

1 Performance fatigability is not regulated to a peripheral critical
2 threshold

3

4 Kevin Thomas¹ Stuart Goodall¹ Glyn Howatson^{1,2}

5 ¹Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne,

6 United Kingdom; ²Water Research Group, School of Environmental Sciences and

7 Development, Northwest University, Potchefstroom, South Africa

8

9 **Short title:** Fatigability is task-dependent

10

11 **Address for correspondence:**

12 Dr Kevin Thomas,

13 Faculty of Health and Life Science,

14 Department of Sport, Exercise and Rehabilitation,

15 Northumbria University,

16 Newcastle-upon-Tyne,

17 NE1 8ST,

18 UK.

19 Tel: +44 191 227 4863,

20 Fax: +44 191 227 4713

21 Email: kevin2.thomas@northumbria.ac.uk

22

23 No funding was received for the work. The authors have no conflicts of interest to

24 declare.

25 **ABSTRACT**

26 The *critical threshold hypothesis* proposes that performance fatigability during high-
27 intensity exercise is tightly regulated by negative-feedback signals from the active
28 muscles. We propose that performance fatigability is simply dependent on the
29 exercise mode and intensity; the consequent adjustments, in skeletal muscle and the
30 other physiological systems that support exercise, interact to modulate fatigue and
31 determine exercise tolerance.

32

33 **KEY WORDS**

34 Afferent feedback; cardiovascular; exercise; fatigue; fatigability; muscle; respiratory

35

36 **SUMMARY**

37 The magnitude of performance fatigability observed after high-intensity exercise is
38 task-dependent, and not regulated to a peripheral critical threshold.

39

40 **KEY POINTS**

- 41 • Fatigue is a symptom, or percept, that limits exercise performance in healthy
42 individuals.
- 43 • The *critical threshold hypothesis* emphasizes a critical role for metabolite-
44 mediated afferent discharge in determining exercise tolerance. Specifically,
45 negative-feedback signals from active muscle act to restrain central motor
46 command to limit metabolic perturbation within locomotor muscle, and therefore
47 constrain decrements in the quadriceps potentiated twitch force (a measure of
48 performance fatigability) to a specific, task-dependent level.

49 • We propose that performance fatigability is simply determined by the mode and
50 intensity of the task; these factors dictate the active muscle mass, and demand on
51 other physiological systems. The consequent adjustments interact to modulate
52 fatigue, which determines exercise tolerance.

53 • We review existing correlative and experimental evidence to demonstrate that
54 performance fatigability of skeletal muscle is but one limiting factor in modulating
55 fatigue and exercise tolerance, the importance of which varies with the exercise
56 task.

57

58

59

60

61 INTRODUCTION

62 The study of fatigue and the factors that limit, or regulate, exercise performance has
63 captivated scientists for centuries, but a thorough explanation of the etiology of this
64 condition remains elusive (1, 2). The classic writings of Angelo Mosso (3) identified
65 the two phenomena that characterize fatigue; i) a physical component represented by
66 a diminution of muscular force, and ii) fatigue as a sensation. Over a century later,
67 debate still ensues over our understanding of fatigue, and specifically the sensation of
68 fatigue. Mosso's original description of fatigue was based on the concept of repetitive
69 contractions that induced neuromuscular adjustments in healthy populations that were
70 reversible by rest.. This idea of an organic cause for a perceptual construct remains
71 pertinent for our conceptualization of fatigue in the exercise sciences (4). For the
72 purpose of this review fatigue will be discussed within the taxonomy proposed by
73 Enoka & Duchateau (2). Specifically, fatigue is defined as a symptom or percept,
74 characterized by feelings of tiredness and weakness, in which physical and cognitive
75 function are limited by interactions between performance fatigability and perceived
76 fatigability (2). Performance fatigability refers to the decline in an objective measure
77 of performance; such as the production of maximal voluntary force, the ability to
78 provide an adequate signal to voluntarily activate muscle, or the involuntary twitch
79 response to stimulation (2). Throughout this review, we will use the reduction in the
80 involuntary twitch force in response to motor nerve stimulation as our indicator of
81 performance fatigability. Perceived fatigability refers to the sensations that regulate
82 the integrity of the performer; these sensations can be modulated by disruptions to
83 homeostasis (e.g. core temperature, hydration status, substrate availability) and
84 modifications in psychological state (e.g. arousal, motivation, mood) that contribute
85 to the perception of effort required for the task (2). Performance and perceived

86 fatigability are interdependent, and interact to modulate and determine the symptoms
87 of fatigue. In healthy participants, the physiological adjustments associated with high
88 intensity exercise are strongly associated with perceived fatigability and changes in
89 the rating of perceived exertion (RPE), such that there is a tolerable degree of fatigue
90 the person performing the exercise is willing to experience at any given point during
91 an exercise task. Such a definition is similar to the idea of a sensory tolerance limit
92 (5, 6), but emphasizes the myriad of modulating factors, both physical and
93 psychological, that could contribute to the symptom of fatigue the exerciser is willing
94 to endure at any given point during an exercise challenge.

95

96 The *critical threshold hypothesis* proposes a pivotal role for metabolite-mediated
97 afferent discharge in regulating ‘central motor command’ (defined as the activity of
98 premotor and motor areas of the brain related to voluntary muscle action; 7) during
99 exercise, and thus exercise performance. This hypothesis proposes that adjustments in
100 contractile function are constrained during high-intensity exercise in healthy
101 participants by negative-feedback signals from active muscles. Specifically, exercise-
102 induced alterations of the intramuscular metabolic milieu are proposed to provoke
103 inhibitory input from group III and IV afferents that act to restrain central motor
104 command in order to protect against excessive disruption to muscle homeostasis (8).
105 This hypothesis has been experimentally tested via studying the decline in the
106 electrically or magnetically evoked twitch response to motor nerve stimulation as an
107 indicator of fatigue-related changes in the muscle. A number of studies (e.g. 8, 9, 10-
108 17) have observed an unvarying post-exercise reduction in the involuntary quadriceps
109 potentiated twitch amplitude ($Q_{tw,pot}$, often defined as peripheral fatigue, or locomotor
110 muscle fatigue, but hereafter referred to as performance fatigability) to a range of

111 exercise tasks and experimental interventions, and provided interpretations in support
112 of this concept.

