Original research

Femoral cortical excitability differs between people with knee osteoarthritis and healthy controls: a pilot study

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ABSTRACT | BACKGROUND: Knee osteoarthritis (OA) is associated with changes in corticospinal and intracortical excitability which may be due to persistent pain. **OBJECTIVE:** To investigate the cortical excitability profile of the femoral quadriceps in people with knee OA and healthy volunteers. **METHODS:** Cortical excitability was assessed using transcranial magnetic stimulation (TMS) in 7 participants with knee OA and 6 age- and sex-matched healthy volunteers. The motor evoked potential (MEP), cortical silent period (CSP), short intracortical inhibition (SICI) and intracortical facilitation (ICF) of the rectus femoris (RF), vastus medialis (VM) and vastus lateralis (VL) were measured using standard single pulse and paired-pulse TMS techniques. Data analysis was performed using Mann-Whitney test considering alpha <0.05. **RESULTS:** Participants with knee OA demonstrated reduced MEP amplitude in the RF and VM muscles and augmented MEP amplitude in the VL muscle. SICI was reduced only in the RF and ICF was reduced in the VM and VL. CSP was reduced in all muscles. **CONCLUSION:** People with knee OA exhibit altered corticospinal and intracortical excitability profile in specific portions of the quadriceps muscle. This suggests a possible adaptive strategy to maintain quadriceps motor activity.

KEYWORDS: Cortical excitability. Evoked potentials, Motor. Osteoarthritis, Knee. Quadriceps muscle.

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Introduction

Knee Osteoarthritis (OA) is a chronic condition characterized by joint degeneration and persistent pain.[1] Weakness and/or muscular imbalance of the quadriceps muscle are strongly correlated with pain aggravation[2], poor functional self-assessment and physical performance[3] in individuals with knee OA. However, quadriceps weakness is multifactorial and involves sensory components of pain and inflammation[4], changes in neuromuscular (cortical, segmental and peripheral) control and muscle cell properties.[5,6] Biomechanical and electromyographic markers have a predictive value for the severity of some symptoms and can be used to guide therapeutic strategies.[7,8] In addition, a lower capacity to produce voluntary electromyographic activity in the quadriceps (central activation deficit - CAD) is associated with poor physical performance in individuals with knee OA.[9,10]

More recently, the corticospinal and intracortical pathways have been investigated in knee OA with transcranial magnetic stimulation (TMS).[9,11-14] Resting Motor Threshold (RMT) and Motor evoked potential (MEP) are measures of corticospinal excitability, whereas Intracortical facilitation (ICF) and Short Intracortical Inhibition (SICI) represent cortico-cortical connectivity through the activity of the neurotransmitters glutamate and GABA, respectively.[15,16] Kittelson et al found no differences in corticospinal (MEP) and intracortical excitability between subjects with OA and controls, and no correlation between TMS and CAD measures, but the RMT of the quadriceps was positively correlated with torque and negatively correlated with pain scores.[13] Accordingly, increased corticospinal excitability (lower threshold) is associated with muscle weakness and more pain. Also, the cortical silent period (CSP) is negatively correlated with pain scores.[11] In fact, a component of the (CSP) is mediated by GABAergic inhibition, via GABAA and GABAB receptors.[17,18] Although it is not consensus, reduction of the (CSP) can also be interpreted as an increase in intracortical facilitation due to reduced GABAergic inhibition.[19]

Evidence indicates that MEP and ICF are positively correlated with pain and functional limitation in knee OA.[12,13,19] However, these studies have recorded the vastus lateralis or rectus femoris.[9,11-13] The quadriceps has four distinct portions and optimal joint function results from integrated neuromuscular control. Interestingly, the cortical representation of the quadriceps of individuals with patellofemoral pain is reduced with the same pattern in the *rectus femoris* (RF), *vastus lateralis* (VL) and *vastus medialis* (MV) portions.[20] Therefore, this study aims to investigate the corticospinal and intracortical excitability of the femoral quadriceps of subjects with OA and controls

Materials and methods

A cross-sectional, descriptive study was carried out at the Laboratory of Functional Electrical Stimulation, Federal University of Bahia, Brazil, between January and October 2016. The study was approved by the Research Ethics Committee of the UFBA Institute of Health Sciences, protocol number 1,378,100.

