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Unihemispheric concurrent dual-site cathodal transcranial direct current stimulation: the effects on corticospinal excitability

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Abstract

We aimed to assess the effects of concurrent cathodal transcranial direct current stimulation (c-tDCS) of two targets in a hemisphere, termed unihemispheric concurrent dual-site cathodal tDCS (c-tDCS_{UHCDS}), on the size of M1 corticospinal excitability and its lasting effect. Secondary aims were to identify the mechanisms behind the efficacy of c-tDCS_{UHCDS} and to evaluate the side effects of this new technique. Twelve healthy volunteers received 20 min c-tDCS under five conditions in a random order: M1 c-tDCS, c-tDCS_{UHCDS} of M1-dorsolateral prefrontal cortex (DLPFC), M1–primary sensory cortex (S1), M1– primary visual cortex (V1), and sham. The M1 corticospinal excitability of the first dorsal interossei muscle was assessed before, immediately after, 30 min, 60 min, and 24 hours after the interventions. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were also assessed, using paired-pulse paradigm. Compared to conventional M1 c-tDCS, CSE significantly increased following c-tDCS_{UHCDS} of M1-DLPFC and M1-V1 for up to 24 hours ($P = 0.001$). Significant increases in ICF were observed following c-tDCS_{UHCDS} of M1-DLPFC ($P = 0.005$) and M1-V1 ($P = 0.002$). Compared to baseline values, ICF and SICI significantly increased at T_{60} ($P < 0.001$) and T_{24h} ($P < 0.001$) following the concurrent c-tDCS of M1 and V1. Sham c-tDCS_{UHCDS} did not induce any significant alteration. The corticospinal excitability increase mainly accompanied with ICF increase, which indirectly indicates the activity of glutamergic mechanisms. The findings may help us to understand the brain function and develop future motor learning studies. No significant excitability change induced by sham c-tDCS_{UHCDS} which suggests that there is no placebo effect associated with this new tDCS technique.

Key words: Unihemispheric dual-site cathodal transcranial direct current stimulation, functional connectivity, Primary motor cortex, corticospinal excitability, Lasting effect

1. Introduction

Cathodal transcranial direct current stimulation (c-tDCS) has been known as a neuromodulatory technique for reduction of corticospinal excitability (Nitsche and Paulus, 2000, Mendonca et al., 2011). Literature indicates, 10 min c-tDCS induces reversible hyperpolarization of neurons in the target area, for up to 60 minutes (Nitsche and Paulus, 2000, 2001). This technique has been applied for different therapeutic purposes in neurological or psychological conditions such as neurological pain (Mendonca, et al., 2011, O'Connell et al., 2011, Riberto et al., 2011, Ngernyam et al., 2015), migraine (Antal et al., 2008, Antal et al., 2011, Dasilva et al., 2012), stroke (Hummel et al., 2005, Boggio et al., 2007, Schlaug et al., 2008), depression (Fregni et al., 2006a, Boggio et al., 2008), and focal epilepsy (Fregni et al., 2006b, Liebetanz et al., 2006).

Conventionally, 1 mA c-tDCS of primary motor cortex (M1) with duration of up to 13 min reduces corticospinal excitability for up to one hour (Nitsche and Paulus, 2000, 2001, Schretlen et al., 2014). Many studies have attempted to optimize this polarity driven effect in terms of both size and its lasting. A number of studies showed that, higher-intensity or longer stimulation durations enhance the inhibitory effects of c-tDCS (Apkarian et al., 2005, Ahumada et al., 2013, Accornero et al., 2014). However, new evidence suggests that depending on the c-tDCS parameters such as current intensity, duration of application, c-tDCS can reduce or enhance corticospinal excitability (Boros et al., 2008, Monte-Silva et al., 2010, Batsikadze et al., 2013, Vaseghi et al., 2015b). In contrary to an implicit assumption that more intensive protocol may enhance the efficacy of the stimulation, Batsikadze et al. (2013) indicated that stimulation parameters have a non-linear effect on corticospinal excitability modulation. They found that 20 min c-tDCS with intensity of 1 mA resulted in a significant decrease in corticospinal excitability, whereas 2 mA c-tDCS, with the same duration, increased the corticospinal excitability (Batsikadze, et al., 2013).

Despite some promising results from above studies, more investigations are needed to optimize c-tDCS effects. An alternative way, which may optimize the effect of c-tDCS on corticospinal excitability modulation, is concurrent stimulation of M1 and one of its functionally connected sites in the same hemisphere. The functional connectivity of M1 and dorsolateral prefrontal cortex (DLPFC), primary sensory cortex (S1), and premotor cortex has been evidenced by some imaging studies (Lang et al., 2005, Kwon et al., 2008, Keeser et al., 2011). In addition, the co-activation of M1 and S1 (Ghai et al., 2000, Vaseghi, et al., 2015b)

and DLPFC (Bikson et al., 2004, Ragert et al., 2008) in planning, execution, and control of movement has been well established. This co-activation also exists during pain processing (Peyron et al., 2000, Apkarian, et al., 2005). The rationale behind the superiority of this novel technique, unihemispheric concurrent dual-site c-tDCS (c-tDCS_{UHCDS}), is based upon Hebbian principle of synaptic plasticity and manipulation of functional connectivities in a network (Rizzo et al., 2009, Koch et al., 2013). Based on the Hebbian principle, if two connected neurons (or two sites of a network) are activated simultaneously the connection strengthens and the connected neurons will be strongly activated together in the future with same stimulus intensity (Arai et al., 2011, Koch, et al., 2013). The Hebbian form of plasticity is dependent of coincident activity (Feldman, 2009, Guzman-Karlsson et al., 2014). Long-term potentiation (LTP) and depression (LTD) are two forms of Hebbian plasticity characterized by modification in neuronal excitability and consequently spontaneous firing rate (Nelson and Turrigiano, 2008, Feldman, 2009, Guzman-Karlsson, et al., 2014). TDCS is neuromodulatory technique which is able to modulate the spontaneous firing rate without causing action potential (Stagg and Nitsche, 2011). As a result, theoretically, repeated coincidence of excitatory and/or inhibitory post-synaptic potentials induced by c-tDCS_{UHCDS} can modulate the neuronal excitability more efficiently than conventional c-tDCS. Regarding the direct relationship between the level of excitability-related changes and motor performance (Aihara et al., 2015) and cognition (Ahmed et al., 2012) improvement, current study may provide primitive evidence to optimize c-tDCS effects in motor performance, cognition, or pain management studies.

