Chapter 19. Anatomy and Physiology

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The initiation and maintenance of chronic pain reflects a combination of peripheral, spinal and brain mechanisms.

Pain assessments based on symptom configurations, rather than existing diagnostic categories, are useful in deciphering mechanisms of referred pain.

Visceral nociceptors are poised to hijack cutaneous nociceptive circuits through spinally-mediated cross-talk.

Introduction

Pain and nociception are indispensable contributors to female sexual function. Nociception refers to the physiological processes that mediate detection of environmental threats and the relay of this information through the peripheral and central nervous systems. In contrast, pain is the cortically mediated subjective experience that can emerge when nociceptive signals are integrated into the neural networks underlying consciousness. Therefore, nociception may not lead to pain perception, and pain perception is not solely dependent on nociceptive input.

Just as a woman's subjective experience of desire and arousal are central to the study of female sexual function, pain perception also guides our understanding of pain physiology. This chapter will review the mechanisms of the acute and chronic pain physiology of genito-pelvic pain. Acute genito-pelvic pain arises from trauma, inflammation, or infection and usually resolves as tissue heals. Given that chronic pain persists beyond the normal healing period, by definition the mechanisms underlying chronic pain maintenance are independent of acute tissue pathology. Therefore the assessment and treatment of genito-pelvic pain requires an understanding of the "rules" of nociception in the periphery, spine, and brain and how these rules are violated in chronic pain states across time.

Nociceptor Structure and Function

Across species, the close correspondence between sensory neuron firing properties and magnitude of pain perception indicates that general properties of neuronal function can be deduced from subjective pain perception (1, 2). Nociceptors are free nerve endings that detect noxious or potentially harmful mechanical, thermal, chemical, and electrical stimuli that are usually perceived as painful. Their cell bodies are located in the dorsal root ganglion, with one peripheral process extending to the target tissue and one process terminating in the ipsilateral dorsal horn of the spinal cord. All nociceptors release the excitatory neurotransmitter glutamate and can be distinguished according to five structural and functional criteria that facilitate

encoding of a broad variety of sensory stimuli: (a) nerve diameter (which determines conduction velocity and response latency) and the presence of myelination, (b) stimulus modality (i.e., mechanical, thermal, and/or chemical input), (c) functional response characteristics (rate of neuronal firing, threshold of activation, adaptation profile), (d) receptor expression modulating these response properties, and (e) functional properties unique to either somatic or visceral tissue (3, 4). These criteria are not absolute, as new subpopulations of nociceptors will inevitably be identified in the coming decades. Nociceptive signals are transmitted by Aδ and C nerve fibers that detect either a single sensory modality (unimodal) or two or more sensory modalities (polymodal) (Table 1). Large, myelinated Aδ fibers rapidly conduct mechanical, thermal, and/or cold nociceptive signals (at rates of 5-30 m/s), terminate in superficial lamina I and deep lamina V of the dorsal horn, and lead to the immediate percept of sharp pain. In contrast, unmyelinated C fibers transmit mechanical, thermal, and/or chemical nociceptive information more slowly (at rates of 0.5-2 m/s) and terminate in laminae I and II_{outer} of the dorsal horn, yielding a gradual pain perception of dull or burning pain. More fine-grained nociception is achieved with specialized receptor proteins and ion channels located on nerve endings. These receptors and channels mediate (a) the transduction, or conversion, of a sensory stimulus into an electrical signal and (b) the encoding, or one-to-one correspondence, of electrical signals to stimulus attributes that the brain can interpret (e.g., modality, location, threshold, intensity, timing). For instance, increased stimulus intensity is encoded by an increased rate of neuronal firing, and the timing of neuronal firing encodes stimulus duration. Collectively, the interface between a sensory stimulus and these functional properties of nociceptors contribute to complex sensory perceptions, such as pain.

Detection of mechanical stimulation is central to sexual arousal because sexual activity involves skin-on-skin contact, including manual, oral, and/or genital stimulation of oneself and/or one's partner. Gentle mechanical pressure is encoded by Aβ mechanoreceptors (including Merkel cells, Pacinian, Ruffini, and Meissner's corpuscles) that terminate in laminae II_{inner}, III, and IV of the dorsal horn, and by a non-nociceptive population of C fibers that mediates pleasant touch, mild heat analgesia, and potentially erotic touch (5, 6). Recently described Piezo receptors encode more nuanced gradations of mechanical pressure and stretch, including stretch in urothelial cells (*piezo 1*) and intraluminal pressure and fullness (*piezo 2*) (7). In particular, piezo2 will play an important role in our future understanding of genito-pelvic pain thresholds. Piezo2 expression mediates reduced pain thresholds (*mechanical allodynia*), is required for Merkel cell mechanosensitivity, and leads to activation of Aβ nerve fibers, which can acquire nociceptor characteristics in certain pathological states discussed later in this chapter (8).

Most noxious stimuli also involve some degree of mechanical stimulation. The transition from non-painful to painful mechanical pressure (i.e., pain threshold) is encoded by the $P2X_3$ subclass of purinoreceptors. $P2X_3$ activation provokes the rapid release and detection of adenosine triphosphate to generate a rapid and time-limited inflammatory response (9). $P2X_3$ expression is inhibited by estrogen receptor-α binding on C-fiber nociceptors (mediated by signaling pathways dependent on cyclic adenosine monophosphate, protein kinase A, and extracellular signal-regulated protein kinases 1 and 2 interactions), which strongly suggests that estrogen-$P2X_3$ interactions modulate nociceptive signaling via immune mechanisms. Reduced mechanical pain thresholds may reflect inadequate estrogen receptor-α regulation of $P2X_3$, leading to $P2X_3$ overexpression (10, 11). This hypothesis is indirectly supported by data in postmenopausal women and rodents showing that tissue depletion of estrogen is associated with mechanical allodynia (12, 13). Similarly, vulvar punch biopsies from women with provoked vestibulodynia exhibit dramatic reductions in estrogen receptor-α expression (14). $P2X_3$ participates in the amplification of persistent pain signals at the peripheral and spinal levels. For instance, increased bladder urothelial $P2X_3$ expression in women with interstitial cystitis/bladder pain syndrome may implicate the presence of altered lumbosacral $P2X_3$ response properties

observed in rodent models of bladder inflammation (15, 16). These data also raise the possibility that aversive feelings of fullness and mechanical allodynia reported by women with persistent genital arousal disorder could, in part, reflect a basal state of $P2X_3$ disinhibition (17).

