

# Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome

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**Abstract** In addition to the debilitating fatigue, the majority of patients with chronic fatigue syndrome (CFS) experience chronic widespread pain. These pain complaints show the greatest overlap between CFS and fibromyalgia (FM). Although the literature provides evidence for central sensitization as cause for the musculoskeletal pain in FM, in CFS this evidence is currently lacking, despite the observed similarities in both diseases. The knowledge concerning the physiological mechanism of central sensitization, the pathophysiology and the pain processing in FM, and the knowledge on the pathophysiology of CFS lead to the hypothesis that central sensitization is also responsible for the sustaining pain complaints in CFS. This hypothesis is based on the hyperalgesia and allodynia reported in CFS,

on the elevated concentrations of nitric oxide presented in the blood of CFS patients, on the typical personality styles seen in CFS and on the brain abnormalities shown on brain images. To examine the present hypothesis more research is required. Further investigations could use similar protocols to those already used in studies on pain in FM like, for example, studies on temporal summation, spatial summation, the role of psychosocial aspects in chronic pain, etc.

**Keywords** Central sensitization · Chronic fatigue syndrome · Chronic pain · Fibromyalgia

## Introduction

Chronic fatigue syndrome (CFS), as defined by the Centers for Disease Control and Prevention (CDCP), is a complex illness characterized by prolonged debilitating fatigue and multiple non-specific symptoms including headaches, recurrent sore throats, fever, muscle and joint pain, and neurocognitive complaints [1, 2]. In addition to the chronic fatigue, widespread and persistent pain is common in individuals with CFS [3–5]. A population-based study revealed that 94% of the persons diagnosed with CFS report muscle aches and pain and 84% report joint pain [6]. Nishikai et al. [7] reported muscle pain in 85 CFS patients of 114 patients (74.6%). Seventy-four patients (64.9%) complained of arthralgia. In another study, 24 of 44 patients suffered from chronic widespread pain [8]. Chronic fatigue accompanied by chronic musculoskeletal impairments such as myalgias and arthralgias could be considered an important subclass of CFS [9]. Evidence supportive of the clinical importance of widespread pain in CFS has been provided [10]: chronic pain accounts for up to 34% of the CFS patients' self-reported activity limitations and partic-

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ipation restrictions. Chronic pain is more disabling than chronic fatigue [10].

Given these facts, it may be surprising that the etiology of these pain complaints has not been studied extensively in patients with CFS. The systematic literature review by Meeus et al. [11] shows that only little progress has been made in understanding chronic widespread pain in patients with CFS. A few hypotheses have been proposed, but they have not been studied in depth or relatively little work has been performed to test these hypotheses. In contrast, a large body of scientific literature regarding the etiology of chronic pain complaints in fibromyalgia (FM) is currently available. The diagnosis of FM is based on the 1990 American College of Rheumatology criteria. Following these criteria, FM patients present with 11 of 18 positive tender points and with widespread pain [12]. Validity of both the definition for CFS and FM has been shown [12, 13].

Especially, investigations focusing on the phenomenon “central sensitization” are presented in force in FM. In CFS, the theory of central sensitization has only been suggested, to our knowledge [14]. Given the great overlap between CFS and FM [15] and given the dearth of studies focusing on the explanation for the chronic widespread pain in patients with CFS, it would be interesting to propose a theoretical model for the chronic pain in CFS based on the current knowledge of CFS and on the evidence for central sensitization in FM, giving rise to further research on that matter. Besides the knowledge on chronic pain in FM, it is necessary to gather knowledge on musculoskeletal pain in CFS.

The syndromes may overlap, but despite the similarities between the two syndromes, there are also differences. For example, immunological dysregulations such as the abnormal 2–5A synthetase/RNase L pathway [16] have been revealed in CFS but have never been detected in FM patients. Furthermore, there is not yet any good evidence for similar pain mechanisms in CFS and FM. Some authors already found evidence suggesting differences in pain processing. For example, patterns of functional brain activity in patients with FM are quite different from those in patients with CFS.

Patients with CFS, relative to controls, showed significantly lower blood perfusion in the brain stem [17, 18]. Patients with FM exhibited significantly lower rCBF levels, during rest, in the thalamus and the caudate nucleus [19]. Furthermore, Substance P has been found to be elevated in CSF of FM patients [20] and not in patients with CFS [21]. Therefore, the knowledge on pain in FM cannot be applied on CFS patients without further study. Based on the similarities and differences between the two syndromes, further research on pain in CFS is advised to get an image of pain processing in the two diseases.

