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No significant effect of transcranial direct current stimulation (tDCS) found on simple motor reaction time comparing 15 different simulation protocols

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ABSTRACT

Background: Research exploring the behavioral impact of transcranial direct current stimulation (tDCS) over M1 has produced homogenous results. The most common explanations to address this homogeneity concerns the differential impact of varied tDCS parameters (such as stimulation intensity or electrode montage). To explore this, we systematically examined the effects of 15 different tDCS protocols on a well-elucidated neurobehavioral system: simple visual motor reaction time (smRT).

Methods: For the initial phase of this study, 150 healthy participants were randomly assigned to one of 5 experimental groups (2 mA anodal, 2 mA cathodal, 1 mA anodal, 1 mA cathodal, or sham) across 3 different conditions (orbitofrontal, bilateral, or extracephalic reference electrode location). The active electrode was always placed over M1 and tDCS lasted for 20 min. Starting ~5 min prior to stimulation and running continuously for ~30 min, participants were repeatedly presented with a visual cue centered on a computer monitor and asked to press a response button as quickly as possible at stimulus onset (stimuli number: 100 pre-, 400 during-, and 100-post stimulation - interstimulus interval: 1–3 s). Ex-gaussian distribution curves, miss, and error rates were determined for each normalized batch of 100 RTs and compared using a two-way ANOVA. As the largest group differences were seen with 2 mA anodal (compared to sham) stimulation using an orbitofrontal montage, an additional 60 healthy participants were recruited to further test for significance in this condition.

Results: No significant impact of tDCS was seen on any parameter of smRT distribution, error rate, or miss rate, regardless of polarity, stimulation intensity, electrode montage, or stimulation-to-task relationship.

Conclusion: Our results suggest that tDCS over M1 might not have a predictable or reliable effect on short duration smRT. Our results raise interesting questions regarding the mechanisms by which tDCS might modulate more complex motor behaviors. Additional research utilizing multiple tDCS protocols as undertaken here will help address and clarify these concerns.

1. Introduction

Transcranial direct current stimulation (tDCS) uses weak electric current passed between two electrodes (an anode and a cathode) fixed to the scalp to modulate neuronal activity (Nitsche and Paulus, 2000). It has been proposed that tDCS modulates neural firing rates during stimulation and synaptic strength following long-duration stimulation (Stagg and Nitsche, 2011). The effect of tDCS on neuronal populations has been shown to rely on the polarity of the electrode overlaying said population; more specifically, anodal stimulation over the primary motor cortex (M1) in healthy individuals has been demonstrated to increase whilst cathodal stimulation has been demonstrated to decrease motoneuronal excitability as measured using transcranial magnetic stimulation generated motor evoked potentials (for review: (Nitsche and Paulus, 2011); for debate: (Horvath et al., 2015a)).

Despite evidence for the impact of tDCS on motoneuronal excitability, the impact of this tool over M1 on resultant motor behaviors is less clear (Horvath et al., 2015b). For example, of the three comparable studies published to date utilizing a sham-controlled reach-based motor tracking paradigm, one reported a significant improvement following cathodal stimulation (Antal et al., 2008), one reported a significant impairment following cathodal stimulation (Shah et al., 2013), and one reported no effect of cathodal stimulation (Antal et al., 2004). Similarly, using a

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sham-controlled sequential finger tapping task, two studies have reported a significant improvement in performance following anodal stimulation (Tecchio et al., 2010; Karok and Witney, 2013) whilst one has reported a significant impairment following anodal stimulation (Stagg et al., 2011). Similar homogeneity can be found in studies exploring the effects of tDCS over M1 using pinch-force matching (Vollmann et al., 2013; Saucedo Marquez et al., 2013), the Purdue pegboard test (Kidgell et al., 2013; Bastani and Jaberzadeh, 2014) and the Jebsen-Taylor hand function task (Sohn et al., 2012; Convento et al., 2014).

The effects of tDCS over M1 on simple motor reaction time (smRT) are equally contradictory. Of the twelve papers reporting smRT in healthy adults, five report a significant effect of stimulation (Nitsche et al., 2003; Muller et al., 2008; Leite et al., 2011; Devanathan and Madhavan, 2016; Lopez-Alonso et al., 2015) whilst seven report no significant effect of stimulation (Stagg et al., 2011; Kuo et al., 2008; Tanaka et al., 2009; Reidler et al., 2012; Pellicciari et al., 2013; Iyer et al., 2005). As smRT is a relatively lower-level motor behavior, this suggests that the conflicting motor behavior results outlined above cannot simply be due to task complexity.

Arguments put forward to explain the heterogonous motor behavior results in the tDCS literature, including smRT, commonly revolve around the differential effects of three adjustable parameters: 1) current density (stimulation intensity), 2) reference electrode position (stimulation montage), and 3) stimulation-to-task relationship ('online' vs 'offline'). With regards to current density, a number of researchers have demonstrated density-dependent effects of tDCS (Jefferson et al., 2009; Batsikadze et al., 2013; Bastani and Jaberzadeh, 2013) (interestingly, several recent reports suggest current-density does not, in fact, modulate tDCS effects (Kidgell et al., 2013; Cuypers et al., 2013; Hoy et al., 2013)). With regards to reference electrode position, several modeling studies suggest montage significantly alters current flow through the brain and, consequently, tDCS effect (Sadleir et al., 2010; Datta et al., 2011; Neuling et al., 2012) – though this has not yet been measured in vivo. Finally, with regards to stimulation-to-task relationship, some researchers argue that tDCS is only effective if stimulation occurs *during* task performance whilst others argue that tDCS is only effective if stimulation occurs *prior to* task performance (For review: (Bastani and Jaberzadeh, 2012)).

