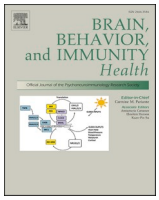
Brain, Behavior, & Immunity - Health 44 (2025) 100964

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



How does chronic psychosocial distress induce pain? Focus on neuroinflammation and neuroplasticity changes

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ARTICLE INFO

Keywords:
Chronic pain
Chronic primary pain
Chronic stress
Fibromyalgia
Unmet medical need
Neuroinflammation
Neuronal plasticity
Mood disorders

ABSTRACT

Chronic primary pain including fibromyalgia for the musculoskeletal system persists for more than 3 months. Its etiological factors and the pathophysiological mechanisms are not known, and therefore, there is no satisfactory therapy, it is an unmet medical need condition. The only etiological and aggravating factor is chronic psychosocial distress, which is known to cause neuroimmune and endocrine changes both in the periphery and the central nervous system. In this short review, we introduce our research perspective by summarizing the recent literature on the interactions between chronic pain, stress, and commonly co-morbid mood disorders. Immune activation, autoimmunity, neuro-immune-vascular crosstalks and neuroinflammation play roles in the pathophysiology of these conditions. Data on stress-induced neuroplasticity changes at cellular and molecular levels were also collected in relation to chronic primary pain both from clinical studies and animal experiments of translational relevance. Understanding these mechanisms could help to identify novel therapeutic targets for chronic primary pain including fibromyalgia.

1. Chronic primary pain as an unmet medical need condition, focus on fibromyalgia (FM)

According to the latest definition of the International Association for the Study of Pain chronic primary pain (CPP) is defined as pain lasting for more than 3 months without any specific underlying cause (Nicholas et al., 2019). It has substantial negative impact not only on the patients' quality of life and working abilities, but also on the healthcare system and the society (D'Onghia et al., 2022). Chronic psychosocial distress is known to be the only etiological and/or aggravating factor of these conditions (Barke, 2019; Nicholas et al., 2019; Scholz et al., 2019). Fibromyalgia (FM) and complex regional pain syndrome (CRPS) represent two out of the five main CPP categories. FM is a chronic widespread musculoskeletal pain without any known underlying background damage condition (Buskila and Sarzi-Puttini, 2006; Harden et al., 2010), with an incidence of 7–12 per 1000 per year (Creed, 2020; Weir et al., 2006). CRPS develops after a minor tissue trauma on the affected limb with excessive swelling and, with an incidence of 5–26 per 100,000 per year (de Mos et al., 2007; Ott and Maihöfner, 2018). These conditions share several common features as chronic primary pain syndromes; such as the lack of definitive etiology and pathophysiology, involvement of chronic psychosocial distress, potential autoimmunity, common mood disorders and psychological co-morbidities. However, they have many distinct characteristics regarding the localisation of the pain and concomitant autonomic nervous system disorders. In CRPS, a minor injury always precedes the condition, however, the extent of the chronic pain in the injured limb is disproportional to the original trauma. In contrast, FM develops without tissue damage, muscular tender points are specific, but there are no demonstratable lesions. Depression and anxiety are common comorbidities in FM patients, which suggests several common pathophysiological mechanisms and interactions between the pain and mood regulation pathways.

This review focuses on FM, which is the most common musculoskeletal chronic primary pain condition with no identified causative factors besides psychosocial distress and abnormal stress-coping capacities. This is still an under-diagnosed and often misunderstood disease, in which not only the diagnosis, but also the therapy is greatly challenging. The classical analgesic drugs such as non-steroid anti-inflammatory drugs and opioids are not or only minimally effective in FM conditions. The first line therapy are the adjuvant analgesics including

This article is part of a special issue entitled: Future of PNI 2nd edition published in Brain, Behavior, & Immunity - Health.

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https://doi.org/10.1016/j.bbih.2025.100964
Received 30 November 2023; Received in revised form 30 January 2025; Accepted 10 February 2025
Available online 10 February 2025

Table 1
Chronic stress-induced behavioral and molecular alterations in animal models of stress-induced pain, related to fibromyalgia.

