

during periods of unpredictable stress that lead to NFOR and investigate the role of an increased inflammatory state and oxidative stress in mediating these changes; admittedly a difficult proposition under controlled laboratory conditions.

Acknowledgements

DSM Food Specialities, Delft, The Netherlands funded this study.

There are no conflicts of interest for any of the authors.

References

1. Meeusen R, Duclos M, Foster C, et al. Prevention, Diagnosis, and Treatment of the Overtraining Syndrome: Joint Consensus Statement of the European College of Sport Science and the American College of Sports Medicine. *Med Sci Sports Exerc.* 2013;45(1):186-205.
2. Gustaffson H, Holmberg HC, Hassmén P. An elite endurance athlete's recovery from underperformance aided by a multidisciplinary sport science support team. *Eur J Sport Sci.* 2008; 8(5):267-276
3. Knaepen K, Goekint M, Heyman E, Meeusen R. Neuroplasticity: the effect of acute and training on peripheral brain-derived neurotrophic factor; a systematic review of experimental studies in human subjects. *Sports Med.* 2010;40(9):765-801.
4. Mattson MP, Maudsley S, and Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *TRENDS Neurosci.* 2004;27(10):589-594.
5. Suri D and Vaidya VA. Glucocorticoid Regulation Of Brain-Derived Neurotrophic Factor: Relevance To Hippocampal Structural And Functional Plasticity. *Neuroscience.* 2013;239:196–213.
6. Marosi K and Mattson MP. BDNF mediates adaptive brain and body responses to energetic challenges. *Trends Endocrin Met.* 2014;25(2): 89-98.
7. Meeusen R, Piacentini MF and De Meirleir K. Brain Microdialysis in Exercise Research. *Sports Med.* 2001;31(14): 965-983.
8. Neeper SA, Gomez Pinilla F, Choi J and Cotman C. Exercise and Brain Neurotrophins. *Nature.* 1995; 373:109.
9. Cotman CW and Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *TRENDS Neurosci.* 2002; 25(6):295-301.
10. Yau SL, Lau BWM, Zhang ED, et al. Effects Of Voluntary Running On Plasma Levels Of Neurotrophins, Hippocampal Cell Proliferation And Learning And Memory In Stressed Rats. *Neuroscience.* 2012;222:289-301.
11. Numakawa T, Adachi N, Richards M, Chiba S, Kunugi H. Brain-Derived Neurotrophic Factor And Glucocorticoids: Reciprocal Influence On The Central Nervous System. *Neuroscience.* 2013;239:157–172.
12. Duman RS and Monteggia LM. A Neurotrophic Model for Stress-Related Mood Disorders. *BIOL PSYCHIATRY.* 2006;59:1116–1127.
13. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci.* 1995;15:1768–77.
14. Calabrese F, Molteni R, Racagni R, Riva MA. Neuronal plasticity: A link between stress and mood disorders. *Psychoneuroendocrino.* 2009; 34S, S208—S216.

15. De Pauw K, Roelands B, Cheung SS, de Geus B, Rietjens G, and Meeusen R. Guidelines to Classify Subject Groups in Sport-Science Research. *Int J Sports Physiol Perf.* 2013;8:111-122.
16. Witard OC, Jackman SR, Kies AK, Jeukendrup AE, and Tipton KD. Effect of Increased Dietary Protein on Tolerance to Intensified Training. *Med. Sci. Sports Exerc.* 2011;43(4):598–607.
17. Witard OC, Turner JE, Jackman SR, et al. High dietary protein restores overreaching induced impairments in leukocyte trafficking and reduces the incidence of upper respiratory tract infection in elite cyclists. *Brain Behav Immun.* 2014;39:211–219.
18. Jeukendrup A, Saris WH, Brouns F, Kester AD. A new validated endurance performance test. *Med Sci Sports Exerc.* 1996;28(2): 266–70.
19. Borg GA. Perceived exertion: a note on “history” and methods. *Med Sci Sports.* 1973;5:90–3.
20. Achten J, Halson SL, Moseley L, Rayson MP, Casey A, Jeukendrup AE. Higher dietary carbohydrate content during intensified running training results in better maintenance of performance and mood state. *J Appl Physiol.* 2004; 96(4):1331–40
21. Bosch JA, Berntson, GG, Cacioppo JT, Marucha PT. Differential mobilization of functionally distinct natural killer subsets during acute psychologic stress. *Psychosom. Med.* 2005; 67, 366–375
22. Grove RJ and Prapavessis H. Preliminary evidence for the reliability and validity of an abbreviated Profile of Mood States. *Int J Sport Psychol.* 1992; 23:93-109.
23. Rojas Vega S, Strueder HK, Vera Wahrman B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Research.* 2006; 1121:5 9 – 6 5
24. Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J and Duda K. Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. *Journal Of Physiology And Pharmacology.* 2008; 59(7):119-132.
25. Seifert T, Brassard P, Wissenberg M, et al. Endurance training enhances BDNF release from the human brain. *Am J Physiol Regul Integr Comp Physiol.* 2010;298: R372–R377.
26. Schiffer T, Schulte S, Hollmann W, Bloch W, Struder HK. Effects of Strength and Endurance Training on Brain-derived Neurotrophic Factor and Insulin-like Growth Factor 1 in Humans. *Horm Metab Res.* 2009; 41:250– 254.
27. Duman RS. Neurotrophic factors and regulation of mood: Role of exercise, diet and metabolism. *Neurobiol Aging.* 2005;26S:S88–S93.
28. Schaaf MJM, de Kloet ER, Vreugdenhil E. Corticosterone effects on BDNF expression in the hippocampus. Implications for memory formation. *Stress* (Amsterdam, Netherlands). 2000; 3:201–208.

