

Prefronto–cerebellar transcranial direct current stimulation improves visuospatial memory, executive functions, and neurological soft signs in patients with euthymic bipolar disorder

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Objective: The aim of the study was to improve neuropsychological functioning of euthymic patients with bipolar disorder (BD) using transcranial direct current stimulation (tDCS) applied to cerebellar and prefrontal cortices.

Methods: Twenty-five BD outpatients underwent prefrontal (anodal) and cerebellar (cathodal) tDCS for 3 consecutive weeks. All participants were assessed through the Rey Complex Figure Test delay and copy and the Neurological Examination Scale at baseline and after therapy with tDCS.

Results: After tDCS treatment, patients showed significant improvements in visuospatial memory tasks. Patients with worse baseline cognitive performances also showed a significant improvement in executive functioning tasks. Neurological Examination Scale total score and motor coordination subscale significantly improved.

Conclusion: Prefrontal-excitatory and cerebellar-inhibitory stimulations in euthymic BD patients may lead to better neurocognitive performances. This improvement could result from the modulation of prefronto–thalamic–cerebellar circuit activity pattern, which can be disrupted in BD.

Keywords: cerebellum, dorsolateral prefrontal cortex, neuropsychology, cognition

Introduction

Bipolar disorder (BD) is a severe and disabling disease. The course of BD has traditionally been viewed as episodic, ie, with symptomatic, functional, and cognitive recovery between mood episodes.^{1,2} However, clinical evidence recently showed that many BD individuals experience difficulties in daily functioning (eg, higher rates of unemployment and disability than healthy controls)^{3–5} as well as neuropsychological and social deficits even during the euthymic phase of the disease, despite symptomatic mood improvements.

Consistently, an increasing number of clinical observations have been considering the cognitive and social impairments observed in BD as trait-associated, rather than state-associated, characteristics of the disorder.^{6–10} In particular, visuospatial memory and executive functions have been found to be the neuropsychological domains that are more significantly impaired in euthymic BD patients in comparison with healthy controls.^{8–10}

The neurological soft signs (NSS) are minor neurological abnormalities in sensory and motor performances well established in schizophrenia.^{11,12} They have been

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described in patients with BD^{13,14} not only during the mood dysregulation episodes, but also in the euthymic phase of the disease.¹⁵ In addition, various research has observed deficits in NSS expression and deficits in executive functions, suggesting that the disturbances in the two areas of brain functioning domains may result from the alteration of similar underlying neurobiological substrates.^{15,16}

Recent studies hypothesize that cognitive impairments in BD patients could be related to prefronto–thalamic–cerebellar circuit dysfunction and, in particular, to the loss of the physiological inverse metabolic activity between the dorsolateral prefrontal cortex (DLPFC) and subcortical areas.^{17–21} In particular, some studies suggest that hypoactivation of the left DLPFC observed in BD could lead to hyperactivation of subcortical structures such as the right cerebellar hemisphere.^{17,18,20} A disruption of prefronto–cerebellar circuitry in severe mental disorders was first suggested by Andreasen et al who specifically coined the term of “cognitive dysmetria”.²²

Transcranial direct current stimulation (tDCS) is a brain-modulating technique using constant, low current delivered directly to the brain areas of interest via inhibitory (cathodal) and excitatory (anodal) electrodes.^{23–25} Intracerebral current flow between the two electrodes excites neurons in the regions of interest, producing both neurophysiological and behavioral changes in the participant.^{23–25} Considering the modulatory properties of tDCS, it is possible to hypothesize that concomitant excitatory stimulation of left DLPFC and inhibitory stimulation of right cerebellar hemisphere might modulate prefronto–cerebellar circuitry, potentially resulting in neurological and neuropsychological improvements.

Previous studies showed that anodal stimulation of DLPFC can improve cognitive performances in both patients and healthy individuals,²⁶ while one study showed that cathodal stimulation of cerebellum increased cognitive performances in healthy people.²⁷ To the best of our knowledge, anodal stimulation of DLPFC and cathodal stimulation of cerebellum have never been applied: 1) concomitantly and 2) in a sample of euthymic bipolar patients.

