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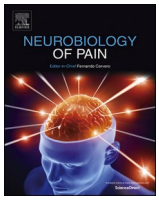

Review

Pain-sensorimotor interactions: New perspectives and a new model

Greg M. Murray [a,*], Barry J. Sessle [b]

[a] Discipline of Restorative and Reconstructive Dentistry, Sydney School of Dentistry, Faculty of Medicine and Health, The University of Sydney, Darcy Road, Westmead, NSW 2145, Australia
[b] Faculty of Dentistry and Temerty Faculty of Medicine Department of Physiology, and Centre for the Study of Pain, University of Toronto, 124 Edward St, Toronto, ON M5G 1G6, Canada

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ABSTRACT

How pain and sensorimotor behavior interact has been the subject of research and debate for many decades. This article reviews theories bearing on pain-sensorimotor interactions and considers their strengths and limitations in the light of findings from experimental and clinical studies of pain-sensorimotor interactions in the spinal and craniofacial sensorimotor systems. A strength of recent theories is that they have incorporated concepts and features missing from earlier theories to account for the role of the sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions of pain in pain-sensorimotor interactions. Findings acquired since the formulation of these recent theories indicate that additional features need to be considered to provide a more comprehensive conceptualization of pain-sensorimotor interactions. These features include biopsychosocial influences that range from biological factors such as genetics and epigenetics to psychological factors and social factors encompassing environmental and cultural influences. Also needing consideration is a mechanistic framework that includes other biological factors reflecting nociceptive processes and glioplastic and neuroplastic changes in sensorimotor and related brain and spinal cord circuits in acute or chronic pain conditions. The literature reviewed and the limitations of previous theories bearing on pain-sensorimotor interactions have led us to provide new perspectives on these interactions, and this has prompted our development of a new concept, the Theory of Pain-Sensorimotor Interactions (TOPSMI) that we suggest gives a more comprehensive framework to consider the interactions and their complexity. This theory states that ***pain is associated with plastic changes in the central nervous system (CNS) that lead to an activation pattern of motor units that contributes to the individual's adaptive sensorimotor behavior. This activation pattern takes account of the biological, psychological, and social influences on the musculoskeletal tissues involved in sensorimotor behavior and on the plastic changes and the experience of pain in that individual. The pattern is normally optimized in terms of biomechanical advantage and metabolic cost related to the features of the individual's musculoskeletal tissues and aims to minimize pain and any associated sensorimotor changes, and thereby maintain homeostasis. However, adverse biopsychosocial factors and their interactions may result in plastic CNS changes leading to less optimal, even maladaptive, sensorimotor changes producing motor unit activation patterns associated with the development of further pain.*** This more comprehensive theory points towards customized treatment strategies, in line with the management approaches to pain proposed in the biopsychosocial model of pain.

1. Introduction

Pain is a complex multi-dimensional experience reflecting sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions (Dubner et al., 1978; Fillingim, 2017; Kuner and Flor, 2017; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021; Sessle, 2021). The sensory-discriminative dimension reflects such aspects as the location and intensity of pain that are commonly described by humans experiencing pain, in particular acute pain which is a transient form of pain that is typically associated with a clearly identifiable noxious stimulus. This dimension relies heavily on nociceptive transmission and processing along ascending nociceptive pathways within the central nervous system (CNS), although these processes themselves can be modulated by projections from CNS areas involved in the various dimensions of pain (Kuner and Flor, 2017; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021). The motivational-affective and cognitive-

* Corresponding author.
E-mail addresses: greg.murray@sydney.edu.au (G.M. Murray), Barry.Sessle@dentistry.utoronto.ca (B.J. Sessle).

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evaluative dimensions of pain and their modulatory influences especially come into play in conditions of chronic pain which is typically defined as pain lasting longer than the normal healing time and which is present for at least 3 months (Kuner and Flor, 2017; Sessle, 2021). Contemporary views consider that chronic pain can be broadly classified into nociceptive pain (associated with ongoing nociceptive afferent input related to tissue injury), neuropathic pain (associated with injury or disease of the somatosensory nervous system), and nociplastic pain (associated with altered function of pain-related somatosensory pathways) (Treede et al., 2008; Fitzcharles et al., 2021; Henning et al., 2022; Treede et al., 2022). Pain is generally considered nowadays within the framework of the biopsychosocial model of pain where the experience of pain is proposed to be driven by dynamic and complex interactions involving many biological, psychological, and social factors that encompass cultural and environmental influences (see Fig. 1) (Melzack, 1999; Loeser, 2000; Gatchel et al., 2007; Fillingim, 2017; Nicholas, 2022).

The biopsychosocial model and descriptions of the multidimensional nature of pain also have briefly noted reactions to pain as well as coping strategies and other adaptive responses that involve changes in sensorimotor behavior (Melzack, 1999; Loeser, 2000; Gatchel et al., 2007; Fillingim, 2017; Nicholas, 2022). They also have drawn attention to the variability between individuals in pain experience as well as in their responses and adaptation to pain, and have revealed that this variability underscores the differences between many individuals in how they use each of the dimensions to express or modify their pain (Gatchel et al., 2007; Fillingim, 2017; Nicholas, 2022). Sensorimotor behaviors are clearly included in these responses to pain, whether the pain is acute or chronic. An acute pain example in the spinal sensorimotor system is the change in limb movement when a person's hand unexpectedly contacts a hot stove, or a person inadvertently steps on a nail. A comparable example in the craniofacial sensorimotor system is the sudden interruption of jaw closing when a person accidentally bites their cheek or tongue during chewing. In addition to these not uncommon instances of transient sensorimotor reflex responses to an acute noxious stimulus, sensorimotor changes may also take place if the person is experiencing chronic pain. For example, chronic pain is commonly experienced by patients with arthritic limb joints or low back pain and is often accompanied by considerable limitation of movements. Movement limitations are also common in chronic craniofacial pain conditions, as typified by patients suffering from pain associated with temporomandibular disorders (TMD) where limitations in jaw movements are manifested as slower jaw movements, and/or reductions in the range of jaw movements; TMD patients also may experience reductions in their ability to control bite force (Schiffman et al., 2014). The sensorimotor systems of some individuals can readily adapt to these acute or chronic pain conditions, and these individuals can perform sensorimotor behaviors that allow them to function at levels comparable to a pain-free state, but other individuals do not readily adapt and indeed may even adopt maladaptive sensorimotor behaviors.

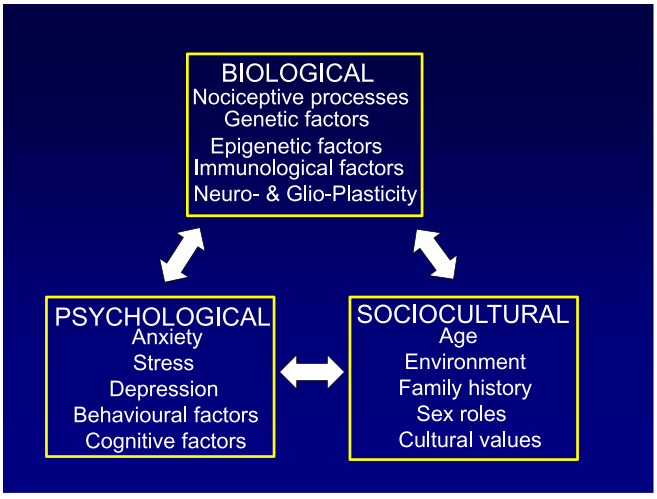

Fig. 1. Components of the biopsychosocial model of pain. Several examples are noted of the components that comprise the biological, psychological, and sociocultural aspects of the model and that influence pain.

What accounts for these sensorimotor behaviors in relation to acute or chronic pain, and for their variability between individuals? The interactions between sensorimotor behaviors and pain or noxious stimuli have been the subject of research and debate in humans and laboratory animal models for many decades, and several theories have been proposed to address the interactions. This article first briefly reviews these theories and outlines their strengths and limitations. It then reviews data sets from earlier and more recent experimental and clinical findings related to these interactions in first the spinal and then the craniofacial sensorimotor systems, and that subserve somatosensory functions and sensorimotor behaviors respectively in the neck, trunk, and limbs, and in the craniofacial region. This includes findings of nociceptive pathways and mechanisms and related behavioral observations of the sensorimotor and psychosocial features of pain and its multi-dimensionality and the wide range of influences and mechanisms that may account for the sensorimotor adaptive behavioral responses associated with pain, and the variability between individuals in their experience and adaptability. In keeping with the biopsychosocial model of pain (see Fig. 1), these influences range from biological factors encompassing genetic and epigenetic influences as well as nociceptive mechanisms and glioplastic and neuroplastic changes in sensorimotor and related CNS circuits in conditions of acute and especially chronic pain, to psychological factors and the broad range of social factors that encompass environmental and cultural influences. The review also recognizes a role in pain-sensorimotor interactions for the various biological, psychological, and social influences on the musculoskeletal tissues *per se* that are involved in sensorimotor behavior. The review then considers these findings in the light of recent and earlier theories of the interactions. While a strength of the recent theories is their incorporation of some concepts and features missing from earlier theories, findings acquired since these recent theories were formulated indicate that additional features need to be considered in pain-sensorimotor interactions. The literature reviewed and the limitations of the theories bearing on pain-sensorimotor interactions have led us to provide new perspectives on these interactions, and prompted our proposal of a new theory, the Theory of Pain-Sensorimotor Interactions (TOPSMI). We suggest that this theory provides a more comprehensive framework to consider pain-sensorimotor interactions and their complexity, including the underlying mechanisms and factors influencing them.

2. Theories of Pain-Sensorimotor interactions

In this review, pain-related sensorimotor behaviors are viewed in terms of the kinematics, dynamics, and/or related electromyographic (EMG) activity patterns associated with skeletal muscle-driven movements or forces, recognizing the integral role of multiple CNS circuits and somatosensory information in the generation and modulation of any movement or force. We do not consider possible pain-related sensorimotor alterations involving the autonomic nervous system innervation of tissues (e.g. smooth or cardiac muscle, glands) although we do recognize that such alterations may produce changes (e.g. in blood flow) that indirectly could influence skeletal muscle function. Rather, we focus on skeletal muscle function since previous theories of pain-sensorimotor interactions have centered on effects of pain on skeletal muscle activity. Indeed, several theories have been developed to characterize the interactions between pain and sensorimotor behaviors and possible underlying mechanisms.

Two of the most influential theories from the last century are the Vicious Cycle Theory (VCT) and the Pain Adaptation Model (PAM). The

VCT has evolved from a vicious "pain-muscle activity-pain" circle or cycle hypothesis originally proposed in 1942 by Travell and colleagues (Travell et al., 1942) (for review, see (Johansson and Sojka, 1991; Lund et al., 1991; Stohler, 1999; Merkle et al., 2020)). Some of the more recent formulations of the VCT propose that an initiating event in the form of stress or an abnormality in posture, structure, or movement leads to increased muscle EMG activity that produces muscle spasm, fatigue and pain in agonist and/or antagonist muscles (one arm of the VCT), and the pain then produces, via segmental reflex mechanisms, more EMG activity (the other arm of the VCT) thus setting up a self-perpetuating cycle. The basic tenets of the VCT are countered in the Pain Adaptation Model (PAM) (Lund et al., 1991). In contrast with the VCT where increased levels of muscle activity are viewed as contributing to the pain, the PAM does not attempt to explain the origin of the pain but proposes that pain, via segmental motor circuits in the CNS, leads reflexly to a reduction in agonist muscle activity and an increase in antagonist muscle activity, with the net effect being a limitation of movement that protects the musculoskeletal system from further injury and thereby promotes healing (Lund et al., 1991; Lund, 2008). Both models have been well studied since their initial formulations (Stohler, 1999; Svensson and Graven-Nielsen, 2001; van Dieën et al., 2003; Murray and Peck, 2007; Hodges and Tucker, 2011; Murray and Lavigne, 2014; Hodges and Smeets, 2015) and even though each has provided simple frameworks that appear in some patients to assist in the clinical management of pain in both spinal and craniofacial sensorimotor systems, many clinical and experimental data sets from studies using rigorous design and control procedures have shown considerable variability in pain-related changes in muscle activity between individuals and between muscles within individuals, and have provided no or limited support or indeed contradictory evidence bearing on the fundamental proposals of either theory (for review, see (Stohler, 1999; Svensson and Graven-Nielsen, 2001; van Dieën et al., 2003; Murray and Peck, 2007; Hodges and Tucker, 2011; Murray and Lavigne, 2014; Hodges and Smeets, 2015)). In addition, it should be noted that both models are incongruous and misleading given that they are segmentally based models erroneously equating pain with nociception and inferring that pain *per se* can evoke a nociceptive reflex that involves activity in segmental motor circuits that results in changes in muscle activity. As noted above, pain is a multi-dimensional experience encompassing a number of biopsychosocial factors reflecting complex processing and modulation in nociceptive and possibly also non-nociceptive circuits at many CNS levels (segmental spinal cord and/or brainstem, other brainstem regions and subcortical and cortical regions). Nociception on the other hand refers to the processing of nociceptive information in nociceptive circuits at one or more of many different levels of the CNS. A nociceptive reflex is a segmental motor response to a noxious stimulus evoking nociceptive activity in segmental motor circuits in the CNS and thereby a change in muscle activity; although a nociceptive reflex may be part of the experience of pain, the reflex is not generated by pain itself.

Other models have paid greater attention to the possible contribution to pain-sensorimotor interactions from factors such as psychological and social influences. One psychological factor that has attracted particular attention is pain-related fear of movement that is captured in the Fear-Avoidance Model of Pain (FAM), which was originally introduced in 1983 and incorporates classical (i.e. Pavlovian) and operant (i.e. respondent or instrumental) conditioning in its conceptualization (Lethem et al., 1983; Vlaeyen et al., 1995; Leeuw et al., 2007; Vlaeyen et al., 2016). This model proposes that if an acute pain experience is interpreted as essentially non-threatening, then patients will essentially maintain their daily activities and functional recovery will likely occur. If, however, the pain is misinterpreted (e.g. through catastrophizing), then the acute pain being experienced can lead to excessive pain-related fear and avoidance and other safety-seeking behaviors including hypervigilance. This may provide short-term pain minimization but in the long term may give rise to disuse, disability, and paradoxically more pain. The FAM has received some criticism because it upholds a phobia-based model of psychopathology, and because some of the psychophysiological components have not been reliably demonstrated, e.g. some studies have failed to demonstrate increased muscular activations in studies of pain-related fear (for review, see (Meulders, 2020)). Related to this concept is the Avoidance-Endurance Model (AEM) (Hasenbring and Verbunt, 2010; Hodges and Smeets, 2015) which proposes that the beliefs and expectations of a patient lead the patient, despite the pain, to persevere so as to complete a motor behavior which may however result in overuse of the motor system and further injury and pain. Other theories are the Integrated Pain Adaptation Model (IPAM) (Murray and Peck, 2007; Peck et al., 2008) and the New or Contemporary Theory for the Motor Adaptation to Pain (NTAP) (Hodges, 2011; Hodges and Tucker, 2011) which share some similarities as both have proposed that, in response to pain, there is a reorganization or redistribution of muscle activity that leads to alleviation of the pain but in some cases may lead to a worsening of the pain. The IPAM also acknowledges the role of the sensory-discriminative, motivational-affective, and cognitive-evaluative components of pain in influencing the sensorimotor response to pain. The NTAP and the IPAM have been recently encapsulated in the Protective Response Theory (Merkle et al., 2020). Other related concepts include the Strength Inhibition Theory (SIT) that "peak muscle force is inhibited by pain" (Merkle et al., 2020), a "stiffness model" which implicates EMG-free changes in stiffness as influencing the effects of a painful or damaged state of a muscle on movement (Turker, 2010), and the Cinderella Hypothesis which proposes that overuse of low-threshold motor units leads to fatigue and pain (Zennaro et al., 2003).

