International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: informahealthcare.com/journals/ihyt20

Heat reactions in multiple sclerosis: An overlooked paradigm in the study of comparative fatigue

Frank E. Marino

To cite this article: Frank E. Marino (2009) Heat reactions in multiple sclerosis: An overlooked paradigm in the study of comparative fatigue, International Journal of Hyperthermia, 25:1, 34-40, DOI: 10.1080/02656730802294020

To link to this article: https://doi.org/10.1080/02656730802294020

Int. J. Hyperthermia, February 2009; 25(1): 34–40

informa
healthcare

Heat reactions in multiple sclerosis: An overlooked paradigm in the study of comparative fatigue

FRANK E. MARINO

School of Human Movement Studies & Exercise & Sports Science Laboratories, Charles Sturt University, Bathurst, New South Wales, Australia

(Received 30 April 2008; Revised 31 May 2008; Accepted 22 June 2008)

Abstract
Multiple sclerosis (MS) is a demyelinating and debilitating disease characterised by a range of symptoms such as motor dysfunction and muscle weakness. A significant MS symptom is heat sensitivity so that exposure to heat will increase body temperature and consequently the appearance of neurological signs. Although some people with MS can undertake exercise, it is thought to be limited by the sensitivity to heat and the subsequent rise in body temperature which occurs. It has been found that central fatigue is a determining factor in muscle activation and performance in normal healthy subjects. However, it is unknown whether thermal strain also induces central fatigue in MS even though muscular fatigue in MS is due mainly to central rather than peripheral factors. This review focuses on the similarities in the manifestation of central fatigue in both MS and healthy subjects with reference to thermal strain and heat reactions.

Keywords: *Central activation, fatigue, heat reactions, multiple sclerosis, thermoregulation, effort sense*

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease which affects about 2.5 million people worldwide and is more prevalent in women than in men by ~2:1 (http://www.msaustralia.org.au/msinformation/faqs.htm#2). The disease is characterised by axonal loss and demyelination and as a consequence is debilitating so that a range of symptoms including motor dysfunction and muscle weakness are typically experienced [1, 2]. These symptoms can also include depression, spastic paresis, poor balance, ventilatory muscle weakness and elimination dysfunction [3]. However, a particular symptom which seems to be a predominant outcome of the disease is excessive fatigue [4, 5]. Excessive fatigue is a significant problem as it reduces the time that people with MS can spend on activities of daily living and consequently the opportunities, enjoyment and health benefits which can be derived from long term employment and recreational pursuits.

A further outcome of symptomatic fatigue in MS is the potential development of secondary conditions such as cardiovascular disease and obesity [6, 7]. The positive effects of exercise as an intervention in these secondary diseases in a range of populations is well documented and indeed arguably overwhelming [8]. The effect of exercise as a therapy has not been systematically studied in patients with MS compared to healthy people or to other conditions; although a recent review on this topic highlights the benefits of the therapeutic role of exercise in the MS treatment plan [3]. Studies have shown positive benefits of exercise in people with MS in addition to a reduction in the incidence of secondary diseases and maintenance of better functional independence [9–11].

A positive outcome of prescribed exercise in healthy people is increased tolerance to symptoms of fatigue [12]. However, in MS an increased tolerance to fatigue is much more difficult to ascertain for several reasons. First, because the disease is characterised by demyelination and

Correspondence: Frank E. Marino, Head, School of Human Movement Studies & Exercise & Sports Science Laboratories, Charles Sturt University, Bathurst, NSW 2795, Australia. Tel: 61 2 6338 4268. Fax: 61 2 6338 4065. E-mail: fmarino@csu.edu.au

ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.1080/02656730802294020

subsequent slowing of axonal conduction velocity, gait and balance is disturbed which inhibits the ability to undertake sustained activities, making it difficult to distinguish between the ability to complete a task due to compromised sustained coordination or whether specific symptomatic fatigue itself is the predominant cause. Second, in MS there is muscle atrophy due to reduced physical activity and so relative premature fatigue is expected. This is a circular effect as changes in the physical structure of affected axons gives rise to gait and balance changes and muscle atrophy so it is unclear which of these is the predominant cause in the development of premature fatigue. Third, physical and chemical changes in the axonal characteristics are primarily peripheral in nature and thus cannot fully explain findings which show overwhelmingly a definitive central component of fatigue in this disease [13, 14]. Fourth, physical activity provides an avenue for increased body heat which in individuals with MS apparently reduces functionality and is known to hasten fatigue [15]. This is an interesting and most salient observation as increased thermal strain has also been shown to hasten fatigue in healthy individuals [16, 17]. Recent evidence indicates that increased thermoregulatory strain either through exercise or through passively induced rises in body temperature, reduces central drive [18, 19]. However, this mechanism of heat-strain induced fatigue has not been explored as a possible cause of premature fatigue in MS.

