

## 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.**

## REFERENCES

- [1] Adamczyk WM, Saulicz O, Saulicz E, Luedtke K. Tactile acuity (dys)function in acute nociceptive low back pain: a double-blind experiment. *Pain* 2018;159(3):427-436.
- [2] Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004;24(46):10410-10415.
- [3] Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Mohr Drewes A. Assessment and manifestation of central sensitisation across different chronic pain conditions. *Eur J Pain* 2018;22(2):216-241.
- [4] Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. *PLoS One* 2011;6(10):e26010.
- [5] Bannister K, Patel R, Goncalves L, Townson L, Dickenson AH. Diffuse noxious inhibitory controls and nerve injury: restoring an imbalance between descending monoamine inhibitions and facilitations. *Pain* 2015;156(9):1803-1811.
- [6] Chen X, Hodges PW, James G, Diwan AD. Do Markers of Inflammation and/or Muscle Regeneration in Lumbar Multifidus Muscle and Fat Differ between Individuals with Good or Poor Outcome Following Microdiscectomy for Lumbar Disc Herniation? *Spine (Phila Pa 1976)* 2020.
- [7] den Bandt HL, Paulis WD, Beckwee D, Ickmans K, Nijs J, Voogt L. Pain Mechanisms in Low Back Pain: A Systematic Review With Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People With Nonspecific Low Back Pain. *J Orthop Sports Phys Ther* 2019;49(10):698-715.
- [8] Elgueta-Cancino E, Marinovic W, Jull G, Hodges PW. Motor cortex representation of deep and superficial neck flexor muscles in individuals with and without neck pain. *Hum Brain Mapp* 2019;40(9):2759-2770.
- [9] Gagne M, Cote I, Boulet M, Jutzeler CR, Kramer JL, Mercier C. Conditioned Pain Modulation Decreases Over Time in Patients With Neuropathic Pain Following a Spinal Cord Injury. *Neurorehabil Neural Repair* 2020;34(11):997-1008.
- [10] Harvie DS, Edmond-Hank G, Smith AD. Tactile acuity is reduced in people with chronic neck pain. *Musculoskelet Sci Pract* 2018;33:61-66.
- [11] Jenkins L, Chang WJ, Buscemi V, Cunningham C, Cashin A, McAuley JH, Liston M, Schabrun SM. Is there a causal relationship between acute stage sensorimotor cortex activity and the development of chronic low back pain? a protocol and statistical analysis plan. *BMJ Open* 2019;9(12):e035792.
- [12] Khan AN, Jacobsen HE, Khan J, Filippi CG, Levine M, Lehman RA, Jr., Riew KD, Lenke LG, Chahine NO. Inflammatory biomarkers of low back pain and disc degeneration: a review. *Ann N Y Acad Sci* 2017;1410(1):68-84.
- [13] Kim H, Mawla I, Lee J, Gerber J, Walker K, Kim J, Ortiz A, Chan ST, Loggia ML, Wasan AD, Edwards RR, Kong J, Kaptchuk TJ, Gollub RL, Rosen BR, Napadow V. Reduced tactile acuity in chronic low back pain is linked with structural neuroplasticity in primary somatosensory cortex and is modulated by acupuncture therapy. *Neuroimage* 2020;217:116899.
- [14] Krock E, Rosenzweig DH, Chabot-Dore AJ, Jarzem P, Weber MH, Ouellet JA, Stone LS, Haglund L. Painful, degenerating intervertebral discs up-regulate neurite sprouting and CGRP through nociceptive factors. *J Cell Mol Med* 2014;18(6):1213-1225.
- [15] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;10(9):895-926.
- [16] LeResche L, Turner JA, Saunders K, Shortreed SM, Von Korff M. Psychophysical tests as predictors of back pain chronicity in primary care. *J Pain* 2013;14(12):1663-1670.
- [17] Luomajoki H, Moseley GL. Tactile acuity and lumbopelvic motor control in patients with back pain and healthy controls. *Br J Sports Med* 2011;45(5):437-440.
- [18] Marcuzzi A, Dean CM, Wrigley PJ, Chakiath RJ, Hush JM. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J Pain Res* 2016;9:599-607.
- [19] Marcuzzi A, Wrigley PJ, Dean CM, Graham PL, Hush JM. From acute to persistent low back pain: a longitudinal investigation of somatosensory changes using quantitative sensory testing-an exploratory study. *Pain Rep* 2018;3(2):e641.
- [20] McPhee ME, Graven-Nielsen T. Recurrent low back pain patients demonstrate facilitated pronociceptive mechanisms when in pain, and impaired antinociceptive mechanisms with and without pain. *Pain* 2019;160(12):2866-2876.
- [21] McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. *Pain* 2020;161(3):464-475.

