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1 **Acute effects of bi-hemispheric transcranial direct current stimulation on the**
2 **neuromuscular function of patients with chronic stroke: a randomized controlled study.**

3 Geiger, M.^{1,3,4,6}, Roche, N.^{1,6}, Vlachos, E.⁵, Cattagni, T.^{1,6,7}, Zory, R.²

4 ¹AP-HP, Raymond Poincaré Teaching Hospital, Inserm Unit 1179, Team 3: Technologies
5 and Innovative Therapies Applied to Neuromuscular diseases, UVSQ, CIC 805, Physiology–
6 Functional Testing Ward, Garches, France

7 ²Université Côte d'Azur, LAMHESS, France

8 ³CIAMS, Univ. Paris-Sud, Université Paris-Saclay, 91405 Orsay Cedex, France

9 ⁴CIAMS, Université d'Orléans, 45067, Orléans, France

10 ⁵ AP-HP, Raymond Poincaré Teaching Hospital, CIC Inserm Unit 1429, Garches, France

11 ⁶Fondation Garches, Garches, France

12 ⁷Laboratory Movement, Interactions, Performance (EA4334), Faculty of Sport Sciences, University of
13 Nantes, Nantes, France

14

15 Corresponding author: Maxime Geiger, 104 Boulevard Raymond Poincaré, 92380 Garches,
16 maxime.geiger@gmail.com

17 Funding: Fondation Garches

18 Mails :

- 19 • Maxime Geiger : maxime.geiger@u-psud.fr
20 • Nicolas Roche : roche.nicolas@aphp.fr
21 • Erica Vlachos : erica.vlachos@aphp.fr
22 • Thomas Cattagni : thomas.cattagni@uvsq.fr
23 • Raphaël Zory : raphael.zory@unice.fr

24

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27 **NR and RZ:** Funding acquisition. **MG, NR and RZ:** Conceptualization, Methodology. **MG**
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33 **Abstract**

34 *Background:* Muscle weakness in patients with chronic stroke is due to neuromuscular disorders such
35 as muscle atrophy, loss of voluntary activation or weak muscle contractile properties which are
36 majored by the imbalance of interhemispheric inhibition following stroke. In patients with chronic
37 stroke, unilateral transcranial direct current stimulation improved the maximal isometric strength of
38 paretic knee extensors, but bilateral transcranial direct current stimulation failed to improve concentric
39 strength. This study aimed to assess if a bilateral current stimulation improves isometric maximal
40 strength, voluntary activation and contractile properties of knee extensors in patients with chronic
41 stroke.

42 *Methods:* Thirteen patients with chronic stroke and eight young healthy individuals participated in this
43 randomized, simple-blinded, crossover study that included two experimental sessions: one with sham
44 bilateral transcranial direct current stimulation and another with effective bilateral transcranial direct
45 current stimulation (20 min, 2 mA). In the stroke patients, the anode was placed over the primary
46 motor cortex of the affected hemisphere and the cathode over the contralateral primary motor cortex.
47 In healthy participants, the brain side targeted by the anode and the cathode was randomly assigned. In
48 each session, participants performed three assessments of strength, voluntary activation and contractile
49 properties: before, during and after effective/sham bilateral transcranial direct current stimulation.

50 *Findings:* bilateral transcranial direct current stimulation had no effect on any neuromuscular
51 assessments in both groups (All P values>0.05, partial eta-squares varied from 0.02 to 0.06).

52 *Interpretation:* a single session of bilateral transcranial direct current stimulation did not compensate
53 muscular weakness of knee extensors in patients with chronic stroke.

54 *Key words:* stroke, voluntary activation, tDCS, knee, MVC, contractile properties

55 **Abbreviations:**

- 56
- 57 • ANOVA Analysis of variance
 - 58 • EMG electromyography
 - 59 • HRT Half relaxation time
 - 60 • iMVC isometric maximum voluntary contraction
 - 61 • M1 primary motor cortex
 - 62 • RF rectus femoris
 - 63 • RMS Root Mean Square
 - 64 • tDCS transcranial direct current stimulation
 - 65 • Twpot Potentiated Twitch
 - 66 • VA voluntary activation
 - 67 • VL vastus lateralis

68 **Introduction**

69 Muscle weakness is one of the major symptoms after stroke (Teixeira-Salmela et al., 1999). The
70 mechanisms underlying muscle weakness in patients with chronic stroke are generally attributed to
71 muscle atrophy (Hunnicutt and Gregory, 2017), reduced ability to fully activate muscles during
72 voluntary effort (i.e. voluntary activation, VA) (Miller et al., 2009) or changes in muscle contractile
73 properties (Li et al., 2014). Consequently, clinical rehabilitation aims to strengthen patients' muscular
74 function and, increasingly, to improve motor neural drive from supra-spinal (Nudo, 2013). The
75 difficulty in inducing cortical adaptations in stroke patients is that, motor disorder is exaggerated by
76 transcortical asymmetry of interhemispheric inhibition, where the unaffected hemisphere excessively
77 inhibits the affected hemisphere (Murase et al., 2004). The clinical challenge is therefore to develop
78 new methods to improve the motor function of stroke patients. In this context, the use of cortical
79 neuromodulation approaches, such as transcranial direct current stimulation (tDCS), could be of
80 interest (Lindenberg et al., 2010).

81 tDCS is a non-invasive technique based on neuromodulation of cortical excitability (Nitsche and
82 Paulus, 2000), which has been used to improve motor function of lower limbs in patients with stroke
83 (Lefaucheur, 2016). The modulation of excitability is related to the polarity of the applied current.
84 When targeting the motor area, a cathodal current (cathodal tDCS) leads to reduced excitability of the
85 neurons under the electrode, as revealed by the reduced motor evoked potential induced by
86 transcranial magnetic stimulation. In contrast, increased motor evoked potential size under anodal
87 current (anodal tDCS) highlights that anodal-tDCS increases excitability of neurons under the
88 electrode (Nitsche and Paulus, 2000). When targeting the lower limb, for which cortical representation
89 is deep and close to the interhemispheric fissure, anodal-tDCS effectively increases the cortical
90 excitability of the lower limb cortical representation but cathodal-tDCS had minimal effect (Jeffery et
91 al., 2007). The effects of tDCS are characterized by large inter-individual variability (Wiethoff et al.,
92 2014). Furthermore, anodal-tDCS over leg representation of primary motor cortex (M1) in healthy
93 participants and in stroke patients has demonstrated increased excitability of targeted M1 and a
94 concomitant decreased excitability in the contralateral M1 (Madhavan and Stinear, 2010). As
95 previously mentioned, motor deficit in stroke patients results in interhemispheric inhibition (Murase et
96 al., 2004). To decrease the asymmetry of interhemispheric inhibition, bilateral-tDCS could be used to
97 increase the excitability of the affected hemisphere and decrease the excitability of the unaffected
98 hemisphere (Lefebvre and Liew, 2017). Some findings demonstrate that bilateral-tDCS induces a
99 larger decrease in interhemispheric inhibition from the unaffected hemisphere to the affected
100 hemisphere than unilateral tDCS (Tazoe et al., 2014).