$P2X_3$ frequently co-localizes with the capsaicin receptor (i.e., the transient receptor potential cation channel subfamily V member 1 receptor, previously the vanilloid 1 receptor) which is a cation channel receptor located on polymodal C fiber nociceptors in skin and especially visceral organs. Under normal physiological conditions, the capsaicin receptor activates with noxious thermal (> 43° C), chemical, and acidic stimuli (pH < 5) and facilitates the perception of burning heat pain (18). Women with provoked vestibulodynia exhibit increased capsaicin receptor expression in sub-epidermal vulvar nerves, which implicates a greater capacity to detect noxious vulvar stimulation (19). Capsaicin receptor expression in keratinocytes may also contribute to nociceptive signaling (20). Capsaicin receptors exhibit a range of unique functions that can contribute to symptom variability in genito-pelvic pain. Under acidic conditions capsaicin receptors activate at room temperature (20-25 °C), which would allow these receptors in acidic vulvar tissue (pH 3.8-4.5) to transmit burning heat sensations in the absence of high temperatures. Sustained activation of these receptors with topical capsaicin promotes a calcium–dependent decrease in channel activity that prevents nerve firing for an extended period (21). This desensitization mechanism may explain the treatment of vulvar pain with topical capsaicin, and brief trials combining capsaicin and lidocaine (for comfort) can be used to assess the degree of peripheral nerve contributions to vulvar pain (22). Capsaicin receptors can sensitize the activity of neighboring receptors, like $P2X_3$, and provide a feasible mechanism for mechanical pressure-induced sensations of burning pain. Note that this phenomenon does not require nerve injury—it represents a phenotypic shift in how sensory input is detected (21). Collectively, these data suggest that nociceptors encoding both mechanical and heat pain are functionally poised to play major roles in genito-pelvic pain. Use of $P2X_3$ antagonists, capsaicin receptor antagonists or extended treatment with agonists (e.g., topical capsaicin) to induce depolarization blockade, and/or estrogen receptor-α agonists may prove fruitful in managing pain.

The actions of receptors may differ between basal, inflammatory, and neuropathic states. For instance, acute inflammation is characterized by thermal hyperalgesia that is dependent on capsaicin receptor expression and mechanical hyperalgesia that relies on expression of transient receptor potential ankyrin 1 (18). Blockade of transient receptor potential ankyrin 1 normalizes mechanical sensitivity without affecting inflammation or capsaicin receptor expression. Receptors that express transient receptor potential cation channel subfamily V member 4 encode innocuous warmth in basal conditions and mediate inflammation-induced visceral mechanical sensitivity. Notably, these three receptors, in variable combinations, are expressed by most abomino-pelvic visceral afferents.

HORMONAL REGULATION

Estrogen is implicated in sensation and nociception at the peripheral, spinal, and supraspinal levels. In the brain, estrogen promotes endogenous opioid analgesia and spinal inhibition of pain, yet it also facilitates hippocampal capsaicin receptor-mediated pain hypersensitivity (23-25). Spinal estrogenic regulation of μ- and/or κ-opioid heterodimer expression is critical for a female-specific neural pathway for opioid analgesia (26-28). Estrogen receptors are present in lumbosacral dorsal root ganglia and on peripheral terminals of putative nociceptors, with estrogen receptor-α expressed in the vulva, vagina, uterus, bladder, and ovaries, and estrogen receptor-β intensely expressed in the ovaries (29, 30). Both receptors are distributed throughout the vaginal epithelium, labia minora epidermis, and vaginal smooth muscle (31). In the periphery, rapid 17β-estradiol signaling of membrane-bound estrogen receptors -α and –β plays a key role in regulating mechanical nociception (9). For example,

$P2X_3$-dependent painful bladder distension is inhibited by estrogen receptor-α binding, and ovariectomy increases bladder P2X3 receptor expression by 300% (32, 33). The respective roles of estrogen receptors -α and -β remain poorly understood, and their functions vary based on site(s) of action (peripheral or central), levels of bioavailable sex steroid hormones in local tissue and in free circulation, presence of inflammation or disease, states of hormone depletion (e.g., oophorectomy, menopause, lactational amenorrhea, etc.), and physiological adaptations resulting from long-term supplementation (e.g., oral contraceptive use).

It is feasible that nociceptor signaling could qualitatively differ across the cycle as hormones fluctuate. During pre-ovulatory periods of high circulating estrogen, enhanced structural integrity of tissue and estrogenic inhibition of $P2X_3$ may allow genital tissue to withstand the physically rigorous act of intercourse. In contrast, depletion of female gonadal hormones in rodents induces mechanical and thermal pain hypersensitivity that parallels a threefold increase of P2X3 receptor expression in the dorsal root ganglion (13, 34, 35). Restoration of sexual function with combination oral/topical estrogen treatment in hormonally deficient women may therefore reflect improved physical integrity of the vaginal epithelium and normalized mechanical pain thresholds (36-39). Given the pivotal role of estrogen in bladder and uterine visceral nociception, it likely plays an important role in referred and comorbid pelvic pain (40, 41).

