Chronic pain:

We should not underestimate the contribution of neural plasticity

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ABSTRACT

Disability associated with chronic pain is a prevalent worldwide problem. Much of our understanding of how and why chronic pain develops has been provided through developments in neural imaging and assessment techniques. Such investigations have highlighted the substantial amount of neural plasticity, or neural reorganisation, that is possible within the nociceptive system. While this plasticity is often physiologically beneficial and usually reverses over time, persistent plasticity can occur following long term activation or damage to the nociceptive system. These adaptations are associated with the development and maintenance of chronic pain conditions. This review provides an outline of the nociceptive system and describes the evidence for plasticity of the system at peripheral, spinal, and supraspinal levels. A number of clinical symptoms associated with chronic pain are described along with the possible neural mechanisms that may contribute to the presentation. Finally, chronic pain management approaches that promote reorganisation of the nociceptive system are discussed. These include sensory training, non-invasive brain stimulation, and mechanisms-based treatment.

Key words: chronic pain, neural plasticity, hyperalgesia, central sensitisation
I. INTRODUCTION

Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain persisting for more than 3 months, or beyond the expected time of tissue healing.\(^1\)

Worldwide, chronic pain has a prevalence of approximately 15-20% of the adult population.\(^2\)–\(^5\) It is therefore one of the most disabling chronic conditions, yet it suffers from a distinct lack of identity, recognition, and acceptance. Pain is so often viewed as a symptom of another condition, e.g. arthritis or spinal cord injury, that the neural changes that occur with long term pain are rarely acknowledged. Part of the problem contributing to the limited recognition of chronic pain is that pain is a purely subjective experience and there are no valid physical tests that can be used for diagnosis. It is also complicated in that pain is multidimensional, being both a sensory and emotional experience, and is commonly associated with adaptations in other areas of the nervous system, including somatosensory, motor, autonomic, and cognitive functions. However, chronic pain is now receiving recognition as its own disease entity, and with advances in neural imaging and assessment techniques, greater insight has been provided on the plasticity that occurs within the nervous system in long term pain conditions. This paper will highlight evidence of this neural plasticity and attempt to link it to the common symptoms present in chronic pain.

II. OVERVIEW OF THE NOCICEPTIVE SYSTEM

To more fully understand the neuroplastic changes in the nociceptive system associated with long-term pain, an overview of the system is presented first. There are a wealth of textbooks and review articles that provide this information in detail,\(^6\)–\(^9\) so a brief and simple version is presented here. Receptors that are sensitive to noxious stimuli (nociceptors) are present in most tissues of the body. These nociceptors are free nerve endings that respond
to harmful or potentially harmful chemical, mechanical, and thermal stimuli and relay this information via Aδ and C fibre axons (also termed group III and IV fibres, respectively) to the dorsal horn of the spinal cord. Aδ fibres are lightly myelinated and relatively fast conducting, while C fibres are non-myelinated and have a small axon diameter, making them the slowest conducting of our sensory afferents. In the dorsal horn, nociceptive afferents predominantly synapse with onto second order neurons in superficial laminae I and II as well as deeper into laminae IV-VI. Second order neurons in laminae I and II are primarily nociceptive specific neurons that only receive input from Aδ and C fibres. In lamina IV-VI, nociceptors synapse with wide dynamic range (WDR) second order neurons that receive input from multiple afferents. WDR neurons are principally located in laminae IV-VI but can also be found in laminae I and II. In comparison to Aδ and C fibres, axons from non-noxious touch and proprioceptive receptors, known as Aβ fibres, synapse in the deeper laminae III-V only.

Nociceptors predominantly communicate using the neurotransmitters glutamate, an amino acid, and substance P, a slow-acting neuropeptide. In normal conditions, glutamate binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the dorsal horn cells and causes a short acting excitatory potential. Substance P binds to the neurokinin-1 receptor, a G-protein couple receptor, to generate a much slower and longer acting depolarisation. Glutamate may also bind to N-methyl-d-aspartate (NMDA) receptors but at resting membrane potential the NMDA receptors are blocked by the ion Mg²⁺. Dorsal horn neurons themselves are connected both within the same spinal cord layer through interneurons that traverse laminae, and within close spinal segments through ascending and descending propriospinal interneurons.
From the dorsal horn, nociceptive information ascends to brainstem and cortical regions in medial and lateral pathways. Key areas in the brainstem that receive direct nociceptive input are the midbrain periaqueductal grey (PAG), the rostral ventromedial medulla (RVM), and the reticular formation. These areas have notable roles in the modulation of the ascending nociceptive signal. Cortical and subcortical regions receiving direct nociceptive input reflect a highly connected network of sites involved in the perception, interpretation, and behavioural response to nociceptive input. These areas include the thalamus, primary and secondary somatosensory cortices, anterior cingulate cortex, amygdala, prefrontal cortex, and the insula, and are collectively referred to as the neuromatrix. It is when nociceptive information arrives in the neuromatrix that the lived experience of pain is created, with the lateral system providing the sensory-discriminative component of pain and the medial system contributing to the emotional-aversive component. The neuromatrix itself has bilateral projections to brainstem modulatory areas, providing a means for cognitive and emotional modulation of the ascending nociceptive signal. The hypothalamus is also intimately connected with neuromatrix and brainstem regions, facilitating interaction between the autonomic and nociceptive components of the nervous systems.

Modulation of the ascending nociceptive signals can be both facilitatory and inhibitory and occurs at multiple levels of the nociceptive system. Descending excitatory and inhibitory modulatory pathways are tonically active, with the extent of activation influenced by nociceptive input, psychological stress, or other forms of nervous system stimulation. Shifts in the balance of inhibitory and excitatory activation therefore determine the overall modulation of nociceptive signals. In the periphery, nociceptive signals can be facilitated through sensitisation of nociceptors that occurs following tissue injury and inflammation,
while activation of non-noxious mechanoreceptors can activate the dorsal horn spinal gating mechanism and reduce nociceptive input. Within the dorsal horn, a multitude of inhibitory and excitatory interneurons serve to modulate the transmission from nociceptors to ascending pathways. GABAergic inhibitory interneurons play a particularly important role at this level in reducing the ascending signal. In key modulatory regions of the brainstem, including the RVM and PAG, there are classes of neurons termed ON and OFF cells. These cells activate descending facilitatory and inhibitory pathways, respectively, that act directly or indirectly on dorsal horn neurons. Two of the main neurotransmitters associated with inhibitory pathways are serotonin, released following activation of the raphe magnus nucleus, and noradrenaline, released following activation of the locus ceruleus. A further, well established inhibitory system involves the activation of diffuse noxious inhibitory control neurons located in the caudal medulla. At a cortical level, the strong bi-directional interaction with brainstem centres affords a means for cognitive and emotional factors to modulate the nociceptive signal. These include psychological factors such as attention, expectations, mood, arousal, and beliefs regarding pain. Finally, the hormonal system provides an additional important source of nociceptive modulation. Circulating endogenous opioids can act to inhibit the nociceptive signal through receptor activation at peripheral nociceptors, spinal cord dorsal horn, brainstem, and cortical sites. Importantly, opioid receptor density and distribution is dynamic and is regulated by activation of the nociceptive system, nerve and tissue damage, and the peptide hormone cholecystokinin (CCK).

