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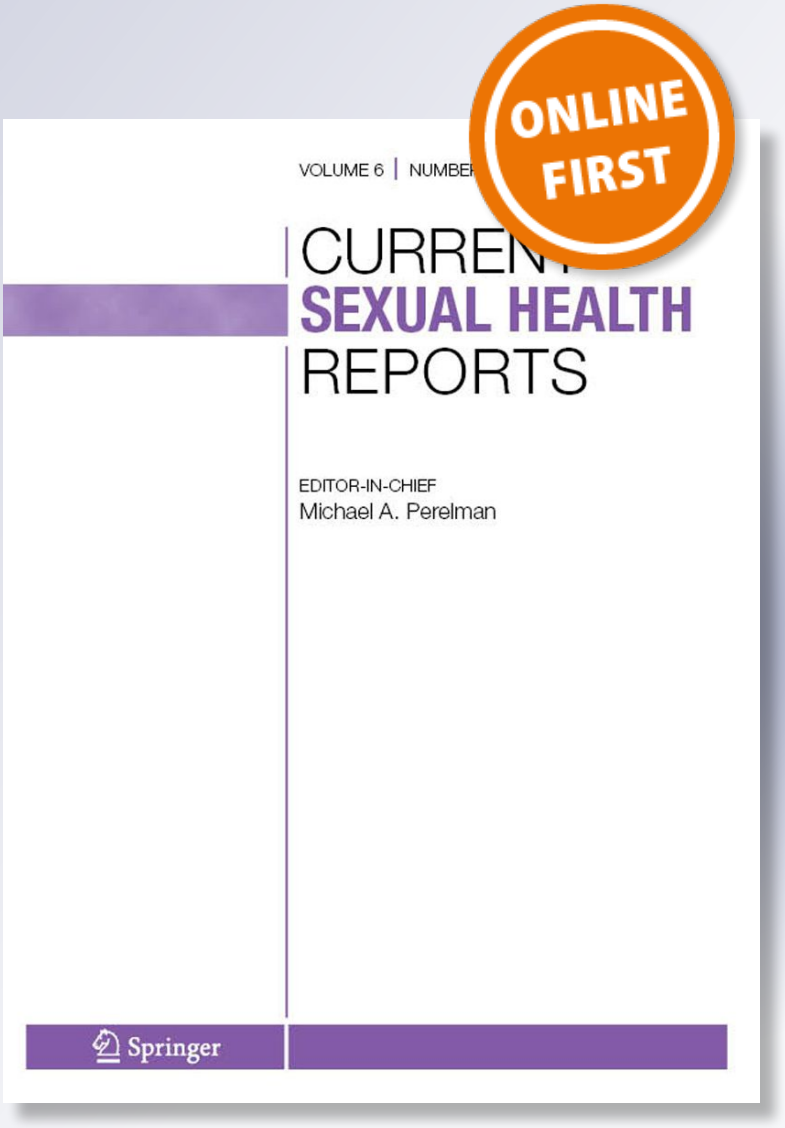

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New Developments in the Pathophysiology of Genital Pain: Role of Central Sensitization

Caroline F. Pukall · Catherine M. Cahill

Abstract Medically unexplained chronic vulvar pain, or vulvodynia, is a common condition that affects many aspects of a woman's life. The most common subtype of vulvodynia is provoked vestibulodynia (PVD), and recent research has demonstrated that its pathophysiology likely involves both peripheral and central dysregulation. In this review, the phenomenon of central sensitization is specifically described and linked to relevant findings in the PVD literature. Recommendations for further research in the area of vulvodynia are made, in particular, the examination of other vulvodynia subtypes and of subtypes within the PVD samples. In addition, support is given for the validation of an existing animal model of provoked vulvar pain in order to understand further spinal involvement and also mechanisms involved in the genesis and persistence of this condition.