The present study aimed to manipulate these three parameters to determine if/how each influences the impact of tDCS on smRT. First, we varied the strength and polarity of the tDCS current - using 1 mA anode and cathode, 2 mA anode and cathode, and sham stimulation. Next, we varied the stimulation montage by keeping the active electrode over M1 whilst positioning the reference electrode over contralateral orbit, contralateral M1 (bilateral), and contralateral wrist (extracephalic). Finally, in each of these conditions, smRT performance was measured both during and following stimulation. Through this systematic parametric manipulation, we hope to clarify the contradictory literature relating to tDCS effects of smRT and motor behavior.

2. Method

2.1. Participants

For the initial phase of this study, 150 healthy University of Melbourne students (Male=70; Total Age Range=18–34, M=21.43, SD=4.53) participated in this study. For the second phase of the study, an additional 60 healthy University of Melbourne students (Male=34; Total Age Range=18–33, M=23.08, SD=13.29) were recruited. Each was right-handed and reported normal or corrected-to-normal vision.

2.2. tDCS

tDCS was delivered through two saline soaked sponges (35 cm^2) using a battery-driven constant-current stimulator (Chatanooga Ionto 2). As the device was not commercially designed for tDCS purposes, we had it independently assessed by an electrical biomedical engineer with expertise in intracranial stimulation in the context of epilepsy seizure management. The device was confirmed to generate and maintain a constant current with a compliance of 56 V@1 mA, which falls well within the compliance voltage required for tDCS at that power (Hahn et al.., 2013). Electrodes were held in place using flexible rubber straps adjustable via non-conductive clips. The active electrode was centered over the left M1, corresponding to position C3 of the 10–20 system (Homan et al., 1987; Okamoto et al., 2004). For the contralateral orbit (CO) condition, the reference electrode was fixed at the forehead over the right eyebrow. For the bilateral (BL) condition, the reference electrode was fixed over the right M1, corresponding to position C4 of the 10–20 system (Homan et al., 1987; Okamoto et al., 2004). For the extracephalic (EC) condition, the reference electrode was fixed to the dorsal surface of the right wrist.

In each condition, current intensity was either 1 mA (0.02857 mA/cm^2), 2 mA (0.0571 mA/cm^2), or sham and applied for 20 min with approximately 30 s ramp-up and –down times. For sham stimulation, current flow was increased gradually (to 1.5 mA) then decreased gradually (to 0) over the course of approximately 30 s to mimic the sensation of stimulation.

2.3. Reaction time task

Simple reaction time was recorded to the onset of a high luminance contrast gabor patch (1 cycle per degree, space constant 1 degree) which appeared in the center of a Sony GPD520 CRT monitor (vertical refresh rate of 100 Hz; mean luminance of 40 cd/m2). Contrast was ramped on and off for 10 frames within a single frame resulting in an exposure duration of 100 ms. Participants were asked to press a single button on a response box (RTbox: accurate to the milisecond) using a digit of their right hand as quickly as possible in response to the appearance of each stimulus. In total, 600 stimuli were presented with an ISI of 1.5–3.5 s. The task took ~30 min to complete.

2.4. Experimental design

A sham-controlled, single-measure design was carried out. During the first phase of the study, each participant was randomly assigned to one condition according to reference electrode position (CO, BL, or EC) and assigned a single intensity (1 mA, 2 mA, or Sham: Fig. 1). During the second phase of the study, participants were randomly assigned to either the 2 mA anodal or sham CO condition. After signing standardized consent forms, participants were verbally administered a tDCS side-effects questionnaire exploring current levels of sleepiness, headache, etc..

Following this, participants were seated 60 cm away from a computer monitor in a small, sound-proofed, dimly-lit testing booth and the tDCS electrodes were attached according to condition. Once the system was set up, the participant was presented with a brief training period (10 stimuli: ~30 s) to get used to the button box and stimuli.

Afterwards, the program was started. After the first 100 presentations, stimulus presentation stopped and the experimenter activated the tDCS device. Once stimulation reached the appropriate level, the RT program was resumed and continued non-stop for the remaining 500 stimuli. After approximately 20 min (~400 stimuli), the tDCS device would ramp-down and generate an audio beep alerting the experimenter that stimulation was complete. Although

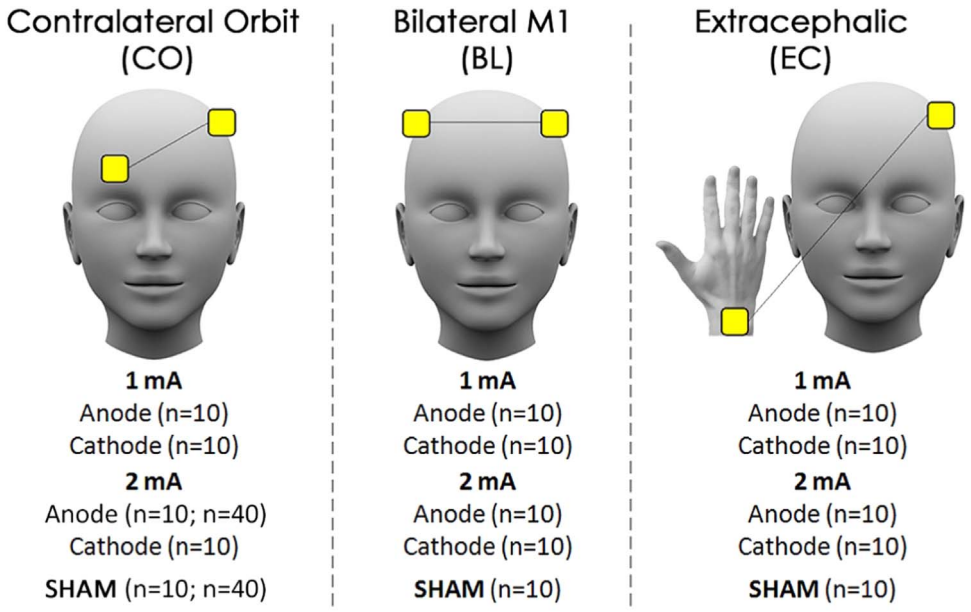

Fig. 1. Group condition and subject number schematic.

participants were likely able to hear this beep, it was never explained to them what the beep signified. At this point, the experimenter would shut off the device (without the awareness of the participant) as the program continued to completion (~100 stimuli; ~5 min).

