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CHRONIC PAIN (R STAUD, SECTION EDITOR)

Predictors of Osteoarthritis Pain: the Importance of Resilience

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Abstract
Purpose of Review Osteoarthritis (OA) is one of the most common and disabling forms of arthritis worldwide, with joint pain being a primary symptom. Given that clinical symptoms often show poor concordance with tissue damage in OA, processes other than joint remodeling likely play a role in the condition. Using the biopsychosocial model of pain as a guiding framework, the purpose of this review is to highlight the extra-articular mechanisms that contribute to pain and dysfunction in OA, with a specific focus on resilience.
Recent Findings Whereas previous research has mostly focused on risk factors for worsening of OA pain, recently emerging evidence places greater emphasis on the identification of protective mechanisms that enhance pain adaptation and palliate the negative effects of joint pain.
Summary In view of this new and important research, more emphasis should be placed on endogenous pain modulation and, in particular, pain attenuation. The result of such work could serve as a basis for optimizing treatment in the OA population.

Keywords Osteoarthritis · Mechanisms · Biopsychosocial · Risk · Vulnerability · Resilience

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Introduction

Chronic pain is rapidly becoming one of the nation's top public health concerns, affecting over 100 million US adults and resulting in tremendous societal burden. Costs are estimated to supersede that of cancer, diabetes, and heart disease combined [1], and patients are often at risk for substantial physical disability and psychological comorbidities (e.g., anxiety, depression). By and large, osteoarthritis (OA) represents one of the most prevalent and disabling chronic pain conditions, with an estimated 26 million people in the USA being affected [2]. While any diarthrodial joint of the body can be affected, OA most often occurs in the hands, knees, and hips, with incidence rates highest for the knee [3]. Women and adults over the age of 50 tend to be disproportionately affected by OA [4], and various demographic, lifestyle, physiological, and psychosocial factors have been implicated in its pathogenesis. Because OA is a chronic condition affecting the joint and surrounding tissues, radiological evidence of joint pathology is traditionally used for diagnosis. However, diagnosis is also strongly influenced by clinical symptomatology, with joint pain, aching, and stiffness being the most frequently reported symptoms [5].

When OA becomes symptomatic, the effect is often staggering, leading to significant decrements in emotional and

physical health, social functioning, and activities of daily living. OA pain is considered to be a leading cause of mobility impairment in older adults, with hip and knee OA ranked as the 11th highest contributors to global disability (from 291 conditions) [6]. In addition to these effects, OA pain results in substantial economic burden with annual direct and indirect costs totaling $5700 per individual, as well as lost productivity due to reduced work capacity [7]. These rates are estimated to rise as a result of longer life expectancies, increased obesity prevalence, and the rapid growth of aging adults in the USA.

Biopsychosocial Model of Pain

Traditionally, a biomedical approach focusing on physiological contributions to symptoms has been the cornerstone to understanding OA and other pain conditions. The problem of the biomedical model is that despite often readily detectable pathology, there is a poor concordance between pain and pathology, especially in the context of OA [8]. In fact, individuals with a high degree of pain and disability from OA may show minimal signs of osteoarthritic changes on clinical exam or imaging. What is more, significant inter-individual differences exist in the experience of OA pain, even in the presence of similar joint abnormality, suggesting that factors other than pathophysiology contribute to pain-related outcomes.

In contrast to the biomedical model, the prevailing biopsychosocial model recognizes the contribution of all relevant biological, psychological, sociological, and behavioral factors that dynamically interact with one another to generate the experience of pain (Fig. 1). A fundamental tenet of this theory is that pain is affected by a combination of factors. Supporting this, considerable evidence suggests that pain and disability have profound influences on social and psychological functioning, and multiple psychosocial factors such as mood, personality traits, and coping styles can heighten the pain experience. While much of previous research has focused on vulnerability or risk factors that worsen pain-related outcomes, there is also increased recognition of protective mechanisms that mitigate the negative effects of chronic pain to enhance resilience.

