Perspective

Addressing Neuroplastic Changes in Distributed Areas of the Nervous System Associated With Chronic Musculoskeletal Disorders

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Abstract

Present interventions utilized in musculoskeletal rehabilitation are in large part guided by a biomedical model where peripheral structural injury is believed to be the sole driver of the disorder. There are however neurophysiological changes across different areas of the peripheral and central nervous system including peripheral receptors, dorsal horn of the spinal cord, brain stem, sensorimotor cortical areas and in the meso-limbic and prefrontal areas associated with chronic musculoskeletal disorders including chronic low back pain, osteoarthritis, and tendon injuries. These neurophysiological changes appear to be not only a consequence of peripheral structural injury but play a part in the pathophysiology of chronic musculoskeletal disorders. Neurophysiological changes are consistent with a bio-psycho-social formulation reflecting the underlying mechanisms associated with sensory and motor findings, psychological traits, and perceptual changes associated with chronic musculoskeletal conditions. These changes therefore have important implications in the clinical manifestation, pathophysiology and for rehabilitative treatment of chronic musculoskeletal disorders. Musculoskeletal rehabilitation professionals have at their disposal tools to address these neuroplastic changes including top down cognitive based interventions (such as education, cognitive behavioral therapy, mindfulness meditation and motor imagery), and bottom up physical interventions (such as motor learning, peripheral sensory stimulation, and manual therapy) that induce neuroplastic changes across distributed areas of the nervous system and impact outcomes in patients with chronic musculoskeletal disorders. Furthermore, novel approaches such as the use of transcranial direct current stimulation and repetitive transcranial magnetic stimulation may also be utilized to help renormalize neurological function. Comprehensive treatment addressing peripheral structural
injury as well as neurophysiological changes occurring across distributed areas of the nervous system may help to improve outcomes in patients with chronic musculoskeletal disorders.
Traditionally, treatments for chronic musculoskeletal disorders (CMSD) such as chronic low back pain (CLBP) have been anchored in a biomedical model. This model is based upon a structural-pathology paradigm where insult to anatomical structures is believed to be the sole driver of the condition. Over the last two decades evidence has emerged of neurophysiological changes within the peripheral and central nervous systems associated with CMSD. Studies suggest that CMSD do not simply result from ongoing structural pathology to peripheral tissues but involve a complex interplay between peripheral structural injury, altered afferent information conveyed from peripheral receptors towards the spinal cord, brain stem and cortical areas, changes in neuronal processing of noxious stimuli and psychosocial factors\(^1\). These neurophysiological changes are consistent with experimental and clinical findings of altered sensory transmission including sensory amplification of pain, motor control changes such as altered muscle recruitment patterns, changes in perceptual processes including altered body image, psychological traits such as catastrophization and somatization, and behavioral changes such as fear-avoidance that appear to be implicated both in the clinical manifestation and the pathophysiology of CMSD (Table).

Neurophysiological changes, or neuroplasticity, refers to changes in structure, function and organisation within the nervous system that occurs continuously throughout our lifetimes in response to internal stressors such as cognitive processes, internal changes in sensory afference, and external stressors such as motor learning and peripheral sensory stimulation\(^2\). Neuroplasticity is the method by which the brain encodes new experiences, learns, and develops new behaviors. Neuroplastic changes associated with CMSD have been demonstrated in the (1) peripheral nervous system and spinal cord, (2) brain stem, (3) sensorimotor areas, and (4) mesolimbic and pre-frontal areas of the cortex (see \(^1,\,^3\)).
(1) Neurophysiological changes occurring within peripheral receptors and the dorsal horn of the spinal cord include increased responsiveness to nociceptive stimuli resulting from anatomical insult to musculoskeletal structures and neuropathic stimuli in sensory amplification, a process called sensitisation resulting in hyperalgesia, increased pain perception, and in allodynia, innocuous stimuli is perceived as painful. Peripheral sensitization involving increased responsiveness of the peripheral nociceptors, and central sensitization involving changes in the spinal cord amplifying the transmission of pain is a natural process that has a biological advantage in helping to protect the injury from re-injury. However sensitization should be transient and peripheral and dorsal horn plastic changes should return to their pre-injury state with normalized afferent peripheral input associated with tissue repair.

