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Individual Differences in Pain: Understanding the Mosaic that Makes Pain Personal

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Abstract

The experience of pain is characterized by tremendous inter-individual variability. Multiple biological and psychosocial variables contribute to these individual differences in pain, including demographic variables, genetic factors, and psychosocial processes. For example, sex, age and ethnic group differences in the prevalence of chronic pain conditions have been widely reported. Moreover, these demographic factors have been associated with responses to experimentally-induced pain. Similarly, both genetic and psychosocial factors contribute to clinical and experimental pain responses. Importantly, these different biopsychosocial influences interact with each other in complex ways to sculpt the experience of pain. Some genetic associations with pain have been found to vary across sex and ethnic group. Moreover, genetic factors also interact with psychosocial factors, including stress and pain catastrophizing, to influence pain. The individual and combined influences of these biological and psychosocial variables results in a unique mosaic of factors that contributes pain in each individual. Understanding these mosaics is critically important in order to provide optimal pain treatment, and future research to further elucidate the nature of these biopsychosocial interactions is needed in order to provide more informed and personalized pain care.

Introduction

It has long been appreciated that individuals differ from each other in important ways. More than 2,000 years ago Plato said: “No two persons are born exactly alike; but each differs from the other in natural endowments (360 B.C.).” Such individual differences are a hallmark of the experience of pain and have been a topic of keen interest to pain researchers for many years. Indeed, more than 70 years ago, in describing the rationale for their psychophysical study of pain sensitivity in healthy adults, Chapman and Jones [13] stated that “A striking variation in the intensity of pain, experienced in diseases with apparently similar lesions, is a common observation.” Historically, this inter-individual variability in pain response was more often viewed as a nuisance than a fruitful area of scientific inquiry; however, the genomic revolution and the ensuing promise of precision medicine have reinvigorated and legitimized scientific interest in individual differences [12; 18; 21; 52]. The purpose of this article is to provide an overview of factors contributing to individual differences in pain. Given the abundance of potential individual difference factors, I will not

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attempt a comprehensive review of this field, rather provide examples of individual differences from our own research as well as the work of other investigators. First, I will introduce the topic of individual differences in responses to pain and its treatment, including a biopsychosocial context for conceptualizing individual differences. Then, I will present findings regarding demographic factors that are associated with individual differences in pain. Next, I will discuss genetic and psychosocial contributions to individual differences, and I will present examples of interactions among these multiple individual difference factors. I will describe the clinical implications of individual differences in pain, followed by conclusions and recommendations for future research.

By definition pain is a subjective and highly personal experience, which presents challenges for both the researcher and clinician. A well-recognized challenge resulting from the *subjective* nature of pain is that direct measurement of pain is impossible, rather we must rely on individuals' self-report, and to some extent their behavior, to provide a glimpse into their experience. However, an equally important but less often discussed challenge results from the *highly personal* nature of the pain experience; the experience of pain is sculpted by a mosaic of factors unique to the person, which renders the pain experience completely individualized. That is, there are pervasive and important individual differences in pain, and these individual differences produce pain experiences that are completely unique to the person experiencing them (i.e. they make the pain personal). For purposes of this paper, I will define individual differences in pain as between person differences in the pain experience that are independent of the initiating stimulus. Perhaps the simplest manifestation of individual differences is that an experimental stimulus delivered at a standardized intensity elicits subjective pain reports that vary dramatically between individuals (**Figure 1**), as noted decades ago by Chapman and Jones [13] and more recently by others [16; 26; 71; 86]. Interestingly, these differences in self-reported pain are corroborated by inter-individual differences in cerebral activation evoked by the same painful stimulus [14] and are in part predicted by individual differences in brain morphology [25], suggesting that these individual differences are not simply a product of idiosyncrasies in the reporting of pain. Such individual differences also emerge in the clinical environment. For example, pain reports following the same surgical procedure vary greatly across patients [7; 43; 83]. Similarly, responses to pain treatments are characterized by robust individual differences [3; 5; 11; 52]; however, a discussion of factors contributing to variability in treatment responses is beyond the scope of this article, which will focus on the individual difference factors impacting the experience of pain.

The biopsychosocial model provides an ideal framework for conceptualizing individual differences in pain. This model posits that the experience of pain is influenced by complex and dynamic interactions among multiple biological, psychological, and social factors [37]. Importantly, the ensemble of biopsychosocial factors contributing to the experience of pain and its expression varies considerably across people. Thus, pain is sculpted by a mosaic of factors that is completely unique to each individual at a given point in time, and this mosaic must be considered in order to provide optimal pain treatment.

