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RESEARCH ARTICLE

Influence of neurovascular mechanisms on response to tDCS: an exploratory study

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Abstract

The beneficial effects of transcranial direct current stimulation (tDCS) for stroke rehabilitation are limited by the variability in changes in corticomotor excitability (CME) after tDCS. Neuronal activity is closely related to cerebral blood flow; however, the cerebral hemodynamics of neuromodulation in relation to neural effects have been less explored. In this study, we examined the effects of tDCS on cerebral blood velocity (CBv) in chronic stroke survivors using transcranial Doppler (TCD) ultrasound in relation to changes in CME and described the neurovascular characteristics of tDCS responders. Middle cerebral artery (MCA) CBv, cerebrovascular resistance (CVRi) and other cerebral hemodynamics-related variables were continuously measured before and after 15 min of 1 mA anodal tDCS to the lesioned lower limb M1. tDCS did not modulate CBv in the whole group and upon TMS-based stratification of responders and non-responders. However, at baseline, responders demonstrated lower CME levels, lower CBv and higher CVRi as compared to non-responders. These results indicate a possible difference in baseline CME and CBv in tDCS responders that may influence their response to neuromodulation. Future trials with a large sample size and repeated baseline measurements may help validate these findings and establish a relationship between neuromodulation and neurovascular mechanisms in stroke.

Keywords Cerebral blood velocity · Transcranial direct current stimulation · Corticomotor excitability · Responders · Non-responders · Chronic stroke

Abbreviations

CME	Corticomotor excitability
CBF	Cerebral blood flow
CBv	Cerebral blood velocity
MBv	Mean blood velocity
CVRi	Cerebrovascular resistance index
PI	Pulsatility index
$Et\text{-}CO_2$	End-tidal carbon dioxide
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
MCA	Middle cerebral artery

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Introduction

Over the last decade, transcranial direct current stimulation (tDCS) has being increasingly investigated as a neuromodulatory adjunct to optimize recovery of motor function in stroke survivors (Kang et al. 2015). Anodal tDCS to the lower limb motor cortex, applied before or during a motor task, has shown to improve task-specific practice in healthy individuals and in those with stroke (Tanaka et al. 2009, 2011; Sohn et al. 2013; Sriraman et al. 2014; Chang et al. 2015; Devanathan and Madhavan 2016). However, variability in the expected response (both inter-subject and intra-subject) highly limits clinical translation, underscoring an urgent need for exploration of predictors that determine the effects of tDCS (López-Alonso et al. 2014; Wiethoff et al. 2014; Chew et al. 2015; Strube et al. 2015; Madhavan et al.

2016a; Strube et al. 2016; Tremblay et al. 2016). Modulation in underlying cortical neuronal activity produced by tDCS is associated with changes in corticomotor excitability (CME), typically measured as changes in the size of motor-evoked potentials (MEPs), elicited with single-pulse transcranial magnetic stimulation (Dissanayaka et al. 2017). Studies examining MEP responses as an indicator of successful modulation with tDCS indicate that only 50–60% of individuals ('responders') show the expected change (López-Alonso et al. 2014; Wiethoff et al. 2014). Amongst the various biological and experimental factors that may influence neuromodulatory success, TMS-related factors such as TMS sensitivity (Labruna et al. 2016) and baseline CME (Wiethoff et al. 2014), and tDCS related factors such as stimulation duration and current density (Dissanayaka et al. 2017) have been shown to influence the observed inter-individual variability in healthy subjects. In addition to these factors, changes in neuronal architecture associated with stroke, the location and extent of the stroke lesions, attention, genetics, and previous neuronal excitability may also influence the current distribution of tDCS in stroke survivors and thereby increase variability of responses (Kamke et al. 2012; Li et al. 2015; Puri et al. 2015).

The influence of cerebral blood flow (CBF) on tDCS-induced neuromodulation has been less explored. Neurovascular coupling is the close temporal and spatial relationship between neural activity and CBF in response to metabolic demand. Neuronal activity increases metabolic demand, triggering the hemodynamic response to increase CBF (Lecrux and Hamel 2011; Muoio et al. 2014). Neurovascular coupling helps to maintain the fine balance between neuronal activity and subsequent changes in CBF, which is critical to maintain cerebral homeostasis (Rosengarten et al. 2001). Facilitatory anodal tDCS increases baseline neuronal activity thereby triggering a change in CBF. Several neuroimaging studies using functional magnetic resonance imaging (fMRI), arterial spin labeling (ASL), functional near-infrared spectroscopy (fNIRS) and positron emission topography (PET) scan with tDCS have reported changes in local cerebral blood flow and blood oxygenation that occur in parallel to the changes in neural activity in healthy adults (Lang et al. 2005; Merzagora et al. 2010; Zheng et al. 2011; Nord et al. 2013; Stagg et al. 2013). This increase in blood flow could be due to the increased activation of excitatory neural networks creating an energy demand, modulating glutamatergic activity, thus leading to long-term potentiation (Stagg and Nitsche 2011; Giordano et al. 2017) or simply a direct effect of tDCS on blood vessels. Others have proposed that the increase in CBF following tDCS could also be due to changes in the properties of astrocytes, which outnumber neurons and are polarized by tDCS thereby playing a role in synaptic efficacy (Merzagora et al. 2010). These neuroimaging studies provide some evidence that the cerebral hemodynamic response is altered with the administration of tDCS and that changes in CBF can be used as a measurable outcome making exploration of possible neuromodulatory interventions in chronic stroke patients desirable.