Keywords Vulvodynia · Provoked vestibulodynia · Dyspareunia · Peripheral sensitization · Central factors · Central sensitization · Pathophysiology · Genital pain · Sensory innervation · Allodynia · Hyperalgesia · Receptive field expansion · GABA · Neuronal-glial interactions · Nociceptors · Pain pathways · Quantitative sensory testing · Diffuse noxious inhibitory control · Functional brain imaging

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Introduction

Genital pain presents in many varieties, from diffuse and constant chronic pelvic pain to pain in a specific vulvar area (e.g., vaginal entrance) that is experienced in response to pressure. It is critical to gather information regarding pain characteristics, such as location, temporal pattern, description, and functional interference in order to understand the pain and its effects [1]. One common manifestation of genital pain is that of dyspareunia, or pain during sexual intercourse. Despite this common presenting complaint, it is necessary to look beyond this single characteristic in order to understand the specific type, or types, of pain that may plague a patient [2••]. This review will focus on vulvodynia, defined as medically unexplained chronic vulvar pain, and consider the involvement of central sensitization that contributes to the genesis and persistence of its expression.

Vulvodynia

Vulvodynia is defined by the International Society for the Study of Vulvovaginal Disease (ISSVD) as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder" [3] (see Table 1). It is important to note that, in vulvodynia, the vulva has a normal appearance other than some possible erythema [4]. The term *vulvodynia* is an umbrella term that captures a wide range of chronic vulvar pain presentations; as such, subtypes can be delineated based on variables related to pain presentation [3]. Two main categorizations of vulvodynia exist, based on whether the pain is *localized* to a specific vulvar area, or *generalized*, affecting the entire vulvar region. Further subtypes of each categorization can be made depending on whether the pain is *provoked* (by sexual, nonsexual, or both types of activities), *unprovoked* (i.e., pain characterized by

Table 1 International Society for the Study of Vulvovaginal Disease (ISSVD) classification of chronic vulvar pain conditions

Two major classifications
1: Vulvar pain related to a specific disorder (i.e., infectious, inflammatory, neoplastic, neurologic)
2: Vulvodynia (vulvar pain that is not related to a specific disorder)
Location of pain must be documented: generalized or localized?
Within each location, the *temporal characteristics* (when the pain occurs) need to be elucidated: provoked, unprovoked, mixed?

(*Adapted from* Haefner [3].)

ongoing pain in the absence of sensory input; otherwise known as spontaneous pain), or *mixed*.

This review will focus on the most common subtype of vulvodynia, provoked vestibulodynia (PVD), formerly termed vulvar vestibulitis syndrome. PVD is believed to affect approximately 16 % of premenopausal women in the general population [5]. Women with PVD typically experience a severe, sharp/burning pain in response to pressure upon the portion of the vulvar vestibule surrounding the vaginal entrance [6]. The vulvar vestibule is derived from the embryonic endoderm and is visible when the labia minora are spread apart. It extends from the clitoris to the posterior fourchette [7]. Its medial boundary is the hymen and its lateral boundary is defined by Hart's line, a distinct line of demarcation visible at the base of the inner aspects of each labium minus. Hart's line separates the keratinized epithelium of the labia minora from the non-keratinized squamous epithelium of the vestibule [7]. The vestibule includes the vaginal and urethral openings and the ducts of the greater vestibular glands, which open into the vestibule [6]. It is innervated by the pudendal nerve [8] and contains three types of sensory afferents, A-beta, A-delta, and non-myelinated C-fibers, the latter of which are believed to constitute the majority of the sensory innervation [9]. The vestibule is composed of mucosal tissue that is innervated by the same sensory afferents as non-glabrous skin; thus, it has the capability of perceiving sensations of touch, temperature, and pain.

Typically, the vestibule acts as a source of pleasure during vaginal penetration [10]; however, in women with PVD, even light pressure to the vestibule can elicit intense pain. The pain usually occurs during sexual activities involving vaginal penetration (i.e., dyspareunia), but it can also occur in response to nonsexual activities involving vaginal entry or pressure (e.g., tampon insertion, internal pelvic examinations, bicycle or horseback riding) [11]. To date, an emphasis has been placed on identifying peripheral factors that contribute to the occurrence of PVD, including altered sensory innervation, infiltration of pro-nociceptive cytokines, and peripheral sensitization. Nevertheless, central factors contributing to its expression should not be discounted. Indeed, several studies have established that central sensitization is an important factor in the chronicity of PVD pain. Central sensitization is well accepted as a contributing element in many chronic pain syndromes, including neuropathic pain of various etiologies [12].