It is apparent that the nociceptive system is a multi-faceted and dynamic network that affords enormous capacity for short- and long-term plasticity. Nociception facilitation and
inhibition is normally regulated physiologically to provide a useful response that at first alerts us to actual or potential tissue damage, promotes recovery and restoration, and then enables increasing use and activity as the body recovers. Thus, the pain experience is temporally matched to tissue damage and repair. When this process escapes tight regulation and pain continues far beyond the period of tissue recovery, the consequences can be catastrophic for an individual. It is indeed not surprising that chronic pain is commonly associated with depression, anxiety, reduced participation, and impaired quality of life.\textsuperscript{2,10-12} There is increasing evidence that this dysregulated response of the nociceptive system arises through persistent plasticity. The following sections of this review will examine in more depth the neural changes that have been identified in the nociceptive system following tissue damage and how these may underlie the common clinical features of chronic pain conditions.

III. PLASTICITY IN THE NOCICEPTIVE SYSTEM

There are many mechanisms that can underlie neural plasticity and many levels within the nociceptive system at which plasticity can occur. In general, the adaptive responses to acute, nociceptive pain are physiologically useful and predominantly serve to augment the ascending nociceptive signal to promote awareness of tissue injury and recuperative behaviour. However, much of the reorganisation that occurs with chronic pain appears to serve no biological purpose, and may even be profoundly detrimental, contributing to the maintenance of pain. The following provides a description of potential neural plasticity at each level of the nociceptive system.
A. Peripheral nociceptors

Tissue damage or inflammation and the subsequent activation of nociceptors result in almost immediate changes in peripheral nociceptive system function. A soup of chemical mediators, including inflammatory substances, catecholamines, and neuropeptides are released locally. These substances can directly activate free nerve endings and rapidly increase their excitability, a process termed peripheral sensitisation. Peripheral sensitisation is characterised by a reduction in nociceptor activation threshold and the development of spontaneous nociceptor discharge, leading to an increased nociceptor response to a given noxious stimulus. Nerve growth factor is a particularly important sensitising agent that is implicated in the development of longer-term neuronal changes.  

Nociceptors themselves play a contributory role in peripheral sensitisation through the antidromic propagation of action potentials and subsequent release of substance P and calcitonin gene related peptide (CGRP) from their sensory terminals into the peripheral tissue. These substances cause enhanced vascular permeability, vasodilation, and increased synthesis of prostaglandins, further enhancing nociceptor activation and sensitisation. As well as these effects on functioning nociceptors, a group of nociceptors that are normally dormant, termed silent nociceptors, become activated during inflammation and sensitisation. These newly awakened receptors respond intensely to both noxious and non-noxious stimuli, increasing the peripheral afferent barrage into the spinal cord. Additionally, glial cells (microglia and astrocytes), long thought to play a strictly structural role in the nervous system, are now known to contribute to peripheral sensitisation. Glia are activated by pathogens and inflammation and release pro-inflammatory cytokines that further facilitate nociceptor sensitisation. Emerging evidence from animal studies suggests that peripheral sensitisation can cause nociceptors to respond more vigorously the next time they are exposed to
inflammatory mediators, a phenomenon termed “hyperalgesic priming”. In their primed state, the resulting sensitisation of nociceptors is much stronger and longer lasting when exposed to a second dose of inflammatory mediators. The length of time the exposed nociceptors remain in this primed state is unknown but appears to be at least a few weeks after the initial inflammatory response.

Nociceptor axons that are damaged through demyelination or a lesion can fire spontaneously, sending a constant volley of signals to the dorsal horn. Termed ectopic discharge, the spontaneous activation can begin early following nerve damage, can be rhythmic or irregular depending on the fibres involved, and appears to arise through upregulation and altered trafficking of Na\(^+\) channel expression. Damaged axons are particularly sensitive to circulating catecholamines, which can lead to further axonal firing. Traumatic axonal damage commonly results in the formation of neuroma, or an accumulation of nerve tissue. Neuroma themselves facilitate spontaneous firing of action potentials due to the accumulation of Na\(^+\) channels. Nerve injury also causes the expression of novel receptors in the neuroma that are sensitive to inflammatory chemicals, adding to the spontaneous axonal firing. Ectopic discharge from axons or neuroma can continue for lengthy periods of time, providing a continuous input to second order neurons within the spinal cord.

Damage or demyelination of multiple axon types also can lead to ephaptic discharge. In this case, afferent signals jump across axons in areas of damage. Thus, ephaptic transfer may lead to an action potential along an A\(\beta\) fibre transferring to a neighbouring nociceptor axon and subsequently ascending to the cortex in normally nociceptor-specific pathways. Additionally, a phenotypic switch in non-noxious A\(\beta\) fibres to release substance P has been
documented following nerve damage or inflammation.\textsuperscript{24,25} This enables non-noxious stimuli to activate dorsal horn neurons that are usually responsive to noxious input only.

\textbf{B. Spinal Cord Dorsal Horn}

Prolonged nociceptive input, particularly from deep tissue afferents, instigates additional neuroplastic changes within the spinal cord dorsal horn. The release of the slow-acting neurotransmitter substance P causes sustained depolarisation of dorsal horn neurons, instigating changes in neurotransmitter receptor availability. Depolarisation of second order neurons stimulates the removal of the Mg\textsuperscript{2+} block from NMDA receptors, making them available for glutamate binding.\textsuperscript{26} Activation of pre- and post-synaptic NMDA receptors in the dorsal horn causes a large and prolonged depolarisation, increased intracellular Ca\textsuperscript{2+} influx, and can stimulate the additional release of neuropeptides, such as substance P.\textsuperscript{27-29} NMDA receptor activation also enables the phenomenon of windup to occur in WDR neurons. Windup is instigated by temporal summation of high frequency (>0.3 Hz) nociceptive input that gives rise to a progressively increased depolarisation of WDR neurons.\textsuperscript{26,30} This process results in an increase in firing frequency of the second order neurons. In addition, sustained depolarisation leads to an expansion of the receptive zone of WDR neurons,\textsuperscript{31} may cause new receptive fields to be established,\textsuperscript{32} and increases the sensitivity of WDR neurons to both noxious and non-noxious inputs.\textsuperscript{31} These are the first and fundamental steps of central sensitisation. The overall effect is an increased number of action potentials generated in nociceptive pathways ascending to neuromatrix regions.

Glial cells, substance P, and the enzyme cyclo-oxygenase-2 (COX-2) also play a role in facilitating nociceptive transmission at the dorsal horn and a spread from local to more diffuse effects. Glial cells are incredibly well interconnected and communicate via gap
junctions, facilitating a rapid spread of activation. Activated glial cells facilitate the release of substance P from nociceptors \(^{16}\) and pro-inflammatory cytokines, \(^{33}\) increasing depolarisation of second order neurons and enhancing COX-2 expression in the dorsal horn. The extended release and slow re-uptake properties of substance P enable the peptide to diffuse to adjacent synapses or even across the dorsal horn, \(^{34}\) contributing to the sensitisation of second order neurons in remote areas. The enzyme COX-2 is used in the synthesis of prostaglandins from arachidonic acid. COX-2 that is produced in the dorsal horn does not remain local but travels through the spinal cord and to supraspinal regions. \(^{35}\) This can lead to increased prostaglandin production in cerebrospinal fluid and widespread facilitation of dorsal horn sensitisation.