Transcranial Doppler (TCD) ultrasound, a non-invasive clinically available tool, allows for measurement of cerebral blood velocities (CBv) in the vessels that arise from the circle of Willis (Kassab et al. 2007; Willie et al. 2011). TCD ultrasound uses high-frequency sound waves to detect instantaneous changes in velocity of large basal cerebral arteries that have shown to be correlated with blood flow changes in arteries supplied by these blood vessels (Kontos 1989; Jørgensen 1995). TCD is routinely used in the clinic to facilitate diagnosis of a variety of conditions that affect CBF such as cerebral embolism, subarachnoid hemorrhage and transient ischemic attacks. Although ASL, fMRI, NIRS and PET may provide a more comprehensive brain imaging picture in vivo, in this study, we chose to use TCD to understand CBv effects of tDCS as TCD presents several advantages relative to these techniques. Advantages of TCD include high temporal resolution, ease of administration, relative insensitivity to movement artifacts, less expensive technology, more clinical accessibility and bedside availability (Willie et al. 2011). Numerous studies have reliably and accurately measured neurovascular coupling using TCD related to sensorimotor and cognitive stimulatory effects. These studies have demonstrated consistent changes in CBv during or after verbal, motor and cognitive tasks using TCD (Matteis et al. 2001, 2003; Salinet et al. 2012, 2013; Williams et al. 2017). Neurovascular coupling becomes significantly altered after stroke; individuals with stroke present with impaired cerebrovascular reactivity to CO_2 measured by TCD (Maeda et al. 1993; Matteis et al. 2001; Krainik et al. 2005; Lin et al. 2011). Matteis et al. (2003) observed that the change in CBv of the ipsilesional middle cerebral artery (MCA) during the acute phase of stroke was a significant prognostic indicator of clinical recovery.

Despite the prevalence of TCD ultrasound as a clinical diagnostic tool, our recent systematic review indicated there is limited evidence regarding the use of TCD to capture the neuromodulatory effects of tDCS (Iyer and Madhavan 2018). Only three studies have explored changes in tDCS using TCD and these results are limited to individuals without a stroke (Vernieri et al. 2010; Giorli et al. 2015; List et al. 2015). Giorli et al. (2015) reported an increase in CBv after tDCS of the upper limb M1 in healthy adults. Vernieri et al. (2010) reported no changes in CBv but found changes in vasomotor reactivity in healthy adults. Vernieri et al. (2010) and Giorli et al. (2015) applied the reference electrode to the ipsilateral shoulder which is a not a commonly used montage and may not be optimal for tDCS affecting some of their results. List et al. (2015) measured only vasomotor reactivity and reported no changes in healthy and older adults. The

cerebral hemodynamics of tDCS-induced neuroplasticity has not been characterized in stroke, especially in relation to the lower limb M1. In addition, the relationship between changes in CBv and CME has not been explored. Hence, in this study, we aimed to assess the instantaneous changes in CBv in relation to CME after tDCS in chronic stroke survivors. This study focused on answering these questions: Does anodal tDCS modulate CBv in chronic stroke survivors as measured with TCD? Do changes in CBv relate to change in corticomotor excitability after anodal tDCS? Does anodal tDCS have a differential effect on CBv for responders and non-responders to tDCS, categorized based on the expected upregulation in CME? To account for effects of higher blood pressures and impaired vasomotor reactivity on CBF, which is commonly seen in stroke survivors, we also included the measures of vascular resistance and CO_2 changes to draw careful interpretations of CBv changes.

Methods

Study participants and protocol

We recruited 20 chronic stroke survivors (aged 45–72 years; female = 7) with a single episode of stroke, post-stroke period of at least 6 months, and with the presence of detectable MEPs from paretic tibialis anterior (TA) muscle. As this was an exploratory study, we selectively recruited those with MEPs so we could study changes in CME using TMS in the lesioned hemisphere to fully understand the effects of tDCS on cerebral hemodynamics. We excluded pregnant women, persons with history of other neurological conditions, multiple strokes, cardiac surgery/abnormal cardiac rhythms, and participants contraindicated for TMS, which included those with metal implants in the head, recurrent headaches, seizures, and medications that alter CME. The study was approved by the Institutional Review Board at the University of Illinois at Chicago and all subjects participated after providing written informed consent prior to participation.

Subjects participated in three sessions with a crossover design for sessions 2 and 3 (Fig. 1). The first session included clinical measures and TMS measurements before and after anodal tDCS. Participants were block randomized into anodal and sham stimulation for sessions 2 and 3. All experimental sessions were conducted in the morning and the participants were instructed to avoid caffeine, alcohol, smoking, exercise, and medications for at least 12 h before testing.

Clinical outcomes

Clinical assessments were performed to obtain a baseline assessment of participants' functional status. Gait speed was assessed using the 10-meter walk test (10MWT) at each participant's self-selected (SS) and fastest speed (FS). Self-selected and fast walking tests were performed twice and averaged. Lower limb sensorimotor recovery was assessed using lower limb Fugl Meyer scale (FMLE). FMLE test included the sensory (touch and proprioception) and motor (movement ability, reflexes, speed and coordination) assessment of the paretic and non-paretic legs.

