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► **To cite this version:**

Pauline Eon, Sidney Grosprêtre, Alain Martin. Neuromuscular electrical stimulation at submaximal intensity combined with motor imagery increases corticospinal excitability. *European Journal of Applied Physiology*, 2024, 10.1007/s00421-024-05615-y . hal-04720900

HAL Id: hal-04720900

<https://hal.science/hal-04720900v1>

Submitted on 4 Oct 2024

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1 **TITLE**

2 Neuromuscular electrical stimulation at submaximal intensity combined with motor imagery increases
3 corticospinal excitability

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30

31 **Abstract**

32 **Purpose:** There is sparse evidence in the literature that the combination of neuromuscular electrical
33 stimulation (NMES) and motor imagery (MI) can increase corticospinal excitability more than the
34 application of one or the other modality alone. However, the NMES intensity usually employed was
35 below or at motor threshold, not allowing a proper activation of the whole neuromuscular system. This
36 questions the effect of combined MI+NMES with higher intensities, closer to those used in clinical
37 settings. The purpose here was to assess corticospinal excitability during either MI, NMES or a
38 combination of both at different evoked forces.

39 **Methods:** Seventeen healthy participants were enrolled in one session consisting of 6 conditions
40 targeting flexor carpi radialis muscle (FCR): rest, MI, NMES at 5% and 20% of maximal voluntary
41 contraction (MVC) and MI and NMES performed simultaneously (MI+NMES). During each condition,
42 corticospinal excitability was assessed by evoking MEP of FCR by using transcranial magnetic
43 stimulation. Maximal M-wave (Mmax) was measured by using the stimulation of the median nerve.

44 **Results:** MEPs during MI were greater as compared to rest ($P = 0.005$). MEPs during MI were
45 significantly lower than during MI+NMES at 5% ($P = 0.02$) and 20% ($P = 0.001$). Then, MEPs during
46 NMES 5% was significantly lower than during MI+NMES 20% ($P < 0.005$).

47 **Conclusion:** The present study showed that MI+NMES increased corticospinal excitability more than
48 MI alone. However, corticospinal excitability was not higher as the intensity increase during
49 MI+NMES. Therefore, MI+NMES targeting FCR may not significantly increase the corticospinal
50 excitability between different low-submaximal contractions intensities.

51 **Keywords:** Motor evoked potential, M-wave, imagined movement, stimulated contractions,
52 electromyography, palmar flexors

53

54 **Abbreviations**

55	ANOVA	Analysis of variance
56	EMG	Electromyography
57	FCR	Flexor carpi radialis
58	ECR	Extensor carpi radialis
59	FTI	Force-time integral
60	GM	Gastrocnemius medialis
61	MEP	Motor evoked potential
62	MI	Motor imagery
63	MIQ-3Sf	Motor Imagery Questionnaire French version

64	M _{MAX}	Maximal M-wave
65	MVC	Maximal voluntary contraction
66	NMES	Neuromuscular electrical stimulation
67	NRS	Numerical rating scale
68	RMT	Resting motor threshold
69	TMS	Transcranial magnetic stimulation
70		

71 **Introduction**

72 Alternative methods to physical activity play a pivotal role in the motor rehabilitation of patients with
73 the main objective to reduce the loss of muscle strength and restoring functional autonomy in daily life
74 (Belfiore et al. 2018). Among these methods, the scientific community has particularly paid attention to
75 motor imagery (MI) and neuromuscular electrical stimulation (NMES) presented as efficient methods
76 to improve the muscle strength. MI is defined as the mental simulation of contraction without its
77 corresponding motor output (Jeannerod 1995) whereas, NMES consists in evoking muscle contractions
78 by applying an electrical current over the muscle using surface electrodes without inducing voluntary
79 activation (Seyri and Maffiuletti 2011). Studies showed that the improvement of muscle strength was
80 associated with an increase of the corticospinal excitability, measured as the size of the motor evoked
81 potential by using transcranial magnetic stimulation applied over the motor cortex (Grosprêtre et al.
82 2016b; Olsen et al. 2020). Indeed, we know that MI activates cortical motor areas (Lotze et al. 1999;
83 Hardwick et al. 2018), which likely contributes to an increase of the corticospinal excitability (Kaneko
84 et al. 2014; Mouthon et al. 2015; Grosprêtre et al. 2016b). On the other hand, it is known that during
85 NMES muscle fibers can be recruited directly, through motor axon depolarization as well as indirectly,
86 through activation of spinal motoneurons by the afferent volley (Collins et al. 2001). In the same way
87 than MI, NMES can enhance the corticospinal excitability through afferent input which has the
88 potential to modify the primary motor cortex excitability (Mang et al. 2011). In this respect, studies have
89 examined the effect of the combination of MI and NMES on the corticospinal excitability (Saito et al.
90 2013; Kaneko et al. 2014). Hence, it has been shown that the combination of NMES and MI induces a
91 higher corticospinal excitability compared to each method applied alone (Saito et al. 2013; Kaneko et
92 al. 2014). These studies reported that this effect occurred when the evoked contractions are applied
93 above the motor threshold at very low stimulation intensities [e.g. 1.56% of maximal voluntary
94 contraction (MVC)]. However, there is no evidence that higher intensities of NMES, most often
95 employed in clinical settings to restore skeletal muscle mass and function after a period of reduced use
96 (from 5% to 30% of MVC) (Enoka et al. 2020), combined with MI are efficient in increasing the
97 corticospinal excitability. Such knowledge is of interest since NMES evoking moderate force level can
98 acutely modify spinal excitability (Papaiordanidou et al. 2014; Grosprêtre et al. 2017, 2018a), the
99 activation of cortical motor regions (Muthalib et al. 2015) and corticospinal excitability of the stimulated
100 muscles (Mang et al. 2011).

101 It has been widely shown that the activation of the primary motor cortices during MI induces an increase
102 of the corticospinal excitability compared to rest (Fadiga et al. 1998; Rozand et al. 2014; Mouthon et al.
103 2015; Grosprêtre et al. 2016b). In addition, the generation of a subliminal cortical output during MI can
104 also impact spinal structures such as primary afferent depolarization (PAD) interneurons which mediates
105 spinal presynaptic inhibition (Grosprêtre et al. 2016a, 2019) and could account for the higher
106 corticospinal excitability during MI as well. Regarding NMES, studies demonstrated that a higher

107 corticospinal excitability compared to rest was attributed to the activation of afferent fibers when NMES
108 is applied at an intensity just above motor threshold (sufficient to create a visible contraction) (Saito et
109 al. 2013). By combining both, it has been suggested that the afferent input from the muscle spindle
110 during NMES might enhance the cortical activity induced by MI resulting in higher corticospinal
111 excitability when NMES is applied above the motor threshold at very low stimulation intensities (Saito
112 et al. 2013; Kaneko et al. 2014). Thus, since NMES applied at higher intensities (evoking a significant
113 percentage of maximal force) as it is usually used in clinical setting is known to induce nervous
114 alterations, the combination of NMES at these intensities with MI question the impact that could occur
115 on the corticospinal excitability. It is reasonable to think that underlying mechanism during the
116 combination of MI and NMES may be accentuated with the increase of the stimulation intensity due to
117 the greater number of afferent fibers activated.