The Phenomenon of Central Sensitization

Synaptic plasticity of sensory transmission appears to be a key element in the genesis of chronic pain. Various mechanisms proposed to underlie synaptic plasticity pertinent to the development and persistence of chronic pain include: peripheral sensitization [13, 14]; central sensitization, which involves alterations in glutamatergic excitatory neurotransmission [12] and changes in GABAergic inhibitory transmission [15]; and neuronal-glia interactions, particularly products released from activated astrocytes and microglia [16–18]. Central sensitization is defined as a state of facilitation, potentiation, augmentation, or amplification of response in second-order or higher-order neurons and circuits within the nociceptive transmission pathway. It is caused by an increase in membrane excitability and synaptic efficacy of pain neurons within the spinal cord and brain structures responsible for the sensory, affective, and cognitive components of pain.

Various mechanisms account for the occurrence of central sensitization. A strong argument can be made that without peripheral sensitization, central sensitization would not transpire. Peripheral sensitization is the process by which high threshold nociceptors transition into low threshold nociceptors; this transition is induced by the release of various chemicals at the site of injury [19]. In this case, many diverse inflammatory mediators, such as prostaglandins, cytokines, and neuropeptides, are released from the injured tissue and unite with others being transported by the circulation [20]. Pain-transmitting sensory fibres, A-delta and C fibres, innervating the injured tissue enter a state characterized by ongoing discharge, a lowered activation threshold, and excitation elicited by suprathreshold stimulation and accounts for primary hyperalgesia (an exaggerated response to a painful stimulus in and around the original site of injury) [21]. Secondary hyperalgesia (expansion of the receptive field) is a consequence of central sensitization [22], and the most prominent feature of secondary hyperalgesia is touch-evoked pain, or pain evoked by dynamic tactile stimuli applied to areas adjacent to or remote from the originating injury [23]. Hence, central sensitization results in changes within the circuitry such that pain is no longer coupled to the presence, intensity, and duration of a noxious peripheral stimulus, as is acute pain [12]. Rather, as the result of central sensitization, pain is now produced by a sensory stimulus that would normally elicit a non-painful response, such as touch, pressure, and/or vibration (Fig. 1a).