Further, longer lasting changes in the dorsal horn occur with prolonged stimulation. Sustained activation of nociceptors or nerve damage causes upregulation of c-fos, an immediate early gene and a marker of neuronal activity. Several seconds of activation is enough to induce transient labelling in superficial laminae of the dorsal horn, while 4-5 hours of stimulation can lead to labelling in deeper laminae. \(^{36}\) Such activation can cause alterations in the expression of neurotransmitters, receptor availability, ion channel function and numbers, and even structural reorganisation. Following inflammation or nerve damage, there is an increase in receptor availability for glutamate and substance P in dorsal horn cells \(^{37}\) and enhanced release of these neurotransmitters. \(^{29}\) There are also alterations associated with inhibitory pathways. Changes in the opioid system at the dorsal horn include a reduction in opioid receptor numbers, \(^{38}\) up-regulation of opioid receptor antagonists, \(^{39}\) and increased CCK release that reduces the ability of morphine to bind to receptors. \(^{40}\) There also may be loss of inhibitory glycine receptors, \(^{41}\) depression of gamma-
aminobutyric acid (GABA) inhibitory interneurons,\textsuperscript{42} or even a functional switch of GABA-mediated synapses from inhibitory to excitatory.\textsuperscript{43}

Peripheral nerve damage may also lead to alterations in neuronal firing properties and dorsal horn connectivity. Dorsal horn neurons can alter from a tonic firing pattern to the formation of plateau potentials,\textsuperscript{44} which enhances and amplifies signal transmission. Glia present in the dorsal horn can be upregulated following nerve damage,\textsuperscript{45} reinforcing their sensitising effect on second order neurons. Interneurons present within the dorsal horn that connect deeper to superficial laminae are normally inactive, but following nerve injury these pathways may be facilitated.\textsuperscript{46} This polysynaptic pathway provides a means for non-noxious Aβ input into deeper laminae to indirectly activate superficial dorsal horn neurons and ascending nociceptive pathways.

Structural changes around the dorsal horn can also occur. Peripheral axonal damage can lead to fibre death; this appears to be more predominant in non-myelinated C fibres.\textsuperscript{47} With the death and withdrawal of C fibres, Aβ fibres have been shown to invade the superficial laminae of the dorsal horn and make functional synapses with nociceptive specific neurons.\textsuperscript{48,49} The release of nerve growth factor in the dorsal horn can also instigate C fibre sprouting,\textsuperscript{50} increasing the number of functional synapses from nociceptors to second order neurons. Apoptosis, or death, of dorsal horn GABA inhibitory interneurons may also occur,\textsuperscript{42} although more recent findings have challenged this assertion.\textsuperscript{51}

These factors may all contribute to central sensitisation at the spinal cord level. While acute central sensitisation may be useful in nociceptive pain, long-standing sensitisation of dorsal horn neurons is pathological. A number of the mechanisms of plasticity described above can
lead to sensitisation persisting after removal of incoming nociceptive stimuli, or result in very little input needed to sustain sensitisation.\textsuperscript{52,53}

C. Brainstem Regions

Neuroplasticity is not limited to the dorsal horn but can continue into supraspinal regions. There is now good evidence of alterations in brainstem descending pain inhibitory and facilitatory pathways in many chronic pain populations. Although it is difficult to establish the chronology of such alterations, several studies have provided evidence that inflammation and peripheral nerve damage can give rise to subsequent changes in brainstem modulatory regions, suggesting a causative effect.

After acute tissue injury or inflammation, there is net increase in both descending inhibition and facilitation from multiple supraspinal sites, particularly the RVM and locus ceruleus.\textsuperscript{54} As well as altered activity in existing ON and OFF cells, a phenotypic switch of neurons may occur. A third class of cells in brainstem regions, termed NEUTRAL cells, do not normally respond to nociceptive input. However, following activation of the nociceptive system, these NEUTRAL cells can be converted to ON or OFF cells, potentially mediating the increased descending activity.\textsuperscript{55} Although the overall modulation of ascending nociceptive signals is upregulated, there are distinct temporal shifts in the balance between inhibition and facilitation. Facilitation dominates early after injury, with inhibition taking time to build.\textsuperscript{56} The delayed inhibition predominates with time and likely serves as a mechanism to dampen dorsal horn hyperexcitability. However, in a chronic inflammatory model, it has recently been shown that despite descending inhibition being increased, the mechanical threshold for an OFF cell pause (i.e., removal of descending inhibition) is significantly
lowered,\textsuperscript{57} perhaps providing a basis for mechanical hypersensitivity in prolonged inflammatory states.

More sustained changes in the balance of descending facilitation and inhibition occur with ongoing nociceptive input. Following nerve injury, there is evidence of reduced inhibition and increased facilitation from the medulla\textsuperscript{58,59} and death of some RVM cells may occur.\textsuperscript{60} Additionally, the normally inhibitory locus ceruleus, which gives rise to the descending ceruleospinal pathway, may switch to a facilitatory input.\textsuperscript{61} Long-term exposure to morphine also has been shown to increase the number of ON cells in the RVM.\textsuperscript{62} Such changes would give rise to a shift in the balance of descending modulation towards tonic facilitation. In support of this, increased activity in the RVM and PAG has been documented in people with chronic allodynia following nerve injury\textsuperscript{63} and is associated with punctuate hyperalgesia in chronic hip osteoarthritis,\textsuperscript{64} suggestive of enhanced facilitation of nociceptive input by these supraspinal centres.

It is also now established that several chronic pain populations have impaired conditioned pain modulation,\textsuperscript{65} a paradigm used to assess the function of the diffuse noxious inhibitory control system. Impaired inhibition by this system has been documented in people with arthritis,\textsuperscript{66,67} fibromyalgia,\textsuperscript{68,69} chronic headache,\textsuperscript{70-72} irritable bowel syndrome,\textsuperscript{73-75} and temperomandibular joint disorder.\textsuperscript{76,77} Thus, it appears to be a phenomenon that is not specific to any particular chronic pain pathology. Of note, there is evidence that impaired conditioned pain modulation can be restored with pain relief.\textsuperscript{67,78} These studies provide evidence that conditioned pain modulation is modifiable over time and is temporally associated with the pain experience. Animal models of mild or chronic stress also have shown that brainstem regions are involved in the development of hyperalgesia.\textsuperscript{79-81}
providing evidence for a “top-down” modulation of plasticity in brainstem pathways by cortical regions.