When considering individual difference factors, it is important to distinguish characteristics of the individual that are statistically associated with pain responses (i.e. markers) from

biological and psychosocial mechanisms that directly influence pain responses. Notably, some markers may reflect mechanisms underlying pain, while others do not. Examples of the former include demographic factors, such as sex, race/ethnicity and age. While each of these variables has been associated with pain responses (as discussed below), they reflect proxies for mechanisms influencing pain rather than mechanisms themselves. That is, the sex of an individual does not directly influence pain, rather sex differences in pain reflect the effects of other biological and psychosocial processes (e.g. sex hormones, inflammatory responses, gender roles, pain coping). Alternatively, a study could assess biological marker(s) related to pain, in which case the biological marker(s) represents both an individual difference factor and a potential mechanism directly influencing pain. Thus, while individual differences in pain response present challenges to the scientist and clinician, they also provide important opportunities. Indeed, investigating the factors contributing to individual differences in pain can provide important insights into pain mechanisms, which may lead to the development of novel treatments. Also, incorporating an understanding of individual differences into assessment and diagnosis of pain in the clinical setting may allow the clinician to select treatments that are tailored to the patient, thereby improving treatment outcomes.

Demographic Influences on Pain

As noted above, demographic factors do not directly influence pain, however they represent valuable individual difference factors, because they are easily measured and they provide important public health information regarding large population groups that may be at risk for increased pain. In addition, demographic associations with pain reflect the influence of underlying mechanisms, a better understanding of which can elucidate the pathophysiology of pain. That is, the prevalence of joint pain generally increases monotonically with age, and explanations for this association will enhance our mechanistic understanding of joint pain. Below, I will briefly review research examining sex differences, racial/ethnic differences, and age-related differences in pain, and the interested reader can find additional information regarding each of these topics in several recent reviews [2; 29; 32; 51; 62; 67; 78].

Sex Differences

Abundant epidemiologic evidence demonstrates that chronic pain is more prevalent among women than men [29; 67]. For example, recent findings from a large scale nationally representative study in the United States (US) found that a higher proportion of women than men reported any pain over the last 3 months [69]. Interestingly, women also were more likely to report pain that was persistent and bothersome, but only among non-Hispanic whites and non-Hispanic blacks. No such sex difference emerged for Hispanic whites. (Note: this reflects an interaction between sex and ethnic group, and such interactions among individual difference factors will be discussed further below) These findings relate to chronic pain in general, but sex differences in the prevalence of specific pain conditions have also been reported. Indeed, women are at greater risk for most common chronic pain conditions, including migraine and tension-type headaches, low back pain, fibromyalgia and widespread pain, temporomandibular disorders, irritable bowel syndrome, and osteoarthritis [29; 67]. Some studies have examined sex differences in the severity of acute and chronic

pain, and in general any sex differences that have emerged have been inconsistent and small in magnitude [29; 83].

While multiple explanations for these sex differences in pain prevalence can be offered, one possibility is that fundamental differences in the functioning of female and male pain processing systems renders women at increased risk for clinical pain. This has motivated investigators to explore sex differences in responses to experimentally-induced pain. Multiple reviews of this topic are available [29; 46; 67; 78], and while some differences in interpretation of findings have emerged, the pattern of findings is indisputable. For virtually all standard measures of experimental pain sensitivity women display greater sensitivity than men, including pain threshold (the minimum stimulus intensity required to produce pain), pain tolerance (the maximum stimulus intensity an individual is willing to tolerate), and ratings of suprathreshold stimuli. Notably, the magnitude of the sex difference varies considerably across studies and across pain measures and stimulus modalities, but the direction of the difference is highly consistent. Also, women have shown greater temporal summation of pain (a measure of transient central sensitization) and less conditioned pain modulation (a measure of endogenous pain inhibition)[77], suggesting a pain modulatory balance that is tuned more strongly toward pain facilitation than pain inhibition among women. In contrast, in response to sustained and repeated thermal stimuli, females have shown greater habituation than men, suggesting a stronger pain inhibitory response to these types of stimuli [44; 45]. Multiple mechanisms have been proposed to explain these sex differences in pain, including the effects of sex hormones, differences in endogenous opioid function, cognitive/affective influences, and contributions of social factors such as stereotypic gender roles [29; 67].

