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Chronic Headaches and the Neurobiology of Somatization

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Abstract Pain sensitivity is an adaptive process affected by expectation, mood, coping, operant conditioning, and the preconscious allocation of attention. Underlying mechanisms may include encoding of similar experiences (eg, depression, loss, pain-distress) in overlapping patterns of activation, failure of common regulatory mechanisms, direct top-down activation of the pain matrix, and changes in descending pain facilitatory and inhibitory tone. In theory, the combination of glial cell activation from psychological stress and neural firing from nociceptive input may be particularly likely to lead to pain sensitization and long-term structural changes in pain processing regions of the brain. In these ways, headaches in which chronicity, diffuseness, and distress seem better accounted for by psychological than by medical variables can be understood in neurobiological terms. This can allow psychological treatment of physical distress to be objective, nonthreatening, and relatively precise.

Keywords Somatization disorder · Conversion disorder · Pain disorder · Catastrophizing · Depression · Glia

Introduction

That psychological factors can influence the nature of physical symptoms or even cause them de novo traces at least to Paracelsus in the 16th century AD. It may even trace to Plato in the 4th century BC, for whom the Greeks' belief that hysterical symptoms were caused by a "wandering womb" was perhaps not meant literally, but as a metaphor for the frustrated desires of childlessness [1]. In somatization, physical symptoms seem better explained by psychological factors than by any medical diagnosis. Anxious preoccupation with the body, idiopathic pain syndromes, and the amplifying effects of depression, anxiety, and stress are prototypical subtypes [2].

Nowhere do psychological factors seem more evident than in primary headaches, for which the exacerbating effects of stress are often a commonplace to sufferer and clinician alike. In this review, however, we will eschew the well-trodden paths of headache psychophysiology. We will leave aside the possible subtle perturbations in cerebral blood supply from stress-related platelet activation or vasoconstriction, the increased cognitive demands from over-recruitment of attention, and the priming of mast cells (all of potential relevance to migraines). We will also leave aside any effects of stress on muscle tension or trigger point activity in tension-type headaches.

Rather, our focus here will be on people whose headaches do not conform to one of the standard episodic types, but whose pain has become chronic, or seems disproportional, or for whom headache is but one component of a more global presentation of poorly defined illness. For them, we must understand those psychological processes that act deep in the brain and spinal cord to determine pain sensitivity. Thus, we will examine the ways in which cognitive, emotional, and behavioral factors can influence the perception of pain, seeking out wherever possible the underlying neural mechanisms.

Attention

Focusing on a nociceptive stimulus increases the intensity and unpleasantness of the resulting pain, whereas distrac-

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tion reduces these quantities, the somatosensory evoked potential, and the activation of such pain-relevant cerebral structures as midcingulate cortex [3, 4].

The literature is divided about whether mere information processing demands are sufficient to reduce pain, or whether the distraction must also include an "appetitive motivational state," in which the competing activity is absorbing, enjoyable, and actively sought after.

Implicit in this controversy is the fact that attention includes both an effortful focusing and the automatic access to consciousness afforded to stimuli relevant to a goal [3]. The former, effortful aspect of attention seems to correlate with activation in the dorsolateral prefrontal cortex and is of limited capacity and easily fatigued. The latter, automatic aspect involves priming or preactivation of stimuli that are part of a cognitive set. (Thus, depressing or angry thoughts about the pain, in which the pain is relevant by virtue of being embedding in a cognitive schema—a network of associations—generate more pain-distress than nonspecific negative mood [5].) The maintenance of a cognitive set seems to correlate with activation in the intraparietal sulcus [3]. It appears that both regions can have facilitatory and inhibitory effects on the pain matrix.

Pain coping strategies can most likely engage these two aspects of attention in opposite ways. For example, deliberately suppressing pain, which is an intuitive but counterproductive strategy, draws on effortful focusing but at the cost of making pain a relevant stimulus. In contrast, accepting pain so that emotional energy can be reinvested into more meaningful projects, a strategy formalized in Acceptance and Commitment Therapy [6], is likely effective by changing the cognitive set.

Expectation

In the laboratory, the anticipation of pain seems to exert a direct priming effect: The subjective intensity of a pain stimulus is an additive function of expectation and actual stimulus intensity [7]. In neuroimaging studies, correlates of this effect have been found in regions encoding the subjective intensity of pain (anterior insular cortex), pain-unpleasantness (dorsal anterior cingulate cortex), and the pain's sensory qualities (posterior insula, thalamus, and secondary somatosensory cortex [7]).

