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## Exercise-induced fatigue in young people: advances and future perspectives

--Manuscript Draft--

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<b>Funding Information:</b>	
<b>Abstract:</b>	<p>Purpose: In recent decades, the interest for exercise-induced fatigue in youth has substantially increased, and the effects of growth on the peripheral (muscular) and central (neural) mechanisms underpinning differences in neuromuscular fatigue between healthy children and adults have been described more extensively. The purpose of this review is to retrieve, report and analyse the findings of studies comparing neuromuscular fatigue between children and adults. Objective measures of the evaluation of the physiological mechanisms are discussed. Method: Major databases (PubMed, Ovid, Scopus and Web of Science) were systematically searched and limited to English language from inception to September 2017. Result: Collectively, the analysed studies indicate that children experience less muscular and potentially more neural fatigue than adults. However, there are still many unknown aspects of fatigue regarding neural (supra-spinal and spinal) and peripheral mechanisms that should be more thoroughly examined in children. Conclusion: Suitable methods, such as transcranial magnetic stimulation, transcranial electrical stimulation, functional magnetic resonance imaging, near-infrared spectroscopy, tendon vibration, H-reflex, and ultrasound are recommended in the research field of fatigue in youth. By designing studies that test the fatigue effects in movements that replicate daily activities, new knowledge will be acquired. The linkage and interaction between physiological, cognitive, and psychological aspects of human performance remains to be resolved in young people. This can only be successful if research is based on a foundation of basic research focused on the mechanisms of fatigue, whilst measuring all three above aspects.</p>
<b>Response to Reviewers:</b>	

## Response to the general comment

Submission: EJAP-D-17-00784

I should have caught this earlier: Would you please develop a figure, in color, to accompany section 2. Conceptual framework of fatigue? This would help the reader visual key relationships, inputs and outputs in the fatigue process.

As suggested, we added a figure in color to accompany section 2 (please see figure 1 in file attached). This is now specified lines 148 and 186 in the manuscript. Furthermore, we added a legend to this figure page 36 as follows:

*“Figure 1. Schematic framework of fatigue with the possible sites and mechanisms that may contribute to it.”*

1       1    **Review article**

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6       4    **Exercise-induced fatigue in young people: advances and future perspectives**

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1   34   **Abstract**

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3   35   **Purpose:** In recent decades, the interest for exercise-induced fatigue in youth has  
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5   36   substantially increased, and the effects of growth on the peripheral (muscular) and  
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7   37   central (neural) mechanisms underpinning differences in neuromuscular fatigue  
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9   38   between healthy children and adults have been described more extensively. The purpose  
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11   39   of this review is to retrieve, report and analyse the findings of studies comparing  
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13   40   neuromuscular fatigue between children and adults. Objective measures of the  
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15   41   evaluation of the physiological mechanisms are discussed. **Method:** Major databases  
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17   42   (PubMed, Ovid, Scopus and Web of Science) were systematically searched and limited  
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19   43   to English language from inception to September 2017. **Result:** Collectively, the  
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21   44   analysed studies indicate that children experience less muscular and potentially more  
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23   45   neural fatigue than adults. However, there are still many unknown aspects of fatigue  
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25   46   regarding neural (supra-spinal and spinal) and peripheral mechanisms that should be  
26  
27   47   more thoroughly examined in children. **Conclusion:** Suitable methods, such as  
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29   48   transcranial magnetic stimulation, transcranial electrical stimulation, functional  
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31   49   magnetic resonance imaging, near-infrared spectroscopy, tendon vibration, H-reflex,  
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33   50   and ultrasound are recommended in the research field of fatigue in youth. By designing  
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35   51   studies that test the fatigue effects in movements that replicate daily activities, new  
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37   52   knowledge will be acquired. The linkage and interaction between physiological,  
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39   53   cognitive, and psychological aspects of human performance remains to be resolved in  
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41   54   young people. This can only be successful if research is based on a foundation of basic  
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43   55   research focused on the mechanisms of fatigue, whilst measuring all three above  
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45   56   aspects.

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1 58 **Keywords:** Fatigue; Children; Etiology; Perspectives  
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1	59	<b>Abbreviations</b>
2	60	
3	61	<b>CNS:</b> central nervous system
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5	63	<b>E-C:</b> excitation-contraction
6	64	
7	65	<b>MRI:</b> magnetic resonance imaging
8	66	
9	67	<b>MTU:</b> muscle-tendon unit
10	68	
11	69	<b>MVC:</b> maximum voluntary contraction
12	70	
13	71	<b>NIRS:</b> near infrared spectroscopy
14	72	
15	73	<b>PCr:</b> phosphocreatine
16	74	
17	75	<b>PICs:</b> persistent inward currents
18	76	
19	77	<b>sEMG:</b> surface electromyography
20	78	
21	79	<b>TMS:</b> transcranial magnetic stimulation
22	80	
23	81	<b>VA:</b> voluntary activation
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## 1. Introduction

Compared to adult studies of fatigue, there is much less known about fatigue in children and adolescents. Whilst the consequences of fatigue are just as important to understand in children and adolescents as for adults, the necessity to require youngsters to exercise until exhaustion, presents some ethical dilemmas that, no doubt, have limited its investigation (Williams and Ratel 2009). However, in the last 20 years fatigue, induced mainly by exercise related studies, has received more attention in children (Ratel et al. 2002a; De Ste Croix et al. 2009; Gorianovas et al. 2013; Hatzikotoulas et al. 2014; Murphy et al. 2014). A significant reason for this interest is the translation of results into children's and adolescents' high-level sports participation. Today's youth are experiencing training regimens that are considered as highly demanding as those of adult athletes. In some sports, such as female gymnastics, youth athletes excel and reach world standards, often commencing this specialized training early in the first decade of life. However, most fatigue-related studies are still experimental laboratory based and fatigue assessment in sports tend to be observational by design and usually related to injury prevention. Therefore, knowledge of the demands of exercise and its ensuing fatigue is fundamentally important for coaches and practitioners in paediatric research, but research design and measurement outcomes need to demonstrate better external validity to youth sports performance. More encouragingly, research studies in assessing fatigue in a clinical setting have been more valid to the functional setting of the young patient.

In a recent review, Ratel and Blazevich (2017) analysed the effects of growth and maturation on energy metabolism during exercise and showed how differences between prepubertal children and untrained adults could be analogous to those observed between

1 106 well-trained endurance adult athletes and untrained adults. However, while some  
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3 107 aspects of fatigue were discussed between children and adults, those concerning the  
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5 108 neuromuscular features, were not referenced. Since the latest reviews regarding muscle  
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7 109 fatigue in children were published more than a decade ago (Falk and Dotan 2006; Ratel  
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9 110 et al. 2006a) and this topic has gained the interest of researchers over the last years, the  
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11 111 main objective of this review is to provide a synthesis of the literature, as related to the  
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13 112 exercising child and adolescent and the consequences of fatigue, with a particularly  
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15 113 emphasis on neuromuscular research and the approaches/methods currently used. The  
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17 114 following databases were systematically searched, and limited to English language:  
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19 115 PubMed, Ovid, Scopus and Web of Science from inception to September, 2017. To  
20  
21 116 retrieve papers that compared neuromuscular fatigue between children and adults, the  
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23 117 following search terms and Medical Subject Headings (MeSH) were used to source  
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25 118 pertinent peer-reviewed literature: muscle fatigue (MeSH) OR children (All Fields),  
26  
27 119 adolescent (All Fields) AND exercise (MeSH) OR exercise (All Fields).

