How to cite this article: Chipchase L, Baptista AF, Te M, Summers JS. TMS-guided physiotherapy reduces pain and induces plasticity in the motor cortex in chronic knee osteoarthritis. J Phys Res. 2018;8(2):269-278. doi: 10.17267/2238-2704rpf.v8i2.1960

Case study

Journals BAHIANA
SCHOOL OF MEDICINE AND PUBLIC HEALTH

TMS-guided physiotherapy reduces pain and induces plasticity in the motor cortex in chronic knee osteoarthritis

Fisioterapia guiada por EMT reduz a dor e induz a plasticidade no córtex motor na osteoartrose crônica do joelho

Lucy Chipchase[1], Abrahão Fontes Baptista[2], Maxine Te[3], Simon John Summers[4]

[1]Corresponding Author. School of Science and Health. Western Sydney University. Campbelltown Campus. Penrith, New South Wales, Australia. ORCID: 0000-0003-0228-3326. l.chipchase@westernsydney.edu.au

[2]Center for Mathematics, Computation and Cognition. Federal University of ABC. São Bernardo do Campo, São Paulo, Brazil. ORCID: 0000-0001-7870-3820. a.baptista@ufabc.edu.br

[3]School of Science and Health. Western Sydney University. Campbelltown Campus. Penrith, New South Wales, Australia. ORCID: 0000-0003-4682-9992. M.Te@westernsydney.edu.au

[4]School of Science and Health. Western Sydney University. Campbelltown Campus. Penrith, New South Wales, Australia. ORCID: 0000-0003-2114-6239. s.summers@westernsydney.edu.au

RESUMO | INTRODUÇÃO: A osteoartrite do joelho (OA) está associada à dor crônica, comprometimento da função e perda da qualidade de vida. A plasticidade mal-adaptativa do cérebro pode estar envolvida, impedindo efeitos benéficos de exercícios e outras intervenções. A neuromodulação com estimulação elétrica periférica guiada pelo mapeamento da EMT pode influenciar especificamente as modificações mal-adaptativas. **OBJETIVO:** Comparar a organização cortical e excitabilidade de três músculos (reto femural, vasto lateral e vasto medial) em uma participante com OA joelho. **MÉTODOS:** Este estudo de caso único envolveu uma mulher de 66 anos com OA de joelho que estava considerando se submeter a uma artroplastia. Ela foi avaliada para dor (EVA), função (WOMAC, ICOAP) e força do quadríceps uma vez por semana, durante 10 semanas (A - avaliação de quatro semanas; B - avaliação de duas semanas e intervenção; A - avaliação de quatro semanas). O mapeamento de EMT foi realizado no início do estudo, após o período de intervenção de duas semanas e no final do estudo. Esse exame inicialmente revelou uma diminuição proeminente no volume da porção do músculo quadríceps do vasto medial sobre o córtex motor primário (M1), que determinou um protocolo de estimulação elétrica periférica projetado especificamente para aumentar a excitabilidade desse músculo. Durante o período de intervenção, a participante também realizou exercícios específicos diariamente. **RESULTADOS:** Os escores do WOMAC e a força do quadríceps não foram alterados durante o período do estudo. Melhoras foram observadas nas três subescalas do ICOAP após a intervenção. Esta alteração clínica foi associada a um aumento do volume de representação cortical do músculo vasto medial e também do vasto lateral, e uma diminuição nos volumes do mapa da EMT do músculo reto femoral, que foram mantidos até a última avaliação. **CONCLUSÃO:** O mapeamento com EMT pode guiar intervenções específicas para contrabalançar a plasticidade mal-adaptativa do córtex motor e influenciar positivamente a dor e a função na OA do joelho.

PALAVRAS-CHAVE: Estimulação magnética transcraniana. Osteoartrite do joelho. Fisioterapia.

