When pain goes weird: central sensitisation and its implications for physiotherapy practice

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Information from the body is conveyed to the brain through receptors, peripheral nerves and the spinal cord. In the dorsal horn, inhibitory mechanisms under control of local, peripheral and brain influences keep sensory transmission under control. Nociceptive input from persistent inflammation and neuropathy can reduce inhibition and lead to an enhanced perception of pain. This central sensitisation is thought to underlie a number of persistent pain conditions. Physiotherapists can enhance their approaches to examination and treatment by considering the somatic tissues as well as the processing status of the sensory nervous system.

Learning outcomes

1. Understand sensory processing, both under normal and pathological circumstances.
2. Understand the principles for assessment, management and treatment of patients thought to have central factors contributing to their pain.

Introduction

When I trained as a physiotherapist in The Netherlands, the role of the nervous system was discussed frequently. We were discouraged from thinking about pain purely as a phenomenon that originated in, was maintained by and could be treated through the musculoskeletal tissues. Once I started working it became clear that this view was far from common. I once taught on in-service training about the sensory nervous system and colleagues asked whether I invented these different neurones just to make a point!

I realised that I was not alone when, in 1997, I attended a two-day lecture series by Louis Gifford entitled The Clinical Biology of Aches and Pains. Here was a man who had studied neural and endocrine physiology, psychology and musculoskeletal physiotherapy in order to make sense of pain. He was a highly reflective practitioner who asked himself how consistent our practice was with modern science. He used the answers he found to empower rather than belittle physiotherapists, putting them straight on some opinions and practices while encouraging them to capitalise on others. He presented practitioners with an integrative framework to enable them to deal with pain on a rational basis. My interest in the nervous system was rekindled and became the basis of my practice.

With regard to pathobiology, Louis pointed to clinical reasoning categories (Jones 1995) and extended them to include the nervous system; input from the tissues, processing by peripheral neurones, processing by the central nervous system, and output through efferent systems including autonomic and endocrine. He urged us to make a reasoned hypothesis of the contribution in each category for every patient, and, if we could not achieve this, either to find out more from the patient or gain more knowledge. In other words, he suggested that we make all features fit (Maitland 1986) and deal with the consequences.

Plasticity in the central sensory nervous system is one of the factors that may prevent us from making the musculoskeletal features fit in patients with persistent pain. Under normal circumstances, there is a reliable correlation between what the patient perceives and what is happening in their somatic body; pressure, tissue damage, cooling, etc. In this situation, the sensory nervous system can be viewed as a simple conduit between the tissues and the brain. Clinically, this means that the patient's descriptions of their sensations offer a relatively direct window on the state of the tissues. However, the patient's presentation is influenced by a number of subjective factors (Glenton 2003; May *et al* 2000; Osborn & Smith 1998; Toye & Barker 2010) and persistent pain is associated with changes in how the central nervous system processes sensory information. This phenomenon, sometimes referred to as central sensitisation, leads to exaggerated pain responses and pain in physically unaffected body regions (Latremoliere & Woolf 2009). In Louis' words, when plasticity starts to get involved, "the pain goes weird."

Basic pain neurophysiology

Information about the somatic body is conveyed to the central nervous system through activation of receptors in the tissues and their sensory neurones. Receptors may be specialised for a specific stimulus or polymodal, and can be subdivided into

nociceptive, i.e. activated by noxious stimuli, and non-nociceptive. Generally, non-noxious mechanical stimuli such as stretch or pressure are activate sets of highly specialised receptors and transmitted by their thick and fast conducting myelinated Aβ fibres (Gardner & Johnson 2013a, 2013c).

Nociceptive neurons, type Aδ or C, have a high stimulation threshold and generally respond only to stimuli associated with actual or potential tissue damage. Thin, but myelinated Aδ fibres respond and accommodate quickly, thus providing a quick first response to noxious input due to injury. The fast response characteristics provide discriminatory information about location and duration of the problem, also referred to as first pain. On the other hand, thin and unmyelinated C fibres respond and accommodate more slowly and provide a second pain which is more dull and aching in nature (van Cranenburgh 2000). These response characteristics are observed in experimental acute pain; persistent inflammation lowers the stimulation threshold of both types of nociceptor, manifesting as primary or peripheral hyperalgesia. Hyperalgesia is defined as increased pain from a response that normally provokes pain (www.iasp-pain.org).