In the present study we used tDCS on both the right cerebellum hemisphere (cathodal, ie, inhibitory modulation) and left DLPFC (anodal, ie, excitatory modulation) to investigate the effects on visuospatial memory, executive functioning, and NSS performances in euthymic BD patients.

Methods

Participants and study design

Twenty-seven outpatients with a diagnosis of BD type I or II referring at the Policlinico Umberto I University Hospital,

Sapienza University of Rome, have been enrolled in the study. Patients were in the euthymic phase of the disorder (this was as assessed by Hamilton Depression Rating Scale score <7 and Young Mania Rating Scale <7).^{28,29} Some of these participants had previously been enrolled by our research team in other studies with different aims and objectives.^{19,30}

Exclusion criteria were: concomitant neurological diseases, other axis I diagnosis, hospitalization in the last 12 months, left handedness, pharmacological treatment with typical antipsychotics, Hamilton Depression Rating Scale score >7, Young Mania Rating Scale >7, and mental retardation (IQ <70).

tDCS was administered as an add-on treatment to patients who had been stable on a standard course of pharmacological maintenance therapies for at least 2 months. All participants were assessed at baseline and the day after the last tDCS session.

All participants signed written informed consent. The research protocol was approved by the Ethical Committee of Human Experimentation of Policlinico Umberto I University Hospital and was in accordance with the Helsinki Declaration of 1975.

tDCS

tDCS was applied through two sponge electrodes (surface area =25 cm²) moistened with a saline solution. The electrode montage was: cathodal tDCS on the right cerebellar cortex, 1 cm under, and 4 cm lateral to theinion (approximately comparable to the projection of cerebellar lobule VII onto the scalp); anodal tDCS over the left DLPFC (electrode position was determined by the International 10/20 System for EEG Electrodes, such as that Fp1 corresponded to the DLPFC). The onset and offset of the intervention involved current being increased and decreased, respectively, in a ramp-like manner over 10 seconds. The intensity of stimulation was set at 2 mA and delivered for 20 minutes every working day (Monday to Friday) for 3 consecutive weeks using a Magstim DC Stimulator Plus and was considered a safe level of exposure, well below the threshold for causing tissue damage.^{27,31}

Neuropsychological and neurological assessment

To test visuospatial memory, participants completed the Rey Complex Figure Test (RCFT) after short and long (immediately and 20 minutes, respectively) delays, while the RCFT copy was used to measure executive functioning.³² To minimize the “learning effect”, parallel (ie, different) versions of RCFT were used in pre- and post-treatment evaluations.

The neurological examination was performed through the Neurological Evaluation Scale (NES),³³ which includes

26 items listing the more frequent and significant NSS. Trained evaluators administered the scales based on the original scoring instructions, and items were scored as 0 (no abnormality), 1 (mild but definite impairment), and 2 (marked impairment). Two items (the suck and snout reflex) were scored 0 (absent) or 2 (present). The results show the total score and the three main subscale scores (sensorial integration, motor coordination, and motor sequencing).

Statistical analysis

The data were analyzed through SPSS software version 20. Data were normally distributed and a paired sample *t*-test was used to compare pre- and post-treatment measures. The significance threshold was $P < 0.05$.

Results

Two patients did not complete the stimulation protocol because of the onset of migraine. The remaining 25 patients tolerated tDCS without complications with the exception of three patients complaining of a transient burning sensation surrounding the electrode site. Demographic and clinical characteristics of these patients are given in Table 1.

Visuospatial memory (measured through the RCFT delay test) improved significantly ($P < 0.01$) after the treatment, although no significant changes were observed in the executive functions domain (measured through the RCFT copy test) (Table 2). NES total score and motor coordination subscale showed significant improvements after tDCS treatment ($P < 0.01$) (Table 2; Figure 1).

