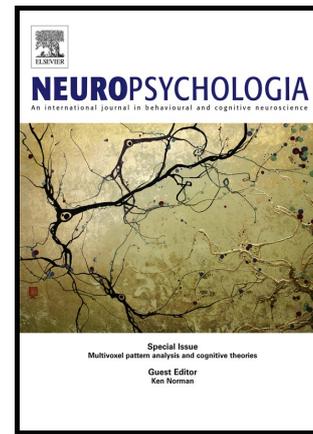


Author's Accepted Manuscript

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PII: S0028-3932(18)30123-4
DOI: <https://doi.org/10.1016/j.neuropsychologia.2018.03.030>
Reference: NSY6733

To appear in: *Neuropsychologia*

Received date: 10 September 2017
Revised date: 21 February 2018
Accepted date: 22 March 2018

Cite this article as: Beth L Parkin, Mayank Bhandari, James C. Glen and Vincent Walsh, THE PHYSIOLOGICAL EFFECTS OF TRANSCRANIAL ELECTRICAL STIMULATION DO NOT APPLY TO PARAMETERS COMMONLY USED IN STUDIES OF COGNITIVE NEUROMODULATION, *Neuropsychologia*, <https://doi.org/10.1016/j.neuropsychologia.2018.03.030>

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**THE PHYSIOLOGICAL EFFECTS OF TRANSCRANIAL ELECTRICAL STIMULATION DO NOT
APPLY TO PARAMETERS COMMONLY USED IN STUDIES OF COGNITIVE
NEUROMODULATION**

Beth L Parkin^{1,2}, Mayank Bhandari¹, James C. Glen¹, & Vincent Walsh¹

¹Institute of Cognitive Neuroscience, University College London.

²Department of Psychology, Univeristy of Westminster

Corresponding author: Beth L Parkin

Department of Psychology, 115 New Cavendish Street, London, W1W 6UW.
Parkinb@Westminster.ac.uk

Keywords: TMS, tDCS, tRNS, MEP, Cognition.

Abstract

Transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS) have been claimed to produce many remarkable enhancements in perception, cognition, learning and numerous clinical conditions. The physiological basis of the claims for tDCS rests on the finding that 1mA of unilateral anodal stimulation increases cortical excitation and 1mA of cathodal produces inhibition. Here we show that these classic excitatory and inhibitory effects do not hold for the bilateral stimulation or 2mA intensity conditions favoured in cognitive enhancement experiments. This is important because many, including some of the most salient claims are based on experiments using 2mA bilateral stimulation. The claims for tRNS are also

based on unilateral stimulation. Here we show that, again the classic excitatory effects of unilateral tRNS do not extend to the bilateral stimulation preferred in enhancement experiments. Further, we show that the effects of unilateral tRNS do not hold when one merely doubles the stimulation duration. We are forced to two conclusions: (i) that even if all the data on TES enhancements are true, the physiological explanations on which the claims are based are at best not established but at worst false, and (ii) that we cannot explain, scientifically at least, how so many experiments can have obtained data consistent with physiological effects that may not exist.

INTRODUCTION

There are now many reports of transcranial electrical stimulation (tES) having positive effects on perception, cognition, learning, performance and a range of clinical conditions. One of the methods through which these claims are made is transcranial direct current stimulation. A cornerstone of our understanding of the effects of tDCS on the human cortex is that it induces polarity dependent shifts in cortical excitability, with anodal stimulation exerting an excitatory effect and cathodal stimulation an inhibitory effect in the area underlying the electrodes (Nitsche & Paulus, 2001; Nitsche et al., 2003). The physiological basis of these effects has been widely explored through the study of motor cortex plasticity (for a summary see Stagg & Nitsche, 2011). The classical studies of Nitsche & Paulus (2001) and Nitsche et al (2003), which originally demonstrated anodal excitation and cathodal inhibition, examined modulation of the amplitude of motor evoked potentials (MEPs) induced by single pulse TMS. MEPs are a global parameter of corticospinal excitability and changes in their amplitude are thought to reflect a sub-threshold depolarization (anodal) or hyperpolarization (cathodal) of resting membrane potentials (Tergau & Paulus, 2008). At a conceptual level, these changes make it more (anodal) or less (cathodal) likely that stimulation of a neuron will produce an action potential (Bestmann, de Berker, & Bonaiuto, 2015). The work that provided the groundwork of the anodal excitatory and cathodal inhibitory model of tDCS has applied DC stimulation using precise and consistent parameters. In particular, as studies aim to investigate anodal and cathodal effects in isolation, a unilateral electrode

array is almost always applied. This is where the 'active' electrode, the one that is the focus of study, is placed over the primary motor cortex (M1). The alternate 'reference' electrode is placed over the contralateral orbit, a region conceptualized as a dead spot unimportant to inducing effects (Parkin et al., 2015). Another common reference position is away from the head (e.g. the upper arm). In addition to this, almost all of this work has delivered tDCS at an intensity of 1mA. There is a much more limited understanding of the physiological effects of tDCS outside of these stimulation parameters (Lindenberg, Sieg, Meinzer, Nachtigall, & Flöel, 2016).

In line with the capacity to modulate neuronal excitability, tDCS has been widely applied to modify human brain function in both healthy controls (Jacobson, Koslowsky, & Lavidor, 2012) and clinical populations (Flöel, 2014). These studies use the anodal excitation cathodal inhibition model of tDCS to guide the mechanistic rationale for application and to explain findings. The majority of studies within the field, however, have applied tDCS using parameters that differ from those used to induce the classical effects of anodal excitation and cathodal inhibition, yet have assumed these effects remain (e.g. Boggio et al., 2010; Chi, Fregni, & Snyder, 2010; Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010; Hecht, Walsh, & Lavidor, 2010).

