European Journal of Applied Physiology (2019) 119:597–609
https://doi.org/10.1007/s00421-018-4027-4

ORIGINAL ARTICLE

Anodal transcranial direct current stimulation does not influence the neural adjustments associated with fatiguing contractions in a hand muscle

Achraf Abdelmoula[1] · Stéphane Baudry[1] · Jacques Duchateau[1]

Received: 1 May 2018 / Accepted: 24 October 2018 / Published online: 13 November 2018

Abstract

Purpose The objective of the current study was to investigate the mechanisms responsible for the briefer time to failure of a submaximal contraction (C2) when performed 60 min after a similar contraction (C1), and the influence of anodal transcranial direct current stimulation (a-tDCS) applied over the motor cortex on these mechanisms.

Methods In two sessions, ten adults sustained two isometric contractions (35% of maximum) to failure with the abductor pollicis brevis (APB). Before C2, either a-tDCS or sham stimulation was applied over the motor cortex. Fatigue-related changes in Hoffmann (H) and long-latency (LLR) reflexes, motor-evoked potential (MEP) induced by transcranial magnetic stimulation and associated silent period (SP), maximal motor wave (M_{max}), voluntary activation (VA), electromyographic (EMG) activity and peak force (PT_3) evoked by a 3 pulse-train (100 Hz) were investigated.

Results The results indicate that regardless of session, the time to failure was briefer (− 13%, $p < 0.05$) for C2 than C1, with no a-tDCS effect. During C1, MEP amplitude, SP duration and LLR amplitude increased, H-reflex amplitude did not change, and M_{max}, VA and PT_3 decreased ($p < 0.05$). Except for EMG activity that was greater during C2 than C1 ($p < 0.001$), all variables were similar in C1 and C2 ($p > 0.05$), and recovered their initial values after the 60-min rest, except PT_3.

Conclusions The results of the current study indicate that a-tDCS did not influence corticospinal excitability and time to failure of C2 when performed with the APB. These observations may reflect a peripheral origin of the briefer C2 time to failure in the APB.

Keywords Electromyography · Fatigue · Motor-evoked potential · Transcranial magnetic stimulation · H reflex · Long-latency reflex

Abbreviations

C1	First sustained submaximal contraction
C2	Second sustained submaximal contraction
a-tDCS	Anodal transcranial direct current stimulation
APB	Abductor pollicis brevis
H reflex	Hoffmann reflex
LLR	Long-latency reflex
TMS	Transcranial magnetic stimulation
MEP	Motor evoked potential
SP	Silent period
M wave	Motor wave
M_{max}	Maximal motor wave
VA	Voluntary activation
EMG	Electromyogram
MVC	Maximal voluntary contraction
PT_3	Peak torque evoked by 3-pulse train
Pt	Twitch force
TP	Twitch time to peak
TR1/2	Twitch half-relaxation time

Communicated by NicolasPlace.

✉ Stéphane Baudry
sbaudry@ulb.ac.be

[1] Laboratory of Applied Neurophysiology and Biology, Faculty for Motor Sciences, ULB Neuroscience Institute (UNI), Université libre de Bruxelles (ULB), 808 Route de Lennik, CP 640, 1070 Brussels, Belgium

Introduction

The corticospinal pathway consists of monosynaptic (cortico-motoneuronal) and oligosynaptic cortical projections to the spinal motor neurones pool (Pierrot-Deseilligny 1996). In human, this pathway is classically investigated by

transcranial magnetic stimulation (TMS) applied over the motor cortex (Rothwell et al. 1991). Single TMS produces a short-latency motor-evoked potential (MEP) that reflects the net excitation of the corticospinal pathway. During sustained submaximal voluntary contractions, the increase in MEP amplitude indicates a progressive augmentation of the corticospinal tract responsiveness (Lévénez et al. 2008; Sacco et al. 1997; Taylor et al. 1996). Submaximal fatiguing contractions can also lead to peripheral alterations involving several intramuscular processes (Place et al. 2010; Debold et al. 2016; Kent et al. 2016). These peripheral changes likely promote the increase in descending drive converging onto spinal motor neurones to maintain the required force level (for a review, see Taylor et al. 2016).

Transcranial direct current stimulation (tDCS) is a non-invasive technique of neuromodulation that consists of a weak direct electrical current (1–2 mA) delivered to the brain through surface electrodes (Nitsche and Paulus 2000). The anodal tDCS (a-tDCS; the anode was positioned over the motor cortical area) was found to prolong the time to task failure of a second sustained submaximal contraction performed with the elbow flexor muscles 60 min after a similar contraction (Abdelmoula et al. 2016; Cogiamanian et al. 2007) although contradictory results on elbow flexor muscles were observed using similar fatiguing protocol. (Kan et al. 2013; Muthalib et al. 2013). These divergent results may partly reflect differences in shoulder and forearm positions which influence the time to task failure of submaximal contractions and the underlying mechanisms (Enoka et al. 2011). Surprisingly, the increase in time to task failure was not accompanied by an increase in MEP amplitude (Abdelmoula et al. 2016). Similarly, a-tDCS increased the time to exhaustion of a submaximal contraction performed with the knee extensors, without influencing neural adjustments (Angius et al. 2016). As during a sustained contraction, changes in cortical excitability can be counteracted by opposite changes at spinal level (McNeil et al. 2011), a-tDCS effect on corticospinal excitability may have been masked. This is supported by the observation that a-tDCS may influence the excitability of a spinal inhibitory networks between forearm muscles (Roche et al. 2009), suggesting that effects of tDCS should not only be considered at a cortical level. Understanding the effects of a-tDCS on neural adjustments during contractions sustained to failure, therefore, requires assessing changes in different parts of the corticospinal pathway.

The present study was performed on the abductor pollicis brevis (APB) because we expected a greater a-tDCS effect as monosynaptic projections from cortical to spinal motor neurones are more pronounced in hand compared with arm muscles (Maertens de Noordhout et al. 1999). In agreement with this rationale, a-tDCS has been shown to increase corticospinal excitability in small muscles (Furubayashi et al. 2008). Furthermore, short-latency [Hoffmann (H) reflex] and long-latency reflexes (LLR) can be easily evoked in APB during voluntary contractions (Duchateau et al. 1993, 2002). As the H reflex is conveyed through a spinal loop whereas the LLR follows a transcortical pathway, at least in hand muscles (Mariorenzi et al. 1991), investigating the modulation of these two reflex responses, in addition to MEP, may provide relevant information on a-tDCS effects, and more specifically on possible opposite changes within the corticospinal pathway during the sustained contraction performed after a-tDCS. In addition to investigating the influence of a-tDCS on the time to task failure, the present study also questioned whether changes of neural and peripheral factors may limit the time to task failure of C2. We hypothesized an increase in corticospinal excitability and LLR amplitude during C2 when performed after 10 min of a-tDCS, these changes being associated with a longer time to task failure.

Materials and methods

Ten healthy men (25.5 ± 1.7 year; 2 left-handed) volunteered to participate in this investigation. None of them were engaged in regular strength training programme or reported signs of neurological disorders, cardiovascular disease or orthopaedic injury of the right upper limb that could limit their ability to perform the protocol.

After informed consent was obtained, subjects participated to two experimental sessions and were asked to refrain from exercising the arm and hand muscles for 24 h before testing. Approval for the project was obtained from the local Ethics Committee.

Experimental apparatus

Subjects were seated in an adjustable chair with the right forearm supported in a horizontal position to minimize activity in shoulder and arm muscles. The arm was slightly abducted (~ 20°) and the elbow joint flexed at 90°. The right hand was placed midway between pronation and supination in a custom-made orthosis that prevented wrist movements. The thumb was secured to a force transducer (TC 2000-50; Kulite, Basingstoke, UK) by means of a U-shape block positioned at the level of the joint between the proximal and distal phalanxes. The signal from the force transducer was A/D sampled at 200 Hz (Power 1401, 16-bit resolution, Cambridge Electronic Design, Cambridge, UK), and displayed on a monitor located in front of the subject (see "Experimental procedures").

Electromyographic recordings

The electromyogram (EMG) was recorded with surface electrodes (silver–silver chloride electrodes, 8-mm diameter) placed over the ABP after the skin was rubbed with a solution of alcohol, ether and acetone to reduce the impedance at the skin–electrode interface. The electrodes were filled with gel and held on the skin by means of adhesive tape. One electrode was placed over the muscle belly and the other over the distal tendon (monopolar recordings). The reference electrode was placed on the wrist, over the styloid process of the radius. Anatomical landmarks were used to place the electrodes at the same locations during the two experimental sessions. The EMG signals were amplified (1000×) and bandpass filtered (10–1000 Hz) prior to being A/D sampled at 2 kHz (Power 1401) and stored on a computer.

