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Enzo Piponnier, Vincent Martin, Pierre Bourdier, Brice Biancarelli, Virginie Kluka, Sebastian Garcia-Vicencio, Anne-Gaelle Jegu, Charlotte Cardenoux, Cedric Morio, Emmanuel Coudeyre, et al.

► **To cite this version:**

Enzo Piponnier, Vincent Martin, Pierre Bourdier, Brice Biancarelli, Virginie Kluka, et al.. Maturation-related changes in the development and etiology of neuromuscular fatigue. *European Journal of Applied Physiology*, In press, 119 (11-12), pp.2545-2555. 10.1007/s00421-019-04233-3 . hal-02301647

**HAL Id: hal-02301647**

**<https://hal.science/hal-02301647>**

Submitted on 30 Sep 2019

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1 **Original article**

2 **Maturation-related changes in the development and etiology of**  
3 **neuromuscular fatigue**

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21 **ABSTRACT**

22 **Purpose:** The aim of the present study was to investigate the role of maturation on the etiology  
23 of neuromuscular fatigue induced by repeated maximal voluntary isometric contractions  
24 (MVIC).

25 **Methods:** Nine prepubertal boys ( $9.9 \pm 1.3$  yr.), eight male adolescents ( $13.6 \pm 1.3$  yr.) and  
26 eleven men ( $23.4 \pm 3.0$  yr.) performed a series of repeated isometric MVICs of the knee  
27 extensors until the MVIC torque reached 60% of its initial value. Magnetic stimulations were  
28 delivered to the femoral nerve every five MVICs to follow the course of voluntary activation  
29 level (VA) and the potentiated twitch torque ( $Q_{tw_{pot}}$ ).

30 **Results:** Task failure was reached after  $52.9 \pm 12.7$ ,  $42.6 \pm 12.5$  and  $26.6 \pm 6.3$  repetitions in  
31 boys, adolescents and men, respectively. VA remained unchanged in men whereas it decreased  
32 significantly and similarly in boys and adolescents ( $p < 0.001$ ). In contrast,  $Q_{tw_{pot}}$  remained  
33 unchanged in boys and decreased significantly less in adolescents than adults ( $p < 0.05$ ).

34 **Conclusions:** Children and adolescents experience less peripheral and more central fatigue than  
35 adults. However, adolescents experience more peripheral fatigue than children for a comparable  
36 amount of central fatigue. This finding supports the idea that the tolerance of the central nervous  
37 system to peripheral fatigue could increase during maturation.

38 **Keywords:** Adolescent, central fatigue, peripheral fatigue, electromyography, peripheral  
39 magnetic stimulation

40 **Abbreviations:**

41 %CoAct: Level of antagonist co-activation

42 %REP: Percentage of the number of repetitions

43  $\eta^2$ : Partial eta-squared

44 ANOVA: Analysis of variance

45 APHV: Age from peak height velocity

46 BF: Biceps femoris

47 CI: Confidence interval

48 EMG: Electromyography

49 KE: Knee extensors

50  $M_{max}$ : Maximal M-wave amplitude

51 MVIC: Maximal voluntary isometric contractions

52 M-wave: Compound action potential

53  $Q_{tw_{pot}}$ : Potentiated twitch torque

54  $Q_{tw_s}$ : Superimposed twitch torque

55  $Q_{tw_{unpot}}$ : Unpotentiated twitch torque

56 RF: Rectus femoris

57 RMS: Root Mean Square

58 VA: Voluntary activation level

59 VL: Vastus lateralis

## 60 INTRODUCTION

61 Neuromuscular fatigue is commonly defined as “any exercise-induced reduction in the ability  
62 of skeletal muscle to produce force or power irrespective of task completion” (Bigland-Ritchie  
63 and Woods 1984). Historically, potential factors involved in neuromuscular fatigue were  
64 classified into two categories, (i) central factors involving the central nervous system and neural  
65 pathways, and (ii) peripheral factors occurring within the muscle, beyond the neuromuscular  
66 junction (Gandevia 2001). As a result, it is possible to distinguish both central, *i.e.* neural, and  
67 peripheral, *i.e.* muscular fatigue. As the neuromuscular system is highly adaptable (Enoka and  
68 Stuart 1992), neuromuscular fatigue varies in response to different conditions. For instance,  
69 numerous studies examined the differential effect of age (Streckis et al. 2007), ageing (Kent-  
70 Braun et al. 2002), sex (Hunter et al. 2004), training status (Mira et al. 2018) and the mode of  
71 contraction (Souron et al. 2018) on neuromuscular fatigue. However, less attention has been  
72 paid to the impact of maturation on the development and etiology of neuromuscular fatigue.

73 Current knowledge suggests that fatigue increases progressively from childhood to adulthood  
74 during intermittent whole-body dynamic activities or repeated maximal voluntary contractions.  
75 For instance, during repeated cycling sprints, the decline of peak power output is higher in  
76 adolescents than children and lower than adults (Ratel et al. 2002). This finding has been  
77 confirmed during a series of isokinetic maximal voluntary contractions of the knee extensors  
78 (KE) and knee flexors (Zafeiridis et al. 2005; Dipla et al. 2009). Similarly, when muscle  
79 contractions include an eccentric phase (*i.e.* a stretch of the active muscle), the decline of peak  
80 torque during exercise is higher in adolescents than children and lower than adults (Chen et al.  
81 2014). Moreover, the magnitude of symptoms appearing during the days following a series of  
82 eccentric contractions (*i.e.* stiffness, oedema, decreased range of motion) is higher in adults  
83 than adolescents, and higher in adolescents than children (Chen et al. 2014).