Race/Ethnic Group Differences

The concepts of race and ethnicity are complex biological and social constructs that remain poorly defined. In the United States, it is typical to categorize individuals according to both ethnicity (Hispanic/Latino vs. non-Hispanic/non-Latino) and race (e.g. Asian, African-American, white), while different approaches may be taken in other parts of the world. Whether individuals from different racial and ethnic backgrounds experience pain differently has long been a topic of interest. From an epidemiologic perspective, limited evidence suggests racial or ethnic differences in pain prevalence. Nahin [69] found that pain prevalence was lowest among Asians compared to other race/ethnic groups in the US. Other studies of adults in the US have reported higher prevalence of persistent pain among whites compared to other racial/ethnic groups [53; 54]. Among older adults some studies have reported higher pain prevalence among minorities compared to whites, while others reported no differences in pain prevalence [57]. While there is conflicting information regarding pain prevalence may be lower among minority versus majority ethnic groups, studies consistently suggest that the severity and impact of pain appears to be greater among minorities who are experiencing chronic pain [2; 57; 64]. Indeed, our own studies demonstrate greater pain severity and functional limitations among African Americans compared to non-Hispanic whites with knee osteoarthritis [17]. In addition, differences in pain perception between racial/ethnic groups may contribute to differences in severity of clinical pain. A meta-analytic review of studies examining pain perception in generally healthy adults found that

African Americans display greater experimental pain sensitivity compared to non-Hispanic whites [79]. Similarly, our recent findings among adults with knee osteoarthritis showed greater pain sensitivity and temporal summation of pain among African Americans [17].s These findings are largely based on work conducted in the United States, where racial and ethnic disparities in health are a substantial national concern. Similar findings have emerged in other developed countries throughout the world; however, little data related to ethnic group differences in pain have been reported from less developed countries.

The mechanisms underlying racial/ethnic group differences in the experience of pain are inevitably multifactorial, and include factors related to socioeconomic standing and access to adequate health care. For example, in most developed countries, members of minority groups on average have lower socioeconomic status, which has been associated with increased pain prevalence and more severe pain [64; 76]. In addition, considerable evidence suggests that minority patients are at greater risk for undertreatment of their pain, which could obviously contribute to the greater clinical pain severity observed among members of minority groups [2; 75]. Pain coping also differs significantly across racial/ethnic groups [48; 65], and it is possible that biological factors, such as genetic contributions, may play a role in racial/ethnic differences in pain responses [49; 79].

Age-Related Differences

Given the aging of the world's population, whether the experience of pain changes with age has drawn increasing attention in recent years [10; 32; 33; 62; 68; 73]. Patterns of pain prevalence across the lifespan are complex and they vary across pain conditions (see **Figure 2**)[32]. Briefly, the prevalence of joint pain, lower extremity pain and neuropathic pains tend to increase monotonically with age. General chronic pain increases in prevalence until middle age, at which time the prevalence plateaus. In contrast, pain conditions such as headache, abdominal pain, back pain and temporomandibular disorders show peak prevalence in the third to fifth decades of life, after which their frequency decreases. It is important to note that these epidemiologic findings are based almost exclusively on cross-sectional studies, such that cohort effects (e.g. earlier mortality among people with certain pain conditions) could influence the results. Beyond pain prevalence, multiple studies have examined age-related changes in the severity and impact of pain. Older adults have reported lower acute pain intensity in some studies [34; 83], but not others [4; 35]. Similarly, age-related differences in the intensity and impact of chronic pain have not been consistently demonstrated [32; 33].

Age-related changes in responses to experimental pain have been widely studied. Taken together these findings suggest that older adults show less sensitivity to brief, cutaneous pains (e.g. heat pain threshold); however, sensitivity to more sustained pain stimuli that impact deeper tissues increases with age [32; 55]. Moreover, several studies have demonstrated increased temporal summation of pain among older adults [23; 56; 70], while conditioned pain modulation consistently has been found to decrease with age [24; 80]. This pattern of results suggests that aging is associated with a shift in pain modulatory balance, such that older adults show enhanced pain facilitation combined with decreased pain inhibition.