113

114 Recently, the authors of the critical threshold hypothesis revisited the sensory
115 tolerance limit concept proposed by Gandevia (6) to offer a more holistic explanation
116 for understanding the limits to exercise tolerance (5). The sensory tolerance limit
117 concept proposes it is the sum of all neural feedback, feedforward signals, and
118 associated sensations that interact to limit exercise performance. Such an idea is
119 qualitatively similar to the taxonomy proposed by Enoka & Duchateau (2) discussed
120 previously. This notwithstanding, the idea that group III/IV afferent feedback acts to
121 reduce central motor command and the subsequent development of performance
122 fatigability to a specific level remains a key feature of these updated proposals, but
123 with an acknowledgement that the magnitude of adjustments varies between
124 individuals and the exercise task (5).

125

126 The aim of this review is to propose that performance fatigability is not constrained to
127 a task-specific, critical peripheral threshold, but rather simply depends on the muscle
128 mass engaged during the task, and the associated disruption to homeostasis in
129 multiple physiological systems. The muscle mass recruited during exercise is
130 dependent on the intensity and mode of the task; these two critical factors will dictate
131 the magnitude of performance fatigability. Specifically, we propose that for the same
132 mode of exercise, reductions in $Q_{tw,pot}$ will increase with exercise intensity, primarily
133 because a greater proportion of the active musculature will be activated and exhausted
134 as the force requirements of the task increase. Furthermore, we propose the
135 adjustments as the active muscle mass increases during different exercise modes (e.g.

136 single limb < double limb < whole body locomotor) are progressively dictated by the
137 demand placed on maintaining the homeostasis of other competing physiological
138 systems that support exercise (e.g. cardiovascular, respiratory). As a consequence, the
139 magnitude of performance fatigability is lower as other adjustments contribute to the
140 maximum tolerable symptom of fatigue the exerciser is willing to endure. We propose
141 the observation of a consistent magnitude of end-exercise performance fatigability is
142 due to the characteristics of the task, and not a result of regulation to a critical
143 threshold. Disruption to the metabolic milieu of the muscle tissue is but one potential
144 modifier of fatigue, and varies in importance depending on the exercise task. This
145 notwithstanding, the ability of skeletal muscle to meet the demands of exercise is
146 likely to be the primary modulator of fatigue and thus exercise performance, as
147 skeletal muscle will incur greater metabolic stress relative to its maximum capacity
148 in comparison to the cardiac and respiratory muscle systems that support exercise
149 (18). This elegant design feature of the human body ensures that the homeostatic
150 physiological systems responsible for supporting life, do not approach exhaustion
151 during, and continue maintaining homeostatic functions after, exhaustive exercise
152 (18). However, while skeletal muscle will typically be the primary limiter of exercise,
153 the increased demand on cardiac and respiratory muscle systems, particularly at the
154 point of task failure, will still contribute to modulating the symptom of fatigue.
155 Ultimately, we propose it is the percept of fatigue that is regulated during exercise,
156 underpinned by changes in the factors that modulate performance and perceived
157 fatigability, which will vary in their importance depending on the exercise task.
158 These ideas are explicated in this review, alongside a reinterpretation of the
159 correlative and experimental evidence that seemingly supports the critical threshold
160 hypothesis.

161

162 **Performance fatigability and active muscle mass**

163 For the same relative intensity, we propose the magnitude of active muscle mass
164 required for the exercise task will modulate the degree of performance fatigability,
165 because of the consequent challenge to whole-body homeostasis that will contribute
166 to the tolerable magnitude of fatigue. Data from comparisons between modes of
167 exercise within (13, 14), and between studies (9, 19-21) support this idea.

168

169 Rossman *et al.* (13, 14) directly investigated the effect of varying the active muscle
170 mass on the magnitude of end-exercise performance fatigability. In the first of these
171 studies (14), participants voluntarily exercised to the limit of tolerance at 85% of
172 modality-specific maximal intensity in two exercise modes; isoinertial knee
173 extension, and locomotor cycling exercise. The magnitude of performance fatigability
174 was higher after knee extensor exercise when the active muscle mass was small,
175 compared to cycling exercise when the active muscle mass was larger (-53 ± 2 vs.
176 $-34 \pm 2\%$ reduction in $Q_{tw,pot}$, respectively). The same authors subsequently
177 confirmed these observations studying single-leg knee extension exercise compared to
178 double-leg knee extension exercise, thereby circumventing the potential confounding
179 factor of mode-specific exercise responses (13). Specifically, participants completed
180 single-leg and double-leg knee extension exercise to their self-determined limit of
181 tolerance at the same relative modality-specific exercise intensity. The magnitude of
182 performance fatigability was higher after single leg knee extension exercise ($-44 \pm$
183 6%) compared to double-leg knee extension exercise ($-33 \pm 7\%$). In both studies the
184 higher active muscle mass was also concurrent with higher cardiorespiratory
185 responses (13, 14), and in the second of these studies, the increase in the *vastus*

186 *lateralis* integrated electromyogram signal (iEMG) from the first to the last minute of
187 exercise, was higher during single-leg compared to double-leg exercise (147 ± 24 vs.
188 $85 \pm 15\%$) indicative of a progressively greater recruitment of additional muscle mass
189 during the single-leg trial. These data demonstrate that when the active muscle mass
190 is smaller, a greater proportion of the available musculature is engaged during the
191 task, and the demand on other physiological systems is lower. In concert, these factors
192 lead to a greater post-exercise reduction in $Q_{tw,pot}$, as the exerciser can tolerate greater
193 local muscular stress before the perception of effort becomes excessive.

