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PAIN MANAGEMENT

BRAIN PAIN SUPPLY

Common sources of neurological amplification: nociceptive fibres

BY ALEJANDRO ELORRIAGA CLARACO

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

This definition contains two important agreements that comprise the foundation of understanding pain syndromes: First, that pain is a conscious experience (i.e. psychological and therefore by definition a brain event), and second, that this brain event may or may not be associated with detectable tissue damage anywhere in the body – although it is, also by definition, usually felt as if it was associated to tissue damage.

Regarding this last point, and again according to IASP: "…*many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.*"

This paragraph suggests that psychological is a realm separated from neurological, which is not compatible with contemporary science and neurophysiology.

Despite Descartes insistence in separating reality into the *res cognitas* (consciousness, mind) and the *res extensa* (matter, extension), and impregnating Western philosophy for more than 300 years with his intellectually appealing, but inaccurate concept of dualism, we know now that there is no such a thing as a mind separated from the matter responsible for the phenomena of consciousness and emotions (i.e. the human brain as well as the brain of other animals).

At one time, dualism allowed for the separation of sciences and the non-physical realm (allowing scientists to conduct their research without fear of being considered heretics by religious groups). Nowadays, dualism creates a serious problem for anybody approaching the study of mind-related events, such as the aforementioned pain syndromes. Interestingly, it was Descartes himself, in his famous 1637 Discours de la Méthode, who advocated the systematic doubting of knowledge, believing that sensed perception and reason deceive us and therefore, man cannot have real knowledge of nature. The only thing that he believed could be certain was that he was doubtful, leading to his famous phrase *Cogito ergo sum*: I think therefore I am – which, in an updated version relevant to our subject today, it could read "I doubt, therefore I am scientific."

This may seem philosophical, but it is highly relevant to the topic because as I have just demonstrated, science in general and pain medicine in particular are still impregnated with the biases of past centuries, which in turn are conditioning the way we see and treat these pain problems in everyday clinical practice. To help clinicians with an updated approach to the management of pain problems, we must discuss the many possible contributors of a complex pain experience. Because pain is a brain event and all brain events are by nature the product of non-linear physiological processes, they are therefore complex. We seem to have failed so far in pain medicine because of the use of linear models, mostly structure based, that simply cannot explain the observed non-linear behaviour of these complex clinical problems.

As a complex central nervous system by-product, where sensory, cognitive and emotional contributors are all part of the unpleasant experience, pain is deemed to have numerous physiological contributors that I'd like to call "pain contributors." Obviously, the pathophysiology of pain contributors is complex and not fully understood, and

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it may involve "up regulatory" and "down regulatory" mechanisms on the nociceptive pathways, including phenomena such as peripheral and central sensitization, silent nociception, and neuronal plasticity. Also related to the neurophysiology of inflammation, sympathetic nervous system hyperactivity is known to be a majorcontributor to all pain problems.

Less understood contributors include dysfunction of pre- and post-ganglionic sympathetic neurons, abnormal visceral autonomic activity, lack of sufficient non-noxious information from these or adjacent segments related to the kinetic chain (proximal and distal joints, synergistic and/or antagonistic muscles, etc.). It is even possible that any nociceptive signal from any innervated tissue, regardless of topographic location, could become a source of amplification in a given pain problem.