Most of these theories relating to pain-sensorimotor interactions have recognized the protective aspects of the manifestation of sensorimotor behavioral responses, and that cognitive and/or other aspects of the multi-dimensional nature of pain play a role in pain-related sensorimotor interactions. Nonetheless, little or no attention has been paid in any of these theories to the importance of the broad range of psychosocial influences, to the related biological processes encompassing nociceptive mechanisms, glioplasticity and neuroplasticity in the CNS and the role that plasticity may play in the expression of these interactions and in motor adaptation (or not) to pain, and to other biological factors (such as genetic and epigenetic factors) that may contribute to the variability between individuals in adapting to the pain and associated sensorimotor changes. Over the past decade, considerably more findings bearing on these influences and processes have emerged in clinical and experimental studies in humans and animal models, thereby warranting a reassessment of pain-sensorimotor interactions that takes account of this new information as well as the limitations of these theories. Therefore, the following focusses particularly on these recent findings and points to the need for a new theory that is more comprehensive and consistent with the currently available literature stemming from studies in animal models and humans.

3. Pain and sensorimotor interactions

3.1. Pain-related sensorimotor behaviors

3.1.1. Animal studies

Numerous studies in the spinal and craniofacial sensorimotor systems of humans and laboratory animal models have documented a wide variety of sensorimotor behaviors that may be associated with noxious stimulation or pain. In animals, a range of acute and chronic pain models has been developed to study pain and in some cases to investigate pain-related sensorimotor behaviors or provide insights into underlying mechanisms. The behavioral responses in these animal models closely mimic key components of many acute and chronic pain conditions that occur in humans, such as facial grimacing and guarding behaviors, and behavioral features indicative of allodynia, hyperalgesia, and extraterritorial spread of sensitivity (Kuner, 2010; Zhang and Ren, 2011; Sessle, 2021; Sadler et al., 2022). Models of acute pain in animals have included

the application to cutaneous, musculoskeletal, or visceral tissues of noxious stimuli (mechanical [e.g. pinprick], thermal [noxious heat, noxious cold], chemical [e.g. hypertonic saline, capsaicin]) that generate so-called physiological or nociceptive pain where there is usually only limited tissue damage and the evoked nociceptive behaviors may last for less than a second to a few hours (Kuner and Flor, 2017; Kuner and Kuner, 2021; Sadler et al., 2022). Animal models of chronic pain have included inflammatory pain models and neuropathic pain models; both model types typically manifest spontaneous and/or evoked pain-like behavioral features that last several days or weeks and include changes in sensorimotor behaviors in comparison with control pain-free animals (Zhang and Ren, 2011; Kuner and Kuner, 2021; Sadler et al., 2022). The chronic inflammatory pain models have used approaches typically involving the application of noxious stimuli having sustained actions in tissues supplied by spinal or trigeminal nerve afferents (e.g. chemical irritants or inflammogens such as formalin, mustard oil, carrageenan, or complete Freund's adjuvant) or mechanically induced damage to tissues or restrictions of movement. Although these animal models do not necessarily simulate every feature associated with chronic inflammatory or mechanically induced pain in humans, the persistent pain-like behavior in these models has led to them generally being regarded as animal models of chronic pain (Zhang and Ren, 2011; Ren, 2020; Kuner and Kuner, 2021; Sadler et al., 2022). Chronic neuropathic pain models have included approaches that directly compromise some pain-related CNS circuits, but more commonly have involved injury (e.g. transection or chronic constriction injury) of a somatosensory nerve.

In terms of pain-related sensorimotor behaviors in the spinal sensorimotor system subserving somatosensory functions and sensorimotor behaviors involving the neck, trunk, and limbs, transient noxious stimulation of tissues supplied by spinal primary afferent nerves can evoke a variety of acute reflex sensorimotor behaviors that include reflex withdrawal (e.g. tail flick, paw lift, limb withdrawal) or flinching. These behaviors in animals involve relatively simple, segmentally based circuits in the spinal cord and are readily quantifiable and they have been extensively used in acute pain models to explore nociceptive mechanisms in peripheral tissues and the CNS, such as glioplasticity and neuroplasticity and changes in gene expression in dorsal root ganglia and spinal and supraspinal CNS regions (Kuner, 2010; Descalzi et al., 2015; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021). Chronic inflammatory or neuropathic pain models on the other hand usually involve more extensive CNS circuitry and more complex behaviors often manifesting as a change in sensorimotor behavior. In comparison with pain-free animals: these behaviors include spontaneous or evoked pain-like behaviors reflecting allodynia or hyperalgesia for example, as well as other behaviors that can be quantified through studies of conditioned behavioral paradigms measuring motivational or affective aspects of pain (e.g. anxiety, stress), as well as studies of survival behavioral measures (e.g. avoidance behaviors), elective or natural behavioral measures (e.g. cage hanging, nest building, social interaction, wheel running), and other measures of overt nocifensive sensorimotor behaviors (e.g. writhing, licking, gait changes, guarding, immobility, vocalizations) (Zhang and Ren, 2011; Dubner et al., 2014; Tappe-Theodor et al., 2019; Sadler et al., 2022). Some of these behaviors (e.g. wheel running, nest building) in these models may be reduced or impaired whereas others (e.g. writhing) may be adopted or increased when the animal is experiencing pain. Like the acute pain models, these approaches have been used to provide insights into the peripheral and central mechanisms involved, such as peripheral sensitization, central sensitization, and modulatory processes. It is also noteworthy that the sensorimotor outcome measures from many of these acute or chronic pain studies can show considerable variability between individual animals subjected to the same nociceptive stimulus or chronic pain-producing procedure and many factors can contribute to this variability. One of these factors is sex since robust sex differences have been demonstrated in nociceptive behavior and analgesia in animal models; this and other factors contributing to this variability will be elaborated further below (see sections 3.3.1. and 3.4.1.).

In the craniofacial sensorimotor system subserving craniofacial somatosensory functions and sensorimotor behaviors, analogous animal models of acute craniofacial nociceptive or inflammatory pain include acute pain models where noxious stimuli have been applied to superficial tissues (e.g. facial skin, oral mucosa) or deeper tissues (e.g. temporomandibular joint [TMJ], jaw muscle, meninges, tooth pulp). These noxious stimuli activate trigeminal nociceptive afferent nerves that typically elicit acute reflex sensorimotor responses such as a jaw-opening reflex involving excitation of jaw-opening muscles (e.g. anterior digastric) and inhibition of jaw-closing muscles (e.g. masseter) or reflex changes in other orofacial muscles and neck muscles (e.g. contributing to a head withdrawal reflex) (Dubner et al., 1978; Sessle, 2006; Avivi-Arber and Sessle, 2018). Like the nociceptive reflexes in the spinal sensorimotor system, these reflex responses are relatively simple, segmentally based (in this case, brainstem based), and readily quantifiable. Chronic craniofacial inflammatory pain models have included those utilizing the application to craniofacial tissues of chemical irritants or inflammogens analogous to those mentioned above, and mechanically induced tissue damage or alterations such as ligation of a muscle tendon and changes to the dental occlusion that induce inflammation of oral tissues (Cairns et al., 2014; Dostrovsky et al., 2014; Shinoda et al., 2019; Chung et al., 2020; Sessle, 2021). The craniofacial neuropathic pain models have included those replicating spinal nerve injury models (e.g. chronic constriction injury or transection of branches of the trigeminal nerve) and also have included approaches producing compression of the trigeminal ganglion or sensory root or disruption of trigeminal pathways in the CNS as models of trigeminal neuralgia or other trigeminal neuropathic pain states (Dubner et al., 2014; Shinoda et al., 2019; Sessle, 2021). In contrast with the acute pain models, these chronic models are typically associated with a more complex array of spontaneous and evoked behaviors, including sensorimotor behaviors analogous to some of those noted above for chronic pain models in the spinal sensorimotor system and reflecting features such as allodynia or hyperalgesia as well as peripheral and/or central sensitization (Cairns et al., 2014; Dostrovsky et al., 2014; Dubner et al., 2014; Shinoda et al., 2019; Chung et al., 2020; Sessle, 2021). These nocifensive sensorimotor behaviors may include changes in grooming and exploratory activity, facial grimacing, increased licking and guarding behaviors, and disruptions in chewing, biting, feeding, drinking, or other motor behaviors as well as operant responses involving complex craniofacial behaviors (Abdalla et al., 2022; Chung et al., 2020; Dubner et al., 2014; Ro, 2005; Rocha Barreto et al., 2022; Sessle, 2021; Shinoda et al., 2019). It is notable that, like the pain models used in the spinal sensorimotor system, sex differences and inter-individual variability in pain-related sensorimotor behavior are not uncommon in the acute or chronic craniofacial pain models (Cairns, 2007; Cairns et al., 2014; Zhang et al., 2014; Sessle, 2021). The mix of psychosocial, genetic, and epigenetic factors that may contribute to these features in both spinal and craniofacial sensorimotor systems in animals are detailed below in sections 3.3.1 and 3.4.1.

3.1.2. *Human studies*

Studies of pain-related sensorimotor behaviors in human subjects have involved investigations using experimental induction of pain in healthy pain-free individuals or investigations of patients who have acute or chronic pain. The experimental pain studies have mostly involved experimentally induced acute pain, whereas the clinical pain studies have mainly covered a variety of chronic musculoskeletal pain conditions, such as low back pain, fibromyalgia, and TMD, as well as some neuropathic pain conditions. Several sensory-discriminative and motivational-affective features of the human experimental pain models are similar to those manifested in the chronic pain conditions that the experimental pain models have been designed to emulate (Stohler and Kowalski, 1999; Castrillon et al., 2008; Graven-Nielsen and Arendt-Nielsen, 2008), and therefore experimental data sets are important in

understanding acute or chronic pain-sensorimotor interactions. However, experimental pain models may not readily address several factors commonly associated with chronic pain in humans and the possible role of these factors in the experience of pain. These factors include the high levels of psychosocial distress typically associated with chronic pain, the plastic changes in CNS circuits associated with chronic pain (i.e. longer than 3 months), as well as other adverse psychosocial factors such as negative life experiences, sleep disruption, and other adverse social and cultural factors and events that may contribute to a chronic pain condition. One feature of acute and chronic pain that the experimental pain models do indeed emulate is the large variation between individuals in the experience of pain; for example, it has been frequently demonstrated that a standardized noxious stimulus evokes pain that is rated more highly in females than males (Berkley, 1997; Mogil, 2012b; Fillingim, 2017; Mogil, 2020) and that also may be very variable between individuals in its rated intensity (Cairns, 2007; Mogil, 2012a; Fillingim, 2017). A wide range of factors has been implicated as contributing to the sex differences and inter-individual variability in pain experience (see sections 3.3. and 3.4.) and these include biological (e.g. genetic, epigenetic, glioplastic and neuroplastic influences), psychological (depression, anxiety, stress, pain catastrophizing), and social (e.g. environmental, experiential, cultural, economic) factors. These many factors exert their effects on the expression and experience of pain, including pain-related sensorimotor behavior, through several neural mechanisms such as peripheral and central sensitization processes, the interplay between nociceptive afferent inputs and descending pain-modulatory systems as well as interactions with other systems (e.g. hypothalamic–pituitary–adrenal axis, sensorimotor circuits) (Bushnell et al., 2013; Kucyi and Davis, 2015; Fillingim, 2017; Malfliet et al., 2017; Timmers et al., 2019; Mogil, 2020).

In the human spinal sensorimotor system, many studies have addressed the associations between pain and sensorimotor behavior by investigating the activity of spinal and supraspinal CNS regions projecting to spinal cord motoneurons as well as the activity of motor units in a variety of upper and lower limb and trunk muscles in acute experimental pain or acute or chronic clinical pain conditions. These studies have included investigations of reflexes (e.g. nociceptive withdrawal reflex EMG latency and amplitude, effects of noxious stimulation on H-reflex amplitude), corticospinal excitability and primary motor cortex (MI) organization and motor representation characterized by features such as motor evoked potential (MEP) threshold or amplitude and motor map areas revealed through transcranial magnetic stimulation (TMS). Studies have also been made of multi-unit or single motor unit EMG activities (e.g. single motor unit recruitments or firing rates) during rest or during voluntary movement or force generation associated with motor task performance. Recent studies have also explored the potential utility of machine learning to use the variability (e.g. in motor behavior, brain activity) in experimental or clinical presentations to enhance clinical predictions regarding diagnosis and management. There have been many wide-ranging systematic or narrative reviews addressing one or more of these aspects (e.g. (Andersen, 2007; Bank et al., 2013; Wager et al., 2013; Hodges and Smeets, 2015; Burns et al., 2016; Chang et al., 2018; van der Miesen et al., 2019; Falla and Gallina, 2020; Merkle et al., 2020; Falla et al., 2021; Sanderson et al., 2021; Devecchi et al., 2023; Graven-Nielsen and Arendt-Nielsen, 2008) and some findings particularly relevant to this present review are highlighted below.

In terms of nociceptive reflex effects, it is a very common experience that an acute noxious stimulus applied to cutaneous or musculoskeletal tissues typically evokes a withdrawal reflex motor response as a mechanism of protection against potentially damaging stimuli. It is also a commonplace experience that nociceptive reflexes can readily interrupt rhythmical movements such as walking, running, and breathing. In the spinal sensorimotor system of humans, the nociceptive withdrawal reflex has been well characterized in the limbs and may be evoked by Group III and IV muscle, joint, and cutaneous nociceptive afferents (Clarke and Harris, 2004; Sandrini et al., 2005; Andersen, 2007). There is evidence in humans that the excitability of this reflex may be influenced by physiological or psychological factors (e.g. stress, attention, sleep) and pathological factors (e.g. spinal lesions, chronic pain conditions) (Sandrini et al., 2005), and there may be sex differences in some features of the reflex (e.g. lower thresholds in females (Mylius et al., 2005)).

