

Repeated noninvasive stimulation of the ventromedial prefrontal cortex reveals cumulative amplification of pleasant compared to unpleasant scene processing: a single subject pilot study

Constantin Winker^{1,2,#}, Maimu A. Rehbein^{1,2,#}, Dean Sabatinelli³, & Markus Junghofer^{1,2,*}

¹Institute for Biomagnetism and Biosignalanalysis, University of Muenster, Germany

²Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Muenster, Germany

³Department of Psychology and BioImaging Research Center, University of Georgia, USA

***Correspondence:**

Markus Junghofer

markus.junghofer@uni-muenster.de

#CW and MAR contributed equally to this work and should be considered as joint first authors.

Keywords: Emotion, Brain Stimulation, tDCS, Depression, MEG, EEG, Scenes.

Abstract

The ventromedial prefrontal cortex (vmPFC) is a major hub of the reward system and has been shown to activate specifically in response to pleasant / rewarding stimuli. Previous studies demonstrate enhanced pleasant cue reactivity after single applications of transcranial direct current stimulation (tDCS) to the vmPFC. Here we present a pilot case study in which we assess the cumulative impact of multiple consecutive vmPFC-tDCS sessions on the processing of visual emotional stimuli in an event-related MEG recording design. The results point to stable modulation of increased positivity biases (pleasant > unpleasant stimulus signal strength) after excitatory vmPFC stimulation and a reversed pattern (pleasant < unpleasant) after inhibitory stimulation across five consecutive tDCS sessions. Moreover, cumulative effects of these emotional bias modulations were observable for several source-localized spatio-temporal clusters, suggesting an increase in modulatory efficiency by repeated tDCS sessions. This pilot study provides evidence for improvements in the effectiveness and utility of a novel tDCS paradigm in the context of emotional processing.

1 Introduction

The prioritized processing of emotional information within early (<100 ms; e.g. Steinberg et al., 2012) or mid-latency (<300 ms; e.g. Schupp et al., 2006) time intervals strongly supports the idea that environmental emotional stimuli are of high relevance to humans. One important aspect of emotion processing is the differentiation between aversive / unpleasant and rewarding / pleasant information. In this context, the ventromedial prefrontal cortex (vmPFC) is known to play an important role. More precisely, the vmPFC shows increased activation patterns specifically for stimuli with pleasant content in comparison to unpleasant or neutral stimuli (Carlson et al., 2011; Costa et al., 2010; Keuper et al., 2013; Knutson et al., 2003; Milad et al., 2007; Sabatinelli et al.,

Cumulative emotional modulation after repeated vmPFC-tDCS

2007a). Furthermore, several psychiatric disorders were shown to be linked—amongst others—to dysfunctional processing in vmPFC regions (Greenberg et al., 2013; Laeger et al., 2014; Milad et al., 2009; Pizzagalli et al., 2001; Sabatinelli et al., 2015).

To investigate the valence specificity of vmPFC and its potential to be modulated noninvasively, several studies within our lab were conducted that assessed neuronal effects of excitatory and inhibitory transcranial direct current stimulation (tDCS). In an fMRI and a separate MEG sample, participants showed valence modulation effects for passively viewed emotional scenes with increased neuronal activation for pleasant compared to unpleasant scenes after excitatory vmPFC-tDCS and vice versa after inhibitory vmPFC-tDCS (Junghofer et al., 2017). Comparable effects were found during the processing of happy compared to fearful faces (Winker et al., 2018). In addition, several studies from other groups point to a more general modulation capability of vmPFC by tDCS that is not limited to the mere viewing of emotional stimuli (Abend et al., 2018; Chib et al., 2013; Dittert et al., 2018; Mungee et al., 2014; Van 't Wout et al., 2016). All these studies investigated effects of a single tDCS session. However, there is evidence that multiple sessions of tDCS might induce cumulating effects and increase efficacy (Alonzo et al., 2012) although others even reported cancelation of effects with a second stimulation after 24 hours (Monte-Silva et al., 2010; 2013). To probe the limits and expandability of our newly developed tDCS paradigm, in this pilot study we investigated the possible cumulative effects of tDCS across 5 days of consecutive sessions—with author MJ as single participant. Therefore, the event-related paradigm was similar to the MEG assessment described by Junghofer and colleagues (2017), featuring a passive viewing task with pleasant and unpleasant emotional scenes during MEG measurement of neuronal activation. With respect to a planned extension of this study to healthy controls, a further goal was to identify possible negative physiological or psychological side effects of repeated stimulation such as headaches, negative feelings during inhibitory or manic feelings during excitatory stimulation. Weighing false positive less critical than false negative findings of detrimental side effects, we decided against a blinding of tDCS conditions. Since negative side effects of inhibitory stimulation could be masked by previous excitatory stimulation effects, we decided to start with inhibitory stimulation.

Consistent with our prior research, we hypothesized an induction of a positivity bias after excitatory vmPFC-tDCS with increased brain activation for pleasant compared to unpleasant stimuli and vice versa after inhibitory vmPFC-tDCS by comparing neural activation after vmPFC-tDCS stimulation (post-tDCS) with baseline activity (pre-tDCS). Furthermore, in the case of accumulating tDCS effects, both effect patterns (positivity bias due to excitatory, negativity bias due to inhibitory tDCS) were predicted to intensify across sessions. Finally, the course of pre-tDCS data was separately investigated to test for any cumulative effects reflecting changes of vmPFC baseline activation (i.e. increasing positivity or negativity biases of baseline activity across days). Based on our previous findings on emotional scenes (Junghofer et al., 2017), we expected multiple effects to occur in spatio-temporal clusters distributed across the entire interval of analysis (0-600 ms after stimulus onset). However, due to the exploratory nature of this study, analyses reported here were conducted without predefined regions of interest. Only temporal limitations by fixed intervals that divided the whole time window into subgroups (for a detailed description see Junghofer et al., 2017; Winker et al., 2018) were applied.

Method

1.1 Participant

MJ (male; age: 48 years) gave informed consent in accordance with the Declaration of Helsinki.

Cumulative emotional modulation after repeated tDCS

1.2 tDCS

tDCS was applied by means of a DC Stimulator Plus (NeuroConn). The procedure was identical to previous studies (Junghofer et al., 2017; Winker et al., 2018; 2019): in a two-electrode design with a 3 x 3 cm square electrode placed at 10-20 electrode position Fp and a 5 x 5 cm square electrode placed below the chin as extracephalic reference, a current strength of 1.5 mA was applied over 10 min. Both electrodes were covered in saline soaked sponges to enable sufficient conductivity.

1.3 Stimuli

Stimuli employed in the MEG measurement have been reported previously (Junghofer et al., 2017). They consisted of pleasant and unpleasant scenes with 32 different stimuli per category. Each stimulus contained a grayscale picture with 1024 x 786 resolution (12.3° horizontal field of view). Stimuli were controlled for luminance, contrast, and complexity (90% JPEG file size) across categories.

1.4 Procedure

The study consisted of 10 daily sessions of pre-tDCS and post-tDCS MEG measures summing up to 20 MEG data sets. Participant MJ first passed 5 sessions of inhibitory stimulation and a month later, 5 sessions of excitatory stimulation on 5 consecutive weekdays each. The post-tDCS MEG measurement always followed the tDCS in direct succession (< 5 minutes). During MEG assessment, a passive viewing task was conducted. MJ relaxed and kept his gaze fixated on a central red dot to reduce artifacts from eye-movement. Stimuli were presented in a pseudo-random order with controlled transitions between scenes from Pleasant and Unpleasant categories which did not repeat until the complete set of 64 individual scenes had been presented. Overall, 192 stimuli (3 x 64 scenes) were presented per MEG run.