28  
29 120 The following count of papers were found in the respective databases with the keywords  
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31 121 shown in square brackets (date of retrieval: 27<sup>th</sup> September 2017):

- 32 122 • Pubmed: 82 [muscle fatigue AND child AND exercise[MeSH]]
- 33 123 • Scopus: 139 [“muscle fatigue” AND child AND exercise]
- 34 124 • Web of Science: 171 [muscle fatigue AND child AND exercise]
- 35 125 • Ovid: 60 [muscle fatigue AND child AND exercise]

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37 126 The search was supplemented by manually cross-matching reference lists, key author  
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39 127 searches, and citation searching of all retrieved papers to potentially identify additional  
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41 128 studies. Grey literature including monographs was searched also through databases,  
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43 129 cross referencing in conference proceedings and personal communications.  
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## 130 2. Conceptual framework of fatigue

### 131 2.1. Definition

132 There are as many definitions for fatigue as there are theories for its causality. The lack  
133 of a consistent and agreed upon definition has led to a divisive field of study (Enoka and  
134 Duchateau 2016). A part of this inconsistency reflects the relative ease at which the  
135 diminution of muscle force can be measured compared to the assessment of the  
136 sensation of fatigue. This dichotomy proposed by Mosso (1904) who stated it is easier  
137 to measure the physical but not the ‘psychic’ reflects much of the mechanistic  
138 physiological type literature focused on rate limiting processes, central or peripheral,  
139 and less on regulation of sensations. A commonly accepted definition of fatigue is by  
140 Gandevia (2001) who defined it as ‘any exercise-induced reduction in the ability of a  
141 muscle to generate force or power; it has peripheral and central causes’. The  
142 operationalisation of fatigue as a reduction in force or power is easy to measure,  
143 however it is limited in respect to acknowledging changes in sensation associated with  
144 fatigue. Enoka and Duchateau (2016) have recently proposed combining these two  
145 concepts and further unifying the nomenclature of Kluger (2013), related to  
146 performance fatigability and perceived fatigability so as to define fatigue as “a disabling  
147 symptom in which physical and cognitive function is limited by interactions between  
148 performance fatigability and perceived fatigability” (p. 2230) (Figure 1). Whether  
149 ‘disabling’ is the correct term to adopt, as it might imply a negative consequence of the  
150 fatigue rather than as a protective consequence, remains to be seen.

151

## 152 2.2. Topography

153 As outlined earlier operationalising fatigue in the context of a reduction in muscle force  
154 or power simplifies the identification of the fatigue, if not the mechanism. Furthermore,  
155 a distinction is made between the muscle fatigue and the completion of the task  
156 protocol. In this context, muscle fatigue represents the decrease in maximal power or  
157 force production and develops soon after, depending on the nature of the physical task.  
158 But the fatigue does not represent the point of the task failure or when exhaustion  
159 occurs. That is to say, fatigue can be investigated as a process that apparently will lead  
160 to task failure. For example, during a submaximal isometric contraction the task of  
161 keeping a target force constant may be successful whereas fatigue, captured by  
162 increased values of EMG, may also develop in the background. To distinguish between  
163 the fatigue and task failure, the use of brief maximal muscle contractions (either  
164 voluntary or electrically evoked), which interrupts a fatiguing protocol and measures the  
165 decline in the MVC score, thus quantifying muscle fatigue (Merton 1954; Bigland-  
166 Ritchie et al. 1986). Equally valid, is the procedure whereby the decline in maximal  
167 power or force is measured after a fatiguing protocol (Taylor et al. 1996; McNeil et al.  
168 2006). However, the faster recovery observed in children (see below section 3), should  
169 be taken into account as a differentiating factor when intermittent fatigue protocols are  
170 used for the evaluation of the MVC between the fatiguing contractions.

171 Potential factors involved in fatigue development have been typically classified into two  
172 categories: central factors involving the central nervous system (CNS) and neural  
173 pathways (Enoka 1995), and peripheral factors occurring within the muscle itself  
174 (Westerblad et al. 1991; Fitts 1994). Enoka and Duchateau (2016) propose that the  
175 adjectives central and peripheral be removed given that multi-processes are likely

1 176 involved and the decline in power or force is task dependent (Asmussen 1979; Enoka  
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3 177 and Stuart 1992). Whether this call to eliminate the description of fatigue as central or  
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5 178 peripheral *per se* is adopted, remains to be shown. For the purpose of this review we  
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8 179 will continue, to be consistent with previous literature, to refer to fatigue as centrally  
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10 180 and peripherally orientated.

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### 14 15 182 2.3. Mechanisms

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18 183 As discussed above and putting to one side the issue of performance fatigability and  
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20 184 perceived fatigability, the factors that contribute to fatigue have been typically classified  
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22 185 into two categories: central factors involving the CNS and neural pathways and  
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24 186 peripheral factors occurring within the muscle milieu (Figure 1). Among the peripheral  
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26  
27 187 factors, a major mechanism leading to the development of fatigue, for example, during  
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29 188 high-intensity exercise would be the failure in muscle contractility and excitation-  
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31 189 contraction (E-C) coupling. This could be associated with an impairment of  
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33 190 myofilament function, sarcolemmal excitability and/or calcium release from  
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35 191 sarcoplasmic reticulum (Allen et al. 2008). However, there is little information  
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37 192 regarding muscle activation during fatiguing tasks for young people, where surface  
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39 193 electromyography (sEMG) and evoked twitch techniques have been used. The  
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41 194 inferences from fatigue involving the CNS mechanisms, including the changes in the  
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43 195 motor cortex and spinal excitability require methods that are more difficult to apply in  
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45 196 healthy individuals due to ethical concerns i.e., transcranial magnetic stimulation,  
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47 197 neurotransmitters derived from blood, and have been studied less in young people.  
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### 199 3. Current knowledge about neuromuscular fatigue in children

200 Until now, it has been widely demonstrated that prepubertal children fatigue less than  
201 adults when performing whole-body dynamic activities, such as maximal cycling (Ratel  
202 et al. 2002a, b, 2004) and short running bouts (Ratel et al. 2004, 2006b), resistance  
203 exercise (Faigenbaum et al. 2008), or MVCs under isometric (Halin et al. 2003;  
204 Armatas et al. 2010; Hatzikotoulas et al. 2014; Ratel et al. 2015) and isokinetic  
205 contraction conditions (Zafeiridis et al. 2005; Paraschos et al. 2007; De Ste Croix et al.  
206 2009; Dipla et al. 2009). However, prepubertal children seem to fatigue similarly to  
207 young adults during sustained isometric contractions at similar relative submaximal  
208 intensities (Hatzikotoulas et al. 2009; Patikas et al. 2013). Comparatively, women are  
209 more resistant to fatigue than men particularly at similar relative submaximal  
210 contraction intensities (Hunter et al. 2004), whereas prepubertal girls seem to fatigue at  
211 the same rate than their prepubertal male counterparts regardless of the nature of  
212 exercise (Streckis et al. 2007; De Ste Croix et al. 2009; Dipla et al. 2009).

