Neuromodulation of Abdominal and Pelvic Pain

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INTRODUCTION

Over the last 50 years of pain research, we have been obsessed with peripheral nervous system mechanisms of nociception. From the chemical mediators that stimulate afferent nerve endings, to the glycinergic control of central sensitization in the spinal dorsal horn, our view of nociception has largely ignored the role of supraspinal processing. This preoccupation is surprising, given that the field has matured with Melzack and Wall's revolutionary idea that pain perception requires cortical processing [31]. We have, in essence, decapitated pain.

Chronic abdominal and pelvic pain consists of a family of visceral pain conditions initiated by organ pathology and chronically maintained by aberrant peripheral and central processes. The characteristics that define visceral pain emphasize the role of the brain in nociceptive processing. Visceral pain consists of diffusely localized pain that is inherently linked with negative emotion and autonomic reactivity. The implications of this coexistence are that the nociceptive processes underlying the chronification of visceral pain must be accompanied by sustained negative emotion, such as anxiety and/or depression, as well as ongoing autonomic arousal, which may parallel the elevated arousal that characterizes chronic stress, both of which recruit extensive cortical processing [37]. Furthermore, the co-occurrence of visceral pain and negative emotion may enhance the formation of pain-related memories. It has been hypothesized that memory formation relies on arousal mechanisms to modulate memory strength [10] [30] such that memories encoded during emotion-laden situations will be well remembered for future adaptive purposes. In turn, abdominal and pelvic pain may further dysregulate emotional circuitry, as it disrupts some of the most inherently rewarding physiological processes, including eating, sex, urination, and defecation, which are required for the survival of the organism.

This chapter explores how the brain shapes the modulation of abdominal and pelvic pain across different time scales, through changes in brain function and structure. It is argued that limbic, rather than classic nociceptive circuitry is the primary site of central reorganization in visceral pain.

BASIC ASPECTS

Chronic visceral pain, like any learned experience, is subject to the rules of memory formation and maintenance. As a result, the impact of visceral pain is etched into the synaptic patterns that have relayed nociceptive and emotional information with the repeated exposure to painful visceral stimuli. The activity of these individual synapses is not accessible via neuroimaging due to poor spatial resolution, given that a single voxel represents roughly 100,000 neurons [28]. However, in understanding the rules by which these neurons function and interact, we can extrapolate these principles to large populations of neurons that are accessible via imaging.

The Hebbian axiom, "Neurons that fire together wire together," is useful in understanding how brain function relates to anatomy. The relay of neural information is physically

constrained by the properties of individual neurons (such as variations in axonal and dendritic morphology), their interactions with resident glia, the number of synaptic connections they make with neighboring neurons, and their connections with distant neuronal populations. These anatomical constraints are not fixed; rather, these properties can dynamically adapt to reflect new learning, rendering brain function and anatomy interdependent.

Brain function and structure convey a rich amount of information about the progression from acute to chronic pain. A range of imaging modalities can address unique and complementary clinical questions as to how the brain adapts to pain in the short- and long-term. Short-term changes are reflected in brain functional properties, whereas longer-term changes (as well as predispositions) associated with chronic pain are evident in gray and white matter properties, as well as through cross-sectional and longitudinal assessments of brain function related to clinical pain.

Functional activity associated with acute and chronic pain is measured using functional magnetic resonance imaging (fMRI), which infers neural activation from local variations in oxygenated blood flow [27]. Regional changes in the blood oxygen level dependent (BOLD) signal that correlate with painful stimulation or its perception have yielded consistent patterns of activity in the anterior cingulate cortex (ACC), somatosensory cortices (S1 and S2), insula (INS), thalamus (Th), and prefrontal cortex (PFC), which are collectively referred to as the acute pain “matrix” [46]. Functional activation of these regions has repeatedly correlated with clinically important aspects of pain perception (e.g., pain intensity, unpleasantness, duration, etc), potentially providing an “objective” measure of pain [49]. However, critics have questioned the sensitivity and specificity of this acute pain signature because it is also elicited by nonpainful stimulation, as well as by other sensory modalities [21]. Growing evidence also suggests that the neural representation of chronic pain deviates from this acute pain matrix in condition-specific patterns [2]. The literature remains divided as to how abnormal cortical processing of nociceptive information may manifest in the chronic pain state.