84 However, it is still unclear whether the contribution of central and peripheral factors to  
85 neuromuscular fatigue may differ throughout maturation since no objective comparison of  
86 central *vs.* peripheral fatigue has been performed between prepubertal children, pubertal  
87 children (*i.e.* adolescents) and adults. To date, only Streckis et al. (2007) reported a lower  
88 peripheral fatigue and a higher central fatigue during a sustained 2-min maximal voluntary  
89 isometric contraction (MVIC) of the KE muscles in 12-14-year old boys and girls than men and  
90 women. However, in that study, no objective measurement of maturity status (*i.e.* biological  
91 age) was done, hence limiting our knowledge regarding the role of maturation on the etiology  
92 of neuromuscular fatigue. Despite this lack of information, peripheral fatigue could be higher  
93 in adolescent individuals than children, but lower in adolescents than adults because of (i) the  
94 progressive increase in the strength/power-generating capacity (Tonson et al. 2008) and (ii)  
95 potential changes in the metabolic profile throughout maturation, e.g. transformation of slow-  
96 twitch fibers into fast-twitch fibers (Lexell et al. 1992) and progressive increase in the capacity  
97 of the anaerobic energy turnover over maturation (Ratel and Blazevich 2017). Indeed, it has  
98 been shown that the higher neuromuscular fatigue of healthy men *vs.* women was no longer  
99 observed when subjects were matched for absolute MVIC force (Hunter et al. 2004) suggesting  
100 that the higher the MVIC force, the higher the muscle fatigue. In addition, the amount of  
101 peripheral fatigue was found to be greater in individuals with predominantly fast-twitch fibers  
102 (Hamada et al. 2003) and relying more on anaerobic than aerobic energy turnover as in  
103 explosive power-trained athletes (Garrandes et al. 2007). Taken together, these factors could  
104 promote a faster and/or greater development of peripheral fatigue during repeated maximal  
105 contractions in adolescents than children but a lower peripheral fatigue in adolescents than  
106 adults. Consequently, the development of strength/power and the transformation of slow-twitch  
107 into fast-twitch fibers over maturation could be associated with a progressive reduction of time  
108 to task failure from childhood to adulthood. As central fatigue is mainly promoted by prolonged

109 exercise duration (Thomas et al. 2015), this could translate into a lower central fatigue in  
110 adolescents than children as well as in adults than adolescents.

111 Therefore, the purpose of the present study was to verify these assumptions by examining the  
112 consequences of maturation on the development and etiology of neuromuscular fatigue induced  
113 by repeated voluntary maximal contractions.

## 114 **MATERIAL AND METHODS**

### 115 **Participants**

116 A total of nine 8-11 years old boys (Tanner stage 1-2), eight 13-16 years old male adolescents  
117 (Tanner stage 3-4) and eleven 18-25 years old healthy men were recruited. All the participants  
118 were involved in different physical activities such as rugby, basketball, swimming, etc. To be  
119 included, participants had to exercise less than 4 hours per week and to be free of any medical  
120 contra-indication to physical activity. The present study was approved by the local Ethics  
121 Committee (Protection Committee of People for Biomedical Research South East VI;  
122 Authorization Number AU929). All the participants were fully informed of the experimental  
123 procedures and gave their written consent before any testing was conducted. In addition, the  
124 written consent of the parents/guardians was also obtained for the children and adolescents.

### 125 **Experimental procedure (design)**

126 All participants were tested on three experimental sessions separated by at least 1 week. The  
127 first session was dedicated to collecting participants' physical characteristics, familiarization  
128 with the experimental procedures and clinical examination by a medical practitioner or a  
129 pediatrician. During the second session, the participants were asked to perform MVIC of the  
130 KE muscles at different knee angles (30, 40, 50, 60, 70, 75, 80, 85, 90, 100, 110°; 0° = full  
131 extension) in a randomized order to determine the optimal angle for maximal torque production.  
132 Participants performed two MVICs at each knee angle. Finally, during the third session, all the  
133 participants performed the intermittent voluntary fatigue protocol at the optimal knee angle. All  
134 sessions were done in a temperate room (18-22°C).

### 135 **Anthropometric measurements**

136 Body mass was measured to the nearest 0.1 kg using a calibrated scale and height was  
137 determined to the nearest 0.01 m using a standing stadiometer. Height and body mass were  
138 measured without shoes and while wearing underwear only. Sitting height was also measured  
139 while the participants sat on the floor against a wall, using the same stadiometer. Body mass  
140 index was calculated using a standard formula, mass divided by height squared ( $\text{kg}\cdot\text{m}^{-2}$ ). Body  
141 fat and fat-free mass were determined using dual-energy X-ray absorptiometry (HOLOGIC,  
142 QDR-4500, Hologic Inc, Bedford, Massachusetts, USA).

