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Functional near-infrared spectroscopy to assess central pain responses in a non-pharmacologic treatment trial of osteoarthritis

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Abstract

Background and Purpose: Knee osteoarthritis (OA) is a common source of pain in older adults. Although OA-induced pain can be relieved with analgesics and anti-inflammatory drugs, the current opioid epidemic is fostering the exploration of non-pharmacologic strategies for pain mitigation. Amongst these, transcranial direct current stimulation (tDCS) and mindfulness-based meditation (MBM) hold potential for pain-relief efficacy due to their neuromodulatory effects of the central nervous system, which is known to play a fundamental role in pain perception and processing.

Methods: In this double-blind study, we used functional near-infrared spectroscopy (fNIRS) to investigate the effects of tDCS combined with MBM on underlying pain processing mechanisms at the central nervous level in older adults with knee OA. Nineteen subjects were randomly assigned to two groups undergoing a 10-day active tDCS and MBM regimen and a sham tDCS and MBM regimen, respectively.

Results: Our results showed that the neuromodulatory intervention significantly relieved pain only in the group receiving active treatment. We also found that only the active treatment group showed a significant increase in oxyhemoglobin activation of the superior motor and somatosensory cortices co-located to the placement of the tDCS anodal electrode. To our knowledge, this is the first study in which the combined effect of tDCS and MBM is investigated using fNIRS.

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Conclusion: In conclusion, functional near-infrared spectroscopy can be effectively used to investigate neural mechanisms of pain at the cortical level in association to non-pharmacological, self-administered treatments.

Keywords

Functional near-infrared spectroscopy; transcranial direct current stimulation; pain; meditation; knee osteoarthritis

Introduction

Knee osteoarthritis (OA) is one of the leading causes of pain and physical dysfunction in adults who are 45 years and older.^{1,2} The prevalence of knee OA increases with age, and symptomatic knee OA affects more than 14 million people in the United States.³ Primary treatment options of knee OA pain comprise mainly the prescription of analgesic medications. However, the management of OA pain is particularly challenging for older adults because the pain is only partially responsive to existing pharmacological approaches, and these medications often produce significant adverse events (e.g., addiction, tolerance, constipation, nausea, and drowsiness)⁴⁻⁶ and potentially pose a risk of aggravating the current opioid crisis. Recent studies showed alterations in pain-related brain mechanisms in people with knee OA pain,^{7,8} corroborating a growing interest in non-pharmacologic interventions targeting pain-related brain activity in this population.

A growing body of literature suggests that two non-pharmacological pain treatment, namely transcranial direct current stimulation (tDCS) and mindfulness-based meditation (MBM), improve chronic pain. Transcranial direct current stimulation (tDCS) has received significant attention for the treatment of pain due to its neuromodulatory effects of the central nervous system.⁹ tDCS increases the neuronal excitability by applying a low-amplitude direct electric current (i.e., 2mA) to the scalp noninvasively through wet electrodes, and recent clinical trials indicated tDCS to be a safe and effective technique in reducing pain.¹⁰⁻¹³ Also, mindfulness-based meditation (MBM) has been shown to reduce pain in multiple chronic pain conditions.¹⁴ Indeed, Ussher et al. demonstrated that an audio-recorded mindfulness intervention significantly reduced pain-related distress and pain interferences in patients with chronic pain.¹⁵ Also, Liu et al. reported an increase in pain tolerance and a decrease in pain-related distress for resting periods involving mindfulness intervention (through audio recordings) in comparison to listening to light music.¹⁶