A complementary view of brain functional activity is to view the brain as a conglomerate of efficiently communicating neural networks. When activity in two or more network elements (e.g., voxels, regions) consistently correlate across time they are said to be functionally connected. Network connectivity appears to reflect transient states of mind, including intrinsic and task-related states [19], as well as developmental processes and the presence of chronic disease [1] [39]. 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 [17]. As a result, the rich information conferred by neural networks captures activity and communication patterns that are inaccessible via traditional general linear modeling analysis of fMRI data.

Neuroimaging can differentiate broad anatomical features of the brain, such as gray (neuronal) matter and white (axonal) matter properties. Gray matter is visualized with T1-weighted anatomical images, which differentiate types of brain tissue based on their magnetic properties. Although gray matter density is often assumed to reflect regional concentrations of neurons, it may also reflect changes in vasculature, non-neuronal (glial) growth, neuron morphology (e.g., dendritic arborization and spine growth), neurodegeneration, and less often neurogenesis. The regional distribution of gray matter can capture anatomical changes that take weeks to months to occur. Regional changes

in gray matter are associated with the central processes that underlie the maintenance and remission of chronic pain [4] [41]. Indeed, brain morphology continues to adapt to the presence of chronic pain over the course of years [5].

White matter microstructure is deduced using diffusion tensor imaging (DTI), which measures directional water flow within the brain. Whereas the water flow within the physical confines of a neuron is uniform in all directions, the water flow along the length of myelinated axons is directionally dependent, or anisotropic. Chronic pain is typically accompanied by subtle changes in white matter integrity, and these axonal properties may change over the course of days to weeks, indicating that it is a longer-term index of brain reorganization. Alternatively, certain white matter properties may also reflect a predisposition for chronic pain development, as suggested by the first longitudinal neuroimaging study of the transition to chronic back pain [29].

DESCRIBING THE SUBJECT

Genital Pain Vulvar pain syndrome/Vulvodynia, is the most common type of female genital pain, affecting approximately 8% of premenopausal women [36]. In healthy women, vulvar touch and pain perception evoke equivalent patterns of brain activity that are classically observed with acute pain [16]. Similarly, women with provoked vulvodynia exhibit a similar pattern of activity during experimentally-induced vulvar mechanical stimulation. Higher levels of INS and PFC activation were cited as evidence of elevated pain processing in patients, yet equivalent levels of subjective pain in healthy women were not assessed, nor was an innocuous vulvar stimulation control included in the design [35]. This activation pattern was confirmed in a recent study, however, women presenting with different subtypes of vulvodynia did not show elevated regional activity when compared to clinical (fibromyalgia) and healthy controls [20]. Despite this equivocal evidence of altered central nociceptive processing, women with provoked vulvodynia exhibit increased subcortical gray matter density in the basal ganglia and parahippocampal gyrus/hippocampus [38]. These structural changes may reflect longer-term shifts in information processing related to chronic vulvar pain. Indeed, these gray matter properties correlated with multiple clinical indices of vulvar hypersensitivity, as well as with self-reports of pain catastrophizing.

These studies indicate that provoked vulvar pain in women with vulvar pain/vulvodynia recruits the same pattern of nociceptive processing observed during acute pain perception in healthy individuals. On first glance, this finding challenges the hypothesis that abnormal vulvar pain processing plays a role in vulvar pain/vulvodynia. However, multiple methodological and sample biases, noted above, may confound these results. It is also possible that these studies may have failed to elicit clinically-relevant vulvar pain (due to vaginal penetration, for instance) and therefore have limited relevance to the actual mechanisms underlying the condition. The presence of subcortical anatomical abnormalities that correlate with clinical pain parameters, in particular, suggests the presence of either preexisting vulnerabilities that make these women more likely to develop vulvar pain/vulvodynia, or they are indicative of subcortical reorganization related to the maintenance of chronic vulvar pain.

