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

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Abstract:	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.
Response to Reviewers:	

Response to the general comment

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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."

Review article

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

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Abstract

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.

Keywords: Fatigue; Children; Etiology; Perspectives

Abbreviations

CNS: central nervous system

E-C: excitation-contraction

MRI: magnetic resonance imaging

MTU: muscle-tendon unit

MVC: maximum voluntary contraction

NIRS: near infrared spectroscopy

PCr: phosphocreatine

PICs: persistent inward currents

sEMG: surface electromyography

TMS: transcranial magnetic stimulation

VA: voluntary activation

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

The following count of papers were found in the respective databases with the keywords shown in square brackets (date of retrieval: 27th September 2017):

- Pubmed: 82 [muscle fatigue AND child AND exercise[MeSH]]
- Scopus: 139 [“muscle fatigue” AND child AND exercise]
- Web of Science: 171 [muscle fatigue AND child AND exercise]
- Ovid: 60 [muscle fatigue AND child AND exercise]

The search was supplemented by manually cross-matching reference lists, key author searches, and citation searching of all retrieved papers to potentially identify additional studies. Grey literature including monographs was searched also through databases, cross referencing in conference proceedings and personal communications.

2. Conceptual framework of fatigue

2.1. Definition

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

2.2. Topography

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

Potential factors involved in fatigue development have been typically classified into two categories: central factors involving the central nervous system (CNS) and neural pathways (Enoka 1995), and peripheral factors occurring within the muscle itself (Westerblad et al. 1991; Fitts 1994). Enoka and Duchateau (2016) propose that the adjectives central and peripheral be removed given that multi-processes are likely involved and the decline in power or force is task dependent (Asmussen 1979; Enoka and Stuart 1992). Whether this call to eliminate the description of fatigue as central or peripheral *per se* is adopted, remains to be shown. For the purpose of this review we will continue, to be consistent with previous literature, to refer to fatigue as centrally and peripherally orientated.

2.3. Mechanisms

As discussed above and putting to one side the issue of performance fatigability and perceived fatigability, the factors that contribute to fatigue have been typically classified into two categories: central factors involving the CNS and neural pathways and peripheral factors occurring within the muscle milieu (Figure 1). Among the peripheral factors, a major mechanism leading to the development of fatigue, for example, during high-intensity exercise would be the failure in muscle contractility and excitation-contraction (E-C) coupling. This could be associated with an impairment of myofilament function, sarcolemmal excitability and/or calcium release from sarcoplasmic reticulum (Allen et al. 2008). However, there is little information regarding muscle activation during fatiguing tasks for young people, where surface electromyography (sEMG) and evoked twitch techniques have been used. The inferences from fatigue involving the CNS mechanisms, including the changes in the motor cortex and spinal excitability require methods that are more difficult to apply in healthy individuals due to ethical concerns i.e., transcranial magnetic stimulation, neurotransmitters derived from blood, and have been studied less in young people.

3. Current knowledge about neuromuscular fatigue in children

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

3.1. Whole-body dynamic activities

3.1.1. Cycling

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

Similar conclusions were drawn by other researchers when investigating the effects of age and recovery duration on cycling peak power during repeated sprints (Ratel et al. 2002a). Eleven prepubertal (mean ± SD; 9.6 ± 0.7 years) and nine pubertal boys (15.0 ± 0.7 years) and 10 men (20.4 ± 0.8 years) completed ten 10 s cycling sprints separated by 30 s, 1 min, or 5 min of passive recovery. For the prepubertal boys whatever recovery duration was chosen, peak power remained unchanged during the 10 s sprints. In the pubertal boys, peak power decreased significantly by 20% during the 30 s recovery, by 15% during the 1 min recovery, and was unchanged by the 5 min recovery. For the men, peak power significantly decreased by 29%, 11%, and decreased slightly but non-significantly during the 30 s, 1 min, and 5 min recovery periods, respectively.

3.1.2. Running

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

3.2. Resistance exercise

Similar conclusions as cycling and running were reported during resistance exercise. Faigenbaum et al. (2008) assessed bench press performance during three sets with a 10 repetition maximum load and 1, 2 or 3 min rest intervals between sets in boys (11.3 years), male adolescents (13.6 years), and men (21.4 years). Significant differences in lifting performance between age groups were observed within each set with boys and male adolescents performing significantly more total repetitions than men following protocols with 1 min (27.9, 26.9, and 18.2, respectively), 2 min (29.6, 27.8, and 21.4, respectively) and 3 min (30.0, 28.8, and 23.9, respectively) recovery intervals. The authors concluded that boys and male adolescents are better able to maintain muscle performance during intermittent moderate intensity bench press exercise compared to men.

3.3. Maximal voluntary muscle contractions

The lower fatigability in children has been confirmed during sustained or repeated MVC whatever the nature of contraction and the muscle group investigated (Zafeiridis et al. 2005; De Ste Croix et al. 2009; Dipla et al. 2009; Chen et al. 2014; Ratel et al. 2015). Some authors reported a lower reduction of peak torque and total work during repeated concentric maximal knee extensions and flexions on an isokinetic dynamometer in prepubertal children compared to adults (Zafeiridis et al. 2005; De Ste Croix et al. 2009; Dipla et al. 2009). Also, when muscle contractions included repeated eccentric phases, the decline of concentric peak torque of the elbow flexors was found to be lower in prepubertal children compared to adolescents and lower in adolescents compared to adults (Chen et al. 2014). Similar results were obtained during repeated

MVC of the knee extensors under repeated isometric contractions in prepubertal children compared to adults (Ratel et al. 2015). For instance, during a fatigue protocol consisting of repetitions of 5 s isometric MVC of the knee extensors separated by 5 s passive recovery periods until the torque reached 60% of its initial value, Ratel et al. (2015) showed that the number of repetitions was significantly lower in men compared to prepubertal boys (34.0 vs. 49.5 repetitions, respectively), showing a lower fatigability in children.