213

#### 214 3.1. Whole-body dynamic activities

##### 215 3.1.1. Cycling

216 The first study that investigated muscle fatigue in children was published by Hebestreit  
217 et al. (1993). In their seminal study, boys (9–12 years) and young men (19–23 years)  
218 had to complete two consecutive 30-s maximal intensity cycle sprints separated by a 1,  
219 2, and 10 min recovery. It was found that boys' mean power reached 89.9% of the first  
220 sprint value after 1 min recovery, 96.4% after 2 min recovery, and 103.5% after 10 min  
221 recovery. For the men, the values were 71.2%, 77.1%, and 94.0%, respectively. The  
222 authors concluded that boys recovered faster than men from the sprint cycling exercise.

1 223 Similar conclusions were drawn by other researchers when investigating the effects of  
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3 224 age and recovery duration on cycling peak power during repeated sprints (Ratel et al.  
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5 225 2002a). Eleven prepubertal (mean  $\pm$  SD;  $9.6 \pm 0.7$  years) and nine pubertal boys ( $15.0 \pm$   
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7 226  $0.7$  years) and 10 men ( $20.4 \pm 0.8$  years) completed ten 10 s cycling sprints separated by  
8  
9 227 30 s, 1 min, or 5 min of passive recovery. For the prepubertal boys whatever recovery  
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11 228 duration was chosen, peak power remained unchanged during the 10 s sprints. In the  
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13 229 pubertal boys, peak power decreased significantly by 20% during the 30 s recovery, by  
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15 230 15% during the 1 min recovery, and was unchanged by the 5 min recovery. For the men,  
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17 231 peak power significantly decreased by 29%, 11%, and decreased slightly but non-  
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19 232 significantly during the 30 s, 1 min, and 5 min recovery periods, respectively.  
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### 234 3.1.2. Running

235 In contrast to cycling and under laboratory conditions, Ratel et al. (2006b) compared the  
236 effects of ten consecutive 10-s sprints on a non-motorized treadmill separated by 15 s  
237 and 180 s passive recovery between 11.7 year-old boys and 22.1 year-old men. Results  
238 showed that boys decreased their power or force outputs and running velocity much less  
239 than men during the ten repeated sprints with 15 s recovery intervals (power: -28.9 vs. -  
240 47.0%; force: -13.1 vs. -25.6%; velocity: -18.8 vs. -29.4%, respectively). With 180 s  
241 recovery, boys could maintain running performance over the 10 s sprints whereas the  
242 men decreased their power and force outputs significantly (-7.8 and -4.6%,  
243 respectively), although they were able to maintain their running velocity.

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1 245 3.2. Resistance exercise

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3 246 Similar conclusions as cycling and running were reported during resistance exercise.

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6 247 Faigenbaum et al. (2008) assessed bench press performance during three sets with a 10

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8 248 repetition maximum load and 1, 2 or 3 min rest intervals between sets in boys (11.3

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10 249 years), male adolescents (13.6 years), and men (21.4 years). Significant differences in

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12 250 lifting performance between age groups were observed within each set with boys and

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14 251 male adolescents performing significantly more total repetitions than men following

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16 252 protocols with 1 min (27.9, 26.9, and 18.2, respectively), 2 min (29.6, 27.8, and 21.4,

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18 253 respectively) and 3 min (30.0, 28.8, and 23.9, respectively) recovery intervals. The

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20 254 authors concluded that boys and male adolescents are better able to maintain muscle

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22 255 performance during intermittent moderate intensity bench press exercise compared to

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24 256 men.

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29 258 3.3. Maximal voluntary muscle contractions

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31 259 The lower fatigability in children has been confirmed during sustained or repeated

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33 260 MVC whatever the nature of contraction and the muscle group investigated (Zafeiridis

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35 261 et al. 2005; De Ste Croix et al. 2009; Dipla et al. 2009; Chen et al. 2014; Ratel et al.

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37 262 2015). Some authors reported a lower reduction of peak torque and total work during

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39 263 repeated concentric maximal knee extensions and flexions on an isokinetic

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41 264 dynamometer in prepubertal children compared to adults (Zafeiridis et al. 2005; De Ste

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43 265 Croix et al. 2009; Dipla et al. 2009). Also, when muscle contractions included repeated

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45 266 eccentric phases, the decline of concentric peak torque of the elbow flexors was found

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47 267 to be lower in prepubertal children compared to adolescents and lower in adolescents

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49 268 compared to adults (Chen et al. 2014). Similar results were obtained during repeated

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1 269 MVC of the knee extensors under repeated isometric contractions in prepubertal  
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3 270 children compared to adults (Ratel et al. 2015). For instance, during a fatigue protocol  
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5 271 consisting of repetitions of 5 s isometric MVC of the knee extensors separated by 5 s  
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8 272 passive recovery periods until the torque reached 60% of its initial value, Ratel et al.  
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10 273 (2015) showed that the number of repetitions was significantly lower in men compared  
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12 274 to prepubertal boys (34.0 vs. 49.5 repetitions, respectively), showing a lower fatigability  
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15 275 in children.  
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### 20 277 3.4. Sub-maximal voluntary muscle contractions

22 278 Contrary to maximal intensity fatigue protocols, prepubertal children seem to fatigue  
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24 279 similarly to young adults during sustained isometric contractions, which are conducted  
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27 280 at submaximal intensities (Hatzikotoulas et al. 2009; Patikas et al. 2013). Indeed,  
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30 281 Patikas et al. (2013) examined the effects of two submaximal sustained contractions  
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32 282 (20% and 60% MVC) until exhaustion, on the fatigue and recovery properties of plantar  
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35 283 flexors, in untrained prepubescent children (n = 14) and adults (n = 14). The authors  
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37 284 showed that immediately after fatigue, MVC torque decreased similarly in both groups,  
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40 285 compared with pre-fatigue values and children recovered faster than adults in both  
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42 286 protocols. Furthermore, the reduction in agonist EMG during MVC after fatigue,  
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45 287 independent of the protocols, was not significantly different between children and  
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47 288 adults. However, EMG of children recovered to baseline values after 3 min for both  
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50 289 fatigue protocols, whereas adults did not recover and exhibited significantly lower  
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52 290 values (torque & EMG) 3 min after fatigue compared to the pre-fatigue baseline values.  
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54 291 The authors concluded that submaximal (low- and moderate-intensity) sustained  
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1 292 isometric fatigue protocols induced similar fatigue effects in children and adults, and  
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3 293 children recovered faster than adults.  
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8 295 In summary, whatever the nature of the maximal task performed (whole-body dynamic  
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10 296 activities, resistance exercise or MVC) and the muscle group investigated, prepubertal  
11  
12 297 children fatigue less than their older counterparts. This lower muscle fatigue in  
13  
14 298 prepubertal children could be explained by peripheral (i.e. muscular) and central (i.e.  
15  
16 299 neural) changes that occur during adolescence, which we address in the following  
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18 300 sections.  
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25 302 3.5. Mechanisms underpinning differences between children and adults