The long-term consequences of oral contraceptive use on genito-pelvic pain remain poorly understood. On the one hand, estrogen-dependent conditions like endometriosis can benefit from oral contraceptive and aromatase inhibitor use (42). In contrast, extended use of oral contraceptives, especially low estrogen formulations, may confer greater risk for developing provoked vestibulodynia (43, 44). Chronic use of oral contraceptives reduces sex steroid hormones and may lead to insufficient estrogen receptor-α binding of $P2X_3$ receptors, yielding lower pressure and/or distension pain thresholds.

Notably, vulvar vestibule expression of estrogen receptor-β, the receptor subtype associated with increased nociceptive action, is upregulated in women taking oral contraceptives, a population that exhibits lower mechanical pain thresholds than naturally cycling women (45-47). Pain hypersensitivity could develop with long-term alterations in estrogen and/or progesterone levels by promoting *de novo* nerve sprouting and hyperinnervation (48-50). However, oral contraceptive use alone may not be sufficient to enhance the risk of developing chronic vulvar pain. A subgroup of women with low basal androgen receptor transcriptional function and low free testosterone levels may have a greater risk for developing provoked vestibulodynia (51, 52). These data reinforce that acute and adaptive effects of sex steroid hormones on nociception are mechanistically distinct and clinically relevant.

SOMATIC AND VISCERAL PAIN

Nociceptors exhibit unique functional properties based on the tissue type in which they are embedded (Figure 1). “Somatic” nociceptors innervate skin, muscle, and bone and contribute to pain perception that closely correlates with stimulus intensity, duration, and location, and it has distinctive qualities (“sharp,” “pinching,” etc.). Tissue depth can impact the spatial perception of somatic pain: for instance, deep muscle pain may be perceived across the length of the muscle. In contrast, “visceral” pain caused by hollow organ distension and traction is perceived along the midline of the body as diffuse discomfort that may lag seconds or minutes behind noxious stimulation. Visceral sensations include nausea, bladder and stomach filling, distension (vaginal, rectal, intestinal, esophageal), menstrual cramps, and bloating, but many visceral experiences lack an adequate vocabulary (e.g., the sensations associated with catheter insertion, venous cannulation, or having food lodged in one’s throat). The body must be able to tolerate some physiological discomfort associated with normal functions (e.g, with bowel or

bladder distension). The viscera are therefore exclusively innervated with both high threshold nociceptors that transmit innocuous and noxious input and with intensity-encoding nociceptors, which allows visceral pain to emerge only with prolonged and/or intense noxious stimulation (53). Moreover, high threshold nociceptors can create a time delay between visceral stimulation and its subjective perception.

The lower third of the female genital tract, including the vulva, urethra, and proximal vagina, receives a combination of both somatic and visceral innervation (54). As a result, conditions like provoked vestibulodynia may be characterized by complex nociceptive signaling. Dynamic modeling has revealed that vulvar pain perception closely corresponds with the quality and time course of vulvar punctate pressure, whereas the delayed onset of distension-induced vulvovaginal pain is consistent with visceral transduction (55). These findings imply that genital quantitative sensory testing research that uses somatic tissue (e.g., volar forearm) as a "control" for lower genital tract sensitivity may be comparing fundamentally different types of pain (56). The significant anatomical variability in vulvovaginal shape and size may also facilitate visceral pain through simple mechanical traction. Genital sensitivity testing should always be validated against clinical pain reports because different tissues may exhibit variable degrees of hypersensitivity (57).

REFERRED PAIN

Referred pain is one of the least appreciated mechanisms underlying genito-pelvic pain and other comorbid pain syndromes. Referred pain is a regular feature of visceral pain and can also account for many seemingly enigmatic pain symptoms (58). Three major hypotheses should be considered when a woman reports pain in a specific location: (a) her pain is caused by tissue pathology in target tissue, (b) pain is referred from another site exhibiting tissue pathology, and/or (c) pain is cortically mediated as a sensory memory. In practice, genito-pelvic pain rarely fits neatly into existing diagnostic categories, which is not surprising given that vulvodynia, bladder pain syndrome/interstitial cystitis, dysmenorrhea, pelvic girdle pain, and debatably (painful) endometriosis are diagnoses of exclusion. Therefore, pain assessments based on symptom configurations, rather than existing diagnostic categories, are useful in deciphering mechanisms of referred pain.

Somatic afferent fibers account for 90% of nerves that terminate in the spinal cord, while the remaining 7-10% are visceral afferent fibers that may synapse at, above, or below their originating dermatome (or even on the contralateral side of the spinal cord) (54, 59). Visceral nociceptors synapse onto dorsal horn interneurons in laminae I, II, and V that also receive somatic terminations, and the resulting nociceptive signals—regardless of their tissues of origin—are then transmitted along specialized ventro-lateral funiculus projections to the brain. With intense noxious stimulation, the visceral–somatic convergence of nociceptors onto common interneurons allows neural discharges from one afferent to influence the electrical activity of another and to sensitize their shared interneuron (54). Visceral nociceptors are therefore poised to hijack cutaneous nociceptive circuits.

This neuronal "cross-talk" establishes three types of functional interactions between the participating afferent fibers, including viscero-visceral (organ to organ), viscero-somatic (organ to muscle/skin), or somato-visceral (muscle/skin to organ) interactions (Figure 2). Rodent data has confirmed the functional convergence of abdominal and pelvic visceral organs in 13-60% of lumbosacral dorsal horn neurons, with variation observed between spinal segments (60). Importantly, referred pain can manifest in neighboring dermatomes due to the broad arborization of visceral afferents onto multiple spinal cord segments (61, 62). Classic accounts of visceral pain focused on referral between body sites with common embryological origins (e.g., tissue derived from the urogenital sinus, including vulvar vestibule, bladder, urethra, umbilicus, and prostate); however, pain referral regularly deviates from such patterns. Clinical signs of pain