3.4. Sub-maximal voluntary muscle contractions

Contrary to maximal intensity fatigue protocols, prepubertal children seem to fatigue similarly to young adults during sustained isometric contractions, which are conducted at submaximal intensities (Hatzikotoulas et al. 2009; Patikas et al. 2013). Indeed, Patikas et al. (2013) examined the effects of two submaximal sustained contractions (20% and 60% MVC) until exhaustion, on the fatigue and recovery properties of plantar flexors, in untrained prepubescent children (n = 14) and adults (n = 14). The authors showed that immediately after fatigue, MVC torque decreased similarly in both groups, compared with pre-fatigue values and children recovered faster than adults in both protocols. Furthermore, the reduction in agonist EMG during MVC after fatigue, independent of the protocols, was not significantly different between children and adults. However, EMG of children recovered to baseline values after 3 min for both fatigue protocols, whereas adults did not recover and exhibited significantly lower values (torque & EMG) 3 min after fatigue compared to the pre-fatigue baseline values. The authors concluded that submaximal (low- and moderate-intensity) sustained isometric fatigue protocols induced similar fatigue effects in children and adults, and children recovered faster than adults.

In summary, whatever the nature of the maximal task performed (whole-body dynamic activities, resistance exercise or MVC) and the muscle group investigated, prepubertal children fatigue less than their older counterparts. This lower muscle fatigue in prepubertal children could be explained by peripheral (i.e. muscular) and central (i.e. neural) changes that occur during adolescence, which we address in the following sections.

3.5. Mechanisms underpinning differences between children and adults

3.5.1. Central mechanisms

Central factors may be responsible for the lower fatigue in children. These factors could include the capacity to maximally activate the motor units of agonist muscles (i.e. agonist activation) and the coactivation level of antagonist muscles (i.e. antagonist activation).

Agonist activation

Recently, some studies have reported a greater decrement in voluntary activation (VA) of agonist muscles when using the twitch interpolation technique during fatigue protocols in children compared to adults (Streckis et al. 2007; Ratel et al. 2015). For instance, following a sustained 2-min MVC of the knee extensors, Streckis et al. (2007) reported a greater decrement of VA in 13.9-yr-old boys compared to 22.2-yr-old men (around -55 vs. -45%, respectively). Furthermore, after a fatigue protocol consisting in a repetition of 5-s MVC of the knee extensors until the generated torque reached 60% of its initial value, Ratel et al. (2015) showed that VA remained unchanged in 23.9-yr-old men (91.2 ± 2.6 vs. 86.7 ± 2.6%), whereas it decreased significantly by 27% in 9.9-yr-old boys (86.9 ± 7.6 vs. 63.4 ± 17.9%). This result was associated with a lower fatigue regarding peripheral factors in children, as evidenced by a lower twitch torque decrement (Ratel et al. 2015). The interplay of central vs. peripheral mechanisms of fatigue in children remains to be elucidated; however, on the basis of these studies (Streckis et al. 2007; Ratel et al. 2015), it could be suggested that the greater fatigue effect on central mechanisms in children accounts for their lower fatigue at peripheral level. As such, Amann and Dempsey (2008) proposed the existence of a "critical threshold" of fatigue observed at the periphery and demonstrated that when the inhibitory feedback from group III/IV afferents was reduced by pharmacological blockade, the exercising adult subjects "tolerated" the development of peripheral muscle fatigue substantially beyond their critical threshold (Amann et al. 2011). It is currently unknown if this critical threshold is different in children and adults, but the lower contribution of peripheral mechanisms to fatigue development (and higher of central mechanisms) reported previously (Streckis et al. 2007; Ratel et al. 2015) supports the proposition that the critical threshold could be set centrally at a higher level in children. However, the interplay of central vs. peripheral mechanisms of fatigue during childhood requires further research since some authors have reported greater peripheral fatigue in adults compared to children, despite similar central fatigue in plantar flexors between both age groups (Hatzikotoulas et al. 2014).

Beyond the influence of this potential central regulation of agonist activation during a fatiguing task, the exercise duration could promote the development of fatigue at the

CNS in children (Armatas et al. 2010; Ratel et al. 2015). Indeed, the lower fatigue in prepubertal children translates into a longer exercise duration when repeating MVC ~~until the same level of exhaustion, i.e.~~ until a predetermined percentage of initial MVC is reached (Armatas et al. 2010; Ratel et al. 2015). This observation is supported recently by Ratel et al. (2015) showing a positive relationship between the decrement in VA and the number of repeated isometric maximal contractions of the knee extensor muscles ~~until the same level of exhaustion~~ in prepubertal children and adults.

It is also important to note that the ability to fully activate voluntarily the neuromuscular system might be crucial for the development of fatigue. A lower activation level implies higher resistance to fatigue. Some studies have shown that children have lower levels of activation during a brief non-fatigued MVC (Table 1), although this has not always reached statistical significance (Belanger and McComas 1989; Grosset et al. 2008; O'Brien et al. 2009; Kluka et al. 2015, 2016; Martin et al. 2015). However, such potential differences between children and adults in their ability to reach their maximal voluntary activation should be accounted for when interpreting the level of fatigue.

Antagonist coactivation

Regarding the central regulation of the antagonist coactivation under fatigue conditions, studies have reported different patterns between children and adults. Ratel et al. (2015) showed that antagonist activity of the biceps femoris remained constant in adults, whereas it significantly decreased in prepubertal children during repeated maximal voluntary isometric knee extensions. This decrease in antagonist coactivation in children may contribute to limit the loss of force, and therefore to delay fatigue at the peripheral level (Ratel et al. 2015). Also, in this same study, the decrement of coactivation in children was positively correlated with the decrement of VA, which is consistent with the theory of ‘common drive’. Such a phenomenon could serve to maintain the balance between agonist and antagonist force in children, to preserve their joint integrity (Psek and Cafarelli 1993). However, these results should be confirmed since other studies have reported contradictory results (Paraschos et al. 2007; Armatas et al. 2010; Murphy et al. 2014). For example, it has been shown during repeated isokinetic knee extensions that antagonist activity of the biceps femoris remained constant in adults and increased in prepubertal children (Paraschos et al. 2007; Murphy et al. 2014). Furthermore, Armatas et al. (2010) showed during repeated maximal voluntary isometric knee extensions that antagonist activity of the biceps femoris did not change in prepubertal children and adults and this could not explain the differences of fatigability between children and adults. Therefore, this issue remains unresolved and further research into this area is warranted.

