Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients?

Jo Nijs, Marco L. Loggia, Andrea Polli, Maarten Moens, Eva Huysmans, Lisa Goudman, Mira Meeus, Luc Vanderweeën, Kelly Ickmans & Daniel Clauw

To cite this article: Jo Nijs, Marco L. Loggia, Andrea Polli, Maarten Moens, Eva Huysmans, Lisa Goudman, Mira Meeus, Luc Vanderweeën, Kelly Ickmans & Daniel Clauw (2017) Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients?, Expert Opinion on Therapeutic Targets, 21:8, 817-826, DOI: 10.1080/14728222.2017.1353603

To link to this article: http://dx.doi.org/10.1080/14728222.2017.1353603
Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients?

Jo Nijs\textsuperscript{a,b,c}, Marco L. Loggia\textsuperscript{a}, Andrea Polli\textsuperscript{a,b}, Maarten Moens\textsuperscript{a,e}, Eva Huysmans\textsuperscript{a,b}, Lisa Goudman\textsuperscript{a,b,d}, Mira Meeus\textsuperscript{a,f,g}, Luc Vanderweeën\textsuperscript{a,b,h}, Kelly Ickmans\textsuperscript{a,c} and Daniel Clauw\textsuperscript{a}

\textsuperscript{a}Department of physiotherapy, human physiology and anatomy, Pain in Motion International Research Group, Vrije Universiteit Brussel, Brussels, Belgium; \textsuperscript{b}Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium; \textsuperscript{c}Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium; \textsuperscript{d}Department of Neurosurgery and Radiology, University Hospital Brussels, Brussels, Belgium; \textsuperscript{e}Department of Manual Therapy, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium; \textsuperscript{f}Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Ghent, Belgium; \textsuperscript{g}Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp, Antwerp, Belgium; \textsuperscript{h}Private Practice for Spinal Manual Therapy, Schepdaal-Dilbeek, Belgium; \textsuperscript{i}Chronic Pain and Fatigue Research Center, University of Michigan, Ann Arbor, USA; \textsuperscript{j}MGH/HST A. A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA

ABSTRACT

Introduction: The mechanism of sensitization of the central nervous system partly explains the chronic pain experience in many patients, but the etiological mechanisms of this central nervous system dysfunction are poorly understood. Recently, an increasing number of studies suggest that aberrant glial activation takes part in the establishment and/or maintenance of central sensitization.

Areas covered: This review focused on preclinical work and mostly on the neurobiochemistry studied in animals, with limited human studies available. Glial overactivity results in a low-grade neuroinflammatory state, characterized by high levels of BDNF, IL-1\textbeta, TNF-\alpha, which in turn increases the excitability of the central nervous system neurons through mechanisms like long-term potentiation and increased synaptic efficiency. Aberrant glial activity in chronic pain might have been triggered by severe stress exposure, and/or sleeping disturbances, each of which are established initiating factors for chronic pain development.

Expert opinion: Potential treatment avenues include several pharmacological options for diminishing glial activity, as well as conservative interventions like sleep management, stress management and exercise therapy. Pharmacological options include propentofylline, minocycline, \beta-\textsuperscript{2}-adrenergic receptor antagonists, and cannabidiol. Before translating these findings from basic science to clinical settings, more human studies exploring the outlined mechanisms in chronic pain patients are needed.

1. Introduction

Modern pain neuroscience has advanced our understanding about pain, including the role of central sensitization (CS, or central hyperexcitability) in the presence and amplification of (persistent) pain experiences. CS is defined as ‘an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity’ [1] and ‘increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input’ [2]. In many patients with chronic pain, a clear origin for nociceptive input is lacking or is not severe enough to explain the severe pain and other symptoms experienced by the patient. In such patients, CS is often present and can explain the clinical picture. It is now well established that the mechanism of sensitization of the central nervous system partly explains the chronic pain experience in many patients, including those with neuropathic pain [3], whiplash [4], chronic low back pain [5], osteoarthritis [6], headache [7], pain following cancer treatment [8], fibromyalgia [9], chronic shoulder pain [10], chronic fatigue syndrome [11], rheumatoid arthritis [12], temporomandibular disorders [13], patellar tendinopathy [14], orofacial pain [15], and lateral epicondylalgia [16,17].

