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RESEARCH ARTICLE

Cognitive effects and autonomic responses to transcranial pulsed current stimulation

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Abstract Transcranial pulsed current stimulation (tPCS) is emerging as an option in the field of neuromodulation; however, little is known about its effects on cognition and behavior and its neurophysiological correlates as indexed by autonomic responses. Our aim was to identify the effects of tPCS on arithmetic processing and risk-taking behavior, and to further categorize physiological autonomic responses by heart rate variability (HRV) and electrodermal activity measurements before, during, and after exposure to task performance and stimulation. Thirty healthy volunteers were randomized to receive a single session of sham or active stimulation with a current intensity of 2 mA and a random frequency between 1 and 5 Hz. Our results showed that tPCS has a modest and specific effect on cognitive performance as indexed by the cognitive tasks chosen in this study. There was a modest effect of active tPCS only on performance facilitation on a complex-level mathematical task as compared to sham stimulation. On autonomic responses, we observed that HRV total power increased while LF/HF ratio decreased in the tPCS active group compared to sham. There were no group differences for adverse effects. Based on our results, we conclude that tPCS, in healthy subjects, has a modest and specific cognitive effect as shown by the facilitation of arithmetical processing on complex mathematical task. These effects are accompanied by modulation of the central autonomic network providing sympathetic–vagal balance during stressful conditions. Although behavioral results were modest, they contribute to the understanding of tPCS effects and cognitive enhancement.

Keywords tPCS · Math task · HRV · Autonomic response · Cognition

Introduction

Cognitive performance has being studied for the last decades through the investigation of the modulatory mechanisms of neural plasticity (Cai et al. 2014). Several studies aim to improve cognition by potentiating conventional capabilities of healthy individuals, which can then be translated to patients suffering from different conditions affecting cognitive performance or skills that are already acquired (Belleville et al. 2011; Venkatakrishnan and Sandrini 2012; Wingfield and Grossman 2006). In this scenario, noninvasive brain stimulation (NIBS) techniques are increasingly being used to investigate the neural mechanism of cognitive performance and as a possible tool for cognition enhancement by modulation of brain activity

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via weak electrical currents (Vallar and Bolognini 2011). Among these techniques, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are the most used (Demirtas-Tatlidede et al. 2013). Newer techniques have been introduced to the field, and given their potential advantages over traditional NIBS, they have attracted more interest to their possible uses in both healthy and clinical population.

Transcranial pulsed current stimulation (tPCS) is an example of a NIBS technique that has been newly re-discovered and re-investigated. It has been used and approved under the name of cranial–electrical stimulation (CES), and during the past two decades, some studies have investigated the efficacy of tPCS for different clinical conditions such as depression, anxiety, and pain disorders (Gilula and Barach 2004; Kirsch and Smith 2000; Lichtbroun et al. 2001). Despite its safety profile, ease of application, low cost, and potential efficacy, we still know little about tPCS effects on cortical activity and its potential benefits for cognitive functioning (Datta et al. 2013; Fitzgerald 2014). Recently, we reported the results from two mechanistic trials that aimed to find the optimal parameters of stimulation for this technique by using quantitative EEG as an index of cortical activity changes (Castillo Saavedra et al. 2014; Morales-Quezada et al. 2014).

One of the possible neurophysiological mechanisms by which tPCS exerts its effects is through the modulation of cortical functional connectivity, by increasing inter-hemispheric coherence of low-range frequencies, mainly in frontotemporal areas. To further investigate these findings and understand its implications in cognitive performance, we conducted a trial in healthy volunteers to evaluate the effects of tPCS on performance on a mathematical task with three levels of complexity. Moreover, considering the gap in the literature on the physiological mechanisms of this technique, we analyzed physiological response parameters of the autonomic nervous system such as sympathetic–vagal balance and galvanic skin resistance. Our hypothesis is that active tPCS applied through ear clips with a 2-mA intensity, using a random frequency oscillating between 1 and 5 Hz during 20 min in a single session, reduces autonomic balance and improves performance in mathematical activities of medium-to-high complexity when compared to the sham group.