29. Schaaf MJM, Sibug RM, Duurland MF, et al. Corticosterone effect on BDNF mRNA espresso in the rat hippocampus during Morris Water maze training. *Stress*.1999; 3(2):173-183.
30. Russo-Neustadt A, Ha T, Ramirez R, Kesslak JP. Physical activity–antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. *Behav Brain Res*. 2001; 120:87–95.
31. Goekint M, Heyman E, Roelands B, et al. No Influence of Noradrenaline Manipulation on Acute Exercise-Induced Increase of Brain-Derived Neurotrophic Factor. *Med. Sci. Sports Exerc*. 2008;40(11):1990–1996.
32. Saaltink DJ, Vreugdenhil E. Stress, glucocorticoid receptors, and adult neurogenesis: a balance between excitation and inhibition? *Cell. Mol. Life Sci*. 2014; 71:2499–2515
33. Halson SL, Lancaster GI, Jeukendrup AE, and Gleeson M. Immunological Responses to Overreaching in Cyclists. *Med. Sci. Sports Exerc*. 2003;35(5):854–861.
34. Kellmann M. Preventing overtraining in athletes in high-intensity sports and stress/recovery monitoring. *Scand J Med Sci Sports*. 2010; 20(Suppl. 2):95–102.
35. Morgan WP, Brown DR, Raglin JS, O’Connor PJ and Ellickson KA. Psychological monitoring of overtraining and staleness. *British.J.Sports Med*. 1987;21(3):107-114.
36. Piacentini MF and Meeusen R. An online training monitoring system to prevent non functional overreaching. *Int J Sports Physiol Perf*. 2015;10:524-527.
37. Comotto S, Bottoni A, Moci E, Piacentini MF. Analysis of Session-RPE and Profile of Mood States during a triathlon training camp. *J Sports Med Phys Fitness*. 2015; 55:361-367.
38. Dupuy O, Renaud M, Bherer L, et al. Effect of Functional Overreaching on Executive Functions. *Int J Sports Med*. 2010;31(9):617-23.
39. Meeusen R, Watson P, Roelands B, Hasegawa H, Piacentini MF. Brain neurotransmitters in fatigue and overtraining. *Appl Physiol Nutr Me* 2007; 32(5):857-864.
40. Rietjens G, Kuipers H, Adam JJ, et al. Physiological, biochemical and psychological markers of overreaching. *Int J Sports Med*. 2005;26:16–26.

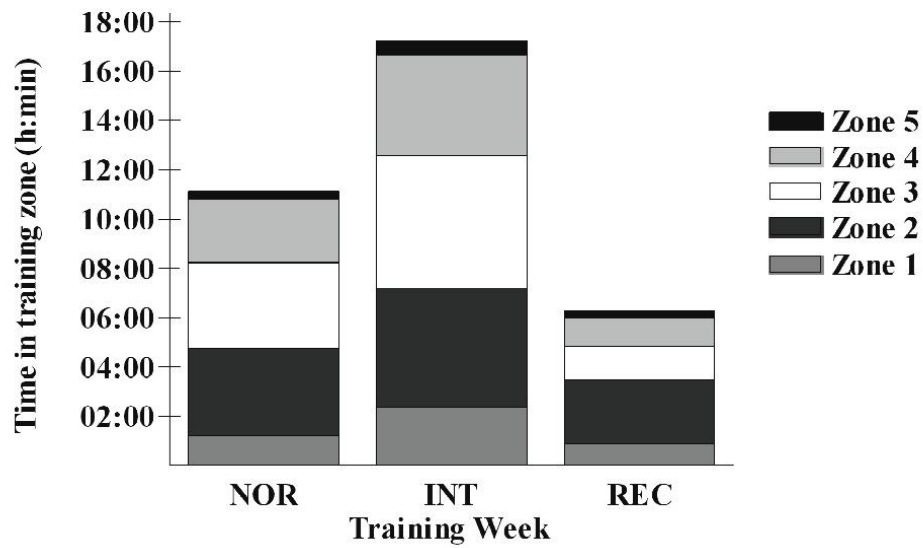


Figure 1: Time spent in each training zone during each training condition. Z1 = < 70%HRmax, Z2 = 70%–80%HRmax, Z3 = 80%–90%HRmax, Z4 = 90%–95%HRmax, and Z5 = > 95%HRmax

INT training showed a significant increase in volume and intensity (time spent in Z4 and Z5).