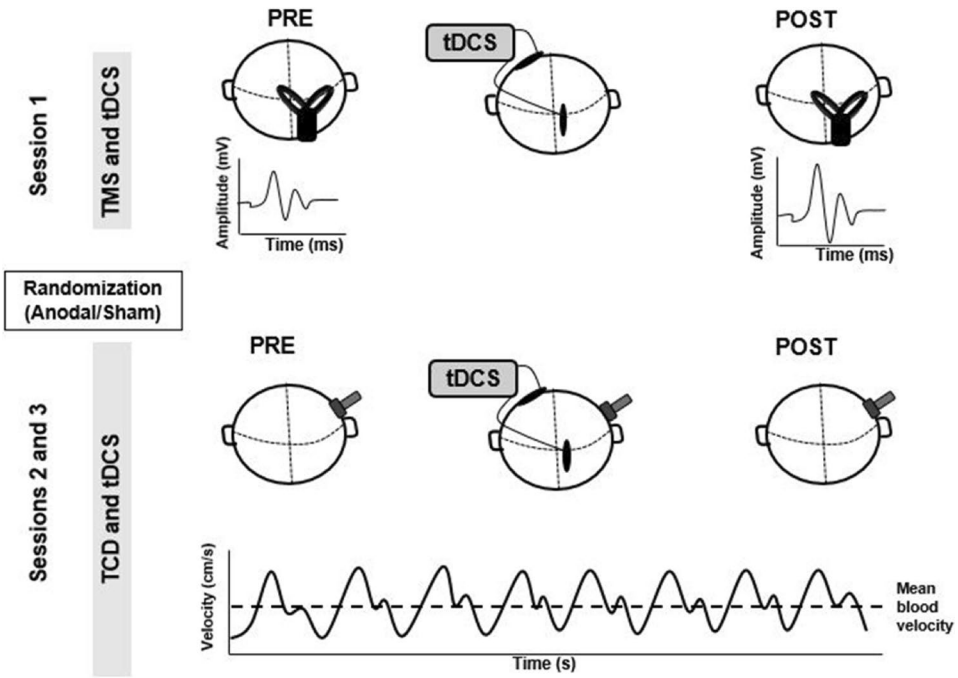

Fig. 1 Schematic representation of the experimental paradigm. Corticomotor excitability before and after transcranial direct current stimulation (tDCS) of the lesioned lower limb M1 was assessed using transcranial magnetic stimulation (TMS). The participant was then randomized to receive anodal or sham tDCS during transcranial Doppler (TCD) ultrasound measurements

Transcranial magnetic stimulation (TMS)

Surface Ag/AgCl electrodes were placed over the paretic and non-paretic TA muscle belly and the reference electrode over the spinous process of C7 vertebra to record muscle activity. Maximum voluntary contraction (MVC) of TA muscle was obtained against maximum resistance. Spike2 software (Cambridge Electronic design, Cambridge, UK) was used for all EMG data collection where EMG data were sampled at 2000 Hz, amplified 1000× and band-pass filtered (10–500 Hz) with a Delsys EMG system (Bagnoli 8, MA USA). Single-pulse TMS was delivered using a 110-cm double-cone coil in a posterior–anterior direction using a single-pulse stimulator (Magstim, Dyfed, Wales, and UK) during weak tonic contraction pertaining to approximately 10% MVC of the TA muscle. Spike2 software was used to automate the TMS trigger and record the trigger pulses. The 'hotspot' for the lower limb M1, referred to as the spot that produced consistent MEPs in contralateral TA muscle, was obtained. This spot was marked relative to the vertex on a tight-fitting cap, to maintain a consistent coil positioning across the session. The location of the hotspot relative to the 10–20 EEG system was carefully noted to be used for tDCS electrode placements in subsequent sessions. Active motor threshold (AMT) was defined as the machine stimulated output (%MSO) resulting in identifiable MEPs of at least 0.4 mV peak to peak in 50% of successive trials from the active contralateral TA (Madhavan and Stinear 2010; Madhavan et al. 2011, 2016a, b; Sivaramakrishnan and Madhavan 2018). For the MEP to be discernible above background activity, we set our criteria for threshold at 0.4 mV as we have typically observed background activity to be between 0.2 and 0.4 mV at 10% MVC. CME of the lesioned and non-lesioned M1, before and after anodal tDCS, was assessed at 80–140% AMT with a 10% increment (Madhavan and Stinear 2010; Sivaramakrishnan et al. 2016). Six MEPs were recorded for each intensity before tDCS stimulation (PRE) and at 10 min post-tDCS (POST).

Transcranial Doppler (TCD)

Participants were comfortably seated on a phlebotomy chair in a quiet environment with their foot on an elevated bench to avoid venous pooling of the lower limbs. The participants were asked to stay awake and the neck was immobilized with a neck pillow to avoid head movements during the recording. The velocity of middle cerebral artery (MCA) of the lesioned hemisphere was measured at the transtemporal window at an average depth of 54 mm (±5 mm) using a cushioned headpiece and a 2-MHz transcranial Doppler ultrasound probe (TOCM Neurovision, MultiGON Industries, INC. Elmsford, NY). The velocity waveform was recorded at 1000 Hz (MP150; BioPac Systems Inc., Goleta, CA) and was stored offline for the analysis of beat-to-beat CBv (WinCPRS, Absolute Aliens Oy, Turku, Finland) (Claassen et al. 2016). Beat-to-beat arterial blood pressure was measured using non-invasive finger photoplethysmography and was calibrated to the brachial pressure (Finometer Pro, FMS, Netherlands) along with beat-to-beat heart rate (HR) from a standard limb lead II electrocardiogram (MP150; BioPac Systems Inc., Goleta, CA) during the TCD recording. End-tidal CO_2 (Et-CO_2) was also measured using a mask covering the nose and mouth for gas collection ($CO_2$100C BioPac Systems Inc., Goleta, CA) during the TCD recording. The CO_2 module was calibrated prior to each test with a gas of known CO_2 concentration (5%). End-tidal CO_2 has a high correlation with arterial CO_2 levels and is considered to affect changes in CBv due to arterial CO_2 levels (McSwain et al. 2010). The tDCS stimulation was applied simultaneously during the TCD recording.

