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Changes in Experimental Pain Sensitivity from Using Home-Based Remotely Supervised Transcranial Direct Current Stimulation in Older Adults with Knee Osteoarthritis

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Abstract

Objective. The present study examined the effects of home-based remotely supervised transcranial direct current stimulation on quantitative sensory testing measurements in older adults with knee osteoarthritis. Participants were hypothesized to experience improved pain measurements over time. **Design**. Open-label, single-arm trial. **Setting**. Southeast Texas between March and November 2018 at a nursing school and participant homes. **Subjects**. Older adults (aged 50–85 years) with self-reported unilateral or bilateral knee osteoarthritis pain who met eligibility criteria set by the American College of Rheumatology. **Methods**. The intervention was applied with a constant current intensity for 20 minutes every weekday for two weeks (10 total sessions). Quantitative measures of pain were collected three times over 10 days (days 1, 5, and 10) and included heat threshold and tolerance, pressure pain threshold, punctate mechanical pain, pain, and conditioned pain modulation. Analyses used nonparametric tests to evaluate differences between day 1 and day 10. Generalized linear mixed models were then used to evaluate change across all three time points for each measure. Bayesian inference was used to provide the posterior probability of longitudinal effects. **Results**. Nonparametric tests found improvements in seven measures, and longitudinal models supported improvements in 10 measures, with some nonlinear effects. **Conclusions**. The home-based, remotely supervised intervention improved quantitative measurements of pain in older adults with knee osteoarthritis. This study contributes to the growing body of literature supporting home-based noninvasive stimulation interventions.

Key Words: Transcranial Direct Current Stimulation; tDCS; Pain Sensitivity; Remote Supervision; Bayesian Statistical Inference; Noninvasive Brain Stimulation

Introduction

Osteoarthritis (OA), a highly prevalent joint pathology in adults over the age of 60, is associated with significant functional impairment, poor quality of life, and a substantial burden on public health care resources [1, 2]. The knee joint is one of the preferential OA sites, and ~14 million American adults report symptomatic knee OA [3]. Pain is one of the primary reasons for individuals with knee OA to seek care [4–6]. OA pain is known to significantly influence clinical and psychosocial outcomes, is persistent in nature, and leads to substantial disability [7]. Per the Global Burden Study 2010 [8], the

number of years lived with disability for knee and hip OA was 17.1 million in 2010, and knee and hip OA is the 11th largest contributor to global disability.

The detrimental influence of pain sensitivity on the clinical course as well as treatment outcomes in chronic pain conditions is well established. Not surprisingly, individuals with OA are found to exhibit higher experimental pain sensitivity, including lower heat pain threshold, lower pain tolerance, and lower pressure pain threshold [2, 9]. Individuals reporting more severe clinical pain in the past 24 to 48 hours show greater sensitivity to experimental stimulation [10]. Such enhanced pain sensitivity is found to be widespread in nature and is not limited to the affected joints. Furthermore, objective radiographic evidence is often not consistent with an individual's self-reported distress, with severe pain and disability being reported in the absence of any radiographic evidence and vice versa. Mounting evidence indicates that OA is likely not limited to peripheral pain processing as traditionally believed, but alterations in central pain processing pathways may lead to enhanced sensitivity to nociceptive stimuli [11].

Treatment options for OA encompass a variety of modalities, including pharmacological and surgical interventions [12]. Most of these traditional therapies target peripheral pain processes, and hypoalgesia remains a significant problem; increasingly, interventions targeting central nervous system (CNS) pain processing have attracted considerable attention [13]. One such pain treatment modality that has shown promising results is transcranial direct current stimulation (tDCS). tDCS exerts a neuromodulatory effect on the CNS [14]. It is a noninvasive and relatively painless process and includes the application of low-amplitude direct electric current to the scalp [15]. Numerous studies have demonstrated and established the effective current intensities and durations and shown the intervention to be safe and well tolerated [16] for a variety of clinical outcomes. tDCS is also valuable for examining pain sensitivity via quantitative sensory testing (QST), and to date there has been limited attention paid to these measurements. A more thorough investigation into the effects of tDCS on QST measurements could provide a foundation for understanding the role of central pain processing in those with knee OA.