1.5 MEG Measurement and Analysis

MEG measurements were conducted with a 275 whole-head sensor system (CTF Systems) with-first order axial gradiometers. Head movement and position were controlled via landmark coils positioned on the nasion and in both earlobes. MEG data were assessed with a sampling rate of 600 Hz. Afterwards, data were down-sampled (300 Hz) and filtered with a 0.1 Hz high-pass filter (zero-phase second-order Butterworth) and a 48 Hz low-pass filter (zero-phase fourth-order Butterworth). Trials were split into 800 ms epochs ranging from -200 to 600 ms relative to stimulus onset. Additionally, trials were baseline-adjusted by subtracting the mean of a -150 to 0 ms interval. In succession, source activation was calculated by Minimum-Norm estimates (L2-MNE; Hämäläinen and Ilmoniemi, 1994). As a source model, a spherical shell with evenly distributed 2 x 350 dipoles in azimuthal and polar directions was applied. L2-MNE topographies were established with a Tikhonov regularization parameter of $k = 0.1$.

Statistical analysis comprised correlational testing of the L2-MNE data. We analyzed data with regard to the three hypothesized effect patterns: (1) To test if previous findings of an induced positivity bias after excitatory stimulation and reduced positivity bias after inhibitory stimulation could be replicated and remained constant across sessions - i.e. without any cumulative effect - the pattern of an identical activation increase per day from Pre-tDCS to Post-tDCS for difference [Pleasant minus Unpleasant] within the excitatory stimulation condition and activation decrease per day within the inhibitory stimulation condition was analyzed. We thus applied differential weights to calculated conditional differences [Pleasant minus Unpleasant] to test for this effect (Pleasant-Minus-

Cumulative emotional modulation after repeated vmPFC-tDCS

Unpleasant-Excitatory-Pre1-5: 2, 2, 2, 2, 2; Pleasant-Minus-Unpleasant-Excitatory-Post1-5: 3, 3, 3, 3, 3; Pleasant-Minus-Unpleasant-Inhibitory-Pre1-5: 2, 2, 2, 2, 2; Pleasant-Minus-Unpleasant-Inhibitory-Post1-5: 1, 1, 1, 1, 1). (2) To investigate a cumulative stimulation effect across sessions, double differences {[Pleasant minus Unpleasant] minus [Post-tDCS minus Pre-tDCS]} were assumed to increase linearly across all five sessions within the excitatory tDCS condition whereas inhibitory stimulation was assumed to show a linear of this double difference decrease across sessions. As we were interested in cumulative Post-tDCS effects, these data were to be baseline-adjusted first for each day to control for varying Pre-tDCS activations, e.g., by additional habituation effects across days (Pleasant-Minus-Unpleasant-Post-Minus-Pre-Excitatory1-5: 1, 2, 3, 4, 5; Pleasant-Minus-Unpleasant-Post-Minus-Pre-Inhibitory1-5: -1, -2, -3, -4, -5). To control for this variance, we accepted the trade-off of losing statistical power by calculating the double difference. (3) We finally investigated if this cumulative effect was already visible prior to consecutive tDCS sessions. Therefore, a correlational analysis of differences [Pleasant minus Unpleasant] at baseline (Pre-tDCS) tested for an increase of the Pleasant > Unpleasant effect across all five sessions of excitatory tDCS and vice versa (i.e., Pleasant < Unpleasant effect) across all five sessions of inhibitory tDCS (Pleasant-Minus-Unpleasant-Excitatory-Pre1-5: 5, 6, 7, 8, 9; Pleasant-Minus-Unpleasant-Inhibitory-Pre1-5: 5, 4, 3, 2, 1). Prevention of α -error inflation was established by the use of a non-parametric cluster permutation (Maris and Oostenveld, 2007). Thereby, clusters containing r -values cumulated across dipole-positions and time-points (spatio-temporal cluster) were tested against a distribution of 1,000 random permutations of the assessed data. In order to add an effect to a cluster, the respective spatio-temporal point had to surpass a p -value of .05 (sensor-level criterion). Subsequently, all effects passing this threshold were added up to a so-called cluster masses (in this case summation of all r -values) and tested against the randomly permuted data. If the cluster mass reached a p -value < .05 in comparison to the biggest cluster of each of the 1,000 permutations (cluster-level criterion), it surpassed the critical cluster mass and thus was considered significant. Cluster mass-analyses were conducted for previously determined intervals (see Junghofer et al., 2017; Winker et al., 2018; 2019) of 0–100ms (early), 100–200ms (early mid-latency), 200–300ms (late mid-latency) and 300–600 ms (late). First- and second-level significant clusters that were cut off by the beginning or end of a pre-defined interval were reanalyzed in an interval extended for 50 ms in the respective direction. By this means it was possible to assess if the found cluster actually began or ended with the borders of the pre-defined interval or if it was temporally extended. Preprocessing and analysis of the MEG data was conducted using EMEGS software¹ (Peyk et al., 2011).

2 Results

All in the following reported significant results reflect positive r -scores, thus confirming the respective hypotheses described above. There were no spatio-temporal clusters with inverted effect patterns with p -values < .2.

2.1 Constant effects of stimulation across sessions

With regard to a constant (non-cumulative) stimulation effect across sessions, three clusters were observed at mid-latency time intervals: in right occipitoparietal cortex (153–257 ms; $p = .01$), medial prefrontal cortex (mPFC; 167–280 ms; $p = .002$), and in right temporal cortex (227–307 ms; $p = .007$). Additionally, the analysis yielded a fourth cluster during late latency in vmPFC (350–470 ms; $p = .005$) (see Figure 1).

¹ emegs.org

Cumulative emotional modulation after repeated vmPFC-tDCS

2.2 Cumulative effects of stimulation: post - pre differences

Analysis of the cumulative effects of stimulation across sessions revealed a later mid-latency cluster at mPFC regions (217-277 ms; $p = .001$) (see Figure 2).

2.3 Cumulative effects of stimulation: pre differences

The investigation of a cumulative effect across pre-tDCS measurements yielded three significant clusters. A first cluster was observed during early mid-latency in primary regions of occipital cortex (127-217 ms; $p = .022$). A second cluster appeared during late mid-latency in secondary occipitotemporal and parietal regions (230-293 ms; $p = .001$), while a third cluster occurred in a late interval in central parietal cortex (323-383 ms; $p = .037$) (see Figure 3).

3 Discussion

In this pilot study, we investigated how repeated vmPFC-tDCS across five days affects the previously reported modulation of valence specificity (Junghofer et al., 2017; Winker et al., 2018; 2019).

An analysis testing for consistent effects across sessions with increased activation for pleasant stimuli compared to unpleasant stimuli after excitatory (i.e. positivity bias) and vice versa after inhibitory stimulation (i.e. negativity bias) yielded three mid-latency (right occipitoparietal, right anterior temporal and mPFC) and one late spatio-temporal cluster (right vmPFC). These relatively stable effects of directed modulation across five daily sessions do not support strong habituation or even cancellation effects of day-to-day carryover as for instance reported by Monte-Silva and coworkers (2010; 2013).

In contrast, we identified cumulative effect patterns due to tDCS repetitions. A significant cluster appeared at mPFC, which spatially and temporally overlapped with the cluster in Figure 1B. Thus, while the earlier activation pattern (~170-220 ms) revealed a main effect of stimulation only, the later part (220-280 ms) suggested increasing positivity and negativity biases across days in this area.

