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Frequency-dependent top-down modulation of temporal summation by anodal transcranial direct current stimulation of the primary motor cortex in healthy adults

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Significance statement:

The analgesic effects of tDCS are dependent on spinal cord excitability. This work provides insight into top-down modulation during acute pain and temporal summation. This knowledge may explain why tDCS has a higher analgesic efficacy in chronic pain patients.

Abstract

Background: Transcranial direct-current stimulation (tDCS) applied over the primary motor cortex has been shown to be effective in the treatment of a number of chronic pain conditions. However, there is a lack of understanding of the top-down analgesic mechanisms involved.

Method: In this study, we investigated the effects of tDCS on the facilitation of subjective sensory and pain scores using a transcutaneous electrically-evoked measure of temporal summation. In this randomised, blinded, cross-over study healthy subjects received a single stimulus given at 0.9 x pain threshold (pTh) over the L5 dermatome on the outer part of the right leg, followed by a train of 5 stimuli given at 0.5, 1, 5 and 20Hz before and after 20 minutes of sham or anodal tDCS (2mA) applied over the primary motor cortex. Ratings of sensation and pain intensity were scored on a visual analogue scale (VAS).

Results: Temporal summation leading to pain only occurred at higher frequencies (5Hz and 20Hz). Sham or real tDCS had no effect over temporal summation evoked at 5Hz, however there was a significant analgesic effect at 20Hz. Sham or real tDCS had no effect over acute, single-stimuli evoked-responses.

Conclusion: These results indicate that anodal tDCS applied to the primary motor cortex preferentially modulates temporal summation induced by high frequency electrical stimulation-induced pain. The inhibitory effects of tDCS appear to be dynamic and dependent on the degree of spinal cord excitability and may explain the higher analgesic efficacy in patients with moderate to severe chronic pain symptoms.

Introduction

Transcranial direct current stimulation (tDCS) can modulate cortical activity by depolarising or hyperpolarising cortical neuronal resting membrane potentials depending on the polarity of current stimulation (Gorman, 1966, Purpura and McMurtry, 1965). There is a growing body of evidence that anodal tDCS applied over the primary motor cortex provides pain relief in a number of neuropathic, visceral and inflammatory chronic pain conditions (Ahn et al., 2017a, Bolognini et al., 2015, Borckardt et al., 2017, Borckardt et al., 2011, Hagenacker et al., 2014, Harvey et al., 2017, Jurgens et al., 2012, Khedr et al., 2017a, Kim et al., 2013, Volz et al., 2016). However, the analgesic mechanisms mediating these effects have been more difficult to elucidate.

Neuroimaging studies have shown that tDCS applied over the primary motor cortex can indirectly activate areas of the brain involved in the modulation of pain perception (Yoon et al., 2014, Ihle et al., 2014, Sankarasubramanian et al., 2017). There is also a growing body of evidence to suggest opioid systems in the midbrain are activated during tDCS (DosSantos et al., 2014, DosSantos et al., 2012) and that patients receiving tDCS may require less opioid-analgesia (Khedr et al., 2017b). The analgesic effects of tDCS have also been enhanced when used alongside conditioned pain modulation (CPM) paradigms in healthy subjects suggesting bottom-up changes in supraspinal sites may be involved (Flood et al., 2016, Reidler et al., 2012). It is therefore possible that tDCS applied over the primary motor cortex may be involved in the top-down modulation of pain processing at the spinal level.

The majority of studies have investigated the effects of tDCS applied over different cortical areas on acute pain thresholds, yielding contradictory results. A combined neuroimaging and pain testing study showed primary motor cortex tDCS could modulate cortical nociceptive processing but had no impact on heat and mechanical pain thresholds (Ihle et al., 2014) and similar observations have been reported following sensory cortex stimulation during acute pain tests (Koyama et al., 2017). Interestingly, others have found that tDCS could preferentially modulate higher-intensity heat stimuli, with no effect over low or moderate heat stimulation (Aslaksen et al., 2014). It is also apparent that the effects of tDCS are enhanced when used in combination with peripheral electrical stimulation in patients with non-specific low back pain (Hazime et al., 2017).

