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Anodal transcranial direct current stimulation over the primary motor cortex attenuates capsaicin-induced dynamic mechanical allodynia and mechanical pain sensitivity in humans

Running title: Attenuation of mechanical sensitivity following tDCS.

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Original article

Conflict of interest statement: The authors report no conflicts of interest.

Funding: Imperial College London

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Significance (80 words): This research shows new evidence that anodal tDCS over the primary motor cortex can reduce dynamic and static forms of mechanical pain sensitivity in the capsaicin model of ongoing pain. By using this approach, it may be possible to provide mechanism-driven analgesia in chronic pain patients who have dynamic mechanical allodynia and/or secondary mechanical hyperalgesia.

Abstract

Background: Anodal transcranial direct current stimulation over the primary cortex has been shown to activate regions of the brain involved in the descending modulation of pain sensitivity. However, more research is required in order to dissect the spinal cord analgesic mechanisms associated with the development of central sensitisation.

Methods: In this randomised, double blind, cross over study 12 healthy participants had baseline mechanical stimulus response (S/R) functions measured before and after the development of capsaicin-induced ongoing pain sensitivity. The effects of 20 minutes of either real or sham transcranial direct current stimulation (tDCS, 2 mA) over the primary motor cortex on dynamic mechanical allodynia (DMA) and mechanical pain sensitivity (MPS) was then investigated.

Results: Topical application of capsaicin resulted in an increase in area under the pain ratings curve for both DMA ($p<0.01$) and MPS ($p<0.01$). The effects of tDCS on the area under the curve ratio (i.e. post/pre-treatment) revealed significant analgesic effects over DMA ($p<0.05$) and MPS ($p<0.05$) when compared to sham.

Conclusions: This study demonstrates that anodal tDCS over the primary motor cortex can reduce both dynamic and static forms of mechanical pain sensitivity associated with the development of DMA and MPS, respectively. The use of tDCS may provide a novel mechanism-driven therapy in chronic pain patients with altered mechanical S/R functions.

Introduction

Chronic pain affects approximately 28 million people in the UK and is associated with poor pain control with conventional use of analgesics. Anodal transcranial direct current stimulation (tDCS) of the primary motor cortex (M1) has shown potential in the treatment of a number of different chronic pain conditions (Ahn et al., 2017, 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., 2017, Kim et al., 2013, Volz et al., 2016). However, more research is required in order to better understand the top-down mechanisms underpinning these analgesic effects.

One of the key features of chronic pain is the development of central sensitisation in the spinal cord, which manifests as the development of allodynia (i.e. pain in response to previously innocuous stimuli) and secondary hyperalgesia (i.e. enhanced pain to previously noxious stimuli) (Arendt-Nielsen et al., 2018, Woolf, 2011). It is possible to measure these perceptual correlates of central sensitisation using the capsaicin model of ongoing pain alongside quantitative sensory testing (QST) in healthy volunteers (Loken et al., 2017, Vollert et al., 2018, Harding et al., 2001). Therefore, we aimed to investigate the top-down analgesic mechanisms of M1-tDCS by measuring the effects on capsaicin-induced allodynia and secondary hyperalgesia.

The mechanical stimulus response (S/R) functions are used to measure changes in dynamic mechanical allodynia (DMA) and mechanical pain sensitivity (MPS) as part of a QST profiling battery in chronic pain patients and in human surrogate pain models (Rolke et al., 2006, Magerl et al., 2001, Magerl et al., 1998, Ziegler et al., 1999). DMA is mediated through changes in the central processing of innocuous Aβ afferent inputs in the dorsal horn, causing pain to slowly moving mechanical stimuli and is known to be difficult to treat pharmacologically (Finnerup et al., 2015, Finnerup et al., 2010, Woolf, 2011). It can be assessed using simple handheld tools such cotton wool or a standardised brush (Rolke et al., 2006) and provides a means by which to determine whether anodal tDCS over M1 exerts any analgesic effects over the central processing of DMA.