26  
27 303 3.5.1. Central mechanisms

28  
29 304 Central factors may be responsible for the lower fatigue in children. These factors could  
30  
31 305 include the capacity to maximally activate the motor units of agonist muscles (i.e.  
32  
33 306 agonist activation) and the coactivation level of antagonist muscles (i.e. antagonist  
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35 307 activation).  
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42 309 Agonist activation

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44 310 Recently, some studies have reported a greater decrement in voluntary activation (VA)  
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46 311 of agonist muscles when using the twitch interpolation technique during fatigue  
47  
48 312 protocols in children compared to adults (Streckis et al. 2007; Ratel et al. 2015). For  
49  
50 313 instance, following a sustained 2-min MVC of the knee extensors, Streckis et al. (2007)  
51  
52 314 reported a greater decrement of VA in 13.9-yr-old boys compared to 22.2-yr-old men  
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55 315 (around -55 vs. -45%, respectively). Furthermore, after a fatigue protocol consisting in a  
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1 316 repetition of 5-s MVC of the knee extensors until the generated torque reached 60% of  
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3 317 its initial value, Ratel et al. (2015) showed that VA remained unchanged in 23.9-yr-old  
4  
5 318 men ( $91.2 \pm 2.6$  vs.  $86.7 \pm 2.6\%$ ), whereas it decreased significantly by 27% in 9.9-yr-  
6  
7 319 old boys ( $86.9 \pm 7.6$  vs.  $63.4 \pm 17.9\%$ ). This result was associated with a lower fatigue  
8  
9 320 regarding peripheral factors in children, as evidenced by a lower twitch torque  
10  
11 321 decrement (Ratel et al. 2015). The interplay of central vs. peripheral mechanisms of  
12  
13 322 fatigue in children remains to be elucidated; however, on the basis of these studies  
14  
15 323 (Streckis et al. 2007; Ratel et al. 2015), it could be suggested that the greater fatigue  
16  
17 324 effect on central mechanisms in children accounts for their lower fatigue at peripheral  
18  
19 325 level. As such, Amann and Dempsey (2008) proposed the existence of a “critical  
20  
21 326 threshold” of fatigue observed at the periphery and demonstrated that when the  
22  
23 327 inhibitory feedback from group III/IV afferents was reduced by pharmacological  
24  
25 328 blockade, the exercising adult subjects “tolerated” the development of peripheral muscle  
26  
27 329 fatigue substantially beyond their critical threshold (Amann et al. 2011). It is currently  
28  
29 330 unknown if this critical threshold is different in children and adults, but the lower  
30  
31 331 contribution of peripheral mechanisms to fatigue development (and higher of central  
32  
33 332 mechanisms) reported previously (Streckis et al. 2007; Ratel et al. 2015) supports the  
34  
35 333 proposition that the critical threshold could be set centrally at a higher level in children.  
36  
37 334 However, the interplay of central vs. peripheral mechanisms of fatigue during childhood  
38  
39 335 requires further research since some authors have reported greater peripheral fatigue in  
40  
41 336 adults compared to children, despite similar central fatigue in plantar flexors between  
42  
43 337 both age groups (Hatzikotoulas et al. 2014).  
44  
45 338 Beyond the influence of this potential central regulation of agonist activation during a  
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47 339 fatiguing task, the exercise duration could promote the development of fatigue at the  
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1 340 CNS in children (Armatas et al. 2010; Ratel et al. 2015). Indeed, the lower fatigue in  
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3 341 prepubertal children translates into a longer exercise duration when repeating MVC  
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5 342 ~~until the same level of exhaustion, i.e.~~ until a predetermined percentage of initial MVC  
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7  
8 343 is reached (Armatas et al. 2010; Ratel et al. 2015). This observation is supported  
9  
10 344 recently by Ratel et al. (2015) showing a positive relationship between the decrement in  
11  
12 345 VA and the number of repeated isometric maximal contractions of the knee extensor  
13  
14 346 muscles ~~until the same level of exhaustion~~ in prepubertal children and adults.  
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17  
18 347 It is also important to note that the ability to fully activate voluntarily the neuromuscular  
19  
20 348 system might be crucial for the development of fatigue. A lower activation level implies  
21  
22 349 higher resistance to fatigue. Some studies have shown that children have lower levels of  
23  
24 350 activation during a brief non-fatigued MVC (Table 1), although this has not always  
25  
26 351 reached statistical significance (Belanger and McComas 1989; Grosset et al. 2008;  
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28 352 O'Brien et al. 2009; Kluka et al. 2015, 2016; Martin et al. 2015). However, such  
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30 353 potential differences between children and adults in their ability to reach their maximal  
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32 354 voluntary activation should be accounted for when interpreting the level of fatigue.  
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40 356 Antagonist coactivation

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42 357 Regarding the central regulation of the antagonist coactivation under fatigue conditions,  
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44 358 studies have reported different patterns between children and adults. Ratel et al. (2015)  
45  
46 359 showed that antagonist activity of the biceps femoris remained constant in adults,  
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48 360 whereas it significantly decreased in prepubertal children during repeated maximal  
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50 361 voluntary isometric knee extensions. This decrease in antagonist coactivation in  
51  
52 362 children may contribute to limit the loss of force, and therefore to delay fatigue at the  
53  
54 363 peripheral level (Ratel et al. 2015). Also, in this same study, the decrement of  
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1 364 coactivation in children was positively correlated with the decrement of VA, which is  
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3 365 consistent with the theory of ‘common drive’. Such a phenomenon could serve to  
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6 366 maintain the balance between agonist and antagonist force in children, to preserve their  
7  
8 367 joint integrity (Psek and Cafarelli 1993). However, these results should be confirmed  
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10 368 since other studies have reported contradictory results (Paraschos et al. 2007; Armatas  
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12  
13 369 et al. 2010; Murphy et al. 2014). For example, it has been shown during repeated  
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15 370 isokinetic knee extensions that antagonist activity of the biceps femoris remained  
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18 371 constant in adults and increased in prepubertal children (Paraschos et al. 2007; Murphy  
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20 372 et al. 2014). Furthermore, Armatas et al. (2010) showed during repeated maximal  
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22 373 voluntary isometric knee extensions that antagonist activity of the biceps femoris did  
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24  
25 374 not change in prepubertal children and adults and this could not explain the differences  
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28 375 of fatigability between children and adults. Therefore, this issue remains unresolved and  
29  
30 376 further research into this area is warranted.

