



Safety and efficacy of transcranial direct current stimulation (tDCS) in the treatment of Anorexia Nervosa. The open-label STAR study



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Dear editor

We report results from an open-label study of the safety and efficacy of transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex (DLPFC) in patients suffering from Anorexia Nervosa (AN). AN is a severe psychiatric illness associated with a high mortality rate and a severely impaired quality of life. However, only a limited number of treatments are available, and specifically, no medication is approved for AN management [1]. Usually, psychotherapeutic interventions and the management of physical complications are recommended. Lately, rTMS has emerged as a safe and somewhat effective treatment option for the treatment of AN. However, results were not conclusive [2,3]. A recent development of tDCS seems to be promising in depression and schizophrenia [4,5] and deserves to be further investigated in AN.

To date, only one pilot study has investigated the effects of tDCS in AN. Among seven patients with AN who received tDCS of 2mA to the left DLPFC, six patients improved, and the procedure was well tolerated [6]. Nevertheless, there were only 10 sessions of stimulation, and cathode was extracephalic. AN is associated with hyperactivity in right-hemisphere frontal regions, and thus a coupled inhibition of right hemisphere might facilitate inter-hemispheric balance. We decided to perform a pilot study using a different design with number of sessions. The primary endpoint of the study was safety and tolerability, and secondary outcomes were efficacy and its persistence.

Ten female patients with a diagnosis of AN according to DSM-5 criteria were recruited in the Eating disorders centre of CHU Montpellier, France. The local ethics committee approved the study and written informed consents were obtained from all participants. The study was registered on the clinical trial database (ClinicalTrials.gov Identifier: NCT02734108). Patients were treated in an inpatient setting, received usual care and their disease was defined as severe (i.e., at least 3 years of progression with the failure of at least one ambulatory and one previous inpatient treatment well conducted

by a specialised team). All patients were taking psychiatric medications of various classes to manage comorbid symptoms. Patients received 20 sessions of anodal 2mA stimulation during a period of two weeks (2 times per day for 25 minutes, 10 days from Monday to Friday). Anode was placed on the left DLPFC, and the cathode was placed on the right DLPFC in accordance with the international 10–20 electrode placement system. The device “DC-stimulator plus” certified CE (CE 0118 EN DIN ISO 13485: 2007) was used for all stimulations. tDCS was delivered in conjunction with the usual multidisciplinary treatment. During the two weeks of stimulation, none of the participants was undergoing a specific refeeding protocol (i.e.: nasogastric refeeding), nutritional intervention, or attending a specialised psychological intervention group. Symptomatology of eating disorder and comorbid conditions were evaluated with validated questionnaires. Patients completed questionnaires before the first procedure and directly after the last procedure, as well as after 1 month. Side effects were registered. Statistical analyses were performed using SPSS version 24. All variables were tested for normality with “Shapiro Wilk” test, and since most of them were normally distributed, “Repeated measures ANOVA” with partial eta squared for effect size were used for comparing scores before and after the procedure. Where the data was distributed non normally, “Friedman” test with Kendall's W for effect size was utilised.

Out of 10 included patients, 9 completed the protocol. As shown in Table 1, the procedure was very well tolerated. No severe side effect (neurological, cardiological, psychiatric) occurred neither during, nor after the procedure. Some minor effects mostly in the anodal side of stimulation appeared. Two-thirds of participants experienced light redness and burning, which may in part be mediated by the skin fragility associated with AN [7]. It makes it even more important for this population to comply with measures to reduce the risk of skin lesions, and carefully inspecting the skin under the electrode before and after the tDCS procedure [8]. All the impacted areas were healed without any scars one month after the procedure, and there was no need for alterations of the treatment protocol.

Concerning efficacy, the total score of the eating disorder inventory questionnaire (EDI) decreased significantly along the study as well as 1 month after the stimulation, with a large effect size of 0.62. Also, the score decreased significantly in following subdimensions: inefficiency, perfectionism, distrust, interoceptive awareness, maturity fears, ascetism with the mean effect size for all those items of around 0.45, indicating high efficacy. The total score of the EDE-Q questionnaire on 1 month was significantly lower with a big effect size of 0.42. Similar results were observed in EDE-Q restraint and eating concern subdimensions, and BSQ-34 questionnaire. Depression symptoms, as measured with the BDI

Table 1
Safety and Efficacy of tDCS in patients who completed the protocol. Significant scores are bolded.