Some experimental and clinical pain studies using measures of motor function (e.g. multi-unit EMG activity, single motor unit properties) have revealed evidence for a reorganization of motor activity reflected in non-uniform pain-related EMG effects within painful and non-painful muscles in comparison with control (Ervilha et al., 2005; Tucker et al., 2009; Madeleine, 2010; Falla et al., 2017; Hodges et al., 2021; Becker et al., 2022). A common feature of both the experimental and the clinical pain studies has been the variability in findings (i.e. increases, decreases, or no changes) in many of the motor outcome measures in association with experimental or clinical pain, not only between different studies but also between individual participants within studies, and between different pain conditions (van Dieën et al., 2003; Hodges and Smeets, 2015; Merkle et al., 2020; Sanderson et al., 2021). Remarkably, analyses for the presence of possible sex differences in pain-sensorimotor behavior have not featured prominently in previous studies, although sex differences have been documented in the changes in trapezius muscle EMG activity during acute experimental noxious stimulation of the trapezius muscle in comparison with control (Ge et al., 2005; Falla et al., 2008), as well as in trunk neuromuscular responses in low back pain (Mueller et al., 2020). While differences in methodology between studies (e.g. tasks performed, analyses used) contribute to the variability between studies in pain-related motor outcome measures, the wide range of biological, psychological, and social factors pointed out above as contributing to the large variation in the experience of pain between individuals likely also contributes to the variability in motor activity between individuals and between studies. These factors were not well defined in most of the above-mentioned studies and are considered further below in sections 3.3. and 3.4.

Many studies in the craniofacial sensorimotor system in humans have also addressed the association between experimental or clinical pain and motor behavior (Dubner et al., 1978; Stohler, 1999; Svensson and Graven-Nielsen, 2001; Sessle, 2006; Murray and Peck, 2007; Lund et al., 2008; Avivi-Arber et al., 2011; Castroflorio et al., 2012; Murray et al., 2014; Avivi-Arber and Sessle, 2018; Maulina et al., 2018; Amhamed et al., 2019; Moura Ferreira et al., 2020; Dinsdale et al., 2021). These have mostly focused on jaw motor function through recordings of EMG activity, movements, and/or forces associated with jaw task performance (e.g. jaw opening or closing, biting tasks, ongoing rhythmical movements as in chewing) during pain in comparison with control. Studies have also recorded EMG activity during noxious stimulation in relation to evoked reflexes manifested in especially jaw-opening (e.g. anterior digastric) or jaw-closing (e.g. masseter, temporalis) muscles, and to corticobulbar excitability and MI organization. Many of the findings from these various studies appear to be generally consistent with the findings from the comparable studies summarized above for the spinal sensorimotor system, including the presence of sex differences and the presence of considerable variability in the effects of pain on some of the outcome measures in comparison with control, not only between different studies of experimental or clinical pain but also between individuals within a study (Torisu et al., 2006; Wiesinger et al., 2016; Maulina et al., 2018; Amhamed et al., 2019; Dinsdale et al., 2020; Moura Ferreira et al., 2020; Dinsdale et al., 2021).

3.2. *Nociceptive pathways, sensorimotor circuits, and their plasticity*

3.2.1. *Animal studies*

In the spinal sensorimotor system, investigations using animal models have revealed that nociceptive signals are conducted along spinal primary afferent nerve fibers via the dorsal root ganglia into the spinal cord. These nociceptive signals are initially processed principally

in the spinal cord dorsal horn and then relayed to local spinal cord regions such as the ventral horn where the spinal motoneurons are located, as well as along ascending pathways that carry the signals to higher levels of the CNS (Bushnell et al., 2013; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Kuner and Kuner, 2021). The targets of these ascending nociceptive signals are numerous and include the brainstem reticular formation, cerebellum, rostroventral medulla (RVM), periaqueductal grey matter (PAG), and thalamus, as well as several areas of the cerebral cortex such as primary (SI) and secondary (SII) somatosensory cortical areas, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and insula. Each of these CNS areas is involved to varying degrees in one or more of the various dimensions of pain and in processes by which sensory-discriminative, cognitive-evaluative, or motivational-affective factors can influence nociceptive transmission and thereby change sensorimotor behavior. There is also evidence for sex differences in some of these influences and processes, e.g. sex-dependent roles of peptides and receptors in nociceptive neural circuits and associated glial cells, as well as in descending pain-modulatory processing (Mogil, 2012b, 2020). It is also notable that many of the above CNS areas are important components of sensorimotor circuits since they may directly or indirectly project to spinal motoneurons and thereby influence sensorimotor behavior.

A major insight gained over the past four decades from animal models of acute or chronic pain following tissue trauma, nerve injury, or inflammation has been the extensive plastic changes that can occur along nociceptive pathways and/or circuits of spinal primary afferent nerves, dorsal root ganglia, spinal cord dorsal horn, as well as brainstem and other CNS regions (e.g. PAG, RVM, insula, amygdala, ACC, hippocampus, SI, MI, cerebellum, basal ganglia, red nucleus) (Latremoliere and Woolf, 2009; Bliss et al., 2016; Lu et al., 2016; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Ji et al., 2018; Da Silva and Seminowicz, 2019; Ji et al., 2019; Kuner and Kuner, 2021; Sawicki et al., 2021). These

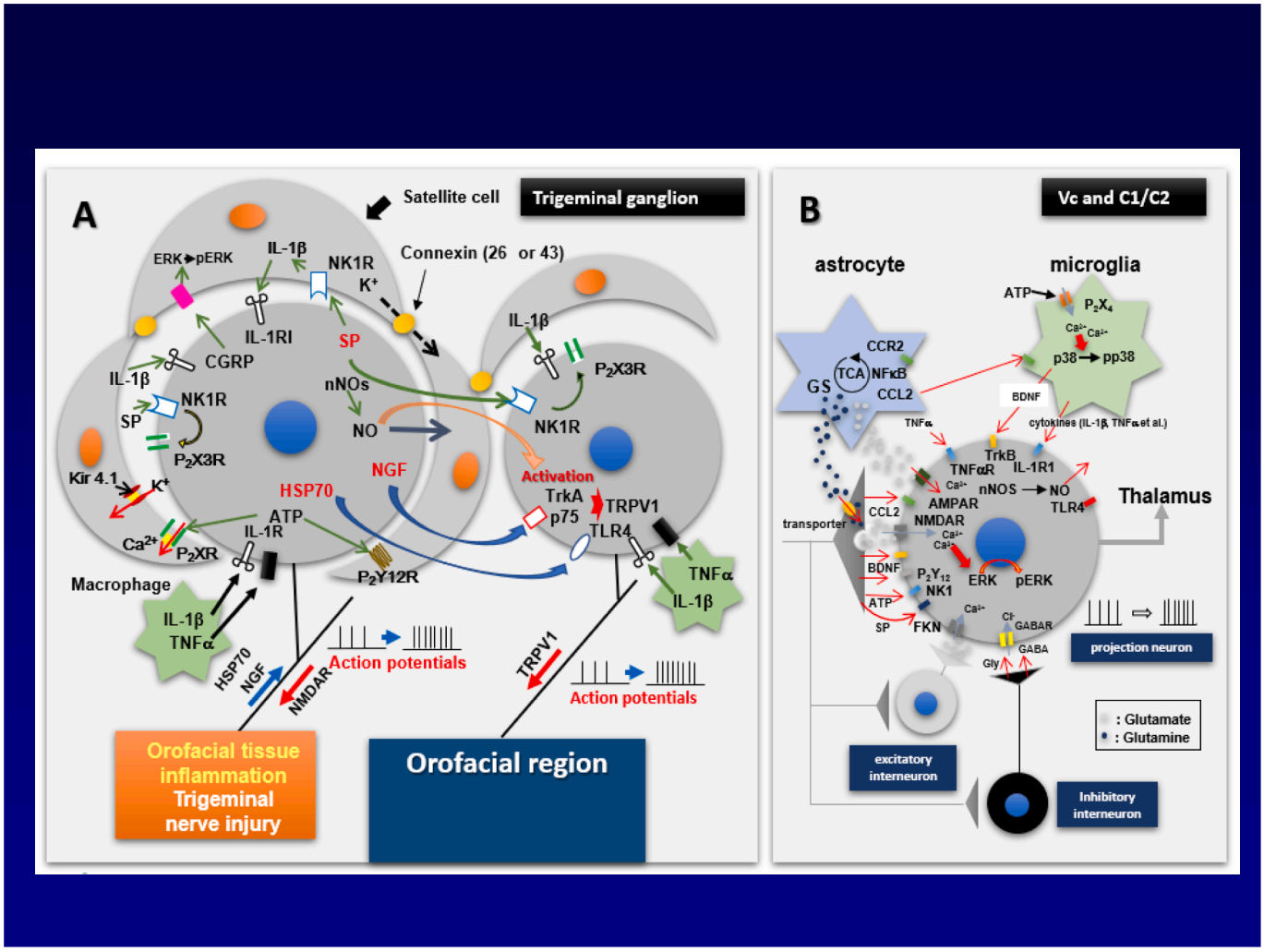

Fig. 2. Peripheral and central mechanisms involved in nociceptive processing associated with tissue inflammation or nerve injury. The mechanisms are portrayed in the context of two parts of the trigeminal sensorimotor system, namely the trigeminal ganglion (TG) and the trigeminal subnucleus caudalis (Vc; also known as the medullary dorsal horn) as well as the immediately adjacent upper cervical spinal cord (C1/C2) dorsal horn. (A) notes that inflammation or nerve injury can elicit a state of hyperexcitability of primary afferent neurons in their peripheral afferent endings (not shown) as well as in their cell bodies in the TG; in addition, satellite glial cell activation and macrophage accumulation may also occur in the TG. The hyperexcitable TG afferent neurons, satellite glial cells and macrophages can communicate with each other through several mediators, receptor processes and signalling mechanisms, and examples are illustrated here. Such inter-communication can produce further enhanced excitability of the TG neurons, resulting in a hyperexcitable afferent input into the trigeminal brainstem sensory nuclear complex, particularly its Vc as well as the C1/C2 dorsal horn. (B) shows input and output features of nociceptive neurons in Vc and C1/C2 dorsal horn in normal conditions and in conditions of inflammation or nerve injury. The hyperexcitable nociceptive afferent input shown in A causes the release of mediators that elicit hyperexcitability of the nociceptive neurons as well as the activation of astrocytes and microglia. Neuron–glial cell communication can occur through the release of chemical mediators, examples of which are shown here. This inter-communication is important in the development and maintenance of the nociceptive neurons' hyperexcitable state, i.e., central sensitization. From Iwata and Sessle (Iwata and Sessle, 2019) Reprinted by Permission of SAGE Publications.

changes include those that are associated with the excitation or inhibition of sensorimotor behavior in acute and chronic pain models and that are manifested as immunohistochemical, molecular, and electrophysiological changes reflecting not only neuroplasticity but also glioplasticity (i.e. plasticity of glial cells, namely, microglia, astrocytes, and satellite glial cells) (Latremoliere and Woolf, 2009; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Ji et al., 2018; Da Silva and Seminowicz, 2019; Ji et al., 2019; Kuner and Kuner, 2021; Sawicki et al., 2021). Hallmarks of this plasticity are sensitization processes reflected in an increased excitability of the nociceptive primary afferents (termed *peripheral sensitization*) and of the neurons in the ascending nociceptive pathways in the CNS (termed *central sensitization*) (Fig. 2) (Latremoliere and Woolf, 2009; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Ji et al., 2018; Kuner and Kuner, 2021; Sawicki et al., 2021; Treede et al., 2022).

The changes reflecting sensitization processes include a critical role not only for neural and glial cells but also for other cellular elements such as immune cells that release chemical mediators (e.g. pro-inflammatory cytokines and chemokines) as part of the neuro-inflammatory response (Fig. 2) (Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Ji et al., 2018; Kuner and Kuner, 2021; Sawicki et al., 2021). Several receptor systems come into play in these processes in both the peripheral and central components of the spinal sensorimotor system; they include purinergic (e.g. P2X, P2Y) and glutamatergic (*N*-methyl-D-aspartate [NMDA] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) receptor-dependent mechanisms. The processes in the CNS also involve Hebbian spike timing-dependent plasticity as well as the disinhibition of inhibitory connections between non-nociceptive and nociceptive circuits and which can contribute to the increased excitability reflecting central sensitization processes (Latremoliere and Woolf, 2009; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Ji et al., 2018; Kuner and Kuner, 2021; Sawicki et al., 2021). It is notable that the central sensitization processes may occur not only in CNS nociceptive neurons receiving afferent inputs from an injured or inflamed region of the body but also in neurons that receive afferents from uninjured or non-inflamed tissues (Devor, 2009; Latremoliere and Woolf, 2009; Ji et al., 2018; Sessle, 2021). Moreover, as Fig. 2 shows, peripheral sensitization may occur not only in primary afferent neurons innervating tissues directly affected by injury or inflammation but also in primary afferent neurons innervating tissues beyond the injured or inflamed area. Thereby, the CNS nociceptive neurons may also be receiving abnormal ectopic afferent inputs. The origin of the nociceptive afferents also appears to play a role in the ensuing degree of central sensitization since deep noxious stimulation produces a greater magnitude of central sensitization than that associated with superficial noxious stimuli (Wall and Woolf, 1984; Yu et al., 1993; Ren, 2020). Furthermore, a common finding from many acute pain models is that the CNS areas that are activated in these models involve areas primarily related to the sensory-discriminative aspects of a noxious stimulus and pain modulation (e.g. SI, insula, thalamus, PAG) (Bushnell et al., 2013; Kucyi and Davis, 2015; Kuner and Flor, 2017; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021). On the other hand, the CNS areas that are activated in chronic pain models are mainly those associated with the cognitive-evaluative and the motivational-affective dimensions of pain (e.g. PFC, ACC, hippocampus), and there is also evidence in these chronic pain models for altered functional connectivity of many of the CNS areas involved in pain (Bushnell et al., 2013; Kucyi and Davis, 2015; Kuner and Flor, 2017; Ji et al., 2018; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021).

The glioplastic and neuroplastic changes that occur in spinal nociceptive afferents and their circuits in the CNS of animal models of pain may indeed be manifested in CNS areas involved in a variety of pain-related and sensorimotor functions. Plasticity comes into play, for example, in CNS processes such as those involved in memory, learning, performance of sensorimotor behaviors or tasks, and the ability to adapt to pain and its associated changes in sensorimotor behavior (Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Omrani et al., 2017; Peters et al., 2017; Papale and Hooks, 2018; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021). The subcortical plastic changes noted above (e.g. in PAG, RVM, hippocampus) undoubtedly play a role here, but plasticity of several cortical areas also may have an important role in sensorimotor behaviors and adaptation to pain. In the spinal sensorimotor system, animal models have demonstrated that pain-related sensorimotor behaviors are associated with plastic changes occurring in several cortical areas involved directly in motor control or in the sensory-discriminative, cognitive-evaluative, and motivational-affective aspects of pain (e.g. SI, ACC, insula, PFC)(Bushnell et al., 2013; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Ji et al., 2018; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021). Sensorimotor cortical plasticity appears to be especially influential in the adaptation of sensorimotor behavior during learning of novel sensorimotor skills or following peripheral manipulations, deafferentation, noxious stimulation, and nerve injuries (Bushnell et al., 2013; Boadas-Vaello et al., 2017; Kuner and Flor, 2017; Omrani et al., 2017; Peters et al., 2017; Papale and Hooks, 2018; Da Silva and Seminowicz, 2019; Kuner and Kuner, 2021). While it is unclear as to the cause-effect relations between MI plasticity, altered somatosensory input, and modified sensorimotor behavior, the crucial role played by MI in processing somatosensory inputs (e.g. via SI) and driving and regulating muscle activity and movements and in the learning of sensorimotor tasks (Omrani et al., 2017; Peters et al., 2017; Papale and Hooks, 2018) suggests that the changes in MI and SI cortical activity are importantly involved in driving the altered sensorimotor activity noted in experimental pain studies in animals and also in experimental or clinical pain investigations in humans (see section 3.2.2.).