In particular, the anterior insula appears to encode the subjective experience of pain, more so than the objective intensity of the pain stimulus [8••]. However, when there is a strong expectation of pain, anterior insular cortex is activated in proportion to this expectation. This preactivation, in turn, predicts the subjective intensity of a subsequent pain stimulus [9]. The priming, at least in part, seems to reflect an overlap in time, between top-down activation generated by a thought and bottom-up activation driven by the nociceptive input.

Moreover, the expectation of pain seems to have subjective and neurobiological effects that are the opposite of a placebo. These effects may involve a descending pain facilitatory pathway that parallels the endorphin system and uses cholecystokinin as a neurotransmitter [7]. The consequences of this descending system can be measured with the nociceptive flexion reflex—the automatic withdrawal (eg, of the lower leg) from an electric shock. The portion of this withdrawal taking place between 85 and 120 ms, too slow to be startle and too fast for the round trip to the brain, is a spinal reflex, thought to reflect the sensitization of nociceptive neurons in the dorsal horn. Not surprisingly, the expectation of pain facilitates the magnitude of this reflex, suggesting that expectation has effects at the spinal level [10•].

The key role of expectation in chronic headaches is suggested by the mediation of psychological, and some pharmacological, treatment effects by increase in self-efficacy—confidence in one's capacity to prevent or ameliorate the pain [11].

Catastrophizing

Originally proposed by Albert Ellis, catastrophizing includes feeling helpless and overwhelmed by the pain, ruminating on it, and markedly overestimating its likely negative consequences [12]. It is usually (but does not have to be) treated as a trait-like quality that affects the processing of all pain, and is assessed psychometrically using either the Pain Catastrophizing Scale or the Coping Strategies Questionnaire. As a cognitive response to pain, it likely encompasses attention, appraisal, and coping [12]. All three aspects may participate in its influence on the intensity and course of pain.

Thus, in acute pain in the laboratory, catastrophizing likely functions in part to increase attention to pain [13], presumably by inducing a cognitive set in which the pain is relevant to current goals. Moreover, catastrophizing implies both an expectation of pain and a strong conviction in that expectation. But the effects of catastrophizing differ from expectation in at least one key way: whereas expectation has a clear pronociceptive priming effect at the spinal level, as measured by the nociceptive flexion reflex, catastrophizing does not [14••, 15].

For catastrophizing, however, the issue is not of an extra increment of intensity added to the pain experience. From its earliest days of study, catastrophization has been found in longitudinal studies to predict a deteriorating course of pain, depression, and disability [16]. In a population-based study, catastrophizing predicted pain that was intense,

chronic, and disabling at 6 months in people who were pain-free at baseline [17]. Although such studies cannot prove causality, they fit with laboratory evidence that catastrophizing increases windup—the short-term buildup of pain sensitization. That is, any spinal effects of catastrophizing seem to emerge only with repeated or sustained stimulation, over seconds to minutes, in increased temporal summation of pain [18] and decreased endorphinergic dampening [19].

Within the brain, the effects of catastrophizing depend on stimulus intensity. When the stimulus is calibrated to be mildly painful, catastrophizing is associated with increased activation in regions associated with the sensory (posterior insula) and emotional (anterior insula) aspects of pain, as well as those involved in pain modulation (rostral anterior cingulate, dorsolateral prefrontal cortex). However, when the stimulus is of stronger, moderate intensity, catastrophizing seems to involve a failure of pain inhibition by dorsolateral prefrontal cortex [20].

Presumably, then, the combined activation from catastrophizing and the pain stimulus facilitates synaptic strengthening along pain pathways. In theory, of course, this could simply reflect the total intensity of activation from summing top-down and bottom-up sources of input. However, on theoretical grounds, the fact that these are two different types of input, one emotional, one sensory, may play a crucial role.

Recall that in the central nervous system, neurons, and the synaptic cleft between them, are surrounded by glial cells: astrocytes and microglia. The glia, in addition to conducting oxygen and nutrients to the neurons, function analogously to white blood cells. Indeed, in embryo, the microglia *are* blood cells that take up residence within the central nervous system [21••].