Rodent Model (rat and mice)		Pain and mood	Neuroinflammation and inflammatory mechanisms
Models using stress paradigms	Repeated swim stress	Mechanical and thermal hypersensitivity (Quintero et al., 2000) Anxiety-like behavior EPM (Nazeri et al., 2018)	↑ CR3 microglia activation in dorsal horn of lumbar spinal cord (Quintero et al., 2003) ↑ IL-1 concentration in spinal tissue (Suarez-Roca et al., 2014)
	Intermittent cold stress	Mechanical and thermal hypersensitivity (Nishiyori and Ueda, 2008) Anxiety and depression-like behavior FST (Hata,' Hata' Eiji et al., 1995), EPM (Montserrat-De La Paz et al., 2013)	↑ Iba1 positive cells in hippocampus(Qu et al., 2017) No IL-1 and TNFα elevation in hypothalamus and prefrontal cortex (Girotti et al., 2011), but IL-1 elevation in the plasma(Liao and Lin, 2021)
	Repeated sound stress	Mechanical and thermal hypersensitivity (Khasar et al., 2005) Anxiety-like behavior OFT(Green et al., 2011), EPM (Hung et al., 2020)	IL-6 but not TNFα elevation in plasma levels in early life sound stress protocol (Alvarez et al., 2013)
	Chronic restraint stress	Mechanical and thermal hypersensitivity (Gamaro et al., 1998) Anxiety and depression-like behavior FST (Platt et al., 1982) TST(Yin et al., 2020), OFT (Liang et al., 2015), EPM (Jeong et al., 2013),	↑ GFAP and Iba1 immunoreactivity in the hippocampus and cerebral cortex (Fülöp et al., 2023) ↑ IL-1 in hippocampus (Guo et al., 2014)
Models without stress application	Reserpine-induced	Mechanical and thermal hypersensitivity (Nagakura et al., 2009) and spontaneous pain (Nagakura et al., 2019) Anxiety and depression-like behavior FST (Hubner de Souza et al., 2014), TST (Yao et al., 2020), OFT (Brusco et al., 2019), EPM (Kaur et al., 2019)	↑ GFAP fluorescence intensity in the lumbar spinal cord.(De La Luz-Cuellar et al., 2019) ↑ Iba1 immunoreactivity activation in the spinal dorsal horn (Taguchi et al., 2015) ↑ glia produced mediators: IL-1, TNFα in cerebral cortex region and in the hippocampus (Arora and Chopra, 2013; Xu et al., 2013)
	Acid saline-induced	Mechanical hypersensitivity (Sluka et al., 2001) Anxiety and depression-like behavior FTS, OFT (Lottering and Lin, 2021)	↑ GFAP expression in hippocampus (Abd-Ellatief et al., 2018; Lambert et al., 2000) ↑ IL-1 and TNFα in hippocampus (Abd-Ellatief et al., 2018)

GFAP = Glial fibrillary acidic protein; Iba1 = Ionized calcium binding adaptor molecule 1; FST=Forced swim test; TST = Tail suspension test; OFT=Open field test; EPM = Elevated plus maze test; IL= Interleukin; TNFα = Tumor necrosis factor alpha

antidepressants (e.g. amitriptyline, nortriptyline, duloxetine, venlafaxine) and antiepileptics (e.g. gabapentin, pregabalin), but they also have only minor effect in a subset of patients (Bellato et al., 2012; Macfarlane et al., 2017). Furthermore, psychotherapy might be effective on a long-term after months, but these treatments usually start together with medications at the earlier stages; further suggesting the complex treatment paradigm: targeting the psychosocial component of these diseases (Gomez-De-Regil and Estrella-Castillo, 2020). Therefore, there is a great need to understand the complex molecular mechanisms and pathways to identify novel, instant and fast acting pain-relievers and specific therapeutic options.