Transcranial direct current stimulation (tDCS)

A 4-cm × 2-cm oblong saline-soaked sponge active electrode was placed over the lower limb M1 hotspot on the lesioned hemisphere. The reference electrode of the same dimension was placed over the supraorbital region on the contralateral side. This electrode was slightly smaller than the reference electrode (35 cm^2) used in previous studies. This modification was performed in response to concerns raised by participants during our pilot phase. As the TCD head strap had to fit snugly on the head to maintain the TCD probe in place, it created an uncomfortable pressure on the forehead when the larger electrode was used. Before placing the electrodes, the scalp and skin were cleaned with alcohol. 1 mA of anodal tDCS for 15 min (current density: 0.125 mA/cm^2 and charge of 1.5 mC) was given using a constant current stimulator device (Chattanooga, Ionto, Hixson, TN, USA) with an initial ramp up of 30 s and final ramp down of 30 s (Madhavan and Stinear 2010; Sriraman et al. 2014; Devanathan and Madhavan 2016; Madhavan et al. 2016a). During sham stimulation, the tDCS device was turned off after initial ramp up of 30 s. Participants were blinded to the type of stimulation and instructed to be at rest during stimulation. tDCS was well tolerated and no adverse effects related to the application of tDCS were observed for any session.

Data analyses

Corticomotor excitability

A linear slope was calculated from the stimulus response recruitment curve (RC) based on averaged MEP amplitudes for each AMT for each individual participant and was considered

as the key measure of CME. The percentage change in CME was calculated using the formula: (POST–PRE)/POST × 100.

Based on previous tDCS response studies, participants with greater than 10% increase in CME after tDCS were classified as responders while those who showed lesser than 10% decrease in CME were classified as non-responders (López-Alonso et al. 2014; Wiethoff et al. 2014; Strube et al. 2015; Madhavan et al. 2016a). There were no participants who fell between these ranges.

CBv and other hemodynamic measures

For TCD data analyses, a 1-min time window was manually set at four time points: baseline (*B*), immediately post-tDCS (P0), 5 min post-tDCS (P5), and 10 min post-tDCS (P10). For baseline measurements, the time cursors were placed to capture data that showed minimal fluctuations in CBv towards the end of the 5-min baseline recording. For the other epochs, the time cursors were placed at the start of each time point mentioned above. Mean blood velocity (MBv) is unaffected by high velocities and low-amplitude signals that originate from small vessels surrounding the major artery studied (Hennerici et al. 1987). Changes in MBv within these time windows were considered to reflect changes in CBv. MBv has been reported to be influenced by changes in cardiac activity, blood pressure, and CO_2 (de Riva et al. 2012; Claassen et al. 2016; Castro et al. 2018). To confirm that change in MBv was a true reflection of the cerebral hemodynamic change induced by tDCS and not because of fluctuations in cardiovascular state, additional measures calculated from blood pressure and beat-to-beat changes in cardiac activity were analyzed. The change in vascular resistance due to change in blood pressure was denoted using cerebrovascular resistance index (CVRi), calculated as a ratio of mean arterial pressure (MAP) and MBv (Claassen et al. 2016). The changes in the resistance to the pulsatile flow were monitored by calculating pulsatility index (PI) (de Riva et al. 2012). PI was calculated from changes in systolic and diastolic CBv and is given by following formula:

$$\mathrm{PI} = \frac{\text{Systolic Velocity} - \text{End-diastolic velocity}}{\text{Mean Blood Velocity}}.$$

Mean blood velocity

Changes in CO_2 levels were represented as changes in end-tidal CO_2 (Et-CO_2) values, where the maximum CO_2 values of the gas capnography wave form recordings were measured and used for statistical analyses.

Statistical analyses

Statistical analyses were performed using SPSS (IBM SPSS statistics 25). Data were found to be normally distributed using the Shapiro–Wilk test. The level of statistical significance was set at $p \leq 0.05$. The following comparisons were performed for changes within the entire group and for between responders and non-responders.

All participants

To study the effect of tDCS on CME across all participants, a two-way repeated measures ANOVA was performed with Hemisphere (Lesioned and Non-lesioned M1) and Time (Pre and Post) as independent factors. Similarly, to examine the effects of tDCS on MBv, MAP, Et-CO_2, PI, and CVRi across all participants, a two-way repeated measures ANOVA was performed with Stimulation (Anodal and Sham) and Time (B, P0, P5, P10) as independent factors. To examine test–retest and the reliability of TCD measures, ICC analyses were performed using a two-way random-effects model on MBv collected at baseline for the sham and anodal TCD sessions.