In contrast, it has recently been shown that direct current stimulation applied over the thoracic spinal cord can modulate temporal summation of the nociceptive withdrawal reflex and pain scores via a segmental inhibitory mechanism (Perrotta et al., 2016). Temporal summation provides a means by which to study how the brain can modulate the central integration of sensory stimuli in the spinal cord. The repetition of a single non-painful stimulus which integrates to cause pain has been previously demonstrated using electrical stimulation delivered at different stimulation frequencies (Arendt-Nielsen et al., 2000). Changes in central excitability can occur following activation of NMDA

receptors present on wide dynamic range (WDR) neurons in the dorsal horn (Dickenson and Sullivan, 1987) and is an important pathological mechanism associated with the development of chronic pain (Woolf, 2011). Despite this, there has been a lack of research into the effects of tDCS on the temporal summation of sensory stimuli leading to pain in healthy adults.

These lines of evidence have led us to investigate the top-down modulation of spinal cord excitability measured via the temporal summation of innocuous tactile stimuli leading to pain perception in healthy subjects. We examined the influence of anodal tDCS and sham stimulation applied over the primary cortex on sensory and pain intensity ratings during single and repeated electrical stimulation delivered at different frequencies.

Materials and Methods

Participants

With ethical approval and written informed consent 15 healthy males (mean ± SD age: 22.5 ± 5.4 years) were recruited into the study. Subjects were excluded if they met the criteria for exclusion for pain testing (i.e. peripheral small-fibre neuropathy, lumbar radiculopathy, rheumatoid arthritis or any other potentially confounding conditions) and tDCS (i.e. metal implants, cardiac pacemaker, history of epilepsy or fits, previous brain injury, neurosurgery, neurological disorders, psychological disorders, actively taking antidepressants or other neuromodulatory drugs).

Electrical stimulation and temporal summation

A pair of Ag/AgCl electrodes (self-adhesive, 2 cm diameter, CareFusion, UK) were positioned over the skin of the right L5 dermatome (Figure 1A). Each transcutaneous electrical stimulus consisted of a standard, constant-current 1-ms duration pulse using a constant current stimulator (DS7A, Digitimer, UK). Temporal summation was measured using a modified version of the protocol used previously (Arendt-Nielsen et al., 2000) by determining the intensity rating after a single transcutaneous electrical stimulus and at the end of a train of 5 stimuli given at 4 different inter-stimulus frequencies (0.5Hz, 1Hz, 5Hz and 20Hz).

Intensity rating scale

Subjects rated the sensation and pain intensity on an 11-point visual analogue scale (VAS; 0 - 10 i.e. 0: no sensation; 1-4: 1 gentle tap; 4: heavy tap; 5: pain threshold; 10: worst pain). Pain threshold (pTh) was determined by increasing the current intensity (in 0.5mA steps) from 1mA until the sensation transitioned from being a ‘‘heavy tapping sensation’’ (i.e. 4 VAS intensity rating) into a ‘‘short, localised or pin-prick pain’’ (i.e. 5 VAS intensity rating).

Primary motor cortex localisation

The site over the primary motor cortex for tDCS stimulation was localised using transcranial magnetic stimulation (TMS). TMS was applied to the cortex using a Magstim 200^2 mono-phasic stimulator (The Magstim Company Ltd., UK) connected to a figure-of-eight coil (wing outer diameter 10cm), positioned over the approximate location of the primary motor cortex at a site which elicited motor evoked potential (MEP) in the tibialis anterior (TA) muscle (i.e. hotspot). The position of the coil was then marked with an indelible to ensure accurate placement of the tDCS anode electrode throughout the experiment.

tDCS

tDCS was delivered by a battery-driven stimulator (neuroConn GMBH, ilmenau, Germany) connected to a pair of electrodes (4 x 4cm). The anode was placed over the primary motor cortex hotspot contralateral to the side receiving pain testing and the cathode was placed over the contralateral supraorbital cortex and were fixed in place using conductive gel (Saturnino et al., 2015) (Figure 1B). A 10-second current ramp-up time was used to reach a 2mA intensity which was applied for 20 minutes, followed by a 10 second current fade-out period which is in line with current safety guidelines (Poreisz et al., 2007, Woods et al., 2016). Sham stimulation consisted of the same electrode placement, but the stimulator was programmed to ramp down after 30 seconds ensuring the initial sensation of tDCS and sham conditions were identical, without producing any stimulation.

