CHAPTER 28

In Search of Pelvic Pain

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The pelvis cradles the reproductive machinery necessary for our species to evolve. As such, pelvic pain represents a critical threat to the survival of the individual and future offspring. Acute pelvic pain signals the presence of bacterial, fungal, or viral infection, or frank tissue damage. Accordingly, traditional assessment and treatment of pelvic pain target the end organs as the primary source(s) of pathology. However, when pelvic pain outlasts the normal healing period, a patient's diagnosis will often depend on the treating physician rather than the unique configuration of symptoms. Gynaecologists investigate potential anatomical, hormonal, and pathophysiological causes; physical therapists assess the tension, controllability, and strength of pelvic floor muscles; urologists biopsy tissue and test the functional capacity of involved organs; neurologists explore potential nerve entrapment or injury; sex therapists focus on anxiety and distraction to enhance sexual function; and psychiatrists seek psychosomatic causes with limited consideration of physical pathology. Like the Indian parable of the blind men and the elephant, each type of clinician emphasizes a narrow aspect of chronic pelvic pain (CPP) to guide diagnosis.

This specialization approach has given rise to three clinical obstacles that influence our understanding of CPP: (a) etiological theories outside a clinician's specialty may not be considered; (b) clinicians rarely communicate across theoretical camps, leading CPP research to evolve as cross-disciplinary islands of unintegrated knowledge; and (c) such specialized approaches have seldom identified physical findings that explain the common symptom of pelvic pain. Indeed, CPP conditions are referred to as a family of clinical "wastebasket" diagnoses because, as diagnoses of exclusion, they are mutually defined by the lack of identifiable pathology. This atheoretical diagnostic approach fails to acknowledge the heterogeneity within each condition that likely points to multiple underlying pain subgroups.

In the context of the pain research field, this fragmented approach to studying pelvic pain is a symptom of long-standing ideological biases within the medical profession. An obsession with end-organ pain mechanisms restricts inquiry to local phenomena (i.e., pelvic pathology, local inflammation, pelvic floor muscles). Similarly, a poor understanding of spinally mediated referred pain and viscerovisceral hyperalgesia reinforces a focus on misleading clinical symptoms characteristic of visceral pain. The common missing element is supraspinal involvement in processing chronic nociceptive input. Perhaps the last place one seeks to find the pelvis is in the brain.

The traditional view of peripheral and central nervous system (CNS) pain mechanisms as independent contributors to CPP reflects an artificial distinction that, surprisingly, continues to fuel controversy within the field [28, 58]. Peripheral and central input may compete, certainly, yet it is more likely that the respective roles of peripheral and central processes shift with pain chronification as the organism adapts to a new baseline state of chronic pain [9, 27]. As a "sentient neural hub," the brain mediates pain perception by

iteratively integrating environmental, nociceptive, and psychological inputs [38]. These inputs culminate in an ongoing neural representation of pain that serves many purposes, including the recruitment of protective behavioural responses such as escape, avoidance, or guarding [14]. The brain is uniquely suited to facilitate these adaptations through experience-dependent neuroplasticity.

LEARNING TO LIVE WITH PELVIC PAIN

Chronic pain has recently been conceptualized as a learned state of suffering [6]. CPP can therefore be characterized as an experience-dependent learned association between pelvic pain perception and functional disability. Functional disability secondary to CPP may take many forms, including hypervigilance to bodily sensations (digestive, urological, and sexual function), restricted movement, limited social interaction, and disrupted sleep, as well as negative emotional states that may diminish motivation to seek reward. By facilitating modified behaviour and motivation, chronic pain essentially redefines how an organism interacts with the environment. The brain adapts to this changing environment through learning, which requires long-term potentiation (LTP), an activity- and postsynaptic NMDA-dependent enhancement of neural synchrony that underlies memory formation (i.e., *consolidation*) and memory revision (i.e., *reconsolidation*), which drives synaptic plasticity throughout the CNS [15], and potentially in the spinal cord [18]. Chronic pain must then be subject to the rules of memory formation and maintenance.

