Individual Differences in Pain Responses

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The experience of pain is characterized by tremendous inter-individual variability. Indeed, an identical noxious stimulus can produce vastly different pain responses across individuals. Historically, scientists have regarded this variability as a nuisance; however, substantial data suggest that these individual differences may provide valuable information that can be used to enhance clinical management of pain. This paper discusses several factors that contribute to individual differences in pain perception, including demographic (ie, sex, age, and ethnicity), genetic, and psychosocial variables. These factors are discussed in the context of the biopsychosocial model of pain, which posits that pain perception is influenced by interactions among biologic, psychosocial, and sociocultural factors. Finally, the clinical and scientific implications of individual differences in pain are discussed.

Introduction

In virtually every setting, human pain responses are characterized by tremendous inter-individual variability. Indeed, two patients with comparable radiographic osteoarthritis (OA) of the knee are likely to report vastly different levels of clinical pain and functional disability. Scientists typically view this variability as a nuisance and attempt to reduce it by exerting vigorous experimental control, such as studying very homogeneous samples (eg, males only) or by statistical adjustment and exclusion of "outliers." Clinicians often respond to the same "outliers" by peppering their pain-related diagnoses with adjectives like "atypical," "unexplained," or "idiopathic." Thus, scientists and clinicians alike are faced with the challenge of accommodating substantial inter-individual variability in pain responses. However, these individual differences become quite understandable when one acknowledges that pain is a complex personal experience, influenced by multiple interactive biopsychosocial processes; therefore, the experience of pain is highly unique and idiosyncratic across individuals. Thus, identical noxious stimuli should be expected to produce different experiences of pain across people, which has been elegantly demonstrated in a recent study involving brain imaging of responses to thermal pain. Using functional magnetic resonance imaging to evaluate cerebral responses to experimentally induced heat pain, Coghill *et al.* [1••] reported greater activation in pain-related regions of the cortex in pain sensitive compared with pain insensitive subjects, suggesting that heightened perceptual responses to heat pain were accompanied by differential central processing of noxious stimuli and not simply the result of response bias or measurement error. This provides compelling evidence that individual differences in pain responses reflect true variability in the experience of pain, and an enhanced understanding of this variability will provide important information that could improve management of clinical pain. Therefore, the primary goal of this paper is to discuss factors that contribute to individual differences in pain responses among humans.

Sources of Variability in Pain Responses

Pain measurement

One nuisance factor that contributes to variability in pain measurement is error. Measurement error refers to the degree to which the obtained pain measure fails to reflect the actual pain experienced. Measurement error is particularly damaging as it cannot be statistically controlled and is not attributable to any variables of interest—it is true error. It can be pre-empted by utilizing reliable and valid pain measurement tools appropriate for the population under study. Multiple scales are available for assessing the subjective experience of pain, including verbal descriptor scales, numerical rating scales (NRS), and visual analog scales (VAS). These scales differ somewhat in their convenience, usability, and statistical properties. For example, NRS are the most widely used scales as they are convenient and easy for patients to use, but NRSs have been criticized as they do not provide ratio-level scaling of pain. VAS, involve patients placing a mark along a line of predetermined length to provide an estimate of their pain level. VASs have excellent statistical properties, including ratio-level scaling; however, they require more time to administer and score and some individuals have difficulty understanding the concept. Moreover, Dionne *et al.* [2•] has argued that the verbal anchors used in constructing pain scales are critically important, because an upper anchor (eg, "Worst pain imaginable") that varies systematically across groups under investigation will produce two quantitatively different pain scales, such that group comparisons may be invalid. A

complete discussion of the strengths and weaknesses of these pain scales is outside the scope of this paper (for more information see [3]); however, it is important to recognize that the choice and implementation of pain scales can influence the degree to which pain ratings are contaminated by error.

Measurement error can be contrasted with error variance, which is a statistical term referring to sources of variance other than those of most interest to the investigator. For example, if an investigator were interested in changes in arthritis pain after administration of a new medication, the proportion of change in clinical pain that is not attributable to the medication is error variance. Some proportion of this error is a result of measurement error; however, many other sources of error variance are present, and to increase the chances of achieving statistical significance, the investigator will try to reduce error variance by statistically controlling for the variance because of these factors (eg, age, sex, ethnicity, body size, and so on). Notably, in addition to using these individual difference factors as control variables to reduce error variance, there is scientific and clinical value to elucidating the mechanisms whereby these various factors influence pain responses. This is the study of individual differences in pain.