Measuring capsaicin-induced changes in MPS in an area surrounding the neurogenic flare response can be used as a further perceptual correlate of central sensitisation in humans (Magerl et al., 2001, Magerl et al., 1998). A leftward shift in the MPS S/R function can result following heterosynaptic facilitation of Aδ fibre inputs at the spinal level and can provide detailed information regarding changes in somatosensory function in both chronic pain patients and human surrogate models of secondary hyperalgesia (Klein et al., 2004, Ziegler et al., 1999, Puta et al., 2012, Stiasny-Kolster et al., 2004, Baumgartner et al., 2002). It has previously been shown that M1-tDCS can reduce temporal summation evoked pain sensitivity and the area of pinprick hyperalgesia which have been attributed to activation of top-down analgesic systems in the brain and brainstem (Hughes et al., 2018a, Hughes et al., 2018b, Meeker et al., 2019), however the effects on spinally mediated changes in mechanical sensitivity are yet to be investigated.

These lines of evidence have led us to examine whether anodal M1-tDCS exerts any top-down analgesic effects over capsaicin-induced changes in DMA and MPS in healthy volunteers.

Methods

Participants

All participants were informed of the experimental protocols and subsequently provided written consent in accordance with the principles of the declaration of Helsinki. All subjects were recruited from Imperial College London and were initially screened to see if they met any of the exclusion criteria for pain testing (i.e. pregnancy, diabetes, blood disorders, neurological conditions, immune-suppression, inflammatory disease, psychiatric conditions, taking steroid, antibiotic or pain medicines). Following initial screening, 15 healthy subjects were recruited onto the study and data from 12 (mean age: 28.85 ±2.14, 7 females) responders to 1% topical capsaicin cream (i.e. a maintained pain intensity rating >50 rating on a visual analogue scale) were included in the final data analysis.

Topical capsaicin pain model

All Participants received topical application of capsaicin cream (1% w/w, Pharmacierge, London, UK). Using a 1 ml syringe, 50 µl was ejected onto a 9 mm diameter clear plastic disc which was then placed face-down on an area of the left L5 dermatome, one third the way along a line from the left lateral femoral epicondyle to the left lateral malleolus, remaining in place for the remainder of the protocol (area of capsaicin skin contact: $64mm^2$) (Harding et al., 2001, Hughes et al., 2019). The participants used a modified visual analogue scale (VAS) used previously (Harding et al., 2001, Hughes et al., 2019) which was anchored at 0 = no sensation; 50 = pain threshold; 100 = worst pain imaginable. Following application of capsaicin cream, the participants were instructed to give a rating whenever they felt a change in sensation or pain. The participants described the sensation initially as ‘’tingling’’ (i.e. <50 VAS rating) which increased in intensity over approximately 40 minutes until a distinct ‘’stinging’’ or ‘’burning’’ pain was perceived (i.e. >50 VAS rating).

S/R (Stimulus/Response) functions: Dynamic mechanical allodynia (DMA) and mechanical pain sensitivity (MPS)

Using the radial lines approach, 8 spokes were marked using a non-permanent marker that radiated outwards from the point of capsaicin cream application. Following the onset of a capsaicin-induced VAS rating greater than 50, areas of altered mechanical pain sensation (i.e. the secondary zone) were mapped using a 128 mN pin prick stimulator starting at the point of capsaicin cream application and moving outwards at 1cm intervals at rate of 1 stimulus/s along the length of each of the 8 spokes and a point was marked on each spoke at the point when the sensation changed from a sharp/burning pinprick sensation to a blunt prodding sensation. During this procedure, the participant was instructed not to observe the testing site. The erythematous flare response (i.e. primary hyperalgesia zone) was defined as the area of skin that was reddened around the capsaicin cream application. This was evaluated visually and the border between the detectable erythema and normal skin pigmentation was marked along each of the 8 spokes. To measure DMA 3 tactile stimuli: a cotton wisp (~3mN), a cotton wool tip attached to an elasticated handle (Q-tip) (~100mN) and a standardised brush (Somedic, Sweden) (~200-400mN) were applied to the skin within the secondary zone in a single sweeping clockwise motion of 1-2cm for ~2 seconds. To measure capsaicin-induced changes in MPS, i.e. secondary hyperalgesia, a set of 7 weighted pinpricks (contact area= 0.5mm tip diameter) with a set force of 8, 16, 32, 64, 128, 256 and 512mN were pressed perpendicularly against the skin within the secondary zone for ~1 second. Pain was rated using a conventional visual analogue scale (VAS) where 0 = no pain and 100 = worst pain imaginable. The 10 stimuli (3 DMA and 7 MPS) were applied a total of 5 times each in a pseudorandom sequence and a pain rating given after each stimulus. There was pause of ~10 seconds between each stimulus to prevent the occurrence of wind up (Rolke et al., 2006).