A variety of biopsychosocial factors have been posited to contribute to these age-related changes in pain processing. First, many pain-related diseases increase in frequency with age (e.g. diabetes, osteoarthritis, many forms of cancer, neurological diseases), which can contribute to increased pain among older adults. Moreover, many of the biological changes that underlie aging can also contribute to increased clinical pain and altered pain modulatory balance, including systemic inflammation, oxidative stress, altered autonomic function, and changes in neuronal structure and function [32]. In addition, psychosocial changes that occur with age could also impact pain. Reductions in cognitive function, sleep quality, and social support are all common in older adults, and these factors are also associated with increased pain [78]. Notably, undertreatment of pain in older adults is common, which could further contribute to greater pain in this population [62; 74].

Interactions Among Biopsychosocial Factors

The biopsychosocial model does not simply propose that factors from biological, psychological and social domains exert important influences on pain. Perhaps the most important aspect of the model is its insistence that these different sets of factors *interact* to create the experience of pain. These interactions are depicted by the three-way bidirectional arrows in **Figure 3**. Though often neglected in pain research, identifying and ultimately understanding these interactions is critical to elucidating the mechanisms driving pain in different groups and individuals. At least three types of interactions should be appreciated: mediation, additive associations, and moderation. As a point of clarification, I use the term interaction here in a general or conceptual sense rather than a statistical one, such that some of these interactions would not necessarily emerge as statistical interactions, though some certainly do. Mediational interactions refer to the phenomenon whereby the influence of an individual difference factor from one domain on pain is mediated through a process from another domain. For example, the influence of psychological stress on pain could be mediated via specific biological processes, such as heightened sympathetic nervous system outflow or increased inflammation. Another common type of interaction is an additive association, in which combining two individual difference factors, each of which increases risk for pain, produces a stronger effect than either factor alone. For example, if both female gender and a particular genetic profile increase the risk for chronic pain, then the combination of being both female and having the genetic profile would produce greater risk than having one or the other but not both. Another type of interaction is moderation, in which the effect of one factor depends on the presence or absence of another factor. In this case, we might find that while both female sex and the genetic profile are risk factors for pain, the association between the gene and pain differs for females and males. That is, the genetic factor may increase risk for pain in females but decrease risk for pain in males. Examples of all three types of interactions will be provided below. The examples I provide are primarily limited to interactions between genetic and non-genetic factors, which is biased by my interests and the research with which I have been involved. It is important to note that many other types of factors can and do interact to shape individual differences in pain.

Genetic Influences on Pain

Genetic contributions to pain have garnered considerable empirical attention in the past 20 years (see [18; 19; 31; 66] for reviews). In addition to representing identifiable individual difference variables, genetic associations with pain can reveal specific biological mechanisms that contribute to pain responses. The most commonly studied gene in pain studies has been the gene that encodes catechol-O-methyl-transferase (COMT), an enzyme that metabolizes catecholamines. *COMT* has been associated with pain-related mu-opioid receptor binding in the brain [87]. In addition, Diatchenko and colleagues [20] identified three *COMT* haplotypes that were related to global pain sensitivity and to risk of developing temporomandibular disorder. Thus, *COMT* has been related to clinical and experimental pain responses. The mu-opioid receptor gene (*OPRM1*) has also been widely studied for associations with pain phenotypes. We previously showed that the A118G single nucleotide polymorphism (SNP) of *OPRM1* was associated with pressure pain sensitivity [28], and others have also demonstrated the same SNP to be related to experimental pain responses [59; 63].

Genetic associations with pain have been found to vary by sex and ethnic group, which reflects moderation as described above. Importantly, such interactions suggest that the biological pathways represented by the gene may differentially influence pain responses in different population groups. For example, *COMT* has been found to interact with sex in predicting pain phenotypes. Belfer and colleagues [6] reported that a haplotype coding for low *COMT* activity predicted increased capsaicin-induced pain among females but not males. In contrast, a *COMT* haplotype from a different haploblock predicted pain and pain interference following motor vehicle collision in males only [9]. Likewise, associations of *OPRM1* with pain have varied across population groups. We found that the A118G SNP of *OPRM1* interacted with sex to influence heat pain responses. Specifically, among males the minor allele was associated with lower rating of heat pain, while among females this allele predicted higher heat pain ratings [28]. Interestingly, a subsequent clinical study produced similar results, finding that the minor allele predicted lower pain levels one year following lumbar disc herniation among males, while females with the minor allele reported higher pain at one year [72], a finding recently replicated by others [50]. We also have reported that associations of this this SNP with experimental pain responses differ across racial/ethnic groups [49]. Among non-Hispanic whites, the minor allele conferred lower sensitivity across multiple experimental pain measures; however, among Hispanic whites the association was in the opposite direction. The study also included African Americans; however, the frequency of the minor allele was too low among African Americans to detect any particular association. Such gene X demographic interactions have profound methodological and clinical implications. Regarding the former, failure to include the interaction term in statistical analysis of the data often results in a null effect of the gene on the outcome, such that investigators fail to discover potentially important findings. Regarding the latter, a treatment targeting the biological process reflected by the gene could produce dramatically disparate outcomes in different population groups, a possibility that would only be identified had the interactions been evaluated.