The aim of the present study was to examine the impact of home-based remotely supervised tDCS on longitudinal changes in QST measurements in older adults with knee OA. As older adults with knee OA have limited mobility, home-based remotely supervised tDCS was used to save the time and cost associated with attending multiple sessions over several days. Moreover, recent technological advances have minimized variability and strengthened the potential applicability of home interventions with real-time monitoring through a secure videoconferencing platform for optimal protocol adherence. The present study hypothesized that the use of home-based tDCS over a period of two weeks would improve participant responses to pain as measured across a variety of pain quantitative indices, including heat pain threshold (HPTH) and tolerance (HPTO), pressure pain threshold (PPT), punctate mechanical pain (PMP), and conditioned pain modulation (CPM) via cold pressor.

Methods

Participants

Older adults (ages 50–85 years) with self-reported unilateral or bilateral knee osteoarthritis pain were recruited in Southeast Texas between March and November 2018. Participants were considered eligible by American College of Rheumatology [17] criteria: 1) had knee pain in the preceding three months, with an average visual analog scale (VAS) pain rating of at least 30 out of 100 mm; 2) could read and speak English; 3) had a device with Internet access that could be utilized for secure videoconferencing (for remote supervision in real time); 4) had access to a distraction-free, clean, well-lit environment with a secure place to store the tDCS device and associated peripherals; 5) had no plans to change their pain medication regimen for the duration of the trial; 6) had the ability to travel to the coordinating center; and 7) were willing and able to provide written informed consent before enrollment. Exclusion criteria included 1) concurrent medical conditions that could confound symptomatic knee OA-related outcomes (prosthetic knee replacement, nonarthroscopic surgery to the affected knee); 2) a history of brain surgery, tumor, stroke, seizure, or intracranial metal implantation; 3) systematic rheumatic disorders (e.g., rheumatoid arthritis, systemic lupus erythematous, fibromyalgia); 4) serious medical illness (e.g., uncontrolled hypertension, heart failure, history of acute myocardial infarction); 5) peripheral neuropathy; 6) alcohol/substance abuse or cognitive impairment, 7) pregnancy or lactation; and 8) hospitalization within the preceding year for psychiatric illness.

This study was approved by the Institutional Review Board of The University of Texas Health Science Center at Houston before commencement and is registered at www.clinicaltrials.gov (NCT03425019). Written informed consent was obtained from all participants before participation.

Design

The design and implementation of the current study have been described fully in previous literature [18]; however, a brief description is provided here. The present study utilized a single-group, open-label design to implement home-based, real-time remotely supervised tDCS [19, 20]. tDCS was applied with a constant current intensity of 2 mA for 20 minutes every weekday for two weeks (Monday to Friday) for a total of 10 sessions. The Soterix 1 × 1 tDCS mini-CT Stimulator (Soterix Medical Inc., NY, USA) [21] was used to implement tDCS, with

headgear and 5 × 7 cm saline-soaked surface sponge electrodes. The sponge electrodes snap into custom headgear, which was secured with fail-safe electrode preparation. This single-position headgear included clearly labeled sponge markers to eliminate room for user error. Participants could only administer a session after being given a single-use code to unlock the device by research staff after proper contact quality was established. The participants could not adjust the device settings. The device timer started after participants entered the unlock code. After 20 minutes, the device automatically turned off, and research staff instructed the participant to remove the device, discard the sponges, and safely store all materials until the subsequent session. Each participant received in-person training to use the device and secure videoconferencing software during the baseline visit. All applications of the home-based tDCS were remotely supervised by the trained research staff using secure videoconferencing software (also provided to each participant).

Participants completed three visits (baseline, day 5, and day 10) to the coordinating center to complete a set of questionnaires and complete a battery of quantitative sensory testing procedures (i.e., pain sensitivity measures).

Measures

Demographic measures (i.e., age, sex, race, height, weight) and osteoarthritis duration were provided by each participant at baseline. A set of pain and clinical assessments were also obtained during each study visit. Clinical assessments for pain included the VAS and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The pain measures were considered the primary study outcomes and were reported in a preceding publication [18], along with details regarding clinical assessment and feasibility. This prior research found support for improvements to clinical pain severity assessments and sleep disturbance after completion of the 10 tDCS sessions.

