Improving working memory and pain inhibition in older persons using transcranial direct current stimulation.

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Running title: Improving cognition and pain with neuromodulation
Key words: neuromodulation, nociceptive, aging, cognition, descending modulation

Total number of pages: 19
Total number of Figures: 7
Total number of Tables: 2

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Conflicts of interest
The authors report no financial or other relationship that may lead to any conflict of interest.

Author's contributions to the manuscript:
1- Zoha Deldar contributed to all aspects of the research.
2- Nabi Rustamov contributed to data acquisition and interpretation.
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4- Mathieu Piché contributed to all aspects of the research and obtained funding for the study.
All authors read and approved the final version of the manuscript.

Abstract

The aim of the present study was to examine whether transcranial Direct Current Stimulation (tDCS) could enhance working memory and pain inhibition in older persons. Fifteen volunteers (7 women, 8 men; mean ± SD: 64 ± 4.4 y.o.) participated in two tDCS sessions during which an n-back task was performed with two levels of working memory load, while painful stimulation was delivered at the ankle. The experiment included five within-subject counterbalanced conditions (pain alone and 0-back or 2-back with or without pain) performed twice during each session. Compared with the pre-tDCS baseline, anodal tDCS decreased response times and improved pain inhibition by working memory in the 2-back condition ($p<0.01$), but not in the 0-back or pain alone conditions, while sham tDCS produced no effect (all $p>0.3$). These results indicate that working memory and pain inhibition can be improved by tDCS in older persons.

Introduction

Recent empirical and theoretical work highlight the important links between pain and cognitive processes, notably attention. The neurocognitive model of attention to pain (Legrain et al., 2009a) describes two modes of attentional selection: bottom-up capture of attention by nociceptive stimuli and top-down attentional modulation of pain. In this model, attention allocation to nociceptive stimuli is affected by the trade-off between bottom-up and top-down processes. Bottom-up processes give nociceptive stimuli, which are intrinsically salient, stronger neuronal representation, leading to involuntary capture of attention. However, this bottom-up attentional capture can be modulated by top-down processes which are determined by cognitive goals represented in the WM.

According to this model, an effective task to reduce attentional capture by pain should be effortful and involve WM engagement. Consistent with this, the more the cognitive task is demanding, the more nociceptive processes will be inhibited, due to limited cognitive resources to be shared between bottom-up and top-down processes. Also, inhibition of nociceptive processing by top-down processes must be supported by WM, which preserves goal priorities and may shield cognition against nociception. While there is empirical evidence to support this prediction of the model in younger adults, this has not yet been investigated in aging, a variable related to pain in multiple ways.

Aging is associated with several physiological changes that affect global functioning, daily activity and quality of life. For instance, cognitive functions progressively decline during normal aging, as evidenced by decreased episodic memory (Moscovitch and Winocur, 1995), attentional resources (Brink and McDowd, 1999), cognitive inhibition (Spieler et al., 1996) as well as working memory (WM) performance (Bopp and Verhaeghen, 2005; Borella et al., 2008; Darowski et al., 2008; De Beni and Palladino, 2004; Fabiani, 2012). Besides, pain conditions commonly occur and persist in the population over 40 years old, with a prevalence of chronic pain over 25% (Frondini et al., 2007; Mansfield et al., 2016). Whether the occurrence of cognitive decline and pain conditions are interrelated is still not clear, but interactions were shown between cognitive performance, pain sensitivity and age (Oosterman et al., 2013). Moreover, a correlational study showed that reduced pain inhibition is associated with reduced cognitive inhibition in older persons (Marouf et al., 2014). In addition, normal aging is associated with a decreased ability to suppress the processing of

distracters. For example, decreased ability to inhibit distracting information when performing a cognitive task mediates age-related effects on WM performance (Darowski et al., 2008; Lustig et al., 2001). As a source of distracting information, pain may decrease cognitive task performance. This may be especially acute in older persons, who may show a greater alteration of cognitive functions. In turn, this alteration of cognitive functions, which results in decreased ability to inhibit distracters such as pain, may worsen pain symptoms and lead to a vicious circle with important impacts. Consistent with this idea, overall cognitive performance is lower in patients with chronic pain, relative to controls, and this is observed particularly in older patients (Moriarty et al., 2017).

Indeed, effective cognitive control during pain perception depends on the disengagement of attention from task-irrelevant pain signals towards the processing of task-relevant information (Legrain et al., 2011; Legrain et al., 2013). WM allows these processes to take place, while inhibiting nociceptive brain activity and pain perception (Legrain et al., 2009a). Accordingly, reduced WM in older persons may decrease top-down inhibition of nociceptive activity and pain (Gazzaley et al., 2005). Thus interventions aimed at improving WM, pain inhibition or pain inhibition by WM are needed. In line with this idea, results from a recent study suggest that anodal transcranial Direct Current Stimulation (tDCS) of the left dorsolateral prefrontal cortex (DLPFC) enhances pain inhibition by improving WM in a sample of young healthy volunteers (Deldar et al., 2018). This type of intervention could present an interesting therapeutic avenue to address the age-related decline in WM performance and pain regulation.

The aim of the present study was to investigate whether anodal tDCS of the DLPFC could improve pain inhibition by WM in older persons. We hypothesized that anodal tDCS of the left DLPFC would improve WM performance, which in turn, would improve top-down pain inhibition during a cognitive task involving WM. Using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission, we also examined whether descending inhibitory pathways contribute to the enhancement of pain inhibition by WM.

Material and Methods

Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of Université du

Québec à Trois-Rivières. All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice and received a compensation of $50 for their travel expenses, time and commitment.

Participants

Fifteen healthy volunteers (7 women and 8 men; range 55-71 years old; mean ± SD: 64 ±4.41) were recruited by advertisements on the campus of Université du Québec à Trois-Rivières and through local associations for seniors. Participants were included if they were between 55 and 75 years old with normal or corrected-to-normal vision. They were excluded if they had taken any medication affecting the nervous system or pain perception within two weeks before the experiment, including antihypertensives, pain killers, anxiolytics, antidepressants and other psychotropic medication and if they had a history of acute or chronic pain, suffered from acute or chronic neurological illness, heart disease, metabolic disorders, vascular disorders or if they were diagnosed with a psychiatric disorder. They were also asked to abstain from consuming alcohol at least 1 day before experimentation. Five participants could not complete experimental procedures; in two participants, the NFR could not be evoked at a stimulus intensity that was tolerable for the participant in the context of this study. The other participants could not perform the n-back task. Therefore, data from these five participants were not collected, leaving a sample of 15 participants.

Experimental design

This experiment is based on a within-subject double-blind sham-controlled design to determine the effect of a single anodal tDCS session applied over the left DLPFC on WM and pain inhibition by WM, as reported in our previous study (Deldar et al., 2018). To elicit WM engagement, a modified n-back task was used. The task consisted in colour discrimination of blue and yellow squares. In order to obtain two different levels of WM load, the n-back task was either 0-back, in which participants responded by reporting the colour of the current stimulus, or 2-back, in which participants responded by reporting the colour of the stimulus presented two trials earlier. Painful stimuli were delivered alone or concurrently to the n-back task to test the interaction between WM and pain. In these conditions, sixty electrical stimuli were delivered randomly, among which ten stimuli were painful and 50 stimuli were non-painful. This increases painful stimulus saliency. Thus, the experiment included five within-subject counterbalanced

conditions (pain alone and 0-back or 2-back with or without pain) performed twice during each session.

