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Mind–body interactions in pain: the neurophysiology of anxious and catastrophic pain-related thoughts

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Abstract

The well-accepted biopsychosocial model proposes that the experience of pain and responses to it result from a complex interaction of biological, psychological, and social factors. However, the separation of these constructs is substantially artificial, and we presume that psychological processes have biological effects, that biological processes affect an individual's psychosocial environment, and so on. Considerable research has demonstrated that pain-coping strategies influence perceived pain intensity and physical functioning, and individual differences in styles of pain coping even shape the persistence of long-term pain complaints in some populations. A good deal of this coping research has focused on catastrophizing, which is a generally maladaptive cognitive and emotional mental set that involves feelings of helplessness when in pain, rumination about pain symptoms, and magnification of pain-related complaints. Collectively, catastrophizing has been consistently associated with heightened experiences of pain across a variety of samples. Although catastrophic thinking regarding pain-related symptoms is often classified under the "psychologic" category within the broader biopsychosocial model, we propose that catastrophizing exerts biologic effects that may account for some of its negative consequences. In general, the cognitive and affective processes captured within the construct of catastrophizing may exert effects on the neuromuscular, cardiovascular, immune, and neuroendocrine systems, and on the activity in the pain neuromatrix within the brain. The interface between pain-related neurobiology and processes such as pain-related catastrophizing represents an important avenue for future pain research.

The pace of chronic pain research seems to have quickened over the last several decades, which includes the present "Decade of Pain Control and Research," perhaps as a consequence of increasing awareness regarding the enormous public health costs and challenges associated with chronic pain conditions. As numerous reviews have noted, the symptom of pain accounts for over 80% of all physician visits; chronic pain affects over 50 million Americans annually, and the annual costs of chronic pain likely exceed \$100 billion in health care expenses and lost productivity.¹ The biopsychosocial model of pain has now almost universally replaced the traditional biomedical characterizations of pain that focused on disease- and injury-related activation of specific receptors in the peripheral nervous system that directly transmitted pain-related information to the brain. These "disease models" of the pain experience assumed a tight correspondence between pain and pathology; this concept has been over-turned by a great deal of research on chronic pain syndromes such as fibromyalgia, lower back pain, and

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osteoarthritis. In the context of these conditions and others, it is now widely accepted that only a modest relationship exists between identifiable physical pathology and a patient's report of pain symptoms. Current biopsychosocial approaches to understanding the experience of pain view it as a dynamic and complex interaction of biological, psychological, and social forces.¹

In particular, we have been interested in studying the biopsychosocial antecedents and consequences of individuals' engagement in various cognitive, affective, and behavioral "coping strategies" to modulate their experience of pain. To date, overwhelming evidence identifies catastrophizing, which is a set of negative emotional/cognitive processes that involve rumination and pessimism, perceptions of helplessness, and magnification of pain-related symptoms as a critically important risk factor for adverse pain-related outcomes.² Considerable research on catastrophizing demonstrates its strong cross-sectional and prospective relationships with pain, physical functioning, psychologic functioning,³ and even health care use.⁴ Although relatively few researchers have investigated the putative neurobiologic underpinnings of catastrophizing directly, recent work strongly suggests that catastrophizing-related cognitions have effects on the central nervous system. Collectively, this review highlights several potentially important neurophysiologic mechanisms by which catastrophizing may shape the experience of pain.

FUNCTIONAL NEUROIMAGING STUDIES: CATASTROPHIZING IN THE BRAIN

The advent of noninvasive functional neuroimaging methods that can be used to evaluate brain responses to noxious stimulation has to some degree revolutionized the field of pain research.⁵⁻⁷ Not surprisingly, such methods have been instrumental in demonstrating the "effects" of various psychologic processes (eg, attention or mood) on pain processing in the central nervous system. To date, 2 functional magnetic resonance imaging (fMRI) studies have shown, using application of standardized noxious stimuli, that (1) higher levels of catastrophizing in pain patients were associated with enhanced pain-related hemodynamic responses in areas such as dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, and medial frontal cortex,⁸ and (2) healthy subjects exposed to mildly painful electrical stimulation also showed a significant positive relationship between pain catastrophizing scores and pain-related brain responses in the dorsolateral prefrontal cortex, insula, and anterior cingulate cortex,⁹ which are brain regions associated with the mediation of emotional and motivational responses to the experience of pain. Additionally, in a follow-up to a previous study on the attentional modulation of pain, Salomons et al¹⁰ found that participants who perceived uncontrollable noxious stimuli as more painful than identical controllable noxious stimuli had greater activation in perigenual anterior cingulate cortex and insular cortex, which suggests that these areas may be associated with loss of control (eg, helplessness, which is a component of catastrophizing). In a still more recent fMRI study in patients with spinal pain, Lloyd et al¹¹ applied nonpainful tactile stimulation to a painful body region and reported that higher levels of catastrophizing were associated with reduced activation in normal sensory processing channels in brain regions such as the posterior cingulate cortex and the parietal cortices. In another very recent fMRI study, Strigo et al¹² found that in subjects with major depression, helplessness and rumination were associated with greater activity in the amygdala during the anticipation and experience of pain. Finally, our group was recently involved in conducting an fMRI study to examine *in vivo* catastrophizing cognitions during the experience of pain. Participants were scanned while receiving moderately painful electrical stimulation under various conditions, with perceptions of helplessness and threat measured after each stimulus. Individual differences in helplessness- and threat-related cognitions were coded in a network of regions that involved the dorsal anterior cingulate cortex, anterior insula, and prefrontal cortex (Edwards et al, unpublished data). Collectively, these fMRI studies strongly suggest that catastrophizing cognitions are associated with amplification

