Dissociation of Motor Task-Induced Cortical Excitability and Pain Perception Changes in Healthy Volunteers

Citation
Volz, Magdalena S., Mariana Mendonca, Fernando S. Pinheiro, Huashun Cui, Marcus Santana, and Felipe Fregni. 2012. Dissociation of motor task-induced cortical excitability and pain perception changes in healthy volunteers. PLoS ONE 7(3): e34273.

Published Version
doi:10.1371/journal.pone.0034273

Permanent link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:10341922

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
Dissociation of Motor Task-Induced Cortical Excitability and Pain Perception Changes in Healthy Volunteers

Magdalena S. Volz1,2, Mariana Mendonca1, Fernando S. Pinheiro1, Huashun Cui1, Marcus Santana1, Felipe Fregni1*
1 Laboratory of Neuromodulation, Department of Physical Medicine & Rehabilitation, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, 2 Charité Center for Neurology, Neurosurgery and Psychiatry, Campus Charité Mitte, Charité - Universitätsmedizin Berlin, Berlin, Germany

Abstract

Background: There is evidence that interventions aiming at modulation of the motor cortex activity lead to pain reduction. In order to understand further the role of the motor cortex on pain modulation, we aimed to compare the behavioral (pressure pain threshold) and neurophysiological effects (transcranial magnetic stimulation (TMS) induced cortical excitability) across three different motor tasks.

Methodology/Principal Findings: Fifteen healthy male subjects were enrolled in this randomized, controlled, blinded, cross-over designed study. Three different tasks were tested including motor learning with and without visual feedback, and simple hand movements. Cortical excitability was assessed using single and paired-pulse TMS measures such as resting motor threshold (RMT), motor-evoked potential (MEP), intracortical facilitation (ICF), short intracortical inhibition (SICI), and cortical silent period (CSP). All tasks showed significant reduction in pain perception represented by an increase in pressure pain threshold compared to the control condition (untrained hand). ANOVA indicated a difference among the three tasks regarding motor cortex excitability change. There was a significant increase in motor cortex excitability (as indexed by MEP increase and CSP shortening) for the simple hand movements.

Conclusions/Significance: Although different motor tasks involving motor learning with and without visual feedback and simple hand movements appear to change pain perception similarly, it is likely that the neural mechanisms might not be the same as evidenced by differential effects in motor cortex excitability induced by these tasks. In addition, TMS-indexed motor excitability measures are not likely good markers to index the effects of motor-based tasks on pain perception in healthy subjects as other neural networks besides primary motor cortex might be involved with pain modulation during motor training.

Introduction

Pain is a multidimensional, complex, subjective experience. According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Thus, treatment remains a major challenge for health professionals as its acute and chronic pathogenesis are not completely understood.

Recent evidence has shown that the primary motor cortex (M1) might be a useful therapeutic target for behavioral and non-pharmacological interventions such as invasive and non-invasive brain stimulation [2,3,4,5,6,7]. The initial evidence comes from a previous study showing that deafferentation of the spinothalamic pathway results in hyperactivity of thalamic neurons, which can be inhibited solely by electrical stimulation of the M1 [8]. The idea is that stimulation of M1 can change thalamic excitability through thalamo-cortical pathways [8,9]. There are many factors that may explain these effects. For instance, M1 activation may lead to activation of the GABAergic inhibitory system and the reduction of activity in the thalamus [3]. M1 might be therefore an “entry port” to modulate dysfunctional activity in pain-related neural networks [9,10]. Moreover, activation of M1 and thalamus, which are known to be involved with the organization of movements, may be associated with improvement in motor control, an important factor for the interruption of the maintenance of pain [11,12,13]. In line with this knowledge, recent clinical findings have shown that activation of M1 with neuromodulatory techniques is efficient in reducing suffering in patients with chronic pain [6,7,14,15,16,17]. M1 modulation via non-invasive brain stimulation may decrease thalamic hyperactivity and change neuronal plasticity, and these effects are also conveyed to other pain-related areas such as subthalamic areas, cingulate gyrus and spinal cord [18,19,20].
Other techniques with different methods of activation of M1 may also be useful in pain management. Alteration of cortical excitability occurs during the realization of motor tasks which require some type of motion component. In addition, also motor learning (ML) leads to direct activation of M1 [21,22]. This has been demonstrated by studies involving microstimulation in animals [23,24], imaging exam assessments in humans [25,26] and the evaluation of cortical excitability by non-invasive brain stimulation techniques [27,28].