D. Cortical reorganisation

Brain structural and functional imaging techniques have provided evidence of morphological, metabolite, and neuronal excitability changes in people with various long term pain conditions. Numerous magnetic resonance imaging (MRI) studies have shown atrophy of grey matter in neuromatrix regions. These have included populations with low back pain, headache, irritable bowel syndrome, osteoarthritis, complex regional pain syndrome (CRPS), and fibromyalgia. This is not a widespread phenomenon but appears to be a functionally specific atrophy that is regionally different among the various pain conditions. The chronology of such grey matter changes is difficult to determine, but a handful of longitudinal studies have convincingly demonstrated that changes in reported pain intensity over time are mirrored by alterations in structural grey matter volume, suggesting that the latter may be a consequence of the former. One caveat that should be mentioned is that most of these studies have not taken patient co-morbidities into account and some have revealed structural changes in non-neuromatrix regions, so such reorganisation may not always be pain-specific.

Changes in concentration of specific brain metabolites have been demonstrated in neuromatrix regions of people with chronic low back pain, CRPS, spinal cord injury, and post-herpetic neuralgia. In fact, it was some of this early work using magnetic resonance spectroscopy that lead to the hypothesis that morphological changes may be present in the brain. These studies have predominantly reported decreased concentration of N-acetyl-aspartate (NAA; a marker of neuronal function) and glutamate...
metabolites in several cortical and subcortical regions, including the primary sensorimotor
cortex, thalamus, insula, and anterior cingulate cortex. The clinical importance of such
findings is evident in that the concentration of metabolites related to glutamate and NAA in
people with spinal cord injury was able to distinguish between those with pain and those
without. Reduced concentration of these specific metabolites reflects a loss of neurons
or neuronal dysfunction in specific neuromatrix regions. It has been speculated that this
arises through a neurodegenerative processes due to enhanced neural activity in these
regions in people with long-term pain. Of note, individuals with visceral pain who had the
lowest baseline concentrations of glutamate and NAA showed the greatest pain reduction
with treatment, suggesting that lowered concentrations of the metabolites are a marker
of potential pain recovery.

Furthermore, there is evidence for more specific reorganisation occurring within the
primary somatosensory and motor cortices in chronic pain conditions. Flor and colleagues were one of first to document shifts in cortical sensory representation maps of people with
phantom limb pain. Since then, numerous studies have reported similar alterations in bodily
representation in the somatosensory cortex of amputees with phantom limb pain that
are not present in those without pain. It is possible that this plasticity reflects a
compensatory measure to restore function in deafferented cortical regions. However, there
are alterations in cortical representation in other chronic pain conditions that do not involve
amputation, so this reorganisation is not entirely dependent on structural deafferentation.

For example, in people with chronic back pain, a medial shift of the back representation
within the somatosensory cortex has been reported without any reorganisation in other,
non-painful body regions. Additionally, reduced or altered locations of primary
somatosensory cortex representations of the painful body region have been documented in studies involving people with CRPS,\textsuperscript{107-110} spinal cord injury pain,\textsuperscript{111} and those with pain associated with carpal tunnel syndrome.\textsuperscript{112}

There are also structural and functional changes in the primary motor cortex in populations with chronic pain. Shifts in motor cortical representation in people with low back pain\textsuperscript{113,114} and phantom limb pain\textsuperscript{103,104,115} have been reported. Studies using transcranial magnetic stimulation to examine corticomotor excitability in chronic pain have shown altered responses in a number of chronic pain populations. The findings have generally indicated an increase in corticomotor excitability\textsuperscript{115,116} and a reduction in intracortical inhibition\textsuperscript{117-123} in the affected body region. These findings appear to be supported by a functional MRI (fMRI) study showing increased ispi- and contra-lateral primary motor cortex activation in people with CRPS during hand movement.\textsuperscript{124} However, some authors have reported normal\textsuperscript{121} or reduced corticomotor excitability\textsuperscript{122} in chronic pain populations, and it is likely that the outcomes are influenced by the pain condition or methodological differences among studies. Regardless, it seems obvious that ongoing nociceptive input influences cortical motor regions. The noted reduction in intracortical inhibition may be particularly important given the role of these circuits in cortical plasticity.\textsuperscript{125}

In addition to these morphological and neural excitability changes, there is evidence of adaptations in white matter tracts, glia concentration, and cortical opioid binding potential in those with chronic pain. Regional white matter abnormalities, reflecting plasticity of connectivity between neuromatrix regions, have recently been shown in people with CRPS,\textsuperscript{89} irritable bowel syndrome,\textsuperscript{126} spinal cord injury pain,\textsuperscript{127} and chronic back pain.\textsuperscript{94} Similar to the alterations in grey matter, the white matter alterations appear to reflect
anatomically specific adaptations rather than a global reduction or increase in connectivity. Other studies have shown reduced opioid binding potential in several cortical neuromatrix regions. These have included people with fibromyalgia,\textsuperscript{128} rheumatoid arthritis,\textsuperscript{129} and stroke,\textsuperscript{130} although the precise locations involved appear to differ among population groups. These studies raise the possibility that chronic activation of receptors by endogenous opioids in long-term pain conditions leads to a down regulation of receptor availability. Finally, a recent magnetic resonance spectroscopy study showed greater concentration of metabolites related to glial markers in the anterior cingulate cortex of people with severe neuropathic pain following spinal cord injury.\textsuperscript{99} This alteration was not present in those with spinal cord injury without pain or with less severe pain, and provides evidence that proliferation of glia and glial activation within the cortex may contribute to the maintenance of neuropathic pain.

**E. Summary**

These examples of plasticity show the many levels within the nociceptive system that can adapt in response to ongoing stimulation of the system. The time-course of these events can be remarkably rapid. Windup of dorsal horn neurons takes less than 100 ms to manifest, changes in receptor availability and receptive zones can occur within minutes, programmed cell death and unmasking of latent connections may be evident within hours, while dorsal horn sprouting and other anatomical changes can arise in days.\textsuperscript{7} Chronic inputs can serve to reinforce this plasticity, contributing to an ongoing cycle of pain and adaptation. Importantly, such adaptation should not be looked at in isolation. Plasticity in the periphery, dorsal horn, supraspinal regions, and in glia is inter-related and reflects the complexity and marked interaction of the nociceptive system across many levels.
IV. CLINICAL PRESENTATIONS OF NEURAL PLASTICITY IN CHRONIC PAIN

Classic findings in people with chronic pain are an increased response to noxious stimuli at the site of injury (primary hyperalgesia) and at neighbouring regions (secondary hyperalgesia), a pain response to harmless stimuli that would not normally be painful (allodynia), and the presence of spontaneous innocuous (parathesia) and unpleasant (dysesthesia) sensations. Disturbances in additional sensory and perceptual systems as well as motor symptoms are also common presentations in chronic pain. The following section presents some of the possible underlying neural mechanisms associated with these signs and symptoms based on the descriptions of plasticity provided above.

A. Spontaneous pain and phantom pain

Spontaneous pain is common following nerve damage and is commonly described as shooting, burning, or stabbing sensations. Ectopic discharge from damaged neurons or neuromata provide a source of nociceptive input to the spinal cord dorsal horn. If this input is sufficient to activate second order neurons, an ascending signal will be sent to the neuromatrix and may lead to pain being experienced. Spontaneous pain arising solely from ectopic discharge can be blocked by anaesthesia of the nerve, so it is relatively simple to determine if this is the sole contributor to spontaneous pain sensations. Since sympathetic discharge and circulating catecholamines can facilitate ectopic discharge from damaged axons or neuromata, people with chronic pain may report greater spontaneous pain sensations when under emotional stress.