In the craniofacial sensorimotor system, trigeminal nociceptive primary afferent nerve fibers convey nociceptive signals via the trigeminal ganglion to the trigeminal brainstem sensory nuclear complex, notably its rostral components (e.g. subnucleus oralis) and particularly its caudal components (e.g. the trigeminal subnucleus caudalis, also known as the medullary dorsal horn), and to adjacent upper cervical dorsal horn. From here, the signals are passed to motoneurons in the brainstem motor nuclei (e.g. trigeminal motor nucleus) and to neurons in nociceptive circuits and pathways in brainstem and higher areas of the CNS comparable to those noted above for spinal nociceptive signals (Sessle, 2006; Chichorro et al., 2017; Shinoda et al., 2019; Chung et al., 2020; Sessle, 2023). And like the spinal sensorimotor system, these nociceptive circuits and pathways are subject to descending modulation from higher CNS areas, sex differences exist in some of their features, and the pathways and circuits may express plastic changes following noxious stimulation or other peripheral manipulations (e.g. trimming or extraction of teeth, nerve injury) and in association with the acquisition of novel sensorimotor skills (Cairns, 2007; Avivi-Arber et al., 2011; Arce-McShane et al., 2014; Cairns et al., 2014; Chichorro et al., 2017; Avivi-Arber and Sessle, 2018; Yao and Sessle, 2018; Shinoda et al., 2019; Chung et al., 2020; Tashiro and Bereiter, 2020; Sessle, 2021, 2023). Furthermore, like the spinal sensorimotor system, the pain-related plastic changes in the CNS may result in altered sensorimotor behavior through changes to descending pathways such as those from SI and MI that influence brainstem motoneurons and/or through changes to descending pathways contributing to the modulation of central sensitization processes of nociceptive circuits within the trigeminal brainstem sensory nuclear complex and which can influence trigeminal motoneuron activity (Sessle, 2006, 2011a; Chichorro et al., 2017; Avivi-Arber and Sessle, 2018; Shinoda et al., 2019).

3.2.2. *Human studies*

Many of the CNS areas involved in the multi-dimensional experience of pain and its modulation in acute and chronic pain states in the spinal and craniofacial somatosensory systems in humans are generally comparable to those outlined above in animal models, and many of these areas are also involved in motor control (Picard and Strick, 1996;

Moriarty et al., 2011; Sessle, 2011b; Bushnell et al., 2013; Wager et al., 2013; Nguyen et al., 2014; Cona and Semenza, 2017; Kuner and Flor, 2017; Malfliet et al., 2017; Avivi-Arber and Sessle, 2018; Rolls, 2019; Sessle, 2019; van der Miesen et al., 2019). The CNS areas include the thalamus, insula, ACC, PFC, SI, SII, MI, supplementary motor area (SMA), and PAG. Machine learning analyses have identified a pattern of fMRI activation of some of these CNS areas during acute noxious stimulation, and this pattern may constitute a neurologic pain signature as it has been shown, for example, to have high sensitivity and specificity for discriminating between noxious and non-noxious heat stimuli in healthy individuals (Wager et al., 2013; van der Miesen et al., 2019). Machine learning approaches have also been applied to the analyses of brain activity in chronic pain patients with a view to develop biomarkers for pain (van der Miesen et al., 2019). Many of these CNS areas also are components of what has recently been viewed as a 'pain connectome' which reflects the spatiotemporal set of brain network communications subserving all aspects of the pain experience including sensorimotor responses (Bushnell et al., 2013; Kucyi and Davis, 2015; Borsook et al., 2018).

The involvement and functional organization of the various networks in the pain connectome can change during the experience of pain and this may contribute to the inter-individual variability in pain perception and pain-related motor output changes (see section 3.1.2.). For example, the communications between these networks may fluctuate with the level of the subject's attention to the pain, the transition from acute to chronic pain appears to be associated with a shift from CNS networks involved in the sensory-discriminative aspects of pain to networks involved in motivational-affective and cognitive-evaluative aspects, and there is considerable inter-individual variability in terms of pain-predictive weighting within CNS areas processing pain and sensorimotor behavior related to experimental noxious thermal stimulation (Bushnell et al., 2013; Kucyi and Davis, 2015; Kohoutová et al., 2022). Some of this variability may also relate to the sex differences which have been identified in structural and/or functional alterations in several CNS regions in both experimental pain subjects and chronic pain patients (Gupta et al., 2017; Fauchon et al., 2021; Osborne and Davis, 2022). For example, there is evidence that several chronic pain conditions exhibit sex-specific brain changes in a number of CNS areas including sensorimotor (e.g. sensorimotor cortex, basal ganglia), salience (ACC, anterior insula), and limbic (e.g. amygdala, hippocampus) networks (Gupta et al., 2017; Osborne and Davis, 2022).

Studies in the spinal sensorimotor system of humans have, like the studies in animal models, also revealed evidence of neuroplasticity and/or glioplasticity in association with pain or other peripheral manipulations as well as with learning, and it is notable that these plastic changes are associated with altered sensorimotor activity. For example, changes in human brain structure (e.g. in MI) have been identified in various behavioral interventions including motor skill acquisition (Karni et al., 1995; Wenger et al., 2017), and there is evidence that the cellular mechanisms of synaptic plasticity identified in animal models of learning can also occur in MI and some other areas of the human brain (e.g. hippocampus, temporal cortex) (Mansvelder et al., 2019). In the case of pain, acute experimental noxious stimulation of tissues supplied by spinal nerves produces for example a reorganization of the sensory and motor representations of limb, neck, and back muscles within the SI and/or MI as demonstrated through fMRI, TMS, and/or electroencephalographic studies (Hodges and Tucker, 2011; Burns et al., 2016; Sanderson et al., 2021). Chronic pain states in humans are also associated with structural and functional changes in many cortical areas and several other CNS regions in comparison with control. Findings of neuroplasticity in chronic pain patients have included structural and functional changes in CNS areas of patients suffering from low back pain, complex regional pain syndrome, fibromyalgia, rheumatoid arthritis, post-amputation pain, and irritable bowel syndrome. These changes are exemplified in the structural and functional reorganization reflected in cortical representation shifts (e.g. in MI, SI, SII, insula, ACC), changes in grey-matter volume (e.g. in MI, SI, ACC, PFC, hippocampus, thalamus), changes in resting state and pain-evoked functional connectivity (e.g. between regions of the default mode network which includes posterior cingulate cortex, medial PFC, lateral parietal lobe, medial temporal lobe), and changes in structural integrity (e.g. in PFC, and basal ganglia) (Hodges and Tucker, 2011; Tsao et al., 2011; Bushnell et al., 2013; Baliki et al., 2014; Kuner and Flor, 2017; Schabrun et al., 2017; Chang et al., 2018). Other examples include alterations in glial cell activity (e.g. in SI, thalamus), impairments in descending inhibitory control (e.g. in ACC, PAG), and neurochemical changes such as alterations in glutamate, γ-aminobutyric acid, and *N*-acetyl aspartate (a neuronal marker) levels and opioid receptor binding (e.g. in frontal cortices or forebrain of patients with neuropathic pain, low back pain or fibromyalgia) (Bushnell et al., 2013; Loggia et al., 2015; Kuner and Flor, 2017).

Many of these plastic changes in brain regions involved in pain control as well as cognitive-evaluative or motivational-affective functions or sensorimotor behaviors in chronic pain patients in particular, are likely to reflect a maladaptive plasticity (or malplasticity) which refers to plasticity that is likely to disrupt or compromise the normal functions of the CNS areas involved; in the case of chronic pain patients, maladaptive plasticity may lead to disrupted or compromised cognitive-evaluative and motivational-affective functions and sensorimotor behaviors as well as disrupt the ability of the brain to modulate pain experience (Borsook et al., 2013; Bushnell et al., 2013; Kucyi and Davis, 2015; Parker et al., 2016; Lin, 2014). Indeed, these various functions are known to be severely disrupted in chronic pain patients (Schweinhardt and Bushnell, 2010; Moriarty et al., 2011; Borsook et al., 2013; Bushnell et al., 2013; Kuner and Flor, 2017). There is also recent evidence in a variety of chronic pain conditions for associations between maladaptive cognitive and affective factors (e.g. high levels of pain catastrophizing) and the structure and function of a number of CNS regions including those involved in pain processing, emotion, stress, and sensorimotor activity (Malfliet et al., 2017; Vachon-Presseau, 2018; Malfliet et al., 2019).

Consistent with the spinal literature outlined above and findings in animal models, studies of craniofacial sensorimotor function or pain in humans have also provided evidence for CNS plastic changes associated with manipulation of craniofacial afferent inputs (e.g. peripheral nerve block, tooth loss, implant placement), learning of new motor skills, and acute experimental or chronic clinical pain (Avivi-Arber et al., 2011; Avivi-Arber and Sessle, 2018; Gustin et al., 2011; Mills et al., 2018; Moayedi et al., 2011; Sessle, 2006, 2019; Lin, 2014). These include changes in craniofacial MI and SI cortical activity which are important in driving the altered sensorimotor behavior noted with manipulation of craniofacial afferents, and in experimental or clinical pain investigations in humans (Sessle et al., 2005; Sessle, 2006; Yan et al., 2008; Avivi-Arber et al., 2011; Sessle, 2011b; Luraschi et al., 2013; Avivi-Arber and Sessle, 2018; Sessle, 2019). For example, changes in sensorimotor cortical activity have been noted in association with the significantly improved masticatory function occurring in patients receiving renewed complete dentures (Luraschi et al., 2013) and with the enhanced tactile discriminative abilities and masticatory motor function in patients with implant-supported prostheses (Yan et al., 2008). In other studies, fMRI or TMS investigations of participants as they learned a novel orofacial sensorimotor task (Boudreau et al., 2007; Boudreau et al., 2010; Arima et al., 2011) have revealed sensorimotor cortex plasticity occurring with behavioral task learning and notably, both the plasticity and the learning could be disrupted in the presence of acute experimental craniofacial pain. Furthermore, some craniofacial clinical pain conditions such as TMD, trigeminal neuropathic pain, or headache manifest evidence for glioplasticity and/or neuroplasticity in CNS areas involved in sensorimotor behaviors, pain modulation or cognitive-evaluative function (Gustin et al., 2011; Mills et al., 2018; Moayedi et al., 2011; Ye et al., 2021; Lin, 2014). As noted above for the spinal sensorimotor system, many of these plastic changes in the structure and function of

these CNS areas in chronic craniofacial pain patients are likely to be maladaptive and may disrupt or compromise normal nociceptive processing and cognitive-evaluative and motivational-affective functions and sensorimotor behavior.

3.3. Psychosocial factors that influence pain-sensorimotor interactions

3.3.1. Animal studies

In the spinal and craniofacial sensorimotor systems, there is much evidence that psychosocial factors can influence pain and pain-sensorimotor interactions and underlying mechanisms. Significant associations have been demonstrated in acute or chronic pain animal models between markers of some psychosocial features, such as stress, anxiety, depression, pain-related fear, or changes in cognitive processing and nociceptive processing or pain-related sensorimotor behaviors (Ford et al., 2008; Butler and Finn, 2009; Mutso et al., 2012; Okamoto et al., 2012; Jennings et al., 2014; Olango and Finn, 2014; Corcoran et al., 2015; Ferdousi and Finn, 2018; Nakatani et al., 2018). It is notable that these associations can be bidirectional (e.g., pain *per se* may be a stressor, and stress can influence pain; cognition can influence pain, and pain can influence cognition) and can vary between males and females, between individuals, and with changes in environmental and other conditions (Butler and Finn, 2009; Jennings et al., 2014; Olango and Finn, 2014; Bartley and Fillingim, 2016). There is also evidence that the effects that psychosocial factors have on pain-sensorimotor interactions are not limited to the neural and non-neural processes underlying these interactions because some animal models have shown that, independently of pain, high scores on measures of depression or stress are associated with altered structure of the musculoskeletal tissues as well as deficits in sensorimotor control (Yirmiya et al., 2006; Bab and Yirmiya, 2010; Azuma et al., 2015; Wang et al., 2017; Fernández et al., 2018). Psychosocial factors also include other influences such as environmental factors (discussed in section 3.4.1.), and the structure and function of musculoskeletal tissues are subject to environmental influences such as the extent to which a muscle is exercised or its use avoided (e.g. after a painful serious injury) (Baldwin and Haddad, 2001; Wisdom et al., 2015; Gao et al., 2018; Sartori et al., 2021). Such possible changes to the musculoskeletal tissues from psychosocial factors alone may thereby influence how the sensorimotor system responds to nociceptive afferent inputs and pain.

Stress is the most widely studied psychosocial variable in these animal models of pain in both spinal and craniofacial sensorimotor systems, and it has complex effects on nociceptive mechanisms and pain-related behaviors. Several factors can influence whether the stressor results in analgesia or hyperalgesia, and/or the magnitude of these pain-modulatory effects, as assessed through the effects on pain-related sensorimotor behaviors; these factors include the type of physical or psychological stressor (e.g. footshock, repeated forced swim stress conditioning, or social conflict, isolation or defeat), its intensity and duration, and the sex of the animal (Butler and Finn, 2009; Jennings et al., 2014; Meloto et al., 2014; Olango and Finn, 2014; Corcoran et al., 2015; Ferdousi and Finn, 2018; Martin et al., 2019; Mogil, 2020; Sessle, 2021; Sadler et al., 2022). Anxiety-like and/or depressive-like sensorimotor behaviors can also be evoked in some rodent stressor models (e.g. repeated forced swim stress conditioning, repeated social defeat, repeated cold stress, chronic mild stress, changes in social interactions). Enhanced anxiety in these models is considered to be reflected in significantly lower scores on the elevated-plus-maze test, and the open-field test in comparison with sham-stressed animals and is typically associated with hyperalgesia to noxious stimulation (Jennings et al., 2014; Olango and Finn, 2014). Some studies of repeated forced swim stress conditioning have demonstrated reductions in struggling times that may reflect a behavioral despair and may model depression (Quintero et al., 2000; Olango and Finn, 2014), and like the rodent models of anxiety, these depression models may also demonstrate hyperalgesia to noxious stimuli and manifest as changes to motor responses (Jennings et al., 2014).

