A Brief History of Sensitization

Robert Cartwright DO, ND, LicAc., Simeon Niel-Asher BPhil, BSc (Ost)

Our knowledge of the brain and how it is connected to our periphery has been changing at breakneck speed. It's really hard to keep up to date with all the new science, which is, with the advent of modern communications, accreting at the speed of a giant neural network. Recent years of neuro-scientific investigation have been revolutionized with technological marvels, such as the 'functional magnetic resonance imaging' machine (fMRI). An fMRI highlights areas of the brain in real-time whilst the periphery is undergoing specific stimuli. These technologies have given us a fascinating insight into deepest workings of the entire nervous system, both peripheral, autonomic and central. What they reveal is a complex hierarchy of self from the skin on the tips of our toes to the hair on our head.

Most pain signals are initiated by peripheral nociceptors, which enter the dorsal horn (DH) of the spinal cord and from there go to the mid brain housing our emotional, behavioral and cultural centers. Finally, having been modulated these signals are orchestrated and managed centrally by the neo cortex. The way each of us responds to pain is affected by our culture, genotype and phenotype. The complexity at work is both beautiful and terrifying from a body-worker perspective. What is for sure however is that these concepts are relevant, important and potentially game changing if we can understand them in their full beauty. Why do some people feel pain more readily? Why do some patients have a stronger treatment reaction than others? How can we tailor our therapeutic approaches to best serve our patient? Pain perception, sensitization and our reactions to pain are on a spectrum. By the time you have finished reading it, we hope to have explained some of the new science behind pain and show you how it relates to the 'clinical coalface'.

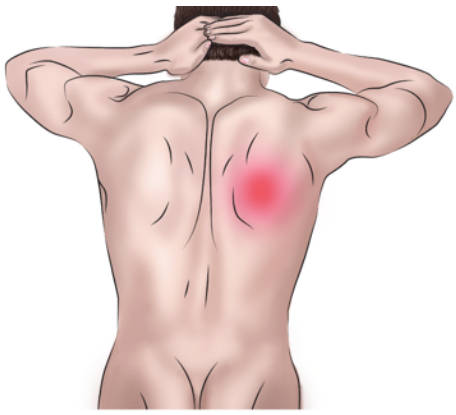
We were both inspired to write this paper independently trying to understand these phenomena from a 'bottom up' perspective. Over many months of collaboration, we have explored the science from an holistic and osteopathic perspective. As we take this journey we will stop on route explore how peripheral nociceptive stimulation can lead to altered motor output, not only within the musculoskeletal system but also in the visceral and endocrine systems. We will follow the science from the 'first order' (very Star Wars) small fiber sensory system, which undergoes sensitization (nee facilitation), peer into the genetics and eventually make our way to the higher centers in the cortex where we will explore the exciting field of neuroplasicticity.

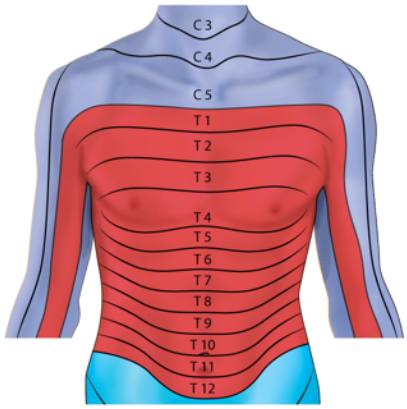
Pain Is a Big Stimulus
Pain is a highly motivating symptom for the nervous system: it is our alarm bell that something is wrong. We are born with a number of protective mechanisms prewired into our nervous system. When we touch something hot, we quickly withdraw our hand; when we smell something unpleasant we turn or move away. Our sensors sift our environment and provide a constant stream of sensory information for body awareness.

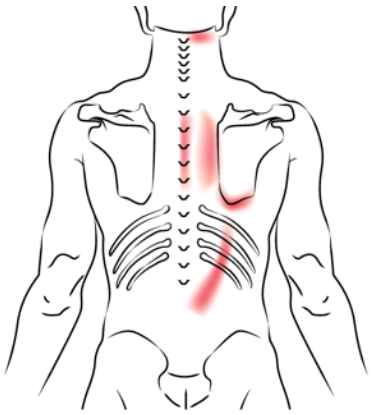
Broadly speaking, pain is there to help to bring awareness that something is wrong and needs addressing. When the body is damaged it tries to do (at least) two somewhat opposing things simultaneously.

1) It tries to avoid further injury and
2) It starts organizing its repair mechanisms to move it back towards homeostasis (homeodynamic balance).

The Three Degrees
Broadly speaking there are three types of pain:







Nociceptive Pain	**Neuropathic Referred Pain**	**Somatic Referred Pain**
Localized Area	Radiating Pain	Facet Joint?
Signs of inflammation	Uni or Bi Lateral	Muscles?
Associated with history of:	Symptoms of neuropathy (eg. Shingles):	Myofascial trigger point MTrP?
• Trauma	• Paranesthesia	Ligament?
• Infection	• Burning/Causalgia	No signs of inflammation
• Cancer	Signs of Neuropathy:	
• Steroid Use	• Allodynia	
• Viscus?	• Hyperaesthesia	
	• Hyperalgesia	
	Look for vertebral damage	

Neuropathic, Nociceptive and Somatic Referred Pain
In back pain, for example, approximately 85% of pain that presents to physicians is somatic referred. Approximately 5% of pain is neuropathic, due to frank nerve damage (Neuropraxia, Neuroptnesis, Axonoptnesis) pathology and 10% of pain is nociceptive i.e. due to nociceptor activity (Vulfson 2015).