CS encompasses various related dysfunctions within the central nervous system, all contributing to altered, often increased responsiveness to a variety of stimuli-like mechanical pressure, chemical substances, light, sound, cold, heat, stress, and electricity [18]. Such central nervous system dysfunctions include sensitization of spinal cord neurons [19], altered sensory processing in the brain [20] with increased brain activity in areas known to be involved in acute pain sensations (primary and secondary somatosensory cortices, thalamus, insula, anterior cingulate cortex, and prefrontal cortex) [21], involvement of several brainstem nuclei (nucleus cuneiformis, periaqueductal gray, parabrachial nucleus, etc.), altered brain neurochemistry [22], poor functioning of descending antinociceptive mechanisms [23,24], and increased activity of brain-orchestrated nociceptive facilitatory pathways [20]. These facilitatory pathways probably relate to the increased brain activity as described above, and they might be (further) activated by cognitive–emotional factors such as...
pain catastrophizing, stress, hypervigilance, lack of acceptance, depressive thoughts, and maladaptive illness perceptions (e.g., perceived injustice, low self-efficacy).

CS is also accompanied by an exaggerated central nervous system response, to nociceptive [25] or even non-nociceptive [26] input, resulting in pain that is disproportionate to the stimulus [27]. CS is often associated not only with severe pain but also with various other symptoms like sleep disturbances and stress intolerance [28,29]. In spite of our increased understanding of the mechanisms explaining (hypersensitivity) symptoms in patients with chronic pain, there is much to learn about the development of chronic pain, including the etiological mechanisms underlying CS. Why do some patients develop CS pain while others do not?

Glia are nonneuronal cells that reside within the nervous system. A subset of glial cells, in particular microglia and astrocytes, resembles physiological functions of immune cells and therefore can be referred to as immune-like [30] or immune competent [31] cells. For too long, neuroscientists have focused on neurons and neglected the glia, probably relating to the fact that basic neuroscience was historically developed from methods monitoring electrical signaling in (between) neurons [32]. Yet, glia far outnumber neurons, as well as having much higher cellular diversity and functions than neurons [33].

An increasing number of preclinical studies suggest that aberrant glial activation might explain the establishment and/or maintenance of CS, and persistent pain [30,34–37], and that poor sleep [38] and severe stress [31,39,40] each can result in such aberrant glial activation. Here, we update the reader with our current understanding of the potential role of aberrant glial activity in explaining (the onset of) CS in patients with chronic pain, together with severe or long-term stress and sleep disturbances as triggers for aberrant glial activation. Finally, potential pharmacological and non-pharmacological treatment avenues for these neuro-immune interactions are discussed. This review focused on preclinical work and mostly on the neurobiochemistry studied in animals, with limited human studies available.

2. Glial activation, neuroinflammation, and the etiology of CS pain

The three major glial cell types are microglia, astrocytes, and oligodendrocytes. While oligodendrocytes have recently been implicated in the development of central pain [41], here we will focus mostly on the first two classes of glia, as their role in pain is more established. Microglia are sometimes referred to as the resident macrophages in the brain: in the presence of injury or infection, they become activated and work together to repair the damage and restore brain homeostasis [31,42]. To allow microglia to perform this important physiological function, it is crucial that they are not static cells but rather hold a high degree of motility within the central nervous system. While in the past, authors would characterize microglia as being either in a ‘resting state’ or an ‘activated state,’ today most accept that microglial cells, when not activated, are in a ‘surveillance’ rather than ‘resting’ state. Microglia are in fact continuously protracting and retracting their processes to scan the molecular and cellular microenvironment, including synapses, in their proximity [31].

In addition, microglia play a crucial role in synapse formation, synapse elimination (e.g. microglia can phagocytose hippocampal synapses), and refinement of neuronal circuits with complement proteins C1q and C3 as critical mediators [31]. Synapse formation/elimination is a crucial mechanism for many functions, including learning (i.e. long-term potentiation and long-term depression) and protection against injury. Rapid eye movement sleep is important in selectively eliminating and maintaining newly formed synapses, which in turn contributes to learning and memory consolidation [43]. Also, microglia motility is regulated by different modes of neuronal transmission: increased by glutamatergic neurotransmission and decreased by GABAergic neurotransmission [44]. Hence, microglia and neurons have bidirectional interactions and are constantly ‘fine-tuning’ each other.

