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Review

Nociception, pain, neuroplasticity and the practice of Osteopathic Manipulative Medicine

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ABSTRACT

There is a growing body of evidence that chronic musculoskeletal injuries are associated with neurophysiological changes in distributed areas of the central nervous system. Traditionally a biomedical model based upon the belief that structural injury to anatomical structures was the sole driver of the condition has guided interventions. In osteopathy, the concept of somatic dysfunction has been the predominant model guiding clinical practice where areas of dysfunction are believed to result from mechanical restrictions that impact normal physiological function. However, despite these models, chronic musculoskeletal disorders such as chronic low back pain remain a challenge for osteopaths and other health care providers. The present article reviews the neurophysiological changes associated with chronic musculoskeletal disorders specifically in the sensorimotor and cognitive-affective-motivational areas of the brain. These neurophysiological changes appear to be part of the pathophysiological process, and are consistent with many of the clinical findings associated with chronic musculoskeletal disorders. Recommendations, inspired by evidence of neurophysiological effects of manual therapy, pain science, and principles driving neuroplastic changes deriving from human and animal studies, are made for osteopathic treatment of chronic musculoskeletal disorders to address these neurophysiological changes. Patient-osteopath interactions may help reconceptualise beliefs and cognitions, may alter behavioural responses, and engage forebrain structures tapping into self-regulatory and homeostatic processes. Neurophysiological effects of Osteopathic Manipulative Treatment may also help renormalize properties and organisation in cortical sensorimotor areas and impact the autonomic nervous system.

Introduction

Chronic Musculoskeletal Disorders (MSD), including chronic Low Back Pain (LBP), impact approximately one quarter of the population, remain significant health care challenges, have important societal direct and indirect costs, and result in personal suffering and disability [1]. The majority of consultations for Osteopathic Manipulative Medicine (OMM) are for musculoskeletal disorders (MSD) [2,3]. Although a systematic review has found that Osteopathic Manipulative Therapy (OMT) is beneficial for Low Back Pain (LBP) and provides greater pain reduction than placebo, these findings were based on a limited number of studies with no long term follow up [4]. Spinal Manipulative Therapy (SMT) appears to have no benefit for chronic LBP compared to standard care [5]. The challenge of practitioners of OMM and other health care professionals are persons with chronic MSD, such as chronic LBP who often respond transiently to OMM and other forms of interventions but suffer with persistent pain and functional limitations.

Traditionally treatment for chronic MSD has been anchored in a biomedical model based upon the paradigm that peripheral structural injury/dysfunction is the sole driver of pain and disability. Treatments based upon a biomedical model fail however to describe, predict and treat chronic MSD effectively [6]. Within OMM somatic dysfunction has been the prevailing paradigm where mechanical restrictions affect self-regulatory homeostatic processes impeding the normal healing processes [7]. Studies clearly indicate that on a population level the relationship between diagnostic findings of peripheral tissue damage and pain is poor and that the relationship between perceived threat in regards to movement and tissue damage is altered in chronic pain states

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Abbreviations

ANS	Autonomic Nervous System
CC	Cingulate Cortex
CNS	Central Nervous System
CRPS	Complex Regional Pain Syndrome
DLPFC	Dorsolateral Prefrontal Cortex
HPA	Hypothalamic Pituitary Adrenal
LBP	Low Back Pain
LRJT	Left-Right Judgement Task
M1	Primary Motor Cortex
MPFC	Medial Prefrontal Cortex
MSD	Musculoskeletal Disorder
MT	Manual Therapy
OMM	Osteopathic Manipulative Medicine
OMT	Osteopathic Manipulative Therapy
PAG-RVM	Periaqueductal Gray- Rostroventral Medulla
PFC	Prefrontal Cortex
PLP	Phantom Limb Pain
S1	Primary Somatosensory Cortex
SII	Secondary Somatosensory Cortex
SEP	Somatosensory Evoked Potentials
SMT	Spinal Manipulative Therapy
VLPFC	Ventral Lateral Prefrontal Cortex

[8–11]. In spite of these findings, both patients and health care practitioners continue to conceptualise pain from a biomedical prospective [12]. The Biopsychosocial model integrates psychological factors and social interactions with the biomedical paradigm. Although the Biopsychosocial model is a better predictor of chronicity, treatment outcomes based upon this model remain low to moderate for treatment of chronic MSD [6,13].

There is an emerging body of evidence that demonstrates that in addition to local peripheral injury and dysfunction, neuromolecular, structural and functional changes occur across the Central Nervous System (CNS) in subjects with chronic MSD and in chronic pain/inflammatory syndromes [8,10,11,14–16] (Fig. 1). Neurophysiological processes may predispose [17,18] and/or contribute to the pathophysiology of these conditions [10,11,19]. Studies in animals and humans demonstrate that the neuromusculoskeletal system and cortex continuously interact, and that peripheral injuries and associated changes in structure and function alter this interaction [16]. Research in animals and humans demonstrates that neuroplastic changes occur rapidly with changes in sensory output and behaviours to the Central Nervous System (CNS) [20] and concurrently with peripheral structural injury and inflammatory mediators [21,22]. These neurophysiological changes in subjects with chronic MSD are consistent with experimental and clinical findings of altered sensory transmission including sensory amplification of pain [23], motor control changes such as altered muscle recruitment patterns [24], changes in perceptual processes including altered body image [25], psychological traits such as catastophization and somatization, and behavioural changes such as fear-avoidance [26].

These findings may have important implications for the treatment of chronic MSD with OMM. The present article aims to (1) highlight the important findings of neuroplastic changes across distributed in areas of the CNS in subjects with chronic MSD and chronic pain states, and (2) provide recommendations on how these findings may influence OMM in the treatment of patients suffering from chronic MSD, utilizing the best available evidence.

Neurophysiological changes associated with chronic musculoskeletal disorders and pain

Injury to musculoskeletal structures, richly innervated with mechanoreceptors, chemoreceptors and nociceptors, alters sensory output [21,27]. These changes in sensory output arise from both injury to anatomical structures and the presence of inflammatory mediators (i.e. cytokines, prostaglandins, bradykinins), growth factors and hormones (i.e. adrenaline) associated with MSD [27]. The altered sensory output contributes to functional changes in sensory perception, tactile acuity, pain thresholds and joint position sense (JPS) [28–50].

Nociception is transduced at the site of injury and are transmitted to the spinal cord. One consequence of repetitive nociceptive transduction and transmission are resultant neuro-molecular, structural and functional changes within the spinal cord. These changes in the spinal cord are implicated in Sensitization, an amplification of nociceptive transmission and processing that occurs in many chronic pain states including chronic MSD [23,51]. Sensitization is the result of lowered membrane potential resulting in increased sensitivity to nociceptive transmission [23]. Sensitization is manifested clinically by hyperalgesia, an increased pain response, and allodynia, where stimuli that do not usually elicit the perception of pain such as light touch is perceived as painful [9]. Although sensitization is beneficial in acute pain states to protect the injured structures, sensitization may persist in chronic pain conditions and is believed to be detrimental to the healing response.

Nociceptive transmission is carried along several pathways from the spinal cord to areas in the brain stem, hypothalamus, and thalamus. The thalamus transmits nociceptive information to sensory discriminative areas in the post central gyrus (lateral system), and to cognitive-affective-motivational areas of the forebrain (medial system) for further processing [52]. Cortical and subcortical areas involved in the transmission and processing of nociceptive stimuli and the perception of pain include the thalamus, primary and secondary somatosensory cortices, insula, cingulate cortex, amygdala, prefrontal areas and the cerebellum [53,54]. Evidence suggests that it is the interaction between the different structures that dictates the pain experience [55,56](see Fig. 1). It is important to note that these structures do not respond only to nociceptive stimuli but are activated in response to behaviourally relevant salient sensory input [55].