Materials and methods

Methods

We conducted a double-blinded, sham-controlled, randomized trial at the Neuromodulation Center, Spaulding Rehabilitation Hospital, to determine the effects of a single session of tPCS versus sham stimulation on performance on cognitive behavioral tasks, heart rate variability, and electrodermal response. This study was approved by the local Institutional Review Board (IRB) and was conducted according to the Declaration of Helsinki. All participants provided written, informed consent.

Participants

Thirty healthy individuals were recruited from the Boston area by posting ads at universities and public areas. The participants were eligible if they fulfilled the following criteria: (1) age between 18 and 65 years; (2) no diagnosis of neurological, psychiatric, or unstable medical disorders; (3) no history of stroke, traumatic brain injury, epilepsy, unexplained loss of consciousness or severe, and frequent headaches; (4) no family history of epilepsy; (5) no history of drug or alcohol abuse or dependence in the last 6 months; (6) no current use of neuropsychotropic drugs; (7) no history of brain surgery or the presence of metallic implants; and (8) no current pregnancy. All subjects completed a mini mental state examination (MMSE), as a brief screening tool to assess cognitive abilities previous to randomization. Sample characteristics are presented in Table 1.

Transcranial pulsed current stimulation (tPCS)

Participants were randomized into one of two study arms: (1) sham or (2) active stimulation. Randomization was carried out according to a computer algorithm that generated permuted blocks of three. Both the investigator assessing the outcomes and the subjects were blinded to the intervention. Stimulation was delivered using two circular metallic plate electrodes cover by a cotton felt to prevent direct skin contact, attached to a plastic ear clip frame and placed in the inferior lobule of each earlobe. Electrodes were previously

Table 1 Baseline characteristics of study population. Mean (SD)

	Active	Sham
Demographics		
n	15 (50 %)	15 (50 %)
Male/female	7/8	6/9
Age, years	30.53 (7.59)	28.40 (5.15)
Gender		
Asian	3	5
Hispanic	8	6
Caucasian	4	4
Highest level of education	1	1
High school	8	9
Bachelor	6	5
Postgraduate		
MMSE	29.73 (0.8)	29.93 (0.26)

soaked in saline solution. The tPCS device used was an investigational and battery-powered, high-frequency cycling stimulator, developed by BrainGear (BrainGear AG). This device delivers a pulsed, low-amplitude electrical current, which is considered a specific type of transcranial alternating current with a biphasic temporal wavelength. Since tPCS generates an alternating bidirectional current, it does not matter where the anode or cathode is positioned following a bilateral pattern (earlobes). The parameters used for this experiment were random frequency oscillating at 1–5 Hz with an intensity of 2 mA during 20 min. This frequency range was chosen based on the results obtained in our previous two studies assessing the effects of tPCS on brain neuronal activity and connectivity indexed by quantitative EEG (Castillo Saavedra et al. 2014; Morales-Quezada et al. 2014). The associated pulse frequency and its relation to the magnitude spectrum randomly oscillates between 0 and 0.637 A.

To evaluate the integrity of blindness, all participants answered a questionnaire that assessed the degree to which they believed they had received active or sham stimulation. All the participants answered the tPCS side effects Questionnaire after the single session of stimulation. Experiment flow design is presented in Fig. 1.

Cognitive behavioral tasks

Balloon analogue risk task (BART)

This risk assessment task consists of a computerized gambling paradigm as a measurement of decision making. In the task, the participant is presented with a balloon and has the chance to earn points by pumping up the balloon by pressing “P” (Fig. 2a). Each press causes the balloon to inflate, and points are being added to a counter until a randomized time point where the balloon is over inflated and explodes. In this case, the participant loses the points for this trial. So each press represents more risk but it also carries a greater potential for reward. The participant can choose at any

