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► To cite this version:

Robin Souron, Adrien Farabet, Guillaume Y. Millet, Thomas Lapole. Reliability of the functional measures of the corticospinal pathways to dorsiflexor muscles during maximal voluntary contractions. *Journal of the Neurological Sciences*, 2016, 369 (11), pp.368-374. 10.1016/j.jns.2016.09.003 . hal-02409556

HAL Id: hal-02409556

<https://hal.science/hal-02409556>

Submitted on 4 Sep 2023

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1 **Reliability of the functional measures of the corticospinal pathways to**
2 **dorsiflexor muscles during maximal voluntary contractions**

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7
8 Running title: Reliability of tibialis anterior corticospinal functional properties

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18 **ABSTRACT**

19
20 This study aimed to evaluate the intra- and inter-day reliability of transcranial
21 magnetic stimulation (TMS)-related measurements recorded from the tibialis anterior
22 (TA) muscle. Thirteen healthy young men and women (23 ± 4 years) performed 3
23 testing sessions to assess intra- (i.e., two sessions performed the same day) and
24 inter-day (i.e. two sessions performed one week apart) reliability of (i) dorsiflexion
25 cortical maximal voluntary activation level (VA_{TMS}), (ii) TA corticospinal excitability
26 assessed through the amplitude of the motor evoked potentials (MEP) recorded
27 during 100, 75 and 50% maximal voluntary contractions (MVC), and (iii) intracortical
28 inhibition investigated via the cortical silent period (CSP) recorded at the same
29 %MVC. Absolute (i.e., coefficient of variation (CV) and standard error of the mean
30 (SEM)), and relative (i.e., intraclass correlation coefficients (ICC)) reliability
31 parameters were calculated. VA_{TMS} demonstrated excellent intra- and inter-day
32 reliabilities (ICC: 0.80 and 0.99; CV: 1.7 and 0.8%, respectively). MEPs and CSPs
33 presented moderate to excellent intra- and inter-day reliabilities, while input-output
34 curves extracted parameters presented highly variable outcomes. These results
35 suggest that most TA corticospinal measurements during voluntary contraction can
36 be used to quantify corticospinal adaptations after acute (e.g. fatigue) or long term
37 (e.g. training) interventions.

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39
40 Keywords: transcranial magnetic stimulation; tibialis anterior; cortical voluntary
41 activation; corticospinal excitability, Boltzmann modelling.

43 **ABBREVIATIONS**

1	44	CSP	Cortical silent period
2			
3	45	CSP ₅₀	Cortical silent period during a 50% MVC submaximal contraction
4			
5	46	CSP ₇₅	Cortical silent period during a 75% MVC submaximal contraction
6			
7	47	CSP _{MVC}	Cortical silent period during a MVC
8			
9	48	CV	Coefficient of variation
10			
11	49	EMG	Electromyographic
12			
13	50	ERT	Estimated resting twitch amplitude
14			
15	51	I ₅₀	Stimulus intensity required to obtain a MEP of half the size of the
16	52		plateau
17			
18	53	ICC	Intraclass correlation coefficient
19			
20	54	k	The slope parameter of the Boltzmann modelling
21			
22	55	M _{MVC}	M-wave amplitude during a MVC
23			
24	56	MEP	Motor evoked potential
25			
26	57	MEP ₅₀	Motor evoked potential amplitude during a 50% MVC submaximal
27	58		contraction
28			
29	59	MEP ₇₅	Motor evoked potential amplitude during a 75% MVC submaximal
30	60		contraction
31			
32	61	MEP _{MVC}	Motor evoked potential amplitude during a MVC
33			
34	62	MVC	Maximal voluntary contraction
35			
36	63	P	The function plateau of Boltzmann modelling
37			
38	64	RMS	Root mean square
39			
40	65	SEM	Standard error of the mean
41			
42	66	SIT	Superimposed twitch amplitude
43			
44	67	SIT _{MVC}	Superimposed twitch amplitude during a maximal voluntary contraction
45			
46	68	TA	Tibialis anterior
47			
48	69	TMS	Transcranial magnetic stimulation
49	70	VA _{TMS}	Voluntary activation assessed with TMS

1. Introduction

It is well established that training, and especially strength training, induces several adaptations to the central nervous system leading, *in fine*, to an augmentation of maximal voluntary contraction (MVC) force. The investigation of maximal voluntary activation is critical to assess neural adaptations. Voluntary activation refers to the neural drive delivered to a muscle during a voluntary contraction. The most common way to estimate maximal voluntary activation is to use the interpolated twitch technique [1], where a supramaximal stimulus is delivered over a motor nerve during an MVC to measure the extra force evoked by the stimulation. Using this method, changes in neural drive can be identified as at or above the site of stimulation of the motor axons, without distinction between spinal and supraspinal mechanisms [2]. Since training may induce both spinal [3] and supraspinal adaptations [4], transcranial magnetic stimulation (TMS) has been proposed as an alternative technique to ascertain whether adaptations occur throughout the corticospinal pathway [5]. Indeed, the evocation of a superimposed twitch elicited by TMS during MVC has been suggested to highlight a suboptimal drive from the motor cortex [5-7], although the cause of VA_{TMS} reduction can be due to modulation at any level of the corticospinal network (i.e. through reduced spinal and/or motoneuronal excitability).

The assessment of cortical voluntary activation using TMS (i.e., VA_{TMS}) cannot be performed for all muscles since some criteria must be met, especially having strong corticomotoneuronal projections [8]. VA_{TMS} has been shown to be reliable for the elbow flexors [9] or the knee extensors [8], but not in dorsiflexor muscles thus far, despite the functional role of these muscles in particular during locomotion [10, 11]. The tibialis anterior (TA), contributing to almost half of the voluntary torque produced in ankle dorsiflexion (the remainder presumably being provided by the long extensors of the toes) [12], is known to have the strongest corticospinal projections among lower limb muscles [13]. Even though dorsiflexor muscles VA_{TMS} has already been assessed in fatigue studies [14, 15], no study has yet investigated VA_{TMS} reliability for this muscle group. Such an approach is necessary since the constant oscillation in the elements of the central nervous system and methodological factors (e.g. subject population, muscle considered, position for magnetic stimulation) are two main sources that may affect the stability of TMS measurements [16]. Indeed, motor-

105 evoked potential (MEP) elicited by TMS, which is known to represent the excitability
106 of cortical neurons and/or motoneuron pools of the stimulated muscles [17], are
107 inherently variable. For instance, MEP amplitude may be influenced by circadian
108 variation [18]. To reduce variability, MEP amplitude is commonly expressed as ratio
109 to M-wave to rise above the membrane excitability and conductivity influence. MEPs
110 should also be measured during a stable voluntary contraction to further reduce
111 variability [16, 19]. Among the studies that investigated TA MEP reliability [14, 16,
112 20], only one met these last two criteria and reported high inter-day reliability for
113 MEPs measured during submaximal lengthening and shortening contractions [16].
114 During maximal isometric contraction, absolute MEP was also reported to be reliable
115 [14], as it was at rest [14, 20]. Hence, intra-day and inter-day reliability of normalized
116 TA MEPs during submaximal and maximal isometric contractions has yet to be
117 determined.. Moreover, although input-output curves (i.e. the relation between TMS
118 intensity and MEP amplitude) [19, 21] are recognized as a more sensitive measure of
119 corticospinal excitability [22, 23], its reliability for the TA muscle has only been proven
120 during a relaxed condition [20].

