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New perspectives on pain management in rehabilitation

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ABSTRACT

Introduction. Pain is a complex and debilitating experience. When pain lasts over three months it becomes chronic, outlasts normal tissue healing time and doesn't serve to protective function. Patients with chronic pain no longer exhibit peripheral tissue damage but continue to feel pain, suggesting an abnormal functioning of the somatosensory system. This process may be due to central sensitization (CS), neuroplastic changes that occur in pain related central networks and boost pain perception independent of peripheral neural activation. Non-invasive brain stimulation (NIBS) seems to reduce chronic pain by directly altering brain activity. Trasncranial direct current stimulation (tDCS), one of the most used NIBS techniques, seems to be efficacy in reducing chronic pain, when used alone or in combination with other treatments. Aim of this PhD project is to investigate efficacy of brain stimulation techniques on chronic pain, specifically due to temporomandibular disorders (TMDs) and low back pain (LBP). Furthermore, we would identify biomarkers related to chronic pain, using electroencephalography and pain threshold assessment in people with chronic orofacial pain.

Methods. In the first research project we proposed tDCS treatment in people with chronic pain due to TMDs. Stimulation was delivered for five consecutive days over primary motor cortex for 20 minutes a day with the intensity of 2mA. Subjects were evaluated before and after treatment and at one-month follow-up for pain perception and psychological symptoms. In the second research project tDCS was combined with group exercise treatment and proposed to people with chronic LBP. Stimulation parameters and assessment points were the same. In the third research project we evaluated people with orofacial pain due to TMDs using EEG recording and pain threshold assessment looking for CS signs.

Results. Our findings support the use of tDCS on patients with chronic pain due to TMDs. The majority of the sample had good results for pain intensity and depressive symptoms. One case, who had severe degenerative disease, did not report any beneficial effects after tDCS. Also in subjects with chronic LBP tDCS seems to be effective in ameliorating pain and psychological wellbeing, but the effects were evident only at one-month follow-up when combined with behavioural intervention. Reduced pain threshold and increased gamma activity in frontal and central brain areas were recorded in people with TMDs as chronic pain's biomarkers.

Discussion and Conclusion. NIBS can be used to reverse maladaptive changes that occur in chronic pain. In people with chronic pain due to TMDs or LBP, tDCS seems to be efficacy on symptoms intensity and pain-related quality of life. tDCS efficacy may be improved combining its top-down effects with a bottom-up approach. Brain modifications due to chronic pain and presence of CS mechanisms can be assessed using EEG. Abnormal EEG activity in central and frontal areas during pain threshold assessment may be recorded as CS signs in people with chronic pain. Interpretation of our findings needs to be confirmed by further studies on people with chronic pain.

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INTRODUCTION

Pain: Definitions, Epidemiology and Models

Pain is a complex and debilitating experience that involves people and clinicians that have to deal with it for assessment process and treatment delivering.

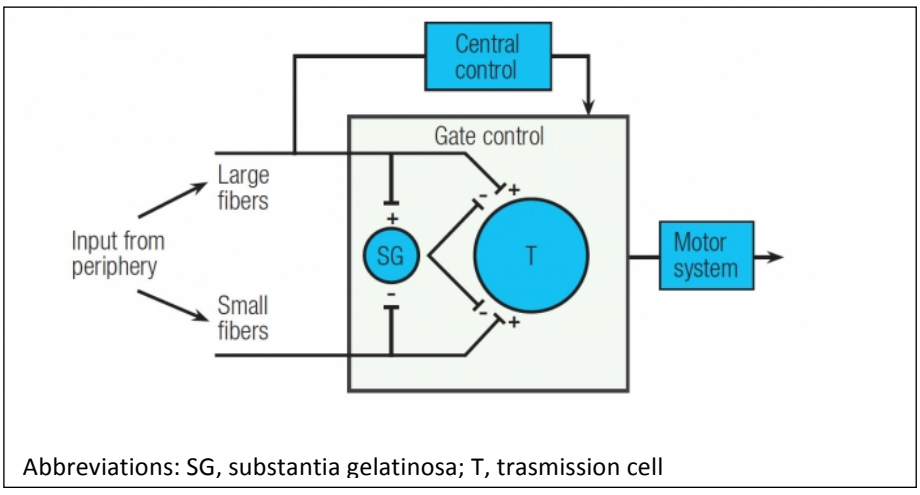
The term pain can refer to acute or chronic pain. The first is a symptom of present or potential tissue damage, with defined onset and duration. Acute pain works to protect the human body from tissue damage and can be adequately treated using conventional therapy (pharmacological or not). Chronic pain occurs also when tissue damage has already been solved and it doesn't serve to protective function. Pain is considered chronic when outlasts normal tissue healing time; impairment is not proportional to injury and occurs in absence of identifiable tissue damage. Normally clinicians classified pain as chronic when it lasts over three months (1); it's difficult to treat and interdisciplinary and bio-psycho-social approach to it is recommended.

The impact of pain in everyday life may go beyond the physical sensation that occurs following lesion to body structures and can affect cognitive and emotional field of a person. For this reason, the impact of pain on activity and participation should be evaluated when pain assessment is performed. Epidemiology of pain is a continuous challenge for clinician due to subjectivity of symptoms and absence of consensus about diagnoses and definitions. Pain conditions need to be studied from its onset at an early age. Pain study in children and adolescents gain great interest in recent years because it seems to be predictive of pain development in adult age, in addition to contribute to physical inactivity and other negative health behaviours (2–4). Most represented pain at a young age seems to be low back pain, headache, and abdominal pain (5). In adulthood the most represented pain is spinal pain and pain due to other musculoskeletal conditions, fibromyalgia and chronic widespread pain. Chronic pain affects 20% of people worldwide and the most common sites reported as sources of pain are the low back (30%), hip (25%), neck and shoulder (25%) and knee (24%) (6). Distress, demoralization and functional impairment often accompany chronic pain, making it a major source of suffering and economic burden. Early life factors as premature birth, very low birth weight and hospitalisation for a motor vehicle accident at young ages seem to be linked to chronic pain in adulthood (7). Advanced age, womankind, socio-economic deprivation and negative health behaviours are associated with higher prevalence of pain (8).

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (9). This definition not only coupled the sensory and emotional dimensions of the experience, but also recognised the association between tissue injury and pain (10). However, pain can be the result of tissue damage that involves nociceptors, but it can occur also without any lesion to body structures. Pain is

damage that involves nociceptors, but it can occur also without any lesion to body structures. Pain is subjective and multidimensional, involving not only the body unpleasant perception of pain but also the emotional experience linked to it.

Many changes occurred in definitions and interpretation of pain in the past years. Initially pain was explained as the only results of cutaneous stimulation of pain receptors ("specificity theory"). When this "nerve endings" were stimulated they produced pain sensation. However, this theory lapses when we thought, for example, to pain arising from a phantom limb, also without peripheral stimulation of pain receptors. The "pattern theory" integrates previous concepts with the idea of central pathways that transmit pain sensation to supraspinal structures. In 1965, Melzack and Wall developed the gate control theory of pain that summarized concepts from specificity and pattern theories (11) (Figure 1). Skin stimulation were transmitted to three specific system located in the spinal cord: the cells of the substantia gelatinosa in the dorsal horn, the dorsal-column fibers that project to the brain and the T cells, the first central transmission in the dorsal horn. Input from large-diameter and small-diameter fibers converges on the substantia gelatinosa that plays inhibitory effect on the T cell and on its function on neural mechanism activation like motor, sensory and autonomic response to pain. Melzack and Wall proposed that pain sensation was determined by interaction between these three structures. When the system is balanced there is no pain sensation. Input from small-diameters fibers inhibits the substantia gelatinosa neurons and the T cell "opens the gate" to the pain to supraspinal structures. An increase in excitatory input from large-diameter afference stimulates the substantia gelatinosa and results in "closing the gate" to pain perception. This theory has been criticised for a long time in the following years, but it was the first attempt to recognize the role of Central Nervous System (CNS) in pain phenomenon and opened the way to multidimensional treatment of pain, not only restricted to peripheral approach.



Abbreviations: SG, substantia gelatinosa; T, trasmission cell

Figure 1 The Gate control model, adapted from Melzack and Wall, 1965 (11)

Three years later, Melzack and Casey proposed a three-dimensional model of pain that comprised sensory discriminative aspects of pain, motivational affective and cognitive evaluative (12). The first component is the sensory component and is influenced primarily by the rapidly conducting spinal systems. The second is subserved by activities of the reticular and limbic structures that are influenced primarily by the slow conducting spinal systems. The latter, that provide cognitive evaluation of the input in terms of past experiences, is controlled by neocortical or higher CNS processes. All the three components interact with each other to provide the complex experience of pain.

In 1991, starting from the gate control theory of pain, Melzack proposed the neuromatrix theory (13) (Figure 2). The neuromatrix is distributed throughout many areas of the brain and comprises a widespread network of neurons that generates patterns and processes information that flows through it. The neuromatrix is initially genetically determined, then adapted on sensory inputs and personal attitude and experiences. Areas involved in pain experience are the thalamus, the cortex and the limbic system; this complex network produces output, the neurosignature, that projects to other brain areas for awareness of pain or motor output. The neurosignature is a fluid and plastic system modulated by sensory inputs, cognitive and emotional aspects of each other, and it produces customised output to every noxious stimulus. The theory of neuromatrix gives to the brain cortex a primary role in awareness of painful sensation but considers also the nociceptor activation following peripheral stimulus, the role of spinal and subcortical structures, in addition to many other neuronal and non-neuronal systems that influence pain experience. All these structures play a key role in sensory, cognitive and affective aspects of pain.

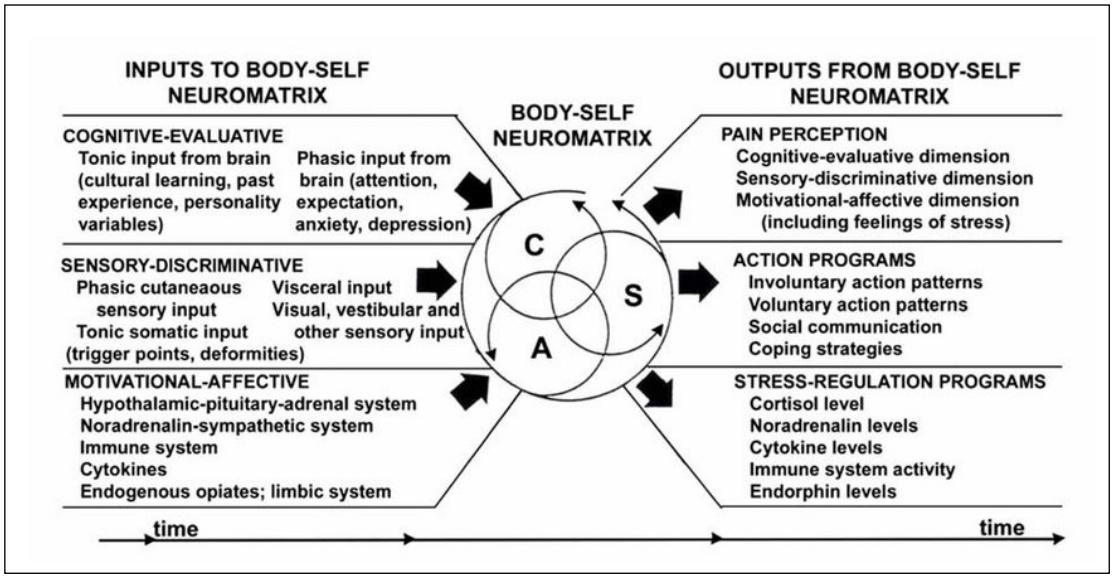
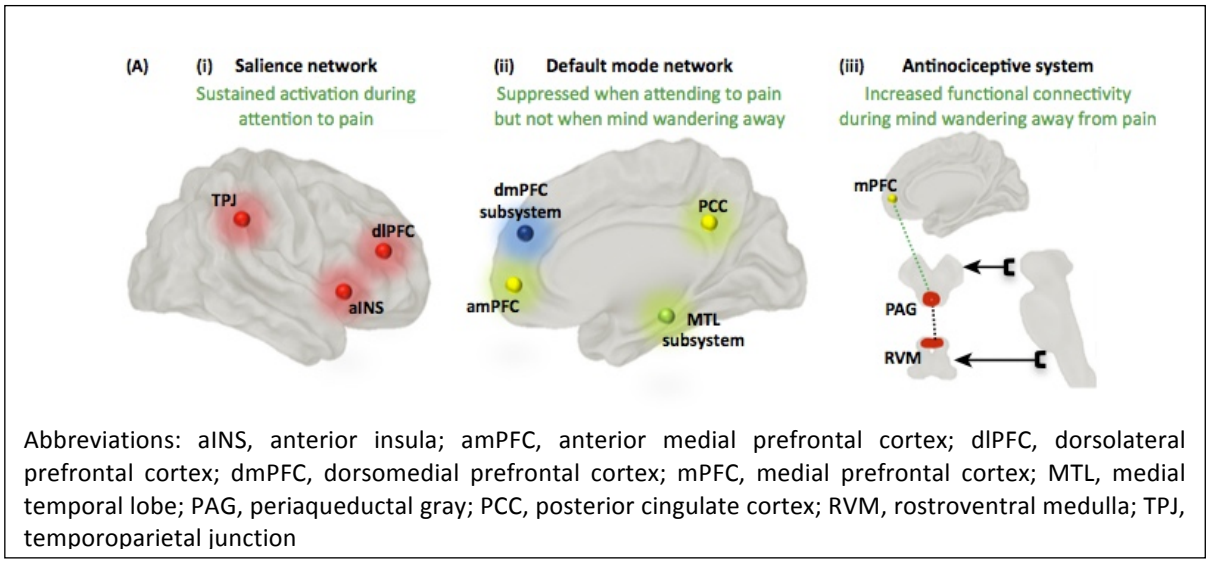


Figure 2 The Neuromatrix theory, adapted from Melzack 1991 (13)

In the following years the neuromatrix theory has been questioned by pain researchers. One of the most criticized aspects of this theory was the attribution of pain sensation and features to specific brain areas, while pain experience seems to emerge from the flow and integration between these areas and their activation in concert (14). In recent years attention shifts from brain areas involved to cognitive and attentional processes that characterized pain experience. Saliency of pain like a way to survive to immediate threat emphasises the role of attention in the study of all processes characterizing nociception. The whole brain-wide network, the connectome, include also pain- and attention-related circuits, and the connection between them is dynamic and spontaneously fluctuating in time. For this reason, pain starts to be considered a dynamic experience encoded by a "pain connectome", a network communication that represents integration of cognitive, affective and sensorimotor aspects of pain (15). Functional magnetic resonance imaging (fMRI) studies identified three key brain systems, and their dynamic interactions, involved in spontaneous attentional fluctuation toward and away from pain (16). One system is the salience network (SN): activity in this region is recorded during attention to pain. A second system, the default mode network (DMN) is activated when subject drives its attention away from the present sensory world. A third system, the antinociceptive system (AS), is characterized by modulatory descending pathways and is associated with pain modulation. The complex interaction between the three brain systems underlies new theories on nociception and attentional-sustained pain (Figure 3).