3.5.2. Peripheral mechanisms

Several studies have shown a lower fatigue at peripheral level, as indicated by a lower twitch torque decrement after sustained or repeated MVC in children or adolescents compared to adults (Streckis et al. 2007; Hatzikotoulas et al. 2014; Murphy et al. 2014; Ratel et al. 2015). Furthermore, after a repetitive stretch-shortening cycle fatigue protocol, which induces muscle damage, Gorianovas et al. (2013) reported a lower low-frequency fatigue, evaluated by the low-to-high frequency tetanic force ratio, in children compared to adults, showing a lower alteration of the excitation-contraction coupling. However, the contribution of sarcolemmal excitability changes to fatigue in children still remains equivocal (Hatzikotoulas et al. 2014; Murphy et al. 2014; Ratel et al.

2015). Indeed, while some authors reported a similar decrement (Hatzikotoulas et al. 2014) or no change of the M-wave (Ratel et al. 2015) in response to exercise in prepubertal children compared to adults, others showed an increase in children and a significant decrease in adults (Murphy et al. 2014). These discrepancies could result from a different balance of potentiation and fatigue on the M-wave during exercise between children and adults. Therefore, despite the underlying factors not being fully acknowledged, there is a consensus that prepubertal children develop a lower fatigue at the peripheral level compared to adults (Streckis et al. 2007; Hatzikotoulas et al. 2014; Murphy et al. 2014; Ratel et al. 2015). This could be attributed to different factors such as absolute force and muscle phenotype.

Absolute force

The higher fatigue observed at peripheral mechanisms in adults during high-intensity exercise could be associated with their larger active muscle mass involved during exercise and their superior maximal force-generating capacity. To the best of our knowledge in the only study testing this assumption, Ratel et al. (2015) showed a significant positive relationship between the first MVC and the twitch torque decrement during repeated maximal contractions of the knee extensors in children and adults. Furthermore, when the initial MVC torque was used as covariate, no significant difference in the course of the twitch torque was observed between groups, supporting the importance of MVC torque in the development of fatigue. This finding is also consistent with other studies that showed the fatigability of the knee extensors during repeated MVC was no longer different between obese and non-obese adolescent girls when the initial MVC torque was used as a covariate in statistical analysis (Garcia-

Vicencio et al. 2015). In addition, other studies reported that the greater fatigue observed in men versus women was eliminated when subjects were matched for absolute force (Hunter et al. 2004). This greater muscle mass involved during exercise in adults could be the cause of a greater vascular occlusion and therefore greater metabolic disturbances that are usually observed during high-intensity exercise in adults compared to children (Kappenstein et al. 2013). However, this suggestion is speculative because this has not been tested in adults compared to children. Studies with fatigue protocols using variable intensities controlling for blood vascular occlusion are required to elucidate this speculation.

Muscle phenotype

Muscle phenotype, which is more oxidative than glycolytic in prepubertal children regarding muscle fibre type composition and muscle metabolism (Ratel and Blazevich 2017), could also account for the differences in fatigue between children and adults.

The distribution of muscle fibre types in the muscle can determine not only its force production capacity and contractile properties, but its resistance to fatigue as well. It has been previously shown that individuals with predominantly fast-twitch fibres in their vastus lateralis develop a greater fatigue during knee extension compared to subjects with a higher proportion of slow-twitch fibres (Hamada et al. 2003). Furthermore, it has been reported that adults have a lower percentage of slow-twitch fibres in the vastus lateralis muscle than children (Lexell et al. 1992; Glenmark et al. 1994). For instance, Lexell et al. (1992) reported individual values of 63, 65, 67 and 69% in four children aged between 5 and 13 years and values comprised between 47 and 57% in sixteen adults aged between 18 and 37 years. However, the influence of muscle type on the fatigue in children remains to be established since other studies showed no difference in muscle fibre type composition in the vastus lateralis between children and adults (Berg and Keul 1988).

Furthermore, several studies provided evidence that children rely more on oxidative relative to anaerobic metabolism during exercise (Berg and Keul 1988; Ratel et al. 2008; Tonson et al. 2010). Indeed, using ^{31}P-magnetic resonance spectroscopy, it has been shown that post-exercise phosphocreatine (PCr) resynthesis rates are higher in children compared to adults, suggesting a higher muscle oxidative activity during exercise in children (Taylor et al. 1997; Ratel et al. 2008; Fleischman et al. 2010; Tonson et al. 2010). This specific metabolic profile in children could lead to a lower accumulation of muscle by-products (i.e. H^+ ions and inorganic phosphate) and a lower PCr depletion during high-intensity intermittent exercise in children compared to adults (Kappenstein et al. 2013). As inorganic phosphate is strongly associated with the decrease of myofibrillar force production and Ca^{2+} sensitivity as well as sarcoplasmic reticulum Ca^{2+} release (Allen et al. 2008), its lower accumulation in exercising muscle in prepubertal children could constitute the major cause of their lower fatigue at the periphery (Streckis et al. 2007; Hatzikotoulas et al. 2014; Murphy et al. 2014; Ratel et al. 2015). The lower decrement in intramuscular pH in prepubertal children may also account for this; however, the reduction in pH obtained under physiological circumstances, could have far less inhibitory (or restraining) effects on the contractile apparatus efficiency and Ca^{2+} release than previously assumed (Allen et al. 2008).