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### 34 35 378 3.5.2. Peripheral mechanisms

36  
37 379 Several studies have shown a lower fatigue at peripheral level, as indicated by a lower  
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40 380 twitch torque decrement after sustained or repeated MVC in children or adolescents  
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42 381 compared to adults (Streckis et al. 2007; Hatzikotoulas et al. 2014; Murphy et al. 2014;  
43  
44 382 Ratel et al. 2015). Furthermore, after a repetitive stretch-shortening cycle fatigue  
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47 383 protocol, which induces muscle damage, Gorianovas et al. (2013) reported a lower low-  
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49 384 frequency fatigue, evaluated by the low-to-high frequency tetanic force ratio, in children  
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52 385 compared to adults, showing a lower alteration of the excitation-contraction coupling.  
53  
54 386 However, the contribution of sarcolemmal excitability changes to fatigue in children  
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57 387 still remains equivocal (Hatzikotoulas et al. 2014; Murphy et al. 2014; Ratel et al.  
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1 388 2015). Indeed, while some authors reported a similar decrement (Hatzikotoulas et al.  
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3 389 2014) or no change of the M-wave (Ratel et al. 2015) in response to exercise in  
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5 390 prepubertal children compared to adults, others showed an increase in children and a  
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7 391 significant decrease in adults (Murphy et al. 2014). These discrepancies could result  
8  
9 392 from a different balance of potentiation and fatigue on the M-wave during exercise  
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11 393 between children and adults. Therefore, despite the underlying factors not being fully  
12  
13 394 acknowledged, there is a consensus that prepubertal children develop a lower fatigue at  
14  
15 395 the peripheral level compared to adults (Streckis et al. 2007; Hatzikotoulas et al. 2014;  
16  
17 396 Murphy et al. 2014; Ratel et al. 2015). This could be attributed to different factors such  
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19 397 as absolute force and muscle phenotype.  
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25 398

26  
27 399 Absolute force

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29 400 The higher fatigue observed at peripheral mechanisms in adults during high-intensity  
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31 401 exercise could be associated with their larger active muscle mass involved during  
32  
33 402 exercise and their superior maximal force-generating capacity. To the best of our  
34  
35 403 knowledge in the only study testing this assumption, Ratel et al. (2015) showed a  
36  
37 404 significant positive relationship between the first MVC and the twitch torque decrement  
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39 405 during repeated maximal contractions of the knee extensors in children and adults.  
40  
41 406 Furthermore, when the initial MVC torque was used as covariate, no significant  
42  
43 407 difference in the course of the twitch torque was observed between groups, supporting  
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45 408 the importance of MVC torque in the development of fatigue. This finding is also  
46  
47 409 consistent with other studies that showed the fatigability of the knee extensors during  
48  
49 410 repeated MVC was no longer different between obese and non-obese adolescent girls  
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51  
52 411 when the initial MVC torque was used as a covariate in statistical analysis (Garcia-  
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1 412 Vicencio et al. 2015). In addition, other studies reported that the greater fatigue  
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3 413 observed in men versus women was eliminated when subjects were matched for  
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5  
6 414 absolute force (Hunter et al. 2004). This greater muscle mass involved during exercise  
7  
8 415 in adults could be the cause of a greater vascular occlusion and therefore greater  
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10 416 metabolic disturbances that are usually observed during high-intensity exercise in adults  
11  
12 417 compared to children (Kappenstein et al. 2013). However, this suggestion is speculative  
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14 418 because this has not been tested in adults compared to children. Studies with fatigue  
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16 419 protocols using variable intensities controlling for blood vascular occlusion are required  
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18 420 to elucidate this speculation.  
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23 421

24  
25 422 Muscle phenotype

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27 423 Muscle phenotype, which is more oxidative than glycolytic in prepubertal children  
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29 424 regarding muscle fibre type composition and muscle metabolism (Ratel and Blazevich  
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31 425 2017), could also account for the differences in fatigue between children and adults.  
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34  
35 426 The distribution of muscle fibre types in the muscle can determine not only its force  
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37 427 production capacity and contractile properties, but its resistance to fatigue as well. It has  
38  
39 428 been previously shown that individuals with predominantly fast-twitch fibres in their  
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41 429 vastus lateralis develop a greater fatigue during knee extension compared to subjects  
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43 430 with a higher proportion of slow-twitch fibres (Hamada et al. 2003). Furthermore, it has  
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45 431 been reported that adults have a lower percentage of slow-twitch fibres in the vastus  
46  
47 432 lateralis muscle than children (Lexell et al. 1992; Glenmark et al. 1994). For instance,  
48  
49 433 Lexell et al. (1992) reported individual values of 63, 65, 67 and 69% in four children  
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51 434 aged between 5 and 13 years and values comprised between 47 and 57% in sixteen  
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53 435 adults aged between 18 and 37 years. However, the influence of muscle type on the  
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1 436 fatigue in children remains to be established since other studies showed no difference in  
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3 437 muscle fibre type composition in the vastus lateralis between children and adults (Berg  
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5  
6 438 and Keul 1988).

7  
8 439 Furthermore, several studies provided evidence that children rely more on oxidative  
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10 440 relative to anaerobic metabolism during exercise (Berg and Keul 1988; Ratel et al.  
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12  
13 441 2008; Tonson et al. 2010). Indeed, using  $^{31}\text{P}$ -magnetic resonance spectroscopy, it has  
14  
15 442 been shown that post-exercise phosphocreatine (PCr) resynthesis rates are higher in  
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18 443 children compared to adults, suggesting a higher muscle oxidative activity during  
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20 444 exercise in children (Taylor et al. 1997; Ratel et al. 2008; Fleischman et al. 2010;  
21  
22  
23 445 Tonson et al. 2010). This specific metabolic profile in children could lead to a lower  
24  
25 446 accumulation of muscle by-products (i.e.  $\text{H}^+$  ions and inorganic phosphate) and a lower  
26  
27 447 PCr depletion during high-intensity intermittent exercise in children compared to adults  
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29  
30 448 (Kappenstein et al. 2013). As inorganic phosphate is strongly associated with the  
31  
32 449 decrease of myofibrillar force production and  $\text{Ca}^{2+}$  sensitivity as well as sarcoplasmic  
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34  
35 450 reticulum  $\text{Ca}^{2+}$  release (Allen et al. 2008), its lower accumulation in exercising muscle  
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37 451 in prepubertal children could constitute the major cause of their lower fatigue at the  
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40 452 periphery (Streckis et al. 2007; Hatzikotoulas et al. 2014; Murphy et al. 2014; Ratel et  
41  
42 453 al. 2015). The lower decrement in intramuscular pH in prepubertal children may also  
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44 454 account for this; however, the reduction in pH obtained under physiological  
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47 455 circumstances, could have far less inhibitory (or restraining) effects on the contractile  
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50 456 apparatus efficiency and  $\text{Ca}^{2+}$  release than previously assumed (Allen et al. 2008).