Abbreviations: aINS, anterior insula; amPFC, anterior medial prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; mPFC, medial prefrontal cortex; MTL, medial temporal lobe; PAG, periaqueductal gray; PCC, posterior cingulate cortex; RVM, rostroventral medulla; TPJ, temporoparietal junction

Figure 3 The dynamic pain connectome by Kucyi et al. 2015 (15)

Physiology of pain

Peripheral Nociceptive Pathways

Pain is widely mediated by activity of peripheral nervous system that participates in pain perception and transmission to the CNS. After an acute injury a cascade of events occurs in the site of lesion and in the whole body. Pain signal is mediated by nociceptors. All pain messages are driven to the CNS by thinly myelinated Aδ fibers and unmyelinated C fibers. A nociceptor is a sensory receptor that responds to noxious stimulation: its role is to convert mechanical, thermal and chemical energy into electrical sign and carry this information to the spinal cord. Cutaneous nociceptors are characterized by free nerve endings of Aδ fibers and C nociceptors that respond to mechanical and thermal stimuli, polymodal nociceptors for multiple noxious stimuli. Muscle and joint nociceptors are characterized by free nerve endings activated by capsular joint stretching or muscle pressure and ischemia. Visceral nociceptors are polymodal and they are triggered by distention. Some nociceptors are normally silent and are triggered by inflammatory mediators activated following tissue damage. Activity of nociceptors is sensitive to peripheral stimulation and can change in response to noxious stimulation on the basis of the state of the all the somatosensory system.

Central Nociceptive Pathways

The processing of nociceptive information to the CNS is mediated by three systems of neurons involved in transmission of painful sensation through primary afferent fiber, spinothalamic tract (STT) and thalamo-cortical neuron. At spinal level sensory fibers lead noxious information to the most superficial layers of spinal cord, laminae I, II and V. In the dorsal horn of the spinal cord, neurons that project to the thalamus are classified as high-threshold, wide dynamic range (WDR) and low-threshold neurons. Nociceptive information activates high-threshold and WDR neurons. Many neurotransmitters and receptors are involved in nociceptive transmission at spinal level, like glutamate, neuropeptides, adenosine and γ-Aminobutyric Acid (GABA). An increase of neurotransmitters in the dorsal horn contributes to hyperalgesia and sensitization to pain.

From the spinal cord, nociceptive information is driven to supraspinal structures through several ascending pathways. The STT is the main pathway for transmission of noxious stimulus to the thalamus and to higher centres involved in pain processing. Other ascending pathways are involved in visceral pain transmission (dorsal column), integration for descending inhibition or autonomic response to pain (spino-mesencephalic and spino-reticular pathway).

The STT projects directly to neurons located in the ventral posterolateral (VPL) nucleus and medial and posterior nuclei of thalamus. The VPL projects to primary and secondary somatosensory cortex for sensory-

discriminative component of pain; projections from medial and posterior thalamic nuclei are more diffuse and participate to motivational-affective component of pain.

Descending modulation of pain

Supraspinal structures can participate in descending modulation through facilitation or inhibition of pain transmission. Periaqueductal grey (PAG), pontine nuclei, amygdala and anterior cingulate cortex (ACC) facilitatory activity is mediated by rostroventromedial medulla (RVM). The RVM projects to the spinal cord for modulation of dorsal horn neuron activity and nociceptive information. Amygdala and its connection to prefrontal cortex play an important role in emotional aspects of pain; altered or sensitized connection was found in pain patients (17). ACC is involved in nociceptive processing and avoidance of noxious stimuli (18). Decreased grey matter volume was found in people with chronic pain.

Inhibition of pain transmission is mediated by PAG and nucleus raphe magnus (NRM) through the RVM. Activation of these nuclei produces analgesia and inhibits spinal neurons that respond to noxious stimulation. Many others cortical and non-cortical areas relay directly or indirectly to the RVM that produces the final pathway to the spinal cord for pain suppression. Different types of neurons with facilitatory or inhibitory effect located in the RVM explain their role in descending nociceptive modulation. Actors involved in descending pain modulation, with different role in pain facilitation or inhibition, are opioid receptors located specifically on peripheral terminals of primary afferent fibers, serotonin in PAG and RVM and norepinephrine terminals in the spinal cord.

Sensitization to pain

Sensitization is defined by the IASP as an increased responsiveness of nociceptive neurons to their normal input or recruitment of a response to normally sub-threshold inputs (19). Sensitization can occur at peripheral or central level.

Peripheral sensitization is characterized by increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields (19). This phenomenon occurs in response to chemical mediators released by nociceptors and other inflammatory cells at the site of tissue lesion or inflammation. Furthermore, silent nociceptors can be activated by peripheral inflammation and begin to respond to stimulation, not only noxious but also innocuous. All these messages are driven to the spinal cord and the CNS as painful. Pain and sensitization can be produced by primary afferent fibers itself or by non-neuronal activators and inflammatory mediators. Neurogenic inflammation is mediated by the release of the neuropeptides from nociceptors (20). Neuropeptides act in the development and maintenance of peripheral inflammation, as

glutamate and other molecular mediators (nitric oxide, eotaxin). Inflammatory cells participate in nociceptors sensitization through release of substances that can directly activate or sensitize primary afferent fibers. Between them we can found cytokines released by macrophages, nerve growth factor produced by muscles and during tissue injury, and adenosine triphosphate, released from muscle fibers during exercise and cause of enhanced nociceptive activity.

Central sensitization (CS) is defined as an increased responsiveness of nociceptive neurons in the CNS to their normal or sub-threshold afferent input and it was first described by Woolf in 1983 on animal models (21). What Woolf was explaining was a disorder recorded in spinal mechanism responsible of increased ongoing peripheral nociceptive input. The phenomenon described by Woolf differed from "windup", a progressively increasing output during the course of a train of identical stimuli; CS was characterized by facilitation that appears after the end of the conditioning stimuli and that remain autonomous for some time once triggered, or required sub-threshold nociceptive input to be activated or sustained. Furthermore, in CS condition, the nociceptive input amplified response of CNS also to other non-painful stimuli. This was the first attempt to manage the concept that pain we experience might not necessarily reflect the presence, or the entity, of a peripheral noxious stimulus. Pain perception is instead a particular function of the CNS and of its state. After CS discovery, became more clear that a noxious stimulus while sufficient was not necessary to produce pain (22). Sub-threshold inputs can activate pain pathways and pain sensation can be evoked by innocuous stimuli. In this case pain cannot be termed as nociceptive, but rather it reflects hypersensitivity of CNS that produces pain sensation. After many years of discussions about uncertainty of pain without any causal mechanism, CS was recognized as an amplification of neural signalling within the CNS that elicits pain hypersensitivity (23).

Starting from pain perception, sensitization occurs when high-threshold and WDR neurons become more sensitive to noxious and innocuous stimuli (allodynia), they develop or increase their spontaneous activity, reduce their activation threshold to peripheral stimuli, increase their response to supra-threshold stimulation and enlarge their receptive fields. At spinal level central sensitization is driven by neurotransmitters and receptors activities. An increase of glutamate in the dorsal horn contributes to hyperalgesia and maintenance of painful sensation.

Proceeding in perception of pain stimulation towards supra-spinal level, the STT, the most important ascending pathway that drives noxious information, can become more sensitive to painful and non-painful stimulation and its responsiveness enhanced after inflammation. STT originates primarily by laminae I and V; sensitization of WDR cells located in lamina V may be responsible of pain perception also with non-painful stimulation. Furthermore, increased sensitiveness in the spinal cord seems to be mediated by nitric oxide that contribute to development of hyperalgesia (24).

At supra-spinal level sensitization involves neurons in thalamic and cortical areas that become more sensitive to spinal afferences after inflammatory or neuropathic processes. In sensitization, central processing of pain activates brain areas not normally involved in pain perception or that are silent when painful stimulation is removed

Many studies on healthy volunteers were made to explain mechanisms responsible for CS (22). However, all the attempts made to sensitize the CNS through different ways of activating nociceptors may not reflect over activation of a sensitized NS, rather than pain hypersensitivity mediated by peripheral sensitization. For this reason, pain hypersensitivity by itself is not enough to make diagnosis of central sensitization. Many other features of patient whose pain can be associated to CS need to be identified, like spread of pain sensitivity in areas not involved by pathology, after-sensations, enhances temporal summation, and the maintenance of pain by low frequency stimuli that normally do not evoke any pain. All these signs should be associated to objective measures of central activity related to pain stimulation, like fMRI parameters or electroencephalography (EEG) activity (25).

CS seems to play a role in a multitude of painful and other medical conditions, in particular in chronic pain, representing a third core mechanism for pain, beyond the well-known nociceptive and neuropathic pain mechanisms (26). Pathologies where CS found a primary role in their development and maintenance are fibromyalgia (27,28), irritable bowel syndrome (29,30), temporomandibular disorder (31–33), low back pain (34,35), migraine (36), chronic pelvic pain (37), chronic whiplash (38), rheumatoid arthritis (39).

Pain Assessment

Due to its subjective nature, pain cannot be directly observed in patients or measured through objective evaluation, and pain assessment relies largely on the use of self-report. Assessing pain requires valid and reliable measurement, as well as an ability to communicate through the use of language and movements. Another challenge in pain assessment is the definition of the time frame when pain need to be evaluated, due to variable nature of pain experience. Most of the scales used for pain assessment consider the current pain or pain over the past one/two weeks but longer time frames may be necessary for pain assessment, introducing memory biases that can influence the evaluation. In addition, pain is a multidimensional experience and all its components should be assessed separately.

Most of tools used for pain assessment focus their attention on pain intensity, rated over a relatively brief period of time. The most commonly used methods to quantify pain intensity in clinical practice are Verbal Rating Scale (VRS), Numerical Rating Scale (NRS) and Visual Analog Scale (VAS) (40–42). Self-reported questionnaires are used to evaluate quality of pain, its multidimensional aspects and its impact on quality of

life. One example of them is the McGill Pain Questionnaire (MPQ), used to investigate sensory-discriminative, affective-motivational, and cognitive-evaluative dimension of pain (43). Particular assessment instruments were developed for the evaluation of pain due to specific medical conditions, like the Low Back Pain Rating Scale (LBPRS) (44) or the Neck Disability Index (NDI) (45) for musculoskeletal conditions or linked to specific health status like the King's Parkinson's disease pain scale (KPDPS) (46) or Pain Assessment in Advanced Dementia Scale (PAINAD) (47). Shifting the focus on pain research, Dworkin et al. with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) reviewed measures of pain intensity, physical functioning, emotional functioning, and other pain-relevant outcome domains, making recommendations for the selection of outcome measures for clinical trials of pain treatments (48). Different assessment tools were proposed on the basis of mechanism responsible of pain production. One of them is the PainDETECT questionnaire (PD-Q), a self-report questionnaire to identify neuropathic components of low back pain (49), or the Neuropathic Pain Questionnaire (NPQ) to identify the presence of components of neuropathic pain (50). The use of standardized noxious stimulation under controlled conditions constitutes an important strategy to perform an objective evaluation of pain. The use of quantitative sensory testing (QST) is proposed in pain assessment and is characterized by pain induced through several modalities of noxious stimulation (thermal, mechanical, chemical etc.); typical parameters that are measured include pain threshold, pain tolerance, and ratings of supra-threshold noxious stimuli using NRS, VAS, or VRS (51).

The disparity between chronic pain manifestation and the severity of tissue damage make the assessment of this condition particularly challenging. Chronic pain assessment can be performed through self-reported questionnaires; QST are particularly helpful in chronic pain assessment and to identify mechanisms underlying it. However, the un-proportionality recorded in people suffering from chronic pain may be due to sensitization processes that characterize people with pain lasting beyond the tissue healing time. Many misconceptions arise from differentiation of sensitization and neuropathic mechanism. As sensitisation phenomena are readily recognised across neuropathic pain conditions, the CS features have often been interchanged with the neuropathic pain terminology and caused some confusion (52). Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system (53); pain with CS features instead, does not require lesion or disease of CNS and can underlie many chronic pain conditions. Starting from IASP definition of CS, the term “central” may refer to several manifestations of pain, like ipsilateral sensitisation associated with the local nociceptive focus, segmental and extrasegmental sensitisation contralateral to the local nociceptive focus, extraterritorial spreading sensitisation around local nociceptive focus, or generalised widespread sensitisation. In practice, the assessment of clinical history (e.g. intensity, character/modality, spatial and temporal characteristics, spontaneous/provoked, and possible

exacerbating factors of the pain), bedside sensory testing (hypo- or hyper-phenomena, windup like pain and after-sensation), and mapping of areas with sensory abnormalities can be used to identify sensitization phenomena. The above-mentioned QST can be used in more research-based environments to study the nociceptive excitability of the nervous system, testing the excitability of different pain pathways, providing information about pain transduction, transmission and perception under normal and pathophysiological conditions (54).

Assessing sensitization is important to distinguish between peripheral and central mechanism. Recently, topographical pain sensitivity mapping techniques have been developed to assess pain threshold of a defined body area (52). The topographical mapping technique permits to identify areas characterized by changed pain sensitivity. Peripheral sensitization can be addressed when a minimum of two locations from two different segmental levels show differences when compared with normative data provided from a pain-free population. If CS is present, all threshold or pain ratings, assessed locally and distantly to injured tissue, will be affected and relevant at the comparison with pain-free normative data. Furthermore, CS is most pronounced in pain conditions with a neuropathic component (22,55).