Experimental procedures

Subjects were seated on a couch with knee extended to 180° and hip flexed to 90°. Each subject underwent 2 experimental sessions (separated by at least a week) involving single stimulation and temporal summation measurements pre- and post-anodal or sham tDCS given in a randomised, blinded manner. Before the experiment started, each subject was trained in using the intensity rating scale. The training consisted of increasing the current intensity from 0 mA until the sensation was first detected (i.e. light tap; 1 VAS), followed by 0.5 mA increments until the sensation transitioned from a light tap into moderate tap (i.e. 2-3 VAS) and from a heavy tap (i.e. 4 VAS) into a sharp, pin prick pain (i.e. 5 VAS). It was made clear to all subjects what the difference between a heavy tap and pin prick pain before starting the experiment. The pTh was determined by increasing the stimulus intensity in 0.5mA steps until the sensation moved from a heavy tapping sensation into a pin-prick pain. Stimulus frequencies were normalised according the pTh and in order to evaluate the facilitation of innocuous stimuli leading to pain, 0.9x pTh was determined in each participant. During each 90-minute session, VAS ratings after a single stimulus at 0.9x pTh were determined and at the end of the train of 5 at 0.5, 1, 5 and 20Hz given at the same intensity before (baseline) and immediately after anodal or sham tDCS. Trains of stimuli at different frequencies were delivered in a random order, separate by 1 minute

to reduce potential carry-over effects, pre- and post- tDCS or sham-tDCS. Acute, single stimulus pain VAS ratings at 1.0x pTh were also determined before and after anodal or sham tDCS.

Statistical analysis

All data are normally distributed, expressed as mean ± SEM and were analysed using SigmaPlot 12.5 (Systat Software Inc, UK). The temporal summation of innocuous stimulation leading to pain (i.e. > 5 VAS intensity rating) at different stimulation frequencies were compared using one-way RM ANOVA with Holm-Sidak multiple comparison post-hoc tests against the control single stimulus-evoked VAS intensity rating. Mean pre- versus post-anodal or sham tDCS VAS intensity ratings were compared using paired t-tests. Statistical significance was set at $p<0.05$.

Results

Temporal summation leading to pain occurs at 5Hz and 20Hz stimulation frequencies

There was a significant facilitation of VAS intensity rating scores when the frequency of stimulation at 0.9x pTh was increased ($F_{4,14} = 23.8$, $P<0.001$; figure 2). Multiple comparison post-hoc analysis revealed that there was a significant increase in VAS intensity rating compared to a single stimulation (0.9x pTh: 3.93 ± 0.28) when temporal summation induced by electrical stimulation at 5Hz (5.66 ± 0.27; $p<0.001$) and 20Hz (6.33 ± 0.32; $P<0.001$), but not at 0.5Hz (4.07 ± 0.32; $P=0.5$) or 1Hz (4.27 ± 0.21; $P=0.4$).

Anodal primary motor cortex tDCS reduces temporal summation induced by electrical stimulation at 20Hz stimulation frequency

tDCS had no effect on VAS ratings during 0.5Hz (0.5Hz pre-tDCS: 4.06 ± 0.31 versus post-tDCS: 3.66 ± 0.25; $P=0.3$; 0.5Hz pre-sham: 4.13 ± 0.19 versus post-sham: 4.07 ± 0.23; $P=0.8$) or 1Hz (1Hz pre-tDCS: 4.27 ± 0.21 versus post-tDCS: 4.27 ± 0.23; $P=1.0$; pre-sham: 4.33 ± 0.16 versus post-sham: 4.33 ± 0.25; $P=1.0$) stimulation frequencies (i.e. at temporal summation frequencies that did not lead to pain). tDCS was still without effect when temporal summation lead to pain at 5Hz (pre-tDCS: 5.67 ± 0.27 versus post-tDCS: 5.27 ± 0.18; $P=0.08$; sham-tDCS: 5.53 ± 0.40 versus post-sham 5.33 ± 0.32; $P=0.7$), however there was a significant analgesic effect at 20Hz stimulation frequency (pre-tDCS: 6.33 ± 0.32 versus post-tDCS: 5.67 ± 0.25; $P=0.03$; pre-sham 5.87 ± 0.32 versus post-sham: 6.13 ± 0.35; $P=0.2$; figure 3A). Difference score analysis (figure 3B) before and after tDCS revealed a significant change in VAS intensity rating compared to sham following 20Hz stimulation (tDCS: -0.66 ± 0.27 versus sham: 0.27 ± 0.30; $P=0.02$), but not 5Hz (tDCS: -0.40 ± 0.21 versus sham: -0.20 ± 0.47; $P=0.7$), 1Hz (tDCS: 0.00 ± 0.24 versus sham: 0.00 ± 0.26; $P=1.0$) or 0.5Hz (tDCS: -0.40 ± 0.36 versus sham: -0.06 ± 0.24; $P=0.4$).