2. Chronic psychosocial distress as an etiological and aggravating factor of chronic primary pain: stress-pain interactions in FM

2.1. Clinical data

Positive correlations were found between the baseline stress levels and pain intensity scores in FM and other chronic widespread pain conditions in a longitudinal long-term clinical study (Bergenheim et al., 2019). Furthermore, both stress and pain catastrophizing showed strong positive correlations with pain severity and the co-occurrence of multiple painful diseases (Fillingim et al., 2020). Different psychosocial stressors influence the pathogenesis of low back pain, another chronic primary pain. The inflammatory cytokine interleukin-6 (IL-6), the sympathetic mediator norepinephrine, and resting heart rate were suggested to have predictive values in this condition (Wippert et al., 2022). The impact of chronic pain on stress levels, anxiety, and depression is confirmed, and the psychopathological profile, stress, and differences in coping mechanisms are associated with FM symptoms and pain threshold decrease (Weber et al., 2022). Psychotherapeutic tools like mindfulness in combination with exercise to reduce stress level was also effective for chronic pain (Deegan et al., 2023).

Trier Social Stress Test - a standardized and reliable acute psychosocial stress task that decreases both thermo- and mechanonociceptive thresholds resulting in hyperalgesia (increased pain sensitivity) and allodynia (pain induced by a non-painful stimulus, such as touch or stroke) in FM patients (Crettaz et al., 2013).

Besides the clinical, psychological and neuroimaging (e.g. fMRI) outcomes, postmortem brain tissue examination with high-resolution microscopic techniques and omics (transcriptomic, metabolomic, proteomic) analysis could provide information about the molecular mechanisms of the disease. Nevertheless, these approaches are not applicable in FM patients, since it is not a lethal disease and postmortem samples are not available without other serious concomitant diseases. Therefore, it is inevitable to perform extensive research on brain samples obtained from translationally relevant animal models.

2.2. Preclinical models to investigate chronic primary pain: stress-related pain mechanisms

Although no animal models are suitable for reflecting all aspects of the complex symptomatology of human diseases, they can provide a good basis for understanding the cellular and molecular pathophysiological processes.

Several FM rodent models including chronic stress as an etiological factor are currently used in the literature which mimics different aspects of the disease (Table 1.). To draw strong conclusions, more of these models are suggested to be parallelly investigated and validated by functional techniques (e.g. behavioral outcomes for pain, anxiety and depression), morphological and imaging methods (e.g. microscopy, fMRI), and pharmacological tools using drugs currently registered for FM therapy (e.g. antidepressants, opioids).

Different types of chronic stress paradigms, such as repeated swim stress (Quintero et al., 2000), intermittent cold stress (Nishiyori and Ueda, 2008), sound stress of four different frequencies combined with bradykinin hind paw injection (Khasar et al., 2005) as well as chronic immobilization stress induce both mechanical and thermal hyper-nociception similar to the FM patients (Da Silva Torres et al., 2003; Gamaro et al., 1998; Scheich et al., 2017). However, literature data suggests that not all stress types can mimic the basic symptoms of

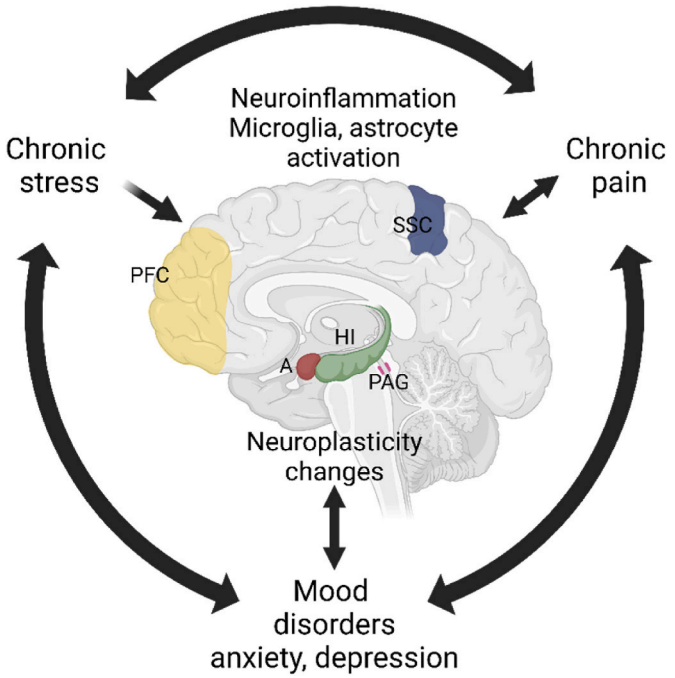

Fig. 1. Interactions of chronic pain, mood disorders and stress: chronic psychosocial distress induces neuroinflammation and neuroplasticity changes in brain areas involved also in pain processing, e.g. the prefrontal cortex (PFC), amygdala (A), hippocampus (HI), periaqueductal gray (PAG) and somatosensory cortex (SSC). Created with BioRender.com.