Experimental tools have been developed to test the presence of CS. QST permit to identify the presence of widespread sensitization in CS, comparing patients' assessment with pain-free normative data. A clinical feature of sensitised subject is the presence of temporal summation, a progressive increase in neuronal output during the course of a train of identical afferent nociceptive stimuli. Pain in these patients lasts over nociceptive generator removal. Subject with CS frequently present also spatial summation phenomenon, an increase in pain intensity when the size of the stimulated area is expanded. Descending pain modulation system is generally affected in people with CS and may contribute to development and maintenance of symptoms. The assessment of the descending pathways is named conditioning pain modulation (CPM) (56–59). When pain patients have impaired CPM, it's difficult to establish if the inhibition is reduced or the facilitation is increased. All this features of CS can be easily identify in patients with chronic pain due to temporomandibular disorders, low back pain, myofascial pain, fibromyalgia, tension-type headache, irritable bowel syndrome, pelvic pain (52).

New insights on pain assessment come from brain imaging. Brain imaging technologies, including fMRI, positron emission tomography (PET), EEG and magnetoencephalography (MEG), have the potential to provide objective measurements of patterns of brain activity that underlie pain experience (25). During brain imaging assessment problems arise because nociceptive stimuli trigger a great variety of cognitive, emotional, autonomic and motor mechanisms that are not specific to pain, but, due to multifactorial dimension of pain experience, are part of it. Most of the features of brain activity recorded during pain are not specific to it and

make inferences about personal experience of pain is difficult. Generally, functional brain imaging can be used to measure three different types of activity relevant to chronic pain: evoked activity, task-free resting state brain activity and activity related to particular attribute of ongoing clinical pain (25). During pain stimulation, brain responses can be recorded to differentiate between patients with chronic pain and healthy individuals, or between responses elicited by stimuli applied to affected and unaffected areas of the same patient (60–63). Brain activity in chronic pain can be out of sync or completely disconnected from the timing and duration of the applied stimulus (64–67). Resting-state brain activity involves the acquisition of brain response in the absence of any stimulus or task. During this type of assessment can be measured brain connectivity related to spontaneous processes, included those involved in ongoing pain (15). However, in absence of defined chronic pain patterns, it's difficult to establish if a particular resting-state connectivity is related to pain itself or thoughts or other spontaneous processes. Finally, brain activity related to ongoing pain can be recorded to assess brain areas and networks related to emotional, cognitive and motivational processes of pain (15,68).

Imaging of pain-related processes in patients is challenging due to variability in imaging within and between patients, specificity of the imaging findings, the possibility of reverse inference and various technical and statistical issues (25). Defined set of brain areas responding to nociceptive stimulation has been identified but these findings are subjected to personal variability, influenced by sensitive, cognitive and emotional processes linked to pain and, for this reason, variable across time, people and context (69,70). Furthermore, brain imaging linked to pain lack of specificity. No brain areas or networks have been specifically and exclusively linked to chronic pain yet. The complex network recorded in people suffering from chronic pain is also present in depression, anxiety and other mental disorders frequently associated to long-lasting pain. Last but not least the reverse inference problem must be take into account. Reverse inference means the inference of a particular mental state (for example, the perception of pain) from a given pattern of brain activation (25). Accurate assessment of whether a reverse inference is true requires not only assessment of how often the pattern of brain activity occurs when pain is experienced, but also how often the pattern is present when pain is not experienced.

On the basis of these considerations, even though recordings from different brain areas can be associated to chronic pain, it's not possible to say with any degree of certainty that a person does or does not have chronic pain based on brain imaging (25).

Central sensitization in chronic low back pain

Chronic low back pain (CLBP) is one of the pathology we investigated in our project. CLBP seems to present typical features of CS. Studies on animal models shown activation of glial cells and release of cytokines

comparable to those observed in other neuropathic pain models (71). QST measurements have found localised or generalised hyperalgesia in patients with CLBP, in particular pressure pain thresholds, frequently impaired in CS (72–74). Another positive finding of CS in CLBP patients is temporal summation of nociceptive stimuli. Temporal summation during QST has been significantly associated with pain severity and disability (75). Several studies provided evidence about impaired descending modulation in CLBP, supporting the idea of CS mechanism (75–77). Furthermore, it is demonstrated that continued painful stimulation may results into cortical changes and growing evidence supports changes in the brain structure, brain function, and brain chemistry in CLBP patients (78–82). fMRI studies revealed that people with CLBP have functional connectivity reorganisation in several brain regions: increased activation in the medial prefrontal cortex (22,83–86), cingulate cortex (84,85,87), amygdala (84,85), and insula (87,88), and a disrupted default mode network connectivity (89–92). Studies that explored the brain responses to noxious stimuli in people with CLBP found increased activation in brain regions involved in somatosensory-discriminative, affective, and cognitive processing of pain, including the primary/secondary somatosensory cortex, anterior and posterior cingulate, insula, prefrontal cortices, and the thalamus (93,94).

Central sensitization in temporomandibular disorders

Chronic pain due to temporomandibular disorder (TMD) is investigated across this project. TMDs are frequently associated with other pathologies where CS has been widely documented, like myofascial pain syndrome, tension-type headache and migraine, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and multiple chemical sensitivity (95–97). As in other chronic pain pathologies, altered CPM was found also in TMDs and, in particular, in PAG functioning (98–100). Brain imaging studies revealed consistent functional and structural changes in the thalamus and the primary somatosensory cortex of subjects with chronic pain due to TMDs, in addition to neuroplastic modifications in the prefrontal cortex and basal ganglia, supporting the role of cognitive involvement in chronic orofacial pain (101). In TMDs, like other chronic pain pathologies, CS starts from a peripheral injury or dysfunction. In this case, temporomandibular joint (TMJ) dysfunction due to muscular or articular impairment or dental malocclusion can be considered the peripheral triggers (102,103). Once established, the CS process becomes independent from injury or damage at the peripheral tissue level and maintains pain despite healing or disappearance of the original damage (104).

Indirect evidence of the presence of CS in TMD subjects is given by the effectiveness of centrally acting drugs in several studies where the use of benzodiazepines (105,106), tricyclic antidepressants (106,107), beta blockers (108), gabapentinoids (109,110), and melatonin (111,112) seems to reduce pain and other related symptoms (sleep disorders and affective-emotional disorders). Recently, a systematic review on CS in TMDs

revealed increased pressure pain sensitivity in patients with TMDs when compared with asymptomatic subjects, which is suggestive of sensitization of peripheral and CNS (32). Signs of TS and widespread mechanical hyperalgesia were found in these patients, proving the existence of a process of CS (104).

Central Sensitization treatment

Treatment of chronic pain with CS components represents a continuous challenge for clinicians. Chronic pain usually starts from a peripheral nociceptive input that should be the first target of the treatment. Many approaches can be used to eliminate peripheral nociceptive input, according to the nature of the trigger (bottom-up approach). Pharmacological treatments like non-steroidal anti-inflammatory drugs have peripheral effects and can be the first attempt to reduce nociceptive input to the somatosensory system. Physiotherapy or cognitive behavioural treatments can be proposed when the primary nociceptive input arises from the musculoskeletal system. Surgery procedures can be an alternative in more serious conditions like osteoarthritis, where nociceptive pain starts from structural joint damage (113). However, limited evidence supports treatment strategies that eliminate peripheral nociceptive input in patients with chronic pain due to CS (114–118). Hence, the focus of the treatment of chronic pain should be targeted at the brain if CS is considered the dominant feature underlying the pain (top-down approach).

Pharmacological options can be considered for predominant CS pain. Centrally acting drugs such as antidepressants can be considered for the treatment of CS in patients having chronic pain (119), but not opioids as their effects are small in size and long-term use results in opioid-induced hyperalgesia and consequently aggravation of CS, as well as problems associated with dependence (120,121). Preferred pharmacologic treatment includes tricyclic compounds, serotonin-norepinephrine reuptake inhibitors, and $\alpha_2\delta$ ligands (122). All these approaches target key mechanisms that are often dysfunctional in patients having chronic pain and CS, like dysfunctional endogenous analgesia, increased activity in descending nociceptive facilitation and neuro-inflammation. Unfortunately, observed effects of centrally acting drugs in patients having chronic pain and CS are often limited, and the prevalence of side-effects is high (121,123). The uncertainty about efficacy of pharmacological treatments should be due to the high variability of mechanisms underlying CS: this phenomenon is complex and comprises several pathological processes and each of the tested drugs targets one or two of those mechanisms from a purely biomedical viewpoint. A multimodal and complex biopsychological approach should be recommended. Exercise therapy is often a crucial part of evidence-based guidelines for chronic pain disorders (124–126). Exercise therapy has the capacity to activate brain-orchestrated endogenous analgesia in patients with chronic pain (127). In healthy people and patients with chronic pain (CLBP (128,129), shoulder myalgia (130), rheumatoid arthritis (131)), exercise activates

powerful top-down pain inhibitory action, typically referred to as exercise-induced endogenous analgesia (132). However, many studies on patients with CS pain, including chronic whiplash associated disorders (125), chronic fatigue syndrome and fibromyalgia (124,130), describe inability of sensitized subjects to activate endogenous analgesia following exercise (127). Looking at a multidimensional approach to CS, combination of exercise therapy and modern pain neuroscience education should be the right way to trigger mechanisms involved in CS. Several studies shown that pain neuroscience education combined with cognition-targeted time-contingent exercise therapy resulted in marked improvements in self-reported symptoms of CS as well as psychophysiological evidence of decreased CS in patients with chronic spinal pain (119). Pain neuroscience education is therapeutic on its own, with level A evidence supporting its use for changing pain beliefs and improving health status in patients with CS pain (e.g., fibromyalgia, chronic fatigue syndrome, CLBP) (133). Detailed pain neuroscience education is required to reconceptualise pain and to convince the patient that hypersensitivity of the CNS rather than local tissue damage may be the cause of their presenting symptoms. Therapeutic pain neuroscience education can change inappropriate pain beliefs and cognitions, such as pain catastrophizing, anxiety, hypervigilance and kinesiophobia, that contribute to sensitization of the dorsal horn spinal cord neurons (through inhibition of descending tracks in the CNS) (134–137).

To address the cognitive-emotional aspects of chronic pain, interventions such as cognitive behavioural therapy target maladaptive pain cognitions (138). Cognitive behavioural strategies increase the ability of subject to cope with their pain. This approach aims to increase self-control over the cognitive and affective responses to pain, deactivating brain-orchestrated top-down pain facilitatory pathways (139).

In addition to more cognitive approaches, rehabilitation provides opportunities for treating CS. Manual therapy, originally aimed at exerting peripheral effects, seems to produce central analgesia through activation of descending anti-nociceptive pathways (140–143). However, the short-term nature of the central analgesic effects of manual therapy limits is clinical utility as a treatment strategy for desensitizing the CNS. Transcutaneous electric nerve stimulation (TENS) is frequently used in patients with chronic pain. TENS targets mechanisms known to be involved in central sensitization, activating large diameter afferent fibers, which in turn activate descending nociceptive inhibitory mechanisms through the ventrolateral PAG and the rostral ventromedial medulla (144,145).

For several years non-invasive brain stimulation (NIBS) techniques are getting growing interest for chronic pain treatment. NIBS aims to induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity. Between them, the more used in chronic pain treatment are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (146). rTMS involves stimulation of the cerebral cortex by a stimulating coil applied to the scalp. Electric currents are

induced in the neurons directly using rapidly changing magnetic fields (147). Trains of these stimuli are applied to the target region of the cortex to induce alterations in brain activity both locally and in remote brain regions (148). tDCS involves the safe and painless application of low-intensity (commonly ≤ 2 mA) electrical current to the cerebral cortex (147,149,150). tDCS has been developed as a clinical tool for the modulation of brain activity and uses relatively large electrodes that are applied to the scalp over the targeted brain area to deliver a weak constant current (151). Both tDCS and rTMS have been shown to modulate brain activity specific to the site of application and the stimulation parameters. The observed alterations in cortical excitability following rTMS and tDCS that last beyond the time of stimulation are the result of long-term synaptic changes (151). NIBS can be used to trigger many different brain areas and to modulate their role on sensory, motivational or cognitive components of pain experience. However, a recent systematic review found lack of high-quality evidence to support or refute the effectiveness of NIBS techniques for chronic pain treatment (146).

Aim of the study

The aim of this PhD project is to identify features of pain in subjects with chronic pain and to test efficacy of NIBS in treatment of this pathological condition.

In particular we would like to identify biological marker related to pain in people with chronic orofacial pain due to TMDs. We would also propose treatment using transcranial direct current stimulation to reduce pain related to TMDs and CLBP.

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Effects of transcranial direct current stimulation (tDCS) on patients with chronic temporomandibular joint disorders: A case series

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Abstract

Chronic orofacial pain caused by temporomandibular disorders (TMD) is a challenge for clinicians for the presence of associated psychological symptoms and central sensitization mechanisms. Modulation of brain activity using transcranial direct current stimulation (tDCS) seems to be effective in the treatment of chronic pain syndromes for its effect on neuroplastic maladaptive changes defined as central sensitization. Hereby, we present three cases of chronic orofacial pain by temporomandibular disorders resistant to any other medical treatments. After monitoring their pain perception for ten days, we applied tDCS over their primary motor cortex for five days with encouraging effects on pain perception, psychological symptoms and jaw function.

Keywords: Orofacial pain, temporomandibular disorder, tDCS, chronic pain, case series

Introduction

Temporomandibular disorders (TMD) are a very common cause of orofacial pain characterized by a complex and multifactorial etiopathogenesis. Chronic orofacial pain caused by TMD is about the 4-12% of the population affected by this symptom (1).

The Research Diagnostic Criteria for TMD (RDC/TMD) Axis I and Axis II protocols are a useful instrument for a biopsychosocial assessment of chronic pain and allow for the identification of patients with a wide range of simple to complex TMD presentations. Treatment is often oriented towards symptoms referred by patients and to restore mandibular masticatory functions and recovery in activities of daily living. When conservative treatments fail, surgical procedures such as

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arthroscopic infiltrations or arthroplasty are necessary. It is well known the presence of central sensitization mechanisms among patients with TMD (2). Recently, new findings pointed out the role of transcranial direct current stimulation (tDCS) on chronic pain treatment. The rationale for its use is the neuroplastic maladaptive changes into the central nervous system defined as central sensitization which is present in some unexplained chronic pain originated from musculoskeletal disorders. Central sensitization is an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity or an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors.' tDCS is a noninvasive brain stimulation technique that applies weak electrical currents (1-2 mA) through the skull to modulate the activity of neurons in the brain and augment opioids receptors. In this report, the use of tDCS in three cases with TMD resistant to any other medical treatment and its efficacy of on pain, function and psychological symptoms, are discussed.