The Role of Resilience in Pain

Over the years, pain research has provided considerable evidence regarding vulnerability factors that worsen the risk for pain outcomes. Stemming from this research has been the proliferation of both pharmacological and psychological treatments of pain that focus on the reduction of negative symptoms, such as pain severity and negative mood. While many important answers have been gained from this research, less attention has been directed toward identifying factors that confer successful adaptation to pain. In light of this, recent years have seen a paradigm shift in search of positive factors that enhance resilience and promote optimal functioning. Much of the push in this direction has been derived from numerous studies demonstrating that not all individuals with persistent pain show the same pattern of disability and loss of functioning.

Broadly, resilience is a dynamic process resulting from the ability to adjust to challenges and sustain successful adaptability to adversity. The quantification of resilience can be challenging due to its many variations in definitions; however,

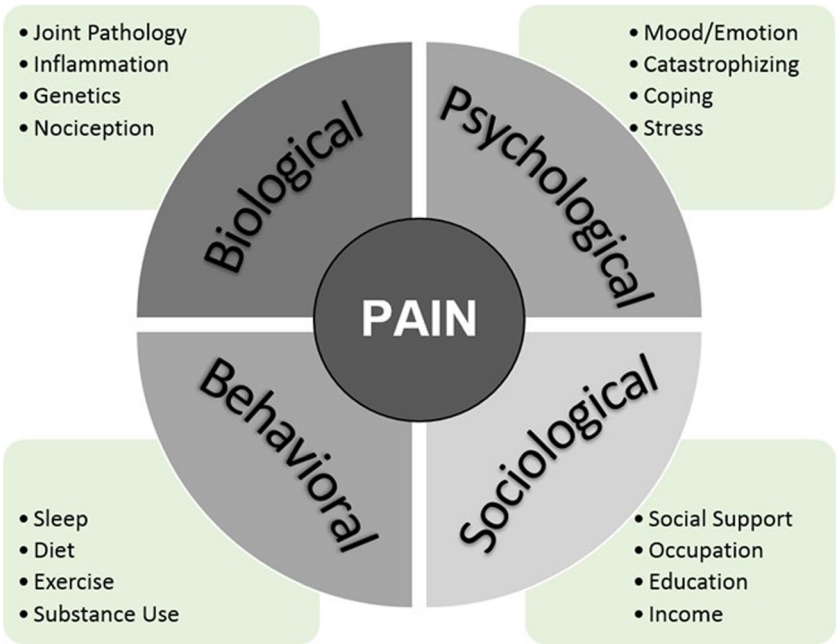

Fig. 1 Biopsychosocial model of pain. Illustration of the biological, psychological, social, and behavioral factors that independently influence and dynamically interact with one another to impact the pain experience

recent models [9] conceptualize this construct as a process through which dispositional resources (e.g., trait positive affect, social ties) and mechanisms (e.g., state positive affect, positive social interactions) enhance adaptive pain coping, thereby resulting in recovery, sustainability, and growth—outcomes which are central to the characterization of a resilient system. It is important to note that resilience is not simply the opposite of vulnerability, nor does it mean the absence of pathology. In fact, people can have varying levels of both, and effects may be contingent upon the type or duration of stressor present.

In essence, individuals with greater levels of resilience have the ability to quickly rebound from physiological or emotional stress, persist in meaningful activities despite ongoing hardship, and experience personal growth as a result of the adversity [9]. While factors such as catastrophizing and depression may increase one's risk for pain vulnerability, psychosocial facets including optimism and self-efficacy (among others) may promote greater pain-related resilience [10, 9]. However, this is not simply relegated to psychosocial variables, as numerous genetic, environmental, neurochemical, and behavioral factors have been found to confer resilience.

Mechanisms Underlying Osteoarthritis Pain

In the following sections, we briefly review the empirical literature by evaluating contributory mechanisms that underlie osteoarthritis pain and functioning. Using the framework of the biopsychosocial model, factors associated with vulnerability and increased risk for OA will be reviewed, as well as protective resources that attenuate risk and promote resilience in osteoarthritic conditions. While this review is not intended to be exhaustive, we will highlight the most salient factors with a specific focus directed toward recent discoveries implicated in the pathogenesis of and protection against negative pain outcomes in OA.