referral from viscera to somatic tissue include cutaneous and deep muscle hyperalgesia (but not altered detection thresholds), which emerges over minutes to hours and may outlast the original visceral pain (63). Referred visceral pain can generate one or more regions of referral to somatic tissue (e.g., referred uterine pain that is experienced in the lower back), or it can manifest as a radiating, burning, aching, prickling, and/or electrical shock-like pain that moves throughout the pelvic cradle, which is reminiscent of neuropathic pain features (64, 65). Therefore, referred pain is an umbrella term that can indicate a) pain referred from a visceral structure to muscle, with no muscle hyperalgesia, b) pain referred from a visceral structure to muscle, resulting in muscle hyperalgesia, and c) expansion of referred hyperalgesia following intense and/or persistent nociceptive input and/or presence of co-occurring visceral pain conditions. Accordingly, more frequent visceral pain episodes are associated with greater pain threshold reductions at sites of pain referral (64). Similarly, presence of comorbid chronic visceral pain conditions may promote increased intensity and greater spatial spread of referred hyperalgesia (66).

Referred deep muscle hyperalgesia in the pelvic floor musculature may contribute to diffuse pain sensations, given that muscle pain can be perceived along the length of the muscle (67). It is hypothesized that this hyperalgesia results from a viscero-muscular reflex that induces painful muscle contractions that can ultimately become maintained independent of the original visceral input. Muscle hyperalgesia referred from the viscera can, in turn, cause secondary referred pain across multiple dermatomes and promote a broad spectrum of extra-pelvic pain symptoms that are not due to sensitization, *per se*. It is plausible that localized muscle pain, or "trigger points" are the product of visceral pain referral, rather than primary dysfunctions. Care should be taken to parse referred muscle pain from reactive muscle tension, which is a natural defensive response to pain, and from the muscle tension and pain that emerge as the body attempts to compensate for functional deficits caused by genito-pelvic pain. Pelvic floor physical therapists have the ideal education and training to help disentangle the causes and consequences of referred genito-pelvic pain within a larger biopsychosocial framework (68).

Spinally mediated cross-talk can intensify or strategically alleviate pain symptoms. Viscero-visceral hyperalgesia caused by cross-organ sensitization in animals and humans confirms that referral can mutually influence pain generated at either site (69). Accordingly, the successful treatment of pain originating in one visceral organ can partially alleviate pain symptoms associated with other organs sharing overlapping innervation (69). Pain referral is ultimately dependent on continued nociceptive input and its spinal mediation; as a result, anesthetic blocks at the site of pain referral provide only partial relief (70, 71).

VASCULAR PAIN

The discrepancy between pain perception and degree of arterio-venous pathology is a classic feature of visceral pain (54). In general, vascular pain arises either from inadequate or excessive blood flow to a body region. Circulation is impaired when tissue, muscles, and tendons are deprived of oxygen or constricted by edema leading to elevated internal venous pressure. Visceral vasculature can also be compressed by surrounding muscle and fascia, depending on regional differences in pelvic floor muscle architecture. For example, shorter coccygeus muscle fibers can generate greater force than longer pubovisceral muscle fibers (67). The generated biomechanical forces result in stretch, compression, shear, or injury of vasculature that contribute to pelvic pain through local inflammation and/or direct nerve compression. The resilience of vasculature is compromised by estrogen-mediated signaling cascades that promote vasodilation, compromise vascular smooth muscle contraction, alter vascular remodeling, and weaken venous walls.

Acute venous dilation is rarely painful, yet chronic venous reflux is considered a diagnostic indicator of pelvic congestion syndrome, a symptom complex characterized by

aching, burning pain with muscle exertion (e.g., claudication) that radiates from the buttocks to feet, as well as neuropathic symptoms like numbness, paresthesia. Pelvic congestion syndrome is characterized by venous insufficiency, as corroborated by evidence of pelvic, abdominal, and thigh varicose veins. However, pelvic venous dilation and compromised venous integrity are also present in many healthy women who do not have these symptoms (72). Again, this is not surprising given that superficial and deep venous reflux are not correlated with pain perception.

INFLAMMATION

As a normal feature of female reproductive physiology, inflammation is not an inherently pathological process. Menstruation is thought to be initiated by progesterone withdrawal-induced pro-inflammatory responses (73). The lower genital tract (vagina and vulva) exhibits ongoing low-grade inflammation, presumably as a defense against pathogens introduced with invasive sexual contact or migrated from nearby body sites (e.g., anorectal bacteria) (74-76). The degree of inflammation can vary based on a woman's vaginal and bladder flora (which changes across the menstrual cycle), presence of injury (e.g., vaginal fissures), tissue-specific inflammatory profiles (e.g., upper versus lower genital tract), exposure to new immune threats (e.g., sexually transmitted infections), priming by past immune threats, host resilience to new immune threats, genetic polymorphisms that bias the inflammatory response, and interactions between these factors (56, 77-79). Therefore, inflammation results from, mediates, and fine-tunes nociception to enhance the sensitivity and specificity of nociceptive signaling. The presence of inflammation may reflect immune responses to current as well as past immune threats. As a result, inflammation *per se* may be a poor indicator of underlying pain pathology. Given the complexity of this process, the dynamics of inflammation are discussed in relation to the pathogen-host interactions that may facilitate emergence of the most common cause of dyspareunia, provoked vestibulodynia.

The standard clinical assumption is that vestibulodynia pain arises from vulvar vestibular inflammation that is secondary to repeated exposure to biological or synthetic inflammagens (e.g., recurrent yeast infections), neuroproliferation, and hormonal antagonists (not mutually exclusive). Regarding the first hypothesis, non-autoimmune inflammation reflects an interaction between stimulus severity (e.g., a pathogen's virulence, pathogen load, frequency of repeated exposures, etc.) and host resilience (e.g., genetic and developmental influences, microbial abundance/richness, immune suppression, etc.). Although the detection of pathogenic viruses, yeast, and bacteria by epithelial toll-like receptors immediately triggers a nonspecific "innate" immune cascade (80), each of these pathogens in isolation may contribute to clinically relevant pain: repeated yeast exposures cause persistent vulvar pain, post-viral neuropathic pain can last years beyond primary infections, and bacteria may modulate nociception (81-83). Some of these microorganisms have even evolved unique adaptations to evade dominant immune responses in human hosts (84). Therefore inflammation *per se* may account for a limited degree of pain pathophysiology observed in women with genito-pelvic pain.