Psychosocial Influences on Pain and Gene X Psychology Interactions

Abundant evidence demonstrates strong associations between psychosocial factors and the experience of pain. The examples below represent selected findings from work with which I have been involved, and there are many other important psychological processes that contribute to individual differences in pain (e.g. traumatic experiences, developmental influences, personality). On average, compared to individuals without pain, people with chronic pain conditions report increased psychological distress, greater life stress, and more non-pain somatic symptoms [22; 61; 84]. Moreover, when assessed in pain-free individuals, these psychosocial variables represent premorbid risk factors for future development of chronic pain [8; 58]. For example, in the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) Study, we assessed multiple psychological variables in a large sample of generally healthy adults with no history of TMD pain. We found that poorer psychological functioning across two broad domains, global psychological symptoms (e.g. somatic symptoms, general psychological distress) and stress and negative affectivity (e.g. perceived stress, trait negative affect), predicted significantly increased risk for future development of TMD [30].

Importantly, psychological processes can interact with other individual difference variables, including demographic and genetic factors, to influence pain responses. George and colleagues [41] found that *COMT* interacted with pain catastrophizing (a maladaptive cognitive approach to pain characterized by rumination, magnification, and helplessness) to predict pain intensity in patients with chronic shoulder pain. Specifically, this additive interaction demonstrated that the subgroup of individuals who were both high in pain catastrophizing and had a high pain sensitive *COMT* haplotype reported greater pain than those who had only one or none of these two risk factors. These investigators subsequently replicated and extended these findings, demonstrating additional gene X psychology interactions in another clinical cohort of patients with shoulder pain as well as in healthy individuals experiencing experimentally-induced shoulder pain due to delayed onset muscle soreness [38-40; 42]. These findings suggest that the combination of genetic and psychological risk factors are associated with substantial increases in likelihood of experiencing pain of greater duration and higher intensity.

Additional findings from the OPPERA study also provide evidence of interactions between genetic and psychological factors. As noted above, perceived stress at the time of enrollment was a premorbid risk factor for development of new onset TMD. However, repeated measurements of stress also revealed that stress increased over time in those people who subsequently developed TMD but not among individuals who remained TMD-free [81]. More interestingly, increasing stress predicted TMD onset only among people who had a *COMT* haplotype associated with low COMT activity. Thus, increasing stress heightened risk for development of pain only in individuals with a genetic profile that rendered them more sensitive to the effects of catecholamines. While these findings emphasize risk factors, increasing research is focused on potential resilience factors that may protect against pain, which is an area of profound scientific and clinical significance [47; 82].

Clinical Implications

Individual differences in pain, and the biopsychosocial interactions that create them, have profound implications for assessment and management of pain. First, perhaps the most important implication is that awareness of individual differences in the clinical setting is critical. Those providers who approach each patient with a recognition of the importance of individual differences in pain will deliver better care and their patients will realize better outcomes. Thus, educational interventions to enhance provider understanding of individual differences in pain could enhance pain care. Second, the complexity of the biopsychosocial mosaic that influences pain demands an equally sophisticated approach to pain assessment and treatment. As recently highlighted in the ACTTION-American Pain Society Pain Taxonomy (AAPT), classification of chronic pain conditions should include not only core diagnostic features and associated symptoms, but should also incorporate information regarding biopsychosocial mechanisms and consequences [27]. This approach is also important for acute pain, which is likewise profoundly influenced by biopsychosocial factors [85], as noted in many of the examples above. Identifying the multiple biological and psychosocial processes and interactions contributing to a patient's pain, whether acute or chronic, serves as the basis for developing an effective treatment plan. Unfortunately, the time and resource constraints that characterize most current health care environments conspire against this approach, which requires a level of time and expertise that is typically available only in the context of a multidisciplinary treatment team. Perhaps our inability to consistently achieve this standard of care partially explains why chronic pain is among the costliest health conditions in the developed world, and a leading cause of disability worldwide [1; 15; 36]. Third, pain treatment should target the multiple biopsychosocial drivers of a patient's pain. Medical monotherapy is the norm; however, the suboptimal outcomes achieved by this approach are quite predictable given the complex and unique panoply of factors contributing to pain in each individual. The goal is to deploy personalized pain management, which is not simply pharmacotherapy based on genetic profile, rather truly personalized therapy is comprised of multiple treatment modalities designed specifically for each patient to target her or his singular mosaic. A final clinical implication is that an understanding of individual differences in pain can inform approaches to prevention of chronic pain. Indeed, identifying at risk individuals based on biopsychosocial profiles and developing prevention and early intervention programs based on those profiles has the potential to reduce the incidence of chronic pain appreciably (e.g. [60]).

