ORIGINAL RESEARCH

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Differential effects of conventional transcranial direct current stimulation (tDCS) and high-definition transcranial direct current stimulation (HD-tDCS) of the cerebellum on offset analgesia

Niamh O'Connor[1,3*]

Hannah Ashe[1*]

Max Wragan[1,3*]

Ruairí O'Flaherty[1*]

Eoin Deevy-Gray[1]

Alice G. Witney [1,2,3]

[1] Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland

[2]Trinity Centre for Biomedical Engineering, Trinity College Dublin, Ireland

[3]Discipline of Physiology, School of Medicine, Trinity College Dublin, Ireland

*These authors contributed equally to this work

Correspondence:

Department of Physiology,

2nd Floor Trinity Biomedical Sciences Institute,

152-160 Pearse Street,

Dublin D2

Tel +353 1 896 2080

Email : Dr Alice Witney awitney@tcd.ie

Abstract

Background : Endogenous analgesic systems in the brain modulate pain perception. Offset analgesia (OA) describes the large decrease in perceived pain in response to a minor decrease in applied painful thermal stimulus. Here non-invasive brain stimulation (NIBS) of the cerebellum is used to probe OA.

Methods : An OA protocol individualized to heat pain threshold (HPT) was applied via TSA-II (Medoc, Israel). Heat was ramped to HPT, with a transient temperature increase of HPT+1°C. NIBS interventions were applied prior to OA in 46 participants within a sham controlled repeated measures design. Cathodal cerebellar transcranial direct current stimulation (tDCS) and high-definition (4X1) transcranial direct current stimulation (HD-tDCS) were applied in separate experimental sessions to examine whether diffuse (tDCS) or focal (HD-tDCS) stimulation differentially modulates OA.

Results : OA induced hypoanalgesia was robust, with 90% of responses showing a substantial drop in perceived pain (δVAS) following the 1°C fall in temperature, with an average VAS decrease of 38 in response to the 1°C fall in temperature. Cathodal cerebellar HD-tDCS enhances the analgesic impact of OA on four OA parameters ($OA_{latency}$, $VAS_{minimum}$, VAS_{mean} and $VAS_{2nd\ max}$) relative to pre-stimulation. Conventional tDCS modulates two OA metrics relative to pre-stimulation ($OA_{duration}$, $VAS_{2nd\ max}$) with an increase in $OA_{duration}$ following sham tDCS.

Conclusion : There is a differential influence of conventional and high-definition cerebellar NIBS on OA. This is suggestive of cerebellar modulation of OA and highlights the importance of electrode montage in delineating the influence of the cerebellum in pain processing.

Introduction

Endogenous pain modulatory pathways, that alter the pain experienced in response to nociceptive stimuli, are obvious therapeutic targets. However, these pathways are not fully elucidated. Offset analgesia (OA) is a pain modulation phenomenon where an individual experiences a disproportionately large decrease in pain sensation in response to a small decrease in experimentally applied thermal stimulus [20]. The hypoanalgesia evoked by OA experimental protocols has potential to provide valuable insights into the function of endogenous pain regulation systems. Previous studies have demonstrated abnormal OA responses in chronic pain patients relative to healthy participants, including neuropathic pain and osteoarthritis [1; 41; 43; 57] thus validating the potential clinical utility of this protocol. This study aims to further characterize the OA response and examine whether non-invasive brain stimulation (NIBS) of the cerebellum modulates these pathways.

The cerebellum contributes to pain modulation, but the precise role has not been elucidated [27; 38; 54]. fMRI pain studies report cerebellar activity in response to nociceptive stimuli, with cerebellar lobules IV-VI and crus I consistently showing increased activity during nociceptive stimulation [12; 36]. Thermal nociceptive stimuli increase activity in cerebellar lobules III-VIII [4; 37; 38]. Injury typically leads to increases in cerebellar activity ipsilateral to injury, whereas thermal and chemical nociception can cause bilateral increases in cerebellar activity [24; 27; 47]. Cerebellar lesions in humans are associated with increased pain sensation in response to mechanical and thermal stimulus, suggesting the cerebellum modulates pain via connectivity with sensorimotor, limbic, executive and reward regions [48]. A NIBS technique, repetitive transcranial magnetic stimulation (rTMS) of the cerebellum has been found to modulate pain thresholds with mechanisms thought to be related to peripheral nerve effects rather than the pathway to motor cortex [68]. Animal models show evidence of both anti-nociceptive and pro-nociceptive role of the cerebellum [49; 50] on pain thresholds that is thought to be due to the involvement of the anterior and posterior cerebellar cortex respectively.

Imaging studies show the cerebellum increases in activity during an OA protocol relative to tonic pain, with close correlation demonstrated with the periacqueductal gray (PAG) [22]. The

cerebellum's connectivity between the cerebellum and PAG are highly indicative of the cerebellum's important role in mediating pain perception [38]. Further, patients with cerebellar lesions demonstrated poor OA responses relative to age-matched healthy participants[48].

