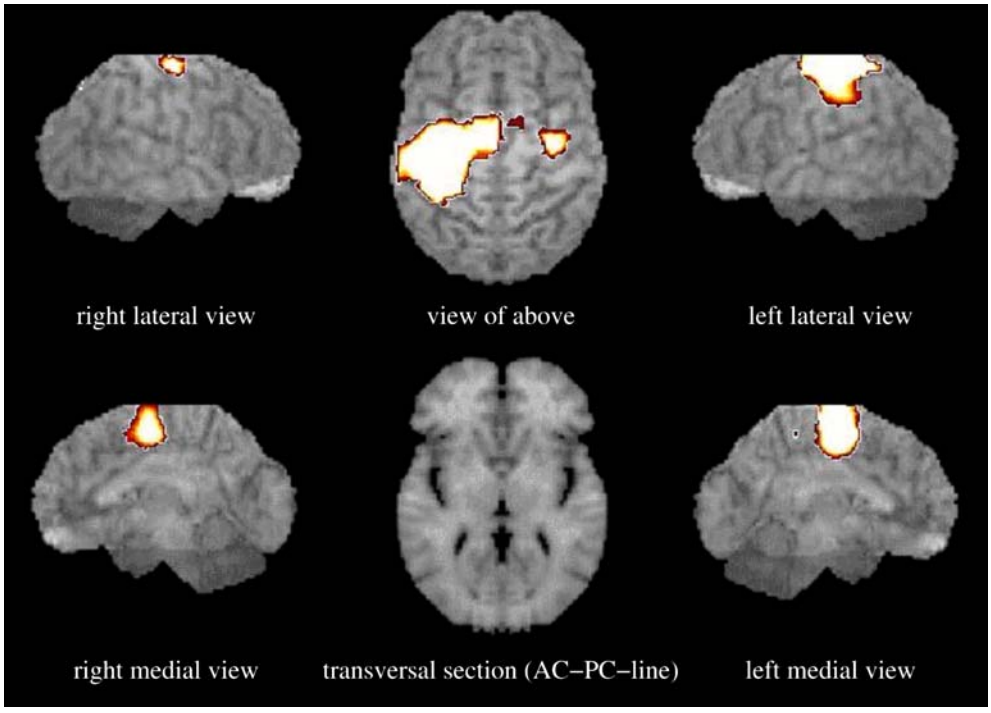

Fig. 4. Neural activation compared to rest *after* the application of RPMS.