Similarly, the cognitive and clinical effects of transcranial random noise stimulation (tRNS) are often assumed to be a simple reflection of MEP effects in unilateral conditions. tRNS applies alternating current (AC), at random frequencies, via electrodes placed on the scalp. The amplitude and frequency of oscillations are generated at random, within a range set by the experimenter. Frequencies from a spectrum of 0.1-640 Hz can be selected, with narrower bands within this range routinely applied, namely 0.1-100Hz for low frequency tRNS (lf-tRNS), or 100-640 for high frequency tRNS (hf-tRNS) (Moreno-Duarte et al., 2014). Using standard stimulation parameters (electrode position, intensity and duration) imported from the direct current literature, hf- tRNS has been shown to increase corticospinal excitability (Chaieb, Antal, & Paulus, 2015; Chaieb, Paulus, & Antal, 2011; Inukai et al., 2016; Moliadze, Antal, & Paulus, 2010; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). The classical

study revealing the excitatory effects of hf-tRNS was Terney et al., (2008) who applied hf-tRNS using an M1/contralateral orbit montage for a duration of ten minutes. Here sustained elevations in MEP amplitude lasting up to ninety minutes post stimulation were demonstrated.

In this paper we pose four simple questions that are important to be able to interpret the physiological basis of tES enhancement effects. (1) Do the 1mA unilateral effects of tDCS apply to anode and cathode when the electrode montage stimulates homotopic sites bilaterally? This is important because this array is used frequently in enhancement studies. (2) Do the 1mA effects of unilateral stimulation apply to bilateral, homotopic montages at 2mA? This is important for the same reason as question 1 and because it has already been shown that 2mA unilateral tDCS does not simply have additive effects over 1mA (Batsikadze et al, 2013). (3) Do the excitatory effects of tRNS, observed with unilateral stimulation, hold for bilateral montages as used in many enhancement experiments? (4) Does the effect of unilateral tRNS hold when the duration of stimulation is increased from 10 to 20 minutes? We ask this last question because an assumption in the cognitive literature is that “more is more” and that increasing duration or intensity produces a simple linear increase of effects at lower durations and intensities.

MATERIALS AND METHODS

Participants

Five conditions were tested over two experiments. In Experiment 1a we attempted to replicate the classic, unilateral 1mA tDCS finding in eight subjects (6 female, mean age = 20; age range 18-27). In Experiment 1b we tested whether the 1mA effects extended to bilateral 1mA stimulation in nine subjects (6 female, mean = age 21; age range 18-21). In Experiment 1c we tested whether the anodal/excitation – cathodal/inhibition finding extended to 2mA bilateral tDCS in nine subjects (6 female, mean age = 21; age range 18-21). In Experiment 2a ten subjects were stimulated for 10 minutes with unilateral tRNS and seven subjects were stimulated for 10 minutes with bilateral tRNS (10 female, mean age: 21 age range 19-25). In Experiment 2b eight participants

took part in the unilateral-tRNS 20 minutes condition (4 female; mean age 20; age range 19-23). These data was compared to the unilateral-tRNS 10 minutes condition collected in experiment 2a.

On expressing an interest in participating, subjects were screened to determine their eligibility to take part in brain stimulation research (no history of acute or chronic medical, neurological or psychiatric diseases, not currently taking any medication and no problematic metallic implants). Those with any contraindications were not recruited. All participants were right hand dominant as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971). In accordance with previous work there was a wash out period of at least 3 days during which participants must not have taken part in brain stimulation research for this duration to avoid carry over effects (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). All participants gave written informed consent and were financially compensated at the standard rate for cognitive neuroscience studies (£10 per hour). The study and consent procedures were approved by UCL ethics committee in accordance with the declaration of Helsinki.

Experimental Protocol

Experiment 1: A within subject design was used, participants were randomly assigned to anodal or cathodal stimulation conditions and the order of these sessions was counterbalanced across subjects.

Experiment 2: A between subjects design was used. In experiment 2a the participants were randomized by gender to one of two conditions (unilateral or bilateral tRNS). In experiment 2b unilateral tRNS was performed for 20 minutes and this was compared to the unilateral condition of experiment 2a that delivered stimulation for 10 minutes.

In both experiments, each experimental session followed the same procedure, regardless of condition (**Figure 1**). Following consent procedures, participants were seated in a chair with their hands resting on a pillow. Participants were instructed to keep their arms still but relaxed throughout the experiment. First, the site for TMS assessment was identified using single pulse TMS (the coil

position that produced the largest MEP amplitude in the FDI muscle) and marked with a pen. The optimal coil orientation was identified by drawing a line on the scalp to outline the contour of the coil. These marks were used to ensure consistency in the placement throughout the experiment. In experiments stimulating bilaterally (experiment 1b,1c,& 2a), the motor hotspot was located on both hemispheres to ensure precise electrode placement.

FIGURE 1 ABOUT HERE

Once the site for TMS assessment was located, the TMS intensity was adjusted to elicit MEPs with peak-to-peak amplitudes of approximately 1mV, and baseline MEPs were then recorded. Following this, the placement of the electrodes, intensity and duration was determined according to condition. Immediately after stimulation the electrodes were removed and the participant's scalp briefly cleaned. MEPs were then recorded at five-minute intervals for thirty minutes post stimulation (5, 10, 15, 20, 25, 30 minutes post stimulation). At the end of the experiment the participants were appropriately debriefed and paid for their participation.