FM. Although chronic variable mild stress is an appropriate depression model, it is not suitable to investigate stress-induced pain mechanisms (Liu et al., 2018; Shi et al., 2010).

Systemic reserpine injection depleting monoamines mimics spontaneous pain, thermal and mechanical hyperalgesia (Nagakura et al., 2009). Meanwhile, acid saline (pH 4 hydroxyethyl-piperazineethane-sulfonic acid buffered saline) injection into the gastrocnemius muscle results in mechanical hypersensitivity, but the development of thermal sensitivity is debated (Sluka et al., 2001).

The characteristics of rodent FM models are summarized in Table 1.

3. Mood disorders as common comorbidities of chronic pain

Chronic pain patients often suffer from comorbidities of mental illnesses, such as depression and anxiety disorders (Dahan et al., 2014; McWilliams et al., 2003). Chronic psychosocial distress particularly in vulnerable patients with inappropriate coping abilities and resilience, induces rumination, consequent anxiety, mood negativities and depression (Bø et al., 2023; Bylsma et al., 2008; Richter-Levin and Xu, 2018). Higher percentage of mood disorders are present in FM patients compared to the healthy population (Galvez-Sánchez et al., 2019; Henao-Pérez et al., 2022; Wan et al., 2019). Depression as a comorbidity is also suspected to worsen the treatment outcomes in FM patients (Munipalli et al., 2022). In women, pain severity and catastrophizing were associated with both higher depression and anxiety levels (Hadlandsmyth et al., 2020). Personality traits such as neuroticism, conscientiousness and extraversion are associated with FM symptoms including pain, depression, anxiety and stress level (Seto et al., 2019). As a stress management method, cognitive behavior therapy significantly improved coping and self-reported depression ratings in FM (Karlsson et al., 2023).

Stress has a huge negative impact on patients' mental health and illness course, which often leads to depression. Similarly, in mice, chronic unpredictable stress results in anxiety and depression-like behaviors combined with severe cognitive impairment (Liu et al., 2020). Social defeat stress and subthreshold social defeat paradigm also induces depression-like behavior in mice accompanied by long-lasting hyperalgesia further suggesting interactions between mood disorders and pain (Pagliusi et al., 2020; Piardi et al., 2020).

In different rodent FM models, such as reserpine-, direct muscle harm- and stress-induced paradigms anxiety and depression-like behavior were also observed (Blasco-Serra et al., 2015; Liu et al., 2014; Scheich et al., 2017) which correlated with the extent of hyperalgesia (Zhao et al., 2022).

Both chronic pain and depression have been suggested to induce neuroinflammation via glia-neuron interactions and neuroplasticity alterations by remodeling of the neural networks in the affected brain regions, making the treatment more difficult (Lithwick et al., 2013).

4. Neuroinflammation and neuroplasticity changes as common mechanisms of chronic primary pain: interaction of pain, mood and stress pathways

Neuroinflammation is defined as the activation of the innate immune system of the central nervous system (CNS) in response to noxious stimuli like trauma, infarction, infection, or even chronic stress. It is characterized by cellular (glia cells and neurons) and molecular changes (cytokines, chemokines, neuropeptides, neurotransmitters). Microglia and astrocytes also contribute to the regenerative and/or apoptotic processes (Calcia et al., 2016; DiSabato et al., 2016; Patani et al., 2023). (Fig. 1.)

