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Original Report

Multifocal tDCS Targeting the Motor Network Modulates Event-Related Cortical Responses During Prolonged Pain

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Abstract: **Multifocal transcranial direct current stimulation (tDCS) targeting several brain regions is promising for inducing cortical plasticity. It remains unknown whether multifocal tDCS aimed at the resting-state motor network (network-tDCS) can revert N2-P2 cortical responses otherwise attenuated during prolonged experimental pain. Thirty-eight healthy subjects participated in 2 sessions separated by 24 hours (Day1, Day2) of active (n = 19) or sham (n = 19) network-tDCS. Experimental pain induced by topical capsaicin was maintained for 24 hours and assessed using a numerical rating scale. Electrical detection and pain thresholds, and N2-P2 evoked potentials (electroencephalography) to noxious electrical stimulation were recorded before capsaicin-induced pain (Day1-baseline), after capsaicin application (Day1-post-cap), and after 2 sessions of network-tDCS (Day2). Capsaicin induced moderate pain at Day1-post-cap, which further increased at Day2 in both groups (P = .01). Electrical detection/pain thresholds did not change over time. N2-P2 responses were reduced on Day1-post-cap compared to Day1-baseline (P = .019). At Day2 compared with Day1-post-cap, N2-P2 responses were significantly higher in the Active network-tDCS group (P<.05), while the sham group remained inhibited. These results suggest that tDCS targeting regions associated with the motor network may modulate the late evoked brain responses to noxious peripheral stimulation otherwise initially inhibited by capsaicin-induced pain.**

Perspective: ***This study extends the evidence of N2-P2 reduction due to capsaicin-induced pain from 30 minutes to 24 hrs. Moreover, 2 sessions of tDCS targeting the motor network in the early stage of nociceptive pain may revert the inhibition of N2-P2 associated with capsaicin-induced pain.***

Key words: *tDCS, multifocal tDCS, motor network, non-invasive brain stimulation, event-related evoked potentials, event-related potentials, experimental pain, capsaicin.*

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[57] At the cortical level, pain triggers a dynamic interaction between widespread brain networks that include regions such as somatosensory, operculoinsular, and cingulate cortices.[4,14,36,68] Maladaptive pain-related neuroplasticity in those regions may contribute to the development of clinical pain conditions.[3,5,14,36,61] In this context, 1 way to probe the pathways also involved in pain[10,41] is the N2-P2 components of event-related potentials (ERPs). They represent an electrophysiological outcome of the cortical integration, cognitive evaluation, and modulation of salient stimulation, and, when

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noxious stimulation is delivered, they have been reported to correlate with pain perception[12,38,65] and its associated saliency.[49] Indeed, pain is an intrinsically salient experience.[35]

Modulating such processing and potentially antagonizing pain symptoms may be done by non-invasive brain stimulation (NIBS), eg transcranial direct current stimulation over the motor cortex (M1 tDCS), which is a feasible, tolerable, patient-friendly, and safe[53] treatment option.[52] An overall rationale for using M1 tDCS to modulate the effects of pain is to restore the balance of the endogenous inhibitory pain pathways and to prevent or revert the maladaptive plasticity associated to persistent pain[23] through the modulation of the cortical and subcortical activity of the thalamus, anterior cingulate, and prefrontal cortices.[51] However, low effect sizes and inconclusive findings in experimental[50] and clinical settings[39] of traditional and high definition M1 tDCS have motivated the use of new methodologies examining the stimulation of functionally associated areas through multifocal tDCS[21,28] using a number of small-sized electrodes in order to facilitate cortical and corticospinal responses.[11,20,27,28,46] Those studies report higher effect sizes than traditional tDCS montages. In fact, even though some tDCS studies targeting solely the M1 have shown an effect,[39] M1 does not function in isolation; it interacts within the motor network.[25,32] Stimulation of more regions of this network have resulted in increased corticospinal excitability and after-effects persisted for a longer period compared with traditional M1 tDCS in healthy individuals.[20] Therefore, if there is a certain effect of M1 tDCS on the maladaptive plasticity associated to persistent pain[23] and pain perception processes,[39] it is likely that to stimulate all the network could increase its restorative effects.

In a healthy population, anodal tDCS of the left primary motor cortex facilitates early sensory ERPs.[47] Conflicting evidence on late ERPs after NIBS has been reported. Whereas anodal M1 tDCS was found to increase the event-related N2-P2 responses compared to baseline,[26] other studies show that anodal M1 tDCS[13] and M1 repetitive transcranial magnetic stimulation[9] did not modulate these potentials in healthy individuals. Moreover, NIBS-induced modulation has been speculated being state-specific, promoting antagonizing effects in sensitized pain pathways[40] rather than in pain-free non-sensitized subjects.[9]

Experimental models of prolonged pain, in contrast to clinical pain, allow measures before pain induction. Indeed, experimental pain models often induce relevant clinical characteristics such as dysfunctional pain mechanisms and cortical responses. For example, prolonged topical application of capsaicin produces ongoing pain, long-lasting hyperalgesia,[7,33] reduced corticomotor excitability,[19,20] impaired conditioned pain modulation (CPM),[6] and reduced N2-P2 ERPs although without affecting latencies.[64,67] At present, no studies have tried to normalize the reduced cortical ERPs during prolonged pain through sessions of tDCS.