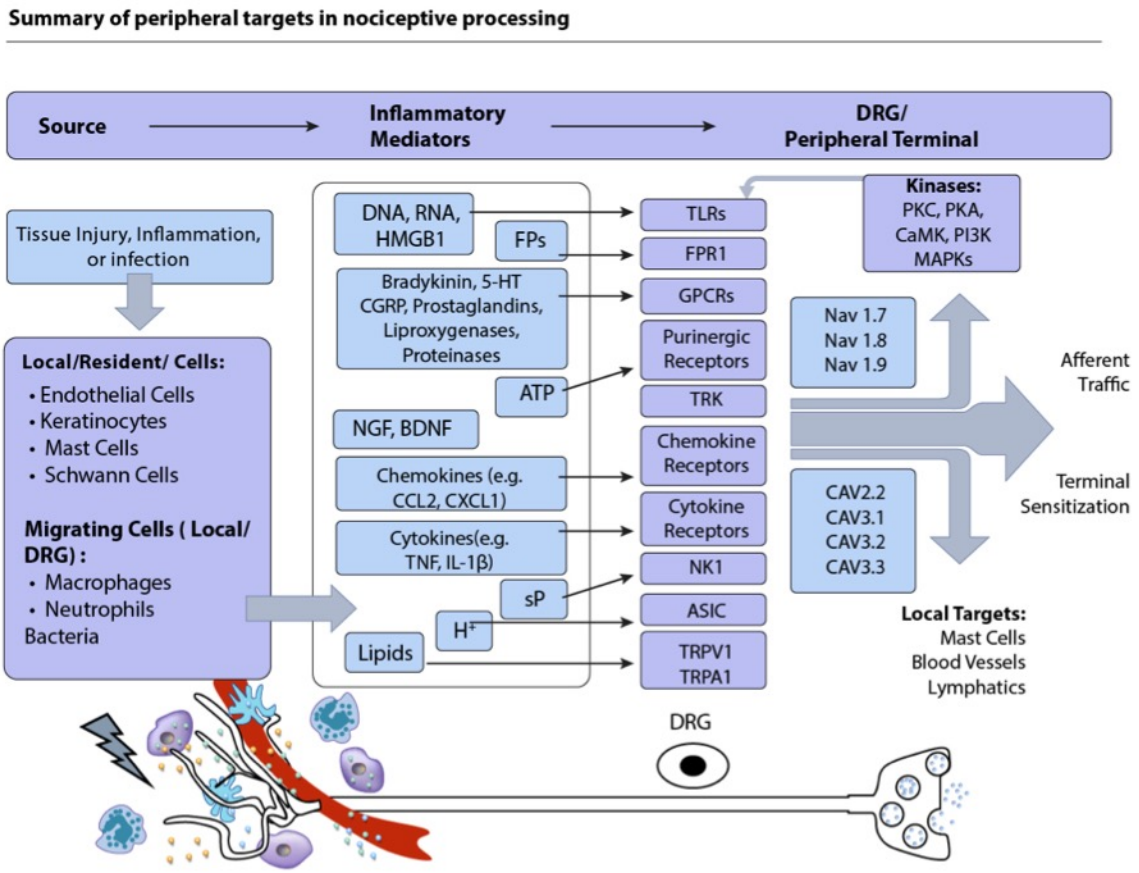
Nociceptive pain is the type of pain you get from a pathological viscus or the pain associated with cancer. Neuropathic, is the type of pain associated with sciatica or shingles. Somatic referred pain has also been called 'myofascial' pain (Gerwin 2015)[10], and that's the stuff we like to treat.

Nociceptors
Nociceptors inhabit virtually every nook and cranny of the body (apart from nucleus pulposus, parenchymal tissue of the CNS and hyaline articular cartilage) especially muscles (Type III & IV) they are part of our holism. They are responsible for incoming information about the external environment which enables the CNS to make reflex and considered responses.

In broad terms, there are two main classes of nociceptor:

Medium fiber myelinated	these afford acute "first order" well defined pain
C-fiber unmyelinated	slow pain which is less well localized

Nociceptive processing
In order for nociceptors to fire there must be both sufficient input or summation to reach the firing threshold sufficient to overcome the dampening down or innate inhibitory mechanisms of the cortex. The following graphic will give you some insight into the complexity of nociception from stimulation, to the dorsal root ganglion, and onwards from there. As you can see, a number of factors can induce nociceptors to reach action potential including tissue damage and inflammation. Once these factors have initiated the stimulus other factors such as ion channels within the receptor can up-modulate or down-modulate the signal and change it to subthreshold if required. These channels are mainly Sodium (NaV), Calcium (CaV) or Potassium. The ion channels themselves are subject to genetic variation each of us therefore has a different baseline for 'action potential' stimulation.



Trigger points and somatic referred pain

Somatic referred pain has also been shown to be related to the presence of myofascial trigger points (MTrP's) within muscles. Trigger points are discrete exquisitely painful nodules embedded in taut bands of muscle. They make the muscle shorter, fatter and less efficient. If untreated trigger points can add not only be a source of nociceptive pain but their ongoing presence can be a source of ongoing afferent signals to the nervous system. This barrage can contribute towards ongoing sensitization/ facilitation of the spinal cord. Kawakita et al (2002) suggested that trigger points themselves maybe "sensitized neural structures" called polymodal receptors (PMR's). These PMR "sensory terminals" exist in situ within muscles in the form of free nerve endings (receptors). The theory is that these "PMR" are switched on under certain physiological stimuli making them tender, morphing into what we now call trigger points.

A Brief History of Sensitization

"Yes, Osteopaths knew all about it first – remember facilitation?"

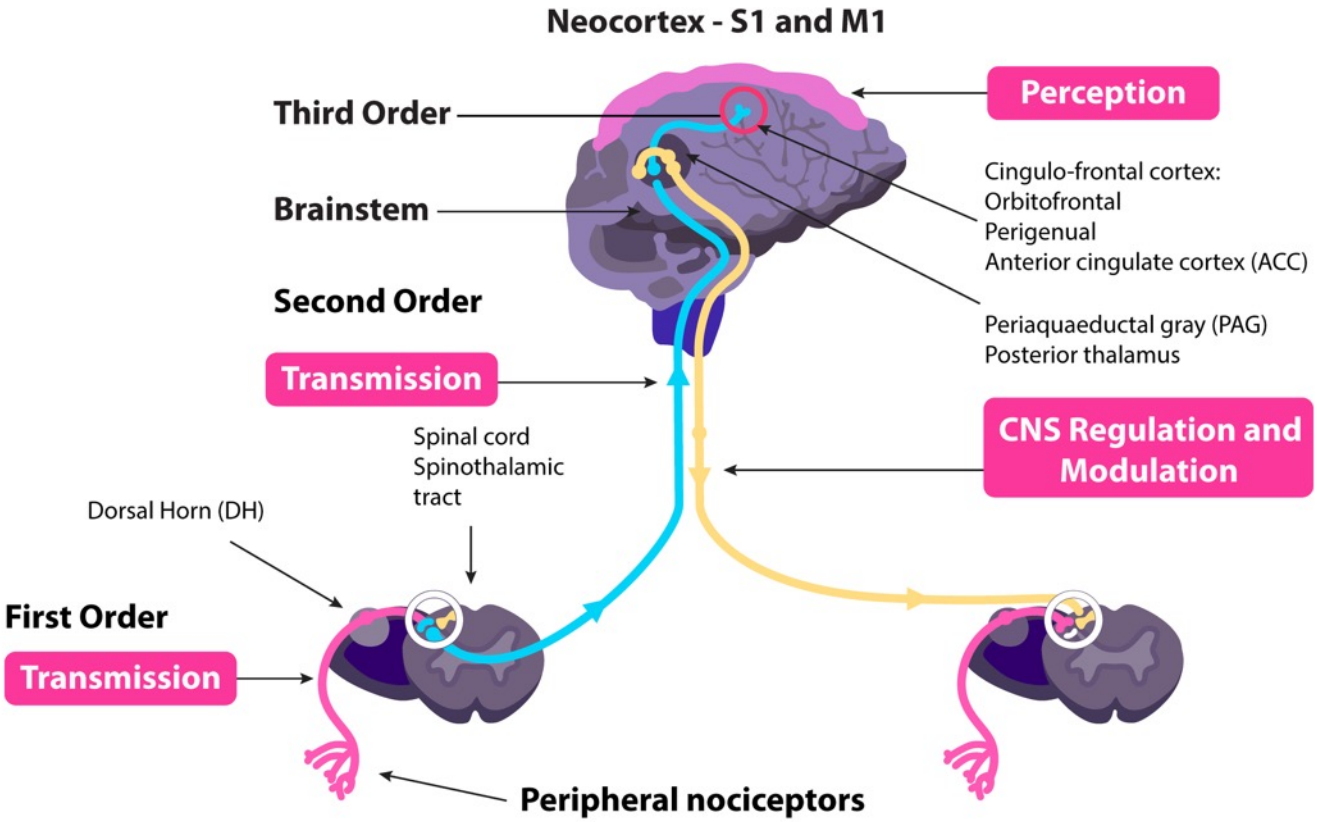
In the 1940's pioneering research was undertaken at the Still Memorial Research Trust by the researcher John Stedman Denslow DO. Denslow (and later by Irvin Korr PhD) demonstrated that when a person is lying prone in a resting position, some areas of paraspinal muscles had increased tone in relation to others. After repeated experimentation it was reasoned that these areas where caused by 'osteopathic spinal lesions', now referred to as somatic dysfunction (SD). What was the cause of this phenomenon? Denslow and Korr both asserted that a range of issues might be underlying such as postural adaptation/loading to stress and strain, previous injury or stimulation from a viscus (viscero-somatic reflex). These areas of paraspinal hypertonia varied from one individual to another. Measurements were made using a pressure meter (algometry), the pressure applied to an area had to be sufficient to provoke action potentials on EMG; these were then compared to the "normal" areas. What Korr noticed was that areas of somatic dysfunction needed far less pressure to provoke an action potential when compared to "normal" regions.