Following stimulation, side-effects questionnaire was verbally administered and the participant was free to leave.

2.5. Analysis

smRTs were divided into six blocks of 100 RTs each. The first block (generated prior to stimulation) was labeled baseline (BL), the next four blocks (generated during active stimulation) were labeled T1-T4, and the final block (generated following stimulation) was labeled T5 (Table 1). T1-T5 were normalized to BL and analyzed as percent-of-baseline measures.

Within each block, the total number of misses (failure to respond to a stimulus within 1000 ms) and errors (responses between 1 and 110 ms) were calculated and removed from further analysis. Using the DISTRIB toolbox for MatLab, each block of RTs was fit with an exponentially modified gaussian (ex-gaussian) curve to model the distribution shape for each block (Lacouture and Cousineau, 2008). The ex-Gaussian curve contains three parameters: mu (the mean of the Gaussian-portion of the curve), sigma (the variance of the Gaussian-portion of the curve) and tau (the mean and variance of the exponential-portion of the curve). When combined, these three parameters are believed to confer the strongest representation of RT distribution as they offer the average (mu) and variance (sigma) of a normally distributed RT distribution whilst accounting for the fact that RTs will be minimally constrained by the physiologic time required to sense, interpret, and react to the 'go-signal' stimuli (tau). Put another way, because it takes time for a person to process a stimulus and generate a response, there will necessarily be a period of time following stimulus presentation where a RT cannot occur (typically <110 ms); it is this processing time that the exponential 'tau' parameter accounts for. Maximum likelihood estimates were obtained using the "fminsearch" function of the aforementioned Matlab toolbox (based upon the Nelder-Mead simplex search algorithm – (Lagarias et al., 1998)). -LogL values ranged between -304.86 and -45.38 ($M=-173.72$, $SD=48.04$). Finally, goodness-of-fit for each ex-gaussian curve was measured using chi-squared. Bins for the chi-squared analysis were initially set to intervals of hundredths of a millisecond with the constraint that there had to be more than 5 expected observations per bin (Hays, 1994). If there were 5 or fewer observations, adjacent bins were pooled until the observations exceeded 5 (Palmer et al., 2011). Total bin values ranged between 8 and 14 ($M=11.46$, $SD=1.27$) and X^2 ranged between 3.21 and 48.87 ($M=15.88$, $SD=8.66$). Each was non-significant suggesting a good fit between the model and the data.

Once ex-gaussian distribution curve parameters were determined, comparisons for each parameter were made within each condition (CO, BL, EC) using a two-way ANOVA (group x time). Any significant findings were compared using post-hoc, bonferroni corrected *t*-tests. As a secondary analysis, all stimulation intensities (regardless of reference electrode location) were pooled and compared using a two-way ANOVA (group x time). This was done to increase the N within each group (to $N=30$) to determine if any reference-independent effects were present. Finally, visual inspection of the Mu parameter and effect size measures revealed the largest differential occurred between the 2 mA CO and Sham CO groups. To explore this relationship further, an additional 30 individuals were added to each of these groups and analyses were undertaken (as outlined above).

3. Results

3.1. Contralateral orbit (CO) condition

3.1.1. Errors

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 225)=0.530$, $p=0.753$; *stimulation intensity*: ($F(4, 45)=0.687$, $p=0.924$) nor the interaction effect ($F(20, 225)=1.249$, $p=0.217$) were significant (Fig. 2a).

3.1.2. Misses

A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 225)=6.230$, $p<0.001$, such that the number of misses increased significantly within each group across the study. Neither the main effect of stimulation intensity, $F(4, 45)=1.140$, $p=0.350$, nor the interaction effect, $F(20, 225)=0.582$, $p=0.923$, were significant (Fig. 3a).

Table 1
shows the average and standard deviation of each group's absolute smRT values (in ms).

	Baseline	T1	T2	T3	T4	T5
OrbFro (N=10)						
1 mA Anode	228.7 (25.3)	235.4 (25.2)	240.1 (27.0)	248.2 (35.0)	250.6 (38.6)	249.6 (37.4)
2 mA Anode	229.9 (29.4)	233.6 (32.6)	239.0 (36.7)	245.8 (47.0)	245.2 (44.7)	242.2 (35.7)
1 mA Cathode	232.3 (32.4)	233.6 (23.9)	245.2 (33.2)	263.6 (51.6)	251.0 (40.9)	255.9 (38.1)
2 mA Cathode	261.4 (45.3)	260.0 (41.2)	266.7 (38.1)	276.6 (49.5)	280.6 (61.5)	270.7 (52.3)
Sham	236.9 (29.5)	234.7 (29.7)	250.3 (39.3)	260.0 (48.5)	266.6 (58.8)	265.9 (55.8)
BiLat (N=10)						
1 mA Anode	230.0 (26.2)	242.8 (33.9)	252.1 (39.1)	245.1 (40.6)	248.4 (40.8)	251.1 (36.6)
2 mA Anode	227.0 (39.7)	232.9 (45.1)	247.8 (56.8)	244.7 (53.1)	253.1 (57.9)	245.9 (52.7)
1 mA Cathode	237.7 (32.1)	245.2 (36.6)	251.8 (38.6)	248.3 (38.7)	256.0 (42.8)	251.5 (41.1)
2 mA Cathode	232.8 (39.8)	248.9 (60.5)	248.9 (57.4)	247.2 (63.1)	253.1 (59.8)	257.4 (70.1)
Sham	234.1 (31.4)	240.7 (34.4)	247.2 (36.0)	254.3 (41.2)	250.8 (34.6)	251.0 (37.6)
ExCeph (N-10)						
1 mA Anode	237.1 (24.0)	244.3 (18.5)	248.5 (40.8)	264.1 (64.0)	255.1 (47.8)	259.0 (45.8)
2 mA Anode	237.9 (28.9)	254.1 (50.6)	252.9 (50.3)	256.2 (53.5)	260.9 (58.7)	262.3 (53.9)
1 mA Cathode	241.4 (19.5)	255.5 (33.9)	268.8 (44.7)	267.2 (38.1)	265.6 (45.5)	272.0 (40.5)
2 mA Cathode	219.7 (33.3)	239.3 (57.9)	241.3 (50.1)	242.8 (56.4)	238.7 (49.1)	238.3 (48.9)
Sham	236.6 (35.3)	240.5 (40.6)	250.9 (39.2)	263.4 (44.9)	261.8 (39.2)	267.8 (53.0)
OrbFro (N=40)						
2 mA Anode	227.3 (26.8)	234.5 (32.7)	244.8 (42.1)	248.0 (42.3)	245.1 (36.6)	242.1 (33.1)
Sham	237.2 (34.3)	240.2 (36.7)	247.3 (41.5)	251.1 (45.8)	252.6 (46.2)	252.4 (46.9)