121
122 Although several studies have investigated the reliability of TA TMS-related
123 parameters [14, 16, 20], this topic needs further investigation. Specifically, dorsiflexor
124 VA_{TMS} must be examined to better understand short- and long-term adaptations
125 within the central nervous system during acute and long term interventions. This
126 would provide complementary knowledge with regard to previous TMS studies
127 demonstrating changes in TA corticospinal excitability after strength training [24, 25].
128 Therefore, the present study is intended to evaluate the intra- and inter-day reliability
129 of VA_{TMS} and associated corticospinal functional properties (e.g. MEP amplitude) for
130 dorsiflexor muscles.

131 **2. Material and methods**

132

133 **2.1. Participants.** Thirteen young, healthy young subjects (9 men and 4 women, $23 \pm$
134 4 years; height: 177 ± 8 cm; body mass: 69 ± 10 kg) participated in this study. The
135 subjects' level of weekly physical activity was reported to be between 0 and 5 hours
136 per week. Written, informed consent was obtained from all subjects prior to their
137 participation and this study conformed to the standards from latest revision of the
138 Helsinki Declaration and was approved by the local ethics committee. All subjects
139 were free of lower-limb injury during the previous three months, contraindications to
140 TMS, acute and chronic neurological disorders, and trauma. Before testing, each
141 subject was informed about the nature and the aim of this study, as well as risks and
142 discomfort associated with electrical and magnetic stimulation. They were instructed
143 to abstain from caffeine for a minimum of 12 h before each session.

144

145 **2.2. Design of the study.** Subjects came for three visits to the laboratory at the
146 same time of the day with a 1-week interval between visits. The first visit was a
147 familiarization session of the entire experimental protocol. In order to assess the
148 inter-day reliability, the same protocol was performed during the second and third
149 visits, i.e., session 1 (S1) and session 3 (S3), respectively. Except for the TMS
150 recruitment curve and the peripheral nerve stimulation setup (see below), the whole
151 experimental protocol was performed twice with a 30-min resting period between
152 measurement sessions during one of these visits (randomly designed), allowing the
153 assessment of intra-day reliability (S1 and session 2 (S2)) (Fig. 1). The 30 minutes
154 resting period began at the end of S1 and finished at the beginning of S2. Hence,
155 subjects were invited to stay in a sitting position on the custom-built chair during the
156 30-min period.

157

158 **2.3. Torque and electromyographic recordings.** Dorsiflexion torque was measured
159 during voluntary contractions by a calibrated, instrumented pedal (CS1060 300 Nm,
160 FGP Sensors, Les Clayes Sous Bois, France). Subjects were seated upright in a
161 custom-built chair with a hip, knee, and ankle angle of 90, 120, and 90°, respectively.
162 The foot was securely attached to the pedal with a custom designed hook and loop
163 fastener. Electromyographic (EMG) activity of the right TA and soleus (SOL) was
164 recorded with pairs of self-adhesive surface electrodes (Meditrace 100, Covidien,

165 Mansfield, USA) in bipolar configuration with a 30-mm interelectrode distance and the
166 reference on the medial malleolus. SOL electrodes were placed 2 cm inferior to the
167 insertion of the gastrocnemii on the Achilles tendon. TA electrodes were placed on
168 the muscle belly parallel to the longitudinal axis of the muscle at one-third of the
169 distance between the head of the fibula and the tip of the medial malleolus, according
170 to SENIAM recommendations [26]. Skin impedance was measured using a classic
171 impedance analyser (Fluke 87V Ex, Fluke, Wallisellen, Switzerland) and low
172 impedance (<5 k Ω) between electrodes was obtained by shaving, gently abrading the
173 skin and then cleaning it with isopropyl alcohol. Signals were amplified with an octal
174 bio-amplifier (ML138, ADInstruments; common mode rejection ratio = 85 dB, gain =
175 500), bandpass filtered (5-500 Hz), and analogue-to-digital converted at a sampling
176 rate of 2000 Hz by PowerLab system (16/30—ML880/P, ADInstruments, Bella Vista,
177 Australia). All data was analyzed offline using Labchart 7 software (ADInstruments).

2.4. Stimulation. Two types of stimulation were used. Specifically, electrical
180 stimulation of the tibialis anterior motor nerve (i.e., peroneal nerve) and transcranial
181 magnetic stimulation (TMS) over the motor hotspot for the TA muscle. For stimulation
182 of the tibialis anterior motor nerve, a bipolar bar stimulating electrode with 30-mm
183 anode-cathode spacing (Bipolar Felt Pad Stimulating Electrode Part number
184 E.SB020/4mm, Digitimer) was positioned next to the fibular head. Single rectangular
185 pulses with 0.5ms duration and 400 V maximal output voltage were delivered to the
186 right peroneal nerve via a constant-current stimulator (DS7A, Digitimer, Welwyn
187 Garden City, Hertfordshire, UK). The optimal site of stimulation was determined as
188 the location eliciting the greatest TA M-wave for a given stimulus intensity. This site
189 was marked with semi-permanent ink. To determine the optimal intensity of electrical
190 stimulation, the intensity was increased by 5 mA until the magnitude of resting TA M-
191 wave plateaued. The number of stimulations to find the optimal stimulating intensity
192 varied among subjects (i.e., between 3 and 10). This optimal stimulating intensity was
193 then increased by 50% to ensure supramaximal intensity of stimulation during
194 contraction. Electrical stimulation configuration was determined at the beginning of
195 the S1 and S3 to avoid any potentiation effects. The stimulation intensity used to
196 evoke M-wave during MVC ranged between 30 and 97.5 mA. The mean stimulation
197 intensities were 47.6 ± 20.2 mA in S1 (the same intensity was used for S2) and 48.2

198 ± 17.0 mA in S3. The whole procedure of determining stimulation site and intensity
199 was performed in approximately 3 min.