Primary motor cortex localisation

The site over the right motor cortex for tDCS stimulation was localised using transcranial magnetic stimulation (TMS) (Hughes et al., 2018b). TMS was applied to the motor 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 left tibialis anterior (TA) muscle. The position of the coil was then marked with an indelible pen to ensure accurate placement of the tDCS anode electrode throughout the experiment.

M1-tDCS

tDCS was delivered by a battery-driven stimulator (HDCkit; Magstim, Whitland, Carmarthenshire, UK) connected to a pair of electrodes (5 x 5 cm^2) placed within saline soaked sponges which were fixed in place using a cap. The anode was placed over the right M1, contralateral to the side receiving pain testing (left leg) and the cathode was placed over the contralateral (left) supraorbital cortex (Nitsche and Paulus, 2000, Hughes et al., 2018b, Hughes et al., 2018a, Ngernyam et al., 2013). 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 protocol

The effects of either real or sham M1-tDCS were investigated using a double-blind, randomised cross-over design (Figure 1). Participants were seated on a physiotherapy couch, with both legs fully extended at the knee. All participants were first familiarised with the mechanical S/R function tests. Baseline DMA and MPS measurements were then taken before 1% topical capsaicin cream was applied and changes in VAS ratings were recorded. When capsaicin had induced an ongoing pain state (VAS >50; total post-sensitisation testing time = 40 minutes; Figure 1A) the mechanical S/R function tests were then re-measured within an area surrounding the neurogenic flare response. The effects of 20 minutes stimulation of either real or sham 2mA M1-tDCS were then examined by re-measuring the effects on the DMA and MPS S/R functions.

Statistical analysis

All data were initially entered into Microsoft Excel before being analysed for statistical significance and normality in GraphPad Prism (v8.0.1. GraphPad Software, Inc.). To avoid a loss of zero values for the calculation of DMA and MPS S/R function area under the curve (AUC) ratios, a small constant (0.1) was added to all raw data (i.e. zero and non-zero values) (Klein et al., 2004, Magerl et al., 2001, Puta et al., 2012, Ziegler et al., 1999). Changes in pain perception after topical capsaicin application were calculated from the areas under the pain rating curves (Magerl et al., 2001). The effects of either real or sham tDCS on DMA and MPS were calculated from the ratio of the post stimulation AUC divided by pre-stimulation AUC. Prior to statistical analysis, all data were checked for normality using the Shapiro-Wilks test. Differences between pre and post-capsaicin or between real and sham tDCS were analysed using paired t-tests or Wilcoxon signed rank test, where appropriate. Statistical significance was set at $p<0.05$ and all data are presented as mean ± SEM in the figures and text.

Results

Topical capsaicin caused the onset of DMA and changes in MPS in healthy volunteers

Following the onset of a sensitised pain state (i.e. when the VAS rating reached >50, which was ~40 minutes post capsaicin cream application), there was a significant increase in the DMA AUC (pre-capsaicin AUC: 0.2 ± 0.1 versus post-capsaicin AUC: 3.3 ± 0.9; $p<0.01$; Figure 2A) measured within the secondary zone. There was also a leftward shift in the MPS S/R function in the secondary zone which was reflected in an increase in the MPS AUC (pre-capsaicin AUC: 23.1 ± 6.3 versus post-capsaicin AUC: 44.6 ± 10.2; $p<0.01$; Figure 2B).