194

195 Further comparisons between exercise modes also illustrates how the active muscle
196 mass modulates performance fatigability. For high intensity cycling exercise (80-90%
197 of peak intensity measured during an incremental test to the limit of tolerance, usually
198 abbreviated as P_{max}) numerous research groups, including our own, have shown a
199 relatively consistent post-exercise reduction in potentiated twitch force of
200 approximately 35% (8, 9, 19, 20, 22). When the task requires a smaller active muscle
201 mass, the absolute reduction in twitch force after exhaustive exercise is higher. For
202 example, we observed a reduction in $Q_{tw,pot}$ of $60 \pm 13\%$ after 3×30 s MVCs (23),
203 and as previously demonstrated Rossman *et al.* (13, 14) reported absolute reductions
204 in $Q_{tw,pot}$ of 44% and 53% after single limb knee extension exercise. Conversely,
205 during running exercise, when the active skeletal muscle mass is increased, the
206 absolute decline in potentiated twitch is lower; even for maximal repeated sprint
207 exercise ($-24 \pm 9\%$; 21). Finally, prior high-intensity arm cycling reduces exercise
208 tolerance during leg cycling, and the worsened leg cycling exercise performance is
209 associated with a lower reduction in $Q_{tw,pot}$ ($-38 \pm 13\%$ vs. $-26 \pm 10\%$; 19). This last
210 finding underlines the effect that engaging a higher active muscle mass has on

211 modulating fatigue. Even though the upper limbs do not directly contribute to cycling
212 exercise, the higher sensory input from engaging and exhausting a greater volume of
213 skeletal muscle was proposed to limit subsequent cycling performance and constrain
214 performance of the locomotor muscles because the maximum tolerable degree of
215 fatigue the exerciser was willing to endure was reached more rapidly (19). Figure 1
216 provides a simplified summary of our proposal that the active muscle mass modulates
217 the maximum tolerable symptom of fatigue, and the magnitude of performance
218 fatigability. Specifically, as the active muscle mass increases, the degree of
219 performance fatigability is lower as the sensory input from a larger muscle mass and
220 greater disruption to homeostasis in other physiological systems (e.g cardiovascular,
221 respiratory) increases; ultimately these adjustments summate to collectively modulate
222 the symptom of fatigue the exerciser experiences

223

224 Rossman *et al.* (13, 14) acknowledged the task-specificity of performance fatigability,
225 and proposed that a reduction in the exercising muscle mass permits the development
226 of greater performance fatigability because of a reduction in the source of group
227 III/IV afferent feedback to a more local, and less diffuse, signal. Central to this
228 interpretation remains the idea that feedback from group III/IV afferents act to inhibit
229 central motor command to skeletal muscle to restrict the development of performance
230 fatigability to a specific critical level. While conceptually similar, we propose that the
231 higher magnitude of performance fatigability observed after single compared to
232 double leg exercise is not tightly regulated to a task-specific level, but rather is simply
233 a consequence of a greater recruitment and subsequent stress of a greater volume of
234 skeletal muscle. The smaller active muscle mass (both involved and non-involved
235 skeletal muscle), and lower activation of cardiac and respiratory muscle systems

236 affords a greater mass-specific blood flow to the exercising muscle (24), and a
237 progressively greater recruitment of additional muscle fibers (17). This smaller active
238 muscle mass permits the exerciser to endure greater perturbations to contractile
239 function as the threat to homeostasis is predominantly restricted to a single muscle
240 group, and as such a larger magnitude of performance fatigability can be incurred
241 before the fatigue elicited by the task is perceived as intolerable. As previously
242 described, it is the symptom of fatigue that is the likely “regulated” variable
243 determining exercise tolerance, modulated by interactions between the factors that
244 underpin performance and perceived fatigability.

245

246 **Performance fatigability and exercise intensity**

247 The active muscle mass engaged during exercise interacts with exercise intensity (and
248 consequent duration) to determine the magnitude of performance fatigability. Before
249 any discussion of the importance of exercise intensity in determining performance
250 fatigability, consideration of the well-established intensity-duration relationship
251 characteristic of exercise performance is necessary. Briefly, the peak intensity of any
252 mode of activity declines as the duration of the task increases. The relationship
253 between intensity and duration can be described by a hyperbolic function with two
254 key features; i) the intensity asymptote of the intensity-time hyperbola corresponds to
255 a maximum sustainable intensity (the critical intensity, CI) and ii) the curvature
256 constant of the hyperbola denotes a finite amount of work that can be performed
257 above CI, termed W' (25). The CI denotes the boundary between the “heavy” and
258 “severe” exercise intensity domains. Sustained activity above CI, in the severe
259 domain, elicits perturbations to intramuscular homeostasis that ultimately result in
260 task failure. Exercise below CI is theoretically fatigue-free, though in reality this

261 prediction is not correct (26). The performance and physiological characteristics of
262 the intensity-duration relationship are critical to consider when discussing any
263 integrated model of fatigue. For the most part, we will discuss data from exercise
264 tasks completed to the limit of tolerance at intensities above the CI.

