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MEDICINE

Chronic Primary Pain of the Spine: an Integrative Perspective Part 1

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Abstract

The aim of this study is to conduct a narrative review of the literature emphasizing current models of non-specific low back and neck pain with an emphasis on chronic and disabling pain. We include its risk factors, etiology, pathophysiology, and differential diagnosis. Emphasis is also placed on variables of chronification and the persistence of this type of pain. Our secondary aim was to provide foundational knowledge before advancing the discussion to a proposal of evidence-based management strategies for patients suffering from chronic primary spine pain in a subsequent follow-up article. A review of the English medical literature was performed using search terms "chronic low back pain" OR "chronic neck pain" AND "primary," "differential diagnosis," "pathophysiology," "functional imaging" and "risk factors." Additional searches were made using Google Scholar and PubMed search engines through January 17, 2020. A total of 112 articles were used. Acute and chronic spine pain differ significantly in risk factors, pathophysiology, prevalence, and differential diagnosis. Chronic spinal pain is multifactorial in nature, and that proposed causes of chronicity and pain-related disability span the entire spectrum of the biopsychosocial domain. Chronic low back and neck pain poses a significant global threat of disabling and burdensome quality of life. Because pain is a complex multifactorial integrative experience, the scientific literature reports an abundance of multidimensional risk factors associated with the persistence of pain beyond normal healing times. Understanding the nature of chronic primary spinal pain will provide clinicians with necessary and valuable insights for patient care along the complex and variable spectrum of the biopsychosocial approach.

Keywords Chronic pain · Spine · Low back pain · Neck pain · Risk factors · Pathophysiology

Abbreviations

DALYs	disability-adjusted life years
IASP	International Association for the Study of Pain
ICD-11	International Classification of Disease 11th Edition
QST	quantitative sensory testing
cLBP	chronic low back pain
PTSD	post-traumatic stress disorder
PHQ-9	patient health questionnaire-9
SES	socioeconomic status
BMI	body mass index
HPA	hypothalamic-pituitary-adrenal
PET	positron emission tomography
MRI	magnetic resonance imaging
TSPO	translocator protein 18 kDa
LTP	long-term potentiation
LTD	long-term depression
DMN	default mode network
mPFC	medial prefrontal cortex
PAG-RVM	periaqueductal gray-rostral ventromedial medulla
dACC	dorsal anterior cingulate cortex
NAcc	nucleus accumbens

Introduction

Spinal pain is the single greatest cause of disability worldwide, responsible for 87 million disability-adjusted life years (DALYs) [1, 2]. DALYs associated with chronic back and neck pain have increased by 61.6% between 1990 and 2016 with a precipitous increase of 19.6% between 2006 and 2016 [3]. Despite increasing healthcare expenditures and medical costs dedicated to the care of spine-related pain, no

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corresponding decreases in prevalence have been observed. In 2011, it was estimated globally that one in five adults suffer from chronic pain, while that number increased to one in three adults by the year 2018 [4, 5]. Clearly, a new and integrative approach to managing these conditions is required. The purpose of this narrative review is twofold. Part 1 will explore current models of spine pain including epidemiology, risk factors, and pathophysiology of pain chronification; part 2 will discuss contemporary management, emphasizing methods by which clinicians may care for patients with primary spinal pain using an integrative, behavioral, and biopsychosocial model of care.

Review

In 1977, George Engel, MD introduced the medical community to the biopsychosocial model as a new perspective for understanding patient conditions in which the biomedical, or pathoanatomical, approach failed to fully appreciate and appropriately guide treatment [6]. This model proposed that psychological, social, and environmental factors influence symptomatology and could overcome pain and avoid prolonged disability.

The following narrative review will provide and expand on the current models regarding chronic spine pain as a biopsychosocial construct. The design of this paper is to first discriminate differential diagnoses of both acute and chronic spine pain before focusing on the nature of chronic back and neck pain, collectively, particularly chronic primary spine pain. The discussion first evaluates established risk factors associated with chronic pain conditions and pathophysiological processes. A neurophysiological mechanism for the chronification and persistence of pain is provided from research focused on central sensitization, neuroinflammation, psychoneuroimmunology, and further supported by more recently emerging studies of human brain mapping utilizing functional magnetic resonance imaging of the brain and cortical/subcortical networks associated with nociception, pain and emotional learning in clinical pain models.