To evaluate if the degree of the baseline cognitive impairment in BD patients could influence the

Table 1 Clinical and sociodemographic data

| | |
|--|-------------------|
| Patients (n) | 25 |
| Age, years (mean \pm standard deviation) | 41.9 \pm 12.62 |
| Sex | |
| Males (n) | 8 |
| Females (n) | 17 |
| Civil status | |
| Married (n) | 8 |
| Single (n) | 11 |
| Others (divorced + widowed) (n) | 6 |
| Number of years in school | |
| ≤ 9 (n) | 6 |
| > 9 (n) | 19 |
| Diagnosis | |
| Bipolar disorder I (n) | 15 |
| Bipolar disorder II (n) | 10 |
| Disease duration, years (mean \pm standard deviation) | 17.08 \pm 12.05 |
| Age at onset of illness, years (mean \pm standard deviation) | 28.79 \pm 12.60 |
| Psychiatric medication | |
| Lithium (n) | 12 |
| Anticonvulsants (n) | 17 |
| Atypical (n) | 17 |
| Benzodiazepines (n) | 10 |
| Antidepressants (n) | 5 |

neuropsychological outcomes of the tDCS treatment, we performed supplementary analyses dividing the whole sample into two subgroups of patients: 1) high baseline performances (HBP) group comprised patients with an average baseline score above the median value of the neuropsychological domain of interest; 2) low baseline performances (LBP) group comprised patients with an average baseline score below the median value of the neuropsychological domain of interest. LBP patients showed a more relevant improvement than HBP patients in both visuospatial (RCFT delay test) and executive functions (RCFT copy test) domains (Table 2).

Table 2 Mean scores of neuropsychological and NES assessments pre-tDCS and post-tDCS

| | Pre-tDCS evaluation | Post-tDCS evaluation | P-value |
|--------------------------------------|---------------------|----------------------|---------|
| Neuropsychological evaluation | | | |
| RCFT copy | 26.29 \pm 5.76 | 28.00 \pm 7.66 | 0.41 |
| LBP patients | 21.95 \pm 4.50 | 27.19 \pm 4.58 | 0.01* |
| HBP patients | 31.00 \pm 1.99 | 28.91 \pm 10.41 | 0.50 |
| RCFT delay | 8.42 \pm 6.22 | 13.71 \pm 6.51 | 0.01* |
| LBP patients | 3.37 \pm 3.41 | 9.04 \pm 4.26 | <0.01* |
| HBP patients | 13.37 \pm 4.26 | 17.74 \pm 5.67 | 0.06 |
| NES | | | |
| Motor coordination | 1.91 \pm 1.54 | 0.39 \pm 0.65 | <0.01* |
| Motor sequencing | 3.77 \pm 2.84 | 2.22 \pm 2.61 | 0.06 |
| Sensory integration | 2.00 \pm 1.48 | 1.43 \pm 1.85 | 0.26 |
| Total score | 11.77 \pm 6.48 | 5.91 \pm 4.44 | <0.01* |

Note: * $P < 0.05$. Data are presented as mean \pm standard deviation.

Abbreviations: HBP, high baseline performances; LBP, low baseline performances; NES, Neurological Evaluation Scale; RCFT, Rey Complex Figure Test; tDCS, transcranial direct current stimulation.

