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Transcutaneous Vagus and Trigeminal Nerve Stimulation: New Perspectives in the Treatment of Psychiatric Disorders

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Abstract: *The advances in the understanding of brain circuitry underlying mental disorders have contributed to the development of new therapeutical strategies as Non-invasive brain stimulation techniques (NIBS). NIBS are techniques that might aid to overcome some of the current challenges related to pharmacotherapy. Ideally, NIBS should be not only as effective as pharmacotherapy but also present a low rate of adverse effects, thereby increasing treatment adherence. Neuromodulation techniques include novel techniques, such as trigeminal nerve stimulation (TNS) and transcutaneous vagus nerve stimulation (tVNS).In fact, these cutting-edge neuromodulation interventions are driven by data from both neuro-functioning and experimental research that help targeting specific brain areas related to psychiatric disorders. Different brain sites can be modulated throughout the use of electrical currents, what could restore balance to impaired circuits leading to clinical amelioration of symptoms.*

Keywords*: neuromodulation, psychiatry, Trigeminal nerve Stimulation, Vagus nerve stimulation*

1. PSYCHIATRIC DISORDERS: ASSESSING BRAIN FUNCTIONING

With the development of new tools to assess brain function and cerebrovascular health such as functional magnetic resonance imaging, new understanding of disrupted mechanisms underlying psychiatric conditions has been proposed. Findings regarding neuroplasticity-related pathways for the therapy of mental disorders, such as major depressive disorder (MDD), supports the hypothesis that abnormalities associated with psychiatric conditions go beyond neurochemical imbalances [1][2].

Specific impairments in brain circuitry are under growing evidence in psychiatric research. For instance, patients diagnosed with major depressive disorder (MDD) present with altered functioning of dorsolateral prefrontal cortex (DLPFC). In fact, in MDD there has been exhibited a reduction in neuronal activity in the DLPFC [3][4]. For other disorders, such as schizophrenia, similar impairments have been systematically reported [5].

The advances in the understanding of brain circuitry underlying mental disorders have contributed to the development of new therapeutical strategies as Non-invasive brain stimulation techniques (NIBS). NIBS are techniques that might aid to overcome some of the current challenges related to pharmacotherapy. Ideally, NIBS should be not only as effective as pharmacotherapy but also present a low rate of adverse effects, thereby increasing treatment adherence. Neuromodulation techniques include novel techniques, such as trigeminal nerve stimulation (TNS) and transcutaneous vagus nerve stimulation (tVNS).

In fact, these cutting-edge neuromodulation interventions are driven by data from both neuro-functioning and experimental research that help targeting specific brain areas related to psychiatric disorders. Different brain sites can be modulated throughout the use of electrical currents, what could restore balance to impaired circuits leading to clinical amelioration of symptoms [6][7].

2. TRIGEMINAL AND VAGUS NERVE STIMULATION: TARGETING ANATOMY-BASED SITES

The rational for using trigeminal or vagus nerves for delivering electric current toward specific brain areas is the anatomical correlation these nerves maintain with sites related to psychiatric symptoms such as the amygdala, insula, precentralgyrus, hippocampus, thalamus and prefrontal cortex (structures widely related to cognitive functioning and mood regulation). Therefore, both TNS and

tVNS modulate brain structures throughout the "bottom-up"hypothesis, in which stimulation of these nerves would propagate to its cortical and subcortical projections [7].

Following this hypothesis, Cook et al. have initially proposed transcutaneous stimulation of thesupraorbitary branch of the trigeminal nerve (TNS) with interesting results for MDD[8][9][10][10, 11]andotherpsychiatricconditions[12]. Following the leading results of Cook et al., Shiozawa et al. proposed an innovative brief 10-day TNS protocol [13] that has been tested for depressive symptoms in a randomized sham-controlled clinical trial with positive results. The authors found significant interaction between the mean percentage change in depressive symptoms in the two groups over time with mean reduction of 6.32 points in the Hamilton Depression Rating Scale (HDRS17); p=0.002 [14].

The same protocol was further used for anxiety disorders with promising results for symptoms ameliorations in post-traumatic stress disorder [15] and generalized anxiety disorder [16].

Regarding tVNS, its use in clinical research is still scant. However, the rational for stimulating a superficial branch of the X cranial nerve is similar to the TNS given common neural pathways shared by both trigeminal and vagus nerves. Regarding depressive MDD, Hein and colleagues found transcutaneous vagus nerve stimulation to be an effective treatment. The authors evaluated a total of 37 patients over a randomized sham controlled add-on study. Patients were stimulated five times a week on a daily basis over two weeks. The vagusnervewasaccessedontheouter canal oftheear, in a novel techniqueof auricular transcutaneouselectricnervestimulation. Active treatment group presented markedly clinical amelioration of symptoms in comparison to sham stimulation [17].

Interestingly, once we observe potential clinical benefits of TNS and tVNS, it is reasonable to infer that stimulating other specific areas innervated by these nerves we would obtain the same neuromodulatory effects. Considering those hypothetical areas of interest, different cranial sites would be under focus. Trevizol and colleagues [18] have recently proposed a new tVNS assessment trough the auricular branch of the vagus nerve using the transcutaneous electrical nerve stimulation (TENS) technology. The auricular branch of the vagus nerve, also known as Arnold's nerve or Alderman's nerve, originates in the superior ganglia of the vagus nerve and penetrates the mastoid canaliculi, accessing the temporal bone and emerges trough the tympanomastoid fissure, between the mastoid process and the tympanic portion of the temporal bone. It then originates two branches, one that enervates the occipitofrontal muscle with the posterior auricular nerve and another branch that enervates the skin over the mastoid process and the posterior wall of the ear canal. The authors proposed the stimulation with a TENS equipment with the electrodes placed bilaterally over the mastoid process area, juxtaposed to the ear, near the tympanomastoid fissure.

The same group has reported interesting findings in a case in which ten daily 30-minute sessions were performed with the following parameters: 120 Hz frequency and 250 μs ofpulse wave duration, with successful amelioration of the patient's depressive symptoms[19]. The findings, however, are limited to a case report and further phase II clinical trials have yet to be performed. The possibility of developing an easy access, with a easy-to-use, safe, non-invasive technology such as a TENS equipment, with the results previously described for VNS, would enable easier access to a neuromodulation strategy for patients with psychiatric disorders in which the neurobiology involves the vagus nerve subcortical and cortical connections, such as the amygdala, the hippocampus and the DLPFC.

3. ADDRESSING SAFETY

Finally, the use of both TNS and tVNS protocols in clinical research are a safe strategy. In fact, no severe adverse effect has been reported hitherto. Regarding skin injury, the techniques have been innocuous in contrast to similar non-invasive neuromodulation strategies astranscranial direct current stimulation (tDCS), which markedly present safety concerns regarding skin integrity in different reports [20].

4. PERSPECTIVES AND FINAL REMARKS

The results on the use of TNS and tVNS protocols for treating psychiatric disorders have been relevant, however, there is a continuous need for additional research as to guarantee a more robust use of these promising techniques in daily clinical practice.

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