| SAFETY AND TOLERABILITY | | | | | |
|---|--------------------------------------|-------------------------------------|--------------------------------------|-----------------|-------------------------|
| | During and just after the protocol | | | After 1 month | |
| SYSTEMIC SIDE EFFECTS | | | | | |
| Serious side effects (neurological, cardiological, psychiatric) | 0% | | | 0% | |
| LOCAL SIDE EFFECTS | | | | | |
| Tingling | 100% | | | 0% | |
| Itching | 100% | | | 0% | |
| Burning sensation | 66% | | | 0% | |
| Redness | 66% | | | 0% | |
| SCORES OF EATING DISORDER QUESTIONNAIRES | | | | | |
| | Pre-sessions mean \pm SD N = 9 | Post sessions mean \pm SD N = 9 | 1 month mean \pm SD N = 9 | Global p-value | Effect size |
| EDI | | | | | |
| Drive for thinness ^a | 12.89 \pm 5.28 | 12.11 \pm 5.62 | 10.78 \pm 4.09 | 0.31 | 0.14 ^a |
| Bulimia ^a | 6.00 \pm 5.68 | 4.33 \pm 5.98 | 5.11 \pm 4.78 | 0.11 | 0.24 ^a |
| Body dissatisfaction ^a | 11.67 \pm 4.58 | 11.44 \pm 5.36 | 10.89 \pm 4.23 | 0.67 | 0.05 ^a |
| Inefficiency^a | 14.56 \pm 6.37 | 11.00 \pm 7.62 | 12.44 \pm 6.43 | <0.05 | 0.32^a |
| Perfectionism^a | 8.67 \pm 5.55 | 7.44 \pm 5.15 | 7.00 \pm 4.90 | 0.03 | 0.62^a |
| Distrust^a | 5.22 \pm 3.38 | 3.56 \pm 3.17 | 4.78 \pm 3.37 | 0.03 | 0.36^a |
| Interceptive awareness^a | 10.78 \pm 6.32 | 7.22 \pm 6.42 | 8.11 \pm 6.03 | <0.01 | 0.47^a |
| Maturity fears^a | 8.33 \pm 5.61 | 5.62 \pm 5.90 | 5.22 \pm 5.29 | <0.01 | 0.52^a |
| Ascetism^a | 6.11 \pm 3.41 | 4.00 \pm 2.35 | 4.78 \pm 2.82 | 0.01 | 0.43^a |
| Impulse control ^a | 3.56 \pm 2.79 | 2.44 \pm 1.81 | 3.33 \pm 1.80 | 0.19 | 0.19 ^a |
| Insecurity ^a | 7.56 \pm 4.10 | 5.78 \pm 3.15 | 6.78 \pm 2.99 | 0.14 | 0.22 ^a |
| EDI total^a | 95.11 \pm 38.41 | 79.38 \pm 35.35 | 78.67 \pm 34.01 | <0.01 | 0.62^a |
| EDE-Q | | | | | |
| Restraint^a | 4.67 \pm 2.03 | - | 4.17 \pm 1.94 | <0.05 | 0.42^a |
| Eating concern^a | 3.18 \pm 1.19 | - | 2.31 \pm 1.47 | 0.03 | 0.46^a |
| Shape Concern ^a | 4.78 \pm 1.23 | - | 4.11 \pm 1.20 | 0.13 | 0.27 ^a |
| Weight Concern ^a | 3.60 \pm 1.49 | - | 3.00 \pm 1.28 | 0.18 | 0.21 ^a |
| EDE-Q Total^a | 3.68 \pm 1.12 | - | 3.07 \pm 1.09 | <0.05 | 0.42^a |
| BSQ34^a | 114.22 \pm 32.79 | - | 101.67 \pm 23.21 | <0.05 | 0.41^a |
| SCORES OF MOOD DISORDERS QUESTIONNAIRES | | | | | |
| BDI^a | 16.89 \pm 5.16 | 12.67 \pm 5.20 | 14.00 \pm 6.96 | <0.01 | 0.47^a |
| YMRS ^b | 0.67 \pm 1.12 | 0.44 \pm 1.01 | 1.11 \pm 2.03 | 0.44 | 0.09 ^b |
| MOCI ^b | 17.00 \pm 3.20 | - | 17.67 \pm 2.45 | 0.71 | 0.02 ^b |
| C-SSRS ^b | 6.67 \pm 8.53 | - | 7.44 \pm 9.85 | 1 | 0.00 ^b |
| SCORES OF FUNCTIONING QUESTIONNAIRES | | | | | |
| WSAS ^a | 26.11 \pm 4.65 | - | 25.11 \pm 5.99 | 0.59 | 0.04 ^a |
| GAF ^a | 61.11 \pm 8.94 | - | 59.00 \pm 10.26 | 0.70 | 0.02 ^a |
| SCORES OF PHYSICAL ACTIVITY QUESTIONNAIRE | | | | | |
| EDS-R ^a | 37.38 \pm 10.70 | - | 36.78 \pm 17.85 | 0.74 | 0.02 ^a |

Pre-sessions – initial visit, post-sessions – scores after 2 weeks of procedure, 1 month – scores one month after the procedure ended; EDI – Eating Disorder Inventory; EDE-Q – Eating Disorder Examination Questionnaire; BSAQ34 – The Body Shape Questionnaire; BDI – Beck Depression Inventory; YMRS – Young Mania Rating Scale; MOCI – The Maudsley Obsessive Compulsive Inventory; C-SSRS – The Columbia Suicide Severity Rating Scale; WSAS – Work and Social Adjustment Scale; GAF – Global Assessment of Functioning; EDS-R – Exercise Dependent Scale Revised.

^a Repeated Measures ANOVA with partial eta squared for effect size.

^b Friedman test with Kendall's W for effect size.

questionnaire, also significantly decreased after the procedure and were lower at 1 month ($p < 0.01$, effect size 0.47). There were no differences in terms of mania, obsessive-compulsive symptoms, general functioning, suicidality, and physical activity.

The main limitation of this study is the absence of a control group that does not allow any inference on the effect of neuromodulation versus improvements secondary to the other part of the management.

In conclusion, nine of ten patients with severe AN safely completed the treatment protocol. The only patient who did not complete the protocol stopped for reasons unrelated to the stimulation. No severe side effects were registered, and some minor side effects at the anodal stimulation site disappeared quickly after the procedure. In terms of efficacy, significant improvements in AN

symptoms were achieved. Improvements in comorbid depression symptoms were also noted. The decrease in symptoms lasted 1 month. Given the lack of available therapeutic options in the AN and relatively low prices of tDCS devices, which could be done safely in outpatient settings [9,10], these results strongly call for further investigation. Future studies and randomised controlled trials are warranted to confirm if tDCS could be a safe and effective adjunctive treatment option for patients suffering from AN.

Conflicts of interest

None.

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