ABSTRACT | BACKGROUND: Knee osteoarthritis (OA) is associated with chronic pain, impaired function and loss of quality of life. Maladaptive plasticity of the motor cortex may be involved limiting the beneficial effects of exercises and other interventions. Neuromodulation with peripheral electrical stimulation guided by TMS mapping may specifically influence those maladaptive plasticity. **OBJECTIVE:** To compare the cortical organization and excitability of three muscles (rectus femoris, vastus lateralis and vastus medialis) in a subject with knee OA. **METHODS:** This single case (ABA) study involved a 66 years old woman with knee OA that was considering an arthroplasty. She was assessed for pain (VAS), function (WOMAC, ICOAP), and quadriceps strength once a week, for 10 weeks (A – four weeks assessment; B – two weeks assessment and intervention; A – four weeks assessment). TMS mapping was performed at baseline, after the two-week intervention period and at the end of the study. The baseline examination revealed less volume of the vastus medialis portion of the quadriceps muscle over the primary motor cortex (M1), which determined a peripheral electrical stimulation protocol specifically designed to increase this muscle's excitability. During the intervention period the participant also performed other specific exercises daily. **RESULTS:** WOMAC scores, and quadriceps strength were not changed during the study period. However, improvements were seen in the three subscales of the ICOAP following the intervention. This clinical change was associated with an increase in vastus medialis and also vastus lateralis, and a decrease in rectus femoris TMS map volumes, which were maintained until the last evaluation. **CONCLUSION:** TMS mapping may guide specific interventions to counteract motor cortex maladaptive plasticity and positively influence pain and function in knee OA.

KEYWORDS: Transcranial magnetic stimulation. Knee osteoarthritis. Physiotherapy.

Submitted 05/08/2018, Accepted 05/11/2018, Published 05/21/2018
J Phys Res, Salvador, 2018 May;8(2):269-278
Doi: 10.17267/2238-2704rpf.v8i2.1960 | ISSN: 2238-2704

Introduction

Transcranial magnetic stimulation (TMS) is a relatively new non-invasive brain stimulation technique that has been used widely to measure changes in cortical networks in a variety of pathologies[1]. In particular, changes in the excitability and organization of the primary motor cortex (M1) have been demonstrated using TMS in chronic musculoskeletal pain conditions including low back pain[2], lateral epicondylalgia[3], patellofemoral pain[4], and following anterior cruciate rupture[5]. In these conditions, altered excitability and organization of M1 has been demonstrated and in some cases has been associated with motor control dysfunction, symptom severity or duration[6]. Also, chronic pain has been linked to intracortical excitability deficits such as decreased GABAergic inhibition[7], assessed with TMS.

To show M1 organization/reorganization, TMS mapping is made by assessing variables such as differences in map volume, center of gravity position (CoG) for each muscle and their relation between each other, and discrete peaks[8]. This methodology has improved since its initial use as a consequence of the development of new equipment, such as neuronavigation systems[9], signal processing and analysis[10], becoming more rapid and accurate. As TMS is able to demonstrate changes in M1 organization, it may be very useful to guide interventions, especially those with a highly focal effect such as those provided by physiotherapists (e.g. electrotherapy, manual therapy, acupuncture). Hence, given the ability of TMS mapping to detect changes in cortical networks, there is a potential to use TMS to guide treatment for chronic musculoskeletal pain conditions, so that interventions can target specific changes in central nervous system activity.

Neuromodulatory techniques, such as peripheral electrical stimulation (PES), have been demonstrated to alter cortical excitability and organization. For example, depending on the parameters applied, PES can increase or decrease excitability of the cortical networks to the muscle stimulated[11]. Using PES prior to other interventions provides a method by which the corticomotor pathway may be primed to enhance the effect of other interventions[12]. However, there is heterogeneity in findings, with some studies showing that the influence of PES on corticomotor excitability is variable and does not correlate with improved function. One possibility to explain this controversy is that the focal application of PES may alter only the representation of one muscle, but not the neighboring muscles. If this is the case, TMS mapping could be useful to guide PES interventions to specific muscles, changing their M1 representation, and possibly function.

For the purpose of this study, knee OA is used as a model of a chronic musculoskeletal pain condition. In knee OA, altered cortical processing, particularly central sensitization and hyperexcitability of the sensory pathways and sensory cortex has been demonstrated[13]. However, little attention has been paid to the impact of altered cortical processing of the motor cortex on pain and function. This is important as altered neuromuscular activity and kinematics have been demonstrated during functional and postural tasks in people with knee OA with neuromuscular activity being controlled by descending inputs from M1[14]. Thus, the first aim was to compare cortical organization and excitability of three muscles (rectus femoris, vastus lateralis and vastus medialis) in a subject with knee OA to an age and sex matched control subject. Based on the TMS findings, an exercise and PES intervention was developed and evaluated using a single case study in a subject with knee OA.