In the same vein, another series of cumulative effect analyses investigated changes of baseline activation across days. Here, another three clusters (mid-latency: occipital cortex; occipitoparietal cortex; late latency: parietal cortex) also supported cumulative effects consistent with our hypotheses, as pleasant stimulus reactivity showed increasing activation in comparison to unpleasant stimulus reactivity after excitatory stimulation and vice versa after inhibitory stimulation across days. An explanation for these cumulative effects could be a shift in the baseline activation level of vmPFC or the network that is affected by it. These effects support the often proposed activation of neuroplastic changes (see Lefaucheur et al., 2017) and by that point to a possibility to increase efficacy of this paradigm of repeated stimulations.

Through the course of both weeks of tDCS, MJ reported mild signs of disturbed sleep with more than usual nocturnal wake-ups that both times dissolved with the end of the tDCS. No other signs of physiological or psychological side effects could be reported neither during the active stimulation nor in the weeks of stimulation or in the weeks after stimulation.

3.1 Limitations

It is noteworthy that all spatio-temporal clusters revealed the proposed direction of effects but differed with regard to temporal and spatial characteristics from previous findings (Junghofer et al.,

Cumulative emotional modulation after repeated vmTFC-tDCS

2017). These differences might reflect inter-individual differences in brain activation patterns and brain anatomy. However, effects can be interpreted as typical emotion related activation patterns like the early posterior negativity (EPN) and the late positive potential (LPP) that have been localized in occipitotemporal as well as parietal regions (Junghofer et al., 2010; Sabatinelli et al., 2007b). Nevertheless, these pilot findings need to be tested in a representative sample to see if previously presented effects are actually cumulative or if the here presented effects are at least partly distinct from those.

Due to the intentional non-blinding of MJ to the tDCS conditions, it is possible that focused top-down attention—although unintentional—might have increased valence specific processing as for instance shown for explicit directed attention by Schupp and coworkers for emotional scenes (2007) or Schindler and Kissler (2016) for emotional words. While such implicit effects might potentially explain the non-cumulative effects across sessions it is unlikely to explain the cumulation of effects. It is also possible that implicit, unintentional reappraisal processes have influenced scene valence perception. For instance, Li and colleagues (2018) presented results of successful upregulation of pleasant stimulus material. With regard to the cumulative effects, a study of Denny and Ochsner (2014) pointed to possible additive effects of downregulation of negative emotions over the course of four sessions. However, in that study, two reappraisal methods were compared and only one showed cumulative effects that were not attributable solely to habituation. It therefore might require a clear regulation strategy in order to cumulatively downregulate emotions over sessions. MJ, in contrast, passively viewed all presented images without explicitly directing attention to one specific category and without applying any specific strategy. Nevertheless, as in our previous studies, follow-up studies should keep the participants naïve to the stimulation conditions.

In this pilot study we also checked for potential physiological or psychological negative side effects of the repeated stimulation, but side effects—especially on cognitive processes—have not systematically been assessed. Therefore, while this study does not speak against repeated tDCS in healthy controls, a first test of a single tDCS repetition and a systematic assessment of side effects and symptoms of stimulations is highly recommended.

4 Conclusion

This pilot study provides a first indication of cumulative effects of repeated tDCS on the valence processing of emotional stimuli. These cumulative effects were also visible in the MEG baseline measurement around 24 h after the preceding stimulation and thus, in the absence of acute aftereffects. Repeated stimulations did not lead to more than mild negative side effects. Of course, these results should be viewed only as preliminary as only one person participated in this study. Nevertheless, due to the absence of more systematic investigations of tDCS paradigms in the context of emotion processing, this pilot data might help to stimulate further research in this field.

5 Ethics Statement

This study was approved by the Ethics Committee of the Department of Psychology and Sports Science at the University of Muenster, Germany.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Cumulative emotional modulation after repeated vmPFC-tDCS

7 Author Contributions

MJ, CW, MAR and DS conceptualized the work and implemented the study design. MJ conducted data acquisition. MJ and CW analyzed and interpreted the data. CW, MAR, DS and MJ drafted and revised the work.

8 Funding

This work was funded by the Interdisciplinary Center for Clinical Research of the University of Muenster (Ju2/024/15) and the Collaborative Research Center (SFB-TRR58/C08).

9 Acknowledgments

We thank Karin Wilken, Hildegard Deitermann, and Ute Trompeter for their help with the MEG data collection, and Andreas Wollbrink for technical assistance.

10 References

- Abend, R., Sar-el, R., Gonen, T., Jalon, I., Vaisvaser, S., Bar-Haim, Y., & Hendler, T. (2018). Modulating Emotional Experience Using Electrical Stimulation of the Medial-Prefrontal Cortex: A Preliminary tDCS-fMRI Study. *Neuromodulation*, 2018. <https://doi.org/10.1111/ner.12787>
- Alonzo, A., Brassil, J., Taylor, J. L., Martin, D., & Loo, C. K. (2012). Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimulation*, 5(3), 208–213. <https://doi.org/10.1016/j.brs.2011.04.006>
- Carlson, J. M., Foti, D., Mujica-Parodi, L. R., Harmon-Jones, E., & Hajcak, G. (2011). Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: A combined ERP and fMRI study. *NeuroImage*, 57(4), 1608–1616. <https://doi.org/10.1016/j.neuroimage.2011.05.037>
- Chib, V. S., Yun, K., Takahashi, H., & Shimojo, S. (2013). Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. *Translational Psychiatry*, 3(6), e268. <https://doi.org/10.1038/tp.2013.44>
- Costa, V. D., Lang, P. J., Sabatinelli, D., Versace, F., & Bradley, M. M. (2010). Emotional imagery: assessing pleasure and arousal in the brain's reward circuitry. *Human Brain Mapping*, 31(9), 1446–1457. <https://doi.org/10.1002/hbm.20948>
- Denny, B. T., & Ochsner, K. N. (2014). Behavioral effects of longitudinal training in cognitive reappraisal. *Emotion*, 14(2), 425–433. <https://doi.org/10.1037/a0035276>
- Dittert, N., Hüttner, S., Polak, T., & Herrmann, M. J. (2018). Augmentation of Fear Extinction by Transcranial Direct Current Stimulation (tDCS). *Frontiers in Behavioral Neuroscience*, 12(April), 1–16. <https://doi.org/10.3389/fnbeh.2018.00076>