(2) Neuroplastic changes also occur within the brainstem, specifically in areas involved in the descending modulation of nociceptive and neuropathic stimuli including the Periaqueductal Grey (PAG) and the Rostral Ventral Medulla (RVM). The PAG & RVM are influenced by meso-limbic and opioid systems which in turn influence the transmission of noxious stimuli in the dorsal horn of the spinal cord. Evidence suggests that these descending modulatory systems are affected in chronic pain states and may perpetuate sensitization within the spinal cord.

(3) The sensory discriminative areas involved in the transmission and processing of noxious stimuli includes the primary (S1) and secondary somatosensory cortices (S2) and the insula. The insula appears to be at the crossroads between the sensory discriminative and affective aspects related to pain sensation in the caudal portion and pain affect in the anterior portion. Changes in structure, function and in the somatotopic organization in S1 and the primary motor cortex (M1) have been demonstrated in chronic pain conditions including CLBP and Complex
Regional Pain Syndrome (CRPS) but have also been found in patella femoral pain syndrome, patellar tendinopathy, osteoarthritis (OA), and rotator cuff pathology (see\(^1\)). Changes in pressure pain thresholds and bilateral findings including decreased strength, range of motion, and presence of inflammatory mediators in the contralateral homologous structure also allude to the presence of altered neural transmission and processing in a number of CMSD. The neuroplastic changes in the cortical sensorimotor areas are consistent with sensory (i.e., changes in tactile acuity), perceptual (i.e., altered body image) and motor disturbances (i.e., motor control) apparent in different CMSD. The neurophysiological changes in the sensorimotor cortical areas often correlate with pain intensity and symptom duration\(^9,10\). Evidence suggests a two-way causality between pain/injury and cortical plasticity in S1 and M1, as the elimination of pain may result in cortical reorganization, and interventions that address cortical reorganization may result in decreased pain and improved function\(^{16}\).

(4) The cognitive-affective-motivational areas involved in pain processing receive input from ascending projections via the brainstem and the thalamus\(^7\). This includes the structures within the meso-limbic and prefrontal areas such as the insula, Anterior Cingulate Cortex (ACC), amygdala, and Prefrontal Cortex (PFC)\(^7\). Arguably the most important neuroplastic changes associated with CMSD occur within the meso-limbic and prefrontal areas, regions associated with threat, fear, aversive conditioning, attention, motivation (dis)engagement, and executive control\(^{17}\). The best biomarker identified for the transition from acute to chronic conditions\(^{18}\), and for the presence of chronicity in subjects with low back pain and OA involves activity within these regions\(^3\). Altered structure, function and activity within meso-limbic and prefrontal areas correlate with psychological traits that are often implicated in chronic conditions such as fear-avoidance and catastrophization (a tendency to focus and magnify actual or anticipated pain...
experience and to feel hopeless in the face of such experience\textsuperscript{19})\textsuperscript{20, 21}. Meso-limbic structures, specifically the PFC, ACC and amygdala also influence motor areas and functioning of the descending modulatory systems including the PAG-RVM pathway that are affected in chronic pain states\textsuperscript{6, 7}. The PFC and meso-limbic activity appears to lay the foundation for increased vigilance, attention and salience attributed to the injury, and may therefore contribute to central sensitisation resulting in hyperalgesia and allodynia, and provide conditions ripe for inducing neuroplastic changes in the sensorimotor and subcortical areas. Increasing attention and salience directed to the injury, threat, and perception of pain appears to result in implicit and explicit learning linking movement with pain\textsuperscript{16}.

In summary, neurophysiological changes associated with CMSD include alterations in structure (decrease in grey matter in meso-limbic and prefrontal)\textsuperscript{22, 23}, function and organisation (i.e. changes in response properties and cortical representation in S1 and M1)\textsuperscript{1} and neurobiology (changes in brain chemistry concentrations have been found in subjects with CLBP in an area of the PFC and in M1)\textsuperscript{24}.