101 In stroke patients, previous studies showed that tDCS may facilitate the motor performance of lower
102 limbs (Elsner et al., 2013). Specifically, for lower limb strength, two studies reported an improvement
103 in the isometric maximum voluntary contraction (iMVC) torque of knee extensors compared to the
104 sham condition after 10 min at 2 mA of anodal-tDCS in patients with chronic stroke (Sohn et al.,
105 2013; Tanaka et al., 2011). Based on the larger modification of interhemispheric inhibition after
106 bilateral-tDCS compared to unilateral-tDCS and on the results of Tanaka et al, (2011), Montenegro et
107 al., (2016) assessed the effects of 20 min at 2 mA of bilateral-tDCS on the torque during concentric
108 maximum voluntary contraction (MVC) of knee extensors and knee flexors in patients with chronic
109 sub-cortical stroke (Montenegro et al., 2016). While they found improved force steadiness for both
110 muscle groups after bilateral-tDCS, they did not report changes in concentric MVC knee extensors.
111 Montenegro et al., (2016) assumed that the dissimilarity between their results (no effect of tDCS) and
112 those of Tanaka et al., (2011) (torque improvement with tDCS) may be attributed to different
113 contraction modes (concentric vs isometric), given that the processes underlying these two types of
114 contractions are different (Babault et al., 2006). Montenegro et al., (2016) indicated that concentric
115 contraction could induce a hamstring stretch reflex exaggeration that could inhibit knee extensors, as
116 previously observed in spastic paraparetic patients (Knutsson et al., 1997; Montenegro et al., 2016).
117 This mechanism could explain why no maximal neuromuscular performance effect was observed in
118 the Montenegro et al., (2016) study. However, these authors did not address outcomes for the neural
119 and/or muscle mechanisms that underlie the maximal performance of the neuromuscular function in
120 stroke patients.

121 The aim of this randomized sham-controlled study was to assess the effects of bilateral-tDCS on
122 maximal isometric force production and muscle activation of knee extensors for the paretic leg of
123 stroke patients. We therefore assessed iMVC torque, voluntary activation, EMG activity of knee
124 extensors after, during, and before the application of bilateral-tDCS. We hypothesized that, compared
125 with the sham condition, knee extensors iMVC and activation would increase during and after
126 bilateral-tDCS. To assess whether potential bilateral-tDCS-related changes in neuromuscular
127 performance are linked to stroke, a control group, including healthy participants was also included.

128 **Methods**

129 **Subjects**

130 The sample size for patients with chronic stroke was predetermined using the G*Power software
131 (Universität Kiel, Kiel, Germany) and calculated based on the results of the study of Tanaka et al.,
132 (2011). For an expected increase in iMVC torque of 20%, a standard deviation (SD) of iMVC of 20%,
133 a statistical power of 0.9, a required sample size of 11 patients with chronic stroke was obtained to

134 investigate potential bilateral-tDCS-related changes in maximal knee extensors performance. Then, it
135 was decided to include 14 participants in the experiment, to account for potential dropouts. Initially,
136 14 patients were included but one patient did not complete all the study protocol. Finally, 13 patients
137 with chronic stroke [2 women, 6 right hemiparesis, age: 57.3 (11.6) years, anteriority of stroke: 8.7
138 (5.1) years, mean (SD)] were included in this study. All characteristics of patients with chronic stroke
139 are displayed in Table 1. Stroke patients were recruited during routine follow-up visits in the Physical
140 Medicine and Rehabilitation department of the university teaching hospital. They were eligible for
141 inclusion if: they had signed the information memorandum; were at least 18 years of age; were
142 hemiplegia post-stroke for more than 6 months; were walking with or without technical assistance;
143 were able to follow recommended guidelines. All patients with stroke gave their written consent prior
144 to participation. The study was approved by the local Ethics Committee (“Comité de protection des
145 personnes Ile de France IV”; reference number: 14025 / ClinicalTrials.gov: NCT02109796). In
146 addition, a control group of 8 young healthy participants [3 women, age: 24.8 (2.3) years] was also
147 included to this work. These participants have been evaluated prior to the beginning of this clinical
148 trial. They also gave their written consent prior to participation. The study was performed in
149 accordance with the ethical codes of the World Medical Association (Declaration of Helsinki, last
150 update from October 2013).

151 --Table1—

152 **Study design and experimental procedure**

153 This study used a randomized, sham-controlled and simple blind crossover experimental method. The
154 study design is available in Figure 1. Each subject participated in two randomized visits separated by
155 at least 7 days: one with effective bilateral-tDCS and one with sham bilateral-tDCS. For each visit, a
156 neuromuscular assessment of knee extensors was performed before (pre-stimulation), during (per-
157 stimulation) and immediately (post-stimulation) after bilateral-tDCS. The knee extensors of the paretic
158 limb were tested in stroke patients while the knee extensors of dominant or non-dominant limb
159 (randomly assigned) were tested in healthy participants. A standardized warm-up including 5
160 submaximal isometric contractions was performed by each participant 5 minutes before the first
161 neuromuscular assessment (pre-stimulation). Each neuromuscular assessment included 2 iMVCs
162 without superimposed electrical nerve stimulation and then 2 iMVCs with electrical nerve stimulations
163 during (superimposed twitch) and after (potentiated twitch). For each iMVC, participants were asked
164 to contract their knee extensors as strong as possible, and to maintain the effort for 5 seconds (to
165 observe a torque plateau when possible). A rest period of 30 seconds was included between each
166 MVC. iMVCs with superimposed stimulation were performed to assess voluntary activation level
167 using the "interpolation twitch technique" (Gandevia, 2001). This technique consists of superimposing

168 a percutaneous electric stimulation (a twitch) on the femoral nerve during the torque plateau phase of
169 iMVC and three seconds after iMVC at rest (potentiated twitch) (Krishnan and Williams, 2010).
170 iMVCs with superimposed stimulation were obtained in all healthy participants and only in 10 patients
171 with chronic stroke. Indeed, for 3 patients with chronic stroke, electrical nerve stimulation induced too
172 much discomfort (i.e. >5 on a 0-10 visual analogue scale, where 0 is no discomfort and 10 is an
173 extremely important discomfort). The entire experiment, including data collection, was performed by
174 the same operator.

