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Sustained Effects of a Neural-based Intervention in a Refractory Case of Tourette Syndrome

Dear Editor:

There are only a few treatments available for Tourette syndrome (TS). These treatments frequently do not work in patients with moderate to severe TS [1]. Neuroimaging studies show a correlation between tics severity and increased activation over motor pathways, along with reduced activation over the control areas of the cortico-striato-thalamo-cortical circuits [2]. Moreover, the temporal pattern of tic generation suggests that cortical activation especially in the SMA precedes subcortical activation [3]. Following this assumption, here we explored the brain effects of 10-daily sessions of cathodal transcranial Direct Current Stimulation (tDCS) delivered over the pre-SMA in a patient with refractory and severe TS and also assessed whether those changes were long lasting (up to 6 months).

Case presentation

A 16-year old boy, with simple and complex vocal and motor tics, diagnosed with severe refractory TS (age-of-onset 6 years old), was referred by a neurologist to non-invasive brain stimulation treatment as a compassionate treatment given the failure of other treatments. Since the age of seven, this patient had experienced a series of unsuccessful treatments, including several pharmacological interventions alone or in combination with speech and cognitive-behavioral therapies. Upon enrollment, he was on stable medication (Pimozide (4 mg), trihexyphenidyl HCl (2 mg) and Clonidine (0.15 mg)) for the past three years, and had mildly responded to Cognitive Behavioral Therapy [4]. At the start of the trial, the patient scored 36 in tic severity and 76 in the total score of YGTSS. The patient received 10–daily sessions (1.425 mA for 30 min) of cathodal tDCS over the pre-SMA (25 cm^2), with a right deltoid muscle reference (100 cm^2). The present electrode montage and parameters of stimulation focalize tDCS effects over the pre-SMA and avoid current intensities that could cause significant skin irritation [5]. tDCS was delivered by a battery driven Eldith Stimulator DC+ (Neuroconn, Germany) using saline-soaked sponge electrodes. Each daily session of cathodal tDCS was performed at approximately the same time in the afternoon, and the patient was asked to remain comfortably seated during the entire session. Assessments were conducted prior to the intervention (T0), at the end of the first (T1) and second (T2) weeks of cathodal tDCS, and then followed up until 6 months (T7) after the intervention. fMRI scan were performed before and immediately after the 10 daily sessions of tDCS intervention. Resting state fMRI data were acquired on a clinical approved Siemens Trio Tim 3T, pre-processed and processed as previously described [6]. The resulting Z-score maps for each component were subtracted (T0 and T2) and the results were considered significant if Z-scores

differences were above 2.25 with a minimum cluster size of 200 voxels. The study started after local ethical committee approval (School of Psychology, University of Minho, Portugal) and was in accordance with the Declaration of Helsinki. Both parents gave written informed consent prior to commencement of treatment. Informed assent was also provided by the patient.

10 sessions of cathodal tDCS were well tolerated in a severe case of TS. After the first week of cathodal TDCS (T1), total tic severity decreased by 22%, with a global decrease in the YGTSS (Tic severity + Deficit) of 23%. At the end of tDCS week 2 (T2) tic severity decreased by 41%, with a global score decrease of 46%. At the 3 and 6 month follow up (T6 and T7), the tic severity and the global score were still decreased 39% and 44%, respectively, when comparing to the baseline. The tic decreases during the first week were mainly on the verbal component (40% reduction compared to 9% in motor). At the end of the second week of cathodal tDCS there was a decrease of 40% in verbal and 42% in motor tics. At the 3 and 6 months follow up, verbal tics were still decreased by 47% and motor by 33%. These results reflect clinically significant reduction in both motor and phonic tics, with the overall rating of the patient moving from the severe category to mild. The present case report suggests but certainly does not prove, that 10-sessions of cathodal tDCS applied bilaterally over the pre-SMA might be effective in decreasing both motor and vocal tics in a resilient case of TS. Moreover, improvements were apparent up to 6 months after cathodal tDCS has ended.

The resting state fMRI showed that after cathodal tDCS, activity decreased in the left precentral region and in the left cerebellum of the sensorimotor resting state network.

10 sessions of cathodal tDCS decreased the activity in the left precentral region of the sensorimotor resting state network. In fact, previous studies have found that increased activation in the sensorimotor region is associated with symptom severity in several movement disorders [7]. A decrease in the activation of the left cerebellum was also evident. The cerebellum has been reported in the literature, as being more activated in TS patients, with spiking activity just prior to the tic occurrence [8]; overlapping in time with abnormal discharges in the primary motor area. If those two areas function as a "gating mechanism" in order to release tic movement, the down regulation of these two areas by cathodal tDCS may explain the clinical improvement.

Given the long-lasting effects of our intervention in a subject non-responsive to several treatments in addition to the neuroimaging findings, it is conceivable to assume that cathodal tDCS induced significant neuroplastic changes in these neural circuits; providing the initial support for further investigation of this potential intervention as a clinical treatment for refractory TS. Due to the uncontrolled design of the present case report, future systematic studies are needed in order to test this hypothesis, especially as tic symptoms wax and wane over time, particularly in adolescence. In fact most patients with tics at age 12 do not have tics as adults. Thus the improvements in this patient may simply reflect the normal spontaneous fluctuations of TS.