Arousal mechanisms inherent to pelvic pain ensure that a pain memory is strongly encoded from its inception. Pelvic visceral pain—or any visceral pain, for that matter—is inherently emotional because it is accompanied by increased autonomic arousal and strong negative emotional responses. McGaugh and others [35, 37] have hypothesized that memory consolidation relies on arousal mechanisms to modulate memory strength, such that memories encoded during stressful situations will be well remembered for future adaptive purposes. The basolateral amygdala plays a pivotal role in emotional (fear) memory formation because it is optimally responsive to norepinephrine produced during the stress response [39]. When paired with nociceptive input funnelled through the central nuclei of the amygdala, the negatively valenced sensory information can modulate (and amplify) pain behaviour. Conversely, the pharmacological inhibition of amygdala activity inhibits spinally mediated pain behaviour, suggesting that spinally mediated central sensitization may be dependent on supraspinal mechanisms [16, 42]. Furthermore, the reactivation of established emotional memory pathways with each subsequent episode of intense pain may facilitate reconsolidation (and further strengthening) of the salient pain memory [21] (but see [1]). CPP patients are then left with repetitive exposure to stress-enhanced pelvic pain.

Repeated emotional experiences with pelvic pain may alter the perception of other emotionally salient situations. Pelvic pain disrupts some of the most intrinsically rewarding physiological processes: sexual arousal, orgasm, urination, and defecation. The literature is rife with examples of how pelvic pain can frequently interfere with these rewarding processes. A subset of men with chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) experience excruciating pain with ejaculation during masturbation and/or intercourse, thereby dampening sexual motivation for future sexual encounters [5, 52]. Similarly, women with vulvodynia report exquisite pain with light vulvar touch, and also diminished sexual pleasure and sexual motivation [56]. The latter results are consistent with an animal model showing suppressed pacing mating behaviour—and therefore reduced sexual

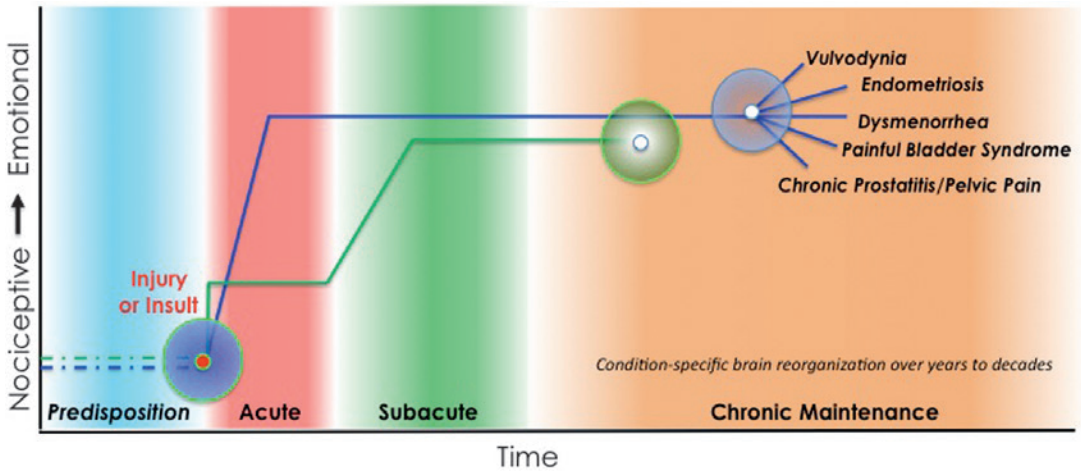

FIGURE 28-1 Hypothesized divergence of pain chronification for pelvic visceral versus somatic pain. Pain chronification is depicted across time (*x* axis) and by dominant cortical systems involved in pain processing (*y* axis), ranging from regions mediating nociceptive processing (including primary and secondary somatosensory cortices, insula, anterior cingulate cortex, prefrontal cortex, and thalamus) to regions mediating emotion processing (limbic and mesocortical regions). In addition to the impact of predisposing factors (*blue shading*) prior to injury onset, it is hypothesized that the type of pain properties can also determine the trajectory of pain chronification. Acute pelvic visceral pain (*red shading*), defined by strong negative emotion and autonomic arousal, creates optimal conditions for arousal-enhanced fear learning of pelvic pain. In contrast, existing evidence suggests that emotional learning during the subacute phase (*green shading*) drives chronification of chronic low back pain—a prevalent form of somatic pain. Further changes in brain function and structure that characterize unique pelvic pain diagnoses emerge during the chronic pain phase (*orange shading*), forging condition-specific trajectories.