Differential Diagnosis

Acute Spine Pain

In order to fully understand chronic spine pain, a brief introduction to the origins of new-onset spine-related pain must be addressed. The differential diagnosis of acute spine pain includes a variety of conditions that can be potentially life-threatening, physically disabling, or cause severe emotional and social impairment with reduced quality of life. In order to effectively triage patients reporting with low back and neck pain, it is recommended that the cause of their symptoms be classified into one of four diagnostic categories [7, 8]:

- Non-specific pain (~ 90% of spine pain) [7, 9, 10]
- Disorders of the nerve root or spinal cord (radiculopathy, myelopathy, stenosis with neurogenic claudication, cauda equina syndrome)
- Spinal pathology (axial spondyloarthropathy, compression fracture, metastatic or primary malignancy, spondylodiscitis)
- Visceral diseases (pancreatitis, nephrolithiasis, pelvic inflammatory disease)

The latter three diagnostic categories are considered subtypes of *specific* spine pain, for which an anatomical pain generator can be identified with appropriate clinical exam, laboratory testing, and/or diagnostic imaging. Of all patients reporting to primary care with complaints of low back or neck pain, Deyo and Weinstein report that roughly 4% will be attributed to compression fracture, 3% to spinal stenosis, 2% will have visceral disease, and less than 1% will be suffering from cancerous or infectious diseases of the spine [11]. Street, White, and Vandal were the first to determine spinal pathology-specific prevalence rates in secondary and tertiary care levels, noting a sequentially higher percentage at each level of care; the combined prevalence of serious spinal pathology (fracture, cauda equina compression, malignancy, infection) in the tertiary care (public health) setting was as high as 14.8% [12]. It is recommended that extensive testing to identify a pathoanatomical cause for a patient's pain complaint be reserved for instances when there is suspicion of a specific pain diagnosis.

Chronic Spine Pain

In order to address the burden of chronic spine pain around the globe, the IASP recently developed a Task Force for the Classification of Chronic Pain to more accurately define and classify various forms of chronic pain disorders to best allocate treatment interventions based on subtype. As a proposal for the 11th edition of the International Classification of Disease (ICD-11), Treede and colleagues organized various forms of chronic pain into the following categories [13]:

- Chronic primary pain
- Chronic cancer pain
- Chronic postsurgical/posttraumatic ain
- Chronic neuropathic pain
- Chronic headache/orofacial pain
- Chronic visceral pain
- Chronic musculoskeletal pain

While an acute bout of low back and neck pain is considered a symptom, persistence for an extended duration of time without a known cause qualifies this as a disease of its own—chronic pain. Non-specific back and neck pain, which are diagnoses of exclusion, should be considered sufficient diagnoses to begin guideline-mediated care; any further diagnostic exploration to identify the pain source (intervertebral disc, facet joint, sacroiliac joint, myofascial structures, etc.), although commonplace in many practices, is not supported by reliability studies and is unlikely to change the course of first- or second-line treatment [10, 14]. Quantitative sensory testing (QST) studies have displayed a decrease of pain-pressure thresholds in body regions distant from the low back (scapula) in patients suffering from chronic low back pain (cLBP), indicating a failure of descending pain inhibition, rather than abnormal increases of nociceptive summation in dorsal horn neurons exclusive to dermatomes correspondent with the lower back [15]. These findings further support the notion that nonspecific pain is unlikely to be caused by a specific pain generator anywhere in the anatomy of the spine or local tissues, but perhaps is a failure of top-down antinociceptive mechanisms within the central nervous system in response to altered homeostatic and behavioral priorities [16]. This notion expresses the core principles of the biopsychosocial model and will provide the spine clinician with a more appropriate perspective when evaluating and treating the patients they serve.

Chronic Primary Pain

Chronic primary pain is defined as "pain in one or more anatomic regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or significant functional disability (interference with activities of daily life and participation in social roles) and that cannot be better explained by another chronic pain condition" [13]. Chronic, non-specific low back and neck pain fall within the diagnostic domain of "chronic primary pain" and should not be confused with "chronic musculoskeletal pain." Assigning the diagnosis of "chronic musculoskeletal pain" implies that the patient's pain can be attributed to an identifiable lesion or complicating condition (persistent infection, autoimmune or inflammatory disease, metabolic disorders, or structural symptomatic changes, e.g., osteoarthritis).

Because non-specific pain significantly outnumbers other causes of spine pain, the primary focus of this review will target chronic, non-specific low back pain and neck pain, or "chronic primary pain" according to proposed ICD-11 terminology. The following sections will examine the risk factors and pathophysiological mechanisms known to have either a causal or correlative relationship with patients suffering from chronic primary spinal pain.