The goal of this article is to provide a rational basis for future investigations. First, the concept of central sensitization as a cause of chronic pain will be explained. This theoretical background will then be applied to FM and an overview of the evidence for central sensitization in FM will follow. Finally, based on the theoretical background and the findings in FM, the hypothesis concerning central sensitization in CFS will be unfolded, supported with the present knowledge on CFS.

## Central sensitization

**Introduction** Pain is a complex perception that is influenced by prior experience and by the context within which the noxious stimulus occurs; “nociception” is the physiologic response to tissue damage or prior tissue damage [22]. The definition of pain is endorsed by the International Association for the Study of Pain: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [23]. There are a host of physiologic mechanisms by which injuries lead to nociceptive responses and ultimately to pain [22]. However, not all nociceptive signals are perceived as pain and vice versa, not every pain sensation originates from nociception. Nevertheless, acute pain almost always originates from nociceptors in somatic or visceral tissue. Mainly two types of pain receptors are activated by nociceptive input. These include low-threshold nociceptors that are connected to fast conducting A-delta pain fibers, and high-threshold nociceptors that conduct impulses in slow (unmyelinated) C fibers. Within the dorsal horn of the spinal cord, these pain fibers synapse with spinal neurons via synaptic transmission. Many neurotransmitters (i.e., glutamate, substance P, etc.) are able to modulate the postsynaptic responses with further transmission to supraspinal sites (thalamus, anterior cingulate cortex, insular cortex, and somatosensory cortex) via the ascending pathways [22, 24, 25].

The simplest form of plasticity in nervous systems is that repeated noxious stimulation may lead to habituation (decreased response) or sensitization (increased response) [26]. Prolonged or strong activity of dorsal horn neurons caused by repeated or sustained noxious stimulation may subsequently lead to increased neuronal responsiveness or central sensitization [25, 27]. Neuroplasticity and subsequent CNS sensitization include altered function of chemical, electrophysiological, and pharmacological systems [22, 28, 29]. These changes cause exaggerated perception of painful stimuli (hyperalgesia), a perception of innocuous stimuli as painful (allodynia) and may be involved in the generation of referred pain and hyperalgesia across multiple spinal segments [25, 30–33].

While the exact mechanism by which the spinal cord becomes sensitized or in “hyperexcitable” state currently remains somewhat unknown, some contributing factors have been proposed.

*Temporal summation or wind-up* “Wind up” refers to a central spinal mechanism in which repetitive noxious stimulation results in a slow temporal summation that is experienced in humans as increased pain [34]. In 1965, animal experiments showed for the first time that repetitive C-fiber stimulation could result in a progressive increase of electrical discharges from the second-order neuron in the spinal cord [35]. This mechanism of pain amplification in the spinal cord is related to temporal summation of second pain or wind-up. Second pain, which is more dull and strongly related to chronic pain states, is transmitted through unmyelinated C fibers to dorsal horn nociceptive neurons. During the C-fibres transmitted stimuli, *N*-methyl-D-aspartate (NMDA) receptors of second-order neurons become activated.

It is well-known that NMDA activation induces calcium entry into the dorsal horn neurons [36]. Calcium entry into sensory neurons in the dorsal horn induces activation of nitric oxide (NO) synthase, leading to the synthesis of NO [37]. NO can affect the nociceptor terminals and enhance the release of sensory neuropeptides (in particular, substance P) from presynaptic neurons, therefore contributing to the development of hyperalgesia and maintenance of central sensitization [38]. Substance P (SP) is an important nociceptive neurotransmitter. It lowers the threshold of synaptic excitability, resulting in the unmasking of normally silent interspinal synapses and the sensitization of second-order spinal neurons [39].

Furthermore, SP can extend for long distances in the spinal cord and sensitize dorsal horn neurons at a distance from the initial input locus. This results in an expansion of receptive fields and the activation of wide dynamic neurons by non-nociceptive afferent impulses [24].

Wind-up can be elicited in human patients if identical nociceptive stimuli are applied to the skin or muscles more often than once every 3 s. The resulting progressive increase of pain sensations represents wind-up and has been demonstrated to result from a central rather than a peripheral nervous system mechanism, because the input from C nociceptors has been shown to decline or stay the same with stimulus repetition [40].