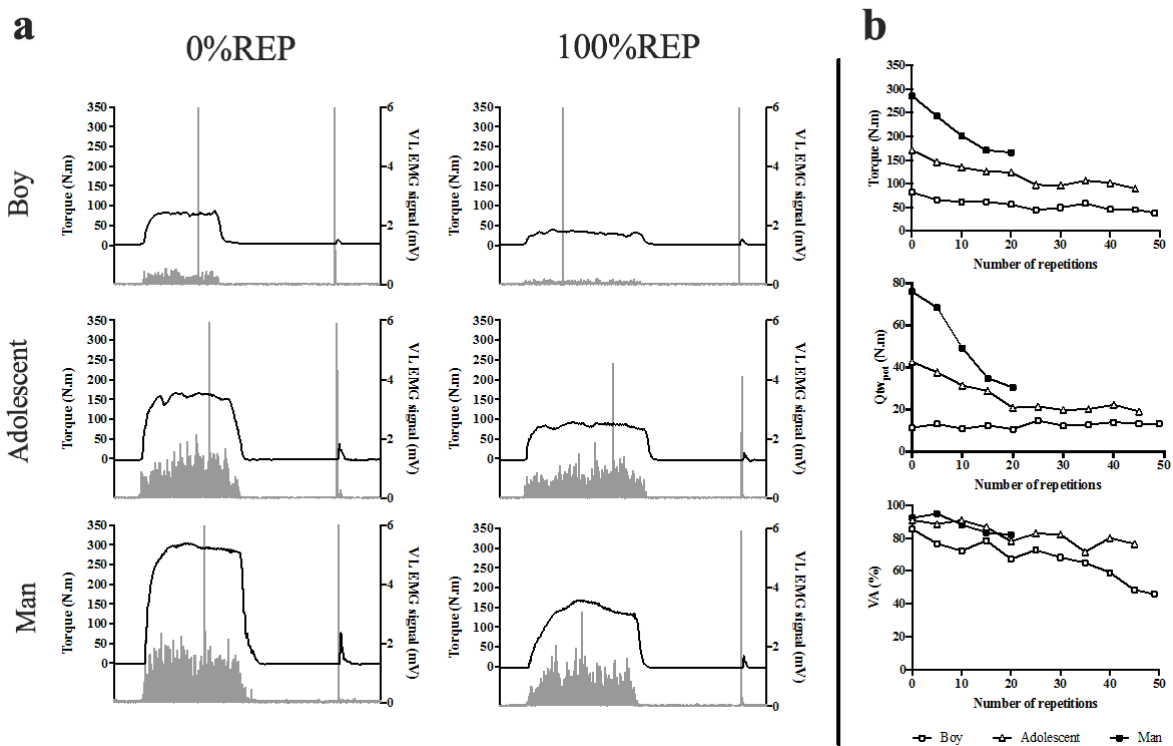
### 143 **Maturity status assessment**

144 Two methods were used to assess children and adolescents' maturity status: 1) Tanner stages  
145 were determined from self-reported assessment based on pubic hair and testicular/penis  
146 development (Tanner and Whitehouse 1976), the children and adolescents being assisted by  
147 their parents while completing the questionnaire; 2) Age from peak height velocity (APHV)  
148 was used to assess somatic maturity and determined by using height, sitting height and body  
149 mass (Mirwald et al. 2002).

### 150 **Intermittent voluntary fatigue protocol**

151 Participants performed an intermittent voluntary fatigue protocol consisting of a repetition of  
152 isometric 5-s MVICs of the KE muscles interspersed with 5-s passive recovery periods until  
153 the voluntary torque failed to reach a target value of 60% of its initial value over three  
154 consecutive MVICs. The participants had no visual feedback of torque output during the

155 exercise. However, they were strongly encouraged by the investigators during the entire  
 156 fatiguing task. During the fatigue protocol, all participants were allowed to drink water ad  
 157 libitum. The knee joint was fixed at the optimal angle for maximal torque production ( $75.6 \pm$   
 158  $5.3^\circ$ ,  $90.0 \pm 0.0^\circ$  and  $81.8 \pm 7.5^\circ$  in boys, adolescents and men, respectively;  $p < 0.001$ ), which  
 159 was determined from the torque-angle relationship during the second visit. The number of  
 160 repetitions was considered as the performance criteria to quantify neuromuscular fatigue. Single  
 161 magnetic stimulations were delivered to the femoral nerve every five MVICs to determine the  
 162 maximal level of voluntary activation (VA) by using the twitch interpolation technique (see  
 163 below for further details). The electromyographic (EMG) activity of the *vastus lateralis* (VL)  
 164 and *rectus femoris* (RF) muscles was recorded during the entire fatigue protocol. The amplitude  
 165 of the potentiated twitch torque ( $Q_{tw_{pot}}$ ; see below) and VL and RF concomitant compound  
 166 action potential amplitudes (maximal M-wave;  $M_{max}$ ) were considered as indicators of  
 167 peripheral fatigue. The time-course of VA and normalized EMG (see below) of the VL and RF  
 168 muscles throughout the protocol were considered as indexes of central fatigue. Examples of  
 169 raw data (MVIC torque and VL EMG; panel A) and time-courses of MVIC torque,  $Q_{tw_{pot}}$  and  
 170 VA during the fatigue protocol in a typical boy, adolescent and man are presented in Figure 1.



171 **Fig. 1:** (a) Example of raw data for MVIC torque and VL EMG obtained at 0%REP and  
 172 100%REP in a typical boy (top), adolescent (middle), and man (bottom). (b) Example of time-  
 173 courses of MVIC torque (top),  $Q_{tw_{pot}}$  (middle), and VA (bottom) during the intermittent fatigue  
 174 protocol in a typical boy, adolescent and man.

### 175 Torque measurements

176 Voluntary and evoked contractions were assessed in isometric condition with an isokinetic  
 177 dynamometer (Cybex Norm, Lumex, Ronkonkoma, NY, USA). Participants were comfortably  
 178 positioned on an adjustable chair with the hip joint flexed at  $30^\circ$  ( $0^\circ =$  neutral position). The  
 179 dynamometer lever arm was attached 1-2 cm above the lateral malleolus with a Velcro strap.  
 180 The axis of rotation of the dynamometer was aligned with the lateral femoral condyle of the  
 181 right femur. Torque data were corrected for gravity using the Cybex software and were digitized

182 to an external A/D converter (Powerlab 8/35, ADInstruments, New South Wales, Australia)  
183 driven by the Labchart 7.3 Pro software (ADInstruments, Australia).

#### 184 **Femoral nerve stimulation**

185 Evoked contractions of the KE muscles were triggered by a single magnetic stimulus, delivered  
186 to the femoral nerve using a 45-mm figure-of-eight coil connected to a magnetic stimulator  
187 (Magstim 2002, peak magnetic field strength 2.34 T, stimulation duration 0.1 ms; MagstimCo,  
188 Whiteland, Dyfed, UK). The coil was placed high in the femoral triangle in regard of the  
189 femoral nerve. Small spatial adjustments were initially performed to determine the optimal  
190 position where the greatest unpotentiated KE twitch amplitude ( $Q_{tw_{unpot}}$ ) and the greatest VL  
191 and RF  $M_{max}$  were evoked. The optimal stimulation intensity, *i.e.* the intensity where maximal  
192 twitch and concomitant M-waves amplitudes started to plateau, was determined from a  
193 recruitment curve.  $Q_{tw_{unpot}}$  and  $M_{max}$  plateaued at  $85.0 \pm 4.3\%$ ,  $84.4 \pm 7.8\%$  and  $85.0 \pm 6.7\%$   
194 of the stimulator power output for prepubertal boys, adolescents and men, respectively. In order  
195 to overcome the potential confounding effect of axonal hyperpolarization (Burke 2002), the  
196 stimulation intensity was set to 100% of the stimulator output during the subsequent testing  
197 procedures (*i.e.* voluntary intermittent fatigue protocol). This intensity corresponded to  $117.9 \pm$   
198  $6.0\%$ ,  $119.5 \pm 11.7\%$  and  $118.4 \pm 10.1\%$  of the optimal intensity in the boys, adolescents and  
199 men, respectively, and was not significantly different between groups. This supramaximal  
200 intensity of stimulation ( $\approx 120\%$ ) has been demonstrated as being optimal for an adequate  
201 assessment of central and peripheral fatigue of the KE muscles (Neyroud et al. 2014).