Although the recent studies on invasive and non-invasive brain stimulation have provided robust data supporting the critical role of motor cortex modulation for pain control, it is not clear whether other behavioral tasks aiming at motor cortex modulation would induce similar effects. Therefore, our study intends to increase our understanding on the role of M1 modulation for the modulation of pain perception by testing the hypothesis that pain perception can be modified with different motor tasks and whether these tasks produce changes in the M1 excitability as assessed by transcranial magnetic stimulation (TMS) in healthy male individuals.

Methods

Study Design

We conducted a blinded (assessor was blinded to subject’s intervention, and subjects were not aware to expected outcomes), randomized (randomization in blocks of 3 with a random list), controlled (right hands as within-individual control), cross-over (every subject completed three interventions in a random order) trial to determine effects of different motor tasks on pressure pain threshold and M1 excitability in healthy male volunteers. This study conformed to the ethical standards of the Declaration of Helsinki and was approved by the local IRB (Spaulding Rehabilitation Hospital, Boston, MA, USA). All participants read and signed written informed consent before initiating any study procedures.

Subjects

Fifteen healthy right-handed male subjects (mean age: 25 years, SD 7.69, range: 19–42 years) were recruited from general population by postings in universities, internet and public places in the Boston area. Interested individuals were screened for eligibility by phone. Subjects were eligible to participate if they fulfilled the following criteria: (1) age between 18–45 years; (2) right-handed; (3) male; (4) no rheumatologic disease; (5) no clinically significant or unstable medical or neuro-psychiatric disorder including chronic pain disorders (as assessed by a clinician); (6) no history of alcohol or substance abuse within the last 6 months; (7) no contraindication to TMS; and (8) no use of central nervous system-effective medication. All study participants provided written, informed consent. All study participants provided written informed consent. Since the menstrual cycle and age play a role in cortical excitability [29,30,31], we only recruited male subjects younger than 45 years of age to control for these effects. Additionally, we only included right-handed subjects in order to avoid motor ceiling effects and to ensure significant learning effects with these tasks as we trained the non-dominant left hand [32,33].

The sample size calculation was based on a study also assessing pain threshold levels in healthy volunteers after targeting M1 excitability [34]. We assumed a type I error of 5%, a type II error of 10%, and a power of 90%, and a mean difference of 8% (±6%) in the active group and a difference of 1% (±1%) in the other groups. Using a sample size calculation for normal distribution, eight volunteers would be necessary. However given attrition rate and other unexpected factors including also the addition of a third comparison group we increased the sample size to total of fifteen subjects.

Experiment

Subjects completed a total of three study visits. There was an interval of at least one day between each visit to avoid carryover effects. Every visit included one of the three different tasks (see below), which were performed with subjects’ left hand, each for 20 minutes. The right hand served as a control as there were no tasks performed with this hand. Participants were randomly assigned to a given order of interventions. Before and after the intervention, pressure pain threshold levels were determined for both hands; thus as mentioned before, the results of the right hand served as the control group for each individual to avoid inter-individual variability. Additionally, the visits included several assessments scales and tasks (see below) as well as TMS measurements before and after the intervention.

Motor Tasks

Participants were requested to perform the following tasks in a randomized and counterbalanced order:

**Motor Learning with Visual Feedback (MLblindfold).** This task consisted of four 5 min blocks of tracing a set of shapes and words, which were shown to subjects on a computer screen. Tracing was performed on an electronic board using an electronic pen with the left hand. To enhance learning, the complexity of shapes and words were increased over time. ML component was measured by comparing the number of completed shapes and words between the first and last block.