118 The increase of corticospinal excitability during the combination of both MI and NMES could be
119 beneficial especially during the early period of limb immobilization during which a decrease of
120 corticospinal excitability is usually associated with the decrease of muscle strength (Campbell et al.
121 2019). If NMES with high intensities, i.e. sufficient to evoke certain levels of force, are already used in
122 clinical setting, the effect while combined with MI is unknown. Thus, the present study aimed to
123 evaluate the effect of NMES at submaximal intensities (sufficient to create a muscle force) when it is
124 combined with MI compared to one or the other modality alone. Most of studies investigating NMES
125 protocols on the corticospinal excitability used low-stimulation intensities (around the motor threshold)
126 which limit the improvement of muscle force and/or muscle mass. Yet, the stimulation intensity is one
127 of a determinant parameter to generate optimum muscle strength gains which may optimize the motor
128 rehabilitation process. The purpose of the present study was to investigate the corticospinal excitability
129 during MI, NMES and combining MI and NMES at different levels of evoked force on the wrist flexors.
130 We hypothesized a higher corticospinal excitability during MI and NMES combined than each method
131 alone. Then, we hypothesized that the corticospinal excitability during MI and NMES combined will
132 depend on NMES stimulation intensity since the amount of fibers activated may modified the
133 corticospinal excitability.

134 **Methods**

135 *Participants*

136 Seventeen healthy participants (16 males and 1 female; age: 25.7 ± 6.1 years; height: 177.3 ± 6.9 cm;
137 weight: 71.6 ± 10.6 kg) with no history of neurological and muscular disorders gave written informed
138 consent to participate in this study. The sample size calculation was based on the primary efficacy
139 outcome that relates to changes in neurophysiological marker during MI+NMES (Takahashi et al. 2019),
140 and calculated using G-power Software (version 3.1.9, Universität Düsseldorf, Germany). Considering
141 a significance level of 5% and a power of 90%, 17 participants were included to satisfy the sample size
142 requirements. Prior to the first experimental session, participants were asked to complete a transcranial

143 magnetic stimulation (TMS) questionnaire to determine whether or not the TMS was contraindicated
144 (Rossi et al. 2009). In addition, participants completed the Movement Imagery Questionnaire (MIQ-
145 3Sf) to determine their self-estimation of MI ability (Robin et al. 2021). The mean MIQ-3Sf was $5.0 \pm$
146 1.2 (mean \pm SD) out of 7 indicating a satisfactory imagery capacity. Participants were instructed not to
147 perform any strenuous exercise 48 hours before the experimental session.

148 The sample size calculation was performed using the software G*power (Kiel, Germany). The
149 experimental protocol was approved by an institutional review board (CPP COOM III number 2017-
150 A00064-49 ; ClinicalTrials.gov identifier NCT03334526) and conducted in conformity with the latest
151 version of the Declaration of Helsinki.