The present exploratory study aimed at investigating whether the effects of experimental pain during 24 hours on behavior and its associated cortical processing may be reverted by 2 sessions of multifocal tDCS targeting the resting state motor network (network-tDCS). It was hypothesized, that 1) experimental pain for 24 hours would increase pain scores, reduce detection and pain thresholds, and inhibit the amplitude of the N2-P2 ERPs in the sham group, and 2) active network-tDCS in contrast with sham tDCS would reduce pain scores, and modulate the reduction of detection and pain electrical thresholds, as well as revert the amplitude reduction of the N2-P2 ERPs responses.

Methods

Participants

Healthy, right-handed subjects (N = 38, 16 females) between 21 and 36 years old were recruited in this parallel, double-blinded, and randomized study. Before experiments, all subjects were informed about the procedures in writing and orally, and completed a tDCS safety screen questionnaire.[2] Subjects were randomly assigned into 1 of 2 independent and sex-matched groups by employing a stratified randomization (www.random.org): Active (n = 19; 8 females; age: 26.0±4.2 years; height: 1.74±.12 m; weight: 79.8±12.8 kg) and Sham network-tDCS (n = 19; 8 females; age: 27.1±2.7 years; height: 1.75±.09 m; weight: 73.1±15.3 kg). All subjects reported to be free of chronic pain or acute pain at the time of the experiment, chili (capsaicin) allergies, pregnancy as well as neurological, musculoskeletal, and mental conditions. These data are secondary outcomes from a previous study and the sample size estimation was performed based on primary outcome parameters (corticomotor excitability to single-pulse TMS)[24] and previous publications using a similar approach.[29,34] The protocol was approved by the local ethics committee (VN-20180092), registered in clinicaltrials.gov (NCT04165980), and procedures were in conformity with the declaration of Helsinki.

Experimental Design

The effect of 24 hours of capsaicin-induced pain and 2 daily network-tDCS treatments (active/sham) were studied in 2 sessions on successive days (Fig 1) at the Center for Neuroplasticity and Pain (CNAP), Denmark. All participants were familiarized with the testing procedures before baseline assessments. The detection and pain threshold to electrical stimulation at the right volar wrist area, as well as ERPs evoked by painful electrical stimulation and their perceived pain intensity were recorded at the beginning of Day1 (Day1-baseline). Topical capsaicin was then applied on the right hand to induce experimental pain lasting 24 hours. Given that approximately 1 hour of topical capsaicin induces a robust pain and changes in cortical networks,[1] the assessment of the initial impact of capsaicin was conducted similarly to Day1-baseline approximately 50 minutes after the capsaicin application (Day1-post-cap). Subsequently, the first

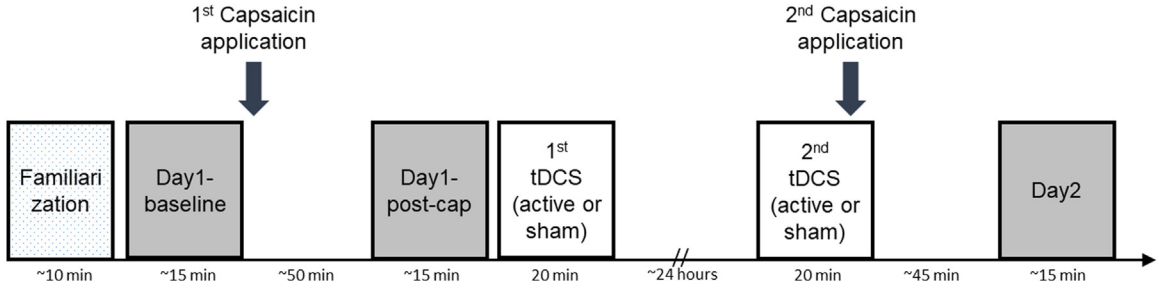

Figure 1. Experimental design of the study. After familiarization, the detection and pain thresholds to electrical stimulation as well as the event-related potentials (ERPs) to noxious electrical stimulation and self-reported pain scores due to electrical pulses delivered during ERPs recordings were registered at the right volar wrist area at the beginning of Day1 (Day1-baseline), 50 minutes after the first capsaicin application on the right hand (Day1-post-cap), and 50 minutes after the second capsaicin application on Day2 (Day2). Immediately after Day1-post-cap and after 24 hours, 20 mininutes of network-tDCS (active or sham) was applied. NRS pain scores due to capsaicin were reported every 20 minutes at the lab after first and second capsaicin patch application on Day1 and Day2, respectively.

session of network-tDCS was applied. The next network-tDCS session took place 24 hours after. Five minutes before the end of the second session of network-tDCS, capsaicin was reapplied on the right hand (beside the original capsaicin site) to ensure that pain-related responses would not be affected by the phenomenon of habituation. After 50 minutes of the second capsaicin application (Fig 1) the last assessment of ERPs and pain sensitivity were done (Day2, identical to the Day1-baseline and Day1-post-cap).