Menstrual Pain

One of the most common forms of female pelvic pain is menstrual pain, or dysmenorrhea, which causes severe pain in 2-29% of premenopausal women [23] [48]. During menstruation, pain-related brain activity does not differ between women with and without

dysmenorrhea. Specifically, painful thermal lower abdominal and arm stimulation evoked similar activation patterns in the secondary somatosensory cortex (SII), premotor cortex (PMC), INS, ACC, posterior cingulate cortex (PCC), orbitofrontal cortex (OFC), and subcortical regions (e.g., putamen, thalamus [Th], caudate, and brainstem [48].

Women with dysmenorrhea exhibit a range of cortical and subcortical anatomical changes that correlate with clinical parameters. A well-designed study of this population discovered nuanced gray matter changes during menstrual and peri-ovulatory phases [47]. Compared to menstrual phase-matched controls, women with dysmenorrhea exhibited increased gray matter in the left medial OFC, left PMC, right postcentral gyrus within S1, right precuneus (PC), and right hypothalamus, as well as decreased gray matter in S2, ACC, and dorsal PCC. Menstrual pain intensity positively correlated with increased right caudate nucleus and hypothalamus gray matter and negatively correlated with left Th gray matter density [47]. Furthermore, during menstruation, women with pain had increased gray matter density in the left orbital gyrus, left precentral gyrus within the PMC, left inferior temporal gyrus, right hypothalamus, as well as decreased gray matter in left S2 and left anterior/dorsal PCC. These findings may not generalize to other types of female pelvic pain, however, given that women with endometriosis-related pain exhibit reduced gray matter restricted to the left Th, left cingulate gyrus, right putamen, and right INS, compared to controls [3].

The Tu study [47] is significant in the visceral pain imaging field, as it demonstrates the impact of chronic, intermittent visceral pain on the brain. Specifically, rapid fluctuations in gray matter properties closely correlate with variations in clinical pain severity. These data suggest that visceral pain conditions that are characterized by cyclic exacerbations of pain may show greater cortical reorganization with increased pain frequency and severity. These short-term pain fluctuations are of particular clinical interest given our poor understanding of pain “flares,” a term used to describe exacerbations of pain that may last minutes, days, or weeks [45]. Importantly, a subset of the observed anatomical changes may reflect the ongoing central maintenance of visceral pain, whereas other morphological features may signify the short-term structural changes resulting from repeated peripheral insults related to menstruation. These findings stand in stark contrast to data from musculoskeletal pain populations, who show sustained reductions in regional gray matter density across the course of months [4].

Urological Pelvic Pain Prostate pain syndrome/chronic pelvic pain syndrome (PPS/CPPS) occurs in 5-8% of men [12]. PPS/CPPS is characterized by a combination of spontaneous or provoked pelvic or genital pain, as well as pain with ejaculation in approximately a third of the clinical population [14]. Symptoms may be accompanied by bladder dysfunction similar to that observed in bladder pain syndrome/interstitial cystitis (BPS/IC), including pain with urination, as well as urinary urgency and frequency. No imaging studies have evaluated neural correlates of experimental or naturalistic pain in men or women with BPS/IC, yet imaging work has begun to explore neural correlates of PPS/CPPS. In an early study, men with PPS/CPPS continuously rated the intensity of their spontaneous pain during a 10 minute scan, and this activity was contrasted with activity from a sensorimotor and cognitive-evaluative control task [18]. The contrast yielded a unique map of pelvic pain-related brain activity, including the INS, dorsolateral PFC, PPC, SI, primary motor cortex (M1), and precuneus regions. Anterior INS activity and gray matter density were associated with the magnitude of pelvic pain, whereas anterior ACC gray matter density increased with longer pain duration. In addition to regional alterations, the relationship between whole-brain gray and white matter was