The lateral pain system – sensory discrimination cortical areas

The lateral pain system involves the Primary Somatosensory Cortex (SI), Secondary Somatosensory Cortex (SII) and posterior parietal areas involved in sensory discrimination. Changes in sensory input can result in adaptation of the somatosensory representation of the injured area within the brainstem, thalamic nuclei, and the primary somatosensory cortex (S1) [16]. Numerous experiments have demonstrated changes in structure and function of S1 as the result of changes in sensory input [57–60]. In subjects with a history of LBP, peripheral stimulation of the lumbar region is associated with decreased evoked potentials [61,62] and changes in somatotopic organisation within S1 compared to healthy controls [63–65]. These changes in representation are similar to those that have been found in other chronic pain conditions including Complex Regional Pain Syndrome (CRPS) and Phantom Limb Pain (PLP) [66–69]. Behavioural treatments such as sensory discriminative

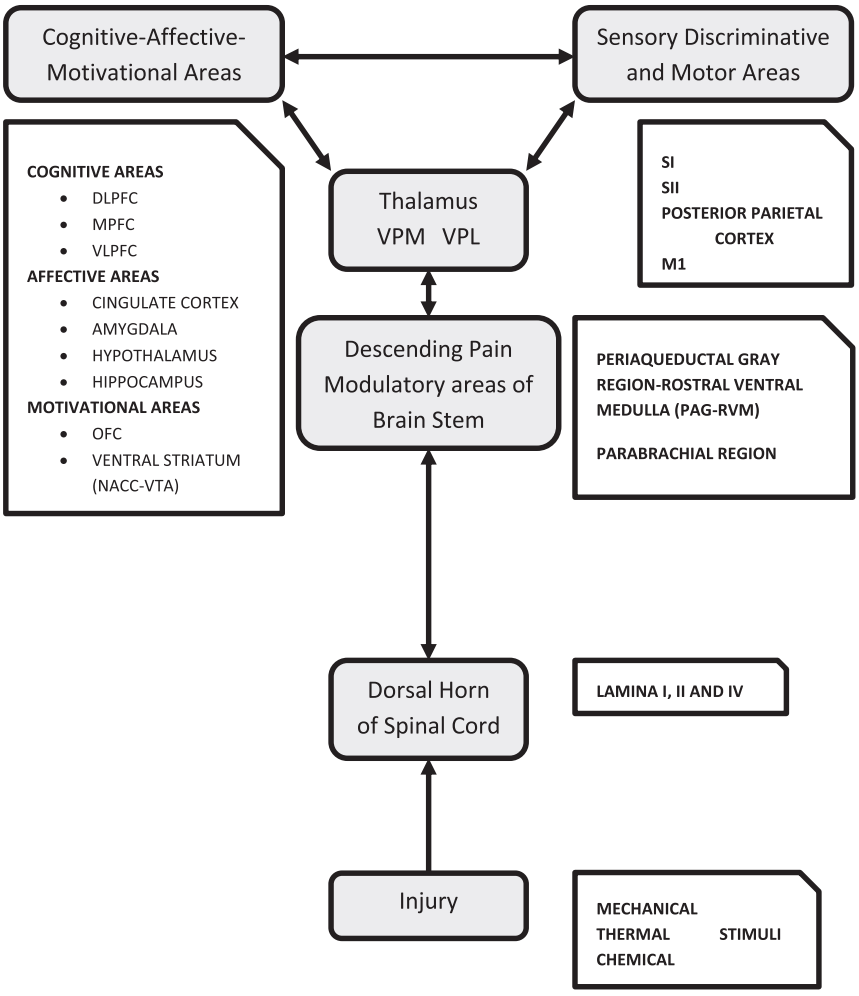

Fig. 1. Nociception transmission and transduction and pain pathways. Abbreviations: VPM: Ventral Postero Medial; Ventral Postero Lateral; PFC: Prefrontal Cortex; DLPFC: Dorsolateral Prefrontal Cortex; MPFC: Medial Prefrontal Cortex; VLPFC: Ventrolateral Prefrontal cortex; OFC: Orbital Frontal Cortex; NACC: Nucleus Accumbens; VTA: Ventral Tegmental Area; S1: Primary Somatosensory Cortex; SII: Secondary Somatosensory Cortex; M1: Primary Motor Cortex.

training [70–72], motor imagery [73–75] and mirror therapy [73,76] targeting changes in S1 have been found to both renormalize somatotopy and decrease pain in subjects with CRPS, PLP, carpal tunnel syndrome, and focal hand dystonia [10,77]. These findings are consistent with the belief that these neuroplastic changes contribute to the pathophysiology of these conditions.

Changes in properties and organisation within the sensory cortical areas have functional consequences. Tactile acuity has been found to correlate with changes in somatotopic organisation in S1 [78] probably resulting in changes in both Body Image and Body Schema [25]. Lotze and Moseley (2007) define Body image "as the way one's body feels to it's owner" [79]. Subjects with chronic pain complain of changes in the size of the injured area, which may feel larger, smaller or distorted [25]. The Body Schema is a real time internal representation of the body in peripersonal space derived from incoming sensory and proprioceptive input [79]. The Body Schema is assessed utilizing the Left Right Judgement Task (LRJT). Imaging studies have demonstrated that the LRJT is associated with activation of subcortical and cortical areas including frontal, premotor areas, basal ganglia, cerebellum and associative areas in the parietal cortex involving neural mechanisms associated with sensorimotor integration, movement planning and execution [80,81]. Some studies have found that subjects with chronic MSD, when presented with images corresponding to their area of injury, demonstrate changes in accuracy and/or reaction time to determine the laterality of the image suggestive of an altered Body Schema [82–85].

Primary Motor Cortex and chronic musculoskeletal disorders

In addition to sensory areas, changes in cortical properties and organisation occur in motor areas following MSD. Changes in corticospinal properties and organisation have been found in the Primary Motor Cortex (M1) in subjects with patella femoral syndrome [86], knee osteoarthritis [87], lateral epicondylitis [88], hand injuries including arthritis [89,90], shoulder [91], cervical [92] and chronic LBP [93–95]. These include changes in inhibitory processes, corticospinal excitability, and an overlapping of the corticospinal projections within M1 of the muscles innervating the injured area [88–90,92,94,95]. The overlapping of corticospinal projections emanating from M1 to the injured area is consistent with co-contraction and modifications in motor unit recruitment demonstrated in subjects with MSD [24].

Medial pain system – cognitive-affective-motivational areas of the forebrain

Pain is a perceptual experience that is affected by a confluence of

factors including gender, age, culture, experience, expectancies, and attention and are largely mediated by processes in the forebrain [96]. The medial pain system involves cognitive-affective-motivational centers of the forebrain including the prefrontal cortex, limbic and mesolimbic (reward center) areas. With chronic pain, imaging studies demonstrate a shift form activity in the lateral pain structures to areas of the medial pain system, where different forebrain structures have demonstrated structural and functional changes including changes in gray matter volume, altered functional activity, decreased neuronal cell health, and alterations in white matter tracts interconnecting different structures [8,14,18,97] (see Fig. 2).

These forebrain areas are implicated in chronic pain states including chronic LBP resulting in affective states, which help to impact arousal, motivation, and behavioural responses. The prefrontal structures are involved in cognitive aspects related to pain, including executive functions, working memory, attentional resources, cognitive appraisal, risk assessment, decision making, self referential thought, and mediate behavioural responses [98,99]. Other subcortical structures involved in nociceptive processing include the amygdala (imprinting of emotional salience to incoming sensory input), insula (involved in homeostatic monitoring, valuation of intensity, salience, attention), cingulate cortex (error prediction, emotional valence, motor functions). Recent evidence has also demonstrated changes in the motivational-dopaminergic areas of the brain (ventral tegmental area and the nucleus accumbens) [17,100] that are integral to the reward circuitry of the brain. The reward centers interact with other forebrain areas to affect motivational drive, influence cognitive appraisal, behavioural choices, and engage motor actions [99,101]. Activity within these forebrain areas helps to shape behavioural responses to the injury [99] and are implicated in self regulatory and homeostatic processes involved in pain modulation (i.e. arousal, placebo response) [102].

Descending modulatory pain system

Many of these forebrain structures have direct or indirect connections with the descending modulatory pathways in the brain stem [103]. The brain stem areas involved in descending pain modulation include the Periaqueductal Gray Region (PAG) and Rostral Ventral Medulla (RVM), parabrachial region, and dorsal reticular nucleus [104]. Under normal circumstances, activity in the descending modulatory pathways results in a net state of inhibition and decreases the transmission of nociceptive stimuli within the dorsal horn of the spinal cord [105]. Under chronic conditions these modulatory systems are affected and appear to shift from a state of inhibition to a state of facilitation contributing to Sensitization [97,104–107].