Recent evidence has revealed one innate immune pathway that may play a major role in the initiation and maintenance of provoked vestibulodynia in women with histories of recurrent vulvovaginal candidiasis. An experimental mouse model of chronic vulvar pain following recurrent Candida albicans infections provided causal evidence that prolonged yeast exposure can initiate persistent pain and vulvar hyperinnervation (82). The role of yeast exposure in the maintenance of provoked vestibulodynia is supported by the differential cytokine expression induced by yeast-exposed fibroblasts isolated from vestibule versus non-vestibule punch biopsies in women with and without the condition (75). In both groups, vestibule fibroblasts expressed more interleukin-6 and prostaglandin than non-vestibule fibroblasts. This cytokine expression is mitigated by blocking Dectin-1 gene expression and is almost abolished with inhibition of nuclear factor-κB phosphorylation (85). Estrogen receptor-α binding directly inhibits

nuclear factor-κB pathways, which suggests a critical role of estrogen in regulating nociception and related immune reactivity (86). Note that yeast-induced nociception can sensitize nociceptive pathways that are ultimately independent of the presence or absence of yeast, and such mechanisms are difficult to study *in vitro*.

These studies highlight the importance of anatomical and genetic factors in provoked vestibulodynia, a pain condition that is frequently comorbid with pelvic, abdominal, and temporomandibular pain. The unique immune profile of the vulvar vestibule, a urogenital sinus-derived tissue, may be shared by tissues of common embryological origin (urethra, bladder, umbilicus) (87, 88). These shared immunological abnormalities may therefore predispose women with vulvar pain to develop comorbid bladder and/or urethral pain, a diagnostic overlap that is consistently observed in the literature (89). Moreover, women with provoked vestibulodynia are 2.5 times as likely to exhibit loss-of-function melanocortin-1 receptor polymorphisms that may interfere with the downregulation of proinflammatory cytokines and adhesion molecules generated by the nuclear factor-κB pathway (90, 91). This polymorphism may impact a broad range of pain mechanisms because the melanocortin-1 receptor mediates κ-opioid analgesia in women, modulates μ-opioid analgesia, and pain thresholds in women (92-95). Indeed, most of the genetic polymorphisms identified in genito-pelvic pain populations appear to impact inflammatory cascades, host-pathogen interactions, and pain sensitivity (88).

The body cannot afford to sustain a biologically expensive response like inflammation indefinitely because these resources must be available to defend against new threats. Inflammation promotes physiological adaptations that maintain efficient nociceptive signaling as chronic pain persists, and these adaptive solutions will change over time. Sensory neurons are the only afferents that can regenerate in mammals, and *de novo* nerve sprouting is a well-documented consequence of chronic pain pathology observed with frank tissue injury, skin scratching, infection, and even radiation in rodent models (82, 96, 97). Indeed, women with provoked vestibulodynia exhibit increased density of vulvar calcitonin gene-related peptide expressing C fiber nociceptors and area vulvar vestibular nerve fibers, compared to healthy controls (98, 99). Therefore vulvar neuroproliferation may in some cases evolve as a long-term consequence of inflammation. A pervasive bias continues to influence the field's understanding of inflammation and is based on the expectation that chronic inflammation will resemble the acute inflammatory state. Instead, one of the most common findings across pelvic pain populations is evidence of increased mast cell count and/or mast cell degranulation (100-103).

PERIPHERAL & CENTRAL SENSITIZATION

The term "sensitization" is not in itself mechanistically useful because amplified nociceptive signaling can be sustained by the nociceptor that detects noxious input, and/or the spinal cord interneurons that relay these signals, and/or the brain that interprets and learns from these signals. However, this concept can be used to better interpret configurations of pain symptoms (Figure 3).

Repeated noxious stimulation can enhance the firing properties of C fiber nociceptors in a process called peripheral sensitization (65, 104). Peripheral sensitization is defined by the following five functional changes in nociceptors: (a) reduced activation thresholds due to changes in membrane potentials; (b) enhanced magnitude of signaling, (c) generation of spontaneous signaling with no stimulus (i.e., ectopic discharges), (d) enhanced magnitude of signaling with repeated stimulation (wind-up), and (e) recruitment of "silent nociceptors," which are previously non-nociceptive Aβ afferents that switch phenotypes to become nociceptors (105). Inflammation is the most common cause of peripheral sensitization, and it is a normal physiological process from which our bodies usually recover. It can generate clinical symptoms like mechanical and heat allodynia and hyperalgesia at the site of injury, without the independent participation of spinal cord interneurons.

Central sensitization is a powerful idea, as it provides a physiological mechanism for sustained pain in the absence of the precipitating stimulus. Prolonged activation of peripheral nociceptors can trigger enhanced activity of spinal cord cephalad projecting neurons in proportion to intensity, repetition, and duration of the nociceptive input (106). Symptoms consistent with central sensitization include touch but not thermal hypersensitivity around the perimeter of the primary injury. This may include increased punctate pain sensitivity (*hyperalgesia*) mediated by A delta fibers, pain with moving tactile pressure (*dynamic tactile allodynia*) mediated by "silent nociceptors" (Aβ fibers), and pain sensations that persist long after vulvar or bladder stimulation has ceased (65). Thermal hyperalgesia is rarely observed. When central sensitization and referred pain co-occur, secondary hyperalgesia may take a different form: silent nociceptors can mediate new regions of cutaneous or deep muscle hypersensitivity (64). However, the most distinctive signature feature of central sensitization is the temporal dissociation between removal of the noxious stimulus and continued spinal interneuron firing that underlies pain after-sensations. This can be contrasted with the period of quiescence that separates the removal of a visceral stimulus and prolonged visceral pain. Mechanisms underlying central sensitization of visceral nociceptive signals remain poorly understood and do not follow the same "rules" as sensitization of somatic nociceptive signals.