Electrical Stimulation and Related Sensations

Electrical stimulation was delivered through a stainless steel cutaneous pin electrode[43] placed on the right volar wrist at the level of the styloid process (proximal to application of experimental pain). Stimuli were delivered in 3-pulse trains (each pulse duration was 200 μs) and inter-pulse period of 5 ms[54] using an isolated electrical stimulator (NoxiTest IES 230; NoxiTest, Aalborg, Denmark). The electrical detection thresholds (EDT) and electrical pain thresholds (EPT) were assessed using an ascending method-of-limits.[54,60] An ascending ramp of stimulus intensities was delivered using steps sizes of 0.02 mA and an inter-stimulus interval of 1 seconds. EDT was defined as the minimum current value at which the participant reported a tingling sensation. EPT was defined as the minimum current value at which the participant reported a painful pricking sensation. Three trials were run for both EDT and EPT, respectively, and the resulting values were averaged for further use. Forty ERPs were recorded with variable inter-stimulus intervals between 8 to 12 seconds to avoid habituation to the frequency of the stimulation, and the stimulus intensity was fixed as 2 times the EPT[54] measured at Day1-baseline to keep stimulus intensity constant across days. At the end of the stimulation for ERPs, subjects rated the electrically-induced pain on a numerical rating scale (NRS; anchored at 0: no pain, and at 10: worst pain imaginable). EDT and EPT values were normalized by computing the ratio between the individual values and the group mean value at Day1-post-cap and used for further analysis.

Recordings of Evoked Potentials

Electroencephalographic (EEG) activity was acquired through a 32-channel system (Starstim 32, Neuroelectrics, Spain) in the 10-10 international configuration using an EEG neoprene cap (NE056 Headcap R, Neuroelectrics, Spain) with Ag/AgCl electrodes (Neuroelectrics, Spain). Thirty-one EEG channels were used for EEG acquisition referenced to the right earlobe and the remaining channel (O2) was used to convey trigger information in order to synchronize EEG activity to electrical stimulation. Electrode impedance was secured below 5 kΩ. Sampling frequency was set at 500 Hz and a band-pass filtering was applied between .5 Hz to 40 Hz. The position of the EEG neoprene cap was systematically fixed considering the nasion-to-inion and tragus-to-tragus distances of each individual, and monitored throughout the experiment. During EEG recordings, participants sat relaxed in an armchair and kept their eyes open during the electrical stimulation (approximately 7–8 minutes).

Analysis of Evoked Potentials

Offline analysis was performed using EEGLAB v14.1.2b[17] running under MATLAB (The Mathworks, Natick, MA). Visual inspection was done to identify noisy channels and movement artifacts. A linear band-pass filter with cutoff frequencies of .5 to 40 Hz was applied. Independent component analysis (ICA) of the filtered recordings was performed and this was followed by thorough inspection of ICA maps and ICA continuous recordings to extract eye movement, eye blinks, cardiac, muscle, and stimulation artifacts. Data were epoched with a duration of 3 seconds each, stimulus-locked from -1 to 2 seconds with time 0 corresponding to stimulus onset. Baseline correction was made using the -1 to 0 seconds window. The resultant baseline-corrected epochs were averaged to extract the ERPs of interest and stored for further analysis. The N2 and P2 components were identified with the recommended central-earlobe montage (Cz-A1), where the N2 was defined as the first major negative deflection after stimulus onset, and P2 was defined as the first major positive

deflection. The N2-P2 peak-to-peak amplitude was determined by combining the voltage of each peak of the biphasic component. Latencies were measured at the peak of each component. N2-P2 amplitudes as well as N2 and P2 latencies were normalized by calculating the ratio of each individual value and their group mean value at Day1-post-cap. Grand average (across all subjects) of N2-P2 responses and scalp maps of averaged N2 and P2 responses considering the range of mean latency (± SD) were performed for illustrative purposes.