175 -- Figure 1 --

176 **Randomization**

177 The randomization was performed at the hospital's Clinical Investigation Technological Innovation
178 Centers. The allocation of the first visit (effective or sham tDCS) was concealed in sealed envelopes.
179 The envelopes were opened by the investigator at the end of the pre-evaluation of the first visit.

180 **Transcranial Direct Current Stimulation**

181 Anodal-tDCS was administered through a pair of electrodes covered by saline-soaked sponges (7 cm×
182 5 cm, 35 cm²). The current was delivered by a constant-current stimulator (Eldith-DC, NeuroConn
183 GmbH, Germany). In stroke patients, the anode was placed over M1 of the affected hemisphere and
184 the cathode over M1 of the unaffected hemisphere, both with regard to the leg's cortical
185 representation: laterally to Cz of the international electroencephalogram 10–20 system (Klem et al.,
186 1999). In healthy participants, the placement of the anode and the cathode was randomized: the anode
187 was placed either on the dominant hemisphere or on the non-dominant hemisphere (the cathode was
188 placed contralaterally), also with regard to leg's cortical representation (Figure 2). During the effective
189 bilateral-tDCS visit, the stimulation intensity was 2 mA and the duration of stimulation was 20
190 minutes, the current had a ramp time of 8 seconds at the beginning and at the end of stimulation.
191 During the “sham” visit the electrodes were placed in the same way as the effective tDCS visit, but the
192 current was only applied for 120 seconds to induce a pruritic sensation, as well as the effective
193 bilateral-tDCS condition. As shown by Nitsche and Paulus (2000), this duration is not sufficient to
194 induce changes in neuronal excitability, which would need the current to be applied for at least 3
195 minutes (Nitsche and Paulus, 2000).

196 -- Figure 2 --

197 **Data collection**

198 **Torque recordings**

199 iMVCs were assessed by an isokinetic dynamometer (Biodex, Shirley Corporation, NY, USA;
200 sampling frequency: 150Hz). The participants were sitting down on the isokinetic dynamometer chair
201 with a hip angle of 85° (0°: complete hip extension) and a knee angle of 85° (0°: complete knee
202 extension). To avoid muscular compensation of other parts of the body during the knee extensors
203 assessment, the trunk and the assessed limb positions were maintained using straps placed around the
204 chest, the waist and the thigh. The axis of the dynamometer arm was visually aligned with the articular
205 center of the tested knee, defined by a line passing between the medial and lateral femoral
206 epicondyles. The distal attachment of the lower limb with the arm of the dynamometer was set at 3 cm
207 above the lateral malleolus.

208 **Electrophysiological recordings**

209 Participants were equipped with an electromyographic (EMG) analysis system composed of 2 surface
210 electrodes (Bagnoli-4, Delsys Inc., Boston, USA; Sampling frequency: 2000Hz). The EMG activity of
211 the rectus femoris (RF) and the vastus lateralis (VL) of the limb studied (paretic lower limb in stroke
212 patients, dominant or non-dominant in healthy participants) was recorded during all assessments. The
213 surface electrodes were placed on the participants' skin. The VL electrode was placed at the 2/3 point
214 along the line from the great trochanter to the lateral side of the patella, the RF electrode was placed 5-
215 10 cm above the patella to limit the stimulation artifact of the electrical stimulation (used to study the
216 superimposed MVC) (Pierrot-Deseilligny and Burke, 2012).

217 **Electrical stimulation**

218 The electrical stimulation was manually delivered using a Digitimer DS7A (Digitimer Ltd;
219 Hertfordshire, United Kingdom); the spherical cathode was placed above the femoral triangle and held
220 in place by a bag of sand; the rectangular anode was placed under the thigh. A single rectangular pulse
221 with a 1-ms duration was used and the stimulation intensity was set to induce the maximum peak-to-
222 peak amplitude of compound action potential (M wave) (Fimland et al., 2011). Since the number of
223 pulses (single vs. double pulse) does not affect the assessment of voluntary activation (Allen et al.,
224 1998; Scaglioni and Martin, 2009), we chose to stimulate the nerve trunk using single pulse rather than
225 multiple pulses to optimize the comfort of participants, especially that of patients with chronic stroke.

226 **Data analysis**

227 Throughout the analysis, we used data from the highest standard iMVC torque and highest
228 superimposed iMVC torque. The iMVC torque was considered as the highest peak torque value

229 measured over each two standards and two superimposed trials. The voluntary activation level was
230 estimated according to the following formula (Hureau et al., 2016; Strojnik and Komi, 1998):

$$231 \quad VA (\%) = 100 - [d (\text{Superimposed torque} / \text{Voluntary torque}) / \text{Potentiated twitch}] * 100$$

232 Where VA means voluntary activation, d is the difference between superimposed torque and torque at
233 stimulation artefact.

234 The Root Mean Square (RMS) of RF and VL EMG was calculated over a time interval of 500 ms
235 around the maximum force value of MVC. The RMS value was then normalized to the corresponding
236 M-wave (induced by the electrical stimulation at rest, after the contraction) for the RF ($RF_{EMG-RMS/M}$)
237 and VL ($VL_{EMG-RMS/M}$). EMG-RMS is mainly influenced by central and peripheral factors whereas M-
238 wave is influenced by peripheral factors (Rodriguez-Falces and Place, 2018). M-wave amplitude and
239 duration were subsequently used to assess neuromuscular transmission (Rodriguez-Falces and Place,
240 2018) and EMG-RMS/M was used to assess central activation. Contractile properties were assessed by
241 measuring potentiated twitch amplitude, contraction time and half-relaxation time (Miller et al., 1987).

242 **Statistical Analyses**

243 All statistical analyses were carried out using the Statistica ® version 7.1 software. The level of
244 statistical significance was set at $p < 0.05$.