200
201 For the TMS technique, motor evoked potentials (MEPs) and superimposed twitches
202 (SITs) were evoked during voluntary isometric dorsiflexion via a Magstim 200²
203 magnetic stimulator (Magstim 200², The Magstim Company Ltd, Whitland, UK) with a
204 110-mm double cone coil. The coil was positioned over the leg area of the left motor
205 cortex along the nasal-inion axis to induce a postero-anterior current. The coil
206 position to obtain an optimal activation of the TA is known to be 0.5-1 cm posterior
207 and along the anteroposterior plane of the vertex [21]. This location was drawn on
208 the swim cap every centimeter from 1 cm anterior to 3 cm posterior to the vertex
209 along the nasal-inion line and also to 2 cm over the left motor cortex area (i.e., 8
210 marks on the swim cap). Thus, a single stimulation was delivered at each of the
211 specified anatomical positions (i.e. 8 stimulations in total) and the optimal coil position
212 was chosen as the site eliciting the largest SIT and TA MEP amplitude with minimal
213 SOL MEP amplitude in response to stimulation at 50% maximal stimulator output
214 during brief voluntary dorsiflexion at 10% MVC. The whole procedure was performed
215 in approximately 2 min.

216
217 Subjects were provided with real-time feedback of their target force, which was
218 displayed on a screen. This position was marked on a swim cap that was secured to
219 the scalp. During voluntary contractions, TMS was delivered once the subject had
220 stabilized the force on the target level. Subjects were instructed to re-contract as
221 strongly and as fast as possible immediately after TMS delivery to permit accurate
222 measurement of the cortical silent period (CSP). Electrodes for peripheral nerve
223 stimulation as well as the TMS coil were placed and hand-held by the same
224 investigator for all subjects and all visits.

2.5. Neuromuscular measurements.

227 **2.5.1. MVC.** After a standardized warm-up consisting of 10 submaximal voluntary
228 contractions performed between 30-80% of the MVC obtained during the
229 familiarization session, subjects performed three maximal dorsiflexion contractions
230 lasting approximately 3 s, with a 1-min resting period between trials to avoid fatigue.
231 Electrical stimulation was delivered during MVCs to obtain the maximal M-wave

232 peak-to-peak amplitude recorded during MVC (M_{MVC}) (Fig. 1.B). MVC was
233 determined as the highest torque value achieved before the electrical stimulation. TA
234 EMG root mean square (RMS) was calculated as the mean over a 500-ms period
235 after maximal force had reached a plateau and was then normalized to M_{MVC} .

236
237 **2.5.2. Input-output curves.** TA TMS input-output curves were only assessed once
238 during each visit to the laboratory to determine the optimal stimulation intensity.
239 Hence, only inter-day reliability was investigated for this curve. TMS was delivered
240 over the hotspot. Since corticospinal excitability is increased with muscle activity [27],
241 input-output curves were determined during brief voluntary dorsiflexion at 20% MVC.
242 Four consecutive 2-3 s contractions, with a 10 second rest between contractions,
243 were performed at 20, 30, 40, 50, 60, 70 and 80% maximal stimulator output
244 (randomly ordered), and a TMS pulse was delivered during each of these
245 contractions (i.e., 28 stimulations were initially delivered). If a TA MEP plateau was
246 not confirmed from these intensities, higher TMS intensities were investigated. The
247 optimal stimulation intensity obtained from the input-output curves was chosen when
248 TA MEP and SIT plateaued. The MEP evoked in the antagonist SOL was also
249 measured to ensure it stayed at a low value (Fig 3). The whole procedure was
250 performed in approximately 10 min.

251
252 The aforementioned method has been recently reported to be appropriate for
253 determining TMS intensity in the quadriceps [28]. The size of the TA MEPs was
254 measured as the peak-to-peak amplitude of the non-rectified EMG response and
255 expressed relative to M_{MVC} , and then averaged and plotted against the stimulus
256 intensity. Then Boltzmann modelling was performed on input-output curves in order
257 to apply a nonlinear regression analysis (Fig. 2.A) [21, 24, 29]:

$$\text{MEPampl} = \frac{P}{1 + \exp\left[\frac{150 - I}{k}\right]}$$

258 This function allows the determination of the relation between MEP amplitude
259 (MEPampl) and the TMS intensity (I, in percentage of the stimulator output). Three
260 parameters can be extracted from this relationship: the maximum MEP defined by the
261 function (P, in % M_{MVC}), the stimulus intensity at which the MEP size is 50% of the
262 maximal MEP (I_{50} , in percentage of the stimulator output), and the slope parameter (k)

263 that is inversely proportional to the maximal function steepness [21]. The peak slope
264 of the function was also calculated to provide an indication of the maximal rate of
265 increase in MEP amplitude with stimulus intensity. The peak slope of the function is
266 its tangent at I_{50} [19] and was further calculated by the following equation, taking into
267 account the slope parameter (i.e., k) and the maximum MEP defined by the previous
268 equation (i.e., P) [19, 24]:

$$\text{Peak slope} = \frac{k \times P}{4}$$

2.5.3. Cortical voluntary activation. Cortical voluntary activation (VA_{TMS}) during
maximal effort was calculated with the modified twitch interpolation technique as
initially developed by Todd et al. [7]. Stimulus intensity used for the investigation of
cortical voluntary activation was defined as the lowest stimulus intensity tested
eliciting maximal SIT and TA MEP amplitude from the input-output curve test
performed for corticospinal excitability measurement. The same intensity was used
for intra-session reliability, but was not necessarily the same between S1 and S3
(i.e., inter-day). The stimulus intensities used to assess VA_{TMS} were $65.3 \pm 7.7\%$ and
 $65.3 \pm 8.7\%$ of the maximal stimulator output in S1 and S3, respectively.
Corticospinal excitability increases substantially during the transition from relaxed to
contracted muscle states [30], thus underestimating TMS evoked twitch in the
relaxed muscle. Hence, estimated resting twitch (ERT) was determined by linear
regression of the relation between SIT amplitude evoked when TMS was delivered at
100, 75 and 50% MVC and voluntary force (Fig. 2.B) [7]. This relation was
extrapolated and the y-intercept was interpreted as the ERT amplitude (Fig. 4).
 VA_{TMS} was assessed with the equation:

$$VA_{TMS} = (1 - SIT_{MVC} / ERT) \times 100$$

where SIT_{MVC} is the superimposed twitch evoked during MVC. Three series were
performed and averaged with contractions separated by 30 s and series by 2 min.
Thus, the linear regression was run out with the 3 values from each series, and
 VA_{TMS} was then averaged. ERT was excluded and VA_{TMS} was not calculated when
the linear regression was not linear within a series ($r^2 < 0.9$) [31]. One series was
excluded from the data analysis for 5 subjects (out of 39 series in total) and the
average was done with 2 series rather than 3 in this case. ERT and SIT_{MVC} were
determined on each series separately before being averaged. Mean R^2 of the linear

294 regression was 0.97 ± 0.04 , 0.97 ± 0.05 and 0.95 ± 0.03 for S1, S2 and S3,
295 respectively. MEPs and CSPs elicited by TMS during 100, 75 and 50% MVC
296 contractions were also calculated and averaged over the 3 sets. Peak-to-peak
297 amplitude of MEPs were measured and normalized to M_{MVC} (MEP_{MVC} , MEP_{75} and
298 MEP_{50} , respectively). Since it was difficult to precisely determine the beginning and
299 the end of the MEP, due to its polyphasic form, MEP area was not calculated. The
300 duration of the CSPs were determined visually and defined as the duration from the
301 TMS stimulus to the return of continuous voluntary EMG (CSP_{MVC} , CSP_{75} and CSP_{50} ,
302 respectively) (Fig. 2.C) Two investigators performed the CSP analysis, and the two
303 values were averaged. The treatment was redone by a 3rd investigator when the
304 difference between the two was higher than 5%. This large error occurred only for
305 one subject (in that case, the average was performed on the values that were these
306 closest to each other), showing that analysing CSP duration visually was not
307 investigator-dependant and was thus an appropriate method.