265

266 Within the same exercise mode, the intensity of the task can modulate the level of
267 performance fatigability such that increases in intensity result in greater reductions in
268 $Q_{tw,pot}$ (20, 22). However, the effect of intensity on performance fatigability is
269 negligible when the active muscle mass is small, the intensity is above CI, and the
270 relative demand on other modulators of fatigue is minimized (17). When the active
271 muscle mass is higher, (such as during whole body locomotor exercise), the exercise
272 intensity will influence performance fatigability; higher exercise intensities result in a
273 greater recruitment and subsequent adjustment of the active musculature, and a
274 greater reduction in potentiated twitch. These proposals are explained below.

275

276 During locomotor exercise (cycling and running) to volitional exhaustion, the degree
277 of performance fatigability is modulated by exercise intensity. Specifically, data from
278 our laboratory showed the reduction in $Q_{tw,pot}$ is exacerbated with increased exercise
279 intensity (20, 22). For example, during constant-load cycling at relative intensities of
280 100%, 76% and 64% of P_{max} , we observed physiological responses consistent with
281 exercise above CI in the severe domain, and post-exercise reductions in potentiated
282 twitch force of -33%, -16% and -11%, respectively (20). Additionally, the greatest
283 reductions (>50%) observed in potentiated twitch after cycling exercise have been
284 reported after repeated sprint cycling exercise, which theoretically offers a model
285 where exercise intensity is “all-out” or maximal (15, 16). The same pattern has also

286 been observed in running exercise; reductions in potentiated twitch after repeated
287 sprint running (-24%; 21) are higher than after 90 min of intermittent exercise
288 (-14%; 27), and after marathon running, where no significant decline in $Q_{tw,pot}$ has
289 been observed (28). In all of these studies there was a short time delay (typically 1-2
290 min) between the cessation of exercise and the measurement of performance
291 fatigability that could potentially confound comparisons both within- and between-
292 studies (29). However, even with this confound, the magnitude of difference observed
293 both between- and within-studies supports the supposition that locomotor exercise-
294 induced performance fatigability (measured by reductions in $Q_{tw,pot}$) is exacerbated
295 with increasing exercise intensity.

296

297 In contrast to whole body cycling exercise, the magnitude of performance fatigability
298 after exhaustive single limb exercise above CI is unvarying (17). Additionally,
299 magnetic resonance spectroscopy studies show a similar post-exercise metabolic
300 derangement after exhaustive single-limb exercise at different intensities above CI
301 (30), although these metabolic responses have previously been dissociated from
302 measurements of performance fatigability (31). Whilst these observations contradict
303 the proposal that exercise intensity can modulate the degree of performance
304 fatigability, they can be explained by the interactive effect of exercising with a small
305 active muscle mass. Specifically, when the active muscle mass is smaller there is a
306 lower demand on maintaining homeostasis in other physiological systems. As such,
307 the exerciser is able to tolerate a higher magnitude of performance fatigability specific
308 to reductions in contractile function before the maximum tolerable symptom of
309 fatigue is attained. The reader is referred back to Figure 1 for a graphical illustration
310 of this concept; during single-limb exercise the stress to other modulating factors is

311 minimized, such that a greater (perhaps maximum volitional) magnitude of
312 performance fatigability can be attained before the symptom of fatigue becomes
313 intolerable. This premise explains why exercise intensity modulates performance
314 fatigability after exhaustive exercise above CI in locomotor, but not single-limb
315 exercise modes.

316

317 **Challenges to the model; afferent blockade.**

318 Thus far our proposal has been based on correlative evidence, and observations
319 between studies. The strongest challenge to the idea that performance fatigability is
320 task-dependent and not regulated to a critical threshold is provided by experimental
321 studies that used an intrathecal opioid analgesic (fentanyl) to attenuate the activity of
322 group III/IV afferent feedback during exercise. These elegant studies have
323 consistently demonstrated that, when group III/IV afferent feedback is blocked by
324 fentanyl, participants voluntarily incur a higher degree of performance fatigability (8,
325 9, 32). The subsequent interpretation of these observations emphasize the decisive
326 role that group III/IV feedback from exercising skeletal muscle plays in determining
327 exercise tolerance, via sensory input that mediates central motor command during
328 exercise to constrain the development of performance fatigability to a specific,
329 unvarying, task-dependent level.

330

331 Although seemingly in opposition to our proposal, a reinterpretation of the data from
332 these studies provides support to the idea that the magnitude of performance
333 fatigability is dependent on the active muscle mass engaged, and disruption to
334 homeostasis in multiple physiological systems, which collectively combine to
335 modulate the symptom of fatigue and thus determine exercise tolerance. In addition to

336 attenuating the activity of group III/IV afferents, the administration of fentanyl also
337 compromises the exercise pressor reflex, which results in an attenuation of the
338 cardiopulmonary response to exercise (33). Consequently, the disruption to these
339 physiological systems, and the demand for cardiac and respiratory muscle work, is
340 attenuated, which theoretically reduces their input to modulating the symptom of
341 fatigue (see Figure 4, Amann et al., 2009 (8), and Figure 3, Amann et al., 2011 (9)).
342 We contend this enables the exerciser to recruit and exhaust a greater volume of the
343 knee extensor musculature during the task for the same symptom of fatigue because
344 there is less sensory input from, and/or demand on, the respiratory and cardiovascular
345 systems, not because there is a compromised regulation to a critical threshold. In
346 support of this proposal, the attenuated cardiovascular and respiratory response
347 observed in these studies was concurrent with a greater recruitment of the knee
348 extensor musculature during the cycling bout (see Figure 2, Amann et al., 2009 (8),
349 and Figure 2, Amann et al., 2011, (9)) when group III/IV afferent feedback was
350 blocked. Estimates of muscle activation via surface EMG are subject to a number of
351 valid critiques (34-36), particularly a lack of sensitivity in detecting small differences
352 in exercise intensity. Considering this, it is perhaps particularly striking that
353 participants had a consistently higher surface EMG after fentanyl administration even
354 though they were cycling at the same absolute intensity (9). Figure 2 illustrates this
355 alternative reinterpretation; in panel A, the symptom of fatigue is modulated to a
356 greater extent by adjustments in cardiovascular and respiratory systems, probably
357 mediated primarily by the stress to cardiac and respiratory muscle. This sensory input
358 indirectly limits the adjustments in contractile function by providing a greater
359 contribution to the tolerable fatigue the exerciser is willing to endure. Panel B
360 illustrates how these inputs change when group III/IV afferent feedback is blocked;