51  
52 457 Collectively, these studies report a lower peripheral fatigue and a potentially greater  
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55 458 neural fatigue in children. However, further studies are required to better investigate the  
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1 459 neuromuscular mechanisms underpinning differences in fatigue between children,  
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3 460 adolescents and adults (Table 2).

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8 462 ===== Table 2 near here =====

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#### 11 464 **4. Challenges and future perspectives**

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13 465 To better investigate the exercise-induced fatigue, it is necessary to examine the whole  
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15 466 chain of events that occur from the generation of the movement to its execution.

16  
17 467 However, this process should not overlook the importance of the sensory feedback and  
18  
19 468 its integration to the motor command. In general, it is important to evaluate all possible  
20  
21 469 neural and mechanical properties of the neuromuscular system as thoroughly as possible  
22  
23 470 and to understand how they adapt and interact during the development of fatigue.

24  
25 471 Therefore, the objective evaluation of fatigue and its underlying mechanisms is essential  
26  
27 472 for understanding the strategies that the neuromuscular system develops to sustain an  
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29 473 external load. Numerous methods are available to investigate neuromuscular fatigue and  
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31 474 some of these that have been applied in children are shown in Table 3.

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35 476 ===== Table 3 near here =====

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39 478 Additionally, this research should not only be focused on well-controlled experiments  
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41 479 that isolate one mechanism under certain, mostly laboratory, conditions. One major goal  
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43 480 of research should be the documentation of the interaction between different  
44  
45 481 mechanisms with the utmost perspective to describe fatigue universally, in real-world  
46  
47 482 conditions (i.e. during training and everyday activities, to increase the ecological

1 483 validity of the experiment) and to determine the weakest link or links in the chain of  
2  
3 484 events producing muscle force.  
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5 485 Although there are ethical limitations for using some methods, especially invasive ones,  
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8 486 in healthy young and adult people, there are more instruments and methods available to  
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10 487 examine fatigue compared to twenty years ago. Many of the assessments described in  
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12 488 the present review have drawn useful conclusions about the fatigue development and  
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14 489 recovery, and their underlying causes. However, fatigue remains a complex and  
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16 490 multifactorial process. This situation demands the assessment of carefully designed  
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18 491 experimental setups, that could limit controversial findings and accept or reject possible  
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20 492 candidate theories explaining the mechanisms that are responsible for any differences in  
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22 493 fatigability between youth and adulthood.  
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26  
27 494 It is important to note, that some studies regarding fatigue in youth have revealed  
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29 495 controversial findings. This could be attributed to methodological issues such as  
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31 496 different fatigue protocols, the characteristics of the participants (sample size and  
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33 497 homogeneity), and the methods used, which might not be sensitive or accurate enough  
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35 498 to capture any systematic differentiation (Table 2). Therefore, cross-validation of the  
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37 499 current findings is of major importance. The direct or indirect evidence that earlier  
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39 500 findings have shown can be replicated, thus building a sound foundation for future  
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41 501 research. This will not only verify that our current knowledge is valid but may also  
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43 502 enlighten any current discrepancies. Finally, the importance of the sensation of fatigue  
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45 503 should be also considered in future research since its effect, which has not been studied  
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47 504 extensively in this age group, might be responsible for current controversial findings in  
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52 505 various parameters measuring performance.  
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## 507 **5. What remains to be discovered?**

508 The studies shown in Tables 2 and 3 illustrate the current status of the literature  
509 regarding the investigation of exercise-induced fatigue in healthy young population.

510 Considering all the available methodological approaches, it is apparent that there are  
511 still many unknown aspects of fatigue that need to be more thoroughly examined using  
512 methods such as transcranial magnetic stimulation (TMS), transcranial electrical  
513 stimulation, functional Magnetic Resonance Imaging (MRI), near infrared spectroscopy  
514 (NIRS), tendon vibration, H-reflex, and ultrasound. This knowledge may reveal new  
515 insights in fatigue and would cross-validate previous findings.

516 More specifically, by means of electrical or magnetic stimulation it is possible to  
517 identify more precisely the site of fatigue (spinal, supraspinal or both). Methods such as  
518 TMS (Gandevia et al. 1999; Taylor et al. 2000, 2006) that examine the cortical  
519 excitability, and electroencephalography, functional MRI, or NIRS that examine the  
520 activation of the brain, have not yet been applied in children during different fatigue  
521 protocols. Moreover, application of methods such as the H-reflex (Tucker et al. 2005)  
522 and the development of persistent inward currents (PICs) (Heckman et al. 2005) could  
523 give an insight in the spinal excitability and the function of different spinal mechanisms,  
524 such as the IA reciprocal inhibition (Crone et al. 1987), the Ia presynaptic inhibition  
525 (Hultborn et al. 1987), the recurrent inhibition (Pierrot-Deseilligny and Bussel 1975),  
526 and the post-activation depression (Crone and Nielsen 1989).

527 Regarding the evaluation of the muscle, the low-frequency electrical/magnetic  
528 stimulation could be applied to the motor nerve during a fatiguing protocol to quantify  
529 the consequences of low-frequency fatigue, i.e. the reduction of  $Ca^{2+}$  release from  
530 sarcoplasmic reticulum (Chin et al. 1997), on differences in peripheral fatigue between

1 531 children and adults. Additional studies using surface EMG and electrical/magnetic  
2  
3 532 stimulation are also required to get a better understanding of the effects of fatigue on M-  
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6 533 wave or sarcolemmal excitability in children and adults. NIRS could be also applied on  
7  
8 534 the surface of a muscle to quantify deoxygenation and oxygenation rates in the muscle  
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10 535 during strenuous exercise (Racinais et al. 2007; Smith and Billaut 2010), but only a few  
11  
12 536 researchers have assessed measurements in children during fatigue (Moalla et al. 2006,  
13  
14 537 2012; Callewaert et al. 2013). The findings from studies using NIRS measurement will  
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17 538 be even more valuable if they are coupled with methods measuring directly blood flow  
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20 539 velocity and arterial size, such as Doppler ultrasound. Furthermore, structural changes  
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22 540 on the muscle-tendon unit (MTU) captured with ultrasound (fascicle length, MTU  
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24 541 stiffness, pennation angle), affect force production and transmission (Folland and  
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26 542 Williams 2007) have not been studied in children yet under fatigue conditions.  
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29 543 Although such MTU properties are affected by fatigue (Mademli and Arampatzis 2005)  
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31 544 and are different between children and adults (Waugh et al. 2012), this is an area that  
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33 545 requires more research.  
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36 546 It is also important to underline that since all methods have their limitations, it is  
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39 547 important to cross-validate previous findings with other approaches and from a different  
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41 548 perspective. For example, the estimation of the level of VA by means of the twitch  
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43 549 interpolation technique (Herbert and Gandevia 1999), has its limitations (Shield and  
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45 550 Zhou 2004) and particularly in children, the application of a train of electrical  
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47 551 supramaximal nerve stimuli might be a limiting factor due to potential pain. Therefore,  
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50 552 it is recommended to apply electrical single or double nerve stimuli, or magnetic nerve  
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52 553 stimulation or muscle electrical stimulation (Belanger and McComas 1989; Streckis et  
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55 554 al. 2007; Grosset et al. 2008; O'Brien et al. 2009; Hatzikotoulas et al. 2014; Ratel et al.  
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1 555 2015). Another example regards the sEMG that might be influenced by cross-talk,  
2  
3 556 signal cancelation, motor unit synchronization and muscle fibre conduction velocity  
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6 557 (Farina et al. 2004). Due to these limitations, the MRI with T2 enhancement could be  
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8 558 used to identify which portion and to what extent the muscle is activated (Ploutz-Snyder  
9  
10 559 et al. 1994; Kinugasa et al. 2004). Furthermore, specific experiments using advanced  
11  
12 560 decomposition techniques of the surface EMG would need to be also performed to  
13  
14 561 determine the recruitment thresholds and firing frequencies of active units (De Luca et  
15  
16 562 al. 2015) before and after fatigue in children compared to adults.