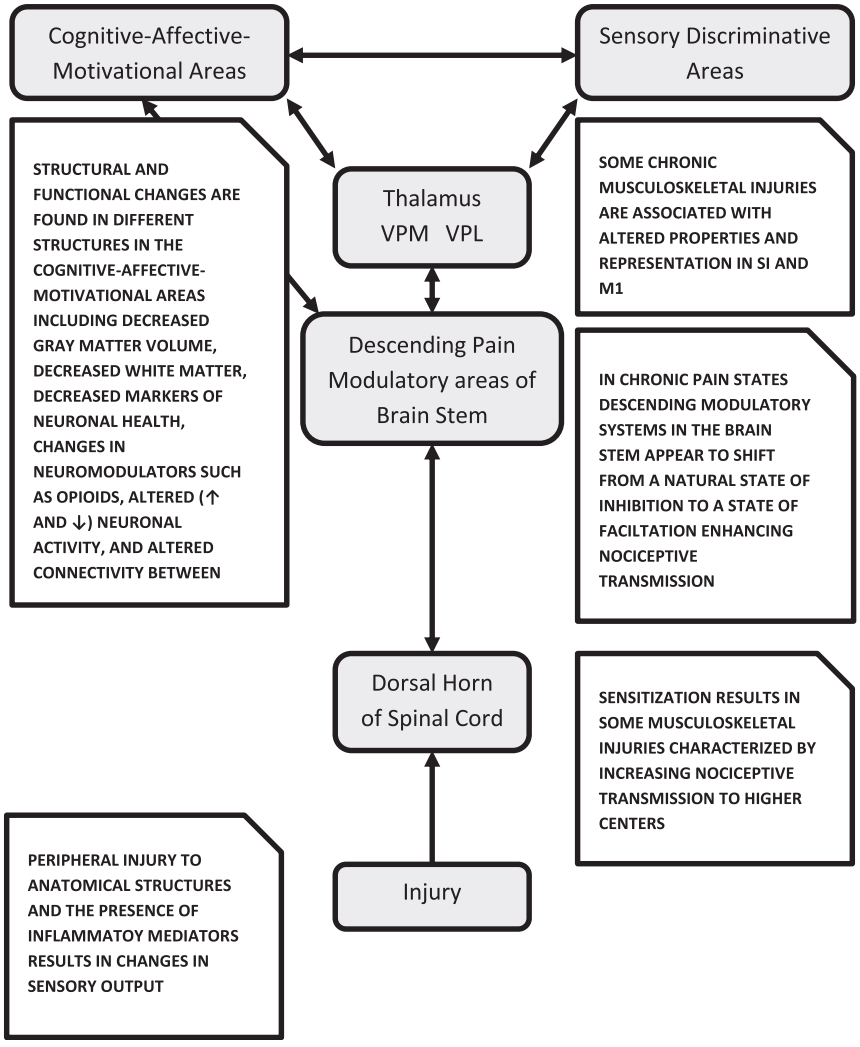

Fig. 2. Neurophysiological changes associated with chronic musculoskeletal disorders and chronic pain states.

The autonomic nervous and neuroendocrine systems

Both the Autonomic Nervous System (ANS) and the nociceptive system involve several extensively interconnected anatomical regions which include the insula, prefrontal cortex, cingulate cortex, amygdala, hypothalamus and the PAG [108]. There is evidence that the ANS is implicated in both the development and the maintenance of pain associated with chronic MSD [109]. Autonomic imbalance, with an increase in sympathetic activity and a decrease in parasympathetic activity, has been demonstrated in subjects with chronic LBP [110] and neck pain [109]. The limbic and forebrain structures that are implicated in the processing of nociceptive input as well as to other mental and physical stressors also influence the Hypothalamus-Pituitary-Adrenal (HPA) system forming a nociceptive reflex circuit [111]. The CNS is able to control inflammatory processes via primary afferent nociceptive neurones, efferent connections from post-ganglionic sympathetic nerve fibers, and the neuroendocrine systems by impacting inflammatory mediators such as cytokines secreted in the area of injury [112]. Sympathetic neurons found within tissues is necessary for the control of local inflammation [112] (see Table 1).

Pain, neuroplasticity and Osteopathic Manipulative Medicine

The neurophysiological changes that occur across distributed areas of the CNS with chronic MSD may have important implications for practitioners of OMM. OMM treatments have been guided by the concept of somatic dysfunction. Somatic Dysfunction is defined as “impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and neural elements.” [113]. Clinically, the regions of somatic dysfunction are characterized by the acronym TART (Tenderness, Asymmetry, Restricted Motion, Tissue texture changes). Although OMT may have an impact on peripheral structures and areas of somatic dysfunction these interventions may not specifically address neuroplastic changes associated with chronic MSD and pain [114]. It is therefore important for patients to reconceptualise the belief that pain is associated with structural damage and (somatic) dysfunction and that injury/dysfunction to anatomical structures alone is the sole driver of chronic pain [115]. CNS changes resulting from changes in areas of the brain involved in pain processing and psychological states contribute to the pain and altered function they experience. Experimental findings in subjects with chronic pain, including chronic LBP, demonstrate that psycho-social factors [116] and neuroplastic changes in the Cognitive-Affective-Motivational areas are the best predictors of chronicity [17,18,117].

It is therefore logical to believe that treatment provided to patients with chronic MSD should address peripheral structural injury, areas of somatic dysfunction, but also maladaptive neuroplastic changes in the CNS to improve treatment efficacy. In addition, treatment should address factors such as erroneous beliefs regarding pain, attempt to minimize fear and anxiety, maladaptive behaviours such as avoidance, and include the performance of exercises and interventions that also target sensorimotor processes.

Studies performed with animals and humans in subjects with and without injury, has elucidated principles that may be harnessed to induce positive neuroplastic changes [118]. These principles suggest that the stimuli necessary to promote neuroplastic changes must be behaviourally salient engaging attentional resources, repetitive, of sufficient intensity, and involve learning [118,119]. Neuroplastic changes will be specific to the neuronal structures implicated in the task [118]. As chronic MSD involves neuroplastic changes across different regions of the CNS, OMM treatment should be directed across the different affected structure (see Fig. 3).

Non-specific effects of OMT and the forebrain

Non-specific effects of OMT are influenced by the context of application and by the patient's expectancies, experiences, values, beliefs, credibility of the treatment, and health care provider-patient interactions [120–124]. The context of application of OMT impacts treatment outcomes similar to other forms of complimentary and alternative therapies and can be parcelled to different aspects of the treatment comprised of the patient's response to being observed and assessed, the administration of a therapeutic ritual associated with the treatment, and the patient-practitioner interaction [125]. Physiological effects attributed to context are governed by processes found within the forebrain and limbic areas underlying physiological processes of cognitive-affective-motivational aspects related to OMT [102]. Contexts perceived as positive engage self-regulatory homeostatic mechanisms involving opioids, cannabinoids and dopamine and require proper structure and function of the reward circuitry [96].

Specific effects of OMM – patient-osteopath interactions and the forebrain

In regard to the neuroplastic changes found within the Cognitive-Affective-Motivational areas of the brain in response to pain processing and the psychological states that may be associated with persons with chronic MSD (i.e. fear, anxiety, depression) the following is recommended:

1. **Recognize:** The osteopath should be attentive for erroneous beliefs and misguided behaviours that may be displayed regarding pain and injury [126]. These include patient's stringent belief in a biomedical model where structural pathology and peripheral areas of dysfunction are the source of all pain. Fear-avoidance [127], catastophization [128], somatization [116] all have documented evidence suggesting that they contribute to the development of chronicity of injuries and are associated with poorer outcomes. Catastrophization [129,130] and

Table 1
Signs and symptoms suggestive of neurophysiological changes in the CNS with chronic Musculoskeletal Disorders.

Forebrain (medial pain system)	Spontaneous fluctuations in pain. Motivation is oriented to avoidance and escape from pain Psychological aspects related to pain including fear-avoidance, anxiety, depression, catastrophization, somatization, worry, increased vigilance.
Descending pain modulatory systems	Sensitization Increase/exaggerated pain perception in the area of injury (hyperalgesia) Cutaneous stimuli perceived as painful (allodynia) Pain
Dorsal Horn of the Spinal cord	Thresholds may be decreased (pressure and thermal).
Somatosensory cortex	Altered Two Point Discrimination Impaired performance in the Left Right Judgement Task Change in perception of body image including size of the limb, altered body midline.
Primary motor cortex	Changes in motor control including co-contraction and loss of ability to selectively recruit individual muscles.