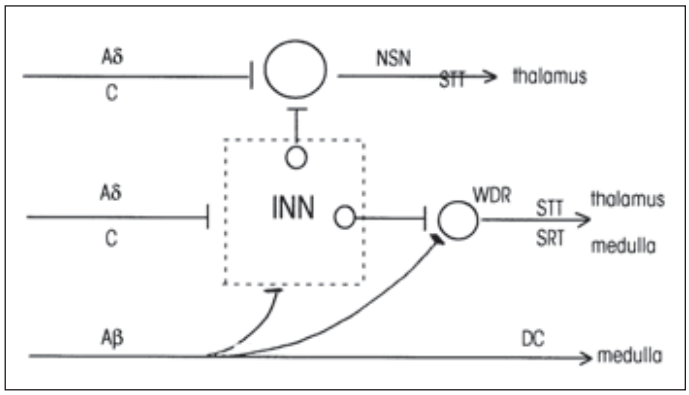

***Figure 1:** Representation of three sensory pathways from periphery (left), via the dorsal horn (middle) to brain (right). Some Aδ and C fibres enter the spinal cord and synapse with nociception-specific neurones (NSN) which ascend to the thalamus via the spino-thalamic tract (STT). Others synapse with wide dynamic range cells (WDR) via a network of interneurones (INN) which project to the medulla or the thalamus via the spino-reticular tract (SRT) or the STT. Aβ fibres ascend via the dorsal column (DC) to the medulla, but also have branches that influence WDR and IIN*

Simplifying spinal cord neurology for the sake of clarity, we can identify three main sensory pathways as shown in figure 1 (Galea 2013; Gardner & Johnson 2013b). Some Aδ and C fibres synapse with secondary nociception-specific neurones (NSN), which cross the midline and ascend to the thalamus via the spino-thalamic tract (STT). Others synapse with a network of interneurones which, in turn, connect with neurones that follow either the STT or go to the medulla via the spino-reticular tract (SRT) (Basbaum & Jessell 2013). An important set of these neurones respond to both non-noxious Aβ stimulation and nociceptive input and are therefore called wide dynamic range (WDR) cells. Finally, although Aβ fibres ascend directly in the dorsal column to synapse in the medulla, they have branches into the spinal cord at the level of entry. These branches synapse with the WDR via the interneurones (ibid). This link is thought to form the physiological substrate for allodynia, the production of pain due to a stimulus that does not normally produce pain (www.iasp-pain.org).

Primary sensory neurones terminate in the dorsal horn. The main excitatory neurotransmitter released by nociceptive and non-nociceptive primary neurones is glutamate, which opens ion channels of the AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) type in the post-synaptic membrane. This leads to depolarisation of the secondary neurone and therefore transmission of the signal. The dorsal horn also contains a large population of inhibitory interneurones (IIN), which when stimulated can release inhibitory neurotransmitters such as glycine and γ-aminobutyric acid (GABA). These transmitters have a moderating effect on nociceptive transmission in several ways (Sandkühler 2009, 2013) as illustrated in figure 2. When there is no noxious stimulation, the response of nociceptive neurones is kept under control (muting). When there is, IIN limit the response of the secondary neurone (attenuation). The input from adjacent neurones is also controlled, thus preventing spreading excitation from both nociceptive and non-nociceptive neurones which would manifest as spreading hyperalgesia and allodynia (separating and localising). Finally, stimulation of Aβ fibres can have an inhibitory effect on nociceptive transmission, as described in the gate theory (Mendell 2014; Wall 1978).

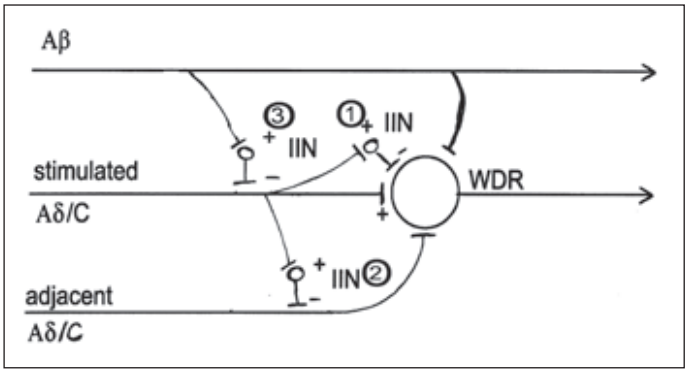

***Figure 2:** Representation of three inhibitory mechanisms at spinal cord level:*
1) When a nociceptive fibre is stimulated, it activates inhibitory interneurones (IIN) which limit the response of the secondary neurone.
2) The input from adjacent neurones is also controlled to prevent spreading excitation.
3) Stimulation of Aβ fibres inhibits nociceptive transmission