NIBS is effective for pain modulation[3; 16; 17; 25; 28; 35]. Currently, the greatest efficacy is associated with high frequency repetitive transcranial magnetic stimulation (rTMS) of primary motor cortex (M1) and anodal transcranial direct current stimulation (tDCS) of primary motor cortex (M1) [18; 26; 30]. Anodal M1 HD-tDCS has been found to modulate pain thresholds [62] with increased focality. The cerebellum is currently a relatively unexplored target for pain modulation. Cerebellar NIBS protocols and electrode montages are developing [14; 31; 60] but there is increasing evidence that the choice of optimal electrode montage and 'dosage' is critical for an optimal effect [46]. Cerebellar NIBS may aid understanding of endogenous pain modulation [25; 63]. A recent study has suggested that anodal and cathodal tDCS enhance and inhibit endogenous pain pathways [53] respectively with small effect sizes. Given the substantial evidence behind cerebellar involvement in OA, further research into cerebellar NIBS protocols is appropriate to further understand this finding, as consideration of stimulation polarity effects should be treated cautiously[7]. Folding of the brain region underlying stimulation will likely result in the direction of current flow on neurons being difficult to predict [3] and perhaps distort or diminish effect. This presents a particular challenge to NIBS of the cerebellum, due to its complex cytoarchitecture [60] . Additionally the cerebellum contains the highest density of neurons in the brain, making interpretation of diffuse current application as occurs in conventional tDCS particularly challenging [64]. Therefore, cerebellar NIBS may benefit from the more focused HD-tDCS method for optimizing behavioural effects. This study compares two forms of transcranial direct current stimulation (tDCS) of the cerebellum on OA, conventional tDCS and the more focal HD-tDCS on the OA response.

Material and methods

The study protocol was approved by the Faculty of Health Science Research Ethics Committee, Trinity College Dublin, Ireland and conducted in accordance with the Declaration of Helsinki (2013). Participant eligibility was evaluated with a medical questionnaire, which excluded participants with neurological and psychiatric conditions. 46 participants (22

110 females, mean age 22.35 years) completed all experiments in the study. A sham-controlled
111 repeated measures design was used, with tDCS and HD-tDCS completed in two sessions,
112 separated by at least one week, to ensure no overlap in NIBS effects between experimental
113 sessions.

114 *Offset analgesia protocol*

115 A TSA-II Neurosensory Analyzer, Medoc, Israel [34] applied heat via the 16x16 mm peltier
116 thermode to the participants right forearm, secured with Velcro©. A computerized visual
117 analogue scale (CoVAS, Medoc, Israel) [33] continuously recorded participants' pain report at
118 9 Hz [67] with the displacement of a marker between two endpoints of 'no pain' and 'most
119 intense pain imaginable' corresponding to values between 0 and 100. Trained using the
120 CoVAS occurred prior to testing.
121 Heat pain threshold (HPT) individualized the subsequent OA protocol [2; 39; 51; 55; 56].
122 HPTs were determined by increasing the temperature of the thermode applied to the right
123 forearm at a rate of 1.5°C/s from a baseline of 32-35°C until pain was reported. HPT trials
124 were repeated three times, with 10 s rest intervals between trials.
125 The OA protocol comprised of an OA trial and a control trial, presented in random order. To
126 ensure data accuracy, 60 s of rest followed data collection trials in addition to slight thermode
127 repositioning on the forearm to prevent sensitization [66]. On an OA trial (Figure 1), three
128 sequential temperatures (T1-3) were utilised: the initial stimulus temperature (T1) is the
129 participant's HPT, ramped from the baseline temperature representing normal skin
130 temperature (32-35°C) at a rate of 1.5℃/s. T1 (HPT) was held constant for 7 - 10 seconds.
131 The duration of T1 varied to decrease participants' expectation of a temperature change at
132 temperature 2 (T2). The T2 phase elevates the temperature a single degree to HPT + 1℃ for
133 5 s, and the Temperature 3 (T3) falls to HPT for 30 s before returning to baseline skin
134 temperature at a rate of 6℃/s. (Figure 1). The transition from T2 to T3 is where OA is
135 experienced, the characteristic disproportionate decrease in pain sensation relative to the
136 associated temperature decrease. This OA protocol differs from some previous OA protocols
137 [20; 66] because the T3 phase was extended to characterize the duration of OA, previous
138 studies show ongoing OA at the termination of T3 [2; 20; 58].

139 Control trials consisted of the same T1 temperature as the OA trials (HPT), similarly ramped
140 from baseline skin temperature at a rate of 1.5℃/s. However, in contrast, T1 was sustained
141 for 30s, before ramping down to baseline skin temperature at rate of 6℃/s.