Capsaicin-Induced Pain

Sustained pain was provoked for 24 hours, by applying a 4 cm x 4 cm patch of topical capsaicin (8%, Qutenza, Germany) on the distal skin area of the first metacarpus[20] on Day1 and on the center of third metacarpus on Day2 on the right hand. Both patches were kept on the same positions until the completion of the experiment on Day2. During the sessions at Day1 and Day2, subjects reported current pain intensity ratings due to topical capsaicin every 20 minutes. At the end of Day1 assessments, participants received a pain diary and were instructed to rate their pain every hour (off-lab hours) until they returned to the laboratory the following day (sleep hours excluded). Averaged NRS pain ratings were quantified at 6 different time points: using current pain NRS ratings reported during 1) first 50 minutes of capsaicin application on Day 1 (Day1−50minutes-cap), 2) after the 50 minutes of capsaicin application and before 1st tDCS session (Day1-before1st-tDCS), 3) during off-lab hours on Day1 (Day1-evening), 4) during morning hours on Day2 before the experiment (Day2-morning), 5) after 2nd tDCS session and 2nd capsaicin application (Day2-50minutes-cap), and 6) during the final 30 minutes of Day2 (Day2-final30minutes).

Transcranial Direct Current Stimulation

Network-tDCS delivered an anodal current over bilateral motor cortices (C1, C2, C3, C4, and T8) and a cathodal current over posterior parietal (P3 and P4) and frontal (F_Z) cortices using the electrode configuration designed in a previous study.[20] Using the 10−10 international EEG system, 3.14 cm^2 Ag/AgCl circular electrodes (PiStim, Neuroelectrics, Spain) were placed on the following positions administering the indicated currents: C1 = 872 μA, C2 = 888 μA, C3 = 1135 μA, C4 = 922 μA, F_Z = -1843 μA, P3 = -1121 μA, P4 = -1036 μA and T8 = 183 μA.[20] Sessions of double-blinded tDCS were conducted using tDCS system (Starstim 32, Neuroelectrics, Spain) and specific software (NIC2, Neuroelectrics, Spain). Following evidence-based guidelines on the clinical use of tDCS,[39,59] 2 consecutive daily sessions of tDCS were delivered. Administration of active and sham network-tDCS lasted 20 minutes per session during which subjects were requested to keep their eyes open and remain relaxed. Active network-tDCS applied a constant current during the 20-minute period, whereas the sham network-tDCS administered a ramped current during the first 30 seconds and the last 30 seconds of the 20-minute period while in-between no current was delivered. The examiner doing all psychophysical and electrophysiological recordings were blinded to the type of stimulation the subjects received.

Statistics

Data are presented as mean and standard deviation (SD) in text, figures and tables. Statistical analysis were carried out using SPSS (SPSS, v25.0, IBM) and significance was set at $P<.05$. Analysis of normal distribution was performed using visual inspection and Shapiro-Wilks' test. Data that did not show normal distribution (EDTs) were log-transformed and normality assessments were reconducted to apply parametric tests. Current intensity for eliciting ERPs in the 2 groups (Active and Sham network-tDCS) was compared by an independent t-test. Changes in averaged capsaicin-induced pain NRS scores were analyzed with a 2-way analysis of variance (ANOVA) with *time* (Day1-50minutes-cap, Day1-before1sttDCS, Day1-evening, Day2-morning, Day2-50minutes-cap, and Day2-final30minutes) as repeated factor, and *group* (Active or Sham network-tDCS) as the between-group factor. The impact of topical capsaicin on EDT, EPT, latencies and peak-to-peak amplitudes of N2-P2 responses, and pain NRS ratings due to electrical stimulation during EP recordings, was tested by a 2-way ANOVA performed with the factors, *time* (Day1-baseline and Day1-post-cap) as the repeated factor and group (Active or Sham network-tDCS) as the between-group factor. The impact of 2 sessions of tDCS on EDT, EPT, latencies and peak-to-peak amplitudes of N2-P2 responses, pain NRS ratings due to electrical stimulation during EP recordings, and capsaicin-induced current NRS pain scores was evaluated by a 2-way ANOVA with time (Day1-post-cap and Day2) as the repeated factor and *group* (Active or Sham network-tDCS) as the between group factor. When ANOVA factors or interactions were significant, post-hoc analysis was performed using Bonferroni corrections for multiple comparison.

Results

Capsaicin-Induced Pain

Current pain NRS ratings were zero at Day1-baseline, 3.6±1.8 and 4.3±2.5 at Day1-post-cap, and 4.4±2.2 and 5.5±2.6 at Day2 in the active and sham network-tDCS group, respectively. ANOVA of current pain NRS ratings revealed a main effect of *time* ($P<.01$) showing that the current pain was increased on Day2 compared with Day1-post-cap. No main effect of *group* nor interactions were observed.

ANOVA of averaged pain NRS ratings (Table 1) revealed a main effect of *time*. Compared to Day1-post-cap, the averaged NRS pain ratings were increased at all time points ($P<.001$). There was no significant interaction, and no significant main effect of *group*.