encounters—in female mice with inflammatory genital pain [24]. In addition to sexual disturbances, previously rewarding processes such as urination and defecation are disrupted with pelvic pain. Individuals with interstitial cystitis may report ongoing or intermittent lack of relief or pain with urination, pain with bladder filling, and heightened urinary urgency that persists [55]. Similarly, some men with CPP report a "golf ball in the anus" sensation that worsens with defecation and may trigger additional pelvic pain. These clinical reports suggest that, when previously pleasurable events become painful, the emotional valence of reward may shift, as well. Such a phenomenon has been observed in chronic back pain patients who show abnormal nucleus accumbens activity associated with pain relief [11]. It is feasible that a maladaptive limbic circuit maintaining CPP may also influence processing of hedonic information.

Considering the emotionally salient origins of pelvic pain, it is reasonable to assume that factors driving the transition to CPP chronicity may differ from somatic pain conditions, for which pain is localized to the skin, muscles, and/or bone (Fig. 28-1). In the first longitudinal neuroimaging study examining brain changes that parallel the transition to a common somatic pain condition, chronic back pain, functional representation of pain shifted from sensory nociceptive brain regions to limbic regions as pain persisted [9, 27]. These observations support the hypothesis that back pain is increasingly processed through more emotion-related regions as it becomes chronic. In contrast, pelvic visceral pain begins with strong nociceptive and emotional involvement, suggesting that limbic circuitry would likely be recruited soon after pelvic pain onset. It has been established that a predisposition to emotional learning can manifest in altered features of brain function and structure [13]. One possibility is that larger volumes of subcortical regions prior to visceral pain onset may

uniquely facilitate the transition to chronic visceral pain. This hypothesis is supported by single reports of increased hypothalamic, anterior cingulate, orbitofrontal cortex, dorsolateral prefrontal cortex volume in irritable bowel syndrome (IBS) [17, 48], as well as increased grey matter density limited to bilateral hippocampus, lenticular nuclei, and substantia nigra in a sample of young women with vulvodynia [46]. The extent of emotional involvement in pelvic pain onset may be a decisive factor mediating this transition and can be influenced by genetic vulnerabilities, early life experiences, chronic stress, pain frequency, and/or intensity of pain. Future longitudinal research is needed to determine whether visceral and somatic pain conditions share similar trajectories as they become chronic.

WHAT THE CHRONIC PHENOTYPE CAN AND CANNOT TELL US

The neuroimaging of pelvic pain is a young field. Unfortunately, the field has inherited ideological biases that will continue to limit the advancement of pain neuroimaging if left unchallenged. For instance, it is commonly assumed in pain neuroimaging that the chronic brain phenotype can reflect the etiological mechanisms that initiated the pain. This assumption has evolved across many clinical and scientific environments that were limited by many unknowns: (a) the inciting factors triggering pelvic pain are frequently unknown; (b) the extent of peripheral injury rarely correlates with the features of chronic pain; (c) the few clinically relevant animal models of pelvic pain have yet to experimentally validate popular etiological theories (with the exception of [23]); and (d) a general disinterest in supraspinal mechanisms of pain chronification has focused inquiry to primary afferents and their spinal terminations. It is therefore critical to recognize that distinct mechanisms underlie the initiation and maintenance of chronic pain. This distinction has clear significance for assessment and treatment approaches for CPP, as clinicians often obsess about how the pain began rather than how the body has adapted to maintain persistent pelvic pain.