Upon activation, microglia transform morphologically from a ramified (resting) to an ameboid (phagocytic) phenotype [42]. Not every activated microglia present a pro-inflammatory pattern. Microglia inflammatory actions depend on the activation subtype: the pro-inflammatory subtype (i.e. M1) secretes pro-inflammatory cytokines (e.g. tumor necrosis factor α [TNF-α], interleukin 1β [IL-1β], IL-6), neurotrophic factors (e.g. brain-derived neurotrophic factor or BDNF), and free radicals that are toxic to the surrounding cells [42], while the anti-inflammatory subtype (i.e. M2) secretes anti-inflammatory cytokines (e.g. IL-10) for resolving inflammation and trophic factors for promoting tissue healing [45]. Such generation of inflammatory responses is mediated through the activation of p38 mitogen-activating kinase (MAPK) in spinal microglia, at least in male (but not in female) animals [46], which plays a pivotal role in wide dynamic range neuronal hyperexcitability [47].
M1–M2 polarization of microglia also has different effects on synaptogenesis: M2-microglia stimulate synaptogenesis, while M1-microglia in inflammatory state result in synapse elimination (synaptic stripping, a mechanism linked to learning processes) [31]. The concept of M1 versus M2 polarization of microglia is currently being debated, since it may represent a continuous process rather than different subtypes [48]. Also, the fact that glial cells have different dynamics and a different order of activation after stimulus might also explain differences across patients, possibly even explaining in part why some people develop chronic pain after a certain event (e.g. physical trauma), while others do not.

In the acute or subacute phases of injury and pain, glial activation likely plays an adaptive role, as it favors tissue healing and recovery. When glial activation does not resolve, and becomes chronic, it can become pathogenic and lead to collateral damage of nearby neurons and other glia [42]. Resulting low-grade chronic neuroinflammation is an underlying feature of many neurological disorders like major depressive disorder [42], Alzheimer’s disease [42], Parkinson’s disease [42], schizophrenia [42], traumatic brain injury [49], diabetic retinopathy [50], and brain tumors [51]. Similar chronic neuroinflammation might also be involved in the pathogenesis of chronic pain [36,52–55].

Aberrant glial activity has the potential to initiate CS through several mechanisms. Activated microglia have been identified as a major source for the synthesis and release of BDNF which is responsible for increasing neuronal excitability by causing disinhibition in dorsal horn neurons in the spinal cord [56,57]. This microglia-to-neuron communication includes not only attenuation of the pain inhibitory action of gamma-aminobutyric acid (GABA) but also of glycine receptor-mediated inhibition [57]. Increased glial synthesis of BDNF in the nociceptive pathways in patients with CS pain can be considered a pathophysiological response [58].

Elevated IL-1β gene expression in microglia has been linked to long-term potentiation induction and maintenance (and consequently to learning, fear, and memory processes) [31]. Likewise, gliosis is accompanied by increased TNF-α availability, which in turn induces long-term potentiation [59] and consequent enhanced synaptic efficacy [31] and pain sensitization [59]. Long-term potentiation and enhanced synaptic efficacy are (partly overlapping) key mechanisms underlying increased excitability of the central nervous system pain [60–62] and the formation of (maladaptive) pain memories [63,64] in patients with chronic pain and CS, possibly coordinated by gliosis. Likewise, pro-inflammatory mediators, produced by activated microglia during neuroinflammation, directly activate nearby neurons, which express receptors for these pro-inflammatory cytokines, which in turn become hyperexcitable [31].

While structurally and functionally very different from microglia, astrocytes have been convincingly demonstrated to play a key role in the pathogenesis of persistent pain in animal models [65–67]. Astrocytes are capable of detecting the presence of an insult, such as an inflammatory challenge [68] or nerve injury [69], to which they respond by exhibiting hypertrophy, and increasing expression of a variety of molecules that contribute to hyperalgesia and allodynia, such as the enzyme nitric oxide synthase [70], the pro-inflammatory cytokine IL-1 [68], and the chemokines CXCL1 [71].