Anodal primary motor cortex tDCS has no effect on acute VAS intensity ratings

tDCS and sham stimulation had no effect on single stimulation given at 0.9x pTh (pre-tDCS: 3.93 ± 0.28 versus post-tDCS: 4.14 ± 0.23; P=0.7; pre-sham: 3.86 ± 0.18 versus post-sham: 4.0 ± 0.32; P=0.7; figure 4A) and 1.0x pTh (pre-tDCS: 5.14 ± 0.23 versus post-tDCS: 5.07 ± 0.24; P=0.7; pre-sham: 5.00 ± 0.18 versus post-sham: 4.93 ± 0.34; P=0.4; figure 4B).

Discussion

We investigated the top-down modulation of temporal summation in healthy adults. Using an electrical stimulus applied over the L5 dermatome, we showed that a single, innocuous tapping sensation can summate leading to pain perception when repeated at a frequency of either 5Hz or 20Hz. When anodal tDCS was applied at 2mA for 20 minutes over the primary motor cortex, there was a significant reduction in pain intensity rating when temporal summation was induced by electrical stimulation at 20Hz stimulation frequency. tDCS had no effect over acute sensory and pain responses and was also without effect at 0.5Hz, 1Hz and 5Hz stimulation frequencies. These findings indicate that primary motor cortex stimulation with tDCS dynamically modulates spinal nociceptive processing and is dependent on the degree of temporal summation, indicative of central excitability. They may also provide insight into the efficacy of tDCS in both clinical and non-clinical settings.

There is a growing body of evidence that suggests tDCS is more effective in patients with chronic pain (Ahn et al., 2017a, Bolognini et al., 2015, Borckardt et al., 2017, Borckardt et al., 2011, Hagenacker et al., 2014, Harvey et al., 2017, Jurgens et al., 2012, Khedr et al., 2017a, Kim et al., 2013, Volz et al., 2016) compared to studies that have attempted to dissect the analgesic mechanisms in healthy subjects (Csifcsak et al., 2009, Hansen et al., 2011, Jurgens et al., 2012, Ihle et al., 2014, Aslaksen et al., 2014, Boggio et al., 2008). These lines of evidence have now not only shown a reduction in pain intensity in chronic pain patients, but also distinct changes in the brain regions involved in the top-down modulation of pain processing. In a recent study, tDCS improved clinical pain and mood ratings in fibromyalgia patients which was correlated with changes in serum endorphin levels (Khedr et al., 2017a). This suggests activation of the opioid system, in part, mediates the analgesic effects of primary motor cortex tDCS and others have shown the release of opioids in the midbrain in both healthy subjects (DosSantos et al., 2014) and during chronic pain (DosSantos et al., 2012). Similar clinical pain-relieving effects have been seen in elderly patients with chronic musculoskeletal pain (Harvey et al., 2017, Ahn et al., 2017b), small-fibre neuropathy (Kim et al., 2013) and in patients with chronic visceral pain (Volz et al., 2016). Further positive results have demonstrated that primary motor cortex stimulation may provide an effective treatment in drug-resistant neuropathic pain conditions; showing analgesic effects in phantom limb pain (Bolognini et al., 2015) and trigeminal neuralgia (Hagenacker et al., 2014).

The results from human mechanistic studies in healthy volunteers have been more contradictory, with a number of authors reporting either weak or non-existent analgesic effects (Csifcsak et al., 2009, Hansen et al., 2011, Jurgens et al., 2012, Ihle et al., 2014, Aslaksen et al., 2014, Boggio et al., 2008). This could be because tDCS is often delivered over a number of days in chronic pain patients which may result in an accumulation of top-down analgesia (Khedr et al., 2017a). Additionally, it could be due to the variability in the tDCS montages used in healthy subject studies. A number of studies have shown more beneficial analgesic effects following 2 mA stimulation of the primary motor cortex (Aslaksen et al., 2014, Boggio et al., 2008) than 1 mA stimulation (Csifcsak et al., 2009, Hansen et al., 2011, Jurgens et al., 2012, Ihle et al., 2014). In this study, we found no effect on acute pain, however there was a preferential modulation of the highest temporal summation-induced pain intensity following 2 mA tDCS. This is in line with a study showing the same tDCS montage could modulate the response to a thermal wind-up testing paradigm (Borckardt et al., 2012). Taken together, these lines of evidence suggest that tDCS may have a higher analgesic efficacy when used in chronic pain patients or in experimental models of pain hypersensitivity.