**Implications of distributed neuroplastic changes associated with CMSD for rehabilitation**

Neuroplasticity associated with CMSD have important implications for the treatment of conditions such as CLBP, OA and possibly other CMSD\textsuperscript{25}. Conventional rehabilitation interventions are in large part directed towards input (i.e. peripheral structural injury addressing inflammation, repair and remodelling) and output (i.e. muscular strength, endurance, motor control and proprioception) mechanisms associated with CMSD\textsuperscript{26}. Although these interventions may have an impact on peripheral structures they in themselves may not be sufficient to restore cortical properties and function and alleviate pain particularly in chronic injuries\textsuperscript{27}. In
musculoskeletal rehabilitation limited resources have been directed to the problems of transmission, processing, and control mediating afferent stimuli and motor output\textsuperscript{26}. Failure to effectively treat conditions such as CLBP may stem from the fact that these central neuroplastic changes occurring across distributed areas associated with this condition have largely been ignored and may explain why treatment effects are consistently small regardless of the type of intervention \textsuperscript{1,28}.

Principles of neuroplasticity emerging from animal and human studies can be harnessed to induce positive neuroplastic changes. Studies in subjects with and without neurological injury suggest that the stimuli necessary to promote neuroplastic changes, at least in sensorimotor cortical areas, must be repetitive, of sufficient intensity to stimulate adaptive changes, require attention and behavioral salience, involve learning, and that changes will be specific to the neuronal structures implicated in the task \textsuperscript{2,29}. Neuroplasticity is stimulus driven and the stimuli can be mediated by top-down, from higher to lower hierarchical structures within the nervous system, and bottom-up, peripheral to central structures of the nervous system, processes \textsuperscript{30}. As CMSD involves neuroplastic changes within distributed areas, it is logical to believe that treatment should be directed across the different affected structures in the nervous system including the sensorimotor areas and the meso-limbic prefrontal areas. Although this area of study is in its infancy it appears that rehabilitation professionals have at their disposal tools and resources to promote adaptive changes in the sensorimotor areas as well as the meso-limbic and pre-frontal areas associated with CMSD.

\textit{Interventions}

\textit{Top-down}
Reconceptualising Pain

Health care practitioners and persons with CMSD tend to view pain with a bio-medical focus in spite of the failings of this model both to explain clinical and experimental findings and to guide effective rehabilitative strategies. Studies indicate that the relationship between threat and tissue damage is altered in chronic pain states, the stimulus response relationship between structural injury and pain perception is nebulous, neuroplastic changes associated with chronic pain is mal-adaptive, and no longer performs the biological function of protection. It is imperative that updated and current knowledge regarding pain and a biopsychosocial perspective stemming from the wealth of research findings that has emerged over the last two decades be transferred to health care professionals and in health care curriculum.

Recognition of misguided beliefs, values, and behavioral strategies that persons with CMSD may display regarding pain and their injury that are incongruent with the rehabilitation principles of graded activity to promote mobilization and positive adaptive changes should be addressed early and continuously in the rehabilitative process. The conceptualisation that pain and movement is associated with structural damage and belief that the structural insult to anatomical structures is the source of all pain needs to be reformulated.

Experimental findings demonstrate that neurophysiology education of pain (NEP) which includes information regarding the anatomy, physiology and processing of noxious stimuli, the perceptual nature of pain, and the altered processing with chronic pain is associated with improvement in function and attenuation of pain. The information and concepts presented in the NEP programs are accessible to patients experiencing chronic pain and can have an immediate impact on behavior. Although the scientific literature is limited in regards to these
programs they would appear to perform better than educational programs that stem from a biomedical model to explain structural pathology and biomechanics as the driver of the CMSD
36, 37. A single session of neurophysiology education of pain in subjects with CLBP has proven to result in a transient decrease in pain and improvement in function 35 and may be associated with changes in brain activation patterns 38. For more permanent changes in belief and behavior the concepts stemming from neurophysiology education will most probably need to be repeated consistently in the rehabilitation program 32. Although education has been demonstrated to be beneficial in outcome for chronic back pain 39, recent meta-analysis and systematic reviews of neurophysiological pain education demonstrate that these programs are promising but that results are presently tenuous due to the limited number of studies 36, 37.