However, few studies have investigated the effects of tDCS combined with MBM on brain mechanisms using functional optical neuroimaging methods. Because tDCS facilitates neuroplasticity,^{17,18} it may increase the effect of MBM, which also stimulates adaptive changes in the brain.^{19,20} Since the therapeutic effects of MBM are at least partially due to adaptive changes in pain-related brain activity, combining tDCS with MBM may strengthen the adaptive brain changes that occur with MBM. In this work, since persons with knee OA have limited mobility and considerable time and cost are needed to travel multiple times for clinic-based interventions, we used home-based interventions with remote supervision. All home-based intervention sessions were remotely supervised by trained research team via

secure videoconferencing software (i.e., WebEx) to ensure optimal protocol adherence. We used functional near-infrared spectroscopy (fNIRS), i.e. an optical neuroimaging technique measuring cortical hemodynamic activity, to investigate the effects of tDCS combined with MBM on underlying pain processing mechanisms at the central nervous level in older adults with knee OA.

In the last decade, fNIRS has been used to investigate pain perception and its therapeutic interventions, as well as to measure the effect of tDCS on cortical activation.²¹⁻²⁴ Recently, we explored the longitudinal effect of tDCS on the hemodynamic response to thermal pain in knee osteoarthritis patients using fNIRS²⁵ and found that cortical activity increased over time. However, to our knowledge no study has yet investigated the neuromodulatory effect of a combination of tDCS and MBM on the same population.

Methods

Participants

Detailed selection criteria and enrollment procedures were described in our previous work.²⁶ Briefly, 30 participants between ages 50 and 85 with self-reported knee OA pain level of at least 30 on the Numerical Rating Scale (0: no pain; 100: most intense pain imaginable) in the past three months were recruited in Southeast Texas. According to the American College of Rheumatology criteria,²⁷ participants met at least 3 of 6 criteria for symptomatic knee OA, namely age more than 50 years, stiffness less than 30 minutes, crepitus, bony tenderness, bony enlargement, and no palpable warmth. Participants were excluded if they had concurrent medical conditions that could hinder the completion of the protocol, including history of strokes, seizure, brain surgery, brain tumor, cognitive impairment, alcohol or substance abuse, or serious medical illness. The experimental protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at Houston.

Neuromodulation and Meditation Paradigms

The study was a double-blind, randomized, sham-controlled clinical trial designed to evaluate the efficacy of 10 daily sessions of tDCS paired with MBM administered at home for 20 minutes daily over two weeks (Monday through Friday) in older adults with knee OA. Participants who met selection criteria were randomly assigned to either an active treatment (n = 15) or a sham intervention group (n = 15) for the ten sessions in a 1:1 ratio. Neither participants nor investigators were aware of the group assignment prior to experimentation. By using the method of minimization,²⁸ participants were allocated to the study arms considering distributions of age, race, and sex. For ensuring the use of proper technique and monitoring any adverse events, participants were remotely supervised by investigators at each home-based intervention session via secure videoconferencing software (e.g., WebEx). Active tDCS treatment consisted of a constant electrical direct current (2 mA) delivered through a pair of saline-saturated rectangular sponge electrodes (5 x 7 cm) controlled by a commercial tDCS stimulator (1x1 tDCS mini-CT Stimulator, Soterix Medical Inc., NY). The anode electrode was placed over the primary motor cortex of the hemisphere contralateral to the affected knee, while the cathode electrode was placed over the

supraorbital region contralateral to the anode.²⁹ For sham tDCS, the electrodes were located in the same position, but the stimulator delivered no electrical current except a ramp-up/down period of 30 seconds at the beginning and end of trials in order to mimic somatosensory perception of an active tDCS treatment. During each tDCS session, participants assigned to the active tDCS group were instructed to practice MBM by listening to a guided meditation recording through earphones on a CD player. MBM was performed for 20 minutes, concurrently to the tDCS intervention. The MBM intervention included three different recordings that gradually take the participant into a deeper meditation practice. Meditation 1 for the first 3 days focused on learning basic breathing mindfulness techniques to help focus and calm one's mind. Meditation 2 for days 4-6 included the techniques learned in Meditation 1 and incorporated directions to help the participant connect to the stillness of one's body, the silence of one's speech, and the openness of one's mind. Meditation 3 for the remaining days included the techniques learned in Meditation 2 and incorporated directions for staying deeper in one's connection by mindfully maintaining and deepening the connection through breathing with more openness and awareness, and connecting to one's qualities of warmth (i.e., kindness, compassion, joy). In contrast, participants in the sham treatment group were instructed to relax and take deep breaths every three minutes without any specific mindfulness-based instructions.²⁶

Differences in clinical pain and OA-related symptoms before and after the experimental protocol were measured in all subjects using the well-established Numerical Rating Scale (NRS)³⁰ and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)³¹ scores, respectively.