17  
18 563 The multifaceted nature of fatigue implies its investigation using a wide variety of  
19  
20 564 fatigue protocols, that differ in intensity, duration, type of contraction  
21  
22 565 (dynamic/isometric, eccentric/concentric, sustained/intermittent), number of active  
23  
24 566 muscles and joints, and the source of muscle activation (volitional or evoked) is  
25  
26 567 encouraged. This serves to highlight the importance of selecting appropriate fatigue  
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28 568 protocols that limit factors, which may influence the variability of the outcome  
29  
30 569 variables. Nonetheless, the variety of fatigue protocols makes comparisons between  
31  
32 570 studies difficult to evaluate. Therefore, there needs to be common agreement on the  
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34 571 selected fatigue protocols when attempting to elucidate contributing mechanisms to  
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36 572 fatigue and whilst designing studies to document the effects of fatigue protocols with  
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38 573 different outcome properties.

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42  
43 575 In conclusion, the cited references related to exercise-induced fatigue in children and  
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45 576 adolescents of this review reveals that more in-depth and systematic research is required  
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47 577 to understand the broader topic of fatigue. This goal can be achieved by designing  
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49 578 studies that test the fatigue effects in movements to replicate daily activities. However,  
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1 579 this can only be successful if it is based on more basic research focused on the  
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3 580 mechanisms of fatigue, whilst accounting for physiological, cognitive, and  
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5  
6 581 psychological aspects of performance. Some objective measures of the evaluation of the  
7  
8 582 physiological mechanisms have been cited in the current review, however, the linkage  
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10 583 and interaction between all three above aspects remains to be resolved in young people.

11 584

### 12 585 **Conflict of interest**

13 586 The authors report no conflict of interest. This work is known to and agreed by the co-  
14  
15 587 authors identified on the manuscript's title page.

16 588

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1 803 **Figure legend**

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3 804 Figure 1. Schematic framework of fatigue with the possible sites and mechanisms that

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6 805 may contribute to it.

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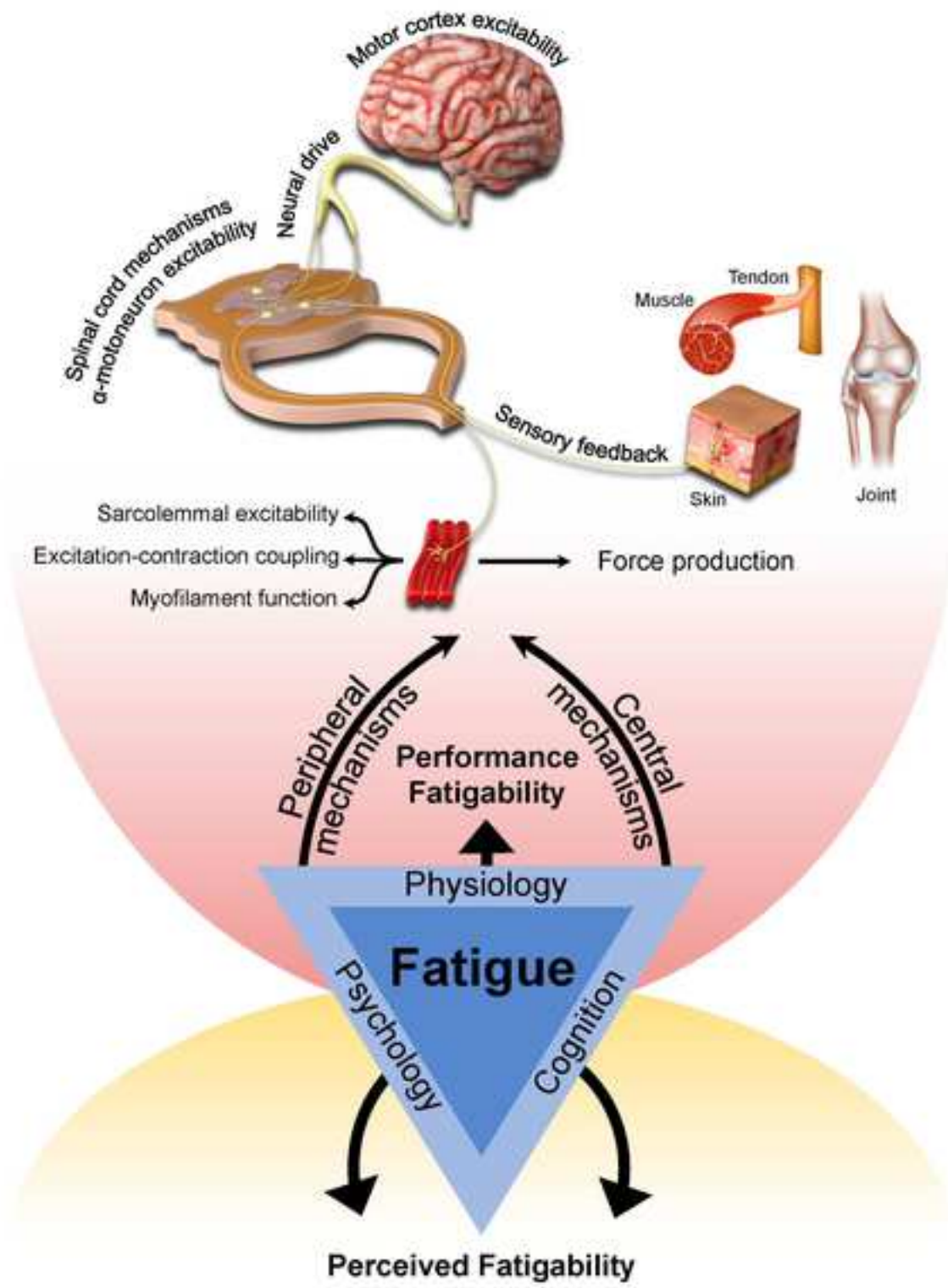
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1 **Table 1.** Voluntary activation (VA) during a brief non-fatigued maximal contraction in children and adults.