Addressing Maladaptive Thoughts and Behavior

Cognitive Behavioral Interventions (CBI) seeks to identify and address thoughts, ideas and beliefs that are inconsistent, erroneous and unproductive resulting in maladaptive behavior patterns such as worry and avoidance 40. These include traditional Cognitive Behavioral Therapy (CBT) that is a control-oriented treatment attempting to address catastrophic thinking through cognitive re-structuring, promotion of problem solving skills and addressing mal-adaptive behaviors through exposure-oriented interventions to address avoidance behaviors 41, 42. CBT appears to result in improvement in function, decrease in anxiety, and depression which are correlated with increases in activation within the prefrontal cortex 40, 42. These findings suggest that CBT results in an increase in executive control that modulates dysfunctional activity in the meso-limbic areas 40, 42. A prospective study of CBT in subjects with chronic back pain demonstrated decreased functional connectivity between the areas in the PFC and ACC with the amygdala/PAG which positively correlated with decreased pain and improved self-efficacy 43.
Systematic reviews of CBT in subjects with chronic pain indicate that CBT has small to moderate effects on mood, catastrophization and pain intensity and to a lesser extent pain related disability and avoidance behaviors for up to 6 months\textsuperscript{40,44}.

**Acceptance Based Interventions**

Other forms of CBI have also been studied in regards to pain including approaches that involve the development of awareness and non-judgemental acceptance of pain in contrast to attempting to control or fight pain. Two such approaches include Acceptance Commitment Therapy (ACT) and Mindfulness Based Stress Reduction (MBSR)\textsuperscript{41,45}. ACT involves the acceptance of positive and negative experiences, the elucidation of values, commitment to these values, and appropriate goals and actions that support these values\textsuperscript{45}. Pain is seen as an interference to goal directed, value driven action \textsuperscript{41,45}. MBSR incorporates meditation, yoga, and a body scan/relaxation technique providing instruction on acceptance without cognitive assessment, to minimize anxiety and its detrimental effects on pain processing, encourages movement and relaxation and the transference of these skills and mindset to everyday life\textsuperscript{46}. Different variants have been developed including Mindfulness Based Cognitive Therapy that incorporates principles of CBT within MBSR. MBSR decreases stress, anxiety and depression associated with chronic pain states and, similar to CBT, has an impact on prefrontal structures and their control of mesolimbic structures\textsuperscript{46,47}. In healthy subjects a six-week program of MBSR resulted in neuroplastic changes in the insula, S1 and changes in functional connectivity between the medial prefrontal cortex and the insula (increased connectivity between these structures is found in OA patients\textsuperscript{3}), changes that also correlated with the improvement on psychological indexes including worry, anxiety and depression\textsuperscript{47}. In healthy subjects exposed to a noxious stimulation, MBSR resulted not only in the activation of areas in the PFC involved in the reformulation of the contextual
evaluation of the noxious stimuli, but also influenced activity within S1 and the thalamus, areas involved in the transmission and sensory discriminative aspects of pain, alluding to possible gating mechanism of noxious transmission 48.

There is positive evidence for the use of CBI in the treatment of chronic pain, however outcomes are variable and the effects are small for pain intensity, anxiety, depression, quality of life and physical well-being 41,45. The beneficial effects are greatest for mood, catastrophizing thoughts and disability and there is evidence that effects are maintained at six months49,50.

In summary, reconceptualisation involves education that challenges negative and faulty beliefs regarding pain. Issues regarding stress/anxiety/worry that contribute to a heightened response to pain, guarding and fear-avoidance need to be addressed continuously and patients should be provided with the tools to better understand and manage their pain and disability including information regarding pain neurophysiology and a bio-psycho-social formulation of CMSD26. Collectively these interventions appear to improve self-efficacy, the ability of the person to self-manage through actions and interventions to cope with their pain and disability, and promote active coping styles 43, 51. Greater self-efficacy is associated with better outcomes in patients with chronic pain 51. Cognitive-based interventions also address the mesolimbic and prefrontal changes associated with chronic pain, which in turn may impact descending pain modulatory systems within the brain stem (that perpetuate sensitization) and cortical sensorimotor areas 7. NEP and CBI should be addressed at the onset of treatment, even in acute and sub-acute phases and should be continuously addressed during the rehabilitation process. Failure of these interventions to demonstrate more positive effects and for longer durations may stem from the fact that substantial changes in neurophysiological correlates of faulty beliefs and values have not been reconceptualised sufficiently.
Priming the Brain for Movement

The creation of adaptive changes in musculoskeletal structures requires graded and progressive interventions, performed repetitively and with sufficient intensity. These principles appear to apply equally in addressing neuroplastic changes to promote positive adaptive outcomes.