of cortical activation in the context of pain, as well as potentially maladaptive responses to even nonpainful somatosensory input.

CATASTROPHIZING AND OPIOID ANALGESIC SYSTEMS

Some developing evidence also suggests that high levels of catastrophizing may produce dysregulation or dysfunction in endogenous opioid pain-control systems. Endogenous opioids are central neurochemical players in multiple pain-inhibitory systems, and opioids such as beta-endorphins act both in the periphery and in the central nervous system to modulate incoming information related to noxious stimulation. In several studies, elevated catastrophizing has been associated with a greater need for postoperative opioid analgesics to control post-surgical pain,¹³ which suggests that the opioids produced, on a per-unit basis, less analgesic benefits in individuals who reported higher levels of catastrophizing. In addition, several reports of individual differences in analgesic responses to opioids with kappa agonist activity have appeared in the literature. In the first report, butorphanol was shown to be ineffective in managing cardiac pain, unless catastrophizing was taken into account.¹⁴ That is, the effects of catastrophizing on reported chest pain symptoms “overshadowed” the analgesic effects of opioids, which potentially suggests (although formal moderational analyses were not performed) that only a subgroup of patients (eg, those low in catastrophizing) may have demonstrated butorphanol-related reductions in pain. Similarly, a study of intravenous pentazocine in healthy adults revealed that increased indices of catastrophizing were associated with less subsequent analgesic benefit of pentazocine, especially among men.¹⁵ Finally, indirect evidence that supports the hypothesis that catastrophizing interferes with effective functioning of the endogenous opioid system can be derived from a psychophysical study in which high-catastrophizing healthy participants demonstrated less effective functioning of endogenous pain-inhibitory systems, which was measured using a counterirritation paradigm.¹⁶ Such counterirritation analgesic effects had been shown to be opioid mediated in prior studies that used competitive antagonists, such as naloxone.¹⁷ Finally, our laboratory has recently examined the effects of distraction, which is a potent behavioral analgesic technique possibly mediated by endogenous opioids, on experimentally induced pain. Interestingly, distraction produced analgesia for low catastrophizers more quickly than for high catastrophizers, which potentially suggests that high catastrophizers are less equipped to mobilize opioid-dependent pain inhibitory processes. Collectively, although these studies are generally cross-sectional in nature and provide only indirect evidence, they offer an intriguing hint that catastrophizing may interfere with the optimal functioning of endogenous opioid analgesic systems. However, whether such effects might be mediated by changes in opioid receptors, opioid receptor binding, the generation of postsynaptic potentials, or in the activation of cortical pain-modulatory networks is not clear currently. Longitudinal studies that use other assessment methods will be necessary to identify the molecular mechanisms involved in catastrophizing’s putative interference with opioid-mediated analgesic processes.

CATASTROPHIZING AND INFLAMMATION

We recently reviewed the literature on catastrophizing’s influence on pain in the context of rheumatic diseases,² and we suggested that catastrophizing might be associated with activation of systemic inflammatory processes. For example, studies in patients with rheumatoid arthritis have reported positive associations between helplessness (a key component of catastrophizing) and elevated indices of inflammatory disease activity.^{18–22} Several of these investigations are longitudinal and suggest that high levels of catastrophizing at a given “base-line” time point prospectively predicted worsening erythrocyte sedimentation rates.^{23,24} Moreover, the putative proinflammatory effects of catastrophizing may be relatively specific; a recent study in rheumatoid arthritis patients suggested that helplessness was strongly positively associated

with elevated C-reactive protein levels, whereas anxiety and depression were largely unrelated.²⁵

Similarly, our laboratory has recently assessed the association between catastrophizing and the proinflammatory cytokine interleukin-6 (IL-6). In this study, 42 healthy adults underwent a series of standardized pain testing procedures that involved the administration of noxious pressure, heat, and cold.²⁶ Catastrophizing cognitions were measured immediately after the pain induction procedures, and blood samples were taken at baseline and then at several time points from the end of the procedures to 1 h after testing. Samples were assayed for serum levels of IL-6, which increased during the posttesting period. Individual differences in catastrophizing were strongly related to individual differences in IL-6 reactivity to pain, with higher levels of catastrophizing predicting elevated IL-6 levels for at least 1 h after the experience of acute pain.²⁶

