

# Principles and Practice of Clinical Research

A Global Journal in Clinical Research



# PPCR

ISSN: 2378-1890

## Assessing potential neurophysiological signatures of chronic corneal pain and its modulation through non-invasive brain stimulation: A commentary

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Received August 20, 2015; accepted August 26, 2015; published September 16, 2015.

### Abstract:

Chronic corneal pain (CCP) is a highly disabling condition and its diagnosis is typically made based on patients' self-report. Recent advances in the understanding of the pathophysiology of chronic pain syndromes have led to the hypothesis that sensitization of both peripheral (i.e. trigeminal) and central (i.e. thalamocortical) pathways may be involved, resulting in pathological alterations of brain activity. However, no objective neurophysiological biomarker associated with symptom presence or severity has been identified to date. Moreover, the lack of effective therapeutic options for medically-refractory cases further complicates the management of CCP. In recent years, several techniques such as electroencephalography (EEG) and transcranial magnetic stimulation (TMS) have been used to investigate the neurophysiological signatures of several chronic pain conditions. Additionally, transcranial direct current stimulation (tDCS) has emerged as a promising alternative for the treatment of chronic medically-refractory pain. In this commentary, we discuss the interest of EEG and TMS as potential clinically relevant tools to identify biomarkers of chronic corneal pain reflecting disrupted cortical and/or thalamocortical processing. Furthermore, these techniques could be used to guide the development and application of alternative therapeutic options such as tDCS to reduce the symptoms associated with this condition.

DOI: <http://dx.doi.org/10.21801/ppcrj.2015.12.3>

### INTRODUCTION

Chronic corneal pain (CCP) can be caused by several conditions including dry eye disease (e.g. Sjogren's syndrome), direct injury to the ophthalmic branch of the trigeminal nerve (e.g. surgical ablation) and infectious disease (e.g. herpes zoster ophthalmicus) [1]. Recent advances in the understanding of chronic pain pathophysiology have led to the hypothesis that CCP may be associated with both peripheral (i.e. trigeminal pathway) and central (e.g. thalamocortical pathway) sensitization [1]. However, the diagnosis and treatment of this condition remains a challenge. The diagnosis of CCP is typically made based on patients' self-report [1, 2] and, although nerve microscopic changes have been occasionally observed [3], to date no objective reliable

biomarker has been described, possibly leaving a number of patients undiagnosed. Furthermore, when an accurate diagnosis is made, available therapeutic options including pharmacological intervention [4-8] and decompression of the trigeminal nerve root [9] have shown limited efficacy [1]. Given the current challenges in the diagnosis and treatment of CCP, the identification of neurophysiological signatures associated with this condition has the potential to significantly improve diagnostic accuracy and guide the development of new therapeutic approaches, particularly those based in the use of non-invasive brain stimulation.

In this commentary, we discuss two potential tools that could be used to identify neurophysiological signatures in CCP: electroencephalography (EEG) and

transcranial magnetic stimulation (TMS). EEG is a safe, portable, and low-cost tool that provides reliable measures of cortical activity with a high temporal resolution, while TMS, a non-invasive brain stimulation technique, can inform on maladaptive plasticity by assessing changes in cortical excitability. In this context, several EEG and TMS studies have described specific cortical changes related to chronic pain [10-13] suggesting that both techniques could be relevant to identify novel biomarkers for CCP.

As an example of a promising novel strategy for the management of CCP, we here also discuss the use of transcranial direct current stimulation (tDCS) as a non-invasive brain stimulation technique able to modulate cortical excitability. Although tDCS has shown promising results in the management of chronic pain [14, 15], its potential in the case of CCP remains to be assessed.

### **Electroencephalography (EEG) as a potential tool to identify neurophysiological signatures of chronic corneal pain**

EEG is a widely used technique to assess cortical activity. Several EEG measures, such as power, peak frequency and event-related potentials (ERP) are commonly used in research and clinical settings to evaluate cortical processes in both healthy and clinical populations [16, 17].

Chronic pain has been related to changes in EEG measures. For example, neuropathic pain after spinal cord injury (SCI) has been associated with a slowdown of background EEG activity, as indexed by lower EEG peak frequencies [11, 18-21]. Moreover, this shift in the peak frequency toward slower EEG rhythms has been reported to distinguish SCI patients with pain from SCI patients without pain [21]. Consistent with this shift in peak frequency, an increase of power in the EEG theta band (4- 8 Hz) has also been reported in other chronic pain conditions including chronic pancreatitis and neuropathic pain with central and peripheral causes [10, 22-26]. One of the mechanisms that could explain these EEG changes associated with chronic pain is known as thalamo-cortical dysrhythmia and it involves alterations in thalamic processing and thalamocortical pathways [23, 27]. Moreover, reduction in pain symptoms and normalization of EEG activity after thalamic surgery strongly suggest a role of the thalamus and thalamic connections in the pathophysiology of chronic pain [11] while emphasizing the interest of EEG as a potential tool to identify biomarkers associated with this condition.

