Transcranial direct current stimulation (tDCS) priming of 1 Hz repetitive transcranial magnetic stimulation (rTMS) modulates experimental pain thresholds

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HIGHLIGHTS

- Priming motor cortex with tDCS before 1 Hz rTMS standardizes its effects.
- This technique is applied to experimental pain thresholds.
- Cathodal tDCS – 1 Hz rTMS increased heat and cold pain thresholds.
- Anodal tDCS – 1 Hz rTMS decreased cold pain thresholds.
- tDCS priming may have applications in pain relief in the clinic.

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ABSTRACT

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) of primary motor cortex (M1) modulate cortical excitability. Both techniques have been demonstrated to modulate chronic pain and experimental pain thresholds, but with inconsistent effects. Preconditioning M1 with weak tDCS (1 mA) standardizes the effects of subsequent stimulation via rTMS on levels of cortical excitability. Here we examine whether 1 Hz rTMS, primed with tDCS, could effectively standardize the modulation of pain thresholds. Thermal pain thresholds were determined using quantitative sensory testing (QST) of the palmar thenar of both hands in 12 healthy males pre and post tDCS – 1 Hz rTMS over the hand area of the left M1. Cathodal tDCS preconditioning of 1 Hz rTMS successfully reversed the normal suppressive effect of low frequency rTMS and effectively modulated cold and heat pain thresholds. Conversely, anodal tDCS – 1 Hz rTMS led to a decrease in cold pain thresholds. Therefore, this study supports that preconditioning M1 using cathodal tDCS before subsequent stimulation via 1 Hz rTMS facilitates the production of analgesia.

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1. Introduction

Pain is a global health problem that decreases patient quality of life. Due to the multiple different causes of pain, and the complexity of the pain network, it may be that alone, pharmacology will never provide adequate pain relief. Non-invasive cortical neurostimulation techniques offer an alternative or supplement to pharmacological interventions in pain relief, and are less costly than implanted stimulation [28]. Two major neurostimulation techniques: transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), particularly of primary motor cortex (M1), have recently emerged as successful in the modulation of chronic and experimental pain [4,16]. Recent studies on the preconditioning effects of tDCS applied to M1 on subsequent rTMS suggest that this method may act to stabilize neural circuits and enable neurostimulation protocols appropriate for clinical applications. Here this preconditioning protocol is used to assess effectiveness in modulating experimental pain thresholds.

1.1. tDCS

tDCS is a neuromodulatory technique, where weak electrical current (~1 mA) is non-invasively applied to cortical targets. tDCS does not function to induce action potentials in the neurons, but rather to influence spontaneous neuronal activity already occurring in the brain in a polarity dependent fashion [15,17,27]. Anodal tDCS has been found to induce an increase in cortical excitability via the depolarisation of neuronal membrane potentials and
cathodal tDCS has been shown to decrease cortical excitability via the hyperpolarisation of these [13]. Short lasting effects of tDCS on cortical excitability are mediated by the activity of sodium and calcium channels, whereas long term after effects depend on both changes in the membrane potential and modulations of the N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptor efficacy [13].

Previous studies using tDCS to modulate pain thresholds have shown effectiveness of both anodal [1] and cathodal [2] stimulation in increasing pain thresholds [16]. This may be due to tDCS being somewhat non-focal, as the electrodes used to deliver the modulatory current are large; different electrode montages; and heterogeneous patient groups in clinical studies. fMRI studies have revealed that tDCS not only affects the underlying cortex, but also provokes sustained and widespread changes in regional neuronal activity [7]. It remains to be determined how these distant areas are affected, but it is probably through interconnections between the principally stimulated area and these structures [9]. These findings make the optimum polarity for consistent pain threshold reduction difficult to establish [16].