Transcranial magnetic stimulation

MEPs were elicited in the APB of the right thumb by TMS applied over the left motor cortex via a double-cone coil (Magstim 200 stimulator, Magstim, Dyfed, UK). The site of stimulation was determined by moving the coil until the site eliciting a response with the largest amplitude at a given intensity was identified ("hotspot"). The coil was then held in place by means of a custom made fixing system (Abdelmoula et al. 2016) and the position of the coil relative to the nasion and the tragus was checked throughout the experiment. The motor threshold was defined as the intensity at which three evoked responses out of five stimulations with an amplitude of at least 100 µV were discerned above background EMG level during voluntary contractions performed at the same intensity that the fatiguing contractions (see below). Thereafter, the stimulus intensity was set at 30% of stimulator output above the motor threshold (Lévénez et al. 2008) and ranged between 60 and 90% of maximal stimulator output for all subjects.

Electrical nerve stimulation

Electrical stimuli (rectangular pulses, 1 ms duration) were delivered to the median nerve at the wrist via a constant current stimulator (DS7A, Digitimer, Hertfordshare, UK) to evoke an H reflex, LLR and motor wave (M wave) in APB during steady isometric contractions [35% of maximal voluntary contraction (MVC) force]. The optimal stimulation site of the median nerve was determined by searching with a pen electrode (cathode) the location that elicited an H-reflex in the APB with the largest amplitude at a given stimulus intensity. The recruitment curve for H reflex was determined with trains of 10 stimuli at 3 Hz by progressively increasing the stimulus intensity in steps of 0.5 mA from subthreshold H-reflex intensity to intensities at which the M wave reached a plateau (M_{max}). Thereafter, the stimulus intensity for the H reflex was set to obtain a response corresponding to 50% of its maximal amplitude. In agreement with results obtained in soleus (Stein et al. 2007), the 3-Hz frequency did not induce postactivation depression of the H reflex during voluntary contractions of the APB in our experimental conditions. For M_{max}, the stimulus intensity was set 50% above the lowest intensity associated with the maximal M wave to ensure a maximal activation of the muscle throughout the experiment.

The APB force-generating capacity was assessed by recording the mechanical response induced by a train of 3 supramaximal stimuli (3-pulse train) delivered at 100 Hz.

Sustained submaximal contractions

Two submaximal voluntary contractions (C1 and C2) sustained to failure were performed by the subjects in each session. Each contraction consisted of maintaining an isometric contraction at 35% of MVC force for as long as possible with the APB. The visual gain was standardized across sessions and subjects, as follows: the standard deviation (SD) of the force measured during a brief contraction performed at 35% MVC prior to the first fatiguing task was measured and the scale of the feedback was adjusted so that the distance between the upper and lower edges of the screen to the target force corresponded to SD × 100. The intraclass correlation coefficient (ICC) for the SD of force used to setup the visual gain was 0.91 between the two experimental sessions. The contraction ended when subjects were unable to maintain the force within a range of 10% of the target value for more than 5 consecutive seconds. The same force level (35% of the maximal force measured before the first fatiguing task) was used to setup the target force for C1 and C2. C2 was performed 60 min after C1 ended.

Transcranial direct current stimulation

The a-tDCS was delivered by an electrical stimulator through a constant-current unit and an isolation unit (NeuroConn DC Stimulator, Germany) connected to a pair of electrodes (35 cm^2 electrodes), one on the scalp over the left motor cortex over the hotspot for TMS stimulation, (~ 4 cm lateral to the vertex) and the other above the right shoulder (Cogiamanian et al. 2007). We used an extracephalic reference electrode to avoid the confusion regarding the source of the after-effect as it could originate from the anodal as well as the cathodal electrode. In this regard, a single cephalic electrode on the scalp helps to resolve this ambiguity, as the observed after-effects are unlikely to be related to the extracephalic reference electrode (Priori et al. 2007). During a-tDCS, a continuous current (1.5 mA) was applied for 10 min, to produce effects lasting for up to 1 h after the

stimulation in the human motor cortex (Nitsche and Paulus 2000). The sham a-tDCS (Sham) consisted of 90 s of a-tDCS at 1.5 mA. In both a-tDCS and Sham sessions, the current was ramped-up and down over 8 s at the beginning and end of the stimulation to prevent electrical transients. Only one type of stimulation (a-tDCS or Sham) was applied during each experimental session, and the order of the sessions was counterbalanced across subjects. None of the subjects knew whether a-tDCS or Sham stimulation was applied, as underscored by the fact that after completing the two experimental sessions, participants stated that they were unable to differentiate a-tDCS and Sham sessions.

Experimental procedures

Each experimental session began by recording maximal thumb abduction force produced during MVCs lasting 4–5 s. When force of two MVCs was within 5% of each other, the greatest value was taken as the maximum and used as a reference for the submaximal contractions. Otherwise, additional trials were performed until the 5% criterion was achieved (a maximum of five trials were required to meet this criterion). The location and stimulation intensity for MEP, M_{max}, reflex responses were determined during contractions performed at 35% of maximum. Visual feedback of the force signal was provided from a monitor placed 1.5 m in front of the subject and he was asked to match a target line with the force signal. Then, to assess subject's capacity of voluntary activation (VA), they performed two MVCs during which a train of 3 supramaximal electrical stimuli (100 Hz) was triggered when the force plateaued and another one, at rest, 3 s after the MVC. Thereafter subjects performed the fatiguing contraction (C1) that was followed by a resting period of 60 min during which a-tDCS or Sham was applied in the last 10 min. At the end of this period, subjects performed an MVC, with a superimposed train of stimuli, followed by a train of stimuli triggered at rest, 3 s after the end of the MVC. Next, subjects performed C2 at the same absolute force than C1. At both C1 and C2 completion, subjects performed an MVC without relaxation between the end of the sustained contraction and the MVC. During and 3 s after the MVC, one train of electrical stimulations was triggered.

During C1 and C2, one electrical stimulus (M_{max}), four TMS pulses (MEP; 5 s between each successive stimuli), and one train of 10 submaximal stimuli (3 Hz) to elicit H-reflex and LLR responses were delivered every minute, starting 10 s after the beginning of the contraction (Figs. 1, 2).

To further document peripheral changes, six subjects came back to the lab for a third session during which C1 and C2 were performed without tDCS. During this session, the mechanical response to a single electrical pulse (muscle twitch) and 1-s train of supramaximal stimulation intensity delivered at 20 Hz and 80 Hz were recorded before and after C1 and C2.

Data reduction

The MVC force defined as the greatest value measured when the force plateaued was measured and taken as the subject's maximum force capacity. The average value of the rectified EMG (aEMG) of APB was determined over a 1-s epoch around MVC force and used as a reference to normalize voluntary EMG activity during the fatiguing contractions. Furthermore, the aEMG at task failure was normalized to the aEMG recorded during postfatigue MVC to provide a more accurate index of aEMG amplitude at task failure (Lévénez et al. 2008). During the fatiguing contractions, aEMG was measured over 3-s epoch without stimulation at the beginning, 25%, 50%, 75% and 100% of the time to failure. VA level (% of maximum) was determined according to the following equation (Allen et al. 1995): VA = [1 – (superimposed response/control response)] × 100; where the superimposed response is the force increment induced by the 3-pulse train triggered during the MVC and the control response is that evoked in the relaxed muscle 3 s after the MVC. The onset of H reflex and LLR was determined, from the rectified

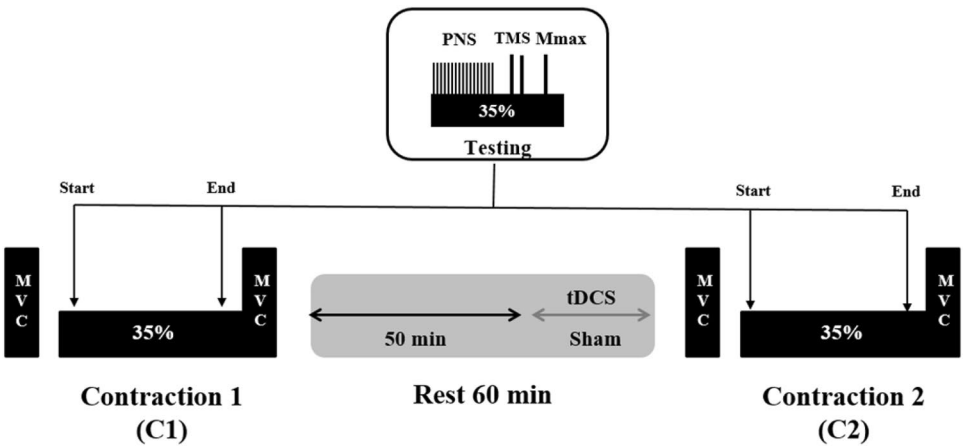

Fig. 1 Schematic description of the experimental protocol. PNS: peripheral nerve stimulation to evoke H reflex and long-latency reflex (LLR). *TMS* transcranial magnetic stimulation to evoke the motor evoked potential (MEP). *MVC* maximal voluntary contraction