Quantitative Sensory Testing Procedures

Participants completed a multimodal quantitative sensory testing (QST) battery, including heat pain threshold (HPTH) and tolerance (HPTO), pressure pain threshold (PPT), punctate mechanical pain (PMP), and conditioned pain modulation (CPM) via cold pressor. The order of heat and mechanical testing was counterbalanced, while CPM always occurred last to avoid carryover effects. Each measure in the battery has a unique developmental history that is beyond the scope of the present article; however, several original research articles and reviews [22–25] have documented the evolution of these procedures. The battery of QST measures as specifically implemented in the current study follows directly from previous work by the present research team [26–29].

Thermal Testing Procedures

Thermal stimuli were assessed using a computer-controlled TSA-II NeuroSensory Analyzer (Medoc Ltd., Ramat Yishai, Israel) to measure HPTH and HPTO on the index knee and the ipsilateral ventral forearm using an ascending method of limits. The thermode position was relocated between trials to circumvent habituation/sensitization. From the baseline of 32°C, the temperature increased by 0.5°C per second until participants opted to quit by pressing a stopping button when the sensation "first becomes painful" (for HPTH) or when they "no longer feel able to tolerate the pain" (for HPTO). Average scores across three trials at each site were computed to provide one overall measurement for both heat pain tolerance and threshold.

Mechanical Testing Procedures

Mechanical pain response was measured via two approaches. First, PPT was measured by applying blunt mechanical pressure to deep tissues using a handheld digital pressure algometer (Wagner, Greenwich, CT, USA). Pressure was increased by 0.3 kgf/cm^2 per second to measure PPT at three sites: the medial and lateral aspect of the index knee and the trapezius. Participants opted to quit by informing the experimenter when the sensation "first becomes painful." The results of three trials were averaged to provide an overall measurement at each site.

Subsequently, punctate mechanical pain (PMP) stimuli evaluated cutaneous mechanical sensitivity on the index patella and the back of the ipsilateral hand. A calibrated nylon monofilament delivered a target force of 300 g to provide verbal ratings of pain intensity on a scale from 0 (no pain) to 100 (maximum imaginable pain) following 10 contacts at one contact per second. An overall score for each site was calculated by averaging across two trials.

Conditioned Pain Modulation

Pain inhibition via CPM was measured by determining the change in PPT on the trapezius immediately following immersion of the contralateral hand up to the wrist in a cold water bath (12°C) for up to one minute. A cold pain intensity rating (PIR; 0–100) was provided by participants at 30 seconds into the trial. Water was constantly circulated and maintained at a constant temperature by a refrigeration unit (Neslab, Portsmouth, NH, USA). An increase in PPT following cold water immersion demonstrated pain inhibition.

Statistical Analyses

Sample characteristics were evaluated by descriptive statistics (i.e., frequency; central tendency). Participant characteristics (i.e., sex, race) were screened as potential confounding variables of the relationship between time and QST measures following recommendations in the literature [30, 31]. None of the screened variables

demonstrated a relationship to both time and QST measures, and therefore they did not meet criteria for inclusion in statistical models as a potential confound.

Visual inspection of histograms indicated that the distribution of each QST measure in the present study deviated from normality. As such, preliminary analyses that relied on the nonparametric Wilcoxon signed-rank test (analogous to the parametric paired-samples *t* test) were used to evaluate differences between baseline and the end of study for each measure. As in previous work [18], effect size was calculated via Rosenthal's formula ($R = Z/\sqrt{2N}$), where Z is the z-score of the Wilcoxon signed-rank test statistic and N is the number of participants in the study [32]. Spearman's rank order correlation was used to evaluate broad patterns of relationships between changes (i.e., difference scores: end of treatment – baseline) on QST measures and clinical pain measures.