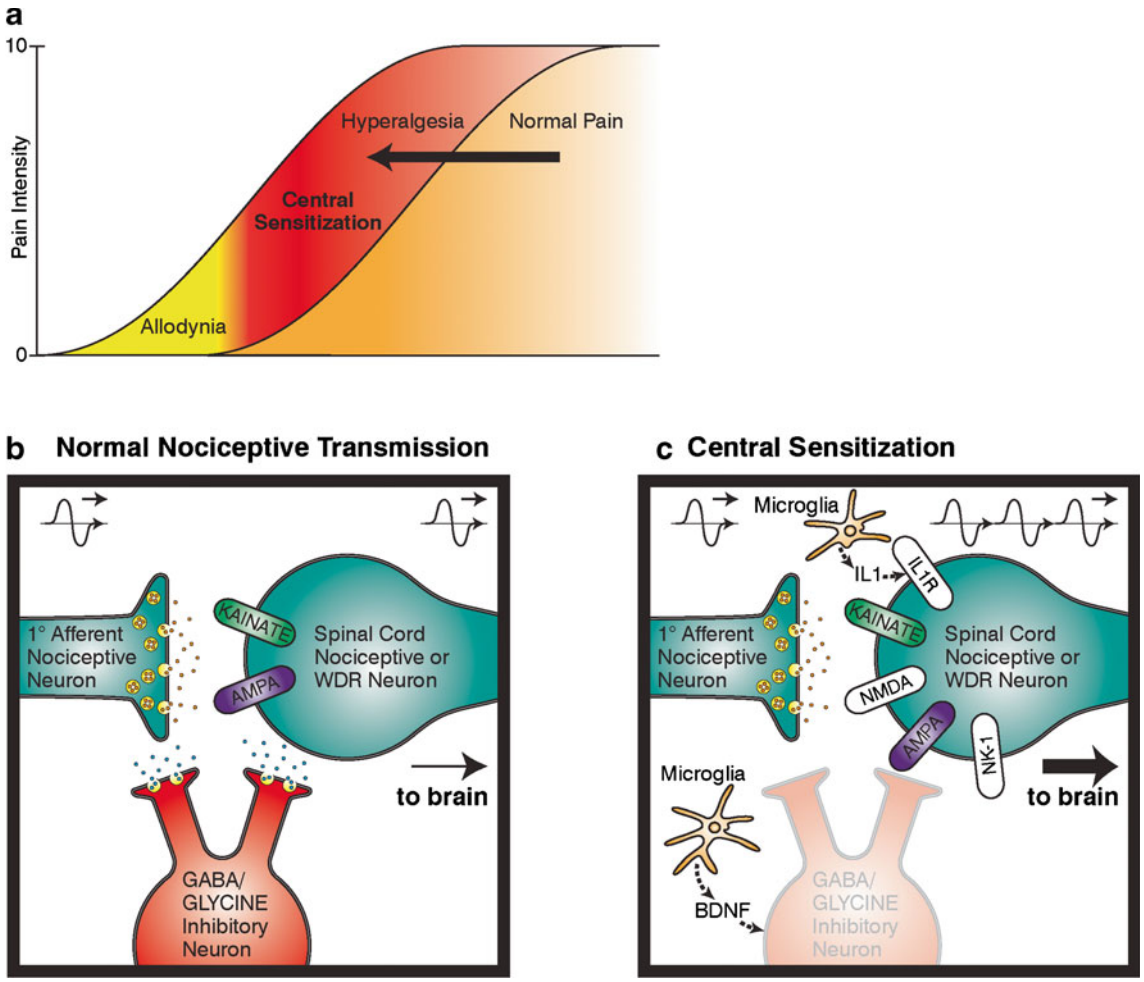

Fig 1 Processes involved in central sensitization. 1°= Primary; WDR=wide dynamic range; AMPA=amino-3-hydroxy-5-methyl-4-isoxazole propionate; BDNF=brain derived neurotrophic factor; IL1=interleukin 1; IL1R=interleukin 1 receptor; NMDA=N-methyl-D-aspartate; NK-1=neurokinin 1

To expand on the mechanisms of central sensitization, most of our knowledge emanates from studies at the level of the spinal cord, where primary afferent nociceptive neurons terminate on second-order nociceptive and wide dynamic range neurons within the dorsal spinal cord (Fig. 1b). However, it is known that central sensitization occurs throughout the neural axis, including the posterior part of the ventral medial thalamus, a brain structure within the spinothalamic tract pathway that relays sensory information about pain location and intensity [24]. Additionally, central sensitization also occurs in brain regions important for pain affect (the emotional experience associated with pain), including the amygdala [25, 26] and anterior cingulate cortex [27]. Imaging studies of chronic pain patients have noted activity-dependent changes in several brain regions consistent with increases in excitability due to central sensitization (e.g., [28]).

In the spinal cord, there is a conversion of nociceptive specific neurons to wide dynamic range neurons (Fig. 1c), such that they no longer respond to only painful stimuli but can now be activated by stimuli that normally produce only innocuous sensations. This conversion is due to many factors. First, activity-dependent central sensitization results from an increase in the functional activity of the ionotropic calcium permeable glutamate receptor, N-methyl-D-aspartate (NMDA), and trafficking of another glutamatergic ionotropic amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor to excitatory synapses within nociceptive transmission pathways [29, 30]. Changes in transcription and channel properties of NMDA receptors are critical for the expression and development of central sensitization. Sustained release of nociceptor primary afferent transmitters such as glutamate and neuropeptides from peptidergic C-fibers allows for the activation of this receptor, which is normally inactive due to the receptor pore being blocked by magnesium. However, the magnesium block is voltage dependent, and ongoing activity due to peripheral sensitization allows for its removal from the channel pore allowing NMDA receptor activation. NMDA receptor activation in turn engages multiple intracellular signaling pathways responsible for central sensitization. Second, accompanying an increase in activity via glutamate receptor signaling is a decrease in inhibitory transmission. In the spinal cord, GABA and glycine are inhibitory transmitters but

inhibition of nociceptive transmission also occurs via activation of descending modulatory circuitry originating from the periaqueductal gray area. The loss of inhibition occurs via various mechanisms and results in a change in the excitability (change in threshold of activation) of second-order spinal cord neurons, resulting in more excitatory input from primary afferents.