1.2. rTMS

rTMS is a non-invasive neurostimulation technique that can be used to modulate cortical excitability to suppress or facilitate underlying cortical activity. Stimulation of M1 with low frequency rTMS (1 Hz or less) is associated with decreased cortical excitability, whereas higher frequencies (20–50 Hz) have been associated with an increase in excitability [14].

rTMS of M1 has proven efficacious in the treatment of chronic pain [16,19]. Further, high frequency rTMS of M1 in healthy populations show this technique can modulate experimental pain thresholds [16,26]. It is thought rTMS acts to modulate pathways from the insula and orbitofrontal cortex to the posterior thalamus in order to upregulate these pain thresholds [12]. The effects of high frequency rTMS on pain thresholds have been demonstrated to last up to eight days [11].

1.3. tDCS primed rTMS

Siebner et al., demonstrate that tDCS may be used to “prime” or “precondition” the brain before subsequent stimulation via rTMS so that baseline cortical excitability can be standardized [25]. Low frequency (1 Hz) rTMS applied on its own, normally results in an inhibition of cortical excitability in relation to the targeted brain area. Siebner et al., found that preconditioning with cathodal tDCS altered the expected suppressive effect and led to cortical excitation. Similarly, preconditioning with anodal tDCS [6] resulted in an overall cortical inhibition after subsequent stimulation using 1 Hz rTMS, again altering the expected effects. These findings are thought to be due to cortical homeostatic plasticity [5].

In our study the technique of tDCS primed 1 Hz rTMS is applied to experimental pain threshold modulation. The aim is to prime M1 using a preconditioning inhibitory session of cathodal tDCS, to cause an initial inhibition of cortical activity, reducing neuronal thresholds, thereby facilitating the overall increase in cortical excitability upon subsequent stimulation of low frequency rTMS. The prediction is that this increased cortical excitation will in turn, increase pain thresholds.

2. Materials and methods

2.1. Participants

Twelve healthy males (mean age, 21.5 years, 10 right handed); naive to the experimental aims, participated in the study. No participants reported any previous or concomitant psychiatric or neurological disease, any conditions associated with acute or chronic pain or with somatosensory abnormalities. The study was performed in accordance with the Declaration of Helsinki and approved by the Faculty of Health Sciences Research Ethics Committee, Trinity College Dublin, Ireland.

2.2. Quantitative sensory testing (QST)

To determine thermal detection and pain thresholds, QST was performed using a TSA-2001 NeuroSensory Analyzer apparatus (Medoc, Ramat Yishai, Israel) that applied thermal stimuli and recorded participants’ responses [6]. Standardized instructions provided with the TSA-2001 were given to each participant. The psychophysical method of limits was used to determine: cold sensation threshold (CS); warm sensation threshold (WS); cold pain threshold (CP) and heat pain threshold (HP). A 3 cm × 3 cm thermode was attached to the palmar thenar with a Velcro® strap, with thresholds determined for the hand both ipsilateral and contralateral to M1 stimulation. For CS and WS, the threshold decreased/increased in temperature (Min temp: −10 °C; Max temp: 50 °C) at a linear rate of 1 °C/s and a return rate of 1 °C/s with an adaptation temperature of 32 °C. The threshold for CP/HP was tested 4 times with an interval of 4–6 s between each separate, successive trial. The average value of the 4 trials was expressed in degrees centigrade (°C) and taken as the participant’s detection threshold. In determining CP/HP thresholds, the thermode decreased/increased in temperature, but at a linear rate of 1.5 °C/s and return rate of 10 °C/s. These thresholds were measured over 3 successive trials with an interval of 10 s between each trial, before averaging. These threshold measurements were not counterbalanced; rather innocuous sensation perception threshold measurements (CS/WS) preceded pain perception thresholds (CP/HP) in order to avoid possible sensitivity changes caused by painful stimulation [5] (Fig. 1(a)).
2.3. Electromyograms and determination of stimulation parameters

Electromyograms (EMGs) were recorded from the right abductor pollicis brevis (APB) muscle using conductive adhesive Ag/AgCl electrodes (Tyco Healthcare, Mansfield, UK) in a belly tendon montage. EMGs were recorded through an Octal BioAmp (AD Instruments, Oxford, UK). The optimal placement for subsequent rTMS stimulation was defined as the site where single pulse TMS resulted in the largest motor evoked potential (MEP) in a consistent fashion. TMS was applied using a Magstim Rapid² stimulator (Magstim Company Limited, Whitland, Wales, UK) connected to a figure of eight coil (70 mm). The coil was angled 45° from the midline and held tangentially to the skull during stimulation as proven successful in previous studies [18]. The resting motor threshold (RMT) was defined as the minimum TMS intensity which achieved peak-to-peak MEP amplitude of ≥50 μV in the resting APB muscle, in 3 out of 5 stimulations. The RMT was measured using a reference coil [19].