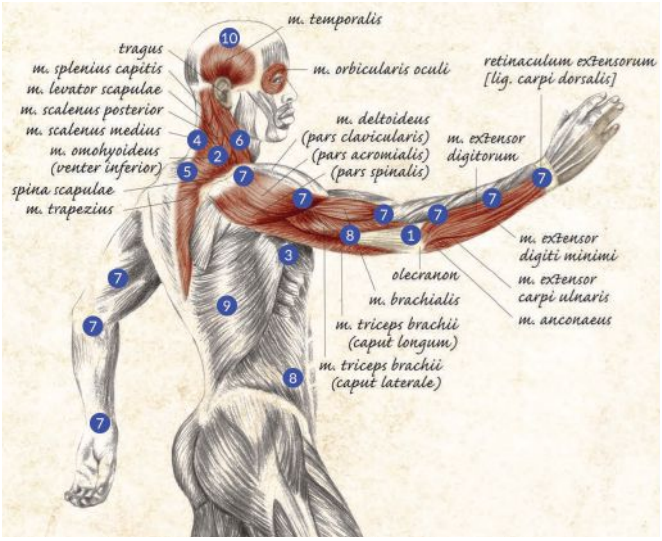
Practitioners of pain medicine need to be able to evaluate and identify these common contributors to pain syndromes. Being able to provide a timely, relevant treatment to optimize functional recovery requires a systematic, yet holistic approach. A practical neurofunctional treatment model (See: "The neurofunctional era: Optimizing the use of therapeutic resources" on Canadianchiropractor.ca) will be best to help practitioners select the most appropriate neuromodulatory interventions for the most relevant levels involved in each pain problem.

For the sake of making this discussion as clinically relevant as possible, a hypothetical elbow pain problem has been selected to illustrate the discussion, and an accompanying diagram (page 26) has been provided to reflect the 10 kinds of contributors to the pain experience, visually. Discussion of each contributor is signalled with the same number used in the diagram.

1. Local contributors: nociceptive fibres with receptor fields on dermatomal, myotomal, and sclerotomal tissues

Nociception is a neurological segmental phenomenon related to peripheral nervous system and spinal cord activity. Nociceptive signals are generated in response to chemical, mechanical and thermal stimuli acting over free nerve endings (belonging to C fibres and A-delta fibres) located on dermatomal, myotomal or sclerotomal structures.

These C and A-delta fibers are functionally referred to as nociceptive fibers, because of their ability to inform the central nervous system (CNS) about noxious stimuli, i.e. potentially harmful or unpleasant stimuli, whether there has been already tissue damage or not. These are the only nerve fibers capable of detecting noxious activity in the tissues, and to convey it to the CNS. These nociceptive signals are



first processed at the dorsal horn of the spinal cord, and then carried to the brain stem, the thalamus, and other brain areas where they will be consciously perceived as pain.

While not all pain experiences originate on peripheral nociceptive signals, most pain experiences are contributed to by nociceptive activity, overt or silent.

Let's remember that different sensory stimuli in the periphery of the body are detected and conducted by different receptors associated to particular type of nerve fibres. Each kind of sensory signal is processed differently at the spinal cord and at supraspinal levels.

For instance, some neurons possess thick myelinated axons that end in specialized encapsulated receptors in the peripheral tissues, each type of receptor devoted to a particular type of sensory input (e.g. vibration, light touch, tension, angular velocity). These receptors can only be stimulated by the specific stimulus they are designed to codify for, and no amount of other stimuli, including the presence of terrible tissue damage, could ever make these neurons contribute to the messages that eventually will become a pain experience in the brain; for instance, even if someone burns alive by fire or in a bath of acid (I apologize for the crude example, it is provided just to illustrate the physiological point), all the horrible pain experienced as a result of the massive tissue damage, will be solely contributed by nociceptive fibres in the affected tissues. None of the encapsulated specialized receptors (mechanoreceptors, proprioceptors, extereoceptors) will contribute any signals.

Some facts about nociceptive fibres:

- Nociceptive fibres have their cell bodies on the dorsal root ganglia and their axons in the peripheral tissues ending as free nerve endings (C and A-delta fibres): skin, periosteum, arterial walls, joint surface, capsules and ligaments, meninges, tentorium and faux cerebelli, viscera, and nervi nervorum. They contain substance P (vasodilation, increase permeability of microvasculature, and inducing histamine release from mast cells), calcitonin gene-related peptide (CGRP), and somatostatin.
- Free nerve endings in skeletal muscle typically end in the adventitia surrounding arterioles, while the muscle fibres proper are not supplied with neuropeptide-containing free nerve endings – a fact that may explain the lack of pain in response to massive tissue destruction in muscular dystrophies in contrast with the increased sensitivity associated with chemical pain due to disturbances of microcirculation.
- Nociceptive fibre density along the length of the muscle seems uniform but it is higher in the peritendon while almost absent in the tendon tissue proper. Corollary, tendons are not a main source of nociceptive information.
- Nociceptive fibres' depolarization requires either physiological stimuli (mechanical, thermal, chemical) or pathological (inflammation, ischemia, necrosis, or neuropathic behavior = peripheral/spinal sensitization).
- Although large myelinated fibres respond only to specific sensory modalities, under situations of intense peripheral stimuli involving inflammation, some large calibre sensory fibres may undergo a phenotypic change, such that they can now activate dorsal horn neurons by producing substance P. (Neumann S. et al. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature 1996;384-:360-364)
- Examples of nociceptive pain on deep somatic tissues of the musculoskeletal system that are difficult to characterize include:

Osteomielitis (bacterial, fungal, viral): From cursing with pain and fever on an acute standard presentation, to becoming painless on a chronic situation. This pain is usually worse with movement, can radiate to the chest, abdomen, or limbs, and the affected vertebrae are tender on palpation.

Osteoporosis: The pain is due to bone fractures (vertebrae, hip, wrist, humerus, tibia), and it also behaves mechanically like osteomielitis.

Bone tumors: Severe pain due to neoplasic tissue invasion of bone.

Joint disease: Multiple pain mechanisms involved: inflammation (septic, crystal induced, immune reactions), joint effusion (increased intra-articular pressure), release of cartilage-derived macromolecules and calcium-containing crystals, irritation of periarticular structures and subchondral bone.

- Muscle pain syndromes: mechanical and chemical factors involved such as inflammation, ischemia, toxic necrosis, myofascial pain syndromes, or inflammatory myopathies such as polymyositis, dermatomyosistis and the polymyalgia rheumatica.

It is hard to argue that local nociceptors are the number one contributors to a pain experience, but as we have discussed, nociceptors and nociceptive fibres do not necessarily require tissue damage to be activated. The remaining nine kinds of contributors to pain syndromes will be discussed in the next issue (May 2019). Interestingly, all of them can become at times, more important contributors to a pain syndrome that any local nociception.

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May 2019

Reframing pain

Developing a healthy narrative

PAIN MANAGEMENT

COMPLEX PAIN

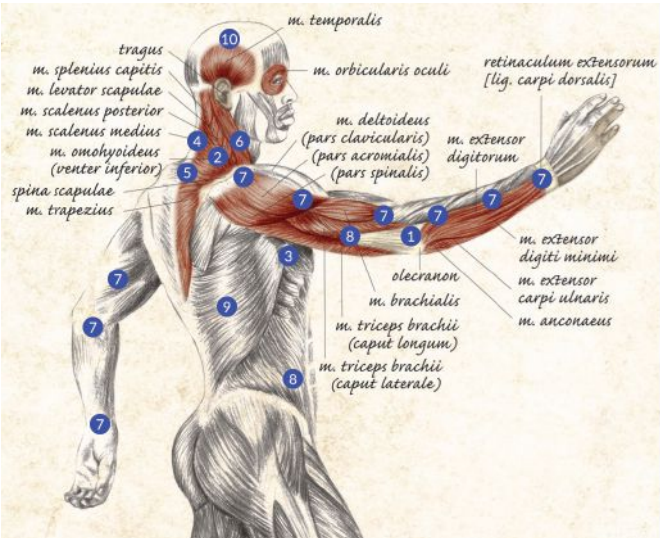
Common sources of neurological amplification: Part 2