There are now a number of lines of evidence which suggest that the analgesic effects of tDCS are enhanced in both experimental and clinical settings in response to bottom-up activation supraspinal sites involved in the modulation of pain (Hazime et al., 2017, Flood et al., 2016, Reidler et al., 2012, DosSantos et al., 2014). Our results are in-keeping with these studies, in that tDCS was only effective during high frequency repeated stimulation associated with the highest pain intensity rating. Others have also suggested that tDCS was more effective during a high intensity thermal stimulation which the authors suggest was at a pain intensity rating more comparable to clinical pain syndromes (Aslaksen et al., 2014). It is possible that the analgesic efficacy of tDCS may be dependent on a baseline level of cortical network activity associated with pathological or abnormal pain. This has been shown to be case for pharmacological agents such as ketamine, which has a greater effect during experimentally induced increased spinal cord excitability compared to acute testing (Arendt-Nielsen et al., 1995). It may therefore be that non-invasive brain stimulation techniques are more effective during pathological pain states or when pain pathways become sensitised (Bradley et al., 2016).

The temporal summation of repeated electrically-evoked sub-threshold inputs to the dorsal horn leading to pain involves the integration of a train of incoming sensory signals in dorsal horn neurons (Arendt-Nielsen et al., 1994). It is the human equivalent of the wind-up phenomenon observed in animals and is a form of transient synaptic plasticity dependent on the activation of NMDA receptors present on WDR in the dorsal horn (Arendt-Nielsen et al., 1995, Dickenson and Sullivan, 1987). Interestingly, we found that both 5 Hz and 20 Hz stimulation over the L5 dermatome resulted in the temporal summation of innocuous stimuli leading to pain, but only saw a significant analgesic effect of tDCS in the 20 Hz condition. We found that higher stimulation frequencies were associated with a

higher pain intensity rating which may indicate a greater degree of NMDA-mediated neuronal plasticity at WDR neurons. This is in line with previous research using temporal summation of the nociceptive withdrawal reflex at increasing stimulation frequencies (Arendt-Nielsen et al., 2000) and may be associated with a stronger bottom-up activation of supraspinal sites (Flood et al., 2016). In line with this, functional neuroimaging studies have shown that changes in spinal cord excitability can increase the bottom-up activation of cortical and brainstem regions involved in pain control (Bosma et al., 2015, Perrotta et al., 2017). We have shown that tDCS can reduce the perception of pain in response to temporal summation-induced plasticity in pain pathways; it is therefore possible that the effects of tDCS are dynamic and dependent on the degree of bottom-up activation and functional connectivity in pain-related brain regions. This is in agreement with a recent study which demonstrated that changes in the functional connectivity in endogenous analgesic circuits could predict the analgesic response to tDCS in fibromyalgia patients (Cummiford et al., 2016).

In summary, this study demonstrates the dynamic modulation of pain perception using tDCS applied over the primary motor cortex in healthy subjects. We have shown that tDCS is only effective during temporal summation of electrically-evoked stimuli when delivered at higher frequencies and the highest pain ratings over the L5 dermatome, showing no analgesic effects during acute or lower-frequency stimulation. Together, this indicates that a degree of spinal cord plasticity is required for tDCS to show a beneficial modulation of pain perception. We suggest that tDCS may play a key role in the top-down modulation of endogenous analgesic mechanisms present in both healthy subjects and chronic pain patients and could also provide a novel treatment for patients suffering from chronic pain in lower limbs as a result of radiculopathy.

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Figure legends

Figure 1. Electrode placement. A) A pair of Ag/AgCl electrodes was positioned (~30mm inter-electrode distance) over the skin of the L5 dermatome. B) The tDCS electrodes (16cm^2) were placed over the primary motor cortex hotspot contralateral to the side receiving pain testing (anode) and the cathode was placed over the contralateral supraorbital region (cathode) using conductive gel.