Participants

We included in this study 13 participants (seven OA and six controls) recruited from health services in Salvador, Bahia, Brazil. Subjects were over 50 years of age, presented knee pain on most days of the last month, a score on the Chronic Pain Grade18 equal to or greater than II, and a medical report confirming knee OA. Healthy controls were paired by sex, age, and body weight. Healthy controls could not present any pain in the moment of the assessment or have any knee injury in the past. Subjects with contraindications to TMS, history of disorders with confounding factors (fibromyalgia, rheumatoid arthritis, ankylosing spondylitis, low back pain and spinal and lower limb surgeries) and people unable to understand the content of the assessment tools were excluded. All subjects signed the Free and Informed Consent.

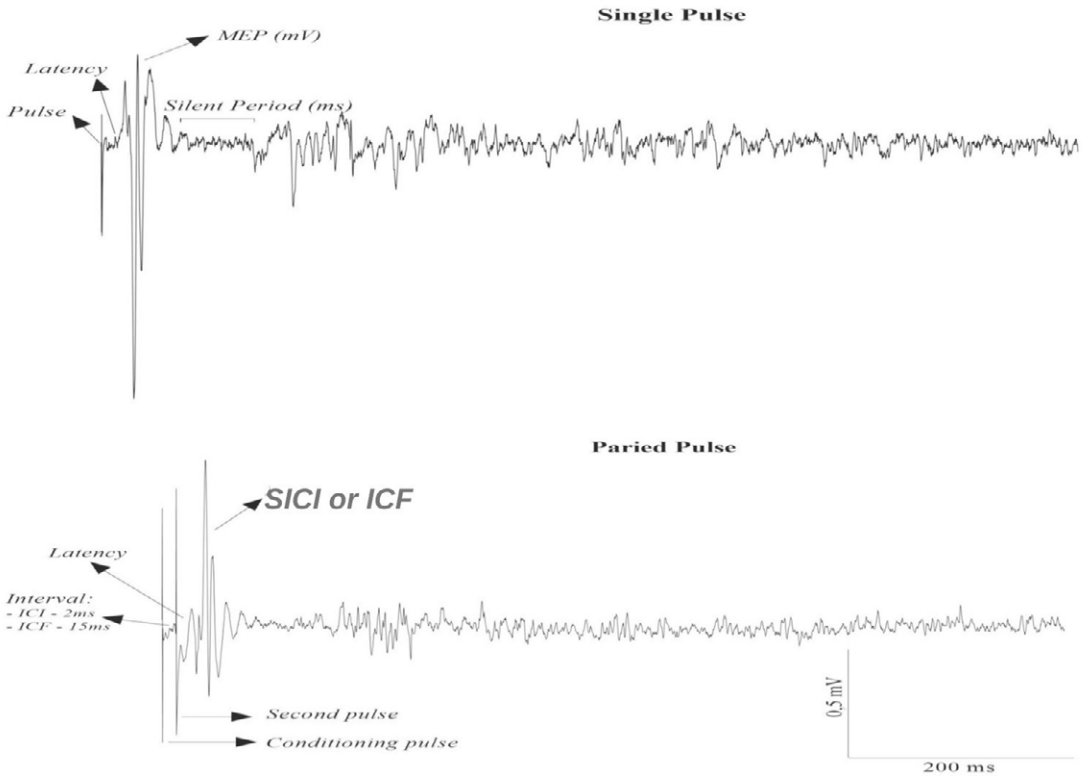
Procedures

The subjects were positioned in a comfortable chair. Electromyography electrodes (Miotec, Brazil) were placed in the RF, VM and VL of the most painful knee, according to the SENIAM.[21] The reference electrode was positioned on the ipsilateral patella. For the controls, the knee of the dominant limb was selected. EMG activity was pre-amplified, filtered at 1-2000Hz and captured at a sampling rate of 4000Hz using a 1401/1902 acquisition system and Signal v.6 software (Cambridge Electronic Design, Cambridge, UK).

Corticospinal and intracortical excitability were evaluated with TMS (BiStim, Magstim, UK). A 70mm figure-of-eight coil was used. For positioning of the coil, the vertex (Cz) was located through the use of the international 10/20 EEG localization system. A pre-marked polyester cap with a 1x1cm grid oriented in the Cartesian plane was used as reference for TMS procedures. A light contraction of the quadriceps was performed, and RF activity was standardized around 100 μV during TMS. Signal v.6 software was used to record and analyze the EMG MEP.