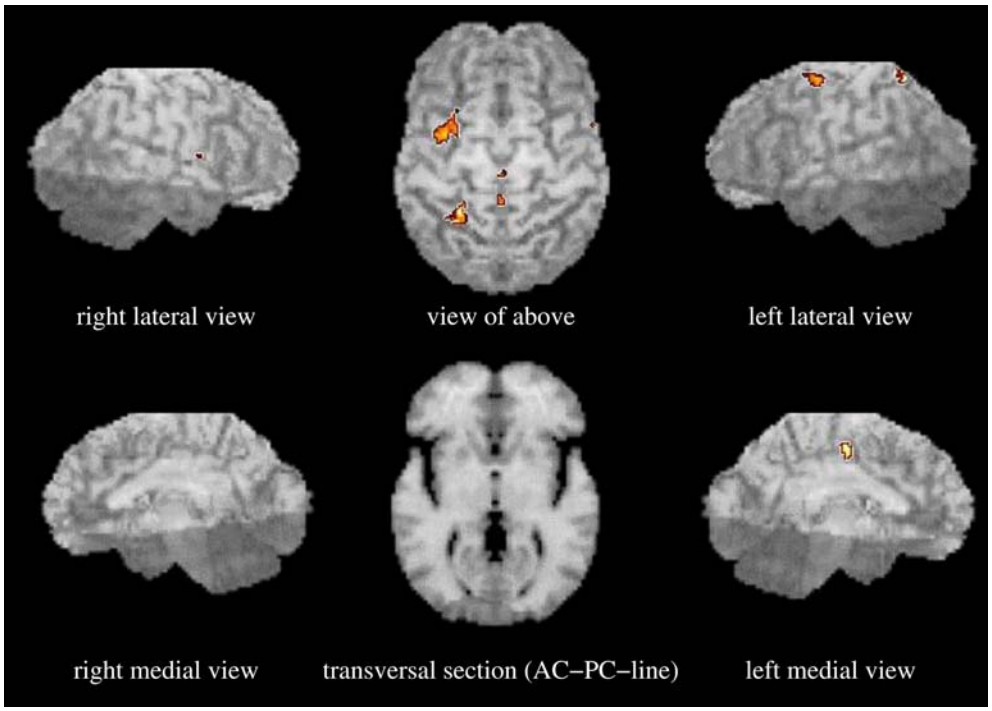

Fig. 5. Significant *higher increase* of the task induced rCBF before (see Fig. 3) and after (see Fig. 4) RPMS. This means a positive difference of differences.

on the right side. The second row shows the shift of neural activation due to RPMS of a patient with the lesion on the left side.

Semiquantitative analysis of the activation pattern within a single subject

Using the additional ROI analysis (region of interest) higher increases of rCBF related to the RPMS could be found in all patients. Significant higher increases could be found in the ipsilateral sensorimotor cortex and in the cingulum in almost all patients. These results are described in detail in Tables 4 and 5.

A lower increase of the motor task specific rCBF due to RPMS is found in the contralateral striatum and thalamus, ipsilateral in the insula and in the uppermost part of the cerebellum in almost all patients. This means a negative difference of differences which can be seen in Tables 4 and 5.

In the statistical analysis the significance level of $p \leq 0.05$ was reached in the ipsilateral sensorimotor cortex (higher increase), in the motor cingulum (higher increase) and in the vermis (lower increase). Using a threshold of $p \leq 0.01$ a significant higher increase of rCBF related to RPMS could be found in the contralateral premotor and parietal cortex. These results are summarized in Table 6.

Discussion

The aim of the current PET study was to test if the improvement of motor functions after repetitive peripheral magnetic stimulation (RPMS) is caused (at least in part) by plastic changes at the central level, due to proprioceptive inflow from the stimulated finger and hand muscles. The positive and lasting effect of RPMS of arm

Table 3
Areas with significant higher increases (upper part) and significant lower increase (lower part) of the rCBF due to RPMS (see Table 2; difference to differences)

	Area (Brodmann area)	Talairach coordinates			*Z*-score	Level of significance (p)
		x	y	z		
Higher increase due to RPMS	Left premotor cortex (BA 6)	30	−4	43	3.6	0.003
	Right premotor cortex	−24	−17	52	2.3	0.03
	Left sup. post. Parietal lobe (sPPL) (BA 7)	21	−46	50	3.2	0.008
	Left sup. post. Parietal lobe (sPPL) (BA 7)	30	−51	61	2.6	0.02
	Left sup. post. Parietal lobe (sPPL) (BA 7)	26	−51	63	2.3	0.04
	Left anterior cingulate (BA 24)	6	−10	45	3.1	0.009
	Right cingulum (BA 24/31)	−15	−4	36	2.9	0.001
Lower increase due to RPMS	Right cerebellum	−3	−44	−4	3.8	0.002
	Left neostriatum	26	3	0	3.6	0.004
	Left thalamus	15	−19	0	3.4	0.006
	Right putamen	−24	10	11	2.3	0.04
	Right insula	−39	17	4	3.1	0.009
	Right ant. Cingulum (BA 24)	−1	14	27	2.4	0.03