Biopsychosocial Factors Associated with Pain Perception in Humans

The biopsychosocial model of pain posits that the experience of and response to pain is determined by complex and dynamic interactions among three types of factors: biologic, psychologic, and sociocultural [4]. This model supplants the clearly inadequate disease model, which insists on a high correspondence between pain and pathology. It is important to recognize that the conceptual distinction of factors as biologic versus psychosocial is somewhat artificial, based more on the level of analysis than on the actual mechanism of action. For example, at a psychosocial level, anxiety may be associated with increased pain report; however, at a more biologic level, the neurobiologic underpinnings of anxiety likely influence nociceptive processing. Thus, when considering the putative mechanisms underlying individual differences in pain responses, it is important to recognize that "psychosocial" and "biologic" explanations may refer to the same underlying processes described at different levels of analysis. The biopsychosocial model is represented in Figure 1. Abundant evidence demonstrates that pain and tissue damage are poorly correlated, that there are tremendous inter-individual differences in the perception of pain, and that multiple factors above and beyond pathophysiology contribute to pain and related symptoms. For example, in rheumatoid arthritis and OA, measures of disease activity (eg, tender and swollen joints, radiographic measures) are relatively poor predictors of pain and function [5,6]. Also, in several chronic pain conditions (eg, temporomandibular disorders, irritable bowel syndrome, and fibromyalgia) no clear pathophysiology has been identified. Moreover, psychosocial factors consistently account for significant variance in pain reports among patients with clinical pain [7].

Consistent with the biopsychosocial model, it is well-documented that numerous social and environmental variables are associated with pain perception among humans. This brief paper will highlight demographic (ie, sex, ethnicity, and age), genetic, and psychosocial factors that may be associated with pain perception, as these factors represent clinically relevant individual difference variables that contribute to the complexity of pain.

Sex Differences in Pain

Sex differences in pain responses have been widely reported. Of relevance to the rheumatology setting, several pain-related rheumatologic conditions are more common among women than men, including rheumatoid arthritis, OA, systemic lupus erythematosis, and fibromyalgia [8]. Moreover, Keefe *et al*. [9] have reported greater arthritis pain and disability among women compared with men. Sex-related influences on pain perception could contribute to these differences in clinical pain. Indeed, abundant evidence suggests that relative to men, women exhibit more robust perceptual responses to experimentally induced pain. Specifically, women report lower pain thresholds and tolerances than men across multiple stimuli [10,11]. Also, women demonstrate greater temporal summation of heat [12,13] and mechanical pain [14], suggesting enhanced sensitization of spinal nociceptive neurons in response to repetitive noxious input. Also, injection of the excitatory amino acid glutamate into the masseter muscle produced greater and longer lasting pain among women than men [15]. Thus, sex differences in pain perception have been consistently reported across multiple measures and stimulus modalities.

Ethnic Differences in Pain

Considerable evidence suggests that the experience of clinical pain differs among ethnic groups [16,17••]. Of particular relevance to this paper are findings that arthritis is more prevalent among blacks and Hispanics than in whites, and these minority groups experience greater arthritis-related pain and activity limitations [18,19]. In addition, laboratory research has reported increased experimental pain sensitivity among blacks as compared with whites. Indeed, findings of lower heat pain thresholds and tolerances among blacks compared with white subjects date back more than six decades [20]. Similarly, whites had higher tolerance for cold pressor pain compared with a combined group of blacks and Hispanics [21]. Recent studies have suggested that the greater pain sensitivity among blacks compared with whites may be more robust for the affective versus sensory dimension of pain [22,23].