Between responders and non-responders

Independent sample *t* tests were used to examine differences for the following baseline measurements between responders and non-responders: CME, MBv, MAP, Et-CO_2, PI, and CVRi. To study the effect of tDCS on CME between responders and non-responders, a three-way mixed model ANOVA (Hemisphere × Response × Time) was applied to test with Hemisphere (Lesioned and Non-lesioned M1) and Time (Pre and Post) as within-subject factors, and Response (responders and non-responders) as the between-subject factor. Similarly, to study the effects of tDCS on MBv, MAP, Et-CO_2, PI, and CVRi between responders and non-responders, a two-way mixed model ANOVA (Response × Time) was conducted with Time (B, P0, P5, P10) as the within-subject factor and Response (responders and non-responders) as the between-subject factor. Pairwise post hoc comparisons were carried out using *t* statistics with Bonferroni correction. Cohen's *d* value was calculated to interpret the effect size of the observed results. Cohen's *d* values between 0.20 and 0.49, 0.50 and 0.79, and greater than 0.8 were considered as small, moderate, and large effect sizes, respectively.

Results

Out of 20 participants, 6 participants (African American ethnicity, female = 5) were unable to participate in the TCD sessions due to inefficient acoustic window resulting in inability to detect their MCA. 14 subjects completed all three sessions. During data analyses, we found irregular ECG recordings for one participant and their data were excluded

from the study. Data from 13 participants were included in the final analyses (Table 1).

All participants

The two-way repeated measures ANOVA (Hemisphere × Time) examining changes in CME after tDCS revealed a main effect of Hemisphere ($F_{1,\ 10} = 5.868$, $P = 0.032$, $d = 0.89$). The non-lesioned M1 revealed 38% greater CME than the lesioned M1 (Table 2). The two-way repeated measures ANOVA (Stimulation × Time) revealed no significant main effects or interactions of tDCS for any of the TCD outcomes: CBv, PI, MAP, Et-CO_2, and CVRi. Test–retest reliability of baseline MBv between the two TCD sessions was high (0.967, $P = 0.001$).

Subgroup analyses

Out of 13 participants, 7 were classified as responders and 6 as non-responders. At baseline, the independent sample *t* tests revealed that the responders had 38% lower CME than non-responders in the lesioned M1 ($t_{11} = 6.348$, $P = 0.001$, $d = 0.60$) and 47% higher CME in the non-lesioned M1 ($t_{11} = 2.689$, $P = 0.021$, $d = 1.50$) (Table 2). The independent sample *t* tests revealed that the responders had 35% lower MBv ($t_{11} = 2.835$, $P = 0.016$, $d = 1.69$) and 26% greater CVRi as compared to non-responders ($t_{11} = -2.288$, $P = 0.043$, $d = 1.14$). The independent sample *t* tests on MAP, PI and Et-CO_2 did not note any significant differences between responders and non-responders (Table 3).

The three-way mixed model ANOVA (Hemisphere × Response × Time) for CME between responders and non-responders revealed a significant Hemisphere × Response × Time effect ($F_{1,\ 11}$ (1, 11) = 6.559, $P = 0.026$, $d = 1.05$). Further analyses showed a significant Response × Time ($F_{1,\ 11} = 5.863$, $P = 0.034$, $d = 0.98$) and Hemisphere × Time ($F_{1,\ 6} = 6.113$, $P = 0.048$, $d = 1.01$) interactions (Table 2, Fig. 2). Paired sample *t* tests revealed that only in responders, tDCS increased CME of the lesioned M1 by 85% ($t_6 = -2.656$, $P = 0.038$, $d = 0.74$). No difference was seen in CME for the non-lesioned M1. The CME in lesioned M1 differed from non-lesioned M1 before ($t_6 = 6.015$, $P = 0.001$, $d = 2.5$) and after tDCS ($t_6 = 6.787$, $P = 0.001$, $d = 0.87$).

Table 1 Participant characteristics

	All participants	Responders	Non-responders
Number of participants (*n*)	13	7	6
Sex			
Male (*n*)	10	6	4
Female (*n*)	3	1	2
Age (years)	56.4 (8.8)	55.9 (6.7)	57 (9.6)
Stroke history			
Type of stroke (*n*) (ischemic/hemorrhagic)	10/3	5/2	5/1
Post-stroke period (years)	6.5 (4.9)	6.4 (4.0)	7.8 (6.1)
Hemisphere affected (R/L) (*n*)	9/4	4/2	5/3
Motor impairment post-stroke			
FMLE (sensory) (total: 12)	10.9 (2.6)	11 (2.2)	10.7 (3.3)
FMLE (motor) (total: 34)	21.5 (5.7)	21.7(5.6)	22 (5.9)
10-meter walk test (m/s)			
Self-selected speed	0.9 (0.1)	0.8 (0.1)	0.9 (0.2)
Fast speed	1.2 (0.3)	1.2 (0.3)	1.2 (0.2)

Values are mean (standard deviation)

R right, *L* left, *FMLE* Fugl Meyer Lower Extremity assessment

Table 2 Corticomotor excitability of the paretic tibialis anterior muscle

	Pre		Post	
	Non-paretic TA	Paretic TA	Non-paretic TA	Paretic TA
All participants	0.013 (0.01)	0.007 (0.003)	0.013 (0.001)	0.009 (0.01)
Responders	0.017 (0.001)	0.006 (0.0003)	0.016 (0.001)	0.011 (0.001)
Non-responders	0.009 (0.001)	0.008 (0.001)	0.009 (0.001)	0.007 (0.001)

Mean CME slope values before and after tDCS are shown for all participants, responders, and non-responders. Values are mean (standard deviation)