Experiments by Denslow found strong evidence which indicated that the different thresholds to pressure stimuli were due to both peripheral and central factors (Denslow 1944).

Three years later Denslow had refined his research and along with Korr and Krems published a paper called "Quantitative studies of chronic facilitation in human motor neuron pools" (1947). The research presented confirmed that the reduction in threshold causing action potentials at lower pressures was a measure of 'facilitation' in the dorsal horn (DH) or what is now called "sensitization." During his research, Korr hypothesized that inflammation around nerve endings was the principle triggering factor. We now know that this is only partially true. Localized inflammation does indeed initiate the propagation of a number of chemicals such as histamine, substance P and cytokines within the fascia as part of the organization of the healing process. We now know that this is only a part of the story, but thanks to Denslow and Korr's insights, the notion of the 'facilitated segment' was born (Korr 1947) – and this is a great place to start our journey.

Inflammation, first, second and third order

Inflammatory substances excite the local free nerve endings of the **small fiber peripheral afferent** receptors (SFPA's) enough to trigger an action potential; these fibers are connected to the ganglia in the Dorsal Root (DRG) of the spinal cord (Sessle 2007). ***First order*** SFPA's carry information from the periphery about nociception and the region of potential injury to the Dorsal Horn (DH) and synapse with **second order** neurons which ascend the spinal cord. From the brainstem and thalamus afferent information is spread to multiple regions in the brain. These neurons ascend cranially and sprout into a multitude of brainstem nuclei sending collateral branches to other nuclei and networks. Finally, they synapse with **third order neurons** and from there onwards to the cerebral cortex.



Inflammation, Nerve damage and Sensitization – the science

The effects of inflammation on nociceptors have been extensively studied. Inflammatory mediating substances such as prostaglandin E_2, Bradykinin, Tumor Necrosis Factor (TNF) and Nerve Growth Factor act on the 'G-protein coupled receptors' or tyrosine kinase receptors on nociceptor terminals. By activating intracellular signaling pathways, phosphorylating receptors and ion channels in the nociceptor terminals, inflammation effectively reduces or lowers the action potential threshold. This has the effect of amplifying the volume of action potentials activating several signaling pathways in post synaptic DH neurons that mediate the induction and maintenance of DH sensitisation (Zhou 2002, Ji et al 2003, Scholz and Woolf 2002). Action potentials caused by peripheral nerve damage have also been demonstrated to initiate the release of the neurotransmitter glutamate and other neuro-modulatory substances. In other words, inflammation can trigger a series of events that cause pain to be felt more readily.

Perception, response and activation

The small fiber system is an important route to the activation and arousal of (wakefulness) the brainstem where it forms an elaborate network of connections. This activation leads to homeostatic (homeodynamic) changes throughout the body (Bremner 2006), via activation of the endocrine, immune and emotional 'centers'. The targets of these small fibers include the reticular formation, the parabrachial nucleus, the periaqueductal grey, the hypothalamus, pre-frontal cortex, hippocampus and the

amygdala (Foltz 1969). Some of the neurons which pass into the lower regions of the brainstem send fibers to the medial nuclei of the thalamus and then on to the prefrontal and anterior cingulate cortices which are components of and connected to the emotional center in the brain (the limbic system).

The problem with Korr

What Korr omitted in his paper "The emerging concept of the osteopathic lesion" was, DH facilitation *doesn't* go **directly** to the ventral root it follows a pathway up the spinal cord towards the cortex and en-route triggers a myriad of neuroendocrine and visceral responses via highly complex reflex mechanisms. Although, in his diagrams Korr did indicate the ascending direction of the impulses, the huge advances in neurobiology made since his seminal work have given us deeper insights. We now know that higher centers are also involved in facilitation (or sensitization). The afferent input from the periphery doesn't just cause a facilitated segment, ***it causes a facilitated or sensitized nervous system***. Impulses don't just pass through the facilitated area of the cord; they also create a sensitization pathway to the cortex. From the cortex they then send signals back to the target tissues, affording a path of lowered resistance.

So Korr was on the right path, muscle hypertonia, inflammation and an enhanced pain response. What is the current explanation for this paraspinal hypertonia? Let's pause a little on the science of these hypertonic muscles and explore this phenomenon from another angle. What are the other sources of stimulation that can trigger pain?

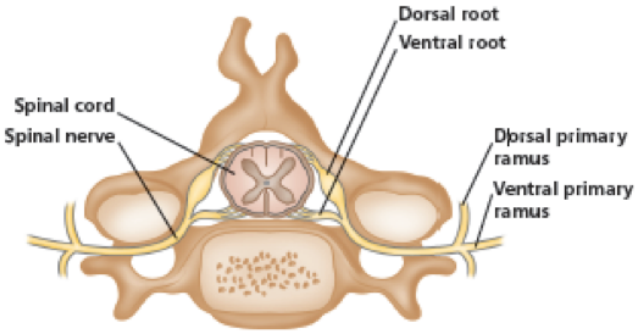
Referred Pain & Muscle Hypertonia

We are all used to the notion of a viscus such as the heart causing referred pain to the jaw and the left arm but we now know that this type of pain is also associated with increased muscle hypertonia, tenderness and frank trophic tissue changes. There is also a tendency for the stimulated muscle to atrophy, as revealed by a decreased thickness and section area of the muscle belly.