Risk Factors Associated with Chronic Primary Spine Pain

Genetic Predisposition

Pain sensitivity is partially influenced by genetic factors. Genetic polymorphisms in genes involving both the serotonergic and adrenergic neurotransmitter pathways have been linked to people at higher risk of suffering from chronic pain conditions [17]. These pathways further lend to the previous mention of neuroinflammation and HPA axis dysfunction as a neurobiological explanation for the conversion from acute to chronic spine pain. In the adrenergic neurotransmitter pathway, expression of the catechol O-methyltransferase (*COMT*) gene lends to the breakdown of epinephrine, norepinephrine, and dopamine—key elements in the normal functioning of the autonomic nervous system. Polymorphisms in this gene are the most common genetic abnormality seen in chronic musculoskeletal pain disorders [18, 19]. Additionally, beta-2 adrenergic receptor gene (*ARDRB2*) polymorphisms are associated with an increased risk of acquiring fibromyalgia and other chronic pain conditions [20]. In the serotonergic neurotransmitter pathway, it is most common to identify polymorphisms in the 5-hydroxytryptamine receptor 2A (*HTR2A*) and 5HT transporter (*SLC6A4*) genes. Disruption of both pathways leads to many of the risk factors and pathophysiological mechanisms associated with the perpetuation and persistence of spinal pain—autonomic dysregulation, altered pain processing, sleep disruption, and mood disorders. Caspi and colleagues found that persons displaying one or two copies of the short allele for said genes exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events compared to individuals homozygous for the long allele [21].

Battié et al. used twin studies to support claims of the heritability of intervertebral disc desiccation as high as 46% through genetic polymorphisms [22]. Kraatari et al. recently discovered a genetic polymorphism in two alleles (MAML1 and HSPG2) associated with cartilage health in the vertebral endplate, promoting Modic changes in affected individuals—a greater predictor of low back pain than disc degeneration alone [23]. Other researchers have concluded similar percentages of heritability, while the exact mechanisms are still debatable [24, 25]. El-Metwally and colleagues argue that genetic factors play a minor role, at most, in the development of non-specific pain in twin children, and that environmental factors are a much more important prognosticator [26]. An enhanced understanding of risk factors for chronic primary pain will emphasize the minimal involvement necessary for physical factors and the overwhelming contribution of psychosocial and behavioral elements that chronify pain symptoms over time.

Psychological Risk Factors

Numerous studies have demonstrated the effects of poor psychological health on physiological markers of stress and inflammation in humans with chronic spinal pain [27–29]. Emotional distress and comorbid mental health disorders show a strong correlation with other risk factors for persistent pain including physical disability, work-related disability, greater health care expenditure, mortality, and suicidal tendencies [30–34]. In contrast, it appears that populations with chronic pain who identify as being more "spiritual" regardless of any particular religious affiliation showed small but noticeable associations with greater psychological well-being and decreases in pain and physical dysfunction [35]. This response may have also been the expression of a social support interaction, known to reduce depression in chronic stroke victims [36]. The most common psychological risk factors known to contribute to chronic spine pain development are summarized below [37–40].

- Depression (present in up to 40–60% of cLBP patients)
- Anxiety
- Fear-avoidant behaviors
- Passive coping
- Post-traumatic stress disorder (75% of PTSD patients suffer chronic pain)
- Childhood trauma and adversity
- Unsupportive social and interpersonal relationships
- Catastrophizing thoughts
- Low self-efficacy
- Maladaptive beliefs
- Addiction and substance use disorders

The Flag System

These risk factors, most often termed yellow flags, can be categorized further to delineate those requiring specialized clinical care from less concerning contributors [41]. Orange flags are reserved for diagnosable or previously diagnosed psychiatric disorders such as clinical depression or personality disorder. Numerous studies have found depression to be the strongest predictor of an acute episode of low back pain and persisting spine pain symptoms, while others have identified strong associations between both chronic pain symptoms in depression patients, and depressive-like symptoms in chronic pain patients [39, 42–45]. Clinical depression and similar mental health disorders are potentially life-threatening conditions and should be co-managed by a behavioral health specialist. The PHQ-9 Questionnaire is a reliable outcome measure for clinical depression and is recommended as a screening tool for patients suspected of suffering from moderate-to-severe psychiatric symptoms [46, 47]. Yellow flags include a patient's pain-related beliefs, emotional responses, or coping strategies and are considered manageable by the primary care practitioner. This will be discussed further in the companion article (part 2) of this review. Blue flags encompass the perceptual influences of a person's workplace, considering the emotional stresses of perceived injustice and/or helplessness, for example. White flags, introduced by Vlaeyen et al. [7], are regarded as potentially iatrogenic expectancies secondary to the messages clinicians deliver to patients (e.g., take it easy, stay in bed, do not flex your spine, you will have pain for the rest of your life). Lastly, black flags consider social and cultural influences on pain and will be expanded upon in the next section (Table 1).