Methods

Case description

The subject was a 66-year-old women diagnosed with OA of her right knee. The patient had intermittent knee pain that was made worse by standing from sitting and going down stairs.

Design

A single subject experimental ABA design was used with the subject acting as her own control. Data were collected over three phases consisting of an initial baseline phase without intervention for 4 weeks (A), an intervention phase lasting 2 weeks (B), and a final baseline phase in which the intervention was withdrawn (A') (Table 1). During all phases, the

subject continued to participate in her usual exercise regimes (e.g. exercise class, swimming and walking) but did not start any new treatment other than the one proposed in this study. The study was approved by the institutional Human Research Ethics Committee of the University of Western Sydney (#H10184). Informed consent was obtained from the participant following a detailed explanation of the study procedure and requirement for regular testing. The same investigator took all the evaluation procedures to ensure reproducibility in the study.

Outcome measures

Clinical evaluation

At the first appointment the participant was screened for pain location with a body map, and completed the Chronic Pain Grade, Douleur Neuropathique 4, Western and McMaster Universities Osteoarthritis Index (WOMAC)[15], Intermittent and Constant Osteoarthritis Pain (ICOAP),[16] and TMS safety questionnaires. During the recording of objective measures the participant was seated on an examination table, which was raised until there was no foot contact to the floor. Objective measures included: a) Pressure pain thresholds (PPT) – PPTs were assessed over the most medial and lateral aspects of the joint lines in both knees, and at the most lateral aspect of joint line in the contralateral elbow, using a handheld pressure algometer with a probe size of 1cm^2 (SenseBox, SOMEDIC, Sweden). The probe was applied perpendicular to the skin (rate 1Kgf/sec) until the participant first reported that the sensation of pressure had changed to the first sensation of pain; b) Quadriceps strength – a rigid belt was secured around the distal tibia at a 90° angle to the leg. Measures of strength were taken using a hand-held dynamometer (Lafayette, USA). The test followed the make test paradigm, where the participant was verbally encouraged to perform maximal knee extension against the dynamometer that was positioned between the belt and the anterior margin of the tibia. All objective measures were repeated three times, and the average used for analysis. Clinical evaluation was repeated weekly, until the last day of the study (10 weeks).

TMS evaluation

Prior to the commencement of phase A, TMS was conducted to measure M1 excitability and organization (representational plasticity) of the rectus femuris (RF), vastus lateralis (VL) and vastus medialis (VM) of the affected leg. Motor representational maps derived by TMS were collected as these have been shown to be stable over time and therefore suitable to study the effect of various interventions. The results were then compared to that of a healthy control matched for sex and age with no knee pain, to determine the neuromodulatory intervention.

Electromyographic (EMG) activity was used as the TMS/EMG parameter and also to determine the degree of quadriceps activation during TMS evaluation. Surface EMG silver/silver chloride snap dual self-adhesive electrodes (Noraxon, USA) were used to record EMG from RF, VL and VM. The skin site was abraded with skin gel (Nuprep, Weaver & Company, USA) and cleaned with alcohol. Electrodes were positioned at the midpoint between the superior edge of the patella and anterior superior iliac crest (ASIS) for RF, while the electrodes for VM and VL were placed at an angle of 55° medially and 15° laterally from the femur's vertical axis respectively. The ground electrode was positioned over the ASIS. The EMG signals were pre-amplified at 1000x, filtered at 20-1000Hz and sampled at 2000Hz using Power 1401 data acquisition system and Spike 2 software (Cambridge Electronic Design, Cambridge, UK).

Transcranial magnetic stimulation was performed using a Magstim 200 stimulator (Magstim Co, Ltd, Dyfed, UK) with a figure of eight coil (diameter 7cm). The subjects' vertex was located and marked according to the 10/20 EEG system[17]. The vertex was used to place the center of a polyester cap that had been marked with a 10x10cm grid and orientated to the vertex (0.0). This allowed for identification of stimulation co-ordinates and ensured accuracy for repeated measures.

Prior to the TMS procedure, the subject performed three maximal voluntary contractions (MVC), and the average root-mean-square (RMS) EMG amplitude of the RF was used to determine 10% of MVC. As

MEPs of the lower limb are difficult to elicit at rest, the participant activated the quadriceps muscle to 10% of their MVC during mapping[4]. Visual feedback of RF EMG activity was provided on a computer monitor with a horizontal line representing the target EMG activity (10%) to ensure a consistent level of activation was maintained during mapping. The belt used for strength measures was positioned at the same place over the symptomatic leg, to work as a resistance against knee extension, and facilitate quadriceps activation.