Electrical stimulation

Transcutaneous electrical stimulation (trains of 10 x 1 ms pulses at 333 Hz) was delivered with two isolated DS7A constant current stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA, USA). Stimulators were controlled by a script running in a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). The degreased skin over the retromalleolar path of the right sural nerve was stimulated by two adjacent pairs of custom-made surface electrodes (1 cm^2; 2 cm inter-electrode distance) for the painful and tactile stimuli, respectively. For the painful stimulus, the NFR threshold was determined using the staircase method (Ladouceur et al., 2017; Ladouceur et al., 2012; Piche et al., 2011). For the tactile stimulus, the detection threshold was determined as the first stimulus intensity that produced a tactile sensation under the electrodes. The painful and tactile stimuli were always delivered with the same pair of electrodes. In both sessions, stimulus intensity was adjusted individually to 120% of the NFR threshold for painful stimulation and to 150% of the detection threshold for non-painful stimulation.

Nociceptive flexion reflex measure and analysis

Electromyography (EMG) of the short head of the biceps femoris was recorded with a pair of surface electrodes (EL-508, Biopac Systems, Inc., Goleta, CA, USA). Signal was amplified 2000 times, band pass filtered (10-500 Hz), sampled at 1000 Hz (Biopac Systems, Inc., Goleta, CA, USA) and stored on a personal computer for off-line analyses. The raw EMG recordings were full wave rectified and the resulting signal was used to quantify the amplitude of NFR to each shock by extracting the integral value between 90 and 180 ms after stimulus onset. This amplitude was standardized using a within-subject z-transformation. For group analyses, the mean response to 10 painful stimuli was calculated for each condition.

Pain and pain-related anxiety ratings

Participants verbally rated pain intensity and pain-related anxiety using numerical rating

scales (NRS) with two anchors on the left and right extremities (0, no pain/anxiety and 100, extreme pain/anxiety). These scales were displayed horizontally on a computer screen after each condition.

Transcranial Direct Current Stimulation

A direct current of 2 mA was generated by a battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) and delivered continuously using a pair of rubber electrodes (35 cm^2 surface) covered by conductive sponges moistened with saline. To enhance the activity of the left DLPFC, the anodal electrode was placed on the scalp over the F3 site, according to the international 10-20 system of electrode placement. The cathode was placed over the right deltoid muscle to make sure that tDCS effects were due only to anodal stimulation (Wolkenstein and Plewnia, 2013). During the first 30 seconds of stimulation, the current was ramped up to 2 mA and then delivered for 22 minutes. The first 3 minutes allowed participants to get used to tDCS before beginning the task. At the end of stimulation, the current was ramped down to 0 mA over 30 seconds. For the sham stimulation, electrodes were placed in the same positions but the current was only applied for 40 seconds. Pre-defined codes assigned to either sham or anodal stimulation were used to start the stimulator. These codes allowed for a double-blind study design. The order of tDCS and sham stimulation was counterbalanced across participants with a one-week inter-session interval.

Psychometric assessment

Participants completed validated questionnaires. Anxiety was assessed using the Spielberger State-Trait Anxiety Inventory (STAI-Y) in its original English or validated French version (Vigneau, 2009), depending on participant's mother language. Pain catastrophizing was evaluated using the French or English version of the Pain Catastrophizing Scale (PCS) (French DJ, 2005). To measure how participants pay attention to pain in daily life, they also completed the pain vigilance and awareness questionnaire (PVAQ) (Roelofs et al., 2003). To measure individual differences in attentional control, they completed the Attentional Control Scale (ACS) (Derryberry and Reed, 2002). Depressive symptoms were measured using the French or English version of the Geriatric Depression Scale (GDS) (Yesavage et al., 1982). Cognitive impairment was evaluated using the Montreal Cognitive Assessment (Nasreddine et al., 2005).

Cognitive task

A modified n-back task was used in which the participant had to discriminate between blue and yellow squares with two levels of WM load (0-back and 2-back conditions) (Deldar et al., 2018). In the 0-back condition, participants discriminated the colour of the current stimulus directly after its presentation. In the 2-back condition, they responded to the stimulus presented two trials before. WM performance was examined with response time (RT) and response accuracy (RA: percentage of correct responses). The mean RT was calculated for each condition by including RTs from each trial with a correct response. Trials defined as anticipated responses (RT < 150 ms) or missed responses (RT > 1500 ms) were excluded from the mean RT calculation.

For conditions with electrical stimulation during the n-back task, one series of task-relevant stimuli (blue or yellow squares presented for 500 ms) was shortly preceded by a task-irrelevant electrical stimulation (non-painful: 200 ms before; painful: 300 ms before; see Figure 1). 83 % of electrical stimuli were non-painful and 17 % were painful, following the procedure described previously (Deldar et al., 2018). The inter-stimulus interval (ISI) between the onset of the electrical stimulus and the onset of task-relevant stimulus was either 220 ms for tactile trials and 300 ms for painful trials, in order to account for the conduction velocity of tactile and nociceptive fibres. The inter-trial interval (ITI) between the onsets of two consecutive task-relevant stimuli was 3000 ms.

Experimental procedures

Participants completed two 180-minute sessions on separate days with a 1-week interval. All participants received anodal brain stimulation and sham stimulation; the order was counterbalanced across participants. The same protocol was carried out in both sessions. After individual adjustment of stimulus intensity for ankle stimulation, the tDCS electrodes were placed as described above and participants were familiarized with the n-back task. Familiarization included twenty trials for each condition, during which participants received feedback (correct or incorrect response) (Deldar et al., 2018). After this practice, the experimental protocol began with the pre-tDCS baseline conditions (pain alone and 0-back or 2-back with or without pain) followed by the same five conditions during tDCS (see Figure 2). Each condition included 60 trials. For the 0-back and 2-back conditions, the 60 trials were

presented without any electrical stimulation. For the pain condition, the 60 trials included 50 tactile stimuli and 10 painful stimuli without the n-back task, as in our previous study (Deldar et al., 2018). For the 0-back and 2-back with pain conditions, 50 trials of the n-back task were preceded by a tactile stimulus while 10 trials were preceded by a painful stimulus. The order of the five conditions was counterbalanced between subjects but the same order was kept within-subject for the pre-tDCS baseline and tDCS conditions, as well as for both sessions (anodal and sham).

Statistical Analysis

Data analysis was conducted using Statistica v13.1 (Dell Inc., Tulsa, OK, USA). All results are expressed as mean ± SEM and statistical threshold was set to $p \leq 0.05$ (two-tailed). Distribution normality was confirmed using the Kolmogorov-Smirnov test and data was transformed (1/x) for variables which distribution deviated from normality (RT and RA). A priori hypotheses were tested with planned contrasts and the type I error rate was controlled for using the Bonferroni correction for multiple comparisons, based on the number of comparisons for each independent analysis. All reported p-values are therefore corrected for multiple comparisons for all variables, including RT, RA, pain, pain-related anxiety and NFR amplitude. Effect sizes are reported based on partial eta-squared (η^2_p).