Optical Neuroimaging During Pain Stimulation

To compare the neuronal response to pain before and after the tDCS+MBM regimen, we induced thermal pain using a temperature-controlled, 16x16 mm thermode (Medoc TSA-II Neurosensory Analyzer) applied onto the forearm ipsilateral to the OA-affected knee, as in King, Sibille, Goodin et al.³² The thermal stimulation was produced in a timed block design paradigm as follows. After an initial baseline period of 60 seconds with the thermode at room temperature (i.e., no pain experienced), the temperature was risen to 45°C to induce a moderate-to-intense sensation of pain for 20 seconds, followed by a recovery period of 30 seconds in which the thermode was reset to room temperature. The temperature was quickly transitioned between baseline (room temperature) and 45 degrees by physically applying the thermode to the forearm and then removing it at the end of the stimulation period.

During this experimental paradigm, the hemodynamic cortical response to thermal pain was measured using a continuous-wave fNIRS imaging system (LIGHTNIRS, Shimadzu, Kyoto, Japan) comprising eight multi-wavelength emitters (lasers at 780, 805, and 830 nm) and eight photodetectors optically coupled to the scalp via optical fibers. The optodes were arranged in two regions covering the prefrontal cortex (bilaterally) and the primary motor and somatosensory cortices on the hemisphere contralateral to the thermal stimulation side. More specifically, Figure 1 shows the optode layout and the corresponding cortical sensitivity map of the optical probe on subjects affected by OA on the right knee primarily, hence thermally stimulated on the right forearm to elicit a pain-related cortical response on

the left hemisphere. In contrast, the cortical response in subjects suffering from OA-related pain in the left knee was measured by placing optodes S2-S8 and D2-D8 symmetrically on the right hemisphere, while leaving the anterior optical probe layout unchanged. The distance between adjacent sources and detectors was set at 30 mm to ensure the probing of the cerebral cortex in all 20 optical channels.

Optical neuroimaging scans were performed twice: prior to the beginning of the first tDCS +MBM session (either active or sham) and after the last session. All 60 scans (two scans on 30 subjects) were evaluated for data quality by visual inspection and by quantitative measures of fNIRS signal integrity previously proposed by our group.³³⁻³⁵ As a result of this assessment, we excluded 22 noisy scans (11 subjects, 4 of whom were from the active treatment group) from further analysis, reducing the cohort to 19 subjects (9 males and 10 females, 60 ± 7.7 years old). Subsequently, raw data were converted to optical density and then to changes of concentration of oxygenated and deoxygenated hemoglobin over time, according to the Modified Beer-Lambert law.^{36,37} In each subject, cortical hemodynamic activity, i.e. changes of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) over time during thermal stimulation was evaluated with a general linear model based on an autoregressive iteratively-reweighted least squares approach (AR-IRLS), as described in Barker, Aarabi and Huppert³⁸ where only optical channels with a statistical q-value (i.e., p-value corrected for multiple comparisons³⁹) lower than 5% were considered significantly active (i.e., beta weight statistically different from zero). The general linear model was designed by assuming a canonical (double-gamma function³⁹) hemodynamic response concurrent to the train of 20-second stimulation followed by 30 seconds of rest, repeated six times. We do not find any evidence indicating that a habituation effect was produced by the repetitive stimulation, hence we did not account for it in the GLM analysis. Although it is possible that healthy individuals could habituate after few minutes of noxious stimuli, existing literature indicates that this is unlikely to happen in populations with chronic pain.^{40,41} At the group level, we assessed the relationship between the estimated beta coefficient of each optical channel (the predicted variable) and the combined effect of time and treatment using a linear mixed-effects model with the subject-specific intercept set as a random effect. Of relevance, the AR-IRLS method automatically accounts for the expected presence of extracerebral components in the optical signals due to cardiac pulsation and respiration, and it automatically excludes artifact movements as statistical outliers. Hence, a bandpass signal filtering step was not explicitly required to remove these components.