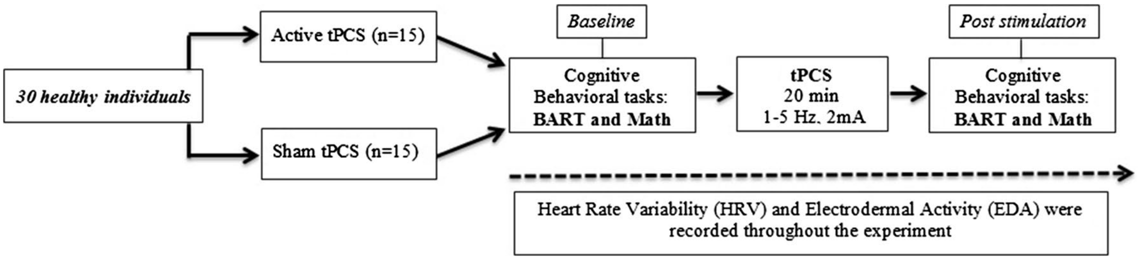
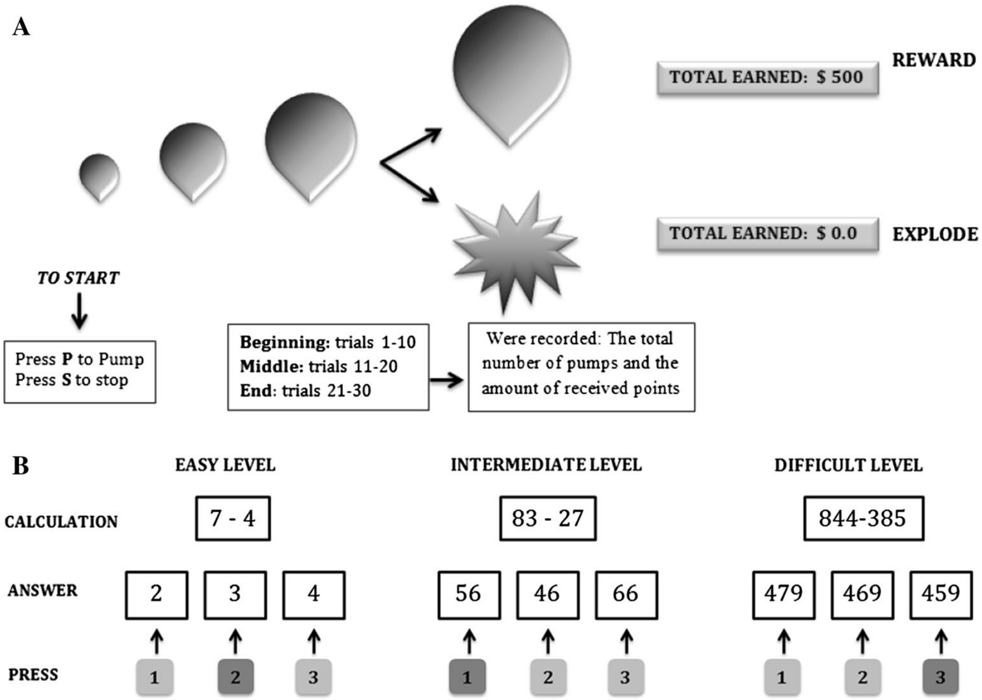


Fig. 1 Study design

Fig. 2 **a** BART task paradigm used for the assessment of risk-taking behavior. **b** Mathematical Task—subtractions with three levels of difficulty: easy level, intermediate level, and difficult level



moment to stop the balloon inflation by pressing "S" and earn the points he collected. This test assesses subject's ability to balance the potential for reward versus loss. This task consisted of 30 trials, and we recorded the number of pumps and the amount of received points at three points during the experiment: at the beginning (1–10 trials), in the middle (11–20), and at the end (21–30).

Math task

This task involves the evaluation of cognition pathways for the processing of mental arithmetic (Hauser et al. 2011). We used subtractions as the main arithmetic procedure, and it was divided into three levels of complexity, easy, intermediate, and difficult (Fig. 2b), which were randomized through the duration of the experiment. The outcomes of this task were accuracy (those who are more accurate complete more tasks in the same amounts of time than those who are not as accurate) and number of correct answers.

Stroop task

We used a computer version of the Stroop color-word task. Different stimuli were presented individually on a computer screen and subjects had to press the key corresponding to the color in which the stimulus was presented. Three types of stimuli were presented such as: (1) congruent stimuli: color words printed in the same color as the meaning of the word; (2) incongruent stimuli: color words printed in a different color; and (3) neutral stimuli: color words printed in black ink, for this type of stimuli participants had to press the key corresponding to the printed color.