361 the relative input of cardiopulmonary adjustments to modulating fatigue is reduced,
362 which permits the exerciser to stress a greater degree of the locomotor skeletal muscle
363 before the maximum tolerable perception of fatigue is attained. These data also
364 demonstrate that, although skeletal muscle is the ultimate “limiter” of exercise
365 performance, disruption to other physiological systems can modulate the symptom of
366 fatigue even if such disruptions are submaximal relative to the higher capacity of
367 these systems (18).

368

369 **Does group III/IV afferent feedback from skeletal muscle contribute to fatigue?**

370 The activity of group III/IV afferent feedback from exercising skeletal muscle clearly
371 contributes to the optimal regulation of exercise by instigating adjustments in multiple
372 physiological systems in response to the homeostatic threat that exercise might
373 impose (33, 37). Without such feedback, exercise regulation is almost certainly
374 compromised, at least for high-intensity locomotor exercise lasting < 10 min (8, 9,
375 32). Indeed, Amann *et al.* (8, 9) clearly demonstrated that when such feedback is
376 blocked participants self-select exercise intensities and/or inappropriate recruitment
377 strategies that result in significant additional performance fatigability in comparison
378 to a control, with no improvement in exercise performance. These data clearly support
379 the idea that group III/IV afferent feedback is important for the regulation of exercise,
380 at least indirectly.

381

382 The critical threshold hypothesis proposes that metabolite-mediated, non-nociceptive
383 feedback also acts directly, in a negative feedback loop, on the central nervous system
384 to restrain central motor command to limit reductions in contractile function to a
385 specific level (7). In this review we have argued that adjustments in skeletal muscle as

386 a consequence of exhaustive exercise are intensity- and mode-dependent, and not
387 regulated to a critical threshold. Additionally, it is questionable whether non-
388 nociceptive group III/IV afferent feedback from skeletal muscle has any impact
389 beyond the appropriate stimulation of the exercise pressor reflex. The potential
390 modulating role of nociceptive (i.e. pain-related) discharge of group III/IV afferents
391 on the recovery of muscle force and voluntary activation has been demonstrated using
392 models of post-exercise circulatory occlusion (38-42), however whether non-
393 nociceptive afferents act on the CNS is debatable (43-45). In this review we have
394 conceptualized that disruptions to multiple physiological systems (including skeletal
395 muscle) combine to modulate the symptom of fatigue via sensory “input”, but the
396 relative importance of such “inputs” is open to debate. Indeed, the neurophysiological
397 basis of fatigue, and the extent to which afferent feedback determines endurance
398 exercise performance remains the subject of fervent debate (44-48). Some theorists
399 propose the fatigue experienced during exercise is mediated primarily by the
400 integration of multiple afferent sensory inputs (49), whereas opponents cite the
401 processing of corollary discharge from premotor/motor areas as the primary factor
402 mediating the perception of effort experienced during exercise (50). A limitation
403 within these debates is the concept of the RPE as a measure of fatigue is not described
404 in detail to afford a valid comparison between studies (51). A detailed discussion is
405 beyond the scope of the current review. Regardless of whether the fatigue experienced
406 during exercise can be explained by afferent or efferent mechanisms, understanding
407 the significance of different adjustments (both physiological and psychological) that
408 contribute to fatigue, how these vary with the exercise task, and how the tolerance of
409 fatigue can be modulated by intervention remain key questions for our understanding
410 of human performance (2).

411

412 **CONCLUSION**

413 The critical threshold hypothesis proposes that group III/IV afferent feedback from
414 skeletal muscle acts directly on the central nervous system to restrain central motor
415 command and limit performance fatigability to a specific, unvarying level. Here we
416 propose the reduction in skeletal muscle contractile function observed after exercise is
417 task-dependent, and determined primarily by the active muscle mass engaged in the
418 exercise bout, the exercise intensity, and the associated disruption to whole body
419 homeostasis. When the active muscle mass is small, greater reductions in contractile
420 function specific to the exercising muscle can be tolerated before fatigue becomes
421 intolerable as the sensory input is confined to a small muscle mass, and disruptions to
422 other physiological systems are smaller. When the active muscle mass is increased,
423 the demands placed on a larger skeletal muscle mass, and the extra disruption to
424 homeostasis in the physiological systems that support exercise, combine and summate
425 to modulate the symptom of fatigue. Consequently, the tolerable level of fatigue the
426 exerciser is willing to endure is mediated less by adjustments in the involved skeletal
427 muscle, as other adjustments in whole body homeostasis contribute to the perception
428 of fatigue. For locomotor exercise the intensity of the task also modulates the
429 magnitude of performance fatigability, as higher exercise intensities will result in the
430 recruitment and subsequent stress of a greater volume of skeletal muscle. This
431 explains why performance fatigability is: i) exacerbated with greater exercise
432 intensity during locomotor exercise, ii) larger at termination of single-limb exercise
433 than double-limb exercise, and locomotor cycling compared with running exercise,
434 iii) is consistent between trials of the same exercise task, and iv) is altered in
435 conditions of “blocked” afferent feedback when the subsequent force or muscle

436 activation strategies are also altered. The hypothesis put forth in this review provides
437 a plausible alternative interpretation to the idea of a critical threshold, and further
438 experimental work to test this hypothesis is warranted.

