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Individual Differences in the Subjective Experience of Pain: New Insights into Mechanisms and Models

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Abstract

Individual differences in pain sensitivity have long remained a perplexing and challenging clinical problem. How can one individual have a sensory experience that is vastly different than that of another, even when they have received similar sensory input? Developing an understanding of such differences and the mechanisms that support them has progressed substantially as psychophysical findings are integrated with measures of brain activation provided by functional brain imaging techniques. Continued delineation of these mechanisms will contribute substantially to the development of combined psychophysical/psychological models that can be used to optimize pain treatment on an individual-by-individual basis.

Keywords

pain; fMRI; expectations; placebo; anterior insular cortex

Across all sensory modalities, our subjective experiences are individually unique. One texture may be pleasant to one individual, and uncomfortable to another. One flavor may be appealing to one individual and aversive to another. These experiences can rapidly shift within one individual - for example even too much chocolate in chocolate lovers becomes a negative rather than a positive experience (1). These differences underscore the fact that sensory experiences are far more than a mere extraction and appreciation of the features of an afferent signal. Instead, they are constructed from a complex convolution of afferent input with information related to our past experiences, present context, as well as the future implications and meaning of the afferent input. This process is supported by genetically determined hardware but heavily modified by psychological and cognitive factors.

Clinical importance of individual differences

Individual differences in sensory experiences are of profound importance in the treatment of pain. Subjective ratings are essential for the diagnosis and treatment of pain, but profound individual differences in sensitivity complicate treatment. Is the patient reporting extremely high pain from a given procedure simply a histrionic personality, or engaging in drug seeking behavior, or do they really have much more pain than the other patients? Do they need to be treated more aggressively? Conversely, does the patient reporting minimal pain from the same procedure need the standard analgesic regimen, or can they avoid the risks and costs by having more conservative treatment?

Appreciation of the sensory experience of another

Such individual differences in the first person subjective experience are profoundly difficult to appreciate from a third person perspective. However, in experimental studies using carefully controlled noxious stimuli, tremendous individual differences are consistently observed. When reporting pain intensity using a visual analog scale with a range of 0–10 (with 0 being anchored by no pain sensation, and 10 being anchored by the most intense pain imaginable), healthy volunteers report ratings that range from slightly above 1 to slightly below 9(2). Simultaneous brain imaging identified patterns of activation that were consistent with these subjective reports. Highly sensitive individuals activated a number of brain regions important in the experience of pain more frequently and to a greater magnitude than insensitive individuals (2). These regions included the primary somatosensory cortex, a brain region important in early processing of both intensity and spatial features of noxious stimuli; the anterior cingulate cortex, a region involved in pain-related affect, attention, and decision-making; and the prefrontal cortex, an area important in working memory and emotion. Previous studies focused on within-individual differences in perceived pain indicate that the primary somatosensory cortex and anterior cingulate cortex both exhibit activation that increases monotonically with increases in both stimulus intensity and the perceived magnitude of pain intensity (3). Thus, the between subjects differences observed in these regions are consistent with the inter-individual differences in the reported magnitude of pain intensity, and provide evidence that subjective reports of pain are sufficiently sensitive to reflect underlying differences in the neural state. Moreover, these findings underscore the fact that individual differences in pain are real and not simply artifacts of scale usage.

Mechanisms contributing to individual differences

The study of individual differences in pain has only recently been a topic of focused examination. Historically, reliance on subjective reports dampened enthusiasm for such lines of investigation, but the increasing confidence in psychophysical assessment of pain, in combination with increasing capability to explore genetic contributions to pain, has led to a growth in the output of this aspect of pain research. Moreover, the contributions of functional imaging studies to the determination of the neural mechanisms supporting cognitive and psychological modulation of pain has opened new realms for the investigation of individual differences. However, the development of a full understanding of individual differences in pain remains challenging, due to the myriad of genetic, environmental, psychological, and cognitive variables that can shape such differences.