In the present study, primary sensory cortex (S1) and dorsolateral prefrontal cortex (DLPFC) are chosen as two functionally connected cortical sites of M1. The primary aim was to investigate the effect of c-tDCS_{UHCDS} of M1-DLPFC and M1-S1 on M1 corticospinal excitability and its lasting effects, compared to conventional M1 c-tDCS. We hypothesized that c-tDCS_{UHCDS} of M1-S1 and M1-DLPFC is more efficient than the conventional M1 c-tDCS in corticospinal excitability reduction. Due to the novelty of the proposed approach, and the need for better understanding of mechanisms behind the efficacy of c-tDCS_{UHCDS}, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were also measured. It is hypothesized that corticospinal excitability enhancement in c-tDCS_{UHCDS} of M1-S1 and M1-DLPFC conditions is accompanied with increasing the level of SICI and decreasing the level of ICF. As c-tDCS_{UHCDS} is a new technique, we also aimed to systematically assess its

side effects. We hypothesized that concurrent stimulation of two sites in a same hemisphere is a safe with minimum side effects.

2. Methods

2.1. Study design

The study was conducted as a randomized, sham-controlled, cross-over design study with at least seven days of wash-out. All experimental procedures were approved by the Monash University Human Research Ethics Committee and conformed to the Declaration of Helsinki (1964). The current study is registered as a clinical trial on the Australian New Zealand Clinical Trial (registry number: ACTRN12614000817640, <http://www.anzctr.org.au/>).

2.2. Participants

We recruited 12 healthy volunteers (eight women and four men, all Monash University students) with mean age of 24 ± 2.11 (age range 19-34). The sample size was calculated (with power of 80%) based on the result of a pilot study on six participants. All participants were right-handers as determined by the Edinburgh Handedness Inventory (10-item version, mean laterality quotient = 89 ± 9.3) (Valle et al., 2009). The method and procedure of the study were explained to the participants before they received the written informed consent form. None of the participants reported contraindications to Transcranial magnetic stimulation (TMS) or tDCS, and all were medication-free before and during the study. None declared a history of neurological or psychiatric disease or pain during the three months before the study.

2.3. M1 corticospinal excitability assessment

Participants were comfortably seated in a fully adjustable treatment chair (MagVenture, Denmark) with head and arm rests. Single-pulse TMS of the left M1, using a MagPro $\times 30$ (MagOption) stimulator (MagVenture, Denmark) with a flat 70 mm figure-of-eight coil (max. initial dB/dt 28 KT/s near the coil surface) was applied to record motor-evoked potentials (MEPs) from the right first dorsal interossei (FDI) muscle. The coil was placed over the left M1 with a posterior-anterior orientation and set at angle of 45° to the midline. The area of stimulation with largest MEP responses was defined as the hotspot and marked on the scalp to be used throughout the tests to ensure the consistency of the coil placement. Resting motor threshold (RMT) was defined as the minimal stimulator output needed to elicit five MEPs in

a series of 10 with minimum amplitude of 50-100 μ V in the relaxed FDI muscle (Rossini et al., 1994, Hallett, 1996, Wassermann et al., 2008). Single-pulse MEPs were recorded with the TMS intensity adjusted to elicit $\sim$ 1 mV peak-to-peak amplitude at baseline. Stimulation intensity was kept constant for the post-intervention assessments.

2.4. Intracortical inhibition and facilitation assessment

In order to evaluate the function of intracortical inhibition and facilitation circuits in the M1, paired-pulse TMS was used to measure SICI and ICF (Kujirai et al., 1993). In this method, a subthreshold TMS stimulus is followed by a suprathreshold TMS pulse with an inter-stimulus interval (ISI) of 1-5 msec or 8-15 msec to measure SICI or ICF respectively (Kujirai, et al., 1993). In the present study, subthreshold test stimulus intensity was applied as 80% of RMT ($0.8 \times$ RMT), followed by a suprathreshold test stimulus (Di Pino et al., 2014). The test stimulus intensity was adjusted to achieve a baseline MEP of around 1 mV (Zoghi et al., 2003, Kothari et al., 2014). The ISI was set at 3 msec to measure SICI and 10 msec to measure ICF (Di Pino, et al., 2014, Opie and Semmler, 2014). Five blocks of ISI were designed to deliver both single- and paired-pulse TMS randomly. Each block of ISI contained 20 single-pulse and 40 paired-pulse TMS (20 ISI of 3 and 20 ISI of 10 msec). One of five blocks was randomly selected in each time point of measurement to minimize the bias induced by the order of stimuli. Blocks of MEPs in which the muscle was not relaxed were excluded from the analysis. In order to avoid any profound effect of inter-pulse interval on MEP size, a ten-second interval was applied between Stimulations (Vaseghi et al., 2015a).

2.5. Experimental procedure

Volunteers were comfortably seated in a fully adjustable treatment chair (MagVenture, Denmark) with head and arm rests. After finding the hotspot of M1 FDI by single-pulse TMS, the stimulus intensity was adjusted to elicit single-pulse MEPs with averaged amplitude of 1 mV. 80% of RMT was calculated as the subthreshold test stimulus. In the next stage, 20 single-pulse TMS-induced MEPs, 20 pair-pulsed induced MEPs with ISI of 3 msec, and 20 with ISI of 10 msec were recorded in a random order as a baseline measurement. Then participants received tDCS under each of five different experimental conditions in random order: c-tDCS of M1, c-tDCS_{UHCDS} of M1-S1, c-tDCS_{UHCDS} of M1-DLPFC, c-tDCS_{UHCDS} of M1- primary visual cortex (V1), and sham c-tDCS_{UHCDS}. The experimental sessions were separated by at least seven days to avoid interference or carry-over effects of tDCS, and

completed at the same time of day to avoid diurnal variation (late mornings or early afternoon). Duration of intervention was 20 minutes in both active and sham conditions. All outcome measures were measured before (T_{pre}), immediately after (T_0), 30 minutes (T_{30}), 60 minutes (T_{60}) and 24 hours (T_{24h}) after each intervention (Fig. 1).

