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Letter to the Editor

Rapid therapeutic response to anodal tDCS of right dorsolateral prefrontal cortex in acute mania

Dear Editor

Transcranial direct current stimulation is a method of non-invasive brain stimulation (NIBS) that has been intensively investigated in the last few years [1,2]. In tDCS, a weak and continuous electrical current over the scalp is applied for several minutes. If electrodes are appropriately placed and adequate parameters of stimulation are used, tDCS changes cortical excitability significantly [3].

Given the modulatory effects of tDCS, this method has been tested for mood disorders such as major depression [5,6] and bipolar disorder [6]. Although tDCS has been used for the treatment of bipolar patients, it has been used to treat depression rather than mania symptoms. Given the positive effects of other techniques of non-invasive brain stimulation for the treatment of mania such as rTMS and these initial results of tDCS for mood modulation; it is conceivable that tDCS can also induce significant reduction in symptoms of mania. Based on the neurophysiological effects of anodal stimulation and initial evidence suggesting that high frequency rTMS over the right dorsolateral prefrontal cortex might induce reduce mania symptoms [7–9], we applied 5 sessions of anodal tDCS over the right dorsolateral prefrontal cortex as an off-label treatment for a patient with an episode of mania with sexual hyperactivity.

Case report

A 41 year-old white man who carried the diagnosis of bipolar disorder since his twenties, according to DSM-IV [10] presented, in June 2012, to the psychiatric inpatient unit of Hospital de Clinicas de Porto Alegre with an acute psychomotor agitation and concomitant auditory hallucinations. This patient had obsessive-compulsive symptoms as comorbidity, characterized by intrusive contamination thoughts that produce uneasiness and by repetitive cleaning behaviors. He had 2 manic episodes in the last year that were related to side effects of tricyclic antidepressants used for anxiety complaints. He was clinical stable for the past 3 months using lithium carbonate 900 mg/day, olanzapine 10 mg/day and sertraline 50 mg/day.

The current symptoms were accompanied by repetitive masturbation, as well as perseverant and inappropriate sexual behavior. In the first hours of hospital admission he tried to have sexual intercourse with a nurse and a female patient, but sometimes his sexual feelings were directed toward to male patients or male members of the staff. He was clearly not upset about his behavior and the diagnosis of psychotic mania was made by consensus of two psychiatrists after clinical interview. Lithium dosage was then increased and sertraline was gradually tapered-down with no significant improvement in agitation after 5 days. Because a rapid response was desired and given the past history of seizures (normal MRI), a 5-day-course of transcranial direct current stimulation (tDCS) was provided, instead of electroconvulsive therapy (ECT). For that, patient and their relatives filled an informed consent, agreeing with the use of off-label tDCS. The set up for tDCS was the following: 2 mA/20 min/day with the anode over the right dorsolateral prefrontal cortex and cathode over contralateral supraorbital region using a current density of 0.06 m^2/A. He was also receiving oxcarbazepine and clozapine in increasing dosages. For oxcarbazepine, 1200 mg was reached after 1 week, and for clozapine 350 mg was reached after 3 weeks. In the third day of combined treatment the patient showed a rapid and significant decrease in the episodes of sexual disinhibited behavior, as well as in *Young mania rating scale* (YMRS) and *Nurses' Observation Scale for Inpatient Evaluation* (NOSIE) scores (See Fig. 1). A decreased number of medical intercurrences per night and a report of improvement in clinical global impression from his relatives were also noted. After the end of tDCS, the improvement lasted for approximately 72 h, when the symptoms—especially those related to his sexual drive—reappeared but in a lower intensity. The same drug regiment was maintained and patient started to improve again after 10 days with a stable evolution in the following 30 days. No further tDCS sessions were administered.

Discussion

According to Fig. 1 there was some improvement in both agitation and manic symptoms, measured by NOSIE [11] and YMRS [12] scales, respectively. For a better comprehension of the clinical evolution of the patient the effects should be analyzed separately.

Regarding the psychomotor agitation (measured by NOSIE), after concomitant tDCS and drugs, there was a significant and sustained effect up to the 20th day. We believe that both tDCS and the medication had synergic effects since the beginning regarding agitation. It is conceivable to consider that the acute effect of tDCS on that was helped by the sedative effect of both drugs over the first 2 weeks. After the third week, medication probably improved psychomotor agitation via their anti-manic effects (see dashed arrow).