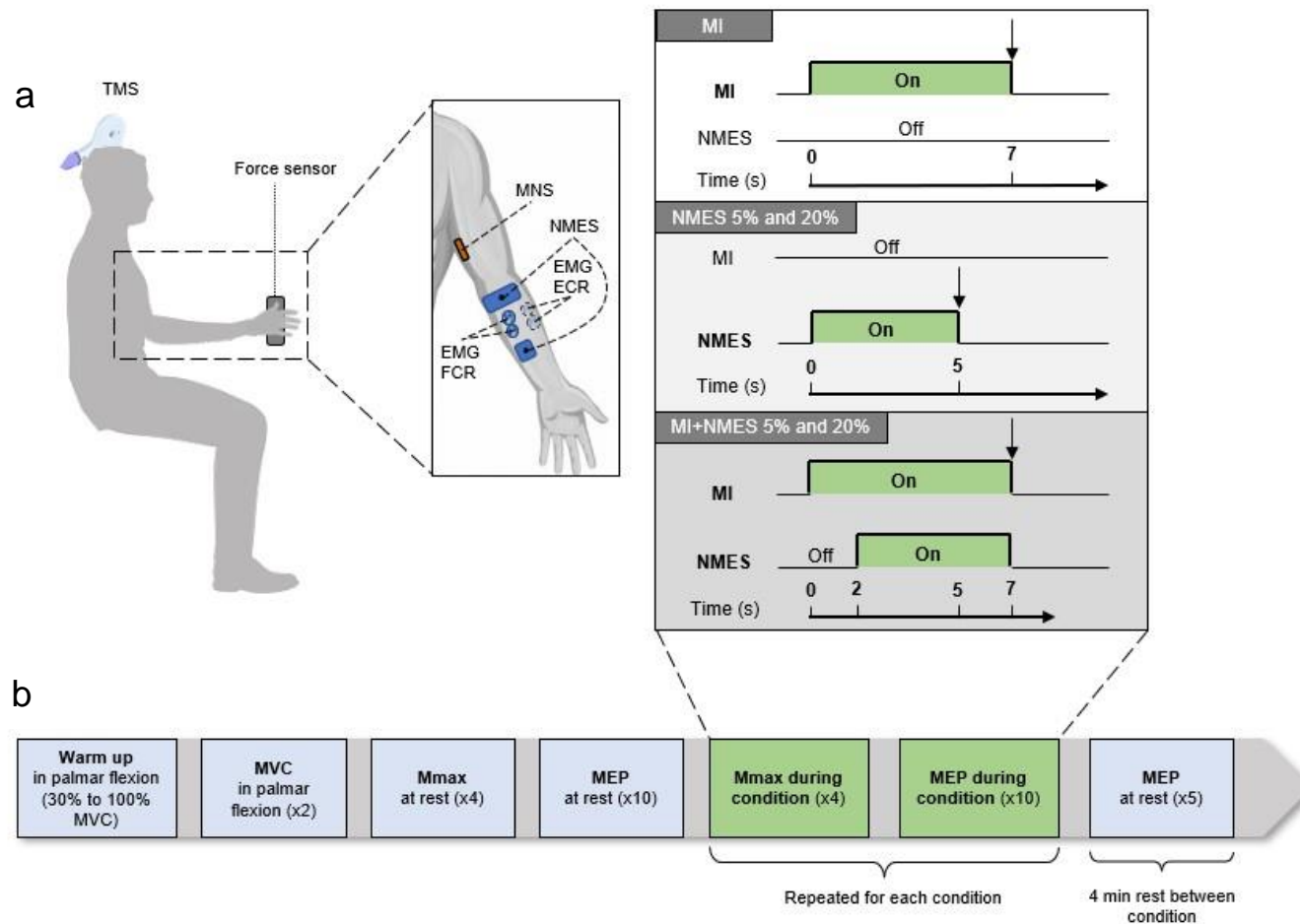
152 *Experimental design*

153 Participants were enrolled in one familiarization session of 30 minutes and one experimental session of
154 about 3 hours separated by at least 48h. All measurements were assessed on the dominant arm defined
155 as the preferential arm for throwing a ball. All participants were right-handed. Participants were seated
156 on a chair with the arm on a homemade device equipped with a force sensor (Grip force sensor,
157 ADInstruments, Sydney, Australia) that enables to record instantaneous muscle force (in Newtons) at a
158 sample frequency of 4000 Hz. Participants were placed with elbow joint at 90° (angle between the
159 forearm and the arm) and the hand in neutral anatomical position with the force sensor on the palm (Fig.
160 1). Straps were tightened to secure the forearm. During the first session, participants were familiarized
161 to nerve stimulation of the median nerve, transcranial stimulation over the motor cortex and muscular
162 stimulation of the flexor carpi radialis (FCR). Then, participants were accustomed to voluntary wrist
163 flexion on the homemade device. The second session, the main experiment, was designed to assess
164 mechanical and electrophysiological responses of the FCR induced by electrical nerve stimulation at
165 rest and during 5 conditions : motor imagery (MI), neuromuscular electrical stimulation evoked at 5%
166 (NMES 5%) and 20% MVC (NMES 20%) and motor imagery and neuromuscular electrical stimulation
167 performed simultaneously with both NMES intensities, 5% (MI+NMES 5%) and 20% (MI+NMES
168 20%) (Fig. 1). First, participants performed a warm-up consisting of contractions in palmar flexion from
169 30% to 100% MVC. Two MVC were performed first, with 1-min rest in-between. Evoked contractions
170 with 1 s stimulation train on the FCR were then used to set the intensity of NMES at 5% and 20% MVC.
171 Then, a recruitment curve of the M-wave of the FCR at rest was performed by evoking single electrical
172 pulses on the median nerve to record the maximal M-wave. A supramaximal response of M-wave at
173 120% of the maximal M-wave (Mmax) was used. The MEP of FCR was elicited by evoking transcranial
174 magnetic stimulation (TMS) on the left motor cortex evoked at 120% of the participant's resting motor
175 threshold (RMT). Once the parameters of the stimulation intensity were fixed, single stimulations were
176 evoked to measure Mmax and MEP at rest. Ten MEP and 4 Mmax of the FCR were evoked at rest.
177 Then, participants performed imagined contractions (MI condition), evoked contractions at 5% and 20%
178 MVC (NMES conditions) and imagined and evoked contractions at 5% and 20% MVC (MI+NMES

179 conditions) in randomized order. During each condition, 14 trials were performed (10 MEP and 4
180 Mmax) with 4 min of rest between conditions. Each stimulation was elicited 100 ms after each repetition
181 with 1 min of rest between MEP and 20 s between Mmax. The stimulator program from LABCHART
182 was used to program the evoked stimulation 100 ms after the last stimulation of NMES in NMES and
183 MI+NMES condition. During MI, the stimulation was evoked 100 ms after 7 s of MI (see below the
184 training condition). Between conditions, 5 MEP were elicited at rest with 10 s of rest in-between to
185 ensure stability of stimulations condition (e.g. positioning of the coil). During all the measurements,
186 electromyographic activity of ECR was always recorded simultaneously with the FCR.

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202 **Fig. 1** Graphical overview of the experimental setup (a) and experimental protocol (b). The experimental session was performed composed of 5 conditions
 203 randomized: MI, NMES 5%, NMES 20%, MI+NMES 5%, MI+NMES 20%. MI was performed during 7 s, NMES during 5 s and MI+NMES during 7 s while
 204 NMES was applied 2 s after MI. The motor evoked potential (MEP) and the maximal M-wave (Mmax) were measured 100 ms after each condition. Ten and 4
 205 repetitions were performed to measure the MEP and Mmax, respectively. Vertical arrow indicates stimulations. MI, motor imagery; NMES, neuromuscular
 206 electrical stimulation; MI+NMES, motor imagery and neuromuscular electrical stimulation performed simultaneously; MNS, median nerve stimulation; TMS,
 207 transcranial magnetic stimulation; EMG, electromyography; ECR, extensor carpi radialis; FCR, flexor carpi radialis.

208 *Training sessions*

209 *Motor imagery (MI)*

210 Participants were instructed to imagine the kinaesthetic sensation of maximal isometric palmar flexion
211 pressed on the force sensor during 7 s. Participants were asked to imagine pushing as hard as they could
212 on the sensor without moving the wrist (isometric contraction), taking as an example the MVC they did
213 in pre-experimentation. They were asked to feel the intensity of muscle contraction normally elicited
214 during actual movement. The kinaesthetic imagery was performed due to its particular effectiveness to
215 induce modulations of corticospinal excitability (Stinear et al. 2006). Fourteen repetitions were
216 performed according to the number of stimulation (4 Mmax and 10 MEP). Each imagined trial began
217 by oral signals of the experimenter (“get ready”, “go”) and ended after the stimulation evoked. After the
218 MI condition, participants quoted their quality of the imagery on a Likert scale following the MIQ-3Sf
219 recommendations from 1 (poor) to 7 (excellent) (Robin et al. 2021).

220 *Neuromuscular electrical stimulation (NMES) 5% and 20%*

221 NMES condition consisted in evoking stimulated contractions of the FCR during 5 s at constant intensity
222 allowing to reach 5% and 20% MVC preliminary recorded. Fourteen repetitions were performed
223 according to the number of stimulation (4 Mmax and 10 MEP). Two electrodes were placed over the
224 FCR belly. The upper NMES electrode (5 x 10 cm Medicompex SA, Ecublens, Switzerland) was placed
225 over the FCR proximally to the EMG and the lower one (5 x 5 cm Medicompex SA, Ecublens,
226 Switzerland) distally to the EMG. Trains of monophasic rectangular electrical stimuli (1 ms width) were
227 evoked to the FCR belly by using high voltage (400 V) constant-current stimulator (Digitimer DS7R,
228 Hertfordshire, UK). By using LABCHART software (LABCHART 8, AdInstruments, Sydney,
229 Australia), a program of NMES stimulation train was used to set the parameters of NMES condition.
230 The frequency of stimulation was set at 100 Hz. The stimulation intensity was preliminary set to reach
231 5% and 20% MVC in palmar flexion with 1 s stimulation train. The intensity was increased with 1 mA
232 increment until 5% and 20% MVC were reached. Then, the stimulation intensity was constant during
233 the whole session. To determine 5% and 20% MVC, a mean of two MVCs in palmar flexion was
234 performed. After the NMES 5% and NMES 20% conditions, participants quoted the discomfort induced
235 by NMES on a pain numerical rating scale (NRS) following a score from 0 (no discomfort) to 10
236 (intolerable pain) (Ferreira-Valente et al. 2011).

237 *MI+NMES 5% and 20%*

238 In this session participants performed imagined and evoked contractions of the FCR concomitantly. MI
239 was performed during 7 s while NMES trains was applied 2 s after the beginning of MI to limit the
240 disturbance of participants cause by NMES. Fourteen repetitions were performed according to the
241 number of stimulation (4 Mmax and 10 MEP). To check if the EMG activity of imagined contractions

242 during MI+NMES was similar to imagined contractions alone, one of the 14 contractions at each
243 condition were performed without NMES without warning the participant (MI+NMES_{sham}). To ensure
244 that participants were ready the experimenter asked them (“get ready”) before to give an oral signal
245 (“go”) to begin the imagery at each trial. Each MI and NMES trials were performed with the same
246 modality of single MI and NMES session described above. After each MI+NMES repetitions,
247 participants gave a mark of the quality of their imagery on a Likert scale following the MIQ-3Sf from 1
248 (poor) to 7 (excellent) (Robin et al. 2021). After the MI+NMES 5% and MI+NMES 20% conditions,
249 participants quoted the discomfort induced by NMES on a pain NRS following a score from 0 (no
250 discomfort) to 10 (intolerable pain) (Ferreira-Valente et al. 2011).