Cortical plasticity may also underlie spontaneous and phantom pain. Reorganisation within the primary somatosensory and motor cortices has been associated with the magnitude of reported phantom limb pain. While some report that these representational
shifts are not present in congenital amputation or those without phantom limb pain,\textsuperscript{102} others have provided evidence of reorganisation in amputees who do not experience pain.\textsuperscript{132} It is known that deafferentation or amputation itself can lead to sensory and motor cortical plasticity.\textsuperscript{132,133} Thus, alterations in cortical sensory and motor map representations do not necessarily give rise to phantom pain in amputees, but may contribute to its maintenance. People with phantom limb pain appear to have disordered motor control of the phantom limb compared to those without pain, and it is speculated that an inability to move the phantom limb and generate afferent feedback to the sensory cortex may contribute to this pain.\textsuperscript{134}

B. Allodynia

Allodynia is the perception of pain in response to a non-noxious stimulus. It is commonly assessed using brush, touch, thermal, or vibration stimuli and is a frequent symptom in chronic pain conditions such as CRPS\textsuperscript{135} and whiplash.\textsuperscript{136,137} According to international criteria, the term allodynia must only be used when it is certain that the stimulus does not activate nociceptors, and therefore it is primarily associated with Aβ fibre activation. Evidence for the involvement of Aβ fibres is provided by the rapid activation of cortical regions following application of allodynic stimuli, which is consistent with involvement of fast conducting axons.\textsuperscript{138}

Allodynia can arise through several of the mechanisms described in the preceding section. This includes sensitisation of WDR neurons and subsequent increased responsiveness to non-noxious input, ephaptic discharge between Aβ and nociceptive fibres, invasion of Aβ fibres into the superficial laminae of the dorsal horn, activation of latent interneurons from deep to superficial dorsal horn laminae, and release of substance P by Aβ fibres.
evidence for the occurrence of these processes is difficult to provide in man, there is substantial evidence of such plasticity in animal work described in the preceding section.

In humans, cortical imaging studies have perhaps provided the best evidence of altered neural processing in allodynia. Several studies undertaken with neuropathic pain patients have shown cortical activation networks in allodynia that are different from that seen during the presentation of equivalent, non-painful stimuli or during nociceptive pain.\textsuperscript{139-142} Maihöfner and colleagues\textsuperscript{143} also have shown altered neuromatrix activation during skin brushing in healthy people who have been given experimentally induced allodynia. Thus, the experience of allodynia clearly arises through altered processing of non-noxious input.

While not all of the clinical studies elicited common activation networks, in general there is evidence of a larger extent of cortical activation during allodynia and a shift to more lateral or sensory-dominant neuromatrix regions.

\textbf{C. Hyperalgesia}

Consistently, people with chronic pain have reduced pain thresholds, or, for a given intensity of noxious stimulation, will report a higher pain rating. Localised reductions in threshold that are specific to the area of tissue injury or pathology are common. For example, significantly reduced pain thresholds in local pain areas have been reported in fibromyalgia,\textsuperscript{144,145} whiplash,\textsuperscript{146,147} visceral pain syndromes,\textsuperscript{75,148} low back pain,\textsuperscript{149} arthritis,\textsuperscript{66} and headache.\textsuperscript{150} This hyperalgesia could reflect peripheral sensitisation of the nociceptors, localised central sensitisation within the dorsal horn, or sensitisation of cortical regions.

The clinical detection and differentiation of peripheral and central sensitisation can be challenging, but surprisingly detailed conclusions can be made on the basis of routine sensory examinations and slightly more sophisticated quantitative sensory testing
procedures. Evidence that the threshold for eliciting the lower limb nociceptive flexion reflex is reduced in people with chronic whiplash and fibromyalgia\textsuperscript{151} shows that there is a definite spinal level adaptation in these conditions as the flexion reflex is not dependent on subjective pain report. If reductions in pain threshold can be ameliorated or eliminated by local anaesthesia, then it is likely that sensitisation is at least partly mediated by a short-term mechanism that is sustained by peripheral nociceptive. If sensitisation or hyperalgesia is not abolished through peripheral analgesia, it is indicative of central structural alterations or changes in neurotransmitter or receptor types. Sprouting of nociceptor terminals, opening of dorsal horn latent connections, reduced glycinergic or GABAergic inhibition of second order dorsal horn neurons, switches from inhibitory to excitatory transmission, shifts in the balance of descending regulation, and reduced responsiveness to endogenous opioids can all contribute to central sensitisation and localised hyperalgesia.

There is also evidence of cortical plasticity associated with hyperalgesia. The intensity of current or ongoing pain has been correlated with primary somatosensory cortex reorganisation in CRPS,\textsuperscript{107,110} spinal cord injury,\textsuperscript{111} and phantom limb pain.\textsuperscript{152} Others have reported that cortical metabolite concentrations\textsuperscript{98,99} and the extent of atrophy of the insula\textsuperscript{89} correlate with pain intensity. Stronger evidence of a relationship between pain and cortical plasticity has been shown in a few longitudinal studies. Functional connectivity involving the primary sensorimotor cortex was modulated in healthy individuals during sustained (6 minutes) experimental pain, with a shift towards a salience network evident.\textsuperscript{153} Additionally, Birbaumer and colleagues\textsuperscript{105} found that an anaesthetic block both reduced the extent of phantom limb pain and gave rise to a normalisation of primary somatosensory cortex representation in amputees. The somatosensory cortex was unchanged in those who
did not experience analgesia. Reorganisation within the primary somatosensory cortex also has shown to be reversed in people with CRPS coincident with clinical improvement,\textsuperscript{109} while brain metabolite concentrations of glutamate and NAA increased with treatment in people with visceral pain.\textsuperscript{100} In the latter study, the reduction in clinical pain correlated with changes in metabolite concentration. Thus, it is likely that these cortical adaptations reflect neural plasticity in response to the ongoing nociceptive signals, but they may serve to maintain or facilitate pain over time.

The knowledge that a history of pain,\textsuperscript{154-156} multiple sites of pain,\textsuperscript{157-159} and prior trauma\textsuperscript{160} are predictors of the development and impact of chronic pain following injury suggests that some individuals may be more susceptible to central sensitisation and hyperalgesia. Their baseline nociceptive system is likely to be in a state that is more likely to lead to persistent plasticity and transform an innocuous event into a chronic problem.

**D. Windup**

Windup is an exaggerated pain response following repeated, high frequency nociceptor activation. It is evident clinically as rapidly increasing pain during application of repetitive noxious stimuli and serves as a biomarker of central sensitisation. High frequency nociceptive input induces temporal summation in WDR dorsal horn neurons, the perceptual correlate of windup, and the presence of an exaggerated response indicates that sensitisation of the WDR neurons has taken place. Indeed, the temporal summation response is a more sensitive indicator of central sensitisation than the response to a single noxious stimulus.\textsuperscript{66,144}

Evidence of a relationship between peripheral tissue damage and an enhanced windup response is provided by a study that induced delayed onset muscle soreness in healthy
individuals. Following the induction of muscle soreness, temporal summation threshold was significantly reduced in the painful muscle. This suggests that sensitisation of WDR neurons contributed to the induced muscle hyperalgesia. Clinically, enhanced susceptibility to temporal summation means that persistent, minor nociceptive input from the periphery can lead to the perception of pain when it would normally remain subthreshold. The relevance of windup and temporal summation for chronic pain conditions is further evident in that the duration of pain symptoms has been correlated with temporal summation threshold in people with osteoarthritis.