**Motor Learning without Visual Feedback (MLblindfold).** Subjects used the left hand to draw different shapes (triangle, square, and pentagon). As subjects were blindfolded, the shapes were marked with pins at each corner to give feedback of where the angles of the shape were located. To enhance learning, the difficulty of shapes was increased over time. ML was measured by counting the total amount of completed shapes comparing the first and last sequence.

**Motor Activation with Simple movements (MA_simple).** Participants were requested to perform sequences of different simple hand movements (opening/closing, pronation/supination, flexion/extension of the wrist, abduction/adduction of fingers). M1 activation and attention were ensured by alteration and increased complexity of movements over time [35,36].

Pain Assessment

Pressure pain thresholds were the primary outcome of this study and assessed with an electronic algometer (J Tech Medical Industries, USA) before and after the intervention for both hands. The device had a 1-cm² hard-rubber probe, which was pressed against the thenar surface of the hand. The investigator, who assessed the pain threshold levels (MSV), was trained to this procedure and blinded to the intervention and not able to view the display of pressure intensities. Subjects sat comfortably in a chair, with arms placed on the arm rest, and instructed to say when the stimulus became painful and to be consistent with notification of painful sensation. This procedure was repeated 3 times.

Transcranial Magnetic Stimulation (TMS)

Only one trained assessor (MSV), who was blinded to the intervention, conducted TMS measurements in all subjects to ensure a homogeneous assessment. TMS measurements (secondary outcome) were performed with a Bistim™ stimulator (Magstim Company LTD, UK) and a commercially available 70 mm
Dissociation of Cortical Excitability and Pain

For TMS data, we performed a mixed ANOVA model in which the dependent variable is the measurement of cortical excitability (RMTs, MEPs, SICIs, ICFs, CSPs) and the independent variables are the tasks (MLsighted, MLblindfold, MAsample) and time (pre, post) for each experiment. Moreover, one-way ANOVAs were performed for change in MEP amplitude/integral over time versus task to reveal differences among the task. When appropriate, post hoc comparisons were carried out using Bonferroni’s correction.

The results of the exploratory GNG before and after the intervention were described in means and SD for amount of errors, omissions and correct answers. Furthermore, we compared differences in errors, omissions and correct answers using two-tailed, paired t-tests for pre-/post-comparison.

Following descriptions of statistical significance refer to a p-value<0.05, and a statistical trend is considered to indicate a p-value<0.1.

Results
No adverse effects were experienced throughout the entire procedure including assessment with single and paired-pulse TMS. Of the 15 subjects enrolled, 14 completed all three visits, thus, one subject dropped out, because of scheduling difficulties. We did not include his data, as he only completed one of three visits as this was a cross-over trial.

Learning effect for the motor learning tasks
Sequences comparison showed significant results for both ML tasks: comparing 1st to 4th block of 5 min (p = 0.0003), 1st to 2nd 5 min (p = 0.0014), 1st to 2nd 5 min (p = 0.0036) and 2nd to 4th 5 min (p = 0.0109) of MLsighted (Figure 1), and comparing first and last sequences of MLblindfold (triangle: p = 0.0250; square: p = 0.0052; pentagon: p = 0.0024) (Figure 2). All participants improved their performance on the tasks sequence over time, which indicates that successful learning had occurred.
Pain threshold across the three motor tasks and both hands (left trained and right untrained control hand)

We initially conducted an ANOVA with two factors (motor task and hand). This analysis showed only an effect for hand (differential effect when comparing left trained vs. right control hand, p = 0.0001). We therefore conducted separated models for each hand. For the left trained hand, there was a similar increase in pain threshold across the three motor tasks. Analyses showed a significant increase in pain threshold of MLblindfold (p = 0.0037, threshold increase of 17.96%), MLsighted (p = 0.0182, threshold increase of 15.85%), and MA simple (p = 0.006, threshold increase of 31.24%). Although the simple task had a larger magnitude increase in pain threshold, this was not statistically significant (p = 0.15) when compared to the other two motor tasks (Figure 3).