Transcranial Electrical Stimulation (tES)

tES was delivered by a battery-driven current stimulator (Neuroconn, Germany) via a standard pair of rubber conductive electrodes (5x7cm, surface area of 35cm² each). The electrodes were attached to the scalp with conductive paste and held in place with two rubber straps.

Experiment 1

In each condition tDCS was applied for 10 minutes, with a 15 second fade in / fade out period. The stimulation parameters employed did not exceed safety limits (Bikson, Datta, & Elwassif, 2009). Two types of electrode montage, unilateral and bilateral, were used across three conditions (**Figure 2**).

Experiment 1a - Unilateral 1mA tDCS

tDCS was applied using a unilateral montage, the active electrode was fixed over left M1, with the centre of the electrode positioned over the site identified for TMS assessment. The reference electrode was placed horizontally over the right contralateral orbit. For unilateral anodal stimulation the anode was placed over left M1 and the cathode over the contralateral orbit. For unilateral cathodal stimulation the cathode was placed over left M1 and the anode over the contralateral orbit. Unilateral stimulation was delivered at 1mA, creating a current density of $0.029\text{mA}/\text{cm}^2$.

Experiment 1b – Bilateral 1mA tDCS

In experiment 1b, tDCS was applied using a bilateral montage where the active electrode was fixed over left M1 and the reference electrode over right M1. In measuring the MEP we used left hemisphere anode to measure excitation and reversed the polarity to use left hemisphere cathode over M1 to measure inhibition. In each case electrodes were centered over the motor hotspot identified by TMS. Stimulation was delivered at 1mA creating a current density of $0.029\text{mA}/\text{cm}^2$.

Experiment 1c- Bilateral 2mA tDCS

tDCS was applied using the same electrode montage as described in experiment 1b, but with an increased current of 2mA to create a current density of $0.057\text{mA}/\text{cm}^2$.

Experiment 2

High frequency tRNS (hf-tRNS) was used with alternating currents randomly selected between 101-640 Hz and an offset of 0. The current intensity was 1mA peak-to peak, with each sample being drawn from a normal distribution with

mean 0 μA , and with 99% of all generated amplitude values lying between $-500 \mu\text{A}$ and $+500 \mu\text{A}$. A 20 second fade in/ fade out period was used. Two different electrode montages were examined in experiment 2a, and an extended duration in experiment 2b (**Figure 2**).

Experiment 2a: Unilateral and bilateral hf-tRNS

hf-tRNS was applied using either a unilateral montage or bilateral montage. In the unilateral montage condition, one electrode was fixed over the left M1, the other was placed horizontally over the right contralateral orbit. For the bilateral montage the electrodes were placed over the left and right M1. M1 electrodes were centered over the motor hotspot. In both conditions stimulation was delivered for a duration of ten minutes.

Experiment 2b: Unilateral 20 minutes hf-tRNS

hf-tRNS was applied using a unilateral montage, where the electrodes were fixed over the left M1 (placed over the site located for TMS assessment), and over the right contralateral orbit, stimulation was delivered for 20 minutes.

Measurement of Motor Cortex Excitability

In all experiments, to detect changes in corticospinal excitability, MEPs elicited by single pulse TMS were recorded from the right First Dorsal Interosseous muscle (FDI).

TMS was delivered to the left M1 using a Magstim Rapid 200 Stimulator (Magstim Company, Whitland, Dyfed, Uk) and a 70 mm figure of eight shaped coil. The coil was held tangentially over the scalp positioned laterally at 45° from the midline, such that the current flowed in a posterior-anterior direction in the brain. The optimum stimulus location, marked as the site for TMS assessment, was defined as the region that consistently elicited the largest MEP. This was determined by first identifying the C3 position of the EEG 10-20 grid, and then moving the coil in 0.5 cm steps around the region to locate the motor 'hotspot'. All TMS safety guidelines were adhered to (Rossi, Hallett, Rossini, & Pascual-

Leone, 2009). In the bilateral tDCS conditions the same procedure was also implemented to locate the motor hotspot on the right hemisphere, using the EEG 10-20 C4 position as an initial starting point. This was used to guide placement of the bilateral reference electrode.

Surface electromyography (EMG) was recorded with disposable adhesive disc electrodes (Ag-AgCl) placed in a belly tendon montage on the right hand. To ensure good surface contact and reduce skin resistance, a standard skin preparation procedure of cleaning and abrading was performed at each electrode site. Peak-to-peak MEP amplitude was acquired with a sampling rate of 3kHz via an automatic acquisition system (Brainsight, Rogue Research, Montréal, Québec, Canada). The TMS intensity was adjusted per subject to elicit MEPs with amplitudes of approximately 1mV, the intensity was recorded and then used throughout the testing session. An MEP height of 1mV was used as this is moderate amplitude that allows for possible enhancements or reductions without ceiling or floor effects (Wiethoff, Hamada, & Rothwell, 2014). Fifteen consecutive MEPs were collected as baseline measurements prior to tDCS. Post tDCS, blocks of 10 consecutive MEPs were recorded at each timepoint. Similar paradigms of identifying and measuring MEP amplitude have been used by several experiments in this field (for example by, Batsikadze et al., 2013; Nitsche & Paulus, 2000; Nitsche et al., 2003).

Data Analysis

For evaluation of corticospinal excitability, the peak-to-peak amplitude of MEPs was measured in the 15-50 ms window after the TMS trigger. This was carried out automatically using BrainSight 3.10b software (Brainsight, Rogue Research, Montréal, Québec, Canada). The mean peak-to-peak amplitudes were calculated for each time point per subject. These included the first 10 (post stimulation) or 15 (baseline) consecutive MEPs that were recorded. Trials with more than 15 microvolts background EMG activity for 100ms pre-stimulation were discarded. The mean peak-to-peak amplitudes recorded post stimulation were then normalized to baseline and expressed as the ratio of MEP amplitude

obtained after stimulation compared to the MEP amplitude obtained before stimulation (amplitude after/ amplitude before).