In the spinal sensorimotor system, short-duration, intense stress typically results in stress-induced analgesia (SIA) that has protective or survival value as it is part of the fight-or-flight response. In animal models, SIA usually manifests as diminished pain-like sensorimotor behaviors (e.g. higher tail flick latencies) to noxious stimuli in comparison with control (Ford and Finn, 2008; Butler and Finn, 2009; Sadler et al., 2022). On the other hand, prolonged or repeated exposure to physical or psychological stress is usually associated with stress-induced hyperalgesia (SIH) manifesting as enhanced pain-like sensorimotor behaviors to noxious stimuli (e.g. algesic chemical application) in comparison with control animals not subjected to these stressor paradigms (Butler and Finn, 2009; Jennings et al., 2014; Olango and Finn, 2014; Corcoran et al., 2015; Ferdousi and Finn, 2018). These sensorimotor behavioral changes induced by noxious stimuli during prolonged or repeated stress include reductions in latency and/or changes in the number or duration of a pain-related motor response (e.g. increases in hindpaw withdrawal/lift, hindlimb licking, jumping behavior, or tail flick; decreases in grip force) (Imbe et al., 2006; Bardin et al., 2009; Jennings et al., 2014). An important observation from many of these studies is that the sensitivity to SIA and SIH (quantified in terms of changes to the sensorimotor responses to noxious stimuli) can vary between individuals, animal strains, pain models, and with age, sex, and nutrition of the animal, and can also be influenced by environmental factors such as prenatal stress, animal housing room characteristics, and sleep disruption (Butler and Finn, 2009; Jennings et al., 2014; Miguez et al., 2014; Olango and Finn, 2014; Corcoran et al., 2015; Sadler et al., 2022).

Changes in pain-like behavior in the spinal sensorimotor system also occur in animal models of anxiety and depression. Noxious stimulation in these animal models of anxiety or depression typically evoke hyperalgesia manifesting as enhanced motor responses to the noxious stimulation (e.g. reductions in latencies and/or increases of motor activity such as hindpaw lifting or licking or flicking, or writhing responses) compared to control rats receiving the same noxious stimulation (Jennings et al., 2014; Baptista-de-Souza et al., 2015). It is notable that the Wistar-Kyoto (WKY) rat in comparison with some other rat strains naturally displays increased levels of anxiety-like behavior (Olango and Finn, 2014), reduced hot plate response latencies, enhanced formalin-evoked pain-like motor behavior (Olango and Finn, 2014), and increased visceromotor responses to colorectal distension in colons sensitized with low concentrations of acetic acid (Gunter et al., 2000). The WKY rat also displays increased levels of depression-like behavior compared to other rat strains (e.g. the Wistar strain) (Zeng et al., 2008; Wang et al., 2017), and its immobility times (an index of depression) have been reported to be inversely related to the lowest mechanical threshold for a brisk paw withdrawal reflecting allodynia in a model of neuropathic pain; these inverse relations have not been observed in the Wistar rat strain (Zeng et al., 2008). These differences between some rat strains suggest that genetic factors may influence the effects that anxiety and depression may have on pain-sensorimotor interactions, a feature that is further considered in section 3.4.

Changes in pain-related sensorimotor behavior in comparison with control have also been noted in animal models of pain-related fear conditioning or of changes in cognitive processing. For example, sham-operated mice have been shown to extinguish a pain-related conditioned fear to a context paired with a noxious foot shock (as evidenced by a progressive reduction in freezing sensorimotor behavior over successive extinction trials), whereas mice subjected to a spared nerve injury do not exhibit this reduction but instead exhibit a significantly higher occurrence of the freezing behavior than the sham mice (Mutso et al., 2012; Meulders, 2020). In terms of cognitive processing, studies in animals have shown that attentional state or placebo can modulate nociceptive sensorimotor behavior (Seminowicz and Davis, 2007; Ford et al., 2008; Moriarty and Finn, 2014). For example, formalin-evoked nociceptive sensorimotor behaviors have been shown to be significantly reduced in

rats exposed to a novel object or environment in comparison with control rats; the lack of both aversive behavior and changes in plasma corticosterone levels appear to rule out increased levels of stress as the reason for the reduction in nociceptive behaviours (Ford et al., 2008; Moriarty and Finn, 2014).

In animal models of acute or chronic stress, anxiety, depression, or fear conditioning and in animal models of acute or chronic pain, changes in neural, glial (e.g. microglial activation), neurotransmitter, and cytokine processes and pathways reflecting glioplasticity and neuroplasticity have been documented in spinal and supraspinal regions (e.g. thalamus, PFC, PAG, ACC, hippocampus, and amygdala) (Mutso et al., 2012; Grace et al., 2014; Jennings et al., 2014; Olango and Finn, 2014; Wang et al., 2018; Hore and Denk, 2019; Sawicki et al., 2019; Sawicki et al., 2021). Chronic stressors have also been associated with the activation of bidirectional communication pathways between the peripheral immune system and the CNS which leads to enhanced chronic neuroinflammation and immune dysregulation and increased sensitivity to noxious stimuli, and may contribute to the etiology of chronic pain conditions and other disorders such as psychiatric disorders (Powell et al., 2013; Grace et al., 2014; Hodes et al., 2015; Hore and Denk, 2019; Grace et al., 2021; Sawicki et al., 2021). Taken together, these various observations indicate that stress, anxiety, and depression may be associated with enhanced central sensitization and can contribute to abnormal pain processing and sensorimotor responses in acute or chronic pain (Butler and Finn, 2009; Grace et al., 2014; Jennings et al., 2014; Olango and Finn, 2014; Wang et al., 2018; Hore and Denk, 2019; Sawicki et al., 2019; Sawicki et al., 2021).

Analogous observations to some of the above findings have also been made from comparable experiments in the craniofacial sensorimotor system. For example, in comparison with control, repeated stress has been shown to induce craniofacial hyperalgesia manifesting as increases in the number of nociceptive motor reflexes or flinching or rubbing behaviors, or to lead to decreases in the threshold for head withdrawal to noxious jaw muscle mechanical stimulation (Gameiro et al., 2005; Huang et al., 2011; Okamoto et al., 2012; Lin et al., 2019). Repeated stress has also been shown to result in enhanced masseter muscle EMG activity evoked by noxious (adenosine triphosphate, ATP) injection into the TMJ and enhanced excitability of TMJ-responsive neurons within the trigeminal subnucleus caudalis (Okamoto et al., 2012), and to contribute to the enhanced expression within trigeminal subnucleus caudalis of c-Fos (a marker of neuronal activity) evoked by masseter muscle noxious stimulation (Nakatani et al., 2018). These observations are consistent with the view that repeated psychosocial stress has a facilitatory effect on nociceptive circuits and their plasticity, likely mediated at least in part via changes in the balance of activity in descending pain-modulatory systems and resulting in enhanced sensorimotor behavior (Gameiro et al., 2005; Butler and Finn, 2009; Ossipov et al., 2014; Nones et al., 2017; Ferdousi and Finn, 2018). There is also some limited evidence suggesting that anxiety or depression may be associated with enhancement of pain-related sensorimotor responses in the craniofacial sensorimotor system (Huang et al., 2011; Okamoto et al., 2012).

3.3.2. *Human studies*

The evidence outlined above from animal models that psychosocial factors can influence pain-related processes and behaviors is consistent with analogous findings from many experimental and clinical pain studies in both the spinal and craniofacial sensorimotor systems of humans. Some of these studies have demonstrated significant associations between psychosocial factors (e.g. depression, anxiety, stress, pain-related fear, and some cognitive factors such as expectations, levels of attention, and pain catastrophizing) and nociceptive processing, pain experience, and/or motor activity, and with neural activity in sensorimotor, motivational-affective, and pain-modulatory CNS regions (e.g. (Bushnell et al., 1985; Leeuw et al., 2007; Alschuler et al., 2008; Campbell and Edwards, 2009; Henchoz et al., 2013; Jennings et al., 2014; Luijcks et al., 2016; Pakzad et al., 2016; Pinheiro et al., 2016; Harvie et al., 2017; Malfliet et al., 2017; Niles et al., 2018; Meulders, 2020; Sarabzadeh et al., 2020; Matheve et al., 2022)). As pointed out above for animal studies, other psychosocial factors such as environmental factors also show associations with nociceptive processing or pain-related sensorimotor behaviors, and they are also discussed in section 3.4.2. In addition, sensorimotor CNS areas (e.g. MI, SI, ACC, insular cortex) as well as other systems (e.g. the hypothalamic–pituitary–adrenal axis) may undergo plastic changes in association with psychosocial distress, resulting in dysregulations or alterations in the brains of chronic pain patients (Apkarian et al., 2011; Borsook et al., 2013; Bushnell et al., 2013; Hashmi et al., 2013; Jennings et al., 2014; Fillingim, 2017; Malfliet et al., 2017; Ferdousi and Finn, 2018; Vachon-Presseau, 2018; Timmers et al., 2019; Ellingsen et al., 2021; Sawicki et al., 2021). Again, as noted above for animal studies, there is evidence that psychosocial factors may also have an influence on the structure and function of musculoskeletal tissues *per se* since associations have been reported between pain-related fear, depression, or pain catastrophizing, and one or more of muscle sarcopenia, dynapenia, physical task performance, impaired muscle coordination, deteriorations in body composition and/or decreases in aerobic fitness levels (Verbunt et al., 2003; Leeuw et al., 2007; Chang et al., 2017; Walther et al., 2017; Bertoni et al., 2018; Wada et al., 2019; Paquet et al., 2022). Furthermore, in human as well as animal studies, there is evidence that chronic stress is associated with bone loss and osteoporosis (Bab and Yirmiya, 2010; Azuma et al., 2015).

In the spinal sensorimotor system, stress has been intensively studied in relation to its influence on pain in humans given the critical role of stress and stress-related affective disorders such as anxiety and depression in acute and chronic pain in humans (Davidson and McEwen, 2012; Jennings et al., 2014; Ferdousi and Finn, 2018; Timmers et al., 2019). Like investigations in animal pain models, many studies in human subjects have shown that exposure to an acute, robust, intense stress event leads to a reduction in pain responses (i.e. SIA). However, repeated exposure to physical or psychological stressors (e.g. stressful interview, mathematical task, threat of an electrical stimulus) typically results in SIH as evidenced by, for example, reductions in acute experimental pain thresholds or worsening of existing pain in chronic pain disorders (Jennings et al., 2014; Ferdousi and Finn, 2018; Timmers et al., 2019). There is also evidence of sex differences in the effects of stress on responses to noxious stimuli (e.g. on measures of temporal summation of acute pain) in healthy adults (Geva et al., 2023). Some studies have reported, although not consistently, that stress-inducing events lead to increased muscle activity (e.g. in the trapezius muscle) in healthy controls and also significantly greater increases in muscle activity in patients with some chronic pain conditions in comparison with healthy controls (Leistad et al., 2006; Nilsen et al., 2006; Westgaard et al., 2013; Zetterman et al., 2021). Sex differences have been reported in the neuroendocrine responses to stress and this may contribute to the sex differences in many stress-related pain disorders (e.g. fibromyalgia, irritable bowel syndrome, tension-type headache, TMD) that are more common in women than men (Bartley and Fillingim, 2016). Whether there are sex differences in the effects of stress on EMG activity in chronic pain does not appear to have been explored.

In addition to stress, pain-related fear of movement has been extensively studied in the spinal sensorimotor system. Classical and operant conditioning associated with pain-related fear of movement has been implicated as influencing sensorimotor behavior and associated EMG activity patterns (Harvie et al., 2017; Meulders, 2020). For example, in a classical conditioning paradigm in healthy pain-free individuals, a voluntary joystick hand movement in a direction which has been paired with an acute noxious wrist stimulus, has been shown to exhibit significantly increased velocity, acceleration, and accuracy of joystick movements, together with elevated auditory-evoked startle responses, than a voluntary joystick hand movement in the opposite direction and which has not been paired with the noxious stimulus

(Meulders et al., 2011; Karos et al., 2017; Meulders, 2020). A pain-related operant conditioning paradigm in healthy individuals has also revealed that individuals can generalize avoidance to novel joystick movements which have some similarities with pain-associated movements but which themselves have not been paired with noxious stimulation (Glogan et al., 2023). In chronic pain patients, there is some evidence that conditioning processes can become disrupted or maladapted (Schneider et al., 2004; Klinger et al., 2010; Glombiewski et al., 2015; Harvie et al., 2017; Meulders, 2020). For example, in comparison with healthy controls, some chronic pain patients (e.g. with low back pain or tension-type headache) may exhibit significantly greater conditioned muscle EMG activity (e.g. from trapezius and flexor digitorum muscles) in response to a conditioned stimulus (a visual image or a sound) that has been paired with a noxious unconditioned stimulus (Schneider et al., 2004; Klinger et al., 2010). Chronic pain patients, in comparison with healthy controls, have also been shown to exhibit fear-potentiated startle responses to a broader range of cues dissimilar to the threat cues; these findings suggest that patients with chronic pain may show reductions in their ability to learn selectively (Harvie et al., 2017; Meulders, 2020).

In terms of cognitive factors, it was noted above that cognition and pain may interact reciprocally: pain can influence cognition and cognition can influence pain. For example, many cognitive-related interventions, including placebo, nocebo, distraction, meditation, and mindfulness, may lead to reductions or modifications of experimental and/or clinical pain intensity and/or pain-related sensorimotor behaviors (Legrain et al., 2011; Moriarty and Finn, 2014; Colloca and Barsky, 2020). While there have been some inconsistent findings, there is evidence that tasks that distract attention (e.g. Stroop task execution requiring high cognitive load) may have an effect on experimental pain intensity and sensorimotor reaction time (Bushnell et al., 1985; Seminowicz and Davis, 2007; Van Ryckeghem et al., 2013; Silvestrini and Corradi-Dell'Acqua, 2023). There is also evidence that distraction leads to decreases in brain activity in the sensorimotor cortical areas of humans in response to nociceptive stimuli (Legrain et al., 2009). Pain catastrophizing is another cognitive factor that has received particular attention in recent years since it has been implicated as playing a role in the transition from acute to chronic pain. High pain catastrophizing individuals exhibit an excessive focus on pain (termed rumination), a tendency to exaggerate the threat of pain (magnification), and a sense of helplessness (Sullivan et al., 1995; Sullivan et al., 2001; Leeuw et al., 2007; Borsook et al., 2013). Across different musculoskeletal pain conditions, pain catastrophizing is not only related to pain severity, affective distress, muscle and joint tenderness, and adverse pain-related outcomes but also to sensorimotor measures such as pain-related disability, and escape or avoidance motor behavior (Edwards et al., 2006; Leeuw et al., 2007; Campbell and Edwards, 2009; Quartana et al., 2009; Velly et al., 2011; Wertli et al., 2014; Timmers et al., 2019; Zetterman et al., 2021). The various studies of the associations between psychosocial factors and pain-related sensorimotor activity have reported sometimes positive or sometimes negative correlated parameters, and associations have not been consistently observed. The variability in findings between studies may relate to the possible contribution to pain-sensorimotor interactions from other psychosocial factors as well as genetic and epigenetic factors (which are discussed below in section 3.4).