Therefore, the purpose of this review is to draw together the findings which describe fatigue in both MS and healthy individuals and explore the basis on which heat sensitivity in MS might contribute to premature fatigue either through passively induced rises in body temperature or through exercise. A further purpose is to review the common methods used to measure and evaluate peripheral and central fatigue and establish an experimental paradigm which could be used to determine the relationship between heat sensitivity and the development of premature fatigue in MS.

Heat reactions (HR) in multiple sclerosis

Heat sensitivity or heat reactions (HR) in MS can be traced back to the reports of Uhthoff (1890) describing changes in visual acuity during heating. The interesting observation which seems to have escaped scrutiny is that Uhtoff found changes in visual acuity, colour perception, and other neurological signs specifically following exercise and thus concluded that an exercise-induced increase in body temperature was the primary cause for these neurological signs. However, a review of the literature pertaining to HR has highlighted the inconsistencies and citation errors dealing with Uhtoff's original work suggesting that almost any form of heat exposure induces neurological signs in people with MS [20]. Nevertheless, the neurological signs commonly referred to as 'Uhtoff's symptom' provide a fundamental neurological link between HR and fatigue. Initial theories included vasoconstriction [21], humoral substance release [22], and neuroelectric blocking [23]. More current thinking describes heat reaction blockade of the action potentials in demyelinated neurons termed, frequency-dependent conduction block (FDCB) [20]. Presumably, demyelination is thought to cause slowing of nerve conduction velocity and lead to conduction block so that the affected axons can only transmit single or low frequency impulses but not high frequency trains [24]. This observation is particularly important in studies that have shown a slowing or blocking of nerve impulses in demyelinated fibres with increasing temperature [25]. Accordingly, it is thought that when demyelination is present only a small increase in temperature is able to completely block action potentials [20].

The sensitivity to heat in MS is exacerbated by elevated environmental heat, humidity and exercise [15]. Premature fatigue has been shown in healthy persons exercising in the heat, but with no long lasting detrimental effects. It is thought that, in healthy individuals exercising in the heat to exhaustion, a critical limiting core temperature (T_c) of $\sim$39.5°C develops at which point exercise is terminated [17, 26]. Originally it was thought that during exercise heat stress, physiological responses such as cardiovascular and thermoregulatory control approach their limit, motivation to continue exercise is reduced and exercise terminates [16]. The mechanism responsible for limiting motivation is not well understood but it could be linked to a centrally mediated reduction in motor drive [18]. Interestingly a critical limiting T_c of $\sim$39.5°C in people with MS has not been reported even though heat sensitivity reduces exercise tolerance time in this condition [27]. In addition, it is unknown whether the severity of MS contributes to the heat sensitivity as appearance of neurological signs with heating is inconsistent among those with MS [28].

Heat reactions and exercise

Although FDCB has physiological significance, it is still unknown whether heating, either passively or by exercise causes nerve and brain temperatures to rise. This is a key consideration as fatigue in the heat is thought to be due to a mechanism protecting the brain from high temperature. This may not be the

case in MS as rises in body temperature of as little as 0.05–1.0°C can induce neurological signs where core temperature only ever reaches ~38°C (rectal temperature) during exercise [27] and well below the temperature thought to induce premature fatigue in healthy persons [17].

Figure 1 shows data redrawn from the studies of White et al. [27] where MS subjects were either cooled before exercise (precooled) or not precooled, and the study by Easton et al. [29] examining thermoregulatory responses in well trained subjects. In each study rectal temperature was monitored and subjects cycled at a work rate equivalent to ~60% of maximal oxygen uptake (VO_{2Max}). Figure 1 (panel A) shows a uniform change in rectal temperature in MS from beginning to end of exercise regardless of initial temperature; whereas, in healthy subjects the increase seems steeper from start to finish. Figure 1 (panel B) confirms that the rate of rise in rectal temperature is indeed lower in MS than in control over about the same exercise duration (38–40 min). These data suggest that in MS, the rise in body temperature is much more constant than in healthy individuals. However, a definitive study examining this relationship has not been reported.