Table 1. Mean (± SD) Pain Numerical Rating Scale (NRS) Ratings Following Capsaicin Application at Day1

	Active Network-tDCS	*Sham Network-tDCS*
Day1-post-cap	2.3±1.3	2.6±1.7
Day1-beforetDCS	4.2±1.8	5.1±2.5
off-lab hours on Day1	4.7±1.9	6.1±2.6
off-lab hours on Day2	4.6±1.9	5.7±2.8
Day2-after2ndtDCS	3.9±1.7	4.9±2.3
Day2-final30min	4.6±2.0	6.1±2.5

Electrical Stimulation

The ANOVAs of EDT and EPT (Table 2) showed no significant main effect of *time, group* nor interactions (Table 3). Likewise, the ANOVA of pain NRS scores during electrical stimulation for ERPs (Table 2) showed no significant main effect of *time, group*, or interactions (Table 3).

N2-P2 Components of Evoked Potentials

Recordings from 2 subjects in the sham group were excluded due to technical trigger issues. Therefore, recordings from 19 participants in the active and 17 participants in the sham group were analyzed. Stimulation intensity was 0.56±0.16 mA and 0.63±0.25 mA in the active and sham group, respectively, without significant differences between groups (t=-1.44, P = .260). The topographical maps of the evoked responses (Fig 2A-D) show the scalp distributions with maximum activity on central electrodes. The N2 and P2 ERPs were clearly detectable in the active and sham network-tDCS groups (Fig 2E, F)

The ANOVA of the N2-P2 peak-to-peak amplitude at Day1-baseline and Day1-post-cap showed a significant main effect of *time* (Table 3, Fig 2E-H). No significant main effect of *group* or interaction was observed. The ANOVA of the N2-P2 peak-to-peak amplitude at Day1-post-cap and Day2 showed a significant time-x-group interaction (P<.025, Table 3). Post-hoc analysis showed a significant N2-P2 increment at Day2 compared to Day1-post-cap (P<.05) only in the active tDCS group. Posthoc results also revealed significant group differences at Day2 (P<.05), showing the impact of active network-tDCS on N2P2 amplitudes, compared to sham network-tDCS.

Latency of N2-P2 Components

ANOVA of the N2 latency as well as P2 latency showed no significant effects over *time, group* and interactions

Table 2. Mean (± SD) Raw Electrical Detection Thresholds (EDT), Electrical Pain Thresholds (EPT), Latencies of the N2 and P2, as Well as Pain Numerical Rating Scale (NRS) Scores Due to the Electrical Stimulation at Day1-Baseline, Day1-Post-Cap, and Day2 in the Active and Sham Network-tDCS Groups

	Active Network-tDCS			*Sham Network-tDCS*		
	Day1-Baseline	*Day1-Post-Cap*	*Day2*	*Day1-Baseline*	*Day1-Post-Cap*	*Day2*
EDT (mA)	.12±.06	.11±.03	.12±.04	.10±.05	.10±.05	.11±.04
EPT (mA)	.28±.08	.32±.10	.30±.12	.31±.13	.33±.16	.30±.14
N2 Latency (ms)	162.8±31.7	159.1±34.5	150.8±47.6	160.2±32.6	160.0±34.3	170.9±30. 2
P2 latency (ms)	302.6±26.2	304.3±39.2	297.1±41.7	302.8±23.1	305.8±22.6	294.8±31.7
Pain NRS during stim. (0−10)	3.6±1.3	4.0±1.2	3.9±1.6	4.4±1.8	4.6±1.9	4.3±2.0

Table 3. Results of ANOVA (F and p values) for Normalized Electrical Detection Thresholds (EDT), Electrical Pain Thresholds (EPT), Latencies and Peak-to-Peal Amplitudes of N2-P2 Event-Related Potentials, N2P2 Amplitudes, and Pain Numerical Rating Scale (NRS) Scores Due to the Electrical Stimulation at Day1-Baseline, Day1-Post-Cap, and Day2 in the Active and Sham Network-tDCS Groups

	Results of ANOVA from Day1-baseline to Day1-Post-Cap			*Results of ANOVA from Day1-post-cap to Day2*		
	Main Effect of Time	*Main Effect of Group*	*Time x Group Interaction*	*Main Effect of Time*	*Main Effect of Group*	*Time x Group Interaction*
EDT	F = .01 P = .928	F = 2.04 P = .161	F = . 00 P = .996	F = .41 P = .524	F=2.39 P = .131	F = .21 P = .652
EPT	F = 3.56 P = .067	F = .11 P = .741	F = .47 P = .496	F = 2.54 P = .120	F = .07 P = .791	F = .52 P = .475
Latency N2	F = .30 P = .588	F = .03 P = .870	F = .23 P = .633	F = .04 P = .846	F = .81 P = .375	F = 2.23 P = .144
Latency P2	F = .21 P = .650	F = .01 P = .942	F = .01 P = .908	F = 2.72 P = .108	F = .03 P = .858	F = .12 P = .735
N2P2 amplitude	F = 6.08 P = .019	F = .40 P = .529	F = 1.03 P = .318	F = .07 P = .793	F = 1.33 P = .258	F = 5.61 P = .024
Pain NRS during stimulation	F = 2.76 P = .105	F = .07 P = .791	F = .51 P = .480	F = .97 P = .330	F = .02 P = .885	F = .15 P = .704