Case story 1

A 57-year-old woman. She complained a bilateral TM pain for two years without specific radiations of pain that worsened during chewing. Pain arose from a yawn with no joint dislocation or block. According to RDC/TMD from history, instrumental and clinical exams, she could be classified as affected by a slight degenerative joint disease, disc displacement without reduction with limited opening and an overlapping myofascial pain with the referral.

Case story 2

A 44-year-old woman. She complained TM pain and masticatory problems for six years after a microdiscectomy and stabilization intervention for cervical myelopathy. Her pain widespread involving neck and shoulders bilaterally, without a metameric distribution for the upper limbs. According to RDC/TMD she could be classified as affected by a moderate degenerative joint disease, disc displacement without reduction with limited opening and an overlapping severe myofascial pain with the referral.

Case story 3

A 46-year-old woman came to our attention complaining bilateral TM pain that was radiating to the neck, frontal head and jaw since three years before. According to RDC/TMD, from history, instrumental and clinical exams Case 3 could be classified as affected by a severe degenerative joint disease, disc displacement without reduction on the left side with limited opening and an overlapping myofascial pain with the referral. The degenerative joint disease was more severe, according to radiological evaluation, compared to the other cases.

All patients in their past medical history underwent a twelve-session rehabilitation program at our department with laser therapy, TM analytic mobilization, masticatory muscles electromyography biofeedback, isometric-isotonic strengthening and ergonomic posture advice. Case 1 and Case 2 also received arthroscopic infiltrations procedures with hyaluronic acid. Case 1 and Case 3 started to use oral byte made by our dental technician. Case 2 started pharmacological treatment with pregabalin and alpha lipoic acid for persistent pain with paresthesia and neuropathic characteristics.

In all patients, we assessed daily pain intensity for ten days before stimulation using Visual Analogue Scale (VAS) (see Table 1).

For five consecutive days we stimulated their left primary motor cortex area (M1) using anodal transcranial direct current stimulation (tDCS) for 20 minutes a day with the intensity of 2 mA (5 sessions). The anode was placed over M1 area contralateral the side of pain and the cathode over the opposite supraorbital area. The current was delivered through a pair of sponge electrodes (7cm x 5 cm), soaked in saline solution and it was generated by a constant current stimulator (Brainstim, EMS, Italy).

Before treatment (T0), after treatment (T1) and at one-month follow-up (T2) they were evaluated using VAS for pain, Patient Health Questionnaire (PHQ-9) for depression, Symptoms Checklist-90-Revised (SCL-90-R) for psychological symptoms and Jaw

Functional Limitation Scale-20 items (JFLS-20) for jaw function. The pain was evaluated daily following stimulation. After positive consensus from the Ethics Committee, informative letter regarding our procedure was given to patients and their primary care doctors and patients' written informed consent was obtained.

Results

Case 1 presented a high variability at the VAS scale for pain in the two weeks before treatment (4.7 ± 4.1 cm). After treatment Case 1 showed pain reduction at the VAS scale from 6.5 cm at T0 to 0.7 cm at T1 and 1.3 cm at T2. Depression at the PHQ-9 decreased from 10 at T0 to 6 at T1 and seven at T2. Psychological symptoms at the SCL-90-R decreased from 11 at T0 to 8 at T1 and 2 at T2. After treatment, jaw function decreased from a score of 52 to 57 at the JFLS-20. Jaw function increased at 1-month follow-up (44 points at the JFLS-20). Case 2 showed low fluctuations in pain intensity in the two weeks before treatment (8.9 ± 1). Following treatment, Case 2 reported a pain reduction from 8.9 cm at T0 to 6 cm at T1 and 1.3 cm at T2 at the VAS scale. Depression at the PHQ-9 decreased from a score 6 at T0 to 3 at T1 and T2. Psychological symptoms and jaw function remains unchanged during assessments.

Case 3 presented a high variability at the VAS scale for pain in the two weeks before treatment (4.9 ± 4). Following treatment, Case 3 reported an increase in pain from 4 cm at T0 to 5.6 cm at T1 and 6.2 cm at T2 at the VAS scale.

Depression at the PHQ-9 decreased from a score 5 at T0 to 4 at T1 and 3 at T2. Psychological symptoms remain unchanged during assessments. Jaw function at the JFLS-20 decreased from a score of 48 to 59 and 56 at T0, T1, T2 respectively.

Considering average scores for all three cases, pain, depression and psychological symptoms, measured by VAS, PHQ-9 and SCL-90-R, decreased after tDCS and results were retained after one month. No adverse effects were reported following tDCS treatment

Table 1. Clinical and demographic characteristics of the cases

	Case 1	Case 2	Case 3
Age, y	57	44	46
Sex	F	F	F
DC/TMD Axis I	Degenerative joint disease Myofascial pain with referral Disc displacement without reduction with limited opening	Degenerative joint disease Myofascial pain with referral Disc displacement without reduction with limited opening	Degenerative joint disease Myofascial pain with referral
Side of pain	Bilateral	Bilateral	Bilateral
Symptoms duration, y	2	6	3
Physiotherapy	Yes	Yes	Yes
Surgery	Yes	Yes	No
Byte's use	Yes	No	Yes
VAS pain results[a] mean, cm	4.7	8.9	4.9

F: female. DC/TMD: Diagnostic Criteria for Temporomandibular Disorders. VAS: Visual Analogue Scale.
[a] 10-days-pain-assessment before treatment.

Table 1. Outcome measures

		Case 1	Case 2	Case 3	Mean (SD)
VAS pain	T0	6.5	8.9	4	6.5 (2.4)
	T1	0.7	6.0	5.6	4.1 (2.9)
	T2	1.3	1.3	6.2	2.9 (2.8)
PHQ-9	T0	10	6	5	7.0 (2.6)
	T1	6	3	4	4.3 (1.5)
	T2	7	3	3	4.3 (2.3)
SCL-90-R	T0	11	0	3	4.7 (5.7)
	T1	8	0	2	3.3 (4.2)
	T2	2	1	2	1.7 (0.6)
JFLS-20	T0	52	46	48	48.7 (3.1)
	T1	57	49	59	55.0 (5.3)
	T2	44	45	56	48.3 (6.7)

VAS: Visual Analogue Scale; PHQ-9: Patient Health Questionnaire-9; SCL-90-R: Symptoms Checklist-90-Revised; JFLS: Jaw Function Limitation Scale-20 items.
T0: pre-treatment assessment; T1: post-treatment assessment; T2: one-month follow-up assessment.

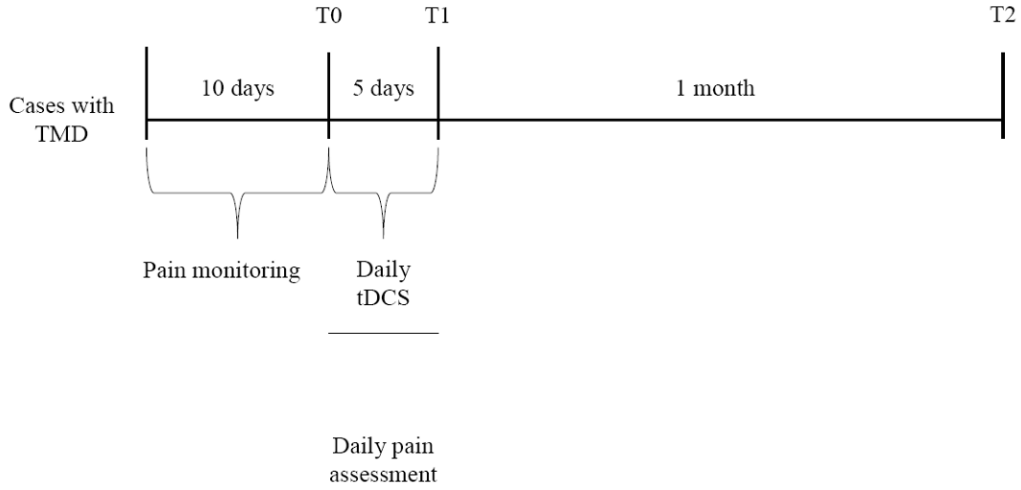

Figure 1. Timeline of the study.

Discussion

Anxiety, depression, catastrophization, chronic fatigue and sleep disorders are symptoms often represented in chronic pain syndromes such as TMD. All together this procession of symptoms badly influences quality of life and social participation of patients. Our preliminary findings support the use of tDCS on pain perception, depression and psychological wellbeing. Our three cases had a similar diagnosis, according to RCD/TMD and the common denominator was a chronic persistent pain, unresponsive to conventional treatments with a strong psychological impact on health and quality of life. The care pathway was very fragmentary and this is typical for all patients who suffer from chronic pain. In this report, we propose the neuromodulation approach, according to the hypothesis that chronic pain patients have central sensitization mechanisms and maladaptive neuroplastic changes which can be

modified by neuromodulation itself. There are already two papers regarding tDCS effects on pain for TMD, from Donnel et al. (3) and Oliveira et al. (4) and a study protocol from Brandão Filho et al. (5) which involves dorsolateral prefrontal cortex stimulation. Donnel et al. (3) tried to define the neuromodulatory effect of five daily 2 x 2 motor cortex high-definition tDCS (HD-tDCS) sessions on clinical pain and motor measures in chronic TMD patients. They considered twenty-four females with chronic myofascial TMD pain and concluded that putative M1 stimulation by HD-tDCS selectively improved meaningful clinical sensory-discriminative pain and motor measures during stimulation, and up to four weeks post-treatment (4). Oliveira et al. (4) combined tDCS and exercise to treat TMD and they concluded for no additional benefits in adding tDCS to exercise even if it would be better to use tDCS before or during exercises to improve synaptic activity. In our small sample, 2/3 of cases had good results for pain intensity and depressive symptoms after treatment and up to 4 weeks. Conversely, one case, who had a severe degenerative disease, did not report any beneficial effects after tDCS. One possible explanation for our results is that chronic pain is related to emotional disorders and maybe stimulation over the dorsolateral prefrontal cortex could have a more pronounced effect than anodic stimulation over M1, such as Brandão Filho et al. (5) considered in their study protocol. Nowadays, correlations among degenerative and articular disease, chronicity of pain and psychological profiles for muscular pain for these patients are still to be correctly identified. We can speculate that a complex pain, both articular and muscular, need to be treated with a "bottom up" and a "top-down" approach. In the future, with a better classification of TMD and the possibility to identify central sensitization mechanisms, it will be possible to design an RCT study, with a bigger sample size to test the efficacy of this procedure.

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Ethical compliance

The authors have stated all possible conflicts of interest within this work. The authors have stated all sources of funding for this work. If this work involved human participants, informed consent was received from each individual. If this work involved human participants, it was conducted in accordance with the 1964 Declaration of Helsinki. If this work involved experiments with humans or animals, it was conducted in accordance with the related institutions' research ethics guidelines.

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Original Article

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The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial

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Abstract

Objective: To test the efficacy of transcranial direct current stimulation (tDCS) in addition to group exercise on non-specific chronic low back pain.
Design: Double-blinded randomized control trial.
Subjects: Patients with non-specific chronic low back pain.
Methods: A total of 35 subjects were recruited and allocated to real- or sham-tDCS followed by a group exercise protocol. Each patient underwent five sessions of brain stimulation followed by 10 sessions of group exercise. Subjects were evaluated before and after tDCS, after group exercise and one month after the combined treatment. Outcome measures were Visual Analog Scale for pain intensity, Roland Morris Disability Questionnaire, EuroQuol-5 Dimension and Patient Health Questionnaire-9.
Results: Significant between-group difference in pain intensity (–27.7 ± 30.4 mm in real-tDCS group compared to –2.2 ± 30.1 mm in sham-tDCS group) and Patient Health Questionnaire-9 (–4.9 ± 4.2 in real-tDCS group compared to –1.1 ± 2.7 in sham-tDCS group) was found one month after the combined treatment ($P < 0.05$).
Conclusion: Our results showed that real-tDCS can induce significant larger effects on pain and psychological well-being, compared to sham-tDCS, when it is associated with a group exercise program. The effects were observed mostly in the follow-up.

Keywords

Non-specific chronic low back pain, transcranial direct current stimulation, neuromodulation, group exercise

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Introduction

Non-specific chronic low back pain is a widespread condition with significant personal, social and economic burden.[1]

According to the most recent guidelines for treatment of chronic low back pain, a multidisciplinary approach including group exercise treatment is recommended.[2] Moreover, research studies have shown how transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, can be considered a reliable tool for the management of chronic pain syndromes, such as fibromyalgia or central pain related to spinal cord injury.[3–5] tDCS applied over the motor cortex is able to decrease the intensity and duration of pain, modulating the activity of brain areas involved in pain regulation.[6] It has been hypothesized that combining tDCS with a rehabilitative technique can foster the effects of single treatments. For example, it was combined with a multidisciplinary approach for fibromyalgia or a cognitive behavioral therapy in chronic low back pain with inconclusive results.[7,8] Although a recent large randomized trial did not show significant differences between real- and sham-tDCS for chronic low back pain, one of the reasons may have been the type of behavioral intervention combined with M1 tDCS.[8] In this study, we therefore aimed to test the feasibility of combining tDCS preceding a group exercise program in subjects with non-specific chronic low back pain. Specifically, we tested the effects on pain intensity, disability, quality of life and psychological well-being.

The differences between this study and previous reports with negative results can be explained by the type of behavioral intervention and also regimen of stimulation, underscoring the important notion that tDCS does not enhance the effects of any type of behavioral intervention, but it does when there is a temporal and spatial correlation between stimulation and task.

Methods

This is a double-blinded randomized control trial. Participants were contacted by a short phone interview and subsequently assessed for eligibility with a medical examination. This trial was approved by Ferrara University Hospital Ethics Committee (Italy), and all procedures were conducted according to the ethical standards of the Declaration of Helsinki only when a written consent was provided. The trial protocol has been registered (NCT01875029).