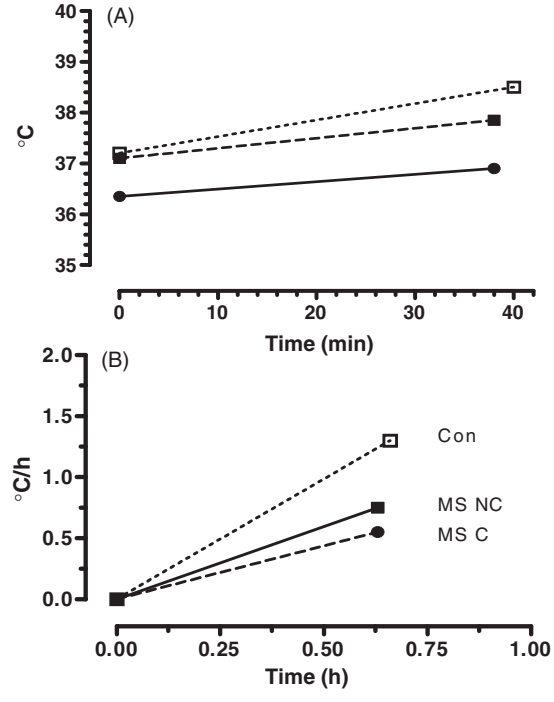

Figure 1. Rectal temperature data redrawn from White et al. (2000) in MS patients either precooled (MS C) or not precooled (MS NC) vs. well trained subjects (Con) from the study of Easton et al. (2007) exercising at ~60% maximum oxygen uptake. Panel A is the absolute change in rectal temperature from start to end of exercise. Panel B is the rate of increase in rectal temperature.

Thermal strain and autonomic dysfunction

There could be several reasons for the paradoxical difference in exercise rectal temperature response between MS and healthy subjects described in the previous section and as shown in Figure 1. A normal consequence in MS is autonomic dysfunction. Surprisingly, research into the sweating response in MS is scant, with only few studies reporting altered autonomic function [30–34]. Davis et al. [34] examined the sweating characteristics of MS versus healthy controls before and after a 15-week aerobic training programme. These authors reasoned that since aerobic training induces adaptive sweating responses, a greater production of sweat may be available for cooling following a training programme. However, this study confirmed that sweat rate and sweat gland output of the MS group was significantly less than controls and that autonomic response following a 15-week period of aerobic training was not significantly altered. If a reduced sweating response is a common observation in MS, then in the precooling study by White et al. [27] where only a modest increase in T_c was observed (~1.0°C) during exercise in both precooled and control subjects, a suppressed sweat response should have resulted in a higher rate of increase in T_c; but this was not the case. White et al. [27] did not report skin temperature during exercise but as previously shown [35], maintaining a cooler shell (skin) reduces thermal strain and provides a larger gradient for heat transfer so that a more modest sweat rate would be sufficient to provide MS subjects with the evaporation needed to maintain a lower temperature. Differences in thermal strain between exercising MS subjects and controls might be explained by differences in aerobic capacity where tolerance to a higher T_c has been shown in trained subjects [36]. A further autonomic problem in MS is the possibility of an upward shift in the thermoregulatory set point so that the threshold for invoking effector mechanisms such as sweating would be delayed, thereby attenuating the sweating response, although this seems to be equivocal [32, 33]. It has also been suggested that about 80% of MS patients have paradoxical heat sensation when cooling the skin [37]. It is unknown how this particular 'side effect' of MS might contribute to the heat tolerance or 'interpretation' of heat sensation during exercise. In addition, lesions within the central nervous system (CNS) could develop in areas which affect thermoregulatory control such as the hypothalamus. However, the relationship between lesion load and fatigue in MS is not well understood as studies in this area have shown equivocal results [38, 39].

Anticipatory regulation and perceived effort

It has been argued that the rate of rise in T_c is an integral part of the ability to anticipate cellular catastrophe during exercise in healthy persons [40, 41]. Given that the CNS is susceptible to demyelination in MS, it is unknown how this might affect the perceived effort during physical work and thus inhibit the ability to anticipate impending cellular damage. This seems a plausible line of enquiry as subjective feelings of fatigue are potentiated in MS [42].