We then conducted the same analysis for the control hand (right untrained hand). The results showed that there was no significant change in the control hand for these three tasks (MLblindfold, p = 0.5773, threshold increase of 1.81%; MLsighted, p = 0.9821, threshold increase of 0.13%; MA simple, p = 0.1356, threshold increase of 6.53%) (Figure 4). This indicates that the effects of pain alleviation were side specific and thus induced by the motor tasks.

TMS

ANOVA revealed a significant difference in MEP amplitude change across motor tasks (p = 0.0233), and a trend for change in MEP integral (p = 0.0697). This indicates that there was a difference in M1 excitability changes across the tasks. P-values and means/SD for post-hoc comparisons for all TMS measures are shown in Table 1. Comparing MEP, ICF and CSP before and after the intervention, significant effects could be revealed mainly for MA simple, showing that cortical excitability increases after this task (increase in MEP and CSP shortening). SICI and RMT did not change in all tasks.

Further Assessments

The mean of PP - control task for motor function changes - for the left hand before intervention was 13.51 (SD 1.46), and 13.63 (SD 1.46) afterwards. T-test for pre-/post-comparison did not show significance (p = 0.4112). Similar results were obtained for the right hand (mean-before: 14.33, SD 1.51; mean-after 14.62, SD 1.26; p = 0.09).

No changes in mood, affective and/or cognitive capability were present as indicated by GNG and VAS. The t-test for VAS for anxiety showed no differences (p = 0.84) between pre-/post-comparison. For the GNG, there were no differences in the amount of correct answers (p = 0.95; pre = mean: 27.37; SD 1.98; post = mean: 27.39; SD 1.97), omissions (p = 0.95; pre = mean: 2.61; SD 1.99; post = mean: 2.59; SD 2.09) and errors (p = 0.36; pre = mean: 3.93; SD 1.81; post = mean: 4.24; SD 2.45) between pre-/post-comparison.

Figure 2. Behavioral results of task MLblindfold. Box-and-whisker plots show amount of completed shapes of the first and last sequence of each shape. T = Triangle; S = square; P = Pentagon. * = p<0.05. ** = p<0.01.
doi:10.1371/journal.pone.0034273.g002

Figure 3. Results of pain thresholds: left hand. Pressure pain threshold levels before and after the tasks for the left trained hand. * = p<0.05. ** = p<0.01. *** = p<0.001.
doi:10.1371/journal.pone.0034273.g003

Figure 4. Results of pain thresholds: right hand. Pressure pain threshold levels before and after the tasks for the right untrained control hand. Ns = not significant.
doi:10.1371/journal.pone.0034273.g004
Discussion

In this study, we showed that three different motor tasks increase pressure pain thresholds in healthy volunteers and accordingly might alleviate perception of pain sensations. This effect was specific for the hand being tested as the control hand did not show any significant difference. Interestingly, although the three motor tasks induced similar behavioral pain effects, they induced different changes in motor cortex excitability. This result suggests that motor training induced pain threshold changes may be mediated through different neural mechanisms as it is motor task specific.

Our results confirm the notion that motor learning can modulate pain threshold. Both motor learning tasks confirmed that a significant learning has taken place (behavioral improvement) and we measured a significant increase in pain threshold of 15.85% for ML_{sighted} and 17.96% for ML_{blind} whereas the control condition (untrained hand) showed very small pain threshold increase of 0.15% and 1.81%, respectively. Our findings are in line with other studies, which encourage cognitive effort during motor training in pain rehabilitation [28,41]. Even though, our observations were gained in healthy subjects and may be different in chronic pain patients. In fact EEG- and PET-imaging studies support the beneficial effects of cognitive involvement during execution of complex movements [35,42]. One interesting finding was the result of ML_{blind} condition - as it was also significant and even larger compared to ML_{sighted} (though this difference was not significant). In fact, one possibility that needs to be explored further is whether visual deprivation can enhance the effects of motor learning on pain modulation as visual deprivation can divert attention toward other senses [43,44].