In patients with chronic kidney stones/calculosis in the urinary tracts, for example, muscle hyperalgesia is also associated with a lowered pain threshold (sensitization) and localized tissue tenderness. Another example of this can be seen with acid reflux in the lower oesophagus. The reflux causes viscera-visceral referred pain and also hypersensitivity in the upper oesophagus, over time this may also cause viscera-somatic referred pain (allodynia) to the chest wall (Sarkar et al 2000).

These changes are believed to start very 'early on' in the disease process and are proportional in extent to the number and intensity of visceral pain episodes and duration (Vecchiet L, Vecchiet J 1999). [This may mean that a patient presenting to us with somatic pain may be sometimes be suffering from an (early) visceral cause]. This is an early change that can sometimes be palpated before medical testing can reveal pathology. Korr noticed this phenomena working in the labs at the Kirksville campus, research subjects that were followed over several years would develop pathology in the neurologically related viscera to the dermotomes exhibiting increased sweat gland activity.

The latest evidence for viscero-viscero-somatic reflex
Again, we as Osteopaths are back on familiar territory and the mechanism for the muscle hypertonia is both fascinating and relevant too. Explored experimentally on rats by Giamberardino et al (2004), it seems to start at the level of the dorsal horn of the spinal cord and involve a peripheral nociceptor stimulation. "The visceral barrage, … is … likely to activate a reflex arc towards the periphery (afferent branch: visceral afferent fibers, efferent branch: somatic efferents) towards the muscle resulting in sustained muscle contraction and subsequent local sensitization of nociceptors". So here is some proof that the paraspinal muscle hypertonia may result from reflex phenomenon within the **peripheral** nervous system.



Somato-Visceral reflex
The same is true in reverse. Ventral nerve roots carry visceral efferent fibers innervating glandular and vascular tissue from the DH. This includes messages to smooth muscle, tissue of the viscera, fascia and also immunocytes. Evidence from Sato and Schmidt (1973) has previously demonstrated that DH sensitization alters the output in the ventral horn (now we know this is via the higher centres) and, that this is responsible for the vasomotor, sudomotor and organ specific changes seen in SD (Patterson and Wurster 2004) and from myofascial trigger points (MTrPs).

Sensitization and the Neuro-Endocrine Axis
Persistent incoming action potentials from the SFPA's, increase arousal and stress hormone production. In this environment, raised stress levels further increases cortisol levels. In turn, this increases the propensity to sensitization in a vicious circle of stress, afferent action potential, increased arousal susceptibility to sensitization and increased glutamate secretion. The nervous system responds by sending a motor response appropriate to the incoming sensory information. The resulting neuroendocrine reflex response leads to a cascade, stimulating not just target tissues, but also, secondary glandular, visceral and somatic structures. These reflex motor responses cause (secondary) symptoms if they are extensive enough.

Allostatic loading
The **allostatic load** is "the wear and tear on the body" which grows over time when the individual is exposed to repeated or chronic stress. In an individual with high allostatic loads, the persistent barrage of incoming sensory information overwhelms the inhibitory modulation system and the balance between the two is lost. An increase in allostatic

load can also be due to the presence of SD and MTrP's or from chronic ongoing sensory stimulation from a viscerosomatic reflex.

The lack of parity between incoming ascending and outgoing descending responses may be maintained due to heightened activity from **interoceptive** stimulation (arising from within the organism). An example of interoceptive stimulation is someone eating a diet high in indigestible processed food whilst worrying about things that may never happen.

In summary - action potentials coming from somatic and visceral nociceptive stimuli can be viewed as part of our defense mechanism. Their way of protecting us from tissue damage, injury or death is by initiating reflexes involving cardiovascular, respiratory and neuroendocrine responses, commonly referred to as fight or flight responses (Turrigiano, Nelson 2000). These changes have an immense effect on homeostatic (homeodynamic) regulation and if prolonged, allostasis (the process by which the body responds to stressors in order to regain homeostasis) and general adaptation. Prolonged exposure to stress hormones has a huge effect on many tissues, in general this effect is degenerative (McEwen, Stellar 1993).

CNS, the midbrain and pain modulation

We need to add another factor to the mix. We have a number of self-regulatory inhibitory mechanisms which help to modulate pain from nociception. These also take into account the functions of the emotion and higher centres. After all, we may not want to drop that hot cup of tea, especially when it is in an expensive china cup!

Neuroimaging studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used to investigate healthy volunteers. Ratings for pain intensity and unpleasantness and of pain-related activation have been studied in multiple areas of the brain. According to research, certain areas have been highlighted in response to pain. These are mainly the cingulo-frontal cortex (including the orbitofrontal) and perigenual anterior cingulate cortex (ACC), as well as the periaquaeductal gray (PAG) and the posterior thalamus.

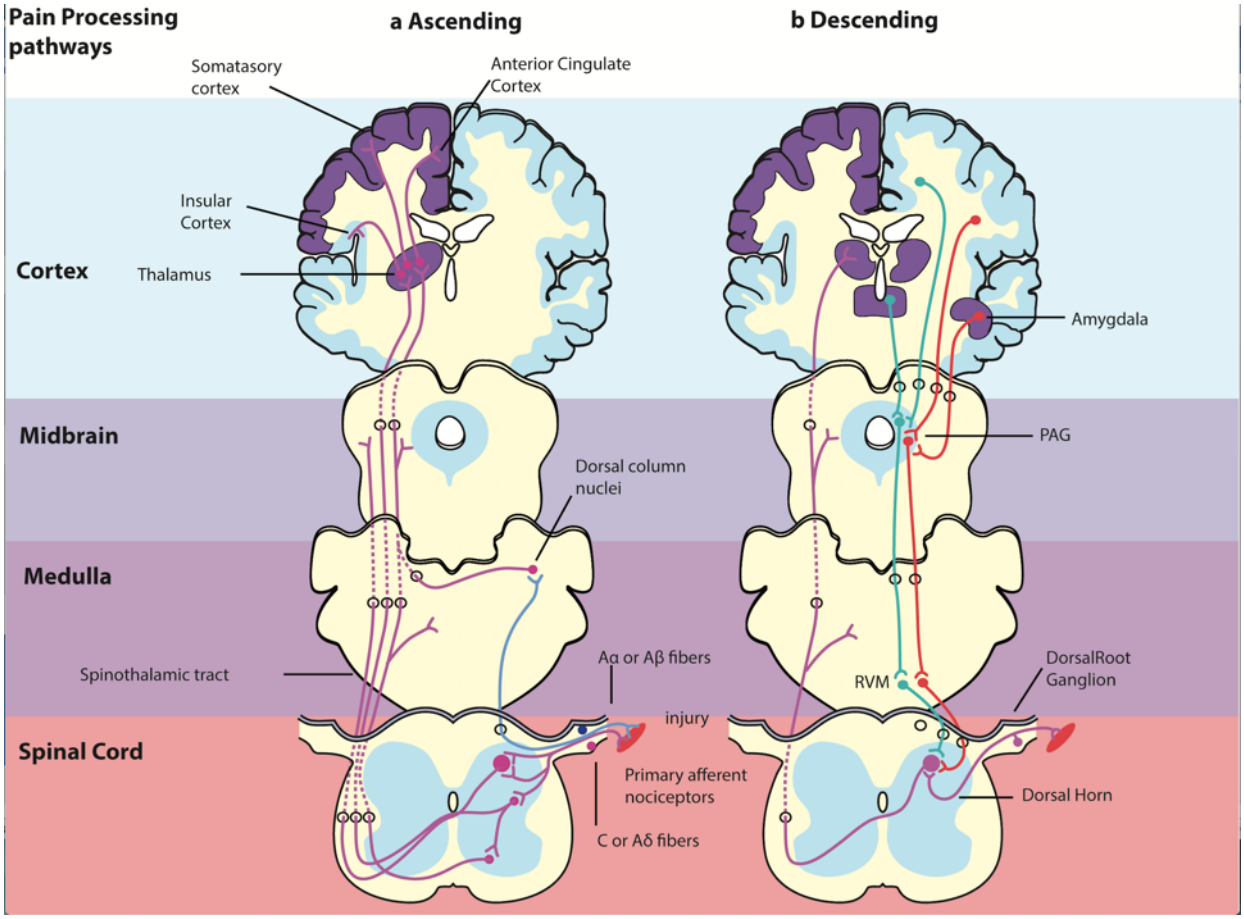
The midbrain takes the second order signals and modifies them. The higher centers and the midbrain work together to downgrade and modulate pain signals. It appears that the midbrain is very important in this process. It is believed that the cingulo-frontal cortex may exert top–down influences on the PAG and posterior thalamus to gate pain modulation.