**E. Referred sensations**

Referred sensations are those that arise from areas distant to a primary location receiving noxious stimulation. Referred sensations are commonly reported in people with CRPS, phantom limb pain, facial pain, whiplash, spinal cord injury, and fibromyalgia. During experimentally induced pain in healthy volunteers, referred pain is usually felt distal to the primary site, but it is often reported to spread proximally in some people with chronic pain. The referred sensations can match the modality of the primary stimulation but also may be different and can be both painful and non-painful. Referred sensations are normally present with a slight time delay (20–40 s) from the primary stimulation.

Referred sensations have been reported to be more common in people with complete spinal cord injury with neuropathic pain compared to those without pain and in amputees with phantom limb pain compared to those without. Because of this association with neuropathic pain, it is likely that referred sensations are related to neural plasticity. A possible mechanism of referred sensation is the spatial summation of noxious afferents
from the primary source and non-noxious afferents from the referred area. The use of anaesthetic blocks has shown that input from the primary source of pain is required for referred sensations to be felt. While some studies have shown that referred muscle pain persists after anaesthetising peripheral nerves innervating the referred area, others have shown a reduction in pain intensity when large afferents are blocked. This suggests that afferent input from the referred area is not necessary for referred sensations to develop but may serve to enhance those that are experienced. Since ongoing stimulation is required to elicit referred sensations in healthy people and there is a time delay between the primary and referred sensation, it is probable that central sensitisation of dorsal horn neurons is required. A sensitised dorsal horn may open the normally latent connections from nociceptors mediating pain from the primary area, activating secondary neurons that normally receive input from the referred pain area.

Interestingly, the number or extent of referred sensations elicited by painful stimuli has been correlated with the extent of primary somatosensory cortex reorganisation in people with phantom limb pain, suggesting a possible cortical contribution. Referred sensations from non-noxious stimuli were also present in the same individuals and have previously been reported in people with subcortical stroke who do not have ongoing pain; however, the extent of cortical reorganisation was only correlated with sensations arising from painful stimuli. Therefore, while referred sensations from non-noxious stimuli may be a manifestation of more general cortical sensorimotor reorganisation, there appears to be a relationship between primary somatosensory cortex plasticity, nociceptive processing, and referred pain.
F. Widespread pain

Many studies in people with regional chronic pain conditions have shown that pain thresholds are also reduced at remote, non-painful body regions. Widespread hyperalgesia is more severe when present across a number of stimulus modalities and locations, in people with longer term duration of pain, and in people with more intense pain. This widespread hyperalgesia cannot be accounted for by peripheral sensitisation as there is no damage or inflammation at the local site; therefore, it must be due to hypersensitivity in the central nervous system.

A potential mechanism of this diffuse central sensitisation is the activation of intersegmental propriospinal interneurons that provide a link between second order neurons in the dorsal horn. An intersegmental mechanism is favoured as the spread of hyperalgesia does not follow dermatomal patterns. Indirect evidence of this has been provided by several studies examining the spread of experimentally-induced pain in chronic pain populations. Following the injection of hypertonic saline into specific muscles, a diffuse spread of pain has been reported in people with osteoarthritis, fibromyalgia, whiplash, and chronic low back pain. Compared to healthy controls, the spread of pain was greater, lasted longer, and was more intense in the chronic pain populations. In some cases, pain spread to other segments of the limb or to the contralateral side. The fact that ketamine, an NMDA receptor antagonist, can block the spread of pain also points to a central sensitisation process involving a change in glutamate receptor availability in the dorsal horn. The substantial evidence that people with a longer duration of pain and more intense current pain are more likely to show widespread pain suggests it may take some time for sensitisation to spread. Ongoing peripheral input is likely to drive this plasticity at central regions. Indeed, evidence for the reversibility of widespread sensitisation with
Changes in nociceptor input has been provided by Graven-Nielsen and colleagues, who showed that pain thresholds at multiple sites increased following knee joint replacement in people with osteoarthritis. At least for this pathological entity, maintenance of central hypersensitivity seems to be reliant on peripheral input.

Alternative possible spinal cord mechanisms contributing to widespread pain are the opening of latent synaptic connections to WDR neurons with ongoing input, similar to the mechanism for referred pain, or the diffusion of substance P within the spinal cord dorsal horn, leading to a spread of activation of WDR neurons. At a supraspinal level, an imbalance in descending inhibition and facilitation may lead to a widespread increase in the excitability of dorsal horn neurons. For example, descending facilitation from the RVM would contribute to secondary hyperalgesia as it can impact at multiple spinal segments, while blocking descending inhibition can increase the number of receptive fields of dorsal horn cells. Glial cell connections also may play a role given their extensive and rapid potential for activation. Any change in connectivity driven by persistent local inflammation may facilitate the sensitising effect of glia at other segmental locations. Finally, if the concentration of the prostaglandin forming enzyme COX-2 is elevated centrally following persistent inflammation, it will facilitate widespread production of prostaglandins in the dorsal horn, which will contribute to sensitisation of dorsal horn neurons at multiple levels. Of note, elevated levels of substance P, CGRP, and excitatory amino acids have been found in the cerebrospinal fluid of people with fibromyalgia and CRPS.

G. Sensory disturbances

Impairments in other sensory modalities are frequently reported in long term pain conditions. For example, in people with CRPS, reduced tactile and touch thresholds.
reduced awareness of limb position, dysgraphesia, body perception disturbances, and neglect have been reported. Similar findings are evident in other chronic pain populations. Decreased kinaesthesia, altered body perception, reduced acuity, or dysgraphesia have been reported in chronic low back pain patients and people with repetitive strain injury, and hypoesthesia to multiple stimulus modalities is common in chronic whiplash. Additionally, telescoping, or the perception of shrinking and retraction of the phantom limb towards the residual limb, is often present in amputees but appears to be more prevalent in those with phantom limb pain than those without pain. The finding in two studies that abnormal sensory function in people with CRPS correlates with pain severity and that reduced joint position sense in whiplash is greater in those with higher levels of pain provides evidence of a relationship between these sensory disturbances and the nociceptive system.