Table 3 Cerebrovascular changes between responders and non-responders

TCD parameters	*B*	P0	P5	P10
MBv (cm/s)				
Responders	37 (8)	37 (8)	38 (12)	36 (12)
Non-responders	49 (6)	50 (9)	50 (8)	49 (8)
MAP (mmHg)				
Responders	108 (14)	109 (10)	110 (13)	105 (8)
Non-responders	106 (13)	109 (15)	110 (15)	110 (15)
PI				
Responders	1.1 (0.1)	1.1 (0.2)	1.0 (0.1)	1.0 (0.2)
Non-responders	1.0 (0.1)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)
Et-CO_2 (%)				
Responders	5.0 (0.1)	5.0 (0.1)	5 (0.1)	5.0 (0.1)
Non-responders	5.0 (0.1)	5.0 (0.1)	4.9 (0.1)	4.9 (0.1)
CVRi				
Responders	3.2 (0.9)	3.3 (0.9)	3.3 (1)	3.4 (0.9)
Non-responders	2.2 (0.4)	2.3 (0.6)	2.3 (0.5)	2.3 (0.6)

TCD ultrasound measurements before and after tDCS. The time points at which the TCD measurements were taken are shown in the top column. Values are mean (standard deviation)

TCD transcranial Doppler, *tDCS* transcranial direct current stimulation, *MBv* mean blood velocity, *MAP* mean arterial pressure, *PI* pulsatility index, *EtCO_2* end-tidal carbon dioxide, *CVRi* cerebrovascular resistance index, *B* baseline, *Po* immediately post-tDCS, *P5* 5 min post-tDCS, P10 10 min post-tDCS

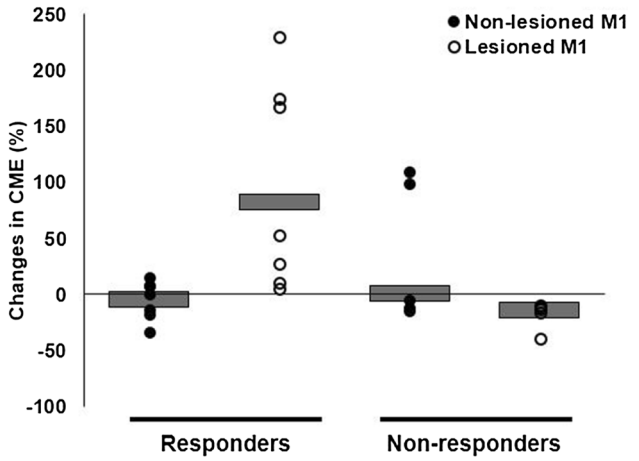

Fig. 2 Changes in corticomotor excitability (CME) of responders and non-responders after tDCS. Changes in CME after tDCS are shown for responders ($n=7$, black circles) and non-responders ($n=6$, open circles) for the non-lesioned M1 and the lesioned M1. Each data point represents percentage change in CME slope. Averages are shown as dark gray bars

The two-way mixed model ANOVA (Response × Time) on MBv revealed a significant main effect of Response ($F_{1, 11}=5.722$, $P=0.036$, $d=1.63$) with responders showing 28% lower MBv than non-responders (Table 3, Fig. 3). The two-way mixed model ANOVA (Response × Time) for CVRi also revealed a significant main effect of Response ($F_{1, 11}=5.255$, $P=0.043$, $d=3.9$). The responders had 27% higher CVRi than non-responders (Table 3, Fig. 4). The two-way mixed model ANOVA (Response × Time) on PI, MAP and Et-CO_2 did not reveal any significant main effects or interactions.

Discussion

In this study, we explored the effects of anodal tDCS on CBv and examined the relationship between changes in CBv and CME after tDCS in chronic stroke survivors. This is the first study to explore neurovascular changes after tDCS of the lower limb M1 in individuals with stroke. We observed that there was no change in CME or CBv parameters due to anodal tDCS in the entire sample of participants. The effects of tDCS on CME was different when participants were stratified into responders and non-responders, with the responders showing about 85% increase in CME of the lesioned M1 after anodal tDCS. It was also interesting to note that the baseline measurements for CME, MBv and CVRi was significantly different between responders and non-responders, perhaps indicating distinct corticomotor and neurovascular characteristics between the two groups.

In the overall sample of participants, it was not surprising that we did not observe a change in CME after tDCS. The lack of a group effect for CME is supported by observations from previous tDCS studies (López-Alonso et al. 2014; Strube et al. 2015; Madhavan et al. 2016a; Strube

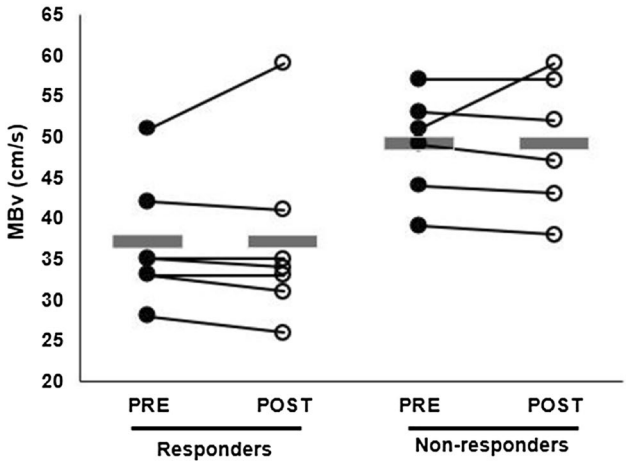

Fig. 3 Mean blood velocity (MBv) in responders and non-responders before and after tDCS. MBv at baseline (PRE, black circles) and after (POST, open circles) tDCS are shown for responders ($n=7$) and non-responders ($n=6$). Post-MBv is a grand mean average across all post-time points (P0, P5 and P10). Averages are shown as dark gray bars