Biological Mechanisms

Biomechanical changes are a prime characteristic of OA development, including compromised hyaline articular cartilage in the joints, joint line spacing, subchondral bone, development of osteophytes, cyst formation, corresponding damage to ligaments, and diminished joint/muscle strength [11]. Although it is generally conceived that the degree of joint and tissue damage should be proportional to the amount of pain and disability arising from OA, this is not always the case. In fact, other biological and neurobiological factors, beyond biomechanical and physiological changes, can confer risk of OA pain development [11]. For instance, peripheral mechanisms (e.g., sensitized nociceptors) can contribute to chronic pain development [12, 13]. Such peripheral sensitization can lead to hyperalgesia (heightened sensitivity/reactivity to painful stimuli and/or reduced pain threshold) and/or allodynia (pain in response to non-noxious stimuli) [14]. Further, abnormalities in central nervous system mechanisms such as central sensitization (hyperexcitability of central nervous system neurons) and decreased descending pain inhibition are thought to be associated with chronic pain risk, including OA pain development [13].

Like many other conditions, OA has a genetic basis, accounting for approximately 50% of hand and hip OA cases, but less so for knee OA [15]. Over the past several years, genome-wide association studies (GWAS) have identified numerous genes and their associated single-nucleotide polymorphisms (SNPs) as being linked to OA (as of 2013, one review identified 28 SNPs) [16, 17]. While a complete synopsis of these SNPs is beyond the scope of this review, it is suggested that the clinical course and progression of OA is influenced by genetic factors and their interactions with multiple environmental determinants.

Growing evidence also supports the relationship between leukocyte telomere length (LTL) and OA. Considered to be a marker of cellular aging, telomeres comprise regions of repetitive DNA that protect the ends of chromosomes from degradation and end-to-end fusion with neighboring chromosomes [18]. LTL is negatively associated with numerous health outcomes including mortality, chronic disease, and psychosocial stress [19]. In the context of OA, shorter telomere length was found in knee osteoarthritis patients with high levels of stress and pain [20], with a later study by the same authors largely confirming these results by observing shorter telomeres among individuals with the greatest burden of chronic knee pain [21]. Interestingly, a recent investigation demonstrated an association between angiogenic cytokines (i.e., hepatic growth factor, vascular endothelial growth factor, granulocyte-colony stimulating factor) and telomere length in knee OA, suggesting a potential role for these factors in cellular aging and OA pathogenesis [22].

The involvement of inflammation in OA is also well recognized, an effect partially attributable to systemic effects associated with aging and adiposity [23]. The strongest support for this relationship is derived from studies demonstrating a link between inflammation and OA pain/function [24], with measures of inflammation (e.g., interleukin-6, tumor necrosis factor alpha, C-reactive protein) independently predicting worsening knee pain [25] and emergence of radiographic knee OA over time [26]. Evidence also points to an association between joint inflammation and heightened experimental pain sensitivity in knee OA [4]. As mentioned, obesity appears to be a large contributing factor to OA prevalence and progression [26, 27]. While increased weight can place greater pressure on the joints, especially on the knee and hip, it has also been shown that metabolic factors, such as central adiposity,

contribute to a low-grade inflammation that directly accelerates cartilage degradation [28••]. For individuals undergoing weight loss, improvements in inflammatory cytokines, as well as pain and function, have been observed [29].

A linkage between omega-3 and omega-6 polyunsaturated fatty acid (PUFA) levels and inflammation exists, since eicosanoids (which regulate inflammation) are derived from these fatty acids. Specifically, omega-3 plays an anti-inflammatory role, while omega-6 has pro-inflammatory properties [30]. Evidence suggests that in those individuals with or at risk for developing knee OA, omega-3 fatty acid may serve a protective role, at least in terms of preventing patellofemoral cartilage damage, while omega-6 fatty acids may have the opposite effect on synovial membranes [30].