Longitudinal analyses were performed via generalized linear mixed modeling (GLMM) [33] to examine changes in each QST pain measure as a function of time across three measurements (baseline, day 5, and day 10). GLMM generalizes a statistical model to evaluate non–normally distributed outcomes while allowing for the inclusion of multilevel (i.e., "random") effects. Given the non-normal distribution of each QST pain measure, outcomes were instead modeled via the skew normal distribution. Correlated observations within persons were accounted for via inclusion of a random intercept term. Given the presence of three time points, a potential nonlinear effect (i.e., a bend in the line) was tested via inclusion of a quadratic effect of time. Models demonstrating weak or no evidence of nonlinearity were reduced to a linear effect of time only.

Bayesian statistical inference was used to evaluate the probability that changes over time were nonzero for each QST pain measure. Detailed descriptions of the utility of Bayesian inference exist elsewhere [34], including the specific context of tDCS [26, 35]; however, a succinct description follows. Bayesian inference has particular utility for evaluating probabilities in smaller-sample-size trials [36–38]. Models used vague, neutral priors ($b = \sim\text{normal}\ [\mu = 0,\ \sigma^2 = 1 \times 10^5]$; *sd* and *sigma* = $\sim\text{Student}\ t\ [\mu = 0,\ \sigma^2 = 1 \times 10^5]$) to maximize the influence of the present data on posterior probabilities. The posterior distribution derived for each model directly provided the probability of the alternative hypothesis (i.e., that an effect of time exists). Consistent with our prior research [26, 35], a posterior probability ≥75% (equivalent to a Bayes factor = 0.33 or 3.00) that an effect of time exists was taken as evidence in favor of the alternative hypothesis. This probability was chosen to emphasize the value in discerning a signal for the effect of change over time; disparate researchers can and should consider their own subjective probability thresholds.

Statistical analyses were performed in the R Statistical Computing Environment [39] via the packages *coin* (for nonparametric tests) [40] and *brms* (for Bayesian GLMM) [41].

Results

Sample Description

Participants were primarily female (75%) with a mean age (SD) of 61.2 (7.2) years. Combined racial/ethnicity characteristics were diverse across participants, with nearly equal representation across African American (N = 6), Asian (N = 6), and Caucasian (N = 7), and there was one Hispanic individual. The sample was well educated, with N = 17 (85%) having completed at least two years of college, and 12 of those having completed four years. Participant BMI was overweight on average (mean [SD] = 28.3 [8.0]). Osteoarthritis duration was highly variable but had lasted for more than two years on average (mean [SD] = 29.6 [26.18] months).

Descriptive Statistics and Nonparametric Tests

Measures of central tendency and results from the nonparametric Wilcoxon signed-rank test are described in Table 1. Statistically significant differences from baseline to post-test were noted for seven of the 11 measures, including HPTO–knee, PPT–medial knee, PPT–lateral knee, PPT–trapezius, PMP–patella, PMP–hand, and CPM. All noted significant differences were in the direction of improved QST measurements (i.e., increased tolerance, lower experienced punctate pain). Spearman rank-order correlation (Table 2) found several relationships between change scores (end of treatment – baseline) within modalities of measurement; for example, changes on the PPT measures (at the lateral knee, medial knee, and trapezius) were related to each other. However, few other relationships between change scores were found in the present analysis.

Generalized Linear Mixed Modeling

Evidence for longitudinal change over time was supported for each QST measure except health pain tolerance at the forearm. Results from the GLMM analyses are summarized in Table 3. As with the nonparametric tests, changes were noted in the direction of improved QST measurements. Purely linear changes were noted for PPT–lateral knee, PMP–patella, PMP–hand, CPM, and PIR during cold water immersion. Nonlinear changes were noted for HPTO–knee, HPTH–arm, HPTH–knee, PPT–medial knee, and PPT–trapezius. For each of these measures, nonlinear changes were characterized by improved QST measurements from baseline to day 5, with a subsequent (smaller) decrease to the end of the study (but not to baseline levels or lower). Posterior probabilities for each of these noted effects exceeded the 75% threshold established in the data analytic strategy, with all effects (except PIR) exceeding 90% probability.