Pain-Related Behavior

To assess patient psychology with a different perspective, Meints & Edwards mention evaluating psychological risk factors as either general or pain-specific psychosocial constructs [48]. General psychosocial constructs (Table 2) can be identified in all people, with or without the presence of pain, and are considered vulnerability factors that pre-determine the risk of developing chronic pain based on their overall health-related behavior. Pain-specific psychosocial constructs (Table 3) are unique to individuals experiencing pain and influence how they integrate and respond to their current pain experience.

Taking a closer look at how these psychological risk factors influence a person's pain-related behavior might provide the necessary information to effectively intervene using a cognitive-behavioral method of care. The introduction of Vlaeyen and Linton's Fear Avoidance Model of Pain has served as a guiding light for behavioral health and spine care clinicians [49]. This model illustrates the cyclical nature of pain chronification as described in the following order:

1. A painful experience occurs ("I hurt")
2. Catastrophizing thoughts and distorted beliefs surface ("I am damaged and in danger")
3. Pain-related fears manifest ("It is not safe to move right now")
4. Avoidant and hypervigilant activity follows ("I must rest and monitor my damaged self")
5. Disuse, depression, and disability ensue ("Because of this pain, I can no longer...")
6. Pain sensitivity increases and the cycle perpetuates

In her book, *Psychological Treatment for Patients with Chronic Pain,* Beth Darnall mentions the cyclical nature of poor pacing strategies commonly observed in anxiety-ridden patients [50]. Patients with underlying anxiety and hypervigilant pain-related behaviors may show pain behaviors which cause them to fluctuate between excessive levels of activity, exacerbation of their pain, followed by a drastic reduction in

Table 1 The Flag System, adapted from Nicholas et al & Vlaeyen et al [7, 41]

Flag	Nature	Example
Orange	Psychiatric symptoms	Clinical depression/anxiety/PTSD, personality disorder
Yellow	Beliefs, appraisals, judgments	Unhelpful beliefs about pain; indication of injury as uncontrollable or likely to worsen; expectations of poor treatment outcome, delayed return to work
	Emotional responses	Distress not meeting criteria for diagnosis of mental disorders—worry, fear, anxiety
	Pain behavior (coping strategies)	Avoidance of activities due to expectations of pain and possible reinjury; over-reliance on passive care
Blue	Perceptions about the relationship between work and health	Belief that work is too onerous and likely to cause further injuryBelief that workplace supervisor and colleagues are unsupportive
White	Iatrogenic expectancies secondary to clinician advice	Recommendations for bed rest or time off from work
		Messages of unsafe postures or physical exposures (i.e., spinal flexion)
		Negative or catastrophic prognosis
Black	System or contextual obstacles	Legislation restricting options for return to workConflict with insurance staff over injury claimOverly solicitous family and health care providersHeavy work, with little opportunity to modify duties

activity until adequate recovery occurs, and a cognitive reinforcement of their anxiety about future tasks. To add, multiple studies have shown that depression, anxiety, and pessimistic thought patterns strongly correlated with susceptibility to nocebo effects following medical treatments [51, 52]. In order to escape this cycle of pain chronification, the primary drivers—fear-avoidance, harmful beliefs, coping strategies—must be removed from the picture and an active confrontational approach must be implemented. Pacing and graded exposure to feared movement (Pavlovian extinction) will be an important concept to consider when designing a rehabilitative exercise program for patients with chronic pain and underlying depression- or anxiety-driven pain behaviors.