Figure 2. Temporal summation at 0.9x pTh. Shown here is the VAS intensity rating after a single stimulus at 0.9x pTh and in a train of 5 at 0.5, 1, 5 and 20Hz during baseline testing. The integration of innocuous stimuli into painful stimuli (>5 VAS intensity rating) occurred when 0.9x pTh was delivered at 5Hz and 20Hz.Data expressed as mean ± SEM; *** P<0.001 versus single stimuli; n=15.

Figure 3. tDCS preferentially modulates temporal summation induced by 20Hz electrical stimulation. A) tDCS reduced pain VAS intensity rating at 20Hz stimulation frequency. B) Only 20Hz stimulation frequency was associated with a reduced intensity rating following tDCS. Data expressed as mean ± SEM; * p<0.05; ns - not significant; n=15.

Figure 4. tDCS has no effect on acute innocuous or noxious pain responses. A) sham and tDCS had no effect on acute innocuous VAS ratings given at 0.9 x pTh. B) sham and tDCS had no effect over acute noxious VAS ratings given at 1.0 x pTh. Data expressed as mean ± SEM; ns - not significant, n=15.

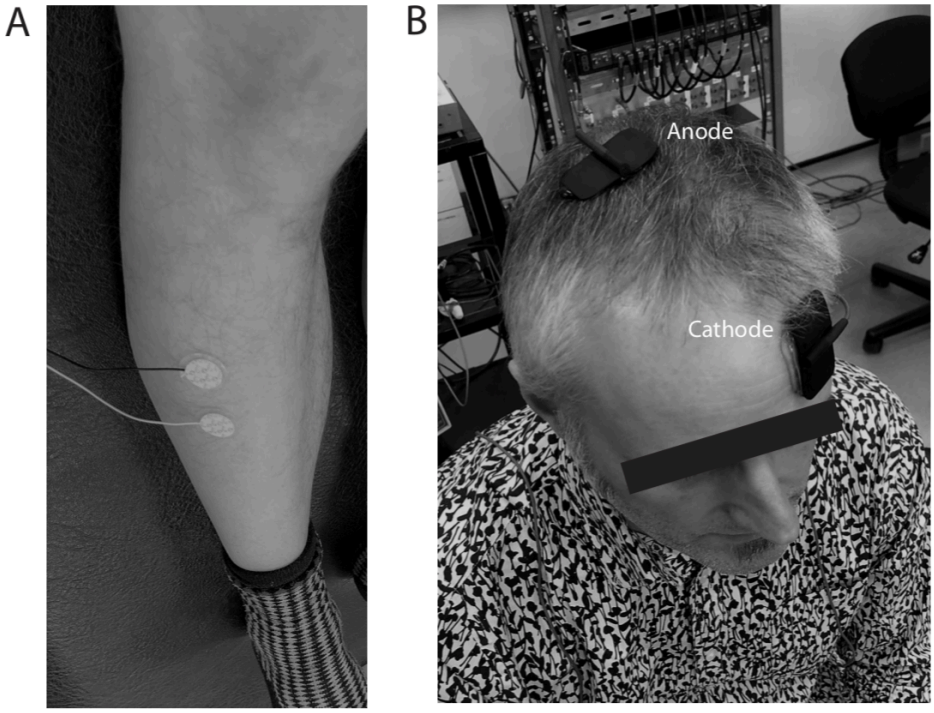


Figure 1.