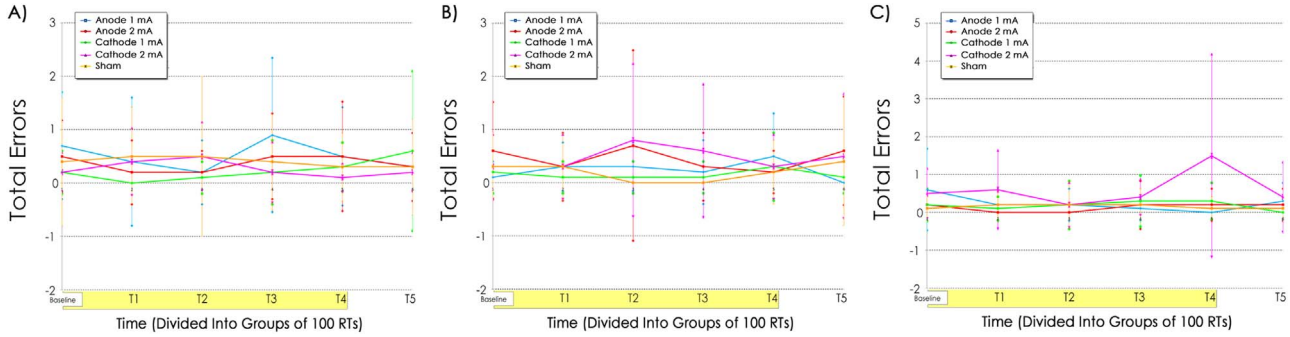

Fig. 2. Average number of errors per RT block for each stimulation intensity. (A) CO Condition; (B) BL Condition; (C) EC Condition.

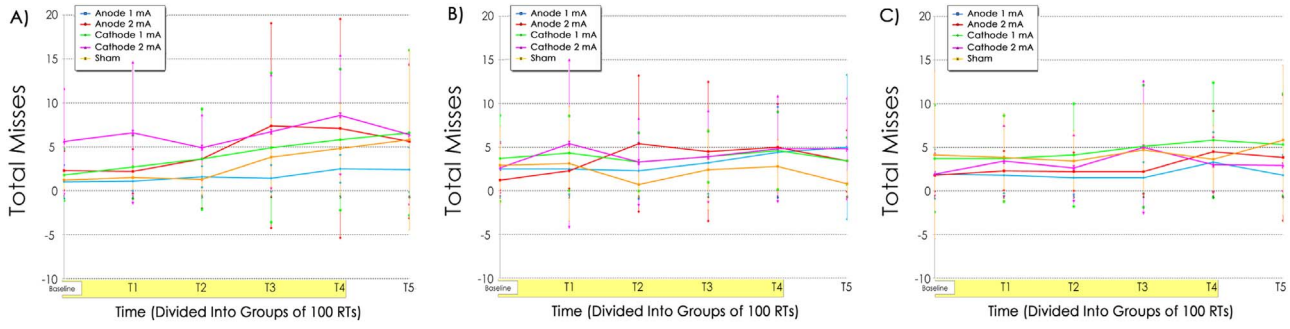

Fig. 3. Average number of misses per RT block for each stimulation intensity. (A) CO Condition; (B) BL Condition; (C) EC Condition.

3.1.3. *Ex-gaussian distribution*

Mu (average) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time ($F(5, 225)=10.797$, $p<0.001$), such that Mu significantly increased within each group across the study. Neither the main effect of group ($F(4, 45)=0.271$, $p=0.895$) nor the interaction effect ($F(20, 225)=0.714$, $p=0.810$) were significant (Fig. 4a).

Sigma (variance) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 225)=2.662$, $p=0.023$, such that sigma changed significantly within each group across the study. Neither the main effect of group, $F(4, 45)=0.714$, $p=0.587$, nor the interaction effect, $F(20, 225)=0.644$, $p=0.877$, were significant (Fig. 5a).

Tau (onset) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 225)=2.662$, $p=0.023$, such that tau changed significantly within each group across the study. Neither the main effect of group, $F(4, 45)=1.337$, $p=0.271$, nor the interaction effect, $F(20, 225)=1.492$, $p=0.086$) were significant (Fig. 6a).

3.2. *Bi-lateral M1 (BL) condition*

3.2.1. *Errors*

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 225)=0.200$, $p=0.962$; *stimulation intensity*: ($F(4, 45)=0.914$, $p=0.464$) nor the interaction effect ($F(20, 225)=0.684$, $p=0.840$) were significant (Fig. 2b).