A further controlling influence on nociceptor activity in the dorsal horn is descending inhibition, the attenuation of the activity of dorsal horn transmission and activity by neurones descending from the medulla (Heinricher & Fields 2013; Villanueva & Fields 2004). Medullary centres involved in this include the peri-aquaductal grey (PAG), rostral ventromedial medulla (RVM) and the locus coeruleus (LC), which respond to nociceptive input. They also respond to input from higher centres, for instance under stressful conditions (ibid). As a consequence, higher centres are able to control the amount of nociceptive information that is transmitted through the dorsal horn; the brain selects and de-selects its own information. On the other hand, the opposite process of descending facilitation has been implemented in the development of hyperalgesia and

allodynia in inflammation and neuropathy (Gardell *et al* 2003; Heinricher & Fields 2013).

Modern understanding of sensory physiology makes it clear that the perception of pain is not a passive process, but one which is normally carefully controlled in several ways. Nociceptive neurones have high stimulation thresholds and normally respond only to extreme stimuli. Inhibitory cells in the spinal cord limit nociceptive activation, both temporally and spatially. Descending systems also exert an inhibitory influence on nociceptive transmission in the dorsal horn. As a consequence, the absence of pain is likely to be the result of constant active control of nociceptive input, rather than the absence of any noxious events. In the course of the day several minor aches and pains can be experienced, but the nervous system suppresses these. However, under certain circumstances these moderating influences become less effective and facilitate the development of central sensitisation.

Central sensitisation at the dorsal horn

The International Association for the Study of Pain (IASP) defines central sensitisation as an *"increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"* (www.iasp-pain.org). The notes, with the definition, explain how central sensitisation involves neurones in the central nervous system, i.e. not the primary neurone coming in from the periphery. The term "central sensitisation" is also referred to as long term potentiation of synaptic transmission strength (Ruscheweyh *et al* 2011). It applies to neurophysiological conditions but is thought to underlie clinical hypersensitivity of various kinds. One aspect of central sensitisation is that the stimulation threshold of secondary neurones comes down. These neurones now begin to respond to peripheral impulses that are normally insufficient to generate an action potential. This is referred to as unmasking of sub-threshold stimuli. A second aspect of central sensitisation is an increase in response to stimuli that are above the stimulation threshold already. Finally, central sensitisation can involve spontaneous neural discharges and increases in receptive field size. The overall effect is one of synaptic strengthening; the signals passed on by the secondary neurone are no longer in proportion with the incoming information, because the responsiveness of the synapse is enhanced. Clinically, this means that the pain is no longer an effective protective signal, but that it becomes maladaptive.

It may be helpful to divide the processes that lead to central sensitisation into peripheral input, descending input from higher centres and changes in dorsal horn cells (Woolf 2014). Peripheral drivers include sustained barrages of primary nociceptive input which lead to increased excitability of the secondary neurone. Descending influences may either be reduced inhibition or enhanced facilitation. Local changes include activation of glial cells and astrocytes, which may in turn facilitate sensitisation. These processes have been shown to contribute to the pain of persistent inflammation or nerve damage (Latremoliere & Woolf 2009).

Once central sensitisation is established, only low levels of C-fibre activity are required to maintain it (Koltzenburg *et al* 1992). The initial process constitutes a strengthening of the synaptic transmission between the stimulated nociceptive neurone and its secondary neurone or homosynaptic potentiation as shown in figure 3 (Woolf 2011). Secondary neurones, however, receive input from many neurones. Normally the contributions of these neurones are controlled by the action of IIN, but when inhibitory activity is reduced, the activation of adjacent primary neurones can also contribute (heterosynaptic potentiation). The contribution of adjacent nociceptive fibres is thought to underlie spreading hyperalgesia, and the contribution to Aβ fibres to allodynia.