4.1. Clinical data

One of the milestone clinical findings for neuroinflammation playing a role in FM was the increased uptake of the radioligand tracer [11C] PBR28 in the prefrontal cortex of these patients positively correlated with their fatigue symptoms. The radioligand is a positron emission tomography (PET) radiotracer binding to a 18pkD translocator protein (TSPO), which is expressed in activated microglia, reactive astrocytes, vascular endothelium, and to a much lower degree in neurons (Albrecht et al., 2019). Choline levels linked to glial activation were also elevated in FM patients in several brain areas assessed by functional magnetic imaging (fMRI), which showed positive correlation with the pain parameters (Jung et al., 2020). Functional connectivity within the salience network involved in the coordination of external and internal stimuli increased in participants exposed to chronic psychosocial stressors compared to unexposed ones. These cortico-striatal connectivity alterations and signal processing abnormalities suggest neuroplasticity changes due to the reorganization of neural networks and synaptic links (McCutcheon et al., 2019). Similarly, increased salience network connectivity was observed in post-traumatic stress disorder patients, which normalized after evidence-based psychotherapy (Abdallah et al., 2019). Maladaptive tuning of several brain functions, more specifically prefrontal processes are suggested to be involved in pain catastrophizing in FM patients (Hubbard et al., 2020; Sandström et al., 2020, 2022). Catastrophizing and ruminations are long known to be involved in the maintenance and aggravation of chronic pain (Gracely et al., 2004) positively correlating with pain intensity in different body regions of FM patients (Ellingsen et al., 2021). Besides the salience network enhanced connectivity was observed in FM patients also in the default mode network representing different brain areas simultaneously activated in response to diverse experimental tasks (Galambos et al., 2019) positive correlating with the pain intensity (Čeko et al., 2020). A recent meta-analysis (Wang et al., 2022) demonstrated gray matter abnormalities in chronic primary pain patients. Neuroinflammation was detected with [^{11}C]-(R)-PK11195, a translocator protein expressed by activated microglia or astrocytes in positron emission tomography, in different brain areas of fibromyalgia and CRPS patients. Distribution volume ratio correlated with stress and anxiety levels which supports

the hypothesis that neuroinflammation is the link between mood disorders and pain (Gritti et al., 2021; Jeon et al., 2017; Seo et al., 2021).

4.2. Preclinical results

Chronic stress-induced microglia and astrocyte activation were demonstrated in animal experiments more than 2 decades ago (O'Connor et al., 2003). Chronic stress paradigms in rats activated microglia shown by increased density of ionized calcium-binding adapter molecule 1 (Iba1) immunoreactivity in the medial prefrontal cortex (Hinwood et al., 2012; Kopp et al., 2013). Several neuroinflammatory parameters were increased in FM models as summarized in Table 1 Pointing out the translational relevance of the models to investigate this pathophysiological component of FM.

In the medial amygdala, loss of neural dendritic spines was shown in mice in response to chronic restraint stress (Bennur et al., 2007) Brain-derived neurotrophic factor (BDNF) is suggested to be involved in the remodeling and neuroplasticity changes of affected brain areas in mice caused by chronic stress (Ammosova et al., 2011; Govindarajan et al., 2006). Deteriorated salience network connectivity was also observed in animal models of chronic stress (Dai et al., 2023; Seewoo et al., 2020). In the acid saline FM mouse model, the default mode network-periaqueductal gray matter functional connectivity showed the strongest positive correlation with the pain threshold decrease (Nasseef et al., 2021). In the reserpine-induced rat FM model moderate electrical forepaw stimulation induced significantly higher activation of the default mode network compared to controls (Wells et al., 2017).

These clinical and pre-clinical results described above may provide a good basis for a more precise understanding of the pathophysiological mechanisms behind stress-induced pain, thus opening novel drug development perspectives in FM. Immunological factors and neuroinflammatory mechanisms are suggested to be involved in FM. In this chapter, we summarized the key mediators, which could serve as potential pharmacological targets.

5. Potential mechanisms and novel therapeutic targets of FM and stress-induced pain

5.1. Autoimmunity, autoantibodies

Autoimmunity has been implicated in chronic primary pain syndromes as a potential pathogenic factor. Systemic injection of purified serum immunoglobulin G (IgG) antibodies of FM patients were shown to bind to the satellite glia cells in the DRGs and induce severe symptoms including hyperalgesia in a mouse model (Krock et al., 2023).