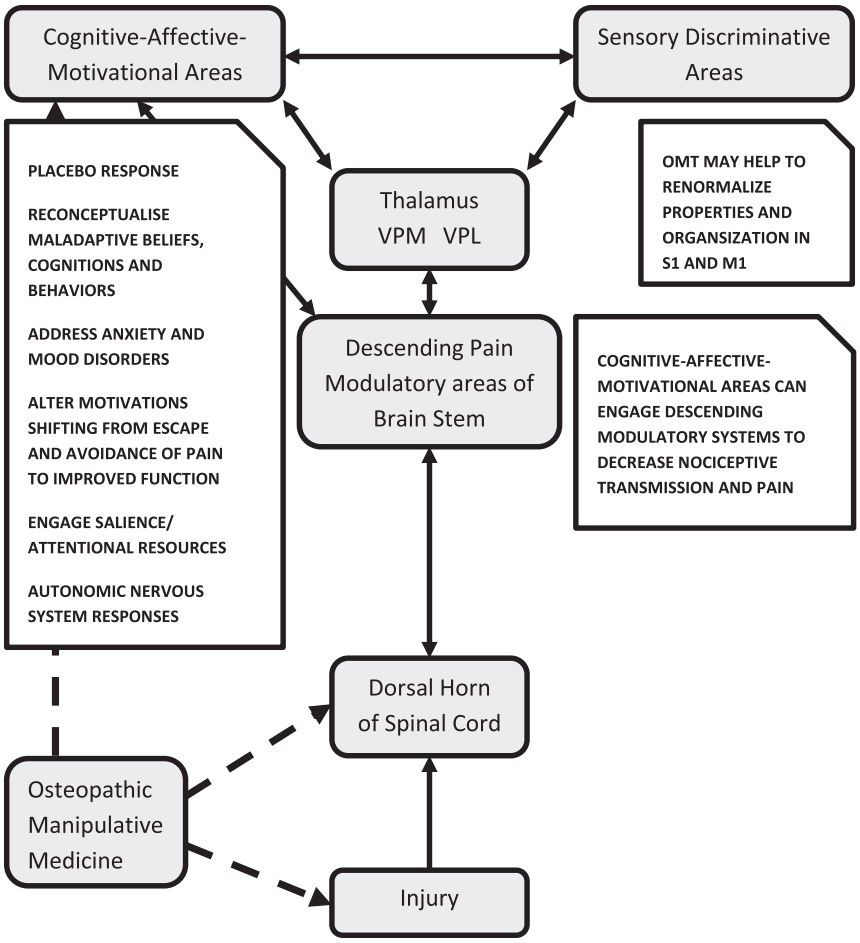

Fig. 3. Osteopathic Manipulative Medicine and neurophysiological changes associated with chronic musculoskeletal disorders: The context of application of OMT and the neurophysiological responses associated with the mechanical application of OMT may result in distributed changes in neurophysiological function locally at the site of application, but also within the spinal cord, sensorimotor cortical areas, forebrain (prefrontal cortex, limbic, and mesolimbic structures), and descending modulatory pathways. These different regions may interact to result in changes in sensorimotor processes, but also engage the autonomic nervous system and the neuroendocrine systems that in turn may influence descending pain modulatory systems and inflammatory responses. The neurophysiological changes may vary depending upon the type of OMT performed. Abbreviations: VPM: Ventral Posterior Medial Nuclei of the Thalamus; VPL: Ventral Posterior Lateral Nuclei of the Thalamus.

conditioned fear responses [26] have been associated with brain changes in the cognitive-affective-motivational areas of the brain in areas also implicated in chronic pain states such as the insula, dorsolateral, ventrolateral and medial prefrontal cortex, cingulate cortex, amygdala, and nucleus accumbens. Addressing erroneous cognitions and beliefs should be assessed and addressed early, even in acute and sub-acute stages following injury.

2. **Educate:** 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 chronic MSD [131]. Programs involving neurophysiology of pain education include information regarding the nociceptive transduction, transmission and processing, neurophysiological changes occurring in subjects with chronic pain, pain as a perceptual experience, the loss of the stimulus-response relationship between structural injury and pain perception, and maladaptive behavioural strategies. The information contained in these programs are accessible to patients experiencing chronic pain [115]. Such programs have also been associated with changes in brain activation patterns in forebrain areas [132]. Neurophysiological pain education appears to result in better outcomes than programs based upon a biomedical model [133,134] and have been found to have an immediate impact on behaviour and function [135]. Meta-analysis and systematic reviews of education on pain neuroscience finds these program to be promising but are based upon a limited number of studies [133,134].
3. **Consistency:** The message conveyed to the patient by the osteopath should not imply, implicitly or explicitly, that local biomechanical/structural problems and areas of somatic dysfunction are the sole driver of the chronic MSD. The perception of the patient, either implicitly or explicitly, of a strictly biomedical paradigm of their injury would be inconsistent with experimental findings previously discussed. Furthermore they could perpetuate faulty beliefs, encourage fear-avoidance, anxiety and guarding, resulting in decreased movement and contribute to a biomedical focus that negatively influence outcomes [131,136]. Biomedical descriptors of injury may also result in passive coping strategies and promote fear and guarding in some patients [137]. Consistency of message **is** important as care giver-patient interaction and communication are integral elements for treatment success [122]. Alignment of health care provider attitudes and beliefs with those of the patient appears to be associated with better outcomes [138].

4. **Collaborate:** Other health care professionals can work with the patient to address maladaptive cognitions, and help address comorbid factors such as anxiety and depression. Examples of such interventions include Cognitive Behavioural Interventions such as Cognitive Behavioural Therapy, Avoidance Commitment Therapy and Mindfulness Based Stress Reductions [123,139,140]. These programs have been found to decrease anxiety and improve function that correlated with increased activation in the prefrontal cortex and appear to modulate activity in the affective areas of the brain [123,140]. Increased activation in prefrontal areas of the brain correlate with decreased pain, greater self-efficacy and improved psychological indexes of worry, anxiety and depression [141–143]. Self-efficacy refers to the perceived ability to self manage their pain and disability [142,144], and greater self-efficacy is associated with better outcomes in patients with chronic MSD [144]. Systematic reviews of CBT in subjects with chronic pain suggest small to moderate effects on mood, catastrophization and pain intensity with some evidence of improved pain related disability and avoidance behaviours for up to 6 months [140,145]. Multidisciplinary biopsychosocial interventions for subjects with chronic LBP experienced less pain and disability than subjects receiving conservative care only [146]. A recent study involving subjects with chronic MSD involving OMT, Avoidance Commitment Therapy, and an adapted Mindfulness practice involving sessions over a 6 week period found the combined approach to be feasible, with positive self-reported effects for pain, function and mood [147].
5. **Repeat:** These cognitions and associated behaviours need to be addressed continuously throughout their treatment sessions with consistency of message between different health care providers [148].

Specific effects — OMT and neurophysiological processes

There is no research of OMT and its ability to drive neuroplastic changes. Physiological effects of MT have however been attributed to neurophysiological mechanisms [103,149–152]. Manipulative therapy results in discharge of muscle spindle afferents, Golgi tendon organs, and low and high threshold mechanoreceptors reflective of stimulation of cutaneous, muscular and articular receptors [153–155]. The ensuing neurophysiological effects of MT are hypothesized to result from changes in localised structure and function that help to renormalize neural sensory input [153] and/or may influence reflex pathways and activity in subcortical and cortical areas [155] (see Fig. 3).

Studies on animal and human subjects suggest that to drive neuroplastic changes in the sensorimotor cortical areas requires repetition, salience, learning and specificity [118]. Based upon these MT literature, findings form peripheral sensory stimulation and their resulting effects on cortical sensorimotor properties and organisation, and modern pain science literature it is suggested that OMT:

(1) **Direct attention to areas of dysfunction:** To foster salience and direct attentional resources to areas of dysfunction. Emphasis should be directed toward altered function and not on pain [10,156].
(2) **Seek patient participation during treatment:** Sensory discrimination training that has been found to be associated with increased pain thresholds, improved function, and renormalisation of properties in S1 in subjects with CRPS, chronic LBP and carpal tunnel syndrome [72,157,158]. It is unclear however if improvement is related to the task specifically or the result of increased attention directed to the intervention. With OMT, patients should be attentive to differences in pressure, mobility and tissue texture during treatment. The patient's focus and motivation should be directed to improving these areas of (somatic) dysfunction and shift their motivation away from escape and avoidance of pain towards improvement of function [99,131].
(3) **OMT will need to be performed repetitively.** Frequency of OMM treatment has never been studied with the goal of renormalizing neuronal properties and organisation. Studies in both animals and humans suggest that neuroplastic changes to behavioural and sensory stimuli occur rapidly [20], but require several sessions over many weeks to be result in long term neuroplastic changes [159]. Some studies however may provide an indication of frequency and duration of treatment. Acupuncture applied 13 times over a 5-week period in subjects with CTS resulted in changes in somatotopic organisation in S1 that correlated with the decrease in paraesthesia [160]. Three to five manual treatments involving both massage and manipulative therapy resulted in self-reported improvement and was associated with improved cerebral evoked potentials [62]. The improvements in cerebral evoked potentials were positively correlated with decreased pain and improved self reported function.
(4) **Stimulate peripheral receptors to engage sensorimotor cortical processes:** Sensory stimulation can be utilized to affect neuronal properties in both S1 and M1 in healthy subjects [161–163]. MT can produce transient changes in somatosensory evoked potentials [164–166]. Somatosensory evoked potentials are the recording of the sequential activation over the spine and the brain of electrical signals generated from sensory stimuli. These altered evoked potentials following MT have been localised to S1, reflecting the initial activation resulting from peripheral stimulation of mechanoreceptors, and a later response that is located in the prefrontal cortex believed to be related to the cognitive appraisal of the stimuli [165–167]. There is preliminary evidence that MT can alter corticospinal excitability in M1. SMT transiently increases corticospinal excitability [168–170] while muscle energy techniques increase inhibitory processes, reflective of a decrease in corticospinal excitability, and decrease motoneuronal excitability [171,172]. Rhythmic OMT techniques such as Facilitated Osteopathic Release [173] may be amenable to drive neuroplastic changes in the sensorimotor areas as they stimulate peripheral receptors in a rhythmic fashion over an extended period.
(5) **OMM should involve functional exercises** that address the areas of dysfunction, are challenging and require learning of movement patterns that implicate the areas of (somatic) dysfunction [131,174].
(6) **MT to engage descending modulatory pain processes:** MT has immediate effects on pressure pain thresholds [175–179] that are superior to a placebo conditions that only involve manual contact [175,179]. These effects are believed to be mediated by descending brain stem mechanisms via the ANS and forebrain mediated pathways [176,180–183]. Although there is conflicting results of manipulative studies on engaging opioid mechanisms [184–188], there is evidence of mood changes and blood serum concentrations of pain and inflammatory biomarkers such as endocannabinoids and serotonin after OMT interventions in healthy subjects and subjects with back pain [189,190]. Soft tissue techniques may stimulate tactile afferents transmitting along unmyelinated C fiber found in glabrous parts of the body that transmit to the