<<Please insert Figure 1 here>>

Participants were blinded to the condition of tDCS (sham or active) and the purposes of the study. To control the effect of female hormonal fluctuation on the size of MEPs, the experimental sessions were carried out between the 7th and 21st day of women's menstrual cycles.

2.6.Active and sham transcranial direct current stimulation conditions

A direct current stimulator (Intelect® Advanced Therapy System, Chattanooga, USA) was set to deliver 0.3 mA (Bastani and Jaberzadeh, 2013b) direct current for 20 minutes, with 10 seconds of linear fade in and fade out. Current intensity of 0.3 mA allowed us to considerably decrease the size of electrodes (Uy and Ridding, 2003), while keeping the current density (0.1 mA/cm^2) in a safe range with limited side effects (Nitsche and Paulus, 2000, Kamen, 2004). The superiority of low intensity in induction of larger corticospinal excitability is supported by some a-tDCS studies (Bastani and Jaberzadeh, 2013a, Parazzini et al., 2013). Unfortunately, there is no c-tDCS study in this regard.

C-tDCS was applied through active and reference saline-soaked surface sponge electrodes sized $2 \times 1.5 \text{ cm}$ (3 cm^2) and $2 \times 6 \text{ cm}$ (12 cm^2) respectively (Fig. 1). The small size of active electrodes produces a highly focused DC current over the target areas, which enabled us to stimulate M1 and S1 with two separated cathode electrodes. Based on the result of some computational modeling studies, the effects of tDCS can be focused by smaller electrodes (Boggio et al., 2006, Christie et al., 2007). In addition, recent anodal tDCS studies illustrated that utilizing the smaller active electrodes over M1 resulted in larger corticospinal excitability even when current density is held constant (Christie, et al., 2007, Bastani and Jaberzadeh, 2013b). However, some computational modeling studies indicated that current intensity to electrode size ratio (current density) is the main factor for induction of larger excitability (Miranda et al., 2009, Roth, 2009, Faria et al., 2011).

The reference electrodes (anode) were conventionally positioned over the contralateral

supraorbital region with the assumption of no or negligible neuromodulatory effects on the subgenual cortex. To reduce the neuromodulatory effects of reference electrodes on the subgenual cortex, we kept them four times as large as the active electrodes (i.e., the density was four times less) (Christie, et al., 2007). Considering the narrow shape of reference electrodes, two reference electrodes administered over the contralateral supraorbital region. The electrodes were fixed with two horizontal and perpendicular straps. The density under each active electrode was 0.1 mA/cm^2 in all experimental conditions.

The cathode was placed over the left M1 for the right FDI muscle. The location of M1 was identified by TMS. The international 10-20 system was used to position the active electrode accurately on S1, and DLPFC. For the c-tDCS_{UHCDs} M1-S1 condition, the cathode was placed over C3 and C'3 (2 cm posterior to C3) and for stimulation of DLPFC, the cathode was placed over F3. V1 is not part of the network involved in movement planning or pain processing. Therefore, to investigate whether the changes induced by c-tDCS_{UHCDs} are site specific or simply due to stimulation of the brain by doubled current density, c-tDCS_{UHCDs} of M1-V1 was included as a control condition. In the sham condition, the electrodes were placed in the same positions as for active M1-S1 or M1-DLPFC conditions, but the stimulator was turned off after 30 seconds of stimulation. All pre- and post-intervention evaluations were kept identical to the ones in other conditions. To stimulate V1, the cathode electrode was placed over Oz.

2.7.Measurement of side effects

During and after all experiments, participants were asked to complete a questionnaire to record their feelings and any side effects. The questionnaire contained rating scales for the presence and severity of side effects such as itching, tingling, burning sensations under electrodes and other adverse effects, including headache and pain during and after stimulation (Poreisz et al., 2007). All participants rated the unpleasantness of any scalp sensation using numeric analogue scales (NAS) (e.g., 0 = no tingling to 10 = worst tingling imaginable).

2.8.Data management and statistical analysis

Peak-to-peak amplitude of 20 single-pulse MEPs were automatically calculated and averaged online for each time point of measurement, using a custom designed macro. Area under the curve of MEPs was also quantified off-line from the digitized averages of rectified EMG for

conditioned and unconditioned stimuli in each trial by using a custom designed macro in Powerlab 8/30 software. The size of the conditioned MEP was expressed as a percentage of the unconditioned test MEPs in order to evaluate the effectiveness of ICI or ICF.

To detect any carry-over effect, one-way repeated measures ANOVA was carried out on the RMT recorded at the starting point of each experimental condition (T_{pre}). A two-way repeated measures ANOVA was performed to assess the effects of two independent variables, experimental conditions with 5 levels (c-tDCS, c-tDCS_{UHCDS} of M1-S1, M1-V1, M1-DLPFC, and sham c-tDCS_{UHCDS}) and time with 5 levels (T_{pre} , T_0 , T_{30} , T_{60} , and T_{24h}), on corticospinal excitability, SICI, and ICF as independent variables. Mauchly's test was used to assess the validity of the sphericity assumption for repeated measures ANOVA. Greenhouse-Geisser corrected significance values were used when sphericity was lacking (Meyers et al., 2006). When ANOVA produced significant results, post hoc comparisons were performed using t-tests (paired samples, two-tailed, $P < 0.05$) adjusted for multiple comparisons to compare MEP, SICI, ICF changes following the intervention at each time point of measurement. Additionally, to test whether the baseline value of each stimulation site differed significantly from post-intervention time points (T_0 , T_{30} , T_{60} , and T_{24h}), a one-way repeated measure ANOVA was applied. In case of any significant main effect, post hoc comparisons were performed, adjusted for multiple comparisons.

In order to assess whether participants were successfully blinded to the stimulation conditions (active or sham), Pearson's chi-square was used on rating scales recorded by questionnaire. In addition, a one-way ANOVA was carried out on the mean values of rating scale recorded by questionnaire to assess any significant differences between the participants' feelings during active and sham conditions. Means are reported $\pm$ standard error (SE). Statistical analyses were performed using SPSS software version 22.