Physiological assessments

Heart rate variability (HRV) and skin conductance level (SCL) were collected on a Powerlab 26T using Labchart 8.1 software (ADInstruments, New South Wales, Australia). Two Ag–Ag–CL SCL electrodes were attached to the second and third fingers of the non-dominant hand, between the first and second phalanges. SCL was analyzed off-line using Labchart 8.1 (ADInstruments, New South Wales, Australia) as a mean value of 5 min of task performance. HRV was acquired using a 3-lead ECG with a lead I configuration. The HRV was acquired for 5 min before, during, and after task performance. After removing ectopic beats, HRV was analyzed off-line using the HRV 2.0 module for Labchart (ADInstruments, New South Wales, Australia).

Statistical analysis

All statistical analyses were performed using SPSS version 21. For the math task, the percentage of variation in accuracy (from pre- to post-experimental condition) was calculated using the following formula: $\frac{\text{Post}-\text{pre accuracy}}{\text{pre accuracy}} \times 100$. Independent sample t tests were used to compare the mean between groups for the simple and the complex level. Additionally, exploratory subgroup analyses were conducted using paired-sample t tests to compare the mean difference in terms of accuracy from pre to post between the active and sham group.

For the BART task, the percentage of variation was calculated using the following formula: $\frac{\text{Post}-\text{pre variation}}{\text{pre variation}} \times 100$. Independent sample t tests were used to compare the mean differences in terms of total points earned and variation in average number of pumps. Given the need to add one additional variable—block-by-block analysis—we additionally conducted two mixed model ANOVAs with *block* as the within-subject factor (with 3 levels: 1–10; 11–20; 21–30) and *group* as the between-subject factor (with 2 levels: active or sham tPCS).

For the Stroop task, we used a similar mixed model ANOVA, with *group* as the between-subject factor (two levels—sham and active), and *congruency* (two levels—congruent stimuli and non-congruent stimuli) and *time* (two levels—pre- and post-experimental condition) as the within-subject factors. We also used two interaction factors in the model: *congruency* × *group* and *congruency* × *time* × *group.*

Heart rate variability measurements included (1) total power $\approx \leq 0.4$ Hz, (2) very low frequencies ≤ 0.04 Hz (VLF), (3) low frequencies 0.04–0.15 Hz (LF), (4) high frequencies 0.15–0.4 Hz (HF), and (5) LF/HF ratio. For each HRV frequency band, we used unpaired t tests. To assess for correlations between changes in HRV and performance in the tested tasks, we conducted a Spearman's rank correlation between HRV parameters and math task performance in both the active and sham groups.

The electrodermal activity was analyzed pre- and post-stimulation (during the Math and BART tasks), and during the stimulation period. We used mixed ANOVAs with *time* as the within-subject factor (pre and post) and *group* as the between-subject factor (active or sham tPCS). The results were considered significant if $p < 0.05$.

Results

Behavioral responses

Math task

We conducted this analysis by the level of task. For the simple level task, there were no significant changes across groups (mean difference: 0.114, SE: 2.387) ($t = 0.048$, $p = 0.962$). For the complex-level task, although the differences across groups were also not significant (mean

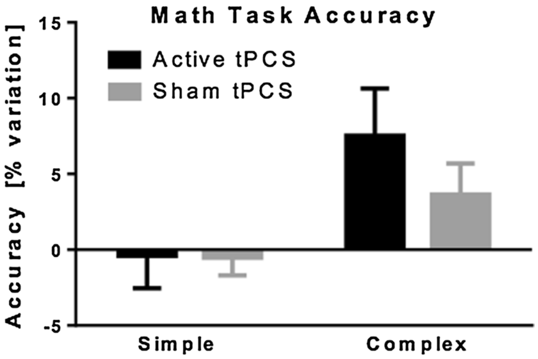


Fig. 3 Accuracy results for the Mathematica task

difference = 3.882, SE = 3.664) ($t = 1.060$, $p = 0.299$), we conducted an exploratory subgroup analysis and observed that active tPCS was able to significantly increase performance from pre to post only for the complex math calculation level, with a mean difference of 5.458 and SE of 2.231 ($t = 2.446$, $p = 0.029$) (Fig. 3). This effect was not observed for sham tPCS.