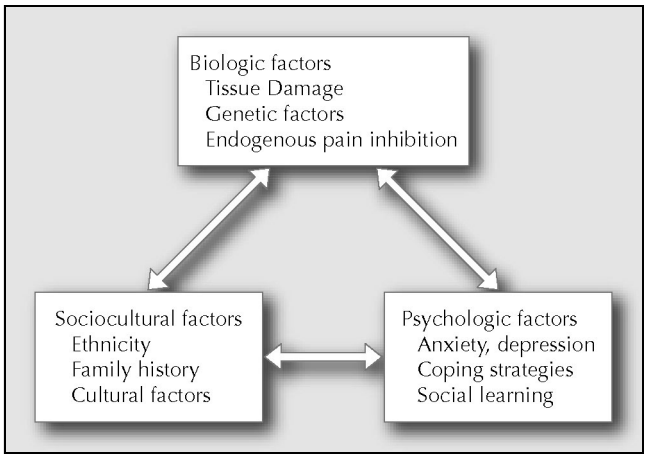

Figure 1. The biopsychosocial model of pain illustrating that the experience of pain is influenced by interactions among biologic, psychologic, and sociocultural factors.

Additionally, recent research has indicated that blacks described ischemic arm pain as more intense and unpleasant compared with whites when using standardized verbal descriptor scales, but not with individualized scales [24], and we recently reported lower pain tolerance across three stimulus modalities (heat, cold, and ischemic pain) among blacks compared with whites [25•]

Age-related Differences in Pain Perception

Recent reviews indicate that the prevalence and impact of pain increases with age [26,27]. For example, older age has been associated with the onset of and persistence of clinical pain [28]. Older adults also appear to expect more pain, report a greater number of body sites affected by pain, and show higher levels of pain-related interference with daily activities [29,30]. In addition to these clinical and epidemiologic findings, there is evidence that pain perception changes with age. In a recent review article Gibson and Helme [31] concluded that age-related changes in pain perception vary across stimulus modality and pain measure. Thus, older adults demonstrate slight increases in pain threshold but show moderate to large reductions in pain tolerance compared with younger adults [31]. Moreover, the greater pain sensitivity in older adults is particularly robust for more clinically relevant experimental pain stimuli, including pain that is tonic, intense, and applied to deeper tissues [31,32]. Older adults also show greater temporal summation of heat pain and demonstrate less effective endogenous pain inhibition [33,34].

Genetic Influences on Pain Responses

Interest in genetic influences on pain-related responses has increased dramatically in recent years. Many clinical pain conditions show significant familial aggregation, including arthritis and fibromyalgia [35,36], and heritability estimates for arthritis [36,37] and several other pain disorders are relatively high [38]. In addition to genes associated with the pathophysiologic processes of specific diseases, genetic influences on pain perception could potentially contribute to the heritability of chronic pain conditions. Substantial evidence from preclinical models suggests that basal nociceptive sensitivity and antinociceptive responses to drugs show significant heritability [38], but evidence of genetic influences on pain sensitivity in humans remains scant. Pressure pain threshold was assessed in monozygotic and dizygotic twins and showed a heritability of only 10% [39]; however, twin studies are typically underpowered for detecting genetic associations for multifactorial traits like pain sensitivity. Interestingly, recent studies have found significant genetic associations between single nucleotide polymorphisms (SNPs) of specific genes and experimental pain responses. One group of investigators reported that a SNP of the δ-opioid receptor gene (*OPRD1*) was associated with thermal pain responses among men but not women, and these authors also found an association between vanilloid receptor subtype 1 (TRPV1) genotype and cold pain perception [40]. Zubieta *et al.* [41] reported that a SNP of the catechol-*O*-methyltransferase gene (*COMT*) was marginally associated with pain report and significantly related to brain m-opioid receptor binding induced by an experimental muscle pain stimulus. Recently, Diatchenko *et al.* [42••] found that *COMT* haplotype was associated with experimental pain sensitivity and risk for subsequent development of temporomandibular pain. We recently reported that a SNP of the m-opioid receptor gene was associated with mechanical pain sensitivity [43]. Thus, emerging evidence indicates that multiple genetic factors may contribute to individual differences in pain sensitivity.

Psychosocial Influences on Pain

A vast literature documents that pain is strongly influenced by a multitude of psychosocial factors, including affective factors, cognitive processes, psychosocial history, social learning, and personality to name a few. A thorough review of this research area is clearly beyond the scope of this paper; therefore, the focus will be on mood and coping and refer the interested reader elsewhere [44]. Among patients with chronic pain, it is well-documented that negative mood (eg, anxiety, anger, depression) is more prevalent and is associated with greater levels of clinical pain. In addition, negative mood predicts greater severity of acute pain and is related to greater pain sensitivity in the laboratory setting. Also, pain coping strategies vary across individuals and are related to clinical pain symptoms [45,46]. Coping has also been related to acute pain. For example, catastrophizing predicted greater severity of postoperative pain [44,47] and has been related to enhanced experimental pain sensitivity [48,49]. Thus, mood states and pain coping strategies are associated with clinical pain symptoms and with experimental pain sensitivity.