Experiment 1

In order to assess the opposing anodal and cathodal polarity dependent shifts in cortical excitability, repeated measures ANOVAs were undertaken for each experiment (using normalized values), with two within subject factors, polarity (2 levels: anodal, cathodal) and time (6 levels: 5, 10, 15, 20, 25, 30 minutes).

Additionally, in order to determine whether there were significant shifts from baseline, paired t-tests (one-tailed) were undertaken for each stimulation type (using the un-normalized values). One-tailed tests were used throughout the analysis due to the strong prior hypothesis that anodal stimulation results in excitatory and cathodal in inhibitory effects. Bonferroni correction was used throughout where multiple t-tests were undertaken.

Experiment 2

Experiment 2a: In order to assess the influence of electrode montage, the shifts in cortical excitability induced by hf-tRNS with unilateral and bilateral electrode montages were compared. A mixed model ANOVA was undertaken on normalized MEP amplitudes with a between subject factor of montage (2 levels: unilateral, bilateral electrode placement) and a within subject factor of time (6 levels: 5,10,15,20,25,30 minutes). Machley's test of Sphericity was performed and Greenhouse Geisser correction applied where necessary. Additionally, in order to determine whether there were significant shifts from baseline, paired t-tests (one tailed) were undertaken for each stimulation condition (using un- normalized values).

Experiment 2b: In order to assess the influence of stimulation duration, the shifts in cortical excitability induced by hf-tRNS applied for 10 and 20 minutes were compared. A mixed model ANOVA was undertaken on normalized MEP amplitudes. This had a between subject factor of stimulation duration (2 levels: 10 or 20 minutes) and a within factor of time post stimulation (6 levels: 5,10,15,20,25,30 minutes). . In order to determine whether there were

significant shifts from baseline, paired t-tests were undertaken for each stimulation type (using un-normalized values).

RESULTS

Experiment 1a: Unilateral 1mA tDCS

A repeated measures ANOVA revealed a significant effect of polarity ($F_{(1,7)}=17.57$, $p<0.01$), a non significant effect of time ($F_{(5,35)}=1.60$, $p=0.19$), and a non significant interaction of time and polarity ($F_{(5,35)}=0.36$, $p=0.87$). Anodal stimulation induced an increase in MEP amplitude (Mean adjusted to baseline: 1.35) in comparison to unilateral cathodal stimulation (Mean adjusted to baseline: 0.78)

(Figure 3).

FIGURE 3 ABOUT HERE

Paired t-tests comparing baseline (i.e. unadjusted) MEP amplitude values to those post stimulation revealed that, for unilateral anodal stimulation MEP amplitude values were significantly higher than baseline ($t_{(7)}=4.74$ $p<0.01$). This suggests that corticospinal excitability is increased by unilateral anodal stimulation of the M1 which is consistent with previous work. For unilateral cathodal stimulation, MEP amplitude following stimulation was significantly lower than baseline ($t_{(7)}=2.29$, $p=0.05$). These results suggest that, in accordance with previous studies, corticospinal excitability is reduced by unilateral cathodal stimulation of the M1.

Experiment 1b: Bilateral 1mA tDCS

One dataset, which was 3 SD above the mean, was excluded from analysis. Repeated measures ANOVA analysis revealed no significant effect of stimulation polarity ($F_{(1,7)}=0.11$, $p=0.75$), no effect of time ($F_{(5,35)}=1.24$, $p=0.31$), and no significant interaction of stimulation polarity * time ($F_{(5,35)}=1.53$, $p=0.21$) on MEP amplitude. Therefore, the opposing anodal and cathode polarity dependent shifts in MEP amplitude described above were not retained following bilateral stimulation at 1mA (**Figure 4**).

FIGURE 4 ABOUT HERE

Paired t-tests comparing baseline (i.e. unadjusted) MEP amplitude values to those collected post stimulation revealed no significant differences following bilateral anodal or bilateral cathodal stimulation at 1mA. Therefore there were no changes in MEP amplitude as a result of bilateral 1mA tDCS.

Experiment 1c: Bilateral 2mA tDCS

A repeated measures ANOVA revealed no significant effect of stimulation polarity ($F_{(1,8)}=0.17$, $p=0.30$), no effect of time ($F_{(5,40)}=0.61$, $p=0.69$), and no interaction of stimulation polarity and time ($F_{(5,40)}=0.44$, $p=0.81$) on MEP amplitude. The opposing anodal and cathodal polarity dependent shifts in MEP amplitude were therefore not retained when stimulation is applied using bilateral montages at 2mA (**Figure 5**).

FIGURE 5 ABOUT HERE

Paired t-tests comparing baseline (i.e. unadjusted) MEP amplitude values to those collected post stimulation revealed no significant differences following bilateral anodal or bilateral cathodal stimulation at 2mA. Therefore there were no changes in MEP amplitude as a result of bilateral 2mA tDCS

Experiment 2a: Unilateral and bilateral hf-tRNS

The ANOVA analysis revealed a significant effect of electrode montage ($F_{(1,15)}=6.23$, $p<0.05$), no significant effect of timepoint post stimulation ($F_{(5,75)}=0.95$, $p=0.46$), and a non significant interaction of time and polarity ($F_{(5,75)}=0.58$, $p=0.72$) (Figure 6). Unilateral tRNS induced an increase in MEP amplitude (Mean adjusted to baseline: 1.32) in comparison to bilateral tRNS (Mean adjusted to baseline: 0.95).