#### 202 **Voluntary activation level**

203 To determine VA, the twitch interpolation was used. Briefly, a superimposed ( $Q_{tw_s}$ ) and a  
204 potentiated ( $Q_{tw_{pot}}$ ) single twitch were delivered during MVIC after the torque had reached a  
205 plateau, and 3-s after the cessation of the contraction, respectively. These superimposed and  
206 potentiated mechanical amplitudes allowed the quantification of VA (%VA) as proposed by  
207 Merton (Merton 1954) (Equation 1):

$$208 \quad VA = \left(1 - \frac{Q_{tw_s}}{Q_{tw_{pot}}}\right) \cdot 100 \quad (\text{Equation 1})$$

#### 209 **EMG recordings**

210 The EMG signals of the VL, RF and *biceps femoris* (BF) muscles were recorded using bipolar  
211 silver chloride surface electrodes (Blue Sensor N-00-S, 30 x 22 mm, Ambu, Denmark) during  
212 voluntary and evoked contractions. The recording electrodes were taped lengthwise on the skin  
213 over the muscle belly, as recommended by SENIAM (Surface ElectroMyoGraphy for the Non-  
214 Invasive Assessment of Muscles) (Hermens et al. 2000) with an inter-electrode distance of 20  
215 mm. The reference electrode was attached to the patella. Low impedance ( $Z < 5 \text{ k}\Omega$ ) at the skin-  
216 electrode surface was obtained by shaving, gently abrading the skin with thin sand paper and  
217 cleaning with alcohol. EMG signals were amplified (Dual Bio Amp ML 135, ADInstruments,  
218 Australia) with a bandwidth frequency ranging from 10 Hz to 500 Hz (common mode rejection  
219 ratio  $> 85 \text{ dB}$ , gain = 1,000) and simultaneously digitized together with the torque signals (2  
220 kHz). During the course of the fatigue protocol, Root Mean Square (RMS) values of the VL  
221 and RF EMG activity were calculated during the MVIC trials over a 0.5-s period before the  
222 superimposed stimulation. This RMS value was then normalized to the maximal peak-to-peak  
223 amplitude of the potentiated VL and RF M-waves ( $\text{RMS} \cdot M_{max-1}$ ).

#### 224 **Antagonist co-activation**

225 The level of antagonist co-activation (%CoAct<sub>BF</sub>) of the BF muscle was computed as the BF  
226 EMG activity during knee extensions, normalized to the maximal BF EMG activity recorded  
227 during a maximal knee flexion at the optimal angle for maximal KE torque production  
228 (Equation 2). To record this maximal BF RMS value, the participants were asked to perform 3-

229 s MVICs of the knee flexors before the fatigue protocol. This measurement was repeated twice,  
230 and the best trial was used for subsequent analysis.

$$231 \quad \%CoAct = \frac{RMS_{anta}}{RMS_{ago}} \cdot 100 \quad (Equation 2)$$

232 Where  $RMS_{anta}$  is the RMS value of BF during intermittent contractions, and  $RMS_{ago}$  is the RMS  
233 value of BF during maximal voluntary knee flexion, recorded before the fatigue protocol.

### 234 **Statistical analysis**

235 The participants were categorized according to their age and maturity level. There were three  
236 groups (prepubertal boys, adolescents and men). Therefore, we considered the group as an  
237 independent categorical variable while the other variables (i.e. neuromuscular parameters) were  
238 dependent variables.

239 All variables measured during the intermittent fatigue protocols were linearly interpolated  
240 between the nearest values at 20%, 40%, 60%, and 80% of number of repetitions (%REP) to  
241 fairly compare the different groups. Values at 0%REP and 100%REP corresponded to pre- and  
242 post-fatigue values, respectively.

243 Data were screened for normality of distribution and homogeneity of variances using a Shapiro-  
244 Wilk normality test and the Barlett's test, respectively. All the data were normally distributed,  
245 and variances were homogeneous. One-way analysis of variance (ANOVA) were used to  
246 compare age and anthropometric characteristics between groups. When ANOVA revealed  
247 significant effects, Tukey HSD *post hoc* tests were applied to test the discrimination between  
248 groups. Differences in absolute values were analyzed using a two-way (group  $\times$  %REP)  
249 ANOVA with repeated measures. When significant differences in initial values were identified  
250 between groups, two-way (group  $\times$  %REP) ANOVA were applied to test differences in percent  
251 changes relative to the pre-fatigue values. The effect size and statistical power were reported  
252 when significant main or interaction effects were detected. When the ANOVA revealed  
253 significant effects or interactions between factors, a Tukey HSD *post hoc* test was applied to  
254 test the discrimination between means. The effect size was assessed using the partial eta-  
255 squared ( $\eta^2$ ) and ranked as follows:  $\sim 0.01$  = small effect,  $\sim 0.06$  = moderate effect, and  $\geq 0.14$   
256 = large effect (Cohen 1969).

257 Moreover, to discriminate the effect of MVIC torque on the etiology of neuromuscular fatigue,  
258 we used a mixed general linear model: the initial MVIC torque was used as a continuous  
259 predictor variable (= co-variable), the group as a categorical independent variable and the  
260  $Qtw_{pot}$  or VA as dependent variables. Pearson's correlation coefficients were used to determine  
261 linear correlations between the initial MVIC torque, the total number of repetitions and  $Qtw_{pot}$   
262 and VA variations over the fatigue protocol. The limit for statistical significance was set at  
263  $p < 0.05$ . Statistical procedures were performed using the Statistica 12.0 software (Statsoft, Inc,  
264 USA).