Inclusion criteria were males and females, aged 18–75 years with non-specific chronic low back pain diagnosed since more than two years with recurrent episodes according to the guidelines.[2] To be enrolled in the study all patients had to have at least an intensity of pain of 20 mm at the Visual Analog Scale (VAS) during the two weeks before treatment.[9] Participants were excluded whether submitted to spine surgery within the previous six months, presented a cognitive impairment assessed with Mini-Mental Status Examination (MMSE)[10] inferior to 24/30 or common contraindications to tDCS: history of epilepsy; implantable devices in the skull; major neurological or psychiatric diseases; severe cardiopulmonary, renal and hepatic diseases or pregnancy. Participants were randomized to real- and sham-tDCS through a block randomization of four. The randomization scheme was generated using the website http://www.randomization.com. The random list was managed by an administrator external to the research groups to prevent selection bias. The experimental group received real-tDCS and group exercise; the control group received sham-tDCS and group exercise. Both subject and investigator were blinded about the treatment group, as well as the physical therapists and medical doctors involved in the study. Pain intensity was measured using the 0–100 mm VAS.[9] Disability was rated using the Roland Morris Disability Questionnaire. It is composed of 24 items designed to assess chronic low back pain–related disability. It is self-administered to patient, and it ranges from 0 (none disability) to 24 (severe disability).[11] We used its Italian version.[12] The EuroQuol-5 Dimension, a widely used questionnaire, was administered to evaluate quality of life and health status in patients with back pain.[13] We used its validated Italian version.[14]

Psychological well-being was assessed with The Patient Health Questionnaire-9 that screened, monitored and evaluated depression severity symptoms.[15] All subjects were evaluated before (T0) and after (T1) tDCS, after the group exercise program (T2) and at one-month follow-up (T3). Pain intensity was also evaluated after every tDCS session. The real-tDCS group received five consecutive daily stimulation immediately before the group exercise program. tDCS was administered as follows: if pain was central in the back or bilateral, the anode was placed on the primary motor cortex (M1) of the dominant hemisphere, whereas the contralateral M1 was stimulated in the presence of pain irradiated to one side. The cathode was placed on the contralateral supraorbital area. The direct current was delivered through a pair of sponge electrodes, with a surface of 35 cm^2 (7×5), soaked in saline solution, with a low-intensity battery-driven stimulation device with rechargeable batteries (BrainSTIM, EMS, Italy). Electrodes were secured using soft elastic straps. The location of the motor cortex was estimated using the international 10–20 electroencephalogram (EEG) system and placing the center of the electrode pad at C3 or C4. This continuous stimulation lasted 20 minutes, with an intensity of 2 mA for five consecutive days.[6] In the sham-tDCS group, the stimulator was turned off after 30 seconds, and the subjects felt the initial itching sensation but receive no current for the rest of stimulation session.[16] A tDCS side-effects questionnaire (headache, neck pain, burning, redness and/or itching at the site of stimulation) was administered after each session to both groups of patients. The Group Exercise intervention included a class of 10 participants starting with one hour lesson where physician explain pain neurophysiology and advised on posture at work with ergonomics information. A physical therapist instructed patients on specific muscle stabilization and mobilization exercises for the trunk for one hour, two or three times a week for about one month. At the end of group exercise (10 sessions), a leaflet with home exercises was given to the patients. Overall, participants received a program of 11 hours. For further details, see Appendix 1.

Data analysis

Descriptive statistics (mean and standard deviation) were reported before treatment, after tDCS treatment, after combined treatment and at one-month follow-up. Baseline characteristics were compared among groups to confirm the quality of randomization (Wilcoxon rank Pearson's chi-square test). Between-group differences were explored with the Wilcoxon rank-sum test. Moreover, a repeated-measures analysis of variance (ANOVA) analysis (within-group factor: TIME; between-group factor: TREATMENT) was conducted to detect main effects for treatment and time. A difference of the percentage of responders among groups was analyzed using chi-square test. A subject was categorized as responder if he or she retained a VAS improvement greater than 30% at the one-month follow-up compared to baseline.[17] An intention-to-treat analysis was carried out on all outcome measures, handling missing data with the last observation carried forward approach. Statistical analysis was performed using STATA 13.1 software. Significance was recognized when $P < 0.05$.

Power and sample size calculation

This was a pilot study, and thus, confirmation of results was not the main goal as we were interested in learning about effect sizes of several outcomes as to plan for future confirmatory trials; thus, we planned this study considering the pilot exploratory nature of it. We were interested in having at least a power to detect a moderate to large effect size of 0.9 (one tail because of the exploratory nature) given a power of 80% and α of 5%. Therefore, for these parameters, we would need a sample of at least 32 subjects (16 in each group); however, an increase in the sample in 10% to 35 subjects is recommended as to account for drop-outs.

Results

In all, 418 subjects with chronic low back pain were screened for this study and 35 were enrolled (mean age = 55.1 ± 12.5 years, nine males and 26

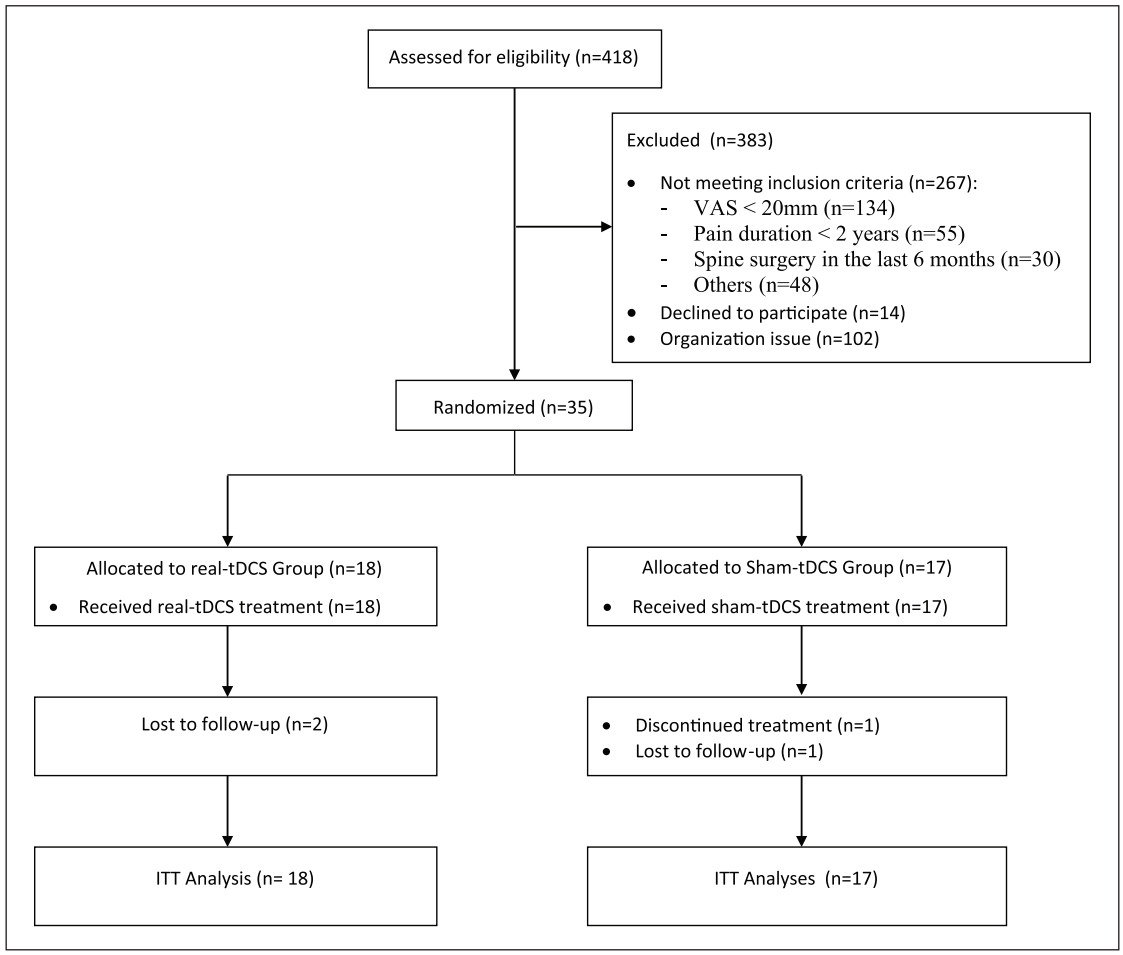

Figure 1. CONSORT flow diagram.
n: number; VAS: Visual Analog Scale; tDCS: transcranial direct current stimulation; ITT: intention-to-treat.

females, 8.7 ± 7.7 years of pain duration) at Ferrara University Hospital. One subject discontinued rehabilitation for personal issue unrelated to the treatment received. The study flow diagram is reported in Figure 1.

The two groups were similar in demographic and clinical characteristics, as summarized in Table 1.

Pain intensity (VAS)

RM-ANOVA analysis revealed a significant interaction of effect time–treatment: $F(3, 99) = 2.8$; $P = 0.042$. Between-group analysis highlighted how the difference among groups was significant at one-month follow-up ($P < 0.05$): −27.7 ± 30.04 mm in real-tDCS group and −2.2 ± 30.1 mm in sham-tDCS group. Results are summarized in Table 2.

Looking at the percentage of responders, a significant difference was found between groups ($P < 0.01$): 72.22% in the real-tDCS group versus 17.65% in the sham-tDCS group. A further analysis to investigate the effects of tDCS on pain intensity after each stimulation session was conducted. We highlighted a positive effect since the first session ($P < 0.05$). See Table 3.

Table 1. Baseline clinical and demographic characteristics.

	Real-tDCS + GE ($n = 18$)	Sham-tDCS + GE ($n = 17$)	Total ($n = 35$)	*P*-value
Age (years)				
Mean (SD)	54.3 (12.4)	56 (12.9)	55.1 (12.5)	0.69
Median	56	54	54	
Sex (M/F)	6/12	3/14	9/26	0.29
CLBP onset (years)				
Mean (SD)	9.4 (9.2)	7.8 (5.3)	8.7 (7.7)	0.57
Median	7	7	7	
Irradiation (yes/no)	11/7	12/5	23/12	0.56
Pain frequency (continuous/intermittent/NE)	10/5/3	9/4/4	19/9/7	0.89
VAS pain baseline (mm)				
Mean (SD)	55.7 (18.3)	50.3 (24.4)	53.1 (21.3)	0.44
Median	53.5	46	50	
RMDQ baseline				
Mean (SD)	9.2 (4.1)	10.2 (4.7)	9.7 (4.3)	0.48
Median	8.5	12	9	
EQ-5D baseline				
Mean (SD)	0.56 (0.2)	0.57 (0.2)	0.57 (0.2)	0.83
Median	0.56	0.59	0.59	
PHQ-9 baseline				
Mean (SD)	9.3 (5.6)	7.5 (3.6)	8.4 (4.8)	0.49
Median	7.5	7	7	
VAS anxiety baseline (mm)				
Mean (SD)	37.3 (22.8)	40.2 (19.3)	38.7 (20.9)	0.68
Median	43.5	47	45	
CGI item 1 baseline				
Mean (SD)	3.6 (1.4)	3.5 (1.4)	3.6 (1.4)	0.77
Median	4	4	4	

tDCS, transcranial direct current stimulation; GE, group exercise; *n*, number; SD, standard deviation; M/F, male/female; CLBP, chronic low back pain; NE, not evaluated; VAS, Visual Analog Scale; RMDQ, Roland Morris Disability Questionnaire; EQ-5D, EuroQol-5D; PHQ-9, Patient Health Questionnaire-9; CGI, clinical global impression; *P*-value, difference between real-tDCS + back school group and sham-tDCS + back school group.

Self-reported questionnaires

An interaction of effect time–treatment was highlighted for psychological well-being: $F(3, 99) = 5.3$ and $P < 0.01$, and the difference among groups was significant at one-month follow-up ($P < 0.05$). Results are summarized in Table 2. Out of 35 patients, 29 reported mild side-effects after stimulation (16 in the real-tDCS group and 13 in the sham-tDCS group). The results of tDCS Adverse Effects Questionnaires are reported in Table 4.

Discussion

Our main findings revealed that tDCS was effective in ameliorating pain and psychological well-being in a convenience sample of non-specific chronic low back pain patients, but the effects were evident only at one-month follow-up and during the behavioral intervention (group exercise program).

Previous studies tested the effects of tDCS and rehabilitation on pain with inconclusive results. Riberto et al.[7] administered tDCS before a weekly

Table 2. Changes in outcome measurements (mean ± SD).

	Changes at T1		Changes at T2		Changes at T3	
	Real-tDCS	Sham-tDCS	Real-tDCS	Sham-tDCS	Real-tDCS	Sham-tDCS
VAS pain (mm)	–16.9 ± 20.4	–8.8 ± 29.2	–21.2 ± 30.7	–7.2 ± 32.5	–27.7 ± 30.4*	–2.2 ± 30.1
RMDQ	3.1 ± 2.9	–2.7 ± 3.8	–3.8 ± 3.7	–3.5 ± 4.2	–4.7 ± 3.9	–3.5 ± 4.4
EQ-5D	0.14 ± 0.2	0.08 ± 0.1	0.16 ± 0.2	0.06 ± 0.2	0.21 ± 0.2	0.11 ± 0.2
PHQ-9	–2.8 ± 3.1	–1.1 ± 2.6	–4.4 ± 4.1	–1.7 ± 2.2	–4.9 ± 4.2*	–1.1 ± 2.7

T1, after tDCS treatment; T2, after combined treatment; T3, at one-month follow-up; tDCS, transcranial direct current stimulation; SD, standard deviation; VAS, visual analog scale; RMDQ, Roland Morris Disability Questionnaire; EQ-5D, EuroQol-5D; PHQ-9, Patient Health Questionnaire-9.
*$P < 0.05$ for the comparison between treatments.

Table 3. Visual Analog Scale for pain intensity (mean ± SD) after each session of stimulation.

	Real-tDCS		Sham-tDCS	
	Mean ± SD	*P*	Mean ± SD	*P*
T0	55.7 ± 18.3	–	50.3 ± 24.4	–
Following I stimulation	43.3 ± 20.4	0.028	42.7 ± 26.7	0.823
Following II stimulation	36.9 ± 19.9	<0.001	47.8 ± 25.8	0.999
Following III stimulation	42.1 ± 25.7	0.012	44.7 ± 22.1	0.945
Following IV stimulation	40.7 ± 27.0	0.004	41.8 ± 26.4	0.745
T1	38.8 ± 23.4	<0.001	41.5 ± 24.2	0.717

tDCS, transcranial direct current stimulation; SD, standard deviation.

Table 4. Frequencies of patients reported side-effects after stimulation (*n* (%)).