251 *Electromyographic recordings*

252 EMG was recorded on flexor carpi radialis (FCR) and extensor carpi radialis (ECR). After shaving and
253 dry-cleaning the skin with alcohol, two silver chloride surface electrodes (8 mm diameter, centre-to-
254 centre distance: 2 cm; Contrôle Graphique S.A., Brie-Comte-Robert, France) were placed over the
255 muscle bellies. The electrodes were positioned at one-third of the distance from the medial epicondyle
256 and the radial styloid for FCR muscle and at one-third of the distance from the lateral epicondyle and
257 the radial styloid for ECR muscle (Bartko and Carpenter 1976). The common reference electrode was
258 placed on the medial epicondyle. EMG signals were amplified (gain=1000) with bandwidth frequency
259 ranging from 100 Hz to 2 kHz (sampling frequency: 4 kHz) by using Powerlab system (Powerlab 16/35,
260 AdInstruments, Sydney, Australia).

261 *Median nerve stimulation*

262 Transcutaneous median nerve stimulation was used to evoke FCR M-wave at rest and during each
263 condition. Single rectangular pulses (1 ms width) were delivered by using a constant current stimulator
264 (Digitimer DS7R, Hertfordshire, UK). A surface bar electrode (ADinstruments) was placed up to the
265 cubital fossa, below biceps’ muscle belly. The optimal stimulation site was first located by hand using
266 the electrode before fixing it with a straps. Then, to determine the intensity of stimulation of maximal
267 M-wave, the intensity was increased with 1 mA increment. Once maximal M-wave amplitude was
268 reached, the intensity was further increased by 20% to ensure that the response lied in the plateau of its
269 maximal value. This last intensity was taken as the one to elicit the actual maximal M-wave (Mmax).
270 Before the whole protocol, 4 single pulses were evoked at rest. Four single pulses were evoked per
271 condition.

272 *Transcranial magnetic stimulation*

273 TMS (Magstim 200; Magstim, Carmarthenshire, UK) was used to elicit MEPs in the FCR and ECR
274 muscle of the right forearm at rest and during each condition. The TMS settings were optimized for the
275 FCR. A figure-of-eight-shaped coil was placed over the left motor cortex held at an angle of 45° to the

276 midsagittal line to be approximately perpendicular to the central sulcus. The coil was held by using a
277 tripod with lockable articulated arm (Magstim, Carmarthenshire, UK). First, the optimal spot for
278 eliciting the largest MEP in the right FCR muscle was identified. This position was marked on a bathing
279 cap worn by the participant. Second, we determined the resting motor threshold (RMT) defined as the
280 minimal TMS intensity required to evoke MEP peak-to-peak amplitudes of 50 μ V of the FCR in 5 out
281 of 10 consecutive trials. Then, the TMS intensity was set to 120% of the participant's RMT.
282 Experimenter checked throughout the experiment that the coil was placed identically for all conditions
283 and checked MEP amplitude during rest trials between each condition. The spatial accuracy of TMS
284 and the proximity of the motor area from FCR allowed to record simultaneously MEPs of the ECR
285 (Fadiga et al. 1998; Neige et al. 2017).

286 **Data analysis**

287 The root mean square (RMS) of EMG activity at rest was determined for each muscle (FCR and ECR)
288 and condition over periods of 500 ms prior to the stimulation. The RMS at rest, during MI (10 imagined
289 contractions) and during MI+NMES_{sham} 5% and 20% (one of the 14 contractions during MI+NMES 5%
290 and 20% performed without NMES) were averaged and normalized by the corresponding Mmax to
291 express the ratio RMS/Mmax for FCR. The force–time integral (FTI), considered as the area under the
292 force–time curve, was analysed for the 14 contractions (imagined and stimulated) performed during
293 each condition that included evoked contractions (NMES and MI+NMES). Then, the mean of the 14
294 FTI was analysed. Peak-to-peak amplitudes of MEP at rest, Mmax at rest and during each condition
295 were averaged for FCR. Peak-to-peak amplitudes of the averaged MEP and normalized to the
296 corresponding averaged Mmax evoked in the same condition for FCR. Therefore, ratios MEP/Mmax
297 during MI, NMES 5%, NMES 20%, MI+NMES 5% and MI+NMES 20% were taken as the analysed
298 variable for the final analysis. Regarding ECR muscle, peak-to-peak amplitudes of MEP at rest and
299 during each condition were averaged and normalized to MEP at rest. For ECR, the ratio
300 MEP_{condition}/MEP_{rest} was taken for the final analysis.

301

302 **Statistical analysis**

303 Statistical analysis was performed using Statistica (8.0 version, StatSoft, Tulsa, Oklahoma, USA). All
304 data are expressed by their mean \pm standard deviation. Data were screened for normal distribution using
305 the Shapiro-Wilk test ($p < 0.05$). The statistical significance was set at $P < 0.05$. A one-way Friedman
306 ANOVA was performed to compare Mmax during each condition compared to rest for FCR. First,
307 statistical analysis was performed to assess the effect of MI on motor imagery ability and
308 electrophysiological responses. A one-way ANOVA was performed between MIQ-3Sf score during MI,
309 MI+NMES session and rest. For each of the two variables, MEP/Mmax and RMS/Mmax, a one-way
310 ANOVA was performed between rest, MI, MI+NMES_{sham} 5% and MI+NMES_{sham} 20% for FCR. In

311 addition, a one-way ANOVA was performed between the pain score during NMES and MI+NMES at
312 5% and 20%. Second to assess the MEP/Mmax during each condition a one-way Friedman ANOVA
313 (condition [MI, NMES5%, NMES 20%, MI+NMES 5%, MI+NMES 20%]) was performed to assess
314 the condition effect on MEP/Mmax for FCR. Then, to assess the effect of each condition on ECR, a one-
315 way Friedman ANOVA (condition [MI, NMES5%, NMES 20%, MI+NMES 5%, MI+NMES 20%])
316 was performed to assess the condition effect on MEP_{condition}/MEP_{rest}. When a main effect was found,
317 a Conover test was performed. A one-way Friedman ANOVA was performed to compare the FTI
318 between NMES and MI+NMES at 5% MVC and between NMES and MI+NMES at 20% MVC. Effect
319 sizes for the ANOVA were calculated and are reported as partial eta squared (η_p^2) with small, moderate
320 and large effects considered for $\eta_p^2 \geq 0.01$, ≥ 0.07 and ≥ 0.14 , respectively and f with small, moderate
321 and large effects considered for $f \geq 0.1$, ≥ 0.25 and ≥ 0.4 , respectively (Levine and Hullett 2002). For
322 paired comparisons the Cohen's d with small, moderate, and large effects considered for $0.2 \leq d < 0.5$,
323 $0.5 \leq d < 0.8$, $d \geq 0.8$, respectively, was used (Fritz et al. 2012). When required, a Bonferroni correction
324 was applied. Pearson's correlation was assessed with P obtained in the Bravais-Pearson table between
325 ratio of MEP expressed as $((MEP_{condition} - MEP_{rest}) / MEP_{rest})$ during MI+NMES 5% and MI+NMES 20%
326 MVC for FCR (degree of freedom = 15).