2.6. Statistical analysis. As recommended by Hopkins [32], intra-session and inter-
308 day reliabilities were assessed using the intra-class correlation coefficient (ICC),
309 standard error of the mean (SEM) and coefficient of variation (CV). The ICC
310 represents a measure of relative reliability showing the degree to which individuals
311 maintain their position in a sample with repeated measurements [33]. According to
312 Fleiss [34], ICC greater than 0.75 represents an excellent reliability; an ICC ranging
313 between 0.74 and 0.40 represents a moderate to good reliability and an ICC smaller
314 than 0.40 represents poor reliability. The SEM scores were also calculated to quantify
315 absolute reliability and give an indication of the precision of a recorded parameter.
316 Thus, a low SEM value means a strong reliability and vice versa [35]. The CV
317 ((standard deviation (SD) / mean) was calculated to represent the degree to which
318 repeated measurements vary for individuals [33]. Data are presented as means \pm
319 SD.
320

321 **3. Results**

1
2 322

3 323 **3.1. MVC and cortical voluntary activation (VA_{TMS})**

4
5 324 The results of intra- and inter-day reliabilities of MVC, M_{MVC} , RMS/M_{MVC} and VA_{TMS}
6
7 325 are presented in Table 1. Intra-day ICCs were 0.96 and 0.80 while inter-day ICCs
8
9 326 were 0.95 and 0.99, for MVC and VA_{TMS} , respectively. For these two parameters, all
10
11 327 CVs for intra- and inter-day conditions were lower than 4.1%, and were associated to
12
13 328 low SEM values. VA_{TMS} across the three testing sessions was $96.0 \pm 4.9\%$. Mean
14
15 329 SIT_{MVC} and ERT values as well as their associated ICC, CV and SEM values are
16
17 330 reported in Table 1.

18 331

19
20 332 **3.2. Corticospinal excitability and intracortical inhibition**

21
22 333 Fig 2.C represents typical torque and EMG recordings (i.e., MEP amplitude and silent
23
24 334 period duration) in response to TMS during 100, 75 and 50% MVC contractions.
25
26 335 Mean results for CSP and MEP recorded at 100, 75 and 50% MVC are presented in
27
28 336 Table 1 as well as their reliability outcomes. For these two parameters, ICCs ranged
29
30 337 from 0.51 to 0.99 and CVs from 3.5% to 14.9%. The parameters of the input-output
31
32 338 curves are presented in Table 2. R^2 of the Boltzmann sigmoid function were $0.83 \pm$
33
34 339 0.12 and 0.88 ± 0.10 for S1 and S3, respectively. For the four parameters extracted,
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36 340 ICC values ranged from 0.71 to 0.87 and CVs from 8.0% to 43.9%.

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341 4. Discussion

1 342 This study aimed to assess the intra- and inter-day reliability of several TMS-related
2 343 measures (VA_{TMS} , MEP amplitude, CSP, input-output curve parameters) related to
3 344 corticospinal output to a voluntarily activated muscle responsible for dorsiflexion in
4 345 healthy subjects. The main findings of the present study are that i) dorsiflexor
5 346 muscles VA_{TMS} was reported for the first time to be highly reliable, ii) MEPs and
6 347 CSPs showed reliable intra- and inter-day outcomes and iii) highly variable results
7 348 are reported for Boltzman modelling extracted parameters.

8 349
9 350 **4.1. MVC and cortical voluntary activation.** As expected, MVC presented good
10 351 intra-and inter-day reliability. To the best of our knowledge, cortical voluntary
11 352 activation level assessment using TMS during MVCs has only been demonstrated to
12 353 be reliable for elbow flexors [9] or knee extensors muscles [6, 8]. Although previous
13 354 fatigue studies investigated dorsiflexor VA_{TMS} [14, 15], the present study is the first
14 355 one to investigate its intra- and inter-day reliability. VA_{TMS} , as well as ERT,
15 356 demonstrated good to excellent intra-and inter-day reliabilities. An important result of
16 357 the present study is that VA_{TMS} recorded between days (i.e., inter-day reliability)
17 358 showed excellent reliability (i.e., 0.99 ICC, 0.8% CV and 0.4 SEM). Since neural
18 359 adaptations have been reported after strength training through CSP [24] and MEP
19 360 [25] increases, our results suggest that VA_{TMS} may be a relevant parameter to inform
20 361 on possible changes in the maximal neural drive from the motor cortex in longitudinal
21 362 studies although this may also reflect on a modification of spinal excitability.

22 363
23 364 VA_{TMS} was found to be $96.0 \pm 4.9\%$ across the three testing sessions, highlighting
24 365 the inability of the nervous drive originating from the motor cortex to fully activate
25 366 motoneurons [5]. Voluntary activation measured in our study appears to be higher
26 367 compared to cortical voluntary activation recorded for elbow flexors (91-95%) [9, 31,
27 368 36-38] or knee extensors muscles (89-93%) [6, 8, 39, 40], and seem to be in
28 369 agreement with others showing that TA activation, quantified by the classical
29 370 superimposed stimulation method, was reported to be maximal or near maximal in a
30 371 healthy young population [41]. This may be explained by the fact that the TA has the
31 372 strongest corticospinal projections among all lower limb muscles [13].

32 373

374 Our values also appear to be greater than those reported by Ross et al., (2007) and
375 Mileva et al., (2012) who found VA_{TMS} to be $75.5 \pm 16.0\%$ and $89.5 \pm 2.9\%$,
376 respectively [14, 15]. These discrepancies may be due to differences in the TMS
377 intensity and/or the type of TMS coil used to evaluate VA_{TMS} . Ross et al., (2007)
378 evaluated the VA_{TMS} at 100% of maximal stimulator output using a 70 mm figure-of-
379 eight coil [15], while a 110-mm double-cone coil was used in the present study. This
380 difference in coil size in the present study may have caused an increased activation
381 of the antagonist muscles leading to misinterpretation of the evoked superimposed
382 twitches. In the study of Mileva et al., (2012), TMS intensity was set at 120% of the
383 resting motor threshold [14]. According to a recent study, this may not have been
384 optimal to fully activate the motor cortical neurons since such intensity selection does
385 not precisely identify the minimum stimulus intensity needed to elicit SIT and MEPs of
386 maximal amplitude [28]. The authors of the present study suggest that determining
387 TMS intensity from an input-output curve (i.e., using optimal intensity identified as the
388 minimum stimulus intensity needed to elicit MEPs of maximal amplitude with minimal
389 co-activation) is more appropriate to assess corticospinal excitability and VA_{TMS} .