BY ALEJANDRO ELORRIAGA CLARACO

In the last issue, a general introduction to the complex topic of "pain with movement" disorders was provided with a detailed discussion of the first contributor to a pain syndrome, i.e. the activity of local nociceptors with receptor fields on dermatomal, myotomal and sclerotomal tissues. An important caveat was provided associated with this idea – the well-known neurofunctional fact that *activity of local nociceptors does not necessarily require tissue damage*. This is one of the most frustrating facts associated to pain syndromes, as in our clinical search for reasons to explain pain symptoms, we tend to naturally believe that some sort of tissue damage has to be present, forgetting that pain is ultimately a brain event and that even at the tissue level, the main contributors to any nociceptive activity have to be either purely neurological (i.e. neuropathic behavior of peripheral nerves) or have an effect on the activity of the nociceptive fibres and/or their receptor fields (e.g. biochemical changes in the perineural space). Let's briefly discuss the next five (of 10) most important contributors to pain syndromes.

#2: REFERRED PAIN FROM TRIGGER POINTS

Referred pain from trigger points (TPs), mostly in muscles and fascia, but also in ligaments and capsules, are neurofunctional clinical entities responsible for the famous Travell and Simons' **myofascial pain syndromes**. In the example provided at right (an elbow pain syndrome), number two corresponds to a supraspinatus muscle trigger point that is referring pain to the elbow, something I've encountered numerous times over the years. The fascinating phenomena of trigger points and referred pain have revolutionized the way we deal with common pain syndromes where a structural problem cannot be found, despite the often-surprising intensity of the pain experienced by the patient. Several decades ago, in their seminal two-volume work *Myofascial Pain and Dysfunction, the Trigger Point Manual*, Janet Travell and David Simons presented to the medical community the foundation for the understanding and effective treatment of many common pain syndromes that were previously a mystery for most health care practitioners. Some important clinical facts associated to TPs:



- Muscles harboring TPs have painfully restricted full range of motion and localized tenderness on palpation. TPs are more common on girdle muscles (shoulder and hip regions, neck and lower back) and mastication muscles. They affect about 30 per cent of the population.
- TPs can be active or latent. When active, these TPs can cause a pain syndrome perceived elsewhere. The territories where pain is perceived by the patient show marked individual variations within a typical referred pain pattern for a given muscle.
- It appears that both peripheral and central mechanisms are involved in the contribution to the phenomena of referred pain from muscles and fascia, and that myelinated fibres are involved in the peripheral component.

Obviously a full discussion of this rather large subject is beyond the scope of this article, but I'd like to encourage

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clinicians to always look for these proximal and distal contributors to the pain experience, even in acute injuries, as an acute event may elicit the activation of previously dormant trigger points, making the clinical picture more difficult to understand. There could be inconsistencies in the symptoms relative to the structural extent of the acute injury that can only be explained by the activation of those pre-existing TPs. Functional "deactivation" of TPs using needling techniques such as neurofunctional electro-acupuncture or dry needling is the current gold standard for dealing with these important contributors to pain syndromes. However, other therapeutic approaches using miscellaneous manual techniques have also proven valuable in the management of these syndromes.

#3: REFERRED PAIN FROM VISCERA

Visceral trigger points (VTPs) are the equivalent to the myofascial TPs discussed above, and curiously, they were known long before Travell and Simons published their books. For instance, in the last half of the 19th century, Dr. Henry Head, later the editor of the journal *Brain*, published a number of articles, with beautiful drawings, presenting the many clinical observations he had gathered from patients with visceral disease that manifested pain on the trunk and girdles. The beautiful image(s) provided on page 20 is from Dr. Head's article "*On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease. Parts I and II*" published on the journal *Brain* in 1893!

