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Low Back Pain

This issue of *Pain: Clinical Updates* examines whether low back pain (LBP) should be considered a straightforward consequence of injury/dysfunction in the spine, or the result of more complex processes involving nervous system processing of sensory information. The focus is on axial LBP rather than radiculopathy, and on chronic LBP rather than on transient episodes of LBP. This article is partly based on a chapter in *Functional Pain Syndromes: Presentation and Pathophysiology,* published by IASP Press in 2009.[1]

Conceptual Models for Low Back Pain

The End-Organ Dysfunction Model (EODM)

Most researchers and clinicians assume that the symptoms of patients with LBP reflect structural abnormalities in the lumbar spine due to some combination of injuries and degenerative changes. The fundamental premise of this model is that patients feel back pain because of a nociceptive focus in the spine. Thus, the pain experiences of patients represent normal functioning of the nervous system in the context of tissue injury or dysfunction.

Altered Nervous System Processing Models (ANSPM)

We believe it is appropriate to group alternatives to the EODM under the general rubric "altered nervous system processing models." The fundamental premise in these models is that patients with LBP suffer from alterations in nervous system encoding or processing of sensory information, rather than from ongoing injury or dysfunction in some structure in the lumbar spine. While various ANSPMs share a rejection of the straightforward link between pathology in the end organ (the lumbar spine) and the experience of pain, they differ in the alternative path postulated. Some models focus on physiological changes in the nervous system precipitated by nociceptive input; others emphasize heightened susceptibility to pain, either because of genetic factors, significant depression or anxiety, or a variety of psychological traits.

This article reviews several domains that are relevant to the two models explaining LBP, specifically: (1) the presence of a distinct event that caused symptoms, (2) symptoms that correlate with a well-defined, characteristic biological abnormality, (3) genetics, (4) co-occurrence with other pain syndromes, (5) co-occurrence with emotional dysfunction, (6) evidence of abnormal functioning in the nervous system, and (7) response to treatment.

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Relevance of the Models

This section focuses on the relevance of the domains to the EODM vs. the ANSPM, rather than on the details of research within each domain. (For details regarding relevant research, see Robinson and Apkarian[1].)

1. A Distinct Event That Caused Symptoms

The EODM is most plausible when a person's symptoms can be traced to a distinct injury involving overwhelming mechanical forces. A striking feature of LBP is that it often begins in the absence of a definable biomechanical load.[2] The absence of any characteristic mechanical trauma at the time when LBP began casts some doubt on the EODM, although one could counter that LBP is best construed as a repetitive trauma disorder rather than a manifestation of a single overwhelming mechanical load.

2. Symptoms That Correlate with a Well-Defined, Characteristic Biological Abnormality

The EODM implies that LBP should be traceable to some derangement in the structure or function of the spine. If so, it should be possible to demonstrate structural abnormalities that reasonably explain the symptoms. LBP has been an enigma precisely because it has proved very difficult to find strong correlations between the symptoms reported by patients and indices of biological pathology in the lumbar spine. Imaging studies have been particularly disappointing—for example, evidence of disk pathology on MRI scans is often seen in asymptomatic patients,[3-5] and longitudinal studies have failed to demonstrate that disk pathology at one point in time predicts later LBP.[6-8] Reasonable conclusions from the abundant evidence now available are that: (a) degenerative changes in lumbar intervertebral disks and facet joints are highly prevalent in individuals with and without LBP, (b) these changes increase as a function of the age of the individuals, and (c) associations between abnormalities in these structures shown on imaging studies and symptoms are modest.

Another approach to diagnosing structural pathology in the spine uses pain provocation and palliation techniques.[9-14] The basic logic is that a pain generator can be identified on the basis of a patient's responses to interventions designed to provoke pain (e.g., by injection of hypertonic saline) or to palliate pain (by injection of a local anesthetic). Pain provocation/palliation techniques have focused primarily on intervertebral disks (via diskography) and facet joints (via medial branch blocks) as sources of LBP. Advocates for this approach argue that pain provocation/palliation techniques reveal a structural basis for LBP in a substantial proportion of patients. Others, however, are skeptical regarding the diagnostic yield of these techniques.[15-18] Limitations in the diagnostic yields of pain provocation/palliation procedures might be attributed to a variety of technical issues, but they could also reflect inherent inadequacies in the EODM.