4.2. Corticospinal excitability. Input-output curves performed in the present study
392 to determine TMS intensity for VA_{TMS} assessment were further used to characterize
393 the excitability of the corticospinal pathway, through the Boltzmann modeling [21, 42].
394 According to the ICC and SEM, the extracted parameters (i.e., the function plateau,
395 the stimulus intensity required to obtain a MEP amplitude of half the size of the
396 plateau, the slope parameter, and the peak slope) demonstrated good reliability and
397 these values are in agreement with previous studies performed on first dorsal
398 interosseous [19] or TA [20]. However, the present study demonstrated high CVs for
399 the slope parameter and the peak slope (43.9 and 40.5%, respectively). The high
400 reported CVs may question the reliability of these two parameters in the current
401 study. Although Carroll et al., (2001) suggested that the slope parameter (i.e., the k
402 parameter in our study) might be a more reliable index of corticospinal excitability
403 than the peak slope for the first dorsal interosseous, similar reliability was reported for
404 these two parameters in the present study [19]. Nevertheless, regarding the high CV
405 described above, it seems difficult to use these two parameters to investigate the
406 chronic and/or acute adaptations of TA corticospinal excitability.

408 While input-output curves were used in the present study to investigate TA
409 corticospinal excitability during a low level of contraction, corticospinal excitability was
410 also assessed at higher levels of contraction (100, 75 and 50% MVC) through MEP
411 recordings. The current results present higher MEP values during submaximal (i.e.,
412 MEP₅₀ and MEP₇₅) than during maximal voluntary contractions (i.e., MEP_{MVC}), which
413 is in agreement with other results obtained on the TA [16]. It has been suggested that
414 the probability for the TMS pulse to be evoked during the refractory period is higher
415 during a maximal (higher discharger rate) rather than a submaximal voluntary
416 contraction, leading to a lower MEP amplitude [8]. MEP_{MVC} presented good intra- and
417 inter-day reliabilities. These results are consistent with a recent study that found that
418 the TA has a good inter-day reliability (ICC: 0.80) for MEPs recorded during MVC
419 [14]. Even if ICC values are lower in our experiment (ICC: 0.51 and 0.52, for intra-
420 and inter-day condition respectively), we can conclude that there was a moderate to
421 good reliability regarding the low associate CV and SEM values, informing about
422 small intra-subject variation. One aim of the present study was to investigate the
423 intra-day reliability of MEP amplitude, which is known to represent corticospinal
424 pathway excitability. Our results have shown that MEPs recorded at maximal or
425 submaximal levels of voluntary contraction may be used as reliable parameters to
426 investigate acute phenomenon such as fatigue. The good reliability observed in the
427 present study is also in agreement with several studies performed on knee extensors
428 [8] or elbow flexors [9]. Yet, unlike the studies where the reliability was independent
429 on force level, in the present study, MEP reliability was higher at low level of
430 voluntary contraction (i.e., MEP₅₀ and MEP₇₅) than during MVC (i.e., MEP_{MVC}). The
431 good reliability observed for MEPs recorded during submaximal contraction is
432 consistent with previous studies investigating the knee extensors [8], first dorsal
433 interosseous [43], elbow flexor [9] or TA [16] muscles. The lower reliability observed
434 for MEPs during MVC is consistent with previous studies, suggesting that high
435 contraction intensities may cause a larger desynchronization of the action potential at
436 the membrane level [16, 19]. Hence, the excitability of corticospinal pathway of the
437 TA muscle can be reliably tested through the recording of MEP amplitude in
438 response to TMS during maximal and submaximal contractions for acute
439 interventions (e.g., fatigue) or longitudinal studies (e.g. training).

441 **4.3. Intracortical inhibition.** Cortical silent periods (CSP) associated with MEPs
1 442 were also measured at 100, 75 and 50% MVC (i.e., CSP_{MVC} , CSP_{75} and CSP_{50} ,
2 443 respectively). When applied during a voluntary contraction, TMS may provide
3 444 information about GABA mediated intracortical inhibition through the assessment of
4 445 the CSP [44]. Although the exact mechanisms of the CSP remain unclear, it is
5 446 accepted that the initial part is mainly due to reduced spinal excitability while the final
6 447 part of the CSP is cortical in origin [45]. CSP results from the activation of inhibitory
7 448 cortical neurons projecting onto the pyramidal cells in the motor cortex [46], and is
8 449 thought to be mainly influenced by GABA (gamma aminobutyric acid)
9 450 neurotransmission [47]. In the present study, CSP_{MVC} was highly reliable, as shown
10 451 by high ICC and low CV-SEM values for both intra- and inter-day comparisons. To
11 452 date, only one study recorded CSP in TA during MVC [14] and similar ICC (0.93)
12 453 were observed. In the present study, CSP_{75} and CSP_{50} were also found to be highly
13 454 reliable, both between S1 and S2 (intra-day) and between S1 and S3 (inter-day), in
14 455 agreement with previous studies that assessed CSP during submaximal voluntary
15 456 contractions in TA [16, 20], first dorsal interosseous [43] and the extensor digitorum
16 457 communis [48] muscles. Hence, CSP can be reliably used during maximal and
17 458 submaximal dorsiflexion to investigate TA intracortical inhibition.
18 459

34 460 As most reliability studies, the principal limitation of the present work is that TMS-
35 461 related parameters were investigated for a healthy young population, and that current
36 462 outcomes may not be applicable to other populations (i.e., clinical, elderly).
37 463

41 464 In conclusion, the present study reports for the first time the excellent intra- and inter-
42 465 day reliability for VA_{TMS} of dorsiflexor muscles. The outcomes were found to be highly
43 466 reliable within and between days. A good reliability in the assessment of corticospinal
44 467 excitability and intra-cortical inhibition directed towards the TA was also observed.
45 468 TMS can thus be used to better understand the effects of training interventions on TA
46 469 neural adaptations (e.g., neural drive from the cortex, corticospinal pathway
47 470 excitability) in a healthy young population. This has important practical consequences
48 471 because, besides the fact that TA has the most corticospinal projections among all
49 472 lower limb muscles, it also plays an important functional role in daily life abilities such
50 473 as lifting the foot in the swing phase during locomotion.
51 474

475 **Acknowledgments**

1
2 476 The authors sincerely thank Régis Bonnefoy for technical assistance as well as Aude
3
4 477 Carlet-Mallet and Michael James Asmussen for revision. The present study was
5
6 478 supported by a doctoral research grant from the University Jean Monnet of Saint-
7 479 Etienne (France) assigned to Robin Souron.
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614 **Figures captions**

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5 617 **Fig.1.** Overview of the experimental design of the study (A) and the neuromuscular
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7 618 testing protocol (B). The measurements were performed during session 1 (S1),
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9 619 session 2 (S2) and session 3 (S3) except for peripheral nerve stimulation (PNS) and
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11 620 transcranial magnetic stimulation (TMS) setup which were performed only for S1 and
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13 621 S3.