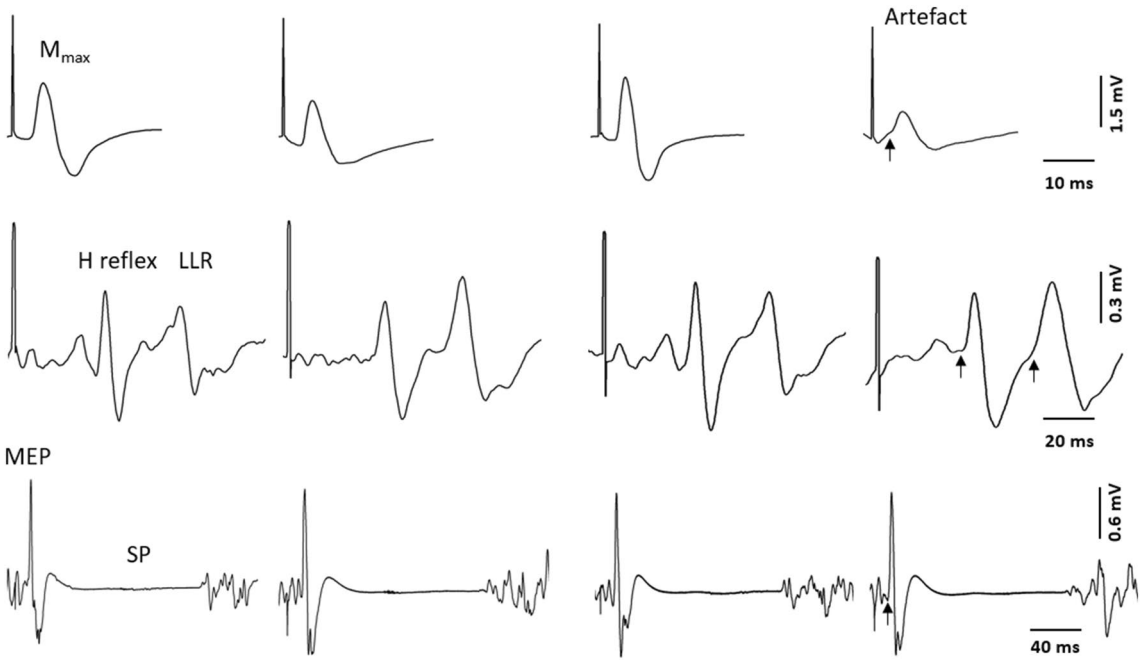

Fig. 2 Typical traces of M_{max}, H reflex, LLR and MEP recordings in the abductor pollicis brevis of one subject at the onset and end of the first (C1) and the second (C2) fatiguing contraction during tDCS session. SP represents the duration of the EMG silent period. The small arrows indicate the onset of each response

EMG signal, as an abrupt and prolonged (5–15 ms) increase above the mean background level at latencies of 25–30 ms (H reflex) and 45–55 ms (LLR) (Duchateau et al. 2002). For that purpose, the background EMG level was measured during the 15 ms preceding the H reflex. The peak-to-peak amplitude of the MEP, M_{max}, H reflex and LLR were measured from the unrectified EMG signal. The MEP, H reflex and LLR were expressed relative to the M_{max} amplitude and the ratio between LLR and H reflex amplitude was computed. The duration of the EMG silent period (SP) evoked by TMS was measured from the stimulus artefact to the return of continuous EMG activity (Lévénez et al. 2008).

The peak force recorded at rest in response to 3-pulse train (PT_3; a-tDCS and Sham sessions), single stimulus (Pt), and tetanic contractions (tetanus) at 20 Hz and 80 Hz (additional experiment, see above) were measured. As the lever arm was not measured because of the lack of precision in the determination of the centre of rotation of the thumb carpometacarpal joint, mechanical responses are expressed as forces. The time to peak (TP) and half-relaxation time ($TR_{1/2}$) for Pt and PT_3 were also measured.

Statistics

The data fitted a Gaussian distribution, as assessed by Kolmogorov–Smirnov test performed for each variable. The time to task failure of C2 was compared with those of C1 by means of 2-way ANOVA [session (a-tDCS vs. Sham) × contraction (C1 vs. C2)]. Furthermore, the duration of C2, expressed relative to the duration of C1, was compared across session by a dependent Student *t* test. This statistical approach allowed taking into account the influence of the duration of C1 on the time to task failure of C2 (Abdelmoula et al. 2016; Cogiamanian et al. 2007). Because the duration of C2 was briefer than 60 s for 2 subjects, only data recorded at the beginning and the end of each sustained contractions were used to analyse changes in evoked potentials. Three-way ANOVAs [session (a-tDCS vs. Sham) × contraction (C1 vs. C2) × time (beginning vs. end)] were used to analyse changes in MVC force, MVC aEMG, VA, MEP, SP, M_{max}, H reflex, LLR and PT_3. Tukey post-hoc test was used when interactions were significant. Cohen'*d* and partial eta squared (η^2_p) were used to estimate the effect size for variables compared with Student *t* test and ANOVA, respectively (Cohen 1988).

For the third session, the Wilcoxon test was used to compare values before C1 and C2. The level of statistical significance was set at $p < 0.05$ for all comparisons. Values are expressed as mean ± SD in the text and mean ± SE in the figures and tables.

Results

Time to task failure No significant session [$F(1,9) = 0.25$, $p = 0.63$, $\eta^2_p = 0.02$] and session × contraction interaction was found for the time to task failure [$F(1,9) = 0.21$,

$p = 0.65$]. The time to failure was significantly briefer for C2 (Sham: 171.1 ± 58 s; a-tDCS: 187.5 ± 98.6 s) compared with C1 [$F(1,9) = 6.1$, $p = 0.03$]. Furthermore, when expressed relative to C1, the time to failure for C2 was similarly reduced in Sham (− 12.7 ± 15.3%) and a-tDCS session (− 12.5 ± 18.2%, Student *t* test, $p = 0.91$, Cohen's $d = 0.01$). The duration of C1 was similar between sessions (Sham: 200.8 ± 80.7 s; a-tDCS: 210.2 ± 95.4 s; $p = 0.70$, Cohen's $d = 0.1$).

MVC force and VA The MVC force was similar before C1 and C2 in both sessions [$F(1,9) = 0.1$, $p = 0.72$]. The MVC force was decreased at the end of C1 (− 37%) and C2 (− 31%) [$F(1,9) = 34.5$, $p < 0.001$], without differences between contractions [$F(1,9) = 2.5$, $p = 0.15$] and sessions [$F(1,9) = 1.1$, $p = 0.33$, $\eta^2_p = 0.10$] (Table 1). VA was similar before C1 and C2 [96.7 ± 7.9%; 96.7 ± 8.0%, respectively; $F(1,9) = 3.4$, $p = 0.10$], and decreased by 19.3 ± 14.6% and 27.2 ± 22.1% for C1 and C2, respectively, regardless of session [$F(1,9) = 1.7$, $p = 0.22$, $\eta^2_p = 0.02$] and contraction [$F(1,9) = 2.4$, $p = 0.15$] (Table 1).

aEMG. The aEMG activity of APB at the end of C1 and C2 did not differ significantly compared with the value recorded at the beginning of the sustained contraction, regardless of the session [$F(4,36) = 0.4$, $p = 0.76$, $\eta^2_p = 0.03$; Fig. 3]. However, aEMG was greater at the beginning of C2 compared with C1 (Tukey, $p = 0.03$).

When normalized to post-fatigue MVC, the aEMG at task failure reached similar values regardless of the contraction [C1: 78.1 ± 21.4% MVC; C2: 80.4 ± 17.1% MVC; $F(1,9) = 0.3$, $p = 0.61$] and session [$F(4, 36) = 0.4$, $p = 0.81$, $\eta^2_p = 0.07$].

Evoked potentials The M_{max} amplitude was similar before C1 and C2 in both sessions [$F(1,9) = 0.3$, $p = 0.63$]. The M_{max} amplitude was decreased at the end of C1 (− 42%) and C2 (− 34%) [$F(1,9) = 53.48$, $p < 0.001$], without differences between sessions [$F(1,9) = 0.3$, $p = 0.92$, $\eta^2_p < 0.01$] (Table 2).