The development of premature fatigue is an accepted consequence of heat stress in healthy adults [26]. However, it has only been within the last decade that a potential mechanism for this premature fatigue has been identified. A series of studies have shown that CNS fatigue is a major component of premature fatigue during hyperthermia. In these studies, a distinct reduction in CNS activation was evident when T_c reached 39.5°C in both exercise and passive hyperthermia [18, 19, 43]. Our own studies have shown that the CNS is selective in down-regulating motor drive to skeletal muscle involved or used during exercise leading to hyperthermia, although motor drive is maintained to the non-involved muscle group [44, 45]. We have speculated that this result might reflect the CNS's ability to discriminate and protect the peripheral structures from ultimate cellular catastrophe as further activation of the involved muscle could only lead to increased metabolic demands and endogenous heat production. However, this mechanism in MS may not be operational due to specific pathology, but if it were it could be much more dangerous to the organism as a higher rate of increase in core temperature in heat sensitive individuals could induce neurological signs prematurely and possibly lead to irreversible cellular damage.

In summary, it is unknown whether heat strain induces fatigue in MS by similar postulated mechanisms as shown in healthy subjects. Studies which can clarify this could also add significantly to the understanding of thermoregulatory control and fatigue across populations.

Muscular fatigue in multiple sclerosis

The most popular definition of fatigue in the healthy intact human is a reduction in sustained muscle force output which can occur as a consequence of changes anywhere along the neuromuscular pathway as depicted in Figure 2.

The cause of the reduced force output is not definitive and is normally classified as either central or peripheral in origin and can be present in varying degrees depending on the physical activity (long duration versus short high intensity). Peripheral fatigue is characterised by changes in the peripheral sites in the motor system whereby conduction in the motor axons and their terminals, neuromuscular transmission, conduction of impulses in the muscle fibres as well as disruption to the excitation-contraction coupling and contractile process is evident [46]. Central fatigue on the other hand is thought to be due to emotional and psychological factors affecting

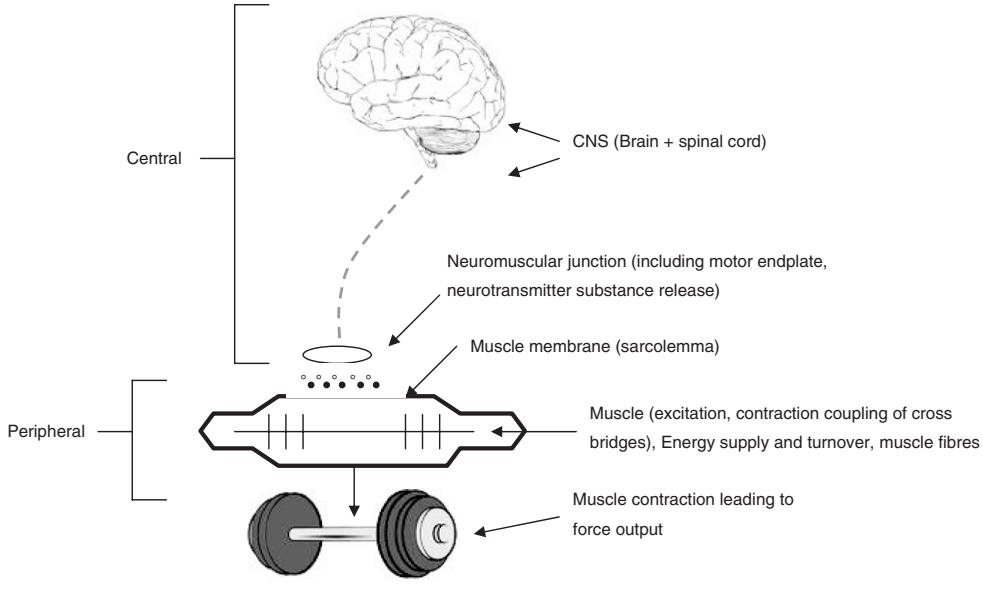

Figure 2. The neuromuscular pathway leading to muscular contraction from the central nervous system (CNS). Neuromuscular fatigue can occur at any point along this pathway and be manifest as a reduction in force output. Note the structures and sites normally thought to be involved in central versus peripheral fatigue as indicated on the left of the figure.

perceived effort in addition to the quantifiable changes in the various descending pathways from the motor cortex to the neuromuscular junction [46].

