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

Journal
Brain Stimulation, 8(3)

ISSN
1935-861X

Authors
Trevizol, Alisson Paulino
Shiozawa, Pedro
Sato, Isa Albuquerque
et al.

Publication Date
2015-05-01

DOI
10.1016/j.brs.2014.12.009

Peer reviewed

[2] Wang Z, Maia TV, Marsh R, Colibazzi T, Gerber A, Peterson BS. The neural circuits that generate tics in Tourette's syndrome. Am J Psychiatry 2011;168(12):1326–37.
[3] Neuner I, Werner CJ, Arrubla J, et al. Imaging the where and when of tic generation and resting state networks in adult Tourette patients. Front Hum Neurosci 2014;8:362.
[4] Lavoie ME, Imbriglio TV, Stip E, O'Connor KP. Neurocognitive changes following cognitive-behavioral treatment in Tourette syndrome and Chronic Tic Disorder. Int J Cogn Ther 2011;4(1):34–50.
[5] Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1(3):206–23.
[6] Soares JM, Sampaio A, Marques P, et al. Plasticity of resting state brain networks in recovery from stress. Front Hum Neurosci 2013;7(919).
[7] Rickards H. Functional neuroimaging in Tourette syndrome. J Psychosom Res 2009;67(6):575–84.
[8] McCairn KW, Iriki A, Isoda M. Global dysrhythmia of cerebro-basal ganglia–cerebellar networks underlies motor tics following striatal disinhibition. J Neurosci 2013;33(2):697–708.

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].

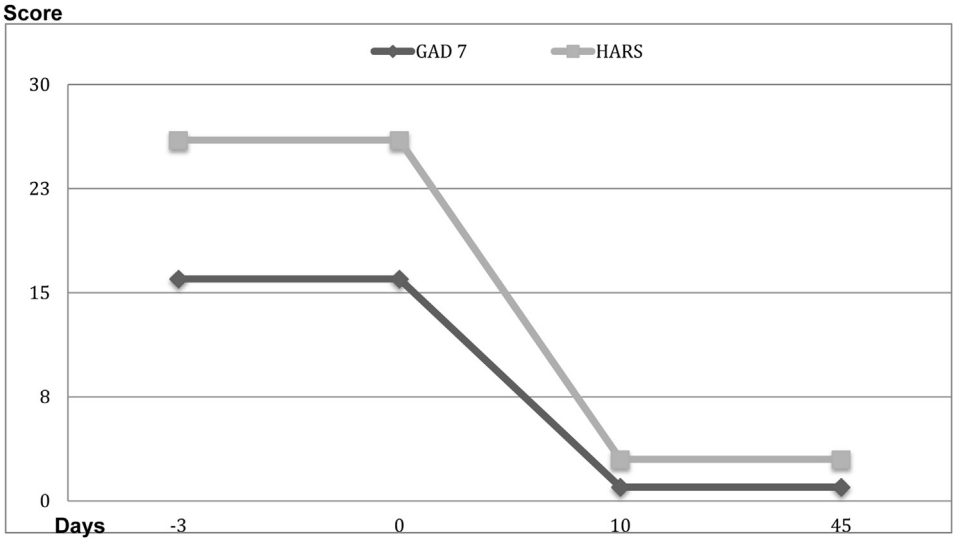

Figure 1. Clinical assessment at baseline, 10 days and 40 days follow up. *GAD-7*: Generalized Anxiety Disorder clinical scale; HARS Hamilton Anxiety Rating Scale. Treatment was administered during the period from Day 0 to Day 10; Day 45 measurements show continued remission one month after the last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

We present this first report of the use of TNS for GAD. Some study limitations, however, should be acknowledged. Our findings are based on a single case study, and thus have limited generalizability. As well, there was no control condition. Nonetheless, these encouraging results should be seen as hypothesis-driving for further controlled, randomized trials exploring the impact of TNS in the treatment of anxiety disorders.

Alisson Paulino Trevizol*
Pedro Shiozawa
Isa Albuquerque Sato
Elie Leal de Barros Calfat
Clinical Neuromodulation Laboratory, Santa Casa Medical School, São Paulo, Brazil

Rodrigo Lancelote Alberto
Centro de Atenção Integrado à Saúde Mental de Franco da Rocha, São Paulo, Brazil

Ian A. Cook
Department of Psychiatry, University of California, Los Angeles, USA

Heloisa H. Medeiros
Centro de Atenção Integrado à Saúde Mental de Franco da Rocha, São Paulo, Brazil

Quirino Cordeiro
Clinical Neuromodulation Laboratory, Santa Casa Medical School, São Paulo, Brazil

* Corresponding author. Departamento de Psiquiatria, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Rua Major Maragliano, 241 Vila Mariana, 04600-010 São Paulo, SP, Brazil.
E-mail address: alisson.trevizol@hotmail.com (A.P. Trevizol)