Cumulative emotional modulation after repeated vmPFC-tDCS

- Greenberg, T., Carlson, J. M., Cha, J., Hajcak, G., & Mujica-Parodi, L. R. (2013). Ventromedial prefrontal cortex reactivity is altered in generalized anxiety disorder during fear generalization. *Depression and Anxiety, 30*(November 2012), 242–250. <https://doi.org/10.1002/da.22016>
- Hämäläinen, M. S., & Ilmoniemi, R. J. (1994). Interpreting magnetic fields of the brain: minimum norm estimates. *Medical and Biological Engineering and Computing, 32*, 35–42.
- Junghofer, M., Kissler, J., Schupp, H. T., Putsche, C., Elling, L., & Dobel, C. (2010). A fast neural signature of motivated attention to consumer goods separates the sexes. *Frontiers in Human Neuroscience, 4*(September), 179. <https://doi.org/10.3389/fnhum.2010.00179>
- Junghofer, M., Winker, C., Rehbein, M. A., & Sabatinelli, D. (2017). Noninvasive stimulation of the ventromedial prefrontal cortex enhances pleasant scene processing. *Cerebral Cortex, 27*(6), 3449–3456. <https://doi.org/10.1093/cercor/bhx073>
- Keuper, K., Zwitserlood, P., Rehbein, M. A., Eden, A. S., Laeger, I., Junghöfer, M., ... Dobel, C. (2013). Early Prefrontal Brain Responses to the Hedonic Quality of Emotional Words - A Simultaneous EEG and MEG Study. *PLoS ONE, 8*(8). <https://doi.org/10.1371/journal.pone.0070788>
- Knutson, B., Fong, G. W., Bennett, S. M., Adams, C. M., & Hommer, D. (2003). A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *NeuroImage, 18*(2), 263–272. [https://doi.org/10.1016/S1053-8119\(02\)00057-5](https://doi.org/10.1016/S1053-8119(02)00057-5)
- Laeger, I., Dobel, C., Radenz, B., Kugel, H., Keuper, K., Eden, A., ... Zwanzger, P. (2014). Of “disgrace” and “pain” - Corticolimbic interaction patterns for disorder-relevant and emotional words in social phobia. *PLoS ONE, 9*(11). <https://doi.org/10.1371/journal.pone.0109949>
- Lefaucheur, J.-P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., ... Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology, 128*(1), 56–92. <https://doi.org/10.1016/j.clinph.2016.10.087>
- Li, F., Yin, S., Feng, P., Hu, N., Ding, C., & Chen, A. (2018). The Cognitive Up- and Down-Regulation of Positive Emotion: Evidence from Behavior, Electrophysiology, and Neuroimaging. *Biological Psychology, 136*, 57–66. <https://doi.org/10.1016/j.biopsycho.2018.05.013>
- Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods, 164*(1), 177–190. <https://doi.org/10.1016/j.jneumeth.2007.03.024>
- Milad, M. R., Pitman, R. K., Ellis, C. B., Gold, A. L., Shin, L. M., Lasko, N. B., ... Rauch, S. L. (2009). Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder. *Biological Psychiatry, 66*(12), 1075–1082. <https://doi.org/10.1016/j.biopsych.2009.06.026>

Cumulative emotional modulation after repeated vmPFC-tDCS

- Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal Cortex and Hippocampus in Concert. *Biological Psychiatry*, *62*(5), 446–454. <https://doi.org/10.1016/j.biopsych.2006.10.011>
- Monte-Silva, K., Kuo, M.-F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of Late LTP-Like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation. *Brain Stimulation*, *6*(3), 424–432. <https://doi.org/10.1016/j.brs.2012.04.011>
- Monte-Silva, K., Kuo, M.-F., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2010). Shaping the Optimal Repetition Interval for Cathodal Transcranial Direct Current Stimulation (tDCS). *Journal of Neurophysiology*, *103*(4), 1735–1740. <https://doi.org/10.1152/jn.00924.2009>
- Mungee, A., Kazzer, P., Feeser, M., Nitsche, M. A., Schiller, D., & Bajbouj, M. (2014). Transcranial direct current stimulation of the prefrontal cortex: a means to modulate fear memories. *NeuroReport*, *25*, 480–484. <https://doi.org/10.1097/WNR.000000000000119>
- Peyk, P., De Cesarei, A., & Junghofer, M. (2011). ElectroMagnetoEncephalography software: overview and integration with other EEG/MEG toolboxes. *Computational Intelligence and Neuroscience*, *2011*. <https://doi.org/10.1155/2011/861705>
- Pizzagalli, D. A., Pascual-Marqui, R. D., Nitschke, J. B., Oakes, T. R., Larson, C. L., Abercrombie, H. C., ... Davidson, R. J. (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *American Journal of Psychiatry*, *158*(3), 405–415. <https://doi.org/10.1176/appi.ajp.158.3.405>
- Sabatinelli, D., Bradley, M. M., Lang, P. J., Costa, V. D., & Versace, F. (2007a). Pleasure rather than salience activates human nucleus accumbens and medial prefrontal cortex. *Journal of Neurophysiology*, *98*(3), 1374–1379. <https://doi.org/10.1152/jn.00230.2007>
- Sabatinelli, D., Lang, P. J., Keil, A., & Bradley, M. M. (2007b). Emotional perception: correlation of functional MRI and event-related potentials. *Cerebral Cortex*, *17*(5), 1085–1091. <https://doi.org/10.1093/cercor/bhl017>
- Sabatinelli, D., McTeague, L. M., Dhamala, M., Frank, D. W., Wanger, T. J., & Adhikari, B. M. (2015). Reduced medial prefrontal-subcortical connectivity in dysphoria: Granger causality analyses of rapid functional magnetic resonance imaging. *Brain Connectivity*, *5*(1), 1–9. <https://doi.org/10.1089/brain.2013.0186>
- Schindler, S., & Kissler, J. (2016). Selective visual attention to emotional words: Early parallel frontal and visual activations followed by interactive effects in visual cortex. *Human Brain Mapping*, *37*(10), 3575–3587. <https://doi.org/10.1002/hbm.23261>
- Schupp, H. T., Flaisch, T., Stockburger, J., & Junghofer, M. (2006). Emotion and attention: event-related brain potential studies. *Progress in Brain Research*, *156*, 31–51.
- Schupp, H. T., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A. I., & Hamm, A. O. (2007). Selective Visual Attention to Emotion. *Journal of Neuroscience*, *27*(5), 1082–1089.

Cumulative emotional modulation after repeated vmPFC-tDCS

<https://doi.org/10.1523/jneurosci.3223-06.2007> Steinberg, C., Dobel, C., Schupp, H. T., Kissler, J., Elling, L., Pantev, C., & Junghofer, M. (2012). Rapid and highly resolving: affective evaluation of olfactorily conditioned faces. *Journal of Cognitive Neuroscience*, 24(1), 17–27. https://doi.org/10.1162/jocn_a_00067

Van 't Wout, M., Mariano, T. Y., Garnaat, S. L., Reddy, M. K., Rasmussen, S. A., & Greenberg, B. D. (2016). Can Transcranial Direct Current Stimulation Augment Extinction of Conditioned Fear? *Brain Stimulation*, 9(4), 529–536. <https://doi.org/10.1016/j.brs.2016.03.004>

Winker, C., Rehbein, M. A., Sabatinelli, D., Dohn, M., Maitzen, J., Roesmann, K., ... Junghoefer, M. (2019). Noninvasive Stimulation of the Ventromedial Prefrontal Cortex Indicates Valence Ambiguity in Sad Compared to Happy and Fearful Face Processing. *Frontiers in Behavioral Neuroscience*, 13(May), 1–16. <https://doi.org/10.3389/fnbeh.2019.00083>

Winker, C., Rehbein, M. A., Sabatinelli, D., Dohn, M., Maitzen, J., Wolters, C. H., ... Junghofer, M. (2018). Noninvasive stimulation of the ventromedial prefrontal cortex modulates emotional face processing. *NeuroImage*, 175(September 2017), 388–401. <https://doi.org/10.1016/j.neuroimage.2018.03.067>

11 Figure captions

Figure 1. Spatio-temporal clusters with stable Stimulation by Valence effects across sessions (days). All clusters reflect a pattern of stronger activation for pleasant compared to unpleasant stimuli after excitatory and vice versa after inhibitory vmPFC-tDCS across all five sessions. Effects were found in (A) right occipitoparietal cortex, (B) mPFC, (C) right temporal cortex, and (D) vmPFC. mPFC = medial prefrontal cortex, vmPFC = ventromedial prefrontal cortex.

Figure 2. Spatio-temporal cluster with cumulative Stimulation by Valence effect across sessions. The cluster reflects an effect pattern of increasingly stronger activation for pleasant compared to unpleasant stimuli after excitatory and vice versa after inhibitory vmPFC-tDCS across all five sessions at the mPFC. mPFC = medial prefrontal cortex.