Table 1. Descriptive statistics and nonparametric testing results

	Day 1		Day 5		Day 10		Day 1 vs Day 10		
Measure	M	SD	M	SD	M	SD	Effect Size	Z Score	*P* Value
HPTH–arm	37.9	3.3	38.3	3.5	37.3	2.0	−0.10	−0.64	0.540
HPTH–knee	39.1	3.5	40.3	3.5	40.1	3.4	0.29	1.83	0.068
HPTO–arm	43.2	3.1	43.9	2.9	43.2	3.2	0.08	0.52	0.622
HPTO–knee	43.1	3.3	45.0	2.9	44.6	3.1	0.35	2.24	**0.023**
PPT–medial knee	3.2	1.4	3.8	1.6	3.7	1.2	0.34	2.13	**0.033**
PPT–lateral knee	3.5	1.5	4.0	1.4	4.4	1.3	0.40	2.54	**0.009**
PPT–trapezius	2.9	1.6	3.9	1.5	3.9	1.3	0.54	3.40	**<0.001**
PMP–patella	84.7	23.4	72.0	28.1	67.4	26.9	−0.33	−2.06	**0.039**
PMP–hand	66.0	27.0	57.7	29.9	54.6	23.9	−0.42	−2.62	**0.007**
CPM	0.9	0.7	1.1	0.8	1.3	0.6	0.40	2.50	**0.011**
PIR	92.3	10.3	84.0	19.8	79.0	25.2	−0.24	−1.51	0.138

Bold font indicates statistical significance at $P < 0.05$. CPM = conditioned pain modulation; HPTH = heat pain threshold; HPTO = heat pain tolerance; PIR = cold pain intensity rating; PMP = punctate mechanical pain; PPT = punctate pain threshold.

Table 2. Spearman rank-order correlations

		1	2	3	4	5	6	7	8	9	10	11	12
1	VAS	1.000											
2	WOMAC	0.394	1.000										
3	HPTO–arm	−0.565**	−0.255	1.000									
4	HPTO–knee	−0.117	0.018	0.293	1.000								
5	HPTH–arm	0.012	−0.064	0.048	0.084	1.000							
6	HPTH–knee	0.029	−0.311	0.003	0.431	0.646**	1.000						
7	PPT–lateral knee	0.026	−0.135	0.183	0.442	−0.149	0.174	1.000					
8	PPT–medial knee	0.067	0.172	−0.048	0.143	−0.081	−0.047	0.617**	1.000				
9	PPT–trapezius	−0.194	0.061	0.205	0.439	−0.186	0.083	0.623**	0.483*	1.000			
10	PMP–patella	0.386	0.451*	−0.35	−0.512*	−0.14	−0.242	−0.367	0.017	−0.045	1.000		
11	PMP–hand	0.018	−0.239	0.073	−0.282	0.055	0.269	−0.131	−0.33	−0.347	0.032	1.000	
12	CPM	−0.369	−0.292	−0.019	−0.327	0.098	−0.117	−0.553*	−0.521*	−0.570*	−0.174	0.244	1.000
13	PIR	0.447*	−0.114	−0.244	−0.218	0.146	0.106	−0.287	−0.29	−0.393	0.172	0.34	0.318

CPM = conditioned pain modulation; HPTH = heat pain threshold; HPTO = heat pain tolerance; PIR = cold pain intensity rating; PMP = punctate mechanical pain; PPT = punctate pain threshold; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

*$P < 0.05$; **$P < 0.01$.

Discussion

The present study examined the impact of open-label tDCS on improving participant responses to pain measured across specific quantitative indices over a two-week period. The results suggested a preliminary signal for tDCS as an efficacious treatment modality for knee OA pain in older adults. Nonparametric tests demonstrated significant improvements to QST measurements from baseline to end of treatment for seven out of 11 QST measures, with small to moderate effect sizes. Longitudinal analyses across all three available measurements found improved QST measurements for 10 of 11 tests, with noteworthy nonlinear patterns for five of the measures, such that improvements to QST measurements were reduced from the halfway point to the end of the study, but not to levels below baseline.

The current study provides preliminary evidence that tDCS is effective for improving QST measurements in individuals with knee OA. These results are consistent with the limited number of previous studies supporting the role of tDCS for improving QST measurements [26, 42, 43], primarily in individuals with a variety of chronic pain conditions other than knee OA (e.g., central post-stroke pain [44]; orofacial pain [45]; fibromyalgia, chronic migraine, and neuropathic pain [46, 47]).