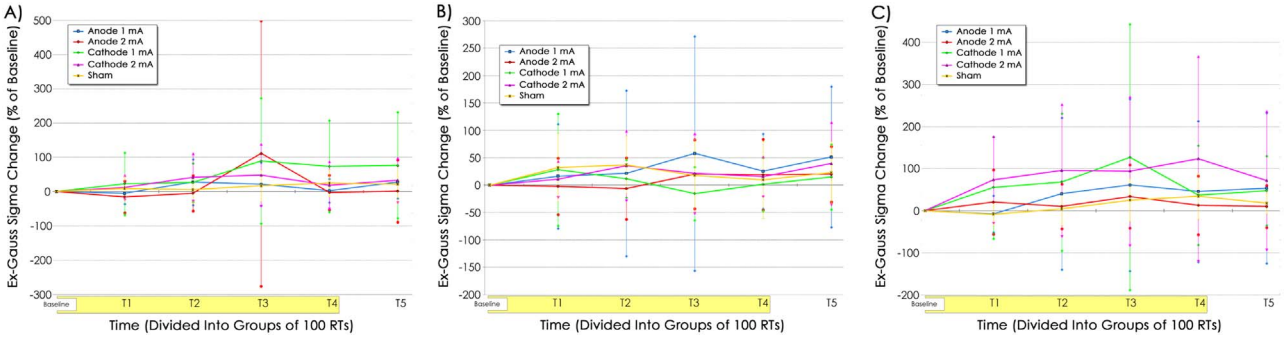

Fig. 4. Average Mu (average) distribution value per RT block for each stimulation intensity. A) CO Condition; B) BL Condition; C) EC Condition.

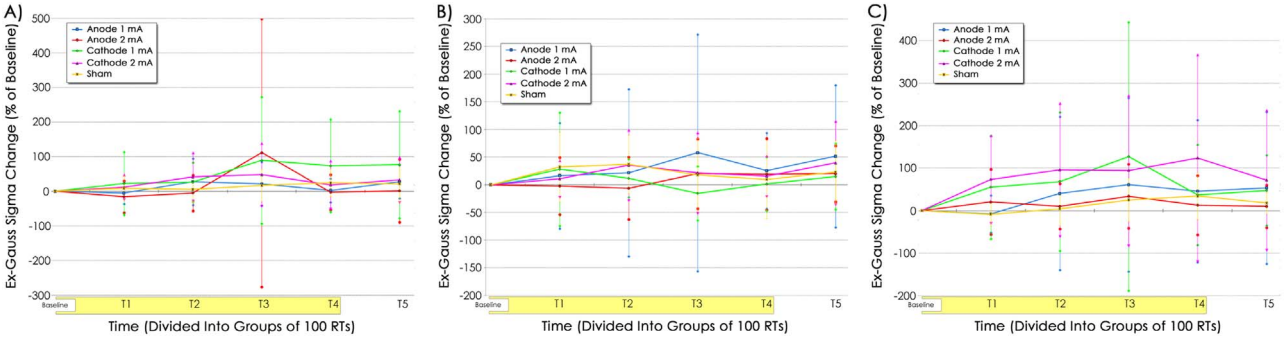

Fig. 5. Average Sigma (variance) distribution value per RT block for each stimulation intensity. (A) CO Condition; (B) BL Condition; (C) EC Condition.

3.2.2. Misses

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 225)=0.254$, $p=0.906$; *stimulation intensity*: $(F(4, 45)=0.687$, $p=0.924)$ nor the interaction effect ($F(20, 225)=0.839$, $p=0.664$) were significant (Fig. 3b).

3.2.3. Distribution

Mu (average) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time ($F(5, 225)=8{,}735$, $p<0.001$), such that Mu significantly increased within each group across the study. Neither the main effect of group ($F(4, 45)=0.212$, $p=0.931$) nor the interaction effect ($F(20, 225)=0.429$, $p=0.986$) were significant (Fig. 4b).

Sigma (variance) - A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 225)=1.555$, $p=0.174$; *stimulation intensity*: $(F(4, 45)=0.262$, $p=0.901)$ nor the interaction effect ($F(20, 225)=0.649$, $p=0.872$) were significant (Fig. 5b).

Tau (onset) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 225)=4.139$, $p<0.001$, such that tau changed significantly within each group across the study. Neither the main effect of group, $F(4, 45)=0.576$, $p=0.681$, nor the interaction effect, $F(20, 225)=0.844$, $p=0.658$, were significant (Fig. 6b).

3.3. Extracephalic (EC) condition

3.3.1. Errors

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 225)=1.105$, $p=0.359$; *stimulation intensity*: $F(4, 45)=2.255$, $p=0.114$) nor the interaction effect ($F(20, 225)=1.462$, $p=0.096$) were significant (Fig. 2c).

3.3.2. Misses

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 225)=1.506$, $p=0.189$; *stimulation intensity*: $F(4, 45)=0.841$, $p=0.506$) nor the interaction effect ($F(20, 225)=0.493$, $p=0.968$) were significant (Fig. 3c).

3.3.3. Distribution

Mu (average) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time ($F(5, 225)=10.832$, $p<0.001$), such that Mu significantly increased within each group across the study. Neither the main effect of group ($F(4, 45)=0.182$, $p=0.947$) nor the interaction effect ($F(20, 225)=0.932$, $p=0.547$) were significant (Fig. 4c).