The stimulus intensity for mapping was set at 110% of active motor threshold (AMT) for RF. Active motor threshold for RF was defined as the minimal intensity required to evoke a 200 μV peak-to-peak motor evoked potential (MEP) during 10% of MVC force. The TMS coil was positioned tangential to the skull with the handle facing posteriorly, to generate a postero-anterior flow of current. Transcranial magnetic stimulations was applied every six seconds with a total of five stimuli at each scalp site. Stimulation extended 1 cm posterior to the vertex, 7 cm anterior and 2cm laterally (7x8cm grid).

Map volume was calculated by summing the mean peak-to-peak MEP amplitudes at all active sites and normalizing to the amplitude of the peak response for each muscle by dividing the amplitude averages of each stimulation spot by the weighted average of all the grid spots. The center of gravity (CoG) was then computed for each muscle as a measure of the amplitude-weighted center of the motor representational map. This is expressed as a bivariate measurement with a lateral (x) and anteroposterior coordinate (y), using the following formula:

$$CoG = \sum Vi \times Xi / \sum Vi, \sum Vi \times Xi / \sum Vi$$

where: Vi = mean MEP amplitude at each site with the coordinates Xi, Yi,

Using these data, the distance between the CoG of the maps of RF, VL and VM were calculated using Pythagoras theorem.

The results were then compared to that of a healthy control matched for sex and age with no knee pain, to determine the neuromodulatory intervention. These results are presented in Table 1.

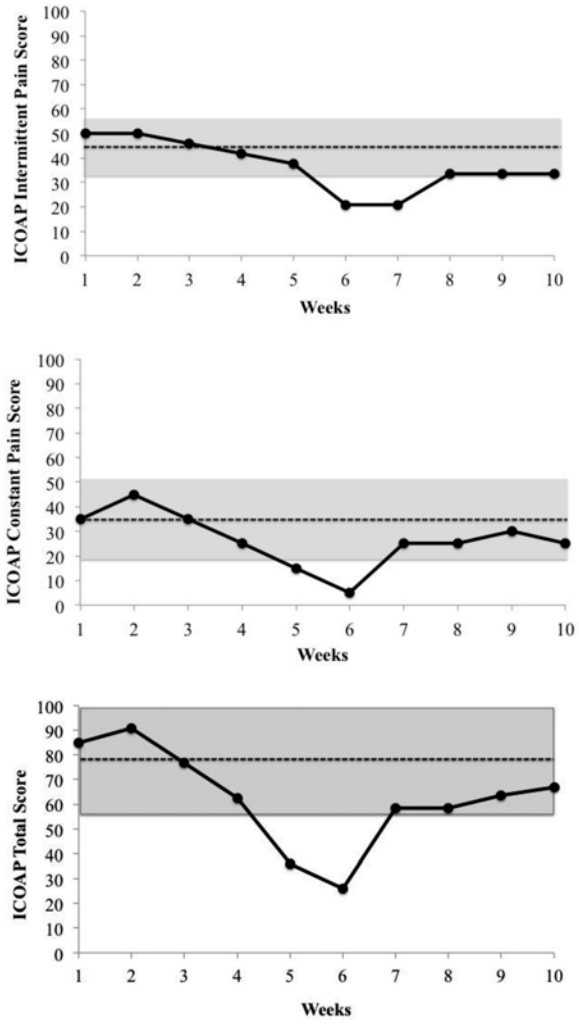
The map volumes for each of the three muscles prior to the intervention (pre-A phase) were compared to those of the control subject (Table 1). Following creation of three-dimensional maps for each muscle, they were first compared qualitatively to the control subject (Figure 1).