A single location (hot spot) in the M1 that represented the best activation of the RF, VM and VL was identified. After the hot spot was found, the active motor threshold (AMT) was estimated. The AMT corresponds to the lowest stimulus intensity capable of generating a potential with a peak-to-peak amplitude of 200μV. The average amplitude of 10 pulses was used to estimate each of the excitability measures (MEP, SICI and ICF) totaling 30 pulses applied randomly in the hot spot. MEP was obtained with suprathreshold AMT intensities (120%). CSP was obtained during MEP collection. The CSP was estimated in milliseconds considering the latency from the start of the MEP until the EMG activity was slightly restored. CSP duration was calculated by subtracting the onset from the offset of the CSP. For ICF and SICI, the TMS paired pulse paradigm was used. The SICI was evaluated with a conditioning pulse at 80% of the MEP and the test pulse at 120%, with an interval of 2 ms between both. The ICF was evaluated with the same values and interval of 15 ms. A schematic representation of the electromyographic recording during TMS can be seen in figure 1.

Figure 1. Representation of the electromyographic record of the simple pulse and the paired pulse of the transcranial magnetic stimulation. In the simple pulse, the amplitude in mV of the MEP and the duration of the CSP were collected. In the paired pulse, the mV amplitude of inhibition and intracortical facilitation



Source: the authors (2023).

Analysis

EMG records were treated offline using Signal software v.6 (Cambridge Electronic Design, Cambridge, UK). MEP was expressed in mV and the calculation of SICI and ICF were based on MEP. The formula used to obtain SICI was: *((SICI average - MEP average)* / MEP average) x 100, and for ICF: *((ICF average - MEP average) / MEP average)* x 100. The Shapiro-Wilk test demonstrated that the data were not normal, and the Mann-Whitney U test was used for comparing data from knee AO and control groups.

Table 1. Clinical and physical characteristics of subjects with OA and controls

	OA (average)	Control (average)	t test *(p valor)*
Age *(years)*	61.9 56.3 – 67.8	58.2 54.3 – 72.8	0.321 *(0.71)*
Weight *(kg)*	72.1 69.7 – 90.5	67.7 65.1 – 77.5	0.546 *(0.62)*
Height *(m)*	1.57 1.51 – 1.65	1.58 1.53 – 1.61	0.927 *(0.19)*
Duration of symptoms *(months)*	38.6 24.5 – 49.7	-	-
Painful knee *(right / left)*	5/2	-	-
Pain *(VAS 0-100mm)*	59.8 25.5– 65.5	-	-

Source: the authors (2023).

Table 2. Records of active motor threshold and hotspot of subjects with OA and healthy

Subject	Group	Sex	HotSpot	AMT (%)
1	Control	female	B4	76,00
2	Control	female	C4	75,00
3	Control	female	C4	75,00
4	Control	female	C3	58,00
5	Control	female	B2	89,00
6	Control	female	C6	68,00
7	OA	female	C4	59,00
8	OA	male	C3	65,00
9	OA	female	B2	62,00
10	OA	female	A0	45,00
11	OA	female	D4	77,00
12	OA	male	D4	77,00
13	OA	female	B3	57,00

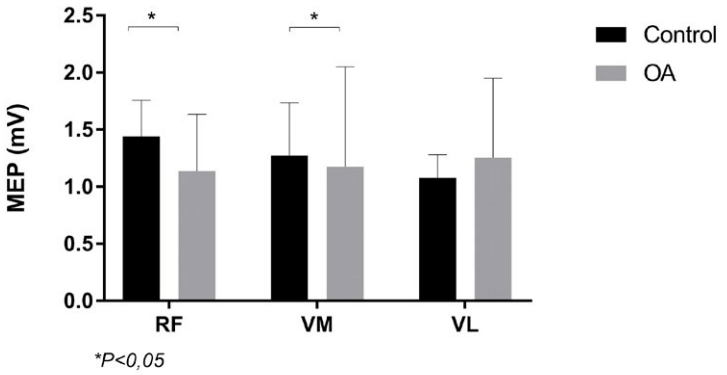
Source: the authors (2023).

Results

The clinical characteristics of the participants are described in Table 1. The data demonstrate that the groups were similar. Regarding the AMT data for each subject, they are described in table 2. RF and VM MEP were lower in participants with knee OA (U = -2.286, p <0.050 and U = -2.429, p <0.050, respectively). VL MEP was similar between groups (U = -0.571, p = 0.628) (Figure 2). Descriptive MEP data suggest different patterns of activation between groups.