One mechanism responsible for the loss of inhibitory transmission in the spinal cord is engaged by neuronal-glial interactions (Fig. 1c). In various animal models of chronic pain, spinal gliosis (microglia and astrocytes) occurs leading to release of pro-nociceptive cytokines, chemokines, and other chemicals that sensitize nociceptive neurons. One example of neuronal-glial mechanisms contributing to central sensitization is release of brain derived neurotrophic factor (BDNF) from activated microglia that contributes to pain hypersensitivities (allodynia and hyperalgesia) by disrupting chloride transport in lamina I nociceptive spinal cord neurons. The resulting dysregulation in chloride causes a change in excitability of these neurons and contributes in the expression of pain hypersensitivities [31]. BDNF is also released by neuronal sources within the dorsal spinal cord in an activity dependent manner. Studies have shown that BDNF enhances NMDA receptor activity, providing an alternative mechanism that contributes to central sensitization [32]. It is important to note that not one single molecular mechanism is responsible for the occurrence of central sensitization, but that many processes will elicit the same outcome. Additionally, synaptic plasticity is critical for the development of central sensitization and the genesis of chronic pain, and although evidence is meager, it is possible that synaptic plasticity could revert nociceptive transmission to 'normal' homeostasis – or signaling that occurs for transmission of acute pain. The challenge is to identify targets that will initiate synaptic plasticity to undermine mechanisms maintaining chronic pain, including PVD.

Is There Evidence of the Role of Central Factors in PVD?

Given the major role central sensitization has been shown to have in chronic pain disorders such as migraine [33], neuropathic pain [34], inflammatory pain including irritable bowel syndrome [35], and fibromyalgia [36], it should not be surprising that this phenomenon most likely contributes to PVD. The involvement of the central nervous system in PVD has been investigated in a variety of studies. What is clear is that the processes involved in the development and maintenance of PVD are not strictly limited to peripheral, local factors in the vulvar vestibule. Rather, a dysregulation of pain processes at the level of the central nervous system is apparent; this dysregulation likely involves some components of central sensitization. For example, there is evidence of allodynia, lowered pain thresholds, spontaneous pain, hyperalgesia, and expansion of peripheral receptive fields in women with PVD. Selected studies are summarized in Table 2.

Allodynia

Allodynia, the experience of pain in response to a normally non-painful stimulus, is the defining characteristic of PVD. In fact, it forms the basis for the diagnosis of PVD. The typical diagnostic test performed is the cotton-swab test, in which various sites of the vestibule and surrounding area are palpated with a cotton-swab [37]. If pain is reported in response to vestibular palpation, which is normally non-painful, and the woman describes painful vaginal penetration/pressure activities, then the diagnosis of PVD is likely. Indeed, although the cotton-swab test is a crude measure of allodynia since the sites and level of pressure of palpation are not standardized [38], allodynia has also been shown to exist in the vestibules of affected women in empirical studies using quantitative sensory testing (QST). For example, several researchers have documented the experience of pain in response to normally non-painful mechanical and thermal stimuli in the vestibules of women with versus without PVD (e.g., [39–41, 42•]), as well as in response to vaginal distension [42•]. Strikingly, Pukall et al. [39] found that vestibular pain thresholds of women with PVD were similar to the tactile detection thresholds of non-affected women, indicating that the process of central sensitization may play a role in the expression of pain in women with PVD. In addition, this study documented that women with PVD were able to perceive non-painful tactile stimuli at levels that were imperceptible to non-affected women, indicating a significant shift in perception of non-painful stimuli as well.

Lowered Thresholds, Hyperalgesia, and Spontaneous Pain

Numerous controlled studies examining sensory function in the vestibules of women with PVD via QST have documented abnormal sensory functioning to a variety of stimuli, including mechanical and thermal. In all sensory modalities studied, except for vibration [40], women with PVD have overwhelmingly been shown to exhibit significantly lower vestibular thresholds (i.e., higher sensitivity) in response to mechanical and thermal stimuli as compared to non-affected women (e.g., [38–41, 42•, 43, 44]). These results indicate that the tissue of the vestibules of women with PVD displays a heightened sensitivity to stimulation, which corresponds with the clinical picture. That is, women with PVD report experiencing intense pain in response to a normally innocuous vestibular palpation with a cotton-swab, and they report pain during typically pleasurable, or at least non-painful, vaginal penetration.