Results

The sample included 15 participants. Results from the psychometric and pain assessments are reported in Table 1**.**

Interactions between pain and working memory

To examine the interactions between pain and WM, pre-tDCS baseline values averaged between sessions were compared between conditions to test whether pain distracters altered WM or whether WM engagement decreased the capture of attention by painful distracters (see Table 2). RT was significantly decreased when painful distracters occurred during the 0-back condition ($p=0.032$, $\eta^2_p=0.35$) and marginally decreased during the 2-back condition ($p=0.054$, $\eta^2_p=0.30$), while response accuracy was not affected by painful distracters either in the 0-back ($p=0.8$, $\eta^2_p<0.01$) or 2-back ($p=0.4$, $\eta^2_p=0.12$) conditions. Besides, pain ratings were significantly

decreased by WM engagement in the 0-back ($p=0.003$, $\eta^2_p=0.52$) and 2-back ($p=0.006$, $\eta^2_p=0.48$) conditions. In contrast, pain-related anxiety ratings were not significantly decreased by WM engagement in the 0-back condition ($p=0.8$, $\eta^2_p=0.05$) and were significantly increased in the 2-back condition ($p=0.04$, $\eta^2_p=0.34$). As for spinal nociceptive activity, NFR amplitude was not significantly altered by WM engagement either in the 0-back ($p=0.9$, $\eta^2_p<0.01$) or 2-back ($p=0.6$, $\eta^2_p=0.07$) condition.

These results indicate that response times were faster when the 0-back and 2-back tasks were performed with painful distracters compared to the respective n-back task alone. In addition, pain perception was decreased when a WM task was performed (either the 0-back or the 2-back), compared with painful stimulation alone, confirming that the engagement of WM can reduce pain perception. In the following analyses, we examined whether anodal tDCS could improve WM performance and pain inhibition by WM engagement.

Effects of transcranial direct current stimulation

Working memory

Compared with pre-tDCS baseline values, anodal tDCS significantly reduced RT in the 2-back condition, with or without pain (both $p<0.01$, $\eta^2_p=0.58$ and 0.52, respectively; see Figure 3A) while no significant effect was observed for the 0-back condition, with or without pain (both $p>0.3$, $\eta^2_p=0.23$ and 0.10, respectively; see Figure 3A). Besides, no significant effect was produced by sham tDCS in the 0-back and 2-back conditions, with or without pain (all $p>0.3$, all $\eta^2_p<0.22$; see Figure 3B). However, anodal tDCS effects were not significantly greater than those produced by sham tDCS (all $p>0.3$, all $\eta^2_p<0.12$). As for RA, no significant change was produced for any condition by either anodal or sham tDCS (all $p>0.1$, all $\eta^2_p<0.34$; see Figure 3C and 3D).

Pain intensity

Anodal tDCS significantly improved pain inhibition by WM in the 2-back with pain condition compared with the pre-tDCS 2-back with pain condition ($p<0.01$, $\eta^2_p=0.55$; see Figure 4A). In contrast, pain and pain inhibition by WM in the 0-back task were not significantly different compared with their respective pre-tDCS condition (both $p>0.8$, $\eta^2_p=0.16$ and 0.01, respectively; see Figure 4A). Sham tDCS produced no significant change in pain intensity for

any of the three conditions (all p>0.9, all η^2_p<0.10; see Figure 4B). However, anodal tDCS effects were not significantly greater than those produced by sham tDCS (all p>0.9, all η^2_p<0.13).

Pain-related anxiety

Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly improved by anodal tDCS compared with their respective pre-tDCS condition (all p>0.1, η^2_p=0.09. 0.01 and 0.38, respectively; see Figure 5A). Similar results were observed for the sham tDCS session (all p>0.9, all η^2_p<0.14; see Figure 5B).

Nociceptive flexion reflex

Figure 6 shows an individual example of NFR in each condition. As for group analyses, anodal tDCS produced no significant change in NFR amplitude for any of the three conditions (all p>0.9, all η2p<0.13; see Figure 7A). Similar results were observed for the sham tDCS session (all p>0.3, η2p=0.03. 0.10 and 0.26, respectively; see Figure 7B).

Discussion

The novel finding of the present study conducted in older persons is that pain inhibition by WM engagement was enhanced by anodal tDCS in the high load WM condition (2-back task), while pain itself was not significantly decreased. This indicates that anodal tDCS can enhance pain inhibition by improving WM in healthy older persons.

Enhancement of working memory and pain inhibition by tDCS

In the present study, anodal tDCS over the left DLPFC decreased mean RTs during the n-back task. This effect was particularly observed in the high WM load conditions while no effect was observed in the low WM load conditions. These results of anodal tDCS on mean RTs replicate our previous findings obtained in younger participants with the same experimental paradigm (Deldar et al., 2018). A study also reported that ten sessions of cognitive training combined with 30 minutes of tDCS over of the prefrontal cortex bilaterally improved accuracy in a verbal working memory task compared with sham tDCS, in older persons (mean age of 69.7 y.o.) (Park et al., 2014). Another study in which ten sessions of cognitive training combined with

sham or anodal tDCS of the right prefrontal, parietal, or prefrontal/parietal cortex were performed reported that older persons (mean age 64.4 y.o.) showed WM improvement, in the anodal tDCS groups only, regardless of tDCS location.

In addition to WM performance, the present results indicate that anodal tDCS could improve pain inhibition by WM. This is also consistent with results from a previous study in young participants (Deldar et al., 2018). Although we suggest that pain inhibition was improved by an improvement of WM, we cannot exclude the possibility that both effects may be produced by independent processes. However, these hypoalgesic effects were observed only with high WM load (2-back task), while no effect was observed with the low WM load condition (0-back task). This suggests that anodal tDCS of the DLPFC may improve pain inhibition by WM but only when the WM task is sufficiently demanding, in accordance with previously described state-dependent or load-dependent effects of tDCS (Roe et al., 2016; Wu et al., 2014). In addition, pain itself was not decreased by anodal tDCS in the present and in our previous study (Deldar et al., 2018), indicating that improvement of pain inhibition by WM with anodal tDCS relies on the interaction of WM with pain-related processes and not on a direct effect on pain-related processes. Also, the lack of significant change in NFR amplitude suggest that this interaction relies on a supraspinal mechanism that do not involve descending modulation.