327 **Results**

328 *Initial checkings*

329 *First*, the mean MIQ-3Sf was 5.0 ± 1.2 (mean \pm SD) out of 7 indicating a satisfactory imagery capacity.
330 The one-way ANOVA did not show significant changes of self-evaluated MI capacity between MI,
331 MI+NMES 5%, MI+NMES 20% and initial MIQ-3Sf score ($P = 0.13$; Table 1). The one-way ANOVA
332 revealed no significant difference on RMS/Mmax between rest, MI, MI+NMES_{sham} 5% and
333 MI+NMES_{sham} 20% for FCR ($P > 0.05$; Table 1). The one-way Friedman ANOVA showed a main effect
334 of condition on MEP/Mmax between rest, MI, MI+NMES_{sham} 5% and MI+NMES_{sham} 20% for FCR ($F_{3, 48} = 10.68$;
335 $P < 0.001$; $\eta_p^2 = 0.4$; $f = 0.81$; Table 1). The MEP/Mmax during rest was significantly lower
336 than MI ($P = 0.005$; $d = 0.26$) and MI+NMES_{sham} 20% ($P = 0.002$; $d = 0.34$). The one-way ANOVA
337 showed a condition effect on pain score between NMES 5%, NMES 20%, MI+NMES 5% and
338 MI+NMES 20% ($F_{3, 48} = 28.99$; $P < 0.001$; $\eta_p^2 = 0.64$; $f = 1.33$; Table 1). The pain score during
339 MI+NMES 20% was significantly higher than NMES 5% ($P < 0.001$; $d = 0.8$) and MI+NMES 5% ($P <$
340 0.001 ; $d = 0.72$). The pain score during NMES 20% was significantly higher than NMES 5% ($P < 0.001$;
341 $d = 0.78$) and MI+NMES 5% ($P < 0.001$; $d = 0.7$). Regarding FTI of evoked contractions, no significant
342 difference was observed between NMES and MI+NMES at 5% MVC ($P = 1.0$), and between NMES
343 and MI+NMES at 20% MVC ($P = 1.0$; Table 1).

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347 **Table 1** Data of MIQ-3Sf, force-time integral (FTI), pain score, motor evoked potential (MEP) and root
 348 mean square (RMS) of FCR. Mean \pm SD. *Significantly higher than rest for MEP/Mmax ($P < 0.005$),
 349 **Significantly higher than NMES 5% and MI+NMES 5% for pain score ($P < 0.001$).

	MIQ-3Sf		FTI (N·s)	pain score		RMS/Mmax	MEP/Mmax
initial score	5.06 \pm 1.21	NMES 5%	40.42 \pm 38.25	2.6 \pm 1.8	rest	0.009 \pm 0.003	0.05 \pm 0.039
MI	5.44 \pm 0.88	MI+NMES 5%	51.78 \pm 40.56	2.7 \pm 1.7	MI	0.01 \pm 0.005	0.12 \pm 0.111*
MI+NMES 5%	5.02 \pm 0.75	NMES 20%	145.43 \pm 72.96	4.0 \pm 2.0**	MI+NMESsham 5%	0.01 \pm 0.004	0.09 \pm 0.06
MI+NMES 20%	5.0 \pm 1.0	MI+NMES 20%	146.57 \pm 72.3	4.1 \pm 1.8**	MI+NMESsham 20%	0.01 \pm 0.005	0.16 \pm 0.12*

350

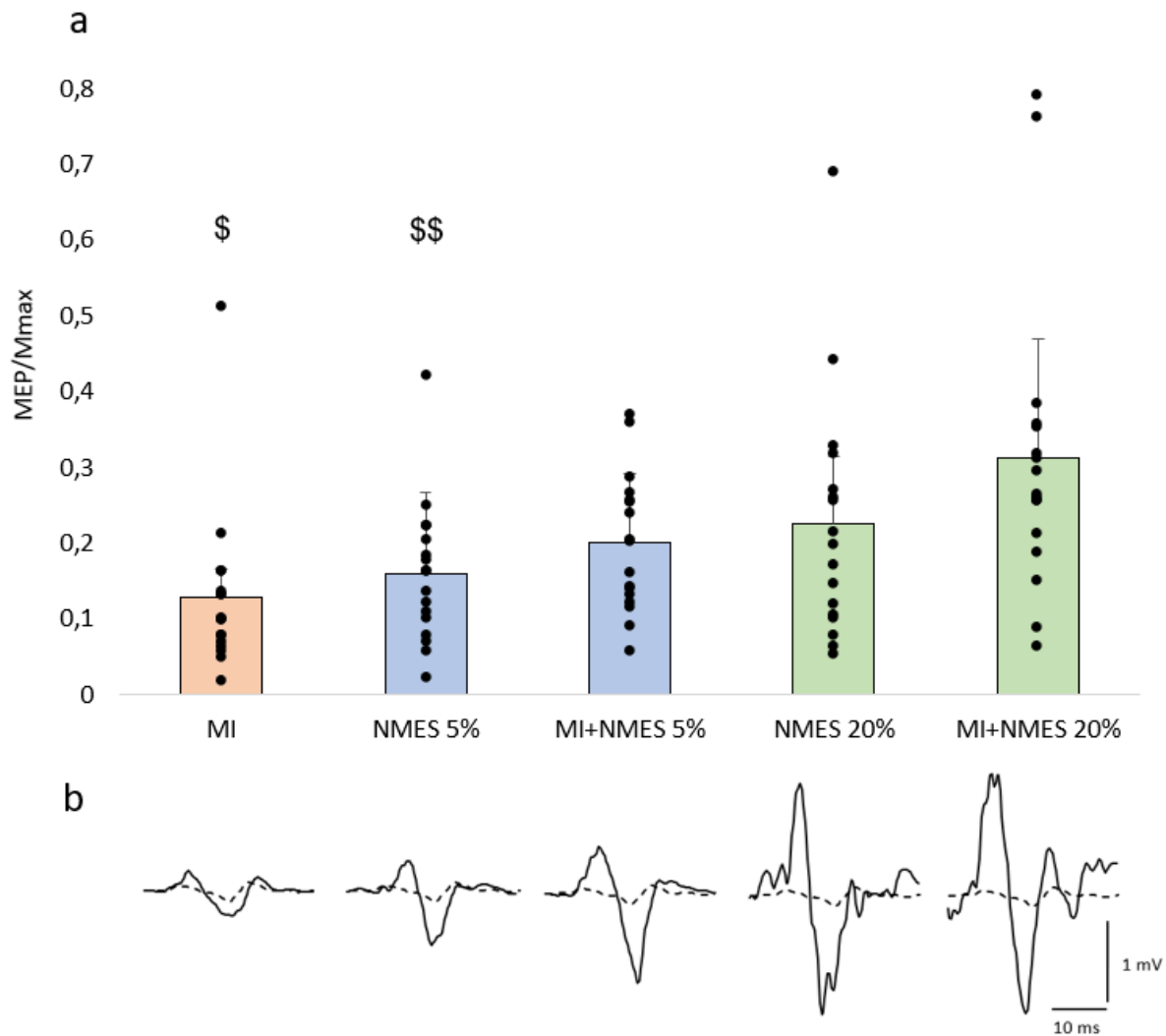
351

352 *M-wave*

353 The one-way Friedman ANOVA did not show significant difference on Mmax between condition for
 354 FCR (rest, 5.59 \pm 2.32 mV; MI, 4.67 \pm 2.15 mV; NMES 5%, 4.95 \pm 2.79 mV; NMES 20%, 4.92 \pm 2.53
 355 mV; MI+NMES 5%, 4.78 \pm 2.26 mV; MI+NMES 20%, 4.75 \pm 3.08 mV; $P > 0.1$).