BART task

There were no significant differences between active and sham tPCS in terms of total earned points from pre- to post-tPCS, reflecting a mean difference of −6.723, and SE of 11.360 ($t = -0.592$, $p = 0.559$) (Fig. 4). There were no significant effects for the average number of pumps (mean difference = −2.017, SE = 11.951) $t = -0.169$, $p = 0.867$. No other significant main effects or interactions were found in the block-by-block analysis.

Stroop task

The mixed model ANOVA showed a main effect of *congruency* ($F_{(1,28)} = 18.872, p < 0.001$) and *time* ($F_{(1,28)} = 25.038$, $p < 0.001$). No effects were found for the interaction factors *congruency × group* ($F_{(1,28)} = 1.340$, $p = 0.257$), or *congruency × time × group* ($F_{(1,28)} = 0.004$, $p = 0.952$). This means that overall, participants were faster during the trials presenting congruent stimuli (M = 1,035.889, SE = 37.851) than during trials with non-congruent stimuli (M = 1,194,668, SE = 64,369) ($p < .001$). They were also faster performing the second time they performed the task (M = 1,013.135, SE = 42.951) than during the first trial (1,217. 422, SE = 62.423) ($p < 0.001$).

Physiological responses

Heart rate variability

Unpaired *t* tests showed a significant increase in HRV total power for the active group compared to sham ($p = 0.05$),

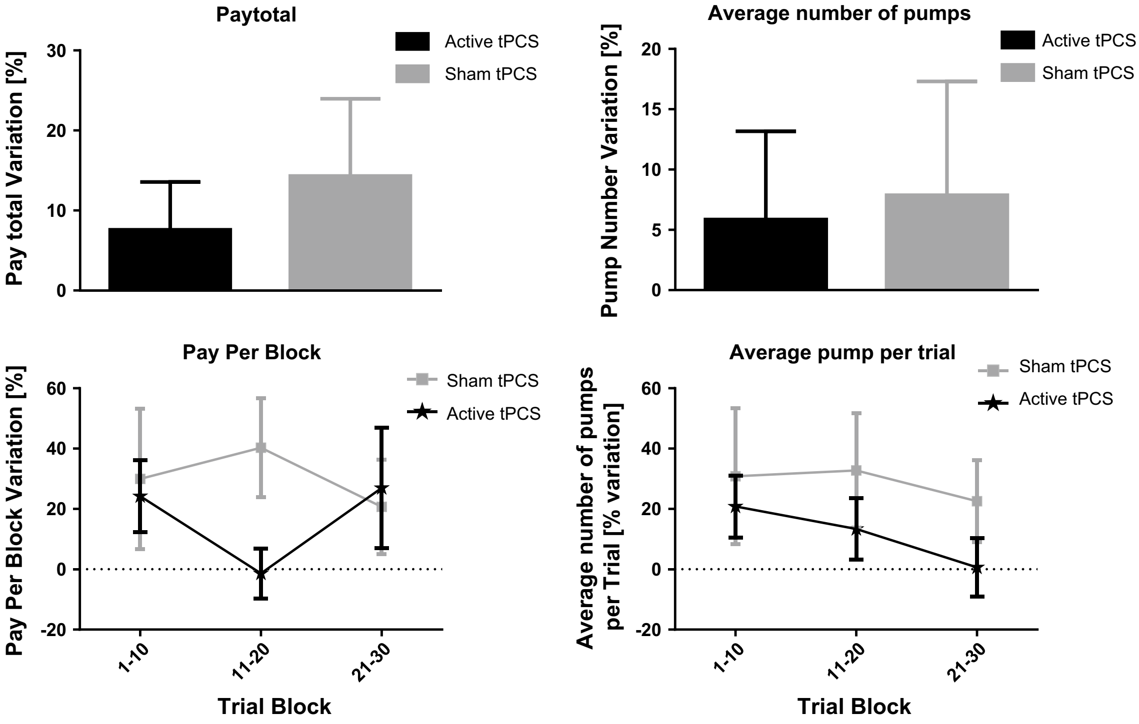


Fig. 4 Results for total pay obtained and average number of pumps for the BART task