Interactions between pain and cognition in older persons

The comparison of WM performance between conditions during pre-tDCS baseline showed that response times were shorter when the 0-back and 2-back tasks were performed with painful distracters compared with the same tasks without painful distracters. There may be experimental conditions or daily situations in which pain is prioritized, resulting in reduced cognitive performance. For instance, patients with fear of pain or with chronic pain may be hypervigilant to pain (Van Damme et al., 2010), which could bias attention towards pain processing at the expense of cognitive task execution. One possibility that should be considered to explain the improvement of WM by anodal tDCS is that anodal tDCS produces a sensation on the scalp that may increase alertness, possibly leading to an improvement in RT. However, this possibility is unlikely since the same sensation did not produce a similar effect in the 0-back condition. In addition, it was reported that when participants prioritize a cognitive task, like the n-back task, RT are decreased (Erpelding and Davis, 2013). Pain was also decreased by the

execution of the 0-back and 2-back tasks, indicating that attentional control was effective and that task execution was prioritized, resulting in reduced processing of painful distracters. Effective attentional control to execute a cognitive task in spite of painful distracters depends on the disengagement of attention from pain and on the allocation of cognitive resources to maintain attention on the processing of task-relevant information (Legrain et al., 2009b). The present results indicate that WM maintenance of the visual targets of the n-back task helped to shift attention away from the painful stimulus.

Significance, future directions and limitations

Chronic pain conditions may advance with the age-related cognitive decline. Besides, pain is associated with changes in the brain that may worsen the cognitive decline observed in older adults. For instance, patients with chronic neuropathic or radicular pain show decreased cognitive performance and this decline is particularly observed in older patients (Moriarty et al., 2011; Moriarty et al., 2017). This suggests that clinical pain can decrease cognitive function and that this effect is moderated by age. Conversely, studies in patients with dementia indicate that cognitive decline is associated with greater amplitude and duration of pain-related activity in regions associated with sensory, affective and cognitive processes (Summers et al., 2016). Based on these interactions between cognition, pain and age, anodal tDCS may be especially useful in older persons affected by cognitive decline, chronic pain or both (Hsu et al., 2015). Besides, It remains to be determined whether anodal tDCS of the DLPFC may be effective at improving pain inhibition by WM in different clinical populations in which an attentional bias to pain was reported (Eccleston and Crombez, 1999; Torta et al., 2017). Another limitation that should be mentioned is that tDCS is not a focal method and other regions and their networks may be stimulated in addition to the DLPFC, over which the anode was placed. Therefore, like in other tDCS studies, the effects reported here cannot be attributed to the DLPFC exclusively.

Conclusion

The present study shows that WM and pain inhibition is enhanced by anodal tDCS in older persons. This warrants future studies to examine whether multiple tDCS sessions with cognitive training may produce long-lasting changes in pain regulation and pain symptoms in healthy older persons and patients with cognitive decline or chronic pain.

Abbreviations

DLPFC: Dorsolateral Prefrontal Cortex; EMG: Electromyography; ERP: *Event-Related Potential*; IASP: International Association for the Study of Pain; ISI: Inter-stimulus Interval; ITI: Inter-trial Interval; NRS: Numerical Rating Scales; M: mean; NFR: Nociceptive Flexion Reflex; RA: Response Accuracy; RT: Response Time; SEM: standard error of the mean; tDCS: Transcranial Direct Current Stimulation; WM: Working Memory.

Acknowledgements

This study was supported by a grant from the Natural Sciences and Engineering Research Council of Canada (MP - grant number 402176). The contribution of MP was supported by the research Chair in Pain Neurophysiology from Université du Québec à Trois-Rivières and the Fonds de Recherche du Québec en Santé (FRQS). The contribution of Zoha Deldar was supported by the department of Anatomy from UQTR and the Centre de Recherche en Neuropsychologie et Cognition (CERNEC) from Université de Montréal.

Conflicts of interest

The authors report no financial or other relationship that may lead to any conflict of interest.

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Figure Captions

Figure 1. Modified n-back task.

Participants performed a modified n-back task in which they had to discriminate the colour of each visual stimulus, consisting in two blue or two yellow squares. In the 0-back condition, they discriminated the colour of the current stimulus immediatly after its presentation. In the 2-back condition, they responded for the stimulus discriminated two trials before. The visual stimulus was preceded by a tactile stimulus in 83% of trials or by a painful stimulus in the remaining trials (17%). The bottom left panel indicates the sequential timings of stimuli in each trial. A fixation cross was presented at the center of the screen during the entire trial. Electrical stimuli were followed by a visual stimulus of 500 ms duration. The interval between the somatosensory and visual stimuli (ISI) was 220 ms for the tactile trials and 300 ms for the painful trials. Task performance was measured in the time window running from 150 to 1500 ms after visual stimulus onset. The next trial began after the response with a fixed inter-trial interval (ITI) of 3000 ms. The placement of the electrodes for painful and tactile stimulation is illustrated at the bottom right of the figure. Two pairs of surface electrodes were placed adjacently on the path of the right sural nerve (painful stimulation) and on the anterior part of the right lateral malleolus (tactile stimulation). Electromyography (EMG) was recorded with a pair of surface electrodes from the short head of the biceps femoris with the ground placed on the medial aspect of the tibial tuberosity.

Figure 2. Experimental design.

The experimental protocol comprised five counterbalanced conditions, including 0-back, 2-back, pain, 0-back with pain and 2-back with pain. This experimental protocol was performed twice during each session, once to establish a pre-tDCS baseline and once during tDCS. The same order was used for the sham and anodal tDCS sessions for a given participant. The condition duration was 3.5 min and each condition contained 60 trials. Participants were instructed to rate pain and pain-related anxiety at the end of each condition comprising painful stimuli using a numerical rating scale (0-100).

Figure 3. Effect of tDCS on working memory

A) Anodal tDCS significantly reduced response times (RT) in the 2-back task with or without pain, compared with pre-tDCS baseline (both $p<0.01$), while no difference was observed for the 0-back task with or without pain compared with pre-tDCS baseline (both $p>0.3$). **B)** No significant effect was produced by sham tDCS for either task, with or without pain, compared with pre-tDCS baseline (all $p>0.3$. **C)** No effect of anodal tDCS was observed on response accuracy (RA) for either task, with or without pain, compared with pre-tDCS baseline (all $p>0.1$). **D)** Sham tDCS did not produce any significant change in response accuracy for any task compared with their respective pre-tDCS baseline (all $p>0.1$). Error bars indicate standard error of the mean. **$p\leq0.01$.

Figure 4. Effect of tDCS on pain intensity.

A) Anodal tDCS significantly increased pain inhibition by WM in the 2-back with pain task compared with pre-tDCS baseline ($p<0.01$). In contrast, pain and pain inhibition by WM in the 0-back task were not significantly different compared with pre-tDCS baseline (both $p>0.8$). **B)** Sham tDCS produced no significant change in pain intensity for any of the three tasks compared with pre-tDCS baseline (all $p>0.9$). Error bars indicate standard error of the mean. **$p\leq0.01$.

Figure 5. Effect of tDCS on pain-related anxiety.

A) Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly modulated by anodal tDCS compared with pre-tDCS baseline (all $p>0.1$). **B)** Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly modulated by sham tDCS compared with pre-tDCS baseline (all $p>0.9$). Error bars indicate standard error of the mean.

Figure 6. Individual example of the raw NFR traces in each condition

A) Average NFR (10 trials) for one participant during pre-tDCS baseline and anodal tDCS in the three conditions (pain; 0-back; 2-back). B) Average NFR (10 trials) for one participant during pre-tDCS baseline and sham tDCS in the three conditions (pain; 0-back; 2-back). In line with group results, anodal tDCS did not improve NFR inhibition.