356 *MEP*

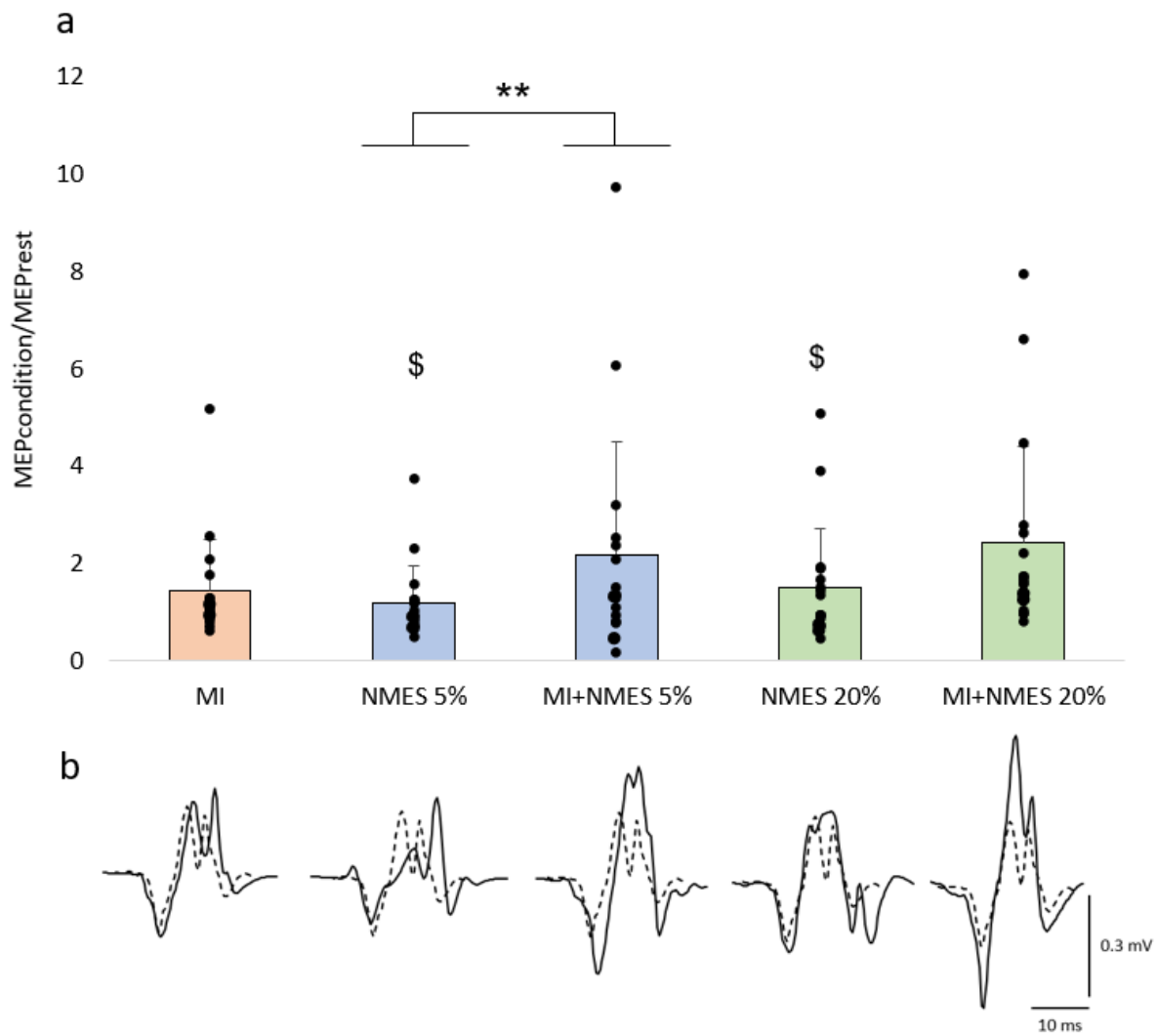
357 The one-way Friedman ANOVA revealed a main effect of condition on MEP/Mmax for FCR ($F_{4, 64} =$
 358 6.76; $P < 0.001$; $\eta_p^2 = 0.29$; $f = 0.63$; Fig. 2). The conover post hoc test showed that MEP/Mmax during
 359 MI was significantly lower than during MI+NMES 5% ($P = 0.02$; $d = 0.73$) and MI+NMES 20% ($P <$
 360 0.001; $d = 0.83$). The MEP/Mmax during NMES 5% was significantly lower than during MI+NMES
 361 20% ($P < 0.005$; $d = 0.79$). The one-way Friedman ANOVA showed a main effect of condition on
 362 MEPcondition/MEPrest for ECR ($F_{4, 64} = 6.46$; $P < 0.001$; $\eta_p^2 = 0.28$; $f = 0.62$; Fig. 3). The conover post
 363 hoc test showed that MEPcondition/MEPrest during MI+NMES 20% was significantly higher compared
 364 to NMES 5% ($P < 0.001$; $d = 0.69$) and NMES 20% ($P = 0.01$; $d = 0.51$) then, MEPcondition/MEPrest
 365 during MI+NMES 5% was significantly higher than NMES 5% ($P = 0.03$; $d = 0.47$). The ratio of MEP
 366 during MI+NMES 5% and MI+NMES 20% were positively correlated for FCR ($r = 0.76$; $P < 0.001$;
 367 Fig. 4).



368

369 **Fig. 2** FCR-evoked responses of MEP/Mmax during each condition (a). Mean \pm SD. Results of each
 370 participant are depicted over bars by black dots. \$Significantly lower than MI+NMES 5% and
 371 MI+NMES 20% ($P < 0.05$), \$\$Significantly lower than MI+NMES 20% ($P < 0.005$). Typical traces of
 372 MEP of the FCR from one representative participant during each condition (b). The MEP was measured
 373 100 ms after each condition (MI, NMES 5%, NMES 20%, MI+NMES 5% and MI+NMES 20%). The
 374 black dotted line represents the MEP at rest.