Alterations in somatosensory cortex representation are perhaps most likely to contribute to the reported features of reduced sensory acuity and impaired body perception disturbance. Tactile threshold is often normal in such populations even though the ability to use this information is impaired, and there is often no evidence of peripheral tissue damage or sensory deficits are present in areas remote from tissue damage. Therefore, impaired sensory function is likely to be of central origin. Some evidence for this is that two-point discrimination ability was shown to be related to the amount of primary somatosensory cortex reorganisation in people with CRPS. Reorganisation of the primary somatosensory cortex in phantom limb pain has also been associated with increased, non-painful stump sensations.
An altered primary somatosensory cortex representation is also likely to increase difficulty in recognising body image. Studies involving people with chronic unilateral pain conditions have consistently indicated laterality recognition impairments compared to healthy individuals. Laterality testing involves assessing the person’s ability to identify the laterality, or side, of a visually presented body limb, most commonly a hand or foot. Such testing has shown that identification of the painful side is slower in populations with CRPS, phantom limb pain, and low back pain. This provides some evidence of a disordered working body schema in these populations and a reduced ability to correctly and rapidly identify body parts. Recent research in both experimental and chronic pain has revealed that visually manipulating body perception of the painful body part can provide pain relief, although the hyper- and an-algesic effects of enlargement and shrinking were not consistent across these studies. Still, they provide further evidence of a strong link between body perception and pain.

While cortical reorganisation may be large contributor to sensory disturbances, it is likely that spinal level plasticity initiated such alterations. Expanded and overlapping fields of WDR neurons that occur when sensitised are likely to alter the ascending input to the primary somatosensory cortex and drive the reorganisation occurring at this level.

**H. Impaired motor control**

Impairments in various aspects of motor control are routinely reported in chronic pain conditions. Indeed, the presence of motor signs and symptoms forms part of the diagnostic criteria for CRPS, with altered range of motion, tremor, weakness, dystonia, and discoordination commonly evident. In people with chronic low back pain, there have been reports of altered postural muscle activation and disturbances in
postural\textsuperscript{193,209} and balance\textsuperscript{210} tasks. Additionally, reduced muscle strength, impaired timing of muscle activation, and reduced range of motion are routinely present in people with whiplash.\textsuperscript{198}

Although motor impairments are common in a variety of chronic pain conditions, why they arise and how they are maintained is currently undetermined. A circular argument exists as to whether ongoing nociceptive input drives plasticity in the motor system and causes movement impairments, or impaired motor function contributes to activation of the nociceptive system and increases pain. Indeed, there have been many theories proposed\textsuperscript{211-213} to account for the relationship between pain and motor dysfunction in people with painful musculoskeletal conditions, none of which completely explain symptoms in chronic neuropathic pain. It is likely that it is a highly complex relationship that may not be uniform among pain conditions.

A large amount of evidence was provided in the preceding chapter of plasticity in motor cortex representation and excitability in chronic pain conditions, and it is likely that this central, motor cortical reorganisation is associated with movement impairments. An fMRI study showed that motor dysfunction in a reach-to-grasp task performed by people with CRPS was related to increased primary motor cortex and supplementary motor area activation during hand movement, with the amount of dysfunction correlated with activation in these regions.\textsuperscript{124} In a further study, the location and volume of trunk muscle representation in the primary motor cortex was associated with deficits in postural control in people with chronic back pain.\textsuperscript{113} The extent of motor reorganisation was correlated with the delayed onset of muscle activity during rapid arm movements. Thus, these studies
provide some evidence of a relationship between cortical motor plasticity and function impairments in people with long-term pain.

One hypothesis is that this motor cortical reorganisation results in a difficulty integrating sensory information and motor output, and that this incongruence may indeed contribute to pain.\textsuperscript{214} It is known that acute experimental pain disrupts motor control,\textsuperscript{215} causes changes in spinal motoneuron\textsuperscript{216,217} and corticomotor excitability,\textsuperscript{216,218,219} and degrades proprioceptive information.\textsuperscript{220,221} In the long-term, such alterations, particularly in the quality and extent of afferent information, may cause more permanent changes in cortical motor representation and lead to sustained impairments in motor function. Plasticity in sensory regions may well contribute to motor impairment. Support for the importance of sensory information in chronic pain is provided by a study showing that tactile acuity was related to impaired motor control in people with low back pain.\textsuperscript{193} However, the cause and effect nature of this finding cannot be determined and the exact reasons for motor impairments in chronic pain populations remain challenging to determine. Perhaps the best insight will come from studies that have manipulated cortical motor excitability and examined the effect on pain and motor function.

V. MANAGEMENT HARNESING NEUROPLASTICITY

While most of the preceding information has shown neuroplastic phenomena that may be causing or contributing to the chronic pain experience, it is also possible to take advantage of the highly plastic nature of the nervous system to identify appropriate treatment strategies and promote restoration of function and management of pain. The remainder of this article will focus on three techniques that aim to achieve this.
A. Sensory training

Sensory discrimination training for chronic pain is not new, but developments in imaging technology have now provided evidence of neural plasticity in response to such interventions and have resulted in refined applications and wider acceptance of its use. Through focusing the patient’s attention on sensory information, sensory training aims to reverse reorganisation within the somatosensory cortex and reduce pain. Flor and colleagues\textsuperscript{222} were one of the first groups to specifically use sensory discrimination training for chronic pain. In this study, people with phantom limb pain were given electrical stimuli over their stump and were asked to discriminate the location and frequency of the stimuli. As well as improvements in the sensory task, there were marked significant reductions in pain and somatosensory cortex reorganisation. Notably, these changes in function, pain, and cortical representation were positively correlated.

Sensory training has since been implemented in other chronic pain populations. In people with CRPS, it has been shown to reduce pain,\textsuperscript{108,223,224} improved sensory acuity,\textsuperscript{108,223,224} and improve function,\textsuperscript{223} while it was also effective in reducing pain and disability in people with chronic low back pain.\textsuperscript{225} Of note, Pleger and colleagues\textsuperscript{108} also reported an increased spatial representation in the primary and secondary somatosensory cortex in people with CRPS following training, suggesting a reversal of cortical reorganisation coincident with improved function and reduced pain. The provision of normal, contextual sensory information may therefore serve to undo the cortical reorganisation that has occurred and restore functional neural connections.

It seems that focussed attention and functional use of the sensory input is integral to the success of sensory discrimination tasks. These factors are likely to prioritise non-noxious
afferent input to the spinal cord and supraspinal regions over any on-going nociceptive input. In support of this theory, there was no change in sensory performance or sensory cortical representation when CRPS patients undertook motor training without a sensory discrimination component. Additionally, Moseley reported that a sensory task involving discrimination of clinically relevant sensory stimuli was effective in reducing pain, but just receiving the equivalent sensory stimuli without the discrimination component was not effective. Visual attention toward the limb during training also appears to be an important factor for modulating the magnitude and duration of analgesia.

It is known that attention and task complexity enhance neural plasticity during motor learning and it is apparent that this also applies to neuroplastic changes in the sensory system during sensory training. Clinically, this would mean that progressively graded sensory discrimination training that requires the patient’s attention would be most beneficial. Functionally relevant stimuli should be used, potentially with multiple modalities, and the training should be individually adapted so that it constantly challenges the ability of the patient. Appropriate tasks include two-point spatial discrimination, identification of object textures, stimulus localisation identification, and graphethesia training.

B. Non-invasive brain stimulation

Stimulation of the primary motor cortex for the treatment of chronic pain originated in the early 1990s using electrodes that were implanted within the cerebral cortex. Whilst effective pain relief was evident, the surgical procedure is highly invasive and comes with the associated risks of brain surgery. The development of non-invasive magnetic and electrical methods of brain stimulation saw these, far safer, techniques applied in people with chronic pain. Repetitive transcranial magnetic stimulation (rTMS) was initially trialled in
the 2000s and early results showed that a modest amount of pain relief could be achieved. More recent studies have made use of transcranial direct current stimulation (tDCS), which involves the delivery of current to the brain through electrodes placed over the scalp.