Graded exposure can begin with interventions that require implicit activation of sensory and associative areas in the parietal cortical areas through interventions such as laterality recognition where the patient is asked to determine the laterality of an anatomical image without moving their body part. Studies have shown that subjects with experimental and chronic pain including CLBP, CRPS, OA and CTS make more errors and the speed in the performance of this task is affected when visualising the injured body part, reflective of altered somatosensory organisation and processes in sensory areas including S1 and the inferior parietal regions. Interventions incorporating implicit imagery results in changes in S1 properties and organisation as well as decreased pain and improved function.

Explicit cognitive exposure involves motor imagery of painful or fearful movements. Motor imagery has a long history of use in kinesiology and has well documented positive benefits for performance. In people experiencing chronic pain, motor imagery may help to improve physical performance but also may help to address cortical changes in meso-limbic and prefrontal areas associated with the physical performance of active movements and possible learned associations (implicit and explicit) of pain and movement. Motor imagery utilized for the learning of a new motor skill results in improvement in performance and changes in the motor areas similar to that from actual physical practice.
Cognitive based interventions such as motor imagery can influence brain function and cortical processes including sensorimotor areas. They may have an advantage in highly anxious and fearful patients as they do not involve physical movement and should not elicit an anxiety response. The progressive nature of these interventions appears to be important at least in certain pain conditions such as CRPS when pain severely limits the capacity for movement, and simply imagining movement can increase pain and swelling\textsuperscript{58,59}. To induce changes in properties and organisation in sensorimotor cortical areas tasks involving motor acquisition of new skills involving sustained attention appears to be necessary.

**Novel Approaches for Promoting Cortical Neuroplasticity.**

Direct non-invasive stimulation of cortical neurons to promote neuroplastic changes both in isolation or in association with other modalities has been investigated in a limited number of research studies\textsuperscript{60,61}. Non-invasive cortical stimulation includes transcranial Direct Cortical Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS). TDCS involves the application of a direct electrical current to the surface of the cranium. Combined tDCS and PES in subjects with CLBP resulted in a map reorganisation in M1, improvement in sensory function and decrease in pain that was superior to their individual application \textsuperscript{30}.

TMS involves an electrical current passing through a coil producing a magnetic field that traverses the skull and results in the depolarization of neurons under the coil. Repetitive TMS (rTMS) applied at low frequencies (below 5 Hz) produces an inhibition of the area of stimulation while rTMS applied at higher frequencies (greater than 5 Hz) results in a facilitation. Studies have been performed in neurologically compromised subjects including stroke patients to help promote positive neuroplastic changes and improve motor function. Repetitive TMS over the
somatosensory cortex can also result in improved tactile acuity. Repetitive TMS and anodal transcranial Direct Current Stimulation of the motor cortex help to attenuate chronic pain. Studies have also been performed that combine peripheral electrical stimulation paired with TMS to promote neuroplastic changes in M1.

**Bottom-up**

**Addressing Changes in Sensorimotor Areas of the Brain**

Bottom up modulation of altered processing and organisation in S1 includes interventions such as sensory discrimination training and Peripheral Electrical Stimulation (PES). Tactile acuity, specifically Two-point discrimination (TPD) utilized as form of treatment has been associated with decreases in pain, improvement in function and with renormalisation of properties and organisation within S1 in subjects with CRPS but only when subjects are attentive to the experimental interventions. These findings are consistent with studies that renormalized cortical organisation in S1 in subjects with CTS and improve pain and disability in subjects with CLBP that appear to be mediated by the discriminative nature of sensory stimulation associated with acupuncture. Sensory retuning programs involving different forms of sensory stimulation have also been performed in patients with CLBP and CTS and although limited in scope preliminary evidence is promising.

PES can be utilised to affect neuronal properties in both S1 and M1 in healthy subjects. PES can cause alterations in the somatotopic map within S1 and improve sensory function. PES can both augment and attenuate neural excitability in both S1 and M1 depending upon the parameters of stimulation. PES of a mixed nerve for 120 minutes, at frequencies <10 Hz, at an
intensity of stimulation at or close to motor threshold, results in increases in corticospinal excitability and in improvement of motor performance in healthy subjects. Higher stimulation frequencies appear to result in decreases in excitability of neurons in the motor cortex. TENS applied daily for three weeks to the hand in healthy subjects’ results in an increase in map volume and area of representation of muscles of the hand within M1.