It was pointed out above that animal models of stress, anxiety, or depression and animal models of pain may exhibit plastic changes within spinal and supraspinal nociceptive processing and pain-related pathways, many of which influence sensorimotor behavior. Likewise, in humans experiencing chronic pain, evidence for brain plasticity in spinal nociceptive processing and pain-related pathways in association with some psychosocial factors has been provided through the demonstration of associations between measures of pain catastrophizing, fear avoidance, anxiety, or depression, and measures of brain structure or function in CNS areas involved in pain, motivational-affective, and cognitive-evaluative processing as well as in sensorimotor behavior (Campbell and Edwards, 2009; Quartana et al., 2009; Borsook et al., 2013; Malfliet et al., 2017; Ellingsen et al., 2021). Also noteworthy is the proposal that chronic pain is a continuous state of learning given that pain is repeatedly associated with adverse affective states and this repeated association may be related to disruptions in CNS structure and function which likely reflect maladaptive plastic changes in the CNS (Apkarian et al., 2011; Hashmi et al., 2013; Mansour et al., 2014; Barroso et al., 2021). For example, the shift from acute to chronic back pain is associated with a shift in brain activations from CNS areas involved in acute pain (e.g. insula, ACC) to CNS areas involved in emotion-related circuitry (e.g. amygdala, orbitofrontal cortex) (Hashmi et al., 2013; Vachon-Presseau et al., 2016). The structure and function of the hippocampus, an important limbic CNS area involved in learning and memory, also appears to be disrupted in chronic pain patients and maladaptive plasticity appears to be involved in this disruption (Apkarian et al., 2011; Mutso et al., 2012; Mansour et al., 2014; Vachon-Presseau et al., 2016; Barroso et al., 2021). Other disruptions likely reflecting a maladaptive plasticity also have been noted such as disruptions in white matter connections of the corticolimbic system (subserving a range of functions including emotion, behavior, memory, and motivation) that may predispose patients to chronic pain (Apkarian et al., 2011; Mutso et al., 2012; Mansour et al., 2014; Vachon-Presseau et al., 2016; Barroso et al., 2021).

It is also noteworthy that many psychosocial factors themselves (e.g. stressful experiential factors such as adverse early life experiences, stressful family environments, post-traumatic stress disorder) are associated with maladaptive plasticity in brain regions involved in social, cognitive, and emotional functioning (Davidson and McEwen, 2012; Popoli et al., 2012) which may influence subsequent nociceptive processing. Psychosocial factors may exert their effects on nociceptive processing via several mechanism, e.g. via modifications to the glioplasticity and neuroplasticity underlying central sensitization processes within nociceptive pathways, via altered processing within descending pain-modulatory pathways via altered brain network functional connectivity, or via altered corticolimbic and hypothalamic–pituitary–adrenal axis responses to pain (Quartana et al., 2010; Apkarian et al., 2011; Bushnell et al., 2013; Hashmi et al., 2013; Jennings et al., 2014; Malfliet et al., 2017; Vachon-Presseau, 2018; Wang et al., 2018; Timmers et al., 2019; Ellingsen et al., 2021; Sawicki et al., 2021). Maladaptive plasticity and maladaptive sensorimotor responses may result from such psychosocial influences. For example, stress-induced changes in nociceptive processing pathways may lead to maladaptive plasticity and changes that not only impair the individual's ability to suppress pain (Jennings et al., 2014; Vachon-Presseau, 2018; Timmers et al., 2019), but also may modify and even impair the individual's ability to select an optimal sensorimotor response to pain; as exemplified by evidence that stress may compromise the selection of flexible goal-directed behaviors in favor of inflexible, rule-governed behaviors (Vachon-Presseau, 2018; Timmers et al., 2019). These motor changes may include reduced force of contraction or avoidance of a movement and disruption of the most optimal motor unit activation pattern in the presence of pain. The effects on brain plasticity from psychosocial factors suggest that, during the experience of pain, individuals with high psychosocial distress may demonstrate alterations or dysregulations in activity in CNS areas involved in the generation or modulation of sensorimotor behavior as well as in motivational-affective and cognitive-evaluative functions, and that the CNS changes may contribute to some of the changes in EMG activity, movement and forces associated with pain and noted above (see section 3.1.2).

In the human craniofacial sensorimotor system, significant associations have also been demonstrated between some pain-related sensorimotor effects (e.g. significant changes in movements, forces, measures of EMG activity, or pain-related disability during pain) and psychosocial factors (e.g. a cognitive-related intervention such as operant conditioning reinforcement and cognitive factors such as pain

catastrophizing, as well as depression, anxiety, stress) in studies of acute experimental or chronic pain conditions (e.g. TMD) (e.g. (Flor et al., 1991; Turner et al., 2001; Brandini et al., 2011; Kunz et al., 2011; Akhter et al., 2014; Shimada et al., 2015; Amhamed et al., 2019; Moura Ferreira et al., 2020)). For example, in an operant conditioning paradigm, facial expression displays of pain have been shown to be sensitive to reinforcement (Kunz et al., 2011). In terms of cognitive factors, healthy individuals scoring higher on pain catastrophizing in comparison with individuals with lower scores exhibit some significantly greater changes in jaw movement kinematic features during repetitive open/close jaw movements during experimental masseter muscle pain in comparison with pain-free jaw movements (Akhter et al., 2014). In addition, patients with TMD exhibit enhanced scores on many psychosocial measures in comparison with healthy controls (Fillingim et al., 2011) and associations have been noted between pain-related disability and depression and somatization scores in TMD patients (Manfredini et al., 2010). Significant associations have also been noted with brain activity. For example, during acute experimental muscle pain (but not in the absence of pain), pain-catastrophizing scores have been reported to be significantly associated with the magnitude of the MRI-detected signal intensity change in CNS areas involved in multi-sensory integrative functions (e.g. PFC, cingulate cortex) and, when repetitive open/close jaw movements were also performed, in CNS areas involved in sensorimotor functions (e.g. trigeminal motor nucleus, posterior insula, cerebellar cortex, dlPFC and MI) (Henderson et al., 2016). Furthermore, this study also reported relationships between the variability in these open/close jaw movements and signal intensity in the dlPFC in the presence of pain. It appears that no studies have addressed the possible associations between fMRI changes in CNS areas, sensorimotor effects and psychosocial factors in chronic craniofacial pain (e.g. TMD, trigeminal neuropathic pain).

3.4. Genetic and epigenetic factors that influence pain-sensorimotor interactions

3.4.1. Animal studies

The role of genetic and epigenetic factors in pain-sensorimotor interactions has been largely overlooked in many studies in animals (and humans) of these interactions and in theories addressing the interactions. However, there is evidence from some studies in both the spinal and craniofacial sensorimotor systems that these factors are likely to play a critical role in not only influencing the experience of pain but also pain-sensorimotor interactions. By way of definitions for this review, genetics refers to genes and genetic variations that are irreversible. In contrast, epigenetics refers to reversible changes in gene expression without changes to the DNA sequence, and epigenetic patterns can be modified by psychosocial factors that include psychological stress, and lifestyle and environmental influences consisting of all biotic and abiotic factors that have a role in the survival, evolution, and development of the organism occupying the environment (Biology Online Dictionary). These environmental influences include an individual's level of physical activity, the nutritional characteristics of the individual's diet, and environmental pollutants. In terms of pain *vis-à-vis* environment and epigenetics, it is notable that environmental influences include the contextual factors within which pain behaviors and experience occur (Jensen, 2011; Karran et al., 2020; Nicholas, 2022), and that one set of environmental factors that is closely allied with epigenetics and its link with genetics is tissue injury or inflammation that represents a noxious stimulus that may or may not evoke pain depending on the individual's genetic makeup and psychosocial factors. It is also noteworthy that genetic, epigenetic, and such allied environmental factors affect not only the neural and non-neural processes underlying pain and pain-sensorimotor interactions but they also play fundamental roles in influencing or contributing to the psychosocial factors that can modulate pain and sensorimotor behavior (Davidson and McEwen, 2012; Polli et al., 2019; Nestler and Waxman, 2020).

Genetics, epigenetics, and allied environmental factors may also affect the very structure and function of the musculoskeletal components of an individual's sensorimotor system (Baldwin and Haddad, 2001; Marini et al., 2017; Chen et al., 2020; Huybrechts et al., 2020). Genetic factors for example influence the structure and function of skeletal tissues such as bones and teeth, as exemplified by sex differences and inter-individual differences in musculoskeletal features and also by disruption of bone growth and form in congenital disorders affecting long bones and/or jaw bones and teeth as a result of alterations in specific genes (Marini et al., 2017; Chen et al., 2020; Huybrechts et al., 2020). Genetic factors also play a crucial role in determining the composition, and distribution of the several different muscle fiber types comprising the contractile elements of muscle as well as other features of muscle structure and function, e.g. the signalling pathways involved in the control of muscle fiber types and contractile processes (Schiaffino, 2010; Verbrugge et al., 2018). Genetics also plays an important role in brain pathways and functions such as in influencing the function of the descending pain-modulatory and thermoregulatory pathways that are associated with a predisposition to high exercise capacity in rodent models (Kitazawa et al., 2021). Both bones and muscles are also affected by epigenetic and allied environmental influences, as evidenced in animal models by the effects on bones and muscular tissues of nutrition (e.g. protein intake, calcium intake), and exercise and motor function on the one hand and disuse on the other hand (Dubner et al., 1978; Baldwin and Haddad, 2001; Wisdom et al., 2015; Chalvon-Demersay et al., 2017; Upadhaya and Kim, 2020). For example, loading or unloading or reductions to the weight-bearing activity of a limb can result in the transformation of one muscle fiber type to another (Baldwin and Haddad, 2001; Wisdom et al., 2015), and experimental manipulation of jaw muscle use or altering the dentitional state can induce analogous plastic changes in jaw muscles (Kawai et al., 2009; Shah et al., 2019). Such versatility in muscle structure and function may contribute to the wide range of biomechanical and functional diversity in muscle fiber properties that are capable of subserving a complex range of functional demands (Baldwin and Haddad, 2001; Schiaffino, 2010; Wisdom et al., 2015). Collectively, findings in animal models point to genetic and epigenetic factors as well as allied environmental factors as contributing to the sex differences and the inter-individual variability in the form and thereby function of bones and their associated muscular tissues in both the spinal and craniofacial sensorimotor systems (Baldwin and Haddad, 2001; Schiaffino, 2010; Wisdom et al., 2015), and indicate that this variability in form and function needs to be recognized when considering pain-sensorimotor interactions and underlying processes.

In the spinal sensorimotor system, there is evidence that genetic factors have an influence on pain and pain-sensorimotor interactions and underlying mechanisms. Rodent sex and strain differences have been documented in pain-related anatomical, electrophysiological, and neurochemical features and these differences likely reflect differences between the sexes and strains in pain-related genes and polymorphisms (Mogil, 1999; Zeng et al., 2008; Mogil, 2012a; Zorina-Lichtenwalter et al., 2016; Mogil, 2020; Millecamps et al., 2023). For example, animal models have revealed differences between males and females and between some different strains of mice or rats in evoked nociceptive behavior (e.g. latencies of withdrawal reflex responses, number of writhing motor responses in response to noxious stimuli) (Mogil et al., 1999; Zeng et al., 2008; Mogil, 2012b; Olango and Finn, 2014; Mogil, 2020; Sessle, 2021). These various sex and strain differences in pain-related sensorimotor features in addition document that genetic factors may also contribute to the inter-individual differences in pain sensorimotor behaviors in the animal model studies noted above.

Epigenetic factors influencing gene expression are also involved in pain and pain-sensorimotor interactions in the spinal sensorimotor system. These changes involve histone acetylation, DNA methylation, and RNA interference, and result in alterations in cellular development and function (Buchheit et al., 2012; Descalzi et al., 2015; Géranton and Tochiki, 2015; Polli et al., 2019). In the context of pain, epigenetic

factors play a role in regulating genes involved in several processes including inflammatory cytokine expression, receptor expression levels at nociceptive neuronal synapses in the spinal dorsal horn, and descending pain-modulatory systems (Buchheit et al., 2012; Descalzi et al., 2015; Géranton and Tochiki, 2015; Geng et al., 2021). Epigenetics may regulate the expression of genes involved in plasticity and peripheral and central sensitization processes in the spinal dorsal horn and supraspinal CNS regions in animal models of nociceptive, inflammatory, or neuropathic pain and, given the close interrelations between the nociceptive and sensorimotor systems, these influences are thereby likely to play a role in pain-related sensorimotor behaviors (Buchheit et al., 2012; Denk et al., 2014; Bai et al., 2015; Descalzi et al., 2015; Polli et al., 2019; Sessle, 2021; Zhou and Verne, 2022). For example, stress-induced visceral hypersensitivity, quantified as the number of abdominal contractions in response to noxious colorectal distension, can be attenuated by a potent histone deacetylase inhibitor, thus supporting a role for epigenetic influences in these motor effects (Tran et al., 2013; Zhou and Verne, 2022). Moreover, epigenetics may play a role in the sex differences in pain and pain-sensorimotor behavior. For example, sex differences have been shown in the epigenetic processes associated with the improvement of low back pain-related behaviors during exercise in a low back pain mouse model (Kawarai et al., 2021), and with the increases in visceromotor responses to colorectal distention following early life stress in rats (Louwies and Greenwood-Van Meerveld, 2020). These sex differences in epigenetic processes associated with pain-related sensorimotor features suggest that epigenetic factors may also contribute to the inter-individual differences in pain-sensorimotor behaviors in the animal model studies noted above.

Epigenetic mechanisms are also increasingly thought to play a crucial role in animal models of acute or chronic pain involving the spinal sensorimotor system through the linkage between gene expression and environmental changes such as injury, inflammation, and diseases, as well as stressors, toxins, and dietary features (Bai et al., 2015; Descalzi et al., 2015; Géranton and Tochiki, 2015; Polli et al., 2019). Injury, inflammation, and diseases are the environmental inciting events for most acute and chronic pains and accompanying sensorimotor behaviors, but a host of other environmental factors has also been shown to be important in the pain experience and behavioral responses including nociceptive sensorimotor behaviors; these factors include features of the diet, animal housing or testing chamber, humidity, past painful experiences, levels of social interaction or physical activity, time of day at which behavior is assessed, sleep disruption, and the sex and other features of littermates as well as the investigator (Mogil, 1999; Chesler et al., 2002; Davidson and McEwen, 2012; Mogil, 2012a; Moehring et al., 2016; Alexandre et al., 2017; Parent-Vachon and Vachon, 2018; Lesnak and Sluka, 2020; Orock et al., 2021; Sessle, 2021; Sadler et al., 2022; Lesnak et al., 2023). There is also evidence that environmental factors can produce epigenetic changes in the expression of pain-related genes and biological pathways that may contribute to the sex and individual differences in pain expression and pain-related sensorimotor behaviors (Polli et al., 2019; Mogil, 2020). For example, some models of thermal or visceral pain hypersensitivity have demonstrated that the effect of environmental influences (e.g. the nature of the testing chamber, or the presence of early life stress) on nociceptive sensorimotor behavior can be sex dependent (Mogil, 2020).