3. Results

3.1. Comparison of baseline values

One-way repeated measures ANOVA illustrated that the RMT elicited by single-pulse TMS at the starting point of each experimental condition were comparable and there was no significant difference between the baseline RMTs ($F_4 = 1.94$, $P = 0.17$) in all conditions.

3.2. Corticospinal excitability changes following c-tDCS and c-tDCS_{UHCDS}

Two-way repeated measures ANOVA showed significant main effects of condition ($F_4 = 13.8$; $P < 0.001$), time ($F_4 = 2.11$; $P = 0.04$), and interaction of condition and time ($F_{16} = 3.53$; $P = 0.001$). Pairwise comparisons indicated that at T_0 there was a significant difference between c-tDCS of M1 and c-tDCS_{UHCDS} M1-DLPFC and M1-V1, and also between c-tDCS_{UHCDS} M1-DLPFC and c-tDCS_{UHCDS} of M1-S1 (Table 1). Significant differences were observed between sham and c-tDCS of M1 and c-tDCS_{UHCDS} of M1-DLPFC at T_0 (Table 1). Post-hoc comparison showed no significant differences between c-tDCS of M1 and c-tDCS_{UHCDS} of M1-S1 and M1-V1 at T_0 (Table 1).

<<Please insert Table 1 here>>

Pairwise comparisons at T_{30} revealed significant differences in corticospinal excitability between c-tDCS of M1 and c-tDCS_{UHCDS} of M1-DLPFC, M1-S1, and M1-V1 and between c-tDCS_{UHCDS} of M1-DLPFC and M1-V1 (Table 1). We measured significant differences between sham and c-tDCS of M1 and c-tDCS_{UHCDS} of M1-DLPFC. There was no significant difference between sham and c-tDCS_{UHCDS} of M1-S1 or M1-V1 at T_{30} (Table 1).

At T_{60} , there were significant differences in corticospinal excitability between c-tDCS of M1 and all other conditions (Table 1). At this time point, there were also significant differences between c-tDCS_{UHCDS} of M1-DLPFC and M1-S1, c-tDCS_{UHCDS} of M1-S1 and M1-V1 at T_{60} (Table 1). The results showed significant differences in corticospinal excitability between sham and all other active conditions except c-tDCS_{UHCDS} of M1-S1 (Table 1).

At T_{24h} there was a significant difference between stimulation of M1 and c-tDCS_{UHCDS} of M1-DLPFC and M1-V1 and also between sham and these two c-tDCS_{UHCDS} conditions (Table 1).

Comparing post-intervention MEP amplitudes with baseline values showed that there was a statistically significant difference between time-points of measurements following c-tDCS_{UHCDS} of M1-V1 ($F_4 = 3.59$, $P = 0.01$) and c-tDCS of M1 ($F_4 = 2.50$, $P = 0.002$). The results of post-hoc tests are summarized in Figure 2. Based on these results, M1 c-tDCS significantly reduced MEPs at T_0 , T_{30} , and T_{60} (Fig. 2). Corticospinal excitability of M1 increased immediately after the c-tDCS_{UHCDS} of M1-DLPFC, whilst no significant change

was found at T₃₀, T₆₀, or T_{24h} (Fig. 2A). In addition, c-tDCS_{UHCDS} of M1-S1 resulted in significant immediate reduction in the size of MEPs. However, compared to baseline value, no significant change was found 30 min, 60 min, and 24 hours after c-tDCS_{UHCDS} of M1-S1 (Fig. 2A). C-tDCS_{UHCDS} of M1-V1 showed significant increase with 60 min delay.

<<Please insert Figure 2 here>>

Comparing baseline values and post-test values showed significant increase in the size of MEPs at T_{24h} following c-tDCS_{UHCDS} of M1-V1 (Fig. 2A). There was no significant change in the size of MEPs following sham c-tDCS_{UHCDS} (Fig. 2A).

3.3. SICI changes following c-tDCS_{UHCDS}

Two-way repeated measures ANOVA showed significant effects of condition ($F_4 = 4.43$, $P = 0.004$), time ($F_4 = 2.77$, $P = 0.01$), and interaction of time and condition ($F_{16} = 4.20$, $P = 0.007$) on SICI. No statistically significant differences were found between conditions at T₀ and T₃₀ ($P > 0.005$) (Table 2). Significant differences were found between c-tDCS_{UHCDS} of M1-V1 and c-tDCS_{UHCDS} of M1-DLPFC, M1-S1, and c-tDCS of M1 at T₆₀ and T_{24h} (Table 2). The results also indicated that there were significant differences between sham and c-tDCS_{UHCDS} of M1-V1 at T₆₀ and T_{24h}.

One-way repeated measures ANOVA results showed that there were statistically significant differences in corticospinal excitability between time-points of measurement following c-tDCS_{UHCDS} of M1-V1 ($F_4 = 12.74$, $P = 0.002$) and c-tDCS_{UHCDS} of M1-DLPFC ($F_4 = 4.06$, $P = 0.01$). No significant SICI alteration was found at any time-points of measurements following c-tDCS_{UHCDS} of M1-S1, c-tDCS M1 and sham. The results of post hoc comparisons are summarized in Figure 2B.

<<Please insert Table 2 here>>

3.4. ICF changes following c-tDCS_{UHCDS}

The results of two-way repeated measures ANOVA indicated significant effect of condition ($F_4 = 5.84$, $P = 0.001$) and time ($F_4 = 4.43$, $P = 0.004$). The interaction of time and condition was also significant ($F_{16} = 6.79$, $P < 0.001$). Post hoc comparisons revealed a significant

difference in ICF between c-tDCS of M1 and c-tDCS_{UHCDS} of M1-DLPFC and M1-V1 at T₀ (Table 2). The result also showed that there were significant differences between M1-V1 and M1-S1 and sham conditions at T₀. The results of pairwise comparison at T₃₀ and T₆₀ were similar; there were significant differences between stimulation of M1 and M1-DLPFC, M1 and M1-V1, M1-S1 and M1-V1, and M1-V1 and sham (Table 2). At T_{24h}, the results showed significant differences between c-tDCS_{UHCDS} of M1-V1 and M1-DLPFC, M1-S1, c-tDCS of M1, and sham (Table 2).