3. Genetics and Low Back Pain

Genetic research could in principle support either the EODM or the ANSMP. For example, research demonstrating a genetic basis for degeneration of the spine would support the EODM. Conversely, evidence that pain sensitivity has a genetic basis would tend to support the hypothesis that LBP is largely the result of heightened pain sensitivity. Research on monozygotic and dizygotic twins has shown that disk degeneration as measured by MRI scans is strongly influenced by genetic factors, with heritability ranging from 51%[19] to 74%.[20] This research appears to support the EODM, although the support is tempered by the weak association between MRI evidence of disk degeneration and symptoms of LBP. There is also evidence from twin studies (on fibromyalgia, for example)[21-23] and from studies of single nucleotide polymorphisms (involving the catechol-*O*-methyl-transferase gene and a few others)[24-26] of a genetic propensity to chronic pain. Thus, genetic evidence cuts both ways with respect to the appropriateness of the EODM vs. the ANSPM.

4. Co-occurrence with Other Pain Syndromes

The EODM suggests that LBP should occur independently of any other painful condition. A patient with LBP obviously might have some other painful disorder, such as chronic headache. But the frequency of co-occurrence of LBP and chronic headache should be no more than the joint probability (p) of occurrence of two independent events: i.e., p(LBP + headache) = p(LBP) × p(headache). In contrast, some versions of the ANSPM imply that people who suffer from chronic LBP are predisposed to painful disorders. Research generally supports the ANSPM because it indicates that individuals with LBP are at higher risk than others to report additional chronic pain syndromes, including neck pain,[27] temporomandibular disorder,[28] arthritis,[29] and headache.[29]

5. Co-occurrence with Emotional Dysfunction

The EODM emphasizes mechanical or biological causes of LBP rather than psychological ones. The model thus implies that prior to the onset of their pain, LBP patients should be indistinguishable from the general public with respect to psychiatric dysfunction. In contrast, at least some ANSPMs invoke psychological vulnerabilities as a key causal factor in chronic LBP. Research has generally supported ANSPMs, since it has shown that premorbid psychological dysfunction or psychological distress increase the risk of LBP.[30-34]

6. Abnormal Functioning in the Nervous System

Peripheral and Central Nervous System Plasticity

There is ample evidence that peripheral sustained injury, be it inflammatory or neuropathic, causes local reorganization of nociceptive and non-nociceptive afferents. These changes lead to alterations in excitability of the afferents to external (painful and nonpainful) stimuli and also to changes in resting membrane properties, such that sensory neurons that are usually silent in healthy tissue can now generate spontaneous action potentials and perhaps subserve pain perception in the absence of external stimuli.[35-39]

The spinal cord dorsal horn is the first relay and central processing site for nociception, and basic science studies on animals provide ample evidence for plasticity of afferent input processing in various experimental models of persistent or chronic pain.[35-39]

Thus, the animal studies point to increased gain in both the periphery and the spinal cord in chronic pain.

Given that descending modulatory circuits integrate supraspinal cortical and subcortical information, changes in properties of descending modulation point to the role of cortical influences on the spinal cord processing of nociception. Studies in rodents show that manipulating local circuitry in the anterior cingulate, amygdala, insula, and medial prefrontal cortex modulates pain behavior and also changes response properties of spinal cord nociceptors. Moreover, there is evidence that in various neuropathic or inflammatory conditions, response properties in multiple supraspinal regions are modified.[40-43] This circuitry must play a role in the mechanisms by which learned behavior can modify responses to painful stimuli, and reciprocally pain experiences induce changes in behavior and learning and memory (fear, anxiety, and depression).

Brain Function in Low Back Pain Patients

Noninvasive brain imaging techniques provide direct access to the brain, and LBP patients have now been studied with a variety of such approaches. The bulk of the evidence in this area comes from the laboratory of one of the authors of this article (A.V. Apkarian), and these findings await validation by other investigators. Still, for almost 10 years, LBP patients' brain properties have been studied and various abnormalities observed. These abnormalities can be divided into three categories: (1) functional, (2) anatomical, and (3) cognitive.

1. Functional abnormalities. Based on the abundant evidence of peripheral and spinal cord plasticity in animal studies, one would expect enhanced nociceptive transmission from the periphery to supraspinal targets in patients with LBP. As the spinothalamic pathway is commonly assumed to be the primary nociceptive signaling system in the central nervous system (CNS), the cortical regions it subserves should indicate enhanced activity either for spontaneous pain or for various external painful, and even nonpainful, stimuli in LBP.