	Real-tDCS (*n* = 18)	Sham-tDCS (*n* = 17)	Total (*n* = 35)
Skin redness	13 (72)	8 (48)	21 (60)
Tingling	6 (34)	8 (48)	14 (40)
Headache	3 (17)	4 (24)	7 (20)
Sleepiness	5 (28)	2 (12)	7 (20)
Trouble to concentrate	2 (11)	2 (12)	4 (11)
Dizziness	1 (6)	–	1 (3)
Mood fluctuations	–	1 (6)	1 (3)

tDCS, transcranial direct current stimulation.

multidisciplinary rehabilitation session for the treatment of patients with fibromyalgia reporting positive results not on pain but on quality of life. Luedtke et al.[8] tested the effects of tDCS and cognitive behavioral management in a large sample of chronic low back pain patients. They concluded that tDCS did not induce further benefits on pain or disability. These differences can be explained by the mechanisms of tDCS and indeed bring important insights for the design of future studies. The first important aspect that explains the difference as compared with Riberto et al. is the regimen of stimulation: weekly (rather than daily) stimulation sessions have less effects.[18] The second important

aspect to explain the differences with Luedtke is the type of combined behavioral intervention. In the Luedtke study, authors chose a cognitive behavioral therapy that engages a different neural area than the one stimulated in the study (M1); therefore, it is possible that effects of tDCS were irrelevant to the type of therapy chosen in that study. There was no spatial correlation between area of stimulation and behavioral task in this case. Also, a ceiling effect in this study is possible given the number of hours of therapy (80 hours versus 11 hours in our study). Therefore, the choice of the combined behavioral therapy plus the number of sessions is critical when designing a therapeutic tDCS trial. Another important point is that in our design, we allowed for the measurement of delayed effects, and in fact, most of the effects in our study were delayed which is similar to two previous tDCS studies in pain.[19,20]

In this context, it is important to understand the neural mechanisms of combined behavioral interventions as (1) to choose the appropriate neural area for stimulation (spatial correlation) and (2) choose a design that allows for an appropriate temporal relationship between both. Given the mechanisms of tDCS to change neuronal membrane threshold, it is critical that the neural area that is affected by the effects of tDCS is the same neural area that is engaged in the behavioral task. This spatial correlation is not as simple as in some cases even the behavioral baseline level affects the main neural area engaged in the behavioral tasks as shown in several tDCS studies.[21,22] In terms of temporal relationship, most of the studies to date have shown that tDCS given before or during the behavioral intervention provides the best outcomes and timing for positive results may be delayed.[19,20,23,24] Thus, it is not only combination of tDCS with a behavioral task, but how this combination is done. Finally, the combination of therapies such as in this study provides improved and also more focal results.[25–28] The main reason for such synergistic effects comes from the mechanism of tDCS that modulates neuronal threshold, instead of inducing action potentials; thus, therapy that does generate action potentials (such as in this study) is important to enhance the effects of tDCS, but only if temporal and spatial relationship discussed is taken into consideration.

Immediately after tDCS, we did not find a significant reduction in pain intensity. We can speculate a placebo effect after the end of stimulation in both groups that is a learned response whereby various types of cues—verbal, conditioned and observational—trigger expectancies that generate behavioral and clinical outcome changes via central nervous system mechanisms.[29] Although other studies found positive results on pain immediately after stimulation, in a mixed population with chronic pain,[3] pelvic pain,[30] neuropathic pain by spinal cord injury[31] or pain in fibromyalgic patients,[4] differences may be related to the type of pain and baseline pain levels and also level of refractoriness.[3,4,30,31] A recent systematic review on the effects of chronic pain induced by tDCS did not find a difference between active and sham stimulation with a very low-quality evidence. Hence, larger better quality studies, rigorously designed, particularly of longer courses of stimulation are mandatory.[32]

In our study, the beneficial effects on pain were retained at one-month follow-up. Specifically, 72% of patients in the real-tDCS group maintained a reduction in pain intensity greater than 30% that can be considered a clinically meaningful improvement.[17] We confirmed our results beyond the time of stimulation, probably indicating a long-lasting retention typical of stimulation in chronic pain patients of visceral or neuropathic origin.[33,34] In addition to pain intensity, we found a superiority of real-tDCS in ameliorating mood symptoms. Pain itself can have a negative effect on emotions and on cognitive function, and it is associated with negative emotions and psychological distress.[35]

In our sample, disability, measured by Roland Morris Disability Questionnaire, improved immediately after group exercise in both groups; this can be related to the patients' care from the rehabilitation team.

Our pilot study has some limitations: (1) our behavioral approach may also be influenced by social aspects (socioeconomic status, family, work and culture) according to a more correct biopsychosocial involvement for chronic pain population, though these factors seemed to be equally distributed

in both groups of stimulation;[36,37] (2) the number of sessions of tDCS may still be insufficient to achieve a larger therapeutic effect and (3) finally, we did not use any clinical or instrumental tool to investigate central sensitization mechanisms involved in chronic low back pain patients.[38]

For a future confirmatory study, we estimated that given a 90% power and an alpha of 1%, we will need 62 patients (31 per arm) to complete the study.

Conclusion

In summary, tDCS can boost the effects of group exercise in patients with chronic low back pain. Looking at the physiological mechanisms underlying tDCS analgesic effects, further research is needed to find out the dose (e.g. number and frequency of treatment sessions) that results in the largest benefits and the long-term effects of treatment on pain intensity, disability, quality of life and psychological well-being.

Clinical Messages

- A neuromodulation approach, such as tDCS, increases the effects of a group exercise program on pain intensity and psychological well-being.
- The beneficial effects are registered after one-month follow-up.
- In a future study, 61 patients will be required to confirm our findings.

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Availability of data and materials

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Hyperalgesia and central sensitization in subjects with chronic orofacial pain: analysis of pain thresholds and EEG biomarkers

An observational study on chronic orofacial pain

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ABSTRACT

Background: Chronic orofacial pain frequently starts from a temporomandibular disorder but continues to be present over tissue healing time for central sensitization process of higher-order neurons. Aim of the study is to describe psychological aspects of patients with chronic orofacial pain, their peripheral pain threshold and EEG recording looking for possible signs of central sensitization.

Methods: Twenty-four subjects with chronic orofacial pain due to temporomandibular disorder were evaluated using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I and Axis II. Pain intensity, catastrophizing and presence of central sensitization were assessed through self-reported questionnaires. Pressure pain threshold was recorded in facial and peripheral sites; EEG activity was recorded during open and closed eyes resting state and while pain threshold assessment was performed. Pain threshold and EEG recording were compared with a cohort of pain-free age- and sex-matched healthy subjects.

Results: Patients with chronic orofacial pain shown a significative reduction in pain threshold compared to healthy subjects in all the sites of assessment. Greater reduction in pain threshold was recorded in patients with more severe psychological symptoms. Increased gamma activity was recorded in cortical and frontal regions of patients during pain threshold assessment compared to the controls.

Conclusions: Generalized reduction in pressure pain threshold was recorded in people who suffer of chronic orofacial pain. Abnormal EEG activity in central areas was recorded during painful stimulation compared to healthy subjects. All these results may be explained by sensitization of the central nervous system due to chronic pain conditions.

INTRODUCTION

Chronic pain is defined as pain that lasts for more than 3 months, over the normal healing time (Treede et al., 2015). Chronic pain impacts working life, somatic, emotional and social wellbeing and quality of life of the affected individuals and it is recognized as a major health care problem in Europe (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). Recently the International Association for the Study of Pain (IASP) distinguished between "chronic primary pain" and "chronic secondary pain". In the first category, chronic pain is conceived as a disease in its own right; in the second, pain is a consequence of an underlying disease and may initially conceived as a symptom (Treede et al., 2019). Orofacial pain (OFP) is usually classified as chronic secondary pain because, in most cases, it can be attributed to an underlying cause (Benoliel et al., 2019). Frequently the pain starts from a TMD, outlasts the initiating event and become the leading cause for continuing treatment need (Benoliel et al., 2019). Patients, following TMD resolution, no longer exhibit peripheral tissue damage but continue to feel pain suggesting an abnormal functioning of the somatosensory system (Sarlani & Greenspan, 2005). This process may be due to an induced sensitization of higher-order neurons, a phenomenon well described by the central sensitization (CS) process (Campi, Jordani, Tenan, Camparis, & Gonçalves, 2017). According to the IASP definition, CS is characterized by an increased responsiveness of nociceptive neurons in the central nervous system (CNS) to their normal or subthreshold afferent input (Loeser & Treede, 2008). With the introduction of the CS concept, pain starts to reflect a functional state of circuits in the CNS instead of being exclusively peripherally driven (Woolf, 2011). Injury or inflammation in peripheral tissue can alter the properties of somatic sensory pathways. This induced peripheral sensitization could trigger CS, leading to pathological pain states (Harte, Harris, & Clauw, 2018). CS has been described in patients with TMD by Dworkin who found no correlation between physical signs of jaw dysfunction and levels of pain in a 3-year follow-up study (Dworkin, 1995). Quantitative sensory testing (QST) like pressure pain threshold (PPT) can be used along to document the somatosensory profile (Svensson et al., 2011). A generalized state of pain sensitivity can justify low PPT, imputable to altered sensory processing, dysregulated endocrine function, hyperinflammatory states, or psychological processes (Lautenbacher, Rollman, & McCain, 1994). In a large prospective study, the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) study, Slade et al. observed that PPT fluctuated in synchrony with the course of painful TMD (Slade et al., 2014). Further, a reduction of PPT in sites related to the temporomandibular joint has been identified as sign of peripheral sensitization (Campi et al., 2017). In case of sensitization due to supraspinal

pathways, the local threshold is further reduced at the local site, but it is also reduced in more distant body sites not related to TMD. The comparison of a TMD cohort with a healthy and pain free sample could be the only way to evaluate the degree of localized and spreading sensitization (Arendt-Nielsen et al., 2018). Involvement of cerebral circuits in chronic pain development has been broadly documented (Apkarian et al., 2004; Ferdek et al., 2019; Kim et al., 2013). Chronic pain seems to be associated to pain related central networks and neuroplastic changes in these circuits may change perception of pain independent of peripheral neural activation (Camfferman, Moseley, Gertz, Pettet, & Jensen, 2017). Thalamus appears to be a key feature in several chronic pain conditions and its connection with cerebral cortex imputable to maintenance of pain (Llinás, Ribary, Jeanmonod, Kronberg, & Mitra, 1999; Stern, Jeanmonod, & Sarnthein, 2006). Many studies tried to identify electroencephalography (EEG) pattern related to pain development and maintenance after physiological tissue healing time (Jensen et al., 2013; Pinheiro et al., 2016; Prichep, John, Howard, Merkin, & Hiesiger, 2011). Despite the lack of certainty about cortical marker of chronic pain, a reduction in alpha activity in frontal lobes and increased theta activity in posterior parietal cortex has been recorded in subjects who suffer of chronic pain for different conditions (Camfferman et al., 2017; Jensen et al., 2013; Sarnthein & Jeanmonod, 2008; Sarnthein, Stern, Aufenberg, Rousson, & Jeanmonod, 2006). The objective of the study is to describe features of chronic OFP due to TMD through the analysis of psychological aspects of patients, peripheral pain threshold and EEG recording, looking for possible signs of CS.

METHODS

This cross-sectional observational study describes factors related to chronic OFP and characteristics of patients in a cohort of twenty-four subjects with OFP due to TMD. This study has been reviewed by the Ferrara University Hospital Ethics Committees. Written informed consent was obtained before all procedures. The study meets the STROBE Guidelines for observational studies (von Elm et al., 2014).

Patients who underwent rehabilitation for TMD at Ferrara Rehabilitation Hospital between January 2018 and January 2019 were assessed for eligibility. Age, sex, occupation, side and duration of TMD, past treatment for temporomandibular joint, comorbidities and medications were recorded. All subjects with a Numeric Pain Rating Scale (NPRS) less than three during the past two weeks or who take medications for pain relief in the two weeks before were excluded from the study (Jensen et al., 2013). Exclusion criteria were also: impaired cognitive

functioning (score less than 24 on the Mini Mental Status Examination), neurological or psychiatric disorders, pregnancy.

A medical doctor expert in temporomandibular rehabilitation evaluated all subjects included in the study following the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I (Schiffman et al., 2014).

The RDC/TMD Axis II was used to assess psychological distress and pain-related disability (Schiffman et al., 2014). For analyses purpose, depression, anxiety and non-specific physical symptoms (NSPS) were treated as dichotomous variables and patients were classified as minimal/mild if their total score was lower than 10; patients with a higher score were classified as moderate/severe (Campi et al., 2017). All subjects included were evaluated using self-reported questionnaire for pain description and PPT for objective assessment of pain perception (Dworkin et al., 2005). Neuronal activity linked to pain sensation was recorded using Electroencephalography (EEG). QST and EEG were also evaluated in a sample of age- and sex-matched healthy controls.

Self-reported questionnaire

Catastrophizing has been defined as "an exaggerated negative orientation towards actual or anticipated pain experiences" and reflects a tendency to misinterpret or exaggerate apparently threatening situations (Sullivan, Bishop, & Pivik, 1995a). The Pain Catastrophizing Scale (PCS) was used to assess the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain (Quartana, Campbell, & Edwards, 2009). A PCS score ≥ 30 was used to detect presence of catastrophizing (Sullivan, Bishop, & Pivik, 1995b).

CS was assessed using the Italian version of the Central Sensitization Inventory (CSI-I) (Chiarotto et al., 2018). A CSI score ≥ 40 has been suggested as the cut-off score to determine if patients display CS (Neblett et al., 2013, 2015; Nijs et al., 2014).

Pressure Pain Threshold (PPT)

PPT is defined as the minimum pressure applied to anatomical regions that can induce pain (Fischer, 1987). PPT measurement was performed with a handled digital dynamometer (Commander Algometer, JTECH Medical USA), consisting of a device with 1 cm^2 flat circular tip used to apply pressure on subjects' skin. A researcher was trained to apply a constant pressure of approximately 1 $lb/cm^2/s$ perpendicular to the skin using the dynamometer, following a protocol well described in literature (Campi et al., 2017). The stimulus intensity increases from zero and the subject was instructed to stop the stimulation at the first

perception of pain by pushing a button. At that moment, the pressure was removed, and the value of pressure applied was recorded. The sites of the stimulation were the muscle belly of the temporal and masseter muscles, the surface of the mandibular condyle, the middle part of the upper trapezius and the centre of the thenar eminence (Fig. 1). During examinations subjects were in a comfortable sitting position with muscles relaxed. The researcher stabilized subject's head gently applying manual resistance contralateral to the point of pressure application. This procedure was repeated three times for every site for both side with an interstimulus interval of 30s (Nie, Graven-Nielsen, & Arendt-Nielsen, 2009). For the patients, the PPT value of painful side was used for the analysis. Value of the more involved side was considered when symptoms were bilaterally. Side of PPT was matched in healthy subjects.