Collectively, these studies report a lower peripheral fatigue and a potentially greater neural fatigue in children. However, further studies are required to better investigate the neuromuscular mechanisms underpinning differences in fatigue between children, adolescents and adults (Table 2).

==== Table 2 near here ====

4. Challenges and future perspectives

To better investigate the exercise-induced fatigue, it is necessary to examine the whole chain of events that occur from the generation of the movement to its execution. However, this process should not overlook the importance of the sensory feedback and its integration to the motor command. In general, it is important to evaluate all possible neural and mechanical properties of the neuromuscular system as thoroughly as possible and to understand how they adapt and interact during the development of fatigue. Therefore, the objective evaluation of fatigue and its underlying mechanisms is essential for understanding the strategies that the neuromuscular system develops to sustain an external load. Numerous methods are available to investigate neuromuscular fatigue and some of these that have been applied in children are shown in Table 3.

==== Table 3 near here ====

Additionally, this research should not only be focused on well-controlled experiments that isolate one mechanism under certain, mostly laboratory, conditions. One major goal of research should be the documentation of the interaction between different mechanisms with the utmost perspective to describe fatigue universally, in real-world conditions (i.e. during training and everyday activities, to increase the ecological validity of the experiment) and to determine the weakest link or links in the chain of events producing muscle force.

Although there are ethical limitations for using some methods, especially invasive ones, in healthy young and adult people, there are more instruments and methods available to examine fatigue compared to twenty years ago. Many of the assessments described in the present review have drawn useful conclusions about the fatigue development and recovery, and their underlying causes. However, fatigue remains a complex and multifactorial process. This situation demands the assessment of carefully designed experimental setups, that could limit controversial findings and accept or reject possible candidate theories explaining the mechanisms that are responsible for any differences in fatigability between youth and adulthood.

It is important to note, that some studies regarding fatigue in youth have revealed controversial findings. This could be attributed to methodological issues such as different fatigue protocols, the characteristics of the participants (sample size and homogeneity), and the methods used, which might not be sensitive or accurate enough to capture any systematic differentiation (Table 2). Therefore, cross-validation of the current findings is of major importance. The direct or indirect evidence that earlier findings have shown can be replicated, thus building a sound foundation for future research. This will not only verify that our current knowledge is valid but may also enlighten any current discrepancies. Finally, the importance of the sensation of fatigue should be also considered in future research since its effect, which has not been studied extensively in this age group, might be responsible for current controversial findings in various parameters measuring performance.

5. What remains to be discovered?

The studies shown in Tables 2 and 3 illustrate the current status of the literature regarding the investigation of exercise-induced fatigue in healthy young population. Considering all the available methodological approaches, it is apparent that there are still many unknown aspects of fatigue that need to be more thoroughly examined using methods such as transcranial magnetic stimulation (TMS), transcranial electrical stimulation, functional Magnetic Resonance Imaging (MRI), near infrared spectroscopy (NIRS), tendon vibration, H-reflex, and ultrasound. This knowledge may reveal new insights in fatigue and would cross-validate previous findings.

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

Regarding the evaluation of the muscle, the low-frequency electrical/magnetic stimulation could be applied to the motor nerve during a fatiguing protocol to quantify the consequences of low-frequency fatigue, i.e. the reduction of Ca^{2+} release from sarcoplasmic reticulum (Chin et al. 1997), on differences in peripheral fatigue between children and adults. Additional studies using surface EMG and electrical/magnetic stimulation are also required to get a better understanding of the effects of fatigue on M-wave or sarcolemmal excitability in children and adults. NIRS could be also applied on the surface of a muscle to quantify deoxygenation and oxygenation rates in the muscle during strenuous exercise (Racinais et al. 2007; Smith and Billaut 2010), but only a few researchers have assessed measurements in children during fatigue (Moalla et al. 2006, 2012; Callewaert et al. 2013). The findings from studies using NIRS measurement will be even more valuable if they are coupled with methods measuring directly blood flow velocity and arterial size, such as Doppler ultrasound. Furthermore, structural changes on the muscle-tendon unit (MTU) captured with ultrasound (fascicle length, MTU stiffness, pennation angle), affect force production and transmission (Folland and Williams 2007) have not been studied in children yet under fatigue conditions. Although such MTU properties are affected by fatigue (Mademli and Arampatzis 2005) and are different between children and adults (Waugh et al. 2012), this is an area that requires more research.

It is also important to underline that since all methods have their limitations, it is important to cross-validate previous findings with other approaches and from a different perspective. For example, the estimation of the level of VA by means of the twitch interpolation technique (Herbert and Gandevia 1999), has its limitations (Shield and Zhou 2004) and particularly in children, the application of a train of electrical supramaximal nerve stimuli might be a limiting factor due to potential pain. Therefore, it is recommended to apply electrical single or double nerve stimuli, or magnetic nerve stimulation or muscle electrical stimulation (Belanger and McComas 1989; Streckis et al. 2007; Grosset et al. 2008; O’Brien et al. 2009; Hatzikotoulas et al. 2014; Ratel et al.

2015). Another example regards the sEMG that might be influenced by cross-talk, signal cancelation, motor unit synchronization and muscle fibre conduction velocity (Farina et al. 2004). Due to these limitations, the MRI with T2 enhancement could be used to identify which portion and to what extent the muscle is activated (Ploutz-Snyder et al. 1994; Kinugasa et al. 2004). Furthermore, specific experiments using advanced decomposition techniques of the surface EMG would need to be also performed to determine the recruitment thresholds and firing frequencies of active units (De Luca et al. 2015) before and after fatigue in children compared to adults.