One study examined enhanced spinothalamic activity in LBP patients and fibromyalgia patients by applying pressure to the thumbnail. In comparison to healthy controls exposed to the same pressure stimuli, LBP patients and fibromyalgia patients reported higher pain perception and demonstrated activation of more brain areas. When stimulus intensity was adjusted so that participants in the three groups reported comparable pain perceptions, then brain activity was not different between the groups.[44] Underlying mechanisms for this finding remain obscure, and trivial explanations cannot be discounted. Yet, the result can also be construed as pointing to a central disposition for enhanced pain, at least for pressure. Importantly, the brain regions where activity was higher in LBP were the same regions responding to more intense stimuli in the control subjects, suggesting that this increase in activity is a pure increase in gain of the system rather than a new representation.

Multiple studies (except for the Giesecke et. al. report[44]) indicate that chronic pain patients respond to noxious stimuli with decreased rather than enhanced activity in brain regions identified for acute pain (assumed to represent spinothalamic inputs).[45-47] Furthermore, inputs seem to cause increased activity in regions that cannot be considered part of the spinothalamic pathway—mainly prefrontal cortical areas and related subcortical structures.[45] Thus, there seems to be a decrease in gain in brain regions involved in acute pain and an increase in gain in areas outside of this representation.

Ongoing spontaneous pain is a common complaint of LBP patients. Recent evidence indicates that the perceived magnitude of this spontaneous pain fluctuates at the scale of seconds to minutes and has temporal characteristics that distinguish LBP from other chronic pain conditions.[48] When brain activity associated with sustained high levels of spontaneous LBP is examined, only one brain area is observed to be activated, the medial prefrontal cortex (mPFC).[49] In contrast, when painful thermal stimuli are applied to the lumbosacral region in patients with LBP, activity in the brain is completely different and closely matches that observed for acute pain in healthy subjects (Fig. 1). As the mPFC is a highly complex region, most elaborated in primates and especially in humans, and is thought to be fundamentally involved in top-down modulation of behavior, one explanation of the difference between spontaneous pain and thermal pain representation would be that the former is mainly driven by emotional centers of the brain, while the latter is a result of activating the end organs. The argument advanced in the study was that a transient signal generated by the end organ invades the cortex, and is then maintained and perpetuated in the

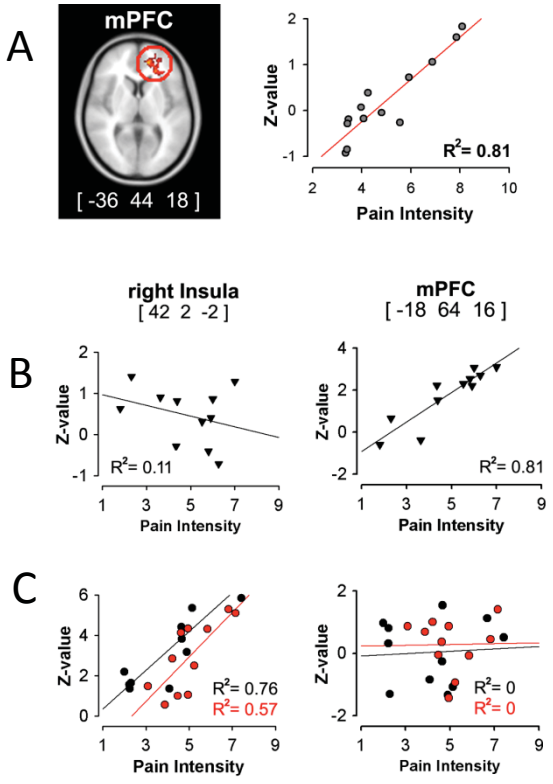

Fig. 1. The brain region identified as best correlated to intensity of back pain is distinct from that for thermal pain. (A) The medial prefrontal cortex (mPFC) is the region best correlated to intensity of pain. The regression shows the relationship of the region to back pain intensity in each patient studied. (B) The mPFC's activity correlates to each patient's intensity of back pain, identified in a new group of patients, while activity in the right insula does not correlate with this parameter. (C) The right insula, but not the mPFC, correlates best to the thermal painful stimuli applied either to the patients or to a group of normal healthy subjects.

mPFC, where the percept becomes more emotional and more self-referential.[49] Curiously, during the time when spontaneous LBP was increasing, increased activity was noted in the insula, and the magnitude of insular activation was tightly and positively correlated with the number of years the patients had experienced LBP. Therefore, the two fundamental properties of LBP, namely its intensity and its duration, are directly associated with brain activity in the mPFC and insula of these patients.