Some insight into pain from visceral origin:

- A number of nerve fibres are involved in this phenomenon, such as C and A-delta fibres: intensity coding receptors, high threshold receptors, and silent nociceptors.
- Multiple causative factors could be involved in the activation of the above-mentioned fibers: distension, necrosis, inflammation, and ischemia.
- Clinically, pain of visceral origin is usually poorly localized, and most of the time is accompanied by reflex autonomic manifestations such as nausea, vomiting, diffuse sweating, anxiety, and unpleasantness. Visceral pain frequently refers to somatic structures that are innervated by fibres in the same spinal segments as the innervation of the diseased visceral organ; these can produce referred muscle hyperalgesia and increased contractions in that territory. Another common examples of this phenomenon include shoulder pain from gall bladder or liver disease, or problems in the ureter felt on the lumbar musculature.

CONTINUED ON PAGE 20

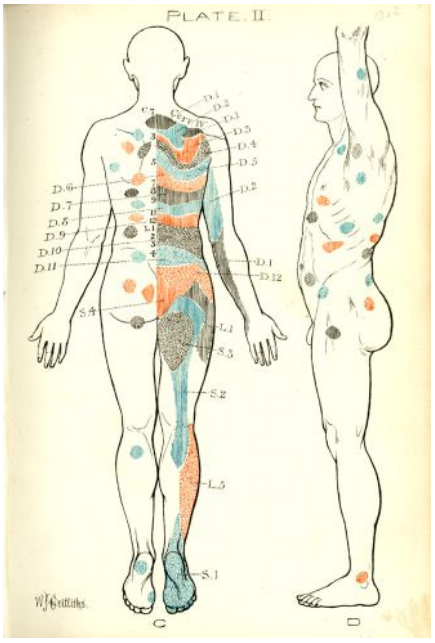
COMPLEX PAIN

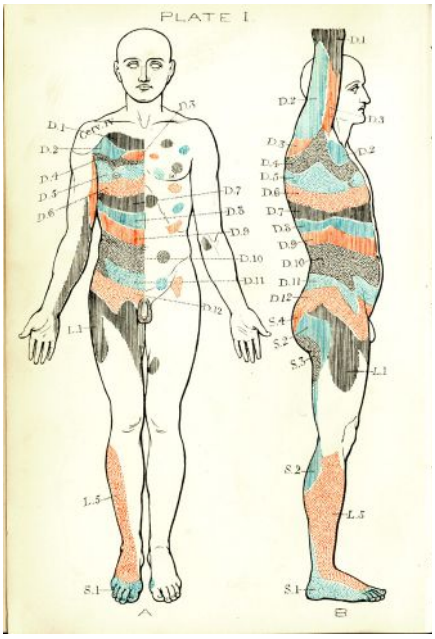
CONTINUED FROM PAGE 17

- A clinical finding from heart disease: angina pectoris pain may refer pain to the neck and jaw. Interestingly, sympathectomy reduces angina pain but not the neck and jaw pain, making very likely that vagal afferents contribute to the expression of this particular referred pain pattern.

#4: SPINAL SEGMENTAL SOMATIC CONTRIBUTIONS

Refers to neurological activity originating in the spinal cord segments that provide innervation to the clinically affected dermatome, myotome and/or sclerotome. The most common reason for this abnormal neurological activity is a "neurofunctional disturbance" in the spinal segment, which triggers some sort of irritation of the afferent sensory neurons whose cell bodies are located in the dorsal root ganglia of the spinal nerves. In turn, this irritation causes the neurons to secrete numerous vasoactive, pro-algic and pro-inflammatory substances such as substance P, CGRP (calcitonin gene-related peptide), neurokinin A, endothelin-3,VIP (vasoactive intestinal polypeptide), 5-HT (serotonin), nitrix oxide, and inflammatory cytokines like IL-1 and IL-6 (interleukines) and tumor necrosis factor alpha, in their own receptor fields (both at the periphery and at the spinal cord). These substances are immune-active and vasoactive and cause leaking of the small vessels with accumulation of liquid and solid materials from the plasma extravasation that eventually leads to a "sensitization" of the receptor field of the neuron both in the periphery of the body and at the dorsal horn in the spinal cord. In a nutshell, the process of neurogenic inflammation that may take place in a very short time after an injury or from exposure to an allergenic substance or an immune system threat, but that usually develops over longer periods of time (months and years) due to non-specific segmental dysfunction. Neurogenic inflammation results in, and is the result of, what has been called Spinal Segmental Sensitization Syndrome, a