Despite the effects of motor learning on pain threshold, we also found that simple hand movements without a learning component were sufficient to increase pressure pain thresholds. This is in line with previous findings, which showed that motor practice is effective to alleviate pain [11,12,13], even if there is no combined learning or highly cognitive demand [45].

One possible limitation we could not control is that the obtained results could have been caused by peripheral effects. Such possible peripheral effect may be altered muscle activity after the exercise of simple hand movements or changes in blood flow or a different blood oxygenation level, which could have influenced the perception of pain [46,47]. However, since all motor tasks, of which each task activated different muscles and also to a different extent, changed perception of pressure pain and varied in changes of cortico-spinal excitability as measured by TMS, it is less likely that analgesic effects result from peripheral mechanisms.

Also possible limitations due to the cross-over design and potential carryover effects need to be mentioned, as it would be possible that the motor tasks changed M1 plasticity for extended period of time [48]. To avoid these problems, we randomized the sequence of tasks which subjects completed and also designed each motor task differently to avoid carryover effects due to motor learning.

Evidence from previous studies showed that hand movements lead to an increase in cortical excitability indicated by an increase in MEP’s amplitude and integral [45,49,50,51]. Furthermore, Roosink et al. (2010) suggested that a complex task leads to a larger corticospinal excitability increase in comparison with simple task [35,36]. Though in this study, the complex task cannot be compared to our motor learning task.

One result that needs to be further discussed is that MA_{simple} led to larger effects on cortical excitability compared to ML tasks. There are several reasons to explain lack of cortical excitability changes in the ML condition. One reason would be associated with the time course of excitability changes. A recently published study showed that MEP does not further increase even after a retention period of motor training, thus, suggesting that the M1 changes in a dynamic time course due to a motor-driven demand [52]. This could explain why the three motor tasks in our experiments changed cortical excitability differently. Nevertheless, the comparison of changes in cortical excitability between studies investigating the effects of ML or simple movements is limited as studies used different paradigms. Firstly, the duration of task execution has a significant effect on M1 activation as shown by a study of Muellbacher et al. (2001) [53]. In this study significant differences between 30 and 60 minutes could be seen; in contrast, in our study subjects conducted each task for 20 minutes.

Table 1. Results of transcranial magnetic stimulation (TMS) measures.

| Transcranial Magnetic Stimulation Measurement | Motor Tasks | ME_{sighted} | ME_{blind} | MA_{simple} |
|---------------------------------------------|-------------|--------------|------------|-------------|
| MEP Amplitude                               | 1.37 [±0.32] 1.27 [±0.35] | 1.39 [±0.25] 1.4 [±0.28] | * 1.28 [±0.23] 1.49 [±0.35] |
| MEP Integral                                | 11.68 [±3.88] 11.13 [±4.08] | 12.2 [±2.92] 12.67 [±4.12] | * 11.57 [±3.28] 14.13 [±4.95] |
| ICF Amplitude                               | 1.027 [±0.188] 1.037 [±0.205] | 1.013 [±0.179] 1.064 [±0.169] | ^ 0.871 [±0.18] 0.982 [±0.223] |
| ICF Integral                                | 0.977 [±0.178] 1.012 [±0.255] | 0.986 [±0.176] 1.011 [±0.215] | * 0.795 [±0.19] 0.977 [±0.269] |
| SICI Amplitude                              | 0.244 [±0.173] 0.268 [±0.236] | 0.216 [±0.160] 0.211 [±0.146] | 0.316 [±0.168] 0.292 [±0.222] |
| SICI Integral                               | 0.249 [±0.248] 0.186 [±0.212] | 0.211 [±0.141] 0.213 [±0.137] | 0.279 [±0.169] 0.259 [±0.197] |
| CSP 110%                                    | * 90.82 [±21.9] 79.43 [±28.97] | 86.15 [±31.59] 83.33 [±27.36] | * 89.68 [±27.28] 79.18 [±24.54] |
| CSP 120%                                    | 114.99 [±20.1] 108.36 [±26.39] | 117 [±33.18] 109.83 [±34.7] | ^ 116.66 [±27] 107.71 [±29.98] |
| CSP 130%                                    | 137.14 [±19.35] 129.27 [±29.44] | 137.99 [±32.7] 130.96 [±38.43] | * 137.29 [±29.3] 125.11 [±30.81] |