Conclusions

The experience of pain is characterized by robust inter-individual differences. This article highlights multiple biopsychosocial factors that contribute to these individual differences. Demographic factors, such as sex, race/ethnicity, and age, represent easily assessed personal characteristics that are associated with pain and can have important public health implications. However, these factors themselves do not directly influence pain, rather they serve as proxies for a host of underlying processes that modulate pain. Genetic factors also represent important individual difference variables, but they have the distinct advantage of reflecting specific biological pathways that potentially directly impact pain. Psychosocial factors also contribute to individual differences in pain, and in addition to their value as risk

markers, many psychological processes are modifiable and thus can be important targets for intervention. Importantly, these multiple biopsychosocial variables interact in complex ways to influence pain, and several examples of such interactions were reviewed above (e.g. sex X gene interactions, gene X psychology interactions). The many variables whose individual and combined influences drive individual differences produce a mosaic that uniquely contributes to pain in each patient. An understanding of these individual differences is critical for effective pain assessment and management, serving as the foundation for personalized pain treatment, an as yet unrealized goal. Future research is sorely needed to further illuminate the interactions among biological and psychosocial processes that importantly influence the experience of pain. In particular, identifying individual difference factors and their interactions that contribute to development and persistence of pain is a high priority. Moreover, determining individual difference factors that predict responses to pain treatments will inform future efforts toward personalized pain treatment. Such research will enhance future pain treatment efforts through identification of novel targets and better matching of therapies to patients' needs.

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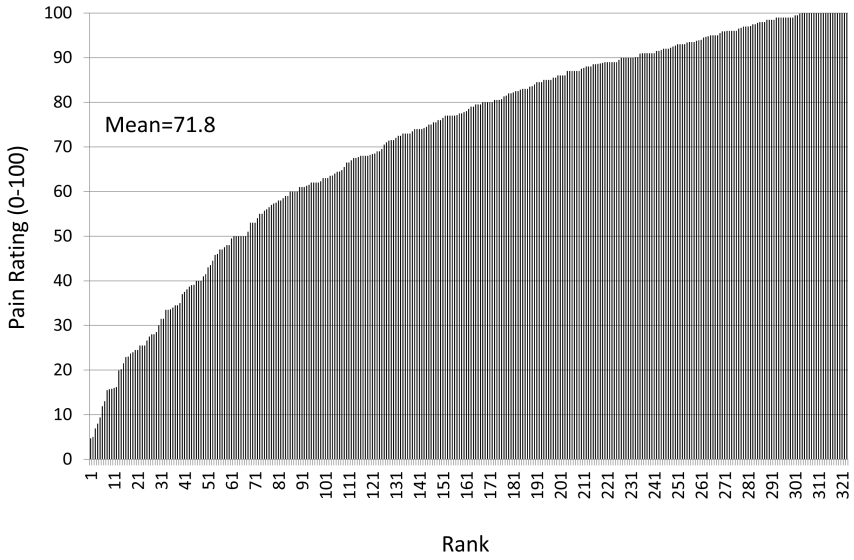

Figure 1.

Pain ratings in response to a heat stimulus (48 deg C) by 321 healthy young adults. Each line represents the pain rating (from 0 [no pain] to 100 [most intense pain imaginable]) by a single person. As can be seen, the mean pain rating was 71.8, but ratings ranged from 4 to 100. These data illustrate dramatic inter-individual differences in responses to a standardized experimental pain stimulus.