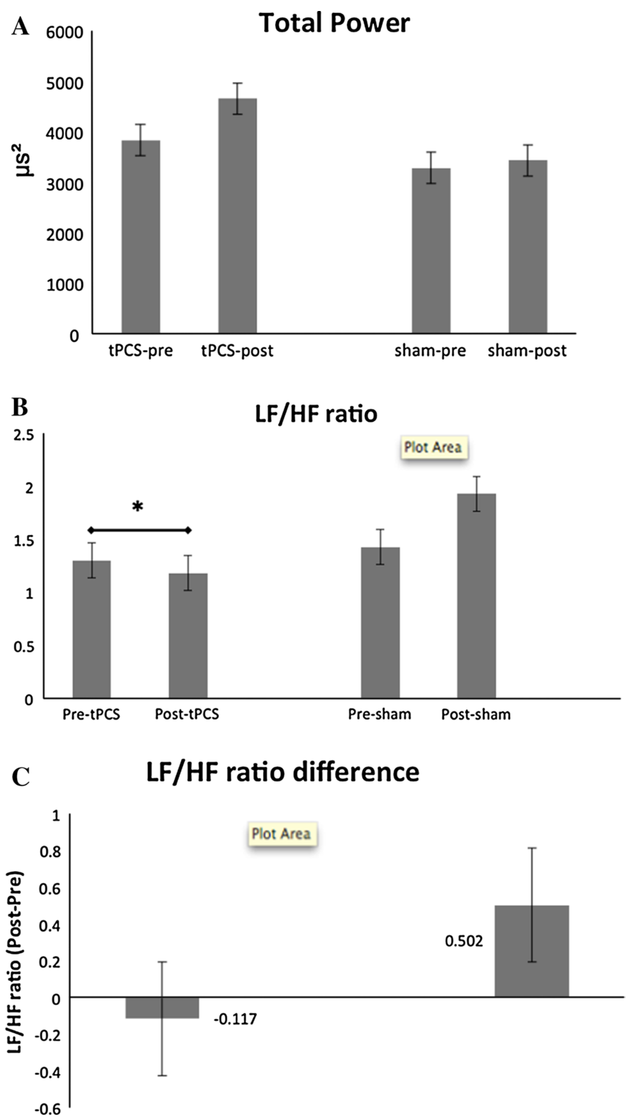


Fig. 5 Changes in heart rate variability (HRV) for active tPCS and sham groups. **a** Changes in HRV total power. No statistically significant changes were found. **b** Changes in low-frequency/high-frequency (LF/HF) ratio. The *asterisks* designate statistical significance. **c** Changes in low-frequency/high-frequency (LF/HF) ratio difference between the post- and pre-experimental period

reflecting a mean increase of 824 units (SE = 72.78). The LF/HF ratio showed a significant decrease in the active group ($p = 0.0227$) with a mean decrease of −0.117 points (SE = .2741), while the sham group showed an increase in the LF/HF ratio ($p = 0.0681$) with a mean increase of 0.502 points (SE = .4866) (Fig. 5a). No significant differences were found for the power of VLF, LF, or HF (Fig. 5b, c).

Electrodermal activity (EDA) pre- and post-tPCS

There were no significant effects of *group* in EDA response for either the BART task ($F_{(1,28)} = 0.697$, $p = 0.411$) nor the Math task ($F_{(1,28)} = 0.576$, $p = 0.454$). No significant effects were found for *time* (pre- and post-experimental condition) for either the BART task ($F_{(1,28)} = 0.753$, $p = 0.393$) nor the Math task ($F_{(1,28)} = 0.803$, $p = 0.378$) (Fig. 6).

Electrodermal activity (EDA) during tPCS stimulation

The mixed ANOVAs did not show significant changes in EDA during the tPCS stimulation between the three time points ($F_{(2,56)} = 1.779$, $p = 0.178$). There was no interaction effect of *time* × *group* ($F_{(2,56)} = 0.346$, $p = 0.709$).

Blinding assessment

Except for one participant, all subjects were able to guess correctly their stimulation condition beyond chance, although the level of confidence for their guess measured in a scale from 1 (not confident at all) to 5 (completely confident) was only 3.166 (±1.315).