Social Determinants of Health

Socioeconomic Status

While current research places a heavy emphasis on understanding the biological and psychological aspects of pain, more frequently overlooked drivers of poor health, both modifiable and nonmodifiable, include the socioeconomic status (SES) and cultural diversities within demographic subgroups. Population stratification based on income, education level, occupation, gender, nationality, ethnicity, and sexual orientation affects a person's ability to access quality care, how they are perceived by their healthcare providers, how their families

Table 2 General Psychosocial Constructs, adapted from Meints & Edwards [48]

Affect	Trauma	Social/interpersonal	Sex-related	Race-related
Anxiety	TBI (physical)	Social environment	Endogenous opioid system	Central pain-inhibitory mechanisms
Depression	PTSD (psychological)	Social interactions	Hormones	SNS response
Negative affect		Social support	Affective distress	Affective distress
Optimism		Therapeutic relationships	Catastrophizing	Catastrophizing
Positive affect			Coping	Coping
			Gender roles	Appraisals
				Expectations
				Socioeconomic strain

TBI, traumatic brain injury; *PTSD*, post-traumatic stress disorder; *SNS,* sympathetic nervous system

Table 3 Pain-specific psychosocial constructs, adapted from Meints & Edwards [48]

Altered pain-related CNS pathways
Catastrophizing
Coping
Expectations
Self-efficacy

CNS, central nervous system

discuss pain and disability, and their vulnerability to health conditions. The most socially disadvantaged and least educated people fall victim to the greatest burden of disease, pain, and pain-related disability leading to earlier retirement [53, 54]. Moreover, socioeconomic inequality gives rise to "double suffering," in that lower classes experience more long-term illnesses and disproportionately experience illnesses with greater intensity.

People of lower SES are faced with greater environmental challenges and fewer resources to achieve optimal health. Lower healthcare access, substandard food quality, undesirable employment opportunities, and persistent exposure to a range of threatening conditions all put this population at greater risk for developing chronic pain disorders [55, 56]. To be seen by a healthcare provider, a patient must typically meet all the following criteria:

- Location—living within reasonable proximity of a healthcare facility
- Transportation—owning a reliable vehicle or mode of transport, having access to public transit, arriving at scheduled appointments on time
- Finances—paying for care, adhering to a management plan, prioritizing preventative check-ups and/or early intervention, missing work to receive care

Living in social disadvantage also creates challenges in regard to nutritional health. Poor food quality may play a role in the rise of obesity prevalence in low SES demographics [57]. High body mass index (BMI) is a risk factor for chronic pain (twofold), just as chronic pain is a risk factor for weight gain [58, 59]. While no single mechanistic cause can account for this complex relationship, it is critical that the clinician be aware of the bidirectional influences of obesity and pain.

Employment opportunities tend to favor manual labor jobs with lower pay rates and directed toward the lower end of the socioeconomic gradient. Strenuous physical activity with excessive bending, lifting, and twisting increases risk for acute low back pain episodes; the same can be said about jobs with monotonous tasks and repetitive activity, predisposing to persistent microtrauma [60]. Coupling this predisposition with the hardships of missing work to pay for healthcare, lends to an experience of increased hardship and negative prognosis. The validity of the "injury model of back pain," however, is being called into question as an overwhelming majority of patients report to clinic without mention of a mechanical, traumatic event initiating their back or neck pain, and recent systematic reviews have failed to identify a causal relationship between spinal postures or physical exposures and new-onset spine pain [7, 61].

The observed risk factors seen in low-SES populations cannot be fully explained by dissociating non-manual and manual labor demands, nor low healthcare access alone, as even those in higher-ranking status with relatively low-labor jobs fall victim to these same non-communicable pain conditions [62]. Singh-Manoux, Adler, and Marmot brought attention to important differences between subjective and objective SES and their associations with health. Their study demonstrated that a person's "cognitive averaging" of their own social measures is what generates their subjective ranking of SES and was found to be a strong predictor of health outcomes [63]. In other words, perceived socioeconomic status might be equally, if not more, prognostic than absolute SES in predicting persistent or disabling pain. This helps to explain why the detrimental effects of the socioeconomic gradient are more prevalent in regions with a broader range of income inequality. This allows for a greater perception of poverty in lower-class citizens—referred to as "poverty amid plenty" [64, 65]. Sapolsky commented on these observations with the following:

"Given food, shelter, and safety sufficient to sustain health, if everyone is poor, then no one is. In modern societies, it is never the case that everyone is equally (non)poor. This paves the way for a key point about the gradient, namely that poor health is not so much the outcome of being poor, but of feeling poor, that is, feeling poorer than others. Therefore, poverty, rather than being an absolute measure, is a subjective assessment that is mired in invidiousness" [66].

Poverty amid plenty is a matter of perception and says more about situational mental health than it does about environmental conditions. To fully appreciate the self-perpetuating cycle of the biopsychosocial model of pain, one must consider all of the ways in which SES (whether subjective or objective) can elicit situational distress, influence behaviors and lifestyle habits that amplify a person's pain, and advance the individual down a spiraling path of disability, worsening depression, and lower perceived SES. Sapolsky goes on to explain, "as one descends the SES slope, the incidence of smoking, drinking to excess, obesity, sedentary lifestyles, poor diets, proximity to toxic dumps, and so on all increase" [66].