M1-tDCS attenuated capsaicin-induced changes in DMA and MPS

The effects of real and sham M1-tDCS on responses measured within the secondary zone were then investigated. There was a significant analgesic effect of M1-tDCS on DMA shown by a reduction in AUC measured following 20 minutes of stimulation (tDCS AUC ratio: 0.75 ± 0.13; sham AUC ratio: 1.4 ± 0.3; $p<0.05$) and a reduction in MPS AUC (tDCS AUC ratio: 0.79 ± 0.1; sham AUC ratio: 1.1 ± 0.1; $p<0.05$) S/R functions when compared to 20 minutes of sham stimulation (Figure 3).

Discussion

In this study we investigated the effects of M1-tDCS on capsaicin-induced changes in mechanical S/R functions. We show the development of an ongoing pain state associated with the development of both DMA and changes in MPS following topical application of capsaicin cream. Following 20 minutes of 2 mA M1-tDCS there was an overall reduction in both DMA and MPS when compared to sham. These results indicate that M1-tDCS can attenuate perceptual correlates of central sensitisation induced following topical capsaicin application in healthy volunteers. We show that M1-tDCS can reduce both dynamic and static forms of pain sensitivity associated with the development of mechanical allodynia and secondary mechanical hyperalgesia, respectively. Taken together, this study shows evidence that M1-tDCS could be used a novel mechanism-driven therapy in chronic pain patients with DMA or changes in MPS.

As part of the German Research Network on Neuropathic Pain (DFNS) QST profiling protocol (Rolke et al., 2006), 13 parameters are measured which can be used to better understand individual differences in pain-generating mechanisms and somatosensory profile (Vollert et al., 2016, Vollert et al., 2018). DMA and changes in peripherally-mediated sensitivity which can detected through changes in heat pain threshold in the primary hyperalgesia zone (Arendt-Nielsen et al., 2018, Rolke et al., 2006). Critically, we have shown the development of DMA and changes in MPS following capsaicin application which has allowed us to model centrally-mediated changes in somatosensory function in healthy volunteers. By doing this, we have measured top-down analgesic effects of M1 non-invasive brain stimulation on these sensitised responses, which could be attributed to activation of descending pain modulation networks (Meeker et al., 2019).

The development of DMA is often seen in neuropathic pain patients, where pain to stroking or brush often accompanies spontaneous pain (Landerholm and Hansson, 2011, Jensen and Finnerup, 2014). The transition of a normally innocuous and slowly moving mechanical stimulation into an unpleasant painful experience is a result of a form of central sensitisation, where low threshold mechanically sensitive Aβ-fibre afferents are thought to activate nociceptive specific cells following activity-dependent plasticity in the dorsal horn (Cervero and Laird, 1996, Campbell and Meyer, 2006). As well as local segmental changes in excitability, there are also thought to be changes in the activity of spinally-projecting pro and anti-nociceptive pathways which contribute to the development of DMA (Hughes et al., 2013). In our study, we demonstrate that anodal tDCS over M1 can reduce pain intensity ratings associated with the development of DMA following topical capsaicin application. As the predominant mechanism underpinning the development of allodynia is the generation of spinal cord plasticity, it can be suggested that anodal activation of M1 can cause top-down modulation of inhibitory descending control pathways which work to reduce excitability in the dorsal horn. This is supported by previous research that has shown that M1 stimulation can cause opioid release and GABAergic inhibition in the periaqueductal grey, an area of the midbrain strongly linked with descending inhibition at the spinal level (DosSantos et al., 2012, DosSantos et al., 2014, Ossipov et al., 2010, Pagano et al., 2012). A recent neuroimaging study has also shown activation of brainstem regions involved in descending inhibitory control following M1-tDCS in a capsaicin-heat pain model in healthy volunteers (Meeker et al., 2019). Taken together, these lines of evidence suggest that there may be top-down changes in pain-related brain activity following anodal M1 stimulation which can cause the activation of spinally-projecting inhibitory pathways which have the ability to modulate altered Aβ-fibre processing in the dorsal horn.