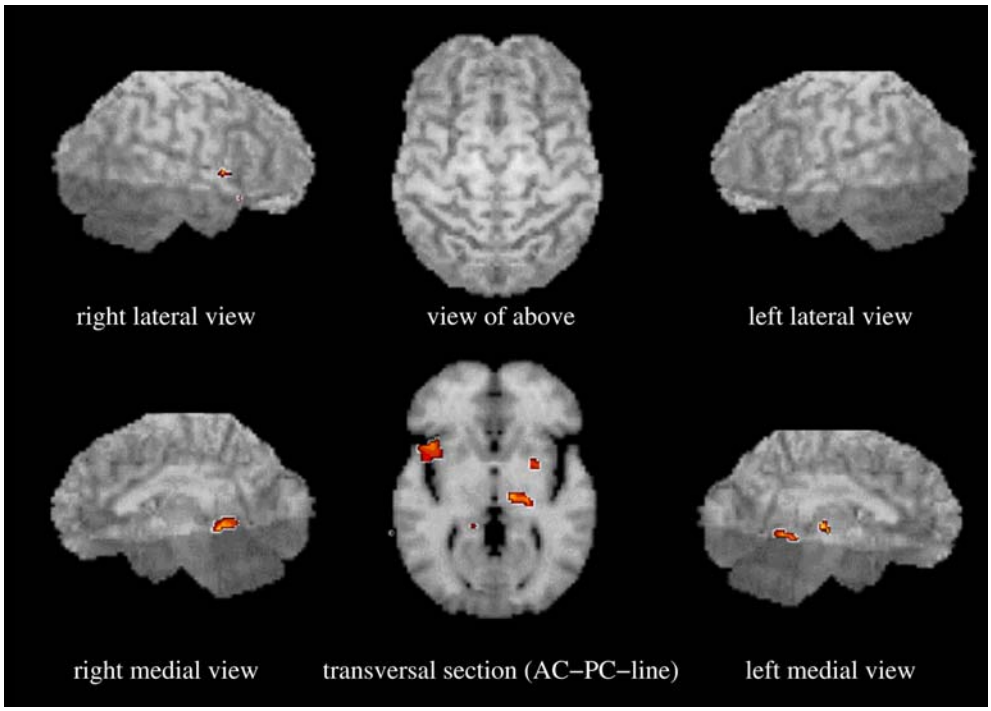

Fig. 6. Significant *lower increase* of the task induced rCBF before (see Fig. 3) and after (see Fig. 4) RPMS. This means a negative difference of differences.

muscles on reduction of spasticity and improvement of hand and finger movements in patients with hemiparesis after stroke has been demonstrated already in previous studies (see Introduction and Struppler et al., 1996).

In confirmation of our hypothesis, the patients' improvement in the motor task (finger extension) was related to an increase of neural activation in the contralateral premotor cortex and the posterior parietal cortex, areas that are known to be functionally tightly interconnected in the higher control of arm and hand movements. An additional increase of activation was also observed in the SMA/CMA complex. Other studies have shown increased activation of the parietal and premotor cortex during different kind of hemiparesis treatments (Seitz et al., 1998; Nelles et al., 1999, 2001; Johansen-Berg et al., 2002), which was correlated with behavior improvement. This is suggesting that RPMS, along with other treatment strategies, is causing adaptive changes in these cortical areas that mediate recovery.

The mechanisms behind the central effects of RPMS

Repetitive peripheral magnetic stimulation (RPMS) applied for rehabilitation of paretic hand and finger muscles stimulates the

Table 4
Changes in % of the motor task depending rCBF increase in four patients with the lesion on the left side: before (*pre*) and after (*post*) RPMS of the left side