Discussion

Previous work generated by our group showed the set of parameters that were able to produce replicable changes in qEEG analysis, specially the inter-hemispheric coherence modulation for the theta and low alpha and subbands in frontotemporal regions (Castillo Saavedra et al. 2014; Morales-Quezada et al. 2014). We also demonstrated that tPCS is a safe technique suitable for human experimentation. To test whether the modulation of such oscillations has an effect on specific cognitive tests, we designed an experiment involving tasks with a functional component linked to the anatomical structures contained within the regions directly influenced by the stimulation, as observed in neurophysiological and modeling studies. In a previous modeling study conducted by our group and using similar parameters as used in this study (Datta et al. 2013), we showed that the ear clip montage used for this experiment induced maximal current densities in the temporal and frontal cortices and diffuse activation of the midbrain, pons, insula, thalamus, and hypothalamus. Our previous studies using qEEG as an index of neuronal activity and connectivity are in agreement with such findings and show that tPCS induces significant modulation of neuronal activity and connectivity of frontotemporal cortical areas.

Our results showed that tPCS has a modest, specific, and marginally significant effect in a complex arithmetic task in healthy individuals. In fact, there were no significant effects in the Stroop and Bart tasks. Although these findings do not fully confirm our main hypothesis, they present critical insights for the future development of this technique

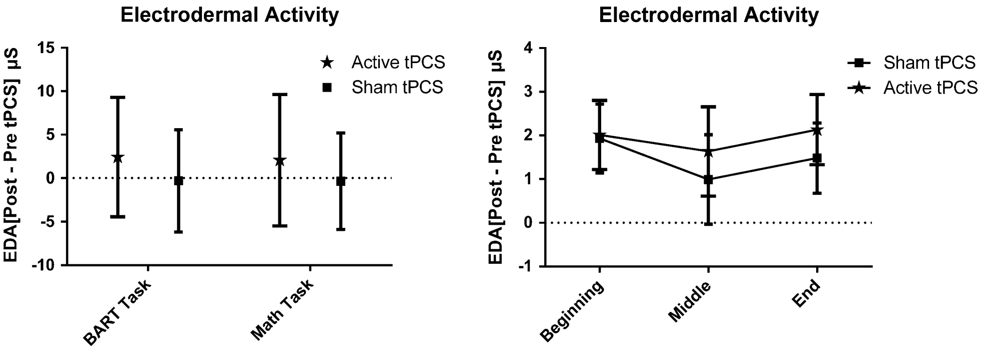


Fig. 6 Changes in electrodermal response for the active and sham group

and for better understanding the main determinants of response. In our previous experiments, we determined the optimal intensity and frequency parameters for transcranial PC stimulation based on measurable changes in neuronal activity and connectivity indexed by quantitative EEG; these parameters were used for this trial (Castillo Saavedra et al. 2014; Morales-Quezada et al. 2014). However, given the small behavioral effects found in this study and the investigation of other parameters (such as intensity), it is likely that a larger number of sessions may increase the effect size of tPCS. This should be tested in further studies. Another possible reason for these results may be the population being investigated: healthy subjects. Given the likely effect of tPCS in strengthening preexisting neural connections and thus inducing cognitive enhancements, individuals with no major impairment in connectivity may have modest or no cognitive effects only with tPCS.

Though effects were modest and marginally significant for complex arithmetic tasks, we present some hypotheses to explain such effects. The parietal cortex, specifically the left angular gyrus, has been involved in arithmetic fact retrieval processing for mental calculations, while a broader area extended over the fronto–parieto–occipital network including the basal ganglia seems to be involved in procedural mental operations (Grabner et al. 2009). Hence, performance in a task with a procedural component requiring approximations for problem-solving can be enhanced by tPCS modulation of the engaged cortical areas, rather than performance in arithmetic activities requiring pure parietal activation for exact problem resolution, which involves the retrieval component. As procedural mental processes demand an extensive network effort, the induction of theta coherence mediated by a random frequency oscillating between 1 and 5 Hz can somewhat facilitate the strategies used for problem-solving; for instance, mental calculation has been proven to increase coherence of the theta frequency band in frontotemporal areas (Nunez et al. 2001) by selective activation. Interestingly, the structures involved in working memory and attention (prefrontal cortex and medial temporal lobe) are located under the area of tPCS influence. Finally, the fact that we only saw a modest effect on the complex-level task strengthens our hypothesis that tPCS has a major effect enhancing existing neural networks.