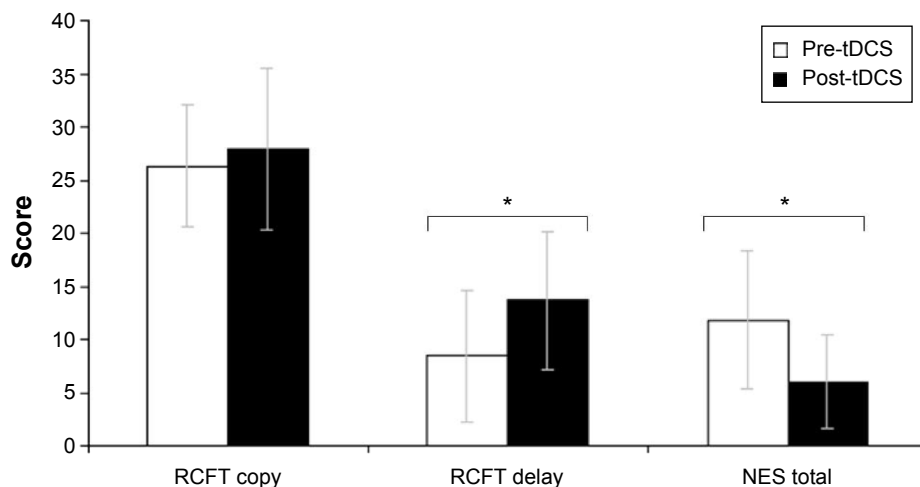


Figure 1 Mean scores and standard deviations of neuropsychological and NES assessments pre- and post-tDCS.

Note: * $P < 0.05$.

Abbreviations: NES, Neurological Evaluation Scale; RCFT, Rey Complex Figure Test; tDCS, transcranial direct current stimulation.

Discussion

To the best of our knowledge, this is the first study investigating the effect of prefronto–cerebellar tDCS on cognitive performances in euthymic BD patients.

Cognitive deficits have gained considerable importance as critical features of a wide range of psychiatric disorders^{10,34–38} and they pose an important therapeutic challenge.^{7,8,39} While there is overwhelming evidence on the efficacy of psychotropic medications in the management of clinical symptoms, cognitive gains are often poor.^{7,8,39} Thus, it is currently accepted that cognitive impairment and symptomatic manifestations of mental disorders require separate and integrated therapeutic approaches.

The results of the present research preliminarily suggest that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS might have a positive effect on visuospatial memory and executive functioning in euthymic BD patients. Andreasen's idea of "cognitive dysmetria" hypothesized that a general loss of mental processes coordination could be the consequence of prefronto–thalamic–cerebellar circuit disruption,²² and this idea has been supported by several subsequent studies.^{17,18,20} It is thus speculatively possible that the cognitive improvements observed in our patients may be at least partially attributable to a functional modulation of prefronto-cerebellar circuitry activity.

Stratifying the patients according to baseline cognitive functions, we found that LBP patients showed significantly improved executive functions and presented more significant benefits in visuospatial memory than HBP patients. This finding suggests that individuals with more severe cognitive

impairments, that are often the most clinically severe and the most difficult to treat, may obtain more substantial benefits from prefronto–cerebellar tDCS.

NSS are indicators of neurological impairment frequently observed in schizophrenia and in other psychiatric disorders;^{11–15} our results showed that prefronto-cerebellar tDCS led to significant improvements of the NES total score and NES motor coordination subscale.

A recent diffusion tensor imaging study found an inverse correlation between NSS severity and the integrity of thalamic–cerebellar tracts,⁴⁰ supporting our study hypothesis. Furthermore, Goswami et al recently found a correlation between NSS and executive dysfunctions in euthymic BD patients, potentially involving an inadequate functioning of prefrontal cortex;¹⁵ this evidence is consistent with our results, as both NSS and executive functions improved after DLPFC stimulation.

Conclusion

In conclusion, the present study provides preliminary evidence that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS in euthymic BD patients may lead to better neurocognitive performances, quantified through neuropsychological and neurological measures. We suggest that this improvement is at least partially attributable to functional modulations of prefronto-cerebellar circuitry activity, which has been proven to be altered in BD as well as in other psychiatric disorders. Prefronto–cerebellar tDCS could potentially represent an inexpensive, easy to administer, non-invasive, and painless therapy to increase the effectiveness of standard BD treatment.

The small sample size and the absence of a sham control group are major limitations of the study. In addition, we assessed a relatively large number of measures and we did not correct for multiple comparisons; therefore, these results are exploratory/hypothesis-generating and further studies are needed.

Acknowledgment

The research was fully funded by the Department of Neurology and Psychiatry of Sapienza University of Rome.

Disclosure

The authors report no conflicts of interest in this work.

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