Genetic contribution to individual differences

The mechanisms that contribute to the construction of individual differences in pain play out on a substrate determined, in part, by genetic factors. Studies of twins provide insight as to the variability that genetic factors can explain (4), (5). For example, genetic factors accounted for approximately 26–32% of the inter-individual variability in heat pain, 21% of the inter-individual variability in chemical pain, but as much as 60% of the variability in cold pressor pain. Surprisingly, genetic factors common to multiple stimulus modalities accounted for a very limited degree (3–7%) of inter-individual variability (4), raising the possibility that a portion of the genetic contribution is situated at a level of the nervous system where sensory information is processed in a modality specific fashion. Such cross modality findings mirror psychophysical results seen in within individual studies. For example, only 23% of the variability in heat pain sensitivity is explained by cold pain sensitivity (6). This observation, when combined with the partial contribution of genetic

factors, suggests that a large portion of inter-individual variability may be accounted for by environmental factors.

Interactions between genetic and sociological factors

Gender and ethnicity are two variables that have a significant genetic component and may contribute substantially to individual differences in pain. Obviously, in the case of gender, individuals who have the XY genotype differ substantially from those who have the XX genotype. Studies of gender differences in large groups of subjects (N=617) receiving acute experimental pain indicate that female subjects are slightly (~8%), yet reliably more sensitive to acute heat pain than males, although within gender variation encompasses the entire range of the scale used (6). In contrast, cold pain tolerance is influenced by gender to a much greater extent. Female subjects withdraw their hand from a noxious cold stimulus nearly 40% earlier than males (6).

Ethnic differences also may have a substantial genetic component and have been observed since the beginning of psychophysical assessment of pain (7). For example, differences were noted between northern Europeans, southern Europeans, Jews, and African Americans. Modern studies confirm that ethnic differences may contribute to individual differences in pain (6). For example, Asian-Americans are more sensitive to heat pain than European Americans, African Americans, or Hispanics. In contrast, European Americans have higher cold pain tolerance.

Ethnic differences may also manifest themselves in a qualitative rather than quantitative fashion. For example, Hispanic subjects frequently report itch from application of capsaicin to the skin, while European Americans and Asians report pain, and African Americans exhibit changes in warmth detection thresholds, but report minimal pain (8).

The interpretation of gender and ethnic differences in a purely genetic context is problematic given the tremendous influence of sociological factors. Manipulations of ethnic role expectations have long been known to influence pain (7). Similarly, modern studies have shown that interpersonally applied manipulations of gender role expectations can dramatically alter pain tolerance and abolish gender differences (9). In addition, other factors such as scaling bias can contribute to apparent gender differences. Female subjects give higher ratings of heat pain than male subjects when using simple numerical (i.e. 0–100) scales. However, these differences disappear when subjects use visual analog scales (VAS) to rate pain (10).

Psychological factors influencing pain sensitivity

A vast diversity of internally maintained cognitive and affective information can substantially shape the experience of pain. At a mechanistic level, such processes can alter the processing of nociceptive information at levels as low as the spinal cord or can shape how it is elaborated into a conscious experience via complex cortical-cortical interactions. Moreover, they may take place at timescales varying from moment-to-moment to being stable over long periods of time.

Neural mechanisms supporting attentional modulation of pain

At any moment in time, we have numerous cognitive processes simultaneously competing for promotion to conscious awareness. Which processes are allowed to win this competition depends on the relative balance between the intrinsic salience of incoming information (bottom-up) and top-down demands to focus on a particular task. Tasks requiring subjects to direct their attention to something other than pain frequently produce reductions in pain.

Functional imaging studies have determined that top-down attentional tasks and noxious stimuli both activate the anterior cingulate cortex, but in distinct sub-regions (11–13). However, cognitively demanding tasks can produce an indirect modulation of pain-related brain activation in regions such as the primary somatosensory cortex and insular cortex (13,14). Under many circumstances, this indirect modulation may be driven by descending inhibitory signals mediated by the periaqueductal gray, and has been demonstrated in studies explicitly examining distraction (15). Thus, at any point in time, a portion of the inter-individual variation in pain can be potentially attributed to which thoughts a subject is currently generating and how focused he or she is on those thoughts.

The direction of attention to pain is less frequently explored, but this topic has substantial clinical implications. The cognitive salience applied to the nociceptive information can alter processing at the lowest levels of the central nervous system. For example, Hayes et al. reported that a neuron in the trigeminal dorsal horn of an awake, behaving monkey expanded its typically contralateral receptive field to encompass ipsilateral portions of the face when the monkey was instructed to attend to that portion of its body (16). Such attentionally driven expansions in receptive fields would be predicted to enhance pain by driving more neurons to receive information from a given body site and may be a mechanistic correlate of how somatization can exacerbate chronic pain. Consistent with this notion, psychophysical studies in humans indicate that direction of attention to a particular body site can enhance radiation of pain (17). However, attentional effects may be complex and highly task dependent. In human subjects, the division of attention between two simultaneously delivered noxious stimuli can abolish spatial interactions that usually enhance pain and can even produce analgesia (18). These findings further indicate that a moment-to-moment situationally dependent tuning of nociceptive processing can potentially contribute to individual differences in pain.