physiopathological state that clinically presents with one or several of the following: segmental hyperalgesia with allodynia and hyperalgesia in the associated dermatome, hyperalgesia in the corresponding myotome (with trigger points), hyperalgesia in the associated sclerotome (with or without structural enthesopathy), and sympathetic hyperactivity (with tissular microedema and/or visceral dysfunction) in the territories supply by the preganglionic sympathetic neurons associated to the involved spinal segments.

In the past, clinical syndromes associated with spinal segmental sensitization and associated intervertebral dysfunction, have been explained clinically by mechanistic concepts that are no longer sustainable, such as the osteopathic lesion or the chiropractic subluxation complex. To me, these mechanistic concepts need to be replaced by the physiologically sound (and evidence-based) Spinal Segmental Sensitization Syndrome briefly described above. Based on research, we know that is associated with complex biochemical, neurological and immune reactions, all functionally related to the peripheral nervous system active role in modulating innate and adaptive immunity, as well as its role in the integrative protective function in host defense and the response to tissue injury.

#5: SPINAL SEGMENTAL SYMPATHETIC NEURONS CONTRIBUTION

Although most studies emphasize the contribution of the primary afferent C fibres to neurogenic inflammation as discussed in #4, there is also evidence for a contribution of sympathetic postganglionic terminals, which are in direct contact with spinal sympathetic neurons, which in turn are connected with spinal somatic neurons at the same levels. It is well established that the sympathetic nervous system is involved in a host of physiological responses evoked by noxious stimulation, including changes in blood flow to muscle and skin, changes in blood pressure, heart rate, sweat glands secretion, and pupil diameter.

Studies in cats have shown that noxious stimulation of the skin caused inhibition of skin sympathetic neurons while most muscle vasoconstrictor neurons in that territory were excited. This occurred in both anesthetized and spinalized cats, suggesting the involvement of a spinal reflex similar to the one on the brain stem. In people with spinal cord injury, it's known that episodes of sudden increases in blood pressure are due to a spinally mediated reflex activation of sympathetic vasoconstrictor neurons supplying skeletal muscle and the gut. It my opinion, the net effect of the spinal segmental sympathetic contribution to

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PAIN MANAGEMENT

NO SIMPLE SOLUTION

Common sources of neurological amplification, part 3

BY ALEJANDRO ELORRIAGA CLARACO

In the first article of this series, a detailed discussion of the number one contributor to a pain syndrome was provided (the activity of local nociceptors with receptor fields on relevant dermatomal, myotomal and sclerotomal tissues) (April 2019). The second article discussed trigger points contribution from both myofascial tissues and viscera, as well as spinal contributions from somatic, visceral, and vascular sympathetic relevant levels of innervation, which also included post-ganglionic neurons from pre-vertebral and visceral ganglia (May 2019).

Let's discuss the remaining contributors to pain syndromes.

#7 KINETIC CHAIN RELATED CONTRIBUTORS

Proximal and distal joints, proximal and distal muscles, and all associated peripheral nerves, whether cutaneous, articular, sympathetic or motor branches. These contributions, although not fully understood and difficult to define by its non-linear nature, are confirmed when pain with movement problems improve greatly and unexpectedly after the kinetic chain is treated.