142 *Transcranial direct current stimulation montages*

143 Conventional cerebellar tDCS was applied using a neuroConn DC stimulator (NeuroConn
144 GmBH, Germany) with sponge electrodes (surface area 25 cm^2) soaked in 0.9% saline. The
145 stimulating electrode was positioned at the mid-point between the inion and the maximum
146 convexity of the right ear with the return electrode on the right buccinator[21; 23; 29].
147 Cerebellar HD-tDCS was applied using the neuroConn DC stimulator connected to a Soterix
148 4x1 HD-tDCS adaptor (Model 4x1-C2; Soterix Medical Inc., New York, USA). A 4X1
149 electrode montage using sintered Ag/AgCl electrodes (EasyCap, GmbH, Germany) filled with
150 conductive gel (Electro-Gel, Brainmaster Inc., USA) were secured with an electrode cap
151 (EasyCap, GmbH, Germany). The central electrode was placed at the mid-point of the inion
152 and the maximum convexity of the right ear, with the four return electrodes spaced 3 cm
153 radially around the central electrode. Impedance values were measured for all electrodes
154 prior to usage to ensure good contact quality [61; 62]. Active NIBS applied current of 2mA of
155 tDCS for 20 minutes for both tDCS protocols. Sham stimulation applied 2mA for 30s to elicit a
156 tingling sensation, with no current applied in remainder of the 20 minute protocol [19; 60].
157 Current flow modelling is critical to NIBS protocol design[15; 45]. The cerebellar tDCS and
158 HD-tDCS protocols were simulated (HD-Explore Version 2.1, Soterix Medical, New York, US)
159 to characterise the current distribution with the given electrode montage and current level of
160 2mA as applied experimentally. All modelling was performed on a 93 standard adult male
161 head model sourced from the Soterix model library. Electrode positioning was based on the
162 10/20 EEG system. For conventional tDCS modelling, O10, PO10, EX2, and EX6
163 represented the cathode sponge electrode and EX14, EX16, and EX18 represented the
164 anodal sponge electrode (Figure 2a). For HD-tDCS modelling, PO10 represented the
165 cathode and PO4, P10, EXZ, and EX4 represented the anodes (Figure 2b).

OA and control trial response characterization

OA and Control response metrics were extracted using a custom written MATLAB script (Version 9.0, The MathWorks Inc., MA, USA). Control trial metrics were mean (VAS_{mean}), minimum (VAS_{min}), maximum (VAS_{max}) and standard deviation (VAS_{sd}) of the VAS score while HPT was applied over a 30s period (T1).

CoVAS profiles were averaged dependent on neurostimulation (pre-stimulation, sham, active stimulation) from the onset T3 for 22 s to qualitatively compare the impact of NIBS on the OA response, which is defined as the VAS ratings made during T3. The OA response metrics used in the study (Table 1, Figure 1) included both magnitude (Figure 1a) and temporal (Figure 1b) features with metrics selected to be consistent with previous studies, VAS_{min} [2; 10; 41], δVAS [1; 10; 41] and VAS_{mean} [10]. Further, in this study, a second maximum VAS was included since the OA protocol extended the T3 phase. Some OA metrics could not be extracted on all trials due to features of the OA response, for example there could be no $VAS_{2nd\ max}$ or $OA_{rate\ up}$ metric if the OA induced hypoanalgesia continued throughout T3.

Statistical analysis

Statistical analysis was performed in SPSS (IBM SPSS Statistics, Version 27; IBM Corp). Descriptive statistics were collected for all OA metrics across conditions (pre-stimulation OA; sham stimulation OA; active stimulation OA). Within day ICC on OA metrics are consistently high in previous research [42] and pilot work in the laboratory. Between day ICC comparing OA metrics at pre-stimulation baseline on each session were moderate or low. Therefore, the tDCS and HD-tDCS experiments were considered separately via two 3X1 repeated measures ANOVA for both control and OA trial metrics. Mauchly's test of sphericity was performed, and when sphericity could not be assumed the Huynh-Feldt estimate was applied. Post-hoc pairwise comparisons were made with Bonferroni corrections for multiple comparisons.

Results

On control trials where T1 was held at HPT for 30s, the VAS_{mean} was 30.07 (SD 18.95), VAS_{max} of 42.31 (SD 22.41), VAS_{min} 15.96 (SD 18.67) and VAS_{sd} was 28.11 (SD 9.06). As expected, there were no consistent periods of hypoanalgesia observed in this VAS response to sustained HPT.

In contrast, the OA protocol successfully consistently induced hypoanalgesia, with only 3% of trials not showing a decrease in VAS at the T2-T3 transition. 90% of trials showed a fall greater than 10 VAS, with most trials eliciting a much larger decrease in pain perception.

The fall of temperature in T3 to HPT gave hypoanalgesia with a minimum VAS (VAS_{min}) at the nadir of the OA response of 12.71 (SD 15.50). The mean δVAS in the current study was slightly lower at 38.13 (SD, 22.39) relative to scores found by previous studies [1; 39; 40]. The T3 VAS_{mean} 30.35 (SD 23.61) for T3 phase was lower than studies that do not individualize OA protocols to HPTs [10]. The $OA_{rate\ down}$ at the T2-T3 transition a mean of 8.45 VAS/s (SD 8.45) was much steeper than $OA_{rate\ up}$, during T3, (1.85 VAS/s, SD 1.71), revealing the rapidity of OA at the transition and the sustained hypoanalgesia that demonstrates the necessity of extending T3 in the protocol. Taken together the protocol used in this study robustly generated OA and provided baseline values consistent with earlier studies in the area [1; 32; 39].

Modelling cerebellar NIBS

Current flow in the conventional tDCS (Figure 2a) is more diffuse than HD-tDCS (Figure 2b). Highest flow intensities with tDCS are near the active electrode, at the cerebellar cortical level in the posterior lobe. Medial structures also receive strong current and spread to the temporal lobe and frontal lobe. Current reached the upper and lower brainstem. For HD-tDCS, current flow was more restricted, with high field intensities in the posterior and anterior cerebellar lobe and posterior aspects of the temporal lobe. Very little current reaches the contralateral cerebellar hemisphere or brainstem.

