Editorial comment

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Pain is common in chronic fatigue syndrome – current knowledge and future perspectives

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In this issue of the *Scandinavian Journal of Pain*, two papers address pain in chronic fatigue syndrome (CFS): Andrea Polli and her co-workers report an association between exercise-induced changes in pressure pain thresholds and complement activity which was not present among healthy controls, suggesting a link between immune and pain modulation in CFS. Elin Bolle Strand and her co-workers found that pain is associated with anxiety and depression, and exerts a strong negative impact on CFS patients' quality of life; these findings emphasize the importance of assessing and relieving pain in clinical care.

Pain is one of the most commonly reported bodily complaints among adult and adolescent CFS sufferers [1, 2], and is included in the most frequently used diagnostic criteria of CFS [3, 4]. Still, a rather limited number of previous studies have specifically addressed pain in CFS. Thus, this symptom seems to be somewhat ignored by clinicians treating patients with CFS as well as researchers studying mechanisms and management of CFS [5].

1 Generalized increased central sensory sensitivity in CFS?

The underlying causes of increased pain experience in CFS remain to be properly understood, and a complex mixture of different mechanisms might be involved. Firstly, *central sensitization* has been advocated by some researchers [6]. Evidence indeed suggests attenuated endogenous inhibitory control of pain [7] as well as overactive endogenous pain facilitation [8]. Accordingly, CFS patients are shown to have abnormally low pressure pain thresholds indicating generalized hyperalgesia [2, 9]. In addition, CFS patients report higher sensitivity towards other sensory stimuli as well, such as sounds and light

[10], and maneuvers causing gentle strain on limb nerves and soft tissues induce pain more easily in CFS patients than in healthy controls [11]. Thus, if there is central sensitization, then other kinds of sensory information may be affected as well [6]. One might therefore speculate whether CFS patients possess a general trait of enhanced sensory-processing sensitivity [12].

2 Autonomic nervous system alterations and generalized low-grade inflammation in CFS

Secondly, *peripheral phenomena* might contribute importantly to pain experiences. CFS is characterized by decreased parasympathetic and increased sympathetic nervous activity [13, 14]. Parasympathetic attenuation has been shown to be directly related to dysfunctional exercise-induced analgesia in CFS [15], whereas sympathetic enhancement is a well-known inducer of pain in many chronic pain conditions [16]. Furthermore, several studies suggest a state of generalized low-grade inflammation in CFS [17, 18]. Inflammation, in turn, might be a possible source of chronic pain [19], corroborating the findings of Polli and co-workers in the present issue. To complicate matter even further, perpetuating effects of vicious circles might be anticipated [20]. For instance, increased sympathetic nervous activity might promote low-grade inflammation in CFS [10] which in turn might evoke a stronger noxious sensory experience due to central sensitization, resulting in a stress response characterized by increased sympathetic activity.

3 Emotional and cognitive alterations in CFS

Thirdly, *emotional and cognitive processes* are likely to be involved in CFS pain experiences. A strong bi-directional relationship between pain and anxiety has been

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documented in several previous studies [21], in line with the results reported by Strand and co-workers in the present issue. Accordingly, anxiety is common in CFS [22], and one CFS study demonstrated an association between pain severity and pain catastrophizing [23]. Furthermore, expectancies are shown to exert a strong, modifying influence on pain experiences and might also have a “self-reinforcing” effect, thus contributing to chronicity [24]. The possible role of expectancies has been only scarcely addressed in previous CFS research. However, one study reported an association between negative symptom expectancies and actual physical performance [25], whereas another study found that expectancies influence autonomic cardiovascular responses to gravity [26]. Finally, a negative association between pain and cognitive performance in CFS was recently reported [27], and cognitive behavioral therapy, which is shown to improve fatigue in CFS [28], also effectively relieves pain [1, 29].

4 Pain and fatigue: expressions of similar alarm systems for disturbed homeostasis?

Summing up, further studies addressing the complex mechanisms underlying chronic pain in CFS are strongly needed. Not only may they contribute to better clinical care. They may also shed important light on the rather enigmatic entity of CFS. This assumption is grounded in some basic observation on the close similarities between pain and fatigue: *Firstly*, at a phenotypical level, there are several overlapping features between CFS and chronic pain states, in particular fibromyalgia [30, 31], and some researchers have suggested that these two conditions should actually be regarded as phenotypical variants of the same underlying pathophysiological process [32]. *Secondly*, at the level of brain organization, a comparison of evidence from functional imaging studies suggests that the experience of fatigue is related to activity in neural networks that share some nodes with pain-associated networks [33, 34]. *Thirdly*, from a functional point of view, both pain and fatigue might be considered evolutionary preserved “homeostatic alarms” that provide salient information to the individual of possible threats to body integrity [33–35]: while pain signals possible or actual tissue damage, fatigue might be related to automatic and unconscious cost-benefit-calculations of energy consumption. In other words, the evolutionary “meaning” of fatigue might be to effectively prevent us from spoiling energy on a task with presumably low gain [35]. Corroborating evidence has