Most pain neuroimaging literature is based on the chronic phenotype. Unique configurations of grey matter changes distinguish between chronic pain diagnoses, including chronic IBS, CP/CPPS, vulvodynia, interstitial cystitis/painful bladder syndrome, low back pain, osteoarthritis, phantom limb, chronic regional pain syndrome, temporomandibular pain, and others [4, 19, 29]. These robust differences across pain populations suggest that neuronal changes driving unique patterns of grey matter reorganization are condition-specific. However, the lack of consistent grey matter changes between—and sometimes within—conditions has frustrated efforts to delineate the meaning of these structural changes. Unreplicated studies of women with chronic vulvar pain [46], interstitial cystitis/painful bladder syndrome [29], and dysmenorrhea [59, 60] have noted regional increases in subcortical grey matter, yet the finding of increased GM is far less common in other pelvic pain neuroimaging studies in men and women [8, 23, 40]. In men with CPP, Farmer and colleagues [23] found that anterior insula activity and grey matter density were associated with the magnitude of pelvic pain. In a separate male CPP cohort, significant reductions in anterior cingulate cortex volume also correlated with pelvic pain severity.

We know that it takes time to translate brain activity, which fuels the synaptic strengthening of pain memory traces, into anatomical changes that can sustain these memories. The formation of lasting memories requires late-phase LTP in the hippocampus to induce the protein synthesis necessary to initiate lasting structural changes (i.e., of terminal boutons,

dendrite morphology, etc.). The rate of hippocampal protein synthesis regulates the time course of these early anatomical changes, and the hippocampus requires approximately 2 weeks to establish long-term cortical networks needed to encode and sustain a pain memory trace. During the early stages of pain chronification, the hippocampus remains continuously engaged via upregulated hippocampal–medial prefrontal connectivity that directly covaries with pain intensity [41], and this ongoing activity may account for incremental voxel-wise changes in neocortical grey matter observed in chronic pain patients over the course of weeks, months, and years [9, 12]. The time frame of this latter process, which is consistent with the timescale of systems memory consolidation [22, 53], strongly suggests that observed alterations in regional grey matter reflect mechanisms underlying the chronic maintenance of pain memories, rather than the inciting processes that initially triggered LTP.

Interestingly, the hippocampus may play a prolonged role in the development of chronic pain. Under normal circumstances, a memory shifts from a hippocampus-dependent to -independent state in which the memory becomes a striatum-maintained habit modulated by the amygdala, which provides an emotional volume control for the memory [3, 30, 36, 50, 57]. Only when novel or high-arousal experiences are paired with a consolidated memory does the hippocampus competitively re-engage the memory [34]. Hypothetically, ongoing hippocampal involvement implies that the pain memory trace is continually reactivated and thus rendered vulnerable to change. Recent longitudinal data support this hypothesis and suggest that ongoing, severe pain is a sufficiently novel stimulus to maintain hippocampal involvement [41], and by extension, the amygdala–striatal modulatory loop that competes with the hippocampus for information [34]. Importantly, reactivated pain memories are susceptible to synaptic strengthening as well as the disruption of the memory trace through the process of memory reconsolidation. Compounds that mediate context-specific memory disruption and/or pain-specific emotional dampening may be promising therapies for central modulation of pelvic pain.

Consistent with evidence that regional grey matter changes in pain patients take months to years to develop, the extent of grey matter changes consistently correlates with the duration of pain. Pain duration correlates with grey matter density of the anterior insula in men with CPP [23], and similar findings have been found in other chronic pain populations [10, 17, 45, 48]. Global grey matter reorganization may continue to shift across the course of years, suggesting that the magnitude of structural changes will evolve as pain persists [12]. Conversely, the reversal of pain-related alterations in grey matter is observed with successful treatment, such that the reduction of clinical pain is accompanied by the restoration of regional grey matter [44, 49]. For these reasons, grey matter properties may best be viewed as indicators of ongoing clinical severity related to pain maintenance. As such, they may be used as indicators of progressing chronification, as well as successful treatment.