Maladaptive neuroplasticity changes have been implicated in OA pain [48], and it is possible that tDCS may revert some of these changes [49]. Further, a body of evidence indicates that tDCS modulates a variety of CNS antinociceptive pathways, including the endogenous opioidergic system as well as the serotonergic, noradrenergic, cannabinoid, GABAergic, and glutamatergic systems [50]. Specifically, regarding the endogenous opioidergic system and the cannabinoid pathway, tDCS may provide a noninvasive adjunct/alternative intervention to several other analgesic treatments for OA pain (e.g., opioids [51]; cannabinoids [52]). Finally, tDCS has been shown to reduce levels of peripheral circulating

Table 3. Generalized linear mixed modeling results

Measure	Effect Linearity	Parameter Estimate	SE	Lower 95% CrI	Upper 95% CrI	Posterior Probability, %
HPTH–arm	Linear	−0.016	0.066	−0.146	0.118	59.9
HPTH–knee	Linear	0.447	0.217	−0.029	0.878	**96.8**
	Quadratic	−0.033	0.021	−0.075	0.013	**93.1**
HPTO–arm	Linear	0.273	0.212	−0.150	0.733	**90.2**
	Quadratic	−0.027	0.021	−0.071	0.014	**90.7**
HPTO–knee	Linear	0.518	0.254	0.040	1.050	**98.2**
	Quadratic	−0.039	0.024	−0.090	0.006	**95.6**
PPT–medial knee	Linear	0.190	0.078	0.021	0.344	**98.8**
	Quadratic	−0.012	0.008	−0.027	0.003	**94.1**
PPT–lateral knee	Linear	0.085	0.025	0.036	0.134	**>99.9**
PPT–trapezius	Linear	0.287	0.073	0.143	0.427	**>99.9**
	Quadratic	−0.018	0.007	−0.032	−0.005	**99.5**
PMP–patella	Linear	−1.026	0.671	−2.407	0.130	**95.6**
PMP–hand	Linear	−1.145	0.436	−2.013	−0.271	**99.5**
CPM	Linear	0.036	0.019	−0.003	0.075	**96.4**
PIR	Linear	−0.203	0.292	−0.896	0.367	**76.6**

Bold font indicates >75% posterior probability threshold. CPM = conditioned pain modulation; CrI = credible interval; HPTH = heat pain threshold; HPTO = heat pain tolerance; PIR = cold pain intensity rating; PMP = punctate mechanical pain; PPT = punctate pain threshold.

cytokines [35] and alleviate symptoms of depression [53]. Considering each of these factors (reverting maladaptive neuroplasticity changes, antinociceptive pathway modulation, reduced inflammation, improved affect), the signal found by the present study for the efficacy of tDCS in improving QST measures may be the result of a complex set of interconnected biological and psychological changes.

The present results should be considered preliminary when considering the lack of a sham-controlled treatment group. Improvements to trial design (i.e., a randomized controlled trial), duration, and sample size are essential to corroborate the present findings regarding the effects of home-based tDCS. These design limitations may specifically affect the interpretation of the present findings: Without a sham treatment comparison, it is difficult to determine if the nonlinear changes in QST measurements (i.e., improvement for the first five days, with some drop-off thereafter) may be due to a placebo effect. Further, the present study was limited in that accommodating participants' daily routines required some slight variability in the timing and intervals between the daily 20-minute sessions. Future studies should also consider adding a follow-up measurement to ascertain the extent to which the noted improved QST measurements last beyond the end of treatment. In light of the nonlinear trends found for some of the QST measures, the longitudinal analyses in the present study may serve as a template for future studies investigating the optimal timing of tDCS treatments. Finally, adding pain-related brain neuroimaging and biological measures would help us understand the mechanism of central pain processing of tDCS.

Conclusions

The present study showed that home-based remotely supervised tDCS provided a preliminary signal as an efficacious pain treatment modality in older adults with knee OA pain. This study contributes to the growing body of literature supporting home-based noninvasive brain stimulation interventions. Future studies with larger samples and well-designed randomized, blinded, controlled methods are needed to validate these findings.

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