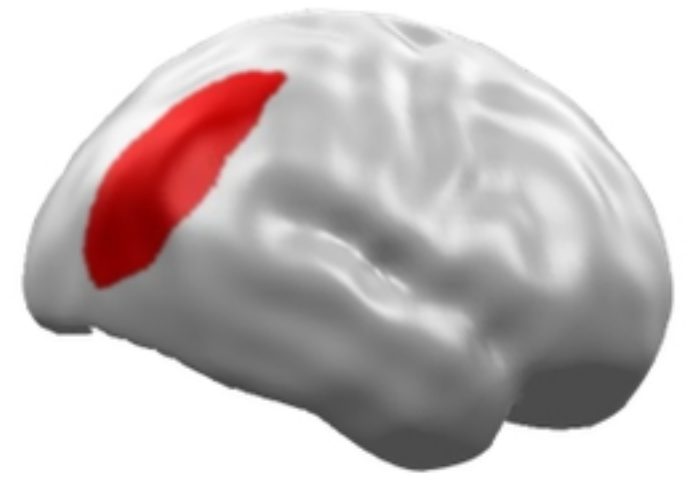
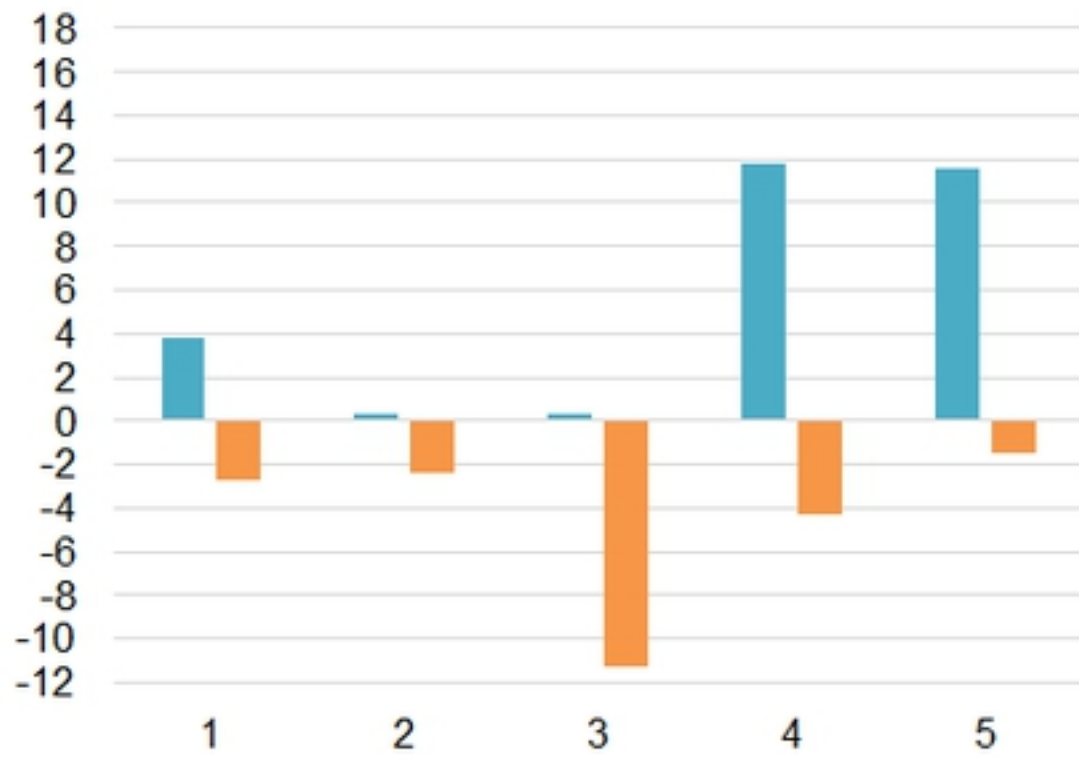
Figure 3. Spatio-temporal clusters with cumulative Stimulation by Valence effects during MEG baseline measurement before stimulation (pre-tDCS) across sessions. Clusters reflect an effect pattern of increasingly stronger pre-tDCS activation for pleasant compared to unpleasant stimuli after excitatory and vice versa after inhibitory vmPFC-tDCS across all five sessions in (A) occipital cortex, (B) occipitotemporal and parietal cortex, and (C) central parietal cortex.

excitatory post – pre & pleasant – unpleasant

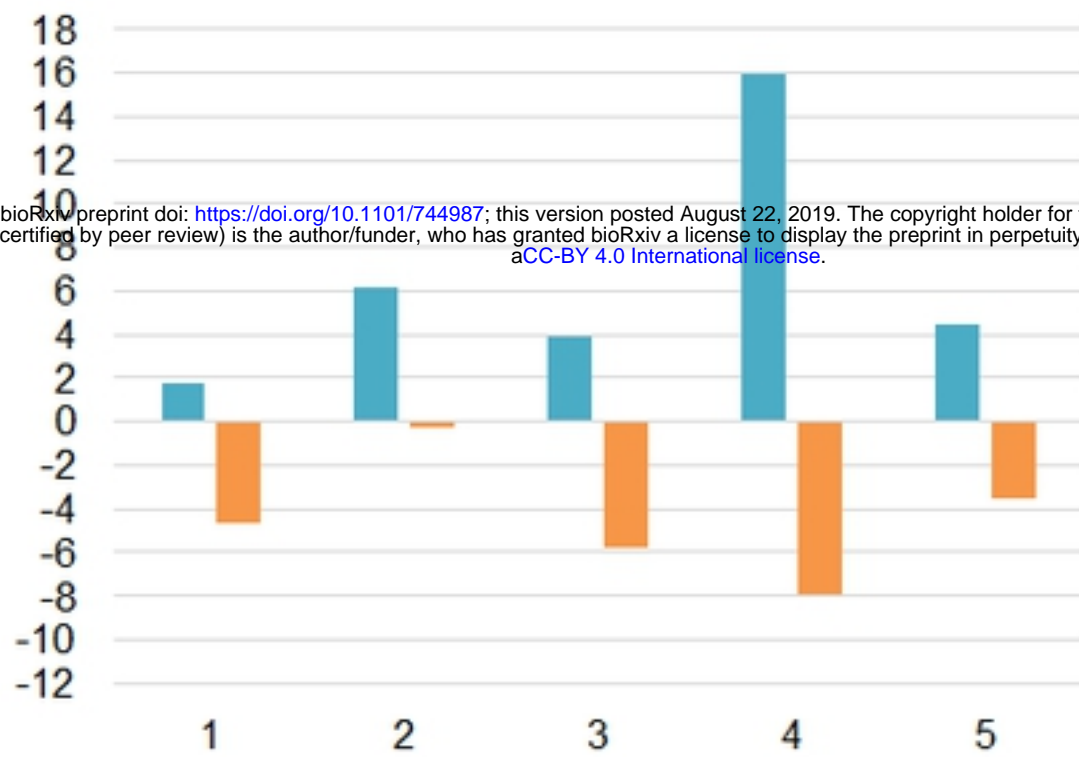
inhibitory post – pre & pleasant – unpleasant