posterior insula and areas on the prefrontal cortex [191]. These C fiber tactile afferents, when perceived as pleasurable, may also engage autonomic responses associated and descending modulatory processes [192]. Massage and light touch have also been found to increase the hormone oxytocin [193,194] which has antinociceptive effects possibly mediated by opioid mechanisms and descending modulatory pathways [195,196].

(7) **Utilize OMT that decrease sympathoexcitation and promote increase parasympathetic activity.** Studies of soft tissue techniques, balanced ligamentous tension, balanced membranous tension, and cranial sacral techniques have been associated with changes in parameters associated with increased parasympathetic activity and increased vagal control of heart rate [197,198]. In contrast, subjects receiving SMT techniques demonstrate changes (heart rate variability measures, skin conductance, increased heart rate and blood pressure) associated with decreased parasympathetic and increased sympathetic nervous system function [187,199–205]. As studies of subjects with chronic pain suggest that parasympathetic activity is heightened, OMM should focus on interventions to increase parasympathetic activation.

(8) **OMT of the upper cervical region may impact vagal nerve function and influence the neuroendocrine reflex arc** to attenuate the serum levels of molecular inflammatory mediators [206]. This hypothesis is presently under study [206]. A decrease in Tumor Necrosis Factor α, a cytokine involved in the inflammatory process, was demonstrated in subjects with LBP who received OMT [207].

Limitations

There are several important considerations that should be considered in the material presented. The neurophysiological effects associated with MT involve a limited number of studies with small sample sizes. Most MT studies have investigated transient neurophysiological changes occurring after one intervention. The long-term effects of repetitive MT interventions on neurological function and clinical outcomes remain undetermined and speculative. The chronic pain literature regarding changes in the forebrain areas were performed in subjects with chronic MSD on subjects with chronic low back and osteoarthritis. The generalizability of these results is therefore limited and requires further investigation. OMM treatment is comprised of a several therapeutic techniques and the combined and interactive effect of these approaches on neurophysiological function has not been thoroughly investigated.

Conclusion

There has been an exponential growth in the study of the neurophysiological processes of nociception and pain over the last few decades. Concurrently, animal and human studies have demonstrated that the CNS is responsive to the internal and external pressures to which it is exposed and is the manner in which the brain learns and encodes new experiences. The findings from these two bodies of research, combined with research of neurophysiological mechanisms of MT would appear to provide information valuable for osteopaths treating patients with chronic MSD.

Chronic MSD remain an important societal, personal and health care challenge. The prevailing Biomedical paradigm is inconsistent with a large body of evidence and has failed to yield efficacious treatment for chronic MSD. The Bio-psychosocial paradigm has greater predictive ability of chronicity, but systematic reviews also suggest that results are modest [146]. The emergent evidence of changes in structure and function distributed across different regions of the CNS with chronic MSD and chronic pain states provides new hope for the development of more efficacious treatment. It is possible that the small to moderate effects seen consistently across different treatments may be the result of the failure to address the neuroplastic changes across different areas of the CNS.

The “soft skills” involved in OMM if conceived by the patient in a positive context, may impact stress, anxiety and worry stemming from the patient's injury. Education may be utilized in an attempt to reconceptualise faulty values and beliefs regarding pain, and address factors such as fear-avoidance, somatization, and guarding. These psychological changes result in altered forebrain activity and mediate behavioural responses to their injury, engage self-regulatory homeostatic mechanisms, descending modulatory systems, help to decrease pain, and promote increased mobility. OMT also is associated with neurophysiological effects that may alter structural and functional changes in sensorimotor cortical areas, alter ANS activity, and engage descending modulatory processes. Although further investigation is necessary, mechanisms of OMM appear to result in at least transient changes in neuronal function, and may, when applied in a manner consistent with findings of studies driving neuroplastic changes, help to renormalize altered structure and function in the CNS associated with chronic MSD hopefully resulting in improved outcomes.

References

[1] Brooks PM. The burden of musculoskeletal disease—a global perspective. Clin Rheumatol 2006;25(6):778–81.
[2] Morin C, Aubin A. Primary reasons for osteopathic consultation: a prospective survey in Quebec. PLoS One 2014;9(9):e106259.
[3] Johnson SM, Kurtz ME. Conditions and diagnoses for which osteopathic primary care physicians and specialists use osteopathic manipulative treatment. J Am Osteopath Assoc 2002;102(10):527.
[4] Licciardone JC, Brimhall AK, King LN. Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials. BMC Musculoskelet Disord 2005;6(1):43.
[5] Rubinstein SM, et al. Spinal manipulative therapy for chronic low-back pain: an update of a Cochrane review. Spine (Phila Pa 1976) 2011;36(13):E825–46.
[6] Foster NE, et al. Understanding the process of care for musculoskeletal conditions—why a biomedical approach is inadequate. 2003. Br Soc Rheumatology.
[7] Lederman E. The science and practice of manual therapy. Elsevier Health Sciences; 2005.
[8] Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 2011;152(3 Suppl):S49.
[9] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152(3 Suppl):S2–15.
[10] Moseley GL, Flor H. Targeting cortical representations in the treatment of chronic pain: a review. Neurorehabil Neural Repair 2012;26(6):646–52.
[11] Pelletier R, Higgins J, Bourbonnais D. Is neuroplasticity in the central nervous system the missing link to our understanding of chronic musculoskeletal disorders? BMC Musculoskelet Disord 2015;16(1):25.
[12] Shaw WS, et al. The effects of patient-provider communication on 3-month recovery from acute low back pain. J Am Board Fam Med 2011;24(1):16–25.
[13] Pincus T, et al. Twenty-five years with the biopsychosocial model of low back pain-is it time to celebrate? A report from the twelfth international forum for primary care research on low back pain. Spine (Phila Pa 1976) 2013;38(24):2118–23.
[14] Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol 2009;87(2):81–97.
[15] Ward S, et al. Neuromuscular deficits after peripheral joint injury: a neurophysiological hypothesis. Muscle Nerve 2015;51(3):327–32.
[16] Wall JT, Xu J, Wang X. Human brain plasticity: an emerging view of the multiple substrates and mechanisms that cause cortical changes and related sensory dysfunctions after injuries of sensory inputs from the body. Brain Res Rev 2002;39(2):181–215.
[17] Baliki MN, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15(8):1117–9.
[18] Mansour AR, et al. Brain white matter structural properties predict transition to chronic pain. Pain 2013;154(10):2160–8.
[19] Wand BM, O'Connell NE. Chronic non-specific low back pain - sub-groups or a single mechanism? BMC Musculoskelet Disord 2008;9(9):11.