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16 623 **Fig. 2.** (A) Typical TA MEP input-output curve. Mean TA MEP amplitudes (white
17 624 squares) are presented as a function of TMS intensity from 20 to 80% of maximal
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19 625 stimulator output. The *solid line* represents the Boltzman sigmoid function fit to that
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21 626 set of data. *Dashed lines* indicate I_{50} (i.e. stimulus intensity required to obtain a MEP
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23 627 amplitude of half the size of the plateau, $\frac{1}{2} P$) and P (i.e. the maximum MEP defined
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25 628 by the function). (B) Superimposed twitch force evoked with TMS during maximal (i.e.
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27 629 100% MVC) and submaximal (i.e. 75% and 50% MVC) voluntary contractions. (C)
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29 630 Example of electromyographic recording in response to transcranial magnetic
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31 631 stimulation (TMS) during maximal (100% MVC) and submaximal voluntary
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33 632 contractions (75% and 50% MVC). The time interval between black and grey arrows
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35 633 represents the way to assess cortical silent period (CSP) duration. Black arrows
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37 634 represent the time of TMS stimulation. Grey arrows represent the resumption of
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39 635 continuous voluntary EMG. Dotted arrows represent the MEP peak-to-peak
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41 636 amplitude. Data are from a representative subject.

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43 637 **Fig. 3.** Input-output curve for a representative subject. The optimal stimulation
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45 638 intensity was selected when MEP TA plateaued and when MEP SOL was small. For
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47 639 this subject, 60% of the maximal stimulator output was chosen.

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49 640 **Fig.4.** Amplitude of superimposed twitches (SIT) produced by TMS during contraction
50
51 641 at 50% (triangles), 75% (circles) and 100% MVC (squares). The linear regression was
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53 642 extrapolated and the y-intercept (dashed line) was interpreted as the ERT amplitude.
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55 643 Data from a representative subject.

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Table 1. Intra- and inter-day reliabilities of neuromuscular parameters recorded during maximal (MVC) and submaximal (75% and 50% MVC) voluntary contractions

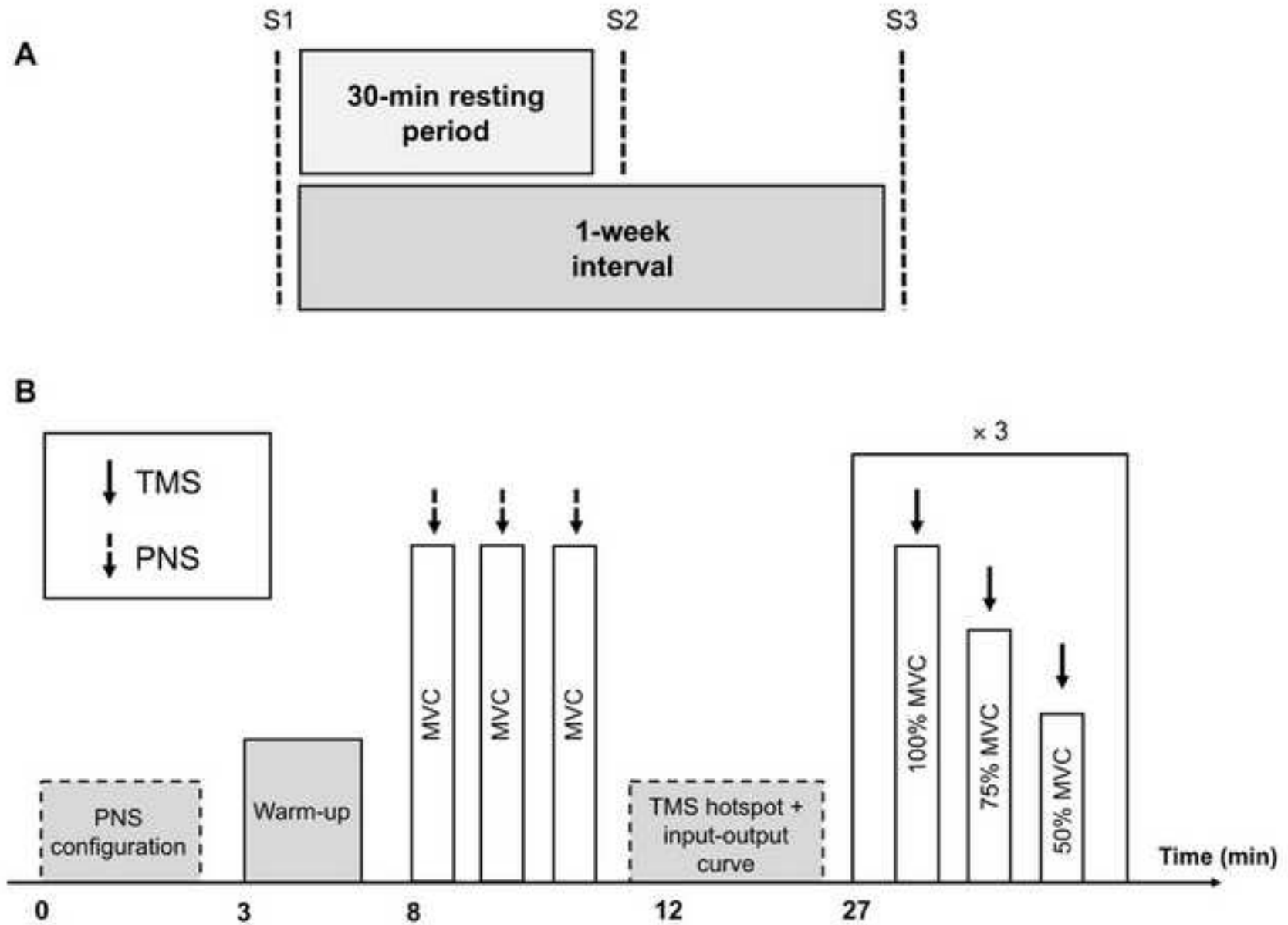
	Mean ± SD			Intra-day			Inter-day		
	S1	S2	S3	ICC	CV (%)	SEM	ICC	CV (%)	SEM
MVC (N.m)	52.4 ± 12.6	52.6 ± 12.9	51.4 ± 12.1	0.96	3.2 ± 2.4	2.7	0.95	4.1 ± 3.0	2.7
RMS / M_{MVC} (%)	9.9 ± 2.3	10.8 ± 2.2	10.5 ± 2.6	0.87	7.7 ± 5.2	0.82	0.68	7.9 ± 6.1	1.4
VA_{TMS} (%)	95.7 ± 5.1	95.9 ± 4.7	96.4 ± 4.9	0.80	1.7 ± 1.5	2.3	0.99	0.8 ± 0.9	0.4
SIT_{MVC} (N.m)	0.76 ± 0.97	0.67 ± 0.88	0.60 ± 0.40	0.73	46.4 ± 40.5	0.5	0.95	38.3 ± 41.7	0.2
ERT (N.m)	16.4 ± 8.1	16.2 ± 4.9	17.4 ± 7.3	0.47	13.2 ± 13.2	4.9	0.94	13.9 ± 14.5	1.8
M_{MVC} (mV)	5.5 ± 1.1	5.7 ± 1.1	6.2 ± 1.7	0.94	6.5 ± 3.7	0.3	0.36	14.1 ± 8.7	1.1
MEP₅₀ (mV)	3.1 ± 0.6	3.1 ± 0.8	3.3 ± 1.2	0.83	8.6 ± 6.3	0.28	0.55	13.1 ± 9.3	0.42
MEP₇₅ (mV)	3.5 ± 0.8	3.5 ± 0.8	3.6 ± 0.9	0.92	5.6 ± 4.6	0.23	0.92	6.7 ± 6.5	0.26
MEP_{MVC} (mV)	3.1 ± 0.6	3.1 ± 0.8	3.3 ± 1.2	0.80	8.9 ± 6.9	0.31	0.47	11.2 ± 10.7	0.67
MEP₅₀ (% M_{MVC})	65.2 ± 14.7	65.3 ± 11.4	61.9 ± 14.9	0.75	10.3 ± 7.5	6.6	0.70	13.4 ± 8.1	8.1
MEP₇₅ (% M_{MVC})	75.8 ± 19.1	74.7 ± 13.7	74.4 ± 18.9	0.86	7.1 ± 5.0	6.1	0.88	7.5 ± 7.4	6.4
MEP_{MVC} (% M_{MVC})	57.0 ± 14.0	50.1 ± 12.3	57.0 ± 14.4	0.51	14.9 ± 8.1	8.7	0.52	9.9 ± 10.4	9.2
CSP₅₀ (ms)	246 ± 58	266 ± 67	230 ± 58	0.84	6.4 ± 7.4	25.2	0.79	7.8 ± 9.2	26.2
CSP₇₅ (ms)	261 ± 64	271 ± 63	246 ± 59	0.99	3.5 ± 3.9	6.4	0.86	7.6 ± 8.3	23.3
CSP_{MVC} (ms)	250 ± 51	267 ± 54	229 ± 62	0.98	7.3 ± 10.9	7.4	0.95	8.6 ± 11.6	13.2