2.4. Preconditioning the left M1 using transcranial direct current stimulation (tDCS)

To prime M1, tDCS (NewRonika, Italy) was applied for 10 min at 1.0 mA through a pair of saline soaked (0.89%NaCl) synthetic buckskin electrodes (25 cm²), with the active electrode above the left motor cortex and the reference electrode positioned contralaterally above the right orbit. The electrodes were held in place with use of a MindCap (NewRonika, Italy). These parameters were consistent with previous studies [25]. For sham stimulation, current flow increased gradually over a 5 s interval reaching the designated 1 mA to mimic the initial itching sensation of real tDCS. The stimulation was then terminated after 10 s, so that a conditioning effect on cortical excitability was not induced [2].

2.5. Stimulation of left M1 with 1 Hz rTMS

The coil was placed tangentially to the scalp with the handle pointing posterolaterally at a 45° angle from the midline. The coil delivered a train of 900 biphasic pulses with 1 s between pulses (15 min total duration) at 90% of the subjects’ RMT. Sham rTMS was administered with the coil tilted at a 45° angle away from the surface of the head, discharging the same number of stimuli at the same rate as Real rTMS. All rTMS protocols were carried out in accordance with the outlined safety guidelines [24].

2.6. Experimental protocol

A sham-controlled, within-subjects single-blind study was conducted, with four experimental conditions (Fig. 1(b)) performed in the order below:

1. Sham tDCS – Sham rTMS.
2. Sham tDCS – Real rTMS.
3. Cathodal tDCS – Real rTMS.
4. Anodal tDCS – Real rTMS.

Each protocol was performed on participants at the same time of day to avoid variation of pain thresholds due to circadian rhythms. There was an interval of one week in active testing conditions, with the two control conditions: (1) Sham tDCS – Sham rTMS and (2) Sham tDCS – Real rTMS presented first, on the same day. The interval was provided to avoid interference between active neurostimulation protocols that would not be controlled for by counterbalancing.

2.7. Statistical analysis

Collected data was first tested for normality of distribution using the non-parametric Kolmogorov–Smirnov test within the SPSS statistical package (version 19, IBM, New York, US). Once normal distribution was determined, it was further confirmed through the analysis of skew and kurtosis. Separate one way ANOVAs of threshold means were conducted for each condition, Pre and Post stimulation. A three-way: protocol × hand × time (4 × 2 × 2) ANOVA with planned comparisons and Bonferroni corrections was then carried out to assess statistical significance within the model. For further analysis and standardization purposes, threshold measurements were Z transformed [2], within MATLAB (version 2011b, Mathworks, Cambridge, UK) using the expression:

\[ Z = \frac{\text{Post neurostimulation score} - \text{Mean of the baseline}}{\text{Standard deviation of the baseline}} \]

where “baseline” refers to a mean of all the pre-test condition values collapsed over all experimental conditions. Differences between Z-scored QST data from the right (contralateral to stimulation) and left (ipsilateral to stimulation) palm, thenar of the hand pre and post each of the 4 individual protocols were compared for each perceptual modality (CS, WS, CP and HP) by another 4 × 2 × 2 ANOVA. Threshold values are presented as the mean of each participant’s mean ± the standard deviation.

3. Results

Twelve healthy male participants completed all protocols, designed to examine how preconditioning M1 using tDCS (cathodal, anodal and sham) may shape the effects of subsequent stimulation via low-frequency rTMS (1 Hz) on innocuous and painful thermal sensory thresholds. None of the participants experienced any adverse effects during or after the neurostimulation sessions.