The close temporal relationship between pain maintenance and neocortical grey matter properties suggests that these structural changes reflect ongoing neuroplastic processes as pain ebbs and flows. This pattern has been observed across numerous chronic pain conditions [7, 12, 33, 51]. Even rapid fluctuations in grey matter properties closely correlate with symptom severity in women with cyclic menstrual pain [60]. Neural correlates of short-term pain fluctuations in CPP are of special clinical interest, given our poor understanding of pain "flares," a term used to describe exacerbations of pain that may last minutes, days, or weeks [54, 55]. Rapid brain structural changes over the timescale of weeks are suggestive of greater cortical reorganization with increased pain frequency and severity.

TRANSLATING THEORY INTO DATA

The pelvic pain field, as a specialty that frequently deals with diagnoses of exclusion, lacks a strong theoretical framework for assessment, diagnosis, and treatment. By conceptualizing CPP as a collection of heterogeneous chronic disease states rooted in emotional learning, unanswered questions about pelvic pain etiology and disease maintenance become accessible and testable. Furthermore, multimodal neuroimaging can be combined to identify the mechanistic interactions between brain function and structure in CPP.

Functional scanning of CPP has yet to be tailored to the stage of chronicity. Given the hypothesis that emotional learning plays a prominent role in the initiation and maintenance of CPP, it follows that brain functional representations of pelvic pain should preferentially reflect limbic involvement. However, emotional involvement may be more pronounced during the initial transition phase to CPP as novel pain information is consolidated and new memories are strengthened. In contrast, most CPP fMRI studies—as well as in the pain field in general—evaluate the chronic phenotype and may not capture the "critical window" of the greatest limbic involvement. To date, functional imaging of CPP has typically yielded nociceptive activity maps consistent with acute pain. For example, painful heat applied to the lower abdomen and arm evokes similar activation patterns in women with and without dysmenorrhea, including the secondary somatosensory cortex, premotor cortex, insula, anterior cingulate cortex, posterior cingulate cortex, orbitofrontal cortex, and subcortical regions (e.g., putamen, thalamus, caudate, and brainstem) [61]. Such approaches have drawn criticism because they have not captured brain activity related to the clinical experience of spontaneous visceral pelvic pain. Even studies that manage to evoke clinically relevant pain, such as provoked vulvar pain in women with vulvodynia, have yielded equivalent activity maps in vulvodynia and pain-free groups (unpublished data) [26, 43]. One strategy AQ1 hypothesized to better capture CPP-related brain activity is to have patients continuously report spontaneous pelvic pain intensity throughout a scan. Continuous ratings of pelvic pain intensity in men with CPP somewhat departed from the standard nociceptive signature, with activity localized to the insula, dorsolateral prefrontal cortex, posterior parietal cortex, primary somatosensory cortex, primary motor cortex, and precuneus regions [23].

Collectively, these findings strongly suggest that functional imaging in CPP populations has yet to produce new information about pelvic pain, with the exception of legitimizing pelvic pain as an objectively measurable clinical state. Methodological and/or analytic limitations can certainly account for a lack of CPP-specific functional activations, whereas other explanations should be considered in future research. (a) A greater magnitude of functional resources recruited for acute pain processing, which is essentially a task-related activity, may overpower our ability to detect lesser underlying CPP-related activity. (b) Pain perception may occur at a network rather than a brain regional level, therefore requiring an analysis of task and task-free (resting-state) activity to identify CPP-specific network dynamics (as seen in [31]). Network connectivity is critical in differentiating transient states of mind, including intrinsic and task-related states [25], as well as developmental processes and the presence of chronic disease [2, 47]. (c) Finally, abnormal brain activity may be more prominent during the initial transition from acute to chronic CPP, as suggested by early changes in nucleus accumbens and prefrontal cortical functional connectivity in predicting pain chronicity in subacute back pain patients [9]. In the latter case, functional imaging of the chronic phenotype may simply be insufficient to detect the critical brain activity underlying CPP. Future work that samples CPP groups at different stages of chronicity, as well as longitudinal neuroimaging studies, are required to detect the "critical window" when CPP-specific brain activity is a dominant feature.