Table 1. TMS map parameters

	Control subject	Single Case Subject - Pre-A phase
Volume RF (cm^2 x mV)	10.17	11.49
Volume VL (cm^2 x mV)	6.60	4.07
Volume VM (cm^2 x mV)	5.0	2.41
CoG RF coord (lat-AP)	2.64 – 1.82	2.67 – 4.01
CoG VL coord (lat-AP)	2.83 – 3.19	2.95 – 4.78
CoG VM coord (lat-AP)	2.82 – 2.19	3.31 – 4.84
Distance (cm) RF - VL	1.38	0.82
Distance (cm) RF - VM	0.41	1.05
Distance (cm) VL - VM	1.00	0.37

Abbreviations: RF – rectus femuris, VL – Vastus lateralis, VM – Vastus medialis, CoG – Center of Gravity, lat – lateral, AP – anteroposterior,

Figure 1. Changes in ICOAP scores (scores out of 100) across each of the three phases (A – 1 to 4 weeks, assessment; B – 5 and 6 weeks, assessment and intervention; C – 7 to 10 weeks, assessment), Dotted lines and shading represent the two standard deviation band and dashed lines the mean of each phase,



TMS based intervention

Table 1 indicates that map volume for VM was less than half of that of the control subject. Thus, PES, using a motor stimulation paradigm to VM was selected to prime the corticomotor pathway as this has been demonstrated to increase excitability of the cortical motor pathway in healthy subjects[16]. The PES protocol (30 Hz, ramped to produce a tetanic contraction, 0.2ms pulse duration to motor threshold) was conducted for 20 minutes three times a day on alternate days to a home exercise program.

The home-exercise program consisted of six exercises designed to strengthen the quadriceps, hip abductors and hamstrings and was based on clinical trials that demonstrate reduction of pain and improvement of function[23]. The intensity of each exercise was determined by the participant's ability to complete 10 repetitions. Exercises were progressed by the subject in conjunction with a physiotherapist by increasing weight or complexity. Weights and resistance elastic bands were provided. The participant performed the prescribed home exercises every other day with a dosage of 3 sets of 10 repetitions.

Evaluation measures

Measures of TMS (map volume, center of gravity coordinates and distance between center of gravity coordinates) were collected on three occasions: at the commencement of the A phase, after the intervention, and at the end of the A' phase (Table 2).

Table 2. Overview of ABA design.

Outcome measure		A				B		A'			
Pain	ICOAP	•	•	•	•	•	•	•	•	•	•
Function	WOMAC	•	•	•	•	•	•	•	•	•	•
Strength	MMT	•	•	•	•	•	•	•	•	•	•
TMS		•						•			•
Week		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Each dot represents the number and type of measurements taken each week.

Statistical analysis

For visual analysis, raw data were plotted on graphs with simple lines connecting adjacent points within each phase. For statistical analysis, the two-standard deviation (2SD) band method was used. This involved calculating the mean ± 2SD of data points within the initial baseline phase and then extending the band to the intervention and final baseline phases. When at least two successive data points in the intervention period fell outside the band, changes from baseline to intervention were regarded as statistically significant at the level of $p<0.05$. In addition, Cohen d statistic effect sizes were calculated to assess clinical significance. The mean scores from the intervention (B) phase and the post intervention phase (A') were each subtracted from the mean of the baseline phase (A) and divided by the corresponding standard deviation. Essentially, the d statistic reflected the change in outcome measures following the intervention divided by an estimate of variance. The magnitude of the effect sizes was considered relative to 0.2, 0.5, and 0.8 as benchmarks for small, medium and large-sized effects, respectively.

Results

The subject completed all 10-measurement sessions and all three TMS sessions (Table 3).

Clinical Measures

There were small changes (small effect sizes) in the WOMAC score or quadriceps strength following the intervention. However, improvements in the three subscales of the ICOAP were seen following the intervention (Figure 2). This change was reflected with a medium effect size for the three scales (Table 2).

Table 3. Mean (SD) values of outcome measures at each phase.

Outcome		A	B	A'	Effect size (B to A)
ICOAP	Constant pain (/100)	34 (7.4)	10 (7.1)	26.3 (2.5)	-3.24
	Intermittent pain (/100)	45 (5.4)	28 (0.0)	35.5 (4.2)	-4.45
	Total (/100)	79 (10.7)	30.8 (7.1)	61.7 (4.1)	-4.52
WOMAC	Pain (/20)	7.8 (1.3)	5.0 (1.4)	6.0 (0.0)	-2.15
	Stiffness (/8)	4.4 (0.9)	4.0 (0.0)	3.5 (0.6)	-0.45
	Physical function (/68)	24.2 (5.9)	17.5 (0.7)	22.0 (0.8)	-1.14
	Total (/96)	36.0 (7.2)	26.5 (0.7)	31.5 (1.0)	-1.32
Strength	Quads affected (lbs)	55.9 (5.9)	58.5 (9.7)	61.2 (5.6)	0.43
	Quads unaffected (lbs)	57.3 (9.5)	52.9 (4.2)	56.8 (3.7)	-0.46