*Endogenous pain modulatory systems* The presence of several pain inhibitory and facilitatory centers in the brainstem is well recognized. The dorsolateral funiculus appears to be a preferred pathway for descending pain inhibitory systems [41]. Experimental evidence for the existence of descending inhibitory pathways, and their

connection with central sensitization, include the observations that bilateral lesions of the dorsolateral funiculus in the rat led to a significant decrease in latency for paw withdrawal to noxious stimulus [42]. Similarly, temporary spinal cord block (lidocaine) caused dorsal horn nociceptive neurons to expand their receptive fields and their responsiveness to afferent input [43]. In addition, selective chemical lesion of serotonergic inhibitory neurons in experimentally “inflamed” animals resulted in demonstrable behavioral “pain” hypersensitivity [42].

The foregoing investigations suggest that disruption of one or more of the elements of the inhibitory system can result in, among other things, the equivalent of central sensitization [44]. One function of the descending inhibitory pathway is to “focus” the excitation of the dorsal horn neurons. The effect is to generate a more urgent, localized, and rapid pain signal by suppressing surrounding neuronal activity [45]. This role is attributed to the “diffuse noxious inhibitory controls” (DNIC) phenomenon [46]. According to this model, descending pathways effectively enhance the biologically valuable pain signal by reducing the level of irrelevant “noise” in the system.

Facilitatory pathways leading from the brainstem have also been identified. There is now behavioral evidence that forebrain centers are capable of exerting powerful clinically significant influences on various nuclei of the brainstem, including the nuclei identified as the origin of the descending facilitatory pathway [44]. The activity in descending pathways is not constant but can be modulated, for example, by the level of vigilance or attention and by stress [47]. Brosschot [48] refers to it as cognitive emotional sensitization. Forebrain products such as cognitions, emotions, attention, and motivation have influence on the clinical pain experience [44].

Dubner and Ren [41] rewarded subjects for responding to a randomly delivered transient tissue threatening peripheral stimulus. It was found that sensitization of second-order pain pathway neurons was directly related to the strength of attention. The evidence suggests that selective attention to relevant stimuli activated descending pain modulatory systems, turning the balance in favor of facilitation. The dominance of descending facilitation then led to sensitization of second-order neurons [44]. Behavioral variables such as attention to a potentially threatening stimulus result in sensitization of dorsal horns spinal cord neurons. Moreover, behavioral modulation associated with selective attention to a perceived threat utilizes the same forebrain and brainstem structures and mechanisms as are involved in the development, amplification, and maintenance of persistent pain after actual tissue damage and inflammation [41].

Certain cognitive styles and personality traits have been associated with amplification of pain and its extension in

the absence of tissue damage. These include somatization, catastrophizing, and hypervigilance [49–52]. Thus, via descending pathways behavioral and cognitive therapies might also effect synaptic transmission in the spinal cord and thereby have the capacity to prevent or reverse long-term changes of synaptic strength in pain pathways [47].

### Evidence in FM

Exaggerated pain is common in whiplash and FM patients. Theoretically, peripheral mechanisms can account for the pain hypersensitivity. In FM, however, there is no evidence for peripheral sensitization as the cause of hyperalgesia, given the absence of real tissue damage. Peripheral sensitization is defined as a reduction in the threshold of nociceptive afferent receptors caused by a local change in the sensitivity of sensory fibers initiated by tissue damage [53]. Peripheral sensitization almost always depends on local inflammation, which may lead to decreased nociceptor thresholds. Despite extensive investigations, no tissue pathology, structural abnormalities, or evidence for a source of chronic stimulation of pain afferents have been detected in fibromyalgic patients [54].

Furthermore, FM pain lacks a distinct spatial localization [55]. This suggests that pathophysiological central mechanisms contribute to or are responsible for FM pain [56]. This has led to the hypothesis that the central nervous system is hyperexcitable in these patients. Central hypersensitivity could explain exaggerated pain in the presence of minimal and undetectable tissue damage, in that the nociceptive signal is amplified by the hyperexcitable neurons [57].

*Pain measurements* Studies in patients with chronic pain after whiplash injury and with FM have demonstrated exaggerated pain responses after sensory stimulation of healthy tissues [55, 58–63]. For example, at same level of thermal stimulation, FM patients perceived pain as 49 and 52% more intense than healthy controls and patients with low-back pain [61]. After-sensations at 15 s after heat taps were regarded as painful on 83% of FM patients, compared to 37% pain reports of healthy controls. The late after-sensations (2 min after heat stimulation) were rated as painful in 55 and 5% of FM and control subjects, respectively [55]. It was not mentioned in the results if all FM patients were subject to increased sensitivity, but there were always significant differences between the FM patients and the healthy controls.