The impact of prior brain activity can be estimated, albeit indirectly, by examining abnormalities in neuronal and axonal structure in the chronic CPP phenotype. The Hebbian axiom "Neurons that fire together wire together" reminds us that observable changes in brain structure result from novel communication patterns that are forged over time. Therefore, voxel-wise grey matter changes, which take weeks to months to develop, likely reflect long-term patterns of activity that have maintained the chronic phenotype of CPP. Perhaps the greatest danger in moving forward is to underestimate the heterogeneity in CPP populations, as this oversight would enhance noise in data and make it more difficult to detect real structural changes that result from specific disease processes leading to CPP.

Moving forward, the priority for pelvic pain neuroimaging is a thorough assessment of brain functional and structural abnormalities that differentiate CPP diagnoses, as well as subtypes within each diagnosis. A longitudinal characterization of brain structure is required to dissociate mechanisms underlying chronic pain initiation versus maintenance, with care taken to avoid extrapolating findings from the chronic phenotype of CPP. These priorities are cornerstones of the first multicentre longitudinal neuroimaging study of CPP populations, the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, conceived by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with collaborations between Northwestern University, University of California at Los Angeles, Stanford University, University of Michigan, University of Alabama, and University of Washington [20, 32]. Pairing detailed MAPP epidemiological data with multimodal neuroimaging data, including resting-state functional, T1-weighted anatomical, and diffusion tensor imaging scans, will drive the identification of behavioural proxies that can be rapidly assessed by clinicians who treat CPP. Such proxies are critical to guiding early interventions in those who are vulnerable to developing CPP, as well as guiding therapeutic use of centrally acting agents and/or psychotherapy in patients who are most likely to respond to these treatment modalities.

ACKNOWLEDGEMENT

This work was supported by the National Vulvodynia Association and the National Institutes of Health (NIH) National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) U01 DK082342, in collaboration with the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network.

AQ2

CONFLICT OF INTEREST

The author has no conflicts of interest.

REFERENCES

1. Akirav I, Maroun M. Stress modulation of reconsolidation. Psychopharmacology 2013;226(4):747–61.
2. Alexander-Bloch A, Raznahan A, Bullmore E, Giedd J. The convergence of maturational change and structural covariance in human cortical networks. J Neurosci 2013;33(7):2889–99.
3. Alvarez P, Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. Proc Natl Acad Sci USA 1994;91(15):7041–5.
4. Alzahrani K, Gandhi R, Debeer J, Petruccelli D, Mahomed NN. Prevalence of clinically significant improvement following total knee replacement. J Rheumatol 2011;38(4):753–9.