Reference	Age (y)	Sex	Contraction	Muscle	Joint angle	VA (%)
Belanger and McComas (1989)	C: $11.0 \pm 2.3$ Ado: $16.5 \pm 0.9$	M M	Isometric	Plantar flexors	Ankle: 20°DF Knee: 90°	C: $94.0 \pm 11.3$ Ado: $99.4 \pm 1.8$ C < A*
Grosset et al. (2008)	C: 7, 8, 9, 10, 11 A: $21.0 \pm 2.3$	M + F	Isometric	Plantar flexors	Ankle: 90° Knee: 120°	C7y: 87.0 C10y: 95.6 C11y: 96.7 A: 98.5 C7y < A
Kluka et al. (2015)	C: $10.2 \pm 1.1$ A: $23.9 \pm 2.9$	M M	Isometric	Knee extensors	Knee: 90°	C: $88 \pm 8$ A: $94 \pm 4$ C < A
Kluka et al. (2016)	C: $10.0 \pm 1.0$ A: $24.6 \pm 4.2$	M M	Isometric	Plantar flexors	Ankle: 10°DF to 20°PF Knee: 180°	C: $87.6 \pm 1.6$ A: $92.4 \pm 1.7$ C < A
Martin et al. (2015)	C: $11.6 \pm 0.1$ A: $25.6 \pm 1.5$	M M	Isometric	Adductor pollicis	Thumb: full abduction	C: $85.0 \pm 2.7$ A: $94.8 \pm 1.4$ C < A
O'Brien et al. (2009)	C: $8.9 \pm 0.7$ C: $9.3 \pm 0.8$ A: $28.2 \pm 3.6$ A: $27.4 \pm 4.2$	M F M F	Isometric	Knee extensors	Knee: 90°	C-M: $75.1 \pm 12.8$ C-F: $66.9 \pm 13$ A-M: $85.6 \pm 8.5$ A-F: $86.6 \pm 6.6$ C-F < A

2 Mean  $\pm$  SD, C: child, A: adult, Ado: adolescent, M: male, F: female, DF: dorsi-flexion, PF: plantar-flexion, \*: not significant.

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1 **Table 2.** Factors underpinning differences in exercise-induced fatigue between children and adults

<b>Mechanisms</b>	<b>Factors involved in the development of fatigue</b>	<b>References</b>	<b>Fatigue protocol</b>	<b>Child-Adult comparison</b>
Central (neural) mechanisms	Motor cortex activation deficit	-	-	-
	Neural drive alteration (cortex → spinal cord)	-	-	-
	Motor unit activation deficit (voluntary activation loss)	Hatzikotoulas et al. (2014) Streckis et al. (2007) Ratel et al. (2015) Gorianovas et al. (2013)	Sustained MVC of PF muscles until 50% of initial MVC 2-min sustained MVC of KE muscles Repeated MVC of KE muscles until 60% of initial MVC 100 repeated drop jumps	Child = Adult Child > Adult Child > Adult Child < Adult
Peripheral (muscular) mechanisms	Sarcolemmal excitability alteration (M-wave alteration)	Hatzikotoulas et al. (2014) Murphy et al. (2014) Ratel et al. (2015)	Sustained MVC of PF muscles until 50% of initial MVC Repeated dynamic knee extensions Repeated MVC of KE muscles until 60% of initial MVC	Child = Adult Child < Adult No alteration in both groups
	Excitation-contraction coupling alteration (Low-Frequency fatigue)	Gorianovas et al. (2013)	100 repeated drop jumps	Child < Adult
	Energy substrates depletion (Glycogen, phosphocreatine)	Kappenstein et al. (2013)	Repeated dynamic plantar flexions	Child < Adult
	Metabolites accumulation	Kappenstein et al. (2013)	Repeated dynamic plantar flexions	Child < Adult
	Contractile properties alteration (twitch torque alteration)	Streckis et al. (2007) Hatzikotoulas et al. (2014) Murphy et al. (2014) Ratel et al. (2015)	2-min sustained MVC of KE muscles Sustained MVC of PF muscles until 50% of initial MVC Repeated dynamic knee extensions Repeated MVC of KE muscles until 60% of initial MVC	Child < Adult Child < Adult Child < Adult Child < Adult
	Blood flow alteration	-	-	-

2 KE: knee extensors, PF: plantar flexors, MVC: maximal voluntary contraction.

- 1 **Table 3.** Studies assessing fatigue in young people with the respective fatigue tests and  
 2 the corresponding physiological analyzed properties.

References	Fatigue test	sEMG	VA	M-wave	Twitch	<sup>31</sup> P-MRS	HR	VO <sub>2</sub>	[La]	Blood pH	CK
Hebestreit et al. (1993)	Cycling sprints						X	X			
Kanehisa et al. (1995)	Isokinetic KE										
Ratel et al. (2002)	Cycling sprints								X	X	
Halin et al. (2003)	Isometric EF	X									
Zafeiridis et al. (2005)	Isokinetic KE KF						X		X		
Ratel et al. (2006)	Running sprints								X		
Paraschos et al. (2007)	Isokinetic KE	X									
Streckis et al. (2007)	Isometric KE		X		X						
Ratel et al. (2008)	Isometric FF					X					
Faigenbaum et al. (2008)	Bench press										
De Ste Croix et al. (2009)	Isokinetic KE KF										
Dipla et al. (2009)	Isokinetic KE KF						X		X		
Hatzikotoulas et al. (2009)	Isometric PF	X									
Armatas et al. (2010)	Isometric KE	X									
Fleischman et al. (2010)	Isotonic KE					X					
Tonson et al. (2010)	Isometric FF					X					
Bottaro et al. (2011)	Isokinetic KE								X		
Gorianovas et al. (2013)	SSC		X		X						X
Kappenstein et al. (2013)	Isotonic PF					X					
Patikas et al. (2013)	Isometric PF	X							X		
Chen et al. (2014)	Eccentric EF										X
Hatzikotoulas et al. (2014)	Isometric PF	X	X	X	X						
Murphy et al. (2014)	Isotonic KE	X			X		X				
Ratel et al. (2015)	Isometric KE	X	X	X	X						
Lazaridis et al. (2018)	SSC	X									

- 3  
 4 KE: knee extension; KF: knee flexion; PF: plantar flexion; EF: elbow flexion; FF:  
 5 finger flexion; SSC: stretch-shortening cycle bouts; sEMG: surface electromyography;  
 6 VA: voluntary activation assessed by means of interpolated twitch technique; NIRS:

7 near infra-red spectroscopy; HR: heart rate; VO<sub>2</sub>: oxygen consumption and gas  
8 exchange; <sup>31</sup>P-MRS: <sup>31</sup>P-magnetic resonance spectroscopy; [La]: blood lactate  
9 concentration; CK: plasma creatine kinase.

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