With respect to manic symptoms, there was an acute, but not sustained effect of tDCS over YMRS, and this can be also related to the sertraline withdrawal. The anti-manic effects started to be more consistent only after the 20th day (see black arrow) probably because of the delayed action of medications. Another possibility is that tDCS would acutely induced neurotransmitter release or increased post-synaptic receptor sensitivity and, after 2 weeks, it might have induced a delayed cortical reorganization followed by

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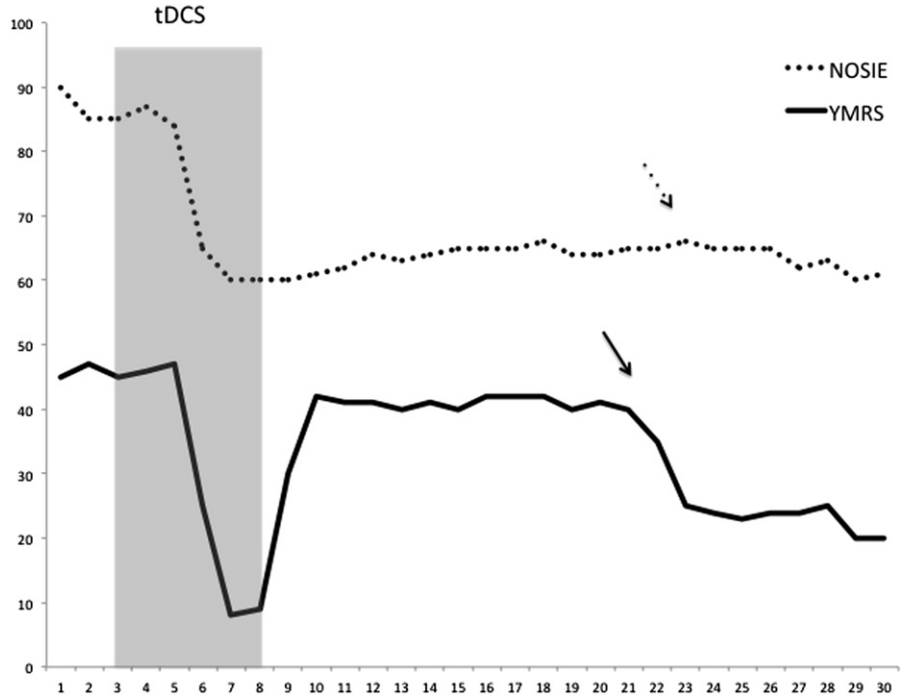

Figure 1. Clinical evolution of the patient on agitation (NOSIE) and manic symptoms (YMRS) after tDCS + drugs. Note the marked response after the intervention in both scales. The duration of the initial effect was longer for general agitation in comparison with the manic symptoms and was probably more related to tDCS rather than to the drug effect. The second improvement by the 20th day was probably secondary to delayed effect of the drugs and/or delayed cortical reorganization induced by tDCS.

a new clinical improvement, according to the tDCS neuroplasticity hypothesis [13].

One important limitation here in this case is whether effects can be attributable to tDCS given that pharmacological agents were also given to this patient. Some reasons provide evidence to support that tDCS had a direct impact such as: (1) the rapid response this patient presented as usually response to drugs has a latency of an average of more than 7 days; (2) the response curve of YMRS ratings suggest a temporal relationship with tDCS as there was a relapse of effects when tDCS was discontinued (see Fig. 1).

In conclusion, our data suggests that the application of right dorsolateral prefrontal cortex anodal tDCS in combination with pharmacological treatment maybe beneficial in acute stages of mania in patients with bipolar disorder type I. This is relevant, since unlike ECT, in which higher electrical doses lead to greater risks of cognitive side-effects [14], no significant side-effects have been described with tDCS, even with repeated sessions [4,5]. Given the characteristics of this case, this approach needs also to be investigated in patients with sexual disinhibition regardless the cause, such as in patients with schizophrenia or substance abuse [15], as well as in patients with epilepsy [16], multiple sclerosis [17] and dementia [18].

The report of this case is important to provide initial data for the design of further studies to evaluate the role of tDCS in the control of manic crisis, using more suitable study design, different tDCS protocols and adequate follow-up assessments.

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