Not surprisingly, the glia are able to secrete proinflammatory cytokines, such as interleukin-1β, tumor necrosis factor-α, and interleukin-6, when stimulated by such triggers as bacterial cell walls or the liberated contents (eg, heat shock proteins, adenosine triphosphate) of stressed, deceased neurons. In turn, these cytokines stimulate nearby neurons to release more neurotransmitters. Further, when glia are shifted to a proinflammatory state, their reuptake of glutamate from the synaptic cleft is slowed, further prolonging the neural signaling [21••].

It is not only the signs of physical stress such as bacterial cell walls that stimulate glia, but also glucocorticoids, stress hormones, in the bloodstream. That is, although glucocorticoids are, at least in the short-term, anti-inflammatory in the periphery, they appear to be proinflammatory in the brain and spinal cord [22•]. Experiencing pain in catastrophic terms may thus combine the emotional stress (glial activation) and sensory stimulation (afferent drive) that would lead to high rates of neural firing. Presumably, this provides the condition for synaptic strengthening as the basis of central sensitization.

An increase in gray matter density in the basal ganglia has been found in several studies of chronic pain. Its relevance is suggested by its correlation with laboratory pain sensitivity and clinical pain level [23•]. Of note, this increase also appears to be correlated with pain catastrophizing, at least in vulvar pain (the only pain for which the question has been studied) [23•]. A causal role has not been proven, but the circumstantial evidence seems to lean toward catastrophizing as a factor in remodeling of pain pathways on both the synaptic and the macroscopic levels.

Moreover, the high rates of firing may do more than simply strengthen synapses. High rates of excitatory signaling can cause the apoptosis of the receiving neuron via glutamate toxicity. In studies of long-term pain, including migraine and tension-type headache, there appears to be progressive loss of gray matter density in brain structures involved in registering (eg, somatosensory cortex, anterior cingulate cortex, insula) and inhibiting (dorsolateral and medial orbital prefrontal cortex, periaqueductal gray region of the brainstem) the pain signal [23•, 24]. The anatomical changes underlying this loss (eg, tissue shrinkage vs neurodegeneration) are not known, nor are its consequences, if any, in terms of pain processing (eg, introducing a deafferentative component or disrupting endorphinergic tone).

Nonetheless, at least in chronic back pain, the loss of gray matter density appears to correlate specifically with the unpleasantness of the pain [24]. Analogously, a loss of gray matter density in the hippocampus is characteristic of posttraumatic stress disorder, as is a loss in prefrontal cortex in depression. Still, a causal role for pain-distress has not been proven. If distress is causal, we do not yet know if it requires prior glial cell activation by, say, a head injury.

Fear of Pain

Fear of pain shows only modest correlations with catastrophizing, and the two constructs differ in their psychophysical and biological correlates. That fear of pain would have a priming effect, increasing the subjective intensity of a subsequent noxious stimulus [25], is perhaps no surprise, for implied by such fear is an expectation—a conviction—of intensity, at least along the pain's affective dimension. It is unclear whether fear also contributes to temporal summation [25].

In the brain, fear of pain adds to the activation of dorsal anterior cingulate cortex (associated with the affective aspects of pain), posterior cingulate cortex (which may be involved in the evaluation of threat), and orbitofrontal cortex (which is involved in self-regulation; its activation

may have been an attempt by subjects to self-manage the fear) [26]. The exact connection between the psychophysical and neuroimaging results is uncertain, but descending pain facilitatory pathways seem to have their starting point in anterior cingulate cortex.

Depression

In clinical studies, major depressive disorder is frequently accompanied by fatigue, a generalized sense of malaise or ill health, and headache of at least moderate intensity [27]. In longitudinal studies, depression increases the risk of new-onset pain [28] and its persistence after an injury [29]. In the laboratory, people who are depressed have lower thresholds and tolerances for ischemic and inflammatory pain (pain that arises from within the body), although a higher threshold for electric shock applied to the skin surface [30]. In this biasing of perception toward internal sensations, depression resembles physical illness.

Depression and the distressing aspects of pain appear to involve activity in overlapping neural structures: the dorsal anterior cingulate cortex, anterior insula, and amygdala [8••, 31]. The implications remain to be worked out, as it is not clear whether the activation corresponds to the experience itself or to an attempt to compensate for, adapt to, or overcome the experience [31]. However, individuals with major depressive disorder show increased activation of these same brain regions when anticipating a painful stimulus, along with lowered pain thresholds and increased pain unpleasantness [32].

