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Precise Neuromodulation in Pain Treatment

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Pain, a known human experience, is not a simple perception of noxious stimuli and instead contains three components of affective, sensory, and cognitive dimensions. Chronic pain is a global health issue affecting approximately 12 - 30% of the population (1). Based on its underlying pathophysiology, chronic pain is categorized into diverse subtypes, including chronic cancer, nociceptive, neuropathic, and functional pain. Fibromyalgia and orthopedic/musculoskeletal pain might also be added, considering the origin of pain.

Pharmacological therapy, such as analgesics and opioid administration, is the most common pain treatment method. However, mentioned treatments do not result in pain relief in all patients, especially those experiencing either non-tolerance or adaptation, leading to later drug addictions (2). Neuromodulation is the targeted delivery of a stimulus, such as electrical, magnetic, or chemical stimuli, to a specific treatment site in the body. Neuromodulation influences pain through distinct mechanisms. At the cellular level, it changes the electrical activity of a neuron or alters neural signaling at synapses through neuroplasticity. At the tissue level, it can change neural circuits that lead to different pain perceptions (3).

Plenty of neuromodulation methods has been studied for pain treatment. In spinal cord stimulation (SCS), pulse generators are implanted beneath the skin and are connected to electrodes. These generators deeply travel into the epidural space behind the spinal cord dorsal columns, activating Aβ fibers and inhibiting interneurons. The frequency of stimulation is an important parameter that needs tuning. For example, high frequency and burst stimulations are recent methods with promising results. In addition to the spinal cord, the blocking of pain fibers from distant sites, such as dorsal root ganglia, is considered in patients with pain in distributed dermatomes.

Deep brain stimulation (DBS) is an invasive neuromodulation technique with controversial results. Complex regional pain syndrome (CRPS), phantom pain, and peripheral neuropathies are pain subtypes with better clinical responses to DBS. A current meta-analysis has reported that DBS has reduced the pain frequency in cluster headaches up to 77%. However, the efficiency of this method in cluster headaches is disputed as there is no consensus on the target region (4). Motor cortex stimulation is another invasive technique using surface electrodes as stimulants that resulted in QoL improvement in patients with CRPS, phantom pain, and facial pain (5).

Moving forward to noninvasive methods, repetitive transcranial magnetic stimulation (rTMS) can change neural excitability by inducing a strong magnetic field. The efficacy of rTMS depends on some variables, including anatomical target, coil orientation, and stimulation frequency. High-frequency stimulation of the primary motor cortex (M1) in neuropathic pain demonstrated definite efficacy, while high-frequency stimulation in left M1 and dorsolateral prefrontal cortex in fibromyalgia resulted in probable beneficences (6). According to the anatomical target, neuropathic pain with peripheral origin responded less favorably to rTMS than central pain, namely post-stroke central pain and trigeminal neuralgia.

Electrical stimulation, such as Transcranial direct current stimulation (tDCS), is the transfer of low-intensity current to the scalp. Although tDCS is an approved treatment method for managing pain in Europe, one may question its efficacy, as the quality of supporting evidence is low. Comparison of headache frequency after tDCS treatment with the sham group showed a significant decrease. In addition, a recent systematic review reported no efficacy for tDCS in treating low back pain (7). Due to the limited number of high-quality studies, difficulty in controlling for the placebo effect, and inter-individual differences in pain sensation and perception, the interpretation of results ob-

tained from neuromodulation studies requires more details.

Functional magnetic resonance imaging has revealed the brain areas involved in experiencing painful stimuli, including prefrontal cortex, periaqueductal gray matter areas, primary motor cortex, anterior cingulate cortex, ventral anterior and lateral thalamus, insula, and basal ganglia. Stimulation of these regions resulted in disparate results in patients. The DBS in periaqueductal gray matter areas was associated with more alleviation in chronic nociceptive pain than DBS in the thalamus, while simultaneous simulating of both sites was accompanied by better outcomes in both sites' neuropathic conditions. On the other hand, the simulation of the primary motor cortex and dorsolateral prefrontal cortex was followed by pain relief in many conditions, such as neuropathic pain, muscle pain, and fibromyalgia (8). The pattern of brain activation in patients experiencing pain might differ substantially. Each of these areas may be involved in a specific aspect of pain processing, and one or more aspects of pain processing might be impaired in each patient. Consequently, we can individualize the target modulation site via obtaining knowledge on the network to be manipulated, called 'endophenotype' (9).

Brain oscillations in chronic pain have been frequently studied. Previous literature considered three components for pain oscillations: strong gamma-band activation over the sensory-motor cortex and strong alpha and beta bands oscillations between regions involved in the contextual aspects of pain processing. By considering attention as a contextual aspect, it was shown that attention to pain changes connectivity between higher pain-relevant brain areas in alpha and beta frequencies (10). Intriguingly, the differences of these components are evident in modulations in a way that bottom-up modulations, such as varying the intensity of the stimulus, affected all components, while top-down modulations had more selectivity in modifying the components. For example, changing attention level influenced all components while music therapy and some placebo manipulations resulted in gamma alterations and alpha suppression, respectively (11). Increased theta oscillations were indicated in chronic pain, referred to as 'thalamocortical dysrhythmia'. In addition, higher beta oscillations in frontal brain areas were reported in studies on chronic pain.

As mentioned previously, Transcranial alternating stimulation (tACS) is one of the electrical stimulation methods similar to tDCS. The tACS is capable of changing a specific frequency band in a defined brain area. For example, tACS has been used to augment alpha oscillations in the left dorsolateral prefrontal cortex and consecutively improved clinical symptoms in patients with major depressive disorder (12). Given the altered oscillation patterns in chronic pain, it may serve as a candidate for tACS modulations. This altered pattern can be investigated using quantitative electroencephalography, and based on this evidence, treatment protocols can be optimized for each patient.

As mentioned before, pain is processed differently in distinct individuals. The sensory threshold for detecting noxious stimuli may vary for each patient. Considering the emotional aspect of pain perception, psychological factors can contribute to the response extent of patients to treatment. In a study by Bendinger et al. (cited in Prabhala et al.), sleep disturbance appeared to predict SCS outcomes. Another study showed improvement in many psychological scores after SCS, including catastrophizing pain scale, McGill pain questionnaire, Oswestry disability index, and Beck Depression Inventory, insisting that this relationship is mutual (13). Age, education level, and smoking status have been consistently reported in the literature to affect the transition from acute to chronic pain after surgery and, therefore, influence treatment response.

Chronic pain, which is highly prevalent as an unavoidable effect of many medical conditions, is frequently resistant to conventional treatments (1). This fact has led to the overconsumption of opioids and the opioid addiction crisis worldwide. Alternative therapies, such as neuromodulation, can be beneficial, and the number of neuromodulation trials is rapidly increasing in trial registry repositories. Pain comprises more than one aspect, and plenty of factors play a role in the efficacy of a treatment for pain relief in each patient. Therefore, individualized therapy of patients renders better outcomes. Precision medicine considers individual differences in response to treatment and optimizes therapy for each patient. Interindividual differences make up a considerable amount of data because humans are different from the most preliminary dimensions of genetics to the broader demographical, psychological, and medical dimensions. Applying artificial intelligence and machine learning to analyze big data has caused much progress in this field. The most useful features for predicting treatment outcomes can be investigated using machine learning models. As a result, the management of complex conditions, such as pain, can be more efficient for each patient. In this regard, further personalized neuromodulation studies based on evidence from data-driven approaches are highly recommended (14).

Footnotes

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authors have read and approved the final version of the manuscript.

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