The effect of cerebellar NIBS on OA

There were no significant differences in the control trial metrics (VAS_{mean}, VAS_{min}, VAS_{max} and VAS_{sd}) dependent on stimulation for either tDCS or HD-tDCS. However, there was a differential impact of NIBS on the OA response (Figure 3).

The average impact of active conventional cerebellar tDCS stimulation relative to pre-stimulation and sham can be seen in Figure (3a).

Statistical analysis revealed there was no effect of cerebellar tDCS neurostimulation on δVAS, VAS_{min}, $OA_{rate\ down}$, VAS_{mean}, $OA_{rate\ up}$ or $OA\ l_{atency}$ metrics of the OA response.

However, the effect of neurostimulation on $OA_{duration}$ was found to be significant $F(2,86)=4.35$, $p = .037$, partial $\eta^2 = .07$. Post-hoc pairwise comparisons with a Bonferroni adjustment indicated there was no significance difference between $OA_{duration}$ at baseline and following sham stimulation, $p=.18$. However, $OA_{duration}$ was significantly longer after active tDCS stimulation (11.17 s, SD 7.97) relative to pre-stimulation (8.11 s, SD 6.75), $p=.048$. Interestingly, there was also no significant difference between $OA_{duration}$ after sham and after active neurostimulation, $p=1$. $OA_{duration}$ represents the length of maximal OA; from the T2-T3 transition to the point at which pain rating begins to rise again (Figure 1b, Table 1, metric 8).

Additionally, there was an effect of stimulation of $VAS_{2nd\ max}$, $F(2,90)=5.40, p=.006$, partial $\eta^2 = .11$. Post-hoc pairwise comparisons with a Bonferroni adjustment showed there was a significant difference between mean $VAS_{2nd\ max}$ at baseline (37.35, SD 26.94) and following sham stimulation, (29.75, SD 25.32) $p=.009$ additionally $VAS_{2nd\ max}$ was significantly lower after active tDCS stimulation, (29.52, SD 25.33), $p=.028$. However, the reduction in $VAS_{2nd\ max}$ also occurred after sham stimulation, with no significant difference between $VAS_{2nd\ max}$ and after active stimulation, $p=1$, suggestive of a placebo effect.

Second, the effect of the more focal 4 X 1 electrode montage was considered. Qualitatively, the effect of active cathodal cerebellar HD-tDCS relative to sham is to enhance the OA effect (Figure 3b). Statistical analysis revealed no effect of cerebellar HD-tDCS neurostimulation was found on $OA_{duration}$, $OA_{latency}$ or $OA_{rate\ up.}$ However, there were differences on four OA metrics. The effect of neurostimulation on δVAS, that is the drop in VAS at the T2-T3 transition was found to be significant $F(1.64,76.09)=3.72$, $p = .036$, partial $\eta^2 = .08$. Post-hoc

pairwise comparisons with a Bonferroni adjustment indicated there was no significance difference between mean δVAS at baseline (32.70, SD 22.63) and following sham stimulation, (38.02, SD 23.51), p=.46. However, δVAS was significantly greater after active tDCS stimulation, (39.80, SD=21.79), p=.007. There was also no significant difference between δVAS after sham and after active neurostimulation, p=.96.

The effect of neurostimulation on $VAS_{rate\ down}$, that is the rate of OA-induced hypoanalgesia, was found to be significant F(1.70,71.18)=3.36, p =.048, partial η^2 = .07. Post-hoc pairwise comparisons with a Bonferroni adjustment indicated there was no significance difference between mean $VAS_{rate\ down}$ at baseline (6.59 VAS/s, SD 4.75) and following sham stimulation, (8.91 VAS/s, SD=8.38), p=.55. However, $VAS_{rate\ down}$ was significantly faster after active tDCS stimulation, (8.31 VAS/s, SD 5.37) p=..021. There was also no significant difference between VAS_{min} after sham and after active neurostimulation, p=.86.

The effect of neurostimulation on VAS_{min} , the VAS at the nadir of the OA response was found to be significant F(2,90)=4.96, p =.01, partial η^2 = .1. Post-hoc pairwise comparisons with a Bonferroni adjustment indicated there was no significance difference between mean VAS_{min} at baseline (16.17, SD=20.25) and following sham stimulation, (10.08, SD 11.62), p=.12. However, mean VAS_{min} was significantly reduced after active tDCS stimulation, (9.79, SD 11.62), p=.018. There was also no significant difference between VAS_{min} after sham and after active neurostimulation, p=1.

There was an effect of stimulation of VAS_{mean}, F(2,90)=4.91, p =.009, partial η^2 = .98. Post-hoc pairwise comparisons with a Bonferroni adjustment indicated there was no significance difference between mean VAS_{mean} at baseline (32.04, SD 23.81) and following sham stimulation, p=.055. However, VAS_{mean} was significantly lower after active tDCS stimulation, (26.02, SD 21.75) p=.023. There was also no significant difference between VAS_{mean} after sham (27.79, SD 18.99), and after active neurostimulation, p=1.

The effect of neurostimulation on $VAS_{2nd\ max}$ was found to be significant F(2,90)=3.56, p =.033, partial η^2 = .07 indicating pain does not rise as much even though OA is reduced relative to the start of T3. Post-hoc pairwise comparisons with a Bonferroni adjustment indicated there was no significance difference between mean $VAS_{2nd\ max}$ at baseline (32.04, SD 23.81) and following sham stimulation, (27.29, SD 18.99), p=.19. However, $VAS_{2nd\ max}$

was significantly reduced after active tDCS stimulation, (26.02, SD 21.75), p=.038. There was also no significant difference between $VAS_{2nd\ max}$ after sham and after active neurostimulation, p=1.