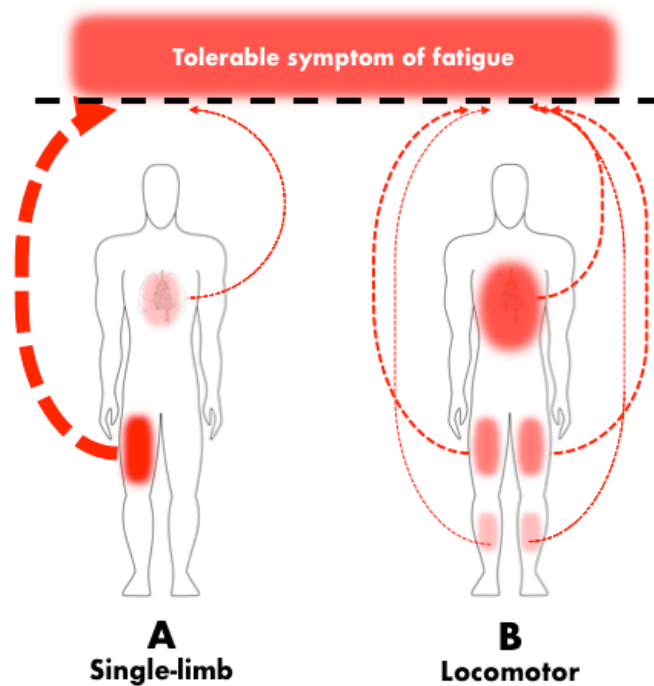
439

440

441

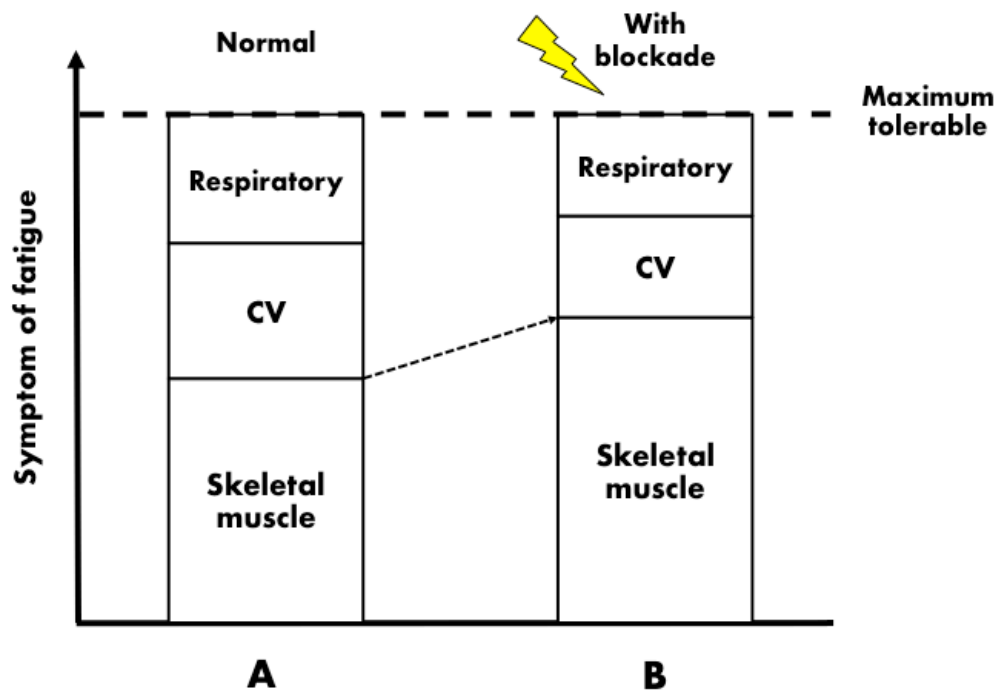
442

443



445

446 **Figure 1.** Simplified illustration of how the active muscle mass required of the
 447 exercise task modulates the symptom of fatigue. In picture A, when a single muscle
 448 group is exercised to the limit of tolerance, a strong, local disruption to the small
 449 muscle mass involved in the task is the primary contributor to the symptom of fatigue
 450 (represented by the thick arrow). In contrast, when the active muscle mass is
 451 increased (picture B), the demands placed on i) a larger skeletal muscle mass (both
 452 involved and non-involved), and ii) the disruption to homeostasis in other
 453 physiological systems (cardiovascular, respiratory), all contribute to modulating the
 454 symptom of fatigue (represented by a number of thin arrows). As a consequence, the
 455 magnitude of performance fatigability, measured by reductions in the involuntary
 456 potentiated twitch response to external stimulation, is reduced in the involved, active
 457 musculature as other adjustments combine to modulate the symptom of fatigue.



458

459 **Figure 2.** Simplified schematic to demonstrate how potential modulators of the
 460 symptom of fatigue are affected by afferent blockade. The compromised exercise
 461 pressor response caused by administration of fentanyl precipitates a reduction in
 462 cardiovascular (CV) and respiratory responses to exercise, and the subsequent work
 463 of cardiac and respiratory muscle is reduced. The reduction in sensory input from
 464 these systems allows the exerciser to incur greater reductions in skeletal muscle
 465 contractile function before the maximum tolerable symptom of fatigue, which in
 466 healthy individuals is strongly associated with the perception of effort, (represented
 467 by the dashed line) is attained.