Values before and after the interventions are given as mean [± standard deviation]. MEP amplitude in mV; MEP integral in mV*ms; SICI and ICF in their index; CSP in ms. Student’s t-test for pre/post-comparison. Statistical significance (p<0.05) indicated with asterisk *. Statistical trend (p<0.1) indicated with ‘.’. MEP: motor evoked potential; ICF: intracortical facilitation; SICI: short intracortical inhibition; CSP: cortical silent period; ML: motor learning; MA: motor activation; SD: standard deviation.

doi:10.1371/journal.pone.0034273.t001
Secondly, examining studies that reported increase in MEP due to ML, it shows that tasks involved fast thumb repetitive abduction movements [54], whereas the task in our study might have involved a larger cognitive demand. Indeed, “learning” component is differently defined and goes from “learn” how to move a finger faster to “learn” how to move the hand to reach a certain goal as it was mandatory in our experiments [49,53]. One important aspect here is that our motor learning task might have engaged other neural circuits and in fact the effects of our ML task on pain threshold might be due to the engagement of these other neural networks. For instance, ML in this study might have activated also working memory-related cortical areas. We showed in a previous study that modulation of the dorsolateral prefrontal cortex (DLPFC) leads to an increase in pain threshold in healthy subjects [34]. Thus motor learning tasks might change pain perception through activation of non-motor neural networks as evidenced in this study.

As we show in this study that simple hand movements without a complex cognitive component is effective to modulate pain and change M1 excitability, this finding might be interesting for the field of physical medicine and rehabilitation and the novel rehabilitation techniques with robotics, as some of these techniques use more repetitive movements; however in some cases in a more passive way [55,56]. As passive movements of upper extremities seems to be sufficient to activate M1 and therefore induces changes in cortical plasticity [54], this intervention might also have a significant impact in pain modulation. In fact these results might extend to mental imagery and motor observation. For instance, imagination of amputated arm movements in chronic phantom pain can induce analgesic effects, which further supports our hypothesis and highlights the clinical relevance of the present findings [37,58]. Seidel et al. (2011) showed an average pain reduction of 2.8 in VAS after mirror visual feedback therapy in phantom limb pain. Similarly Mercier et al. (2009) showed a reduction in 38% in pain as indexed by VAS in phantom limb pain patients. [57,58]. Nevertheless, it is important to underscore that the lack of changes in cortical excitability in motor learning task does not imply that simple movements are better than tasks with a learning component to modulate pain. Further studies are needed to investigate and compare the effects of different motor tasks in patients with chronic pain.

None of the tasks reduced SICI significantly, thus, we could not confirm the reduction of SICI as described by Liepert et al. (1990) [50], even though we found a tendency to reduce SICI [51]. A reason for that might be the different design of the tasks as already discussed. Since the task in their study used line motor control of small hand muscles compared to our task involving multiple hand muscles, a broader cortical representation area might have been activated which therefore resulted in different inhibition patterns. Interestingly, the study of Rosenkranz and Rothwell (2006) could also not reproduce a significant reduction of SICI, which is in line with our findings [54]. In contrast, we revealed significant increase in ICF for one of the tasks (MAsimple), which is in line with the concept proposed by Ziemann et al. (1996) that inhibitory and excitatory neuronal circuits likely act independently [59].