been provided from endurance sports research showing that the experience of fatigue is an important determinant of performance capacity independent on the energetic state of the working muscles [36]. Of note, this functional conceptualization of pain and fatigue implies an unavoidable element of (unconscious) interpretation of the internal body state as well as the external world, which may or may not be correct; corollary, chronic pain and fatigue states might both be regarded as conditions of “misinterpretation”. It has been acknowledged for decades that pain might be experienced without stimulation of peripheral nociceptors [37]. Likewise, it seems reasonable to assume that a sensation of fatigue might arise without any “external cause” immediately explaining it.

5 Implications for further CFS research

Given these basic similarities of pain and fatigue, CFS researchers might benefit strongly from a closer collaboration with pain researchers. On a practical level, this will imply access to a wide range of methodological tools, such as animal models and standardized experimental protocols, which are generally lacking in the field of CFS. On a conceptual level, the scientific tradition in pain research provides a much needed framework with its biopsychosocial perspective and simultaneous warning against body-mind-dichotomy and single-eyed reductionism [38]. The studies by Elin Bolle Strand and her coworkers [39] as well as Andrea Polli and her coworkers [40] should be complemented for bringing pain into the CFS research field. Hopefully, future investigations of pain in CFS might revitalize a scientific field which appears to be somewhat paralyzed by controversies and blind alleys.

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References

- [1] Knoop H, Stulemeijer M, Prins JB, van der Meer JW, Bleijenberg G. Is cognitive behavior therapy for chronic fatigue syndrome also effective for pain symptoms? *Behav Res Ther* 2007;45:2034–43.
- [2] Winger A, Kvarstein G, Wyller VB, Sulheim D, Fagermoen E, Småstuen MC, Helseth S. Pain and pressure pain thresholds in adolescents with chronic fatigue syndrome and healthy controls: a cross-sectional study. *BMJ Open* 2014;4:e005920.