3.1. Quantitative sensory testing (QST) analysis

Comparisons of the QST data within each separate condition revealed significant differences in pain, but not sensory detection thresholds, on the right hand, contralateral to stimulation, as a result of the tDCS preconditioning neurostimulation protocols (protocols 3 and 4). However, thresholds at the left, ipsilateral hand were not affected, Fig. 2.

In Protocol 3, cathodal tDCS priming -1 Hz rTMS (Fig. 2(C)), there was an increase of pain thresholds. Cold pain thresholds (CP) increased significantly from a threshold of 11.5 ± 5.2°C pre-stimulation to 5.8 ± 3.8°C post-stimulation (F(1,11) = 39.63, p < 0.001, \( \eta_p^2 = 0.783 \)), as did heat pain thresholds with mean of 45.9 ± 1.6°C pre-stimulation and 47.8 ± 1.0°C post-stimulation (F(1,11) = 23.11, p < 0.01, \( \eta_p^2 = 0.678 \)).

Contrastingly, Protocol 4, anodal tDCS priming –1 Hz rTMS (Fig. 2(D)) resulted in a decrease in pain thresholds, with a mean CP threshold of 10.5 ± 3.9°C pre-stimulation to a mean of 13.7 ± 3.7°C post neurostimulation (F(1,11) = 8.93, p < 0.05, \( \eta_p^2 = 0.448 \)) and a mean HP threshold of 46.4 ± 1.5°C pre-stimulation to 44.8 ± 2.1°C post-stimulation (F(1,11) = 12.38, p < 0.01, \( \eta_p^2 = 0.530 \)). There were few observable differences in sensory detection and pain threshold in the left hand, ipsilateral to stimulation (Fig. 2(E–H)).

To analyse the effect of neurostimulation protocols in the context of the within-subjects design, a 4 × 2 × 2 ANOVA was conducted. Main effects were seen for the interaction protocol × hand × time for both cold pain (F(3,33) = 11.061, p < 0.001, \( \eta_p^2 = 0.501 \)) and heat pain thresholds (F(3,33) = 4.765, p < 0.01, \( \eta_p^2 = 0.302 \)).
Within subject contrasts identified no differences in thresholds after control conditions (Protocol 1: Sham tDCS – Sham rTMS or Protocol 2: Sham tDCS – 1 Hz rTMS). However, Protocol 3: cathodal tDCS – 1 Hz rTMS resulted in a significant increase of pain thresholds, in regards to contralateral hand to stimulation (Right). Both cold pain thresholds (CP) \( F(1,11) = 5.57, p < 0.05, \eta_p^2 = 0.336 \) and heat pain thresholds (HP) \( F(1,11) = 8.67, p < 0.05; \eta_p^2 = 0.441 \) significantly increased. Therefore the participants experienced a decreased sensitivity for thermal painful stimuli.
Contrastingly, Protocol 4: anodal tDCS – 1 Hz rTMS facilitated a decrease in cold pain thresholds only ($F(1,11)=6.38, p < 0.05, \eta^2_p = 0.367$), but with no effect seen on heat pain thresholds. Cold pain thresholds (CP) were observed to have decreased significantly in comparison to baseline condition. In effect, the subject perceived an increased sensitivity to painful thermal stimuli, meaning they experienced pain at lesser temperatures than compared to baseline.

For standardization purposes, QST data was Z-transformed. Data revealed significant findings for both the cathodal and anodal tDCS – 1 Hz rTMS conditions identical to those seen in the previous ANOVA (Fig. 3).

4. Discussion

This study demonstrates that preconditioning M1 using tDCS prior to 1 Hz rTMS effectively modulated experimental thermal pain thresholds. Further, the direction of pain threshold modulation post-1 Hz rTMS was dependent on the polarity of tDCS priming. For the cathodal (inhibitory) tDCS – 1 Hz rTMS neurostimulation protocol, heat and cold pain thresholds significantly increased. Consistent with the concept that pre-conditioning with tDCS controls the direction of the effect of subsequent rTMS; pain threshold decreases were observed after the anodal (excitatory) tDCS – 1 Hz rTMS neurostimulation protocol [3,25].