Although most comparisons were made to pain-free subjects, some researchers, like Julien et al. [61], even compared the pain responses of FM patients to other pain

patients, such as patients with chronic low-back pain. They could also report significant differences. Despite the lack of research into the contribution of psychological factors in wind-up, these results suggest that input to central nociceptive pathways is abnormally processed in patients with FM. Intramuscular electrical stimulation has been used to assess the efficacy of temporal summation of painful muscle stimuli. Temporal stimulation was found to be more pronounced and to cause stronger pain and larger referred areas in FM patients compared to controls [60].

The increased efficacy of temporal summation in FM has even so been reproduced with cutaneous heat stimulation [55] and with cold and heat taps [59]. Facilitated temporal summation in patients with pain suggests that the efficacy of central processing is increased (central sensitization) in these patients [64]. In addition, after-sensation was greater in magnitude, lasted longer, and was more frequently painful in patients with FM [55]. The prolonged decay together with the augmentation provides evidence for the presence of central sensitization [24, 25]. Immersion of the arm in circulating noxious cold water resulted in a 49% more intense pain in FM patients compared to healthy controls [61]. Further evidence of central sensitization in FM is seen by enlarged referred pain areas. Sørensen et al. [60] found that fibromyalgic patients experienced stronger pain and larger referred areas after intramuscular injection of hypertonic saline.

Moreover, spatial summation effect during increase of the stimulation area was found only in patients with FM and not in healthy controls or in patients with chronic low-back pain [61]. This indicates that pain inhibitory systems are not optimally recruited in patients with FM. FM patients perceived pain at the same intensities and unpleasantness during the ascending and the descending sessions (fingertip to shoulder and shoulder to fingertip immersion). In healthy controls and patients with low-back pain, the noxious stimulation of a large surface area results in an activation of a large population of nociceptive afferents that induce endogenous inhibitory responses, resulting in a decreased response in the dorsal horn neurons, and subsequently leads to lower pain intensities afterward.

Given that FM patients experience similar pain intensities in the descending session after noxious stimulation of the whole arm, this study clearly demonstrated that FM patients present with a lack of activation of endogenous inhibitory systems [61]. Secondly, Lautenbacher and Rollman [65] showed that tonic painful and non-painful thermal stimulation of the foot increased the pain thresholds to electrical stimulation applied to a non-tender point (inner forearm) in healthy controls but had no effect on patients with FM. Kosek and Hansson [66] found that tourniquet ischemic pain in an arm increased the pressure pain threshold in healthy controls but not in FM patients,

suggesting once more a deficiency in the latter of a pain-inhibitory phenomenon termed “diffuse noxious inhibitory control” (DNIC) [66, 67]. Similarly, aerobic exercise has been shown to decrease wind-up pain in normal subjects but increased it in FM patients, suggesting the possibility of reduced endogenous analgesic mechanisms [68]. Also, isometric exercise (i.e., hand-grip exercise) resulted in increased thermal pain ratings and decreased pain thresholds, both ipsilateral and contralateral to the exercised extremity [69]. These investigations support a general hypothesis that FM reflects a disorder affecting modulation of pain sensitivity [66, 67]. In one such scenario, tonic DNIC is present in the normal situation, and its pathological absence results in the spontaneous pain and evoked pain sensitivity associated with FM [34].

*Measurements of excitability* The results of the above-mentioned studies, however, are based on pain reports of the patients and thus subjective in nature, and it was not clear whether this hypersensitivity was the result of central mechanisms or whether the hypersensitivity was the cause of hypervigilance. Banic et al. [57] could provide objective evidence by quantifying the minimal intensity of transcutaneous electrical stimulation of the sural nerve required to evoke flexion reflex in the biceps femoris. This study clearly demonstrates that spinal cord neurons are sensitized in chronic pain after whiplash and in patients with FM; because the stimuli were delivered at random time intervals and the latency of EMG response was measured, voluntary symptom amplification could be ruled out. Moreover, the electrical stimulation bypasses peripheral receptors.

*Cognitive emotional sensitization* Patients with FM or other pain disorders often receive the message that it is “all in their head”. One construct that has been hypothesized to explain the pain amplification in FM is that of hypervigilance [34]. This hypothesis of hypervigilance has been argued by McDermid et al. [70]. FM showed an increased aversiveness to non-painful stimuli such as loud noise. Also, Crombez et al. [71] reported significant correlations between hypervigilance and pain intensity in FM patients. Furthermore, exposure to stressful situations, including noise, lights, and weather, is known to exacerbate symptoms of FM, including pain [72].