647 Absolute data and CV are expressed as mean \pm standard deviation
 1 648 S1: session 1; S2: session 2; S3: session 3
 2 649 MVC: maximal voluntary contraction; RMS: root mean square; VA_{TMS}: cortical voluntary
 3 650 activation; SIT_{MVC}: superimposed twitch amplitude evoked during MVC; ERT: estimated
 4 651 resting twitch amplitude; M_{MVC-PP}: M wave amplitude recorded during MVC; MEP: motor
 5 652 evoked potential recorded at 50% MVC (MEP₅₀), 75% MVC (MEP₇₅) and 100% MVC
 6 653 (MEP_{MVC}). CSP: cortical silent period recorded at 50% MVC (CSP₅₀), 75% MVC (CSP₇₅) and
 7 654 100% MVC (CSP_{MVC}).
 8 655 ICC: intraclass correlation coefficients; CV: coefficient of variation; SEM: standard error of
 9 656 the mean.

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12 657
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14 659 **Table 2.** Intra- and inter-day reliabilities for input-output curves parameters.
16 660

	Mean \pm SD		Inter-day		
	S1	S3	ICC	CV (%)	SEM
k	0.06 \pm 0.03	0.07 \pm 0.03	0.73	43.9 \pm 37.7	0.02
P (%M_{MVC})	55.8 \pm 12.3	49.0 \pm 12.6	0.71	14.8 \pm 11.3	6.7
I₅₀ (% stimulator output)	37.1 \pm 7.4	37.2 \pm 9.1	0.87	8.0 \pm 6.3	3.0
Peak slope	0.81 \pm 0.55	0.88 \pm 0.43	0.71	40.4 \pm 37.9	0.27