Note that central sensitization may coexist with, but is not the same as, the following: (a) peripheral sensitization, (b) "wind-up," which refers to the summation of excitatory input by a subset of hyperexcitable dorsal horn interneurons (without stimulus-response temporal dissociation); (c) referred pain, (d) neuropathic pain, which is caused by an identifiable lesion or disease of the somatosensory system, and (e) the hypothetical diagnoses of "central sensitivity" or "central sensitivity syndrome" (64, 65). Similarly, symptoms like allodynia and hyperalgesia present with peripheral as well as central sensitization, and their relationship to other pain symptoms must be considered to decipher their underlying mechanisms (an overview of mechanisms for distinct types of pain is presented in Table 2) (107).

Central sensitization shares key features with but is not synonymous with neuropathic pain. Although central sensitization is considered a key pathological process used to define the initiation of neuropathic pain, neuropathy encompasses a broader range of symptoms including spontaneous (unprovoked) fluctuations of burning or electrical shock-like pain. Neuropathic pain may include regional numbness or "pins and needles" sensations that indicate a loss of function; central sensitization exclusively reflects gain of function. Importantly, the maintenance of central sensitization, but not neuropathic pain, is dependent on continued provocation of peripheral nociceptors. However, it is possible for these processes to co-exist in a woman with chronic genito-pelvic pain. To date, the presence of central sensitization in many types of genito-pelvic pain has not been supported by evidence due to confusion regarding its definition, variability between diagnoses, and methodological limitations (63, 108).

It is tempting to invoke central sensitization as a catch-all mechanism for unexplained clinical pelvic and non-pelvic pain. However, the mere presence of pain hypersensitivity is not evidence of this phenomenon (107). It is a functional change unique to spinal cord interneurons that requires very specific conditions (moderate, repetitive noxious stimulation) to be maintained and rekindled; otherwise it will extinguish (109). To date, no study has demonstrated a parallel phenomenon in cortical neurons, and therefore no empirical data supports the claims that maladaptive pain behaviors, catastrophization, or other psychological "amplifications" of pain are symptomatic of central sensitization. Similarly, the extrapolation of central sensitization to explain complex symptom patterns found in comorbid pain conditions is purely hypothetical at this point (65). Worst case, the misuse of the term will promote the haphazard mixing and matching of heterogeneous chronic pain conditions in the absence of empirical or clinical data.

The spinal relay of nociceptive information to the brain is influenced by cortically-controlled descending pain modulation, which can be experimentally evaluated using conditioned pain modulation paradigms. Conditioned pain modulation is stable in healthy and

chronic pain populations and may provide prognostic value; however, it has not been assessed in relation to clinical symptom change (110-112). Two of three studies failed to identify abnormal spinal inhibition in vestibulodynia, as evidenced by intact diffuse noxious inhibitory control via conditioned pain modulation (113-115). Indeed, symptoms like temporal summation suggests that spinally mediated facilitation (or gain) plays a more dominant role than descending inhibition. Conditioned pain modulation studies in other populations await replication.

THE BRAIN

Ultimately, pain perception is a cortically-mediated phenomenon. Therefore all content discussed to this point—from the initial detection of sensory stimuli to the dynamic spinal relay of this information—culminates in a nociceptive signal that can be attended to, ignored, or even distorted by brain circuits. Although a thorough treatment of this topic cannot be achieved here, a brief review of the current state of pain neuroimaging is presented.

It was previously believed that the brain regions that mediate pain perception must represent a specialized neural network. This assumption was supported by many studies demonstrating that acute pain perception correlates with functional activation of the insula, anterior cingulate cortex, somatosensory cortices, prefrontal cortex, thalamus, brainstem and other regions, and individual regions mediated distinct aspects of pain location, sensation, affect, intensity, and higher cognitive processing (116-119). More recently, this interpretation has been questioned because the activation of brain regions originally associated with acute nociceptive processing are not specific to noxious stimulation and show limited overlap with neural “signatures” of chronic pain. Recent metaanalyses and large-scale studies have found that acute pain sensitivity has minimal prognostic value across chronic pain populations (120, 121). Instead, more recent evidence suggests that mesocorticolimbic, rather than sensory encoding regions, mediate the transition to and maintenance of pain chronicity (122). For instance, a longitudinal brain imaging study determined that the neural representation of spontaneous fluctuations of subacute low back pain shift from nociceptive to limbic regions as patients transitioned to chronicity (123). These findings highlight the distinction between pain sensation and the long-term suffering it causes, given that both should ideally be targeted in pain management efforts.

Realistically, the transition from acute to chronic pain reflects three broad classes of mechanisms, including peripheral, spinal, and brain processes. The initiation and maintenance of chronic pain reflects a combination of these components that must evolve over time: spinal central sensitization will eventually extinguish without additional peripheral input, and it is not known whether additional insults (e.g., recurrent infections, pain flares) are sufficient to indefinitely sustain central sensitization (109, 124). Likewise, initial formation of a strong emotional memory related to pain is naturally reinforced with continued exposure to the detrimental impact of chronic pain on mood, daily function, sexual relationships, and identity.