Discussion

The individualized offset analgesia protocol provided a robust methodology for inducing hypoanalgesia. Given the recent advances in NIBS as interventions for pain modulation [13], NIBS of the cerebellum is potentially an important means of further elucidating this role and potentially augmenting hypoanalgiesa. A recent study has indicated anodal tDCS of the cerebellum marginally enhances endogenous pain modulation whereas cathodal tDCS suppresses it, with small effect sizes [53]. However, recent research on the optimization of NIBS suggest it is critical to evaluate differing electrode montages and current dosage, with these parameters paramount for the specific effect and yet gaining less attention than target area and polarity[6; 7; 46].

Here cathodal cerebellar HD-tDCS was found to augment the effects of OA relative to pre-stimulation with VAS pain ratings in T3 both lower at the nadir and demonstrating more sustained hyponanalgesia. Conventional cerebellar tDCS increased OA on two metrics relative to pre-stimulation, with an increase in the initial hypoanalgesia experienced. Qualitatively there appears to be a trend towards increased OA after sham (Figure 3), and one metric in the conventional cerebellar tDCS experiment showed a significant difference post sham, suggestive of a placebo effect. However, no other OA metrics showed an effect of sham in either experiment. Further, the differential impact of the NIBS interventions on OA is observable both qualitatively and statistically, indicating that interpretation must include consideration of current flow and the focality of current applied. Additionally, these differential effects indicate that there is not simply an effect of sequential testing of an OA protocol, which has been found in some studies to enhance the analgesia experienced[9]. The study supports increased focality and attention to current flow to different cerebellar regions as critical for further understanding the cerebellum's role in OA. Cerebellar stimulation presents a challenge for NIBS due to the relatively small target regions [59] that may optimally enhance OA. Animal studies show both pro and anti-nociceptive effects of the cerebellum[11;

52], therefore exploration of different high-definition tDCS montages will enhance understanding further in future studies. In parallel, the exact mechanisms of NIBS on the cerebellum are less well established than cortical regions [60] therefore increased understanding of mechanisms from animal studies alongside current flow modelling would further benefit NIBS design [8].

Cerebellar tDCS mediating analgesic enhancement can be explained by several different pathways. First, cathodal cerebellar tDCS may decrease inhibitory effects of Purkinje cells and so increases deep cerebellar nuclei activity to indirectly reduce inhibition of M1 [18]. Numerous studies link analgesia with primary motor cortex excitability and the cerebellum has a known role in modulating corticomotoneuronal activity[44]. Alternatively, increased caudate putamen activity is associated with cathodal and anodal cerebellar tDCS [30]. The caudate is a known region for pain suppression [65] and is critically involved in the reward pathways. The hypoanalgesia experienced after the transient decrease in supra-threshold pain, that is characteristic of the OA protocol, is known to activate reward pathways. Additionally, cerebellar stimulation may impact on OA via connectivity with known pain modulation pathways including the PAG and dorsolateral prefrontal cortex (DLPFC)[5].

To conclude, offset analgesia is a robustly observed form of hypoanalgesia and better understanding of the underlying mechanism could open therapeutic options. The role of the cerebellum in pain processing is further strengthened by this study. High-definition cerebellar tDCS shows promise as a novel neuromodulation protocol to enhance endogenous pain modulation pathways. Further investigation should occur of the optimal electrode montage, current level, and duration for cerebellar stimulation. Such ‘dosing’ effects of neuromodulation are currently under-explored yet likely critical for maximizing NIBS effects, as well as improving mechanistic understanding.

Author contributions

NOC and AW designed the experimental protocol with EDG involved in pilot testing; NOC, HA, ROF collected the experimental data, MW and AW collated the data, MW and AW

performed statistical and data analysis. NOC, HA, ROF, EDG contributed to initial drafts. MW and AW wrote the manuscript.

Disclosure

The author reports no conflicts of interest in this work. A proportion of this work was presented as an abstract at EFIC, Valencia 2019

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Figure Legends

Figure 1: Offset analgesia protocol showing extracted OA metric definitions for magnitude (A) 1: VAS_{min}, 2: VAS_{mean},3: δVAS_{OA} and temporal (B) 5: OA $rate_{down}$, 6: OA $rate_{up}$, 7: OA $_{latency}$ and 8: $0A_{duration}$ of the OA response. See Table 1 for OA metric definitions.

Figure 2: Current flow modelling: 3D representation of current flow (upper panel), current flow through coronal, sagittal and axial slices (lower panel) A) Cerebellar tDCS montage: High intensity in the cerebellum, temporal lobe, frontal lobe and brainstem. B) Cerebellar HD-tDCS montage restricted current to the right cerebellar hemisphere and the posterior occipital lobe, with peak field intensity in the posterior cerebellum.

Figure 3: Average of OA response during T3 period dependent on cerebellar NIBS stimulation for a) tDCS protocol and b) HD-tDCS protocol. Pre-stimulation (red); Sham-stimulation (blue); Active-stimulation (green). Shading represents standard error of the mean.