There is a now a growing body of evidence which suggests that M1-tDCS has little or no effect over measures of acute pain in healthy volunteers (Hughes et al., 2018b, Ihle et al., 2014, Jurgens et al., 2012, Aslaksen et al., 2014, Mylius et al., 2012). Similar observations have been reported following rTMS of the primary motor cortex, which suggests that non-invasive brain stimulation techniques have no effect over normal physiological nociceptive transmission (Bradley et al., 2016). Attempts to explore the discrepancies between healthy volunteers and chronic pain patients have led to a number of studies from our laboratory which have shown that temporal summation, which is associated with the generation of spinal cord excitability, is required in order for an analgesic effect to be measured following M1-tDCS (Hughes et al., 2018a, Hughes et al., 2018b). We have extended these findings to show a beneficial analgesic effect over a spinally-mediated sensitised pain state associated with the development of secondary mechanical hyperalgesia. Taken together, these results indicate that M1-tDCS may only have a top-down effect over sensitised pain networks, which is in line with how some pharmacological agents only show analgesic efficacy during sensitised pain states (Dirks et al., 2002, Arendt-Nielsen et al., 1995)

The majority of clinical studies have assessed changes in self-reported symptom questionnaires as measures of tDCS efficacy in neuropathic pain patients, which have pointed towards little or no overall effect (Lewis et al., 2018, O'Neill et al., 2018, O'Connell et al., 2018). This could be attributed to discrepancies often seen between patient report symptoms and underlying pain-generating mechanisms (Vollert et al., 2016). Our results suggest that future patient stratification studies using QST-based profiling could provide a more targeted and efficacious use of tDCS in specific groups of neuropathic pain patients. By measuring the MPS S/R function we have shown that M1-tDCS can reduce the overall perception of pain to increasing pin prick stimuli in an area surrounding the neurogenic flare response. Measuring changes in the MPS S/R function is often performed in chronic pain patients as part of the DFNS QST-based profiling tool and can help to provide insight into the mechanisms underpinning chronic pain (Stiasny-Kolster et al., 2004, Puta et al., 2012, Rolke et al., 2006, Vollert et al., 2016). The results from our study suggest that M1-tDCS could be used a novel therapy in patients with a leftward shift in their MPS S/R function, which is associated with the development of central sensitisation, with a view to provide personalised and mechanism-driven analgesia. However, it should be noted that the relatively small sample size of the current study means that a larger randomised controlled trial should be performed in order to confirm this approach in a well-defined population of chronic pain patients.

In summary, this study has provided insight into the top-down analgesic mechanisms following anodal M1-tDCS during a sensitised pain state. We show an overall reduction in pain perception associated with the development of capsaicin-induced DMA and MPS which suggests an ability to reduce both dynamic and static forms of evoked pain sensitivity, respectively. The results from this study indicate that M1-tDCS may be beneficial in chronic pain patients with altered DMA or MPS somatosensory profiles.

Acknowledgements

We would like to thank Imperial College London for funding this study and all participants for taking part.

Author contributions

SH developed scientific question and hypothesis, devised protocol, undertook data analysis, prepared draft of manuscript and approved final manuscript. GW collected and analysed data. PS developed scientific question and hypothesis, devised protocol, edited draft of manuscript and approved final manuscript.

Figure legends

Figure 1. Experimental protocol. A) All subjects were first familiarised with the testing procedures before baseline mechanical S/R functions (DMA and MPS) were performed (~10 minutes). Topical capsaicin cream (1%) was then applied to an area of the L5 dermatome, one third the way along a line from the left lateral femoral epicondyle to the left lateral malleolus. Following the development of a sensitised pain state (i.e. >50 VAS rating), DMA and MPS were then re-measured within the secondary zone before and after 20 minutes of either real or sham anodal tDCS of the primary motor cortex. B) Capsaicin-induced primary and secondary zones were mapped using a radial lines approach. The effects of real or sham tDCS on DMA and MPS were examined in the secondary zone.

Figure 2. Development of capsaicin-induced DMA and changes in MPS. The effects of topical capsaicin application on the area under the pain rating curves for A) DMA and B) MPS. Data presented as mean ± SEM; AUC, area under the curve; ** - p<0.01; n = 12.