28 661 Absolute data and CV are expressed as mean \pm standard deviation
 29 662 S1: session 1; S3: session 3
 30 663 K: slope parameter; P: function plateau; I₅₀: stimulus intensity required to obtain a MEP
 31 664 amplitude of half the size of the plateau; ICC: intraclass correlation coefficients; CV:
 32 665 coefficient of variation; SEM: standard error of the mean.
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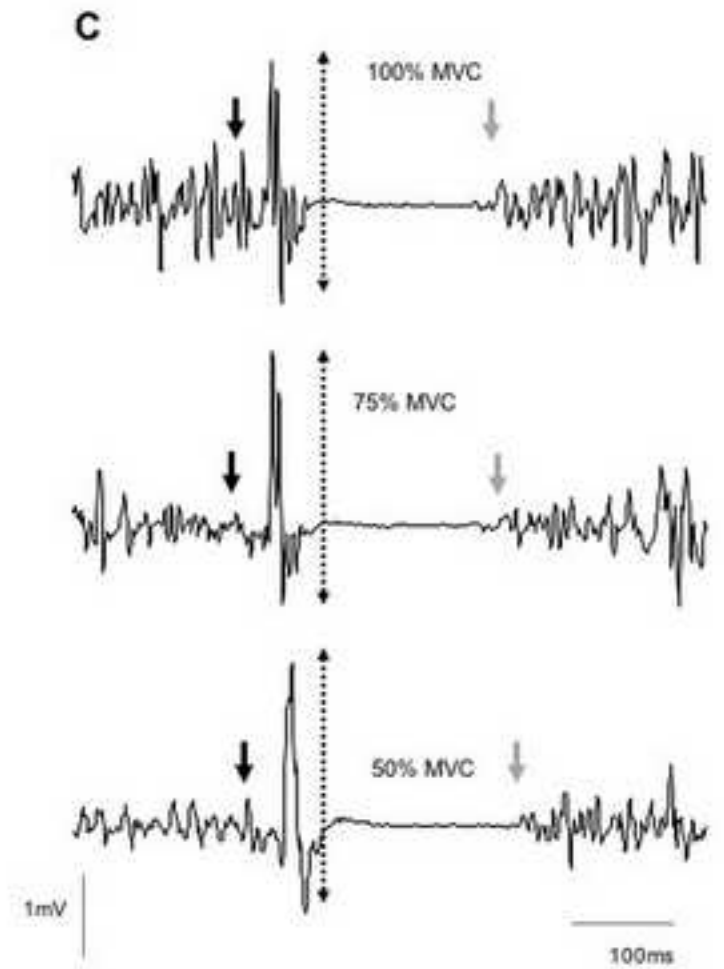
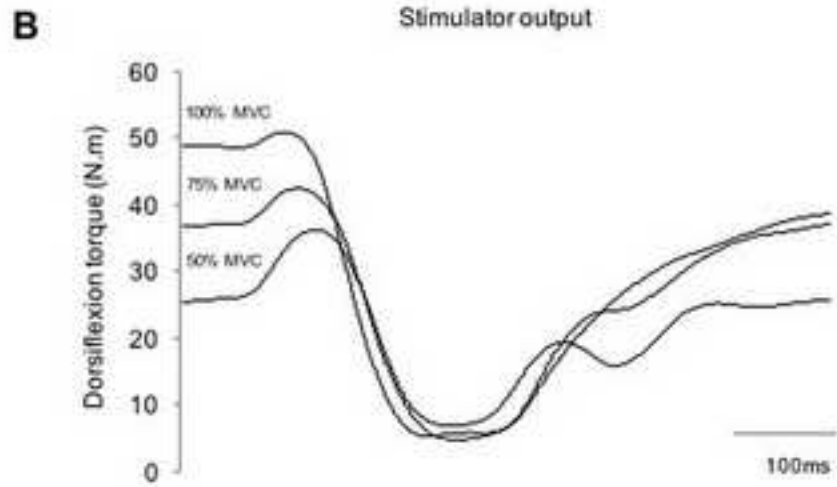
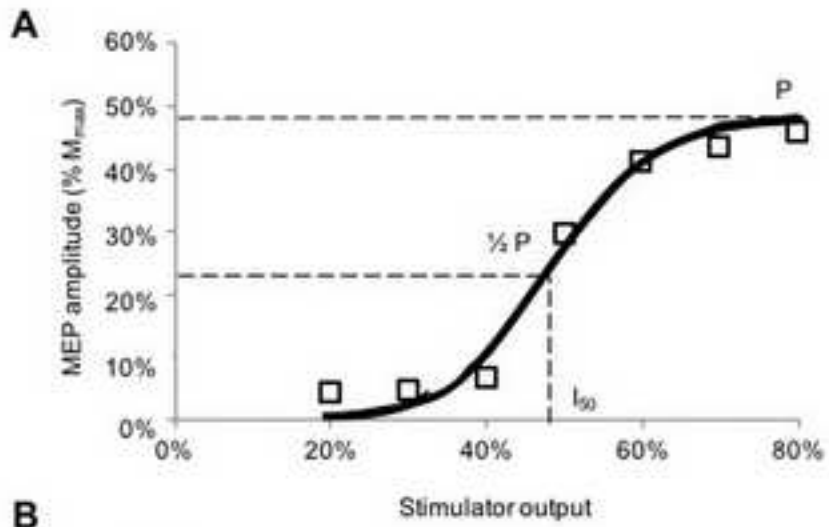


Figure 3

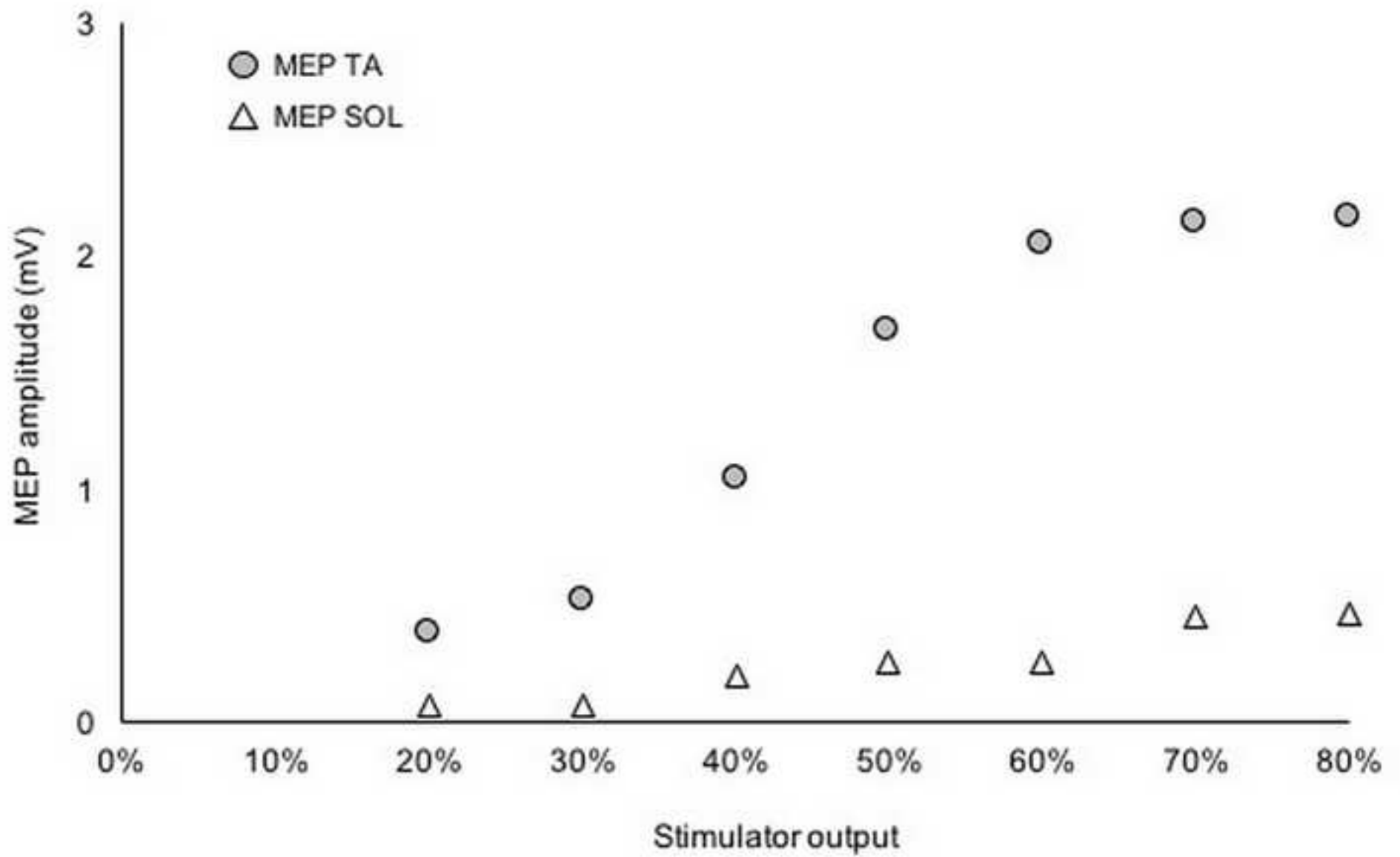


Figure 4