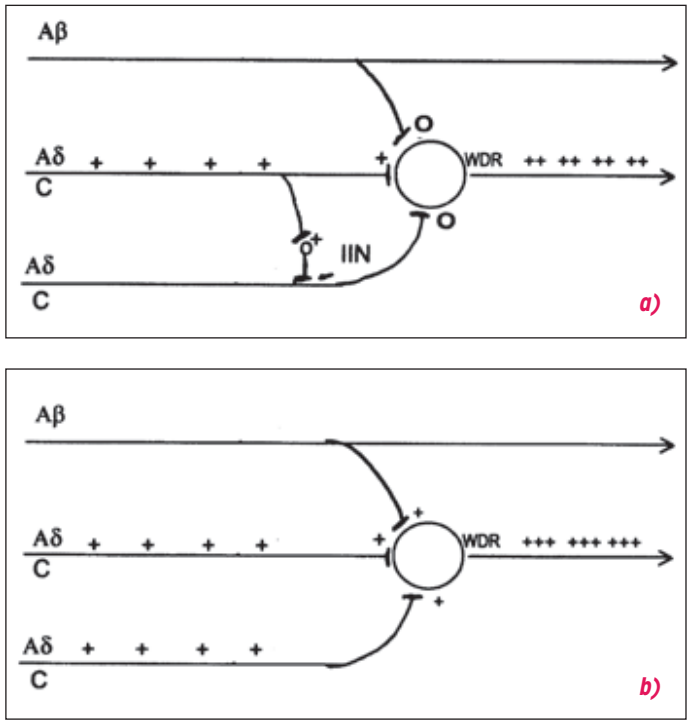

***Figure 3:** Representation of potential changes in synaptic transmission as part of central sensitisation.*
***a)** Under normal circumstances, activation of the wide dynamic range cells (WDR) corresponds with stimulation of one of its nociceptive neurones. Input from adjacent neurones is controlled via inhibitory interneurones IIN.*
***b)** When the secondary neurone is sensitised, adjacent nociceptive and Aβ neurones contribute to the WDR's response*

The mechanisms required for the onset of central sensitisation have been described in a number of texts such as Sandkühler 2013. When activated, primary nociceptive neurones release glutamate at their terminal in the dorsal horn. There it has a number of effects on the secondary neurone. As mentioned, glutamate opens AMPA ion channels which let sodium ions flow into the cell, leading to depolarisation (figure 4). It also opens NMDA (N-methyl-d-aspartate) ion channels which would let calcium ions in, if it were not for the fact that they are normally blocked by a magnesium ion. This positively charged magnesium ion is held in place by the negative intracellular charge. Sustained intensive stimulation leads to a sufficiently low potential across the membrane potential, the magnesium ion is no longer held in place, thus opening the NMDA channels. The resultant influx of

calcium ions leads to a number of intracellular reactions. The overall effect of these is that the secondary neurone responds to stimulation for longer and that the function of the ion channels is enhanced. The unblocking of NMDA and the effects of raised levels of intracellular calcium are thought to be key components of central sensitisation. This effect is further enhanced by the binding of glutamate to kainate receptors (Lerma & Marques 2013), which further enhance the response characteristics of the secondary neurone.