A

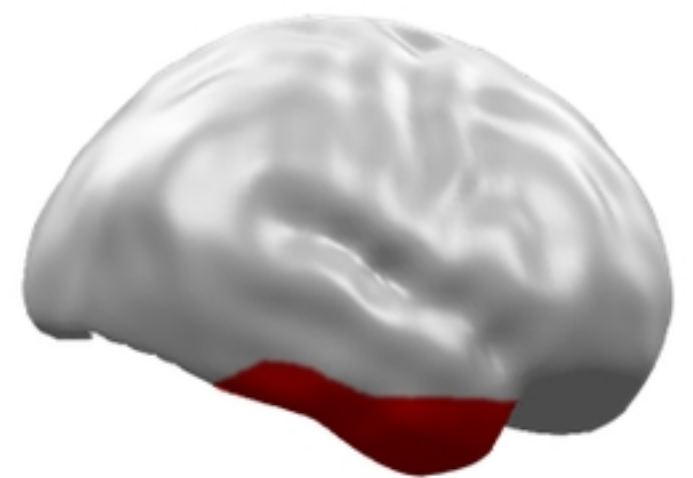
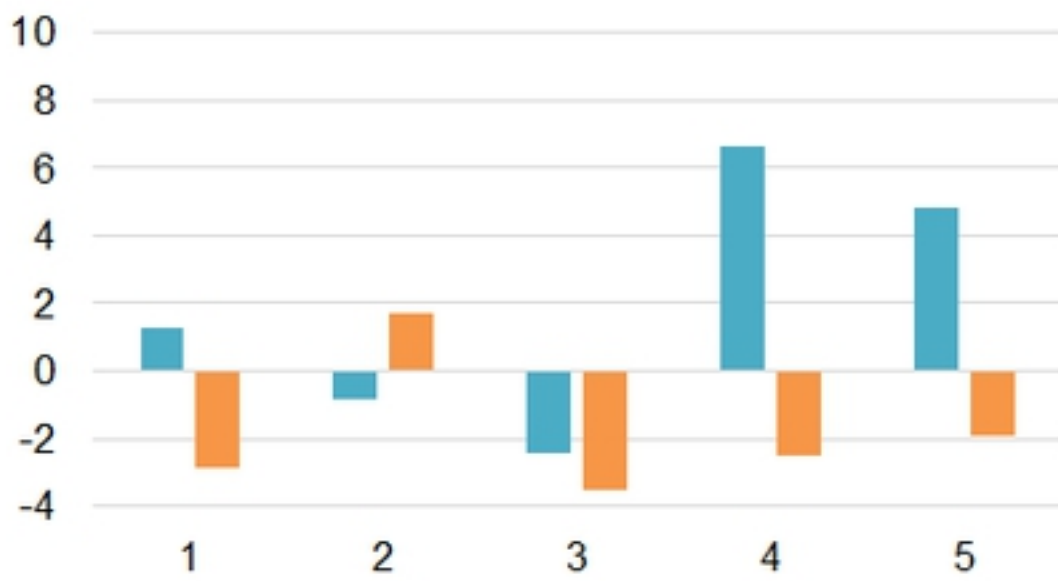
153-257 ms

**B**

167-280 ms

**C**

227-307 ms

**D**

350-470 ms

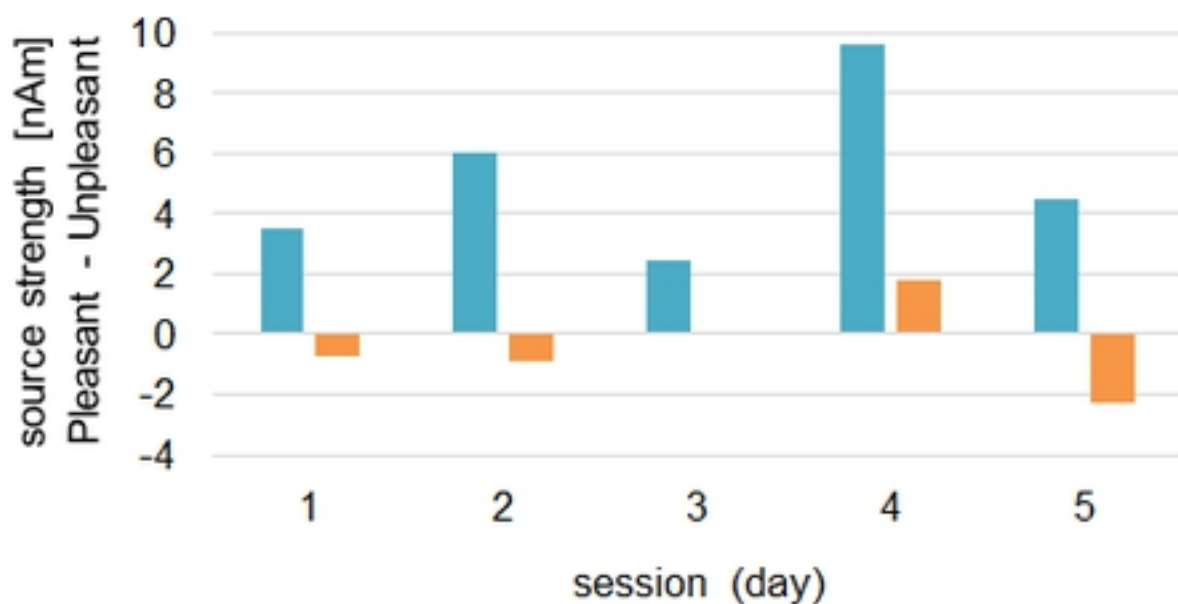


Figure 1

■ excitatory post - pre & pleasant - unpleasant ■ inhibitory post - pre & pleasant - unpleasant