Finally, the most prominent changes besides MEP changes occurred in CSP. Overall, there was a common tendency that CSPs with different intensities of 110–130% decreased in all tasks, and it could reach significance in M1sighted (but only for 110% for this task) and MAsimple. Previous evidence suggested that CSP and SICI have different underlying mechanisms, and that those of CSP can be linked to GABA-B receptor-mediated inhibitory neurotransmission [60]. Furthermore, CSP is evoked through direct stimulation of interneurons in M1 [61], and it is likely that CSP is caused by a decrease in cortical firing induced by activation of inhibitory interneurons. Based on that evidence which suggests that CSP has a cortical origin [62,63,64], it is most likely that excitability of cortical neurons activated by simple hand movements is increased mainly by disinhibition [65]. In fact Lefaucheur et al. have shown that patients with chronic pain have a defective inhibitory activity as indexed by CSP and ICI as compared to healthy subjects [3].

Acknowledgments

The study and its results are part of the MD thesis of Volz MS.

Author Contributions

Conceived and designed the experiments: MSV MM FSP HC MS FF. Performed the experiments: MSV MM FSP HC MS FF. Analyzed the data: MSV MM FSP HC MS FF. Contributed reagents/materials/analysis tools: MSV MM FSP HC MS FF. Wrote the paper: MSV MM FSP HC MS FF.

References

1. Bonica JF (1979) The need of a taxonomy. Pain 6: 247–248.
2. Eisenberg E, Chistyakov AV, Yadushkin M, Kaplan B, Hafner H, et al. (2005) Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. Pain 113: 99–105.
3. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP (2006) Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology 67: 1568–1574.
4. Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouassira D (2010) Alteration of cortical excitability in patients with fibromyalgia. Pain 149: 495–500.
5. Schoenenkreis P, Jansen F, Rommel O, Pleger B, Volk B, et al. (2003) Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology 61: 515–519.
6. Zaghli S, Thiele B, Pimentel D, Pimentel T, Fregni F (2011) Assessment and treatment of pain with non-invasive cortical stimulation. Restor Neurol Neurosci.
7. Ahmed MA, Mohamed SA, Sayed D (2011) Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. Neurol Res 33: 953–958.
8. Tsukubakawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol 14: 151–134.
9. Tsukubakawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 52: 137–139.
10. Tsukubakawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401.
11. van Vliet PM, Heneghan NR (2006) Motor control and the management of musculoskeletal dysfunction. Man Ther 11: 208–213.
12. Buesch AJ, Barber KA, Overend TJ, Peloso PM, Schachtner CL (2007) Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev CD003786.
13. Fransen M, McConnell S, Bell M (2003) Exercise for osteoarthritis of the hip or knee. Cochrane Database Syst Rev CD004256.
14. Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, et al. (2006) A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum 54: 3988–3998.
15. Mhalla A, Baudic S, de Andrade DC, Gautron M, Perrot S, et al. (2011) Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain.
16. Fregni F, Boggs PS, Lima MC, Ferreira MJ, Wagner T, et al. (2006) A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain 122: 197–209.
17. O’Connell NE, Wand BM, Marston L, Spencer S, Dessouza LH (2011) Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis. Eur J Phys Rehabil Med.
18. Strafella AP, Vanderwerf Y, Sadikot AF (2004) Transcranial magnetic stimulation of the human motor cortex influences the neuronal activity of subthalamic nucleus. Eur J Neurosci 20: 2245–2249.
40. Bermpohl F, Fregni F, Boggio PS, Thut G, Northoff G, et al. (2006) Effect of low-frequency transcranial magnetic stimulation on an affective go/no-go task in stable patients with bipolar I disease. PLoS ONE 1: e14–e19.

41. Boudreau SA, Farina D, Falla D (2010) The role of motor learning and neuroplasticity in designing rehabilitation approaches for musculoskeletal pain disorders. Man Ther 15: 410–414.

42. Sadato N, Campbell G, Rabeau V, Deiber M, Hallett M (1996) Complexity affects regional cerebral blood flow change during sequential finger movements. J Neurosci 16: 2691–2700.