The H-reflex amplitude was similar before C1 and C2 in both sessions [$F(1,9) = 2.1$, $p = 0.18$]. The H-reflex amplitude (% M_{max}) did not change significantly during the fatiguing contractions [$F(1,9) = 3.9$, $p = 0.08$], regardless of sessions [$F(1,9) = 0.3$, $p = 0.59$, $\eta^2_p = 0.03$] (Fig. 4). In contrast, the LLR amplitude (% M_{max}) increased during the fatiguing contractions [~ 86.5%; $F(1,9) = 6.5$, $p = 0.03$], regardless of sessions [$F(1,9) = 0.3$, $p = 0.59$, $\eta^2_p = 0.03$] (Fig. 4). Furthermore, change in LLR was positively associated with changes in aEMG during both contractions (C1 and C2) ($r^2 = 0.31$; $p < 0.01$). The LLR/H ratio increased significantly during the sustained contractions [$F(1,9) = 19.5$, $p < 0.01$], but did not differ between sessions [$F(1,9) = 0.1$, $p = 0.93$, $\eta^2_p < 0.01$].

The MEP amplitude (% M_{max}) was similar before C1 and C2 in both sessions [$F(1,9) = 1.6$, $p = 0.23$], and increased during the two fatiguing contractions (35.3%; $F(1,9) = 29.7$, $p < 0.001$], regardless of the sessions [$F(1,9) = 0.13$, $p = 0.72$, $\eta^2_p = 0.02$] (Fig. 5). The SP increased during the two fatiguing contractions (35.3%; $F(1,9) = 50.2$, $p < 0.001$], regardless of the sessions [$F(1,9) = 0.6$, $p = 0.45$, $\eta^2_p = 0.08$] (Fig. 5).

Electrically-evoked contraction At the beginning of each session, no difference was observed for PT_3 ($p = 0.31$) that was decreased significantly [$F(1,8) = 28.3$, $p < 0.001$] after C1 and C2 (Table 1). Furthermore, PT_3 was significantly lesser before C2 than C1 [$F(1,8) = 4.9$, $p = 0.05$; Tukey $p < 0.01$]. The TP did not change significantly at the end of the fatiguing contractions, regardless of sessions [$F(1,8) = 0.2$, $p = 0.64$, $\eta^2_p = 0.04$]. $TR_{1/2}$ tended to increase during the fatiguing contractions [32.2%; $F(1,8) = 4.9$, $p = 0.06$], and was significantly greater before C2 compared with C1 [$F(1,8) = 2.3$, $p = 0.17$; Tukey $p = 0.01$].

Table 1 Mechanical and EMG responses, and voluntary activation before and after each fatiguing contraction

	Sham				a-tDCS			
	C1		C2		C1		C2	
	Before	After	Before	After	Before	After	Before	After
MVC force (N)	48.2 ± 5.4	31.7 ± 3.2*	39.6 ± 4.1	29.7 ± 3.1*	44.9 ± 4.5	27.4 ± 3.3*	39.7 ± 3.6	28.1 ± 3.6*
MVC aEMG (mV)	0.27 ± 0.02	0.17 ± 0.01*	0.21 ± 0.02	0.17 ± 0.02*	0.26 ± 0.03	0.18 ± 0.02*	0.21 ± 0.03	0.16 ± 0.02*
VA (%)	97.1 ± 2.5	75.1 ± 5.6*	95.8 ± 2.6	69.9 ± 6.1*	96.3 ± 2.4	80.1 ± 3.5*	96.7 ± 2.4	70.2 ± 8.2*
PT_3 (N)	9.5 ± 3.1	6.6 ± 2.5*	8.4 ± 2.9	6.6 ± 2.6*	7.8 ± 1.9	5.7 ± 2.1*	7.2 ± 1.7	4.9 ± 1.5*
TP (ms)	89.7 ± 10.4	85.4 ± 10.8	90.7 ± 10.9	87.3 ± 12.2	85.1 ± 6.1	87.2 ± 8.7	93.3 ± 9.9	91.7 ± 11.3
TR 1/2 (ms)	58.7 ± 7.9	82.7 ± 33.4	68.5 ± 11.5	80.8 ± 29.8	56.5 ± 9.4	83.5 ± 24.3	66.1 ± 11.1	83.1 ± 18.3

Data are expressed as mean ± SE

MVC maximal voluntary contraction, *aEMG* average electromyogram during MVC, *VA* voluntary activation, *PT_3* peak force evoked by 3-pulse train, *TP and TR1/2,* respectively, time to peak and time to half-relaxation of PT_3

*Statistical difference with values recorded before the fatiguing contraction (contraction main effect, $p < 0.05$)

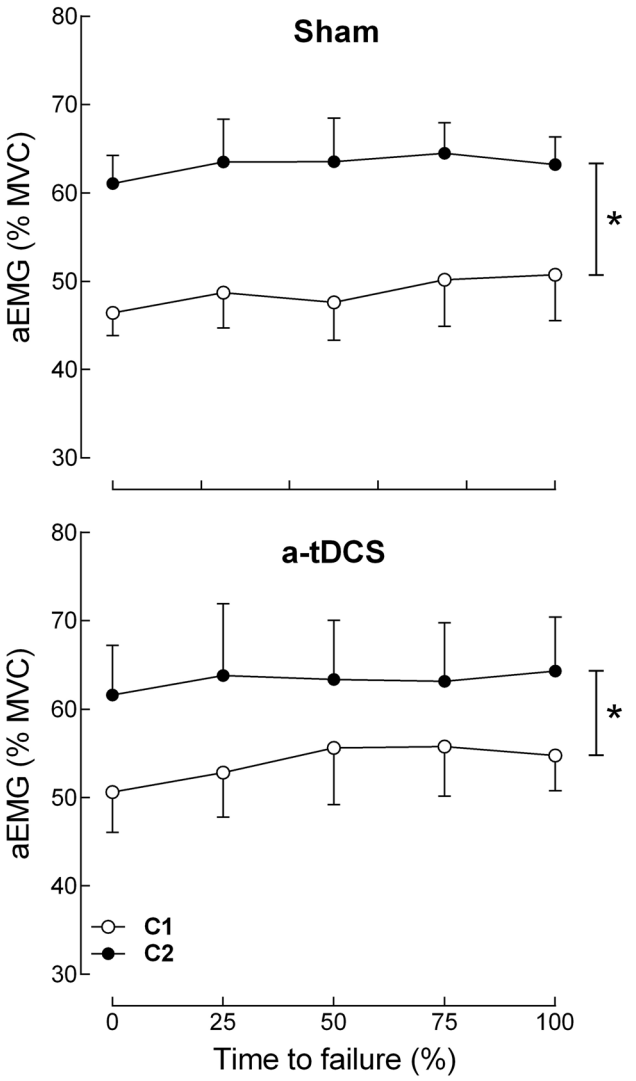

Fig. 3 Average EMG (aEMG) of abductor pollicis brevis at the onset, at 25, 50, and 75% and end (100%) of the time to failure for the first (C1; open circles) and second (C2; filled circles) fatiguing contractions, in sham and a-tDCS sessions. EMG amplitude was normalized to the value obtained during the maximal voluntary contraction (MVC) performed before the fatiguing contraction. Data are expressed as mean ± SE. Asterisk denotes significant differences (main effect) between C1 and C2 at $p < 0.05$

During the third session performed without tDCS, Pt was reduced significantly ($p = 0.03$) after both C1 (47.2%) and C2 (26.9%) and was significantly lesser ($p = 0.02$) before C2 than C1 (Table 3). TP was prolonged significantly ($p < 0.05$) but only after C1 and no difference was observed between values before C1 and C2 ($p = 0.11$). $TR_{1/2}$ increased significantly ($p = 0.03$) after C1 and tended to augment ($p = 0.07$) after C2. As for Pt, $TR_{1/2}$ was greater before C2 than C1 ($p = 0.01$).

The force evoked by the 20-Hz tetanus was reduced significantly (50.9%; $p = 0.04$) after C1 but only tended to decline after C2 (34.2%; $p = 0.07$). Compared with C1, the force was significantly lesser before C2 ($p = 0.02$; Table 3). The force evoked by the 80-Hz tetanus was reduced significantly ($p < 0.05$) after both C1 (41.1%) and C2 (46.7%), but no difference was observed before C1 and C2 ($p = 0.11$; Table 3). The 20/80 Hz tetanus force ratio did not change at the end of C1 and C2 ($p = 0.9$) but was significantly lesser prior to C2 than C1 (16.2 ± 5.3 and 13.5 ± 3.6, respectively; $p = 0.02$).

Discussion

The results of the current study indicate that a-tDCS did not influence corticospinal excitability and the time to failure of C2 when performed with the APB. The present study underscores some limitations in the use of a-tDCS to reduce muscle fatigability that may partly depend on the muscles involved in the task.

