2021 GLOBAL YEAR ABOUT BACK PAIN fact sheet

# Neurobiological Mechanisms Contributing to Back Pain

## There is no single pathophysiological mechanism for back pain.

All of the mechanisms listed below have some empirical support for their role in the experience of back pain and have shown association to back pain features, like pain intensity, duration or related disability. The jury is still out on precisely what causes back pain in the 85-95% of cases that are classified as non-specific. It is likely that many of these mechanisms interplay or reflect overlapping processes that combine with genetic, epigenetic, individual and lifestyle factors to eventually lead to chronic back pain. Precise mechanisms and interactions most probably differ between individuals, meaning continued research efforts aimed at identifying and treating mechanisms relevant to individual patients are essential. This factsheet briefly summarizes some peripheral and mostly central neurobiological mechanisms that may contribute to back pain arising. Specific causes of back pain due to, e.g., fractures, infections, autoimmune disorders, nerve root compression, etc. are not covered, as their pathophysiology and treatment is more clearly understood.

## People with back pain show changes in the peripheral nervous system.

1. Inflammation, sensitization and changes in innervation of spinal structures have been observed in people with back pain and animal models of back pain.

Even in the absence of clear nerve compression following disc herniation (a specific cause of back pain in some cases), changes can occur in the peripheral nervous system that may contribute to the development of back pain. For example, studies have demonstrated the presence of inflammation within musculoskeletal structures in serum and tissue samples from people with back pain [6; 12; 14]. Further, animal models have demonstrated that intervertebral disc compression and degeneration are associated with increases in inflammatory mediators, increased sensory innervation of the disc and plastic changes in both peripheral and spinal sensory neurons [22; 23]. These changes suggest a biological mechanism for pain to arise with intervertebral disc degeneration.

**People with back pain show alterations in sensitivity to painful stimuli.**

2. Sensitivity to painful stimuli, especially pressure, may fluctuate with low back pain but does not appear to be associated with future pain or disability.

Sensitivity to painful pressure stimuli has been assessed extensively in populations with back pain. This has been suggested to reflect peripheral sensitization when assessed locally but may indicate more generalized sensitization of central mechanisms when assessed at remote sites [3]. In the majority of cases, pressure pain thresholds are reduced in people with back pain compared to pain-free individuals [7], suggesting that people with back pain display local hypersensitivity to pressure. Further, there is evidence that patients with severe or widespread back pain in particular also show widespread pressure hyperalgesia[7]. Several studies have now shown that hyperalgesia fluctuates with pain intensity and returns to normal with pain resolution (regardless of whether pain resolution is due to treatment or

natural history) [7; 19; 20; 26; 31]. There is also no evidence of prognostic value from these thresholds [16; 18; 25]. Taken together, this suggests that local and widespread hypersensitivity to pressure, or tenderness on palpation as the clinical correlate, may not give any insight into future prognosis, but may serve as a tool to confirm and/or monitor changes in pain state over time.

3. People with low back pain often show enhanced pain facilitatory measures (pro-nociceptive mechanisms), but this may be the result of ongoing nociception.

By examining increases in pain perception or reflexive withdrawal following repeated noxious stimulation, many research groups have quantified temporal summation of pain in back pain patients. This measure is commonly enhanced in those with low back pain and shows some relation to pain severity [7; 21]. In fact, as this is a relatively homogenous finding, some studies have suggested reflex measures of facilitation to be a potential discriminative tool in low back pain patients. However, recent evidence suggests that this enhancement in facilitation may resolve as pain subsides, thus may just reflect ongoing nociception consistent with the original theoretical underpinnings[15].