disrupted, which is suggestive of large-scale cortical reorganization [18]. In a separate PPS/CPPS cohort, significant reductions in anterior ACC volume, which correlated with pain severity, were identified [33]. However, these findings are difficult to interpret given that the presence of distinct PPS/CPPS subtypes within these samples may increase sample variability and reduce statistical power. Despite the preliminary nature of these findings, these studies provide intriguing initial evidence of local and global brain changes in PPS/CPPS that reflect the severity and duration of pelvic pain.

The use of spontaneous pain ratings to extract pain-relevant brain activity in men with pelvic pain highlights the methodological and clinical biases that are characteristic of the pain imaging field. First, these findings confirm that ongoing, naturalistic pelvic pain shows limited functional overlap with acute pain-related activity, and this conclusion would not have been reached with the experimental pain induction tasks used elsewhere in the literature. Rather, chronic pelvic pain recruits a unique pattern of brain activity that likely reflects neural mechanisms specific to the condition. Second, this study emphasizes the intrinsic temporal variability of the pelvic pain experience. This variability is not adequately captured with a single visual analog scale number, which is widely used by clinicians.

Abdominal Pain

The most common functional gastrointestinal disorder is irritable bowel syndrome (IBS), which may be characterized by a combination of abdominal pain, cramping, bloating, constipation and diarrhea. The majority of IBS pain imaging studies, have evaluated brain activity during acute visceral pain induction using experimentally-induced rectal distension, which admittedly has limited relevance to the clinical state. These studies have yielded mixed support for the hypothesis that chronic abdominal pain is propagated by abnormal nociceptive and descending inhibitory processes. On one hand, nonpainful and painful rectal distension activates a common set of brain regions in IBS and healthy populations, including the ACC, INS, PFC, Th and brainstem [6] [7] [15] [26] [32] [34] [44] [50]. Despite the claims that greater activations in these regions are evidence of abnormal nociceptive processing in IBS, a meta-analysis of 16 studies with comparable methodology concluded that only anterior INS (antINS) activity and its connectivity with other key regions (e.g. posterior INS, Th, PCC, ACC, PFC) is consistently greater in IBS [42]. Given that the antINS regulates interoception (including emotional awareness, based on its rich connectivity to limbic regions) as well as visceral and autonomic responses, these functions may be critically disrupted in IBS.

Specific regions are implicated in the top-down modulation of IBS pain. One study found that greater IBS related functional activity in the ACC and PFC was no longer statistically significant when anxiety and depression were controlled for and these regions may therefore preferentially mediate the affective responses to IBS pain [15]. Reduced activation of the PFC, in particular, is associated with heightened negative emotion [8], potentially suggesting an impaired capacity for top-down control of pain perception. Sex differences in distension-related brain activity, driven by emotion circuitry, appear to mediate this dissociation between sensory and affective aspects of chronic abdominal pain [24] [25].

Structural changes related to IBS remain controversial. Cortical thinning of gray matter in the midcingulate cortex, ACC, and INS has been replicated across multiple laboratories [9] [13] [22] [25]. The INS structural abnormalities are corroborated by a report of increased white matter integrity adjacent to the postINS and antINS, which correlated with pain severity, unpleasantness, and duration [11]. Reports of regional changes in gray matter

volume have been less consistent and have included evidence of increased hypothalamic volume and reduced anterior/medial Th volume [9] [13]. In contrast, the largest IBS study conducted to date determined that, after controlling for anxiety and depression, only increased gray matter in the PFC and PPC remained statistically significant [40], again highlighting the importance of segregating sensory and affect related structural abnormalities.