Compared to baseline values, one-way repeated measure ANOVA results revealed that there were significant ICF changes after c-tDCS_{UHCDS} of M1-DLPFC ($F_4 = 4.03$, $P = 0.007$), c-tDCS_{UHCDS} of M1-S1 ($F_4 = 2.13$, $P = 0.04$), and c-tDCS_{UHCDS} of M1-V1 ($F_4 = 13.81$, $P < 0.001$). Figure 2C summarizes the post-hoc comparison results.

3.5. Safety and side effects of a-tDCS_{UHCDS}

Participants' experiences were recorded at the beginning, middle and end of the 20 min intervention. The averaged sensation score recorded during the intervention is summarized in Table 3. The only reported sensations related to the cathode were itching and tingling. Redness, itching and tingling under the anode electrodes were the most commonly reported side effects. No participants reported a burning sensation or headache during c-tDCS_{UHCDS} application. No adverse effect related to c-tDCS_{UHCDS} or conventional c-tDCS was detected during the follow-up measurements (Table 3).

<<Please insert Table 3 here>>

The participants' judgment on the stimulation conditions is summarized in Table 4. Pearson's chi square showed no significant differences between the active and sham conditions ($\chi^2(4, n = 12) = 8.12$, $P = 0.09$), demonstrating that participants were not able to determine the type of stimulation. The majority of participants were properly blinded and the active or sham conditions were correctly guessed just in 15 % of conditions (excluding the "Cannot say" responses).

<<Please insert Table 4 here>>

The results of one-way ANOVA indicated that sensations were significantly different across the conditions ($F(4, 47) = 6.37$, $P = 0.03$). The post hoc comparisons only showed significant difference between sham and active c-tDCS_{UHCDS} of M1-S1 stimulation ($P = 0.002$) at the

end stage of stimulation. No significant difference was found between sensation of participants in sham and active conditions under the cathode electrode. Under the reference electrode, there was no significant difference between active and sham conditions.

4. Discussion

4.1. Comparison of baseline values

The similarity of the baseline RMTs in each experimental condition indicates that the washout period was adequate and participants experienced no carry-over effect from one intervention to the next.

4.2. Corticospinal excitability changes following M1 c-tDCS

The results showed that 20 min M1 c-tDCS reduced corticospinal excitability, lasting for 60 min. Likewise, it has been previously shown that 13 min c-tDCS with current intensity of 1 mA reduces M1 corticospinal excitability for one hour (Nitsche and Paulus, 2000, Monte-Silva, et al., 2010, Nitsche and Paulus, 2011). In contrast, in some other studies M1 c-tDCS resulted in opposite effects (Batsikadze, et al., 2013, Leon-Sarmiento et al., 2015). As smaller electrodes induce more focused electrical fields over target areas (Bikson, et al., 2004, Christie, et al., 2007), the discrepancy in the result could be easily explained by methodological differences. The second postulated reason behind the opposite effect is the length of c-tDCS application. Batsikadze et al. (2013) compared the effect of 9 and 20 min c-tDCS with intensity of 1 mA on corticospinal excitability (Batsikadze, et al., 2013), demonstrating that 20 min c-tDCS induces excitatory effects. All these studies indicated a non-linear relationship between current density/electrode size and direction of induced changes in corticospinal excitability modulation.

4.3. Corticospinal excitability changes following c-tDCS_{UHCDS}

Unlike conventional M1 c-tDCS, concurrent stimulation of M1 and DLPFC increased corticospinal excitability immediately after stimulation. The finding does not support our hypothesis in which we assumed that concurrent stimulation of two functionally connected sites decrease the M1 excitability more efficient than conventional M1 c-tDCS. The results also showed significant differences between the inhibitory effect of conventional M1 c-tDCS

and excitatory effects of M1-DLPFC c-tDCS_{UHCDS} at all time-points. Basic pharmacological studies indicate that postsynaptic alpha (2)-adrenergic receptors (alpha (2)-ARs) located in the membrane of DLPFC neurons inhibit control of M1 function (Lowe et al., 2000, Rissman et al., 2004, Egorova et al., 2015, Lee and Grafton, 2015). These receptors mediate the function of voltage-gated calcium channels and decrease the level of free intracellular Ca²⁺ ions (Jefferys, 1981, Ghai, et al., 2000). Therefore, the inhibitory effects of c-tDCS may block or disinhibit the inhibitory effects of DLPFC on M1, which increased corticospinal excitability.

The other possible mechanism is activation of homeostatic mechanisms following the doubling of the electrical charges received by target areas. It has been recently indicated that changing the conventional c-tDCS parameters may modulate the Ca²⁺ channels' activity and excitatory mechanisms resulted in opposite cortical (Batsikadze, et al., 2013) and behavioral responses (Pirulli et al., 2014). In fact, L-Type voltage-gated Ca²⁺ channels (L-VGCC) are involved in homeostatic plasticity (Kong et al., 2006, Mansouri et al., 2009) to avoid destabilizing and overpowering changes in the brain and maintain equilibrium (Zubieta et al., 2005, Benedetti, 2008). Hence, it can be hypothesized that concurrent stimulation enhances the activity of L-VGCC and the level of intracellular Ca²⁺ level, activating homeostatic mechanisms, which lasted at least for 24 hours.

Similar to M1 c-tDCS, c-tDCS_{UHCDS} of M1-S1 resulted in immediate M1 corticospinal excitability reduction, which gradually returned to the baseline value. The finding supports our finding in part. There was no statistical difference between inhibitory effects of M1 stimulation and M1-S1 c-tDCS_{UHCDS}. The integrated signals from S1 are projected to M1 through a cortico-cortical interconnection located in superficial layers of the cortex (Diamond et al., 2008, Petreanu et al., 2012, Xu et al., 2012). These projected neurons recruit a type of fast-spiking inhibitory interneurons named Vasointestinal Peptides (VIPs), which are strongly GABAergic interneurons (Lee et al., 2010, Rudy et al., 2011, Lee et al., 2013). Therefore, it can be hypothesized that disinhibition of VIP leads by concurrent stimulation of M1 and S1 results in retuning of corticospinal excitability to baseline value shortly after the immediate corticospinal excitability diminishing.