245 Separate analysis of variance tests (ANOVAs) were performed on the amplitudes for iMVC, voluntary
246 activation, EMG activities and contractile properties; with group ($\times 2$: healthy participants vs. patients
247 with stroke) as the between-participants factor, and stimulation condition ($\times 2$: Sham vs. Effective) and
248 time ($\times 3$: Pre vs. Per vs. Post) as the within-participants factor. Post hoc comparisons were performed
249 using Tukey test. Effect sizes for each ANOVA were calculated as partial eta squares (η_p^2).

250 **Results**

251 All data from stroke patients and healthy participants are available in Table 2 and Table 3,
252 respectively. In the result section, only crucial results as the interaction between condition, time and
253 group or between only time and group will be presented. All the group effects are available as
254 supplementary material.

255 **Mechanical properties**

256 The Figure 3 show the individual response to effective and sham tDCS on iMVC torque in patients
257 with chronic stroke. There was no interaction between condition, time and group on iMVC ($F=0.32$,
258 $df=2$, $p=0.72$, $\eta_p^2=0.02$). The repeated measures ANOVA revealed no effects of interactions between

259 condition, time and group on voluntary activation ($F=0.68$, $df=2$, $p=0.51$, $n_p^2=0.06$). There was no
260 interaction between condition, time and group on the potentiated twitch ($F=0.42$, $df=2$, $p=0.65$,
261 $n_p^2=0.03$). There was no interaction between condition, time and group on contraction time ($F=0.77$,
262 $df=2$, $p=0.47$, $n_p^2=0.05$). A significant interaction between time and group was observed for the half-
263 relaxation time ($F=5.50$, $df=2$, $p=0.01$, $n_p^2=0.31$). The Tukey test showed that, in stroke patients, half-
264 relaxation time increased over time and was higher than in healthy participants. There was no
265 interaction between condition, time and group on the half-relaxation time ($F=0.007$, $df=2$, $p=0.99$,
266 $n_p^2<0.01$).

267 **Electrophysiological properties**

268 There was no interaction between condition, time and group on the $RF_{EMG-RMS/M}$ ($F=0.70$, $df=2$,
269 $p=0.50$, $n_p^2=0.07$) and on the $VL_{EMG-RMS/M}$ ($F=0.95$, $df=2$, $p=0.41$, $n_p^2=0.13$). The repeated measures
270 ANOVA revealed no effects of group, time or condition, and no interaction between these factors on
271 the M amplitude and duration of RF (respectively $F=2.45$, $df=2$, $p=0.11$, $n_p^2=0.21$ and $F=2.81$, $df=2$,
272 $p=0.07$, $n_p^2=0.15$) and VL (respectively $F=1.30$, $df=2$, $p=0.30$, $n_p^2=0.12$ and $F=0.99$, $df=2$, $p=0.37$,
273 $n_p^2=0.06$).

274 --Table 2 --

275 -- Table 3 --

276 -- Figure 3 --

277 **Discussion**

278 The aim of this study was to assess the acute effects of bilateral-tDCS on maximum voluntary strength
279 and activation of paretic knee extensors in patients with chronic stroke compared to healthy
280 participants. No significant improvement of isometric knee extensors performance was found during
281 and after bilateral-tDCS in both groups. This novel observation added to the work of Montenegro et
282 al., (2016) (for concentric contractions) highlights the limits for the use of bilateral-tDCS as an acute
283 treatment for improving neuromuscular function of lower limb in patients with chronic stroke,
284 regardless of muscle contraction mode (isometric and concentric). In this discussion, only the main
285 results will be discussed, however we also performed a comparison of our data with data in the
286 literature such as maximal strength and voluntary activation of healthy participants and patients with
287 stroke in other studies which is available as supplementary material.

288 Our results showed that iMVC torque was not statistically improved by bilateral-tDCS, neither the
289 mechanical properties, nor the electrophysiological properties in both groups. In healthy participants,

290 these results are in accordance with Montenegro et al., (2015) and with the review of Angius et al.,
291 (2017) who reported no improvement on neuromuscular performance in healthy participants after
292 tDCS (Angius et al., 2017; Montenegro et al., 2015). In patients with chronic stroke, the absence of
293 significant effects of bilateral-tDCS treatment is also in accordance with a previous study. Montenegro
294 et al., (2016) found no significant improvement in patients with chronic sub-cortical stroke on
295 concentric MVC torque of knee extensors after 20 min at 2 mA of bilateral-tDCS over both M1
296 (Montenegro et al., 2016). Montenegro et al., (2016) assumed that this lack of effect was due to the
297 concentric contraction mode, but the present study also failed to observed bilateral-tDCS-effects on
298 maximal motor performance with isometric contractions. Our results are in contrast not in agreement
299 with Tanaka et al., (2011) who found an improvement of iMVC torque of knee extensors in patients
300 with chronic stroke after anodal-tDCS (Tanaka et al., 2011). While the contraction mode appears not
301 to be involved in the absence of a bilateral-tDCS-related effect on maximal motor performance, this
302 kind of stimulation deserves to be questioned: is it the use of bilateral-tDCS instead of unilateral-tDCS
303 that leads to an absence of effects? Indeed, Vines et al., (2008) observed that bilateral-tDCS is more
304 efficient than unilateral-tDCS in improving motor learning of the non-dominant hand in healthy
305 participants (Vines et al., 2008). Bilateral-tDCS may also improve motor learning (Lefebvre et al.,
306 2012) and motor recovery in the paretic hand in stroke patients (Lindenberg et al., 2010). Motor
307 learning and motor recovery are closely related processes (Krakauer, 2006) whose responses to tDCS
308 are not identical to the maximal motor performance responses to tDCS (Karok et al., 2017). Thus,
309 perhaps bilateral-tDCS should preferentially be used to improve motor learning rather than maximal
310 motor performance. A final explanation for the absence of significant effects of bilateral-tDCS on
311 motor performance could be the inter-individual variability in response to tDCS. Wiethoff et al.,
312 (2014) showed that in 53 healthy participants, approximately 50% of the participants showed only a
313 minor response or even no response to tDCS (Wiethoff et al., 2014). Furthermore, in anodal conditions
314 about 25% of participants showed an inhibition of cortical excitability and in cathodal conditions
315 about 40% showed an excitation (Wiethoff et al., 2014). Thus, it can be assumed that the participants
316 in our study presented no or low sensitivity to bilateral-tDCS. In this regard, the assessment of cortical
317 excitability under bilateral-tDCS could help us predict the real effects of bilateral-tDCS for each
318 participant.