Figure 7. Effect of tDCS on NFR amplitude.

A) NFR amplitude was not significantly modulated by anodal tDCS compared with pre-tDCS baseline (all $p>0.9$). **B)** NFR amplitude was not significantly modulated by sham tDCS compared with pre-tDCS baseline (all $p>0.3$). Error bars indicate standard error of the mean.

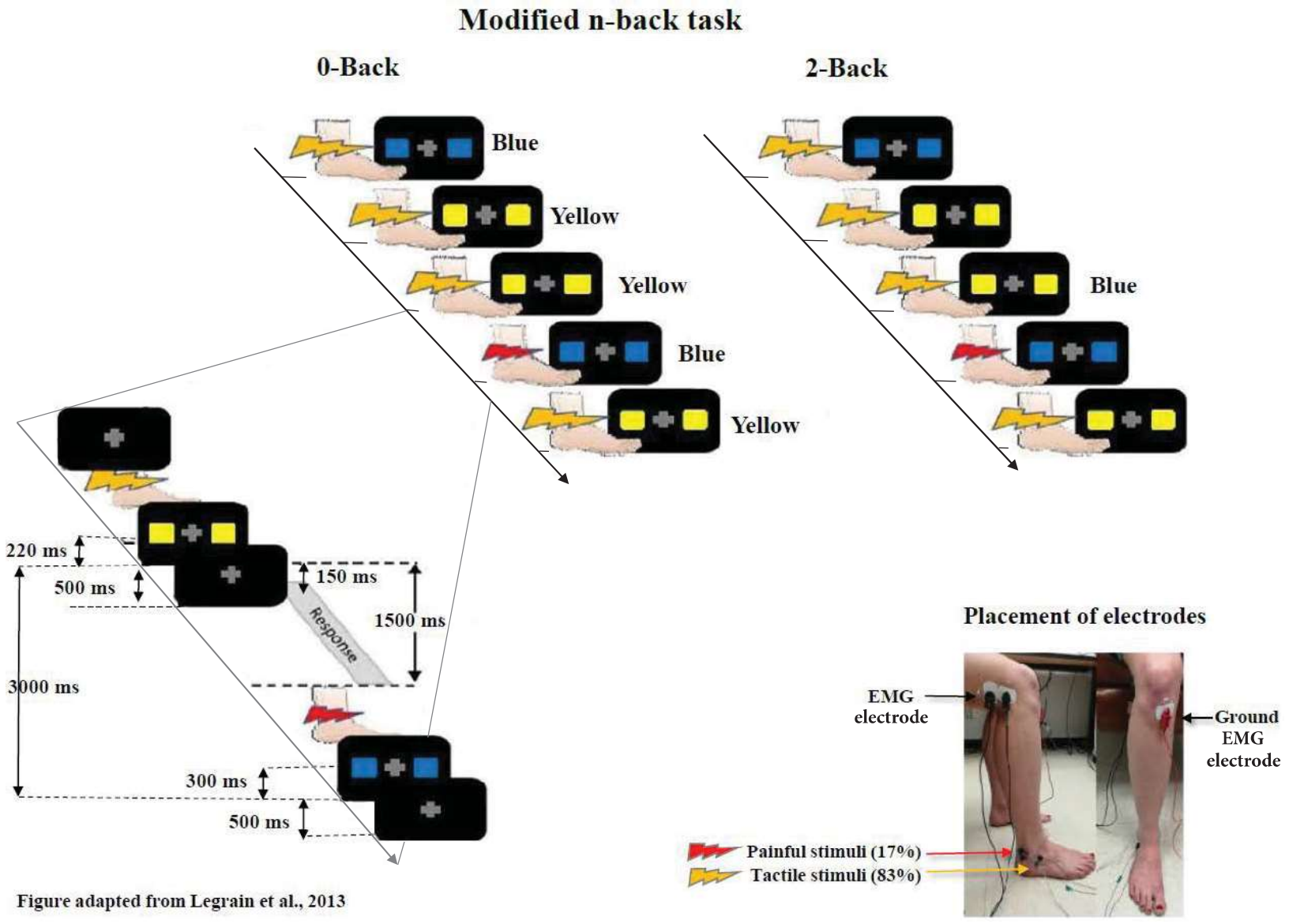
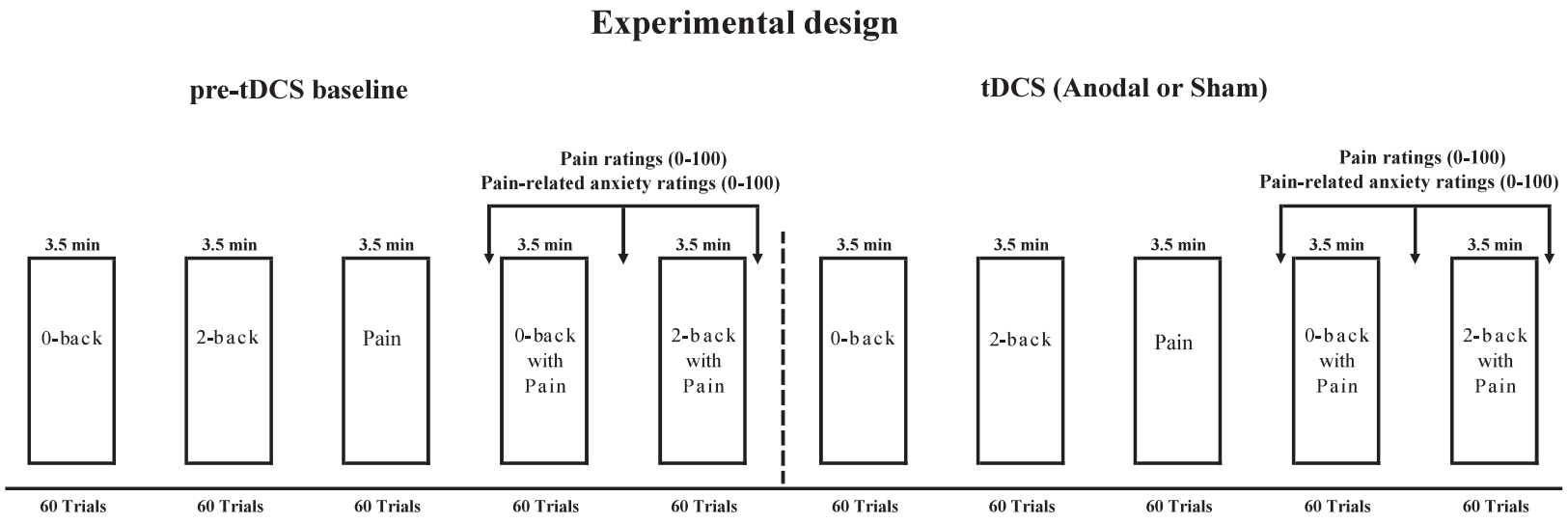
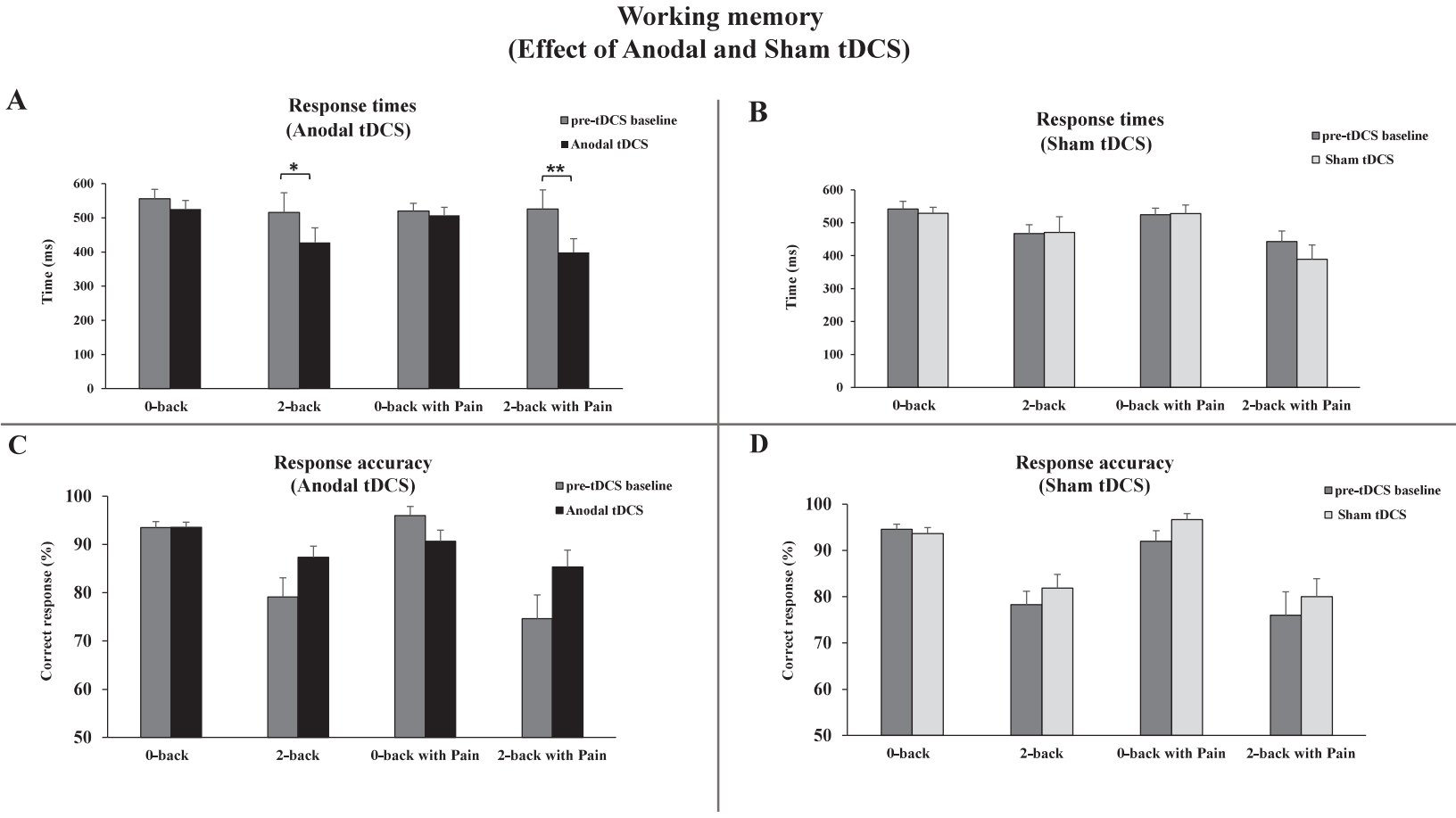
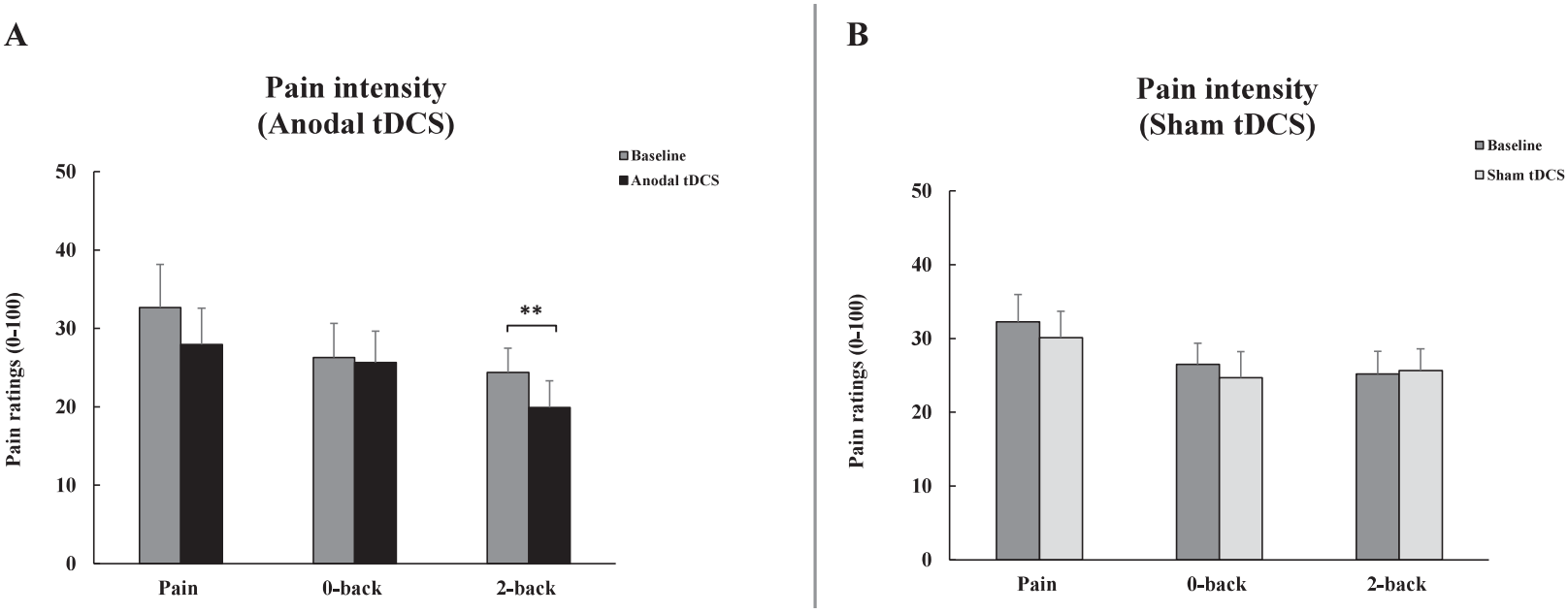