Furthermore, FM symptoms such as mechanical hyperalgesia, reduced grip strength and locomotor activity, increased nociceptor excitability were also mimicked in mice by the passive transfer of FM patients' IgG (Goebel et al., 2021). In this model glial fibrillary acidic protein (GFAP) expression increased in the lumbar DRGs at the level of the primary sensory neuronal cells, but not in the spinal dorsal horn at the level of secondary sensory neurons.

5.2. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)

NGF and BDNF are involved in pain sensitization and hyperalgesia (Sluka and Clauw, 2016). These mediators have recently been investigated in FM, and the results suggested their potential predictive values for pain. FM patients had lower levels of circulating NGF and IL-1β, while BDNF and IL-8 levels were higher than healthy controls. However, no correlation was found between these biomarkers and cytokines with the patients' depressive and anxiety symptoms, pain-catastrophizing, and pain levels (Jablochkova et al., 2019).

In rats, neuroinflammation with Nod-like receptor protein 3 (NLRP3) inflammasome activation in the hippocampus and basolateral amygdala was present in rats in response to CRS (Feng et al., 2019) accompanied by increased expression of the chronic neuronal activation marker c-fos and IL-1β (Yu et al., 2021). Reducing hippocampal CRS-induced proBDNF upregulation resulted in reduced anxiety- and depression-like behaviors in rats (Zhong et al., 2019). CVMS-induced thermal hyperalgesia could be prevented by blocking BDNF signaling (Liu et al., 2018).

5.3. Inflammatory cytokines, chemokines and neuropeptides

The role of inflammatory cytokines are widely investigated in fatigue, pain and psychological disturbances as well (Dantzer and Kelley, 2007). Psychological distress, pain intensity and sensitivity in FM patients showed positive correlations with specific plasma proteins involved in inflammation and immunity (e.g. IL-6, IL-2, haptoglobin) (Wåhlén et al., 2020). Inflammatory response proteins were detected in FM patients' cerebrospinal fluid by proteomic analysis suggesting inflammatory and neuroendocrine disturbances (Khoonsari et al., 2019). Female FM patients' isolated monocytes secreted higher levels of IL-1, IL-5, IL-6 and IL-10 compared to healthy controls. Concentrations of IL-4, IL-5 and the anti-inflammatory cytokine IL-10 showed positive correlations with the pain intensity and related mood disturbances (Merriwether et al., 2021).

The importance of several neuropeptides released from capsaicin-sensitive peptidergic nociceptive fibers has been suggested in chronic pain conditions. Increased levels of tachykinins like substance P and hemokinin-1 (HK-1) were detected in the serum of FM patients compared to controls, which decreased by cognitive behavior therapy (Karlsson et al., 2019; Tsilioni et al., 2016).

Preclinical data demonstrated the important regulatory roles of several neuropeptides released from neurons, glia or mast cells such as neuropeptide Y, pituitary adenylate cyclase-activating peptide, somatostatin and tachykinins, substance P, neurokinin A and B and HK-1 in neuroinflammatory processes (Carniglia et al., 2017; Suto et al., 2014; Theoharides et al., 2019). HK-1 deficiency prevented CRS-induced hyperalgesia in both male and female mice (Borbély et al., 2023).

A recent publication from our laboratory as a part of the PhD project of B. Fülöp showed that CRS-induced hyperalgesia and related neuroinflammation demonstrated by both astroglia and microglia activation in stress and pain-related brain regions do not develop in mice lacking IL-1. This suggests the importance of this cytokine in this pain sensitization mechanism (Fülöp et al., 2023). An important pathway of neuroinflammation is medicated by fractalkine, which predominantly acts at microglial cells in the CNS. Fractalkine receptor 1 (CX3CR1) deficient mice are resistant to chronic unpredictable mild stress-induced depression-like behavior, cognitive impairment and neuroinflammation. Stress-induced elevation of IL-1 in both brain homogenates and plasma samples were not present in CX3CR1 deleted mice, suggesting IL-1 release from microglia in response to fractalkine receptor activation upon chronic stress (Liu et al., 2020).