	Lesion left	SM 1		PM left	Parietal left	Cingulate	Striatum left	Insula right	Thalamus left	Vermis
		Left	Right							
Pre RPMS	Pat. 1	36.6	5.7	16.2	9.9	17.9	7.8	10.6	4.8	19.7
	Pat. 2	47.6	8.4	18.9	17.3	2.0	11.1	4.8	4.3	24.3
	Pat. 3	56.7	1.7	15.2	20.8	24.7	17.0	8.2	8.6	7.9
	Pat. 4	37.0	4.4	8.9	3.6	−.20	11.2	19.4	3.5	21.0
	Mean	44.48	5.05	14.80	12.90	10.65	11.78	10.75	5.30	18.23
Post RPMS	Pat. 1	36.3	2.5	25.4	12.3	15.9	2.6	8.2	3.1	3.4
	Pat. 2	42.8	12.7	32.9	27.5	13.4	−8.4	3.1	5.5	6.5
	Pat. 3	54.7	9.1	20.7	39.8	26.5	21.6	8.9	−0.8	8.3
	Pat. 4	40.1	13.0	11.8	21.6	14.5	0.4	3.2	−4.8	11.4
	Mean	43.48	9.33	22.70	25.30	17.58	4.05	5.85	0.75	7.40
Dif. of dif.	Pat. 1	−0.3	−3.2	9.2	2.4	−2.0	−5.2	−2.4	−1.7	−16.3
	Pat. 2	−4.8	4.3	14.0	10.2	11.4	−19.5	−1.7	1.2	−17.8
	Pat. 3	−2.0	7.4	5.5	19.0	1.8	4.6	0.7	−9.4	0.4
	Pat. 4	3.1	8.6	2.9	18.0	16.5	−10.8	−16.2	−8.3	−9.6
	Mean	−1.00	4.28	7.90	12.40	6.93	−7.73	−4.90	−4.55	−10.83

The comparison of these increases is called *dif. of dif.*

Table 5
Changes in % of the motor task depending rCBF increase in four patients with the lesion on the right side: before (*pre*) and after (*post*) RPMS of the right side

	Lesion right	SM 1		PM right	Parietal right	Cingulate	Striatum right	Insula left	Thalamus right	Vermis
		Right	Left							
Pre RPMS	Pat. 5	3.4	4.5	5.8	−2.5	4.3	10.3	7.6	5.2	19.8
	Pat. 6	56.7	8.7	30.2	19.1	26.7	5.8	10.6	−2.5	17.1
	Pat. 7	40.4	−4.1	−3.6	12.8	1.4	2.5	9.6	9.3	1.4
	Pat. 8	13.6	7.7	5.0	6.7	12.4	6.0	2.9	9.4	2.0
	Mean	28.53	4.20	9.35	9.03	11.20	6.15	7.68	5.35	10.08
Post RPMS	Pat. 5	16.4	17.4	21.8	3.1	9.2	1.2	7.2	1.9	−1.5
	Pat. 6	44.9	9.6	34.0	24.6	40.4	0.3	7.9	2.3	15.2
	Pat. 7	38.6	4.0	0.6	21.6	12.5	2.7	2.4	−3.8	4.9
	Pat. 8	16.5	6.5	14.1	25.5	16.2	3.1	−6.1	−19.6	−27.4
	Mean	29.10	9.38	17.63	18.70	19.58	1.83	2.85	−4.80	−2.20
Dif. of dif.	Pat. 5	13.0	12.9	16.0	5.6	4.9	−9.1	−0.4	−3.3	−21.3
	Pat. 6	−11.8	0.9	3.8	5.5	13.7	−5.5	−2.7	4.8	−1.9
	Pat. 7	−1.8	8.1	4.2	8.8	11.1	0.2	−7.2	−13.1	3.5
	Pat. 8	2.9	−1.2	9.1	18.8	3.8	−2.9	−9.0	−29.0	−29.4
	Mean	0.57	5.18	8.28	9.68	8.38	−4.33	−4.83	−10.15	−12.28