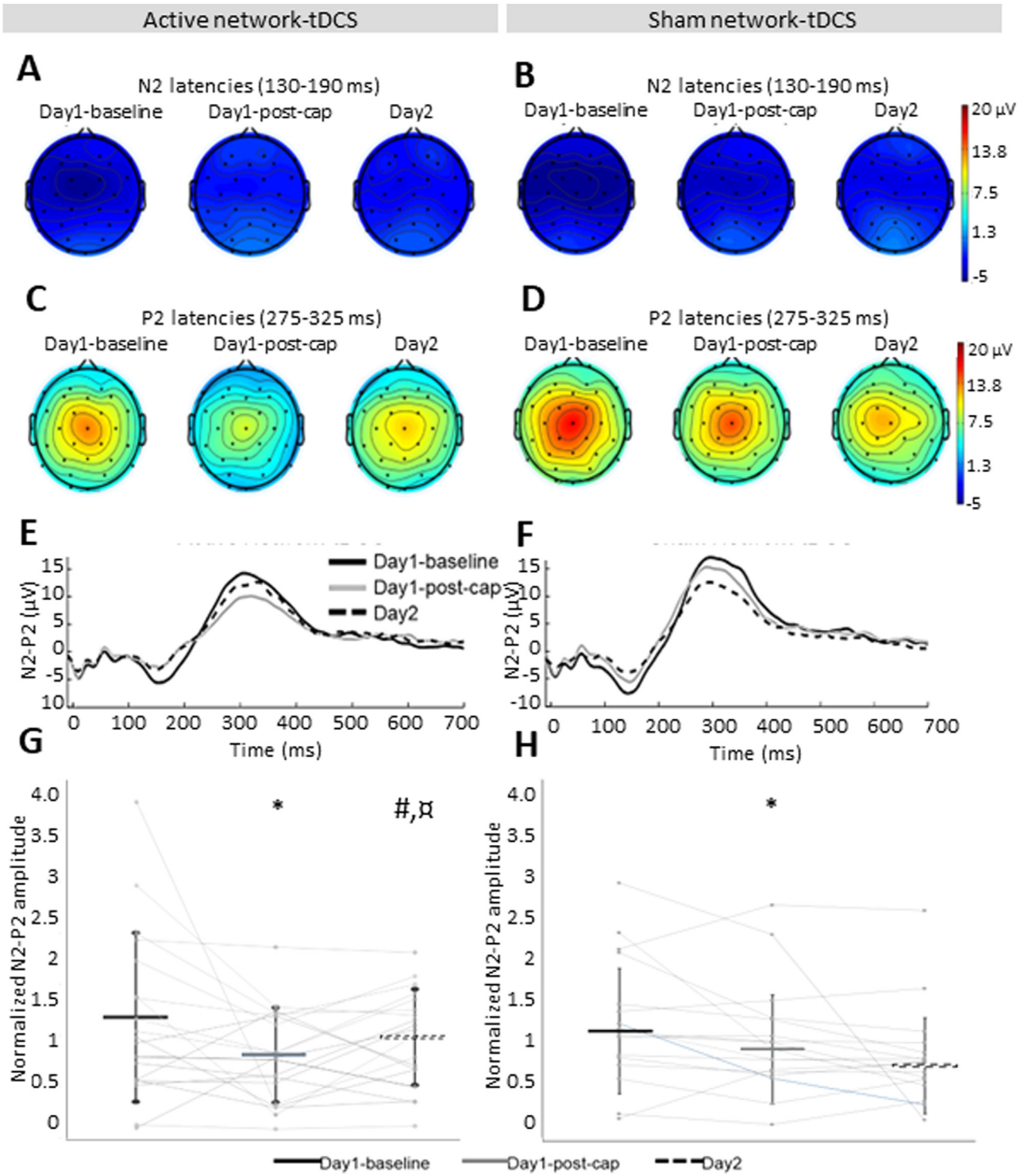

Figure 2. Scalp maps of averaged N2 **(A,B)** between 130 and 190 ms and P2 **(C,D)** between 275 and 325 ms in the active (left) and sham (right) Network-tDCS groups, respectively, at Day1-baseline, Day1-post-cap and Day 2. Grand-average evoked responses **(E,F)** and the mean (standard deviation; **G,H)** of normalized N2-P2 peak-to-peak amplitudes of evoked potentials in the active (left) and sham (right) network-tDCS at baseline (continuous black line), after capsaicin application (continuous gray line) and after active or sham tDCS (dashed line). Individual responses are illustrated in gray. Significantly decreased compared with Day1-baseline (*, $P<.05$). Significantly increased compared to Day1-post-cap (#<.05). Significantly higher compared to the sham network-tDCS group at Day2 (¤, $P<.05$).

at Day1-baseline and Day1-post-cap (Table 3). Likewise, no significant modulation of those latencies was observed over *time, group* nor interactions at Day1-post-cap and Day2 (Table 3).