## 265 **RESULTS**

### 266 **Participants' characteristics**

267 Participants' characteristics are described in Table 1. The boys were prepubertal (Tanner stages  
268 I and II and far from their peak height velocity:  $-3.8 \pm 0.7$  yr.) while the adolescents were circa-  
269 pubertal (Tanner stages III and IV and around their peak height velocity:  $-1.1 \pm 1.3$  yr.).

### 270 **Number of repetitions**

271 Task failure, corresponding to the predetermined 60% decrement of MVIC, was reached after  
272  $52.9 \pm 12.7$  [CI 95% = 43.1-62.6],  $42.6 \pm 12.5$  [CI 95% = 32.2-53.0] and  $26.6 \pm 6.3$  [CI 95% =

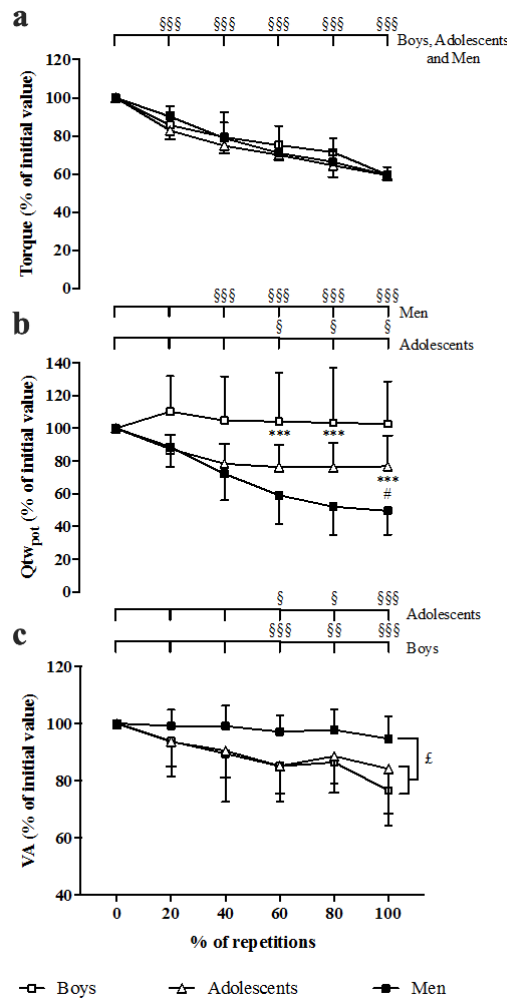


273 22.4-30.9] repetitions in boys, adolescents and men, respectively. ANOVA revealed a  
 274 significant group effect for the total number of repetitions [F(2;25) = 15.80, p<0.001,  $\eta^2$  = 0.56,  
 275 power = 1.0]. The total number of repetitions was significantly higher in boys and adolescents  
 276 than in men (p<0.001). The number of repetitions tended to be higher in boys than adolescents  
 277 (p = 0.056,  $\eta^2$  = 0.81, power = 0.39).

278 **MVIC torque**

279 Significant interactions (group  $\times$  %REP) were found for the absolute MVIC torque [F(10;125)  
 280 = 14.78, p<0.001,  $\eta^2$  = 0.55, power = 1.0]. As expected, initial MVIC torque values were  
 281 significantly lower in boys than adolescents and men, and in adolescents than men (87.4  $\pm$  31.2  
 282 [CI 95% = 63.4-111.3], 184.2  $\pm$  47.9 [CI 95% = 144.2-224.3] and 298.4  $\pm$  50.5 [CI 95% =  
 283 264.4-332.3] N.m in boys, adolescents and men, respectively; p<0.001).

284 A %REP effect was found for MVIC torque changes, i.e. in percentage of initial values  
 285 [F(4;100) = 89.96, p<0.001,  $\eta^2$  = 0.78, power = 1.0]. MVIC torque significantly and  
 286 progressively decreased throughout the fatigue test regardless of group (Fig. 2a).



287 **Fig 2:** Time-courses of (a) MVIC torque of the knee extensor muscles, (b) potentiated twitch  
 288 torque (Qtw<sub>pot</sub>) and (c) voluntary activation level (VA), expressed as a percentage of the initial  
 289 values, during the fatigue protocol in prepubertal boys, male adolescents and men. \*\*\*:  
 290 Significantly different between boys and men at p<0.001 (identified from statistical analysis on  
 291 the relative values); #: Significantly different between adolescents and men at p<0.05  
 292 (identified from statistical analysis on the relative values); £: Significantly different over the

293 fatigue protocol at  $p < 0.05$  (identified from statistical analysis on the absolute values);” §, §§  
294 and §§§ significantly different from the initial value at  $p < 0.05$ ,  $p < 0.01$  and  $p < 0.001$ ,  
295 respectively (identified from statistical analysis on the absolute values).

### 296 **Potentiated twitch torque**

297 During the fatigue protocol, ANOVA revealed a significant interaction of group  $\times$  %REP for  
298 absolute  $Q_{tw_{pot}}$  values [ $F(10;125) = 16.72$ ,  $p < 0.001$ ,  $\eta^2 = 0.57$ , power = 1.0]. Initial absolute  
299  $Q_{tw_{pot}}$  values tended to be lower in boys than in adolescents ( $p = 0.07$ ) and were lower in boys  
300 than in men ( $23.2 \pm 9.3$  [CI 95% = 16.0-30.3],  $56.8 \pm 18.9$  [CI 95% = 38.8-71.3] and  $79.3 \pm$   
301  $28.0$  [CI 95% = 60.5-98.0] N.m in boys, adolescents and men, respectively;  $p < 0.001$ ). No  
302 significant difference was found between adolescents and men for initial  $Q_{tw_{pot}}$  values.  
303 Adolescents and men showed a significant decrement of  $Q_{tw_{pot}}$  during the fatigue exercise,  
304 while it remained unchanged in boys (Fig. 2b).