C-tDCS_{UHCDS} of M1-V1 produced no immediate changes but after a delay of 60 minutes, we observed significant excitatory changes that lasted for at least 24 hours. Such findings are opposite with our hypothesis in which we assumed that concurrent stimulation of two

functionally connected sites decrease the M1 excitability more efficient than conventional M1 c-tDCS. There were significant differences between inhibitory effects of M1 c-tDCS and excitatory effects of concurrent stimulation of M1 and V1 at all time-points of measurement except T₃₀. There is contradictory evidence about the effects of c-tDCS of the visual cortex on visuomotor tasks. Antal et al. (2004) indicated that c-tDCS of V5, the motion-sensitive cortical area, has a facilitatory effect on visuomotor learning. Due to the controlling effect of the visual cortex in complex motor tasks (Antal et al., 2004), they concluded that c-tDCS of V1 disinhibits the inhibitory effects of c-tDCS on M1. In contrast, in another study conducted by Antal et al. (2004), it was observed that V5 c-tDCS has no effect on visuomotor tasks (Antal, et al., 2004). As inhibitory role of V5 occurs only in the early phase of visuomotor coordination, V5 c-tDCS induces no change in M1 corticospinal excitability. One possible mechanism for the excitatory effects of c-tDCS_{UHCDS} of M1-V1 may be disinhibition of the prominent transluminal inhibitory interneurons, which project from V1 to M1 (Katzel et al., 2011, Sultan et al., 2013). Another alternative mechanism behind the excitatory effects of c-tDCS_{UHCDS} of M1-V1 is activation of a homeostatic mechanism to restore the equilibrium in the brain.

Some animal model research demonstrated that low postsynaptic Ca²⁺ enhancement induces long-term depression and increasing the level of calcium causes LTP (Cho et al., 2001, Lisman, 2001). Therefore, one possible mechanism behind the long-lasting effect of c-tDCS_{UHCDS} of M1-V1 is the increase of intracellular Ca²⁺ level and activation of L-VGCC induced by doubled current density. However, more studies are required to discover why concurrent stimulation of M1 and V1, but not other conditions, resulted in an effect lasting 24 hours.

4.4. Physiological mechanisms behind the effects of c-tDCS on M1 corticospinal excitability

The corticospinal excitability reduction immediately after M1 c-tDCS coincided with immediate SICI reduction and no significant ICF change. However, we observed a tendency toward ICF reduction. Nitsche et al. (2005) applied 7 min c-tDCS with intensity of 1 mA over M1 with intensity of 1 mA and showed immediate corticospinal excitability reduction, which accompanied with more inhibition (Nitsche et al., 2005). In line with the current study, Nitsche and his colleagues indicated that there was no significant ICF alteration after the stimulation (Nitsche, et al., 2005). In contrast, Batsikadze et al. (2013) demonstrated that

conventional M1 c-tDCS with intensity of 2 mA and electrode size of 35 cm² enhanced corticospinal excitability, which coincided with immediate SICI reduction and gradual ICF enhancement lasting for 7–8 hours (Batsikadze, et al., 2013). However, they indicated that stimulation of M1 with intensity of 1 mA suppresses the corticospinal excitability and ICF and increases SICI. Batsikadze et al. concluded that intensive parameters like doubling the intensity of stimulation probably overshoot the ceiling targets to keep the neuronal functions at an optimal steady state.

Regardless of decreasing trends in ICF and SICI, the corticospinal excitability reduction at T₃₀ and T₆₀ was associated with no significant change in SICI and ICF. This result is not accordance with those of previous studies. The reason for these effects is unclear at present, but might be related to different c-tDCS parameters. In addition, it was shown that not only do GABA_A and glutamate-based mechanisms, which were indirectly assessed in the present study, play an important role in the corticospinal excitability level, but involvement of other excitatory and inhibitory neurotransmitters like serotonin and dopamine affect the result (Pascual-Leone et al., 1999, Rossi et al., 2009, Medeiros et al., 2012). However, more pharmacological and methodological studies are needed to shed light on the mechanisms behind the efficacy of c-tDCS of M1 on its corticospinal excitability.

4.5. Physiological mechanisms behind the effects of c-tDCS_{UHCDS} on M1 corticospinal excitability

The immediate corticospinal excitability enhancement following concurrent DLPFC and M1 c-tDCS was associated with immediate SICI reduction and ICF enhancement by which our hypothesis is not supported. Corticospinal excitability returning to baseline value also coincided with the return of SICI and ICF to baseline values. Compared to M1 c-tDCS, there was a significant ICF increase with no SICI alteration following c-tDCS_{UHCDS} of M1-DLPFC. Such results indicate that the excitatory effect of c-tDCS_{UHCDS} of M1-DLPFC is the result of increasing the level of glutamate immediately after the stimulation. Glutamate is released by pyramidal neuron synapses located in layer V of the cortex and thalamic synaptic inputs (Ragert, et al., 2008). These synapses are sensitive to electrical fields (Bikson, et al., 2004, Ragert, et al., 2008, Marquez-Ruiz et al., 2012). As a result, it can be speculated that concurrent stimulation of M1 and DLPFC increase the total charge received by pyramidal cells and activate the homeostatic mechanisms to invert the effect of excessive inhibition

induced by c-tDCS_{UHCDS}. As the level of glutamate has an opposing effect on the level of GABA_A (Ragert, et al., 2008, Kabakov et al., 2012), the enhancement of glutamate mechanisms decreases the level of GABA_A and consequently decreases SICI.

For the c-tDCS_{UHCDS} of M1-S1 condition, the results showed no effect on either SICI or ICF although immediate corticospinal excitability reduction was observed after the stimulation. As a result, the results cannot support our hypothesis in which we assumed that c-tDCS_{UHCDS} is more efficient than conventional M1 c-tDCS in SICI enhancement and ICF reduction. The reason behind this result is unclear, but it seems that other mechanisms (in addition to mediating the level of GABA_A and glutamate) are involved in corticospinal excitability reduction following the concurrent stimulation of M1 and S1 in the same hemisphere. Comparing M1 c-tDCS and c-tDCS_{UHCDS} of M1-S1 revealed no significant difference in SICI and ICF at any time point of measurement other than T_{24h}.