[20] Classen J, et al. Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 1998;79(2):1117–23.
[21] Barr AE, Barbe MF, Clark BD. Work-related musculoskeletal disorders of the hand and wrist: epidemiology, pathophysiology, and sensorimotor changes. J Orthop Sports Phys Ther 2004;34(10):610–27.
[22] Coq JO, et al. Peripheral and central changes combine to induce motor behavioral deficits in a moderate repetition task. Exp Neurol 2009;220(2):234–45.
[23] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10(9):895–926.
[24] Hodges PW, Tucker K. Moving differently in pain: a new theory to explain the adaptation to pain. Pain 2011;152(3 Suppl):S90–8.
[25] Tsay A, et al. Sensing the body in chronic pain: a review of psychophysical studies implicating altered body representation. Neurosci Biobehav Rev 2015;52:221–32.
[26] Simons LE, Elman I, Borsook D. Psychological processing in chronic pain: a neural systems approach. Neurosci Biobehav Rev 2014;39:61–78.
[27] Langevin HM, Sherman KJ. Pathophysiological model for chronic low back pain integrating connective tissue and nervous system mechanisms. Med Hypotheses 2007;68(1):74–80.
[28] Swart CM, Stins JF, Beek PJ. Cortical changes in complex regional pain syndrome (CRPS). Eur J Pain 2009;13(9):902–7.
[29] Coombes BK, Bisset L, Vicenzino B. A new integrative model of lateral epicondylalgia. Br J Sports Med 2009;43(4):252–8.
[30] Giesecke T, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50(2):613–23.
[31] Small DM, Apkarian AV. Increased taste intensity perception exhibited by patients with chronic back pain. Pain 2006;120(1–2):124–30.
[32] Farrell M, et al. Pain and hyperalgesia in osteoarthritis of the hands. J Rheumatol 2000;27(2):441–7.
[33] Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. Eur J Pain 2000;4(3):229–38.
[34] Gwilym SE, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum 2009;61(9):1226–34.
[35] Imamura M, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008;59(10):1424–31.
[36] Lee YC, et al. Pain sensitivity and pain reactivity in osteoarthritis. Arthritis Care Res (Hoboken) 2011;63(3):320–7.
[37] Wilgen C, et al. Do patients with chronic patellar tendinopathy have an altered somatosensory profile?–A Quantitative Sensory Testing (QST) study. Scand J Med Sci Sports 2011;23(2):149–55.
[38] Jensen R, Kvale A, Baerheim A. Is pain in patellofemoral pain syndrome neuropathic? Clin J Pain 2008;24(5):384–94.
[39] Fernandez-Carnero J, et al. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral epicondylalgia: a blinded, controlled study. Clin J Pain 2009;25(7):555–61.
[40] Brumagne S, Lysens R, Spaepen A. Lumbosacral position sense during pelvic tilting in men and women without low back pain: test development and reliability assessment. J Orthop Sports Phys Ther 1999;29(6):345–51.
[41] Sharma L, Pai YC. Impaired proprioception and osteoarthritis. Curr Opin Rheumatol 1997;9(3):253–8.
[42] Brumagne S, Cordo P, Verschueren S. Proprioceptive weighting changes in persons with low back pain and elderly persons during upright standing. Neurosci Lett 2004;366(1):63–6.
[43] Garn SN, Newton RA. Kinesthetic awareness in subjects with multiple ankle sprains. Phys Ther 1988;68(11):1667–71.
[44] Warner JJ, Lephart S, Fu FH. Role of proprioception in pathoetiology of shoulder instability. Clin Orthop Relat Res 1996;330(330):35–9.
[45] Georgy EE. Lumbar repositioning accuracy as a measure of proprioception in patients with back dysfunction and healthy controls. Asian spine J 2011;5(4):201–7.
[46] Newcomer KL, et al. Differences in repositioning error among patients with low back pain compared with control subjects. Spine 2000;25(19):2488–93.
[47] Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. Man Ther 2006;11(2):99–106.
[48] Fischer-Rasmussen T, Jensen PE. Proprioceptive sensitivity and performance in anterior cruciate ligament-deficient knee joints. Scand J Med Sci Sports 2000;10(2):85–9.
[49] Lysholm M, et al. Postural control–a comparison between patients with chronic anterior cruciate ligament insufficiency and healthy individuals. Scand J Med Sci Sports 1998;8(6):432–8.
[50] Gill KP, Callaghan MJ. The measurement of lumbar proprioception in individuals with and without low back pain. Spine 1998;23(3):371–7.
[51] Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: a review. PM R 2011;3(12):1116–25.
[52] Almeida TF, Roizenblatt S, Tufik S. Afferent pain pathways: a neuroanatomical review. Brain Res 2004;1000(1–2):40–56.
[53] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55(3):377–91.
[54] Perini I, Bergstrand S, Morrison I. Where pain meets action in the human brain. J Neurosci 2013;33(40):15930–9.
[55] Legrain V, et al. The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol 2011;93(1):111–24.
[56] Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res 2010;205(1):1–12.
[57] Kaas JH, Merzenich MM, Killackey HP. The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. Annu Rev Neurosci 1983;6:325–56.
[58] Merzenich MM, et al. Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 1984;224(4):591–605.
[59] Jenkins WM, et al. Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. J Neurophysiol 1990;63(1):82–104.
[60] Recanzone GH, et al. Topographic reorganization of the hand representation in cortical area 3b owl monkeys trained in a frequency-discrimination task. J Neurophysiol 1992;67(5):1031–56.
[61] Zhu Y, et al. Paraspinal muscle evoked cerebral potentials in patients with unilateral low back pain. Spine (Phila Pa 1976) 1993;18(8):1096–102.
[62] Zhu Y, et al. Do cerebral potentials to magnetic stimulation of paraspinal muscles reflect changes in palpable muscle spasm, low back pain, and activity scores? J Manip Physio Ther 2000;23(7):458–64.
[63] Flor H, et al. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neurosci Lett 1997;224(1):5–8.
[64] Lloyd D, et al. Differences in low back pain behavior are reflected in the cerebral response to tactile stimulation of the lower back. Spine (Phila Pa 1976) 2008;33(12):1372–7.
[65] Kong J, et al. S1 is associated with chronic low back pain: a functional and structural MRI study. Mol pain 2013;9(1):1.
[66] Juottonen K, et al. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain 2002;98(3):315–23.
[67] Maihofner C, et al. Patterns of cortical reorganization in complex regional pain syndrome. Neurology 2003;61(12):1707–15.
[68] Flor H, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995;375(6531):482–4.
[69] Karl A, et al. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci 2001;21(10):3609–18.
[70] Flor H, et al. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. Lancet 2001;357(9270):1763–4.
[71] Flor H. The modification of cortical reorganization and chronic pain by sensory feedback. Appl Psychophysiol Biofeedback 2002;27(3):215–27.
[72] Wand BM, et al. Acupuncture applied as a sensory discrimination training tool decreases movement-related pain in patients with chronic low back pain more than acupuncture alone: a randomised cross-over experiment. Br J Sports Med 2013;47(17):1085–9.
[73] Bowering KJ, et al. The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis. J Pain 2013;14(1):3–13.
[74] Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. Pain 2004;108(1–2):192–8.
[75] MacIver K, et al. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain 2008;131(Pt 8):2181–91.
[76] Nojima I, et al. Human motor plasticity induced by mirror visual feedback. J Neurosci 2012;32(4):1293–300.
[77] Flor H. Cortical reorganisation and chronic pain: implications for rehabilitation. J Rehabil Med 2003;41(supplement):66–72.
[78] Pleger B, et al. Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. Neuroimage 2006;32(2):503–10.
[79] Lotze M, Moseley GL. Role of distorted body image in pain. Curr Rheumatol Rep 2007;9(6):488–96.
[80] Ionta S, et al. The influence of hands posture on mental rotation of hands and feet. Exp Brain Res 2007;183(1):1–7.
[81] Parsons LM. Integrating cognitive psychology, neurology and neuroimaging. Acta Psychol 2001;107(1):155–81.
[82] Stanton TR, et al. Spatially defined disruption of motor imagery performance in people with osteoarthritis. Rheumatol (Oxf) 2012;51(8):1455–64.
[83] Coslett HB, et al. Mental motor imagery and chronic pain: the foot laterality task. J Int Neuropsychol Soc 2010;16(4):603–12.
[84] Botnmark I, Tumilty S, Mani R. Tactile acuity, body schema integrity and physical performance of the shoulder: a cross-sectional study. Man Ther 2016;23:9–16.
[85] Bray H, Moseley GL. Disrupted working body schema of the trunk in people with back pain. Br J Sports Med 2011;45(3):168–73.
[86] On AY, et al. Differential corticomotor control of a muscle adjacent to a painful joint. Neurorehabil Neural Repair 2004;18(3):127–33.
[87] Shanahan CJ, et al. Organisation of the motor cortex differs between people with and without knee osteoarthritis. Arthritis Res Ther 2015;17(1):1–11.
[88] Schabrun SM, et al. Novel adaptations in motor cortical maps: the relationship to persistent elbow pain. Med Sci Sports Exerc 2014;47(4):381–90.
[89] Pelletier R, Higgins J, Bourbonnais D. The relationship of corticospinal excitability with pain, motor performance and disability in subjects with chronic wrist/hand pain. J Electromyogr Kinesiol 2017;34:65–71.
[90] Parker RS, et al. The association between corticomotor excitability and motor skill learning in people with painful hand arthritis. Clin J pain 2017;33(3):

