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Lighting the shades of hidden pain: a role for spinal cord neurons and microglia in vestibulodynia

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Vulvodynia, a chronic pain disorder affecting the vulvar region, represents a significant challenge in both diagnosis and treatment within the field of women's health. This condition is characterized by chronic pain that significantly affects the quality of life of afflicted women. The present perspective paper examines the role of spinal sensitization and microglial activation in vulvodynia. Traditionally, treatment approaches have focused on symptomatic relief without addressing the underlying biological mechanisms, largely due to the condition's complex and poorly understood etiology. Recent scientific advancements underscore the crucial roles of spinal sensitization and microglial activation in vulvodynia's pathophysiology. These findings suggest that microglia, which play a significant role in immune surveillance within the central nervous system, modulate pain pathways through their interactions with neurons, influencing cytokine release and neuronal excitability. This article explores how advancements in understanding these mechanisms could improve clinical practices, offering new, targeted treatments that address the root causes of pain. Thus, it discusses the potential of microglial activation as a therapeutic target, highlighted by successful interventions in various pain models, and considers the implications of these insights for future research and clinical applications. The challenges of translating these findings from animal models to human conditions are acknowledged, emphasizing the need for sophisticated imaging techniques and molecular biology to bridge this gap. Ultimately, the paper highlights a promising direction for improving the management and treatment of vulvodynia through focused research on spinal sensitization and microglial dynamics.

Vulvodynia, characterized by persistent and often debilitating vulvar pain, profoundly impacts the daily lives and mental well-being of affected individuals. Epidemiologically, vestibulodynia is a multifaceted and often underrecognized condition that affects women across various age groups, with a higher incidence during the reproductive years. An estimated 8%–10% of women may experience vulvar pain; however, the precise prevalence is skewed due to significant underreporting and frequent misdiagnosis. Despite the condition's prevalence, effective treatment remains elusive, largely due to its complex and poorly understood etiology. The majority of current therapeutic approaches focus on symptomatic relief, such as pain management, without addressing the underlying biological mechanisms.

Recent scientific advancements, including our seminal study, are reshaping the understanding of vulvodynia cellular and molecular pathways (Boccella et al., 2024a). This research highlights the critical role of spinal sensitization and microglial activation in the pathology of vulvodynia. Microglial cells, long known for their role in immune surveillance within the central nervous system, have come under scrutiny for their involvement in modulating pain pathways as well as other immune-mediated neurological disorders (Mhillaj et al., 2018). These interactions, often mediated through the release of cytokines and other inflammatory mediators, can significantly alter neuronal excitability and pain perception (Wen et al., 2011; Tozaki-Saitoh and Tsuda, 2019).

Studies across various models of chronic pain have consistently shown that microglia play a pivotal role in the development and maintenance of neuropathic and inflammatory pain states (Luongo et al., 2010; Boccella et al., 2024a). For instance, interventions that modulate microglia phenotype, such as pharmacological inhibition of p38 mitogen-activated protein kinase, have demonstrated effectiveness in reducing neuropathic and postoperative pain (Haight et al., 2019). Moreover, research has indicated variable microglial responses between male and female animals following peripheral nerve injuries (Sorge et al., 2015). While both male and female mice exhibit microglia proliferation in the dorsal horn after such injuries, a direct correlation between microglia activation and the development of tactile allodynia has been predominantly observed in male mice (Sorge et al., 2015). A recent study, however, complicates this understanding by demonstrating that the P2X4 receptor, known for its role in mediating spinal neuron hyperexcitability, is crucial in both male and female neuropathic mice, suggesting a fundamental mechanism of pain processing that transcends sex-based differences (Gilabert et al., 2023). These strengths the peculiar nature of microglial activation in pain modulation. Besides the minocycline treatment several inhibitor compounds are under investigation including P2X4 antagonists, cannabinoids, and resolvins. Among those the use of Pexidartinib (PLX3397), a CSF-1 receptor antagonist that depletes microglia, has shown promising applications as a tool to abolish microglia cells. Treatment with PLX3397 effectively prevented the development of tactile allodynia in tested models, suggesting that complete microglial depletion may be a viable strategy for managing this symptom (Boccella et al., 2024a). However, this finding underscores the necessity for further research to explore the full implications of microglial depletion and its potential side effects or long-term impacts on neuronal health and function. This emerging evidence calls for a deeper investigation into the sex-specific roles and mechanisms of microglial activation in pain pathways, particularly in conditions like vulvodynia that exclusively affect women. Understanding these dynamics is crucial for developing targeted therapies that are effective across different patient demographics and can address the underlying biological mechanisms of pain more effectively.

This perspective seeks to delve deeper into these novel insights, exploring how they might revolutionize clinical practices and lead to more effective, targeted treatments for vulvodynia. By understanding the role of spinal sensitization and microglial activation, we could begin to develop therapeutic strategies that address the root causes of pain rather than merely managing its symptoms (**Figure 1**).