Discussion

The current study explored changes in cutaneous sensitivity and event-related potentials in response to electrical noxious stimulation before and after 2 sessions of multifo-

cal tDCS over the motor network while experimental prolonged pain developed through a period of 24 hours. The results show that topical capsaicin induced sustained pain for 24 hours and exerted a reduction of peak-to-peak amplitude of N2-P2 ERPs already after 50 minutes of pain. Compared with a sham condition, network-tDCS did not elicit significant changes on the pain intensity elicited by topical capsaicin and by electrical noxious stimulations. With basis in the reduced N2-P2 ERPs after 50 minutes pain, subjects in the sham network-tDCS group demonstrated a sustained inhibition in the N2-P2 ERPs after 24 hours, while subjects in the active network-tDCS group showed a relative facilitation (towards normalization).

Effects of Network-tDCS on Capsaicin-Induced Pain and Electrical Sensory and Pain Sensitivity

Detection and pain thresholds to electrical skin stimulations were not significantly modulated by topical capsaicin for 50 minutes in line with previous studies where widespread hyperalgesia was not found during capsaicin application for up to 1 hour,[67] 3 hours, and 24 hours.[6] The results of electrical cutaneous sensitivity as well as capsaicin-induced current pain and average pain intensity indicate that two sessions of network-tDCS did not influence these outcomes significantly. Evidence of tDCS-driven pain reduction and hypoalgesia is debated.[23,39,53] In line with the results of the current study, a lack of modulation of sensory and pain sensitivity was reported when applying a battery of quantitative sensory testing (mechanical pain thresholds, pressure pain thresholds, warm detection and heat pain thresholds) after 3 consecutive sessions of either M1, M1 and dorsolateral prefrontal cortex (DLPFC), and DLPFC HD-tDCS[34] in pain-free individuals compared to sham stimulation. However, Boggio and colleagues reported increased electrical detection and pain thresholds when delivering 1 session of anodal M1 tDCS in healthy pain-free individuals.[8] An explanation for the different findings between Boggio's study with the present work may rely on the application of 1 session of traditional anodal M1 tDCS (versus network tDCS), the size and materials of the electrodes (35 cm^2 sponge vs 3 cm^2 vs Ag/AgCl circular electrodes), the use of surface electrodes (versus pin electrodes) to deliver the current stimulation, the type of phasic pain stimulation in pain-free individuals, and, as suggested by previous authors,[9] the antagonizing effects in sensitized pain pathways compared to pain-free non-sensitized subjects. Even though both network-tDCS and traditional anodal M1 tDCS facilitate corticomotor excitability,[20,37] these paradigms could possibly induce differential behavioral responses. Network-tDCS stimulates a number of interconnected regions (left and right M1, medial prefrontal cortex, and posterior parietal cortices), whereas classical anodal M1 tDCS applies an anodal current on the left motor cortex and a cathodal current on the right supraorbital area. However, findings with classical anodal M1 tDCS,[58] M1 HD-tDCS,[22] and network-tDCS[24] support the notion of activation of descending inhibitory pathways using tDCS on the M1. Indeed, network-tDCS improved conditioned pain modulation and normalized corticomotor inhibition induced due to prolonged capsaicin-induced pain in the present study cohort but published elsewhere.[24]

Reduction of N2-P2 Responses During Topical Capsaicin-Induced Pain

The present findings extend the evidence of N2-P2 reduction due to capsaicin-induced pain from 30 minutes[29,67] to at least 50 minutes, and, in the sham group, 24 hours. Moreover, the association between the N2-P2 amplitudes with the pain NRS scores during electrical stimulation across all participants at Day1-baseline and at Day1-post-cap, and only in the sham group at Day2 suggests a pain-related nature of this modulation. Accordingly, previous studies found reduced N2-P2 amplitude when elicited by stimulations in the topical capsaicin-induced secondary hyperalgesic skin area.[29,67] Since self-reported pain during the stimulation were not significantly altered, this N2-P2 reduction was attributed to spinothalamic tract (STT) inhibition.[67] In contrast, intradermal capsaicin amplifies N2-P2 ERPs when based on stimulations in the secondary hyperalgesic area,[44] showing variability of N2-P2 responses among different pain models or pain severity. Equally unexpected are findings based on early somatosensory ERPs, where increased activity in the primary sensory cortex is produced during experimental muscle soreness[16] and clinical disorders,[12] but decreased amplitude of early sensory ERPs were observed in other pain models eg injection of hypertonic saline inducing a short duration but intense pain.[62] A descending inhibitory control effect is unlikely since pain scores during electrical stimulation did not change significantly over time nor between groups. Thus, as a working hypothesis it could be that less intense pain for longer time (topical capsaicin) reduces the amplitude of noxious ERPs whereas more severe pain models for shorter time (intradermal capsaicin) could amplify the noxious ERPs. Since N2-P2 ERPs are mainly generated in the anterior cingulate cortex and the operculoinsular area,[12] they are influenced by salient and attentional factors,[15] and these factors could possibly explain the present results.[45,66] Reduction of N2-P2 amplitudes has been attributed to downregulating saliency of noxious electrical stimulation when delivering nociceptive stimulation at a constant stimulation frequency in comparison to a variable 1.[30] Even though the present work aimed to minimize this effect by applying a variable stimulation frequency, current results were comparable with the study by Iannetti et al,[30] indicating that such reduction may be attributed to a decrement of saliency to electrical stimuli due to attentional reorientation towards the topical capsaicin pain. Moreover, further work elicited N2-P2 ERPs[38] as a result of administrating nociceptive and non-nociceptive sensory, visual and auditory stimuli, suggesting that N2-P2 ERPs are non-specific to pain but correlated with the subjective degree of saliency across all modalities.[49] Therefore, N2-P2 potentials may be an indicator of the