The multifaceted nature of fatigue implies its investigation using a wide variety of fatigue protocols, that differ in intensity, duration, type of contraction (dynamic/isometric, eccentric/concentric, sustained/intermittent), number of active muscles and joints, and the source of muscle activation (volitional or evoked) is encouraged. This serves to highlight the importance of selecting appropriate fatigue protocols that limit factors, which may influence the variability of the outcome variables. Nonetheless, the variety of fatigue protocols makes comparisons between studies difficult to evaluate. Therefore, there needs to be common agreement on the selected fatigue protocols when attempting to elucidate contributing mechanisms to fatigue and whilst designing studies to document the effects of fatigue protocols with different outcome properties.

In conclusion, the cited references related to exercise-induced fatigue in children and adolescents of this review reveals that more in-depth and systematic research is required to understand the broader topic of fatigue. This goal can be achieved by designing studies that test the fatigue effects in movements to replicate daily activities. However, this can only be successful if it is based on more basic research focused on the mechanisms of fatigue, whilst accounting for physiological, cognitive, and psychological aspects of performance. Some objective measures of the evaluation of the physiological mechanisms have been cited in the current review, however, the linkage and interaction between all three above aspects remains to be resolved in young people.

Conflict of interest

The authors report no conflict of interest. This work is known to and agreed by the co-authors identified on the manuscript’s title page.

References

Allen DG, Lamb GD, Westerblad H (2008) Skeletal muscle fatigue: cellular mechanisms. Physiol Rev 88:287–332.

Amann M, Blain GM, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA (2011) Implications of group III and IV muscle afferents for high-intensity endurance exercise performance in humans. J Physiol 589:5299–5309.

Amann M, Dempsey JA (2008) The concept of peripheral locomotor muscle fatigue as a regulated variable. J Physiol 7:2029–2030.

Armatas V, Bassa E, Patikas D, Kitsas I, Zangelidis G, Kotzamanidis C (2010) Neuromuscular differences between men and prepubescent boys during a peak isometric knee extension intermittent fatigue test. Pediatr Exerc Sci 22:205–217.

Asmussen E (1979) Muscle fatigue. Med Sci Sports 11:313–21.

Belanger AY, McComas AJ (1989) Contractile properties of human skeletal muscle in childhood and adolescence. Eur J Appl Physiol 58:563–567.

Berg A, Keul J (1988) Biochemical changes during exercise in children. In: Malina RM (ed) Young athletes/biological, psychological and educational perspectives. Human Kinetics, Champaign, pp 61–77.

Bigland-Ritchie BR, Furbush FH, Woods JJ (1986) Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. J Appl Physiol 61:421–429.

Bottaro M, Brown LE, Celes R, Martorelli S, Carregaro R, de Brito Vidal JC (2011) Effect of rest interval on neuromuscular and metabolic responses between children and adolescents. Pediatr Exerc Sci 23:311–321.

Callewaert M, Boone J, Celie B, De Clercq D, Bourgois J (2013) Quadriceps muscle fatigue in trained and untrained boys. Int J Sports Med 34:14–20.

Chen TC, Chen HL, Liu YC, Nosaka K (2014) Eccentric exercise-induced muscle damage of pre-adolescent and adolescent boys in comparison to young men. Eur J Appl Physiol 114:1183–1195.

Chin ER, Balnave CD, Allen DG (1997) Role of intracellular calcium and metabolites in low-frequency fatigue of mouse skeletal muscle. Am J Physiol 272(2 Pt 1):C550-559.

Crone C, Hultborn H, Jespersen B, Nielsen JB (1987) Reciprocal Ia inhibition between ankle flexors and extensors in man. J Physiol 389:163–185.

Crone C, Nielsen JB (1989) Methodological implications of the post activation depression of the soleus H-reflex in man. Exp Brain Res 78:28–32.

De Luca CJ, Chang SS, Roy SH, Kline JC, Nawab SH (2015) Decomposition of surface EMG signals from cyclic dynamic contractions. J Neurophysiol 113:1941–1951.

De Ste Croix MBA, Deighan MA, Ratel S, Armstrong N (2009) Age- and sex-associated differences in isokinetic knee muscle endurance between young children and adults. Appl Physiol Nutr Metab 34:725–731.

Dipla K, Tsirini T, Zafeiridis A, Manou V, Dalamitros A, Kellis E, Kellis S (2009) Fatigue resistance during high-intensity intermittent exercise from childhood to adulthood in males and females. Eur J Appl Physiol 106:645–653.

Enoka RM (1995) Mechanisms of muscle fatigue: Central factors and task dependency. J Electromyogr Kinesiol 5:141–149.

Enoka RM, Duchateau J (2016) Translating Fatigue to Human Performance. Med Sci Sports Exerc 48:2228–2238.

Enoka RM, Stuart DG (1992) Neurobiology of muscle fatigue. J Appl Physiol 72:1631–1648.

Faigenbaum AD, Ratamess NA, McFarland J, Kaczmarek J, Coraggio MJ, Kang J, Hoffman JR (2008) Effect of rest interval length on bench press performance in boys, teens, and men. Pediatr Exerc Sci 20:457–69.

Falk B, Dotan R (2006) Child-adult differences in the recovery from high-intensity exercise. Exerc Sport Sci Rev 34:107-12.

Farina D, Merletti R, Enoka RM (2004) The extraction of neural strategies from the surface EMG. J Appl Physiol 96:1486–1495.

Fitts RH (1994) Cellular mechanisms of muscle fatigue. Physiol Rev 74:49–94.

Fleischman A, Makimura H, Stanley TL, McCarthy MA, Kron M, Sun N, Chuzi S, Hrovat MI, Systrom DM, Grinspoon SK (2010) Skeletal muscle phosphocreatine recovery after submaximal exercise in children and young and middle-aged adults. J Clin Endocrinol Metab 95:69–74.

Folland JP, Williams AG (2007) The Adaptations to Strength Training Increased Strength. Sport Med 37:145–168.

Gandevia SC (2001) Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 81:1725–89.