6. Conclusions and future perspectives

Chronic psychosocial distress is an important etiological and aggravating factor of chronic primary pain conditions such as FM, and pain further triggers stress, anxiety and depression forming a vitious circle. Stress and pain pathways share several structures in the brain, as well as a range of common mechanisms and mediators. Both have been suggested to induce neuroinflammation via glia-neuron interactions and neuroplasticity alterations by remodeling of the neural networks in the affected brain regions, making the treatment more difficult (Lithwick et al., 2013). A better understanding of the complex interactions between psychosocial distress, pain and inflammation/immunity is crucial to identify preventive and early therapeutic strategies. There has not been original innovative drug development for chronic pain in the last decades as demonstrated by the clinical trial databases, therefore it

Fig. 2. Barbara started her research career as an undergraduate student researcher back in 2017 at the Institute of Pharmacology and Pharmacotherapy at the Medical University of Pécs, Hungary. Her interest focused on stress-induced pain syndromes in animal models. After obtaining her medical degree, she started her Ph.D. studies under the supervision of brilliant researchers of the pain field: Dr. Éva Borbély and Professor Zsuzsanna Helyes (co-authors of this article). After a maternity leave, she continued her studies in the basic research field of chronic stress and pain interactions. Being involved in vivo mouse studies, behavioral testing, and pain measurements as well. She is also performing in vitro immunohistochemical measurements with a focus on neuroinflammation. Currently, she is preparing her Ph.D. thesis about the molecular processes involved in chronic stress in mouse models of pain. For her research work, she received several awards including the Pro Scientia Gold Medal (2019) and the Hungarian New National Excellence Program Scholarship (2019, 2021, 2023, 2024). Besides her family and her 3 kids, her biggest love is her research topic. She hopes that her experimental results can contribute to a more precise treatment of chronic, difficult-to-treat pain conditions in the (not-so-distant) future. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

represents a real unmet medical need.

In agreement with the latest literature data, we conclude that targeting neuroinflammation is a promising novel direction for the treatment of chronic primary pain including FM. Besides extensive human studies, animal models with translational relevance are crucial to determine the key mediators and targets of the neural and immune systems for drug development.

Barbara Fülöp (Fig. 2.) has worked on integrative preclinical investigation of the mechanisms involved in chronic pain conditions related to psychosocial stress. Her focus is on neuroinflammation, glia-neuron interactions and neuroplasticity using mouse models with complex behavioral, molecular biological, biochemical and neuroimaging outcomes. As a neuropharmacology PhD candidate, her deepest belief is that it is crucial to have a holistic approach to identify novel therapeutic targets for these common co-morbidities. In her opinion, preclinical results can substantially promote these efforts.

CRediT authorship contribution statement

Barbara Fülöp: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Éva Borbély:** Writing – review & editing. **Zsuzsanna Helyes:** Writing – review & editing, Conceptualization.

Funding

This research was funded by research grants No. TKP2021-EGA-13 and TKP2021-EGA-16, grants which have been implemented with the support provided from the National Research, Development and Innovation Fund of Hungary, financed under the EGA 13 and EGA 16 funding scheme co-financed by the EU. Supported by the ÚNKP-23-3 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund. Project no. RRF-2.3.1-21-2022-00015 has been implemented with the support provided by the European Union. National Brain Research Program 3.0 (NAP 3.0). Zs. H and É.B. were supported by the National Research, Development and Innovation Office (NKFIH K 138046 and NKFIH FK 137951). B. F. was supported by EKÖP-24-3-II. Hungarian Research Network (HUN-REN), Chronic Pain Research Group, and by The National Research, Development and Innovation Office (Phar-maLab).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors are grateful to Lina Hudhud and Noémi Bencze for the technical help in creating figures.

Abbreviations:

BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CPP	chronic primary pain
CRS	chronic restraint stress
CRPS	complex regional pain syndrome
EPM	elevated plus maze test
FM	fibromyalgia
FST	forced swim test
CX3CR1	Fractalkine receptor
fMRI	functional magnetic resonance imaging
GFAP	glial fibrillary acidic protein
HK-1	hemokinin-1
IgG	immunoglobulin G
IL	interleukin
Iba1	ionized calcium-binding adapter molecule 1
NGF	nerve growth factor
NLRP3	-like receptor protein 3
OFT	field test
PET	positron emission tomography
TST	tail suspension test
TNFα	tumor necrosis factor alpha

Data availability

Data will be made available on request.

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