In addition to the above-explained mechanisms, other pathways could link aberrant glial activation and CS pain. This includes the expression and function of the adenosine A1 receptor (A1AR) on microglia [72]. Selective stimulation of A1AR inhibits the morphological activation of microglia, possibly by suppressing the Ca(2+) influx induced by ATP treatment, and microglial cells, pretreated with the A1AR agonist, exhibit lower capability to facilitate spinal nociceptive neurons [72]. In addition, proteinase-activated receptors are a family of G-protein-coupled receptors available in neurons, microglia, and astrocytes. They are activated by proteases, initiating a series of intracellular signal pathways that result in not only sensitization of pain pathways [73–75] but also activation of the nuclear factor NK-κB [76], which is important for neural plasticity in the nervous system, including synaptogenesis [77]. Activated NK-κB has the capacity to increase the expression of BDNF in central neurons [77].

Importantly, pharmacological disruption of astroglial and microglial function, or of the action of its products, can reduce, reverse, or prevent nociceptive behaviors in animal models [68–70,78]. Taken together, these studies demonstrate that astrocytes, just like microglia, play an important role in the pathogenesis of persistent pain in animals.

In fact, nearly all of the evidence that microglia might play an important role in the maintenance of chronic pain was derived from animal models. The first human study on glial activity used a sensitive in vivo marker of glial cell activation monitored using positron emission tomography (PET) to show that limb denervation (n = 7) induces glial activation, beyond the first-order projection area of the injured neurons, in the human thalamus but not somatosensory cortex [79]. Only the one patient with bilateral nerve injury showed bilateral microglia activation in the thalamus, while the other six patients had only contralateral activation. A more recent human study using PET-magnetic resonance imaging identified a pattern consistent with brain glial activation in patients with chronic low back pain [36], a condition known to be related to CS [5]. Other human studies using cerebrospinal fluid also support a potential role for altered central cytokines and neurotrophic factors, consistent with aberrant glial activation and related neuroinflammation, in a number of chronic pain states despite varying etiologies [35]. Hence, the available evidence supports an association between aberrant glial activity and neuroinflammation in humans with chronic pain, but direct evidence showing that aberrant glial activity and neuroinflammation lead to the development of CS in humans is currently unavailable and requires more research.

If aberrant glial activation or gliosis explains the onset of CS, the next question will be what triggers aberrant glial activation? Neuroscience has provided us with a number of potential answers, including severe stress and sleep disturbances that may primarily target the brain. In the spinal cord, glial activation is mainly triggered by peripheral tissue inflammation or nerve damage. Still, in some instances,
aberrant glial activation may not suffice for pain hypersensitivity, necessitating to look beyond glial-triggered neuroinflammation toward the consequences of such aberrant glial activation and related neuroinflammation on brain morphology and functioning.

3. Stress as a trigger of glial activation and consequent morphological brain changes

Stress can be defined as the continuous struggle of living organisms to preserve an internal dynamic state of equilibrium (homeostasis) [80]. Any factor, being either physical, psychosocial, or emotional, that challenges homeostasis, is labeled as a stressor [80]. High levels of anxiety in the time period surrounding the traumatic musculoskeletal injury predict development and maintenance of moderate-to-severe chronic pain [81]. Likewise, childhood maltreatment (emotional abuse) is not only associated with increased risk of chronic (low back) pain, it also relates to long-lasting CS to nociceptive stimuli as seen in a subgroup of (highly debilitated) people with chronic low back pain [82].

In response to long-term stress, the body is exposed to high levels of glucocorticoids. Glucocorticoids coordinate the expression of subsets of genes involved in signal transduction, neuronal structure, vesicle dynamics, neurotransmitter catabolism, encoding of neurotrophic factors and their receptors [80]. Altogether, stress results in a highly coordinated set of changes in gene expression underlying neuronal plasticity [80], glial activation and consequent neuroinflammation with increased IL-1β and IL-6 mRNA expression [31, 39, 40]. Indeed, stress and the resulting noradrenaline plus glucocorticoids activate microglia (which express α1, α2, β1, and β2-adrenergic and glucocorticoid receptors), resulting in neuroinflammation with increased availability of pro-inflammatory cytokines like IL-1, TNF-α, and IL-6/gliosis as described above [31] (Figure 1). Stress activates glia in a way that they transform into the pro-inflammatory subtype [39, 40], which could then induce CS. Long before they became activated, microglia might have been primed by a traumatic event so that a second ‘hit’ (e.g. another trauma or stress) induces an exaggerated glial response (the ‘double-hit’ hypothesis as described in other neuroinflammatory disorders [83]).