Figure 3. Attenuation of capsaicin-induced DMA and MPS by anodal tDCS. The effects of 20 minutes (2mA) anodal tDCS was compared to sham stimulation by calculating the post/pre-treatment ratios. The graphs show how the area under the pain rating curves change following sham and real tDCS for A) DMA and B) MPS. Data presented as mean ± SEM; AUC, area under the curve; * - $p<0.05$; n = 12.

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Figure 1.

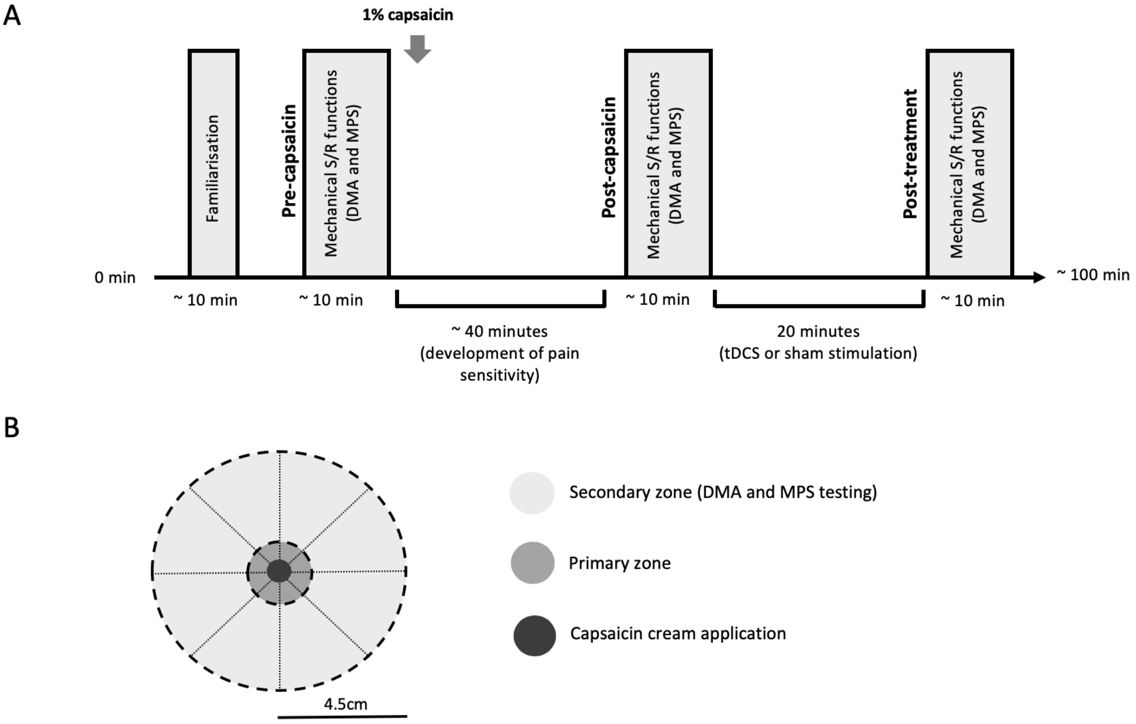

A
1% capsaicin
Familiarisation
Pre-capsaicin
Mechanical S/R functions (DMA and MPS)
Post-capsaicin
Mechanical S/R functions (DMA and MPS)
Post-treatment
Mechanical S/R functions (DMA and MPS)
0 min
~ 100 min
~ 10 min
~ 10 min
~ 10 min
~ 10 min
~ 40 minutes (development of pain sensitivity)
20 minutes (tDCS or sham stimulation)
B
4.5cm
Secondary zone (DMA and MPS testing)
Primary zone
Capsaicin cream application

Figure 2.