Descending pain regulatory neurons in the rostral ventral medulla inhibit nociceptive transmission by several mechanisms:

1) Direct inhibition of projection neurons
2) Inhibition of neurotransmitter release from primary afferents
3) Excitation of inhibitory interneurons
4) Inhibition of excitatory interneurons

FMRI studies have shown that these mechanisms can exert bidirectional control of pain in response to higher order factors such as fear, attention and expectation. Opioid peptide synthesising cells and opioid receptors are distributed throughout the pain

modulating circuit. The release of endogenous opioid ligands (these are binding agents) at receptor sites can produce an analgesic effect. These substances function in part by reducing transmitter release from the dorsal horn terminals in the primary nociceptor terminals. They also direct post synaptic inhibition of central neurons that are activated by noxious stimulation. Endogenous opioids also contribute to pain modulation inhibiting neuropeptide release from the SFPA's.



The Midbrain - Soma, Viscera, Fight and Flight

From an anatomical perspective the reticular formation is the area of the brainstem where the cranial nerves connect, and is also a major target for the ascending visceral and somatic nociceptive fibers. Continued input into these nuclei from the SFPAs could potentially cause sensitization in any one of this array of areas. The nuclei respond and react reflexively to lower thresholds of action potential (sensitization). Stimulation by nociceptive action potentials from the SFPA's affect the reticular activating system and locus caerelius (LC), This stimulates monoamine pathways increasing stress hormones and sensitizing synaptic connections to the effects of **glutamate**.

Sensitizing neurotransmitters

Glutamate is an extremely common amino acid that is used in the biosynthesis of proteins; It also has a secret life – it is essential for the initiation of inflammation-induced central sensitization (Sessle 2007). These pathways have a very powerful effect on the hypothalamic pituitary adrenal axis effecting homeostasis and general adaptation. Glutamate receptors are also known to be more sensitive in the presence of the stress hormones from heightened anxiety or arousal which increases the likelihood of areas of sensitization or facilitation (McEwen, Sapolsky 1995). It is the principal excitatory neurotransmitter in the spinal cord and brain and it acts on a variety of glutamate sensitive receptors (Robinson, Coyle 1987). Some types of receptor are important for the rapid excitatory synaptic transmission of nociception, others such as n-methyl d-aspartate (NMDA) play a critical role in neuroplasticity and sensitization in the CNS. In general neurotransmitters work by increasing the sensitivity of the receptor membrane to glutamate. This neurotransmitter activity increases excitability, eventually induces plasticity centrally and reduces the factors which would normally inhibit excitability. Prolonged exposure to these will be a factor in plasticity[11] and also excitotoxic cell death.

Excitotoxicity is the pathological process by which nerve cells are damaged or killed by excessive stimulation by neurotransmitters such as glutamate and similar substances. This occurs when receptors for the excitatory neurotransmitter glutamate (glutamate receptors) such as the NMDA receptor and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor are over activated by glutamatergic storm. Excitotoxins like NMDA and kainic acid which bind to these receptors, as well as pathologically high levels of glutamate, can cause excitotoxicity by allowing high levels of calcium ions (Ca^{2+}) to enter the cell (Manev et al 1989, Jaiswal et al 2009). Ca^{2+} influx into cells activates a number of enzymes, including phospholipases, endonucleases, and proteases such as calpain. These enzymes go on to damage cell structures such as components of the cytoskeleton, membrane, and DNA.

Synaptic scaling and Hebbian plasticity

Hebbian plasticity is the name used to describe the increase in synaptic efficacy connected to repetitive firing. This is somewhat connected to Heads' and Hiltons' Laws which you may remember studying at college. It follows the notion that "cells that wire together, fire together".

Persistent stimulation of the presynaptic cell affects the postsynaptic cell resting potential – this is called Synaptic scaling (or homeostatic scaling) and it is part of our nervous systems economy/efficiency. The nervous system employs a form of homeostatic plasticity that allows single neurons to regulate their overall action potential firing rate. Like other physiological systems, neural electrochemical activity is subject to homeostasis. Mechanisms modify neural synaptic connections selectively, synaptic scaling works in unison with other homeostatic plasticity mechanisms to attempt to "normalize" all neural synaptic connections (Turrigiano, Nelson 2000).

People and pain

Back to one of our original questions, why do we all feel pain differently?

Phenotype vs Genotype
Recent genetic studies have put forward the notion of 'pain phenotypes'. Pain behaviour and its physiological sequelae are a constellation, a spectrum. The way we react to pain is coloured by a myriad of influences such as childhood, family, culture and disease (remember Charcots' joints?), however, pain is pain and the vast majority of us react to it in a similar way. Phenotypes have been studied from three major classes of initiating conditions:

(a) Acute high intensity stimuli
(b) Tissue injury/inflammation
(c) Injury to a specific peripheral nerve (mononeuropathy, e.g. crush, section), or to all peripheral sensory nerves (polyneuropathy, e.g. diabetes, chemotherapy, or an immune-mediated reaction).