Not surprisingly, in response to stress, microglia are found to become activated in several brain regions, including the prefrontal cortex, the lateral, basolateral, central, and basomedial nuclei of the amygdala and in the CA3 and dentate gyri of the hippocampus [31]. These brain areas undergo morphological changes in response to stress [84–86] and also play a cardinal role in chronic pain [63, 87–89]. Microglia, through several mechanisms including the production of BDNF [90], may explain such stress-induced morphological changes in the brain and even CS (Figure 1). The pro-inflammatory mediators produced by activated microglia during neuroinflammation directly activate receptors on nearby neurons, inducing their hyperexcitability [31].

Surprisingly, the morphological brain changes in response to chronic stress are somewhat site-specific rather than diffuse, and primarily involve hypertrophy in the amygdala and atrophy in the prefrontal cortex and hippocampus [84, 85]. This may be partially related to the distribution of glucocorticoid receptors, which are widely expressed in the brain but have high densities in the medialprefrontal cortex [91], and specificity in the hippocampus and amygdala [80, 91]. Initial experiments regarding the morphological changes in key brain areas in response to chronic stress were conducted on animals, later on backed up in human (mainly observational) studies [84, 85]. These morphological changes can be induced by repeated exposure to mild stressors or brief but intense stress [91]. It is important to emphasize that these stress-induced morphological changes may be reversible [91] and hence do not reflect genuine brain damage but rather a form of plasticity. These morphological changes might protect brain areas from permanent excitotoxic damage and therefore be adaptive [90].

4. Sleep as a trigger of glial activation and neuroinflammation

In the absence of other intrinsic sleep disorders and shift work, insomnia is defined as >30 min sleep latency and/or minutes awake after sleep onset for >3 days/week for >6 months [92, 93]. Stress, sleep, and pain are closely interconnected. Insomnia is highly prevalent among patients with chronic pain, with 53–90% of chronic pain patients suffering from a clinically significant degree of insomnia [94–97]. This might in part be attributed to the role of stress. First, daily life stress (e.g. worry about going to work the next morning) can perturb sleep [98]. Likewise, major stressful life events and/or traumatic events such as natural disasters, combat, or a traffic accident result in sleep architecture changes that reflect poor sleep [98]. Increased awakening and decreased sleep efficiency are the most sensitive sleep architecture variables in response to stress [98]. Second, poor sleep (e.g. lying awake at night or being unable to fall asleep) can be a stressor. Third, the consequences of poor sleep (i.e. feeling itchy and fatigued) result in a marked diminished ability to cope with everyday’s stressors. For all these reasons, it seems logical that sleep management is often included as part of stress management programs.

When addressing sleeping problems in the context of pain neuroscience, it is important to highlight that a single night of total sleep deprivation in healthy people is able to induce
generalized hyperalgesia and to increase state anxiety [99,100]. These findings suggest that sleep problems might not only perpetuate the central nervous system hyperexcitability in patients with chronic musculoskeletal pain but also serve as an initiating factor. Our current understanding of sleep neuroimmunology provides potential links between sleep difficulties and (the onset of) pain.

Melatonin is a neurohormone crucial for (deep) sleep and analgesia. Preclinical studies revealed that selective MT2 melatonin receptor partial agonists hold analgesic properties through modulation of ON/OFF cells of brainstem descending antinociceptive systems in neuropathic pain models [101,102].

Other neural mechanisms may contribute to the close interaction between chronic pain and poor sleep. While proper sleep facilitates immune health, sleep deprivation results in low-grade inflammatory responses [103–105]. This low-grade inflammatory response as a consequence of sleep deprivation includes increased levels of IL-6, prostaglandin E2 [104,105], and nitric oxide [38] possibly mediated by cerebral microglia [38]. Even low levels of inflammatory cytokines are known to affect brain function [106] which correlates with observations of increased sensitivity to painful stimuli following sleep restriction [100,104,107]. Sleep apnea, sometimes diagnosed in patients with chronic pain, is characterized by interrupted hypoxia, which in turn activates brain microglia toward an activated, pro-inflammatory state [108]. Taken together, sleep deprivation imparts a glia-mediated low-grade inflammatory response leading toward increased sensitivity to pain as typically seen in chronic pain sufferers.