319 In the current study, we only focused on the acute effects of bilateral-tDCS on knee extensor
320 performance. Therefore, possible effects for chronic application of bilateral-tDCS (repeated sessions)
321 cannot be thus discarded based on our work. The chronic effects of tDCS on maximal muscle strength
322 has been poorly investigated. Khedr et al., (2013) has shown a small effect of 6 consecutive sessions
323 of anodal and cathodal tDCS cathodal-tDCS (25 min at 2 mA) on muscle strength (hand grip, shoulder
324 abduction, toes dorsiflexion, and hip flexion) in patients with acute stroke (Khedr et al., 2013). In

325 contrast, a recent meta-analysis showed that tDCS (6 studies with an anodal setup and 2 studies with
326 cathodal setup) does not significantly improve the upper extremity impairment of patients with acute,
327 sub-acute or chronic stroke (Tedesco Triccas et al., 2016). Danzl et al., (2013) also found no effect of
328 12 sessions (3 sessions per week for 4 weeks) of anodal tDCS anodal-tDCS (20 min at 2 mA)
329 combined with robotic gait orthosis on several functional assessments (e.g., the timed up and go test
330 and the berg balance scale) in patients with chronic stroke. Taken together, these few studies highlight
331 the low efficacy of repeated tDCS sessions to improve motor function of patients with stroke

332 **Limitations**

333 This study has several limitations. The first limitation is that we did not investigate the cortical
334 excitability of M1 across visits and time, so we cannot be sure that bilateral-tDCS modulated the
335 cortical excitability as expected. The second limitation is that the VA standard deviation of stroke
336 patients was larger than the standard deviation for healthy participants, which may obscure potential
337 differences in VA between groups or during the experiment. The variability of the measure for stroke
338 patients may therefore be a limiting factor for VA comparisons. The third limitation is that the sample
339 of patients was heterogenic, unlike Montenegro et al., (2016) who recruited only patients with
340 subcortical lesions. This possibly added high heterogeneity to our sample of patients, which may
341 interfere with bilateral-tDCS. Indeed, Luft et al, (2004) showed that cortical activation of knee
342 extension is similar between healthy participant and chronic sub-cortical stroke patients but differs in
343 patients with chronic cortical stroke (Luft et al., 2005). However, we performed a statistical analysis
344 by adding the lesion location (i.e., complete and deep location, visible in Table 2) as a categorical
345 variable and it did not reveal any interaction of lesion location on the effects of bilateral-tDCS (data
346 not presented). Despite our small sample size (which was calculated prior to the study), the non-
347 significant results of our main variables are associated with small-to-medium partial eta-squared (0.02
348 for iMVC torque, 0.06 for voluntary activation, according to Cohen (1988) guidelines (Cohen, 1988).
349 The probability of a type 2 error therefore is unlikely. Nevertheless, our results will need to be
350 confirmed in a larger sample size, especially since we based our sample size calculation on the study
351 of Tanaka et al. (2011) in which only 8 patients with chronic stroke were included. Finally, despite all
352 our methodological precautions for installing patients on the isokinetic dynamometer, there is an
353 inevitable difference in dynamometer and knee joint angles that may have affected the results of the
354 present study (Arampatzis et al., 2004).

355 **Conclusion**

356 The results of the present study suggest that a single session of bilateral-tDCS does not significantly
357 improve maximal voluntary strength of the knee extensors muscles by enhancing their efferent neural

358 drive in patients with chronic stroke as well as in healthy individuals. To date, only unilateral-tDCS
359 has demonstrated its effectiveness to acutely compensate, at least in part, the maximal voluntary
360 strength deficit in patients with chronic stroke (Sohn et al., 2013; Tanaka et al., 2011). For clinicians
361 who wish to include tDCS sessions in the clinical management of patients with chronic stroke to
362 improve their maximal muscle activation, we therefore advise to use unilateral-tDCS rather than
363 bilateral-tDCS, pending further studies on bilateral-tDCS with larger sample and greater statistical
364 power (which may confirm or invalidate our results).

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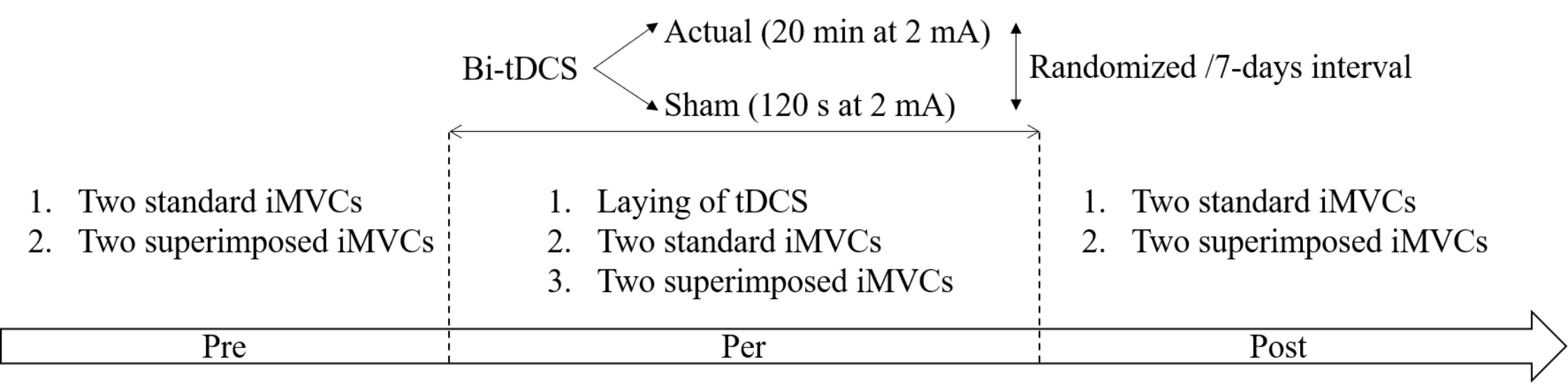
513 **Figure captions**



514 **Fig 1 study design of the two visits and the Pre, Per and Post tDCS evaluations.** iMVC: isometric
515 maximum voluntary contraction; tDCS: transcranial direct current stimulation