2. Anatomical abnormalities. Several morphometric and biochemical studies have demonstrated gray matter atrophy in the dorsolateral prefrontal cortex (DLPFC) and the thalamus (Figs. 2 and 3).[50,51] For LBP, the extent of atrophy could be linked to the number of years the patients were living with the condition, suggesting that at least part of the process is a consequence of the persistence of LBP.

The gray matter atrophy in LBP could also be linked to brain activity observed in these patients. Multiple studies indicate that the DLPFC and mPFC inhibit each other, and this inhibition could be demonstrated for spontaneous pain in LBP.[49] Therefore, it could be hypothesized that the extent of atrophy of DLPFC is linked to the amount of activity in the mPFC. Given that mPFC activity strongly correlates to the intensity of pain, one can then state that the DLPFC atrophy contributes to the increased mPFC activity and thus also to the intensity of LBP.

A recent study performed on complex regional pain syndrome (CRPS) patients[52] clarifies the time course of gray matter atrophy and its association with white matter connectivity. This study found that regional atrophy of the brain is also seen in CRPS, but the brain regions involved are distinct from those of LBP. Also, the study found that gray matter atrophy is coupled with white matter connectivity decreases, especially over long-distance connections, as well as with target-specific increased white matter

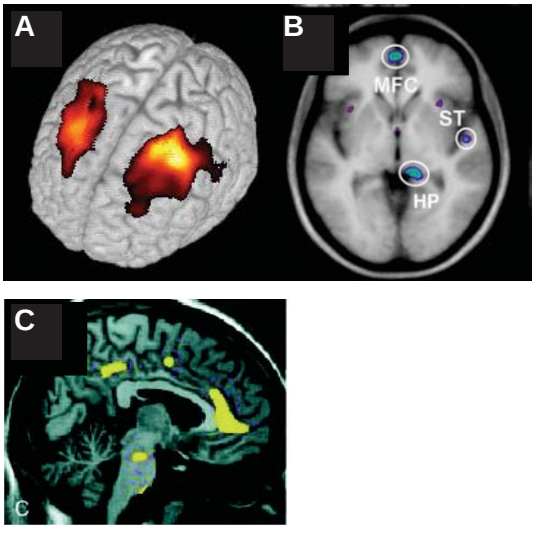

Fig. 2. Brain atrophy in three different clinical populations indicates unique patterns of atrophy. (A) In chronic back pain, atrophy is mainly seen in the bilateral dorsolateral prefrontal cortex. (B) In fibromyalgia, atrophy is seen in the medial prefrontal cortex (MFC) as well as in more posterior regions, namely the superior temporal cortex (ST) and hippocampus (HP). (C) In tension headache, atrophy is seen in the medial prefrontal cortex, in more posterior cingulate regions, and in the brainstem.

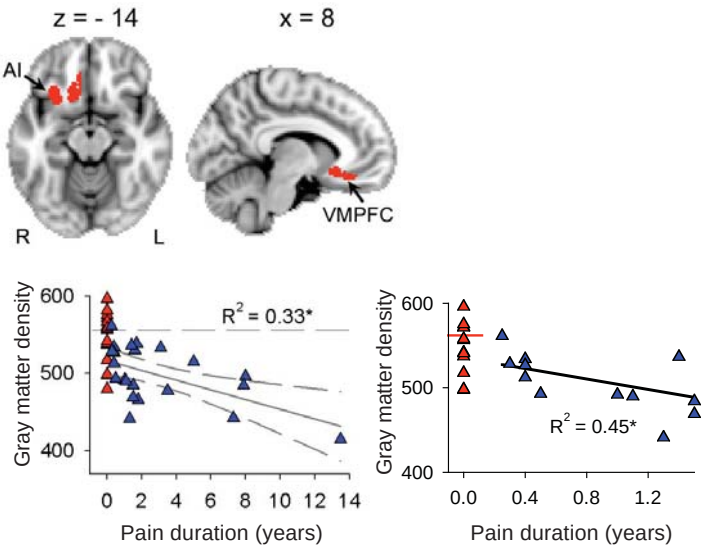

Fig. 3. Brain regional atrophy is shown in patients with complex regional pain syndrome (CRPS). Twenty-two patients were contrasted to 22 age- and gender-matched healthy subjects. Decreased gray matter is seen in a single region in the right hemisphere extending from the anterior insula (AI) to the medial prefrontal cortex (VMPFC). The bottom graph indicates that the extent of gray matter decrease in CRPS is correlated to the duration of living with the condition. Blue symbols are CRPS patients, and red symbols are matched healthy controls. The dashed line shows the mean gray matter density (cm^3) in the healthy subjects. Right graph shows the dependence of pain duration for CRPS patients living with pain for <1.5 years, and their respective matched healthy controls.