Table Legends

Table 1: OA response metric definitions for magnitude and temporal features (see Figure 1 for graphical representation)

554 **Table 1:**

555

Metric Label	Offset Analgesia Metric	Description
1	VAS_{min}	Lowest reported VAS in t3
2	VAS_{mean}	Mean VAS in t3
3	δVAS_{OA}	Magnitude of OA: the change in VAS at t2-t3
4	$VAS_{2nd\ Max}$	Maximum VAS in t3 following hypoanalgesia
5	$OA_{rate\ down}$	Rate of decrease in VAS (δVAS) due to OA
6	$OA_{rate\ up}$	Rate of increase from VAS_{min} to $VAS_{2nd\ Max}$
7	$OA_{latency}$	Time taken for maximum VAS score at the start of t3 to drop to VAS_{min} (the OA induced hypoanalgesia)
8	$OA_{duration}$	Time taken for VAS_{min} to rise again following hypoanalgesia

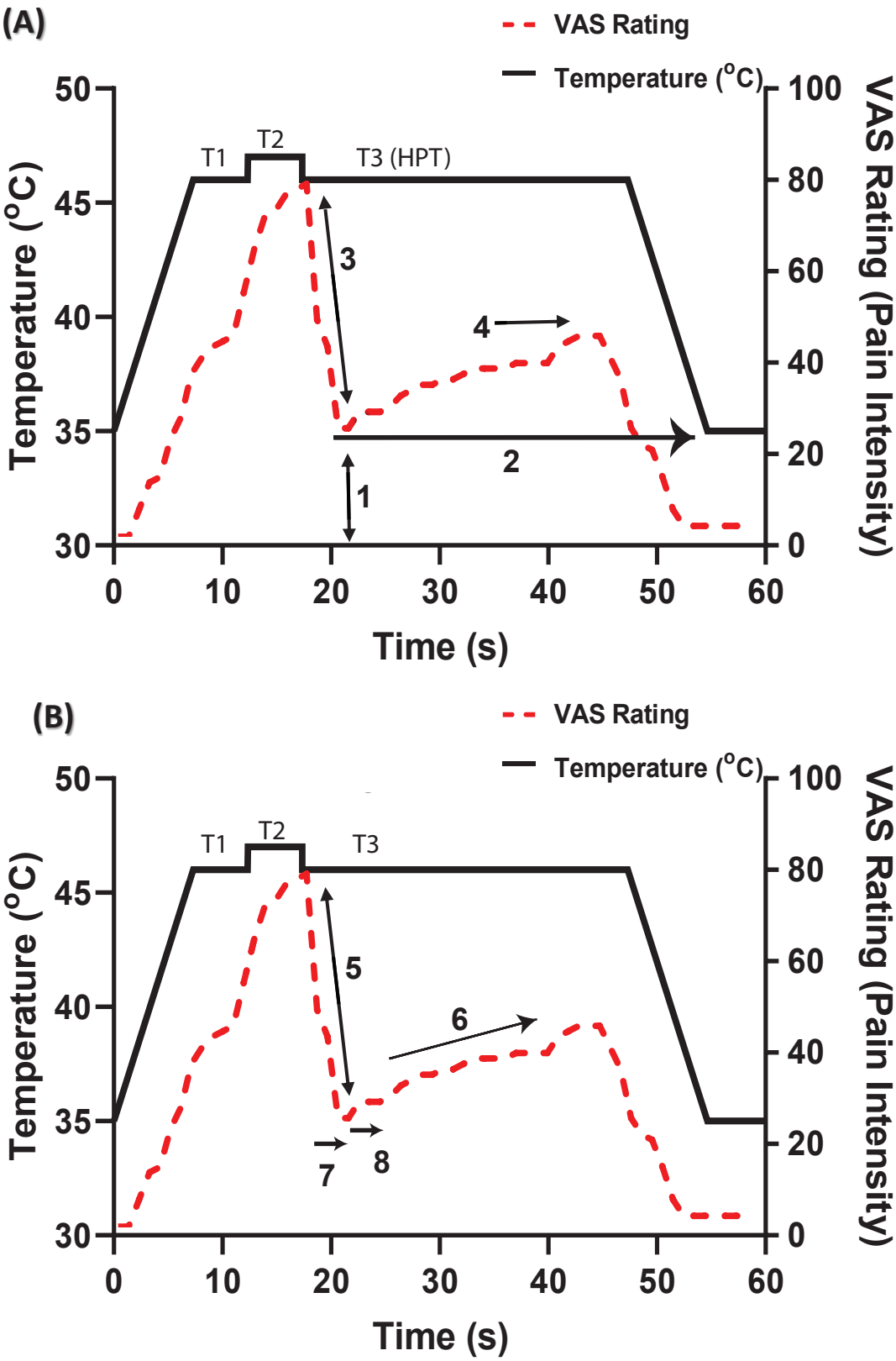
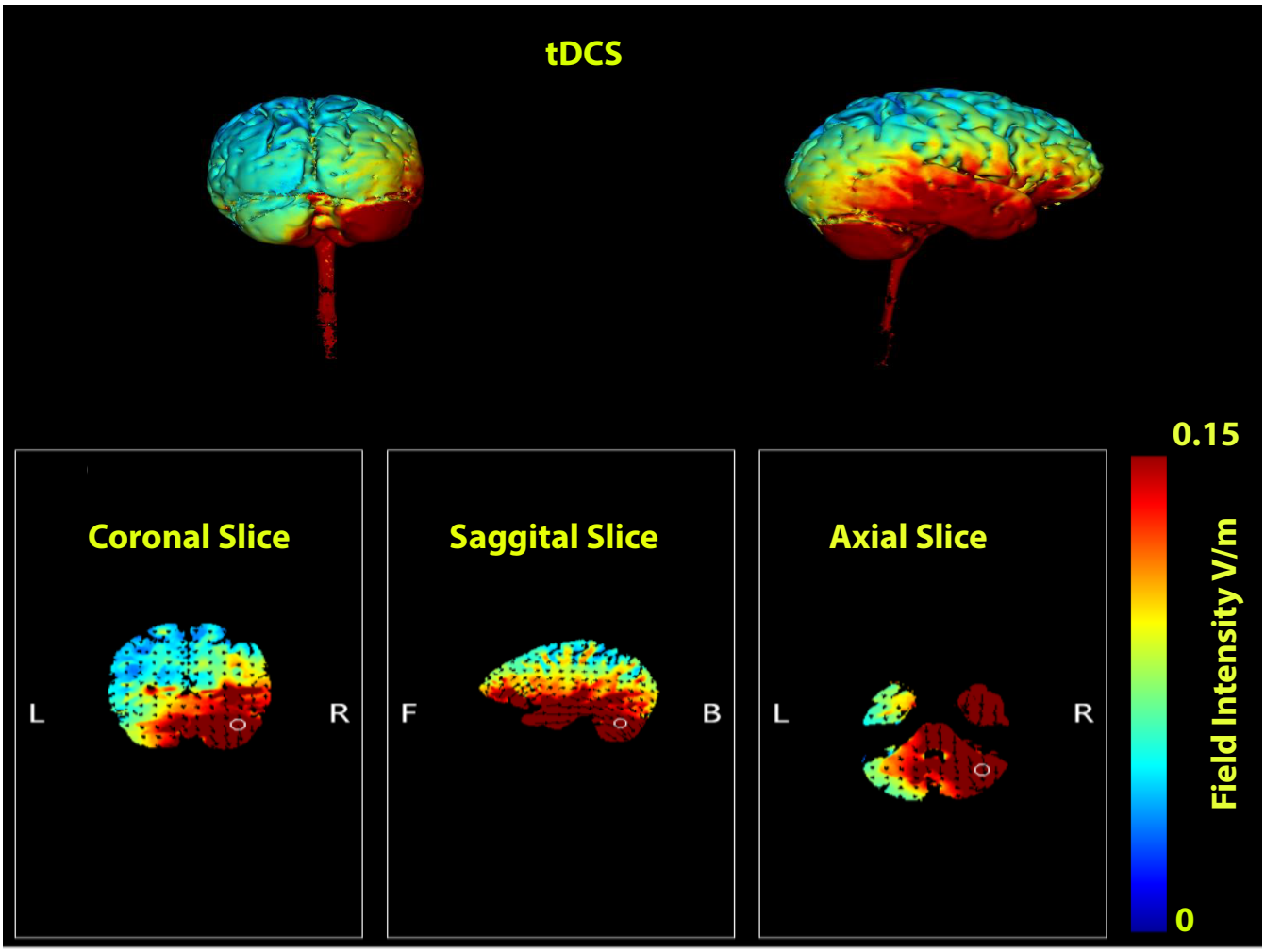
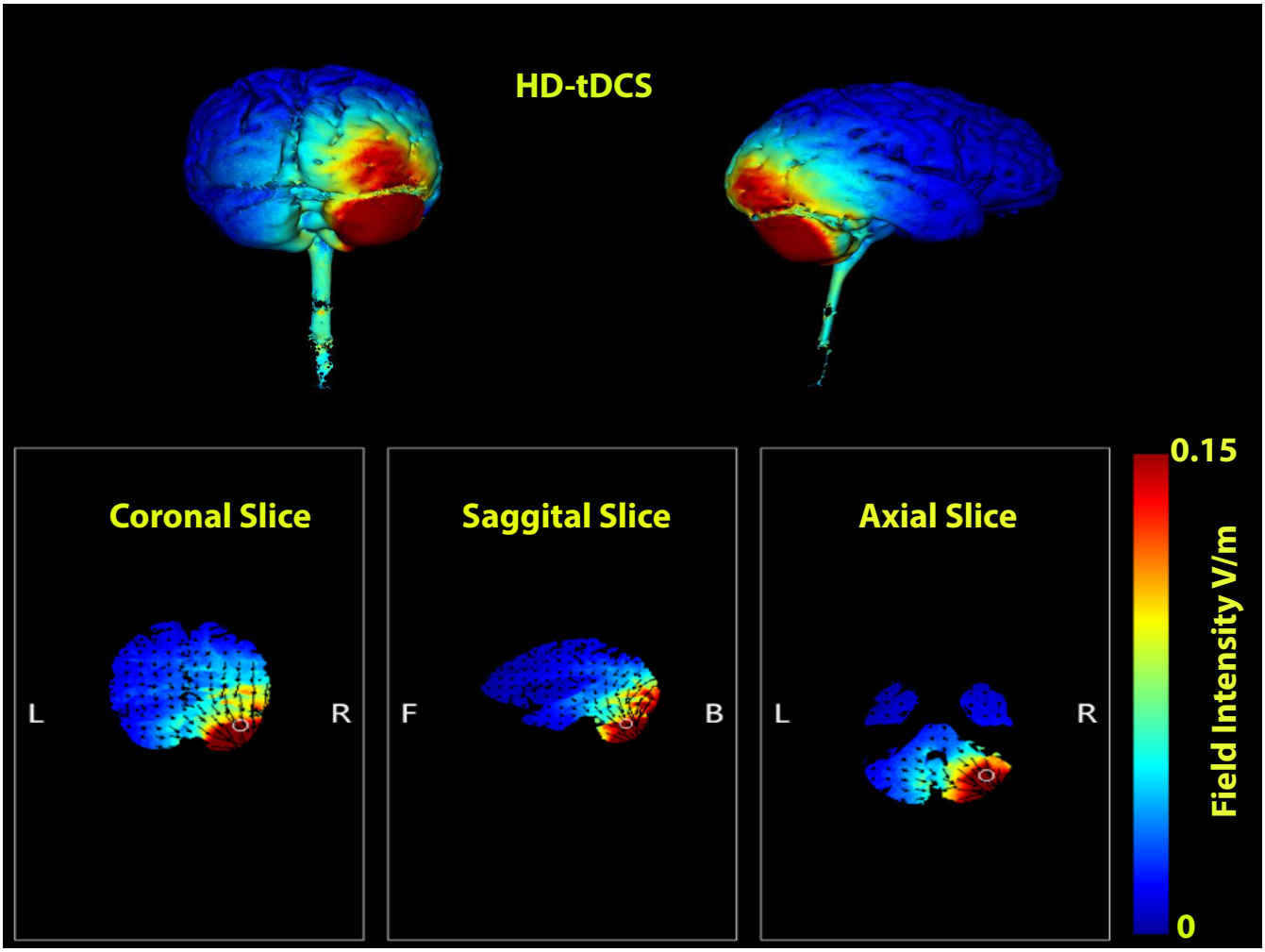
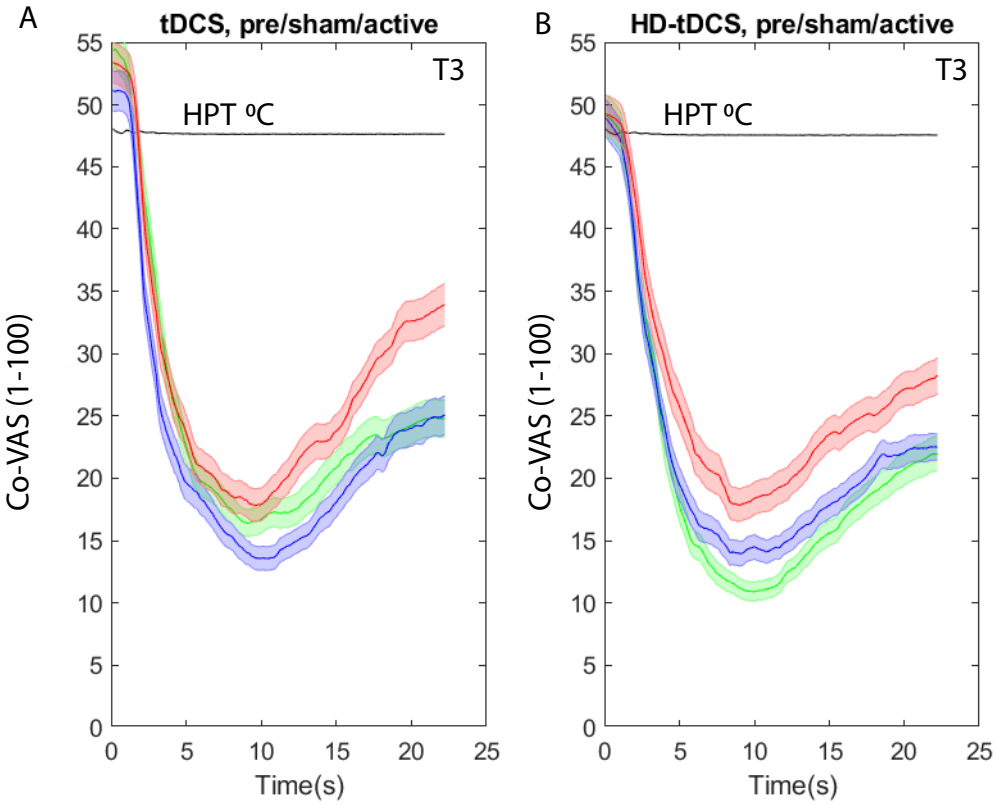

(A)
VAS Rating
Temperature (°C)
T1
T2
T3 (HPT)
1
2
3
4
Temperature (°C)
VAS Rating (Pain Intensity)
Time (s)
(B)
VAS Rating
Temperature (°C)
T1
T2
T3
5
6
7
8
Temperature (°C)
VAS Rating (Pain Intensity)
Time (s)

Figure 1

A


tDCS
Coronal Slice
Saggital Slice
Axial Slice
L
R
F
B
L
R
0.15
0
Field Intensity V/m

B


HD-tDCS
Coronal Slice
Saggital Slice
Axial Slice
L
R
F
B
L
R
0.15
0
Field Intensity V/m

Differential effect of neurostimulation on the OA response