Lack of a-tDCS effect

As already reported, corticospinal excitability increases during sustained submaximal contractions (Taylor et al. 1996; Sacco et al. 1997). In our previous work performed on elbow flexor muscles (Abdelmoula et al. 2016), the increase in time to task failure after 10 min of a-tDCS was not associated with a greater increase in corticospinal excitability compared with the sham session. Similar findings on the same muscle were reported by Williams and colleagues (2013) when a-tDCS was applied during the sustained submaximal contraction. To investigate several loci of the corticospinal pathway, we used different electrophysiological techniques but none of them revealed a-tDCS effect, in agreement with the lack of change in time to task failure of C2.

The decline in VA, tested by a superimposed TMS pulse, during a prolonged exercise is classically associated with a decrease in the drive generated by centres located upstream from motor areas (i.e. supraspinal fatigue; Gandevia 2001; Lévénez et al. 2008; Taylor et al. 2016). In addition, brain activation measured by functional magnetic resonance imaging during sustained submaximal contraction shows a significant reduction not only in the supplementary motor area (Van Duinen et al. 2007) but also in other cortical areas like the primary motor cortex and cerebellum (Benwell et al. 2006a, b). Nonetheless, it should be noted that VA, tested in response to a superimposed electrical stimulation of a motor nerve, as done in our study, does not specifically reflect modulations located at cortical level. The lack of change after a-tDCS suggests, however, that it did not influence the capacity of the nervous system to drive the muscle to its maximum (Angius et al. 2016).

Table 2 Electrically-evoked potentials at the onset and end of each fatiguing contraction

	Sham				a-tDCS			
	C1		C2		C1		C2	
	Onset	End	Onset	End	Onset	End	Onset	End
M_{max} (mV)	3.9 ± 0.4	2.3 ± 0.3*	2.9 ± 0.4	2.0 ± 0.4*	3.9 ± 0.4	2.1 ± 0.3*	3.1 ± 0.3	2.1 ± 0.2*
H reflex (μV)	161.8 ± 29.3	235.9 ± 56.1	177.6 ± 29.1	204.2 ± 38.1	145.7 ± 17.5	174.4 ± 28.2	177.9 ± 20.7	217.6 ± 44.2
LLR (μV)	61.8 ± 6.1	144.1 ± 23.1*	84.9 ± 11.2	125.1 ± 40.3*	54.7 ± 7.1	131.2 ± 32.3*	77.6 ± 13.4	122.1 ± 27.9*
MEP (μV)	514.9 ± 26.3	765.8 ± 81.7	484.6 ± 35.5	599.8 ± 44.3	507.1 ± 32.5	690.9 ± 79.7	539.6 ± 46.3	682.6 ± 54.1
SP (ms)	246.3 ± 21.1	296.4 ± 29.3*	234.8 ± 22.4	315.8 ± 34.1*	214.3 ± 25.7	269.3 ± 32.4*	236.5 ± 21 0.5	272.1 ± 19.3*

Data are expressed as mean ± SE

M_{max} maximal amplitude of compound action potential, *H reflex* Hoffmann reflex, *LLR* long-latency reflex, *MEP* motor-evoked potential evoked by transcranial magnetic stimulation, *SP* duration of EMG silent period

*Statistical difference with values recorded before the fatiguing contraction (contraction main effect, $p < 0.05$)

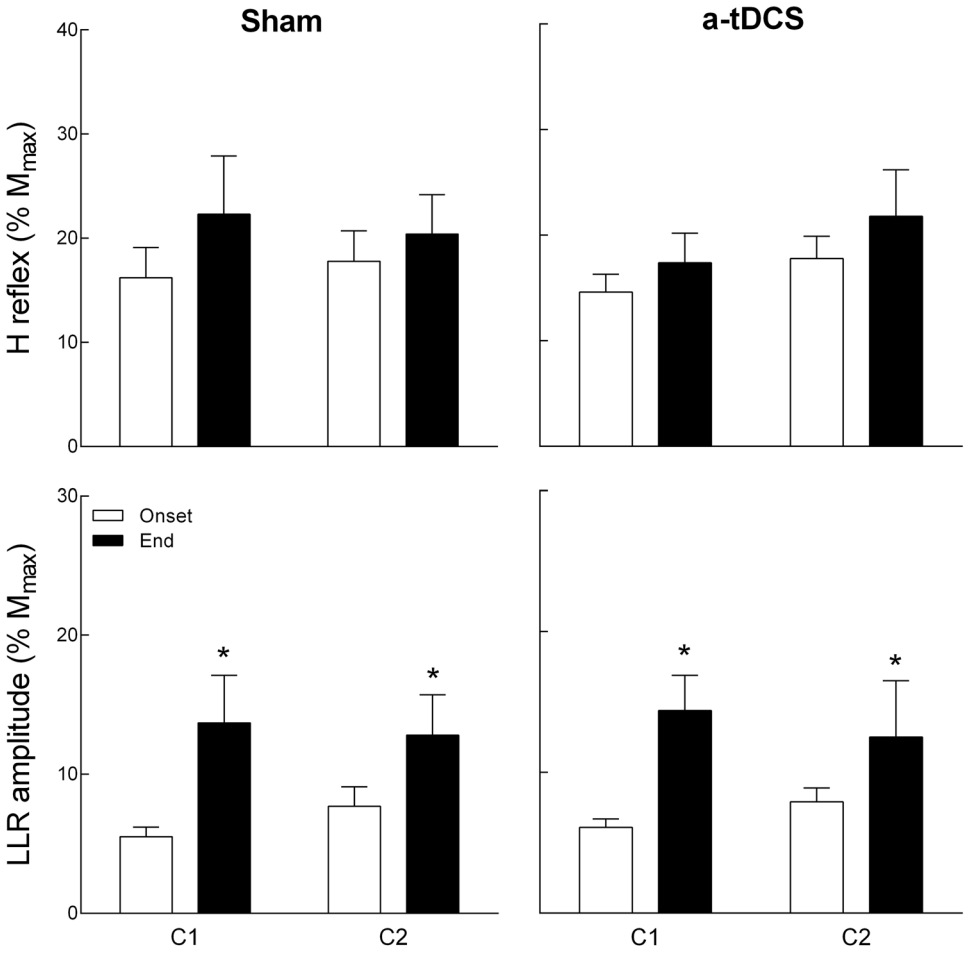

Fig. 4 Amplitude of the H-reflex and the long-latency responses (LLR), recorded in abductor pollicis brevis at the onset (open bars), and just prior to failure (filled bars) for the first (C1) and second (C2) fatiguing contractions, in sham (left panels) and a-tDCS (right panels) sessions. Reflex responses were normalized to M_{max} amplitude recorded at the same time point of the fatiguing contraction. Data are expressed as mean ± SE. Asterisk denotes significant differences with initial values at $p < 0.05$

The lack of change in MEP amplitude following a-tDCS may be related to a ceiling effect in membrane excitability of the cortical neurone resulting from the relatively high level of excitation during prolonged activation, as suggested by the APB aEMG being about 50–60% of maximum at the beginning of the sustained contractions. This may limit the range of resting motor units being susceptible to be activated by TMS. The absence of MEP modulation after a-tDCS in biceps brachii during sustained contraction that involved an activation of only ~ 30% of maximum (Abdelmoula et al. 2016), however, questions the possibility of a saturated state of the cortical neurones as a mechanism underlying the effect of a-tDCS on MEP amplitude. The similar increase in SP duration in the two sessions further supports the assumption