In addition, FM patients with catastrophic thoughts report increased pain intensities [73–75]. Hassett et al. [74] found catastrophizing (27% of the variance) and depression (30% of the variance) to be significant predictors of pain. Finally, kinesiophobia and fear of pain are related to pain severity in patients with FM [76].

The foregoing relations between emotions or cognitions and reported pain severity support the hypothesis of cognitive emotional sensitization in FM.

*Central abnormalities in FM* FM patients differ from healthy persons in regional cerebral blood flow (rCBF) distribution in several brain structures involved in pain processing and pain modulation both at rest and during experimental pain induction. Patients with FM exhibited significantly lower rCBF levels, during rest, in the thalamus and the caudate nucleus [17]. Dysregulation of thalamic activity and hypoperfusion of the caudate nucleus may contribute to the abnormal pain modulation, given the results of previous investigations [77–79]. In addition to nociceptive transmission, the thalamus also plays an important role in pain modulation. Animal studies proved that thalamic stimulation induces analgesia and lesions of the thalamus cause hyperalgesia [77, 78].

Similarly, stimulating the caudate nucleus decreases pain behavior [79]. During pain induction in patients with FM, the absence of significant thalamic activation and a bilateral activation of the somatosensory cortices and the right anterior cingulate cortex was seen [80]. The patterns of cortical activation may be characteristic of patients with allodynia, and pain-induced activation of the right anterior cingulate cortex is associated with the use of maladaptive coping strategies [81]. Patients recruited by Bradley et al. [80] indeed reported significantly greater use of emotion-focused coping strategies (e.g., praying and hoping) during pressure stimulation. In addition, increased right frontal brain activity seemed related to increased pain sensitivity [82].

Furthermore, FM patients are characterized by relatively high cerebrospinal fluid levels of substance P [20]. This finding indicates that abnormal brain activity in persons with FM is associated with abnormal CSF levels of a neuropeptide involved in pain transmission [80]. In addition, it is shown that a subgroup of FM patients present with mycoplasma infections [83]. Infection triggers the release of the pro-inflammatory cytokine interleukin-1 $\beta$ , which is known to play a major role in inducing cyclooxygenase-2 (COX-2) and prostaglandin E2 expression in the central nervous system [84].

Peripheral nerve terminals can be sensitized by elevated COX-2 amounts and prostaglandin E2. Peripheral infections are even able to activate spinal cord glia, leading to the release of NO and proinflammatory cytokines, enhancing the pain response [85]. Physiological symptoms, such as pain, can be explained by these mechanisms (“sickness response”).

### Central sensitization in CFS?

Direct evidence supporting the central sensitization hypothesis in CFS patients is currently lacking. But the present knowledge concerning CFS is suggestive of a central process similar to that seen in FM, given the great overlap between the two diseases and the observed similarities.

First, lower pain thresholds at different sites (hyperalgesia) are reported in patients with CFS, compared to controls [86, 87]. Similar to FM, the lack of peripheral tissue damage and the lack of a distinct localization of the pain complaints are suggestive of a central abnormality responsible for the chronic widespread pain. To our knowledge, there are no investigations that focused on abnormal wind-up, temporal summation, or spatial summation in CFS, to collect evidence for central sensitization in CFS. Yet, evidence of a dysfunctional central anti-nociceptive mechanism in CFS has been proved by Whiteside et al. [88]. They reported a decrease of pain threshold in patients with CFS after graded exercise, while healthy controls present an increased pain threshold. These findings are similar to those of Vierck et al. [68] in FM patients.

Secondly, the frequently reported opportunistic infections [89, 90] may lead to the “sickness response” and complies with the central sensitization hypothesis, as explained above. Indeed, elevated NO levels have been documented in CFS patients [91]. As earlier mentioned, NO plays an important role in the history of central sensitization and, therefore, central sensitization caused by NO would be likely in patients with CFS. The release of excessive amounts of Substance P in the CSF, however, could not be documented in patients with CFS, in contrast to FM patients [21]. The CFS patients in this study, however, did not experience chronic widespread pain, and it is not clear if they fulfilled the 1994 CDC criteria [2]. Given that 70% of the CFS patients do fulfill the ACR criteria for widespread pain [12], it is striking that the patients included in the investigation of Evengard et al. [21] (focused on the source of pain) did not report these pain complaints. Further research on that matter should analyze the CSF of CFS patients (fulfilling the Fukuda criteria) suffering from chronic widespread pain.