One explanation for this non-linear improvement could be the restoration of movement variability and the improvement of tensional behavior on the kinetic chain, both produced by a variety of qualitative changes on different tissues, such as the trophic changes in the subcutaneous tissues, the articular restrictions due to synovial changes or micro-edemas of the periarticular regions, the miscellaneous regional edemas, or the micro-edemas of the peripheral nerves, particularly small articular branches

#8 TENSIONAL INTERRUPTIONS OF THE CONNECTIVE TISSUE NETWORK AND OTHER INTERFERENCE FIELDS

Pervasive connective tissue and tensegrity system of the body extends from the cell cytoskeleton to the thick fasciae that wrap up the muscles, to the skin. The main cause for these interruptions is scars of all sorts, whether in the vicinity of the pain problem or anywhere else in the body, including scars in mucosae (like scars from tonsillectomy or a dental infection). The relationship between scars and pain at a distance is well documented in the scientific literature (particularly in German), and a whole treatment system called "neural therapy" developed by German physician Dr. Ferdinand Huneke, has been widely used in many countries for nearly 100 years. Dr. Huneke considered scars (as well as disorganized tissue from infections) interference fields that cause dysfunction of the autonomic nervous system, therefore affecting the body in different extent at different levels, i.e. locally, regionally and globally. He used a local anesthetic agent to block this interference field and prevent it from continuing sending afferent signals to the central nervous system – signals that were causing abnormal sympathetic nervous system activity and contributing to the pain problem.

#9 METABOLIC, ENDOCRINE, AND SYSTEMIC FACTORS

Together with #10, this could be the most complex aspect due to the intrinsic difficulty in defining (with precision) the many metabolic aspects potentially involved: hormonal, cellular, extracellular, tissular,systemic, gastrointestinal, enzymatic, cytoplasmic, mitochondrial, etc. Here are a few relevant metabolic facts concerning pain problems:

- Hormones influence pain perception by 1) altering the activity of primary afferent nociceptors or their terminal connection at the dorsal horn, and 2) altering the processing of emotions in the limbic system (altering pain perception). Numerous studies indicate that women have greater sensitivity to deep-tissue (muscle) pain than men. The difference decreases after 40 but is still there after 50. Women experience more pain than men in response to the same noxious stimulus. A study of 121 Swedish patients showed that the benefits of cognitive

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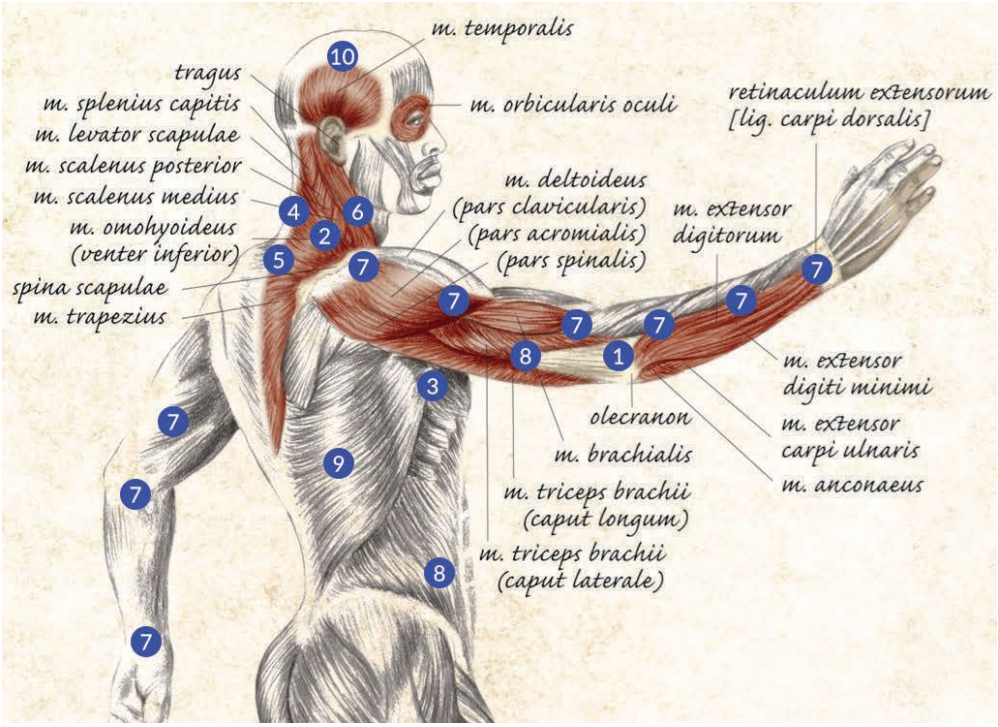

behavioural-based treatments for neck, shoulder, and back pain were confined to women.