Role of spinal neural sensitization and microglia in vulvodynia: The finding that spinal neuron sensitization and microglial activation play central roles in vulvodynia represents a significant paradigm shift in our understanding and approach to this condition. The increased responsiveness of neurons in the spinal cord may lead to heightened pain sensitivity, a characteristic feature of vulvodynia. Microglia, the resident immune cells of the central nervous system, have emerged as key players in this process, primarily through their interaction with neuronal cells and influence on neuroinflammatory processes.

Studies have shown that microglia become activated in various models of pain, where they contribute significantly to the maintenance and enhancement of pain by releasing pro-inflammatory cytokines and modulators of neuronal excitability (Wen et al., 2011; Infantino et al., 2022). This activation is not a simple binary switch but a complex modulation where microglia can adopt various activation states, which may have different implications for pain processing and behavior.

In neuropathic pain models, the role of spinal microglia has been particularly well-documented. For instance, microglial cells in the spinal cord are known to express receptors that are sensitive to environmental changes caused by peripheral nerve injury. Activation of these receptors can lead to an enhanced release of cytokines such as tumor necrosis factor-α, interleukin-1beta, and interleukin-6, which contribute to neuronal sensitization and pain persistence (Ji et al., 2016).

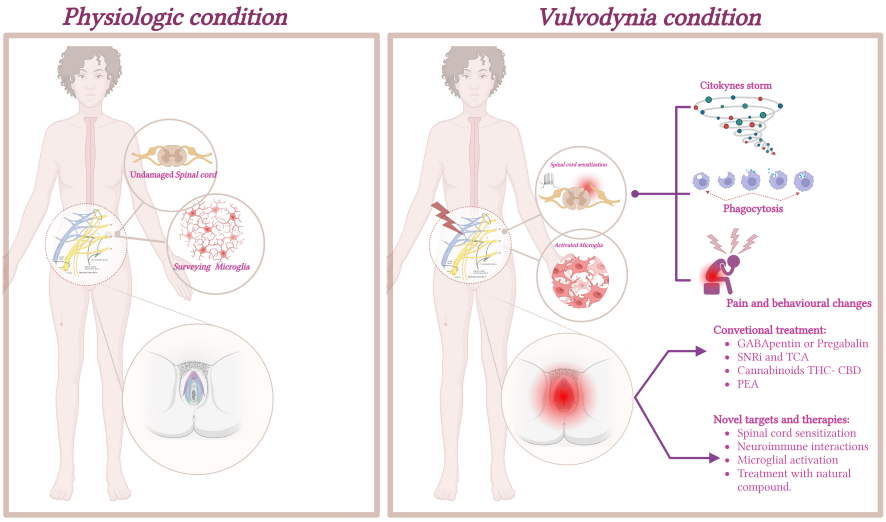

Figure 1 | **Understanding vulvar pain: normal *versus* pathological conditions.**
(Left) Normal physiological condition: In a healthy state, the vulvar region accurately processes painful and non-painful stimuli. The nervous system functions correctly, ensuring that pain signals are appropriately interpreted, leading to normal sensation without discomfort. (Right) Pathological condition: In pathological conditions, there is increased peripheral and spinal cord sensitization. This heightened sensitivity induces plastic changes in the nervous system, resulting in abnormal pain symptoms. These changes manifest as allodynia defined as pain perception from stimuli that would not normally cause pain; hyperalgesia which represents an increased sensitivity to painful stimuli. This altered pain processing contributes to significant discomfort and chronic pain in affected individuals. Pharmacological treatments, still poorly satisfactory, include GABApentinoids such as pregabalin and gabapentin, antidepressant (tricyclic antidepressants [TCA], serotonin-norepinephrine reuptake inhibitors [SNRi]), and local or systemic anti-inflammatory medical supplements such as palmitoylethanolamide (PEA). Future treatments are represented by cannabinoids, which are already used for different forms of chronic pain and natural compounds. Created with BioRender.com.
CBD: Cannabidiol; PEA: N-palmitoylethanolamide; SNRi: serotonin–norepinephrine reuptake inhibitors; TCA: tricyclic antidepressants; THC: tetrahydrocannabinol.

Additionally, microglial cells influence pain through more direct interactions with neurons, affecting synaptic transmission and potentially leading to altered pain perception.

The targeting of microglial activation therefore might be a promising avenue for developing new therapeutic strategies for vulvodynia. For example, pharmacological agents that inhibit microglial activation, such as minocycline, have shown the potential to reduce pain by attenuating pro-inflammatory responses and modulating neuronal excitability (Barcelon et al., 2019). This approach not only offers potential relief for those suffering from vulvodynia but also opens up new research pathways to further understand the intricate connections between the immune system and nervous system in the context of chronic pain.

Potential clinical and research implications: The study of microglial activation in vulvodynia opens several new avenues for research. Understanding how microglia contribute to the transition from acute to chronic pain can inform the development of interventions that prevent chronic pain conditions from taking root. Additionally, as microglial activation has been implicated in various chronic pain conditions, this research could lead to broad-spectrum therapies applicable to multiple pain disorders.