Reduced vitamin D is associated with enhanced sensitivity to pain, including greater pain severity and disability in knee OA [31]. Vitamin D levels can also interact with psychosocial and behavioral factors such as age, ethnicity, and weight. Recent evidence suggests that individuals with knee OA who had normal levels of vitamin D reported less pain severity than those who were vitamin D deficient. In terms of functional capacity, obese individuals with adequate vitamin D were able to perform better on a task of lower extremity functioning, than obese individuals with inadequate levels of vitamin D [32].

Additionally, sex differences in pain are present such that women tend to experience more pain and have higher rates of chronic pain, including OA-related pain [33•, 34]. Moreover, experimental evidence suggests that sex differences in central sensitization may be a risk factor for knee OA, with women demonstrating more enhanced central sensitization compared to men [35]. Although psychosocial and cultural factors may play a role in these differences, sex is likely to contribute in some capacity.

Psychological Mechanisms

Negative Factors

Various psychological factors have been implicated in the development and maintenance of chronic pain conditions such as OA. Such factors likely contribute to the variability in pain severity found among OA patients, especially when divergence is noted between radiographic changes and pain report [36]. For example, negative affect (e.g., general distress or depression), anxiety, and maladaptive coping (e.g., catastrophizing) often result from the experience of persistent or chronic pain, although these psychological variables can also serve as risk factors leading to the development of chronic pain [37••]. In addition to general psychological distress and pain facilitation, some symptoms of depression and anxiety (e.g., muscle tension) may even be directly related to physical findings in OA (e.g., joint stiffness/muscle tension) [36], as well as greater utilization of pain medication after total knee arthroplasty [38]. Factors such as helplessness, stress, and limited self-efficacy can influence OA development and progression [39]. Recent evidence suggests that roughly 20% of individuals with OA report symptoms of depression and/or anxiety [40•], and higher levels of anxiety have been related to poorer physical health in those with knee OA [41]. Although it is currently unclear if rates of mood disturbance are higher than those of the general population, the relationship between negative affect (including depression) and stress/anxiety with pain makes these psychological factors important to consider for OA risk [40•].

Perhaps one of the most widely investigated pain-related psychological factors is catastrophizing—a cognitive–emotional process associated with rumination, magnification, and helplessness related to the pain experience. Individuals scoring high on catastrophizing have been found at risk for heightened pain severity and interference, disability, low functional performance, and negative affect [37••]. A similar pattern also emerges for surgical outcomes, including arthroplasty, as pre-operative catastrophizing is a unique predictor of post-operative pain and physical functioning in OA [42–45]. Pain-related fear is also common among individuals with OA [46], and refers to excessive worry regarding pain-associated activity or (re)injury (i.e., kinesiophobia). Often, this generates a maladaptive cycle whereby negative pain cognitions lead to activity avoidance, thus promoting physical deconditioning and maintenance of pain. Whereas this response may be adaptive after acute pain onset (i.e., facilitation of recovery), it can lead to increased OA pain severity, psychological disability, and functional impairment over time [41, 44, 47, 48], effects which seem to be independent of radiographic severity [47]. While catastrophizing and fear processes can be significant impediments to pain management, cognitive–behavioral and fear exposure therapies can optimize treatment gains.

Though OA risk tends to increase with age, childhood factors may impact the onset of OA later in life. It is known that childhood traumas (e.g., abuse, neglect/maltreatment) often contribute to worse health and pain outcomes in adulthood. Research examining the role of psychosocial stressors on OA development suggests that individuals with a childhood history of two or more adverse psychosocial events are at greater risk of developing OA, which can occur in a dose–response manner [49].