A third important argument in the central sensitization theory for CFS concerns the cognitive, psychological, and behavioral changes in patients diagnosed with CFS. CFS patients often present with depression [6, 92], catastrophizing [93, 94], somatization [95, 96], and kinesiophobia or fear avoidance [97–99]. In CFS, it is known that these psychosocial aspects are important factors in maintaining the complaints of CFS. These cognitions and emotions are able to influence pain perception via modulation of the descending pathways [44]. Furthermore, these “cognitive styles” and “personality traits” have earlier been mentioned to be associated with the amplification and the extension of pain [49–52].

Finally, brain imaging already provided evidence for altered brain activity in CFS. Patterns of functional brain activity in patients with FM are quite different from those in patients with CFS. Patients with CFS, relative to controls, showed significantly lower blood perfusion in the brain stem

[17, 18]. Patients with FM exhibited significantly lower rCBF levels, during rest, in the thalamus and the caudate nucleus [19]. However, the areas are different in FM and in CFS; both the affected areas could be related to central pain processing. Low brain stem rCBF levels may contribute to abnormal function of the locus ceruleus in patients with CFS. The locus ceruleus is involved in controlling descending anti-nociceptive pathways from the brain to the spinal dorsal horn [56]. In consequence, pain experiences of patients with CFS may be related to low resting state levels of functional activity in the brain stem [80].

## Conclusion

Chronic widespread pain can be the consequence of central sensitization. Central sensitization is known as an increased central neuronal responsiveness and causes hyperalgesia, allodynia, and referred pain and hyperalgesia across multiple spinal segments, leading to chronic widespread pain. Possible triggers for sensitization of the spinal cord have extensively been discussed, such as wind-up or temporal summation, dysregulated descending inhibitory pathways, and upregulated facilitatory modulation. Wind-up or temporal summation is the result of repetitive noxious stimuli, leading to an increase in electrical discharges in the dorsal horn. Inhibitory modulation can be impaired by abnormalities in the central nervous system and the facilitatory pain pathways can be stimulated by certain behavioral and cognitive factors.

This theoretical background can be applied to FM. In FM, studies already provided evidence for central sensitization as the cause of chronic pain. Temporal summation was found to be more facilitated, and the inhibitory pain modulation seemed impaired in FM patients. These findings can explain the chronic spontaneous pain in FM. Furthermore, some central abnormalities could be examined/objectified in FM: 1) hyperexcitability of the spinal cord, 2) decreased perfusion of pain-related brain structures, and 3) high levels of substance P in CSF. In addition, FM patients often present with pain hypervigilance, maladaptive coping strategies, and catastrophic thoughts, leading to cognitive central sensitization.

Based on the knowledge on central sensitization, on FM and on CFS, it is suggested that chronic widespread pain in CFS is the consequence of central sensitization. There are arguments and probable mechanisms that could explain this phenomenon in CFS. Also, in other chronic pain populations, central sensitization may play a key role. In fact, there are many similarities between CFS patients and other chronic pain populations such as patients with chronic low-back pain, whiplash, FM, etc. The psychosocial factors, for example, have been proved to contribute to pain perception

in these different pain populations. But the specific nature of CFS such as the immunological abnormalities, elevated NO amounts, preceding infections etc., invites further research, in particular, on the possible contributory role of these abnormalities to pain processing in CFS.

In FM, many researches have been conducted to prove the theory of central sensitization. In CFS, however, it sticks to “supposing.” To give a scientific basis to the theory, the protocols applied in FM investigations could be used for patients with CFS. It would, for example, be interesting to test the efficacy of temporal summation in CFS. The inhibitory control of pain could be another point of interest. The influence of exercise on pain tolerance has already been studied in CFS [88], however, on a relatively small sample. On the contrary, spatial summation has, to our knowledge, never been investigated in CFS. Furthermore, the role of depression, hypervigilance, kinesiophobia, catastrophising, etc. on chronic pain in CFS requires further research. To obtain more direct and objective information on central sensitization, the protocol described by Banic et al. [57] could be used to test the sensitivity of the central nervous system. Clearly, there are many possible research areas to test the hypothesis, but there is still a long way to go to elucidate the nature of the chronic pain in CFS.

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