One of the most intriguing findings from the field of pain neuroimaging is that the degree of brain functional and structural reorganization can reflect clinically meaningful pain properties, such as subjective pain intensity, duration, and even emotional dimensions of pain. Whereas moment-to-moment changes in perception are reflected in brain functional properties, the longer-term consequences associated with chronic pain, such as symptom severity, correlate with neocortical gray matter (neuronal) density/volume and white matter (axonal) microstructure. This suggests that networks can manifest short- and long-term neuroplasticity by (a) adapting to brain state changes in order to optimize the representation of information, as well as (b) evolve over time based on reinforced functional connections, which may in turn promote structural changes (125).

A final comment on the physiological substrates of pain perception: despite the clinical reliance on numerical rating scales, pain perception does not operate on an absolute scale.

Pain is evaluated relative to the state that immediately preceded its onset and relative to predicted outcomes based on past experience (126). A critical principle revealed by investigations of neural encoding of nociceptive input is that the experience of pain begins with pain anticipation. The dynamic nature of pain perception—including peripheral and central sensitization—is adaptive because it facilitates the accurate prediction and detection of future threats. Like somatic pain, fear is tightly coupled with a distinct threat that has a discrete beginning and end. Like visceral pain, anxiety is diffusely focused, without an identifiable threat to defend against (or with all threats being equally salient) and persists long after a significant threat has passed. The difference is that anxiety further distorts sensory and affective dimensions of potential threats (degree of threat, salience, context cues, and avoidance).

NOVEL FUTURE DIRECTIONS

The temporal patterns of genito-pelvic pain may provide insight into the respective contributions of peripheral versus central nervous systems. Theoretically, more variability in pain perception—especially in response to environmental perturbation—may be indicative of a peripheral-dominant pain. In contrast, unprovoked pain with low variability is more consistent with centrally-mediated pain, potentially with intermittent peripheral nerve contributions. Importantly, genito-pelvic pain symptoms may reflect a combination of peripheral and central factors, thereby implying that concurrent treatment approaches targeting peripheral AND central abnormalities may yield the greatest gains. The hypothesis that early and chronic genito-pelvic are maintained by distinct factors suggest the existence of (at least) two subtypes: the subclinical/early onset phenotype and the chronic phenotype. To date, the majority of genito-pelvic pain research has been conducted on the chronic phenotype based on etiological assumptions that preferentially reflect the early phenotype.

Visceral pain deserves special consideration here because it is not purely sensory in nature: it reflects (a) the diffuse sensations by which visceral nociception is currently defined; (b) negative emotion; and (c) increased sympathetic nervous system arousal (53, 54). Targeting any combination of these dimensions can, in theory, diminish the subjective experience of visceral pain (Table 3). The co-occurrence of visceral discomfort with negative affect and sympathetic activation creates ideal physiological conditions for the consolidation and maintenance of robust emotional memories related to visceral pain (127-130).

SUMMARY

Genito-pelvic pain emerges from a series of dynamic interactions between molecular, cellular, systems, behavioral, and psychological factors. Nociceptive signals are functionally amplified by sensory afferent neurons that detect noxious stimuli, spatially generalized by spinal crosstalk, and temporally prolonged by spinal cord central sensitization. Understanding the rules by which these nerves function—and especially how these rules are violated in the chronic pain state—is key in uncovering the mechanisms driving persistent genito-pelvic pain. Therefore, distinct sensory abnormalities can point to unique alterations in peripheral, spinal, and/or brain physiology that bias sensory perception.

Pain pathophysiology—caused by injury, infection, hormonal deficiency, pelvic floor dysfunction, or other insults—reflects the body's adaptations to a threat, not the original threat itself. Etiological factors are distinct from the physiological alterations that eventually become part of the disease of chronic pain over years and decades. The noble goal of identifying and treating suspected etiology (i.e., the acute phenotype) may ultimately detract from opportunities to target mechanisms of the chronic phenotypes of genito-pelvic pain.

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Figure 1.

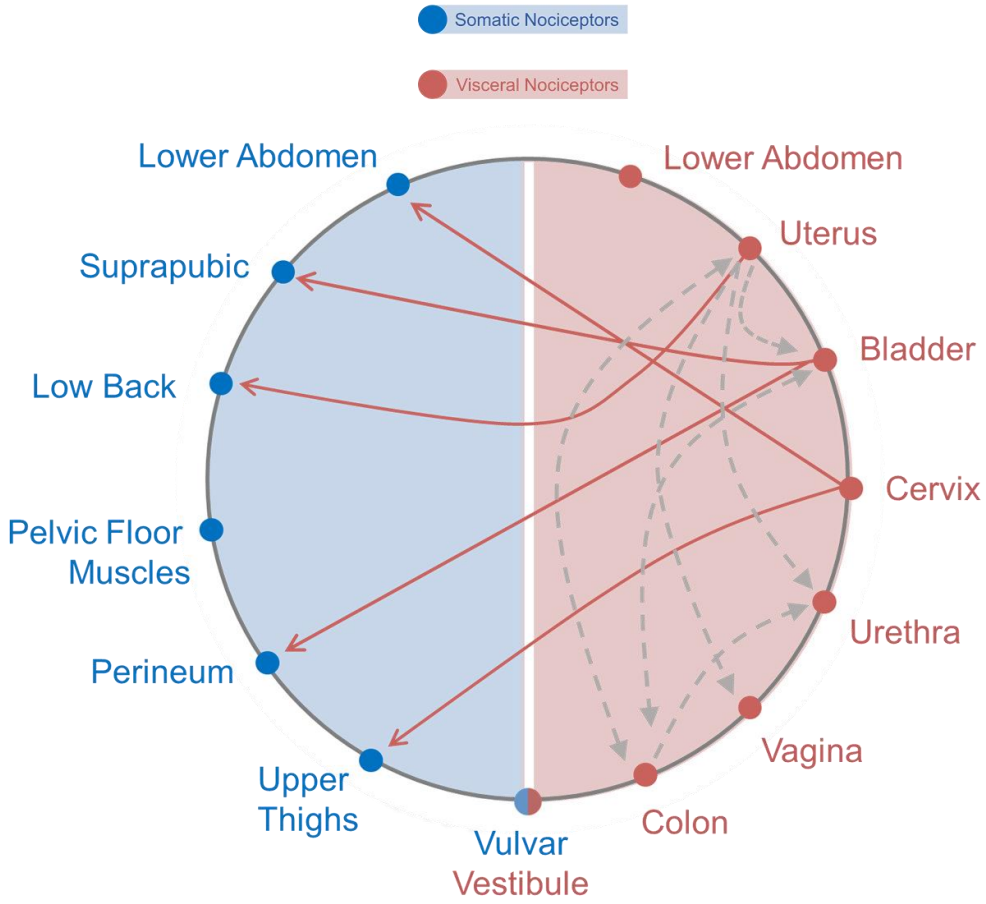
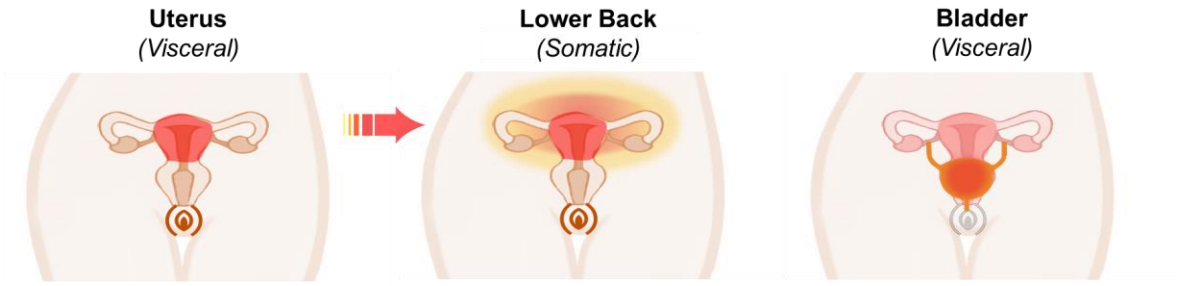