level of saliency of an incoming stimulus,[30,49] in this case affected by the capsaicin-induced pain rather than the perception of electrical-induced pain per se. Future studies should investigate the interplay between attentional reorientation[66] (using eg attention scales) towards the conditioning (in this case capsaicin) and testing stimulus (electrical pulses) when delivering salient noxious and salient sensory stimulation. Indeed, concurrent sensory and/or painful inputs[63] "compete to be represented in the neural system".[42,41]

Effects of Network-tDCS on Cortical Pain Responses During Prolonged Pain

The present findings showed a significant modulation of N2-P2 amplitudes after network-tDCS. Although traditional anodal tDCS on M1 has previously demonstrated inconsistent effects on the N2-P2 amplitude, 1 study showed similar increase of the event-related N2-P2 responses, compared to baseline (not compared to sham).[26] It has been suggested that anodal M1 tDCS induces corticothalamic inhibition and endogenous opioid release as mechanisms of tDCS-induced analgesia. For instance, anodal M1 tDCS has produced a significant increment of functional coupling between the M1 and the ipsilateral thalamus in pain free individuals.[55] There is also evidence of decreased μ-opioid receptor binding after a session of anodal M1 tDCS in the thalamus, nucleus accumbens, ACC and insula,[18] regions that are crucial for processing and integration of pain. Other studies show a reduction in regional cerebral blood flow (rCBF) in anterior insula, an area associated to salience detection and considered to be one of the core nodes of the salience network along with the dorsal ACC,[48] after anodal M1 tDCS compared to cathodal M1 tDCS during heat pain stimulation.[31] However, the anterior insula has also been associated to decision-making relative to salience detection. Future studies are therefore warranted to explore whether tDCS-driven modulation is non-specific to pain intensity but it rather elicits changes on the stimulus saliency, or on the other side, if such modulation is attributed to decision-making or salience detection.

Limitations

Attention and saliency were not evaluated (eg through attentional and saliency scales) during or after delivering electrical pulses (for ERP recordings), limiting the conclusions of capsaicin-induced reduction of N2-P2 potentials as well as the lack of significant modulation of self-reported pain due to tDCS. Second, the aim of this study was to investigate tDCS-driven modulation of N2P2 amplitudes following noxious stimulation during prolonged pain to understand cortical integration of noxious stimuli on sensitized individuals. Given that N2P2 responses are not restricted to nociceptive pathways and that cutaneous pin electrodes may co-activate in some circumstances large myelinated Aβ fibers,[56] future research should investigate the modulatory effects of tDCS on N2P2 ERPs following nociceptive (laser) stimulation. Third, recruited subjects are young healthy individuals. It has been demonstrated that N2-P2 ERPs are age-dependent.[54] Therefore, the results of this study may not be transposable to individuals in different age ranges. The present study evaluated the modulatory effects of 2 sessions of tDCS; more specifically 50 minutes after the delivery of the second tDCS session on each subject since previous research shows significantly increased corticomotor output at 1 hour compared with 30 and 15 minutes after a network-tDCS session.[20] Future studies should evaluate though the immediate effects of tDCS on day 1 on ERPs amplitudes to understand the temporal dynamics of tDCS modulation during pain. Finally, since this is an exploratory study and the sample size was calculated based on primary outcome parameters (corticomotor excitability to single-pulse TMS),[24] future studies are needed to validate the current findings based on a priori sample size estimations.

Conclusions

The present study indicates that tDCS targeting regions associated to the motor network does not induce analgesia in experimental prolonged pain during 24 hours but is effective in the modulation of late event-related potentials in response to noxious peripheral stimulation. These findings extend the basic insight into the neurophysiological effects of tDCS and support further investigation of multifocal tDCS as a tool for modulating cortical evoked-responses. Further basic and clinical studies are necessary to prove the usefulness of tDCS in patients.

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