375

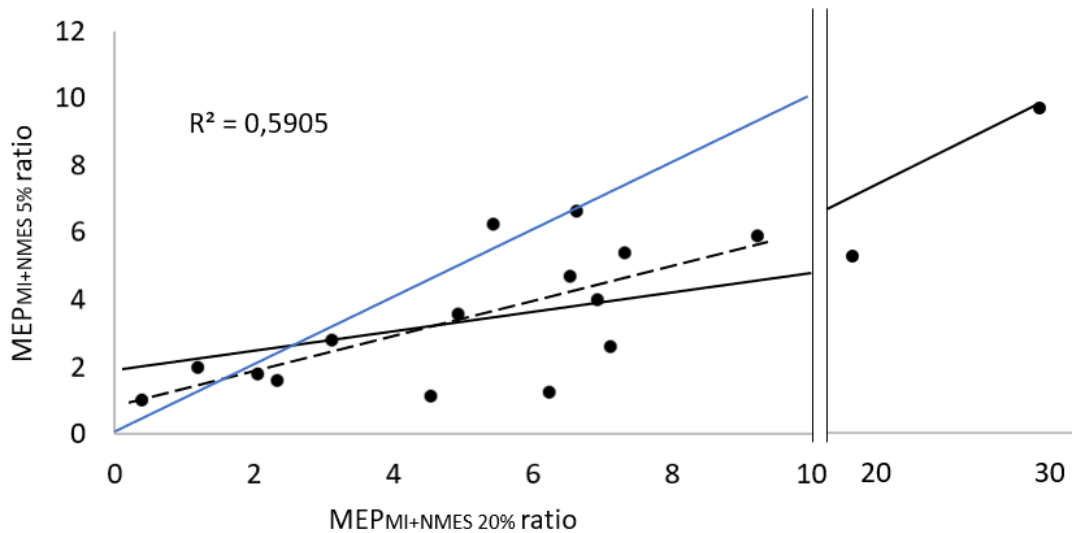


376

377 **Fig. 3** ECR-evoked responses of $MEP_{condition}/MEP_{rest}$ during each condition (a). Mean \pm SD. Results of
 378 each participant are depicted over bars by black dots. \$Significantly lower than MI+NMES 20% ($P <$
 379 0.05), **Significantly lower than MI+NMES 5% ($P <$ 0.05). Typical traces of MEP of the ECR from
 380 one representative participant during each condition (b). The MEP was measured 100 ms after each
 381 condition (MI, NMES 5%, NMES 20%, MI+NMES 5% and MI+NMES 20%). The black dotted line
 382 represents the MEP at rest.

383

384



385

386 **Fig. 4** Correlation between MEP ratio during MI+NMES 5% and MI+NMES 20% of the FCR. MEP
 387 ratio was expressed as $((MEP_{condition} - MEP_{rest}) / MEP_{rest})$. The correlation performed without the two
 388 extreme value for coordinates (18.6; 5.2) and (29.4; 9.6) is still significant ($R^2 = 0.45$; $P < 0.05$). The
 389 latter correlation is represented by the black dot line. The blue line represents the identity line ($x=y$).

390

391 Discussion

392 The aim of this study was to assess the corticospinal excitability during MI, NMES and MI+NMES at
 393 different level of muscle force evoked by NMES (5% and 20% MVC) on the wrist flexors. Our results
 394 showed a main effect of condition on the MEPs amplitude. We found a higher MEP when MI was
 395 combined with NMES at submaximal intensities (5% and 20% MVC), only compared to MI alone.
 396 Furthermore, no significant difference was found between MI+NMES at 5% and 20% MVC. However,
 397 we observed a gradual increase on MEP as the contraction intensity increased. Considering the
 398 hypothesis, these results confirm that MI+NMES with NMES applied at submaximal contraction
 399 intensities increases the corticospinal excitability compared to MI. However, the results did not support
 400 the hypothesis that the intensity effect of NMES could occur during MI+NMES.

401 Motor imagery

402 By using TMS, this non-invasive technique allowed numerous studies to investigate the excitability of
 403 the corticospinal pathway during MI (Stinear et al. 2006; Kaneko et al. 2014; Rozand et al. 2014;
 404 Mouthon et al. 2015; Grosprêtre et al. 2016b). In agreement with previous reports, our results strengthen
 405 the literature stipulating a higher corticospinal excitability during MI compared to rest (Kaneko et al.
 406 2014; Mouthon et al. 2015; Grosprêtre et al. 2016b). Indeed, it is admitted that MI activates the same
 407 brain areas devoted to motor control and execution e.g. supplementary motor area, premotor and primary
 408 motor cortices, cerebellum and primary somatosensory cortex (Lotze et al. 1999; Hardwick et al. 2018),
 409 that likely contribute to an increase of the corticospinal excitability (Kaneko et al. 2014; Mouthon et al.
 410 2015; Grosprêtre et al. 2016b). In addition, by using cervico-medullar stimulation and peripheral nerve

411 stimulation, previous works provided evidence that spinal excitability was also impacted during MI
412 (Grosprêtre et al. 2016a, 2019). It has been shown that kinesthetic MI can increase spinal excitability by
413 the intensity of imagined effort (Cowley et al. 2008). These authors showed that spinal excitability,
414 highlighted by H-reflex, was greater during maximal imagined contraction (MIC) compared to 25%
415 MIC (Cowley et al. 2008). More recently, Grosprêtre et al. (2019) showed that spinal presynaptic
416 inhibitory pathway could be involved during MI practice suggesting that subliminal cortical outputs
417 generated by MI may reach spinal structures with a lower excitability threshold. These results showed
418 that the cortical activity induced by MI was sufficient to create a cortical output addressed to spinal
419 level. Overall, this provides evidence that MI can activate the subcortical regions of the motor pathway,
420 constituting the corticospinal tract, and does not limit to the brain motor regions.

421 *Neuromuscular electrical stimulation*

422 In this current study, when NMES was applied at an intensity sufficient to create a muscle force, we
423 found no intensity effect between NMES 5% and NMES 20% MVC. This could be explained by spinal
424 and/or cortical modifications that NMES can induce by evoking these intensities. Indeed, it is known
425 that NMES applied at submaximal intensities (e.g. 20% MVC) can modify the transmission efficiency
426 of Ia-afferents to motoneuron which alter spinal excitability (Papaiordanidou et al. 2014). Furthermore,
427 it has been shown that the activation of the sensorimotor network and motor areas could be modified by
428 NMES applied at submaximal intensity (Alexandre et al. 2015; Muthalib et al. 2015). Overall, these
429 mechanisms at different nervous level can alter the corticospinal excitability with the increase of the
430 stimulation intensity. However, we noticed that the MEP during NMES was placed between MI and
431 MI+NMES (5% and 20% MVC) conditions suggesting that the intensity of NMES may at least generate
432 an enhancement of the corticospinal excitability. This result suggests that the excitatory afferent inputs
433 induced by NMES applied at submaximal contractions intensities affect the corticomotoneuronal
434 transmission efficacy. Indeed, it is widely known that the activation of afferent receptors (i.e., cutaneous
435 mechanoreceptors, muscle spindles and Golgi tendon organs) increases as the stimulation intensity
436 increases (Maffiuletti et al. 2008; Bergquist et al. 2011; Golaszewski et al. 2012). This activation can
437 generate an afferent volley that are able to reach the somatosensory cortex and can directly project to
438 the motor cortex (Carson and Buick 2021). Together, these results showed that the intensity of NMES
439 evoked at submaximal contractions intensities may modify the corticospinal excitability, which could
440 result to modulations occurring at both cortical and spinal level.