To assess hyperalgesia solely based on self-report measures to pain threshold level stimuli, Pukall et al. [38, 39] assessed pain intensity and unpleasantness ratings in response to

Table 2 Summary of selected controlled studies investigating sensory thresholds in women with provoked vestibulodynia (PVD)

Research group	Type of sensory stimulation	Locations tested	Findings in women with PVD as compared to control women
Bohm-Starke, Hilliges, Brodda-Jansen, Rylander, & Torebjörk, 2001	Punctate mechanical (pain) via filaments	Vestibular mucosa, two sites (anterior [A] and posterior [P]).	Lower punctate mechanical thresholds (A and P locations)
	Perceived warmth and cold (thermal detection) via a thermal stimulator		Lower thermal detection thresholds (P only)
	Heat pain via a thermal stimulator		Lower heat pain thresholds (P only)
	Cold pain		More women with PVD reported pain during cold temperature application
	Vibratory evoked pain		Pain was not elicited in a significant proportion of women
	Distension via a vaginal balloon	Vaginal opening	Lower threshold
Pukall, Binik, Khalifé, Amsel, & Abbott, 2002	Tactile detection via filaments	4 sites around the vestibule	Lower thresholds in all sites tested
		Labium minus	Lower threshold
		Inner thigh	No difference
		Deltoid muscle	Lower threshold
		Forearm	No difference
		Tibia	No difference
	Punctate pain via filaments	4 sites around the vestibule	Lower thresholds in all sites tested
		Labium minus	Lower threshold
		Inner thigh	No difference
		Deltoid muscle	Lower threshold
		Forearm	Lower threshold
		Tibia	No difference
	Pressure pain tolerance via a dolorimeter	Deltoid muscle	Lower threshold
		Tibia	No difference
Giesecke, Reed, Haefner, Giesecke, Clauw, & Gracely, 2004	Pressure pain via a vulvodolorimeter	23 vulvar areas	Lower thresholds in all sites tested
	Pressure pain via a dolorimeter	Deltoid, shin, thumbnail	Lower thresholds in all sites tested
	Pressure pain threshold and suprathreshold via a hydraulic system	Thumbnail	Lower threshold
Granot & Lavee, 2005	Heat pain via a thermal stimulator	Forearm	Lower threshold
	Phasic pain via a thermal stimulator		Lower threshold
	Tonic pain via a thermal stimulator		No difference
Pukall, Baron, Amsel, Khalifé, & Binik, 2006	Pressure pain via manual palpation	9 bilateral nonvulvar sites	Significantly more painful areas

mechanical stimuli applied to the vestibules of women with and without PVD. Ratings were collected on two 0-10 Likert scales where 0 indicated no pain at all/not at all unpleasant and 10 indicated worst pain ever felt/most unpleasant ever to assess the sensory (intensity) and affective (unpleasantness) components of the painful sensation. Results indicated that, although the pain intensity ratings did not differ at the first detection of pain sensation between groups, pain unpleasantness ratings were significantly higher in women with PVD as compared with women in the control group. This finding suggests that women with PVD have a greater affective response to the pain (see also [39, 44]), and supports the presence of hyperalgesia (an increased response to a painful stimulus) in affected women.

In a well-designed study directly assessing some characteristics of central sensitization, Foster and colleagues [45] examined cutaneous response to intradermal capsaicin in the forearm and foot in women with PVD. They found that women with PVD exhibited greater levels of spontaneous pain following capsaicin injection, punctate hyperalgesia to nylon filaments, and dynamic allodynia to a spring wire stimulus in both the forearm and foot as compared with control participants. These results demonstrate a dramatic enhancement of not only evoked pain generated by mechanical and thermal stimuli but also chemical hypersensitivity in women with PVD versus those without PVD. This finding provides support for the presence of some aspects of central sensitization in women with PVD.

Expansion of Peripheral Receptive Fields

Several controlled studies have demonstrated that women with PVD exhibit a generalized (not restricted to the vulva) sensitivity to pain via self-report and QST methods. In terms of the number of other pain conditions experienced, women with PVD report significantly more non-vulvar pain

complaints (e.g., migraine), and they rate these pain issues as more severe and interfering with daily activity than control participants (e.g., [39, 46, 47]). Adding to this finding of self-reported pain is evidence of lowered thresholds in areas outside of the vulvar vestibule as measured by QST.