To induce plastic changes in M1, active interventions need to focus on motor learning. The simple repetition of movement will not result in plastic changes in the motor cortex. Excellent reviews have recently been published on principles of neuroplasticity, motor learning and their utilisation in patients with CMSD. Principles including the utilisation of motor learning, functional reacquisition and external focus of attention can be incorporated into rehabilitation programs to address changes in the sensorimotor areas associated with CMSD. Motor learning requires focused attention and salience and involves increased interaction and feedback. The importance of attention in promoting plastic changes in M1 has been demonstrated in a number of studies. Indeed, it is possible that effects related to motor learning may simply be mediated by the increased attention required to perform new tasks. Active movements to promote motor learning and associated cortical changes should involve functional progressions with increasing task complexity. Finally, an external focus of attention involved with motor learning may be beneficial to shift attention towards the accomplishment of a task, as distraction helps to modulate pain perception, rather than an internal focus, which results in increased vigilance towards pain and can exacerbate pain perception.

Clinical application of treatment addressing distributed neuroplastic changes with CMSD
Active interventions addressing motor and mobility disturbances should also be graded and progressive. The use of laterality recognition training, motor imagery, and mirrors in an approach of graded motor imagery may be helpful in addressing neurophysiological changes associated with CMSD. The question as whether to begin with painful movements to challenge the maladaptive changes in the nervous system or to progressively begin exercise in non-painful ranges and movements or with graded imagery before progressing to movements that are associated with fear and anxiety is a matter of debate. The choice may be dictated by patient attitudes, beliefs and behaviors, the more fearful and anxious, the more non-threatening should be the progression of exercise as early pain may simply re-inforce their existent values and operant learning linking movement to pain. However, pain should not be utilised as the sole measure of progression because of the nebulous relationship between pain and threat of impending further tissue injury in chronic pain states. Exercise should be guided by form, the ability to perform the movement correctly, and functional progressions in volume and intensity (resistance and difficulty of task).

The cognitive strategies reviewed earlier need to be addressed continuously as to dampen the effects of anxiety and fear, to limit guarding, and to progressively integrate movements that were previously perceived as threatening. Patient’s beliefs, apprehension and behaviors must be challenged repetitively. Graded functional progressions should, over time, help extinguish learned associations reflective of neuroplastic changes in the meso-limbic and prefrontal areas, and secondly address the cortical changes in the sensorimotor areas associated with CMSD. Cortical, subcortical and the spinal cord have strong interconnections and interventions targeting one area should impact the others including sensorimotor and meso-limbic areas. Finally, the positive yet limited effects of many of these approaches in isolation suggest that a multimodal
approach that is coherent, consistent, and incorporates interventions specifically targeting neuroplastic changes may yield more positive outcomes.

Reconceptualising treatment provided to patients with CMSD

The growing evidence for changes in distributed areas of the nervous system in chronic pain conditions may also provide greater comprehension of methods of action presently utilized by physical rehabilitation professionals and lead to more effective interventions which may involve neurophysiological changes. Treatment goals in patients with CMSD have largely been directed by a biomedical paradigm which has proven to be limited in efficacy\textsuperscript{28, 73}. Rehabilitation presently performed with patients with CMSD may result in peripheral and central changes. The reconceptualising of treatment provided to patients with CMSD would therefore involve an approach that targets peripheral structural sources of pain, but also interactions and specific interventions to encourage plastic changes in the nervous system by addressing faulty values and beliefs regarding pain, attempting to minimize fear and anxiety, and perform exercises and interventions that target sensorimotor and perceptual changes. It is imperative that the therapist remains consistent in the messages conveyed both explicitly and implicitly through their actions and behaviors. The message conveyed to the patient should not imply implicitly or explicitly that a structural-pathology model alone of local biomechanical problems is the sole driver of the CMSD. The implicit or explicit perception by the patient would be inconsistent with experimental findings and may perpetuate faulty beliefs, encourage fear-avoidance, anxiety and guarding, resulting in decreased movement and contributing to a biomedical focus of local tissue insult as the driver of the condition and possibly negatively impacting self-efficacy and outcomes\textsuperscript{26, 74}. This is important as therapist-patient interaction and communication is important for treatment success\textsuperscript{75}. Our current understanding of principles of neuroplasticity may help
understand the method of action of current interventions and develop interventions that help promote positive long-term adaptive changes within the CNS associated with CMSD.