Understanding that aberrant glial activation or gliosis possibly explains the onset of CS, as summarized in Figure 2, raises the question how to translate these findings to therapeutic targets? Likewise, understanding that aberrant glial activation can be due to chronic stress exposure and/or sleep disturbances raises the question how to account for it in clinical practice? The study of glia’s role in humans with chronic pain, and the mechanism of CS in particular, is still in its infancy, making it too early to translate these findings to clinical practice. However, thinking of potential therapeutic targets provides new innovative avenues for experimental testing of these ideas in humans with CS and chronic pain within a research setting.

5. Treatments that have the potential to normalize glial activity

Pharmacological treatments like minocycline, an antibiotic, theoretically hold the capacity to target aberrant glial activity in patients with chronic pain and CS. Animal work has demonstrated that (postoperative) minocycline antibiotics suppress microglia and astrocytes and reduce hippocampal TNF-α and IL-1β mRNA levels [109,110]. Likewise, minocycline inhibits spinal microglial activation and attenuate diabetic pain in rats with experimentally induced diabetes [111]. A recent small randomized clinical trial has shown that a brief treatment with minocycline was associated with a small, but statistically significant reduction in pain in patients with lumbar radiculopathy [112]. Since patients with lumbar radiculopathy demonstrate increased glial activity [36],) it is possible that minocycline reduces pain by inhibiting microglia in humans, as it does in animals.

Another therapeutic avenue includes pretreatment with β-adrenergic receptor antagonists (e.g. propranolol), which have been shown to reduce microglial activation in an animal model [113]. In vitro work showed that ketamine inhibited some of the inflammatory responses of both astrocytes and microglial cells [114]. In addition, cannabidiol, a major non-psychotomimetic constituent of Cannabis sativa, inhibits microglial activation and consequent neuroinflammation [115]. Still, for all these treatments, it remains to be established whether they are able to normalize glial activity in humans, and if so, whether such glial effects are accompanied by analgesic effects (Table 1).

In addition, inhibitors of cytokine synthesis closely linked to glial activity, including propentofylline, have been explored for the use as therapeutic agents for the treatment of neuropathic pain [116]. Human microglia were less responsive to propentofylline treatment [116], casting doubt whether direct microglial inhibition is a relevant therapeutic target for patients with chronic pain. However, methodological concerns with these studies (the length of the trial, the dosage used, the specific

![Figure 2](image_url). Mechanisms linking glial overactivation to the development of central sensitization. The displayed mechanisms are mainly based on animal studies. BDNF: brain-derived neurotrophic factor; GABA: gamma-aminobutyric acid; IL: interleukin; TNF: tumor necrosis factor.
population targeted, and potential interaction with other drugs or food intake) limit the significance of these negative study outcomes [118].

Also, the reasoning outlined above regarding the possible role of aberrant glial activity and neuroinflammation in relation to CS is focused primarily on the onset of CS. If CS has been initiated and the aberrant glial activity and neuroinflammation has been present for some months or even longer, this has likely resulted in neuroplastic changes including some of the above-discussed changes in brain morphology or connectivity. When neuroplastic changes are already established, targeting aberrant glial activity might be too late or at best can prevent further acceleration of CS in chronic pain patients, rather than serving as a potential treatment for chronic pain. This reasoning is supported by animal work, showing that after spinal nerve ligation, dorsal horn microglia are activated first, followed by the activation of astrocytes, accompanied by a decrease in microglial activity [119]. Hence, targeting the aberrant glial activity might be a new therapeutic avenue for the prevention of the development, rather than the treatment of CS and chronic pain. A preclinical study found positive outcome when glia-suppressing drugs are delivered in the early postoperative phase [110], but this idea requires experimental testing in humans. The possibility to image glial activation in vivo [36] may help to identify patients most likely to benefit from this therapeutic approach, and to identify optimal treatment window, duration, or dosage.