All data quality assessment algorithms were developed by our group, whereas conversion from raw data to hemodynamic parameters and individual and group-level analyses were performed using the software AnalyzIR.³⁹ All code was executed in MATLAB® (Natick, MA, USA).

Results

A comprehensive analysis of the effects of the combined tDCS and MBM treatments in the 30-subject cohort is reported in our previous work.²⁶ In this study, we re-evaluated the most significant pain measures in the subset of subjects considered for the fNIRS analysis, i.e. after the exclusion of 11 subjects due to noisy scans. We confirmed that clinical pain

assessed with NRS was significantly reduced (paired t-test, $p < 0.001$) by the active tDCS +MBM treatment (NRS difference -22.3 ± 13.3), whereas the sham tDCS+MBM regimen did not significantly alter the pain level (NRS difference -3.1 ± 11.6 , $p = 0.36$). We also verified that the initial levels of pain were not significantly different between the active and sham groups prior to the treatment (two-sample t-test, $p = 0.10$). Due to the reduced sample size of this study compared to the full recruitment,²⁶ the WOMAC score was not significantly reduced by the active treatment ($p = 0.11$).

Since existing literature has evidenced a potential gender dependency of pain perception,⁴²⁻⁴⁴ we repeated the statistical comparisons separating males from females, but did not find any significantly different results. In females, NRS was significantly reduced by the experimental treatment (-16.6 ± 10.3 , $p = 0.01$), whereas WOMAC scores decreased non-significantly (-9.33 ± 17.4 , $p = 0.24$). In comparison, female patients assigned to sham treatment did not experience significant pain or symptoms reduction (NRS difference: -6.2 ± 14.9 , $p = 0.46$; WOMAC difference: $+1.75 \pm 11.55$, $p = 0.78$). Consistently with female results, male patients who underwent active treatment experienced a significant reduction of pain assessed with NRS (-28.0 ± 12.5 , $p = 0.007$) and a non-significant decrease of WOMAC symptoms (-5.2 ± 10.82 , $p = 0.34$), whereas the sham male group had non-significant decreases of both NRS (-1.25 ± 8.26 , $p = 0.71$) and WOMAC (-4 ± 8.6 , $p = 0.42$).

Optical neuroimaging showed that a cortical response to thermal pain before the tDCS +MBM protocol was not significantly present in both active and sham treatment groups (Fig. 2).

After the tDCS+MBM treatment, the active treatment group showed a significant HbO activation of the superior motor and somatosensory cortices co-located to the placement of the tDCS anodal electrode, whereas the activation patterns of the sham group were still not significant, as prior to the treatment (Fig. 3).

Discussion

This study reports for the first time on the cortical hemodynamic effects of a combination of two neuromodulatory techniques, namely transcranial direct current stimulation and mindful-based meditation, that have been proposed as non-pharmacological therapies against pain.⁴⁵