**Conclusion**

CLBP, OA and probably other CMSD are associated with neuroplastic changes across distributed areas of the nervous system including the peripheral, spinal cord, brain stem, sensorimotor cortical areas and meso-limbic and prefrontal structures. These changes correlate with the clinical and experimental findings within this population including psychological traits, perceptual and sensorimotor disturbances. Addressing the changes across the distributed network may help to yield greater understanding and outcomes for the treatment of these conditions. This involves cognitive based interventions such as education to reconceptualise beliefs regarding pain, and interventions to modify patients’ thoughts and reactions to help control anxiety and improve self-efficacy. Neuroplastic changes in the sensorimotor cortical areas are also affected in CMSD, and interventions that modulate sensory input and involve motor learning need to be incorporated into existent rehabilitation programs. The focus of interventions oriented towards renormalisation of distributed cortical areas is consistent with a bio-psycho-social paradigm and may result in improved outcomes. Imaging studies of these cortical areas associated with CMSD will help to determine how widespread are these cortical changes, provide an additional means to address efficacy of these interventions, and to determine how well interventions correlate with positive outcomes and renormalisation of cortical properties, processes and organization. Musculoskeletal rehabilitation professionals are well positioned and have resources at their disposition to influence positive adaptive neuroplastic
changes by addressing psychological and biological factors within the nervous system associated with CMSD.
Acknowledgments

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References


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Table. Areas of neuroplastic changes associated with CMSD and possible signs and symptoms manifested by the patient.

<table>
<thead>
<tr>
<th>Neurophysiological changes associated with CMSD</th>
<th>Possible physiological consequences of neuroplastic changes in these areas</th>
<th>Signs and symptoms that may possible indicate neuroplastic changes in these areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meso-limbic and pre-frontal areas. Areas demonstrated to have been affected include: Insula, Cingulate Cortex, Amygdala, Medial and Dorsolateral prefrontal cortex, and Nucleus Accumbens</td>
<td>Altered neuronal responses to pain especially in regards to the “unpleasantness” associated with pain. Implicit and explicit learning associating pain with movement and negative outcomes.</td>
<td>Spontaneous fluctuations in pain. Problems in affective, cognitive and motivational aspects in relation to pain. These changes may be associated with psychological aspects related to pain including fear-avoidance, anxiety, depression, catastrophization, somatization, worry, increased vigilance.</td>
</tr>
<tr>
<td>Descending pain modulatory systems, PAG-RVM pathway. Descending modulatory systems receive input from pre-frontal and mesolimbic structures including the Cingulate cortex, amygdala, and mPFC.</td>
<td>Decreased descending inhibition of pain (disturbed Conditioned Pain Modulation)</td>
<td>Central Sensitization (hyperalgesia and allodynia). Pain Thresholds may be decreased (pressure and thermal).</td>
</tr>
<tr>
<td>Peripheral receptors</td>
<td>Increased transduction of nociceptive stimuli.</td>
<td>Increase pain transmission in the area of injury resulting from changes in input and output characteristics in peripheral nociceptors (Peripheral Sensitization). Contributes to central sensitization (hyperalgesia and allodynia)</td>
</tr>
<tr>
<td>Dorsal Horn of the Spinal cord</td>
<td>Increased transmission of nociceptive and neuropathic stimuli. Result from changes in membrane permeability, decreased inhibition, Influenced by descending modulation pathways including the PAG-RVM</td>
<td>Central Sensitization (hyperalgesia and allodynia) Pain Thresholds may be decreased (pressure and thermal)</td>
</tr>
<tr>
<td>Somatosensory cortex</td>
<td>Altered somatosensory maps including expansion, retraction or shifting of of representation</td>
<td>Increased Two Point Discrimination Impaired performance of laterality recognition</td>
</tr>
<tr>
<td>Region</td>
<td>Changes in muscle/movement representations in motor areas of the brain and corticospinal excitability.</td>
<td>Changes in motor control including co-contraction and loss of ability to selectively recruit individual muscles.</td>
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<tr>
<td>--------------------------------------------</td>
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<tr>
<td>Primary motor cortex</td>
<td>Change in perception of body image including size of the limb, altered body midline.</td>
<td></td>
</tr>
<tr>
<td>Somatosensory associative areas</td>
<td></td>
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