Received 21 December 2014
Available online 31 January 2015

http://dx.doi.org/10.1016/j.brs.2014.12.009

References

[1] Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62(6):617–27.
[2] Ballenger JC. Panic disorder in primary care and general medicine. In: Rosenbaum JF, Pollack MH, editors. Panic disorder and its treatment. New York: Dekker Inc; 1998. p. 1–36.
[3] Craske MG, Edlund MJ, Sullivan G, et al. Perceived unmet need for mental health and barriers to among care patients with panic disorder. Psychiatr Serv 2005; 56:988–94.
[4] Zwanzger P, Fallgatter AJ, Zavorotnyy M, Padberg F. Anxiolytic effects of transcranial magnetic stimulation—an alternative treatment option in anxiety disorders? J Neural Transm 2009;116:767–75.
[5] Shiozawa P, Leiva AP, Castro CD, et al. Transcranial Direct Current Stimulation (tDCS) for generalized anxiety disorder: a case study. Biol Psychiatry 2014 Jun 1;75(11):e17–8.
[6] Shiozawa P, Duailibi MS, da Silva ME, Cordeiro Q. Trigeminal nerve stimulation (TNS) protocol for treating major depression: an open-label proof-of-concept trial. Epilepsy Behav 2014 Aug 19;39C:6–9.
[7] Cook IA, Schrader LM, Degiorgio CM, Miller PR, Maremont ER, Leuchter AF. Trigeminal nerve stimulation in major depressive disorder: acute outcomes in an open pilot study. Epilepsy Behav 2013 Aug;28(2): 221–6.
[8] Cook IA, Espinoza R, Leuchter AF. Neuromodulation for depression: invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). Neurosurg Clin N Am 2014 Jan;25(1):103–16.

Intrasession Reliability of Single and Paired Pulse TMS Evoked From the Biceps Brachii Representation of the Human Motor Cortex

Dear Editor,

Single and paired pulse transcranial magnetic stimulation (TMS) is an established method that can measure corticospinal inhibition and facilitation in healthy individuals, and those with neurological conditions [1]. Magnetic stimulation of the motor cortex results in a motor evoked potential (MEP), which are most often evoked from hand muscle representations, likely because of their high density of corticospinal projections [2]. However, investigations using other motor representations, such as the biceps brachii (BB), have proven valuable. For example, with stroke sufferers experiencing poorer functional outcome in distal than proximal muscles, the analysis of TMS responses measured from the BB muscle has become a valuable tool to assess motor reorganization and recovery [3]. Although the BB is perhaps the most commonly used target muscle of the upper arm, the reliability of outcomes measured from this muscle has yet to be established; to the authors' knowledge, only two studies have investigated the reliability of single pulse TMS measured from the BB, and their results have differed: Kamen [4] demonstrated higher BB reliability in comparison to a muscle of the hand, while Brasil-Neto, McShane [5] showed reduced BB reliability compared to a target muscle within the hand. The present study investigated the intrasession reliability of MEP amplitude and latency using the BB muscle of 14 healthy participants (4 females, mean age 29.6 ± 6.7 years, 13 right handed), in comparison to those obtained from the first dorsal interosseous (FDI) muscle. Intrasession reliability is important to determine given that many investigations using TMS take place over a single testing session, such as those measuring corticospinal excitability immediately following an intervention of repetitive TMS [6], or transcranial direct current stimulation [7].

Data were recorded from the resting muscle under conditions of single pulse TMS and three paired pulse protocols of SICI, SICF, and ICF (see Table 1 for abbreviations). Within each TMS protocol, two sets of 10 MEPs were collected, totaling 80 MEPs per session. Participants returned on a subsequent session, separated by between one and 14 days, for testing of the different muscle. The testing order of muscles was counterbalanced, and the order of TMS protocols was randomized. For both muscles, electromyography activity was recorded using surface electrodes (Powerlab, USA) placed over the participant's dominant hand/arm. A Magstim 200^2 monophasic stimulator (Magstim Co, UK) was used. A 70 mm figure-of-eight coil was held by hand with the handle pointed backward and rotated at 45°. Resting motor threshold (RMT) was defined as the stimulator intensity at which an MEP >50 μV was observed in at least five of ten stimuli. A conditioning stimulus of 80% RMT and test stimulus of 125% RMT were used for SICI and ICF protocols, with an interstimulus interval of 2 ms and 12 ms respectively. For the SICF protocol, an initial stimulus was applied at 125% RMT, followed 1.3 ms later by a stimulus at 80% RMT. MEP amplitude was defined by peak-to-peak measurement of the waveform. MEP latency was measured by visual inspection and defined as the interval from the TMS pulse to the onset of the MEP [8]. Intraclass correlation coefficient (ICC) was