As previously reported in our clinical article,²⁶ the combination of tDCS and meditation had a beneficial effect on the perception of OA-related pain measured with NRS scale. Since no subject was under any pharmacological intervention, it is reasonable to attribute the reduction of pain to the combination of tDCS or MBM, or both, although this study did not quantify which individual technique contributed the most to pain relief. We also investigated if the pain reduction was perceived differently by males and females, but we did not find any significant gender effect as suggested in previous studies on this population.⁴²⁻⁴⁴ It is known from literature that neuromodulation with tDCS has an offline effect in form of an increased localized activity in the tDCS anodal area that endures after the short-lived tDCS session, and that such endurance clearly manifests after few consecutive days of active tDCS

sessions. Since our assessment of pain and OA-symptoms occurred after the last session of a 10-day tDCS regimen, our findings confirm such an offline effect of neurostimulation. A growing body of literature has been showing that also mindful meditation, especially after a training period, has beneficial effects on both experimentally induced and clinical pain.⁴⁶ To assess the contributions on pain relief of tDCS and MBM, as well as the combination of both, our group is currently conducting a larger randomized controlled trial.

Since the neural mechanisms supporting tDCS and MBM-based pain relief, when considered separately, are still poorly understood,⁴⁶ research in this area has been leveraging neuroimaging, especially functional magnetic resonance imaging (fMRI), as a tool to fill this knowledge gap. Despite the lower spatial resolution of fNIRS, our group adopted this optical neuroimaging technology due to its portability enabling deployment to ambulatory, clinical and home settings, and for its lower cost enabling more economical studies on larger populations. In this preliminary study, we found that the cortical response to thermal pain after the active tDCS+MBM regimen was significantly active in the motor and somatosensory areas where the tDCS anode was located, whereas the sham group did not exhibit a significant pain response either before nor after the treatment. We attribute the increased activation in the active group primarily to the offline effect of tDCS in the superior area where the anode was placed during treatment but, speculatively, such effect could have been augmented by the MBM treatment as well. Also, prior fMRI studies have found that the BOLD response were correlated with heat ratings, but not with pain measures like the visual analog scale (VAS)⁴⁷ and the primary somatosensory cortex was a less reliable indicator of pain level than other regions of interests.⁴⁸ Taken together, these elements suggest that the complex spatiotemporal nature of pain processing poses challenges to the quantitative assessment of the relationship between clinical measures and neuroimaging findings, and larger studies are needed to generate further evidence.

Of relevance, our study investigated only the offline effect (i.e., after-treatment) of neuromodulation and meditation on pain perception, whereas existing neuroimaging literature mostly investigated the brain response to pain administered while the subjects are actively meditating, thus making difficult to compare the respective findings. Using fMRI, Zeidan et al have shown that subjects practicing mindful meditation had an increased activity in several brain regions, including the anterior cingulate cortex, anterior insula, and ventromedial PFC in contrast to non-meditating individuals,⁴⁹ and that the level of experience in performing MBM while experiencing pain further underscored these neural response differences.⁴⁶ However, studies have reported benefits such as reduction in stress and pain in a variety of clinical populations ((e.g., pain, cancer, heart disease, depression, and anxiety) practicing meditation therapy,⁵⁰ and is therefore reasonable to assume that the effect of meditation on brain activity may endure beyond the meditative task, as tested in our experimental conditions and in accord with the fNIRS study previously conducted by Gundel et al.⁵¹ Notwithstanding these observations, the neural processes involved in the endurance of meditation effects, the level of meditation experience, the cortical regions of interest and the effectiveness of MBM as an adjuvant therapy to neuromodulation remain to be understood and are indeed objectives of our follow-up investigation.

Although we believe that this study demonstrates the feasibility of assessing central pain responses to a non-pharmacologic treatment of knee osteoarthritis using fNIRS, it is important to state its limitations. In this preliminary trial, we did not administer tDCS and MBM disjointly (i.e., active tDCS + sham MBM, or sham tDCS + active MBM), hence any pre-post treatment differences can be attributed only to the combination of both modalities but without discerning if one of them has a prevailing effect. The sample size of this study is also a limiting factor, especially after the removal of 11 subjects (our of 30) due to noisy fNIRS scans. However, both these shortcomings are being investigated in a larger follow-up study that our group is currently conducting.