6. Conclusion
An increasing amount of animal research data support the idea of aberrant glial activity as a potential underlying, even etiological, mechanism of CS. Such glial overactivation results in a low-grade neuroinflammatory state, characterized by high levels of BDNF, IL-1β, and TNF-α, which in turn increases the excitability of the central nervous system neurons through mechanisms like long-term potentiation and increased synaptic efficiency. Other mechanisms linking aberrant glial activation to the development of CS include attenuation of the nociceptive inhibitory action of GABA and glycine receptor-mediated inhibition. In addition, aberrant glial activity in chronic pain might have been triggered by severe stress exposure, and/or sleeping disturbances, each of which are established initiating factors for chronic pain development. Potential treatment avenues include several pharmacological options for diminishing glial activity, as well as conservative interventions like sleep management, stress management, and exercise therapy. Before translating these findings from basic science to clinical settings, more human studies exploring the outlined mechanisms in chronic pain patients are needed.

The present work is focused on the role of the glia. Other neuro-immune pathways also exist. For instance, in addition to stress and sleep problems, animal work suggests that neuro-trauma results in aberrant glial activation [120]. Also, neuroinflammation observed in animals in response to stress may not be attributed solely to glial activation: stress also induces monocyte trafficking to the brain (e.g. from the bone marrow to the amygdala), resulting in inflammation (i.e. IL-1)-mediated anxiety-like behavior [39,40]. This increased monocyte recruitment to the brain is a unique pathway in which the immune system communicates with the brain [39]. In addition, animal research findings revealed gender differences, including a microglia-independent pathway to mediate pain hypersensitivity [37]. According to those studies, microglia are not required for the development of mechanical pain hypersensitivity in female mice, as they achieved similar levels of pain hypersensitivity using adaptive immune cells, likely T lymphocytes [37,121,122]. Monocyte trafficking might be the preferred pathway for mediating pain hypersensitivity in females [39].

The present review focused on explaining the underlying mechanisms of CS, a mechanism now established to contribute to wide variety of pathologies. It is difficult to combine findings from a large range of different pathologies, studies at different molecular levels and from various types of experiments in one paper. However, the paper aims at creating a bridge between preclinical and clinical data, in order to contribute to translational efforts in the field (or at least stimulate translational work in this area).

7. Expert opinion: non-pharmacological treatment options to normalize glial activity
We emphasized the role of severe stress and sleeping disturbances in triggering aberrant glial activity, implying that aberrant glial activity is not the cause, but instead one part in the long chain of CS initiating events. Hence, conservative interventions like stress and sleep management seem warranted.

Within the field of conservative interventions, exercise is another intervention that is helpful in many chronic pain

### Table 1. Potential therapeutic avenues for normalizing glial activity in patients with chronic pain.

<table>
<thead>
<tr>
<th>Name of treatment</th>
<th>Type of treatment</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline</td>
<td>Antibiotic</td>
<td>Suppresses microglia and astrocytes [109,110]</td>
</tr>
<tr>
<td>Propranolol</td>
<td>β-Adrenergic receptor antagonist</td>
<td>Reduces microglial activation [113]</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA blocker</td>
<td>Inhibits inflammatory responses of astrocytes and microglia [114]</td>
</tr>
<tr>
<td>Propentofylline</td>
<td>Atypical methylxanthine</td>
<td>Inhibits cytokine synthesis [116]</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>A major non-psychotomimetic constituent of Cannabis sativa</td>
<td>Inhibits microglial activation [115]</td>
</tr>
<tr>
<td>Stress management</td>
<td>Conservative intervention</td>
<td>Prevents (further) glial (over)activation?</td>
</tr>
<tr>
<td>Sleep management</td>
<td>Conservative intervention</td>
<td>Prevents (further) glial (over)activation?</td>
</tr>
<tr>
<td>Exercise therapy</td>
<td>Conservative intervention</td>
<td>Reverses astrocyte and microglia hyperactivity [117]</td>
</tr>
</tbody>
</table>