5. Anderson RU, Wise D, Sawyer T, Chan CA. Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training. J Urol 2006; 176(4 Pt 1):1534–8; discussion 1538–9.
6. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol 2009;87(2):81–97.
7. Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 2011;152(3):s49–64.
8. As-Sanie S, Harris RE, Napadow V, Kim J, Neshewat G, Kairys A, Williams D, Clauw DJ, Schmidt-Wilcke T. Changes in regional gray matter volume in women with chronic pelvic pain: a voxel-based morphometry study. Pain 2012;153(5):1006–14.
9. Baliki M, Petre B, Torbey S, Herrmann KM, Huang LS, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15(8):1117–9.
10. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006;26(47):12165–73.
11. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 2010;66(1):149–60.
12. Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. PloS One 2011;6(10):e26010.
13. Baria AT, Baliki MN, Parrish T, Apkarian AV. Anatomical and functional assemblies of brain BOLD oscillations. J Neurosci 2011;31(21):7910–19.
14. Baumgartner U, Iannetti GD, Zambreanu L, Stoeter P, Treede RD, Tracey I. Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: a high-resolution fMRI study. J Neurophysiol 2010;104(5):2863–72.
15. Besnard A, Caboche J, Laroche S. Reconsolidation of memory: a decade of debate. Prog Neurobiol 2012;99(1):61–80.
16. Bird GC, Lash LL, Han JS, Zou X, Willis WD, Neugebauer V. Protein kinase A-dependent enhanced NMDA receptor function in pain-related synaptic plasticity in rat amygdala neurones. J Physiol 2005;564(Pt 3):907–21.
17. Blankstein U, Chen J, Diamant NE, Davis KD. Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. Gastroenterology 2010;138(5):1783–9.
18. Bonin RP, De Koninck Y. A spinal analog of memory reconsolidation enables reversal of hyperalgesia. Nat Neurosci 2014;17(8):1043–5.
19. Chappell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, Brown JP. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2010;11(1):33–41.
20. Clemens JQ, Mullins C, Kusek JW, Kirkali Z, Mayer EA, Rodriguez LV, Klumpp DJ, Schaeffer AJ, Kreder KJ, Buchwald D, et al. The MAPP research network: a novel study of urologic chronic pelvic pain syndromes. BMC Urol 2014;14:57.
21. Diamond DM, Campbell AM, Park CR, Halonen J, Zoladz PR. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. Neural Plast 2007;2007:60803.
22. Dudai Y. The neurobiology of consolidations, or, how stable is the engram? Ann rev Psychol 2004;55:51–86.
23. Farmer MA, Chanda ML, Parks EL, Baliki MN, Apkarian AV, Schaeffer AJ. Brain functional and anatomical changes in chronic prostatitis/chronic pelvic pain syndrome. J Urol 2011;186(1):117–24.
24. Farmer MA, Leja A, Foxen-Craft E, Chan L, MacIntyre LC, Niaki T, Chen M, Mapplebeck JC, Tabry V, Topham L, et al. Pain reduces sexual motivation in female but not male mice. J Neurosci 2014;34(17):5747–53.
25. Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2001;2(10):685–94.
26. Hampson JP, Reed BD, Clauw DJ, Bhavsar R, Gracely RH, Haefner HK, Harris RE. Augmented central pain processing in vulvodynia. J Pain 2013;14(6):579–89.
27. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 2013;136(Pt 9):2751–68.
28. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature 2001;413(6852):203–10.
29. Kairys AE, Schmidt-Wilcke T, Puiu T, Ichesco E, Labus JS, Martucci K, Farmer MA, Ness TJ, Deutsch G, Mayer EA, et al. Increased brain gray matter in the primary somatosensory cortex is associated with increased pain and mood disturbance in interstitial cystitis/painful bladder syndrome patients. J Urol 2015;193(1):131–7.