TMS measures

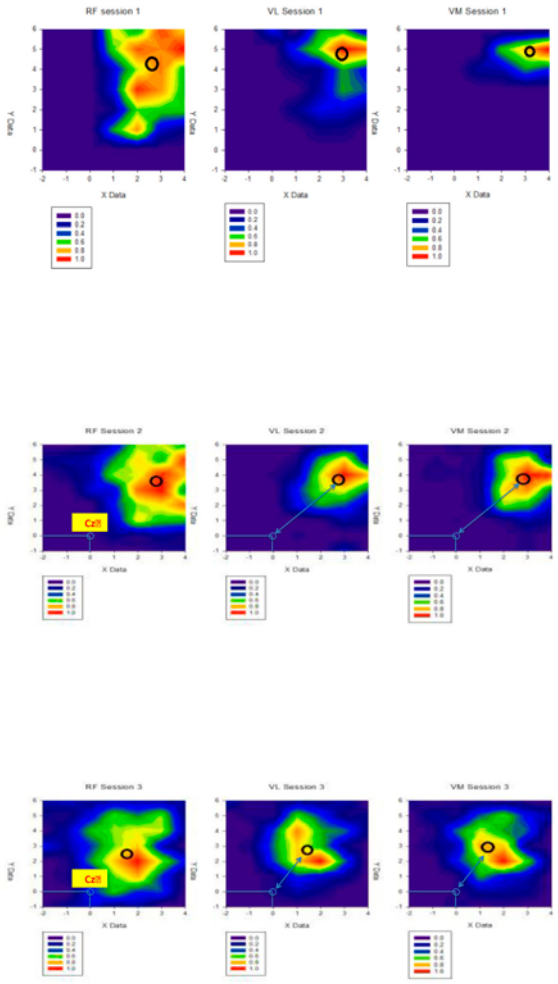
Changes in the TMS measures over the three sessions are presented in Table 4 and Figure 2. Map volume for VM demonstrated a 211% increase in size following intervention, which remained after the post intervention phase. Map volume for VL increased by 144%, while map volume for RF decreased 20.38%.

Table 4. TMS measures

	Control Subject	Single Case Subject A phase *	Single Case Subject B phase *	Single Case Subject A' phase *
RF (cm^2 x mV)	10.17	11.49	11.59 (↑0.86%)♯	9.05 (↓21.24%)♯
VL (cm^2 x mV)	6.60	4.07	5.85 (↑30.43%)♯	5.62 (↑27.59%)♯
VM (cm^2 x mV)	5.90	2.41	5.10 (↑52.75%)♯	5.46 (↑55.86%)♯
CeG RF coord (lat-AP)	2.64 – 1.82	2.67 – 4.01	2.83 – 3.57	1.67 – 2.65
CeG VL coord (lat-AP)	2.83 – 3.19	2.95 – 4.78	2.85 – 3.64	1.61 – 3.00
CeG VM coord (lat-AP)	2.82 – 2.19	3.31 – 4.84	2.80 – 3.73	1.40 – 3.06
Distance (cm) RF - VL	1.38	0.82	0.07	0.35
Distance (cm) RF - VM	0.41	1.05	0.17	0.49
Distance (cm) VL - VM	1.00	0.37	0.11	0.22

* A phase – 4 weeks prior to intervention; B phase – 2 weeks period of intervention; A' phase – 4 weeks after the end of intervention, ♯ Absolute value / % change from baseline

Figure 2. TMS mapping during baseline (up), after two weeks of intervention – end of week 6 (middle), and at the end of the study – week 10 (low), The lowest map volume of VM justified the specific intervention with 30Hz peripheral electrical stimulation over this muscle during weeks 5 and 6, Note that after two weeks of electrical stimulation associated with exercises, VM and VL map volumes increased, and centers of gravity (black circles) approached the center of the head (Cz), RF map volume did not change just after the two weeks intervention, Four weeks after the end of the intervention (lower row) VM and VL map volumes continued to increase and centers of gravity approached Cz, RF map volume decreased, but its center of gravity also approached Cz, VM – Vastus medialis; VL – Vastus lateralis; RF – Rectus femuris,