Gandevia SC, Petersen NT, Butler JE, Taylor JL (1999) Impaired response of human motoneurones to corticospinal stimulation after voluntary exercise. J Physiol 521:749–59.

Garcia-Vicencio S, Martin V, Kluka V, Cardenoux C, Jegu AG, Fourot AV, Coudeyre E, Ratel S (2015) Obesity-related differences in neuromuscular fatigue in adolescent girls. Eur J Appl Physiol 115:2421–2432.

Glenmark BB, Hedberg GG, Kaijser LL, Jansson EE (1994) Muscle strength from adolescence to adulthood--relationship to muscle fibre types. Eur J Appl Physiol 68:9–19.

Gorianovas G, Skurvydas A, Streckis V, Brazaitis M, Kamandulis S, McHugh MP (2013) Repeated bout effect was more expressed in young adult males than in elderly males and boys. Biomed Res Int 2013:218970.

Grosset J-F, Mora I, Lambertz D, Pérot C (2008) Voluntary activation of the triceps surae in prepubertal children. J Electromyogr Kinesiol 18:455–465.

Halin R, Germain P, Bercier S, Kapitaniak B, Buttelli O (2003) Neuromuscular response of young boys versus men during sustained maximal contraction. Med Sci Sports Exerc 35:1042–1048.

Hamada T, Sale DG, MacDougall JD, Tarnopolsky MA (2003) Interaction of fibre type, potentiation and fatigue in human knee extensor muscles. Acta Physiol Scand 178:165–173.

Hatzikotoulas K, Patikas D, Bassa E, Hadjileontiadis L, Koutedakis Y, Kotzamanidis C (2009) Submaximal fatigue and recovery in boys and men. Int J Sports Med 30:741–746.

Hatzikotoulas K, Patikas D, Ratel S, Bassa E, Kotzamanidis C (2014) Central and peripheral fatigability in boys and men during maximal contraction. Med Sci Sports Exerc 46:1326–1333.

Hebestreit H, Mimura K, Bar-Or O (1993) Recovery of muscle power after high-intensity short-term exercise: comparing boys and men. J Appl Physiol 74:2875–2880.

Heckman CJ, Gorassini MA, Bennett DJ (2005) Persistent inward currents in motoneuron dendrites: Implications for motor output. Muscle Nerve 31:135–156.

Herbert RD, Gandevia SC (1999) Twitch interpolation in human muscles: mechanisms and implications for measurement of voluntary activation. J Neurophysiol 82:2271–2283.

Hultborn H, Meunier S, Pierrot-Deseilligny E, Shindo M (1987) Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man. J Physiol 389:757–772.

Hunter SK, Critchlow A, Shin I-S, Enoka RM (2004) Fatigability of the elbow flexor muscles for a sustained submaximal contraction is similar in men and women matched for strength. J Appl Physiol 96:195–202.

Kanehisa H, Okuyama H, Ikegawa S, Fukunaga T (1995) Fatigability during repetitive maximal knee extensions in 14-year-old boys. Eur J Appl Physiol 72:170–174.

Kappenstein J, Ferrauti A, Runkel B, Fernandez-Fernandez J, Müller K, Zange J (2013) Changes in phosphocreatine concentration of skeletal muscle during high-intensity intermittent exercise in children and adults. Eur J Appl Physiol 113:2769–2779.

Kinugasa R, Akima H, Ota A, Ohta A, Sugiura K, Kuno SY (2004) Short-term creatine supplementation does not improve muscle activation or sprint performance in humans. Eur J Appl Physiol 91:230–7.

Kluger BM, Krupp LB, Enoka RM (2013) Fatigue and fatigability in neurologic inllnesses. Neurology 80:409–416.

Kluka V, Martin V, Vicencio SG, Jegu AG, Cardenoux C, Morio C, Coudeyre E, Ratel S (2015) Effect of muscle length on voluntary activation level in children and adults. Med Sci Sports Exerc 47:718–724.

Kluka V, Martin V, Vicencio SG, Giustiniani M, Morel C, Morio C, Coudeyre E, Ratel S (2016) Effect of muscle length on voluntary activation of the plantar flexors in boys and men. Eur J Appl Physiol 116:1043-1051.

Lazaridis S, Patikas DA, Bassa E, Tsatalas T, Hatzikotoulas K, Ftikas C, Kotzamanidis C (2018) The acute effects of an intense stretch-shortening cycle fatigue protocol on the neuromechanical parameters of lower limbs in men and prepubescent boys. J Sports Sci 36:131-39.

Lexell J, Sjöström M, Nordlund AS, Taylor CC (1992) Growth and development of human muscle: a quantitative morphological study of whole vastus lateralis from childhood to adult age. Muscle Nerve 15:404–409.

Mademli L, Arampatzis A (2005) Behaviour of the human gastrocnemius muscle architecture during submaximal isometric fatigue. Eur J Appl Physiol 94:611–617.

Martin V, Kluka V, Garcia Vicencio S, Maso F, Ratel S (2015) Children have a reduced maximal voluntary activation level of the adductor pollicis muscle compared to adults. Eur J Appl Physiol 115:1485–91.

McNeil CJ, Murray BJ, Rice CL (2006) Differential changes in muscle oxygenation between voluntary and stimulated isometric fatigue of human dorsiflexors. J Appl Physiol 100:890–5.

Merton PA (1954) Voluntary strength and fatigue. J Physiol 123:553–564.

Moalla W, Elloumi M, Chamari K, Dupont G, Maingourd Y, Tabka Z, Ahmaidi S (2012) Training effects on peripheral muscle oxygenation and performance in children with congenital heart diseases. Appl Physiol Nutr Metab 57:1–10.

Moalla W, Merzouk A, Costes F, Tabka Z, Ahmaidi S (2006) Muscle oxygenation and EMG activity during isometric exercise in children. J Sports Sci 24:1195–1201.