Sigma (variance) - A two-way ANOVA (stimulation x time)

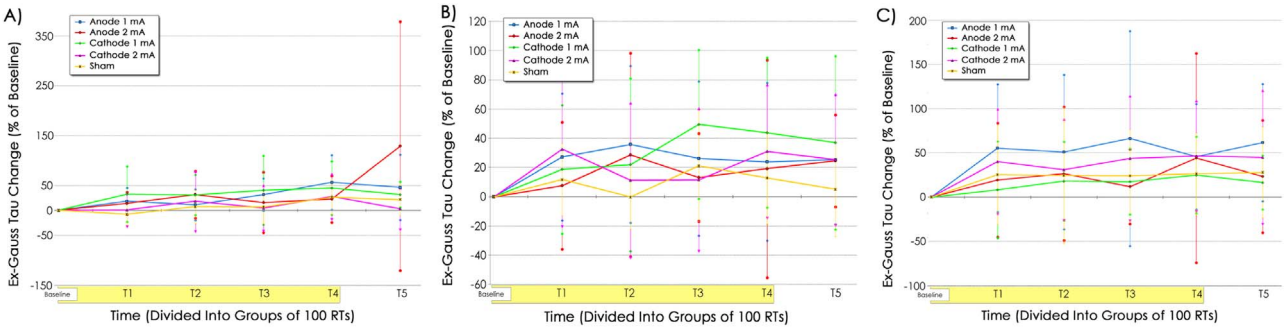

Fig. 6. Average Tau (onset) distribution value per RT block for each stimulation intensity. (A) CO Condition; (B) BL Condition; (C) EC Condition.

revealed a significant main effect of time, $F(5, 225)=3.292$, $p<0.001$, such that sigma changed significantly within each group across the study. Neither the main effect of group ($F(4, 45)=0.818$, $p=0.521$) nor the interaction effect ($F(20, 225)=0.624$, $p=0.893$) were significant (Fig. 5c).

Tau (onset) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 225)=5.676$, $p<0.001$, such that tau changed significantly within each group across the study. Neither the main effect of group ($F(4, 45)=0.706$, $p=0.592$) nor the interaction effect ($F(20, 225)=0.518$, $p=0.957$) were significant (Fig. 6c).

3.4. Combined stimulation intensities (reference electrode location irrelevant)

3.4.1. Errors

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 725)=0.363$, $p=0.874$; *stimulation intensity*: ($F(4, 145)=0.874$, $p=0.481$) nor the interaction effect ($F(20, 725)=0.688$, $p=0.841$) were significant.

3.4.2. Misses

A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 725)=7.795$, $p<0.001$, such that the number of misses increased significantly within each group across the study. Neither the main effect of stimulation intensity ($F(4, 145)=1.229$, $p=0.301$) nor the interaction effect ($F(20, 725)=0.654$, $p=0.872$) were significant.

3.4.3. Distribution

Mu (average) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time ($F(5, 725)=11.242$, $p<0.001$), such that Mu significantly increased within each group across the study. Neither the main effect of group ($F(4, 145)=0.321$, $p=0.863$) nor the interaction effect ($F(20, 725)=0.922$, $p=0.559$) were significant.

Sigma (variance) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 725)=6.497$, $p<0.001$, such that sigma changed significantly within each group across the study. Neither the main effect of group ($F(4, 145)=0.935$, $p=0.446$) nor the interaction effect ($F(20, 725)=0.621$, $p=0.899$) were significant.

Tau (onset) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 725)=12.018$, $p<0.001$, such that tau changed significantly within each group across the study. Neither the main effect of group ($F(4, 145)=0.993$, $p=0.414$) nor the interaction effect ($F(20, 725)=1.080$, $p=0.366$) were significant.

3.5. Increased N analysis (2 mA vs Sham using the CO montage)

3.5.1. Errors

A two-way ANOVA (stimulation x time) revealed neither the main effects (*time*: $F(5, 390)=0.939$, $p=0.455$; *stimulation intensity*: $F(1, 78)=0.693$, $p=0.408$) nor the interaction effect ($F(5, 390)=0.549$, $p=0.739$) were significant (Fig. 7a).

3.5.2. Misses

A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 390)=4.224$, $p=0.001$, such that the number of misses increased significantly within each group across the study. Neither the main effect of group ($F(1, 78)=0.337$, $p=0.563$) nor the interaction effect ($F(5, 390)=0.314$, $p=0.904$) were significant (Fig. 7b).

3.5.3. Distribution

Mu (average) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time ($F(5, 390)=9.235$, $p<0.001$), such that Mu significantly increased within each group across the study. Neither the main effect of group ($F(1, 78)=0.638$, $p=0.427$) nor the interaction effect ($F(5, 390)=0.772$, $p=0.570$) were significant (Fig. 7c).

Sigma (variance) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 390)=2.821$, $p=0.016$, such that sigma significantly increased within each group across the study. Neither the main effect of group ($F(1, 78)=2.791$, $p=0.100$) nor the interaction effect ($F(5, 390)=0.702$, $p=0.622$) were significant (Fig. 7d).

Tau (onset) - A two-way ANOVA (stimulation x time) revealed a significant main effect of time, $F(5, 390)=9.326$, $p<0.001$, such that tau significantly increased within each group across the study. Neither the main effect of group ($F(1, 78)=1.311$, $p=0.256$) nor the interaction effect ($F(5, 390)=0.916$, $p=0.470$) were significant (Fig. 7e).