- [22] Miyagi M, Ishikawa T, Kamoda H, Suzuki M, Murakami K, Shibayama M, Orita S, Eguchi Y, Arai G, Sakuma Y, Kubota G, Oikawa Y, Ozawa T, Aoki Y, Toyone T, Takahashi K, Inoue G, Kawakami M, Ohtori S. ISSLS prize winner: disc dynamic compression in rats produces long-lasting increases in inflammatory mediators in discs and induces long-lasting nerve injury and regeneration of the afferent fibers innervating discs: a pathomechanism for chronic discogenic low back pain. *Spine (Phila Pa 1976)* 2012;37(21):1810-1818.
- [23] Miyagi M, Millecamps M, Danco AT, Ohtori S, Takahashi K, Stone LS. ISSLS Prize winner: Increased innervation and sensory nervous system plasticity in a mouse model of low back pain due to intervertebral disc degeneration. *Spine (Phila Pa 1976)* 2014;39(17):1345-1354.
- [24] Moseley GL. I can't find it! Distorted body image and tactile dysfunction in patients with chronic back pain. *Pain* 2008;140(1):239-243.
- [25] Muller M, Curatolo M, Limacher A, Neziri AY, Treichel F, Battaglia M, Arendt-Nielsen L, Juni P. Predicting transition from acute to chronic low back pain with quantitative sensory tests-A prospective cohort study in the primary care setting. *Eur J Pain* 2019;23(5):894-907.
- [26] O'Neill S, Kjaer P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *Eur Spine J* 2011;20(12):2120-2125.
- [27] Ritchie C, Hendrikz J, Kenardy J, Sterling M. Derivation of a clinical prediction rule to identify both chronic moderate/severe disability and full recovery following whiplash injury. *Pain* 2013;154(10):2198-2206.
- [28] Schabrun SM, Elgueta-Cancino EL, Hodges PW. Smudging of the Motor Cortex Is Related to the Severity of Low Back Pain. *Spine (Phila Pa 1976)* 2017;42(15):1172-1178.
- [29] Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci* 2011;31(20):7540-7550.
- [30] Shahidi B, Curran-Everett D, Maluf KS. Psychosocial, Physical, and Neurophysiological Risk Factors for Chronic Neck Pain: A Prospective Inception Cohort Study. *J Pain* 2015;16(12):1288-1299.
- [31] Slade GD, Sanders AE, Ohrbach R, Fillingim RB, Dubner R, Gracely RH, Bair E, Maixner W, Greenspan JD. Pressure pain thresholds fluctuate with, but do not usefully predict, the clinical course of painful temporomandibular disorder. *Pain* 2014;155(10):2134-2143.
- [32] Stanton TR, Moseley GL, Wong AYL, Kawchuk GN. Feeling stiffness in the back: a protective perceptual inference in chronic back pain. *Sci Rep* 2017;7(1):9681.
- [33] Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. *Pain* 2005;114(1-2):141-148.
- [34] Thapa T, Graven-Nielsen T, Chipchase LS, Schabrun SM. Disruption of cortical synaptic homeostasis in individuals with chronic low back pain. *Clin Neurophysiol* 2018;129(5):1090-1096.
- [35] Tsao H, Galea MP, Hodges PW. Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. *Brain* 2008;131(Pt 8):2161-2171.
- [36] Tu Y, Fu Z, Mao C, Falahpour M, Gollub RL, Park J, Wilson G, Napadow V, Gerber J, Chan ST, Edwards RR, Kaptchuk TJ, Liu T, Calhoun V, Rosen B, Kong J. Distinct thalamocortical network dynamics are associated with the pathophysiology of chronic low back pain. *Nat Commun* 2020;11(1):3948.
- [37] Tu Y, Jung M, Gollub RL, Napadow V, Gerber J, Ortiz A, Lang C, Mawla I, Shen W, Chan ST, Wasan AD, Edwards RR, Kaptchuk TJ, Rosen B, Kong J. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain* 2019;160(6):1308-1318.
- [38] Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *Neuroimage Clin* 2014;6:100-108.
- [39] Yu S, Li W, Shen W, Edwards RR, Gollub RL, Wilson G, Park J, Ortiz A, Cao J, Gerber J, Mawla I, Chan ST, Lee J, Wasan AD, Napadow V, Kaptchuk TJ, Rosen B, Kong J. Impaired mesocorticolimbic connectivity underlies increased pain sensitivity in chronic low back pain. *Neuroimage* 2020;218:116969.

## AUTHORS

Megan McPhee, MSc  
Center for Neuroplasticity and Pain (CNAP)  
Aalborg University, Denmark

Michele Curatolo, MD, PhD  
Department of Anesthesiology and Pain Medicine  
University of Washington, USA

Thomas Graven-Nielsen, DMSc, PhD  
Center for Neuroplasticity and Pain (CNAP)  
Aalborg University, Denmark

#### REVIEWERS

Petra Schweinhardt, MD  
Head, Chiropractic Research  
Balgrist University Hospital, Switzerland

Laura S. Stone, PhD  
Professor, Department of Anesthesiology  
University of Minnesota, USA

©Copyright 2021 International Association for the Study of Pain. All rights reserved.  
IASP brings together scientists, clinicians, healthcare providers, and policymakers to stimulate and support the study of pain and translate that knowledge into improved pain relief worldwide.