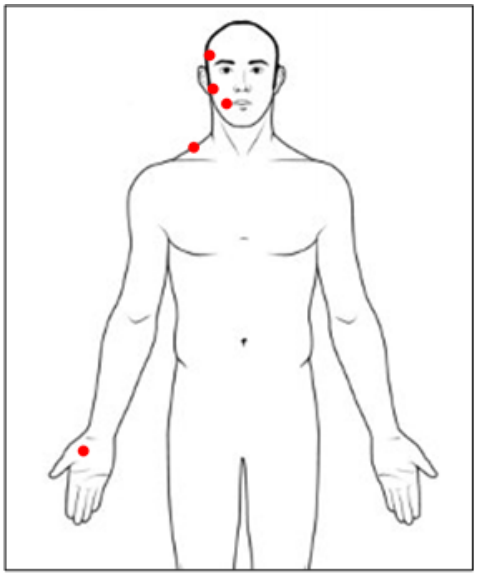

Figure 1. Sites for pressure pain threshold assessment

EEG Recording

EEG assessment was performed using an electrode montage of 32 Ag/AgCl pellet pin electrodes (Easy Cap GmbH, Herrsching, Germany) placed according to the 10-20 International System on a Fast'n Easy cap. A BrainAmp amplifier (Brain Products, Munich, Germany) was used to record EEG activity. All scalp electrodes were referenced to nasion and grounded at AFz during recordings. Horizontal and vertical eye movements were detected respectively with electrodes placed at the left and right outer canthi at Fp1 and below the eye at the non-painful side. The impedance of all the electrodes was kept below 10 kΩ. The EEG signals were recorded with a 1000 Hz sampling rate with a low cut-off frequency of 0.1 Hz and a high cut-off of 1000 Hz.

EEG data was recorded during a 5 minutes resting state task with open eyes and a 5 minutes resting state task with closed eyes. Participants were instructed to stay relaxed and keep their eyes fixed on a cross in front of them during open-eyes recording. EEG was also recorded during the PPT assessment at the thenar eminence following the above-mentioned protocol.

EEG Preprocessing

The EEG data was pre-processed in Matlab, using the EEGlab toolbox (Delorme & Makeig, 2004). A notch filter was applied in post processing for eliminating the power-noise. Then, data was re-referenced to the average reference. Eye movement artifacts were removed by means of an Independent Component Analysis (ICA) procedure. ICA analysis was used to determine the independent components. A visual analysis was used to discard components that were characterized by high-amplitude fluctuations and were mostly located at or close the eye electrodes.

EEG Spectral Analysis

The spectral power in the different EEG bands (theta, delta, alpha, beta, gamma) was calculated, during both resting state tasks, in the middle minute of the 5 minutes of each recording. The power spectral density (PSD) was calculated using Welch's method, using 1 s windows and 80% of overlap over successive windows. The PSDs of all subjects during each trial when then transformed into z-scores. For the pain stimulus trials, the PSD was calculated from the 3-seconds window before reaching the sensory threshold. The PSD calculated during the pain stimulus trials was transformed in z-scores and expressed as a percentage of the PSD calculated from the resting state trials with the eyes open. This choice for normalization was dictated by the fact that subjects had their eyes open during the pain stimulus trials.

Statistical Analysis

Descriptive statistics were used for characterizing the sample. Continuous variables are reported as means and standard deviations, non-continuous variables as counts and percentages. Differences in PPT between patients with OFP and healthy subjects were assessed using the Wilcoxon rank-sum test due to non-normal data distribution. Patients with OFP were also divided according to intensity of pain, presence of psychological disorders, catastrophizing and CS and differences between groups were analyzed. Spearman's rank correlation coefficient was used to measure strength and direction of association between psychological scores and self-reported questionnaires.

Statistical analysis was performed using STATA 13.1 software. Statistical significance was set to $p < 0.05$.

RESULTS

Nineteen subjects of the sample were women. The mean age was 49.8 years, with a minimum of 23 and a maximum of 77 years. Detailed demographic and clinical features of the sample are summarized in Table 1. Most of the sample was classified as myofascial pain with spreading following the Axis 1 of DC/TMD. The mean pain intensity during the 24 hours before at the NRS was 6.42 (1.72 SD), with a minimum of 3 and a maximum of 9. Twenty-four age- and sex-matched healthy subjects were recruited. The assessment in PPT revealed a reduction in pain threshold in subjects with OFP in all the sites of assessment compared to healthy subjects. Differences between groups were statistically significant (Fig. 2). Stratifying patients according to psychological assessment performed with RDC/TMD Axis II we recorded reduction in PPT in all subjects with moderate or severe symptoms compared to those with low or mild, with significative differences for pain related disability and depression (p=0.045 and p=0.023 respectively) (Table 2). No significative differences in pain threshold were identified in patients with CS signs. Positive correlations were found between CS and psychological disorders (depression, non-specific physical symptoms, catastrophizing), without distinction of severity.

Table 1. Descriptive data for the sample

	Sample (n=24) *Mean (SD) or n (%)*
Age (*years*)	49.8 (13.1)
Sex (*n*)	
male/female	5 (21) / 19 (79)
Occupation (*n*)	
employed/unemployed	14 (58) / 10 (42)
Principal comorbidities (*n*)	
rheumatic disease	6 (25)
hypertension	4 (17)
enteric disease	3 (12)
diabetes mellitus	1 (4)
none	10 (42)
Drug use (*n*)	
non steroidal anti-inflammatory drugs	5 (21)
antidepressants	2 (8)
muscle relaxants	2 (8)
analgesics	3 (11)
none	12 (50)
Symptoms duration (*months*)	49.21 (68.59)
Symptoms frequencies (*n*)	
continuous/episodic recurrent	7 (35) / 17 (65)
Pain side (*n*)	
right/left/bilateral	3 (10) / 3 (15) / 18 (75)
Previous treatment	
physiotherapy	11 (45)
arthrocentesis	10 (35)
byte use	16 (65)
DC/TMD AXIS I	
myofascial pain with spreading	21 (90)
myalgia	1 (5)
arthralgia	2 (5)

DC/TMD AXIS II	
Pain related disability (*n*)	
low	9 (37.5)
high	15 (62.5)
Depression (*n*)	
minimal-mild	16 (66.7)
moderate-severe	8 (33.3)
Anxiety (*n*)	
minimal-mild	19 (79)
moderate-severe	5 (21)
Non-specific physical symptoms (*n*)	
minimal-mild	13 (54)
moderate-high	11 (46)
NPRS	6.42 (1.72)
Catastrophizing (*n*)	
not present	12 (50)
present	12 (50)
Central sensitization (*n*)	
subclinical-mild	12 (50)
moderate-severe	12 (50)

n: number; SD: standard deviation; DC/TMD AXIS I and AXIS II: Diagnostic Criteria for Temporomandibular Disorders AXIS I and AXIS II; NPRS: Numeric Pain Rating Scale

Table 2. Pressure pain threshold for classes of impairment

		Mean (SD)	*p*
DC/TMD AXIS II			
Pain related disability	low (*n* = 9)	3.8 (1.3)	**0.045**
	high (*n* = 15)	2.6 (1.1)	
Depression	minimal - mild (*n* = 16)	3.5 (1.3)	**0.023**
	moderate - severe (*n* = 8)	2.3 (1.0)	
Anxiety	minimal-mild (*n* = 19)	3.1 (1.3)	0.749
	moderate-severe (*n* = 5)	2.9 (1.3)	
Non-specific physical symptoms	minimal - mild (*n* = 13)	3.4 (1.4)	0.213
	moderate - severe (*n*=11)	2.7 (1.1)	
NPRS	mild - moderate 3 - 6 (*n* = 12)	3.0 (1.3)	0.954
	severe 7 - 10 (*n* = 12)	3.1 (1.3)	
Catastrophizing	not present (*n* = 12)	3.2 (1.4)	0.427
	present (*n* = 12)	2.8 (0.9)	
Central sensitization	subclinical - mild (*n* = 12)	3.3 (1.5)	0.564
	moderate - severe (*n* = 12)	2.9 (0.9)	

n: number; SD: standard deviation; DC/TMD AXIS II: Diagnostic Criteria for Temporomandibular Disorders AXIS II; NPRS: Numeric Pain Rating Scale

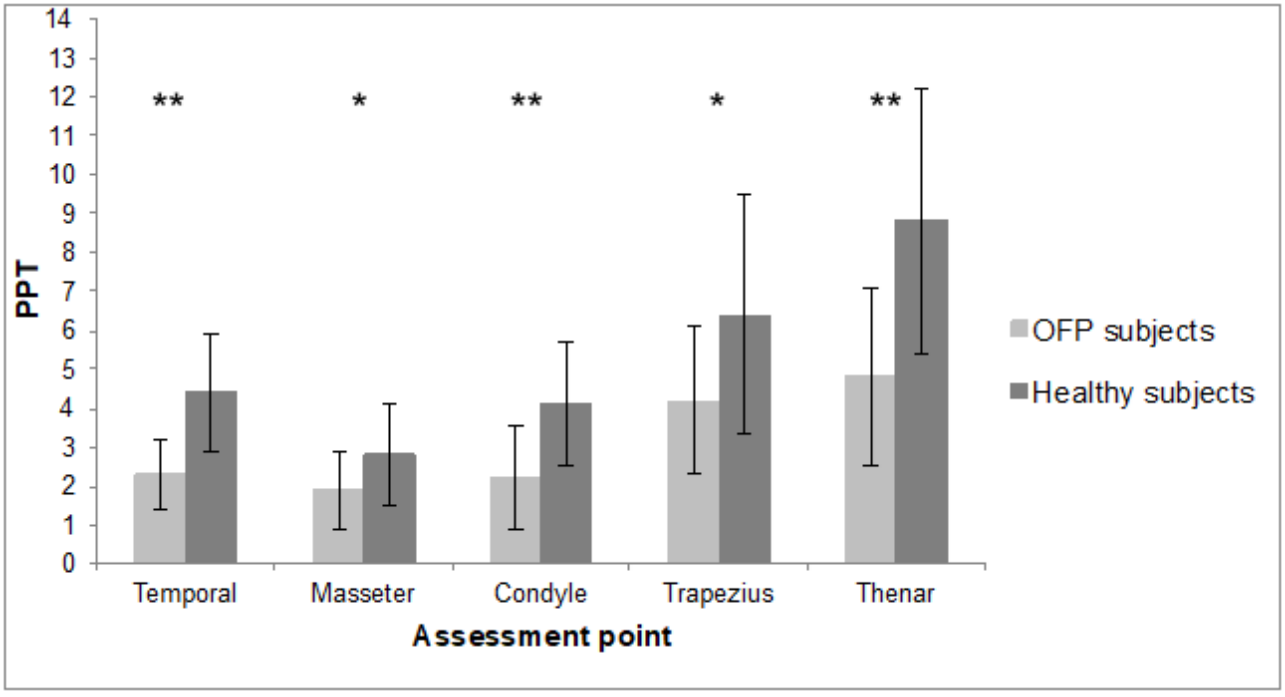

Figure 2. Mean pressure pain threshold of the two samples

PPT: pressure pain threshold; lb: libre; OFP: orofacial pain; *p<0.01 **p<0.001

EEG Results

We did not observe qualitative differences in the PSD between the patients and the control subjects for both the eyes closed and eyes open resting trials across the different frequency bands. For the pain stimulus trials, we noticed increased PSD values (with respect to the eyes open trial) in the gamma band in the controls that was localized mostly in the occipital region. In the patients, differently than the controls, increased values of PSD in the gamma band were instead observed in the cortical and frontal regions (C3/C4 F3/F4 electrodes) (Fig. 3).

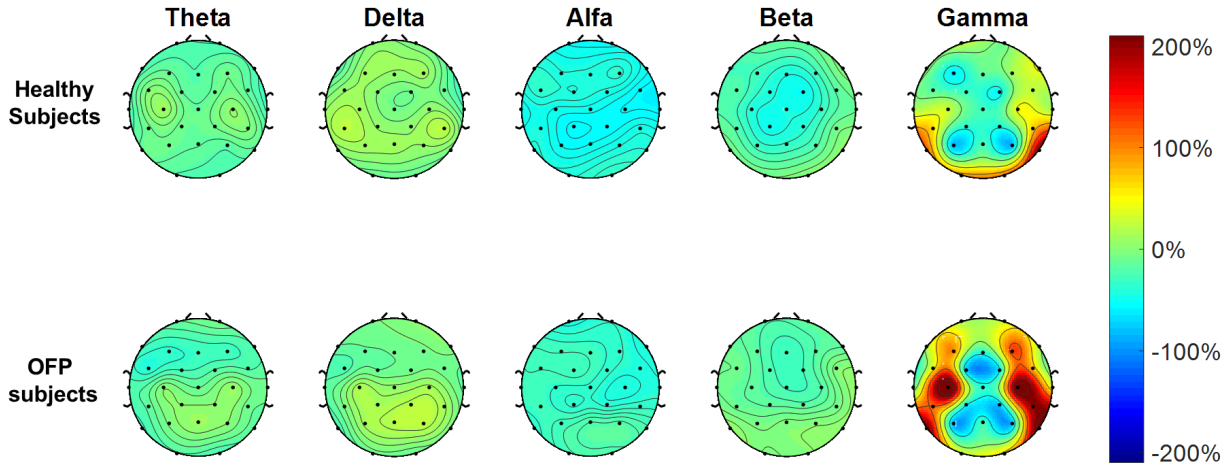

Figure 3. Electrode-level maps of the percentage changes in the z-values of the power spectral density in the different bands between the open eyes resting task and the pain stimulus task. The top row represents the healthy controls, the bottom row the orofacial pain (OFP) patients.