Approximately 20 randomised controlled trials have examined the effect of non-invasive brain stimulation in neuropathic pain populations. The overwhelming majority of these have shown significant reductions in pain and often improvements in function or quality of life, clearly demonstrating the clinical potential of non-invasive brain stimulation. A recent meta-analysis revealed an effect size on pain of approximately 1.5 for tDCS applied to chronic pain populations, which is a clinically important effect. It is noteworthy that the majority of participants involved in these studies are drug-resistant patients who have not responded to other treatment methods.

Both rTMS and tDCS can induce alterations in cortical excitability that outlast the period of stimulation. This lasting effect has important implications as it indicates the development of plasticity within intracortical structures. The excitatory effects of high frequency rTMS appear to arise through a long-term potentiation-like process subsequent to the development of cortical disinhibition. tDCS acts by modifying the transmembrane neuronal potential, influencing the level of resting excitability of individual neurons, and it is speculated that the lasting effects of stimulation are mediated via increased activation of NMDA channels. Importantly, the effects of motor cortex stimulation are not restricted to the area receiving stimulation; the function of distant sites also can be modulated through neuronal network connections.
Exactly how motor cortex brain stimulation elicits its analgesic effects remains a mystery. It may act through direct connections from the primary motor cortex to the thalamus and primary somatosensory cortex. When applied to people with chronic pain, the analgesic effects of rTMS have been associated with normalisation of intracortical excitability, which suggests that the mechanism of action may be related to changes in intracortical modulation. The high connectivity between the primary motor cortex, thalamus, and somatosensory cortex could mean that this modulation of intracortical motor circuits subsequently alters the processing of nociceptive input at these two locations. This mechanism would dictate that the sensory component of pain would primarily be influenced. There is, however, evidence that primary motor cortex stimulation has at least as great an effect on the affective aspect of pain. Alternatively, motor cortical polarisation could give rise to indirect activation of brainstem inhibitory pathways via connections from the motor cortex to other areas of the brain. Altered activation in the anterior cingulate cortex, insula, orbitofrontal regions, and brainstem has been documented following motor cortex stimulation, providing some evidence for this mechanism. It is also been shown that opioids mediate at least part of the analgesic response, and it is known that these brain areas have a high density of opioid receptors. Therefore, primary motor cortex stimulation may instigate opioid release that subsequently initiates activity in these limbic regions. In healthy individuals, direct stimulation over the dorsal lateral prefrontal cortex increases pain tolerance, suggesting that altered activation of this cortical area can modulate the affective experience of pain.

Both rTMS and tDCS are commonly used forms of brain stimulation, but tDCS is a clinically more practical and cheaper option. Indeed, programmable take-home versions of tDCS units
are now commercially available. The most frequently used stimulation parameters are anodal electrical or high frequency magnetic stimulation applied over the primary motor cortex representation. Optimal results appear to be seen with 5 consecutive days of stimulation. There is some evidence that this can provide significant pain relief for up to 3 weeks\textsuperscript{233,234,252,253} but it is likely that the duration of this would be enhanced if further stimulation was provided. In support of this, Mhalla et al.\textsuperscript{245} demonstrated that the cumulative effect of a tapered rTMS protocol gave rise to pain relief for up to 6 months. Given the proposed mechanisms of action, some consideration of the location of application is warranted; stimulation over pre-frontal regions may be indicated for those who are not responsive to primary motor cortex stimulation.

C. Mechanisms-based treatment approach

As outlined in the previous sections, chronic pain may be associated with a multitude of neuroplastic changes at a number of different levels of the nervous system. Even within the same pain condition, there is a large degree of variability in the clinical presentation of pain-related signs and symptoms.\textsuperscript{254-258} This is thought to reflect individual differences in the neuroplastic changes that drive the chronic pain experience for one person compared to another. Conversely, the type of pain treatment an individual receives is usually based on their diagnosed pain condition and the clinical experience of the treating health professional. In recent years, personalised treatment using a mechanisms-based approach has been advocated for chronic pain.\textsuperscript{259} Under this approach, symptom profiling and quantitative sensory testing are used in an attempt to delineate the specific neuroplastic changes underlying an individual’s pain experience and/or identify potential responders from a group of individuals prescribed the same treatment.
There are many examples that individuals who demonstrate marked allodynia and hyperalgesia with quantitative sensory testing may respond better to medications that reduce neuronal hyperexcitability. In people with neuropathic pain due to spinal cord injury, the systemic infusion of lamotrigine was more effective in those with brush allodynia and wind-up to punctuate mechanical input.\textsuperscript{260} Similarly, people with neuropathic pain who reported mechanical allodynia had a significantly greater reduction in ongoing pain with intravenous lidocaine infusion compared to those without alldynia.\textsuperscript{261} In individuals with HIV induced neuropathic pain, pregabalin did not significantly reduce pain compared to placebo;\textsuperscript{262} however, there was a reduction in pain in a subgroup with strong hyperalgesia to punctuate mechanical input. Finally, in a recent study of people with chronic pancreatic pain,\textsuperscript{263} pregabalin was found to be most effective in individuals with localised hypersensitivity to electrical stimulation over the upper abdomen when compared to a control site. Localised electrical hypersensitivity at baseline was able to predict the pain relieving effects of pregabalin with a classification accuracy of 84%.

Further studies in people with painful diabetic neuropathy have shown that assessment of the nociceptive system can predict individual responses to specific analgesic medication. Campbell et al.\textsuperscript{264} categorised patients according to their response to capsaicin prior to undergoing treatment with topical clonidine gel or a placebo. It was hypothesised that a strong capsaicin response would indicate hypersensitive TRPV-1 (non-selective cation channel activated by noxious heat and chemical compounds) cutaneous nociceptors, a potential therapeutic target for clonidine. In people who failed to respond to capsaicin, clonidine was found to be ineffective compared to placebo. However, those who had a painful response to capsaicin showed a significant reduction in ongoing neuropathic pain
with clonidine compared to placebo. Yarnitsky et al.\textsuperscript{265} found that quantitative sensory testing of endogenous pain inhibitory pathways was able to predict the pain-relieving effects of duloxetine, a monoamine reuptake inhibitor. Individuals with less effective conditioned pain modulation at baseline had a greater reduction in pain, a response that is to be expected as conditioned pain modulation is largely determined by descending inhibition from brainstem monoamine pathways. In addition, the treatment-induced improvement in conditioned pain modulation was found to be correlated with medication efficacy.

The observations above support the premise of a mechanisms-based approach to pharmacological management of chronic pain. By relating individual sensory profiles to specific neuroplastic changes that occur in the nociceptive system, it is hoped that individuals may receive more targeted interventions. In turn, this may achieve better therapeutic efficacy while limiting exposure to ineffective treatments and their associated side effects. While there is still a long way to go until such an approach becomes common practice, the evidence presented above suggests that this is a rational approach that holds considerable promise for the future treatment of chronic pain.

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