4. People with back pain show reduced endogenous inhibitory measures (anti-nociceptive mechanisms).

Many psychophysical studies have used conditioned pain modulation, a test of how well individuals inhibit the experience of one painful stimulus in the presence of another tonic painful stimulus, to compare endogenous descending inhibitory function between people with and without back pain. These studies, when meta-analyzed, indicate that people with back pain show impairments compared to controls, which is associated with increased duration and severity of low back pain [7; 21]. Functional magnetic resonance imaging (fMRI) studies also show reduced connectivity between prefrontal regions and the periaqueductal gray [38] – a region critically involved in integrating cortical influences on descending noxious modulatory pathways. This has been interpreted as a reduced ability to cortically initiate descending noxious inhibition. It is not yet clear if impairments in descending inhibitory capacity increase over time with ongoing pain, as observed after nerve injuries in both humans and animals[5; 9], or if this predisposes/contributes to pain development. Some preliminary evidence suggests impaired endogenous inhibition may precede idiopathic neck pain onset [30], but replication and elaboration of this finding is needed.

5. Increased sensitivity to cold stimuli has been found in people with neck pain and may relate to prognosis, but this relationship may be mediated by psychological factors.

Hypersensitivity to cold has been demonstrated in populations with Whiplash-Associated Disorder [33], and was one factor included in a clinical prediction rule for more severe symptom development [27]. However, these research groups have also observed relationships between cold pain thresholds and psychological factors, such as pain catastrophizing or stress, which have also independently been associated with poor prognosis in pain populations.

### People with back pain show changes in cortical structure, excitability and connectivity.

6. Reduced gray matter volume has been observed in people with back pain

Several papers have identified reduced whole-brain gray matter volumes, with gray matter loss primarily in the dorsolateral prefrontal cortex and thalamus of chronic low back pain patients [2; 4]. In these studies, this gray matter loss was more severe in those with neuropathic pain components or increased disability. As these regions participate in processing and modulation of pain-related information, and as some variance in gray matter loss was explained by pain-duration, it was theorized that this was due to overuse. Such changes have also been shown to be reversible [29]. The precise relevance and impact of these differences in cortical gray matter is yet to be elucidated.

7. People with back pain show changes in cortical representation of trunk muscles.

Studies have demonstrated so-called 'smudging' of the motor cortex maps in people with back pain compared to pain-free individuals[8; 28], which shows some association to back pain intensity [28]. This means that when looking at muscle activation in response to magnetic stimulation of the motor cortex, there are less clearly defined regions producing responses in each of the muscles or generating motor patterns. This may be related to the change in postural behavior of these individuals [35], where movement variation is reduced in an effort to avoid provoking pain. A large ongoing trial is examining whether this 'smudging', among other factors, is related to pain progression [11], but results are not yet finalized.

8. People with back pain may show altered cortical homeostatic responses.

When two consecutive bouts of brain stimulation intended to inhibit cortical excitability are applied, pain-free healthy individuals will typically show a homeostatic response. This means that, despite usually being inhibitory, an excitatory response will be observed following the second bout of stimulation, interpreted as a homeostatic mechanism for maintaining excitability within safe limits. In low back pain patients, however, experimental evidence suggests that this mechanism may be impaired, potentially contributing to maladaptive plasticity and pain persistence [34].

9. Connectivity between brain regions may be altered in people with back pain.

A growing number of studies are showing that functional connectivity between specific brain regions in people with low back pain is different from pain-free individuals. Further, these patterns of connectivity seem to change during the transition from acute to chronic pain from sensory-discriminative networks to networks more commonly associated with affective processing [36; 37; 39]. The impact of such changes is yet to be fully understood.

10. Various somatosensory deficits may also be present in back pain populations.

Some studies have shown sensory discrimination, e.g. two-point discrimination and graphesthesia, to be impaired in people with back pain compared to pain-free individuals [1; 10; 13; 17], and have been linked to structural changes in the somatosensory cortex [13]. Further, body image and perceptions of the back's appearance and function can also be distorted in people with low back pain, and these distortions show some relation to both tactile acuity and clinical features [24; 32]. These findings indicate changes in somatosensory processing in people with back pain that may be amenable to intervention by sensory feedback or retraining where relevant.

**As presented here, many different neurobiological mechanisms may play a pathophysiological role in back pain development or maintenance. The precise nature and contribution of each mechanism within individuals and subgroups of people with back pain remains to be elucidated.**

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