Moreover, in clinical writings, depression has long been thought to be triggered by loss, perhaps of social standing or of one's own self-regard, but most prototypically of a loved one. The experience of social rejection entails activation of neural structures encoding the affective dimension of pain (anterior insula and dorsal anterior cingulate cortex), at least in women [33], and increases the unpleasantness of physical pain [34]. Not surprisingly, there is some evidence that pain reports in depression may be accounted for by sensitivity to rejection [35].

Conversely, the affective aspects of pain are antagonized by such "reward centers" as the nucleus accumbens and the ventral tegmentum [36], which tend to be hypoactive in the anhedonia of depression [37].

Dysphoria and pain are also regulated by the same neural structures—dorsolateral, ventral lateral, and orbital prefrontal cortex by way of ventromedial prefrontal cortex—operating on the amygdala and insula. Rostral anterior cingulate cortex similarly seems to play a modulatory role in pain and emotion [4, 38]. Failure of these top-down regulatory circuits can likely contribute to depressive disorder [39] and chronic pain [40]. In major depression and chronic pain, it is not the persistent firing of emotion or pain centers that stands out, but rather the loss of regulatory control [31].

Further, major depressive disorder entails elevated blood levels of the stress hormone cortisol and proinflammatory cytokines, particularly interleukin-1β [41]. Both of these can induce a corresponding "mirror" proinflammatory state in the brain. Thus, depression may increase pain sensitivity through the same glial mechanisms as described for catastrophizing. Patients may become achy with depression in the same way as they become achy with the flu.

In headaches, depression increases the probability of cutaneous allodynia, which is the capacity of nonpainful stimuli to elicit pain. Depression shows a dose-response relationship with allodynia, and its effects are independent of headache frequency and type of diagnosis (episodic migraine, transformed migraine, probable migraine, severe tension-type, or other chronic daily headache). For migraineurs, the effect of depression is also independent of obesity [42]. Because cutaneous allodynia reflects central sensitization, it is thought to be a marker for increased risk of progression in migraine frequency [42]. Major depression also is strongly associated with chronic migraine [43] and with failure to maintain long-term treatment gains in migraine [44].

Stress

Stress is a strong risk factor for the development of widespread pain. In a prospective, population-based study, this effect has seemed to require a preexisting dysfunction of the hypothalamic-pituitary-adrenal cortex axis, as indicated by an attenuated diurnal rhythm and blunted suppression when exogenous steroids were given (the dexamethasone suppression test) [45]. This dysfunction is likely itself due to exposure to high levels of stress in early childhood or in utero [45].

The manner in which cortisol would influence pain levels is uncertain. It may be a marker for more intense emotional reactivity, in which case an anxious or depressive response to stress may be the true trigger [46]. Alternatively, the key variable may be a loss of normal levels of pain inhibition, as the upstream precursor to cortisol, corticotrophin-releasing hormone, has analgesic properties [45].

Stressful life events appear to be a significant risk factor for transformation from episodic to chronic migraine, with a dose-response relationship between the number of stressors and the probability of transformation. Of note, the association pertained only to stressful events occurring in the same year or the year before transfor-

mation; those occurring after transformation showed no association [47].

Culture

Physical symptoms are extraordinarily common in depression and anxiety, yet they are generally regarded as secondary or insignificant. Why? In fact, the tendency to report psychosocial distress in terms of affect (for example, sadness or feelings of worthlessness) rather than physical symptoms (eg, fatigue, weakness, malaise, pain) may be a phenomenon of Western culture [48]. Thus, among the changes in China over the past three decades has been a waning of a diagnostic category corresponding to neurasthenia (comprised largely of the vegetative aspects of depression [49]) in favor of depressive disorder, mirroring a corresponding change in Europe and America in the first part of the 20th century [48].

Analogue data from the laboratory suggest that this may not be a true difference in the experience of distress but rather a difference in verbal behavior—the learned appropriate form of expression [50]. This would make the translation and therapy of distress in psychological terms feasible, even if it were not the natural means of expression in a given culture. However, cultural explanations for nonspecific symptoms can also be dire, leading to catastrophic thinking and anxious preoccupation [2]. We must include in this our own culture, with its emphasis on abstruse, sometimes frightening, almost otherworldly testing, and its focus on anatomic findings of uncertain relevance to the pain. Conversely, health systems that allow a more personal and open physician-patient relationship may also reduce the number of unexplained illnesses because psychological issues can be acknowledged and processed [51].