Discussion

This single case study demonstrates that a TMS directed intervention with peripheral electrical stimulation may be useful to influence muscle activity and related brain plasticity in a person with OA of their knee. Knee OA is a debilitating condition, which involves biomechanical, as well as nervous system modifications[14]. Exercises are generally recommended to improve function and decrease associated pain, and usually aim to increase local (quadriceps, harmstrings) and proximal (gluteus) muscle strength, improve range of motion, gait and balance. However this strategy has low impact in the long term[18]. Although the progression of the disease and poor adherence to the exercise program may explain exercise failure, other possibilities need to be further investigated, including brain maladaptive plasticity, which has been demonstrated through fMRI studies[19].

In our study, VM map volume was markedly decreased in the single case subject. Also, CoG was localized in a more anterior and lateral position than the control subject. Taking into account that this finding matches with biomechanical studies showing that VM may be dysfunctional in patients with knee pain[20], we decided to use a protocol of PES to increase its M1 excitability. Previous studies have shown that 30Hz electrical stimulation with sufficient amplitude to induce muscle contractions and joint movement increases MEP, a marker of cortical excitability[21]. The participant was instructed to maintain her daily activities, and was trained to introduce PES two times a day, three times a week, during two weeks. A protocol of specific exercises was also introduced[22].

The increase in VM (stimulated portion) and VL (non-stimulated portion) map volume and changes in CoG just after the intervention period, and also four weeks after, suggest that there was a change in neuroplasticity secondary to TMS guided PES and associated exercises. Indeed, it could be argued that changes in VL were induced because of its innervation by the femoral nerve. However, RF followed an inverse pattern, showing a decrease in map volume. Rectus femoris CoG changes followed a similar pattern to VM and VL, where the CoG position became more posterior and medial. These findings suggest that a TMS guided PES associated with exercises may exert a plastic influence on the M1, which seems to be specific for the stimulated muscles[23,24]. Ridding et al (2000, 2003) stimulated the adductor policis brevis in the hand, a muscle supplied by the ulnar nerve, and showed that the effects on MEP happened locally, with no changes in muscles supplied by the median nerve[24]. Our study shows that this effect may be more specific than previously demonstrate and may depend on the stimulated muscle, and not on its innervation.

In our study, the specific changes in M1 excitability were temporarily translated into clinical significant functional changes, as there was improved pain and function during the period of intervention. However, this effect was reversed after the interruption of the treatment. This result may signify, that the effects are only maintained during treatment, or that the period of intervention was not sufficient to induce long-term changes. Although previous studies have shown that neuromodulatory interventions are generally short lasting, a maintenance period has been proved to be beneficial in some chronic pain syndromes[25]. The participant of the study was considering the possibility to undergo arthroplasty, and changed her opinion by the end of the study, which led us to consider that the treatment was clinically meaningful. Future studies should continue to investigate if TMS guided PES and associated exercises may add to the functional evaluation in determining specific interventions, including electrotherapy and exercises. If our results are reproduced in representative samples, it is possible to find a new avenue to help people with movement deficits related to chronic pain.

Authors contributions

LSC, AFB, MT and SS were involved in all steps, from designing the study, assessing the participant, analyzing the data, discussing the results and to writing the final draft of the manuscript.

Authors are required to include a statement of responsibility at the end of their manuscript's text that specifies the contribution of every author (see Section 6). Please state that all authors discussed the results and commented on the manuscript.

References

1. Parker RS, Lewis GN, Rice DA, McNair PJ. Is Motor Cortical Excitability Altered in People with Chronic Pain? A Systematic Review and Meta-Analysis. Brain Stimul. 2016;9(4):488-500. doi: 10.1016/j.brs.2016.03.020

2. Tsao H, Galea MP, Hodges PW. Driving plasticity in the motor cortex in recurrent low back pain. European journal of pain. Eur J Pain. 2010;14(8):832-9. doi: 10.1016/j.ejpain.2010.01.001

3. Burns E, Chipchase LS, Schabrun SM. Altered function of intracortical networks in chronic lateral epicondylalgia. Eur J Pain. 2016;20(7):1166-75. doi: 10.1002/ejp.841

