Title
Trigeminal Nerve Stimulation (TNS) for Post-traumatic Stress Disorder: A Case Study

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The participant began experiencing adverse effects as he was traveling home from the laboratory, approximately 30 min after the conclusion of the protocol. The adverse effects started gradually, and included transient paresthesia, hemiparesis of the left side of the body, slurred speech, and ataxia. Due to prolonged hemiparesis for several hours, the participant presented to the emergency department of his local hospital. The treating physician administered a brief neurological screening measure that did not reveal any neurological abnormalities; however the participant requested a second opinion. During this time, the participant experienced several additional symptoms, including: severe headache pain in the right frontal and temporal regions, in addition to pain in the "stem" region; sensitivity to light and sound; hot and cold flashes (without associated fever); nausea; and vomiting. The participant underwent a computerized tomography (CT) brain scan, but no abnormalities were detected. The participant remained in hospital for observation, at the request of the participant's family, for a total of 6 h. Overall, the symptoms lasted for approximately 8 h with the participant returning to normal functioning within 24 h, with no long-lasting side effects. Although a formal clinical diagnosis was not made, treating physicians agreed that the symptoms were indicative of a severe migraine. As a result of the adverse event, the participant was excluded from further participation in the study. The event was reported to the Deakin University Human Research Ethics Committee.

To our knowledge, this is the first report of a combination of TMS and tDCS inducing transient paresthesia. Due to the methodology employed, it is difficult to elucidate which technique is most likely to have caused the adverse event. Both techniques have been previously shown to be safe when applied using accepted parameters, such as those used in this study. The participant had experienced one migraine a year previously, though the symptoms were less extensive and more localized than those experienced following the testing procedure. The previous migraine, which lasted several hours, involved pain around the right temple area and the base of the skull, and photosensitivity. The participant did not seek medical attention for this migraine. Both TMS (in its repetitive form) and anodal M1 tDCS have been investigated as treatments for migraine with no ill effects [1,2]. It is possible that the combination of techniques triggered the adverse event, although TMS is commonly used in conjunction with tDCS as a laboratory measurement of tDCS-induced effects [3] without issue.

The occurrence of headache and other minor adverse effects following non-invasive brain stimulation has been reported under experimental conditions in the literature [1–3]. To the authors' knowledge, there have been no reports of migraine occurrence (with or without transient paresthesia) following single- and paired-pulse TMS and/or tDCS application. However, it has been suggested that anodal tDCS could induce migraine in susceptible individuals via a net increase in cortical hyperexcitability (e.g. Refs. [4,5]). Due to this possibility, Liebetanz et al. [4] concluded that special care should be taken when applying tDCS in migraine patients.

The possibility exists that the symptoms were psychogenic, however this is difficult to determine after just a single episode. It is also possible that psychological factors, such as anxiety or stress, interacted with physiological processes to trigger the migraine. For example, heightened anxiety is a known precipitant for migraine [6]. Anxiety as a trigger seems unlikely in this case, as the participant reported no nervousness on an 11-point numerical rating scale four times throughout the session. However, due to the nature of self-report this possibility cannot be excluded.

In conclusion, though unprecedented, this event highlights the need for continued participant monitoring following tDCS and TMS application. Both techniques should be applied with caution. Participants should be briefed on the possibility of migraine induction following tDCS and/or TMS, particularly in those with a history of migraine.

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Trigeminal Nerve Stimulation (TNS) for Post-traumatic Stress Disorder: A Case Study

Dear Editor,

Posttraumatic stress disorder (PTSD) is an anxiety disorder following a potentially traumatic event. It is best characterized by intrusive thoughts related to the event, avoidance behavior and symptoms of hyperarousal such as sleep disorders, hypervigilance and panic attacks [1]. The lifetime prevalence is estimated to be 7.8% in the United States, with annual costs of about $3 billion [2]. There is no definitive pharmacotherapy for PTSD nuclear

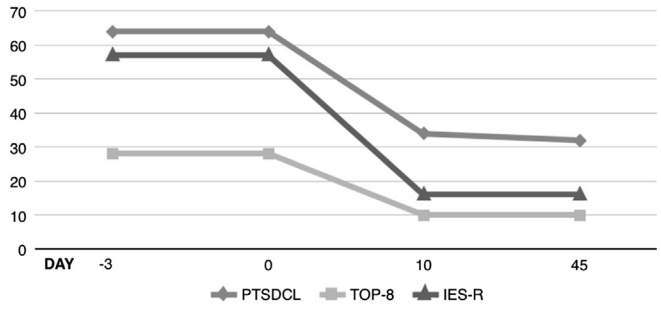

Figure 1. PTSD Check List scale (PTSDCL), the treatment outcome PTSD Scale (TOP-8) and the Impact of Event Scale – Revised (IES-R) at baseline, end of treatment and one-month follow-up.

