



Seeking Brain Homeostatic Compensatory Mechanisms for Pain Control

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Research in novel treatments for pain is not something new. Pain has been a major topic in clinical research. Indeed, it is still an increasingly major public health problem, a source of decreased quality of life, and high healthcare costs (Dahlhamer et al., 2018). According to the CDC, in 2021, the prevalence of U.S adults who experienced chronic pain was 20.9%, and of those, 17.1 million persons experienced high-impact pain leading to substantial restrictions to daily work and life activities (Duca et al., 2022). Despite the great interest in pain research, pain treatment research has been focused mostly on decreasing and modulating pain processing (e.g., modifying the amount of sensory input that enters in the pain circuits). Indeed, an important treatment target for pain control has been largely ignored. That target is the endogenous pain modulation system (EPMS).

The EPMS is a complex system that has mainly inhibitory role in pain perception and has neural components distributed in an extensive neural network including the peripheral neural system, spinal cord, brainstem, thalamic areas, the limbic system, and cortical areas. One example comes from the seminal work of Melzack and Wall, the gate theory, which shows the important role of inhibitory neurons at the dorsal horn of the spinal cord that would serve as a gate for increased sensory afference. In fact, liter-

ature has set “gate control theory” as the origin of potential therapeutic options for pain. For example, Percutaneous Peripheral Nerve Stimulation (PNS) involves a “close-gate” mechanism by stimulating large-diameter sensory neurons with a subsequent reduction of small nociceptive fibers stimuli (Melzack & Wall, 1965). A recent randomized controlled trial, Albright-Trainer et. al (Albright-Trainer et al., 2021) examined PNS with 60 patients with lower extremity amputation, and reported this technique as an effective, safe, and feasible therapy for acute and subacute post-amputation pain with the reduction of pain scores and also opioid consumption.

In this editorial, we want to discuss a relatively unexplored neural target for modulating the EPMS, the cortex. There is increasingly evidence that cortical areas play a major role in modulating the EPMS to induce pain inhibition. Studies testing invasive and noninvasive cortical stimulation, such as epidural cortical stimulation, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) show the importance of cortical regions such as the primary motor cortex and the dorsolateral prefrontal cortex for the modulation of the EPMS. In a randomized controlled trial, Tavares et. al (Tavares et al., 2021) investigated the effects of tDCS of the motor cortex in 104 subjects with chronic pain due to knee osteoarthritis with a disrupted EPMS. The authors showed a significant decrease in pain compared to the sham group and the conditioned pain modulation effect (CPM, a surrogate of EPMS function) was enhanced in the experimental group. In another study, from our team, Gunduz and Pacheco-Barrios

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et al. (Gunduz et al., 2021) explored the impact of M1 tDCS combined with mirror therapy in 132 traumatic amputees with phantom limb. We found that those who received M1 tDCS reported less pain and these changes were correlated with the inhibitory tonus from the motor cortex (intracortical inhibition). These studies confirmed that the EPMS can be modulated targeting cortical networks, especially the primary motor cortex.

Although brain stimulation studies help our understanding of the role of the motor cortex in pain control, it is still unclear the exact mechanisms of cortical control on pain modulation. One possibility is that the damage in the EPMS (e.g., a brain lesion or sensorimotor deafferentation) would disrupt a negotiated equilibrium between pain-generating and the pain-inhibitory networks; thus, induce an increased pain sensitivity (due to lack of an inhibitory counterpart). It is plausible that a brain homeostatic mechanism would be activated to compensate for this unbalance in the system. In this scenario, a change in cortical oscillations (measured by electroencephalography—EEG) could be a marker of this compensatory process activated by the disrupted EPMS. If this is true, we should be able to find neural oscillations that would be increased in subjects with neural lesions and be associated with no or low pain levels. We did find preliminary evidence of these oscillations in a few studies.

One of these studies is a cross sectional analysis of the DEFINE study, a Brazilian prospective cohort proposed by Simis et al. (Simis et al., 2021). In this analysis, Simis et al. (Simis, Imamura, et al., 2022) included 66 chronic pain knee osteoarthritis (OA) patients. Baseline characteristics and assessments in this study, such as demographic variables, pain characteristics, CPM, TMS, and resting-state EEG were analyzed. At that time, this was one of the largest studies testing brain oscillatory activity and chronic OA knee pain in a multivariate approach based on a previous systematic review performed by Pinheiro et al. (Pinheiro et al., 2016).

