Integrity of cognitive functions in trigeminal nerve stimulation trials in neuropsychiatry

Integridade das funções cognitivas em ensaios clínicos de estimulação do nervo trigêmeo em neuropsiquiatria

It is common for both practitioners and patients to have concerns about the possible neurocognitive side effects of neuromodulation techniques and these may also be related to poor adherence.[1] Electroconvulsive therapy (ECT) is currently considered the most effective treatment for severe depression. However, effects such as anterograde and retrograde amnesia and impairment of orientation, processing speed, attention, verbal fluency, and executive functions have been reported after ECT sessions.[1] Clinical trials investigating neuropsychological outcomes after neuromodulation strategies therefore tend to focus on cognitive safety.

Trigeminal nerve stimulation (TNS) is a transcutaneous neuromodulation technique based on the "bottom-up mechanism" in which alternating electric current is administered over the supraorbitary branch of the trigeminal nerve and stimuli propagate towards brain areas related to symptoms of depression and anxiety, modulating their activities. The efficacy of TNS for major depressive disorder has been studied and the results are interesting.[2,3] However, investigations are still ongoing into safety issues related to TNS, such as compromise to skin integrity.[4] We present an exploratory analysis of cognitive assessments conducted in clinical trials undertaken by our neuromodulation group.

As part of clinical trials performed to investigate the efficacy of TNS for neuropsychiatric disorders such as depression, generalized anxiety, fibromyalgia, panic disorder, posttraumatic stress disorder[5] and obsessive-compulsive disorder, 64 patients have been evaluated for cognitive function before and after a TNS protocol, using the Montreal Cognitive Assessment (MOCA).

The TNS protocol used was as proposed by Shiozawa et al.[3] and involves using an external neurostimulator to deliver an electric current with a frequency of 120 Hz and a pulse duration of 200 ms for 30 minutes. Intensity is chosen to achieve non-painful mild paresthesia without muscle contraction, individually reported on each day of stimulation. A total of 10 sessions (one session a day over two weeks) were performed.

Cognitive outcomes were analyzed continuously as the mean difference between baseline and final MOCA scores. Results were tested using analysis of variance (ANOVA). The significance level was set at $p < 0.05$. Statistical analysis was performed using standard statistical software (Stata version 13.1).

A total of 64 patients (55 female) were enrolled. At baseline, patients had a mean age of 48.6±11.9 years. Mean baseline MOCA score was 25.01±4.4. Patients exhibited a mean improvement of 0.92±1.6 points on the MOCA scale after the 10-day TNS protocol with a mean outcome of 25.93±4.16, which remained stable at one-month follow-up (mean outcome = 26.01±4.46). We found no significant differences in cognitive performance between baseline, after 10 days of stimulation and after 1-month follow-up ($F = 1.05$; $df = 2$; $p = 0.35$).

We performed multiple regressions on age, gender, diagnosis and clinical response to treatment in order to test for influences on the clinical effect from clinical or demographical variables. We found no significant confounders in our analysis.

This TNS protocol has been used in several clinical trials in neuropsychiatry and is potentially a safe and non-invasive brain stimulation strategy in terms of cognitive functions. Further studies assessing cognitive safety are of fundamental importance to clarify the effects of TNS on more specific cognitive functions.

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References

1. McClintock SM, Choi J, Deng ZD, Appelbaum LG, Krystal AD, Lisanby SH. Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. J ECT. 2014;30:165-76.
2. 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;39:6-9.
3. Shiozawa P, da Silva ME, Netto GT, Taiar I, Cordeiro Q. Effect of a 10-day trigeminal nerve stimulation (TNS) protocol for treating major depressive disorder: a phase II, sham-controlled, randomized clinical trial. Epilepsy Behav. 2015;44:23-6.
4. Shiozawa P, Cordeiro Q. Trigeminal nerve stimulation for clinical trials in neuropsychiatry: the issue of skin integrity. J ECT. 2015;31:e29-30.
5. Trevizol AP, Shiozawa P, Albuquerque Sato I, da Silva ME, de Barros Calfat EL, Alberto RL, et al. Trigeminal Nerve Stimulation (TNS) for post-traumatic stress disorder: a case study. Brain Stimul. 2015;8:676-8.

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