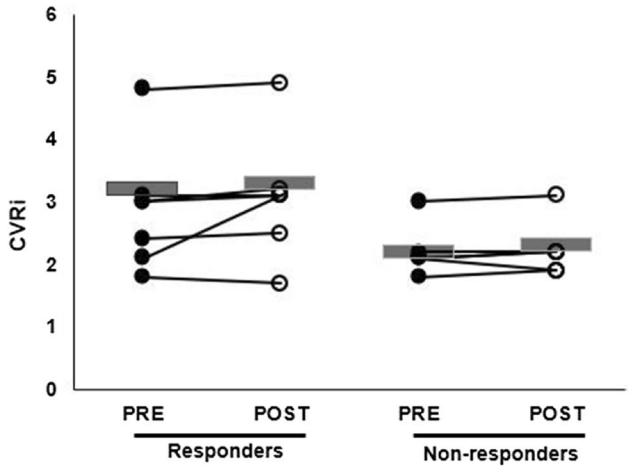

Fig. 4 Cerebrovascular resistance (CVRi) in responders and non-responders before and after tDCS. CVRi at baseline (PRE, black circles) and after (POST, open circles) tDCS for responders ($n=7$) and non-responders ($n=6$). Post-CVRi is a grand mean average of CVRi values across all post-time points (P0, P5 and P10). Averages are shown as dark gray bars

et al. 2016; Tremblay et al. 2016).The inherent variability in the expected neuromodulatory effects of tDCS and our small sample size may have limited our ability to detect the after effects of tDCS in the entire sample. As the parameters of stimulation were consistent across all individuals in this study, some of the factors that may have contributed to inter-individual variability could include biological factors such as age, location and profile of stroke lesion, orientation of neurons, genetic polymorphisms, and individual states (anxiety, motivation) (De Berker et al. 2013; Liew et al. 2017). As expected, our data showed that the CME of the non-lesioned M1 was greater than the lesioned M1 at baseline, supporting the asymmetry in interhemispheric cortical excitability typically seen after stroke (Boddington and Reynolds 2017). The facilitatory effects of anodal tDCS were observed only when our sample was categorized according to changes in CME. Similar to previous studies, responders demonstrated significantly greater upregulation after tDCS than non-responders (Wiethoff et al. 2014; Madhavan et al. 2016a; Strube et al. 2016; Tremblay et al. 2016).

Interestingly, we also found differences in CME between responders and non-responders at baseline, with responders demonstrating 38% lower CME in the lesioned M1. Previous work by Wiethoff et al. (2014) has also supported that individuals with smaller baseline MEPs show a greater facilitatory response to tDCS. One explanation for those with lower CME showing a larger effect size could be that these participants have a greater capacity to respond to tDCS due to their lower starting point, possibly explained by the concept of homeostatic metaplasticity, i.e., ability of neurons to modulate activity based on prior state of synaptic activity (Ziemann and Siebner 2008). This finding is in contrast with the study by Labruna et al. (2016) who demonstrated that individuals who are more sensitive to TMS (i.e., lower motor thresholds and higher MEPs when stimulated at the same intensity) react with larger responses to tDCS (Labruna et al. 2016). And some others have noted no differences in baseline CME between responders and non-responders with healthy brains (López-Alonso et al. 2014; Wiethoff et al. 2014; Tremblay et al. 2016).

Very few studies have reported MBv values for chronic stroke survivors. The average MBv value in our study (42 ± 9 cm/s) was similar to those reported by Aoi et al. (2012) (41 ± 3.5 cm/s) but lower than those reported by Ivey et al. (2011) (50 ± 14 cm/s). The differences in participant sampling may account for these differences in baseline MBv. As expected, MBv values of our sample was lower than the normative values for healthy adults which is reported to be around 56 ± 12 cm/s (Aoi et al. 2012; Tegeler et al. 2013; Krakauskaite et al. 2018). The CBv measures showed similar responses as the CME measures. The absence of a measurable group effect in MBv after anodal tDCS in our study supports and contrasts the two studies that have assessed MBv after tDCS. Vernieri et al. (2010) did not observe any changes in CBv post-tDCS in healthy individuals (Vernieri et al. 2010). However, Giorli et al. (2015) reported a significant increase in CBv by 30% post-1-mA tDCS in healthy individuals (Giorli et al. 2015). It should be noted that both these studies used an electrode montage different from us; the reference electrode was placed on the ipsilateral shoulder and active electrode on the upper limb M1, which may have redirected the currents differently than ours. Even when participants were stratified based on their CME response to tDCS, responders who demonstrated 85% facilitation of the lesioned M1 did not show any tDCS-induced changes in CBv. Our initial hypothesis regarding change in CBF following tDCS was based on previous ASL, PET, fMRI and fNIRS neuroimaging studies on healthy adults that have demonstrated a significant increase in rCBF and widespread increase in oxyhemoglobin after tDCS (Lang et al. 2005; Merzagora et al. 2010; Zheng et al. 2011; Nord et al. 2013; Stagg et al. 2013). We postulate that tDCS may cause a change in local cerebral blood flow limited to the area under the electrode that may not be effectively captured by TCD which measures the response of the large cerebral arteries in response to dilation of the small vessels. An interesting observation was the lower baseline MBv in responders when compared to non-responders, similar to the baseline differences in CME between the groups. Responders and non-responders did not differ in demographics or clinical outcomes such as sex, post-stroke period, motor impairment or walking speeds suggesting that differences in demographics or function may not have influenced our subgroup analyses.