PRACTICAL IMPLICATIONS

One of the most intriguing findings from visceral pain neuroimaging is that the extent of brain functional and structural reorganization can reflect clinically meaningful pain properties, such as subjective pain intensity, duration, and even emotional dimensions of pain. After years of living with pain, these neural adaptations have far-reaching influences on how an individual perceives herself and her world. The sufferer has learned that certain activities such as, sex, eating, and excretion, will reliably elicit visceral pain. She has learned to avoid behaviors that exacerbate this pain, so perhaps she no longer dines in public for fear of abdominal discomfort and its consequences. Perhaps she no longer desires sexual contact or seeks physical closeness with her partner because it will inevitably lead to painful intercourse. She has also learned to carefully adopt physical postures that minimize discomfort, leading to restricted movement and heightened pelvic floor muscle tension. Our traditional focus on end-organ pathology is woefully inadequate to explain these physiological, behavioral, and psychological consequences of chronic visceral pain.

The field has evolved with the assumption that suspected etiology, based on an initial identifiable peripheral injury, should play a primary role in phenotyping and treatment efforts. This fallacy is conceptually and practically counterproductive because it ignores the role of ongoing peripheral and central interactions that determine how the body adapts to the persistence of pain, that is, it neglects critical aspects of the disease process. Central mechanisms of pain maintenance are necessarily part of this process.

Clinicians and researchers are acutely aware of the need for a paradigm shift in how abdominal and pelvic pain is assessed, diagnosed, and treated. A prominent conceptual issue that must be resolved is the problem of accurate clinical phenotyping. Because many of these idiopathic pain conditions are defined by a collection of symptoms rather than clearly defined disease processes, the current diagnostic classifications are based on heterogeneous patient samples that may include a variety of mechanistically-distinct subtypes. Accumulating clinical and basic science research confirms that these subtypes will vary in the respective roles of peripheral and central processes in both the initiation and maintenance of chronic visceral pain. Therefore, the identification of brain functional and anatomical biomarkers that covary with clinically relevant symptoms should be a priority for these classification efforts.

For instance, even the increasingly popular UPOINT classification system for pelvic pain (*U*rinary symptoms, *P*sychosocial dysfunction, *O*rgan-specific findings, *I*nfection, *N*eurologic/systemic, *T*enderness of skeletal muscles) does not currently acknowledge the contribution of brain reorganization in chronic pelvic pain [43]. The UPOINT psychosocial domain, which is restricted to cognitive-emotional responses that can be dissociated from chronic pain, does not reference the cortical processing of nociceptive information. The neurologic/systemic domain refers to pelvic versus extra-pelvic pain, with the implication that extra-pelvic pain may reflect central sensitization, a spinal phenomenon. Inclusion of

brain functional and structural abnormalities within the neurologic/systemic domain would be an appropriate amendment to these criteria.

LOOKING AT THE FUTURE

The priority for visceral pain neuroimaging is the thorough assessment of brain functional and structural abnormalities, or biomarkers, that characterize the natural course of pain development and maintenance. Although visceral pain conditions may share similar patterns of brain reorganization, such as large-scale shifts in subcortical function and structure, the identification of the neural biomarkers that distinguish these diagnoses is necessary. As demonstrated with cyclic menstrual pain, a longitudinal characterization of brain structure is required to dissociate mechanisms underlying chronic pain initiation versus maintenance. The key in translating these findings to the clinic is to identify behavioral proxies of these biomarkers that can be rapidly and accurately assessed by clinicians. Ideally, such proxies can guide early interventions in those who are vulnerable to develop persistent pain and can direct the therapeutic use of centrally acting agents and/or psychotherapy in patients who are most likely to respond.

TAKE HOME MESSAGES

- Central mechanisms underlying abdominal and pelvic pain are accessible via brain imaging techniques.
- Brain functional and structural reorganization reflects pain-related neuroplasticity.
- The chronification of abdominal and pelvic pain is characterized by central nociceptive and emotional abnormalities.
- Condition-specific brain reorganization takes place at the regional and global levels.

Further reading

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