43. Pascual-Leone A, Amedi A, Fregni F, Merabet LB (2003) The plastic human brain cortex. Annu Rev Neurosci 26: 377–401.

44. Gopin CB, Burdick KE, Derosse P, Goldberg TE, Malhotra AK (2011) Gating of somatosensory plasticity and motor learning. J Neurosci 31: 5814–5823.

45. Park JW, Kim YH, Jang SH, Chang WH, Park CH, et al. (2010) Dynamic changes in the cortico-subcortical network during early motor learning. NeuroRehabilitation 26: 95–103.

46. Nosek BA, Banaji MR (2011) The Go/No-go association task. Social Cognition 29: 13–32.

47. Cui RQ, Huter D, Egkher A, Lang W, Lindinger G, et al. (2000) High resolution MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 375: 155–158.

48. Grafton ST, Hazeltine E, Ivy RB (1998) Abstract and effect-specific representations of motor sequences identified with PET. J Neurosci 18: 9420–9428.

49. Karni A, Meyer G, Jeard P, Adams MM, Turner R, et al. (1995) Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 375: 155–158.

50. Grafton ST, Hazeltine E, Ivy RB (1998) Abstract and effect-specific representations of motor sequences identified with PET. J Neurosci 18: 9420–9428.

51. Liepert J, Claessen J, Cohen LG, Hallett M (1998) Task-dependent changes of intracortical inhibition. Exp Brain Res 118: 421–426.

52. Delveneal I, Kuhaake NG, Jung NH, Mainberger F, Croegaer J, et al. (2011) The time course of motor cortex plasticity after spaced motor practice. Brain Stimul 4: 156–164.

53. Zhang W, Sainburg RL, Zatsiorsky VM, Latash ML (2006) Hand dominance and multi-finger synergies. Neurosci Lett 409: 200–204.

54. Sainburg RL, Schaefer SY (2004) Interlimb differences in control of movement and the motor cortex during oculatory and anovulatory cycles: a transcranial magnetic stimulation study. Clin Endocrinol (Oxf) 66: 387–393.

55. Timmermans AA, Seelen HA, Willmann RD, Kingma H (2009) Technology-assisted training of arm-hand skills in stroke: concepts on reacquisition of motor control and therapist guidelines for rehabilitation technology design. J Neuroeng Rehabil 6: 1.

56. Ziemann U, Muellbacher WZU, Boroojerdi B, Cohen L, Hallett M (2001) Role of the human motor cortex in rapid motor learning. Exp Brain Res 136: 431–438.

57. Rosenkranz K, Rothwell JC (2006) Differences between the effects of three plasticity inducing protocols on the organization of the human motor cortex. Eur J Neurosci 23: 822–829.

58. Ziemann U, Ilic TV, Pauli C, Meintzschel F, Rupe D (2004) Exercise-induced changes of motor excitability with and without sensory block. Brain Res 1003: 68–76.

59. Liepert J, Weiss T, Meissner W, Steineruwe K, Wellere C (2004) Exercise-induced changes of motor excitability with and without sensory block. Brain Res 1003: 68–76.

60. Ziemann U, Muellbacher W, Hallen M, Cohen LG (2001) Modulation of the silent period following a fine-motor skill task and motor learning. J Neurophysiol 91: 1570–1578.

61. Chen R, Lozano AM, Ashby P (1999) Mechanism of the silent period following transcranial magnetic stimulation during isometric and maximal voluntary contraction. J Physiol 466: 521–534.

62. Ziemann U, Ridding MC, Hallett M, Cohen LG (2001) Modulation of intracortical inhibition. Exp Brain Res 118: 421–426.

63. Timmermans AA, Seelen HA, Willmann RD, Kingma H (2009) Technology-assisted training of arm-hand skills in stroke: concepts on reacquisition of motor control and therapist guidelines for rehabilitation technology design. J Neuroeng Rehabil 6: 1.

64. Kocabek G, Kollen BJ, Krebs HI (2008) Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehab Neural Repair 22: 111–121.