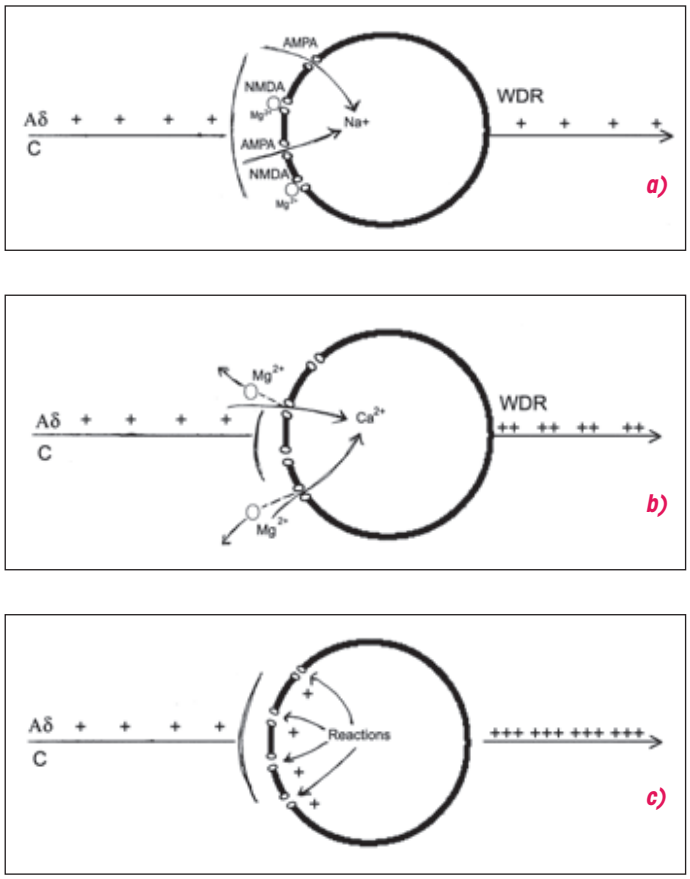

***Figure 4:** Representation of the role of NMDA receptors in the development of central sensitisation.*
***a)** Release of glutamate opens AMPA channels in the secondary neurone. The influx of Na+ ions lowers the membrane potential, leading to depolarisation. NMDA receptors remain blocked by Mg2+ ions.*
***b)** Persistent lowering of the membrane potential removes the Mg2+ block.*
***c)** Raised Ca2+ levels lead to a chain of intracellular reactions which enhances the function of the ion channels*

It is likely that a number of additional neurotransmitters are involved in the sensitisation of spinal cord neurones. Their precise role is as yet unclear (Sandkühler 2013). One such transmitter is the neuropeptide substance P (SP), which may be co-released on strong C fibre stimulation. SP is thought to bind to the neurokinin-1 receptor (NK1) (Porreca 2012) and has been implicated in the enhancement of response characteristics of the secondary neurone (Basbaum & Jessell 2013; Porreca 2012).

Whether central sensitisation is maintained over longer periods depends in part on processes in the cell body (Salter 2012). The influx of calcium and activation of receptors such as NK1, leads to intracellular changes which are signalled to the neurone's nucleus via axonal transport. The nucleus is where genes are transcribed to produce proteins and this production is altered in response to the chemical signals received from the dorsal horn. The proteins, including those which will form receptors and ion channels once they reach their target, are transported down the neurone. The altered proteins can therefore lead to a longer lasting change in response characteristics of the secondary neurone.

Further maintenance of central sensitisation comes from the activation of astrocytes and microglia, collectively referred to as glia. These cells used to be thought of as inert "packing" cells, but it is now clear, as illustrated in figure 5, that they can become "activated" by nociceptive activity (McMahon & Malcangio 2009).

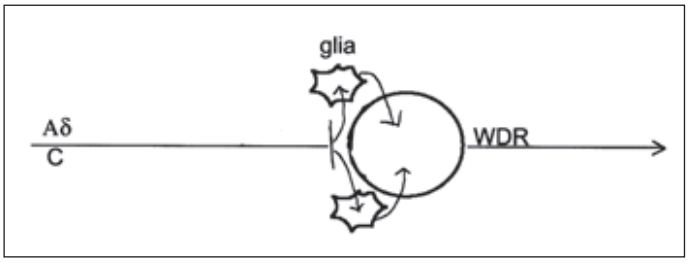

***Figure 5:** Representation of the role of glia in central sensitisation. Neurotransmitters released in nociceptive transmission activate glial cells, which in turn release cytokines and transmitters that alter the secondary neurone's response characteristics*

In their activated state glia release cytokines and neurotransmitters, which have a number of effects on synaptic transmission. For example, release of some cytokines can enhance the efficacy and number of several types of receptors (Milligan & Watkins 2009; Salter 2012). Glia envelop the dorsal horn neurones, so this release has a direct impact on signal transmission in the dorsal horn (Milligan & Watkins 2009). It is however worth bearing in mind that the glial response is complex and is likely to have positive functions as well (McMahon & Malcangio 2009; Milligan & Watkins 2009).