- Two major hormonal systems influence pain: sex steroids and hypothalamic-pituitary-adrenal (HPA) axis: CRH-ACTH (corticotropin-releasing hormone and adrenocorticotropic hormone).
- A number of metabolic deficiencies cause sufficient impairment of muscle metabolism that could be a primary causes of muscle pain. E.g. McArdle's disease (myophosphorylase deficiency that compromises glycolytic metabolism affecting type II fibres), carnitine palmitoyltransferase deficiency (that affects mitochondrial oxidative metabolism), or hypothyroidism (lack of energy in the muscle cell).
- Sympathetic dysfunction will cause abnormal metabolism of the neuromuscular junction.
- Emerging data suggest that the function and health of the CNS is modulated by the interaction between: 1) neurotransmitters, immune signalling, hormones, and neuropeptides produced in the gut. 2) the composition of the gut microbiota, and, 3) integrity of the intestinal wall serving as a barrier to the external environment

#10 CENTRAL NERVOUS SYSTEM FACTORS: SENSITIZATION OF NOCICEPTIVE PATHWAYS AND CENTRAL SUPRASPINAL CENTERS WITH AUTONOMIC, PSYCHOEMOTIONAL, AND STRUCTURAL/NEUROPLASTIC CHANGES

A vast topic, and an area of study in rapid development. Also, as pain is a brain event, all the factors discussed in numbers 1-9 need to be put in context in relation to the effects they may have in each particular brain neuromatrix. Some relevant points:

- Central neuropathic pain may occur associated to post-traumatic hyperirritability syndromes, spinal cord injury, brain injury, stroke, multiple sclerosis, CNS tumours, or complex pain syndromes such as fibromyalgia, where there is a disturbance of central pain processing (neurosensory amplification) but with a peripheral sensitization component (including myofascial TPs).
- The anterior cingulate cortex (ACC), a component of the limbic system, is related to many pain processing functions including anticipation, anxiety, attention and the distress of pain.
- The CNS can adapt to peripheral and central injury by the neuroplastic reorganization of cortical somatosensory somatotopic maps. Due to somatic sensory cortex anatomical and functional divisions, lesions of this region can leave a person capable of feeling pain but incapable of localizing it accurately.
- Preliminary work indicates that interventions that alter peripheral nerve input by utilizing a correlated conditioning afferent stimulus, may trigger beneficial sensorimotor reorganization and improve clinical outcome in chronic pain.
- The insula plays a role in the effective processing of pain. In addition to processing nociceptive input, the insula also processes visceral sensory and motor activity. The insula has descending projections to the brainstem through which it exerts control over the autonomic nervous system as well as apparently regulating the descending pain control systems.
- Thalamic nuclei have widespread cortical efferents projecting to frontal, parietal and limbic regions throughout the cortical and subcortical pain systems.
- A common spinal mechanism of sensitization: increased efficacy of synaptic transmission between primary afferent and spinal neurons with the involvement of NMDA (N-methyl-D-aspartate) glutamate receptors, or activation of NK1 (neurokinin) receptors by substance P.
- There has been a shift towards neuro-inflammation and hence glial cell activations specifically in the dorsal root ganglion and spinal cord as a mechanism possibly driving the transition to chronic pain. This has led to a focus on non-neuronal cells in the peripheral and central nervous system.
- The activation of microglial cells in response to nerve injury has been implicated in the development of neuropathic pain.

After reviewing the 10 most common contributors to pain syndromes, it is clear that the complexity of the pain experience requires clinicians to always take a multi-dimensional approach to the analysis and treatment of these problems.