222–30.
[91] Ngomo S, et al. Alterations in central motor representation increase over time in individuals with rotator cuff tendinopathy. Clin Neurophysiol 2015;126(2):365–71.
[92] Marker RJ, et al. Modulation of intracortical inhibition in response to acute psychosocial stress is impaired among individuals with chronic neck pain. J Psych Res 2014;76(3):249–56.
[93] Tsao H, Galea MP, Hodges PW. Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. Brain 2008;131:2161–71.
[94] Tsao H, Danneels LA, Hodges PW. ISSLS prize winner: smudging the motor brain in young adults with recurrent low back pain. Spine (Phila Pa 1976) 2011;36(21):1721–7.
[95] Strutton PH, et al. Corticospinal excitability in patients with chronic low back pain. J Spinal Disord Tech 2005;18(5):420–4.
[96] Carlino E, Benedetti F. Different contexts, different pains, different experiences. Neuroscience 2016;338:19–26.
[97] Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci 2013;14(7):502–11.
[98] Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med 2010;16(11):1277–83.
[99] Wiech K, Tracey I. Pain, decisions, and actions: a motivational perspective. Front Neurosci 2013;7:1–12.
[100] Baliki MN, et al. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 2010;66(1):149–60.
[101] Navratilova E, Porreca F. Reward and motivation in pain and pain relief. Nat Neurosci 2014;17(10):1304–12.
[102] Benedetti F, et al. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25(45):10390–402.
[103] Zusman M. Forebrain-mediated sensitization of central pain pathways:'non-specific'pain and a new image for MT. Man Ther 2002;7(2):80–8.
[104] Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. J Clin Invest 2010;120(11):3779–87.
[105] Heinricher M, et al. Descending control of nociception: specificity, recruitment and plasticity. Brain Res Rev 2009;60(1):214–25.
[106] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anesthesiol 2010;23(5):611–5.
[107] Zambreanu L, et al. A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. Pain 2005;114(3):397–407.
[108] Benarroch EE. Pain-autonomic interactions. Neurol Sci 2006;27(Suppl 2): S130–3.
[109] Hallman DM, Ekman AH, Lyskov E. Changes in physical activity and heart rate variability in chronic neck-shoulder pain: monitoring during work and leisure time. Int Arch Occup Environ Health 2014;87(7):735–44.
[110] Kalezic N, et al. Physiological reactivity to functional tests in patients with chronic low back pain. J Musculoskelet Pain 2007;15(1):29–40.
[111] Leone M, et al. Neuroimaging and pain: a window on the autonomic nervous system. Neurol Sci 2006;27(Suppl 2(2)):S134–7.
[112] Janig W. Autonomic nervous system and inflammation. Auton Neurosci 2014;182:1–3.
[113] Committee GR. For the educational council on osteopathic principles and the American association of colleges of osteopathic medicine. Gloss Osteopath Termin 2006.
[114] Lundbye Jensen J, Marstrand P, Nielsen J. Motor skill training and strength training are associated with different plastic changes in the central nervous system. J Appl Physiol 2005;99:1558–68.
[115] Moseley L. Unraveling the barriers to reconceptualization of the problem in chronic pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. J Pain 2003;4(4):184–9.
[116] Pincus T, et al. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine 2002;27(5):E109–20.
[117] Mutso AA, et al. Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol 2014;111(5):1065–76.
[118] Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res 2008;51(1):S225–39.
[119] Boudreau SA, Farina D, Falla D. The role of motor learning and neuroplasticity in designing rehabilitation approaches for musculoskeletal pain disorders. Man Ther 2010;15(5):410–4.
[120] Hall AM, et al. The influence of the therapist-patient relationship on treatment outcome in physical rehabilitation: a systematic review. Phys Ther 2010;90(8):1099–110.
[121] Licciardone JC, Russo DP. Blinding protocols, treatment credibility, and expectancy: methodologic issues in clinical trials of osteopathic manipulative treatment. J Am Osteopath Assoc 2006;106(8):457–63.
[122] Ferreira PH, et al. The therapeutic alliance between clinicians and patients predicts outcome in chronic low back pain. Phys Ther 2013;93(4):470–8.
[123] Jensen KB, et al. Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgeia. Pain 2012;153(7):1495–503.
[124] Moerman DE. Meaning, medicine, and the" placebo effect", vol. 28. Cambridge: Cambridge University Press; 2002.
[125] Kaptchuk TJ, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;336(7651):999–1003.
[126] Nijs J, et al. Thinking beyond muscles and joints: therapists' and patients' attitudes and beliefs regarding chronic musculoskeletal pain are key to applying effective treatment. Man Ther 2013;18(2):96–102.
[127] Wertli MM, et al. The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. spine J 2014;14(5):816–36. e4.
[128] Picavet HS, Vlaeyen JW, Schouten JS. Pain catastrophizing and kinesiophobia: predictors of chronic low back pain. Am J Epidemiol 2002;156(11):1028–34.
[129] Gracely R, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127(4):835–43.
[130] Malfliet A, et al. Brain changes associated with cognitive and emotional factors in chronic pain: a systematic review. Eur J Pain 2017;21(5):769–86.
[131] Nijs J, et al. A modern neuroscience approach to chronic spinal pain: combining pain neuroscience education with cognition-targeted motor control training. Phys Ther 2014;94(5):730–8.
[132] Moseley GL. Widespread brain activity during an abdominal task markedly reduced after pain physiology education: fMRI evaluation of a single patient with chronic low back pain. Aust J Physiother 2005;51(1):49–52.
[133] Louw A, et al. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. Archives Phys Med Rehab. 2011;92(12):2041–56.
[134] Clarke CL, Ryan CG, Martin DJ. Pain neurophysiology education for the management of individuals with chronic low back pain: a systematic review and meta-analysis. Man Ther 2011;16(6):544–9.
[135] Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. Eur J Pain 2004;8(1):39–45.
[136] Girbés EL, Meeus M, Baert I, Nijs J . Balancing “hands-on” with “hands-off” physical therapy interventions for the treatment of central sensitization pain in osteoarthritis . Man Ther 2015;20(2) :349–52.
[137] Thomson OP, Collyer K. Talking a different language: a qualitative study of chronic low back pain patients' interpretation of the language used by student osteopaths. Int J Osteopath Med 2017;24:3–11.
[138] Darlow B, et al. The association between health care professional attitudes and beliefs and the attitudes and beliefs, clinical management, and outcomes of patients with low back pain: a systematic review. Eur J Pain 2012;16(1): 3–17.
[139] Wetherell JL, et al. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. Pain 2011;152(9):2098–107.
[140] Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol 2014;69(2):153.
[141] Seminowicz DA, et al. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. J Pain 2013;14(12): 1573–84.
[142] Shpaner M, et al. Unlearning chronic pain: a randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy. NeuroImage Clin 2014;5:365–76.
[143] Santarnecchi E, et al. Interaction between neuroanatomical and psychological changes after mindfulness-based training. PloS one 2014;9(10):e108359.
[144] Jackson T, et al. Self-efficacy and chronic pain outcomes: a meta-analytic review. J Pain 2014;15(8):800–14.
[145] Bernardy K, et al. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials. J Rheumatol 2010;37(10):1991–2005.
[146] Kamper SJ, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. Cochrane Database Syst Rev 2014;9:CD000963.
[147] Carnes D, et al. A mixed methods evaluation of a third wave cognitive behavioural therapy and osteopathic treatment programme for chronic pain in primary care (OsteoMAP). Int J Osteopath Med 2017;24:12–7.
[148] Nijs J, et al. Exercise therapy for chronic musculoskeletal pain: innovation by altering pain memories. Man Ther 2014;20(1):216–20.
[149] Bialosky JE, et al. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. Man Ther 2009;14(5):531–8.
[150] Schmid A, et al. Paradigm shift in manual therapy? Evidence for a central nervous system component in the response to passive cervical joint mobilisation. Man Ther 2008;13(5):387–96.
[151] Zusman M. Spinal manipulative therapy: review of some proposed mechanisms, and a new hypothesis. Aust J Physiother 1986;32(2):89–99.
[152] Pickar JG. Neurophysiological effects of spinal manipulation. Spine J 2002;2(5):357–71.
[153] Pickar JG, Bolton PS. Spinal manipulative therapy and somatosensory activation. J Electromyogr Kinesiol 2012;22(5):785–94.
[154] Sung PS, Kang YM, Pickar JG. Effect of spinal manipulation duration on low threshold mechanoreceptors in lumbar paraspinal muscles: a preliminary report. Spine (Phila Pa 1976) 2005;30(1):115–22.
[155] Clark BC, et al. The biology of manual therapies. JAOA J Am Osteopath Assoc 2012;112(9):617–29.
[156] Nijs J, et al. Exercise therapy for chronic musculoskeletal pain: innovation by altering pain memories. Man Ther 2015;20(1):216–20.
[157] Pleger B, et al. Sensorimotor returning in complex regional pain syndrome