symptoms. Although medications and psychotherapy have been shown to reduce anxiety symptoms, one third of patients remain symptomatic in spite of treatment [3]. In this scenario, new interventions such as neuromodulation strategies have been under growing focus in medical literature [4].

Trigeminal Nerve Stimulation (TNS) is based on the application of an electric current over a branch the supraorbitary branch of the trigeminal nerve. Further stimuli propagates toward brain areas that are related to mood and anxiety symptoms, such as the amygdala and the frontal lobe [5,6]. TNS has been successfully associated on the treatment for depressive disorders [7].

In this report, we describe a 43-year-old female patient with PTSD who successfully underwent a TNS intervention protocol, with amelioration of her symptoms. "Ms. K." experienced the traumatic death of her husband 5 months before TNS treatment. In fact she evolved immediately after the tragic event with anxiety symptoms characterized by hyperarousal, avoidance behavior, nightmares and flashbacks related to the event. The patient was diagnosed with PTSD at an academic psychiatric community center, and underwent pharmacological treatment. Patient had received sertraline 200 mg/daily for three months, without clinical response. Considering the severity of her symptoms and lack of clinical improvement to pharmacotherapy, TNS was started after she provided written informed consent (IRB approved).

Ten consecutive daily TNS sessions were performed. Electric stimulation was performed at 120 Hz with a pulse wave duration of 250 μs for 30 min per day. We used rectangular rubber electrodes of 20 cm^2 wrapped in cotton material moistened in saline solution and placed over supraorbital trigeminal branches (V1) bilaterally following our previously tested protocol [5]. For assessing PTSD symptoms we used the PTSD Check List scale (PTSDCL), the Treatment Outcome PTSD Scale (TOP-8) and the Impact of Event Scale – Revised (IES-R). We also assessed cognitive functions with the Montreal Cognitive Assessment (MOCA). Cognitive functions were unaltered (27 both at baseline and at final outcome) as assessed by MOCA. Core PTSD symptoms substantially improved during the 10-day treatment course and remained stable after one-month follow-up, and the patient reported significant global clinical gains (Fig. 1).

The neural basis for PTSD is related to fear processing and memory acquisition and include structures such as the amygdala, the frontal lobe, and the hippocampus [8]. In fact, neuroimaging and functional brain studies demonstrated hyperactivity of right prefrontal cortex in patients with PTSD. Electroencephalographic (EEG) controlled studies have shown reduction of *alpha* activity in the right hemisphere in PTSD patients when exposed to trauma-related images [9]. Similarly, single photon emission computed tomography (SPECT) studies that have shown increased cerebral blood flow in the right prefrontal cortex in PTSD patients [10].

The rational for using a bilateral protocol is based on the so called "bottom up" mechanism. According to this hypothesis, the propagation of electric stimuli follows an inverse path from peripheral nerves toward the brain stem and central structures. The centrifuges electric propagation throughout neurons contrasts with the well-known "top-down" mechanism of other modulation strategies, such as electroconvulsive therapy and transcranial magnetic stimulation, in which the stimulus acts first on central brain structures, with propagation later to peripheral sites [11].

We present the first report using TNS for PTSD. It is hypothesized that the propagation pathway of the stimuli in TNS may modulate the previously studied areas involved in PTSD symptoms, being responsible for the amelioration of this patient's symptomatology. Some study limitations, however, should be addressed. Our findings are based on a case study, thus having limited generalizability. Nonetheless, these encouraging results should be seen as hypothesis-driving for further controlled, randomized trials exploring the impact of TNS in the treatment of PTSD.

The present work was performed at the Clinical Neuromodulation Laboratory, Santa Casa Medical School, São Paulo, Brazil.
Declaration of interest: All authors confirm that this manuscript has not been published elsewhere and is not under consideration by another Journal. All authors have approved the manuscript and agree with its submission to Brain Stimulation. We here declare no conflict of interest related to the present manuscript.