Culture

Culture is an integrated pattern of beliefs and behaviors within a social group that coexists with the individuality of each

member [67]. This set of beliefs and behaviors can strongly influence a person's perceptions, affective responses, and health-related behaviors when faced with adversity. Variables in culturally driven health behaviors might influence when and where a person decides to seek healthcare, how long or how extensive they believe their treatment should be, who is most responsible for the restoration of their health (doctor, self, guilty third-parties) as well as the definition of treatment success and resolution of symptoms. Further supporting the role of cognitive processing in the pain experience, strong associations have been identified between lower education levels, distorted back pain beliefs, and pain-related disability in the context of non-specific spine pain [53, 54]. The initial diagnosis and explanation given to a patient presenting with new-onset back pain is highly associated with chronicity as well. In a cohort study following 1848 patients presenting with an acute back injury, the 8.9% of patients who were labelled with specific anatomical explanations for their pain, such as "lesion of the disc or vertebrae" rather than nonspecific terms like "pain, strain, or sprain," accounted for 31% of the cases which progressed into chronic low back pain conditions [68]. It is important for the clinician to realize their own messages are known risk factors for pain chronification [69]. The power of a clinician's words can be equally harmful as they can be helpful and will be an important topic of discussion in the next article of this series.

Sleep Hygiene

Another very important risk factor for chronic pain is sleep hygiene. A person's quality of sleep and pain intensity affect one another in a cyclical fashion, with reports of poor sleep correlating to higher inflammatory markers, greater pain intensities and decreases in daily function. This contributes to higher pain- and disability-related stresses and subsequent sleep disruption [60, 70, 71]. Even more importantly, people suffering from chronic pain with higher self-reports of insomnia, sleep disruption, and poor daytime function were significantly more likely to report suicidal ideation, regardless of depression severity [72]. Finan, Goodin, and Smith explored the effects of poor sleep on descending pain inhibition via dopaminergic and opioidergic system dysregulation; their literature review concluded that sleep disruption can strongly predict acute exacerbations of chronic pain complaints as well as mood disorder symptoms [73]. This is important to consider as more than 50% of chronic spine pain patients report a clinically significant degree of sleep disturbance [74].

In summary, the multifactorial nature of pain and the perpetual cycle of risk factors that reinforce and sustain chronification are escalating the prevalence of chronic primary pain. It is paramount that the clinician caring for patients with chronic spine pain keenly assess their patient's social and cultural background, evaluate for false or distorted back pain beliefs, and provide effective education addressing modifiable risk factors and lifestyle habits throughout the course of care. Patient education and other means of counseling/coaching will be an essential component of the next article in this series discussing evidence-based intervention strategies using an individualized integrative behavioral approach.

Pathophysiology of Persistent Pain

Neuroinflammation and HPA Axis Dysfunction

The progression and chronification of the pain experience appear to be mediated, at least in part, by morphological changes occurring in the central nervous system representative of neuronal atrophy and synaptic reorganization. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis and neuroinflammation, induced by the activation of glial cells in response to chronic bombardment of nociceptive signaling, are proposed as the two primary drivers of this phenomenon [75–77]. Both of these pathophysiological events, over a prolonged period of time, can lead to the pruning of functional synapses throughout the cerebral cortex and central sensitization of nociceptive pathways. It is important to note that there is a strong correlation between these two dysfunctional states, although causality cannot be confirmed by present studies [78]. The resulting effect is a functional amplification of the nociceptive system and a low-threshold neuronal network poorly equipped to integrate and respond to incoming noxious, and possibly non-noxious, stimuli.