468

469

470

471 **References**

- 472 1. Marino FE, Gard M, Drinkwater EJ. The limits to exercise performance and
473 the future of fatigue research. *Br J Sports Med.* 2011;45(1):65-7.
- 474 2. Enoka RM, Duchateau J. Translating Fatigue to Human Performance. *Med*
475 *Sci Sports Exerc.* 2016;48(11):2228-38.
- 476 3. Mosso A. *Fatigue.* Translated by Drummond. Putnam's; 1904. p. 154.
- 477 4. Kuppuswamy A. The fatigue conundrum. *Brain.* 2017;140(8):2240-5.
- 478 5. Hureau TJ, Romer LM, Amann M. The 'sensory tolerance limit': A
479 hypothetical construct determining exercise performance? *Eur J Sport Sci.*
480 2016:1-12.
- 481 6. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue.
482 *Physiol Rev.* 2001;81(4):1725-89.
- 483 7. Morree HM, Klein C, Marcora SM. Perception of effort reflects central
484 motor command during movement execution. *Psychophysiology.*
485 2012;49(9):1242-53.
- 486 8. Amann M, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA. Opioid-
487 mediated muscle afferents inhibit central motor drive and limit peripheral
488 muscle fatigue development in humans. *J Physiol.* 2009;587(Pt 1):271-83.
- 489 9. Amann M, Blain GM, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA.
490 Implications of group III and IV muscle afferents for high-intensity endurance
491 exercise performance in humans. *J Physiol.* 2011;589(Pt 21):5299-309.
- 492 10. Amann M, Dempsey JA. Locomotor muscle fatigue modifies central motor
493 drive in healthy humans and imposes a limitation to exercise performance. *J*
494 *Physiol.* 2008;586(1):161-73.
- 495 11. Amann M, Eldridge MW, Lovering AT, Stickland MK, Pegelow DF,
496 Dempsey JA. Arterial oxygenation influences central motor output and exercise
497 performance via effects on peripheral locomotor muscle fatigue in humans. *J*
498 *Physiol.* 2006;575(Pt 3):937-52.
- 499 12. Amann M, Venturelli M, Ives SJ, McDaniel J, Layec G, Rossman MJ, et al.
500 Peripheral fatigue limits endurance exercise via a sensory feedback-mediated
501 reduction in spinal motoneuronal output. *J Appl Physiol.* 2013;115(3):355-64.
- 502 13. Rossman MJ, Garten RS, Venturelli M, Amann M, Richardson RS. The role
503 of active muscle mass in determining the magnitude of peripheral fatigue during
504 dynamic exercise. *Am J Physiol.* 2014;306(12):R394-40.
- 505 14. Rossman MJ, Venturelli M, McDaniel J, Amann M, Richardson RS. Muscle
506 mass and peripheral fatigue: a potential role for afferent feedback? *Acta Physiol.*
507 2012;206(4):242-50.
- 508 15. Hureau TJ, Ducrocq GP, Blain GM. Peripheral and Central Fatigue
509 Development during All-Out Repeated Cycling Sprints. *Med Sci Sports Exerc.*
510 2016;48(3):391-401.
- 511 16. Hureau TJ, Olivier N, Millet GY, Meste O, Blain GM. Exercise performance
512 is regulated during repeated sprints to limit the development of peripheral
513 fatigue beyond a critical threshold. *Exp Physiol.* 2014;99(7):951-63.
- 514 17. Burnley M, Vanhatalo A, Jones AM. Distinct profiles of neuromuscular
515 fatigue during muscle contractions below and above the critical torque in
516 humans. *J Appl Physiol.* 2012;113(2):215-23.
- 517 18. Walsh ML. Whole body fatigue and critical power: a physiological
518 interpretation. *Sports Med.* 2000;29(3):153-66.

- 519 19. Johnson MA, Sharpe GR, Williams NC, Hannah R. Locomotor muscle
520 fatigue is not critically regulated after prior upper body exercise. *J Appl Physiol*
521 (1985). 2015;119(7):840-50.
- 522 20. Thomas K, Elmeua M, Howatson G, Goodall S. Intensity-Dependent
523 Contribution of Neuromuscular Fatigue after Constant-Load Cycling. *Med Sci*
524 *Sports Exerc.* 2016;48(9):1751-60.
- 525 21. Goodall S, Charlton K, Howatson G, Thomas K. Neuromuscular fatigability
526 during repeated-sprint exercise in male athletes. *Med Sci Sports Exerc.*
527 2015;47(3):528-36.
- 528 22. Thomas K, Goodall S, Stone M, Howatson G, St Clair Gibson A, Ansley L.
529 Central and peripheral fatigue in male cyclists after 4-, 20-, and 40-km time
530 trials. *Med Sci Sports Exerc.* 2015;47(3):537-46.
- 531 23. Goodall S, Howatson G, Thomas K. Modulation of specific inhibitory
532 networks in fatigued locomotor muscles of healthy males. *Exp Brain Res.*
533 2018;236(2):463-73.
- 534 24. Bassett DR, Jr., Howley ET. Limiting factors for maximum oxygen uptake
535 and determinants of endurance performance. *Med Sci Sports Exerc.*
536 2000;32(1):70-84.
- 537 25. Burnley M, Jones AM. Power-duration relationship: Physiology, fatigue,
538 and the limits of human performance. *Eur J Sport Sci.* 2016:1-12.
- 539 26. Jones AM, Wilkerson DP, DiMenna F, Fulford J, Poole DC. Muscle metabolic
540 responses to exercise above and below the "critical power" assessed using ^{31}P -
541 MRS. *Am J Physiol.* 2008;294(2):R585-93.
- 542 27. Thomas K, Dent J, Howatson G, Goodall S. Etiology and Recovery of
543 Neuromuscular Fatigue after Simulated Soccer Match Play. *Med Sci Sports Exerc.*
544 2017;49(5):955-64.
- 545 28. Ross EZ, Middleton N, Shave R, George K, Nowicky A. Corticomotor
546 excitability contributes to neuromuscular fatigue following marathon running in
547 man. *Exp Physiol.* 2007;92(2):417-26.
- 548 29. Froyd C, Millet GY, Noakes TD. The development of peripheral fatigue and
549 short-term recovery during self-paced high-intensity exercise. *J Physiol.*
550 2013;591(5):1339-46.
- 551 30. Burnley M, Vanhatalo A, Fulford J, Jones AM. Similar metabolic
552 perturbations during all-out and constant force exhaustive exercise in humans: a
553 (^{31}P) magnetic resonance spectroscopy study. *Exp Physiol.* 2010;95(7):798-807.
- 554 31. Saugen E, Vollestad NK, Gibson H, Martin PA, Edwards RH. Dissociation
555 between metabolic and contractile responses during intermittent isometric
556 exercise in man. *Exp Physiol.* 1997;82(1):213-26.
- 557 32. Blain GM, Mangum TS, Sidhu SK, Weavil JC, Hureau TJ, Jessop JE, et al.
558 Group III/IV muscle afferents limit the intramuscular metabolic perturbation
559 during whole body exercise in humans. *J Physiol.* 2016;594(18):5303-15.
- 560 33. Kaufman MP, Hayes SG. The exercise pressor reflex. *Clin Auton Res.*
561 2002;12(6):429-39.
- 562 34. Farina D, Merletti R, Enoka RM. The extraction of neural strategies from
563 the surface EMG. *J Appl Physiol.* 2004;96(4):1486-95.
- 564 35. Keenan KG, Farina D, Merletti R, Enoka RM. Amplitude cancellation
565 reduces the size of motor unit potentials averaged from the surface EMG. *J Appl*
566 *Physiol.* 2006;100(6):1928-37.