Operant Conditioning

Like other behaviors, those involved in the communication of pain (disability, health care utilization, and verbal and nonverbal expressions) tend to increase when followed by a reinforcer, that is, by a reward or by escape from or avoidance of an unpleasant stimulus.

Three qualities make the process particularly malignant in chronic pain. First, the reinforcement need not be a social or environmental consequence such as sympathy, support, or compensation. Rather, pain reduction itself can be a significant reinforcer. Second, when increments in pain sensitivity are followed by pain reduction, the result seems to be a true increase in pain sensitivity, not merely a change in verbal report. (This has been demonstrated in the laboratory by measuring pain sensation with a response different from that used in the conditioning phase of the study, or by using complex schedules of reinforcement that allow the rate of responding and rate of perceptual change to be disentangled.) Third, the conditioning can take place in the laboratory using reinforcers that are so subtle and infrequent that their relationship to pain goes unnoticed [52, 53].

The neuroanatomical basis of the conditioning has not yet been determined, but its implications seem significant: in the very common practice of persisting in tasks to the point of intense pain, and then using rest, heat, or medications, patients may be inadvertently training their pain systems to a greater degree of sensitivity.

Conversion Disorder

Conversion disorder involves neurological symptoms that lack an organic cause, generally arising after a stressor or in the context of a psychological conflict, in the absence of conscious volition. A diagnosis purely of exclusion like this would seem fraught with inaccuracy, but in modern clinical series only about 4% of patients are later found to have a true neurological illness [54]. Conversion symptoms often distinguish themselves by inconsistencies in presentation, for example, involuntarily extending the “paralyzed” leg when the intact leg is flexed against resistance (“Hoover’s sign”) [54].

At this point, functional neuroimaging consists mostly of data from case studies and small clinical series of patients with sensory or motor deficits. In conversion involving paralysis or focal weakness, primary motor cortex and basal ganglia appear to be inhibited. In contrast to feigned paralysis, however, and in partial contrast to hypnotically induced immobility, the inhibition does not seem to derive from regions involved in self-restraint of movement (eg, the inferior frontal gyrus) but rather those involved in inhibition of emotion, pain, and desire (eg, ventromedial prefrontal cortex) [55].

When the conversion consists of sensory deficits, there appears to be inhibition of primary and secondary somatosensory cortex. This inhibition appears to arise from both the rostral and the subgenual regions of anterior cingulate cortex [56]. The former area is involved in the inhibition of somatosensory experience produced by task absorption, placebo, and hypnosis. The latter area has broad inhibitory influence on emotion and reward centers; its action is most closely associated with treatment-refractory depression [57].

Thus, functional deficits in conversion seem to arise when brain regions involved in the regulation of affect and reward inhibit motor or sensory regions. By analogy, we

might surmise that pathological pain (when it is not due to a musculoskeletal cause such as dystonia or abnormal posture) could arise when these regulatory areas (ventromedial prefrontal cortex, rostral anterior cingulate cortex), which would normally inhibit nociception, are themselves inhibited by limbic areas. This brings us very close to some of the mechanisms proposed for depression, catastrophic thinking, and pain-related affect. Alternatively, perhaps direct stimulation of the basal ganglia, which seem to play a role in pain perception, by limbic structures, could produce a conversion-like pathological pain. However, whether pain can exist as a conversion symptom separate from depression, catastrophic thinking, or the like, does not seem at all clear.

Conclusions

Just as neuropathic pain may arise from attempts by neurons to regenerate damaged axons, so may the psychological influences on pain arise from processes designed to anticipate, represent, and adapt to pain and stress.

Thus, expectation and fear of pain may directly prime portions of the pain matrix. So, too, may experiences that are analogous to pain, such as depression, rejection, and loss. Pain can be a highly relevant stimulus, acutely because of its novelty and biological significance, and chronically because of its social impact, according it more fluent access to consciousness.

Expectation, attention, and possibly fear of pain seem to shift the balance between descending facilitatory and inhibitory influences on pain in favor of the former.

Pain and mood seem to be regulated or otherwise counterbalanced by similar structures, whose failure can contribute to chronicity. Preliminary, circumstantial evidence suggests that the combined effects of pain and distress may be particularly capable of inducing long-term neuroplastic changes in pain and pain-regulatory pathways.

Our awareness of somatization goes back many centuries, but the mind-body dualism that has made it difficult to treat in medical settings is rapidly yielding. This allows us to inquire about, interpret, and treat the psychological sources of physical distress in an objective, nonthreatening, and relatively precise way.

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