Mosso A (1904) Fatigue. New York, London

Murphy JR, Button DC, Chaouachi A, Behm DG (2014) Prepubescent males are less susceptible to neuromuscular fatigue following resistnace exercise. Eur J Appl Physiol 114:825-35.

O'Brien TD, Reeves ND, Baltzopoulos V, Jones DA, Maganaris CN (2009) The effects of agonist and antagonist muscle activation on the knee extension moment-angle relationship in adults and children. Eur J Appl Physiol 106:849-856.

Paraschos I, Hassani A, Bassa E, Hatzikotoulas K, Patikas D, Kotzamanidis C (2007) Fatigue differences between adults and prepubertal males. Int J Sports Med 28:958–963.

Patikas D, Kansizoglou A, Koutlianos N, Williams CA, Hatzikotoulas K, Bassa E, Kotzamanidis C (2013) Fatigue and recovery in children and adults during sustained contractions at two different submaximal intensities. Appl Physiol Nutr Metab 38:953–959.

Pierrot-Deseilligny E, Bussel B (1975) Evidence for recurrent inhibition by motoneurons in human subjects. Brain Res 88:105–108.

Ploutz-Snyder LL, Tesch PA, Biro RL, Dudley GA (1994) Effect of resistance training on muscle use during exercise. J Appl Physiol 76:1675–1681.

Psek JA, Cafarelli E (1993) Behavior of coactive muscles during fatigue. J Appl Physiol 74:170–175.

Racinais S, Bishop D, Denis R, Lattier G, Mendez-Villaneuva A, Perrey S (2007) Muscle deoxygenation and neural drive to the muscle during repeated sprint cycling. Med Sci Sports Exerc 39:268–74.

Ratel S, Bedu M, Hennegrave A, Doré E, Duché P (2002a) Effects of age and recovery duration on peak power output during repeated cycling sprints. Int J Sports Med 23:397–402.

Ratel S, Duche P, Hennegrave A, Van Praagh E, Bedu M (2002b) Acid-base balance during repeated cycling sprints in boys and men. J Appl Physiol 92:479–485.

Ratel S, Kluka V, Vicencio SG, Jegu AG, Cardenoux C, Morio C, Coudeyre E, Martin V (2015) Insights into the mechanisms of neuromuscular fatigue in boys and men. Med Sci Sports Exerc 47:2319–2328.

Ratel S, Tonson A, Le Fur Y, Cozzone P, Bendahan D (2008) Comparative analysis of skeletal muscle oxidative capacity in children and adults: a 31P-MRS study. Appl Physiol Nutr Metab 33:720–727.

Ratel S, Williams CA, Oliver J, Armstrong N (2004) Effects of age and mode of exercise on power output profiles during repeated sprints. Eur J Appl Physiol 92:204–210.

Ratel S, Duché P, Williams CA (2006a) Muscle fatigue during high-intensity exercise in children. Sports Med 6:1031-65.

Ratel S, Williams CA, Oliver J, Armstrong N (2006b) Effects of age and recovery duration on performance during multiple treadmill sprints. Int J Sports Med 26:1–8.

Ratel S, Blazevich AJ (2017) Are Prepubertal Children Metabolically Comparable to Well-Trained Adult Endurance Athletes? Sports Med 2017 47:1477-85.

Shield A, Zhou S (2004) Assessing voluntary muscle activation with the twitch interpolation technique. Sport Med 34:253–267.

Smith KJ, Billaut F (2010) Influence of cerebral and muscle oxygenation on repeated-sprint ability. Eur J Appl Physiol 109:989–99.

Streckis V, Skurvydas A, Ratkevicius A (2007) Children are more susceptible to central fatigue than adults. Muscle Nerve 36:357–363.

Taylor DJ, Kemp GJ, Thompson CH, Radda GK (1997) Ageing: effects on oxidative function of skeletal muscle in vivo. Mol Cell Biochem 174:321–324.

Taylor JL, Butler JE, Allen GM, Gandevia SC (1996) Changes in motor cortical excitability during human muscle fatigue. J Physiol 490:519–528.

Taylor JL, Butler JE, Gandevia SC (2000) Changes in muscle afferents, motoneurons and motor drive during muscle fatigue. Eur J Appl Physiol 83:106–115.

Taylor JL, Todd G, Gandevia SC (2006) Evidence for a supraspinal contribution to human muscle fatigue. Clin Exp Pharmacol Physiol 33:400–5.

Tonson A, Ratel S, Le Fur Y, Vilmen C, Cozzone PJ, Bendahan D (2010) Muscle energetics changes throughout maturation: a quantitative 31P-MRS analysis. J Appl Physiol 109:1769–1778.

Tucker KJ, Tuncer M, Türker KS (2005) A review of the H-reflex and M-wave in the human triceps surae. Hum Mov Sci 24:667–688.

Waugh CM, Blazevich AJ, Fath F, Korff T (2012) Age-related changes in mechanical properties of the Achilles tendon. J Anat 220:144–155.