parallels pain reduction. Ann Neurol 2005;57(3):425–9.
[158] Moseley GL, Zalucki NM, Wiech K. Tactile discrimination, but not tactile stimulation alone, reduces chronic limb pain. Pain 2008;137(3):600–8.
[159] Rosenkranz K, Kacar A, Rothwell JC. Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. J Neurosci 2007;27(44):12058–66.
[160] Napadow V, et al. Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. Hum Brain Mapp 2007;28(3):159–71.
[161] Chipchase LS, Schabrun SM, Hodges PW. Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters. Clin Neurophysiol 2011;122(3):456–63.
[162] Meesen RL, et al. The effect of long-term TENS on persistent neuroplastic changes in the human cerebral cortex. Hum Brain Mapp 2011;32(6):872–82.
[163] Veldman M, et al. Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. Neurosci Biobehav Rev 2014;47:22–35.
[164] Taylor HH, Murphy B. Altered sensorimotor integration with cervical spine manipulation. J Manip Physiol Ther 2008;31(2):115–26.
[165] Haavik H, Murphy B. The role of spinal manipulation in addressing disordered sensorimotor integration and altered motor control. J Electromyogr Kinesiol 2012;22(5):768–76.
[166] Haavik-Taylor H, Murphy B. Cervical spine manipulation alters sensorimotor integration: a somatosensory evoked potential study. Clin Neurophysiol 2007;118(2):391–402.
[167] Lelic D, et al. Manipulation of dysfunctional spinal joints affects sensorimotor integration in the prefrontal cortex: a brain source localization study. Neural Plast 2016;2016:3704964.
[168] Dishman JD, Ball KA, Burke J. First Prize: central motor excitability changes after spinal manipulation: a transcranial magnetic stimulation study. J Manip Physiol Ther 2002;25(1):1–9.
[169] Dishman JD, Greco DS, Burke JR. Motor-evoked potentials recorded from lumbar erector spinae muscles: a study of corticospinal excitability changes associated with spinal manipulation. J Manip Physiol Ther 2008;31(4):258–70.
[170] Haavik-Taylor H, Murphy B. Transient modulation of intracortical inhibition following spinal manipulation. Chiropr J Aust 2007;37(3):106.
[171] Fryer G, Pearce AJ. The effect of muscle energy technique on corticospinal and spinal reflex excitability in asymptomatic participants. J Bodyw Mov Ther 2013;17(4):440–7.
[172] Fryer G, et al. Lumbosacral Muscle Energy Technique produces immediate decreases in corticospinal and spinal reflex excitability in asymptomatic participants. Int J Osteopath Med 2013;16(1):e5–6.
[173] Comeaux Z. Facilitated oscillatory release—a dynamic method of neuromuscular and ligamentous/articular assessment and treatment. J Bodyw Mov Ther 2005;9(2):88–98.
[174] Jensen JL, Marstrand PC, Nielsen JB. Motor skill training and strength training are associated with different plastic changes in the central nervous system. J Appl Physiol (1985) 2005;99(4):1558–68.
[175] Coronado RA, et al. Changes in pain sensitivity following spinal manipulation: a systematic review and meta-analysis. J Electromyogr Kinesiol 2012;22(5):752–67.
[176] Bishop MD, Beneciuk JM, George SZ. Immediate reduction in temporal sensory summation after thoracic spinal manipulation. Spine J 2011;11(5):440–6.
[177] Fernandez-Carnero J, Fernandez-de-las-Penas C, Cleland JA. Immediate hypoalgesic and motor effects after a single cervical spine manipulation in subjects with lateral epicondylalgia. J Manip Physiol Ther 2008;31(9):675–81.
[178] Fryer G, Carub J, McIver S. The effect of manipulation and mobilisation on pressure pain thresholds in the thoracic spine. J Osteopath Med 2004;7(1):8–14.
[179] Voogt L, et al. Analgesic effects of manual therapy in patients with musculoskeletal pain: a systematic review. Man Ther 2015;20(2):250–6.
[180] Bialosky JE, et al. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. Phys Ther 2009;89(12):1292–303.
[181] Wright A. Hypoalgesia post-manipulative therapy: a review of a potential neurophysiological mechanism. Man Ther 1995;1(1):11–6.
[182] Flynn TW, et al. The audible pop is not necessary for successful spinal high-velocity thrust manipulation in individuals with low back pain. Archives Phys Med Rehab. 2003;84(7):1057–60.
[183] Sillevis R, Cleland J. Immediate effects of the audible pop from a thoracic spine thrust manipulation on the autonomic nervous system and pain: a secondary analysis of a randomized clinical trial. J Manip Physiol Ther 2011;34(1):37–45.
[184] Christian GF, et al. Immunoreactive ACTH, beta-endorphin, and cortisol levels in plasma following spinal manipulative therapy. Spine (Phila Pa 1976) 1988;13(12):1411–7.
[185] Sanders GE, et al. Chiropractic adjustive manipulation on subjects with acute low back pain: visual analog pain scores and plasma beta-endorphin levels. J Manip Physiol Ther 1990;13(7):391–5.
[186] Glasziou PP, Sanders SL. Investigating causes of heterogeneity in systematic reviews. Stat Med 2002;21(11):1503–11.
[187] Vicenzino B, et al. Specific manipulative therapy treatment for chronic lateral epicondylalgia produces uniquely characteristic hypoalgesia. Man Ther 2001;6(4):205–12.
[188] Paungmali A, et al. Naloxone fails to antagonize initial hypoalgesic effect of a manual therapy treatment for lateral epicondylalgia. J Manip Physiol Ther 2004;27(3):180–5.
[189] McPartland JM, et al. Cannabimimetic effects of osteopathic manipulative treatment. J Am Osteopath Assoc 2005;105(6):283–91.
[190] Degenhardt BF, et al. Role of osteopathic manipulative treatment in altering pain biomarkers: a pilot study. J Am Osteopath Assoc 2007;107(9):387–400.
[191] McGlone F, et al. Touching and feeling: differences in pleasant touch processing between glabrous and hairy skin in humans. Eur J Neurosci 2012;35(11):1782–8.
[192] Leknes S, Tracey I. A common neurobiology for pain and pleasure. Nat Rev Neurosci 2008;9(4):314–20.
[193] Morhenn V, Beavin LE, Zak PJ. Massage increases oxytocin and reduces adrenocorticotropin hormone in humans. Altern Ther Health Med 2012;18(6):11–8.
[194] Kurosawa M, et al. Massage-like stroking of the abdomen lowers blood pressure in anesthetized rats: influence of oxytocin. J Auton Nerv Syst 1995;56(1–2):26–30.
[195] Yang J. Intrathecal administration of oxytocin induces analgesia in low back pain involving the endogenous opiate peptide system. Spine (Phila Pa 1976) 1994;19(8):867–71.
[196] Breton J-D, et al. Oxytocin-induced antinociception in the spinal cord is mediated by a subpopulation of glutamatergic neurons in lamina I-II which amplify GABAergic inhibition. Mol pain 2008;4(1):1.
[197] Ruffini N, et al. Variations of high frequency parameter of heart rate variability following osteopathic manipulative treatment in healthy subjects compared to control group and sham therapy: randomized controlled trial. Front Neurosci 2015;9:272.
[198] Giles PD, et al. Suboccipital decompression enhances heart rate variability indices of cardiac control in healthy subjects. J Altern Complement Med 2013;19(2):92–6.
[199] Budgell B, Hirano F. Innocuous mechanical stimulation of the neck and alterations in heart-rate variability in healthy young adults. Auton Neurosci 2001;91(1–2):96–9.
[200] Budgell B, Polus B. The effects of thoracic manipulation on heart rate variability: a controlled crossover trial. J Manip Physiol Ther 2006;29(8):603–10.
[201] Roy RA, Boucher JP, Comtois AS. Heart rate variability modulation after manipulation in pain-free patients vs patients in pain. J Manip Physiol Ther 2009;32(4):277–86.
[202] Chu J, et al. Peripheral response to cervical or thoracic spinal manual therapy: an evidence-based review with meta analysis. J Man Manip Ther 2014;22(4):220–9.
[203] Perry J, Green A. An investigation into the effects of a unilaterally applied lumbar mobilisation technique on peripheral sympathetic nervous system activity in the lower limbs. Man Ther 2008;13(6):492–9.
[204] Simon R, Vicenzino B, Wright A. The influence of an anteroposterior accessory glide of the glenohumeral joint on measures of peripheral sympathetic nervous system function in the upper limb. Man Ther 1997;2(1):18–23.
[205] Petersen N, Vicenzino B, Wright A. The effects of a cervical mobilisation technique on sympathetic outflow to the upper limb in normal subjects. Physiother Theory Pract 1993;9(3):149–56.
[206] Cuoco JA, Fennie CN, Cheriyan GK. Hypothetical link between osteopathic suboccipital decompression and neuroimmunomodulation. J Neurol Neurosci 2016;7(S3:133):1–4.
[207] NIH toolbox: negative affect. 2015 [cited 2015 November 11, 2015].