OTHER PHYSIOLOGIC PARAMETERS

Some other studies have provided evidence that catastrophizing may exert a broad influence on physiologic responses to pain, and that its influence may extend across multiple systems. For example, in several studies of healthy young adults, catastrophizing predicted increased systolic blood pressure reactivity to pain²⁷ and enhanced myocardial contractility for a prolonged period of time following a cold pressor task.²⁸ Relatedly, catastrophizing seems to influence the relationship among muscle tension, cardiovascular stress, and pain response;²⁹ electromyography suggests that under specific conditions, catastrophizing is positively related to indices of lumbar paraspinal muscle responses.²⁷ Temporal summation of pain (ie, the increase of perceived pain intensity when repetitive noxious stimuli are delivered), which a frequently studied index of central pain facilitation, is also influenced by catastrophizing.^{30, 31} However, catastrophizing does not seem to affect the nociceptive flexion reflex (NFR), a spinally mediated withdrawal reflex,^{32,33} which suggests that catastrophizing does not engage certain spinal pain-modulatory systems. As reviewed by Edwards et al,³⁰ the neurochemical processes that produce temporal summation of pain are at least somewhat distinct from those mediating the NFR. For example, N-methyl-D-aspartic acid antagonists reduce temporal summation pain, but they do not affect NFR thresholds.³⁰

Several studies have also sought to evaluate the influence of catastrophizing on neuroendocrine responses to pain, and although we previously reported no such relationships among healthy adults,²⁶ clinical samples have yielded more promising observations. In a sample of patients with back pain, higher catastrophizing was associated with a blunted diurnal cortisol rhythm,³⁴ a maladaptive neuroendocrine profile that may indicate a poor pain-related prognosis.^{35,36} Interestingly, catastrophizing has also been associated with a relative enhancement of cortisol response to acute pain among patients with temporomandibular joint disorder who underwent a variety of experimental pain stimuli (Quartana et al, unpublished data). Thus, the neuroendocrine “signature” of catastrophizing may be complex, and dependent on factors such as circadian rhythms.

CATASTROPHIZING AND PAIN GENETICS

Examining the genetic contribution to disease states has become increasingly popular, and pain is no exception.³⁷ To date, a handful of genetic polymorphisms has been linked with risk for chronic pain or with sensitivity to pain, as assessed in the laboratory.³⁷ Although no published studies have yet described a genetic profile associated with catastrophizing, one recent report high-lighted an intriguing interaction between catastrophizing and variability in the catechol-O-methyltransferase (COMT) gene. COMT is an enzyme that influences catecholamine and endogenous opioid systems, and genetic variability in COMT function is associated with individual differences in pain sensitivity. In this study,³⁸ catastrophizing and COMT genotype

together predicted long-term pain complaints, with individuals who had both a high-catastrophizing and a high-pain-sensitive COMT profile experiencing the worst long-term outcomes. These exciting findings suggest either that catastrophizing may modulate the impact of genotype on pain outcomes or that genetic factors may shape the influence of catastrophizing on pain (or both); this area of research represents a fertile avenue for additional research.

CONCLUSIONS

Taken together, this literature provides demonstrative evidence for complex neuroendocrine, neuroimmune, psychophysiological, and functional neuroanatomic “effects” of catastrophizing on the pain experience. Research that examines both physiological and psychosocial factors and how they shape long-term pain outcomes is an exciting area for future study and highlights the truly biopsychosocial nature of the pain experience. Future studies may wish to examine: (1) some potential molecular bases for the identified neurophysiologic underpinnings of catastrophizing, (2) whether reorganization of integrated physiological systems³⁹ takes place following prolonged catastrophic thinking, (3) whether catastrophizing-reducing interventions alter pain-related neurophysiology, and (4) how factors such as individual differences in genotype or in central nervous system pain processing might moderate the effects of catastrophizing on long-term pain outcomes. Such studies will help to establish the neurophysiologic implications of catastrophizing in a more causal fashion. In the future, catastrophizing may well be assessed routinely as part of a “pain phenotype” that has implications for understanding individual differences for pain processing in the central nervous system, as well as for guiding the choice of pain treatments. We already have evidence, for example, that reductions in catastrophizing are responsible for at least some of the apparent analgesic benefit of a variety of treatments, which include “physical” treatments such as exercise.^{40,41} We anticipate that the interdisciplinary field of biobehavioral pain research will be an exciting area in which to work, as researchers with diverse back-grounds attempt to further a common distal goal of refining and developing treatments to improve the quality of life of individuals in pain.

Abbreviations

COMT, catechol-O-methyltransferase; fMRI, functional magnetic resonance imaging; IL-6, interleukin-6; NFR, nociceptive flexion reflex.

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