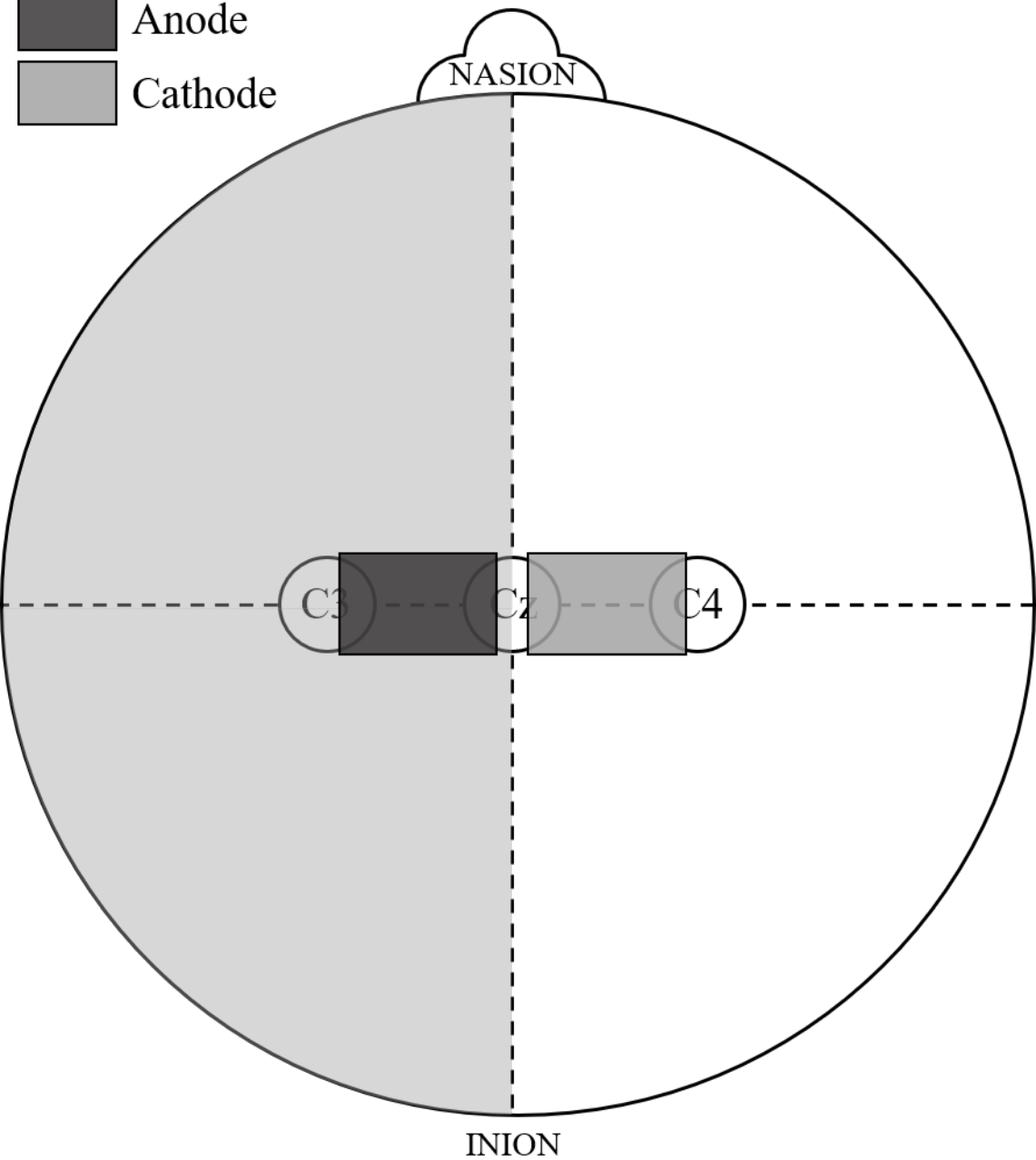
516 **Fig 2 schematic illustration of the bilateral-tDCS setup.** The gray area represents the affected
517 hemisphere for stroke patients and dominant or non-dominant hemisphere in healthy participants

518 **Fig 3 illustration of the evolution of iMVC torque of knee extensors in: A) patients with chronic**
519 **stroke; B) healthy subjects according to tDCS condition (effective or sham) and time (pre, per,**
520 **post).** iMVC: isometric maximum voluntary contraction; tDCS: transcranial direct current stimulation