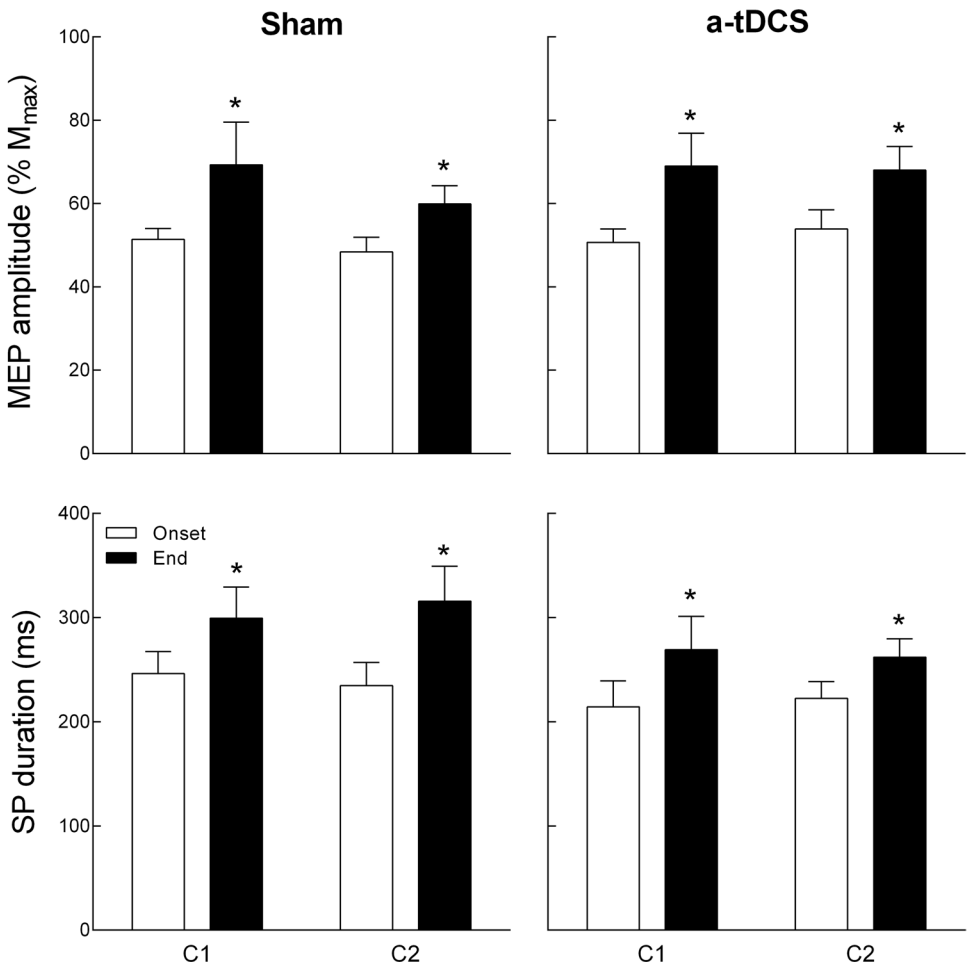

Fig. 5 Amplitude of the motor evoked potential (MEP) and the duration of the EMG silent period (SP), induced by transcranial magnetic stimulation of the motor cortex in abductor pollicis brevis at the onset (open bars), and just prior to failure (filled bars) for the first (C1) and second (C2) fatiguing contractions, in sham (left panels) and a-tDCS (right panels) sessions. MEP amplitude was normalized to M_{max} amplitude recorded at the same time point of the fatiguing contraction. Data are expressed as mean ± SE. Asterisk denotes significant differences with initial values at $p < 0.05$

Table 3 Electrically-evoked contractions before and after each fatiguing contraction without tDCS

	C1		C2	
	Before	After	Before	After
Twitch				
Pt (N)	3.6 ± 1.6	1.9 ± 1.3*	2.6 ± 1.3†	1.9 ± 1.2*
TP (ms)	71.1 ± 4.4	88.1 ± 7.7*	63.4 ± 5.2	72.8 ± 7.2
$TR_{1/2}$ (ms)	51.6 ± 5.1	78.7 ± 10.6*	52.1 ± 3.7†	63.4 ± 5.7(*)
Tetanus				
20 Hz (N)	16.9 ± 3.3	8.3 ± 1.9*	12.2 ± 3.4†	8.1 ± 2.4(*)
80 Hz (N)	25.5 ± 4.6	14.9 ± 2.4*	22.9 ± 4.8	14.2 ± 3.1*

Data are expressed as mean ± SE

Pt twitch force, *TP and* $TR_{1/2,}$ respectively, time to peak and time to half-relaxation of Pt

*Statistical difference with values recorded before the fatiguing contraction (contraction main effect, $p < 0.05$). (*) Indicates a p value of 0.07

†Statistical difference with value recorded before C1 ($p < 0.05$)

that a-tDCS did not induce specific adjustments within the motor cortex. In addition, the similar LLR amplitude before C2 in the two sessions indicates that a-tDCS did not influence the sensori-motor pathway during C2.

Together, these results suggest that the numerous changes occurring within the corticospinal pathway during C2 were not influenced by a-tDCS, likely explaining the absence of change in time to task failure of C2. This is in contrast with previous work which investigated elbow flexor muscles (Abdelmoula et al. 2016; Cogiamanian et al. 2007), questioning thereby the existence of a muscle-dependent effect of a-tDCS (Angius et al. 2017). However, it should be emphasized the lack of consensus on a-tDCS effects on time to task failure of fatiguing contractions performed with elbow flexor muscles (Angius et al. 2017). These divergent results may reflect differences in the initial activation state of the targeted network (Antal et al. 2007), task difficulty and individual cognitive performance differences (Hsu et al. 2016), as well as the absence of a standardized and reliable protocol to assess a-tDCS effect on corticospinal excitability (Madhavan et al. 2016). In addition, in our study which was conducted in healthy young subjects, a 'ceiling effect' of

single stimulation protocols might exist, which cannot be overcome by simply increasing the intensity of stimulation. Indeed, it has been shown that the enhancement or prolongation of tDCS intensity or stimulation duration is not always accompanied by an increase of its efficacy but might even change the direction of effects. (Batsikadze et al. 2013).

Neuromuscular changes during the sustained fatiguing contractions

In contrast to previous studies investigating neural adaptations during sustained contractions in elbow flexor muscles, the aEMG did not increase during the course of the sustained submaximal contractions (Abdelmoula et al. 2016; Booghs et al. 2012). This can be partly due to the smaller recruitment range of the motor neurone pool in APB (~50% MVC) than biceps brachii (~90% MVC), involving a more prominent role of rate coding in the force modulation in hand muscles (Kukulka and Clamann 1981). As changes in rate coding have less influence than motor unit recruitment on surface EMG (Mottram et al. 2005; Carpentier et al. 2001), the above motor unit pool properties may explain the lack of change in APB aEMG during the sustained submaximal contractions. This observation does not, however, preclude a progressive increase in the descending drive to spinal motor neurones, as supported by the increase in MEP amplitude and LLR/H reflex ratio during the sustained contractions (Duchateau et al. 2002). Although these changes may have reflected an increase in spinal motor neurones excitability (Duchateau et al. 2002; Rothwell et al. 1991), this possibility seems unlikely as motor neurones responsiveness is reduced during a sustained submaximal contraction (McNeil et al. 2011; Lévénez et al. 2008; Taylor and Gandevia 2008). In addition, the increased duration in EMG silent period that follows the MEP suggests greater responsiveness of intracortical inhibitory circuits. This may reflect an adaptive modulation in central activation and inhibition processes to optimize the descending drive (Benwell et al. 2006a, b, 2007; Lévénez et al. 2008; Søgaard et al. 2006).

Even if there is a safety margin (Cooper et al. 1988; Duchateau and Hainaut 1985), the reduction in M_{max} amplitude may reflect possible alterations in neuromuscular propagation, contributing thereby to reduce the force developed by the muscle. However, the decrease in the size of the mechanical responses induced by electrical stimulation (PT_3 and 80 Hz tetanus) soon after each fatiguing contraction, at a time M_{max} had completely recovered, indicates a reduction in the force generating capacity of the muscle fibres. Furthermore, the decrease in Pt without change in corresponding M_{max} amplitude when tested after each fatiguing contraction (third session), indicates an impairment in the excitation–contraction coupling (Ditor and Hicks 2000; Duchateau and Hainaut 1985). These peripheral alterations likely promote the increase in descending drive to sustain the target force level (Taylor et al. 2016), as supported by the greater EMG activity in C2.