In all cases the behavioural state initiated by these conditions are intrinsically aversive. Pain is associated with negative effects such as vocalization, facial expression etc. even upon the first (e.g. unconditioned) exposure. This supports the notion pain is somehow fundamental to our survival and it induces complex escape and avoidance behaviours.

Genoytpe
Thanks to cutting edge research we now know pain and sensitization also have a genetic component. Genetic markers have shown that there can be familial and or inherited pain reaction traits, for example in paroxysmal extreme pain disorder (Fertleman 2007) or in the Inherited condition called erythromelalgia where there is a genetic error in NaV 1.7 (Sodium) channel coding.

Where next?
Until now we have explored pain, nociception and the way inflammation affects the dorsal horn. Now we are going to explore what happens to the spinal cord and the midbrain (in more detail). Next we are going to look a little at the effect the peripheral nociceptor stimulation on the neocortex.

Peripheral and Central Sensitization

Pain systems need to be sensitive enough to detect potentially harmful stimuli, but not 'too' sensitive. If they are *not* kept in check, these systems can potentially cause us pain with no benefit. Hypersensitivity or sensitization may also arise because our pain pathways actually increase in sensitivity when they relay pain messages.

Peripheral Sensitization (PS)
It has been shown that up to 50% of muscle nerves are made up of nociceptors (Schaible 2006), and that nociceptors also innervate the connective tissue surrounding muscle. Persistent activation of nociceptors leads to PS. Here, SFPA exhibit an enhanced responsiveness to natural stimuli. PS occurs because of ongoing stimulus from all structures in the periphery innervated by the SFPA systems. It is interesting to note here that persistent MTrPs and SD can also induce peripheral sensitization.

PS occurs, therefore when the cumulative stimuli from muscles, MTrPs, SD, joints or the skin etc. are perpetuated over several weeks. The effect of PS is a lowered threshold for sensing pain. This, again, is part of our 'protect and defend' mechanism, making us more careful around the damaged or inflamed areas. We also know that (as discussed above) visceral structures can be part of the sensitization pathway.

We have already explored how inflammation in these structures can cause the sensitization process to occur. But spookily PS has been shown to occur even after an illness or injury has apparently healed! Furthermore, PS can occur if any of these these tissues have some ongoing stress such as congestion, lymphatic or venous engorgement, from postural strain or even SD and MTrP's. Microneurographical research has confirmed that SFPA's can even be active **without** our conscious knowledge or **without** us feeling pain (Treede et al 1992).

The blurred borderline between Peripheral and Central Sensitization
Over time the ongoing afferent barrage causes neuroplastic changes in the dorsal horn (DH). These ongoing action potentials have an effect not only locally on the spinal cord but also centrally, cascading through a multitude of areas in the upper CNS. When a noxious event occurs at the periphery, a number of gene inducing molecules within the SFPAs are released which enable sensory information to be passed to the CNS.

Stimulation of sufficient numbers of peripheral nociceptors in skin, muscle, connective tissues and joints and their associated tissues or in visceral organs initiates action potentials (summation), which are conducted through the minute SFPA's via second and third order neurons to the cerebral cortex; thus making us aware of the situation at the periphery. The perception depends on specifically dedicated receptors and pathways. Thus sensitization on the periphery starts the process of central sensitization via the DH.

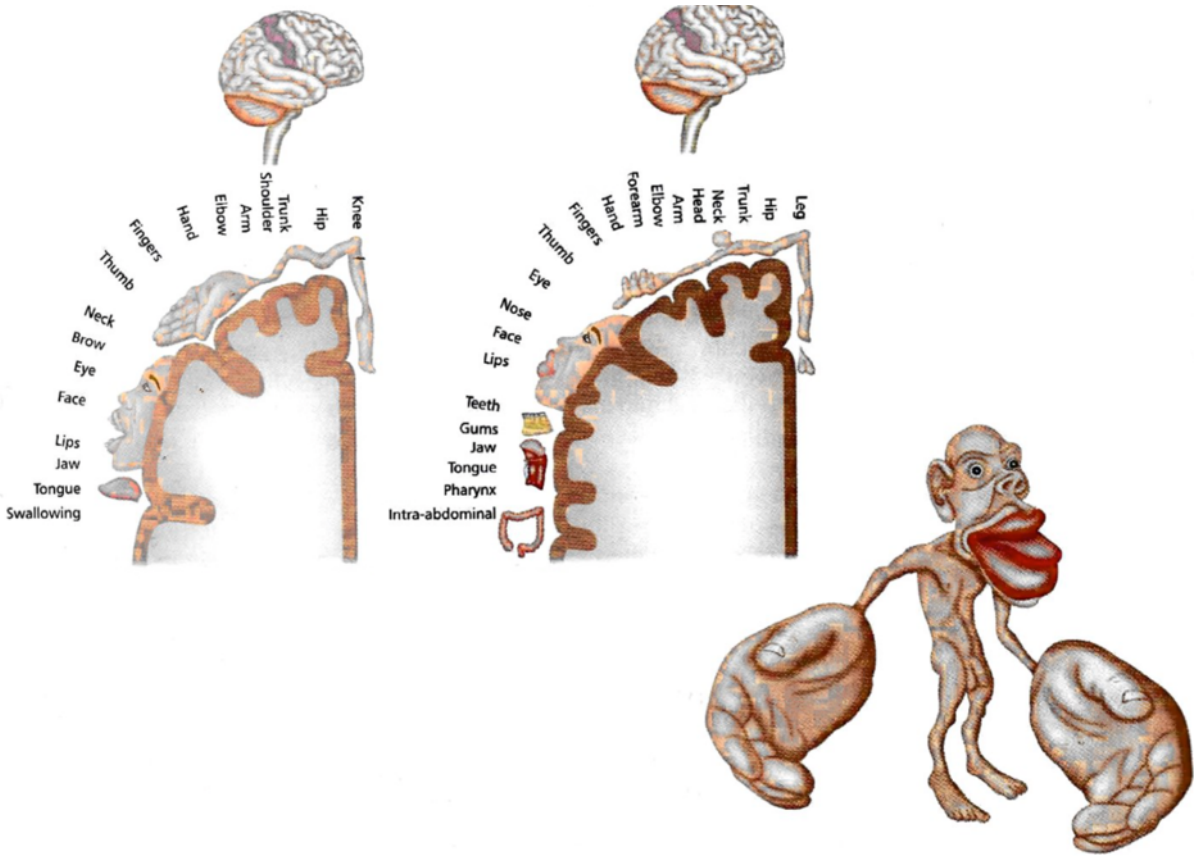
Central Sensitization (CS)