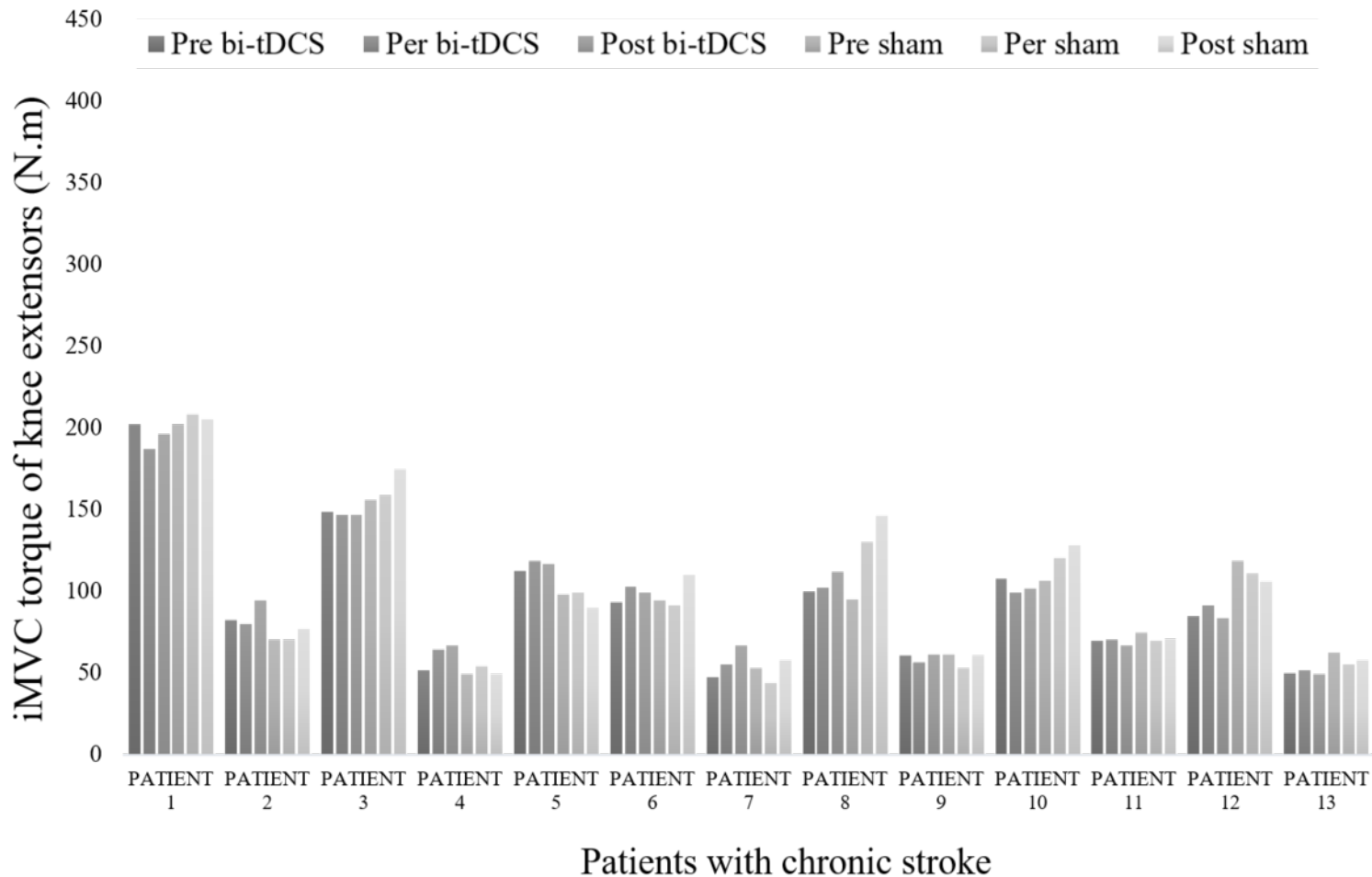
521



 Anode
 Cathode



A



B

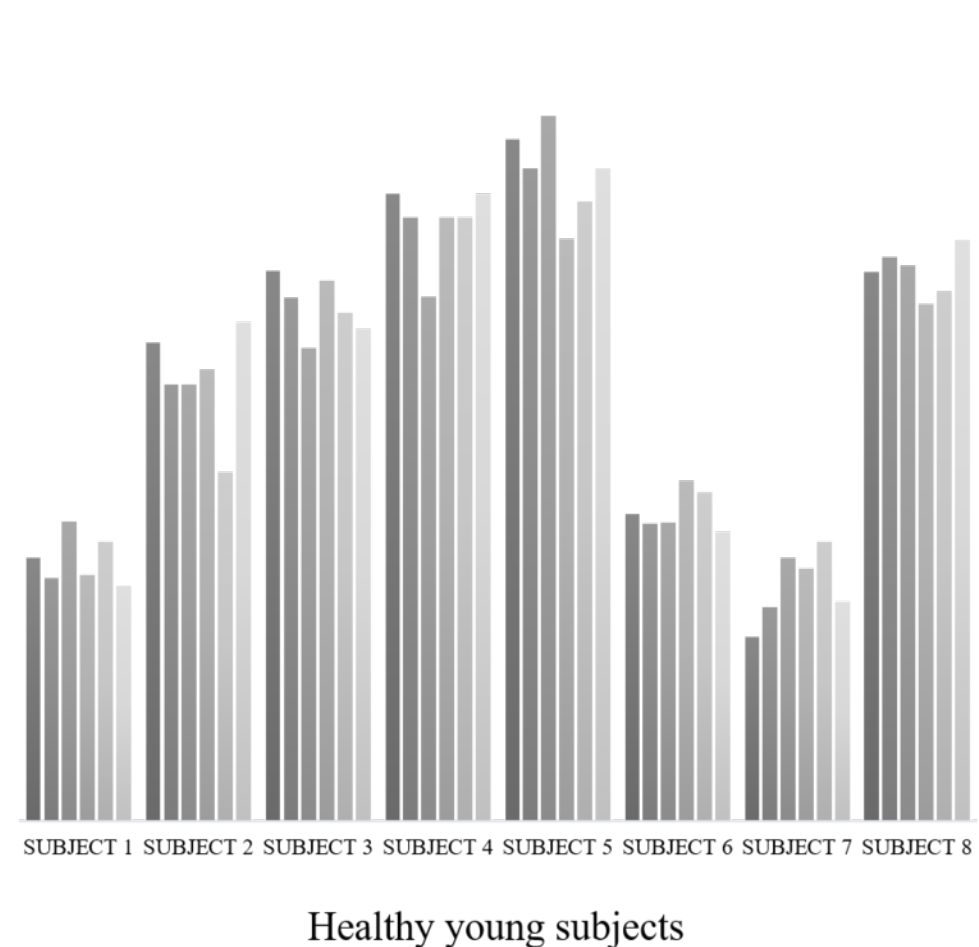


Table 1: Patients' characteristics. A complete stroke location means an involvement of cortical and subcortical lesions, a deep location means only a subcortical lesion.

<i>Patients</i>	<i>Sex</i>	<i>Age (year)</i>	<i>Weight (kg)</i>	<i>Size (cm)</i>	<i>Time since onset (year)</i>	<i>Side of paresia</i>	<i>Stroke type</i>	<i>Stroke location</i>
<i>1</i>	Man	55	106	176	10	Right	Ischemia	Complete
<i>2</i>	Man	55	84	172	1	Left	Ischemia	Deep
<i>3</i>	Man	52	50	160	10	Left	Ischemia	Deep
<i>4</i>	Man	63	70	170	8	Right	Ischemia	Deep
<i>5</i>	Woman	71	58	152	11	Left	Ischemia	Deep
<i>6</i>	Woman	40	55	160	7	Right	Hemorrhage	Deep
<i>7</i>	Man	66	66	178	6	Right	Ischemia	Complete
<i>8</i>	Man	74	80	174	10	Right	Hemorrhage	Complete
<i>9</i>	Man	45	86	186	18	Left	Hemorrhage	Complete
<i>10</i>	Man	39	72	170	12	Left	Hemorrhage	Complete
<i>11</i>	Man	51	57	170	16	Left	Hemorrhage	Deep
<i>12</i>	Man	68	102	175	2	Left	Ischemia	Deep
<i>13</i>	Man	66	105	193	2	Right	Ischemia	Deep
<i>Mean (SD)</i>		57.3 (11.6)	76.2 (19.4)	172 (10.8)	8.7 (5.1)			
<i>Summary</i>	11 Men					7 Left	8 Ischemia	5 Complete
	2 Women					6 Right	6 Hemorrhage	8 Deep

Table 2: Effect of real and sham bilateral-tDCS on electrophysiological and mechanical properties of knee extensors in stroke patients.