Another limitation of this study is that thermal pain was elicited in the forearm ipsilateral to the index knee (i.e., the primary pain site), which may be mapped differently at the cortical level, especially from a sensory perspective, than pain from other body districts and of different type (i.e., thermal vs. mechanical vs. electrical vs. others). Although this study recruited only subjects with knee pain, we aimed at exploring the cortical hemodynamic effect of tDCS and MBM at a general level, with the potential of expanding this non-pharmacological approach to other conditions like fibromyalgia and chronic back pain.

In conclusion, this randomized controlled trial on a knee osteoarthritis cohort shows that combining tDCS and MBM techniques induced significant cortical hemodynamic activity in response to experimentally induced pain alongside a reduction of pain perception, thus suggesting that functional near-infrared spectroscopy can be effectively used to investigate neural mechanism of pain in association to non-pharmacological, self-administered treatments.

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References

- [1]. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35. [PubMed: 18163497]
- [2]. Wallace II, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proc Natl Acad Sci U S A* 2017;114:9332–36. [PubMed: 28808025]
- [3]. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. *Arthritis Care Res (Hoboken)* 2016;68:1743–50. [PubMed: 27014966]
- [4]. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. *Am J Geriatr Pharmacother* 2012;10:331–42. [PubMed: 23036838]

- [5]. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med* 2010;170:1968–76. [PubMed: 21149752]
- [6]. Reid MC, Henderson CR Jr., Papaleontiou M, et al. Characteristics of older adults receiving opioids in primary care: treatment duration and outcomes. *Pain Med* 2010;11:1063–71. [PubMed: 20642732]
- [7]. Phillips K, Clauw DJ. Central pain mechanisms in the rheumatic diseases: future directions. *Arthritis Rheum* 2013;65:291–302. [PubMed: 23045168]
- [8]. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis Rheum* 2013;65:363–72. [PubMed: 22961435]
- [9]. Mori F, Codeca C, Kusayanagi H, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *J Pain* 2010;11:436–42. [PubMed: 20018567]
- [10]. Bikson M, Grossman P, Thomas C, et al. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimul* 2016;9:641–61. [PubMed: 27372845]
- [11]. Ahn H, Woods AJ, Kunik ME, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: An experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study. *Brain Stimul* 2017;10:902–9. [PubMed: 28566193]
- [12]. Ahn H, Suchting R, Woods AJ, et al. Bayesian analysis of the effect of transcranial direct current stimulation on experimental pain sensitivity in older adults with knee osteoarthritis: randomized sham-controlled pilot clinical study. *J Pain Res* 2018;11:2071–82. [PubMed: 30310309]
- [13]. Ahn H, Sorkpor S, Miao H, et al. Home-based self-administered transcranial direct current stimulation in older adults with knee osteoarthritis pain: An open-label study. *J Clin Neurosci* 2019;66:61–5 [PubMed: 31153751]
- [14]. Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther* 2016;45:5–31. [PubMed: 26818413]
- [15]. Ussher M, Spatz A, Copland C, et al. Immediate effects of a brief mindfulness-based body scan on patients with chronic pain. *J Behav Med* 2014;37:127–34. [PubMed: 23129105]
- [16]. Liu X, Wang S, Chang S, Chen W, Si M. Effect of brief mindfulness intervention on tolerance and distress of pain induced by cold-pressor task. *Stress Health* 2013;29:199–204. [PubMed: 22961992]
- [17]. Huang YZ, Lu MK, Antal A, et al. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. *Clin Neurophysiol* 2017;128:2318–29. [PubMed: 29040922]
- [18]. Zhao H, Qiao L, Fan D, et al. Modulation of brain activity with noninvasive Transcranial Direct Current Stimulation (tDCS): clinical applications and safety concerns. *Front Psychol* 2017;8:685. [PubMed: 28539894]
- [19]. Badran BW, Austelle CW, Smith NR, et al. A double-blind study exploring the use of Transcranial Direct Current Stimulation (tDCS) to potentially Enhance Mindfulness Meditation (E-Meditation). *Brain Stimul* 2017;10:152–4. [PubMed: 27839723]
- [20]. Hunter MA, Lieberman G, Coffman BA, et al. Mindfulness-based training with transcranial direct current stimulation modulates neuronal resource allocation in working memory: A randomized pilot study with a nonequivalent control group. *Heliyon* 2018;4:e00685. [PubMed: 30094362]
- [21]. Patel R, Dawidziuk A, Darzi A, Singh H, Leff D. Systematic review of combined functional near-infrared spectroscopy and transcranial direct-current stimulation studies. *Neurophotonics* 2020;7:020901. [PubMed: 32607389]
- [22]. Yücel MA, Aasted CM, Petkov MP, Borsook D, Boas DA, Becerra L. Specificity of hemodynamic brain responses to painful stimuli: a functional near-infrared spectroscopy study. *Sci Rep* 2015;5:9469. [PubMed: 25820289]