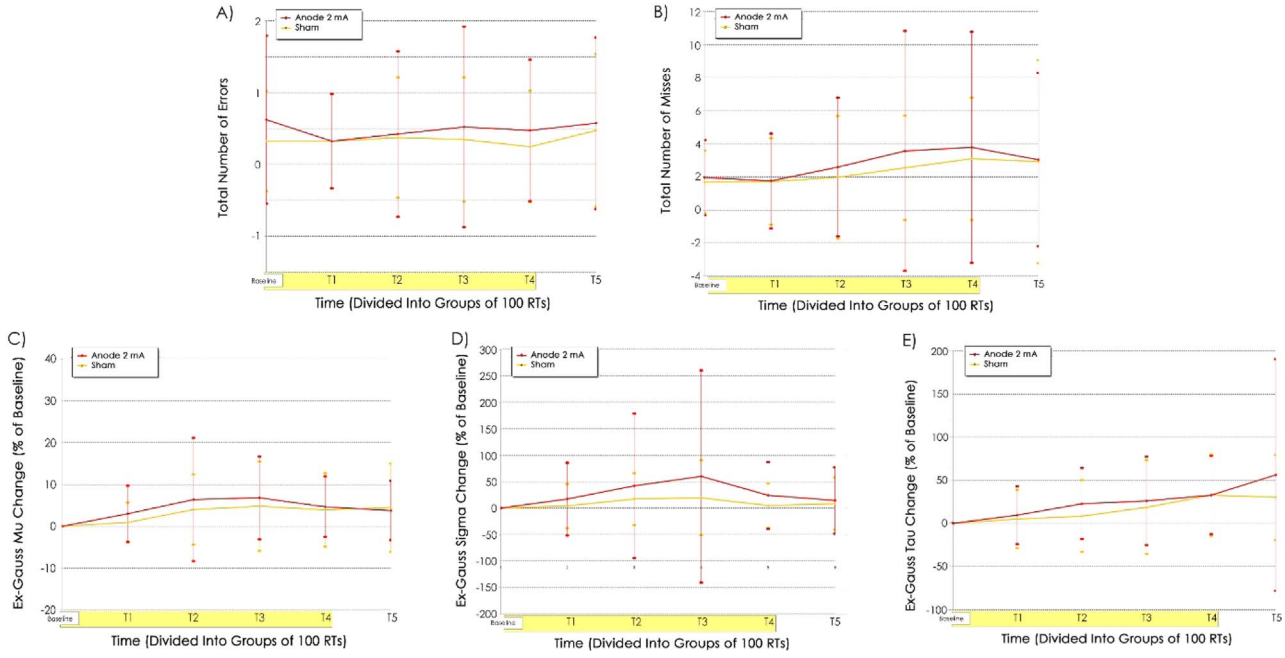

Fig. 7. Outcome values for the increased sample size 2 mA anodal vs sham orbitofrontal stimulation conditions. (A) Error rate; (B) Miss rate; (C) Ex-Gauss Mu value; (D) Ex-Gauss Sigma value; (E) Ex-Gauss Tau value.

4. Discussion

In this study, we set out to determine if and how the unique tDCS parameters of current density, electrode montage, and stimulation-to-task relationship affected smRT. Regardless of how these parameters were varied and combined, we were unable to find a significant impact of tDCS on smRT. More specifically, neither during nor following 20 min of M1 tDCS with 1 mA anodal or cathodal, 2 mA anodal or cathodal, or sham stimulation using a contralateral orbit, contralateral M1, or extracephalic reference location stimulation was any significant effect determined on measures of smRT distribution, miss rate, or error rate.

These results are in-line with other emerging systematic studies suggesting a highly variable behavioral impact of tDCS (Conley et al., 2015; de Hollander et al., 2016) and may help shed light on the contradictory smRT tDCS literature published to date. As noted previously, common explanations for the varied reported findings concern current density, electrode montage, and stimulation-to-task relationship. As this is the first study to explore all major forms of these three parameters (and compare to 3 unique sham-control conditions), we had the unique opportunity to assess these explanations. Interestingly, regardless of parameters or pooling, we were unable to find a significant effect of any form of stimulation. This suggests that the homogenous literature may be due to other sources (such as secondary, non-experimental variables or analytic techniques).

That we were unable to find a significant impact of tDCS over M1 on smRT raises interesting questions concerning the mechanisms by which this tool might modulate higher-order motor behaviors. More specifically, our results suggest that an increase in motor activation speed might not be a mechanistic foundation for the modulation of larger, more cognitively demanding motor behaviors. Including an smRT task in future motor experiments will help clarify the role of tDCS induced motor speed modulation in the modulation of more complex motor behaviors.

It has been noted that the effects of tDCS on more complex motor behaviors are equally homogenous (see above) and that explanations for reported discrepancies revolve largely around the impact of varied tDCS parameters. It is possible that, in line with the results obtained here, that these discrepancies may be found to be driven by other, non-tDCS factors. The utilization of a more comprehensive set of stimulation protocols (as utilized here) in future research will help clarify the impact of varied tDCS parameters on motor behavioral outcomes and allow us to better determine where any sources of outcome variability may lie.

As our results typically demonstrated an impact of time on the Mu parameter (suggestive of a general slowing of smRT speed throughout the study), it is possible fatigue or boredom influenced our findings. However, with the sham-controlled, randomized design utilized here, this influence was likely distributed similarly across all conditions effectively nullifying its overall impact on group differences (it is for this reason we found no significant differences in the pattern of slowing between groups). Despite this, it is possible the impact of fatigue was enough to nullify any impact of tDCS on smRT, effectively making all groups perform at the same level as the sham conditions (although, there is no evidence in the literature to date exploring the impact of fatigue on tDCS). If fatigue generated over a 30 min experiment is enough to nullify or otherwise mask the impact of tDCS, this has important implications about the application of this device during longer sessions or protocols with more cognitively demanding tasks. If the larger goals of neuromodulation research concern clinical or enhancement applications (Brunoni et al., 2012; Pascual-Leone et al., 2012; Halko et al., 2010), then understanding the impact of fatigue on outcome will be of great importance in elucidating the most effective tDCS protocols. Future research should explore the link between fatigue and outcome.