- 567 36. Del Vecchio A, Negro F, Felici F, Farina D. Associations between motor
568 unit action potential parameters and surface EMG features. *J Appl Physiol*
569 (1985). 2017;123(4):835-43.
- 570 37. McCloskey DI, Mitchell JH. Reflex cardiovascular and respiratory
571 responses originating in exercising muscle. *J Physiol*. 1972;224(1):173-86.
- 572 38. Bigland-Ritchie BR, Dawson NJ, Johansson RS, Lippold OC. Reflex origin
573 for the slowing of motoneurone firing rates in fatigue of human voluntary
574 contractions. *J Physiol*. 1986;379:451-9.
- 575 39. Kennedy DS, Fitzpatrick SC, Gandevia SC, Taylor JL. Fatigue-related firing
576 of muscle nociceptors reduces voluntary activation of ipsilateral but not
577 contralateral lower limb muscles. *J Appl Physiol* (1985). 2015;118(4):408-18.
- 578 40. Kennedy DS, McNeil CJ, Gandevia SC, Taylor JL. Fatigue-related firing of
579 distal muscle nociceptors reduces voluntary activation of proximal muscles of
580 the same limb. *J Appl Physiol* (1985). 2014;116(4):385-94.
- 581 41. Gandevia SC, Macefield G, Burke D, McKenzie DK. Voluntary activation of
582 human motor axons in the absence of muscle afferent feedback. The control of
583 the deafferented hand. *Brain*. 1990;113 (Pt 5):1563-81.
- 584 42. Gandevia SC, Allen GM, Butler JE, Taylor JL. Supraspinal factors in human
585 muscle fatigue: evidence for suboptimal output from the motor cortex. *J Physiol*.
586 1996;490(2):529-36.
- 587 43. Jankowski MP, Rau KK, Ekmann KM, Anderson CE, Koerber HR.
588 Comprehensive phenotyping of group III and IV muscle afferents in mouse. *J*
589 *Neurophysiol*. 2013;109(9):2374-81.
- 590 44. Marcora S. Counterpoint: Afferent feedback from fatigued locomotor
591 muscles is not an important determinant of endurance exercise performance. *J*
592 *Appl Physiol*. 2010;108(2):454-6; discussion 6-7.
- 593 45. Amann M, Secher NH. Point: Afferent feedback from fatigued locomotor
594 muscles is an important determinant of endurance exercise performance. *J Appl*
595 *Physiol*. 2010;108(2):452-4.
- 596 46. Marcora S. Is peripheral locomotor muscle fatigue during endurance
597 exercise a variable carefully regulated by a negative feedback system? *J Physiol*.
598 2008;586(7):2027-8; author reply 9-30.
- 599 47. Marcora SM. Viewpoint: Fatigue mechanisms determining exercise
600 performance: integrative physiology is systems physiology. *J Appl Physiol*.
601 2008;104(5):1543.
- 602 48. Burnley M. The limit to exercise tolerance in humans: validity
603 compromised by failing to account for the power-velocity relationship. *Eur J*
604 *Appl Physiol*. 2010;109(6):1225-6.
- 605 49. Gibson AS, Swart J, Tucker R. The interaction of psychological and
606 physiological homeostatic drives and role of general control principles in the
607 regulation of physiological systems, exercise and the fatigue process - The
608 Integrative Governor theory. *Eur J Sport Sci*. 2018;18(1):25-36.
- 609 50. Marcora SM. Do we really need a central governor to explain brain
610 regulation of exercise performance? *Eur J Appl Physiol*. 2008;104(5):929-31;
611 author reply 33-5.
- 612 51. Abbiss CR, Peiffer JJ, Meeusen R, Skorski S. Role of Ratings of Perceived
613 Exertion during Self-Paced Exercise: What are We Actually Measuring? *Sports*
614 *Med*. 2015;45(9):1235-43.
- 615