217-277 ms

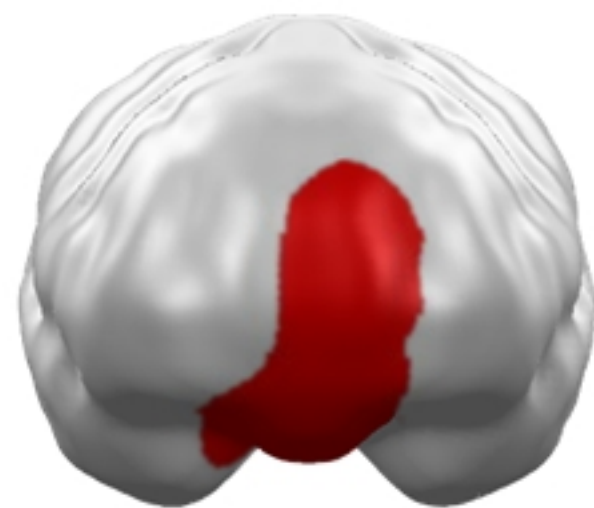
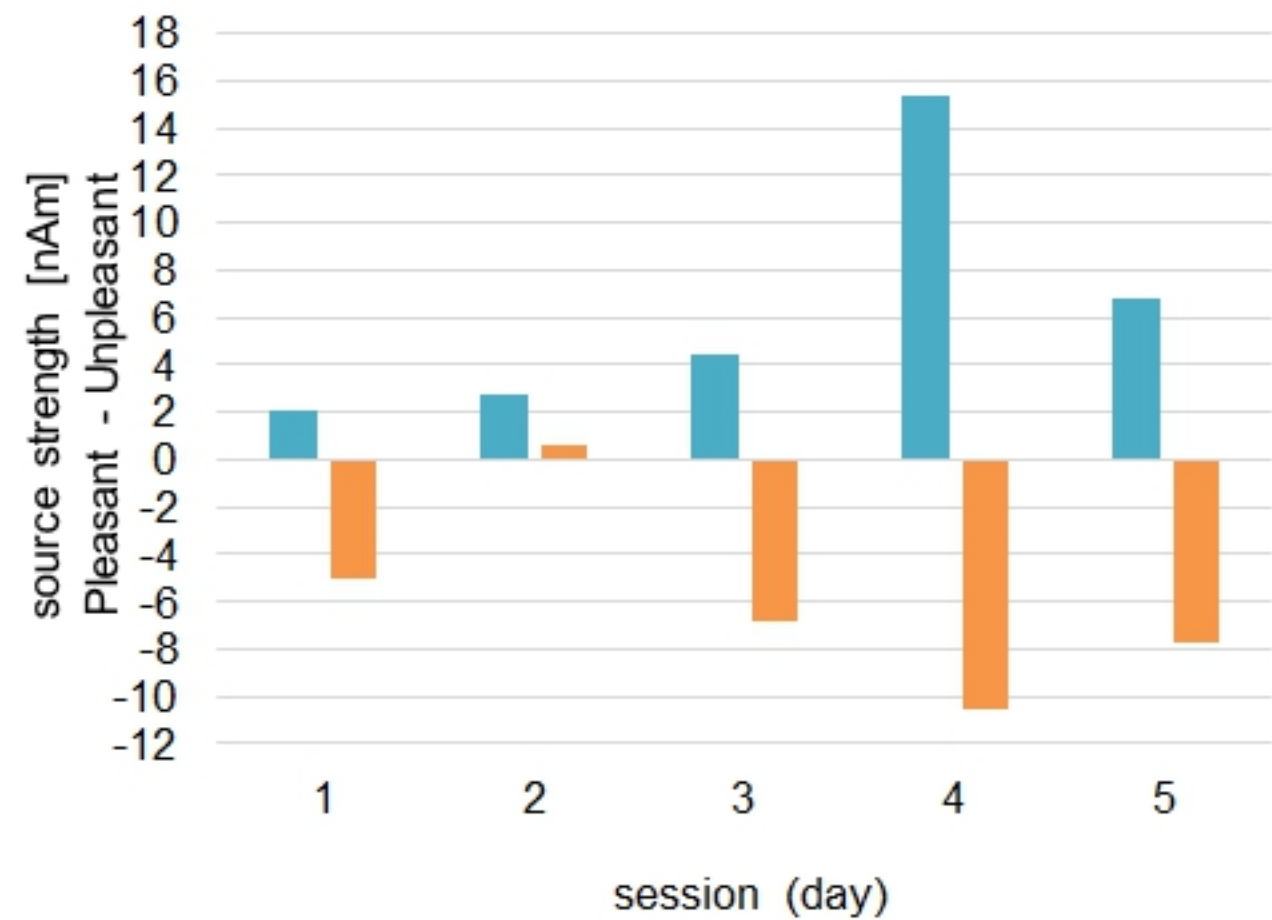
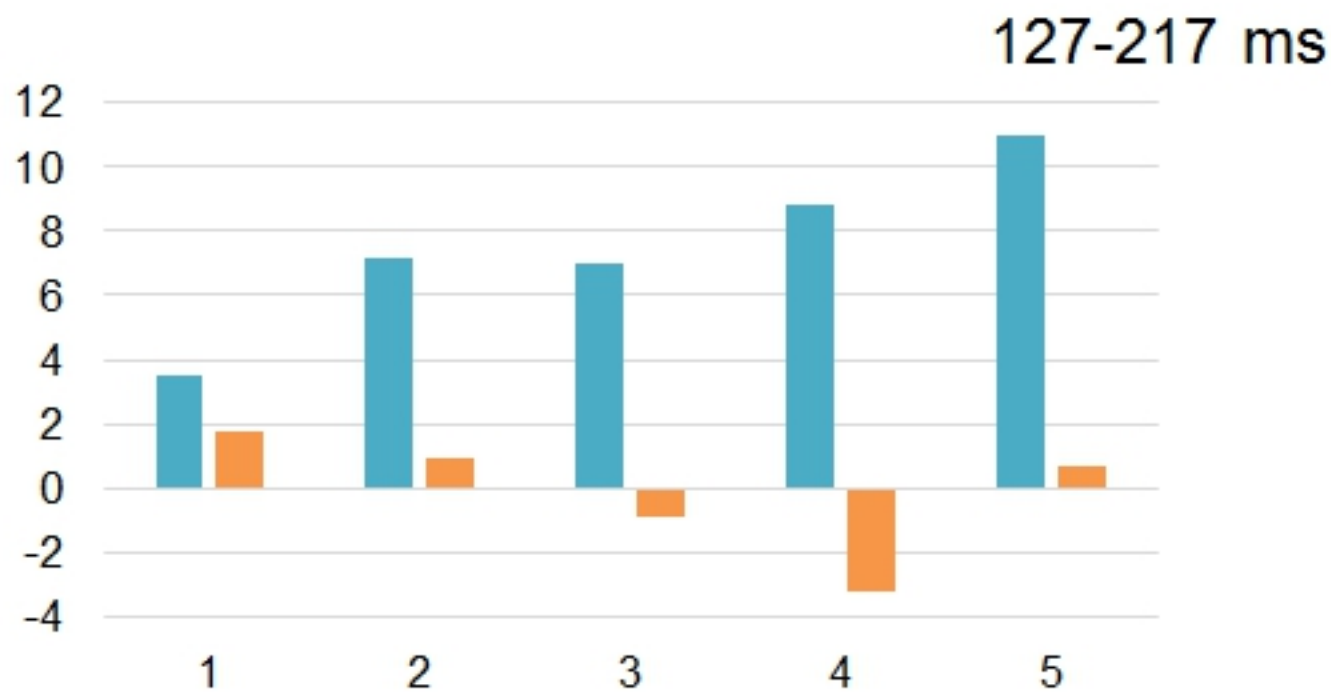