MVC: maximum voluntary contraction; VA: voluntary activation; TW_{pot} : potentiated twitch; Contraction Time; HRT: half relaxation time; $RF_{EMG-RMS/M}$ is the rationalized root mean square (RMS) by the M-wave of the rectus femoris (RF); $VL_{EMG-RMS/M}$ is the rationalized RMS by the M-wave of the vastus lateralis (VL); $RF_{M-wave amp}$ is the amplitude of the M-wave of the RF; $VL_{M-wave amp}$ is the amplitude of the M-wave of the VL; $RF_{M-wave duration}$ is the duration of the M-wave of the RF; $VL_{M-wave duration}$ is the duration of the M-wave of the VL.

	Real bilateral-tDCS			Sham bilateral-tDCS		
	<i>Pre</i>	<i>Per</i>	<i>Post</i>	<i>Pre</i>	<i>Per</i>	<i>Post</i>
MVC (N.m)	82.9 (29.3)	84.0 (28.8)	87.8 (27.3)	87.3 (30.7)	87.4 (34.9)	92.9 (38.2)
VA (%)	66.0 (26.1)	81.5 (13.5)	74.7 (21.8)	71.9 (20.0)	68.3 (21.2)	75.2 (17.5)
TW_{pot} (N.m)	26.5 (12.5)	27.3 (13.4)	25.3 (13.7)	22.9 (11.9)	27.8 (12.9)	26.9 (13.2)
Contraction Time (s)	0.078 (0.022)	0.082 (0.025)	0.081 (0.025)	0.085 (0.024)	0.078 (0.030)	0.082 (0.025)
HRT (s)	0.096 (0.041)	0.108 (0.053)	0.114 (0.069)	0.097 (0.046)	0.106 (0.049)	0.098 (0.046)
$RF_{EMG-RMS/M}$	0.039 (0.02)	0.042 (0.01)	0.040 (0.01)	0.062 (0.02)	0.052 (0.02)	0.051 (0.02)
$VL_{EMG-RMS/M}$	0.043 (0.02)	0.041 (0.01)	0.040 (0.01)	0.048 (0.02)	0.041 (0.02)	0.043 (0.01)
$RF_{M-wave amp}$ (mV)	1.00 (0.53)	1.03 (0.57)	0.99 (0.59)	0.78 (0.52)	0.84 (0.55)	0.98 (0.44)
$VL_{M-wave amp}$ (mV)	1.60 (0.88)	1.80 (1.10)	1.62 (0.96)	1.63 (0.98)	1.72 (1.16)	1.75 (0.93)
$RF_{M-wave duration}$ (s)	0.015 (0.006)	0.015 (0.006)	0.016 (0.006)	0.011 (0.007)	0.013 (0.070)	0.011 (0.006)
$VL_{M-wave duration}$ (s)	0.009 (0.005)	0.009 (0.005)	0.010 (0.006)	0.010 (0.007)	0.011 (0.006)	0.009 (0.005)

Table 3: Effect of real and sham bilateral-tDCS on electrophysiological and mechanical properties of knee extensors in healthy participants. MVC: maximum voluntary contraction; VA: voluntary activation; TW_{pot} : potentiated twitch; Contraction Time; HRT: half relaxation time; $RF_{EMG-RMS/M}$ is the rationalized root mean square (RMS) by the M-wave of the rectus femoris (RF); $VL_{EMG-RMS/M}$ is the rationalized RMS by the M-wave of the vastus lateralis (VL); $RF_{M-wave amp}$ is the amplitude of the M-wave of the RF; $VL_{M-wave amp}$ is the amplitude of the M-wave of the VL; $RF_{M-wave duration}$ is the duration of the M-wave of the RF; $VL_{M-wave duration}$ is the duration of the M-wave of the VL.

	Real bilateral-tDCS			Sham bilateral-tDCS		
	<i>Pre</i>	<i>Per</i>	<i>Post</i>	<i>Pre</i>	<i>Per</i>	<i>Post</i>
MVC (N.m)	248.5 (99.8)	242.2 (93.8)	246.4 (97.0)	242.2 (79.2)	239.6 (78.7)	243.7 (83.5)
VA (%)	80.9 (9.20)	83.9 (11.8)	83.1 (10.9)	86.6 (17.0)	86.9 (12.4)	88.1 (12.0)
TW_{pot} (N.m)	55.9 (16.6)	54.2 (15.7)	53.2 (16.4)	46.5 (26.0)	46.7 (23.4)	40.1 (18.9)
Contraction Time (s)	0.039 (0.008)	0.038 (0.006)	0.035 (0.004)	0.038 (0.007)	0.036 (0.006)	0.037 (0.007)
HRT (s)	0.057 (0.009)	0.059 (0.007)	0.057 (0.005)	0.048 (0.013)	0.050 (0.005)	0.046 (0.011)
$RF_{EMG-RMS/M}$	0.124 (0.07)	0.126 (0.07)	0.099 (0.06)	0.087 (0.04)	0.097 (0.04)	0.087 (0.03)
$VL_{EMG-RMS/M}$	0.091 (0.05)	0.090 (0.05)	0.083 (0.05)	0.088 (0.06)	0.074 (0.03)	0.106 (0.06)
$RF_{M-wave amp}$ (mV)	0.98 (0.54)	0.82 (0.43)	1.00 (0.47)	1.32 (0.30)	1.33 (0.36)	1.12 (0.46)
$VL_{M-wave amp}$ (mV)	1.36 (0.87)	1.35 (0.84)	1.30 (0.82)	1.80 (0.96)	1.94 (1.15)	1.58 (0.96)
$RF_{M-wave duration}$ (s)	0.008 (0.002)	0.010 (0.005)	0.008 (0.002)	0.009 (0.003)	0.009 (0.004)	0.010 (0.004)
$VL_{M-wave duration}$ (s)	0.007 (0.004)	0.007 (0.002)	0.006 (0.002)	0.008 (0.005)	0.007 (0.004)	0.006 (0.004)