Somatic Nociceptors
Visceral Nociceptors
Lower Abdomen
Suprapubic
Low Back
Pelvic Floor Muscles
Perineum
Upper Thighs
Vulvar Vestibule
Lower Abdomen
Uterus
Bladder
Cervix
Urethra
Vagina
Colon

Figure 2.

A) Visceral Pain Referred to Somatic and Visceral Tissue



B) Somatic/Visceral Pain Referred to Visceral Tissue

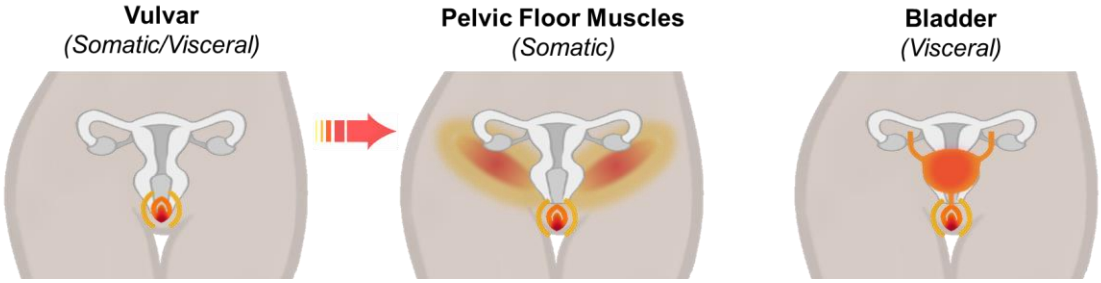
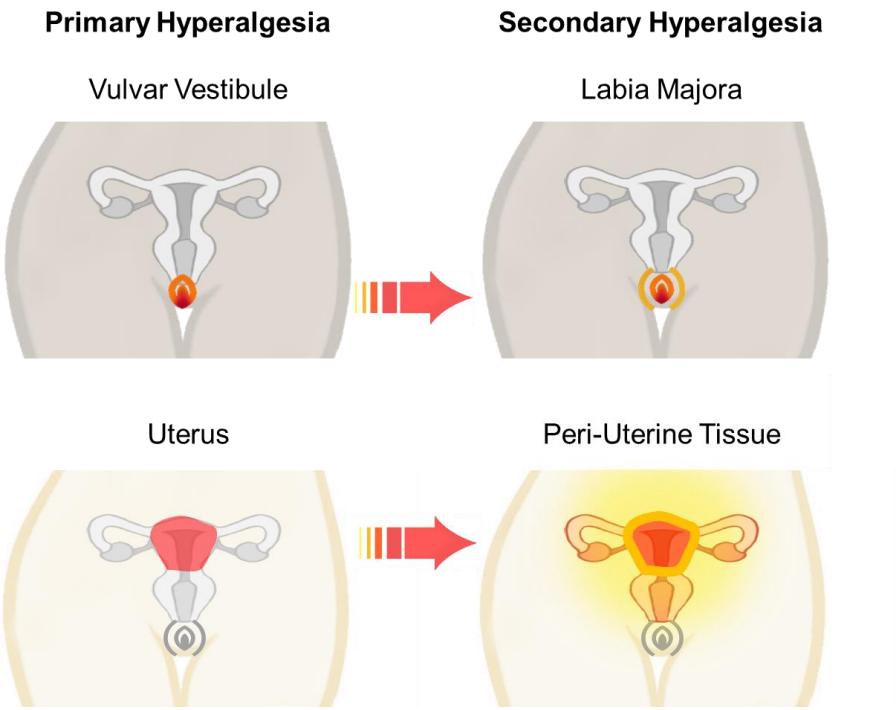


Figure 3.


Primary Hyperalgesia
Secondary Hyperalgesia
Vulvar Vestibule
Labia Majora
Uterus
Peri-Uterine Tissue