Recent advances in imaging technologies such as positron emission tomography allow for the visualization of glial activation *in vivo*, offering a method to directly observe the effects of potential therapies on microglial activity in patients (Haight et al., 2019). Such techniques will enable more personalized approaches to pain management, potentially leading to better outcomes for patients with vulvodynia.

The potential clinical and research implications of understanding spinal sensitization and microglial activation in vulvodynia are vast. By shifting the focus from symptom management to addressing the underlying biological mechanisms of pain, new therapeutic avenues could emerge that offer more effective and long-lasting relief for patients. As the field moves forward, it will be essential to integrate these insights into clinical trials and treatment strategies, to improve pain management and patient care.

Addressing challenges and future directions: While the research into microglial activation and its role in chronic pain, including vulvodynia, offers promising avenues for new therapeutic strategies, several challenges remain. These challenges need to be addressed to fully harness the potential of targeting microglial pathways in pain management. One of the primary hurdles is the translation of findings from animal models to human conditions. Despite robust evidence of microglial involvement in rodent models of pain, replicating these findings in humans is still poorly documented (Wen et al., 2011). The complexity of the human nervous system and the ethical constraints of invasive studies pose significant barriers to direct experimentation. Moreover, individual genetic variability and environmental factors can alter microglial responses, necessitating personalized approaches to treatment.

To overcome these challenges, advancements in non-invasive imaging techniques such as positron emission tomography are very helpful. These techniques enable the visualization of microglial activation *in vivo*, providing a direct link between microglial activity and pain perception in patients (Haight et al., 2019). Further development of specific radiotracers that target microglial markers could enhance the accuracy and reliability of these imaging techniques.

Implications for pharmacological treatment: Conventional approaches targeting peripheral nociceptive pathways have shown limited efficacy in managing vulvar pain, highlighting the need for novel interventions that address central sensitization processes together with the local inflammatory environment. Pharmacotherapy aimed at modulating spinal cord excitability and synaptic transmission represents a promising avenue for achieving better pain control and improving patient outcomes.

Several classes of drugs with known effects on spinal cord function have the potential to be repurposed or developed specifically for vulvodynia treatment: Gabapentinoids such as GABApentin or pregabalin are a class of anticonvulsant drugs that block voltage-gated calcium channel auxiliary subunit Cavα2δ-1 (CACNA2D1). In multiple animal models of chronic neuropathic pain, Cavα2δ-1 is increased in dorsal root ganglion neurons after injury to the peripheral sensory nervous system (Kricek et al., 2024). These drugs are also used in several forms of nociplastic pain including vulvodynia.

Serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants: These antidepressant medications have analgesic properties attributed to their effects on descending pain modulation pathways. By enhancing descending inhibitory control from the brainstem to the spinal cord, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants may attenuate central sensitization and alleviate vulvar pain. These drugs are indeed already used in the clinical practice for treating several forms of neuropathic pain and their clinical use is also employed for the management of pelvic and nociplastic pain in general.

Cannabinoids: Cannabinoid receptors are widely distributed throughout the central nervous system, including the spinal cord, where they modulate pain transmission and processing. Cannabinoid-based therapies, such as delta-9-tetrahydrocannabinol and cannabidiol, have demonstrated analgesic effects in various chronic pain conditions. Exploring the therapeutic potential of cannabinoids in vulvodynia treatment requires further investigation through well-designed clinical trials.

Novel targets and therapies: Advances in neuropharmacology and pain research continue to uncover new targets for pharmacological intervention in chronic pain disorders. Targeting specific molecular or cellular pathways implicated in spinal cord sensitization, such as neuroinflammation, neuroimmune interactions, and glial activation, holds promise for the development of innovative therapies for vulvodynia. Preclinical studies utilizing animal models and translational research efforts are essential for identifying and validating novel drug targets for future clinical trials.

New treatment with natural compounds acting at multitargeted levels would be very helpful in the future. Recently, our lab has identified a combination of two plant extracts (Boswellia serrata and Acmella oleracea) that works demonstrated a synergistic effect in a model of neuropathic pain (Boccella et al., 2024b). These preliminary results could pave the way to test this combination in vulvodynia.

Conclusion: The investigation of spinal sensitization and microglial activation offers a new perspective on vulvodynia, a condition characterized by chronic vulvar pain. This research could significantly shift the current treatment approaches from solely managing symptoms to targeting the biological mechanisms underlying the pain.

Insights from recent studies, such as those by Boccella et al. (2024a), highlight the potential of microglia as key modulators in the pain pathways of vulvodynia. Targeting microglial activation could lead to novel therapeutic strategies that are more effective in addressing the root causes of pain, rather than just alleviating symptoms.

However, the transition from research findings to practical clinical applications presents several challenges. The complex behavior of microglia and their interactions with neural circuits in vulvodynia require sophisticated, precise research tools and methods. Advances in both imaging and molecular biology are crucial for translating these laboratory discoveries into treatments that can be used in clinical settings.

In summary, the path from research to clinical practice is complex, but the potential for microglial research to transform the treatment of vulvodynia is promising. Continued exploration is essential for developing effective treatments that could fundamentally change how this condition is managed, offering hope for improved outcomes for those affected by vulvodynia.

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