FIGURE 6 ABOUT HERE

Paired t-tests comparing baseline (i.e. unadjusted) MEP amplitude values to those post stimulation revealed that, for unilateral hf-tRNS MEP amplitude was significantly higher than at baseline ($t_{(9)}=-2.304$, $p<0.05$). These results suggest that, in accordance with previous studies, corticospinal excitability is increased by unilateral hf-tRNS to the M1. For bilateral hf-tRNS, paired t-test revealed that MEP amplitudes did not significantly differ from baseline post stimulation.

Experiment 2b: Unilateral 20 minutes hf-tRNS

The ANOVA analysis revealed a significant effect of stimulation duration ($F_{(1,16)}=5.50$, $p<0.05$), no significant effect of timepoint post stimulation ($F_{(5,80)}=1.20$, $p=0.32$) and a no significant interaction of stimulation duration and time post stimulation ($F_{(5,80)}=0.50$, $p=0.98$) (**Figure 7**). Unilateral tRNS for a duration of 10 minutes induced an increase in MEP amplitude (Mean adjusted to

baseline: 1.32) in comparison to unilateral tRNS for a duration of 20 minutes (Mean adjusted to baseline: 0.90).

FIGURE 7 ABOUT HERE

A paired t-test comparing baseline (i.e. unadjusted) MEP amplitude values to those post stimulation revealed that, following 20 minutes of hf-tRNS, MEP amplitudes did not significantly differ from baseline ($t_{(7)}=1.037$ $p=0.33$). This was not the case for hf-tRNS delivered for 10 minutes, for which the data is presented in experiment 2a.

DISCUSSION

The literature on the cognitive and clinical enhancing effects of tDCS and tRNS are based on the assumption that the effects of using bilateral montages, high intensities and long durations of stimulation are simple extensions of using unilateral stimulation, low intensities and shorter durations (it is a separate curiosity to consider why all areas of cortex would respond to TES the same as the motor cortex independent of state. We already know this not to be the case with TMS for example, see Stewart et al., 2001; Silvanto et al., 2008). Our findings here show this is not the case and raise some deep problems for the literature.

The aim of the first experiment was to examine whether anodal excitatory and cathodal inhibitory effects of tDCS extend to protocols applying stimulation using bilateral electrode montages at intensities of 1 and 2mA. Experiment 1a replicated the parameters used in classical studies of motor physiology (eg. Batsikadze et al., 2013; Moliadze et al., 2010; Nitsche & Paulus, 2001; Nitsche et al., 2003; Stagg & Nitsche, 2011) on which our knowledge of the effects of tDCS is based, and stimulation was delivered using a unilateral electrode array (M1/ contralateral orbit) at 1mA intensity. The results showed that unilateral anodal and unilateral cathodal stimulation induced polarity dependent shifts in corticospinal excitability these were significantly different both from one another,

and from baseline. The results of experiment 1b and 1c showed that when departing from this typical unilateral arrangement, these polarity dependent shifts in cortical excitability were not induced. In particular, anodal and cathodal stimulation delivered via bilateral electrode montages (left and right M1) at 1mA (experiment 1b) and at 2mA (experiment 1c) did not induce significantly opposing effects on MEP amplitudes, nor did these protocols induce changes to the MEP amplitude in comparison to baseline values.

The bilateral stimulation parameters were chosen for investigation due to their use in an increasing number of cognitive, behavioral and clinical studies. These studies have based their understanding of the effects of tDCS on work using unilateral electrode positioning, assuming that the effects are consistent despite different stimulation parameters. The findings from the current study do not support this premise and raise concerns over the assumptions of polarity dependent shifts in excitation and inhibition underlying studies that stimulate homotopically at 1mA or 2mA (e.g. Boggio et al., 2010; Chi, Fregni, & Snyder, 2010; Cohen Kadosh, Soskic, Luculano, Kanai, & Walsh, 2010; Hecht, Walsh, & Lavidor, 2010; see also Horvath et al., 2015). What is interesting to us is how many of these findings have been explained in terms of anodal excitation and cathodal inhibition without any evidence of physiological evidence underpinning this explanation. Our finding shows that this physiological underpinning, although assumed, does not exist.

Other indications in the literature point to similar conclusions. The foundational work of Nitsche and Paulus. Nitsche & Paulus (2000) explored five different electrode arrays when assessing the rapid induced effect of weak DC stimulation (stimulation applied for 4 seconds at 1mA). It was only the unilateral M1/ contralateral orbit arrangement that produced significant excitability changes, while the four other electrode placements including bilateral motor cortex stimulation yielded no effects. Despite this, the convenient assumption of anodal excitation and cathodal inhibition pervades the literature.

There have also been two previous studies that have similarly examined the aftereffects of bilateral tDCS of motor cortex corticospinal excitability. Mordillo-

Mateos et al., (2012), reported bilateral anodal stimulation at 2 mA to cause an initial increase in MEP amplitude, and bilateral cathodal to cause an initial decrease in MEP amplitude, but these effects were not sustained for the second time point taken at 20 minutes and they also reported the effects of bilateral electrode montages to be less robust in comparison to the unilateral stimulation condition. It is difficult to make direct comparisons due to differences in the stimulation protocol used, for example Mordillo-Mateos et al., (2012) stimulated for 5 minutes, while in the current study stimulation was applied for 10 minutes (a duration closer to those used in cognitive enhancement studies). Comparing the current study to Mordillo-Mateos et al., (2012), it may be that stimulation duration interacts with montage and intensity, making assumptions of transferability between studies even less reliable. An additional study by Kidgell, Goodwill, Frazer, & Daly, (2013) examined the after-effects of bilateral tDCS delivered at 1mA with current densities of 0.04 mA/cm² (stimulation was applied with smaller electrodes than in the current study). Stimulation was delivered for 13 minutes. The study reported excitatory effects of anodal stimulation and inhibitory effects of cathodal stimulation on MEP amplitude, findings which differ from the current study. We used current densities of 0.029 mA/cm² (1mA experiment 1b) and 0.057 mA/cm² (2mA experiment 2a). Taking these two studies along with ours and those of Batsikadze et al, (2013) and Wiethoff, Hamada, & Rothwell (2014), we conclude that any change in stimulation parameters simply weakens the assumptions one can make about physiological effects. The picture increases in complexity when one considers the work of Sehm, Kipping, Schäfer, Villringer, & Ragert, (2013) and Lindenberg et al., (2016) who both found important differences between unilateral and bilateral tDCS.