The comparison of these increases is called *dif. of dif.*

sensorimotor terminal branches of muscle supplying fibers and causes controlled muscle contractions. Hereby the proprioceptive inflow to the CNS is generated in two ways: activation of mechanoreceptors of the stimulated muscles during the induced contraction (adequate, indirect) and via the direct activation of the underlying sensorimotor afferents (inadequate). The afferent inflow to the CNS projects via the fast conducting myelinated nerve fibers primarily to the lemniscal and extra lemniscal systems related to movements of finger and hand. Via thalamus the impulses reach the primary and secondary somatosensory cortex and are processed further in higher associative areas (premotor and parietal areas). Simultaneously to the induced movement, the proprioceptive inflow leads to concomitant perception of movement and vibration. Accordingly, Seitz and Roland (1992) demonstrated that stimulation of the proprioceptive system by application of vibratory stimuli to the right palm of healthy volunteers was associated with increased rCBF in the left primary (S1) and secondary (S2) somatosensory areas, the left anterior posterior parietal cortex, the left primary motor cortex (M1) and the left supplementary motor area (SMA). Further confirmation for the involvement of the

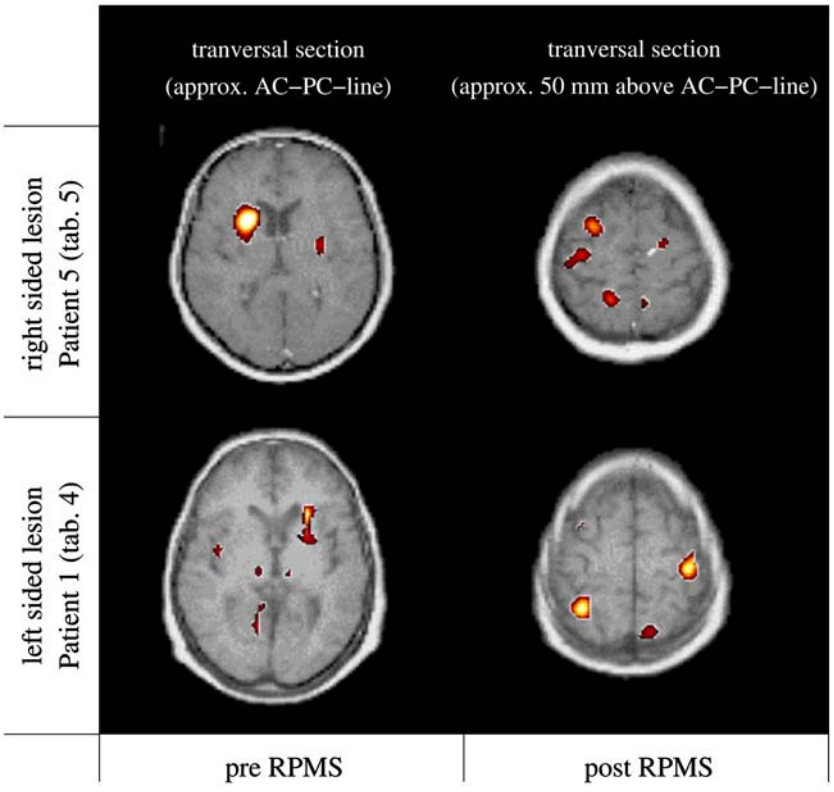

Fig. 7. Example for individual overlay to illustrate the general shift of activation from subcortical to cortical structures due to RPMS (see also Tables 4 and 5).

Table 6
Average changes in % of the motor task depending rCBF increases in all eight patients before (*pre*) and after (*post*) RPMS

8 patients lesion left	SM 1		PM left	Parietal left	Cingulate	Striatum left	Insula right	Thalamus left	Vermis
	Left	Right							
Pre RPMS	36.50	4.63	12.08	10.96	10.93	8.96	9.21	5.33	14.15
Post RPMS	36.29	9.35	20.16	20.75	18.58	2.94	4.35	−2.03	2.60
Dif. of dif.	−0.21	4.72*	8.08**	9.79**	7.65*	−6.02	−4.86	−7.36	−11.55*

The data of the four patients with the infarct on the right side were inverted about the midsagittal plane. Thus in all patients the plegic hand is on the right side. The comparison of the increases before and after RPMS is called *dif. of dif.* Significance level: $*p \leq 0.05$; $**p \leq 0.01$.

sensorimotor areas in the processing of proprioceptive information comes from the study by Radovanovic et al. (2002), who used PET to investigate central structures involved in the perception of passive limb movement and illusory movement generated by muscle tendon vibration. These authors suggested that S2 is involved in stimulus perception generation and that S1/M1 and SMA areas are indeed processing the proprioceptive input. By using a passive and an active index finger movement task to distinguish the involved cortical areas in normal subjects, Mima et al. (1999) could show that performance of active movements was associated with an activation of the contralateral primary sensorimotor cortex, the premotor cortex, the SMA, the bilateral S2, the basal ganglia and the ipsilateral cerebellum. Passive movements activated only the contralateral areas S1 and S2.