Clinical Relevance of Individual Differences in Pain Perception

The information provided above indicates that pain perception is characterized by tremendous inter-individual variability. Interestingly, the reviewed demographic, genetic and psychosocial factors have been associated with clinical pain indices as well as laboratory measures of pain perception. Thus, it seems reasonable to question whether individual differences in experimental pain sensitivity are of direct clinical relevance. Recently, several domains of evidence supporting the clinical relevance of experimental pain assessment have been reviewed [50•]. Specifically, many chronic pain populations demonstrate enhanced sensitivity of painful stimuli, and laboratory pain perception often predicts the severity of clinical symptoms. Indeed, enhanced pain sensitivity has been demonstrated in fibromyalgia, rheumatoid arthritis, and OA [51–54]. In addition, experimental pain perception can predict future pain experiences. Specifically, enhanced pain sensitivity before surgery has predicted greater post-surgical pain [55–57], and greater pre-treatment pain sensitivity has predicted poorer outcomes from treatment for chronic pain [58,59]. Thus, individual differences in pain perception show substantial clinical relevance in multiple chronic pain populations.

Conclusions

The experience of pain is highly complex and influenced by multiple individual difference variables, including age, sex, ethnicity, genetics, and psychosocial factors. To appreciate the contributions of these multiple variables, it is helpful to recognize that pain is a constructed experience. That is, rather than simply "registering" the pain signal to produce pain perception, the brain actively constructs the pain experience by integrating multiple inputs, including biologic factors, current and past psychologic events, and sociocultural influences. Importantly, the available inputs may differ significantly as a function of age, sex, or ethnicity, and all of these factors interact dynamically. For example, the association of biologic and psychologic factors with pain responses has been shown to vary as a function of sex [60]. Thus, the ultimate "mosaic" of information that creates the experience of pain is sculpted by complex interactions among these multiple factors. This conceptualization of pain processing has substantial potential impact on clinical practice and research in rheumatology.

First, the notion that tissue damage or disease severity is the primary determinant of pain and disability must be abandoned. This approach interferes with obtaining a thorough understanding of the multiple biopsychosocial factors contributing to a patient's current health status, which, of course, will be required to create an optimal treatment plan. Relatedly, it is likely that a multimodal approach to pain treatment will be more effective than monotherapy, given the multiple factors that inevitably contribute to a patient's experience of pain. In other words, the biopsychosocial model should serve as the foundation for assessment and treatment of pain in patients with rheumatologic conditions.

Second, increased use of quantitative sensory testing (QST) in the clinical setting may provide valuable information that can be used in diagnosis and treatment. Evidence reviewed above indicates that pain sensitivity assessed through QST is altered in patients with chronic pain resulting from rheumatologic conditions and can predict symptom severity and possibly responses to treatment. For example, one recent study found that lower pressure pain threshold significantly predicted greater disability among OA knee patients who reported clinical pain in the absence of radiographic deformity, but not among patients with radiographic deformity [52]. Thus, QST may be helpful in identifying patient subgroups and may ultimately serve as a useful treatment outcome measure.

Third, there are important individual differences not only in pain symptoms but also in responses to treatment, and efforts to better understand these differences will permit tailoring of treatment in the future. Indeed, individual responder analysis of drug responses (ie, evaluating drug responses for each individual patient) has recently been described and recommended as an approach that may facilitate the development of effective analgesics [2•]. Better characterizing the biopsychosocial factors that contribute to individual differences in treatment response could help identify which patients will benefit from which treatments.

In summary, the experience of pain is influenced by multiple biopsychosocial factors, and there are tremendous inter-individual differences in responses to pain and its treatment. This has profound implications for the management of chronic pain associated with rheumatologic conditions, and efforts to better understand the many factors contributing to patients' pain will permit more effective tailoring of treatment producing improved clinical outcomes.

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