There are a number of reasons that have been proposed to account for why bilateral electrode arrays may produce differing after-effects than unilateral montages. These include differences in, the amount of current reaching the cortex, the position (location and depth) of current flow (Faria, Hallett, & Miranda, 2011), and the possibility of interhemispheric interactions from concurrent stimulation of monosynaptically connected brain regions (Kimura, 1967). Recent computational studies have noted inter-electrode distance as an

important factor in determining efficacy of DC stimulation (Faria, Hallett, & Miranda, 2011). Due to the increased conductivity of the scalp and cerebral spinal fluid relative to the skull and brain, a large portion of the applied current has been calculated to flow through these tissues rather than reaching the brain. Studies have calculated that electrodes which are further apart on the scalp are optimal, with 60% of current calculated to reach the brain when the electrodes are more than 20cm apart, as compared to 35% when electrodes are at a distance of 8cm (Faria et al., 2011). For unilateral montages there are larger inter-electrode distances compared to bilateral arrangements, thus with unilateral arrangements the amount of current entering the brain relative to that shunted across the scalp maybe higher. The absence of significant modulations in cortical excitability from bilateral montages may simply arise from less stimulation reaching the cortex. Given all these differences, the uniformity of behavioural results with different electrode montages and intensities is puzzling.

There are fewer enhancement claims based on Random Noise Stimulation (tRNS) than tDCS, but our results extend the cautionary note to this method. The findings from experiment 2a reveal that electrode montage influences the effects of hf-tRNS. In particular, the effects of hf-tRNS delivered via a unilateral montage were shown to significantly differ from those induced via bilateral montage (at time points 5, 15, 25, 30 minutes post stimulation). Using parameters similar to those which have established the physiological effects of tRNS, namely unilateral montages for 10 minutes, a replication of increased corticospinal excitability (as evidenced by elevations in MEP amplitude in comparison to baseline) were observed (Chaieb et al., 2011; Inukai et al., 2016; Moliadze et al., 2010; Terney et al., 2008). In these studies the excitatory after-effects were observed using an active electrode (over M1) of 4x4cm and reference electrode of 6x14cm. Computational modeling (Faria, Hallett, & Miranda, 2012) and experimental work (Bastani & Jaberzadeh, 2013) suggest smaller electrodes produce more focal, effective and localized neuronal modulation than larger ones. In the current study both electrodes were sized 5x7 (35 cm²) to replicate conditions in studies of cognitive neuromodulation (e.g. Cappelletti et al., 2013; Chawke & Kanai, 2015; Palm, Hasan, Keeser, Falkai, & Padberg, 2013; Popescu et al., 2016).

When stimulation was delivered via bilateral electrode montages (for durations of 10 minutes) there were no significant elevations in MEP amplitudes in comparison to baseline, for the majority of time points post stimulation. There are now two alternate electrode montages explored in the tRNS literature. One is the conventional M1/contralateral orbit montage, and the other is M1/contralateral upper arm, which has additionally been shown to not be effective at inducing increases in corticospinal excitation (Moliadze et al., 2010). Experiment 2b examined the influence of increased stimulation duration on the effects of hf-tRNS. The findings demonstrate duration of stimulation to influence the after-effects of hf-tRNS, in particular hf-tRNS delivered for 10 minutes produced significantly elevated corticospinal excitability in comparison to that delivered for 20 minutes at all time points post stimulation. Moreover there were no significant changes in MEP amplitude following 20 minutes of tRNS, in comparison to baseline, at any timepoint post stimulation. Therefore the classical effects of increased corticospinal excitation were not observed using stimulation with a duration of 20 minutes.

Previous work has shown that durations of five minutes of hf-tRNS stimulation are necessary to induce elevations in corticospinal excitability. Stimulation for 5 minutes induced a significant increase in MEP amplitude at one time point – 10 minutes post stimulation only (Chaieb et al., 2011). With 10 minutes of hf-tRNS these after-effects are much more robust (Terney et al., 2008). The results of the current study show that at longer durations of 20 minutes, this linear relationship of duration of stimulation and magnitude of after effects breaks down and hf-tRNS become less effective at increasing cortical excitability. As tRNS is a less-often used technique its mechanism of action has not been extensively explored (see possible mechanisms outlined in Antal & Herrmann, 2016), the results of the current study suggest however that this mechanism is time dependent. The reason for the reduction in MEP amplitude at longer durations is not clear, although with other neuromodulatory techniques, namely anodal tDCS (unpublished data discussed in Paulus, Antal & Nitsche, 2013) and TBS TMS (Gamboa, Antal, Moliadze, & Paulus, 2010), longer stimulation durations have been reported to change the induced effects on cortical excitability from excitation to inhibition. These findings indicate that there are neuronal inhibitory mechanisms that have a delayed onset when

exposed to excitatory protocols, and similar mechanisms may be at play with tRNS.