In animal models of acute or chronic craniofacial pain, there is some evidence for genetic and epigenetic and allied environmental factors as playing important roles in influencing pain experience and pain-related sensorimotor behavior (Xiao et al., 2016; Sessle, 2021, 2023). Genetic factors may contribute to the sex differences that have been well documented in reflex and more complex behaviors as well as in CNS nociceptive processes in animal models of craniofacial pain (Cairns, 2007; Cairns et al., 2014; Tashiro and Bereiter, 2020; Sessle, 2021). Studies using models of trigeminal neuropathic pain point to a role for genetic factors also in accounting for inter-individual variability in view of the findings of differences between genetically different rodent strains in craniofacial pain-like behavior including sensorimotor behavior (e.g. hypersensitivity, extra-territorial spread of sensitivity) and accompanying glioplasticity and neuroplasticity underlying central sensitization mechanisms (Zhang et al., 2014; Sessle, 2021). Strain differences in volumetric changes documented in sensorimotor and other CNS areas following tooth extraction (Avivi-Arber et al., 2017) implicate genetic factors in the inter-individual variability in dental pain or responses to other orofacial manipulations. There is also some limited evidence that epigenetic factors are involved in craniofacial nociceptive processes (Danaher et al., 2018; Bai et al., 2020; Fox et al., 2020; Sessle, 2021, 2023) and may contribute to the sex and inter-individual variability in pain and pain-related sensorimotor behavior. And like the spinal sensorimotor system, epigenetic processes may have a vital role in linking gene expression changes to environmental influences in the craniofacial sensorimotor system since many of the same environmental factors outlined above in animal models in the spinal sensorimotor system may also play a role in modifying measures of pain experience and pain-sensorimotor behavior as well as contributing to the sex and inter-individual variability in animal models of craniofacial pain (Sessle, 2021). For example, complete Freund's adjuvant-induced masseter muscle inflammation reflecting an environmental change can lead to global reductions in DNA methylation in the trigeminal ganglion, and several pro-nociceptive genes in the trigeminal ganglion may be subject to epigenetic modulation via DNA methylation (Bai et al., 2020). Furthermore, in accord with findings in the spinal sensorimotor system, there is evidence that genetic, epigenetic, and allied environmental factors may influence the psychosocial factors that themselves can influence pain and pain-related sensorimotor behavior in the craniofacial sensorimotor system (see also section 3.3) (Lyons et al., 2015; Sessle, 2021), thus adding to the complex array of interacting influences and processes by which pain and pain-related sensorimotor behavior may be expressed.

3.4.2. *Human studies*

In accordance with the findings in animal models, there is evidence that genetic and epigenetic factors are important in influencing pain experience and pain-sensorimotor interactions in humans and in accounting for the sex differences and inter-individual variability in pain and these interactions. Likewise, these factors have been shown to influence not only neural and non-neural processes underlying pain and its sensorimotor interactions and the psychosocial factors that can influence pain and sensorimotor behavior, but also the structure and function of the musculoskeletal components of spinal and craniofacial sensorimotor systems in humans, and thereby influence sensorimotor behaviors. For example, in humans many genes, genetic polymorphisms, and epigenetic factors have been shown to influence bone structure, metabolic activity, and skeletal muscle structure and function (e.g. muscle fiber type composition) (Ahmetov et al., 2012; Bianconi and Mozzetta, 2022; Hudson and Loots, 2013; Kitazawa et al., 2021; Landen et al., 2023; Maciejewska-Skrendo et al., 2019; Núñez-Álvarez and Suelves, 2022; Simoneau and Bouchard, 1995; Del Coso, 2021). These genes and polymorphisms are likely to play important roles in motor activity, such as for example in the highly characteristic motor activities of handwriting, handedness, gait, and chewing noted in individuals. Sex differences have also been identified in several biomechanical and neuromuscular features in some motor tasks (e.g. motor unit behavior, H-reflex excitability, fatiguability (Mendonca et al., 2020; Lulic-Kuryllo and Inglis, 2022)). Genetic factors alone, however, do not account for these features and their variability since, as in animal models, some environmental factors also contribute; these include the level of an individual's physical activity, dietary features (e.g. levels of essential amino acids, Vitamin D, physical characteristics of the diet), and other lifestyle aspects and stressors determined by the individual's social and physical environment (English et al., 2002; Rennie, 2005; Woda et al., 2006; Ahmetov et al., 2012; Davidson and McEwen, 2012; Popoli et al., 2012; Ozturk et al., 2013; Mangano et al., 2014; Wisdom et al., 2015;

Atherton and Smith, 2017; Bassett and Williams, 2018).

The influence of genetic, epigenetic, and allied environmental factors on pain and pain-sensorimotor interactions is especially evident in the spinal sensorimotor system of humans by the findings of sex and inter-individual differences in pain experience (Mogil, 2012a; Zorina-Lichtenwalter et al., 2016; Fillingim, 2017; Borsook et al., 2018; Mogil, 2020) and pain-related sensorimotor behaviors (Ge et al., 2005; Mylius et al., 2005; Falla et al., 2008; Mueller et al., 2020). In the case of genetic factors, there is evidence that they contribute not only to the sex differences that have been documented in some of the features of pain *per se* in acute or chronic pain states (Mogil, 2012a; Zorina-Lichtenwalter et al., 2016; Mogil, 2020), but also to some of the variability in the outcome measures of sensorimotor behavior in both experimental and clinical pain. For example, several genes have been shown to be associated with experimental or clinical pain features in one sex but not the other (Mogil, 2020). Further, acute experimental pain studies have shown that irrespective of noxious stimulus modality (e.g. electrical, cold, heat, pressure, chemical) or outcome measure (e.g. pain intensity/unpleasantness rating; pain threshold/tolerance; EMG responses), women are more sensitive to pain and/or exhibit a lower pain or nociceptive reflex threshold or tolerance level to pain than men (Mylius et al., 2005; Lautenbacher, 2008; Mogil, 2012b; Fillingim, 2017; Mogil, 2020). In addition, many chronic pain conditions are more common in females, and these include pain-related features expressed in the spinal sensorimotor system (Mogil, 2012b; Bartley and Fillingim, 2013; Fillingim, 2017; Mogil, 2020; Mueller et al., 2020). In addition to the sex differences documented in pain-related sensorimotor behavior (Ge et al., 2005; Mylius et al., 2005; Falla et al., 2008; Mueller et al., 2020) (see section 3.1.2.), sex-related differences have also been noted in brain structure and function across several chronic pain disorders affecting the spinal sensorimotor system (Gupta et al., 2017; Fauchon et al., 2021). Likewise, with regard to inter-individual variability, there is evidence in the spinal sensorimotor system of humans that genetic factors in the form of variations in gene expression and related genetic polymorphisms contribute to the wide inter-individual variability in acute pain sensitivity in response to noxious stimuli, in the expression of chronic pain features such as allodynia, hyperalgesia, and extra-territorial spread of sensitivity, in the variability in ascending nociceptive transmission and descending pain-modulatory signalling pathways, and in the susceptibility of individuals to psychosocial and other risk factors that may predispose an individual to chronic pain (Mogil, 2012b; Mogil, 2012a; Meloto et al., 2014; Zorina-Lichtenwalter et al., 2016; Fillingim, 2017; Borsook et al., 2018; Mogil, 2020). Associations have also been noted between racial/ethnic differences and pain sensitivity (Rahim-Williams et al., 2012; Fillingim, 2017). Given the close interactions between nociceptive and sensorimotor systems identified in this review, it is likely that these many genetically based variable features contribute to differences between individuals in pain-sensorimotor behaviors.

Variations in gene expression in acute or chronic pain and pain-related sensorimotor behavior in the spinal sensorimotor system are explained not only by gene polymorphisms but also by epigenetic processes (Descalzi et al., 2015; Polli et al., 2019; Ghosh and Pan, 2022). For example, changes in DNA methylation or microRNA (miRNA) expression (compared with healthy controls) have been shown in neuropathic pain, fibromyalgia, and irritable bowel syndrome where changes in miRNA expression have also been associated with visceral pain intensity (Bai et al., 2015; Polli et al., 2019; Ghosh and Pan, 2022). It is likely that epigenetics plays an important role in the sex differences and the variability between individuals in pain-sensorimotor behaviors given the evidence for epigenetic processes in pain-related plasticity and in changes in descending pain-modulatory pathways, both of which have been associated with changes in sensorimotor behavior (see section 3.4.1.). Epigenetic mechanisms may also contribute to biological processes whereby psychosocial factors such as fear and stress (e.g. early life adversity and psychological stress during development) play greater roles as risk factors for pain in some individuals more than others (Schouten et al., 2013; Polli et al., 2019). Epigenetic processes may for example enhance glucocorticoid release during stressful events; glucocorticoids have major effects on brain neuroplasticity and synaptic transmission, and with their prolonged release, glial-mediated neuroinflammation is enhanced and may facilitate central sensitization and pain (Schouten et al., 2013; Polli et al., 2019). These changes are likely to have effects on sensorimotor processing in view of the close interactions between the nociceptive and motor systems outlined above.

As in animal models, epigenetic processes link genetic and environmental influences in the human spinal sensorimotor system. Many environmental factors may influence pain and/or sensorimotor behavior. And as in animal models, environmental factors range widely in humans, and include the chemical composition and physical features of the diet, drugs of abuse, toxins, level of physical activity, training and fitness, past pain history, social stressors, sociocultural factors, adverse life circumstances, sleep disruption, and gender roles and expectations, to injury, inflammation, diseases, muscle atrophy, and other alterations of peripheral tissues which can lead to pain (Sanford et al., 2002; Wise et al., 2002; Davidson and McEwen, 2012; Finan et al., 2013; Fillingim, 2017; Bjørklund et al., 2019; Polli et al., 2019; Lesnak and Sluka, 2020; Sessle, 2021; Strath et al., 2022; Lesnak et al., 2023). While many of these factors have not been specifically studied in relation to pain-related sensorimotor behaviors in humans, some of these factors have been shown to contribute to the sex and inter-individual differences in pain sensitivity and sensorimotor behaviors noted above (Mogil, 2012b, 2020; Sawicki et al., 2021). It is clear that injury, inflammation, and diseases in humans, in accordance with findings outlined above for animal models, are the inciting environmental events for many acute and chronic pain conditions, and sensorimotor behaviors are an integral part of the pain experience induced by the environmental-inciting event producing nociceptive or non-nociceptive afferent activity that influences nociceptive circuits in the CNS. Environmental factors in humans can produce epigenetic changes in the expression of pain-related genes and biological pathways that may contribute to pain and pain-related sensorimotor behaviors and the variability between individuals in these behaviors (Meloto et al., 2014; Polli et al., 2019; Woods and Van Vactor, 2021). Many of these factors interact with each other in their effects; for example, environmental stress interacts with genetic factors to influence pain experience and the susceptibility to chronic pain conditions (Diatchenko et al., 2013; Meloto et al., 2014; Slade et al., 2015; Fillingim, 2017).

Consistent with features noted above for the human spinal sensorimotor system, experimental or clinical pain studies have documented some limited evidence that genetic, epigenetic, and environmental factors can influence pain and pain-sensorimotor interactions in the craniofacial sensorimotor system of humans (Cairns et al., 2001; Cairns et al., 2003; Svensson et al., 2003; Smith et al., 2011; Slade et al., 2015; Fillingim, 2017; Fox et al., 2020; Sessle, 2021). These include influences contributing to sex differences as well as to the variability between individuals in the effects that pain has on sensorimotor behavior (Ohrbach et al., 2011; Bhaskaracharya et al., 2015; Shimada et al., 2015; Amhamed et al., 2016; Maulina et al., 2018; Amhamed et al., 2019). In terms of genetic factors, they are linked to the well-documented sex differences in craniofacial pain *per se*, as well as in pain-related motor behavior. For example, experimentally induced acute pain is associated with significantly greater reflex jaw muscle EMG activity and pain intensity and lower pain thresholds and tolerance in women than men (Cairns et al., 2001; Cairns et al., 2003; Svensson et al., 2003). Several chronic pain states in the craniofacial region also have a female predominance, e.g. TMD, migraine headache, and some neuropathic pain conditions (Gatchel et al., 2007; Fillingim et al., 2009; Bueno et al., 2018; Sessle, 2021; Wu et al., 2021), and sex-related differences have also been noted in brain structure and function in migraine, a chronic pain disorder affecting the craniofacial sensorimotor system (Gupta et al., 2017). These various differences may underlie some of the sex

differences in evoked pain and associated sensorimotor behaviors noted above. The specific involvement of genetic factors in some of these sex differences in acute and chronic craniofacial pain conditions is supported by the evidence that some genetic associations with pain have been shown to be different between males and females, e.g. sex differences for single nucleotide polymorphisms of the catechol-O-methyltransferase (*COMT*) gene (encoding an enzyme that metabolizes catecholamines), or of the gene *(OPRM1)* encoding the μ-opioid receptor in some acute craniofacial pain phenotypes (Fillingim, 2017; Nascimento et al., 2019; Lim et al., 2021). There is also evidence of genetically based variability between individuals in trigeminal nociceptive and modulatory pathways in TMD and some trigeminal neuropathic pain conditions (Smith et al., 2011; Meloto et al., 2014; Zorina-Lichtenwalter et al., 2016; Fox et al., 2020; Lim et al., 2021) and variability between different TMD patients in *COMT* gene encoding that can also contribute to the variable effects that psychosocial risk factors (i.e. stress) have on the development of TMD (Slade et al., 2015).

As in the spinal sensorimotor system, the sex differences and the inter-individual variability in the craniofacial sensorimotor system in relation to pain appear to involve not just genetic factors but a specific mix of genetic, epigenetic, and allied environmental factors in an individual's sensorimotor system (Maixner et al., 2011; Meloto et al., 2014; Chichorro et al., 2017; Fillingim, 2017; Fox et al., 2020; Mogil, 2020; Sessle, 2021). While there are currently very limited human data on epigenetic and environmental influences on nociceptive sensorimotor processing and behavioral responses to pain in the craniofacial sensorimotor system, many of the observations made above concerning these influences in the spinal sensorimotor system likely also apply to craniofacial pain and sensorimotor responses (Meloto et al., 2014; Sessle, 2021). For example, several chronic craniofacial pains exhibit a female preponderance that likely reflects significant contributions from gene x environment interactions involving epigenetic factors which may contribute to the sex differences and the inter-individual variability in pain expression and pain sensorimotor interactions observed in these chronic craniofacial pain conditions (Ohrbach et al., 2011; Sessle, 2021). These epigenetic as well as environmental influences and related psychosocial factors may interact and represent risk factors for these conditions (Fillingim et al., 2011; Fox et al., 2020).

There is another clinically relevant "takeaway" from this brief overview of the influence of genetic, epigenetic, and allied environmental factors in pain and associated sensorimotor behaviors. The findings from studies in humans and animal models shed light on the variability between patients with chronic pain in the development, expression, and maintenance of their pain conditions and the contribution that genetic, epigenetic, and environmental factors may each make (Mogil, 2012a; Fillingim, 2017; Borsook et al., 2018; Sessle, 2021). Such insights have significant clinical implications for strategies to customize treatment for individual patients, an approach which is often overlooked in the management of patients in chronic pain, but which is now becoming an increased focus of research (Fillingim, 2017; Borsook et al., 2018). For example, the individual variations in motor effects noted above in human and animal studies exemplify where management strategies might be tailored to the changes in motor-related activity (both within the brain and within muscles) occurring in a patient in pain, just as the type of analgesic medication is tailored to the intensity of the pain experience.