SICI reduction and ICF enhancement peaked 60 min after c-tDCS_{UHCDS} of M1-V1 and lasted at least for 24 hours, consequently enhancing corticospinal excitability. The results do not support the hypothesis. In addition, there were significant differences between ICF changes following concurrent M1 and V1 c-tDCS and the conventional M1 c-tDCS at all time-points of measurement. The finding could be explained by reduction of GABA_A activity and increasing the glutamate level following c-tDCS_{UHCDS} of M1-V1. Regarding the controlling role of V1 on M1 via the visuomotor tract (Antal, et al., 2004), it is possible that V1 c-tDCS blocked/disinhibited the GABA_A receptors and activated the glutamergic mechanisms (Kabakov, et al., 2012). Another possible mechanism is transient homeostatic metaplasticity (Kuo et al., 2007). Overpowering the inhibition induced by c-tDCS_{UHCDS} may activate the LTP mechanisms (Turrigiano and Nelson, 2004, Turrigiano, 2008), which convert the conventional inhibitory effects of c-tDCS to excitatory ones. Activation of LTP mechanisms may cause the long-lasting effects. The prolonged SICI reduction and ICF enhancement following c-tDCS_{UHCDS} of M1-V1 is a valuable finding for future studies investigating new approaches for prolonging the tDCS effect.

The results of sham c-tDCS_{UHCDS} revealed that c-tDCS_{UHCDS} has no placebo effect on corticospinal excitability, SICI, and ICF, and strongly implies all modulations are due to real effects of intervention.

4.6. Safety and side effects of c-tDCS_{UHCDS}

Based on the results, participants were successfully blinded to the experimental conditions. They were not able to distinguish between active or sham conditions (except in ending stage of active M1-S1 c-tDCS_{UHCDS} condition). No significant difference in rating scales was also found under the reference electrodes in sham and active conditions. Similar to M1 c-tDCS, concurrent c-tDCS produced minimal side effects, this new tDCS technique is safe for healthy adults. Itching and tingling were the most frequently reported sensations. Two of 12 participants reported burning and one reported a headache feeling. The reported side effects in this study are comparable with those from conventional single site c-tDCS studies (Kamen, 2004, Miranda, et al., 2009, Turi et al., 2014, Vaseghi, et al., 2015b). Based on these studies, the tDCS-related cutaneous discomfort varies with tDCS parameters, including electrode size and current intensity. In addition, Poreisz et al. (2007) demonstrated that mild tingling and tingling are the most common sensations in healthy adults and there was no significant difference between participants' sensation after stimulation of different cortical targets. (Pascual-Leone, et al., 1999). Small electrodes induce less electro-chemical effect and consequently less inconvenient feelings are received by the sensory cortex (Robertson et al., 2006, Nitsche et al., 2007, Faria, et al., 2011), resulting in less spatial summation and cutaneous discomfort (Wadsworth and Chanmugam, 1983, Robertson, et al., 2006). In addition, Faria and colleagues (2004) illustrated that current intensity but not current density modifies the perceptual threshold for direct currents (Faria, et al., 2011). As a result, it can be assumed that utilizing two small active electrodes in c-tDCS_{UHCDS} is associated with mild cutaneous discomfort, which is comparable with the conventional approach of c-tDCS.

4.7. Limitations

In our study the effect of c-tDCS was only assessed until 24 hours after completion of stimulation, which limits our understanding regarding possible further lasting effects. Corticospinal excitability was evaluated in healthy young adults; older adults or patients with neurological or psychological conditions may respond to c-tDCS_{UHCDS} differently, so the results might not be generalizable to elders or patients. Furthermore, it should be noted that the rater in the current study was not blinded to the experimental conditions which may increase the risk of "experimenter bias" in the current study (Sackett, 1979).

4.8. Suggestions for future studies

Future studies could investigate the impact of c-tDCS_{UHCDS} of M1 on other functionally connected sites of the brain, including the posterior parietal cortex, premotor cortex or supplementary motor area (Ghosh and Porter, 1988, Fink et al., 1997, Munchau et al., 2002, Boros, et al., 2008) on M1 excitability. Such data would help us to better understand the characteristics of c-tDCS_{UHCDS}. The effects of application time, current intensity and electrode size during c-tDCS_{UHCDS} should also be systematically studied to improve our understanding. Pharmacological studies would help to shed light on the mechanisms underlying the efficacy of c-tDCS_{UHCDS} on M1 excitability modulation. To have a better understanding of current flow and penetrated current levels in the s, computational/ fMRI studies are also suggested for the future studies. Moreover, considering the excitatory effects of c-tDCS_{UHCDS} we demonstrated, investigating the efficacy of c-tDCS_{UHCDS} on modulation of pain threshold, working memory, and motor learning is recommended.

5. Conclusion

C-tDCS_{UHCDS} of M1-DLPFC and M1-V1 are new and effective approaches to increasing M1 excitability. As c-tDCS_{UHCDS} is painless, safe and has minimal side effects, it is a promising tool for treatment of conditions in which enhancement of M1 excitability is a therapeutic goal. Modulation of pain and priming of the effects in therapeutic approaches, such as motor training, are potential uses.

Conflict of interest

This manuscript is based on research conducted by Bitá Vaseghi, a PhD candidate at Monash University, Melbourne, Australia. This project had no external funding, and no financial or other relationships pose a conflict of interest.

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Figure legends

Figure 1. Experimental design: Comparing corticospinal excitability (CSE), short interval intracortical inhibition (SICI), and intracortical facilitation (ICF) of left M1 following conventional and unihemispheric dual-site c-tDCS (c-tDCS_{UHCDS}) by single- and paired pulse TMS (A); the electrode montage over the targets in both active and sham conditions (B). * The grey electrodes in sham condition indicate that the electrodes were placed in the same positions as for active M1-S1 or M1-DLPFC conditions.

Figure 2. The effects of different stimulation sites on the peak-to-peak amplitude of MEPs (A), short interval intracortical inhibition (SICI) (B), and intracortical facilitation (ICF) (C) following c-tDCS of primary motor cortex (M1), unihemispheric concurrent dual-site c-tDCS of M1- dorsolateral prefrontal cortex (DLPFC), M1 – primary sensory cortex (S1), M1 – primary visual cortex (V1), and sham.