It has been known for some time that central motor deficits in MS are accompanied by decreased maximal motor unit firing rates [47] and reduced motor unit recruitment [48]. Changes in the electromyography (EMG) recording can be used to infer changes in neuromuscular recruitment. Using the EMG/Force relationship differences in motor pattern have been shown in MS compared with controls [49]. Essentially the findings from these studies indicate that in MS there is an excessive EMG or central motor drive during sub-maximal muscle contractions with the increased central drive correlated to the disease severity.

When central activation, symptomatic fatigue and fat-free cross-sectional area (CSA) and peripheral muscle function were measured in the dorsi flexor of MS and healthy subjects it was confirmed that the augmented weakness in MS was not related to reductions in CSA or peripheral muscle function [14]. However, in healthy subjects the maximum voluntary contraction was not a function of how much muscle was available, but rather how much muscle could be recruited.

In a more direct study of central and peripheral fatigue in MS [50], where force, percentage central activation and compound muscle action potential (M-Wave) were measured, no differences across these measurements at baseline were noted. However, following fatiguing exercise force had decreased ~55% in MS but was not significant in controls. Interestingly, the M-Wave remained unchanged for both groups indicating that reduction in force following fatiguing exercise in MS was a function of reduced central drive and not due to peripheral changes. These findings were subsequently confirmed [51] by measuring the recovery of phosphocreatine (PCr) following sustained maximal handgrip exercise in addition to motor-evoked potentials through transcranial stimulation. The fatiguing exercise resulted in prolonged central motor conduction time in MS but not in control subjects; however, all subjects demonstrated depressed M-Wave amplitude, even after PCr recovery. These findings confirm that fatigue in MS subjects was centrally mediated.

Fatigue and thermal strain in multiple sclerosis

In the case of MS, increasing body temperature either passively or actively through exercise or heat exposure increases the heat reactions and leads to symptomatic premature fatigue. This was recently highlighted by Baker [15] who notes that even swimming in a heated pool induces 'exhaustion' in individuals with MS. However, when MS patients were precooled, it was found that physical performance was significantly improved [27]. In this particular study, the MS subjects exercised at 60% VO_{2Max} for 30 min with either lower body precooling or no cooling. Following exercise in the precooled condition, fatigue scores and the 25-ft walk performance test were improved along with attenuated increases in T_c. Clearly, reducing the 'heat cost' of exercise in MS can improve the likelihood of maintaining an exercise programme. It is worth noting that exercise performance has been found to be significantly improved with the use of precooling in healthy and well trained subjects [52–54]. But it is unclear whether similar mechanisms are in operation for the improvement in exercise duration in MS when precooled. Nevertheless, the conclusion that can be drawn is that reducing thermal strain in both MS and in healthy individuals attenuates the expected reduction in physical performance. A salient point in this regard is the observation that a reduced temperature or cooling results in restoration and alleviation of neurological signs in MS giving credence to the possibility that precooling in MS could allow for an increase in exercise duration with reduced complications in this disease and staving off the development of premature fatigue [15].

In healthy subjects sustained isometric MVCs are significantly reduced following exercise-induced hyperthermia whilst studies in our laboratory indicate that the CNS can discriminate which muscle groups have a reduced central drive in hyperthermia regardless of contraction type – isometric, eccentric or concentric [18, 44, 45]. Interestingly, Morrison et al. [19] have further developed this hypothesis by showing that central activation is attenuated with gradual heating so that passively induced hyperthermia to the level of ~39.5°C is not necessarily needed to invoke a reduction in motor drive. Surprisingly, this paradigm has not been studied in MS and thus it is still not clear whether gradual heating reduces central activation or whether attenuated central activation in MS is independent of heat reactions.

Conclusion

Whether the mechanism for premature fatigue in healthy individuals and in MS is similar in heat stress needs further research and experimentation. However, it seems that in MS fatigue is more likely a central rather than a peripheral phenomenon. It is unclear whether CNS activation is reduced in