305 Furthermore, a significant interaction of group  $\times$  %REP was observed for relative  $Q_{tw_{pot}}$ , i.e.  
306 in percentage of initial values [ $F(8;100) = 8.19$ ,  $p < 0.001$ ,  $\eta^2 = 0.40$ , power = 0.99]. The  $Q_{tw_{pot}}$   
307 decreased respectively up to 20% and 60%REP and then remained unchanged until the end of  
308 the fatigue protocol in adolescents and men. At the end of the fatigue protocol, men showed a  
309 greater relative decrement of  $Q_{tw_{pot}}$  than adolescents ( $-50.5 \pm 14.5\%$  and  $-23.2 \pm 18.9\%$ ,  
310 respectively; Fig. 2b).

311 When the initial MVIC torque value was used as co-variable, a significant interaction of group  
312  $\times$  %REP on the course of  $Q_{tw_{pot}}$  was observed ( $p < 0.05$ ). Post-hoc analyses revealed that the  
313 decrement of  $Q_{tw_{pot}}$  was higher in men than adolescents ( $p < 0.01$ ) and higher in adolescents  
314 than boys ( $p < 0.05$ ).

### 315 **Voluntary activation level**

316 ANOVA revealed a significant interaction of group  $\times$  %REP for absolute VA values [ $F(10;125)$   
317  $= 2.20$ ,  $p < 0.05$ ,  $\eta^2 = 0.15$ , power = 0.90]. Before the fatigue test, the VA values were not  
318 significantly different between groups ( $87.1 \pm 7.6\%$  [CI 95% = 81.2-92.9],  $84.4 \pm 5.5\%$  [CI  
319 95% = 75.5-91.8],  $92.2 \pm 3.2\%$  [CI 95% = 90.0-94.3] in boys, adolescents and men,  
320 respectively). Boys and adolescents showed a significant decrement in VA during the fatigue  
321 protocol, whereas it remained unchanged in men (Fig. 2c). At the end of the fatigue test, VA  
322 decrements were  $-23.4 \pm 12.2\%$  and  $-15.8 \pm 15.7\%$  in boys and adolescents, respectively.

323 However, when the MVIC torque was used as co-variable, no significant interaction or main  
324 effect on the time-course of VA was observed.

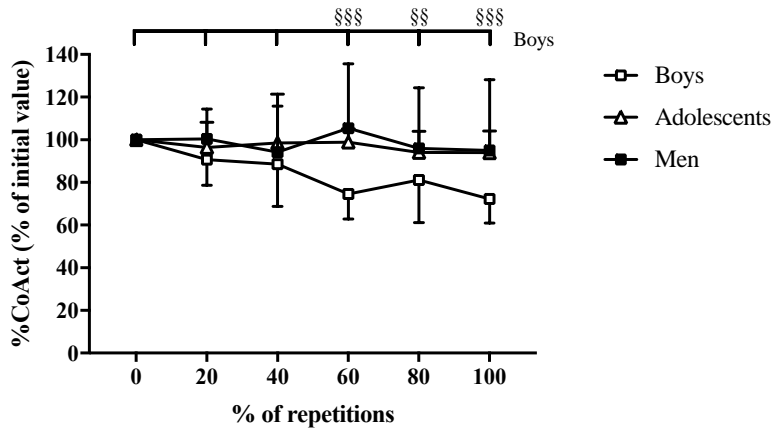
### 325 **EMG activity**

326 No significant main or interaction effect was found for the VL and RF  $M_{max}$  values.

327 However, there were significant interaction (group  $\times$  %REP) effects for VL and RF absolute  
328  $RMS.M_{max-1}$  [ $F(10;125) = 2.01$ ,  $p < 0.05$ ,  $\eta^2 = 0.14$ , power = 0.86 and  $F(10;125) = 2.56$ ,  
329  $p < 0.01$ ,  $\eta^2 = 0.18$ , power = 0.94, respectively]. No difference was found for the initial values of  
330 VL and RF  $RMS.M_{max-1}$  between age groups. *Post hoc* tests only revealed a decrement of VL  
331 and RF  $RMS.M_{max-1}$  in boys (at least  $p < 0.01$ ).

### 332 **Antagonist co-activation**

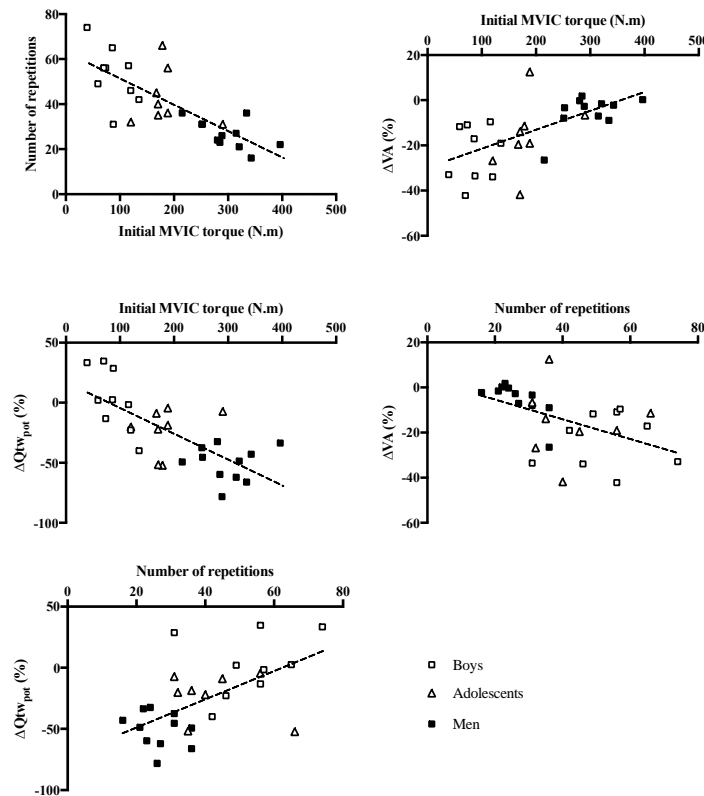
333 ANOVA revealed a significant interaction (group  $\times$  %REP) regarding absolute %CoAct  
334 [ $F(10;125) = 2.72$ ,  $p < 0.01$ ,  $\eta^2 = 0.18$ , power = 0.96]. No difference was found for the initial  
335 value of %CoAct between age groups. %CoAct values remained unchanged in adolescents and  
336 men during the entire fatigue protocol whereas in boys, it decreased significantly at 60%REP,  
337 80%REP and 100%REP compared to 0%REP (Fig. 3).