Lack of CBv changes seen in this study may have been influenced by several factors. For instance, small sample size and the observed heterogeneity in baseline CBv may add to the increased inter-individual variability reducing overall group effect. It is also possible that the choice of testing artery may have influenced our results. Our tDCS currents targeted the lower limb M1, which is mainly supplied by the anterior cerebral artery (ACA) (Ugur et al. 2005). We measured the CBv response in the MCA. We intentionally chose to study the MCA as this is the artery that is commonly measured in most TCD studies including experiments focusing on lower limb movement (Elting et al. 2014; Perry et al. 2014; Nowak-Flück et al. 2018). The ACA is harder to find compared to the MCA and is less studied. It is possible that our tDCS effects on MBv may have been more apparent if we had recorded the ACA and should be considered in future studies. We also used a slightly smaller reference electrode to accommodate for the TCD head strap. It is possible that this electrode parameter may have reduced the modulation induced by tDCS, as most studies use a larger reference electrode. Effects of tDCS may also be influenced by attention. Previous studies have shown that attention load may influence neuroplasticity effects induced with brain stimulation procedures (Kamke et al. 2012, 2014). Although we administered tDCS during rest thereby minimizing the role of attention, it is possible that for those with a right hemisphere stroke (characterized with attention deficits and neglect), the effects of tDCS may be diminished (Parton et al. 2004). CBv is influenced by several physiological factors such as carbon dioxide, temperature, blood pressure, attention or activity some of which we monitored by measuring beat-to-beat HR, blood pressure and end-tidal CO_2. We did not note any changes in these variables after tDCS thereby minimizing the extraneous factors that could cause fluctuations in CBv. Alterations in the resistance of large cerebral arteries feeding into the cerebral system (such as the internal carotid and vertebral arteries) may also influence CBv (Cipolla 2009; Payne 2016). In this study, CVRi calculated as a simple ratio of MAP upon MBv measured resistance to blood flow through the MCA of the lesioned hemisphere (van Beek et al. 2008). This resistance may result from small cerebral arteries lying in periphery of MCA and may be sensitive to the changes in vessel tone possibly indicating potential fluctuation of cerebral vessel responsiveness to maintain constant CBF during MAP perturbations (Smirl et al. 2014). We observed higher CVRi in responders as compared to non-responders with no differences in MAP. Lack of differences in MAP may indicate the influence of vessel diameter on CVRi because according to the Poiseuille's equation, resistance in a vessel segment may be inversely proportional to the fourth power of vessel diameter (Cipolla 2009; Payne 2016). A TCD study on individuals with unilateral carotid stenosis reported that those with greater vessel stenosis have higher CVRi values (O'rourke and Hashimoto 2007). Increase in degree of vessel wall stenosis showed decreased vessel diameter and increased resistance to the blood flow. The extent of blood flow to the ischemic brain may depend on the extent of carotid occlusion and, therefore, may affect changes in CME post-tDCS. We did not find any effects of tDCS on PI. PI has been shown to be determined by the interaction of central pulse pressure, harmonic fluctuations of arterial blood pressure, cerebrovascular resistance, compliance of arterial bed (stiffness of arteries) and heart rate (de Riva et al. 2012). The absence of changes in PI may also be due to insignificant effects of tDCS on arterial blood pressure and MBv.

We recognize several limitations in our study that may warrant caution in interpretation of results. This study reports data from only 13 participants. The study sample was decreased due to the exclusion of 6 participants with inefficient acoustic windows. Previous studies have reported that in older individuals and those of African ethnicity, there is limited access to the cerebral arteries through the temporal windows probably due to differences in skull and bone composition. (Krejza et al. 2007; Suri et al. 2011; Purkayastha and Sorond 2012; Bazan et al. 2015). Our study sample was further reduced when we categorized participants into responders and non-responders. Our statistical power is also limited by the multiple comparisons made within this small sample. We deliberately included participants with detectable MEPs to enable us to find associations between CME and CBF. Hence, the results of this study cannot be generalized to the stroke population. This study was meant to be an exploratory study, and a larger trial with adequate power is required to validate these results. Our study did not account for external carotid stenosis or stroke lesion information for participants, which may have influenced the interpretation of results. Our results are based on a single TMS session for identifying responders to tDCS and studies have shown that corticomotor response to tDCS varies between and within individuals. Although inter-session variability in TCD measurements may influence interpretation of our results, the high agreement for baseline MBv values measured before TCD suggests a minimal influence of TCD measurement variability.

Conclusion

We did not observe modulations in CBv after anodal tDCS in chronic stroke survivors. In addition, TMS-based stratification of responders and non-responders to tDCS did not reveal changes in CBv post-tDCS. In comparison to non-responders, responders demonstrated lower CME levels, lower CBv and higher CVRi at rest. Our interpretation of results warrant caution due to the small sample size tested in this study. Future trials with a larger sample size and

repeated measurements will help validate our findings and establish whether the understanding the relationships between neuromodulation and neurovascular mechanisms using a clinically available tool such as TCD in stroke survivors serves as a prognostic indicator of responsiveness to tDCS.

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Data accessibility Deidentified data that support the findings of this study will be available on reasonable request from the corresponding author (S.M.) after completion of secondary analyses.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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