Shaping of the individual experience of pain by expectations

A priori knowledge about a stimulus can substantially contribute to the tuning of nociceptive processing. Such knowledge may be acquired via the consistent pairing of environmental cues with sensory information and can significantly enhance the processing of afferent information (19) (20). As with attention, subtle differences in the nature and context of the expected information can have a dramatic impact on the processing of noxious information. Uncertain expectations, i.e. those which indicate an impending stimulus, but provide limited information about its nature, may provoke analgesia, while expectations that are more informative have been postulated to enhance pain (21). The influence of expectations on pain can be profound. In a group of 10 healthy subjects, Koyama et al. demonstrated that expectations for decreased pain produced reductions in pain ranging from 10–48% (22). Expectation related activation was detected in a group of brain regions consisting of the anterior cingulate cortex, anterior insular cortex, and prefrontal cortex. This activation increased in magnitude with the expected intensity of the stimulus. Brain activation during experienced pain overlapped with that evoked during the expectation period in portions of the cingulate, insular, and prefrontal cortices, but not more caudal regions such as portions of the posterior insula and primary somatosensory cortex (22). During expectations for decreased pain, activation of numerous brain regions was significantly reduced in comparison with a correctly cued stimulus. At an anatomic level, connections have been identified that would allow top-down information related to expectations to be transmitted from the anterior cingulate cortex, prefrontal cortex and anterior insular cortex to the posterior insular cortex and then to the secondary, and ultimately, primary somatosensory cortex (23).

Lesion studies in both animals and humans suggest that the insular cortex may be a crucial node in a network that contributes to the tuning of somatosensory processing by top-down information. In rats, the insula appears to support the implementation of safety signals in a conditioned fear paradigm (24). In humans, subjects with lesions of the anterior insular cortex exhibited significantly increased pain sensitivity that was partially associated with increased activation of the primary somatosensory cortex (25). This finding contrasts with the widely held view that the insular cortex is more involved with pro-nociceptive process rather than anti-nociceptive processes. One potential explanation for this increased pain sensitivity is that a priori information that the experimental heat stimulus was safe and was not going to cause any injury did not reach sensory processing areas due to the insular lesion. Thus, the afferent nociceptive information was processed in an informational vacuum with less inhibition than normally would occur in that particular experimental context (25).

Expectations are also a fundamental component of the placebo effect. Placebos provide a clear demonstration of how afferent somatosensory information can be altered in a clinically relevant fashion by a priori information. Placebo analgesia can activate both the spinal cord and numerous brain regions including the periaqueductal gray, anterior cingulate cortex and anterior insular cortex (26–28). Together with studies focused on expectation, results from placebo studies further emphasize how a priori information can alter the processing of afferent information and contribute to inter-individual differences in the experience of pain.

Personality attributes and individual differences in pain

Negative personality profiles involving anxiety, catastrophizing, and somatization may alter an individual's pain sensitivity over a longer term than the more moment-to-moment alterations discussed above. In a clinical situation, anxiety is typically seen as a factor that exacerbates pain. However, in healthy individuals without chronic pain or psychological disorders, mild, subclinical anxiety is inversely correlated with pain sensitivity (29). Multiple frontal cortical areas including the dorsolateral prefrontal cortex and medial frontal cortex exhibit relationships with the magnitude of anxiety and catastrophizing (30,31). Given that these regions are involved with the top-down regulation of sensory processing, altered activity may contribute substantially to individual differences in pain.

Towards predicting pain

The development of a better understanding of the factors that underlie individual differences in pain can provide crucial insights to the treatment of both acute and chronic pain. Multifactorial models encompassing both psychophysical and psychological dimensions are now capable of predicting large portions of the variability in acute post-surgical pain, chronic post-surgical pain, and somewhat smaller portions of the variability in treatment requirements. (32–35). As evidence continues to accrue, such models may transition into the clinic and be used to tailor treatment for each individual patient. Thus, complications arising from both under- and over-treatment could be minimized, with the end result of pain therapy being substantially improved.

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