In addition to resting EEG changes, several EEG-ERP studies have reported brain activity disruptions in chronic pain conditions in relation to different cognitive

processes including attention [28], early pre-attentive sensory processing [29], pain-related verbal information processing [30, 31], non-painful sensory [28] and pain processing [32, 33]. Altogether these studies provide evidence of disruptions at the level of sensory, affective, and cognitive processing, in chronic pain conditions [28-34]. Moreover, some of these disruptions may be restored following pain relief [29].

Taken together, all this evidence suggests that CCP may be associated with specific EEG changes and that those could be relevant and potentially employed as objective biomarkers for this condition.

### **Transcranial magnetic stimulation (TMS) as a potential tool to identify neurophysiological signatures of chronic corneal pain**

Single-pulse TMS is a well-suited technique to measure cortical excitability and assess the integrity of the corticospinal tract, whereas paired-pulse TMS has been employed to assess inter-hemispheric and intra-cortical circuits. One of the paired-pulse TMS measures to assess intra-cortical circuits, short interval intra-cortical inhibition (SICI), has been consistently related to chronic pain [12, 13, 35-37]. In particular, decreased SICI has been observed in several chronic pain conditions including Complex Regional Pain Syndromes (CRPS), phantom limb pain, hand pain with neurogenic origins, central post-stroke pain and incomplete peripheral nerve lesions [12, 35-39], suggesting altered inhibitory-excitatory balance in sensory and motor cortices. Given the similarities between CCP and other chronic pain conditions, it is likely that CCP would involve similar changes in intra-cortical circuits that can be indexed by TMS.

### **Transcranial direct current stimulation (tDCS) as a potential tool to modulate cortical excitability and alleviate symptoms in chronic corneal pain**

Conventional therapeutic approaches to chronic pain have yielded modest effects in pain reduction [40]. In this context, non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) and repetitive TMS (rTMS) have emerged as a promising alternative for patients with chronic medically-refractory pain [15, 41].

TDCS is a particularly interesting technique for clinical applications given its high safety profile, simplicity of administration, and low cost [42]. Neural activity modulation by tDCS is based on the delivery of low-intensity (~1-2 mA) electric currents using two electrodes (an anode and a cathode) placed on the surface

of the scalp. Once the current is applied, cortical excitability is increased under the anode and decreased under the cathode electrode [43]. Thus, tDCS can modulate cortical excitability in targeted brain areas according to the underlying pathophysiology of the neuropsychiatric condition of interest. In the case of chronic pain, the primary motor cortex has been the main targeted area [14, 41, 44-46] given its connections to relevant sub-cortical structures, especially the thalamus [47]. Specifically, anodal stimulation of the motor cortex has been reported to be effective in reducing pain as assessed by the visual analogue scale [14, 45, 46].

The dorsolateral prefrontal cortex (DLPFC) has also been targeted with tDCS, given its reported role in the modulation of pain-related networks [48]. Specifically, anodal tDCS of the left DLPFC has been shown to increase pain thresholds to electrical stimulation in healthy volunteers [49], as well as to reduce self-reported pain in clinical conditions like fibromyalgia [45, 50, 51].

An advantage of tDCS techniques over pharmacological treatments is that tDCS could be able to interfere with the maladaptive plasticity occurring in chronic pain. While drugs can provide short-term pain relief, they generally fail in the long-term and can even cause paradoxical increases of central sensitization [52]. In this framework, tDCS should be further investigated and considered as an alternative approach to alleviate pain in medically-refractory CCP.

## CONCLUSION

We here discussed the investigation of potential neurophysiological markers and novel non-invasive stimulation therapeutic approaches for chronic corneal pain with the aim to raise interest and awareness for this type of approaches and encourage collaboration among professionals involved in the management of this condition. Given that both EEG and TMS have been used to investigate neurophysiological biomarkers for other chronic pain conditions they may also prove useful, alone or in combination, to assess pain-related neurophysiological alterations associated with CCP.

While EEG provides information about overall activity in relevant networks, TMS can be used to assess the presence and extent of maladaptive changes in cortical systems. In addition, non-invasive brain stimulation techniques such as tDCS, guided by EEG and/or TMS, could be considered as potential strategies to modulate neurophysiological abnormalities and reduce subjective reports of chronic corneal pain, increasing therapeutic efficacy.

## Acknowledgment

LC was supported by the École des Neurosciences de Paris (ENP) and Fundació "la Caixa". We thank Dr. Perry Rosenthal for his expertise and helpful discussions regarding the pathophysiology of this condition.

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## Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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