Clinical implications of central sensitisation for physiotherapy practice

Central sensitisation has been implicated in the development of pain in patients with rheumatoid arthritis, osteoarthritis and fibromyalgia syndrome (FMS) (Lee *et al* 2011; Meeus *et al* 2012). Patients with conditions such as FMS and chronic fatigue syndrome often display sensitivity to a range of stimuli including bright light, noise, touch and temperature, so asking about these in the subjective examination can provide information about possible central sensitisation (Geisser *et al* 2008; Nijs *et al* 2010). Changes in central processing also have a strong genetic component (Woolf 2011), so questions about a history of other pain problems that the patient and their immediate family experience may be equally informative (Clauw 2012). Examples include dysmenorrhea, migraines, persistent musculoskeletal pains and irritable bowel syndrome. It may also be helpful to

identify potential drivers of sensitisation, including any influences which may interfere with the patient's ability to focus their attention away from their pain by activating their descending inhibitory systems (Bushnell *et al* 2004).

If subjective examination identifies a number of factors suggestive of central sensitisation, this ought to be investigated further. Assessment of the somatic tissues alone is likely to provide only a very partial picture, so the processing status of the central nervous system must also be tested. It is recommended that sensory and other neurological tests are included in the examination (Watson *et al* 2009). Nijs *et al* (2010) recommend testing sensitivity to a range of stimuli, both local to the painful area and at distant sites. This can demonstrate whether hyperaesthesia, hyperalgesia and allodynia are present, and to what extent they are well-localised to the somatic origins of the pain or more widespread.

If the patient is thought to have a strong component of central sensitisation, patient education is essential. For a detailed review and guidance see Nijs *et al* 2012. As mentioned in the introduction, central phenomena make persistent pain "go weird", so patients should understand that this is a function of their pain processing system, not their psychology, and only partially their somatic body. Several qualitative studies have found that patients with persistent pain feel disbelieved and written off (Corbett *et al* 2007; Holloway *et al* 2007; Osborn & Smith 1998). Providing a realistic explanation can help the patient to make sense of their pain and "normalise" it for themselves (Dowrick 2004).

When it comes to treatment or management of the pain, it may be helpful to consider the factors that either drive or inhibit central sensitisation. Reducing contributing factors may include treating the tissues or providing medication with the overt aim of influencing the function of the central nervous system. However, in patients with persistent pain this has often proved inefficient. Adjuvant medication may address central components of the pain (Smith & Muralidharan 2013). Physiotherapists may consider ways of maximising inhibition, using strategies such as general exercise (Daenen *et al* 2015; Foster *et al* 2013), mindfulness (Grabovac *et al* 2011), or selective Aβ stimulation through manual therapy or TENS (Johnson & Paley 2013; McCarthy 2013). Whatever treatment strategy is selected, the overall aim is to enhance the inhibition of central pain processes rather than the mere reduction of nociceptive input in the periphery.

Conclusion

Under normal circumstances, timing and intensity of physical stimuli is transmitted proportionally by the sensory nervous system. Several inhibitory mechanisms keep this transmission under control. However, persistent inflammation and neuropathy can reduce this control and alter nociceptive transmission in the dorsal horn. The patient's pain is out of proportion with the original injury and becomes less predictable and less easy to control. It is up to the physiotherapist to determine whether the patient's sensory nervous system may be in a controlled state or a sensitised state.

About the author

Hubert van Griensven qualified as a physiotherapist in 1988. He completed a three-year course in Chinese Acupuncture in 1996, which led to his appointment as Clinical Specialist in Pain at Guy's and St Thomas' Hospitals. During his time there he completed an MSc in Pain at King's College London and wrote a textbook about the application of pain physiology in manual therapy practice. He was awarded his PhD by the University of Brighton in 2013 and published a second textbook on pain, co-edited with Jenny Strong and Anita Unruh, in the same year. Hubert currently holds posts as Consultant Physiotherapist in Southend and Research Fellow at the University of Brighton. He lives in London and spends his spare time tinkering with soundscapes, practising Chinese exercise, and enjoying music, art and film.

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Further reading

Physiotherapists interested in central sensitisation in clinical practice should read Nijs *et al* 2010 and 2012. An overview of the physiology of central sensitisation is provided by Woolf 2011. For an up-to-date review of its molecular neurophysiology, please see Kuner R. Spinal excitatory mechanisms of pathological pain. *Pain* 2015;156(1):S11-S17