Filled symbols indicate significant deviation of the post transcranial stimulation MEP amplitudes relative to the baseline. Data are reported as mean $\pm$ SE

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Table 1 Summary of pairwise comparison of means differences at each time-point of measurement for the effects of dual cathodal transcranial direct current stimulations on corticospinal excitability (CSE) of M1 measured by single-pulse TMS

		1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
Single-pulse TMS	T _{pre}	0.26	0.84	0.44	0.6	0.74	0.46	0.55	0.67	0.07	0.89
	T ₀	0.001*	0.25	0.002*	0.000*	0.001*	0.22	0.001*	0.005	0.08	0.03
	T ₃₀	0.001*	0.43	0.005*	0.001*	0.002*	0.17	0.004*	0.007	0.01	0.03
	T ₆₀	0.000*	0.001*	0.002*	0.004*	0.003*	0.05	0.003*	0.004*	0.31	0.002*
	T _{24h}	0.003*	0.40	0.001*	0.15	0.07	0.27	0.003*	0.19	0.01	0.001*

The asterisks represent the adjusted p value in multiple comparisons.

1: Stimulation of M1

2: Stimulation of M1-DLPFC

3: Stimulation of M1-S1

4: Stimulation of M1-V1

5: Sham tDCS

Table 2 Summary of pairwise comparison of means differences at each time-point of measurement for the effects of dual cathodal transcranial direct current stimulations on short interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

		1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
SICI (ISI: 3 msec)	T _{pre}	0.27	0.29	0.06	0.02	0.01	0.02	0.27	0.23	0.51	0.81
	T ₀	0.81	0.72	0.67	0.61	0.42	0.87	0.90	0.42	0.24	0.09
	T ₃₀	0.22	0.27	0.24	0.09	0.21	0.11	0.76	0.13	0.02	0.12
	T ₆₀	0.52	0.31	0.000*	0.07	0.41	0.000*	0.21	0.001*	0.61	0.000*
	T _{24h}	0.27	0.31	0.001*	0.45	0.76	0.000*	0.07	0.002*	0.01	0.000*
ICF (ISI: 10 msec)	T _{pre}	0.32	0.46	0.06	0.35	0.10	0.48	0.16	0.08	0.23	0.33
	T ₀	0.005*	0.01	0.002*	0.23	0.004*	0.17	0.07	0.005	0.03	0.003*
	T ₃₀	0.07	0.06	0.004*	0.25	0.67	0.000*	0.12	0.001*	0.09	0.003*
	T ₆₀	0.12	0.28	0.001*	0.31	0.44	0.000*	0.62	0.000*	0.45	0.000*
	T _{24h}	0.05	0.003*	0.000*	0.67	0.85	0.000*	0.33	0.000*	0.48	0.000*

The asterisks represent the adjusted p value in multiple comparisons.

ISI: Inter-stimulus interval

1: Stimulation of M1

2: Stimulation of M1-DLPFC

3: Stimulation of M1-SI

4: Stimulation of M1-V1

5: Sham tDCS

Table 3 Participants' numeric sensation scores during experimental conditions

		Cathode electrode					Reference electrode				
		M1	M1-DLPFC	M1-S1	M1-V1	Sham	M1	M1-DLPFC	M1-S1	M1-V1	Sham
Tingling sensation	Beginning	3.1 ± 0.24	4.1 ± 0.18	3.9 ± 0.41	3.1 ± 0.24	1.9 ± 0.25	1.6 ± 0.19	2.5 ± 0.13	2.3 ± 0.32	2.5 ± 0.29	1.6 ± 0.15
	Middle	2.7 ± 0.14	2.4 ± 0.23	2.3 ± 0.17	1.6 ± 0.15	1.2 ± 0.14	0.8 ± 0.21	1.3 ± 0.14	1.7 ± 0.28	2.1 ± 0.15	1.0 ± 0.04
	End	1.3 ± 0.34	0.9 ± 0.14	1.0 ± 0.21	0.7 ± 0.18	0.6 ± 0.16	0.32 ± 0.1	0.9 ± 0.11	1.1 ± 0.41	1.4 ± 0.16	0.4 ± 0.03
Itching sensation	Beginning	2.7 ± 0.11	2.6 ± 0.26	3.1 ± 0.64	1.3 ± 0.29	1.7 ± 0.17	1.6 ± 0.15	1.2 ± 0.1	1.5 ± 0.2	1.0 ± 0.12	1.3 ± 0.12
	Middle	0.6 ± 0.47	1.2 ± 0.19	2.6 ± 0.12	0.9 ± 0.15	0.5 ± 0.14	0.9 ± 0.21	1.0 ± 0.2	1.1 ± 0.14	0.8 ± 0.27	0.9 ± 0.09
	End	0.3 ± 0.19	0.8 ± 0.27	1.0 ± 0.31	0.7 ± 0.23	-	0.7 ± 0.36	0.4 ± 0.53	0.7 ± 0.09	0.6 ± 0.37	0.3 ± 0.54
Burning sensation	Beginning	-	0.18 ± 0.07	0.52 ± 0.2	-	0.23 ± 0.07	-	-	-	-	-
	Middle	-	-	0.12 ± 0.17	-	0.14 ± 0.01	-	-	-	-	-
	End	-	-	-	-	-	-	-	-	-	-
Not tolerated	Beginning	-	-	-	-	-	-	-	-	-	-
	Middle	-	-	-	-	-	-	-	-	-	-
	End	-	-	-	-	-	-	-	-	-	-

The values are rated using the NAS. 0 is rated as no sensation and 10 rated as the worst sensation imaginable. The sensations are recorded during three phases of stimulation: Beginning (0 to 7 minutes of stimulation), Middle (7 to 14 minutes of stimulation), End (14 to 20 minute of stimulation). Sensations under both active (anode) and reference (cathode) electrodes were recorded during a-tDCS of primary motor cortex (M1), primary sensory cortex (S1), dorsolateral prefrontal cortex (DLPFC), and sham tDCS. Scores are reported in Mean ± SE

Table 4 The judgements of participants on the stimulation conditions

		Actual testing conditions (n = 12)					
		c-tDCS of	c-tDCS _{UHCDS} of	c-tDCS _{UHCDS} of	c-tDCS _{UHCDS} of	Sham	Total
		M1	M1-DLPFC	M1-S1	M1-V1		
Perceived stimulation	Active	2	1	3	2	4	12
	Sham	3	6	3	4	2	18
	Cannot say	7	5	6	6	6	30

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