4. Te M, Baptista AF, Chipchase LS, Schabrun SM. Primary Motor Cortex Organization Is Altered in Persistent Patellofemoral Pain. Pain Med. 2017;18(11):2224-34. doi: 10.1093/pm/pnx036

5. Ward SH, Pearce A, Bennell KL, Peitrosimone B, Bryant AL. Quadriceps cortical adaptations in individuals with an anterior cruciate ligament injury. Knee. 2016;23(4):582-7. doi: 10.1016/j.knee.2016.04.001

6. Schabrun SM, Hodges PW, Vicenzino B, Jones E, Chipchase LS. Novel adaptations in motor cortical maps: the relation to persistent elbow pain. Med Sci Sports Exerc. 2015;47(4):681-90. doi: 10.1249/MSS.0000000000000469

7. Parker RS, Lewis GN, Rice DA, McNair PJ. The Association Between Corticomotor Excitability and Motor Skill Learning in People With Painful Hand Arthritis. Clin J Pain. 2017;33(3):222-30. doi: 10.1097/AJP.0000000000000392

8. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application, An updated report from an I,F,C,N, Committee. Clin Neurophysiol. 2015;126(6):1071-107. doi: 10.1016/j.clinph.2015.02.001

9. Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. Neurophysiol Clin. 2010;40(1):7-17. doi: 10.1016/j.neucli.2010.01.006

10. Cavaleri R, Schabrun SM, Chipchase LS. The number of stimuli required to reliably assess corticomotor excitability and primary motor cortical representations using transcranial magnetic stimulation (TMS): a systematic review and meta-analysis. Syst Rev. 2017;6(1):48. doi: 10.1186/s13643-017-0440-8

11. Chipchase LS, Schabrun SM, Hodges PW. Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters. Clin Neurophysiol. 2011;122(3):456-63. doi: 10.1016/j.clinph.2010.07.025

12. Schabrun SM, Chipchase LS. Priming the brain to learn: The future of therapy? Man Ther. 2012;17(2):184-6. doi: 10.1016/j.math.2011.12.001

13. Kittelson AJ, Thomas AC, Kluger BM, Stevens-Lapsley JE. Corticospinal and intracortical excitability of the quadriceps in patients with knee osteoarthritis. Exp Brain Res. 2014;232(12):3991-9. doi: 10.1007/s00221-014-4079-6

14. Shanahan CJ, Hodges PW, Wrigley TV, Bennell KL, Farrell MJ. Organisation of the motor cortex differs between people with and without knee osteoarthritis. Arthritis Res Ther. 2015;17:164. doi: 10.1186/s13075-015-0676-4

15. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. Arthritis Rheum. 2001;45(5):453-61.

16. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L et al. Development and preliminary psychometric testing of a new OA pain measure - an OARSI/OMERACT initiative. Osteoarthritis Cartilage. 2008;16(4):409-14. doi: 10.1016/j.joca.2007.12.015

17. American Electroencephalographic Society guidelines for standard electrode position nomenclature. J Clin Neurophysiol. 1991;8(2):200-2.

18. Varady NH, Grodzinsky AJ. Osteoarthritis year in review 2015: mechanics. Osteoarthritis Cartilage. 2016;24(1):27-35. doi: 10.1016/j.joca.2015.08.018

19. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015;49(24):1554-7. doi: 10.1136/bjsports-2015-095424

20. Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS One. 2014;9(9):e106133. doi: 10.1371/journal.pone.0106133

21. Mills K, Hunt MA, Leigh R, Ferber R. A systematic review and meta-analysis of lower limb neuromuscular alterations associated with knee osteoarthritis during level walking. Clin Biomech (Bristol, Avon). 2013;28(7):713-24. doi: 10.1016/j.clinbiomech.2013.07.008

22. Chipchase LS, Schabrun SM, Hodges PW. Corticospinal excitability is dependent on the parameters of peripheral electric stimulation: a preliminary study. Arch Phys Med Rehabil. 2011;92(9):1423-30. doi: 10.1016/j.apmr.2011.01.011

23. Charlton CS, Ridding MC, Thompson PD, Miles TS. Prolonged peripheral nerve stimulation induces persistent changes in excitability of human motor cortex. J Neurol Sci. 2003;208(1-2):79-85.

24. Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. Exp Brain Res. 2000;131(1):135-43.

25. Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. Eur J Neurol. 2016;23(10):1489-99. doi: 10.1111/ene.13103