338 **Fig. 3:** Time-course of the coactivation level of the *biceps femoris* (%CoAct) during the fatigue  
 339 protocol in boys, adolescents and men. §§ and §§§§: significantly different from the initial value  
 340 at  $p < 0.01$  and  $p < 0.001$ , respectively (identified from statistical analysis on the absolute values).  
 341

### Correlations

342 When the three groups were pooled in the analysis, the first MVIC torque of the fatigue protocol  
 343 was correlated to the number of repetitions ( $r_2 = 0.59$ ,  $p < 0.001$ ) and relative  $Q_{tw_{pot}}$  changes  
 344 ( $r_2 = 0.52$ ,  $p < 0.001$ ) (Fig. 4); the higher the MVIC torque, the lower the number of repetitions  
 345 and the greater the decrement of  $Q_{tw_{pot}}$ . In contrast, a significant positive relationship was found  
 346 between the first MVIC torque and the relative VA decrement ( $r_2 = 0.41$ ,  $p < 0.001$ ); the higher  
 347 the MVIC torque, the lesser the decrement of VA. Furthermore, the number of repetitions was  
 348 correlated to the relative VA decrement ( $r_2 = 0.23$ ,  $p < 0.05$ ) and to the relative  $Q_{tw_{pot}}$  decrement  
 349 ( $r_2 = 0.33$ ,  $p < 0.01$ ) (Fig. 4).



350 **Fig. 4:** Correlations between initial maximal voluntary isometric contraction (MVIC) torque,  
351 number of repetitions, change in potentiated twitch torque ( $Q_{tw_{pot}}$ ) and change in voluntary  
352 activation level (VA). Boys, adolescents and men were pooled in the analysis.

## 353 **DISCUSSION**

354 The purpose of the present study was to investigate the effect of maturation on the development  
355 and etiology of neuromuscular fatigue induced by repeated MVIC of the KE muscles. The main  
356 results showed that adolescents tended to fatigue faster than prepubertal boys but slower than  
357 men during repeated maximal voluntary contractions. The greater fatigability in adolescents  
358 than prepubertal boys was associated with a greater peripheral fatigue and a similar central  
359 fatigue. In addition, the lower fatigability in adolescents than adults was associated with a lesser  
360 peripheral fatigue and a greater central fatigue. Finally, when MVIC was used as co-variable in  
361 the statistical analysis, differences of peripheral fatigue between groups persisted, suggesting  
362 that factors other than initial MVIC torque may account for the differences of peripheral fatigue  
363 during maturation.

364 The results of the present study confirm that adolescents fatigue faster than prepubertal children  
365 and slower than adults during repeated isometric maximal voluntary contractions of the knee  
366 extensors. The number of repetitions to task failure tended to be lower in adolescents than  
367 prepubertal boys and significantly higher in adolescents than men. Our results agree with the  
368 data published by Ratel et al. (2002) showing a higher decline of peak power output in  
369 adolescents than children or in adults than adolescents during ten repeated 10-s cycling sprints  
370 separated by 30 s of passive recovery. Similarly, it has been reported that during 4 series of 18  
371 concentric knee flexions and extensions, the decline of peak torque is lower in prepubertal boys  
372 than male adolescents and higher in men than adolescents (Zafeiridis et al. 2005; Dipla et al.  
373 2009). Finally, during 5 series of 6 maximal eccentric contractions of the elbow flexors, the  
374 decline of concentric maximal torque was found to be higher in adolescents than children and  
375 higher in adults than adolescents (Chen et al. 2014).

376 Although scientific evidence supports a higher fatigability in adolescents than children and a  
377 lower fatigability in adolescents than adults during high-intensity intermittent exercise, the  
378 mechanisms explaining this phenomenon still remain unclear.

### 379 **Peripheral mechanisms**

380 In prepubertal boys, no significant alteration of  $Q_{tw_{pot}}$  was observed during the fatigue protocol.  
381 In contrast, in adolescents and men,  $Q_{tw_{pot}}$  decreased significantly throughout the fatigue  
382 protocol and the decrement was significantly higher in men than adolescents. This suggests that  
383 contractile properties and/or excitation-contraction coupling were preserved in prepubertal boys  
384 and more strongly altered in men than adolescents. In contrast, the time-course of M-wave did  
385 not differ between groups, suggesting that no maturation-related change in the excitability of  
386 the sarcolemma was associated with fatigue. These results agree with previous studies, showing  
387 a lower alteration of the potentiated twitch torque during fatigue in prepubertal children than  
388 adults (Gorianovas et al. 2013; Murphy et al. 2014; Hatzikotoulas et al. 2014; Ratel et al. 2015;  
389 Piponnier et al. 2018). Furthermore, they concur with those published by Streckis et al. (2007)  
390 showing a lower alteration of twitch torque during a sustained 2-min maximal voluntary  
391 contraction of the knee extensors in 13.6-year-old girls and 13.9-year-old boys than adults.  
392 However, the results of the present study reveal for the first time an effect of maturation.