Mechanisms involved in the briefer time to task failure for C2

As observed in previous work performed on elbow flexor muscles (Abdelmoula et al. 2016; Cogiamanian et al. 2007), the time to task failure was briefer for C2 than C1. This indicates that for both biceps brachii and APB, a resting period of 60 min was insufficient to ensure a complete recovery of the neuromuscular system. As the MVC force and VA had completely recovered prior C2 and the similar change of these parameters after C2 and C1, a deficit in descending drive is likely not responsible for its briefer time to failure. Furthermore, the M_{max} amplitude was similar at the beginning of C2 compared with C1, ruling out possible influence of alteration in neuromuscular propagation (Ditor and Hicks 2000; Duchateau and Hainaut 1985). As a consequence, the briefer time to task failure for C2 appears mainly related to changes located at peripheral level, as supported by the reduced PT_3 response prior to C2 compared with C1. Our complementary results further indicated that whether the tetanic contractions at high (80 Hz) and low frequency (20 Hz) stimulation decreased during each fatiguing contraction, only the high-frequency tetanus recovered after 60-min rest. The so-called "high-frequency fatigue", characterized by significant loss of force at high stimulation frequency, has been attributed to K^+ accumulation in the extracellular environment, particularly in the T tubules (Jones 1996; Allen et al. 2008; Place et al. 2010). Recovery from this type of impairment is usually fast (Cooper et al. 1988). Conversely, the effects of "low-frequency fatigue" (20 Hz), whose mechanism is related to alterations in excitation–contraction coupling, can last for a very long time (Edwards et al. 1977; Jones 1996; Place et al. 2010). The occurrence of peripheral fatigue after C1 and the lack of recovery after 60-min rest may explain the briefer time to failure of C2 compared with C1. Indeed, a reduction in the 20/80 Hz ratio has been correlated with a decrease in intracellular $[Ca^{2+}]$ (Hill et al. 2001). In addition, impairment of Ca^{2+} handling by the sarcoplasmic reticulum, as suggested by the longer TR1/2 before C2 in our study, and alteration in myofibrillar sensitivity for Ca^{2+} (Allen et al. 1995) may have also contributed to reduce C2 duration. The greater EMG activity (Fig. 3) and LLR amplitudes (Fig. 3) observed at the beginning of C2 likely reflect the necessity of an increased descending drive to compensate for the impaired excitation–contraction coupling (Duchateau et al. 2002; Enoka et al. 2011; Taylor and Gandevia 2008). Regardless of the exact underlying muscular mechanisms, the performance of a submaximal contraction performed 60 min after a similar

contraction appears to be mainly affected by alterations involving intracellular Ca^{2+}-controlled processes.

Difference in a-tDCS effect between muscles

Prior to the initiation of the study, we expected a more pronounced effect of a-tDCS on cortical excitability during C2 for APB compared with elbow flexor muscles (Abdelmoula et al. 2016; Cogiamanian et al. 2007). This hypothesis was based on the greater monosynaptic cortico-motoneuronal connections in hand than in arm muscles (Maertens de Noordhout et al. 1999). Our hypothesis was not verified and differences in a-tDCS effect between elbow flexors and APB should rely on other factors such as the muscles involved in the sustained contractions. It is indeed assumed that the capacity to sustain submaximal contractions varies across muscle groups because of differences in fibre-type composition and in motor unit recruitment range and change in the contribution of synergist muscles to the net force produced by the main muscles group during the contraction (Barry and Enoka 2007; Enoka et al. 2011). This likely supports the difference in EMG changes observed during the sustained contractions when performed with elbow flexors (Abdelmoula et al. 2016) and APB. Accordingly, this may influence the a-tDCS efficacy to increase the time to failure of the sustained contraction depending on the muscles involved.

It has also been suggested that a-tDCS may influence the sensorimotor integration and the associated cognitive demand (Abdelmoula et al. 2016; Cogiamanian et al. 2007). Previous work reported that the activity of the elbow flexor muscles could be more sensitive than hand muscles to an increase in cognitive processing associated with accuracy (Bloemsaat et al. 2005), such as those involved in matching the force level to the target force in the present study.

Furthermore, in contrast to thumb abduction, elbow flexion involves a greater number of synergist (biceps brachii, brachioradialis and brachialis), antagonist (triceps brachii) and postural muscles (Abdelmoula et al. 2016; Rudroff et al. 2005). This requires adjusting a greater number of available biomechanical degrees of freedom to maintain steadiness that can be controlled differently between proximal and distal upper limb muscles (Soechting 1984). A muscle-dependent effect of a-tDCS is supported by a recent study showing an increase in time to task failure of a submaximal contraction performed with the knee extensor muscles (Angius et al. 2016). The effect of a-tDCS on muscle fatigability for the elbow flexors and knee extensors but not APB raised the possibility of the influence of the muscle mass involved by the sustained contraction. Future studies are mandatory to investigate such a possibility.

In conclusion, our study indicates that a-tDCS applied over the motor cortex influences neither the time to failure, nor the adjustments within the corticospinal pathway occurring during the second sustained fatiguing contraction performed with the APB. Even if other studies do not exclude possible effects of a-tDCS when applied during the sustained contraction itself (Williams et al. 2013) or before the contraction (Abdelmoula et al. 2016; Angius et al. 2018), the present results underscore some limitations in the use of a-tDCS to reduce muscle fatigability that may partly depend on the muscles involved in the task.

Acknowledgements This study was supported by the "Conseil de la Recherche" of the "Université Libre de Bruxelles".

Author contributions AA, SB and JD conceived and designed research. AA conducted experiments. AA analyzed data. AA, SB and JD wrote the manuscript. All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

References

Abdelmoula A, Baudry S, Duchateau J (2016) Anodal transcranial direct current stimulation enhances time to task failure of a submaximal contraction of elbow flexors without changing cortico-spinal excitability. Neurosci 322:94–103. https://doi.org/10.1016/j.neuroscience.2016.02.025

Allen GM, Gandevia SC, McKenzie DK (1995) Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. Muscle Nerve 18:593–600. https://doi.org/10.1002/mus.880180605

Allen DG, Lamb GD, Westerblad H (2008) Skeletal muscle fatigue: cellular mechanisms. Physiol Rev 88:287–332. https://doi.org/10.1152/physrev.00015.2007

Angius L, Pageaux B, Hopker J, Marcora SM, Mauger AR (2016) Transcranial direct current stimulation improves isometric time to exhaustion of the knee extensors. Neuroscience 339:363–375. https://doi.org/10.1016/j.neuroscience.2016.10.028

Angius L, Hopker J, Mauger AR (2017) The ergogenic effects of transcranial direct current stimulation on exercise performance. Front Physiol 14:8:90. https://doi.org/10.3389/fphys.2017.00090

Angius L, Mauger AR, Hopker J, Pascual-Leone A, Santarnecchi E, Marcora SM (2018) Bilateral extracephalic transcranial direct current stimulation improves endurance performance in healthy individuals. Brain Stimul 11(1):108–117. https://doi.org/10.1016/j.brs.2017.09.017

Antal A, Terney D, Poreisz C, Paulus W (2007) Towards unravelling task – related modulations of neuroplastic changes induced in the human motor cortex. Eur J Neurosci 26: 2687–2691. https://doi.org/10.1111/j.1460-9568.2007.05896.x

Barry BK, Enoka RM (2007) The neurobiology of muscle fatigue: 15 years later. Integr Comp Biol 47:465–473. https://doi.org/10.1093/icb/icm047

Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA (2013) Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 591:1987–2000. https://doi.org/10.1113/jphysiol.2012.249730

Benwell NM, Sacco P, Hammond GR, Byrnes ML, Mastaglia FL, Thickbroom GW (2006a) Short-interval cortical inhibition and

corticomotor excitability with fatiguing hand exercise: a central adaptation to fatigue? Exp Brain Res 170:191–198. https://doi.org/10.1007/s00221-016-4658-9

Benwell NM, Mastaglia FL, Thickbroom GW (2006b) Reduced functional activation after fatiguing exercise is not confined to primary motor areas. Exp Brain Res 175, 575–583. https://doi.org/10.1007/s00221-006-0573-9

Benwell NM, Mastaglia FL, Thickbroom GW (2007) Differential changes in long-interval intracortical inhibition and silent period duration during fatiguing hand exercise. Exp Brain Res 179:255–262. https://doi.org/10.1007/s00221-006-0790-2

Bloemsaat JG, Meulenbroek RG, Van Galen GP (2005) Differential effects of mental load on proximal and distal arm muscle activity. Exp Brain Res 167:622–634. https://doi.org/10.1007/s00221-005-0066-2

Booghs C, Baudry S, Enoka R, Duchateau J (2012) Influence of neural adjustments and muscle oxygenation on task failure during sustained isometric contractions with elbow flexor muscles. Exp Physiol 97:918–929. https://doi.org/10.1113/expphysiol.2011.064303

Carpentier A, Duchateau J, Hainaut K (2001) Motor unit behaviour and contractile changes during fatigue in the human first dorsal interosseus. J Physiol 534:903–912. https://doi.org/10.1111/j.1469-7793.2001.00903.x

Cogiamanian F, Marceglia S, Ardolino G, Barbieri S, Priori A (2007) Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. Eur J Neurosci 26:242–249. https://doi.org/10.1111/j.1460-9568.2007.05633.x

Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Lawrence Earlbaum Associates, Hillsdale, NJ

Cooper RG, Edwards RH, Gibson H, Stokes MJ (1988) Human muscle fatigue: frequency dependence of excitation and force generation. J Physiol 397:585–599. https://doi.org/10.1113/jphysiol.1988.sp017020

Debold EP, Fitts RH, Sundberg CW, Nosek TM (2016) Muscle fatigue from the perspective of a single crossbridge. Med Sci Sports Exerc 48:2270–2280. https://doi.org/10.1249/MSS.0000000000001047