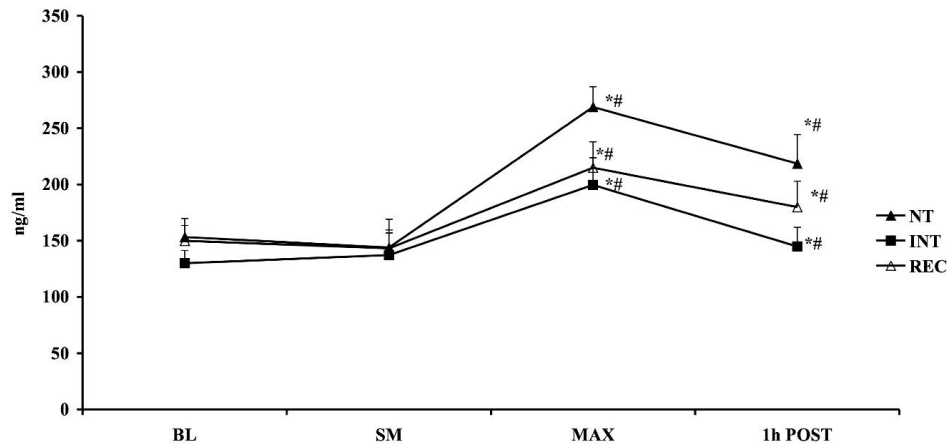


Figure 2. Plasma cortisol concentrations at baseline (BL), at the end of submaximal exercise (SM) at the end of the time trial (MAX) and after recovery (1h POST) in the three training conditions: normal (NT), intensified (INT) and recovery (REC) training. No difference was observed between the three training conditions.

* = statistically different from BL ($p < 0.05$)

= statistically different from SM ($p < 0.05$)

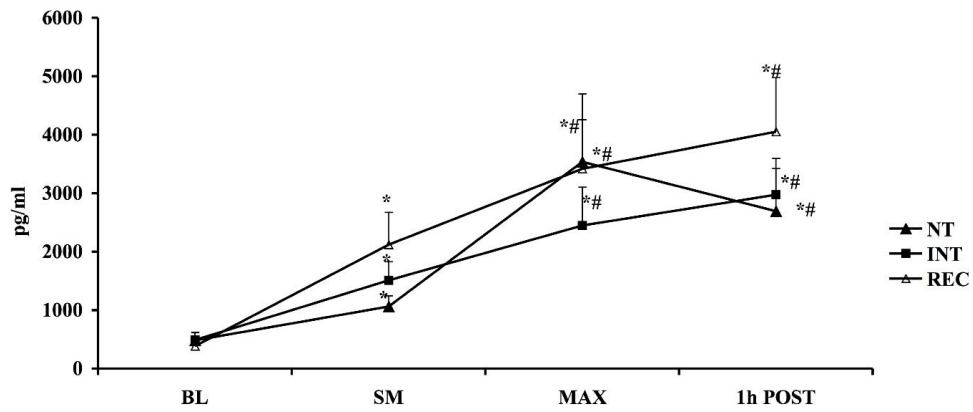


Figure 3. Plasma BDNF concentrations at baseline (BL), at the end of submaximal exercise (SM) at the end of the time trial (MAX) and after recovery (1h POST) in the three training conditions: during normal (NT), intensified (INT) and recovery (REC) training. No difference was observed between the three training conditions.

* = statistically different from BL ($p < 0.05$)

= statistically different from SM ($p < 0.05$)

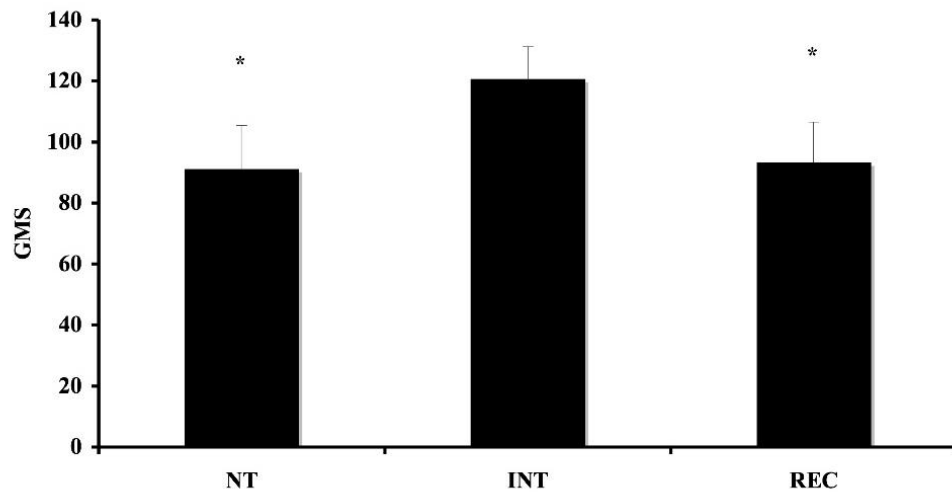


Figure 4. Global Mood Score (GMS) during normal (NT), intensified (INT) and recovery training (REC)

* = statistically different from INT ($p < 0.05$)