Positive Factors

In contrast to maladaptive cognitive and affective processes, positive emotions have long been studied in terms of their health-promoting effects, with positive affect (PA) being an important mediator of pain adaptability (for reviews, see [50,

51•]). PA is found to be protective against weekly increases in pain and negative affect (NA) during exacerbations of pain and stress [52], and appears to be a better predictor of daily OA pain than NA [53]. There is also evidence for conferred benefits to activity promotion, with higher daily step count observed among knee OA patients with higher PA, relative to individuals with low PA and depressive symptoms [54]. Similar to PA, optimism (generalized expectancy toward positive future outcomes) is also known to play a role in pain resilience, effects which are posited to occur from the interplay between positive appraisal and adaptive coping [55]. In OA patients, higher levels of optimism are associated with decreased clinical pain and higher life satisfaction [56], in addition to lower levels of pain catastrophizing and temporal summation (pain facilitatory measure) [57]. Moreover, in a sample of individuals with knee OA, decreased experimental pain sensitivity was observed among those who had high levels of optimism and low negative affect [58]. Comparable findings in surgical outcomes have also been noted; baseline optimism was a significant predictor of less acute pain and anxiety after total knee and hip arthroplasty [59], as well as lower pain severity (but not pain interference) 1 year following knee arthroscopy [60].

Additionally, there is considerable support for greater self-efficacy in the promotion of health and improved pain outcomes [61], although this may be reflected more so for disability than pain [62]. Self-efficacy is broadly defined as the perceived confidence in one's abilities to produce desired outcomes [63], and is predictive of physical performance [64], emotional/physical health, self-reported physical function [44], and lower disability [64, 65]. Further, self-efficacy is known to be a potent mediator between resilience and physical functioning in knee OA [66], while a similar body of literature has linked self-efficacy to post-surgical functional ability [67] and pain-related recovery [68] after knee and hip replacement, respectively. However, results have also been inconclusive in this area as a recent review concluded that post-operative self-efficacy was a more robust predictor of functional outcomes, relative to pre-surgical values [69].

Pain acceptance and mindfulness have also emerged as significant contributors to pain resilience. While pain acceptance reflects a sustainability of life activities/goals and reduced efforts to control or avoid pain [70], mindfulness denotes increased nonjudgmental awareness and self-regulated attention toward one's immediate experience [71]. Highlighting their influence, one study found that greater levels of pain acceptance in women with OA offset the relationship between negative affect and higher weekly pain severity [72]. Additionally, others have demonstrated that mindfulness was associated with adaptive psychosocial functioning and buffered the relationship between pain and perceived stress in patients with knee OA [73].

Behavioral Mechanisms

Physical activity plays an important role in disease prevention, along with symptom management of OA pain [74]. Whereas OA can result in muscle weakness or atrophy, exercise is able to increase muscle and joint health, in addition to reducing body weight [75]. Sedentary behavior is associated with poorer functional performance [76•], while acute exercise has analgesic effects on experimental pain in knee OA patients [77] (although outcomes may be contingent upon differences in endogenous pain modulation) [78]. Intensity of exercise may also play a contributory role in OA progression as a recent study found that low and high levels of physical activity were associated with greater cartilage degeneration than engaging in moderate-intensity exercise [79]. Although the type of physical activity may differentially impact OA-related outcomes [80], regular exercise is generally considered an effective tool in reducing pain and disability in patients.

As may be expected, OA pain is related to sleep disturbance and there is evidence of central sensitization in patients with comorbid insomnia [81]. Although this relationship is most significant in patients with affective disturbance and decreased social support, it is also seen in OA patients lacking psychosocial comorbidities [82–84]. Depression has been found to mediate the relationship between OA pain/disability and sleep disturbance in older adults [82], while high catastrophizing combined with low sleep efficiency worsens central pain sensitivity [81]. Using behavioral approaches for sleep improvement (i.e., CBT) is promising for both acute and long-term pain reductions in OA patients [85–87].

Sociological Mechanisms

Research suggests that social and interpersonal processes such as low socioeconomic status (SES; including education, income, and occupation) and social support are independently associated with risk for OA, as well as pain outcomes [88]. For example, certain occupational demands can lead to increased potential for developing OA due to biomechanical force on the joints arising from strenuous or repetitive physical motions (e.g., lifting, kneeling, bending). Supporting this, some investigators found that physically demanding occupational tasks were associated with higher incidence of hip and knee OA; however, effects were more robust for symptomatic than radiographic changes [89]. A similar pattern of findings was observed in a recent large-scale study, whereby high occupational workload was a significant predictor of hip and knee OA, with risks increasing in relation to the number of years engaged in the occupation [90]. In addition, situational factors such as footwear, type of flooring (e.g., carpet vs. tile), and presence of stairs in an individual's everyday work or home environment can impact the development of knee OA possibly due to mechanical loading on the knee [91].