The mechanisms of action are currently based on animal studies mainly. Any therapeutic choice of pharmacological option for normalizing glial activity in patients with chronic pain will rely on many factors, including the type of chronic pain. NMDA: N-methyl-D-aspartate.
Exercise increases glial fibrillary acidic protein expression in hippocampal astrocytes, more specifically in the stratum radiatum, a region that contains numerous astrocytes and is important for learning and memory [123]. The increased expression of the astrocytic marker ‘glial fibrillary acidic protein’ implies that exercise results in a substantial increase in astroglial metabolism and protein synthesis, consistent with a healthy cellular hypertrophy in response to increased physiological demands [123]. This notion is supported by the observed change in morphology of the astrocytes in response to exercise [123]. This astrocye activation in response to exercise can be explained by the increased production of growth factors like nerve growth factor, fibroblast growth factor, glial cell line-derived neurotrophic factor, and BDNF in response to exercise [42,124,125] – e.g. nerve growth factor and fibroblast growth factor are capable of inducing astrocytic proliferation. Astrocytic activation in response to exercise implies strengthened ‘tripartite’ synapses (astrocyte–presynaptic neuron–postsynaptic neuron), as astrocytes are needed (and change their morphology) around potentiated synapses to accompany neuronal plasticity as seen during long-term potentiation [123].

The immune-modifying, more specifically whole-body anti-inflammatory, effects of moderate physical activity/exercise are now well established [42]. Exercise is known to change the inflammatory state to become anti-inflammatory or neuroprotective in several neuroinflammatory diseases such as multiple sclerosis and systemic lupus erythematosus [45]. Importantly, new research findings suggest that exercise can also have anti-inflammatory effects on the central nervous system [42,45]. More specifically, it seems plausible that exercise (therapy) can diminish the adverse and nonspecific activation of glial cells (gliosis) as typically seen in chronic neuroinflammation [45]. At the level of the glial cells, physical activity/exercise reduces microglial proliferation and triggers a switch toward an anti-inflammatory phenotype [42]. Such a phenotype shift is accompanied by a dramatic change in production of cytokines (i.e. from pro- to anti-inflammatory). This provides a plausible explanation for how regular and moderate exercise maintains glial activity within the healthy range, which in turn might contribute to the reduced incidence of brain disease (characterized by chronic neuroinflammation) in people who exercise regularly [42]. Still, evidence that physical activity/exercise alters glial activity in human brain areas involved in pain integration and perception is currently unavailable and represents an important focus for future research.

It remains uncertain whether we can apply this reasoning of anti-neuroinflammatory effects of exercise therapy to the treatment of CS in patients with chronic pain. One mice study supports this idea: physical training (i.e. swim exercise) in mice after nerve lesion reversed mechanical hypersensitivity, normalized nerve injury-induced nerve growth factor, and BDNF expression in the dorsal root ganglion, reversed astrocyte and microglia hyperactivity in the dorsal horn, which remained normalized after training cessation [117]. Another preclinical study showed that prolonged exercise normalizes early microglia- and astrocytes-mediated brain inflammation following myocardial infarction induction [126]. Also, the possible anti-neuroinflammatory effects of exercise therapy to the treatment of CS in patients with chronic pain are supported by studies showing decreased pain sensitivity following exercise therapy in chronic pain patients [127,128]. A final pathway through which exercise can benefit glial health [129] includes the stimulation of glial heat shock protein 72 expression [129]. Exercise induced increased neuronal and astroglial levels of heat shock protein 72 in normal spinal cord tissue, which facilitated functional recovery after experimental spinal cord injury [129]. Animal work has informed us that increased glial expression of heat shock protein 72 has anti-inflammatory effects and protects against astrogial apoptosis [129,130].

Acknowledgments

The first author is grateful to Boudewijn Van Houdenhove (MD, PhD), for motivating and inspiring him to explore the role of stress in relation to chronic pain.

Funding

K Ickmans, L. Goudman and E. Huysmans are funded by the Applied Biomedical Research Program, Institute for the Agency for Innovation by Science and Technology, Belgium (IWT-TBM project no. 150,180). J. Nijs is holder of the Chair ‘Exercise Immunology and chronic fatigue in health and disease’ funded by the Berekuyl Academy /European College for Decongestive Lymphatic Therapy, The Netherlands. A. Polli is a PhD research fellow funded by ME Research UK, a national charity funding biomedical research in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Declaration of interest

M. Moens received the Lyrica Independent Investigator Research Award (LIIRA) and received consultancy or speaker honoraria from Medtronic and Pfizer.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

43. Hallmark paper regarding the potential anti-inflammatory action of physical activity/exercise in the nervous system in health and disease.


• inspiring paper that potentially explains why and how exercise can diminish central sensitization in chronic pain.