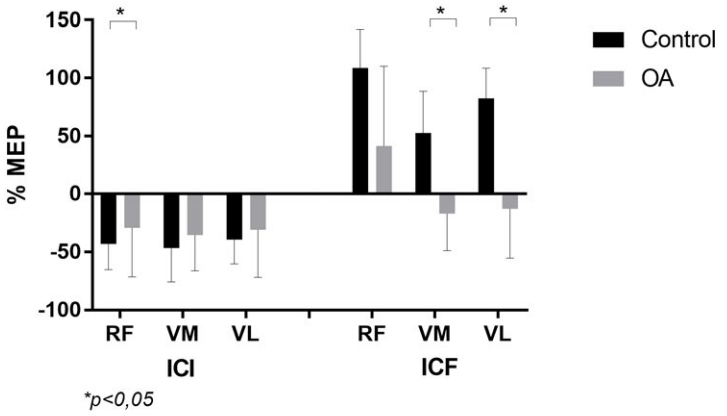
ICF was reduced in the VM and VL portions (U = -2.571, p < 0.010, and U = -2.857, p = 0.005, respectively). RF ICF was similar between the groups (U = -1.571, p = 0.138) (Figure 3). The CSP duration of all assessed portions of the quadriceps was smaller in subjects with knee OA, being RF (U = -2.98, p < 0.010), VM (U = -1.432, p < 0.050) and VL (U = -1.965, p < 0.050) (Figure 4).

Figure 2. Amplitude in mV of the motor evoked potential (MEP) of the femoral rectus (RF), vastus medialis (VM) and vastus lateralis (VL) of subjects with knee OA and controls. Values presented in median and interquartile ranges



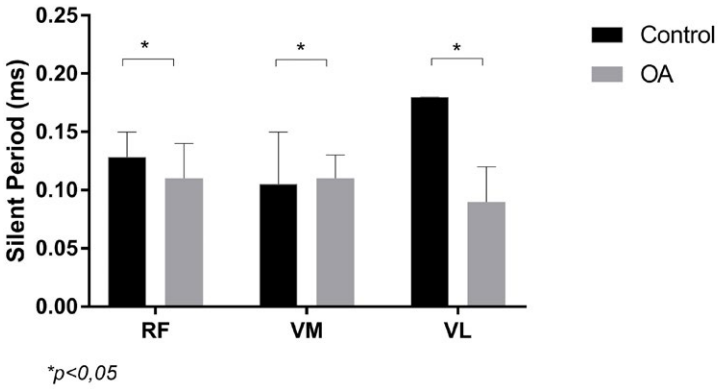
Source: the authors (2023).

Figure 3. Intracortical Inhibition (SICI) and intracortical facilitation (ICF) presented in percentage values regarding the motor evoked potential (MEP) of femoral rectus (RF), vastus medialis (VM) and vastus lateralis (VL) of subjects with knee OA and controls



Source: the authors (2023).

Figure 4. Duration of the Cortical Silent Period (CSP) in milliseconds (ms) of the femoral rectus (RF), vastus medialis (VM) and vastus lateralis (VL) of subjects with knee OA



Source: the authors (2023).

Discussion

Corticospinal and intracortical excitability of the quadriceps may be distinct between subjects with knee OA and controls. Our data show that MEP was reduced in RF and VM, suggesting reduction in corticospinal excitability of these portions. ICI was reduced in the RF, but not in the VM and VL. ICF was reduced in VM and VL, but not in RF. These findings suggest that cortical activity is distinct between subjects with knee OA and controls, and also that it may be different between the portions of the quadriceps. For this reason, we suggest that TMS studies should evaluate all portions of the quadriceps, and not only one. Interestingly, all portions of the quadriceps showed a reduction in CSP in subjects with knee OA, making this measure the only consistent finding across the entire muscle.

The reduction of CSP can be interpreted as a lower intracortical GABAergic inhibition.[17-19] Since, GABAA was only altered in RF muscle, as measured by ICI, GABAB was probably the reason for the VM and VL disinhibition. Therefore, we speculate that individuals with OA present an excitation/inhibition imbalance in cortical circuits related to the quadriceps muscle.