In conclusion, we have shown that across two methods - tDCS and tRNS – one cannot make the assumption that the classic, replicable effects of 1mA, unilateral stimulation are informative about stimulation when the montage, intensity or duration of stimulation are changed. Consequently, we suggest that the absence of a physiological reality underpinning many claims of enhancements now being commercialised in education remediation, clinical conditions, cognitive enhancements, decision making and sport is, at the very least, puzzling.

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FIGURE CAPTIONS

Figure 1: The experimental procedure: The motor hotspot was identified and TMS threshold intensity was adjusted per subject to give a peak-to-peak amplitude of approx 1mA. 15 baseline MEPs of the right FDI muscle were recorded. tES was applied, the parameters used were determined according to experimental condition. Post stimulation MEPs were recorded to determine changes in corticospinal excitability, 10 measurements were taken at 5-minute intervals for half an hour.

Figure 2: The stimulation parameters used in each experiment. Grey = Anode; Dashed line = Cathode.

Figure 3: Results for Experiment 1a- Unilateral 1mA tDCS: Time course of normalised MEP amplitude following 10 minutes of unilateral anodal (anode left M1/ cathode right contralateral orbit; grey line) and unilateral cathodal stimulation (cathode left M1/ anode right contralateral orbit; black dashed line) at 1mA intensity. Unilateral anodal stimulation induced elevations in the MEP amplitude in comparison to unilateral cathodal stimulation. . There were also significant shifts in comparison to baseline for unilateral anodal unilateral cathodal stimulation . * denotes significant differences of MEP amplitudes between unilateral anodal compared to unilateral cathodal . .

Figure 4: Results for Experiment 1b - Bilateral 1mA tDCS: Time course of normalized MEP amplitudes following 10 minutes of 1mA bilateral anodal (anode left M1/ cathode right M1; grey line) and bilateral cathodal stimulation (cathode left M1/ anode right M1; black dashed line). There was no significant effect of stimulation polarity on MEP amplitude, indicating that the opposing anodal and cathode polarity dependent shifts in corticospinal excitability were not retained. Error bars represent SEM.

Figure 5: Results for Experiment 1b- Bilateral 2mA tDCS: Time course of normalized MEP amplitude following 10 minutes of 2mA bilateral anodal (anode left M1/ cathode right M1; grey line) and bilateral-cathodal stimulation (cathode left M1/ anode right M1; black dashed line). There were no significant effects of stimulation polarity on MEP amplitude. Indicating that the opposing anodal and cathode polarity dependent shifts in corticospinal excitability were not retained following bilateral stimulation at 2mA. Error bars represent SEM.

Figure 6: Results for Experiment 2a Unilateral and bilateral hf-tRNS:

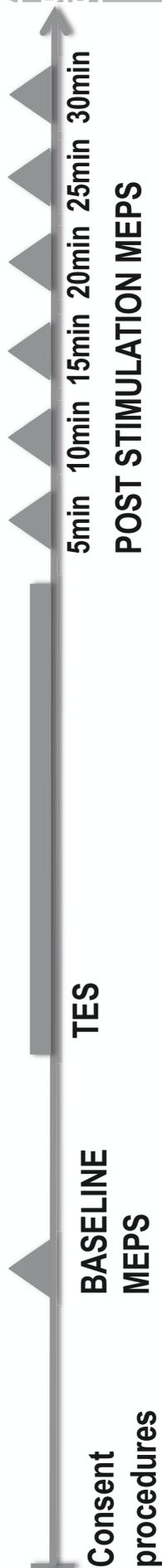
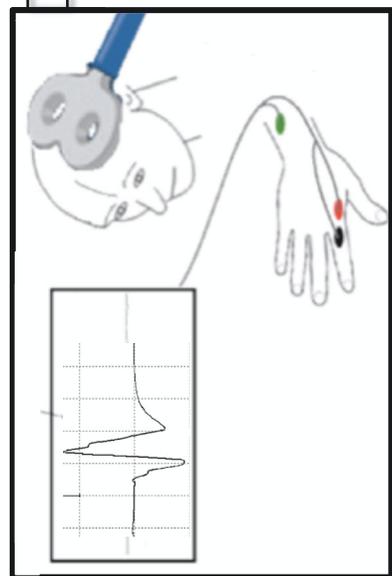
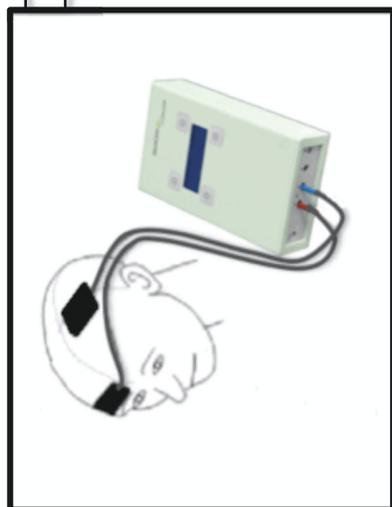
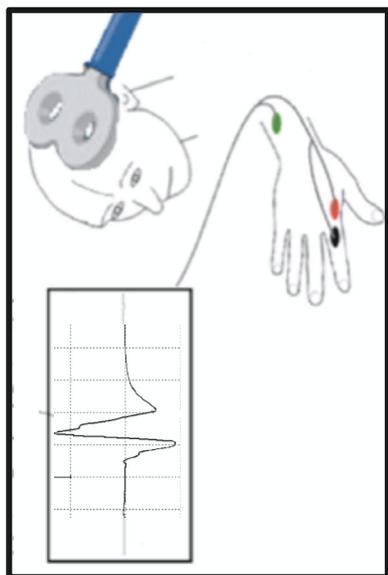
Time course of normalised MEP amplitude following 10 minutes of hf-tRNS applied with unilateral (left M1/ right contralateral orbit montage; black line) and bilateral (left M1/ right M1; grey line) electrode montages. Electrode montage had a significant effect on normalised MEP amplitude. * denotes significant differences between the after effects of unilateral and bilateral electrode montages. MEPs amplitudes post stimulation were significantly larger relative to baseline for unilateral montages, which was not the case for bilateral montages.