### 393 **Central mechanisms**

394 Regarding neural factors, prepubertal boys and male adolescents showed a significant VA and  
395  $RMS.M_{max-1}$  (only in boys) decrement during the fatigue test, whereas no change of VA and  
396  $RMS.M_{max-1}$  was observed in men. Moreover, the decrement of VA was similar in prepubertal

397 boys and male adolescents. The interplay of central and peripheral mechanisms of fatigue  
398 through maturation remains to be elucidated; however, on the basis of these results, it could be  
399 suggested that the greater central fatigue in children and adolescents accounted for their lower  
400 peripheral fatigue than adults. Indeed, according to the central governor theory, the central  
401 nervous system could limit the recruitment of motor units to prevent any extensive homeostasis  
402 disturbance, muscle damage, and biological harm (Noakes et al. 2005). As such, some studies  
403 proposed that the central nervous system may “tolerate” a given peripheral fatigue level  
404 (Amann and Dempsey 2008; Millet 2011; Zghal et al. 2015). It is currently unknown if this  
405 tolerance is different in children, adolescents and adults, but the lower peripheral and the higher  
406 central fatigue reported here in children and adolescents suggest that this tolerance could be  
407 centrally set at a lower level than adults. Furthermore, the greater peripheral fatigue found for  
408 a comparable amount of central fatigue in adolescents than children suggests that the tolerance  
409 could be set at higher level in adolescents. This finding could support the idea that (i) the central  
410 nervous system could not tolerate the development of an extensive peripheral fatigue in children  
411 (Piponnier et al. 2018), contrary to adults, and (ii) the tolerance of the central nervous system  
412 to peripheral fatigue could increase during puberty.

413 Regarding to the central regulation of the antagonist coactivation, the results of the present  
414 study showed different patterns between groups, since it decreased in prepubertal boys whereas  
415 it remained unchanged in male adolescents and men. The progressive decrease of the co-  
416 activation level in prepubertal boys may have contributed to limit the loss of torque, and  
417 therefore to delay the level of fatigue, as previously reported (Piponnier et al. 2018). This  
418 potential mechanism could withdraw through maturation since no significant change of the  
419 antagonist coactivation during the fatigue protocol was observed in adolescents. However, these  
420 results should be confirmed since, to our knowledge, no other studies have investigated the  
421 effect of maturation on the antagonist coactivation associated with fatigue. Furthermore, other  
422 studies have reported opposite results when comparing prepubertal children and adults  
423 (Paraschos et al. 2007; Armatas et al. 2010; Murphy et al. 2014). Therefore, further studies are  
424 required to clarify this issue.

#### 425 **Factors underpinning differences in neuromuscular fatigue**

426 Among the factors that may account for the differences of peripheral fatigue between  
427 prepubertal boys, male adolescents and men, is the absolute torque level. Indeed, when the three  
428 groups were pooled in the analysis, the first MVIC torque of the fatigue test was correlated to  
429 the twitch torque decrement. This suggestion is consistent with other studies that showed that  
430 the greater fatigue observed in men *vs.* women was eliminated if subjects were matched for  
431 absolute strength (Hunter et al. 2004). However, other factors may account for the differences  
432 of peripheral fatigue between prepubertal children, adolescents and adults. Indeed, the  
433 differential time-course of the potentiated twitch torque over repeated maximal voluntary  
434 contractions persisted between groups when the initial MVIC torque was used as co-variable.  
435 This result is consistent with recent reports (Piponnier et al. *in press*), showing that difference  
436 in torque level could not fully account for difference in neuromuscular fatigue at different  
437 muscle-tendon lengths between prepubertal children and adults. Thus, other factors could be  
438 involved in the development and etiology of neuromuscular fatigue during growth and  
439 maturation, such as the metabolic profile (Bontemps et al. 2019). Specifically, the greater  
440 proportion of slow-twitch fibers (Lexell et al. 1992) and the greater reliance on oxidative  
441 metabolism (Tonson et al. 2010) in prepubertal children may also could account for their  
442 reduced peripheral fatigue.

443 The higher implication of central factors in the development of fatigue in children and  
444 adolescents could also be ascribed to their lower absolute MVIC torque and as a result, to the  
445 concurrent longer exercise duration than adults. Indeed, in the present study, the number of

446 repetitions and the associated exercise duration were clearly higher in prepubertal boys and  
447 male adolescents than adults. Furthermore, the relative VA loss was correlated to the first MVIC  
448 of the fatigue test and to the number of repetitions. These findings are consistent with another  
449 study (Thomas et al. 2015), reporting that central fatigue increases with exercise duration. Also,  
450 the results of the present study reveal no significant difference in the time-course of VA between  
451 groups when the MVIC torque was used as co-variable. These results agree with those  
452 published by Russ (2009), which reported similar changes in MVIC decrements and central  
453 activation in strength-matched men and women.

## 454 **CONCLUSIONS**

455 The results of the present study show that male adolescents fatigue faster than prepubertal  
456 children but slower than men during repeated maximal voluntary isometric contractions of the  
457 knee extensors. Furthermore, the contribution of central and peripheral mechanisms to  
458 neuromuscular fatigue differs between groups. Children and adolescents experience less  
459 peripheral and more central fatigue than adults. Moreover, adolescents experience more  
460 peripheral fatigue than children for a comparable amount of central fatigue. This could support  
461 the idea that (i) the central nervous system could not tolerate the development of an extensive  
462 peripheral fatigue in children, contrary to adults, and (ii) the tolerance of the central nervous  
463 system to peripheral fatigue could increase throughout maturation. However, further studies are  
464 required to better understand the origin of these central regulations and the interplay between  
465 peripheral and central mechanisms of fatigue throughout maturation.

## 466 **ACKNOWLEDGEMENTS**

467 Virginie Kluka was supported by a grant of the French National Agency of Technological  
468 Research (ANRT), n°2012/0284.

## 469 **CONFLICT OF INTEREST**

470 The authors report no conflict of interest. A funding from the French National Agency of  
471 Technological Research (ANRT: n°2012/0284; Virginie Kluka) was received for this project.  
472 This work is known to and agreed by the co-authors identified on the manuscript's title page.  
473 This work required more than six people, because of clinical examination (physician or  
474 pediatrician), recruitment of volunteers, experimental procedures, statistical analysis and data  
475 analysis.

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