Women with PVD have been found to exhibit lower thresholds (i.e., higher sensitivity) to touch, pressure-pain, and heat pain at locations such as the labia minora, and the skin over, for example, the deltoid muscle and forearm (e.g., [39, 42•, 48, 49]). These changes appear to be widespread. One study indicated that women with PVD had significantly more painful tender points when nine bilateral areas in locations, ranging from the back of the neck to the knees, were palpated [46]. Furthermore, Foster et al. [45] demonstrated a significant expansion of receptive fields as evidenced by a greater extent of spread of pain sensation at two non-vulvar sites of intradermal injection of capsaicin (forearm and foot) in women with PVD as compared to non-affected control women.

Interestingly, this pattern of findings is not restricted to painful stimuli. Pukall et al. [39] demonstrated that several areas outside of the vestibule (e.g., labia minora, skin over deltoid muscle) were also more sensitive to tactile stimulation. Taken together, these results indicate that the sensory dysregulation exhibited in women with PVD is not restricted to pain. These findings are indicative of widespread hypersensitivity that has also been observed in patients with other chronic pain conditions, such as fibromyalgia [50] and irritable bowel syndrome [51]. Indeed, the characteristic of expanded receptive fields has been documented in women with PVD, demonstrating a key characteristic of central sensitization in this population.

DNIC

Diffuse noxious inhibitory control (DNIC) is a type of central nervous system endogenous pain modulatory mechanism that can be summarized as "pain inhibits pain" [52] and is otherwise known as counter-irritation. Studies of DNIC essentially test the integrity of central pain modulatory pain mechanisms [53], in particular, supraspinal structures [54]. In DNIC, spinal neurons are inhibited by nociceptive stimulation applied outside of their own excitatory and inhibitory segmental receptive fields [52, 55]. DNIC involves a spinal-medullary-spinal pathway; ascending information projects from the ventrolateral quadrant of the spinal cord towards supraspinal centers, whereas descending information projects from supraspinal centers through the dorsolateral funiculi to neurons in the dorsal horn of the spinal cord (e.g., [56]). Key neurons in DNIC inhibitory processes are the wide dynamic range neurons in the dorsal horn and trigeminal nociceptive neurons [55].

Clinically, when one has an intact DNIC system, pain at one body site inhibits pain at a distal body site through the inhibition of nociceptive-specific and wide dynamic range neurons [57], termed a 'positive' DNIC effect. It has been documented that patients with certain pain conditions (e.g., fibromyalgia, irritable bowel syndrome) have an absent or significantly diminished DNIC response, although this pattern of response is not always seen (see [58], for example). Two studies have investigated DNIC function in women with PVD, and both have demonstrated intact DNIC function (i.e., 'positive' DNIC effects) in this population [58, 59]. Sutton et al. speculate that perhaps this positive effect is due to the recurrent, provoked nature of the pain as opposed to the more chronic and constant pain of some other conditions [58]. It is possible that women with vulvodynia subtypes in which the pain is unprovoked and almost always present might have absent or decreased DNIC function. However, this issue has not been investigated systematically, although some preliminary evidence exists that one characteristic of central sensitization may be more likely in women with PVD who have a longer history of pain as compared to those with a shorter pain history (see [60]).

Neural Correlates of Sensation in Women with PVD

Brain imaging of function and structure is a popular method with which to study neural correlates of pain in patients with various pain conditions. Numerous functional imaging studies of pain have indicated that a particular pattern of activation can be more or less reliably observed in response to painful stimulation, including activation of regions such as the amygdala, and the insular, somatosensory, and cingulate cortices (e.g., [61–63]). Functional imaging provides an opportunity to examine central nervous system activity underlying the genital hypersensitivity to touch and pain in women with PVD and to compare activation patterns between PVD and other pain groups. Two such studies have been published, indicating that altered brain responses exist in women with PVD as compared to non-PVD groups.

Pukall et al. [64] compared regions of neural activity in women with and without PVD in response to mild and moderate pressure applied to the posterior portion of the vulvar vestibule. All of the women with PVD reported that the moderate pressure was painful and unpleasant and approximately half described the mild pressure as such. In contrast, none of the stimuli was painful for women in the control group. Results revealed significantly more activated brain regions during pressure intensities that were either painful or non-painful in the PVD group as compared with control participants during comparable pressure stimuli. Painful pressure led to significant levels of activation in somatosensory, insular, anterior cingulate, and frontal cortical regions in women with PVD. In addition, non-painful pressure led to significant levels of activation in insular, frontal, and somatosensory

regions in women with PVD. The results of this study indicate that women with PVD have an increased perception of non-painful and painful stimulation to the vestibule, and this increased perception is reflected in more significantly activated neural regions as compared to control women. Furthermore, the areas activated in response to painful genital stimulation in women with PVD are consistent with many of the areas activated during painful stimulation in non-PVD populations; there are parallels between the activation patterns of women with PVD and those with increased sensitivity due to conditions such as fibromyalgia, low back pain, and neuropathic pain [64].