The researchers mainly found a higher frontocentral beta and high-beta power, and a reduction of theta activity associated with higher pain intensity and OA severity. Furthermore, a higher alpha and beta power was associated with poorer motor function and severe joint degeneration. These results may suggest two EEG-based pain phenotypes in knee OA chronic pain: 1) patients with higher pain intensity and OA severity with higher beta band power in frontocentral regions; 2) and patients with low pain intensity and less OA severity with higher diffuse theta band power (Simis, Imamura, et al., 2022). The associations suggest a potential role of theta and beta

brain oscillations, as drivers of maladaptive and compensatory mechanisms in chronic pain, respectively.

Furthermore, in another cross-sectional analysis of a RCT (Simis, Pacheco-Barrios, et al., 2022), it was found that cortical oscillations in EEG were correlated with pain intensity (VAS) and CPM, when compared in spinal cord injury (SCI) with neuropathic pain versus SCI without pain. Less alpha (central and parietal areas) and less beta power (parietal areas) were suggested to be related to the presence of higher VAS pain levels. Also a different EEG signature was found when looking at CPM, where more theta power (central, frontal and parietal areas) was associated with less CPM efficiency. One possibility here as also to explain larger theta power associated with less CPM efficiency is that a disruption in the CPM process would be associated with a compensatory increase in theta power, which in severe cases is not enough to restore a inhibitory pain activity (likely the case in SCI-related pain). The relationship between spasticity and low CPM efficiency might be related to a disruption in the balance between excitatory and inhibitory cortico-spinal mechanisms, does indicating that low CPM would be a result of neural damage and lack of cortical control.

In addition to these findings, in a recent cross-sectional neurophysiological analysis of fibromyalgia (FM) pain done with RCT data (Uygur-Kucukseymen et al., 2020), the associations between pain intensity (VAS), CPM, and resting-state EEG oscillatory activity were explored. The authors did not find any significant association between pain intensity levels and CPM efficiency, corroborating some previous findings. A potential reading here is that neural disruption results in CPM dysfunction. As for the association between pain intensity and EEG oscillatory activity, which observed negative associations between pain intensity and alpha (frontal, central, and parietal) and beta (central) power activity (lower alpha and beta power over the sensorimotor areas are associated with higher pain intensity). These findings, mainly because they reveal the association of pain levels with beta activity, demonstrate how this activity may reflect impairments of the cortical organization since beta activity is related to changes in the balance of inhibitory and excitatory systems due to disrupted GABAergic inhibition (Rossiter et al., 2014). The fact that these findings reveal a negative association between beta activity and pain intensity reinforces the hypothesis that a greater impairment of the EPMS may reflect different qualitative levels of response to pain (unbalanced response) that may also be influenced by the level of neural damage to other circuits besides the sensory system.

These studies underscore the role of EEG oscilla-

tions, specifically theta, alpha, and beta, in compensating for lesions in the sensorimotor system that are associated with increased pain and decreased pain inhibition. These oscillations seem to be specifically related to levels of pain and neural damage (lower alpha and beta power) and a compensatory mechanism related to CPM (higher theta power). The dichotomy between lower and higher frequencies in the brain oscillatory activity suggests a homeostatic mechanism that is taking place to adapt to the neural damage associated with pain; however, depending on the disease etiology, severity of the condition, and prior brain health, the adaptation process can be challenging (but still possible). One limitation of this hypothesis is that most of the evidence only considers a static and correlational model of the brain oscillatory activity related to pain and EPMS. Therefore, we encourage future research to include the dynamic nature of the pain connectome and assess how the connectivity in the theta and beta frequencies correlates with clinical pain and CPM in chronic pain patients. This approach will likely produce more personalized clinical biomarkers that can be robust to patients heterogeneity. Similarly, to test the causal relationships between these candidate oscillations and EPMS, modulatory studies using alternating electrical current or repetitive stimulation can be used to entrain a specific oscillatory activity in a target area (e.g., increasing theta oscillations in M1) and assess whether the CPM efficacy improves (Hohn et al., 2019). In summary, as we understand the sources of these oscillations and how they can influence EPMS, this would represent a new window into novel treatments of pain.

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Conflicts of Interest

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

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