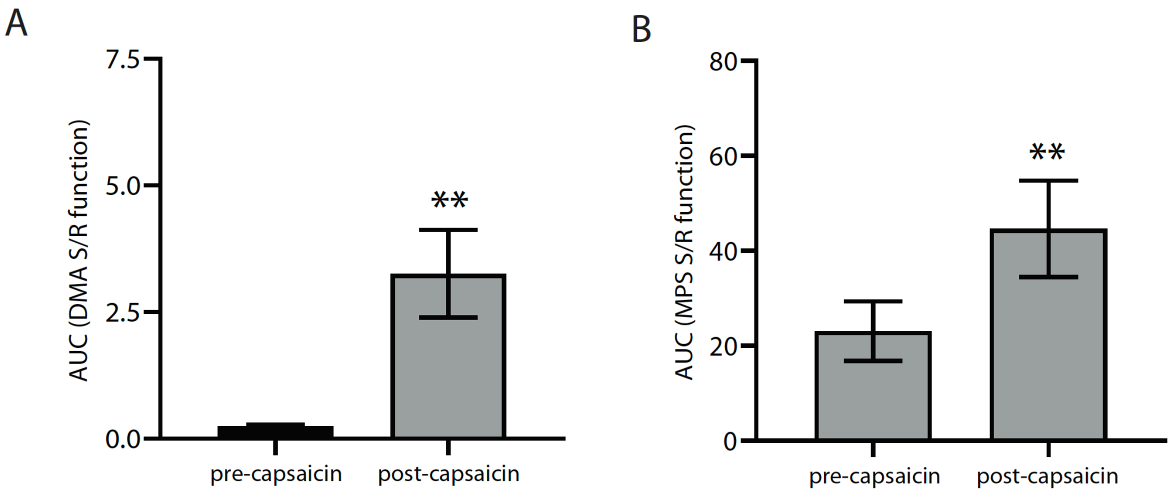
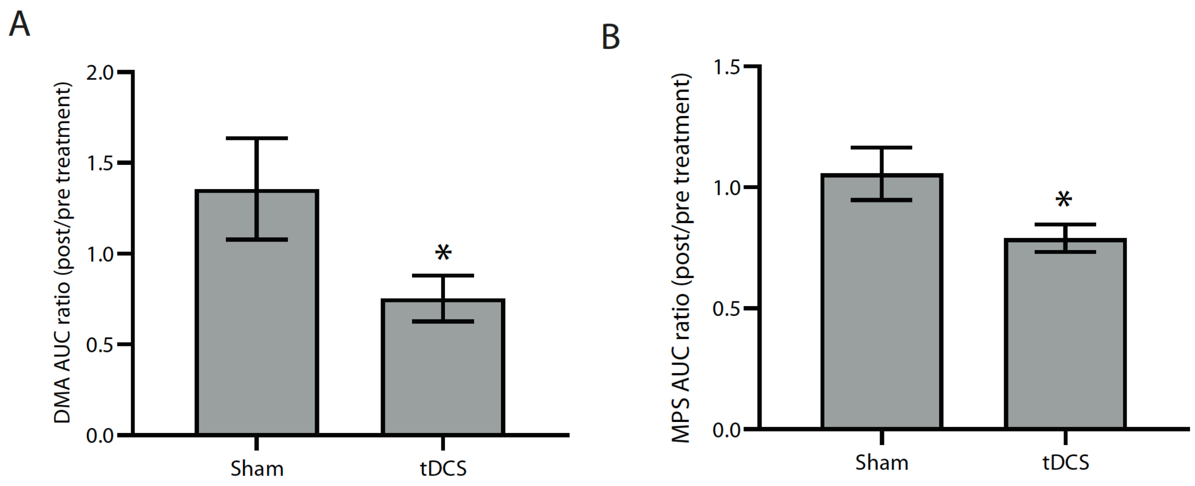

A
7.5
5.0
2.5
0.0
AUC (DMA S/R function)
**
pre-capsaicin
post-capsaicin
B
80
60
40
20
0
AUC (MPS S/R function)
**
pre-capsaicin
post-capsaicin

Figure 3.


A
DMA AUC ratio (post/pre treatment)
2.0
1.5
1.0
0.5
0.0
*
Sham
tDCS
B
MPS AUC ratio (post/pre treatment)
1.5
1.0
0.5
0.0
*
Sham
tDCS