Prefronto-cerebellar tDCS enhances neurocognition in euthymic bipolar patients. Findings from a placebo-controlled neuropsychological and psychophysiological investigation

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ABSTRACT

Objectives: The present double blind placebo-controlled study aimed at investigating the efficacy of 3-weeks prefronto-cerebellar transcranial direct current stimulation (tDCS) on neurocognitive functioning in euthymic BD patients.

Methods: Forty-two outpatients with BD were randomly assigned to receive either active (n=21) or sham (n=21) prefronto-cerebellar tDCS for 3 consecutive weeks. Neurocognitive abilities were assessed with both neuropsychological testing and psychophysiological evaluation with a P300 novelty task.

Results: Our results showed that (i) Trail Making Test-B, a measure of executive functioning, decreased significantly in the active but not in the sham group, (ii) Rey Complex Figure Test Delay Recall, a measure of visuospatial memory, increased significantly in both groups with a greater increase in the active compared to the sham group, and (iii) P3b latency, a measure of brain information processing stream, decreased significantly in the active but not in the sham group. No significant changes were observed in the other explored neuropsychological and psychophysiological measures.

Conclusions: The study suggests that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS in euthymic BD patients may lead to better neurocognitive performance, quantified through neuropsychological and psychophysiological measures.

1. Introduction

Individuals with Bipolar Disorder (BD) can experience difficulties in social and functional outcomes (e.g. higher rates of unemployment and disability than controls) even in the euthymic phase of the disease, despite symptomatic improvements or recovery following mood episodes (Bersani et al., 2013; Dissanayake et al., 2011; Huxley and Baldessarini, 2007; Kessler et al., 2006; Kogan et al., 2004; Tohen et al., 2003).

Increased attention has recently been given to the role of residual neurocognitive deficits of BD subjects and their association with functional impairment. In particular, specific neuropsychological domains such as visuospatial memory, concentration/sustained attention and executive functioning have been found significantly impaired in euthymic BD patients in comparison with healthy control (Deckersbach et al., 2010; Martinez-Aran et al., 2004; Robinson et al., 2006; Mann-Wrobel et al., 2011). Interventions aimed at remediating such cognitive disturbance may therefore have potential for improving patient functioning.

Transcranial direct current stimulation (tDCS) is a brain-modulating technique using constant, low current delivered to the scalp over the brain areas of interest via inhibitory (cathodal) and excitatory (anodal) electrodes (Mann-Wrobel et al., 2011; Bersani and Biondi, 2012; Medeiros et al., 2012; Poreisz et al., 2007; Galea et al., 2009). However, controversial findings on the physiological effects of cathodal and anodal stimulations do exist (Medeiros et al., 2012). Intracerebral current flow between the two electrodes excites neurons in the regions of interest, producing both neurophysiological and behavioural changes (Bersani and Biondi, 2012; Medeiros et al., 2012; Poreisz et al., 2007; Galea et al., 2009; Nitsche and Paulus, 2000).

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Prefrontal cortex, cerebellum, and the prefronto–thamic–cerebellar circuitry have been implicated in certain cognitive processes including those reported as dysfunctional in euthymic BD patients (Tomlinson et al., 2014; Marvel and Desmond, 2010; Ben-Yehuda et al., 2007; Hayter et al., 2007; Frith and Dolan, 1996). The dysfunction of prefronto–cerebellar circuitry may therefore underlie certain aspects of the neurocognitive deficits observed in BD individuals (Strakowski et al., 2004; Monks et al., 2004; Benson et al., 2008; Minichino et al., 2014a). Anodal tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) have led to improved performance on executive tasks, visuospatial memory and sustained attention (Iyer et al., 2005; Fregni et al., 2005; Nelson et al., 2014; Minichino et al., 2015); cathodal cerebellar tDCS stimulation has also been found to improve executive performance in healthy participants (Pope and Mill, 2012). Further, concomitant prefronto-cerebellar stimulations have been preliminarily tested in two recent studies to improve cognitive functions in euthymic BD subjects (Minichino et al., 2015; Martin et al., 2015).

tDCS has the potential to modulate both frontal and cerebellar functioning in a polarity-dependent manner (Galea et al., 2009; Nitsche and Paulus, 2000). Therefore, reduction of relative cerebellar activity using cathodal tDCS together with increase of relative activity of prefrontal DLPFC using anodal stimulation, with the subsequent possible modulation of the prefronto–thamic–cerebellar circuitry, may represent a novel strategy to improve neurocognitive performance in BD patients.

From a psychophysiological point of view, event-related potentials (ERPs) allow the identification of specific neurocognitive deficiencies; in particular, the P300 component has been studied widely, and it is believed to be related to stimuli categorization as an indicator of selective attention and memory updating (Huang et al., 2015; Polich, 2007). One very informative paradigm is the so-called P300 Novelty task. This task is usually used to detect the N1 component, which is related to the early perception and automatic involuntary detection of the acoustic stimulus (Huang et al., 2015; Polich, 2007). Moreover, it can be used to detect two different components with specific psychophysiological meanings, namely P3a and P3b (Huang et al., 2015; Polich, 2007; Friedman et al., 2001). The P3a is elicited by a distracter stimulus, and it has been interpreted as a neural correlate of the orienting response; the P3b component, which is elicited by a target rare stimulus, reflects neuronal activity associated with revision of the mental representation of the previous event within the stimulus environment (Huang et al., 2015; Polich, 2007). This component has been found to be abnormal in a range of psychiatric afflications including BD; in particular, the reduction in the amplitude and the increase in latency of P3b component represent the most common psychophysiological abnormalities observed in euthymic BD patients (Bersani et al., 2015a; Campanella, 2013; Fridberg et al., 2009). Conversely, the orienting response seems to be preserved, as reflected by N1 and P3a parameters, found to be comparable between BD patients and healthy controls (Andersson et al., 2008; Bestelmeyer, 2012).