The possible mechanisms of reorganization induced by RPMS

Rapid changes in excitability of the motor network representing the thumb could be found after half an hour practice of repetitive thumb movements, as tested by TMS (Classen et al., 1998). Such changes in excitability could also be demonstrated from direct magnetic stimulation of the motor cortex by single stimuli (Chen et al., 1999) and by continuous stimulation over 2 h (Ridding et al., 2000, 2001; Conforto et al., 2002; Kaelin-Lang et al., 2002; Khaslavskaia et al., 2002). Especially, simultaneous paired stimulation of the peripheral nerve and the motor cortex has proven to induce longer lasting plastic changes in the sensorimotor networks (Stefan et al., 2001). Evidence that Hebbian type learning could underlie the phenomena is wide ranging, including the application of in vivo-aminobutyrate (GABA) affecting this "use dependent plasticity" (Ziemann et al., 2001). Also, using TMS in humans, cortical plasticity can be blocked by an *N*-methyl-D-aspartate (NMDA) antagonist, indicating that a kind of long-term potentiation plays a role in human M1 motor learning (Stefan et al., 2002). For pure sensory stimuli, such Hebbian learning phenomena at the central level have been demonstrated by Pleger et al. (2003), who showed plastic changes due to perceptual learning in human primary and secondary somatosensory cortex. Thus, there is growing evidence that the proprioceptive input can induce reorganization and plasticity in the cortical sensorimotor system. There is also evidence from neuroimaging that this reorganization at the central level takes place not only in the primary sensorimotor areas, but also at a higher level of processing.

The nature of the increased activation of the ventral premotor and parietal cortex after RPMS treatment

The task used in our PET study contained acoustically triggered selective index finger extensions with the goal to extend the index finger as quickly and as extensively as possible, to hold at constant length and to relax during a given time. The performance of this task required some higher order proprioceptive control and constant motor attention. Accordingly, an increased activation of not only primary sensorimotor areas, but also of a parieto-premotor circuit and of the SMA/CMA complex could be observed.

In the following section we will discuss the increased activation in more detail. As suggested by Rizzolatti et al. (1998) motor and parietal areas are reciprocally connected and form a series of specialized circuits working in parallel. These circuits transform sensory information into action. Each motor area receives afferents from a specific set of parietal areas. The input from one parietal area is rich ("predominant" input), while that from the other areas is moderate or weak ("additional" inputs). In turn, each parietal area is connected with several motor areas, but has privileged contacts with one only. Parietal and frontal areas linked by a "predominant" connection have similar functional properties, whereas this similarity is not so obvious if one compares the functional properties of areas linked by "additional" connections (Rizzolatti et al., 1998). Such parieto-premotor circuits like the PEc–F2 circuit interact closely with each other during the translation of sensory information in suitable movement patterns this circuit is proposed to process of somatosensory guided movements (Battaglia-Mayer et al., 2003; Rizzolatti et al., 1998; Rizzolatti and Luppino, 2001). In monkey area PEc, which is localized in the caudal part of the superior parietal lobule, somatosensory neurons have been found which were activated by active reaching (Breveglieri et al., 2006). An activation of both areas has been found during performance and imagery of somatosensory guided finger movements in man (Binkofski et al., 2000). A common activity of the dorsal premotor cortex and superior parietal cortex have been described by several authors for functions like pointing and grasping, but also for coding of attention and motion direction (Grafton et al., 1996; Astafiev et al., 2003).