Ditor DS, Hicks AL (2000) The effect of age and gender on the relative fatigability of the human adductor pollicis muscle. Can J Physiol Pharmacol 78:781–790. https://doi.org/10.1139/cjpp-78-10-781

Duchateau J, Hainaut K (1985) Electrical and mechanical failures during sustained and intermittent contractions in humans. J Appl Physiol 58:942–947. https://doi.org/10.1152/jappl.1985.58.3.942

Duchateau J, Hainaut K (1993) Behaviour of short and long latency reflexes in fatigued human muscles. J Physiol 471:787–799. https://doi.org/10.1113/jphysiol.1993.sp019928

Duchateau J, Balestra C, Carpentier A, Hainaut K (2002) Reflex regulation during sustained and intermittent submaximal contractions in humans. J Physiol 541:959–967. https://doi.org/10.1113/jphysiol.2002.016790

Edwards RH, Hill DK, Jones DA, Merton PA (1977) Fatigue of long duration in human skeletal muscle after exercise. J Physiol 272:769–778. https://doi.org/10.1113/jphysiol. 1977.sp012072

Enoka RM, Baudry S, Rudroff T, Farina D, Klass M, Duchateau J (2011) Unraveling the neurophysiology of muscle fatigue. J Electromyogr Kinesiol 21:208–219. https://doi.org/10.1016/j.jelekin.2010.10.006

Furubayashi T, Terao Y, Arai N, Okabe S, Mochizuki H, Hanajima R, Hamada M, Yugeta A, Inomata-Terada S, Ugawa Y (2008) Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. Exp Brain Res 185(2):279–286. https://doi.org/10.1007/s00221-007-1149-z

Gandevia SC (2001) Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 81:1725–1789. https://doi.org/10.1152/physrev.2001.81.4.1725

Hill CA, Thompson MW, Ruell PA (2001) Sarcoplasmic reticulum function and muscle contractile character following fatiguing exercise in humans. J Physiol 531:871–878. https://doi.org/10.1111/j.1469-7793.2001.0871h.x

Hsu TY, Juan C, Tseng P (2016) Individual differences and state-dependent responses in transcranial direct current stimulation. Front Hum Neurosci 10:643. https://doi.org/10.3389/fnhum.2016.00643

Jones DA (1996) High- and low-frequency fatigue revisited. Acta Physiol Scand 156:265–270. https://doi.org/10.1046/j.1365-201X.1996.192000.x

Kan B, Dundas JE, Nosaka K (2013) Effect of transcranial direct current stimulation on elbow flexor maximal voluntary isometric strength and endurance. Appl Physiol Nutr Metab 38:734–739. https://doi.org/10.1139/apnm-2012-0412

Kent JA, Ørtenblad N, Hogan MC, Poole DC, Musch TI (2016) No muscle is an Island: integrative perspectives on muscle fatigue. Med Sci Sports Exerc 48:2281–2293. https://doi.org/10.1249/MSS.0000000000001052

Kukulka CG, Clamann HP (1981) Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions. Brain Res 219:45–55. https://doi.org/10.1016/0006-8993(81)90266-3

Lévénez M, Garland SJ, Klass M, Duchateau J (2008) Cortical and spinal modulation of antagonist coactivation during a submaximal fatiguing contraction in humans. J Neurophysiol 99:554–563. https://doi.org/10.1152/jn.00963.2007

Madhavan S, Sriraman A, Freels S (2016) Reliability and variability of tDCS induced changes in the lower limb motor cortex. Brain Sci 6:26. https://doi.org/10.3390/brainsci6030026

Maertens de Noordhout, Rapisarda G, Bogacz D, Gérard P, De Pasqua V, Pennisi G, Delwaide PJ (1999) Corticomotoneuronal synaptic connections in normal man: an electrophysiological study. Brain 122:1327–1340. https://doi.org/10.1093/brain/122.7.1327

Mariorenzi R, Zarola F, Caramia MD, Paradiso C, Rossini PM (1991) Non-invasive evaluation of central motor tract excitability changes following peripheral nerve stimulation in healthy humans. Electroencephalogr Clin Neurophysiol 81:90–101. https://doi.org/10.1016/0168-5597(91)90002-F

McNeil C, Giesebrecht S, Gandevia S, Taylor J (2011) Behaviour of the motoneurone pool in a fatiguing submaximal contraction. J Physiol 589:3533–3544. https://doi.org/10.1113/jphysiol.2011.207191

Mottram CJ, Jakobi JM, Semmler JG, Enoka RM (2005) Motor-unit activity differs with load type during a fatiguing contraction. J Neurophysiol 93:1381–1392. https://doi.org/10.1152/jn.00837.2004

Muthalib M, Kan B, Nosaka K, Perrey S (2013) Effects of transcranial direct current stimulation of the motor cortex on prefrontal cortex activation during a neuromuscular fatigue task: an fNIRS study. Adv Exp Med Biol 789:73–79. https://doi.org/10.1007/978-1-4614-7411-1_11

Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. Physiol 527:633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Pierrot-Deseilligny E (1996) Transmission of the cortical command for human voluntary movement through cervical propriospinal premotoneurons. Prog Neurobiol 48:489–517. https://doi.org/10.1016/0301-0082(96)00002-0

Place N, Yamada T, Bruton JD, Westerblad H (2010) Muscle fatigue: from observations in humans to underlying mechanisms studied in intact single muscle fibres. Eur J Appl Physiol 110:1–15. https://doi.org/10.1007/s00421-010-1480-0

Priori A, Mameli F, Cogiamanian F, Marceglia S, Tiriticco M, Mrakic-Sposta S, Ferrucci R, Zago S, Polezzi D, Sartori G (2007)

Lie-specific involvement of dorsolateral prefrontal cortex in deception. Cereb Cortex 8:451–455. https://doi.org/10.1093/cercor/bhm088

Roche N, Lackmy A, Achache V, Bussel B, Katz R (2009) Impact of transcranial direct current stimulation on spinal network excitability in humans. J Physiol 587: 5653–5664. https://doi.org/10.1113/jphysiol.2009.177550

Rothwell JC, Thompson PD, Day BL, Boyd S, Marsden CD (1991) Stimulation of the human motor cortex through the scalp. Exp Physiol 76:159–200. https://doi.org/10.1113/expphysiol.1991.sp003485

Rudroff T, Poston B, Shin IS, Bojsen-Møller J, Enoka RM (2005) Net excitation of the motor unit pool varies with load type during fatiguing contractions. Muscle Nerve 31:78–87. https://doi.org/10.1002/mus.20241

Sacco P, Thickbroom GW, Thompson ML, Mastaglia FL (1997) Changes in corticomotor excitation and inhibition during prolonged submaximal muscle contractions. Muscle Nerve 20:1158–1166. https://doi.org/10.1002/(SICI)1097-4598(199709)20:9%3C1158:AIDMUS11%3E3.0.CO;2-P

Soechting JF (1984) Effect of target size on spatial and temporal characteristics of a pointing movement in man. Exp Brain Res 54:121–132. https://doi.org/10.1007/BF00235824

Søgaard K, Gandevia SC, Todd G, Petersen NT, Taylor JL (2006) The effect of sustained low-intensity contractions on supraspinal fatigue in human elbow flexor muscles. J Physiol 573: 511–523. https://doi.org/10.1113/jphysiol.2005.103598

Stein RB, Estabrooks KL, McGie S, Roth MJ, Jones KE (2007) Quantifying the effects of voluntary contraction and inter-stimulus interval on the human soleus H-reflex. Exp Brain Res 182:309–319. https://doi.org/10.1007/s00221-007-0989-x

Taylor JL, Gandevia SC (2008) A comparison of central aspects of fatigue in submaximal and maximal voluntary contractions. J Appl Physiol 104:542–550. https://doi.org/10.1152/japplphysiol.01053.2007

Taylor JL, Butler JE, Allen GM, Gandevia SC (1996) Changes in motor cortical excitability during human muscle fatigue. J Physiol 490:519–528. https://doi.org/10.1113/jphysiol.1996.sp021163

Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL (2016) Neural contributions to muscle fatigue: from the brain to the muscle and back again. Med Sci Sports Exerc 48:2294–2306. https://doi.org/10.1249/MSS.0000000000000923

Van Duinen H, Renken R, Maurits N, Zijdewind I (2007) Effects of motor fatigue on human brain activity, an fMRI study. Neuroimage 35:1438–1449. https://doi.org/10.1016/j.neuroimage.2007.02.008

Williams PS, Hoffman RL, Clark BC (2013) Preliminary evidence that anodal transcranial direct current stimulation enhances time to task failure of a sustained submaximal contraction. PLoS One 8:e81418. https://doi.org/10.1371/journal.pone.0081418