connectivity. Therefore, the study shows specific rewiring of the brain in clinical chronic pain. There was also evidence of a very steep decrease in gray matter density during the first 6 months after onset of pain (Fig. 3). This finding suggests an initial atrophy process that then stabilizes, implying a direct link between brain atrophy and the onset of CRPS.

3. Cognitive abnormalities. The brain abnormalities seen in LBP suggest hypotheses about cognitive deficits that may occur in patients. The atrophy in DLPFC and activity in mPFC suggest that chronic LBP is more of an emotional state and that patients may become less sensitive to other emotional stimuli given the distraction that LBP would impose. This hypothesis was tested specifically using an emotional decision-making task. LBP patients were impaired on the task in proportion to the intensity of their pain.[53] Moreover, insular activity was also observed to be abnormal in LBP, and because the insula is known to be the primary gustatory taste region, LBP patients were tested and were found to have better abilities in taste perception than normal subjects.[54] Therefore, LBP patients exhibit specific cognitive abnormalities that can be linked to their brain activity and brain morphological abnormalities.

In summary, research on CNS processing in LBP supports ANSPMs, since it shows that chronic LBP is associated with characteristic functional and anatomic changes in the CNS. Important questions regarding the significance of these changes remain to be explored. In particular, we do not yet know whether the changes should be viewed as causes or consequences of living with ongoing pain, and whether CNS function and structure return to normal after noxious input from the end organ ceases.

7. Response to Treatment

The ultimate practical validity criterion of any model of pathophysiology of a medical disorder is the ability of treatment based on that model to help patients who suffer from the disorder. The EODM has dominated research on the treatment of LBP. The research that is most relevant to this article involves treatment directed toward intervertebral disks and facet joints in the lumbar spine. Injection therapies (e.g., intradiskal electrothermal therapy), spinal fusions, and disk replacement surgery have been studied in relation to diskogenic pain; facet neurotomies have been studied in relation to pain mediated by facet joint pathology. Research on these approaches is complex and often contradictory.[55-67] A reasonable conclusion is that there is some evidence of effectiveness of therapies directed toward disk pathology and facet pathology. However, the studies that have demonstrated positive results have generally been performed in highly selected groups of patients, so the relevance of the results to LBP in general is uncertain.

Research on the effectiveness of antidepressants and anticonvulsants in LBP is relevant to versions of the ANSPM that emphasize relationships between altered CNS functioning and neuropathic pain.[68-70] Results of this research have been unimpressive. A recent Cochrane collection review concluded that there is no evidence that antidepressants are helpful in LBP,[71] and demonstrable benefit from anticonvulsants seems to be limited to patients with radiculopathies.[72]

Research on the effectiveness of psychological therapies in LBP is relevant to versions of the ANSPM that emphasize psychological dysfunction. There is substantial support for these therapies.[73,74]

In summary, there is some evidence to support the efficacy of treatments based on the EODM and various ANSMP models. But all of these therapies have been only modestly effective. None can claim to have cured LBP, or to have been so successful that it proves the pathophysiological theory underpinning it.

Conclusions

In this issue of *Pain: Clinical Updates* we have contrasted the end-organ injury/dysfunction model of LBP with various alternatives that can be grouped as models stressing altered nervous system processing, and we have reviewed the kinds of evidence that would support one perspective over the other. In our view, there is no single answer to the question of which model more accurately reflects the physiology underlying LBP. The pain that most patients experience probably reflects a combination of EODM and ANSPM, with the relative contribution of the two kinds of processes varying from patient to patient. In the face of this ambiguity, clinicians face the difficult task of trying to sort out the relative merits of the two models for individual patients.

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A. Vania Apkarian, PhD
Rehabilitation Institute of Chicago
Departments of Physiology, Anesthesia, and Surgery
Northwestern University, Feinberg School of Medicine,
Chicago IL, USA
a-apkarian@northwestern.edu

James P. Robinson, MD, PhD
Department of Rehabilitation Medicine
University of Washington, Seattle, Washington, USA
jimrob@u.washington.edu

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