- [23]. Yennu A, Tian F, Gatchel R, Liu H. Prefrontal hemodynamic mapping by functional near-infrared spectroscopy in response to thermal stimulations over three body sites. *Neurophotonics* 2016;3:045008. [PubMed: 28018934]
- [24]. Muthalib M, Besson P, Rothwell J, Ward T, Perrey S. Effects of anodal high-definition transcranial direct current stimulation on bilateral sensorimotor cortex activation during sequential finger movements: an fNIRS study In: Elwell CELTS, Harrison DK, ed. *Oxygen transport to tissue XXXVII advances in experimental medicine and biology*. New York, NY: Springer New York; 2016:351–59.
- [25]. Pollonini L, Miao H, Ahn H. Longitudinal effect of transcranial direct current stimulation on knee osteoarthritis patients measured by functional infrared spectroscopy: a pilot study. *Neurophotonics* 2020;7:025004. [PubMed: 32411812]
- [26]. Ahn H, Zhong C, Miao H, et al. Efficacy of combining home-based transcranial direct current stimulation with mindfulness-based meditation for pain in older adults with knee osteoarthritis: A randomized controlled pilot study. *J Clin Neurosci* 2019;70:140–45. [PubMed: 31421990]
- [27]. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039–49. [PubMed: 3741515]
- [28]. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103–15. [PubMed: 1100130]
- [29]. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017;128:56–92. [PubMed: 27866120]
- [30]. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011;63(Supple 11):S240–52. [PubMed: 22588748]
- [31]. Stratford PW, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. *Osteoarthritis Cartilage* 2007;15:266–72. [PubMed: 17046290]
- [32]. King CD, Sibille KT, Goodin BR, et al. Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1243–52. [PubMed: 23973137]
- [33]. Pollonini L, Olds C, Abaya H, Bortfeld H, Beauchamp MS, Oghalai JS. Auditory cortex activation to natural speech and simulated cochlear implant speech measured with functional near-infrared spectroscopy. *Hearing Res* 2014;309:84–93.
- [34]. Olds C, Pollonini L, Abaya H, et al. Cortical activation patterns correlate with speech understanding after cochlear implantation. *Ear Hear* 2016;37:e160–e72. [PubMed: 26709749]
- [35]. Pollonini L, Bortfeld H, Oghalai JS. PHOEBE: a method for real time mapping of optodes-scalp coupling in functional near-infrared spectroscopy. *Biomed Opt Express* 2016;7:5104–19. [PubMed: 28018728]
- [36]. Cope M, Delpy DT. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination. *Med Biol Eng Comput* 1988;26:289–94. [PubMed: 2855531]
- [37]. Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt J. Estimation of optical pathlength through tissue from direct time of flight measurement. *Phys Med Biol* 1988;33:1433–42. [PubMed: 3237772]
- [38]. Barker JW, Aarabi A, Huppert TJ. Autoregressive model based algorithm for correcting motion and serially correlated errors in fNIRS. *Biomed Opt Express* 2013;4:1366–79. [PubMed: 24009999]
- [39]. Santosa H, Zhai X, Fishburn F, Huppert T. The NIRS brain AnalyzIR toolbox. *Algorithms* 2018;11:73.