The primary drivers of neuroinflammation in the central nervous system of a chronic pain patient are attributed to the immune activation of microglia and astrocytes. Using a 3 T PET/MRI scanner combined with radioligand ^{11}C-PBR28, Loggia and colleagues observed glial activation patterns specifically located in areas of the thalamus, somatosensory, and motor cortices consistent with the somatotopic mapping of body regions where chronic and persistent pain had been experienced by patients [79]. ^{11}C-PBR28 is a recently developed radiographic tracer that specifically binds to mitochondrial translocator protein 18 kDa (TSPO), which becomes upregulated or expressed de novo in activated microglia and astrocytes. Along with these observations, noxious stimuli also lead to the production of brain-derived neurotrophic factors, nitric oxide synthase, inflammatory cytokines (TNFa, IL-6, and IL-1B), and other inflammatory mediators (CXCL2). Klyne and colleagues were the first to show a direct relationship between higher initial TNFa levels, along with depressive symptoms, and poor recovery from a bout of acute low back pain. In contrast, patients showing higher baseline levels of C-reactive protein and reporting poorer sleep in the acute phase of pain were associated with better recovery from their back pain at 6-month follow-up [80]. This study sheds light on

physiological prognosticators of pain chronification, but there is still much to say about inflammation and its role in low back pain recovery. While an acute increase of immune and inflammatory activity might be necessary for homeostatic maintenance and tissue healing, pathogenesis lies in the persistence of this response beyond normal healing times.

The HPA axis operates by releasing glucocorticoids as an end-product to promote predictive and reactive homeostatic processes such as cortical arousal, circadian rhythm maintenance, body temperature regulation, food and drink metabolism, and immune activity. These biochemicals also display powerful effects on the morphology of the brain and functional neurological networks [81]. The dysfunction of the HPA axis can be explained by the coexistence of both physical and emotional responses to threatening situations mediated via endocrine and autonomic nervous system activity. In a cyclical fashion, a person's pain state can be perpetuated and amplified by two major pathological functions: chronically elevated serum glucocorticoid levels and heightened activity of the sympathetic nervous system and its associated functions. Chronic hypercortisolemia maintains a humoral state of catabolism, thus causing retraction of dendritic synapses and disconnection of functional networks in the cerebral cortex, particularly regions involved in emotion and learning [82]. The chronic activation of the sympathetic nervous system can explain the trophic effects of brain morphology as vasoconstriction and hypoperfusion of specific cerebral structures would diminish neuronal repair and increase the risk of glutamatergic excitotoxicity.

Trials by Capitanio & Cole found that social relationships impacted the health of rhesus monkeys via corticolimbic modulation of major stress-response systems including the HPA axis (adrenocorticotropic hormone, cortisol), sympathetic nervous system (epinephrine, norepinephrine), and immune system (inflammatory cytokines and mediators). Experimentally unstable social environments caused a greater increase in serum catecholamine levels than direct administration of methamphetamine comparable to dosages in human users [83]. In this same study, it was reported that once the monkeys returned to stable social conditions again, the physiologic stress responses rapidly reversed to homeostatic levels. While this study provides valuable insight into the effect magnitude of unstable social repair conditions in monkeys, it appears that other trials and meta-analytical data show similar findings in human physiology with significant relationships between stress and reductions in immune health, both humoral and cellular [84–87]. This notion, as it applies to humans, provides physiological foundation and evidential support for data examined in previous sections of this review (see *Social and Cultural Determinants of Health).*

Miller and Raison explain these previously mentioned phenomena, using an evolutionary perspective, as a preemptive immune response to what is interpreted as an impending risk of exposure to infectious pathogens [88]. Infection was once the leading cause of death of our ancestors, and evolution favored those generating a psychogenic immune response to stressful scenarios that might result in infection (hunting, being hunted, social adversity). To take this a step further, this pro-inflammatory state promotes (depressive-like) behaviors of social withdrawal and prolonged rest to reduce metabolic demand so that energy reserves can be redirected toward fighting invading pathogens and reducing contagious spread to other members of the community. However, in today's relatively sanitized world, the lack of pathogen exposure causes HPA axis responses to shift toward more emotional expression and away from effective immune activity. What we see, as a result, is a threat-induced proinflammatory state with heightened cortisol levels, sick behaviors, peripherally and centrally sensitized neurons, and nothing for the immune system to assault except tissues of native origin. This might help to explain the strong correlation between stress, autoimmunity, psychological disorders like depression and anxiety, and chronic pain conditions all rising in prevalence worldwide [43, 89–91].

Structural and Functional Brain Adaptations

Central sensitization is a functional upregulation of the nervous system's pain processing network secondary to neuroinflammation (immune), increased membrane permeability (physiologic), synaptic reorganization (anatomical), and activity-dependent changes such as long-term potentiation (LTP) and long-term depression (LTD) of nociceptive synapses (genetic). All of these changes contribute to uncontrollable amplification of nociceptive signaling causing hypersensitivity to noxious (hyperalgesia) or non-noxious (allodynia) stimuli as well as a subjective distortion of the perceived pain experience and associated behavioral responses [92]. Resting-state fMRI (without explicit task) neuroresearch has identified intrinsic and widely anatomically distributed, temporally coherent, and functionally interactive neuronal networks related to somatomotor, visual, auditory, emotional, and executive functions [93]. Brain regions involved in functional networks responsible for attention and emotion, known as the salience network and default mode network (DMN), exhibit maladaptive changes with extensive duration [94, 95].