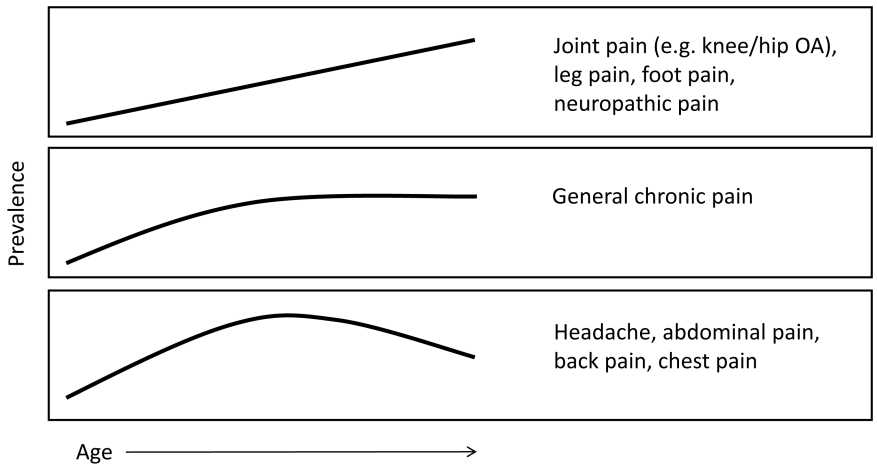

Figure 2.

Patterns of pain prevalence across the adult lifespan. The top panel shows that prevalence increases monotonically with age for several pain conditions, including joint pain, lower extremity pain, and neuropathic pains. The middle panel shows that for general chronic pain, prevalence seems to increase until middle age, at which time it plateaus. The bottom panel shows a pattern of increasing prevalence until middle age followed by a decrease in prevalence in later life for several conditions, including headache, abdominal pain, back pain, chest pain. References supporting these patterns can be found in [32]. It is important to recognize that these prevalence patterns are based on cross-sectional rather than longitudinal data; therefore, one cannot deduce pain trajectories within people from these data.

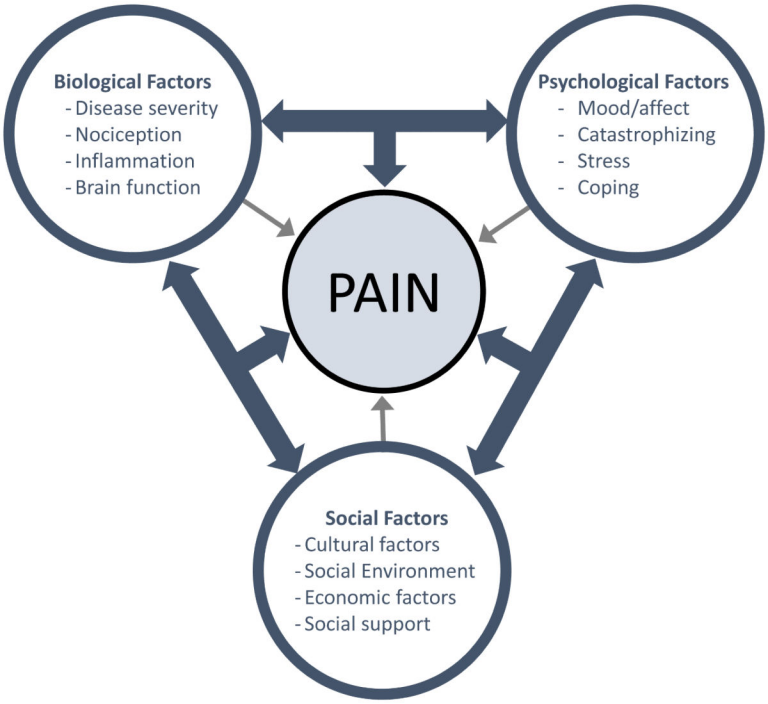

Figure 3.

Biopsychosocial model of pain. The figure illustrates that the experience of pain is sculpted by the influences of biological, psychological and social factors. Notably, while each of these factors can independently influence pain (as depicted by small bidirectional arrows), the more important and complex influences emerge from interactions among the factors, as depicted by the larger three-way arrows. These interactions among multiple biopsychosocial factors results in a unique mosaic of individual difference factors contributing to pain in each person.