a similar way in both healthy persons and in MS during heating, although if this was the case then reduced CNS drive in MS would be invoked at lower core temperatures. However, because precooling is known to alleviate heat reactions in MS and provide for increased exercise time without a potentiated perceived effort, it is possible that one function of precooling might be to maintain CNS activation. At present, there are no studies which have compared CNS activation between healthy and MS subjects during thermal strain or in the case of MS during heat reactions. Studies examining these responses could clarify the nature of the reduction in CNS activation in both MS and healthy people.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: The mechanisms underlying the production of symptoms and the natural history of the disease. Philos Trans R Soc Lond B Biol Sci 1999;354:1649–1673.
2. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938–952.
3. White LJ, Dressendorfer RH. Exercise and multiple sclerosis. Sports Med 2004;24:1077–1100.
4. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. Arch Phys Med Rehab 1984;65:135–138.
5. Bakshi R, Shaikh Z, Miletich R, Czarnecki D, Dmochowski J, Henschel K, Janardhan V, Dubey N, Kinkel P. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000;6:181–185.
6. Slawta JN, McCubbin JA, Wilcox AR, Fox SD, Nalle DJ, Anderson G. Coronary heart disease risk between active and inactive women with multiple sclerosis. Med Sci Sports Exerc 2002;34:905–912.
7. Lambert CP, Lee Archer R, Evans WJ. Body composition in ambulatory women with multiple sclerosis. Arch Phys Med Rehabil 2002;83:1559–1561.
8. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner D, Ettinger W, Heath GW, King AC, et al. Physical activity and public health: A recommendation from the centres for disease control and prevention and the American College of Sports Medicine. JAMA 1995; 273:402–407.
9. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 1996;39:432–441.
10. Mostert S, Kesserling J. Effects of a short term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler 2002;8:161–168.
11. Newman MA, Dawes H, van den Berg M, Wade DT, Burridge J, Izadi H. Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis. Mult Scler 2007;13:113–119.
12. Pfaffenbarger RR, Hyde RT, Wing AL, Hsieh CC. Physical activity, all cause mortality, and longevity of college alumni. N Engl J Med 1986;314:605–613.
13. Garner DJP, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. Muscle Nerve 2003; 27:456–464.
14. Ng AV, Miller RG, Gelinas D, Kent-Braun J. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 2004;29:843–852.
15. Baker D. Multiple sclerosis and thermoregulatory dysfunction. J Appl Physiol 2002;92:1779–1780.
16. Brück K, Olschewski H. Body temperature related factors diminishing the drive to exercise. J Physiol Pharmacol 1986; 65:1274–1280.
17. Nielsen B, Hales JRS, Strange S, Christensen NJ, Warberg J, Saltin B. Human circulatory and thermoregulatory adaptations with heat acclimation and exercise in a hot, dry environment. J Physiol (Lond) 1993;460:467–485.
18. Nybo L, Nielsen B. Hyperthermia and central fatigue during prolonged exercise in humans. J Appl Physiol 2001; 91:1055–1060.
19. Morrison S, Sleivert GG, Cheung SC. Passive hyperthermia reduces voluntary activation and isometric force production. Eur J Appl Physiol 2004;91:729–736.
20. Guthrie TC, Nelson DA. Influence of temperature changes on multiple sclerosis: A critical review of mechanisms and research potential. J Neurol Sci 1995;129:1–8.
21. Brickner R. The significance of localized vasoconstriction in multiple sclerosis. Res Pub Assoc Res Nerv Mental Dis 1950; 28:236–244.
22. Nelson DA, Jeffreys WH, McDowell F. Effects of induced hyperthermia on some neurological diseases. 1958; 79:31–39.
23. Seil FJ, Leiman AL, Kelly JM. Neuroelectric blocking factors in multiple sclerosis and normal sera. Arch Neurol 1976; 33:418–422.
24. Rasminsky M, Sears TA. Internodal conduction in undissected demyelinated nerve fibres. J Physiol (Lond) 1972; 227:323–350.
25. Schauf CL, Davis FA. Impulse conduction in multiple sclerosis: A theoretical basis for modification by temperature and pharmacological agents. J Neurol Neurosurg Psychiatry 1974;37:152–161.
26. González-Alonso J, Teller C, Anderson SL, Jensen FB, Hyldig T, Nielsen B. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol 1999;86(3):1032–1039.
27. White AT, Wilson TE, Davis SL, Petajan JH. Effect of precooling on physical performance in multiple sclerosis. Mult Scler 2000;6:176–180.
28. Ponichtera-Mulcare JA. Exercise and multiple sclerosis. Med Sci Sports Exerc 1993;25:451–465.
29. Easton C, Fudge BW, Pitsiladis YP. Rectal, telemetry pill and tympanic membrane thermometry during exercise heat stress. J Therm Biol 2007;32:78–86.
30. Norohna MJ, Vas CJ, Aziz H. Autonomic dysfunction (sweating responses) in multiple sclerosis. J Neurol Neurosurg Psychiatry 1968;31:19–22.
31. Vas CJ. Sexual impotence and some autonomic disturbances in men with multiple sclerosis. Acta Neurol Scand 1996; 45:23–34.
32. Kurz A, Sessler DI, Tayefeh F, Goldberger R. Poikilothermia syndrome. J Intern Med 1998;244:431–436.
33. Ueno M, Tokunaga Y, Terachi S, Gondo K, Hara T. Asymmetric sweating in a child with multiple sclerosis. Pediatr Neurol 2000;23:74–76.