4. Synthesis of findings in relation to underlying mechanisms and theories of pain-sensorimotor interactions, and a proposal of a new theory

This review has outlined findings from studies in animal models and humans that have revealed the features of pain-sensorimotor interactions, the neural circuits underlying the interactions, as well as the glioplasticity and neuroplasticity of these circuits that normally provide for transient or long-term adaptation to sensorimotor behavior in the presence of pain. The glioplastic and neuroplastic CNS changes, particularly in chronic pain states, reflect processes by which the CNS reorganizes to allow for adaptation and continued sensorimotor performance in the presence of pain. It has been also noted that genetic and epigenetic factors, along with some environmental factors, are at play, influencing not only the form and function of musculoskeletal tissues involved in sensorimotor behavior, but also pain-sensorimotor interactions and the underlying CNS circuits and their plasticity. These factors contribute as well to the sex differences and differences between individuals that may occur in pain *per se*, pain-sensorimotor interactions, and underlying mechanisms. Additional factors operating through CNS areas involved in the psychosocial aspects of pain also may exert powerful influences, in part through influencing the plastic changes within sensorimotor neural networks that occur in association with pain. This review also identified that, particularly in chronic pain, the neural circuits in some of these CNS areas may exhibit plastic changes that reflect a maladaptive plasticity that likely disrupts the normal functions of these brain regions underlying pain-sensorimotor interactions.

Can these various features of pain-sensorimotor interactions and the many biopsychosocial factors that influence them and their underlying mechanisms including glioplasticity as well as neuroplasticity be captured in a comprehensive conceptualization? While previous theories do draw particular attention to a specific factor or factors in contributing to pain-sensorimotor interactions (see section 2), none comprehensively addresses all the biological factors encompassing nociceptive processes, glioplasticity and neuroplasticity in the CNS, and genetic and epigenetic factors, plus psychological factors and the broad range of social factors that encompass environmental and cultural influences and that may be involved in pain-sensorimotor interactions. Nor do any of these theories clearly take into consideration the influences that some of these factors have on the form and function of the musculoskeletal tissues involved in sensorimotor behavior. A new, more comprehensive theory is proposed here that incorporates biological factors, encompassing nociceptive mechanisms, glioplasticity and neuroplasticity as well as genetic and epigenetic factors, that are integrated with psychological and social factors into a more comprehensive perspective of pain-sensorimotor interactions. The Theory of Pain-Sensorimotor Interactions (TOPSMI) states that ***pain is associated with plastic changes in the central nervous system (CNS) that lead to an activation pattern of motor units that contributes to the individual's adaptive sensorimotor behavior. This activation pattern takes account of the biological, psychological, and social influences on the musculoskeletal tissues involved in sensorimotor behavior and on the plastic changes and the experience of pain in that individual. The pattern is normally optimized in terms of biomechanical advantage and metabolic cost related to the features of the individual's musculoskeletal tissues and aims to minimize pain and any associated sensorimotor changes, and thereby maintain homeostasis. However, adverse biopsychosocial factors and their interactions may result in plastic CNS changes leading to less optimal, even maladaptive, sensorimotor changes producing motor unit activation patterns associated with the development of further pain.***

This new theory is based on the features of the biopsychosocial model of pain with the focus being on the sensorimotor aspects of the pain experience. The TOPSMI also acknowledges a role for the individual's musculoskeletal tissues involved in the sensorimotor behavior and defined by biological determinants (i.e. genetic and epigenetic factors) and influenced by psychosocial features of the individual. The theory proposes that the motor unit activation patterns adopted by an individual in pain or encountering a noxious stimulus will depend on the unique mix of biological, psychological, and social factors, and their interactions in that individual. These factors will determine the pain experience as well as how the sensorimotor system responds to and adapts (or maladapts) to the pain or nociceptive inputs induced by the noxious stimulus and the degree of adaptability of an individual's

sensorimotor system. Another feature of the theory is that, depending on the mix of biological, psychological, and social factors, different individuals will be on different parts of the spectrum of sensorimotor network plasticity and activation patterns that drive motor units. For example, one individual experiencing pain might exhibit a large range of options available for sensorimotor neural network plasticity and motor unit activation patterns without the development of further pain, whereas another individual experiencing pain may have fewer options available without the development of further pain and may transition to the worsening of pain or to the development of new pain. The theory emphasizes that "unfavorable" adverse biopsychosocial influences result in maladaptive plastic changes within the sensorimotor networks and the related circuits involved in the multiple dimensions of pain, and therefore effective management strategies should address combinations of targets that take account of the contributing biological, psychological, and social factors. The range of factors may help explain differences in sensorimotor changes during noxious stimulation or pain between sexes, between individuals, and between acute and chronic pain, and may also help explain the possible persistence of sensorimotor effects given that this maladaptive plasticity may not be readily reversible.

Fig. 3 provides a graphic representation of the TOPSMI and shows the sensorimotor neuronal outputs and the strategies for producing associated motor unit activation patterns (motor unit recruitments and/or firing rates) of 2 hypothetical individuals (A, B) encountering a noxious stimulus that may produce pain or experiencing existing pain in, for example, the leg or jaw muscles in response to a leg or jaw injury. Individual (A) has features reflecting a "favorable" mix of biopsychosocial factors (e.g. good anatomical form, genetic and epigenetic profile, sociocultural factors; low psychosocial distress) associated with adaptive glioplasticity and neuroplasticity in nociceptive, modulatory, and sensorimotor circuits. The interaction of these features (bidirectional vertical arrow) can elicit adaptive sensorimotor neuronal outputs allowing for one of several possible motor unit activation patterns to be adopted (blue vertical arrows 'a', 'b', 'c', Fig. 3). Strategic approach 'b' is adopted since it engages motor unit activation patterns associated with a level of biomechanical advantage and low metabolic cost coupled with pain minimization and homeostasis that is not offered at the same level by the other strategies; 'b' may also produce decreased recruitments and firing rates of those motor units that are normally recruited under pain-free conditions. The guiding principle determining the strategic

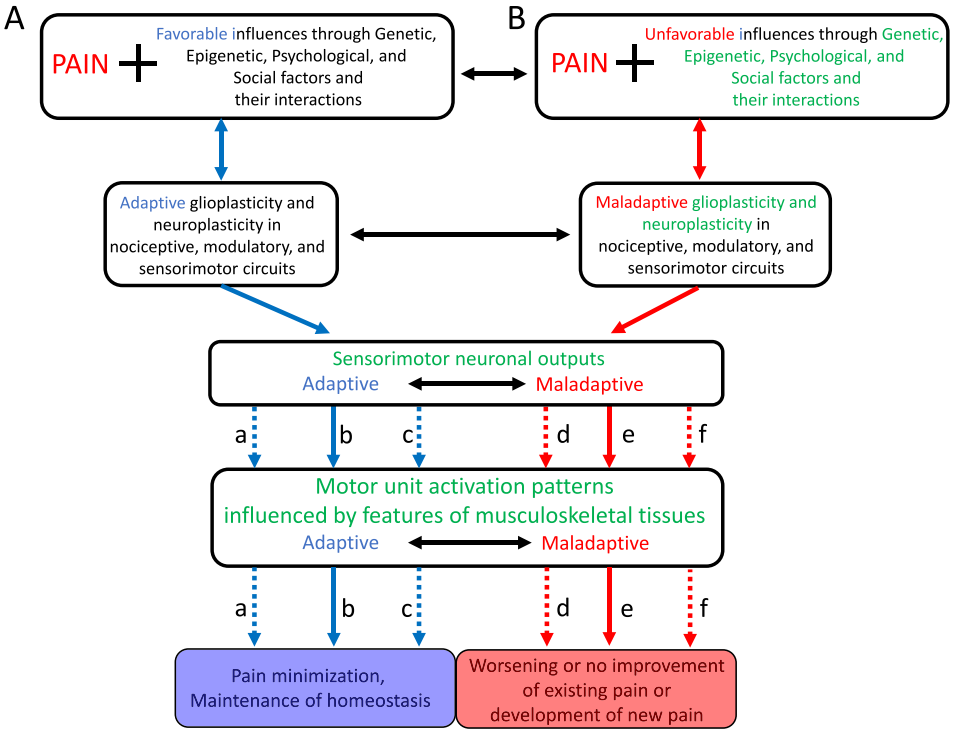

Fig. 3. The Theory of Pain-Sensorimotor Interactions (TOPSMI). The TOPSMI is shown in terms of the sensorimotor neuronal outputs and associated motor unit activation patterns for two hypothetical individuals (A, B) encountering a noxious stimulus that may produce pain or experiencing existing pain. Individual (A) has a "favorable" set of biopsychosocial factors (e.g. good anatomical form, genetic and epigenetic profile, sociocultural factors; low psychosocial distress), and their interaction (blue bidirectional vertical arrow) with adaptive glioplasticity and neuroplasticity in nociceptive, modulatory, and sensorimotor circuits elicits (oblique blue arrow) adaptive sensorimotor neuronal outputs producing adaptive motor unit activation patterns (blue vertical arrows, 'b'). This involves increased firing rates and recruitments of those motor units whose activation is associated with a level of biomechanical advantage and low metabolic cost coupled with pain minimization and homeostasis (blue box), and may also be associated with decreased recruitments and firing rates of those motor units that are normally recruited under pain-free conditions. Several other possible motor unit activation patterns ('a' and 'c' and their dotted vertical arrows are examples) may be available but are not utilized in individual (A) since they do not offer the optimal mix of biomechanical advantage and metabolic cost associated with the same level of pain minimization and homeostasis compared with approach 'b'. Nonetheless, one of these other available strategic approaches could be adopted in an individual with a different mix of favorable features and adaptive processes. Individual (B) in contrast has an "unfavorable" adverse mix of biopsychosocial factors (e.g. poor anatomical form, genetic and epigenetic profile, sociocultural factors; high psychosocial distress) that leads (oblique red arrow) to maladaptive sensorimotor neuronal outputs resulting not in strategies associated with the adoption of motor unit activation patterns that could lead to pain minimization and homeostasis, but rather to (red vertical arrows, 'e') motor unit activation patterns that result in no improvement and indeed there could be worsening of pain or even the development of new pain (red box). The dotted vertical arrows are examples ('d', 'f') of other possible maladaptive sensorimotor neuronal outputs that might be used by an individual with a different mix of unfavorable biopsychosocial factors. The bidirectional horizontal arrows indicate that an individual can shift from favorable to unfavorable and from adaptive to maladaptive, and *vice versa,* depending on the current mix and weightings of factors that an individual might be experiencing. The areas highlighted in green reflect possible targets for muscle pain management. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

approach and the associated motor unit activation patterns may be one that is directed towards pain minimization and maintenance of homeostasis, as previously proposed in several theories. This guiding principle may also take into account the evidence that pain-free motor unit recruitment patterns are likely to reflect the most optimal strategic approach in terms of biomechanical advantage and metabolic cost (Butler et al., 2014; Hudson et al., 2019)offered by the form and function of the individual's musculoskeletal tissues that are determined by genetic and epigenetic factors and psychosocial influences. Thus, one of the other available strategies (e.g. 'blue vertical dotted arrows a' or 'c', Fig. 3) could be adopted in an individual with a different mix of favorable features and adaptive processes if it offers pain minimization and homeostasis together with biomechanical advantage and low metabolic cost. Another feature of the model is that a particular mix of biopsychosocial factors in an individual, coupled with the introduction of, for example pain, may leave that individual with few (or no) adaptive sensorimotor neuronal output options, and instead maladaptive sensorimotor neuronal outputs may be adopted. Indeed, individual (B) in Fig. 3 has a mix of unfavorable biopsychosocial factors (e.g. poor anatomical form, genetic and epigenetic profile, sociocultural factors; high psychosocial distress) that "sets" the nociceptive, modulatory, and sensorimotor neural circuits to a maladaptive plasticity state which modifies and disrupts the adaptive glioplastic and neuroplastic changes that would "usually" or "normally" occur within these neural circuits during noxious stimulation or pain in the absence of these unfavorable factors. These malplastic changes also may interact with (red bidirectional vertical arrow) and reinforce the unfavorable psychosocial factors. Thus, the "usual" guiding principle governing motor unit activation (see above) no longer operates and maladaptive plasticity is driving the sensorimotor neuronal outputs. As a consequence, an approach (e.g. 'e', red vertical arrows, Fig. 3) is adopted in individual (B) that may result in no improvement or even worsening of the pain or the development of new pain. Other possible maladaptive sensorimotor neuronal outputs may be adopted (red dotted vertical arrows 'd' or 'f', Fig. 3) in an individual who has a different mix of unfavorable biopsychosocial factors and is in pain. Nonetheless, the bidirectional horizontal lines in Fig. 3 indicate that an individual could also shift from favorable to unfavorable and from adaptive to maladaptive and *vice versa* depending on the current mix and weightings of factors that the individual might be experiencing e.g. an individual's sensorimotor circuits could shift to maladaptive if the individual experiences markedly deteriorating psychosocial factors. Also at play could be variability in how different parts of a sensorimotor circuit might change in relation to pain or noxious stimulation, even for example in part of a jaw or leg muscle such that one part of a multipennate muscle could be driven by adaptive strategic approaches in response to noxious stimulation or existing pain, while another part of the same muscle could be driven by maladaptive approaches. Effective management therefore should address combinations of targets that take account of the contributing biological, psychological, and social factors, and Fig. 3 highlights in green those areas that potentially could be targeted.

5. Conclusions

The interactions between pain and sensorimotor behavior have been debated for many decades. The main theories in the previous century, the Vicious Cycle Theory (VCT) and the Pain Adaptation Model (PAM), have been shown to be too simplistic to explain all the relevant data sets that have been reported particularly in recent years. Other more recent theories have provided a broader framework for understanding many of the data sets available at the time of their publications. Since the formulations of these recent theories, there have been findings indicating that other features need to be considered in pain-sensorimotor interactions and these include biological factors encompassing nociceptive processes, glioplasticity and neuroplasticity in the CNS, and genetic and epigenetic factors, and psychological factors and a broad range of social factors that encompass environmental and cultural influences. Many of these factors can also influence the form and function of musculoskeletal tissues involved in sensorimotor behavior. To address these limitations, the Theory of Pain-Sensorimotor Interactions (TOPSMI) is presented. In general, it proposes that a range of adverse or unfavorable biopsychosocial factors can modify or disrupt the adaptive plastic changes that would "usually" or "normally" occur within sensorimotor neuronal networks during pain in the absence of these unfavourable factors. These unfavorable factors result in disruptive or maladaptive plastic changes that "set" the sensorimotor neural networks to a maladaptive activity state. Individuals can shift from favorable to unfavorable and from adaptive to maladaptive and *vice versa* depending on the current mix and weightings of factors that an individual might be experiencing. From this perspective, it becomes clear that management strategies directed towards simply treating the muscles in pain are insufficient since the muscles are the end point of a large and complex sensorimotor system that is influenced by many biopsychosocial factors, and so a more holistic approach needs to be considered. This new, more comprehensive theory also points towards consideration of treatment strategies customized to the individual, in line with the management approaches to pain proposed in the biopsychosocial model of pain.

CRediT authorship contribution statement

Greg M. Murray: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – review & editing. **Barry J. Sessle:** Supervision, Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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