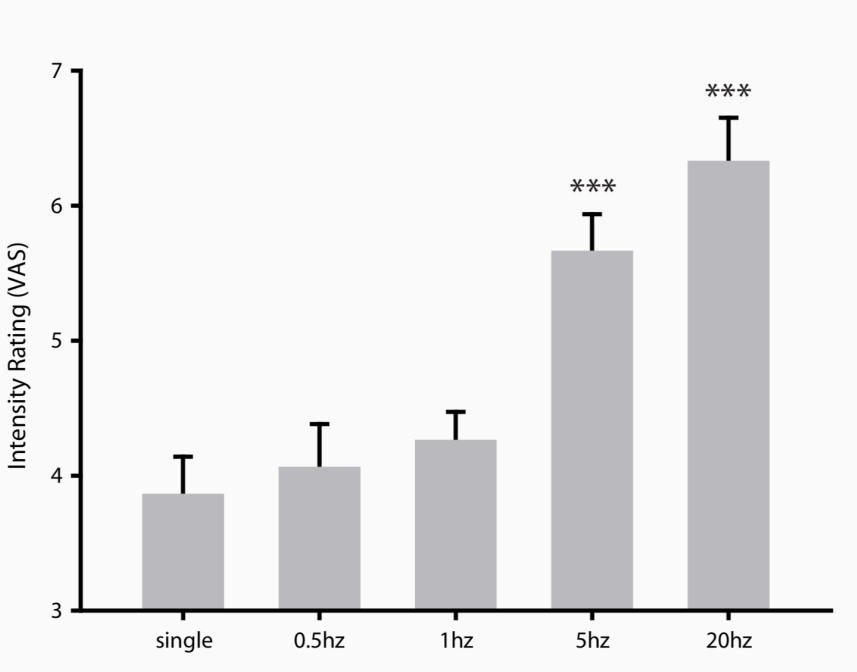


Figure 2.