One of the primary areas of interest involved in resting-state networks is the medial prefrontal cortex (mPFC). Part of the DMN, the mPFC is involved in decision making, executive control, conflict monitoring, error detection, learning, memory, and emotional processing [96]. One of its executive functions is to communicate with the salience network and the Pavlovian fear-conditioning triad (mPFC, basolateral amygdala, hippocampus) to decide if a stimulus is threatening and, if so, modulate behavior and top-down control over antinociceptive and pronociceptive centers residing in

brainstem nuclei (periaqueductal gray-rostral ventromedial medulla, PAG-RVM) [97]. As previously mentioned, QST studies have shown evidence for an apparent loss of descending antinociception in cLBP patients—a net output of fear appraisal and top-down innervation from the fear triad to the PAG-RVM [98].

A systematic review of MRI and fMRI studies in chronic pain patients found that the majority of structural brain changes occurred in emotional and cognitive brain centers, opposed to those related to nociception and sensory integration [99]. Over time, the mPFC displays a loss of connectivity with posterior DMN regions while gaining a stronger connection to regions of the salience network [94]. The salience network, comprised primarily of the dorsal anterior cingulate cortex (dACC) and the anterior insular cortex, functions by evaluating stimuli for their relevance to survival and homeostatic maintenance. The anterior insular cortex is associated with emotion, perception, and self-awareness and helps integrate sensory information to determine how much attention a stimulus deserves. The dACC communicates with the mPFC to induce fear appraisal, while the dACC and nucleus accumbens (NAcc) cause a delay in the perception of reward [95, 100]. As the primary reward center of the brain, the NAcc is crucial for analgesia-related reward and behavioral learning mechanisms, which becomes impaired in patients suffering from chronic pain, depression, and other mood disorders alike [101–103]. In fact, longitudinal studies showed the transition to chronic low back pain could be predicted with > 80% accuracy based on the strength of functional connectivity between the mPFC and NAcc [104, 105].

Eisenberger and colleagues studied the effects of social rejection using fMRI analysis and discovered that the same brain regions activated during social exclusion and cognitive distress are also involved in the integration of pain—namely, the dACC [106]. Considering this, it might be fair to assert that LTP of pain-related neural activity is not necessarily nociception-dependent, as social and other cognitive stressors can serve as a proxy to the chronic bombardment of pain signals, thus promoting functional adaptations independent of a constant somatosensory stimulus. This information supports the argument that the chronification of pain is more strongly dictated by emotionally driven learning experiences rather than the initial magnitude or persistence of pain arising from physical trauma or insult [107]. Perhaps this is why we see that the majority of low back and neck pain occurs insidiously and without any known trauma to the musculoskeletal periphery.

Lastly, it is important to note that these maladaptive neuroplastic changes are likely reversible based on pre- and post-treatment fMRI of patients receiving care for their chronic pain conditions [108–111]. Therefore, clinicians who choose to educate their patients on the topic of cortical reorganization patterns should instill a sense of hopefulness and positive expectancy, rather than one of permanence or irreversibility, as once again, the impact of a clinician's words strongly influences expectations and clinical outcomes [69, 112]. Patient education will be discussed further in part 2 of this review series.

Conclusions

Current evidence supports a myriad of factors that contribute to the experience of back and neck pain and its chronification. Clinicians evaluating patients with spine-related pain should undergo a systematic evaluation, considering the extensive differential diagnosis of both acute and chronic spinal pain. It is imperative that the clinician also understands the multidimensional array of biopsychosocial risk factors that might pose a threat of persisting pain. These conditions require using an integrated approach rather than the reductionist biomedical model. Part 2 of this series will discuss the ways in which evidence-informed care may be optimized to provide the best possible outcomes for chronic primary spine pain utilizing a biopsychosocial approach.

Limitations

This study provides a narrative overview of several pertinent areas of interest within the domain of a highly complex topic of discussion. Because of this, the methodology was less rigorous than an all-inclusive systematic review and relevant articles may have been selectively excluded or overlooked. Although this reduces the level of evidence, the authors believe a systematic review would have been less feasible as an evaluation of the complex multifactorial nature of chronic spine pain.

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