DISCUSSION

In this observational study we tried to describe features and clinical signs of people with chronic OFP due to TMD by comparing them with healthy controls. Our main finding revealed that people who suffer from this debilitating condition present a generalized reduction in PPT. This reduction in pain threshold was observed not only in facial sites but also in areas not involved by pathology, like the upper trapezius or along the upper limb. The phenomenon we observed may be due to CS, an increased responsiveness of nociceptive neurons to subthreshold input (Loeser & Treede, 2008). Fillingim et al. in their longitudinal study found that individuals who transitioned from being TMD-free to a TMD-state tended to show

reduction in PPT limited to the orofacial region and not to other body sites (Fillingim et al., 2018). The discrepancy between these and our results may be explained by the difference in time elapsed between OFP onset and PPT assessment in the two studies. In fact, subjects who developed TMD in the OPPERA study were evaluated for pressure pain sensitivity at a median time of 14 days from symptoms onset (Fillingim et al., 2018; Greenspan et al., 2013). In our study PPT was assessed in patients with OFP from a median time of 33 months. Chronic pain, critical in development of CS, have to last for more than 3 months to be defined as such (Treede et al., 2015). Pain lasting for a shorter time may not contribute to hyperexcitability of the CNS, one of the main features of sensitization process (den Boer et al., 2019). In our study we included patients with fibromyalgia, and this may represent a confounding factor in PPT assessment (Maquet, Croisier, Demoulin, & Crielaard, 2004). However, the analysis performed on the sample after exclusion of fibromyalgia patients showed no differences compared with the whole sample. Stratification of people with OFP based on psychological disorder severity revealed that subjects with moderate or severe depression and high level of pain-related disability showed generalized reduction in PPT. A large systematic review on pain sensitivity and depression found uncertain results about mechanisms underlying their relationship (Thompson, Correll, Gallop, Vancampfort, & Stubbs, 2016). However depression and pain sensitivity frequently occur together (Agüera-Ortiz, Failde, Mico, Cervilla, & López-Ibor, 2011; Bair, Robinson, Katon, & Kroenke, 2003; Lépine & Briley, 2004; Von Knorring, Perris, Eisemann, Eriksson, & Perris, 1983; Von Korff, Dworkin, Le Resche, & Kruger, 1988), probably due to dysfunction at the level of the serotonergic and noradrenergic neurons that affects psychological and somatic symptoms of depression but also physical painful symptoms (Stahl & Briley, 2004). Another possible explanation of the above-mentioned results is that depressed people react negatively to painful stimulation with stronger emotional involvement. A reduction in PPT as sign of CS may explain the link between sensitization of the CNS and emotional comorbidities. Smart et al. in their study on patients with low back pain reported significantly greater levels of pain-related disability, depression and anxiety in people with signs of CS compared to those with nociceptive or neuropathic pain (Smart, Blake, Staines, & Doody, 2012). Strong relationship between CS and psychological symptoms is confirmed by our analysis. What need to be clarified is the causal link between them, establishing if psychological disorders are involved in sensitization or they are consequence of a sensitized system.

To our knowledge, the current study is the first investigating EEG PSD during PPT assessment in people with OFP versus healthy control subjects. In this study we found no differences

between patients and control subjects during resting trials. We noticed instead an increase in central and prefrontal activity in gamma bands during peripheral stimulation just before stimulus was perceived as painful. Other studies investigating resting state EEG in people with chronic pain described significant overactivation of regions involved in pain network. Prichep et al. recorded overactivity in insula areas, parietal lobule, thalamus and the dorsolateral prefrontal cortex; significant differences between normal and pain patients were found in mid and posterior cingulate. Generalized overactivity was described in all areas belonging to the "pain matrix" (Prichep, Shah, Merkin, & Hiesiger, 2018). Our findings about gamma activity in prefrontal areas may further support the model proposed by Baliki & Apkarian on dissociation in processing of longer lasting pain and nociceptive information (Baliki & Apkarian, 2015). The authors described a dissociation of prefrontal component of the default mode network (DMN) in different types of chronic pain (Baliki & Apkarian, 2015). In fMRI studies the DMN was described as one of the tree brain systems that, with their dynamic interactions, are involved in spontaneous attentional fluctuations toward and away from pain (Kucyi & Davis, 2015). The DMN is activated when subject attention is not engaged by sensations from external world (Andrews-Hanna, Smallwood, & Spreng, 2014). In opposition to the DMN, a system known as the salience network (SN) works to track how external stimuli capture attention (Jonathan Downar, Mikulis, & Davis, 2003; Mouraux, Diukova, Lee, Wise, & Iannetti, 2011; Uddin, 2015). Prefrontal areas, in particular dorsolateral prefrontal cortex, are part of the SN (Kucyi, Hodaie, & Davis, 2012; Seeley et al., 2007). An over activity of prefrontal cortex recorded in patients with OFP due to TMD may be representative of an exaggerated engagement of SN in people with long lasting pain and a general tendency to focus attention on external stimuli that could generate pain. Similar results about increased prefrontal gamma activity were reported in chronic back pain patients (May et al., 2019), patients with post-herpetic neuralgia and fibromyalgia (Lim, Kim, Kim, & Chung, 2016; Zhou et al., 2018). Association between gamma oscillations and involuntary attentional effects of pain was well described in literature (Hansen et al., 2017; Hauck, Lorenz, & Engel, 2007; Schulz et al., 2015; Tiemann, Schulz, Gross, & Ploner, 2010), in addition to have great relevance in cortical networks for behavioural and cognitive phenomena (Uhlhaas et al., 2009).

Increased activity of primary motor cortex (M1) area in people with chronic pain was previously described in literature in different musculoskeletal conditions (Di Pietro et al., 2013; Schabrun, Elgueta-Cancino, & Hodges, 2017; Schabrun, Hodges, Vicenzino, Jones, & Chipchase, 2015; Te, Baptista, Chipchase, & Schabrun, 2017). A recent systematic review found inconclusive results about abnormal M1 activation in pain conditions due to

heterogeneity of studies and assessment tools (Chang et al., 2018). Our results seem to underlie abnormal brain activity recorded by C3/C4 electrodes just before the peripheral stimulus became painful. Movement disfunction like unnecessary protective behavior may justify our findings, when patient was undergone to stimulus perceived as threatening. Primary motor cortex was already been target of treatment like brain stimulation with good results on pain relief (Fregni et al., 2006; Straudi et al., 2018). Abnormal function of motor and prefrontal cortex during stimulus perception may due to neuroplastic changes that occur in human brain subjects to long lasting pain. Neurophysiological adaptations occur and seem to persist over peripheral tissue healing time in presence of emotional and behavioral aspects of pain that cause maladaptive changes in areas not normally involved in pain perception (Mansour, Farmer, Baliki, & Apkarian, 2014). Structural changes, as well as functional, were described in frontal and motor areas of patients with chronic pain due to coxarthrosis (Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2013).

Interpretation of our findings is subject to several limitations. Firstly, the small sample size does not allow us to confirm our results on PPT and EEG recordings. Even though CS may be hypothesized looking at our results, we cannot draw any definite conclusion on mechanism underlying sensitization of CNS. Secondly, interpretation of our results must consider the inclusion in our sample of fibromyalgia patients whose sensitivity to pain may influence their PPT.

CONCLUSIONS

In a convenience sample of patients with OFP due to TMD we observed generalized reduction in PPT compared to age- and sex-matched healthy controls, not limited to facial sites. Generalized decrease of pain threshold seems to be linked to severity of psychological symptoms like depression and perceived health-related disability. Abnormal EEG activity in central areas was recorded during painful stimulation led to non-painful sites of patients with OFP due to TMD. This observational study tried to identify potential signs of CS through analysis of sensory and psychological profile and brain activity. Our results can open doors to new strategy for assessment and treatment of patients with CS due to chronic pain conditions.

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AUTHOR CONTRIBUTIONS

AB, SS, S Buja and NB conceived the study and participated in its design. AB and S Borsato performed the instrumented and clinical data collections. AB and GS analyzed the data. AB, GS and SS interpreted the results. AB, GS and SS drafted and revised the manuscript.

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DISCUSSION

Chronic pain represents a disabling condition for many patients that daily come to our rehabilitation departments. The aim of this PhD project was to identify new ways of assessment and treatment for patients suffering from long lasting pain unresponsive to conventional treatment. In the first research project, a small case series on patients with chronic orofacial pain, we proposed tDCS for pain relief. NIBS can be used to modify neuroplastic changes occurring in people with chronic pain, trying to reverse maladaptive modifications that occur in CNS when pain lasts for a long time (146). We treated with tDCS three subjects with orofacial pain due to TMDs diagnosed according to the DC/TMD Axis I. What we found is that tDCS seems to be effective in reducing pain and pain-related psychological symptoms in subjects with less musculoskeletal impairment. Two of three subjects revealed reduction in pain intensity and psychological distress. The third shown any changes after treatment and at one-month follow-up. The subject who shown no modification was the one with more severe degenerative impairment. What we can speculate is that complex pain with peripheral engagement and sensitization may need a multifactorial approach, based on bio-psycho-social model. Many authors reported the need to solve nociceptive peripheral trigger before working on sensitization of CNS (22,152).

Schabrum et al. found positive results on pain and sensitization symptoms combining tDCS and a nociceptive treatment like peripheral electrical stimulation in people with CLBP (153). The reduction in pain severity they recorded following combined treatment was greater in patients with more pronounced primary and secondary hyperalgesia (153). We can assume that a combined treatment including top-down and bottom-up approach can be useful in treatment of patients with chronic pain due to musculoskeletal trigger and sensitization of the CNS.

The above-mentioned results about the need of a combined treatment in complex pain were confirmed by the second research project presented in this PhD project. In a double-blinded randomized control trial on patients with CLBP we found that combination of tDCS and group exercise was effective in ameliorating pain and psychological wellbeing with effects evident at one-month follow-up and during the behavioural intervention. In CLBP sensitization phenomenon are frequently recorded. A recent meta-analysis revealed that reduced pressure pain threshold (PPT) at remote body parts in people with CLBP might be sign of a sensitized CNS (154). What we found is that adding NIBS to behavioural treatment seems to increase positive effects of rehabilitation, especially during the treatment and in the long term. Several studies tested efficacy of combined treatment on pain with uncertain results (155,156). Probably our finding may be explained looking at tDCS mechanisms and stimulation protocol. Stimulation delivered on daily sessions seems to be the better choice to produce the greater effect (157). Furthermore, our combination of treatment seems to be

the more effective in producing positive outcomes. In our study we proposed a behavioural treatment that engage the same neural area that we stimulate, the primary motor cortex (M1). Indeed, spatial correlation between area of stimulation and behavioural task seems to be important to improve effects of both treatments. Behavioural treatment effect on action potential induction may be enhanced by tDCS only if temporal and spatial correlations are respected.

Another crucial point of discussion is about the stimulation area. Changes in M1 were recorded in many studies (158–160) but it's still unclear if they represent an adaptive mechanism to protect against further pain or injury rather than nociplastic modifications due to chronic pain itself (161). Recently, a systematic review by Chang et al. investigated M1 structural and functional changes in people with chronic pain of neuropathic and non-neuropathic origin (162). No conclusive results were found about role of M1 reorganization in chronic pain conditions and larger better quality studies are mandatory to inform treatments targeting the motor area (162). Also assessment techniques like EEG, fMRI, PET or neurophysiological changes need to be further investigated to elucidate their role in M1 investigation during chronic pain conditions (162).

M1 activation during pain assessment was one of our main finding in the observational study we proposed on people with chronic pain due to TMDs. In the third research project presented in this PhD project we investigated features of pain in people with chronic orofacial pain looking for signs of CS. EEG recording performed during pain threshold assessment in a peripheral area not linked to TMJ revealed an abnormal M1 activation in people with chronic pain when compared with healthy subjects. Specifically, we observed increased gamma activity in motor area just before the peripheral stimulus was perceived as painful. Increased gamma activity may indicate increased muscle activity during pain that contaminates EEG signal during pain stimulation (163,164), but we didn't record any muscular activity during pain threshold assessment. Furthermore, a muscular activation would be highlighted also by altered EEG signal during the recording. M1 activation wasn't our only finding; we recorded also prefrontal increased activity during painful stimulation. Prefrontal areas, specifically dorsolateral prefrontal cortex, belong to SN. The SN is activated when an external stimulus captures attention (165–167). We can speculate that people suffering from chronic pain present an exaggerated tendency to focus attention on stimuli that can be perceived as painful. Activation of SN has been recorded in other painful conditions while attending to painful stimuli (168–171), in contrast with the DMN that is activated when subject attention is not engaged by sensations from external world (172). The concept that chronic pain can be due to attentional process may open the doors to new way of treatment aimed at draw attention away from nociceptive stimuli or stimuli perceived as such. The same generalized reduction in pain threshold recorded in people with chronic orofacial pain may be due to exaggerated attention to the evaluation process, in expectation of a nociceptive stimulus. Over activation

recorded in brain areas of people with chronic pain may be target of treatment, helping to define precisely CNS areas involved in sensitization process.

All the considerations made about new way of assessment and treatment of chronic pain can contribute to the management of this disabling condition. The assessment of CNS became crucial when clinicians have to deal people with chronic pain, also when its onset and maintenance appears to be only due to musculoskeletal conditions.

In the next future we would like to confirm our considerations about EEG biomarkers in chronic pain due to different causes, not limited to people with TMDs. The identification of defined EEG recording related to long-lasting pain may open the doors to EEG-tDCS closed loop system, able to detect the predefined EEG pattern of chronic pain and successfully trigger the stimulation. This process should permit customized treatments on the basis of brain activity recorded on the patient.

Finally, the identification of defined brain areas involved in chronicity and sensitization may justify the research of EEG modifications following successful treatments.

CONCLUSION

Chronic pain is a disabling condition, frequently associated to CS mechanisms that promote its development and maintenance. NIBS techniques can be used to reverse maladaptive changes that occur in human brain when pain lasts for a long time. In people with chronic pain due to TMDs or low back pain tDCS seems to be efficacy on symptoms intensity reduction and pain-related quality of life improvement. tDCS efficacy may be improved combining its top-down effects with a bottom-up approach, like physical therapy or group exercise treatment.

Brain modifications due to chronic pain and presence of CS mechanisms can be assessed using EEG. Abnormal EEG activity in central and frontal areas during pain threshold assessment may be recorded as CS signs in people with chronic pain.

Interpretation of our findings needs to be confirmed by further studies on people with chronic pain. However, these results can open the doors to new strategy for assessment and treatment of patients with chronic pain and CS.

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