4.1. tDCS priming to enhance 1 Hz rTMS

Low frequency rTMS (<5 Hz) is thought to facilitate a depression of neuronal excitability and is not efficacious in the modulation of pain thresholds. In contrast, high frequency rTMS (>5 Hz) has been shown to increase neuronal excitability and consequently lead to a parallel increase in pain thresholds [26]. According to a Cochrane review, 2010, [19] low frequency rTMS alone, was not worthy of further research as a possible intervention for chronic pain. However, recent studies have demonstrated that preconditioning via tDCS reverses the expected effects of subsequent administration of low frequency rTMS [8], on the basis of standardizing the primary state of activity of the targeted area of the cortex. Theoretically, this may improve the efficacy of low frequency rTMS for pain modulation. Our study applies Siebner et al.’s [25] findings to modulate experimental pain thresholds. That is, 1 Hz rTMS administered to the M1 following a priming session of cathodal tDCS can reverse the expected depressive effect on the cortex and alternatively cause a lasting increase in cortical excitability. Therefore, their concept provides the basis for the modulation of pain thresholds using tDCS to facilitate the efficient use of low frequency rTMS, which is not associated with the undesirable side effects that are so closely related to that of high frequency rTMS.

4.2. Modulation of pain thresholds

Preconditioning with tDCS before low frequency rTMS, has proven sufficient to increase pain thresholds and similarly rTMS primed anodal tDCS decreases cold pain thresholds. Therefore the study supports the possible importance of cortical homeostatic plasticity in the development of clinically relevant neurostimulation protocols [3]. However, the molecular mechanisms underlying the effects of tDCS preconditioning on rTMS remain speculative. It has been suggested that changes in glutamate release is an important factor, but evidence remains inconclusive and further research is required [3].
M1 as the most appropriate cortical target for pain modulation also remains a topic requiring further study. The mechanisms underlying the analgesic effects after M1 stimulation are not fully understood and the exact nature of the underlying pathways involved remains hypothetical [10]. Functional imaging studies have found that painful cold and heat stimuli activate multiple brain areas associated with pain modulation, including contralateral anterior cingulate cortex (ACC); contralateral primary motor and sensory cortices (M1: primary motor cortex; S1: primary sensory cortex); bilateral secondary sensory cortex (S2: secondary sensory cortex) and mid insular cortex; periaqueductal grey matter (PAG); contralateral VP thalamus; medial ipsilateral thalamus and the vermis and paraventricles of the cerebellum [21]. PET studies later supported these observations as stimulation of the M1 was seen to have resulted in an increased blood flow to the insular and orbitofrontal cortices; the ACC; the thalamus and brainstem [20].

There are a number of proposed mechanisms of pain threshold modulation via high frequency rTMS that may also apply to this tDCS preconditioning study. Firstly transcranial stimulation of the M1 may alter intracortical motor circuitry. According to Raji et al., high frequency rTMS (10Hz) was found to re-establish intracortical inhibition in parallel with pain relief [23]. This inhibition of M1 activity was related to the existence of 20Hz frequency cortical oscillations that are eliminated in the presence of chronic pain. In re-establishing this oscillatory activity, it is possible that transcranial stimulation may restore defective inhibitory mechanisms and thereby result in the modulation of pain thresholds. Alternatively, it has been suggested that of all the areas activated by painful stimulation, the thalamus; being the main relay centre for sensory information to the cortex, may have a key role in the modulation of pain thresholds. It has been hypothesized that part of the pain relief afforded by stimulation of the motor cortex could possibly be through influencing thalamic activity. High frequency rTMS may directly activate the thalamus via corticothalamic projections and thereby suppress the transmission of sensory information via the spinothalamic pathway [22].

4.3. Conclusion

In this study an inhibitory session of cathodal tDCS was observed to have effectively primed M1 resulting in an initial decrease of cortical excitability. This may cause a reduction in neuronal thresholds, thereby facilitating the reversal of the expected suppressive effect of low frequency rTMS, and alternatively producing an overall increase in cortical activity. This increased cortical excitation then in turn, increased sensory detection and pain thresholds of thermal stimuli, and successfully produced a form of analgesia. Overall, preconditioning tDCS before rTMS form a new promising approach to the modulation of pain, and also other clinical applications [3].

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