Figure 7: Results for Experiment 2b: Unilateral 10 and 20 minutes hf-tRNS:

Time course of normalised MEP amplitude following 10 (black line) and 20 minutes (grey dashed line) of hf-tRNS applied with a unilateral montage (left M1/ right contralateral orbit montage). Stimulation duration had a significant effect on normalised MEP amplitudes and 10 minutes of tRNS induced elevations in the MEP amplitude in comparison to 20 minutes of tRNS at all time points post stimulation. *Denotes a significant difference between the after effects of 10 and 20 minutes of hf-tRNS. Hf-tRNS delivered for 20 minutes did not induce significant shifts in MEP amplitudes relative to baseline.

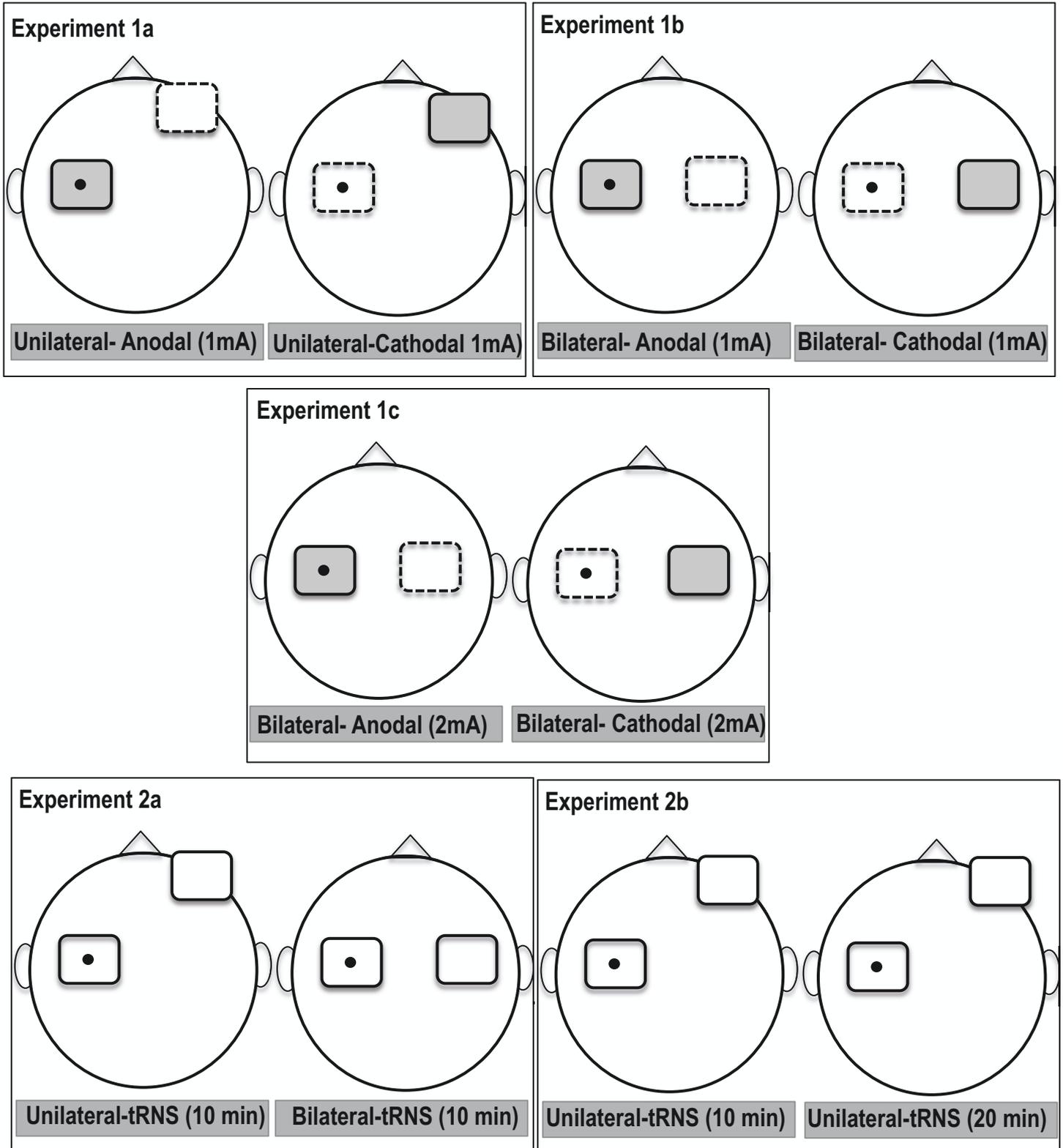
Highlights:

1. We assessed the influence of bilateral electrode placement of 1 and 2mA tDCS on motor evoked potentials.
2. The results show that the assumed physiological effects of anodal/excitation and cathodal/inhibition were not retained using bilateral montages.
3. We also found that the classic excitatory effects of unilateral tRNS do not extend to the bilateral electrode placement.
4. Further, we show that the effects of unilateral tRNS do not hold when one merely doubles the stimulation duration.
5. These stimulation protocols are common practice in studies of cognitive neuroenhancement and therefore findings are important in questioning previously held assumptions.



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● Site of TMS Assessment