AQ3

30. Kensinger EA, Corkin S. Two routes to emotional memory: distinct neural processes for valence and arousal. Proc Natl Acad Sci USA 2004;101(9):3310–15.
31. Kilpatrick LA, Kutch JJ, Tillisch K, Naliboff BD, Labus JS, Jiang Z, Farmer MA, Apkarian AV, Mackey S, Martucci KT, et al. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. J Urol 2014;192(3):947–55.
32. Landis JR, Williams DA, Lucia MS, Clauw DJ, Naliboff BD, Robinson NA, van Bokhoven A, Sutcliffe S, Schaeffer AJ, Rodriguez LV, et al. The MAPP research network: design, patient characterization and operations. BMC Urol 2014;14:58.
33. May A. Chronic pain may change the structure of the brain. Pain 2008;137(1):7–15.
34. McDonald RJ, White NM. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav Neurosci 1993;107(1):3–22.
35. McGaugh JL. Memory—a century of consolidation. Science 2000;287(5451):248–51.
36. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 2004;27:1–28.
37. McIntyre CK, McGaugh JL, Williams CL. Interacting brain systems modulate memory consolidation. Neurosci Biobehav Rev 2012;36(7):1750–62.
38. Melzack R, Wall PD. Textbook of pain. London, UK: Churchill Livingstone; 1999.
39. Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL. Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proc Natl Acad Sci USA 2005;102(30):10706–11.
40. Mordasini L, Weisstanner C, Rummel C, Thalmann GN, Verma RK, Wiest R, Kessler TM. Chronic pelvic pain syndrome in men is associated with reduction of relative gray matter volume in the anterior cingulate cortex compared to healthy controls. J Urol 2012;188(6):2233–7.
41. Mutso AA, Petre B, Huang L, Baliki MN, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV. Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol 2014;111(5):1065–76.
42. Palazzo E, Fu Y, Ji G, Maione S, Neugebauer V. Group III mGluR7 and mGluR8 in the amygdala differentially modulate nocifensive and affective pain behaviors. Neuropharmacology 2008;55(4):537–45.
43. Pukall CF, Strigo IA, Binik YM, Amsel R, Khalife S, Bushnell MC. Neural correlates of painful genital touch in women with vulvar vestibulitis syndrome. Pain 2005;115(1–2):118–27.
44. Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. J Neurosci 2009;29(44):13746–50.
45. Schmidt-Wilcke T, Leinisch E, Straube A, Kampfe N, Draganski B, Diener HC, Bogdahn U, May A. Gray matter decrease in patients with chronic tension type headache. Neurology 2005;65(9):1483–6.
46. Schweinhardt P, Kuchinad A, Pukall CF, Bushnell MC. Increased gray matter density in young women with chronic vulvar pain. Pain 2008;140(3):411–9.
47. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009;62(1):42–52.
48. Seminowicz DA, Labus JS, Bueller JA, Tillisch K, Naliboff BD, Bushnell MC, Mayer EA. Regional gray matter density changes in brains of patients with irritable bowel syndrome. Gastroenterology 2010;139(1):48–57.e42.
49. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011;31(20):7540–50.
50. Sherry DF, Schacter DL. The evolution of multiple memory systems. Psychol Rev 1987;94(4):439–54.
51. Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, et al. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J Pain 2013;14(7):663–75.
52. Smith KB, Pukall CF, Tripp DA, Nickel JC. Sexual and relationship functioning in men with chronic prostatitis/chronic pelvic pain syndrome and their partners. Arch Sex Behav 2007;36(2):301–11.
53. Squire LR, Alvarez P. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 1995;5(2):169–77.
54. Sutcliffe S, Colditz GA, Goodman MS, Pakpahan R, Vetter J, Ness TJ, Andriole GL, Lai HH. Urological chronic pelvic pain syndrome symptom flares: characterisation of the full range of flares at two sites in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. BJU Int 2014;114(6):916–25.
AQ4 55. Sutcliffe S, Colditz GA, Pakpahan R, Bradley CS, Goodman MS, Andriole GL, Lai HH. Changes in symptoms during urologic chronic pelvic pain syndrome symptom flares: findings from one site of the MAPP Research Network. Neurourol Urodyn 2015;34(2):188–95.

56. Sutton KS, Pukall CF, Chamberlain S. Pain, psychosocial, sexual, and psychophysical characteristics of women with primary vs. secondary provoked vestibulodynia. J Sex Med 2009;6(1):205–14.
57. Takashima A, Nieuwenhuis IL, Jensen O, Talamini LM, Rijpkema M, Fernandez G. Shift from hippocampal to neocortical centered retrieval network with consolidation. J Neurosci 2009;29(32):10087–93.
58. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55(3):377–91.
59. Tu CH, Niddam DM, Chao HT, Chen LF, Chen YS, Wu YT, Yeh TC, Lirng JF, Hsieh JC. Brain Morphological changes associated with cyclic menstrual pain. Pain 2010;150(3):462–8.
60. Tu CH, Niddam DM, Yeh TC, Lirng JF, Cheng CM, Chou CC, Chao HT, Hsieh JC. Menstrual pain is associated with rapid structural alterations in the brain. Pain 2013;154(9):1718–24.
61. Vincent K, Warnaby C, Stagg CJ, Moore J, Kennedy S, Tracey I. Dysmenorrhoea is associated with central changes in otherwise healthy women. Pain 2011;152(9):1966–75.

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Chapter: 28

Query Nos.	Query	Remarks
AQ1	Please update the reference cited as unpublished data in the sentence "Even studies that manage to ..." and provide its complete details in the list.	
AQ2	Please confirm whether the heading "Conflict of Interest" introduced here is fine.	
AQ3	Please check whether the edits made to reference [29] are correct.	
AQ4	Please check whether the edits made to reference [55] are correct.	