- [3] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953–9.
- [4] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles AC, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darraqh A, Jo D, Lewis D, Light AR, Marshall-Gradisnik S, et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med* 2011;270:327–38.
- [5] Nijs J, Crombez G, Meeus M, Knoop H, Damme SV, Cauwenbergh V, Bleijenberg G. Pain in patients with chronic fatigue syndrome: time for specific pain treatment? *Pain Physician* 2012;15:E677–86.
- [6] Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, De Clerck LS. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest* 2012;42:203–12.
- [7] Meeus M, Nijs J, Van de Wauwer N, Toebach L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. *Pain* 2008;139:439–48.
- [8] Collin SM, Nijs J, Meeus M, Polli A, Willekens B, Ickmans K. Endogenous pain facilitation rather than inhibition differs between people with chronic fatigue syndrome, multiple sclerosis, and controls: an observational study. *Pain Physician* 2017;20:E489–97.
- [9] Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. *Clin Rheumatol* 2010;29:393–8.
- [10] Sulheim D, Fagermoen E, Winger A, Anders AM, Godang K, Müller F, Rowe PC, Saul JP, Skovlund E, Øie MG, Wyller VB. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatr* 2014;168:351–60.
- [11] Rowe PC, Fontaine KR, Lauver M, Jasion SE, Marden CL, Moni M, Thompson CB, Vieland RL. Neuromuscular strain increases symptom intensity in chronic fatigue syndrome. *PLoS One* 2016;11:e0159386.
- [12] Wyller HB, Wyller VB, Crane C, Gjelsvik B. The relationship between sensory processing sensitivity and psychological distress: a model of underpinning mechanisms and an analysis of therapeutic possibilities. *Scand J Psychol* 2017;4:e15.
- [13] Okamoto LE, Raj SR, Peltier A, Gamboa A, Shibao C, Diedrich A, Black BK, Robertson D, Biaggioni I. Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. *Clin Sci* 2012;122:183–92.
- [14] Wyller VB, Barbieri R, Thaulow E, Saul JP. Enhanced vagal withdrawal during mild orthostatic stress in adolescents with chronic fatigue. *Ann Noninvasive Electrocardiol* 2008;13:67–73.
- [15] Oosterwijck JV, Marusic U, De Wandele I, Paul L, Meeus M, Moorkens G, Lambrecht L, Danneels L, Nijs J. The role of autonomic function in exercise-induced endogenous analgesia: a case-control study in myalgic encephalomyelitis/chronic fatigue syndrome and healthy people. *Pain Physician* 2017;20:E389–99.
- [16] Koltzenburg M, McMahon SB. The enigmatic role of the sympathetic system in chronic pain. *Trends Pharmacol Sci* 1991;12:399–402.
- [17] Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. *Brain Behav Immun* 2012;26:24–31.
- [18] Klimas NG, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. *Brain Behav Immun* 2012;26:1202–10.
- [19] Gerwyn M, Maes M. Mechanisms explaining muscle fatigue and muscle pain in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CF): a review of recent findings. *Curr Rheumatol Rep* 2017;19:1.
- [20] Wyller VB, Eriksen HR, Malterud K. Can sustained arousal explain the Chronic Fatigue Syndrome? *Behav Brain Func* 2009;5:10.
- [21] Gamsa A. The role of psychological factors in chronic pain. I. A half century of study. *Pain* 1994;57:5–15.
- [22] Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. *Curr Opin Psychiatr* 2006;19:67–73.
- [23] Nijs J, Van de Putte K, Louckx F, Truijen S, De Meirleir K. Exercise performance and chronic pain in chronic fatigue syndrome: the role of pain catastrophizing. *Pain Med* 2008;9:1164–72.
- [24] Jepma M, Koban L, van Doorn J, Jones M, Wager TD. Behavioural and neural evidence for self-reinforcing expectancy effects on pain. *Nat Hum Behav* 2018;2:838–55.
- [25] Heins M, Knoop H, Nijs J, Feskens R, Meeus M, Moorkens G, Bleijenberg G. Influence of symptom expectancies on stair-climbing performance in chronic fatigue syndrome: effect of study context. *Int J Behav Med* 2013;20:213–8.
- [26] Wyller VB, Fagermoen E, Sulheim D, Winger A, Skovlund E, Saul JP. Orthostatic responses in adolescent chronic fatigue syndrome: contributions from expectancies as well as gravity. *Biopsychosoc Med* 2014;8:22.
- [27] Ickmans K, Meeus M, De Koning M, Lambrecht L, Pattyn N, Nijs J. Associations between cognitive performance and pain in chronic fatigue syndrome: comorbidity with fibromyalgia does matter. *Pain Physician* 2015;18:E841–52.
- [28] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M; PACE Trial Management Group. Comparison of adaptive pacing therapy, cognitive behavior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011;377:823–36.
- [29] Bourke JH, Johnson AL, Sharpe M, Chalder T, White PD. Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. *Psychol Med* 2014;44:1545–52.
- [30] Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* 2000;160:221–7.
- [31] Norris T, Deere K, Tobias JH, Crawley E. Chronic fatigue syndrome and chronic widespread pain in adolescence: population birth cohort study. *J Pain* 2017;18:285–94.
- [32] Fink P, Schröder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. *J Psychosom Res* 2010;68:415–26.
- [33] Brodal P. A neurobiologist's attempt to understand persistent pain. *Scand J Pain* 2017;15:140–7.
- [34] Brodal P. The central nervous system. New York: Oxford University Press, 2013:541–2.
- [35] Boksem MA, Tops M. Mental fatigue: costs and benefits. *Brain Res Rev* 2008;59:125–39.
- [36] Schipf-Godart L, Roelands B, Hettinga FJ. Drive in sports: how mental fatigue affects endurance performance. *Front Psychol* 2018;9:1383.

- [37] Wall PD, McMahon SB. The relationship of perceived pain to afferent nerve impulses. *Trends Neurosci* 1986;9:254–5.
- [38] Gamsa A. The role of psychological factors in chronic pain. II. A critical appraisal. *Pain* 1994;57:17–29.
- [39] Strand EB, Mengshoel AM, Sandvik L, Helland IB, Abraham S, Nes LS. Pain is associated with reduced quality of life and functional status in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Scand J Pain* 2019;19:61–72.
- [40] Polli A, Van Oosterwijck J, Meeus M, Lambrecht L, Nijs J, Ickmans K. Exercise-induce hyperalgesia, complement system and elastase activation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome – a secondary analysis of experimental comparative studies. *Scand J Pain* 2019;19:183–92.