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Trigeminal Nerve Stimulation (TNS) for Generalized Anxiety Disorder: A Case Study

Dear Editor,

Generalized anxiety disorder (GAD) [1] presents with an overall prevalence of 4–7%. Although available treatment is effective in many patients, treatment-resistance and low adherence due to adverse effects are some issues that compromise optimal treatment. In fact about 25% of patients reportedly fail to respond to treatment [2,3]. Brain stimulation techniques have shown promising results for anxiety symptoms [4,5]. Following previous results of different neuromodulation strategies, Trigeminal Nerve Stimulation (TNS) may also be able to exert anxiolytic effects in the clinical scenario. TNS is a non-invasive strategy based on the application of an low-energy electric signal to stimulate branches of the trigeminal nerve with further propagation of the stimuli toward brain areas related to mood and anxiety symptoms [6]. TNS has been reported to reduce anxiety symptoms in patients with a primary diagnosis of major depression [7] but has not been previously examined as a treatment for primary GAD.

Here, we describe the management of a 39-year-old female patient diagnosed with GAD accordingly to DSM-V criteria. The patient did not present with any psychiatric comorbidity at clinical evaluation. Moreover, no other psychiatric history was reported rather than the development of anxiety symptoms over the last three years. During this period the patient failed to respond to different adequate pharmacological protocols (such as venlafaxine, sertraline, fluoxetine and escitalopram). Considering the severity of her symptoms and lack of clinical response to pharmacotherapy, a experimental TNS protocol was started after written informed consent was provided utilizing IRB-approved materials and procedures. The patient was not under any pharmacological approach at the time she underwent the experimental protocol.

Ten consecutive daily TNS sessions (except for weekends) were performed. Electric stimulation was performed at 120 Hz with a pulse wave duration of 250 μs for 30 min per day. The 25 cm^2 conductive rubber electrodes were wrapped in cotton material, which was moistened with saline so as to reduce impedance. For assessment of anxiety symptoms we used the Generalized Anxiety Disorder 7-item scale (GAD-7) and the Hamilton Anxiety Rating Scale (HARS). We also assessed cognitive functions with the Montreal Cognitive Assessment (MoCA). At the end of the experimental protocol, Ms. E presented with symptomatic remission of her symptoms. Cognitive function exhibited a minor improvement (from 25 at baseline to 27 at final outcome) as assessed by MoCA. Anxiety symptoms substantially improved during the 10-day treatment course (reduction of 93.7% and 88.3% according to GAD-7 and HARS, respectively) and remained stable during one-month follow-up (Fig. 1).

Zwanzger et al. and Pallanti et al. reviewed the use of transcranial magnetic stimulation (TMS) to treat anxiety symptoms, with interesting positive results. Improvements were observed on anxiety symptoms in panic disorder with depression and treatment-resistant depression [4,5]. Trigeminal nerve stimulation may modulate brain activity through bottom-up mechanisms by stimulating a cranial nerve whose nuclei lie in the brain stem, and which, in turn, make extensive connections to the limbic cortex and monoaminergic nuclei. There are a growing number of publications on the use of TNS for psychiatric disorders [6–8].

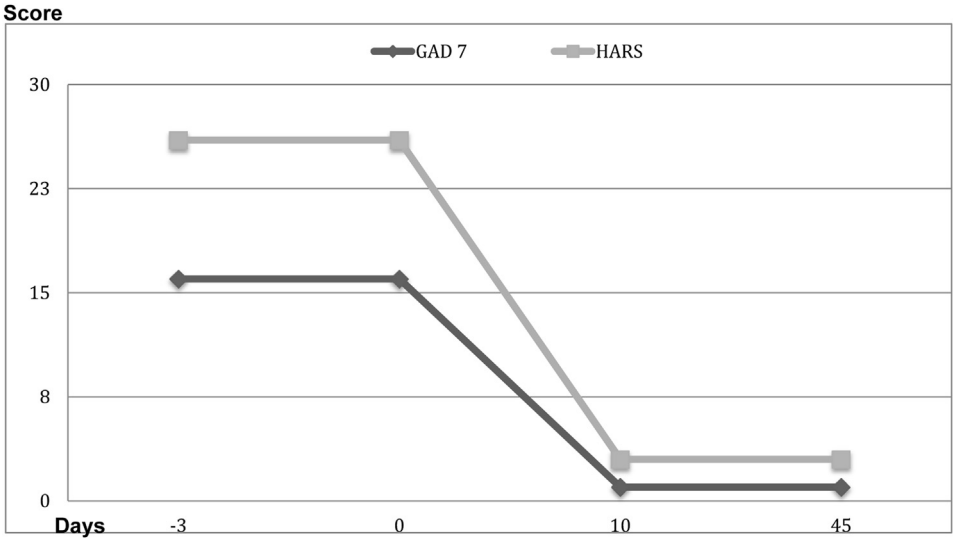

Figure 1. Clinical assessment at baseline, 10 days and 40 days follow up. *GAD-7*: Generalized Anxiety Disorder clinical scale; HARS Hamilton Anxiety Rating Scale. Treatment was administered during the period from Day 0 to Day 10; Day 45 measurements show continued remission one month after the last treatment administration.