A plausible explanation of our findings comes through the presence of Central Sensitization (SC), a phenomenon related to knee OA chronic pain[22,23], and associated with changes in corticospinal and intracortical circuits. Corticospinal (MEP) and intracortical excitability (SICI, ICF and CSP) cannot be predicted, but have a strong correlation with SC.[24] Subjects with SC secondary to knee OA present changes in corticospinal and intracortical excitability.[9,11-13] However, actual data are inconclusive with insufficient methodologies for a parsimonious clinical extrapolation. A case study verified that the mean amplitude of MEP was lower in the RF of the knee affected with OA in relation to the contralateral one.[9] In addition, Tarragó et al.[11] demonstrated that CSP is reduced in individuals with OA in relation to control individuals.

In fact, cortical changes in knee OA have high variability and do not present a characteristic pattern. Our data highlight that these changes may be distinct in the RF, VM, and VL portions. The optimal balance between the three superficial portions of the quadriceps, and also the deep portion (vastus intermedius) requires further studies. Our findings suggest that subjects with knee OA may have a reduction in inhibition in intracortical GABAergic via GABAA receptors (SICI) and via GABAB (CSP) receptors. In addition, ICF was decreased in the VM and VL. In view of this, it is plausible to assume that changes in populations of corticospinal neurons that control motoneurons of different portions of the quadriceps may contribute to muscle imbalance in individuals with knee OA. These findings are preliminary and limited because of our small sample size, limiting external validity of the data. Hence, new studies are stimulated to identify specificities in the excitability of the different portions of the quadriceps of individuals with OA. Measures of cortical excitability guided by neuronavigation may be a strategy to decrease the variability of responses.[25] This strategy may aid in the identification of a pattern of excitability in individuals with knee OA. Studies with larger samples are needed to enable a more robust statistical analysis and to increase the external validity of the results for a possible clinical use.

Conclusion

Our results corroborate the idea of an altered cortical excitability of the femoral quadriceps in individuals with knee OA. In subjects with knee OA, the corticospinal excitability of RF and MV decreased while VL increased. This demonstrates a possible compensatory strategy to maintain motor activity of the quadriceps. In intracortical excitability there is a tendency for decreased facilitation and intracortical inhibition. Identifying differences in the cortical excitability of the quadriceps between subjects with OA and healthy allows us to understand the impact of this condition in the motor cortex. This study is preliminary, future works with larger sample size and methodological robustness are necessary to confirm or refute our findings.

Declaration

Financing

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Ethical approval and consent to participate

We declare that this research was submitted to the Ethics Committee of the Health Sciences Institute, Federal University of Bahia (number: 1,378,100). All participants in the research signed a two-way informed consent form. These and other procedures were based on CNS Resolution 466/12 and the Helsinki Declaration.

Authors' contributions

Castro KVF and Luz-Santos C participated in the conception of the work, data collection, data analysis and interpretation, and drafting the article. Duarte-Moreira RJ worked in the data analysis and interpretation, draft of the article, critical revision of the article, final approval of the version to be published and in the submission to Brain Imaging and Stimulation. Cavalcanti J contributed in the conception of the work, data analysis and interpretation, drafting the article and critical revision of the paper. Noronha D participated in the conception of the work, data analysis and interpretation. Camatti JR worked in the data collection, data analysis and interpretation. Sá KN contributed in the conception of the work, data analysis and interpretation, and critical revision of the article. Okano A and Lee M participated in the data analysis and interpretation, drafting the article and critical revision of the paper. Baptista AF worked in the conception of the work, data analysis and interpretation, drafting the article, critical revision of the paper and final approval of the version to be published.

Competing interests

Authors declare that there is no conflict of interest including any financial, personal or other relationships that could inappropriately influence, or be perceived to influence their work in the field.