Over the course of time, if untreated the peripheral sensory changes move deeper into the nervous system and the pattern becomes established centrally. The superficial, the deep, and the ventral spinal cord show pronounced changes in their response properties (Schaible 2006). Following prolonged sensitization, an increased percentage of neurons in a segment respond to stimulation of injured or inflamed tissue. As with PS, the sensitivity of the spinal cord neurons becomes enhanced, so that an input that was previously subthreshold may now be sufficient to activate the neurons. However, this effect is massively magnified up and down the spinal cord over several segmental levels both caudally and cephalically in something called **'windup'**, this leads to greatly lowered activation thresholds. Central sensitization can persist for weeks, months, and even years, depending on the chronicity of the stimulus. **A patient who presents to us with CS will be very sensitive and almost certainly react strongly to treatment**. **We should thus modify our treatment plan accordingly trying to deal with the reasons why this sensitisation is in the area where it is rather than making a direct assault on the sensitised tissues.**

The suspected mechanism is:

- Repetitive stimulation of primary afferent nociceptors leading to a progressive increase in action potential discharge—a phenomenon called windup, which may lead to a **20-fold** increase in neuronal sensitivity.
- The result is an increase in intensity of pain and sensitization of neurons in the dorsal horn of the spinal cord because of the activation of N-methyl-D-aspartate (NMDA) receptors sensitizing the synaptic membrane to glutamate (the main stimulatory neurotransmitter in the CNS) and increasing the central sensitization.
- Sensory neurons from the dorsal root ganglia become sensitized to mechanical stimuli, so that only mildly painful stimuli become more painful—mechanical hyperalgesia.
- Sustained nociceptive input from active trigger points, irritated visceral structures or somatic dysfunction may not only sensitize dorsal horn neurons, leading to hyperalgesia and allodynia, but also generate expanded referred pain regions as the sensitization makes neuroplastic changes and takes over more cortical real estate.

Neuroplasticity
Neuroplasticity is in some ways a sequelae of longstanding central sensitization. The brains real estate is highly prized, there is a use it or lose it ruthlessness within it. As you may remember from Penfield and his maps (homunculus), different areas of the neocortex are thought to map to different regions of the body, there are Sensory (S1) and Motor (M1) maps.



Our body has an image of self 'soft wired' into the cortex. Soft wired because there is a degree of plasticity. For example, we are born with a map of four limbs which is constantly re-enforced by the summation of afferent inputs from nociceptors, proprioceptors such as tendon organs and muscle spindles and a host of other myelinated and unmyelinated sources.

What happens when we lose a limb?
Well nearly 100% of people develop a phantom limb. There are phantom limbs, nipples, rings and watches to name but a few. Neurosurgeon Dr. Ramachandran in his research on phantoms has demonstrated some startling and relevant experiments. He showed how stroking the face of someone with a phantom arm can reproduce the sensations in the missing am. Similarly, some patients report feeling their missing leg when their penis is stimulated! Why should this be?

Ramachandran explains that the area of the cheek represented in the S1 cortex lies next to the hand, similarly the leg and the penis are in very close proximity. The lack of incoming efferent impulses from the missing limb leads to a lack of signal and stimulus.

Over time this causes apoptosis of the limb afferent nerve cells in the brain. They are reabsorbed and the neighboring nuclei (from the cheek or the penis for example) invade the empty space.

Another interesting finding in the study of phantoms is that many people experience ‘super intense’ pain. Not only is this disconcerting but it is also traditionally difficult to treat. Current thinking is that the last input signal before the limb was lost is the dominant sensation that remains - a type of never ending echo. So if the arm was blown off by a grenade - the excruciating sensation of the arm exploding will continue indefinitely! This, is because the brain remembers the last signal and doesn't receive anything else to update it.

Ramachandran performed a simple but elegant experiment using a mirrored box (Ramachandran and Blakeslee 1998). In this experiment the good limb is put in a box through a hole with a mirror in the middle. The patient is asked to manipulate an object such as an orange and really focus on the mirror image limb. In a significant number of cases, patients reported their phantoms faded away or the pain diminished! Why? Well, the theory is that the body uses a different modality - the visual system to override the lack of efferent sensory referencing from the missing limb.

Think about it! This may have significant implications for physical therapy and Osteopathy, especially once we have looked at the ideas around sensation modification. Maybe therapeutic touch helps guide the nervous system and re-enforce our sense of self. Neuroplasticity is now actively used in rehabilitation after CVA or other neurological conditions. For more information, we highly recommend the books ‘Phantoms in the brain’ (1998) by Dr. Ramachandran and 'The brain that changes itself' by Norman Doidge, chapter 7 – Pain. 2008 Penguin books.

Putting it all together

Summary

Pain is a warning signal that something is wrong, it is part of our 'protect and defend' mechanism. In the healthy non compromised individual there is an even balance between incoming sensory information, the descending motor response and inhibitory systems. The nervous system employs a wide range of mechanisms such as synaptic scaling, Hebbian plasticity and neuroplasticity to help bring us back towards homeostasis (homeodynamic balance). Our body needs to regulate internal stimuli (interoceptive) and external stimuli (exteroceptive) striving towards homeodynamic balance. The SFPA system relays sensory information about the environment via the DH through first and second order neurons to the mid brain: cingulo-frontal cortex (including the orbitofrontal), perigenual anterior cingulate cortex (ACC) and the periaquaeductal gray (PAG) and the posterior thalamus. From there they sprout into a multitude of brainstem nuclei sending collateral branches to other nuclei and networks.

Sensitization (nee facilitation) is the way the nervous system lowers the threshold potential for firing pain signals. It allows us to perceive pain more acutely and act upon it to address the noxious situation. An individual who has persistent afferent bombardment into their CNS releases neurotransmitters such as glutamate causing the environment at the receptor site to overbear inhibitory mechanisms. This afferent bombardment from the periphery causes sensitization at the DH,[21] reducing the threshold for action potential "sensitivity". This then affects the ascending spinothalamic tracts to the brainstem where collateral branches and fibers are disseminated to a multitude of other structures and nuclei which stimulates arousal processes in the reticular activating system and the LC. These centers may also be involved in being sensitized if enough action potentials create the right environment for neuroplastic events to occur. Ongoing SFPA stimulation triggers arousal mechanisms and fight or flight responses within the hypothalamic pituitary axis increasing cortisol and epinephrine secretion causing a vicious circle of nociception-increased arousal-increased susceptibility to sensitization. Again, forcing the body to adapt to move back towards homeostasis.

Professor Bruce Dobson once wrote: "The manipulation of the sensory experience by therapists and patients may be the most formidable tool for the rehabilitation of motor skills." (Dobson 2003). With this in mind, areas of SD and or MTrP's may well be adaptations to the effects of physiological and biomechanical stress and strain. They may also be part of ongoing visceral and/or somatic sensitization. We must take great care not to make the chronic situation worse. Treatment should not be a direct assault on these areas but rather attempt to improve the structural compensations to reduce stress and strain, reducing the afferent bombardment into the CNS. Part of a sensible treatment rationale therefore would be to decrease the incoming action potentials from the small fiber system, this would be inclusive of dietary and manual osteopathic treatment, reduction of trigger points as well as other novel sensory type treatments. The aim of such treatment is to encourage neuroplastic changes to reduce central sensitization and encourage a healthier integration between the CNS and the soma. These are inclusive strategies of the osteopathic principle of "adjustment."