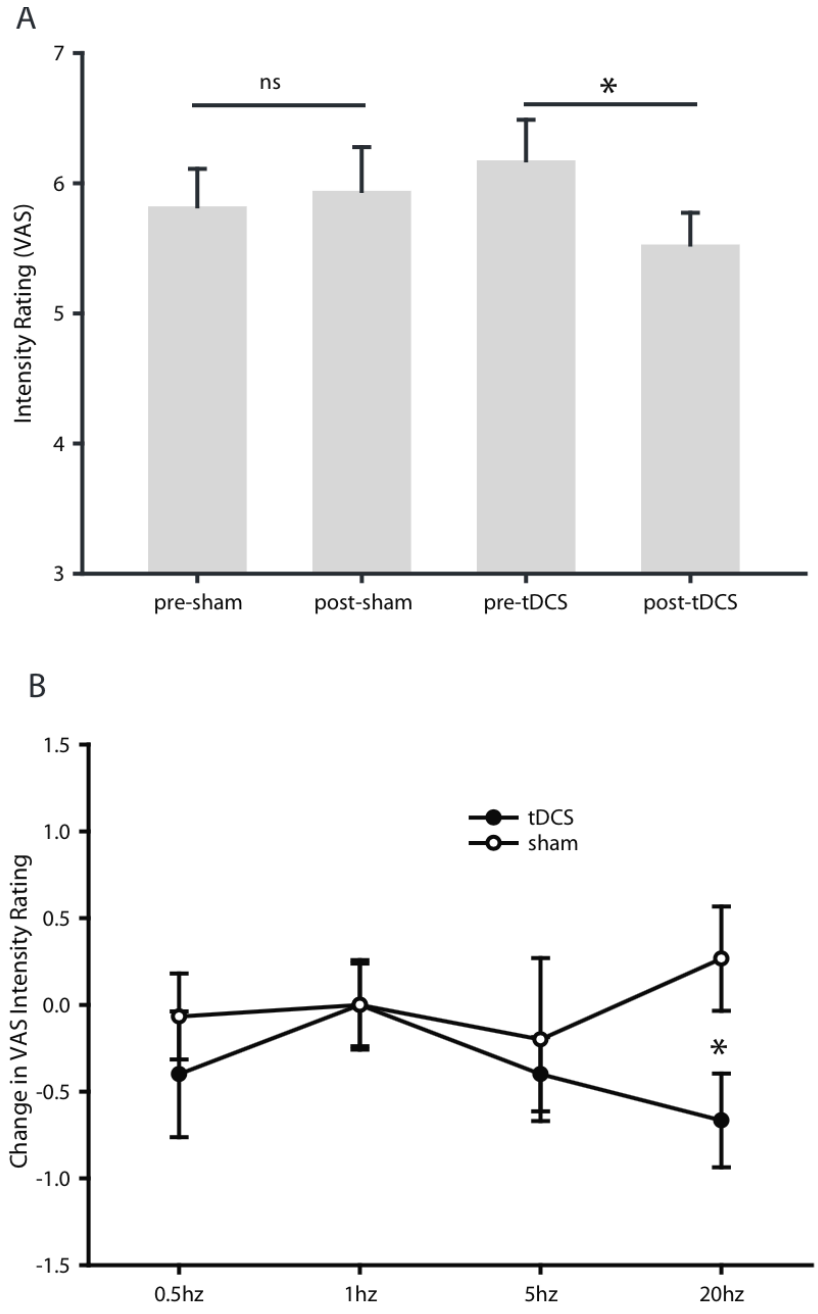
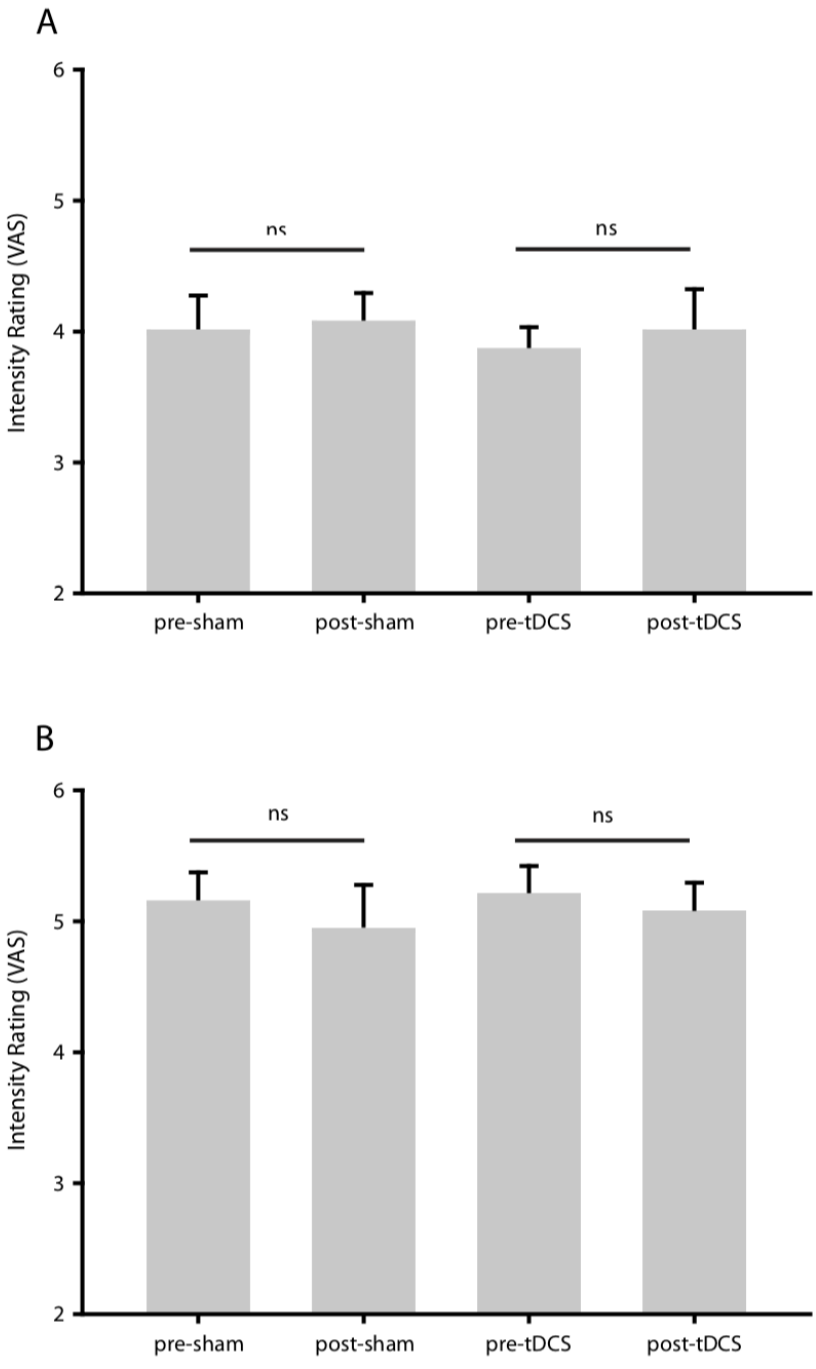

A
7
6
5
4
3
Intensity Rating (VAS)
ns
*
pre-sham
post-sham
pre-tDCS
post-tDCS
B
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Change in VAS Intensity Rating
tDCS
sham
*
0.5hz
1hz
5hz
20hz

Figure 3.


A
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Intensity Rating (VAS)
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post-sham
pre-tDCS
post-tDCS
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6
5
4
3
2
Intensity Rating (VAS)
ns
ns
pre-sham
post-sham
pre-tDCS
post-tDCS

Figure 4.