Socioeconomic disadvantage is also a causative factor for unfavorable pain outcomes. In the National Health and Nutrition Examination Survey (NHANES), lower educational attainment was associated with symptomatic knee OA and self-reported arthritis (but not radiographic OA), even after adjustment for relevant risk factors [92]. Studies from the Johnston County Osteoarthritis Project have reported similar findings, both at the individual and community level. These investigators found that low educational achievement and community poverty (neighborhood household poverty rates >25%) were independent predictors of radiographic and symptomatic knee OA [93], while a later investigation by the same authors demonstrated that occupation and education were associated with self-reported knee pain and physical function, with higher rates of knee pain observed among those living in impoverished areas [94]. Comparable findings have also been noted in OA patients with hip pain and disability [95]. More recently, studies have observed greater incidence rates of hip and knee OA among individuals who were older (≥75 years), obese, had a previous hip/knee injury, and with an annual income less than $15,000 [96, 97]. While these studies support the role of socioeconomic measures in OA-related pain and disability, additional factors, such as obesity, may partially account for these findings [98•].

Social support is one of the most widely explored determinants of health, with evidence supporting the beneficial role that social relationships have on positive emotions, effective pain coping efforts, and reduced disability. Illustrating this, higher levels of perceived social support have been found to moderate the relationship between pain and depression [56], and a positive affiliation with one's partner is known to attenuate pain disability and strengthen pain coping responses during high-pain days in women with OA [99]. Further, higher emotional and instrumental (tangible assistance from others) support as well as social companionship were related to greater health-related quality of life among individuals with hip and knee OA [100]. Emerging evidence indicates that higher spousal empathy and perceived autonomy support for being active are associated with increased physical activity in patients with knee OA [101], whereas positive interpersonal functioning in OA buffers the relationship between pain intensity and negative affect [102]. Although extant research highlights the positive role that affiliative processes have on health outcomes, it is important to note that social relationships are not always supportive and may in fact have detrimental effects on OA. For example, one study found that social strain was related to lower social support and higher levels of pain in individuals with knee OA [103], while another investigation observed an inverse relationship between negative social support and postsurgical improvements in pain and positive affect in patients with knee OA [104]. Taken together, these studies suggest that interpersonal relationships do not guarantee favorable effects on pain. Instead, the quality of the social milieu can yield widely differential effects on OA outcomes.

Conclusions

OA is a multifactorial condition consisting of numerous biopsychosocial factors that potentiate or ameliorate the risk for pain and disability. By and large, much of the extant literature has been problem-focused in nature, with an emphasis on vulnerability and risk factors associated with negative pain outcomes. However, this clearly presents a one-sided view of health as evidence also supports the important contributions of resilience and positive affect on pain. Namely, there is increased realization that individuals with chronic pain, including OA, have the capacity to adapt and manage their pain while simultaneously limiting their disability.

In light of this, we propose that research initiatives be directed toward the factors that mollify the adverse effects of pain. Recognition of the multiple, interactive processes that serve to facilitate or attenuate pain-related outcomes in OA will likely provide a more comprehensive picture of patient functioning that could ultimately inform clinical practice. From a treatment perspective, this will require moving beyond a traditional biomedical approach and instead target the numerous facets (both positive and negative) that comprise the pain experience (i.e., multidisciplinary treatment). Overall, it will be imperative for healthcare professionals to approach OA patient care with this in mind and encourage communication across all pain management specialties (e.g., physicians, psychologists, physiotherapists, social workers).

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Compliance with Ethical Standards

Conflict of Interest Dr. Bartley reports grants from National Institutes of Health/ National Institute on Aging, during the conduct of the study.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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