Figure adapted from Legrain et al., 2013

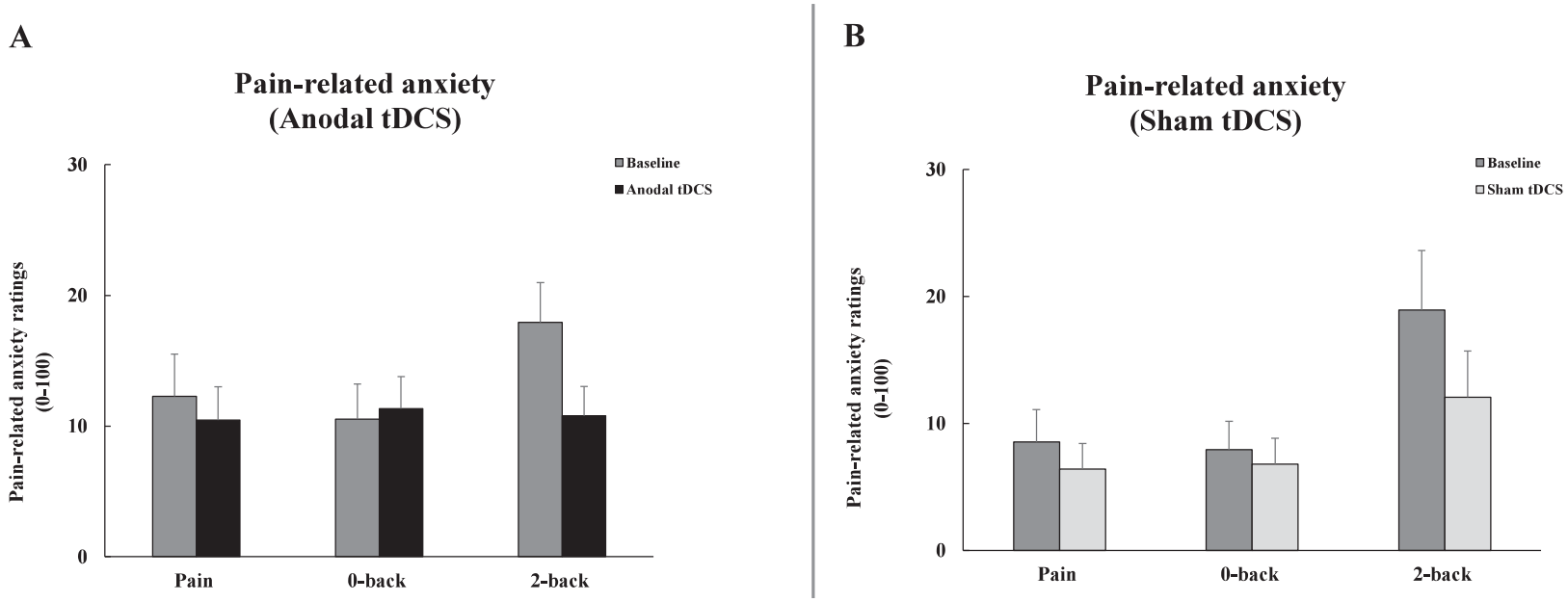

Experimental design
pre-tDCS baseline
tDCS (Anodal or Sham)
Pain ratings (0-100)
Pain-related anxiety ratings (0-100)
Pain ratings (0-100)
Pain-related anxiety ratings (0-100)
3.5 min
0-back
2-back
Pain
0-back with Pain
2-back with Pain
0-back
2-back
Pain
0-back with Pain
2-back with Pain
60 Trials

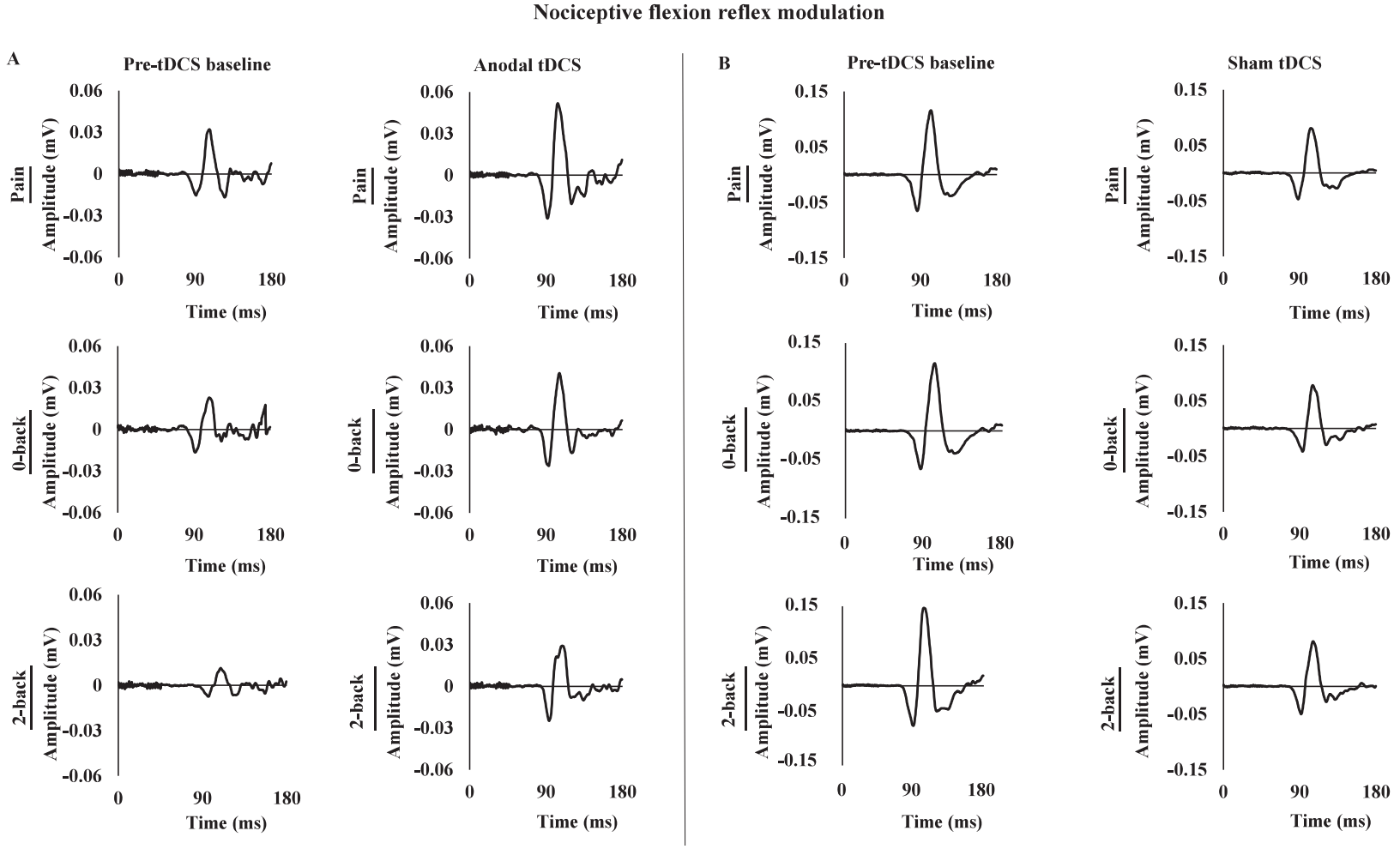

Working memory
(Effect of Anodal and Sham tDCS)
A
Response times
(Anodal tDCS)
pre-tDCS baseline
Anodal tDCS
Time (ms)
600
500
400
300
200
100
0
*
**
0-back
2-back
0-back with Pain
2-back with Pain
B
Response times
(Sham tDCS)
pre-tDCS baseline
Sham tDCS
Time (ms)
600
500
400
300
200
100
0
0-back
2-back
0-back with Pain
2-back with Pain
C
Response accuracy
(Anodal tDCS)
pre-tDCS baseline
Anodal tDCS
Correct response (%)
100
90
80
70
60
50
0-back
2-back
0-back with Pain
2-back with Pain
D
Response accuracy
(Sham tDCS)
pre-tDCS baseline
Sham tDCS
Correct response (%)
100
90
80
70
60
50
0-back
2-back
0-back with Pain
2-back with Pain