441 *Motor imagery combined with neuromuscular electrical stimulation*

442 To allow an optimal concentration on imagined movement during the 5s of NMES, MI was performed
443 2s before NMES during both MI+NMES 5% and 20% MVC. Indeed, it has been shown that NMES can
444 cause discomfort with high stimulation intensity (Theurel et al. 2007) which may disrupt the capacity of
445 motor imagery. It is known that discomfort or pain may be associated with activation of inhibitory

446 mechanism at spinal level which may decrease corticospinal excitability (Rohel et al. 2021). However,
447 our results did not show decrease of MEP during MI+NMES. Furthermore, we found that the capacity
448 of motor imagery was similar between MI, MI+NMES 5% and MI+NMES 20% despite a mild perceived
449 pain (4/10 on pain NRS) quoted during MI+NMES 20%. Thus, this shows that the capacity of motor
450 imagery and the corticospinal excitability have not been altered significantly during NMES.

451 Electrophysiological results revealed an increasing graduated effect of the corticospinal excitability
452 from MI to NMES and MI+NMES at 5% then at 20%. The corticospinal excitability during MI+NMES
453 5% and 20% was higher compared to MI but did not differ to NMES at the same intensity. In comparison
454 to the literature, similar results have been reported that during MI+NMES with a stimulation intensity
455 of NMES applied above motor threshold at very low intensity compared to MI (Saito et al. 2013; Kaneko
456 et al. 2014). This effect observed during MI+NMES could be attributed to a complementary activation
457 of the neuromuscular system from cortical to spinal level that accounts for adaptation of both MI and
458 NMES alone. Indeed, it has been suggested that the afferent input from the muscle spindle induced by
459 NMES may enhance the cortical activity induced by MI resulting in higher corticospinal excitability
460 (Saito et al. 2013; Kaneko et al. 2014). However, in this current study, the supplementary activation of
461 muscle fibers through the increase of stimulation intensity may not increase the corticospinal excitability
462 when it is combined with MI since no intensity effect was observed between MI+NMES at 5% and 20%
463 MVC. It has already been shown that a session of NMES applied at submaximal intensities could
464 modulate other mechanisms at spinal level when combined with MI (Eon et al. 2023) which may limit
465 the enhancement of corticospinal excitability with the increase of the stimulation intensity. This latter
466 study showed that MI+NMES 20% MVC was able to modify the transmission efficiency of Ia-afferents
467 to motoneuron highlighted by a compensation of a decrease in H-reflex induced after a sessions of
468 NMES 20% MVC (Eon et al. 2023). Thus, this suggests that underlying mechanism at spinal level could
469 occur and modulate the corticospinal excitability during MI+NMES. Interestingly, further analysis
470 showed that the gain of MEP amplitude report to rest was strongly correlated between MI+NMES 5%
471 and MI+NMES 20% MVC. This finding demonstrates that the more corticospinal excitability is
472 potentiated at 5%, the more it is potentiated at 20% when it is combined with MI. Together, these results
473 show that the increase of corticospinal excitability during MI+NMES could account slightly higher from
474 adaptations induced by NMES since NMES has an intermediate effect on corticospinal excitability
475 between MI and MI+NMES. In addition, NMES evoking submaximal level of force (5% and 20%
476 MVC) did not differ significantly corticospinal excitability when it is combined with MI.

477 Regarding the antagonist muscle (ECR), our results further revealed that the MEP (%PRE) was
478 significantly higher during MI+NMES at 5% and 20% compared to MI and NMES alone. As antagonist
479 from FCR, it is known that agonist and antagonist muscles exhibit reciprocal activation to smooth
480 voluntary movement via spinal inhibition (Crone and Nielsen 1988; Aymard et al. 1995). Basically,
481 Takahashi et al. (2019) showed that spinal reciprocal inhibition was altered after a session of MI+NMES.

482 These authors stipulating that descending input from corticospinal tract combining with the activation
483 of Ia afferents during MI+NMES may induce plastic changes of the Ia inhibitory circuit (Takahashi et
484 al. 2019). Thus, these adaptations occurred on MEP of the ECR provide evidence that both spinal and
485 cortical mechanisms may have contributed to improve the corticospinal excitability during MI+NMES
486 even when the reverse movement to ECR activation was imagined.

487 Several limitations in this study should be mentioned. Since healthy participants were enrolled in this
488 study, particular care should be taken in generalizing these findings to the clinical context. Nevertheless,
489 MI and NMES are already widely studied and/or used in rehabilitation to improve muscle strength
490 (Grosprêtre et al. 2018b; Olsen et al. 2020) or limit its decline during immobilization (Stevens-Lapsley
491 et al. 2012; Clark et al. 2014) . Thus, further investigations in clinical populations are warranted to test
492 the effect of MI, NMES and their combination. Furthermore, in the present study only one woman
493 participated which limit the generalization of the results to both sexes. To date, few studies have
494 investigated the effect of sex on NMES and MI on neurophysiological markers. However, one study
495 demonstrated that NMES with wide pulse and high frequency evoked larger relative elbow flexion force
496 in women than in men (Ye et al. 2022). This may suggest that the effect of NMES on neuromuscular
497 system may be different between men and women. Therefore, neurophysiological markers during
498 MI+NMES may also differ between men and women.

499 **Conclusion**

500 To conclude, this study showed that the corticospinal excitability was increased during MI compared to
501 rest. In the same way, the corticospinal excitability was increased similarly during MI+NMES at 5%
502 and 20% compared to MI. This study provides evidence of the efficiency of the combination of MI and
503 NMES performed simultaneously with stimulated contractions evoked at submaximal intensities on the
504 corticospinal excitability. Indeed, when NMES is applied at an intensity above motor threshold
505 (sufficient to create a muscle force), the recruitment of afferent fibers could enhance the activation of
506 the cortical motor areas induced by MI which result in enhancement of the corticospinal excitability.
507 Nevertheless, spinal and/or cortical mechanisms may modulate differently the corticospinal excitability
508 for submaximal intensities applied at low muscle contraction avoiding the significant enhancement of
509 corticospinal excitability at 20% compared to 5% MVC. Thus, despite the underlying mechanisms at
510 spinal and cortical level from both MI and NMES applied at submaximal contractions intensities provide
511 a complementary activation of the neuromuscular system able to activate the corticospinal loop, this
512 effect may not significantly potentiate the corticospinal excitability between low submaximal
513 contractions intensities.

514 Overall, the combination of MI and NMES applied at submaximal intensities could be an efficient
515 method to overcome the deleterious effect of physical inactivity on both nervous and muscular

516 alterations. In this way, further investigations are needed to assess the impact of chronic practice on
517 motor performance and neuromuscular system by performing the combination of MI and NMES.

518

519 Acknowledgements

520 We thank all the participants who took part in the experiments.

521 Author contributions

522 AM and SG: conceived and designed research; PE: conducted experiments and extracted results; PE:
523 ran statistical analyses and designed graphs tables; PE, AM and SG: analyzed data; PE: wrote the
524 manuscript. All authors read and approved the manuscript.

525 Funding

526 This work has been supported by the Agence Nationale de la Recherche (ANR) (ANR-20-CE37-0007).

527 **Compliance with ethical standards**

528 Conflict of interest

529 No conflicts of interest, financial or otherwise, are declared by the authors.

530 Ethical approval

531 The experimental protocol was approved by the regional ethic committee (CPP COOM III number 2017-
532 A00064-49 ; Clinical trial.gov identifier NCT03334526) and conducted in conformity with the latest
533 version of the Declaration of Helsinki.

534 Informed consent

535 Participants gave written informed consent to participate in the present study and to its publication.

536

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