The activation of SMA/CMA complex can be explained by the repetitive manner of the task used in our study (Stephan et al., 1999). The lower SMA and the adjacent CMA share a great anatomical similarity and are supposed to work tightly together since motor cingulate is tightly connected with the SMA proper (Rizzolatti and Luppino, 2001). Both structures seem to constitute a functional unit (Stephan et al., 1999), therefore the description SMA/CAM complex is used throughout this paper. SMA proper has significant anatomical connections with the parietal area PEc (Rizzolatti and Luppino, 2001), which was described above and has significant connections with the premotor area F2 (Rizzolatti et al., 1998; Rizzolatti and Luppino, 2001). Increased activation in all three areas due to successful RPMS treatment of motor deficits after stroke is therefore based on improved activation in a physiological network. This network is also involved in processing

parameters of successful sensorimotor control of the task under normal circumstances. The increase of activity in higher order premotor and parietal areas in the course of treatment of hemiparesis seems not to be specific for RPMS. It could be demonstrated that improvement of hemiparesis after arm training, based on task oriented passive arm movements, was also associated with an increase in rCBF in the parieto-premotor network (Nelles et al., 2001). In a group of seven chronic stroke patients receiving constraint induced therapy for hand function (Johansen-Berg et al., 2002) quantified neural changes associated with behavioral improvement have been demonstrated by using fMRI. The results showed that the extent of improvements in hand function correlated with increases in fMRI activity in the premotor cortex, the S2 contralateral to the affected hand and in the superior posterior regions of the cerebellar hemisphere bilaterally.

Also SMA and cingulate play a crucial role in the early phase of good motor recovery after stroke (Carey et al., 2006). The influence of these areas is decreasing in the later course of recovery. Further good motor recovery is reported to correlate with decrease in activity over time in the primary motor cortex, PMC, SMA and cingulate (Ward et al., 2003) consistent with the reduction in SMA (and PMC) activation described in the study of Carey et al. (2006) in patients with initial moderate impairment.

Thus, the behavioral improvement induced by our therapy does not seem to be related to the brain activity changes which occur with spontaneous functional recovery. This increased activity rather suggests adaptive reorganization mediating recovery. The massive proprioceptive input to the sensorimotor cortical system that is provided by different kinds of therapeutic interventions (among others RPMS) obviously seems to trigger such a reorganization. In summary, we could demonstrate that the improvement of motor functions after RPMS is associated with a reorganization process at a cortical level. We suggest therefore that the massive proprioceptive inflow caused by RPMS is re-establishing activity in areas physiologically responsible for coordination of the motor task, which work together in a network.

Interestingly, a concomitant decrease of activation in subcortical structures (contralateral in the thalamus and in the basal ganglia) could be observed after RPMS treatment. It is therefore possible that before treatment the task involved alternative structures, which allowed for some level of suboptimal processing, and that RPMS treatment was able to "shift" the mode of processing from the subcortical to the more effective cortical level. An alternative explanation for this finding could be that before treatment a kind of unselective over-activity was present, which vanished after good improvement of function.

According to a study on goal directed motor tasks (proprioceptive and visual controlled tracking movements) there is evidence that RPMS also improves the efficiency in course control of such movements (asynergy, dysmetry). In this context not only cortical circuits but also cerebro-cerebellar systems have to be taken into account since cerebro-cerebellar systems are involved in maintenance and optimization of a motor program. Therefore the input to the cerebro-cerebellar systems includes proprioceptive afferents as well as a copy of the motor related cortical efferents, while the processed results are projected to the motor related cortical areas. Together, this builds the well known cortico-cerebello-thalamo-cortical loop. In conjunction with the RPMS, we conclude that the induced proprioceptive afferents also improves the function of the motor related cortico-subcortial circuits, which means that RPMS might be able to restore deranged motor programs. Therefore the aim of a further PET study would be to investigate the representation of the RPMS-induced afferents on cerebellar level.

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