One factor worth considering that may have contributed to our null results regards ISI time. As many smRT protocols utilize longer and/or more variable ISIs, it is possible our utilization of a relatively short ISI window (1.5–3.5 s) influenced our result. However, a look at the RT literature (separate from tDCS influence) suggests that shorter ISI times would be more amenable to demonstrating M1 modulation. A common RT model suggests three distinct neurological processing stages: stimulus evaluation (detect, process, and interpret the 'go' signal), task-specific preparation (prepare the motor program required for response), and response generation (execute the motor program: for review and discussion (Pascual-Leone et al., 1992a)). Whereas in paradigms utilizing long ISIs, these three systems are thought to activate in a serial manner, in an explicit smRT task with a short ISI (as utilized here), the stimulus evaluation and task-specific preparation networks are likely activated well in advanced of the stimulus presentation (anticipatory preparation) and held in memory until transferred to the response network (more akin to parallel activation of all three networks: (Coles et al., 1985)). Due to this preactivation, any modulation of smRT using an explicit task with a short ISIs is most likely reflective of changes within the network/s responsible for response generation – in this case, the primary motor cortex. Accordingly, using a relatively short ISI should have increased our likelihood of measuring any M1 modulation (see also (Schupp and Schlier, 1972; Breitmeyer, 1975; Smith, 1995)).

A second factor which may have contributed to our null results is motor interference. Several lines of research suggest that any active motor and/or cognitive activity undertaken during or following tDCS can negatively interfere with or completely abolish the modulatory effects of tDCS (Quartarone et al., 2004; Antal et al., 2007; Miyaguchi et al., 2013) (for review (Horvath et al., 2014)). Although this is compelling, the amount and duration of motor activity in this study is comparable to (if not slightly less) than the studies that have reported significant smRT modulation with tDCS. Accordingly, it is difficult to establish a compelling reason why motor interference would have impacted our findings but not those of others using similar protocols. In addition, using neurophysiologic measures, several studies have demonstrated a delayed plastic response to tDCS protocols in certain populations (Kuo et al., 2013; Fujiyama et al., 2014; Puri et al., 2015). Although this delay was not present in this group's recent quantitative review (largest response occurs immediately following tDCS cessation (Horvath et al., 2015a)), it is possible that any tDCS impact on smRT might require a longer post-stimulation duration than that utilized here. To explore this, future studies should consider testing at longer delays than those used here.

Another factor which may have contributed to our null results is the floor effect. More specifically, as we utilized a relatively simple task with short ISIs, it's possible our participants were already performing at their 'most efficient' level. However, it is worth noting that, using a similar paradigm as performed here, a number of studies have demonstrated the ability of several different drug and/or device classes to accelerate smRT between 6–26% compared to baseline levels (Pascual-Leone et al., 1992b; Farre et al., 1993; Rogers et al., 2013), a pattern we did not find. Beyond the floor effect, it's equally plausible tDCS could serve to inhibit (rather than enhance) smRT. Again, a number of studies have demonstrated the ability of several different drug and/or device classes to inhibit smRT between 9–30% compared to baseline (Hindmarch and Tiplady, 1994; Huang et al., 2005; Tzambazis and Stough, 2000). Accordingly, even with a floor effect, we should have been able to measure any tDCS induced *slowing* of smRT. In the current study, we found no evidence of tDCS induced slowing of response time.

Two additional factors which may have contributed to our null results concern inter-individual tDCS response variability and sample size. With regards to variability, several studies have recently demonstrated that neurophysiologic response to tDCS (as

measured utilizing TMS engendered MEPs) is highly variable between individuals (Wiethoff et al., 2014; Lopez-Alonso et al., 2014; Chew et al., 2015; Horvath et al., 2016). As such, it is possible that individual effects of tDCS were masked within group data. Interestingly, all but one (Horvath et al., 2016) of the above noted papers only explored individual response patterns to *anodal* stimulation with no accompanying control condition. In the absence of a proper sham/control condition, it is impossible to determine if the individual response patterns reported truly represent response to stimulation, or are merely artifacts reflective of typical neuronal fluctuation. It is for this same reason our data is unable to address this question – more specifically, as we utilized a between subject design (as opposed to within), we are unable to identify reliable differences in individual response patterns. Accordingly, it would be important for future researchers to utilize a proper sham-controlled, within subjects design to properly address this question. With regards to sample size, it is possible that our group sizes were too small to detect an effect of stimulation. Interestingly, of the 5 previously published papers to find a significant effect of tDCS on smRT (see above), the average sample size is 18.66 (range between 14 and 25). This value falls below the 30 per group included in our pooled analysis and 40 per group included in our expanded CO analysis. While it might be informative for future researchers to include additional participants to determine whether tDCS effects can be observed with a larger sample size, it will be important for any such studies to clearly discuss the degree of individual variability and the size of group effects observed as this technology is, ultimately, being developed for use by individuals with an expectation that group level findings will hold at the level of the individual.

A final factor to consider with regards to this study concerns the miss-rate patterns displayed by each group within this study (block averages ranging between ~1% to ~7%). Although fatigue almost certainly played a roll in miss-rate values during the course of the study, analyses suggest that this impact was similarly distributed across conditions. However, the miss-rate variance demonstrated within each block suggests large *inter-subject* miss-rate variability. In other words, our data suggest that different individuals demonstrated different miss-rate frequencies. We believe this occurred due to the presentation length of our RT stimuli. More specifically, our visual RT cue (100 ms) was generally shorter than the average duration of a human blink (100–400 ms: (Schiffman, 2001)). It is possible that variations in individual blink-rate and blink-duration led to variations in individual miss-rates frequency. It would be worth undertaking a similar protocol utilizing a longer stimulus presentation duration in order to determine if this is, indeed, the case.

In conclusion, we were unable to find a significant effect of tDCS on any measure of smRT despite exploring a variety of stimulation protocols. As smRT is a relatively lower-level and well explored motor behavior, this finding raises questions as to the mechanistic explanations for how M1 tDCS potentially modulates higher-order motor behaviors. In addition, this finding raise interesting questions regarding the source/s behind the homogenous behavioral tDCS literature. The inclusion of an smRT task and the utilization of varied tDCS parameters as performed here will help future research clarify the true effects of tDCS and aid in the elucidation of a more accurate set of mechanisms of action.

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Appendix A. Supplementary material

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