Take home points

- To become sensitized, a neural structure has to have a degree of ongoing stimulus.

- Neurons, receptors and pain perception are subject to disease, illness and genetic variation; both phenotype and genotype

- Myofascial trigger points, inflammation, somatic dysfunction and nerve damage can all increase the 'sensory input burden' if they are not addressed and lower the threshold for nerve action potentials.

- Stimulus starts on the sensory side and may be maintained by afferent bombardment from any structure in the periphery apart from hyaline cartilage and the nucleus pulposus.

- Ongoing peripheral bombardment first leads to local then peripheral sensitization and from there to central sensitization and neuroplasticity.

- Areas in the spinal cord and suprasegmental regions can become sensitized because of stimulus from the periphery.

- Sensitized circuits of the nervous system can effect immune, endocrine and visceral structures and therefore are a factor in the homeodynamic changes associated with frank pathophysiology.

- The nervous system employs a wide range of mechanisms to allow adaptation and to bring us back towards homeodynamic balance.

- Overlaid on this is are emotional responses learnt from previous experience from the limbic system/midbrain as an additional stimulus on the reticular activating system affecting the HPA axis.

- Patients may present somewhere on the sensitization spectrum. Knowledge of sensitization and neuroplasticity helps us to see the patients' symptoms in context and modify treatment programs so as not to aggravate symptoms, but to provide a rational pathway back to better health.

New References

Bremner JD 2006 Traumatic stress: effects on the brain. Dialogues in clinical neuroscience. 8(4):445-461

Denslow JS 1944 An analysis of the irritability of spinal reflex arcs. Journal of Neurophysiology 7:207-2161

Denslow JS, Korr IM, Krems AD 1947 Quantitive studies of chronic facilitation of human motoneuron pools. American Journal of Physiology 150:229-238

Dobson BH 2003 The Clinical Science of Neurologic Rehabilitation 2nd Edition. Oxford University Press, USA
Chapter 1, Organisational Plasticity in Sensorymotor and Cognitive Networks p.19

Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B, Ostman J, Klugbauer N, Wood JN, Gardiner RM, Rees M 2006 SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron. 52(5):767–774

Foltz EL 1969 The role of the limbic system in pain interpretation. Arizona medicine, 26(12):1033-1040

Gerwin B 2015 Myopain seminars, IMS series, Rambam Hospital, Haifa

Giamberardino MA, Affaitati G, Lerza R, Vecchiet L 2004 Referred Muscle Pain and Hyperalgesia from Viscera: Clinical and Pathophysiological Aspects. Basic Appl Myol 14(1):23-28

Jaiswal MK, Zech WD, Goos M, Leutbecher C, Ferri A, Zippelius A, Carrì MT, Nau R, Keller BU 2009 Impairment of mitochondrial calcium handling in a mtSOD1 cell culture model of motoneuron disease. BMC Neuroscience 10(1): 64. DOI: 10.1186/1471-2202-10-64

Ji R, Kohno T, Moore KA, Woolf CF 2003 Central sensitization and LTP: do pain and memory share similar mechanisms?. Trends in neurosciences 26(12):696-705. DOI:10.1016/j.tins.2003.09.017

Kawakita K, Itoh K, Okada K 2002 The Polymodal Receptor Hypothesis of Acupuncture and Moxibustion, and its Rational Explanation of Acupuncture Points. International congress series1238:63-68. DOI:10.1016/S0531-5131(02)00411-9

Kawakita K, Shinbara H, Imai K, Fukuda F, Yano T, Kuriyama K 2006 How Do Acupuncture and Moxibustion Act? – Focusing on the Progress in Japanese Acupuncture Research. Journal of pharmacological sciences 100(5):443–459

Korr IM 1947 The neural basis of the osteopathic lesion. Journal of the American Osteopathic Association 47:191-198

Korr IM 1948 The emerging concept of the osteopathic lesion. Journal of the American Osteopthic Association 48:127-138

Manev H, Favaron MA, Guidotti AL, Costa ER 1989 Delayed increase of Ca^{2+} influx elicited by glutamate: role in neuronal death. Molecular Pharmacology 36(1):106–112

McEwen B, Stellar E 1993 Stress and the Individual: mechanisms leading to disease. Archives of Internal Medicine 153(18):2093-2101

McEwen BS, Sapolski RM 1995 Stress and Cognitive Function. Current opinion in Neurobiology 5(2):205-216. DOI:10.1016/0959-4388(95)80028-X

Patterson M, Wurster R 2004 Neurophysiological Mechanisms of Integration and Disintegration. Foundations of Osteopathic medicine 2nd edition

Ramachandran VS, Blakeslee S, Sacks OW 1998 Phantoms in the brain: Probing the mysteries of the human mind. New York: William Morrow

Robinson MB, Coyle JT 1987 Glutamate and related acidic excitatory neurotransmitters: from basic science to clinical application. The FASEB journal 1(6): 446-455

Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG 2000 Contribution of central sensitisation to the development of noncardiac chest pain. The Lancet, *356*(9236): 1154-1159. DOI:10.1016/S0140-6736(00)02758-6

Sato A, Schmidt RF 1973 Somatosympathetic reflexes: afferent fibers, central pathways, discharge characteristics. Physiological Reviews 53(4)916-947

Schaible HG, 2006 Peripheral and central mechanisms of pain generation. Analgesia (pp. 3-28). Springer Berlin Heidelberg

Scholz J, Woolf CF 2002 Can we conquer pain?. Nature Neuroscience 5:1062-7. DOI 10.1038/nn942

Sessle B 2007 Astroglial Glutamate–Glutamine Shuttle Is Involved in Central Sensitization of Nociceptive Neurons in Rat Medullary Dorsal Horn. Journal of Neuroscience 27(34):9068-9076. DOI:10.1523/JNEUROSCI.2260-07.2007

Treede RD, Meyer RA, Raja SN, Campbell JN 1992 Peripheral and Central Mechanisms of Cutaneous Hyperalgesia. Progress in Neurobiology 38(4):397-421

Turrigiano GG, Nelson SB 2000 Hebb and homeostasis in neuronal plasticity. Current Opinion in Neurobiology 10(3):358–364. DOI:10.1016/S0959-4388(00)00091-X

Vecchiet L, Vecchiet J, Giamberardino MA 1999 Referred muscle pain: clinical and pathophysiologic aspects. Current Review of Pain 3(6):489–98

Woolf CJ 2011 Central sensitization: Implications for the diagnosis and treatment of pain. Pain 152(3): S2-S15. DOI:10.1016/j.pain.2010.09.030

Zhou, M 2002 Glutamate receptors and persistent pain targeting forebrain NR2B subunits. Drug Discovery Today 15; 7(4):259-67. DOI:10.1016/S1359-6446(01)02138-9