34. Davis SL, Wilson TE, Vener JM, Crandall CG, Petajan JH, White AT. Pilocarpine-induced sweat gland function in individuals with multiple sclerosis. J Appl Physiol 2005; 98:1740–1744.
35. Kay D, Taaffe DR, Marino FE. Whole-body pre-cooling and heat storage during self paced performance in warm humid conditions. J Sports Sci 1999;17:937–944.
36. Cheung SS, McLellan TM. Heat acclimation, aerobic fitness, hydration effects on tolerance during uncompensable heat stress. J Appl Physiol 1998;84(5):1731–1739.
37. Hansen C, Hopf HC, Treede RD. Paradoxical heat sensation in patients with multiple sclerosis: Evidence for a supraspinal integration of temperature sensation. Brain 1996;119: 1729–1736.
38. Codella M, Rocca MA, Colombo B, Rossi P, Comi G, Filippi MA. Preliminary study of magnetization transfer and diffusion tensor MRI of multiple sclerosis patients with fatigue. J Neurol 2002;249:535–537.
39. Colombo B, Martinelli BF, Rossi P, Rovaris M, Maderna L, Filippi MA, Comi G. MRI and motor evoked potential findings in nondisabled multiple sclerosis patients with and without symptoms of fatigue. J Neurol 2000;247:506–509.
40. Ulmer HV. Concept of extracellular regulation of muscular metabolic rate during heavy exercise in humans by psychophysiological feedback. Experentia 1996;52:416–420.
41. Marino F. Anticipatory regulation and avoidance of catastrophe during exercise-induced hyperthermia. Comp Biochem Physiol, Part B 2004;139:561–569.
42. Bailey A, Channon S, Beaumont J. The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. Mult Scler 2007;13:73–80.
43. Todd G, Butler JE, Taylor JL, Gandevia SC. Hyperthermia: A failure of the motor cortex and the muscle. J Physiol (Lond) 2005;563:621–631.
44. Sabiosky J, Marino FE, Kay D, Cannon J. Exercise heat stress does not reduce central activation to non-exercised human skeletal muscle. Exp Physiol 2003;88(6):783–790.
45. Martin P, Marino FE, Rattey J, Kay D, Cannon J. Reduced voluntary activation of skeletal muscle during shortening and lengthening contractions in whole body hyperthermia. Exp Physiol 2005;90:225–236.
46. Jones D, Round J, de Haan A. Skeletal muscle: From molecules to movement. London: Churchill-Livingston; 2004.
47. Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve 1992;15:1123–1132.
48. Sharma A, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. Muscle Nerve 1995;18: 1403–1411.
49. Ng AV, Miller RG, Kent-Braun J. Central motor drive is increased during voluntary muscle contractions in multiple sclerosis. Muscle Nerve 1997;20:1213–1218.
50. Sheean GL, Murray NMF, Rothwell JC, Miller DH, Thompson AJ. An electrophysiological study of the mechanism of fatigue in multiple sclerosis. Brain 1997; 120:299–315.
51. Petajan JH, White AT. Motor-evoked potentials in response to fatiguing grip exercise in multiple sclerosis patients. Clin Neurophysiol 2000;111:2188–2195.
52. Lee DT, Haymes EM. Exercise duration and thermoregulatory responses after whole body precooling. J Appl Physiol 1995;79(6):1971–1976.
53. Booth J, Marino F, Ward JJ. Improved running performance in hot humid conditions following whole body precooling. Med Sci Sports Exerc 1997;29(7):943–949.
54. Marino FE. Methods, advantages, and limitations of body cooling for exercise performance. Br J Sports Med 2002; 36:89–94.