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Visual Sensation by Electrical Stimulation Using a New Direct Optic Nerve Electrode Device

Dear Editors,

Investigations into artificial vision to restore the vision of blind people are ongoing worldwide. There are three targets for artificial vision: the retina, optic nerve, and visual cortex [1–23].

Currently, retinal prostheses for blind people with advanced retinitis pigmentosa (RP) are moving toward practical application. Our research group developed an original artificial vision system that implants wire electrodes directly into the optic disc [20–22]. Electrical stimulations are transmitted to the brain via the optic nerve. Phosphenes are elicited by this system, and the procedure has been named as artificial vision by direct optic nerve electrode (AV-DONE) [23].

AV-DONE has several advantages compared with other artificial vision modalities. Mainly, it allows easy access to the optic nerve, can stimulate a wide visual field, and can elicit small to large phosphenes using just one stimulating electrode. However, it takes a few hours to implant several stimulating electrodes into the optic disc [23]. To address these problems, we developed a new device designed to facilitate one-step implantation of electrode tips into the optic disc (Figs. 1 and 2). The biocompatibility and efficacy of this device has been confirmed in rabbits [24,25].

Case presentation

The patient was a 44-year-old man with autosomal-recessive RP and bare light perception. The patient had no other ocular diseases or systemic disorders that could have caused the visual loss.

The Institutional Ethics Committee Board approved the study, and informed consent was obtained from the patient. The trial adhered to the tenets of the Declaration of Helsinki. All implantation procedures were performed on the left eye of the patient under general anesthesia at Asociacion Para Evitar la Ceguera, Mexico City, Mexico. After a standard three-port pars plana vitrectomy, the electrode device with wires was inserted into the vitreous cavity through the silicon trocar. Then, the electrode tips were inserted into the optic disc, while the rod was manipulated using vitreoretinal forceps. No severe complications developed during any of the surgical procedures. We easily manipulated the electrode device and smoothly and steadily inserted the electrode tips into the optic disc within 10 min in a single step, which exceeded 1 h in a previous study [23].

Electrical stimulation sessions were conducted 9 and 25 months after implantation.

Biphasic, cathodic-phase-first, electrical pulse trains with a 1-s total duration were applied between one of the stimulation electrodes and the reference electrode. The duration of the stimulus pulses was 0.25 ms/phase, and the frequency was 320 Hz.

To access the thresholds of the current required to induce phosphenes, the current was first applied at 100 μA, and if the patient did not recognize the phosphenes, the current was increased. If the patient recognized the phosphenes at 100 μA, the current was increased from 10 μA to a maximum of 500 μA.

The patient was questioned about perception of the phosphenes, their clock position (1–12 o'clock), and the distance of the phosphenes from the center, as previously described [23]. We recorded the positions of the phosphenes in polar coordinates of the visual field. The thresholds of phosphene perception were identified as the stimulation current when more than 50% tests were positive for perception.

The patient identified electrically induced phosphenes through six and five of the seven stimulation electrodes at 9 and 25 months after implantation, respectively. The phosphenes were distributed focally in the visual field. The average central position of the phosphenes differed for each electrode.

The thresholds of electrical stimulation used to induce phosphenes were 100, 150, 150, 150, 200, and 300 μA through each of the six electrodes at 9 months and 100, 200, 300, 300, and 300 μA through each of the five electrodes at 25 months after implantation. There were no significant differences in thresholds among the time points.

The positions of the center of the phosphenes were observed in the second and third quadrants, and some phosphenes were observed in the first quadrant at both 9 and 25 months. No phosphenes were observed in the fourth quadrant.

Before implantation of the electrode device and during the 25-month follow-up, ophthalmologic examinations were performed at least every 6 months. No severe complications developed during 25 months after implantation of the electrode device.

Discussion

This device shortened the surgical time, minimized damage to the optic nerve fibers, and allowed fixation of more electrodes compared with previous devices.

The current patient recognized phosphenes through six of the seven stimulation electrodes when electrical stimulation (maximum current intensity, 500 μA) was applied 9 months after implantation. One electrode could not induce phosphenes. There are two possible reasons for this. First, the silicone board leaned against the surface of the optic disc. If the area of attachment between the uncoated electrode tips and the optic nerve fiber was smaller, the threshold may have increased. The patient did not perceive phosphenes in the fourth quadrant of the visual field, which corresponded to the area where the silicone board leaned against the optic disc, and the distance between the surface of the disc and the silicone board was longest at the supratemporal