References

1. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull. 2013;105(1):185–99. https://doi.org/10.1093/bmb/lds038

2. Palmieri-Smith RM, Villwock M, Downie B, Hecht G, Zernicke R. Pain and effusion and quadriceps activation and strength. J Athl Train. 2013;48(2):186–91. https://doi.org/10.4085/1062-6050-48.2.10

3. Liikavainio T, Lyytinen T, Tyrväinen E, Sipilä S, Arokoski JP. Physical function and properties of quadriceps femoris muscle in men with knee osteoarthritis. Arch Phys Med Rehabil. 2008;89(11):2185–94. https://doi.org/10.1016/j.apmr.2008.04.012

4. Rice DA, McNair PJ. Quadriceps arthrogenic muscle inhibition: neural mechanisms and treatment perspectives. Semin Arthritis Rheum. 2010;40(3):250–66. https://doi.org/10.1016/j.semarthrit.2009.10.001

5. Pietrosimone BG, McLeod MM, Lepley AS. A theoretical framework for understanding neuromuscular response to lower extremity joint injury. Sports Health. 2012;4(1):31–5. https://doi.org/10.1177/1941738111428251

6. Mizner RL, Petterson SC, Stevens JE, Vandenborne K, Snyder-Mackler L. Early quadriceps strength loss after total knee arthroplasty. The contributions of muscle atrophy and failure of voluntary muscle activation. J Bone Joint Surg Am. 2005;87(5):1047–53. https://doi.org/10.2106/JBJS.D.01992

7. Guilak F. Biomechanical factors in osteoarthritis. Best Pract Res Clin Rheumatol. 2011;25(6):815–23. https://doi.org/10.1016/j.berh.2011.11.013

8. Balaguer-Ballester E. Cortical Variability and Challenges for Modeling Approaches. Front Syst Neurosci. 2017;11:15. https://doi.org/10.3389/fnsys.2017.00015

9. Hunt MA, Zabukovec JR, Peters S, Pollock CL, Linsdell MA, Boyd LA. Reduced quadriceps motor-evoked potentials in an individual with unilateral knee osteoarthritis: a case report. Case Rep Rheumatol. 2011;2011:537420. https://doi.org/10.1155/2011/537420

10. Lewek MD, Rudolph KS, Snyder-Mackler L. Quadriceps femoris muscle weakness and activation failure in patients with symptomatic knee osteoarthritis. J Orthop Res. 2004;22(1):110–5. https://doi.org/10.1016/S0736-0266(03)00154-2

11. Tarragó MGL, Deitos A, Brietzke AP, Vercelino R, Torres ILS, Fregni F, et al. Descending Control of Nociceptive Processing in Knee Osteoarthritis Is Associated With Intracortical Disinhibition: An Exploratory Study. Med (Balt). 2016;95(17):e3353. https://doi.org/10.1097/MD.0000000000003353

12. 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. https://doi.org/10.1186/s13075-015-0676-4

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. https://doi.org/10.1007/s00221-014-4079-6

14. Caumo W, Deitos A, Carvalho S, Leite J, Carvalho F, Dussán-Sarria JA, et al. Motor Cortex Excitability and BDNF Levels in Chronic Musculoskeletal Pain According to Structural Pathology. Front Hum Neurosci. 2016;10:357. https://doi.org/10.3389/fnhum.2016.00357

15. Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol. 2012;123(5):858–82. https://doi.org/10.1016/j.clinph.2012.01.010

16. 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. https://doi.org/0.1016/j.clinph.2015.02.001

17. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55(2):187–99. https://doi.org/10.1016/j.neuron.2007.06.026

18. Škarabot J, Mesquita RNO, Brownstein CG, Ansdell P. Myths and Methodologies: How loud is the story told by the transcranial magnetic stimulation-evoked silent period? Exp Physiol. 2019;104(5):635–42. https://doi.org/10.1113/EP087557

19. 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. https://doi.org/10.1016/j.brs.2016.03.020

20. 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. https://doi.org/10.1093/pm/pnx036

21. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol. 2000;10(5):361–74. https://doi.org/10.1016/s1050-6411(00)00027-4

22. Lotze M. Maladaptive Plastizität bei chronischen und neuropathischen Schmerzen. Schmerz. 2016;30(2):127–33. https://doi.org/10.1007/s00482-015-0080-7

23. 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. https://doi.org/10.1371/journal.pone.0106133

24. Mueller S, Wang D, Fox MD, Thomas Yeo BT, Sepulcre J, Sabuncu MR, et al. Individual Variability in Functional Connectivity Architecture of the Human Brain. Neuron. 2013;77(3):586–95. http://dx.doi.org/10.1016/j.neuron.2012.12.028

25. Sparing R, Buelte D, Meister IG, Paus T, Fink GR. Transcranial magnetic stimulation and the challenge of coil placement: a comparison of conventional and stereotaxic neuronavigational strategies. Hum Brain Mapp. 2008;29(1):82–96. https://doi.org/10.1002/hbm.20360