- [40]. Flor H, Diers M, Birbaumer N. Peripheral and electrocortical responses to painful and non-painful stimulation in chronic pain patients, tension headache patients and healthy controls. *Neurosci Lett* 2004;361:147–50. [PubMed: 15135915]
- [41]. de Tommaso M, Federici A, Santostasi R, et al. Laser-evoked potentials habituation in fibromyalgia. *JPain* 2011;12:116–24. [PubMed: 20685171]
- [42]. Elboim-Gabyzon M, Rozen N, Laufer Y. Gender differences in pain perception and functional ability in subjects with knee osteoarthritis. *ISRN Orthop* 2012;2012:413105. [PubMed: 24977076]
- [43]. Glass N, Segal NA, Sluka KA, et al. Examining sex differences in knee pain: the multicenter osteoarthritis study. *Osteoarthritis Cartilage* 2014;22:1100–06. [PubMed: 24999111]
- [44]. Henderson LA, Gandevia SC, Macefield VG. Gender differences in brain activity evoked by muscle and cutaneous pain: A retrospective study of single-trial fMRI data. *Neuroimage* 2008;39:1867–76. [PubMed: 18069004]
- [45]. Jensen MP, Day MA, Miro J. Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nat Rev Neurol* 2014;10:167–78. [PubMed: 24535464]
- [46]. Zeidan F, Baumgartner JN, Coghill RC. The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. *Pain Rep* 2019;4:e759. [PubMed: 31579851]
- [47]. Moulton EA, Pendse G, Becerra LR, Borsook D. BOLD responses in somatosensory cortices better reflect heat sensation than pain. *J Neurosci* 2012;32:6024–31. [PubMed: 22539862]
- [48]. Upadhyay J, Lemme J, Anderson J, et al. Test-retest reliability of evoked heat stimulation BOLD fMRI. *J Neurosci Methods* 2015;253:38–46. [PubMed: 26072245]
- [49]. Zeidan F, Martucci KT, Kraft RA, McHaffie JG, Coghill RC. Neural correlates of mindfulness meditation-related anxiety relief. *Soc Cogn Affect Neurosci* 2014;9:751–9. [PubMed: 23615765]
- [50]. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res* 2004;57:35–43. [PubMed: 15256293]
- [51]. Gundel F, von Spee J, Schneider S, et al. Meditation and the brain - Neuronal correlates of mindfulness as assessed with near-infrared spectroscopy. *Psychiatry Res Neuroimaging* 2018;271:24–33. [PubMed: 28689600]
- [52]. Aasted CM, Yucel MA, Cooper RJ, et al. Anatomical guidance for functional near-infrared spectroscopy: AtlasViewer tutorial. *Neurophotronics* 2015;2:020801. [PubMed: 26157991]

Figure 1:
(a) Location of optical emitters (red markers) and detectors (blue markers) in reference to the International 10-20 System, and (b) correspondent optical sensitivity map⁵² of the optical probe projected onto a brain model (left: frontal view; right: lateral view).

Figure 2:

Cortical hemodynamic activity of all 20 optical channels (emitters-detectors links) before active (left) and sham (right) tDCS+MBM treatment for HbO (top) and HbR (bottom). Red and blue markers denote emitters and detectors, respectively. No optical channels were found to be active at a statistically significant level ($q < 0.05$).

Figure 3:

Cortical hemodynamic activity of all 20 optical channels (emitters-detectors links) after active (left) and sham (right) tDCS+MBM treatment for HbO (top) and HbR (bottom). Red and blue markers denote emitters and detectors, respectively. Color-coded links indicate t-statistics of significantly active channels ($q < 0.05$).