More recently, Hampson et al. [65•] investigated neural activation as assessed by functional imaging in response to vulvar and thumb pressure-evoked pain processing in women with vulvodynia (this group included women with PVD), women with fibromyalgia (used as a positive control group for some analyses), and healthy control women. Results indicated that although no differences were observed in neural activation in response to vulvar stimulation between women with vulvodynia and healthy control women, women with vulvodynia displayed augmented activation as compared with control women in response to slightly intense pressure applied to the thumb. Regions of increased activation for this manipulation included the insula, the dorsal mid-cingulate, posterior cingulate, and ventral posterolateral nuclei of the thalamus [65•]. In addition, results indicated that women with vulvodynia and fibromyalgia exhibited greater activity in the left insular cortex as compared to healthy control participants in response to painful thumb pressure. Furthermore, region of interest analysis demonstrated that women with vulvodynia had great activation levels than healthy control women in areas such as secondary somatosensory cortex, anterior insula, and mid-insula in response to painful thumb pressure. These results, like those of Pukall et al. [64], also demonstrate evidence of augmented sensory processing in women with vulvodynia, and they support a consistency in patterns and levels of activation in patients with other chronic pain syndromes.

Of interest within the pain literature are studies examining gray matter density via voxel-based morphometry (VBM) in various conditions such as neuropathic and non-neuropathic low back pain [66, 67], tension headache [68], irritable bowel syndrome [69], and fibromyalgia [63, 70]. VBM objectively measures the relative amount, or density, of gray matter to all other tissue types in the brain. Predominant changes documented in the pain literature typically involve decreases in the density of gray matter [63, 66–68, 70]; however, some studies report increases in gray matter density, usually in the basal ganglia [67, 68, 70]. In a study of women with and without PVD, results indicated that women with PVD have greater gray matter density in several brain areas, including the parahippocampus, hippocampus, and basal ganglia as compared with a healthy control group [71]. Importantly, these findings indicate that in addition to functional changes in terms of neural responses to stimulation, there are documented changes in the morphology of the brains of women with PVD. However, the issue of whether the changes in neural structure and function reflect central sensitization per se is not clear, as peripheral processes can also contribute to these changes without the presence of central sensitization.

Conclusions

The involvement of central factors in the pathophysiology of PVD has been supported by a number of studies investigating self-report measures, sensory thresholds, functional brain imaging, and morphological analysis of gray matter in the brain. Indeed, the consensus in the literature is that the pain of PVD commences in response to a local (vulvar) issue, but that, with time, increasing distress, negative functional impact (e.g., avoidance of sexual activities because of the pain), and involvement of other bodily areas in terms of pathological responses to pain (e.g., increased tension in the pelvic floor muscles), is maintained by central factors [1, 72••, 73, 74••]. Further research is needed in order to explore the role of spinal cord mechanisms and neural correlates in women with PVD specifically, as well as in women with other types of chronic vulvar pain conditions (e.g., generalized vulvodynia) and in subtypes of PVD (e.g., primary versus secondary).

Perhaps the greatest limitation of investigating the contribution of central sensitization in PVD is due to the lack of a validated animal model. There is promise in this area, however, as Farmer and colleagues [75•] have developed an initial animal model of vulvodynia. Specifically, they demonstrated that repeated, localized exposure of the mouse vulva to *Candida albicans* (the fungal pathogen responsible for yeast infections, a common finding in the histories of many women with PVD [76]) led to vulvar mechanical allodynia and hyperinnervation for a period of at least three weeks after the resolution of the infection and inflammation. This study is important for the field as it demonstrates that hypersensitivity can persist in the absence of observable explanations. This pattern parallels the experiences of many women with PVD, and supports the ISSVD's definition of vulvodynia as medically unexplained chronic vulvar pain [3].

Compliance with Ethics Guidelines

Conflict of Interest Catherine M. Cahill and Caroline F. Pukall declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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