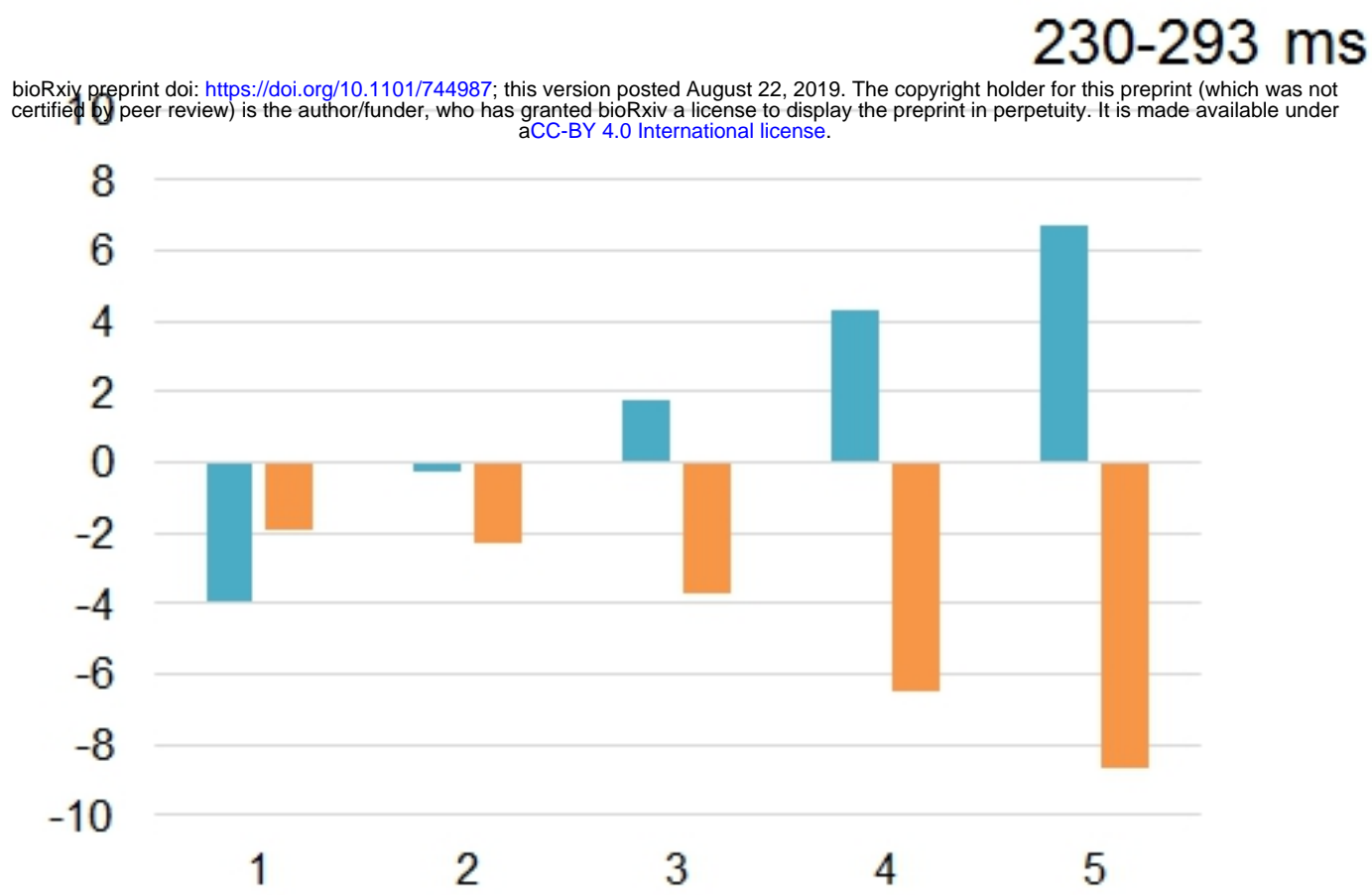
Figure 2

excitatory pleasant – unpleasant (pre-tDCS) inhibitory pleasant – unpleasant (pre-tDCS)

A



B



C

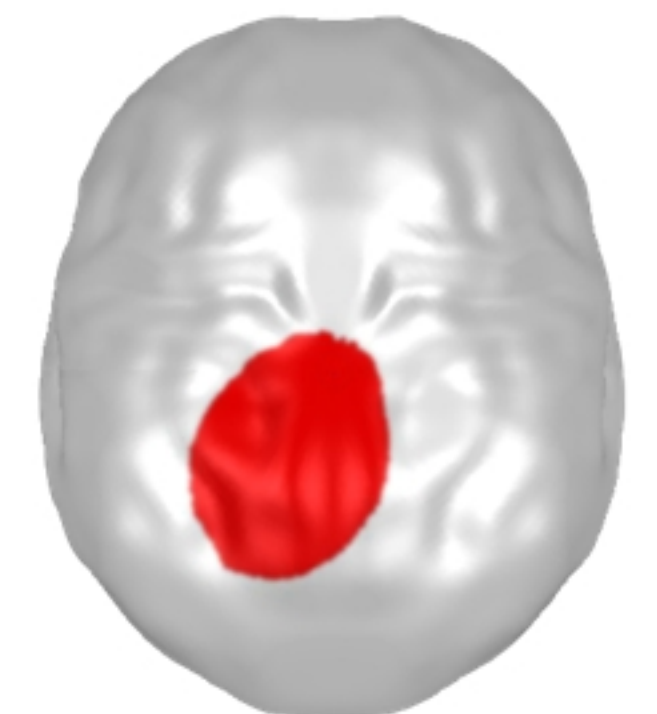
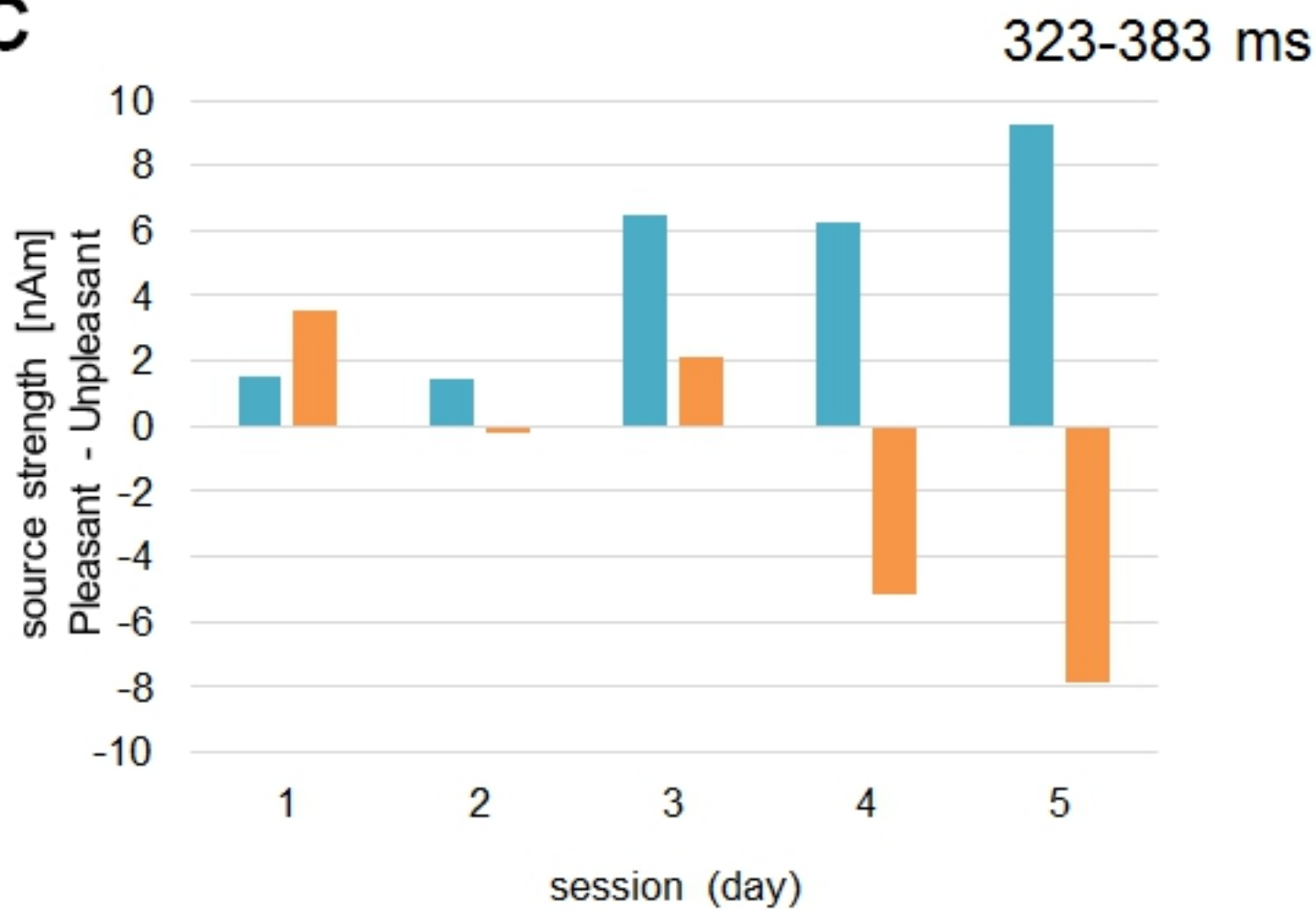


Figure 3