The fact that no significant differences in the pre- and post-experimental measurements were observed on the BART task indicates a different circuitry involvement in the processing of risk-taking which is basically located in the mesolimbic-frontal regions. Nevertheless, there is a clear tendency for the tPCS active group toward a conservative behavior as compared to the sham group, which can indicate a phenomenon of symmetry establishment between the left and right hemisphere as a consequence of the induced theta inter-hemispheric coherence promoted by the random pulsed frequency. It has been mentioned that increased theta power in frontal regions (Schutter et al. 2006) and right–left theta asymmetry in the prefrontal area (Studer et al. 2013) is related to increased risk-taking behaviors. Yet, theta coherence but not power is coupled with gamma oscillations which are present during higher attentional demands in frontal regions; thus, theta coherence serves as inhibitory inter-hemispheric mediator selecting the resources for the rise of gamma activity in decision-making conditions. Taking into account the lack of effect on the Stroop task, we can assume tPCS did not increase cognitive flexibility, nor ability to deal with increased cognitive load; therefore, the effects of tPCS in the arithmetic task can be seen as specific for the network involved in problem-solving.

The observed results in HRV reveal an interesting influence of tPCS over the central autonomic network (CAN). The active group presented an increase in HRV total power accompanied by a decrease in the LF/HF ratio, reflecting a state of sympathovagal balance. It is important to notice that one of the first signs of stress is tachycardia, and this usually precedes a marked reduction in the total power. HRV measurements were recorded throughout the experiment, and the post-recordings were taken immediately after the cognitive tasks were completed; thus, individuals who received tPCS showed better sympathetic control after exposure to stressful conditions. Furthermore, the tPCS group also presented a decrease in the LF/HF ratio, whereas the sham group exhibited an increment of the same ratio, indicating that tPCS conferred sympathetic modulation. Although no significant differences were found for LF and HF power, which are thought to represent sympathovagal control, changes in LF/HF balance and the HRV total power may reflect reciprocal changes in sympathetic and parasympathetic activity in cardiac control (Reyes del Paso et al. 2013). Nonetheless, these contributions of parasympathetic and sympathetic activation to the sympathovagal balance are known to be confounded by the prevailing heart rate and the mechanical effects of respiration; therefore, the present results should be seen as preliminary. Although EDA did not significantly change through the tasks, there is a trend in the tPCS group to increase its response as compared. Therefore, additional studies are needed to assess the effects of tPCS over the CAN.

The role of the autonomic system on emotion and cognition is well known; several imaging and pharmacological studies identified the link between inhibitory prefrontal–subcortical circuits and vagal tone indexed by vagally mediated changes in HRV measurements (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Park and Thayer 2014). Moreover, research has showed that individuals with higher resting HRV (such as total power) exhibit faster response times and better accuracy on executive cognitive tasks (Hansen et al. 2003). Changes in vigilant versus resting state can also have a major impact on sympathovagal balance (Chang et al. 2013) and vice versa. In fact, the changes in LF/HF balance and the HRV total power may reflect reciprocal changes in sympathetic and parasympathetic activity in cardiac control. In fact if tPCS has a direct vagal effect (independent on the brain modulation), the potential explanation for the behavioral results would be a secondary effect on attention/vigilance. However, further studies are needed to confirm this. One potential limitation of this study is that participants guessed correctly their stimulation condition beyond chance, despite most of them not being confident about their guess. This finding may be explained by the fact that several subjects were not naïve to the stimulation procedure. Results could also be associated with limitations in successful blinding of this technique; nonetheless, the results obtained in the performance of the different tasks and changes in HRV parameters still support a central effect of this type of stimulation.

The present study is the first of its kind to demonstrate tPCS properties when applied under controlled conditions. We have provided additional data supporting the modulatory effects of tPCS. Although the behavioral effects were modest, they are helpful to design further studies as to further enhance our understanding of this technique. Additional experiments are needed in order to elucidate the mechanistic attributes of weak pulsed currents and its interactions with endogenously generated oscillations during cognitive processing.

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Conflict of interest None declared.

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