Results of Pain modulation
(Effect of Anodal and Sham tDCS)



Results of Pain-related anxiety modulation (Effect of Anodal and Sham tDCS)




Nociceptive flexion reflex modulation
A
Pre-tDCS baseline
Anodal tDCS
B
Pre-tDCS baseline
Sham tDCS
Pain
0-back
2-back
Amplitude (mV)
Time (ms)
0.06
0.03
0
-0.03
-0.06
0.15
0.05
-0.05
-0.15
0
90
180

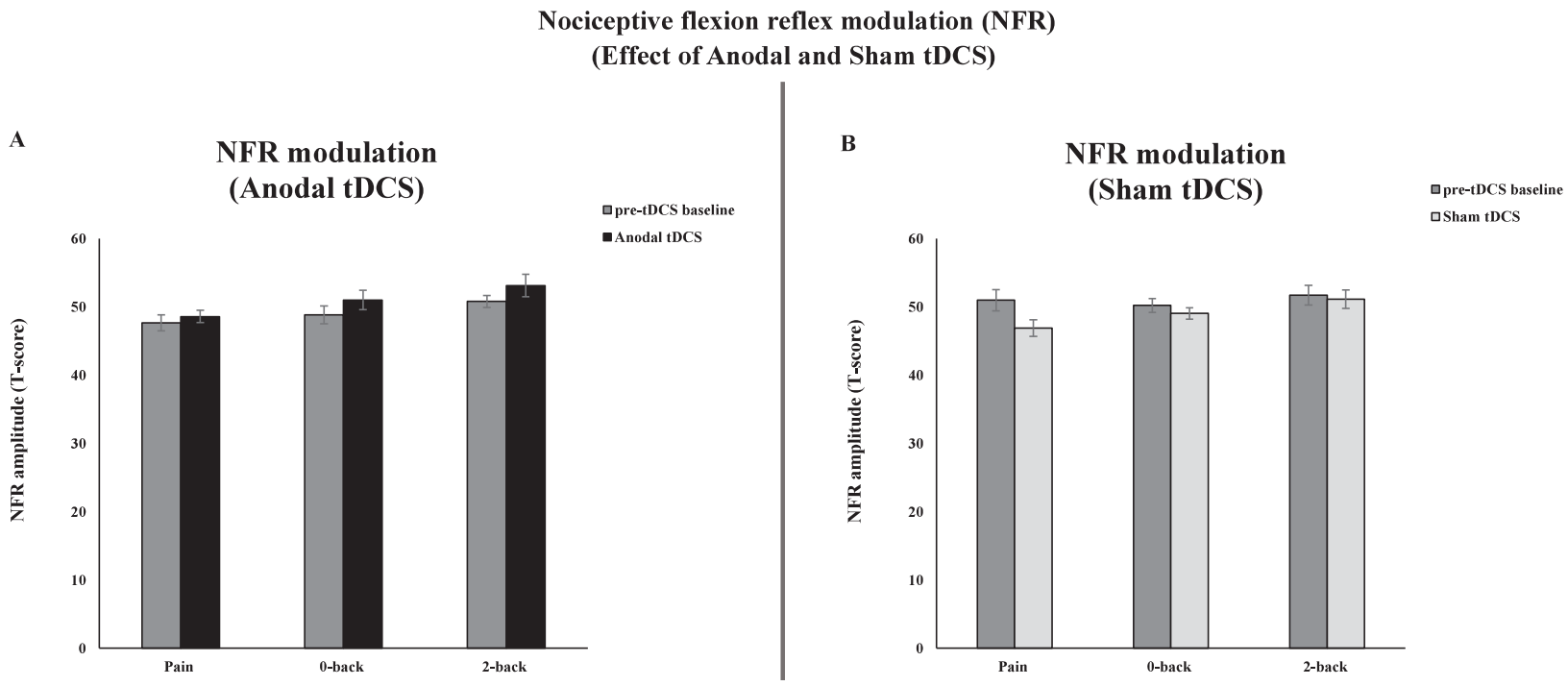

Nociceptive flexion reflex modulation (NFR)
(Effect of Anodal and Sham tDCS)
A
NFR modulation
(Anodal tDCS)
pre-tDCS baseline
Anodal tDCS
NFR amplitude (T-score)
60
50
40
30
20
10
0
Pain
0-back
2-back
B
NFR modulation
(Sham tDCS)
pre-tDCS baseline
Sham tDCS
NFR amplitude (T-score)
60
50
40
30
20
10
0
Pain
0-back
2-back

Table 1. Characteristics of participants

N=15; 7 Females and 8 Males	Mean ± SEM (range)
Age (y.o.)	64 ± 4.41 (55-71)
Depressive symptoms (GDS) (0-30)	3.6 ± 0.8 (0-10)
Pain catastrophizing (PCS) (0-52)	13.7 ± 3.0 (0-37)
Pain vigilance and awareness (PVAQ) (0-80)	36.5 ± 2.4 (22-50)
Trait anxiety (STAI-Y) (0-80)	47.1 ± 0.7 (43-51)
State anxiety (STAI-Y) (0-80)	47.4 ± 0.7 (43-54)
Attentional control scale (ACS) (0-80)	48.9 ± 0.7 (44-53)
Cognitive function (MOCA) (0-30)	29.2 ± 0.4 (25-30)
Pain threshold (mA) for sham and anodal tDCS sessions	7.33 ± 1.33 (3-15)
Nociceptive flexion reflex threshold (mA) for sham and anodal tDCS sessions	8.8 ± 1.60 (3.6-18)

Table 2. Interactions between pain and working memory (pre-tDCS baseline values)

	0-back	2-back	Pain	0-back with pain	2-back with pain
Response time (ms)	548.8 ± 17.8	491.01 ± 31.8	-	521.1 ± 15.2	484.32 ± 32.6
Response accuracy (%)	94 ± 0.9	78.7 ± 2.4	-	94 ± 1.5	75.3 ± 3.5
Pain ratings (0-100)	-	-	32.5 ± 4.1	26.4 ± 3.3	24.8 ± 2.4
Pain-related anxiety ratings (0-100)	-	-	10.4 ± 2.6	9.2 ± 1.9	18.4 ± 3.4
Nociceptive flexion reflex amplitude (T-score)	-	-	49.3 ± 1.3	49.5 ± 1.0	51.3 ±1.0