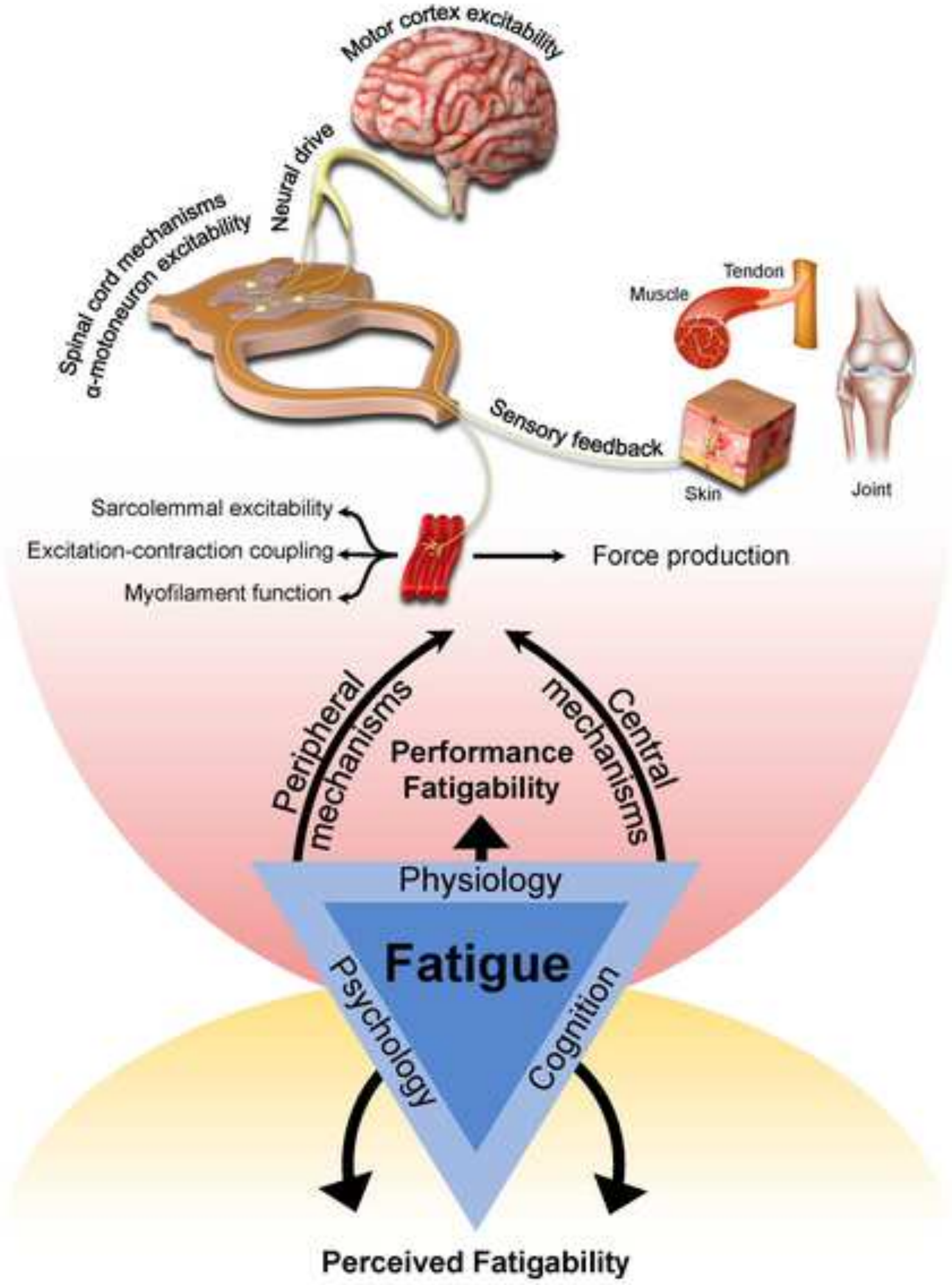
Westerblad H, Lee JA, Lännergren J, Allen DG (1991) Cellular mechanisms of fatigue in skeletal muscle. Am J Med 261:C195–C209.

Williams CA, Ratel S (2009) Human Muscle Fatigue. Routledge, Taylor & Francis Group, London and New York

Zafeiridis A, Dalamitros A, Dipla K, Manou V, Galanis N, Kellis S (2005) Recovery during high-intensity intermittent anaerobic exercise in boys, teens, and men. Med Sci Sports Exerc 37:505–512.

Figure legend

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



Motor cortex excitability
Neural drive
Spinal cord mechanisms
α-motoneuron excitability
Tendon
Muscle
Sensory feedback
Skin
Joint
Sarcolemmal excitability
Excitation-contraction coupling
Myofilament function
Force production
Peripheral mechanisms
Central mechanisms
Performance Fatigability
Physiology
Fatigue
Psychology
Cognition
Perceived Fatigability

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 ± 2.3 Ado: 16.5 ± 0.9	M M	Isometric	Plantar flexors	Ankle: 20°DF Knee: 90°	C: 94.0 ± 11.3 Ado: 99.4 ± 1.8 C < A*
Grosset et al. (2008)	C: 7, 8, 9, 10, 11 A: 21.0 ± 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 ± 1.1 A: 23.9 ± 2.9	M M	Isometric	Knee extensors	Knee: 90°	C: 88 ± 8 A: 94 ± 4 C < A
Kluka et al. (2016)	C: 10.0 ± 1.0 A: 24.6 ± 4.2	M M	Isometric	Plantar flexors	Ankle: 10°DF to 20°PF Knee: 180°	C: 87.6 ± 1.6 A: 92.4 ± 1.7 C < A
Martin et al. (2015)	C: 11.6 ± 0.1 A: 25.6 ± 1.5	M M	Isometric	Adductor pollicis	Thumb: full abduction	C: 85.0 ± 2.7 A: 94.8 ± 1.4 C < A
O’Brien et al. (2009)	C: 8.9 ± 0.7 C: 9.3 ± 0.8 A: 28.2 ± 3.6 A: 27.4 ± 4.2	M F M F	Isometric	Knee extensors	Knee: 90°	C-M: 75.1 ± 12.8 C-F: 66.9 ± 13 A-M: 85.6 ± 8.5 A-F: 86.6 ± 6.6 C-F < A

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

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

Mechanisms	**Factors involved in the development of fatigue**	**References**	**Fatigue protocol**	**Child-Adult comparison**
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	-	-	-

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

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

References	Fatigue test	sEMG	VA	M-wave	Twitch	^{31}P-MRS	HR	VO$_2$	[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									

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

near infra-red spectroscopy; HR: heart rate; VO_2: oxygen consumption and gas exhange; ^{31}P-MRS: ^{31}P-magnetic resonance spectroscopy; [La]: blood lactate concentration; CK: plasma creatine kinase.

Author Contribution Statement

DP, CW and SR wrote the manuscript. All authors read and approved the manuscript.