The present double-blind placebo-controlled study aimed at investigating the efficacy of 3-weeks prefronto-cerebellar tDCS on neurocognitive functioning in euthymic BD patients. Neurocognitive abilities were assessed with both neuropsychological testing and psychophysiological evaluation with a P300 novelty task. We hypothesized that patients in the active groups, compared to patients in the control group, will show (i) significant improvements in the explored neuropsychological domains, and (ii) significant improvements in neurophysiological markers of cognitive processing.

2. Methods

2.1. Participants and study design

Subjects (n=42) were consecutively recruited at the Bipolar Disorder Outpatient Clinic of Policlinico Umberto I University Hospital - Sapienza University of Rome. The institutional review board of Sapienza University of Rome and Policlinico Umberto I University Hospital approved the study. All subjects provided written, informed consent prior to commencing their involvement in the trial.

The inclusion criteria for the study were i) 18–65 years of age, ii) a diagnosis of BD as determined by the Structured Clinical Interview for DSM-IV (First, 1997), iii) patients being in the euthymic phase of the disease as defined by Hamilton Depression Rating Scale < 7 and Young Mania Rating Scale < 7 (Hamilton, 1960; Young et al., 1978), iv) patients being on a stable dose of their psychotropic medications for at least 4 weeks prior to entering the study v) patients being able to grant informed consent and to follow the study procedures. Patients were not included in the study if they: i) had a DSM-IV history of substance abuse or dependence in the 6-months prior to the beginning of the stimulation protocol; ii) had a concomitant, major and unstable medical, or neurologic illness; iii) had a history of seizures; iv) were pregnant; v) had comorbid Axis I or Axis II diagnoses; v) were left-handed, vi) had been hospitalized in the previous 12 months.

Following completion of baseline clinical assessment by two senior psychiatrists (RDC and MB), patients were randomly assigned to receive either active (n=21) or sham (n=21) tDCS. Randomization procedure was completed using a computer-generated randomization list. The study had a double-blind design: only the study coordinators (FSB and AM) were aware of subjects’ treatment condition, while tDCS stimulators (FS, LV, AC), psychophysiological evaluators (DM, CP and FF), neuropsychological evaluator (LB) and patients were blind to treatment group allocation. During the informed consent process, subjects were adequately informed on the possibility to receive a sham or an active stimulation. Patients were instructed not to discuss their treatment experiences with the evaluators, in order to reduce the risk of rating biases.

Fifteen treatments, each lasting 20 min, were administered over the course of 3 weeks (one treatment per weekday). The tDCS was applied to patients in addition to the standard pharmacological maintenance therapies, which remained unchanged along the intervention. Patients underwent a comprehensive psychophysiological and neuropsychological assessment 24–48 h before the beginning of the stimulation (T0) and 24–48 h right after the conclusion of the 15th session (T1).

2.2. TDCS protocol

The tDCS treatment was delivered using a battery-operated, constant current stimulator (BrainSTIM EMS Srl, Bologna, Italy) and transmitted by two rubber electrodes (7 cm×5 cm =35 cm²), each covered by a saline-soaked sponge and affixed to the head with a headband. The anode was directed over the left DLPFC, corresponding to electrode F3 according to the 10–20 EEG system. Neuronavigation studies (Herwig et al., 2001) have indicated that this is a reasonably accurate method of locating the DLPFC, and it has also been used in previous tDCS studies targeting the DLPFC (Bersani and Biondi, 2012; Fregni et al., 2005, 2006; Blumberger et al., 2012). The cathode was directed on the right cerebellar cortex, 1 cm under, and 4 cm lateral to the inion (approximately comparable to the projection of cerebellar lobule VII onto the scalp), consistently with previous studies targeting right cerebellar cortex (Minichino et al., 2015, 2014b; Pope and Mill, 2012; Bersani et al., 2015b; Mannarelli et al., 2016; Picazio et al., 2015).

In the active treatment group, the intensity of stimulation was set at 2 mA and delivered for 20 min every working day (Monday to Friday) for 3 consecutive weeks; this level of exposure was considered safe and
well below the threshold for causing tissue damage (Pope and Miall, 2012; Roggio et al., 2006). Sham stimulation was delivered using parameters identical to those in the active condition with the exception of the stimulator being programmed to turn off after 30 s, allowing the investigators to mimic the initial somatic sensations experienced with active tDCS, but without providing putative therapeutic benefits (Ambrus et al., 2010).

2.3. Neuropsychological evaluation

All participants completed a comprehensive neuropsychological battery administered by a senior neuropsychologist (LB) to assess those domains that are often impaired in euthymic BD patients. i.e. attention, visuo-spatial memory and executive functions (Deckersbach et al., 2010; Martinez-Aran et al., 2004; Robinson et al., 2006). The choice of neuropsychological battery was guided by an extensive review of the scientific literature (Bakkour et al., 2014). All cognitive tests had been translated and validated in the Italian language and all had well-documented norms and excellent estimates of reliability and validity (Lezak, 2012).

Sustained attention was assessed with the Trail Making Test (TMT) part A (Giovagnoli et al., 1996). The domain of executive functioning was assessed with the Wisconsin Card Sorting Test (WCST) (Heaton et al., 2000), TMT part B (Giovagnoli et al., 1996) and Rey Complex Figure Test (RCFT) copy version (Bennett-Leyt, 1984). Visuo-spatial memory abilities were assessed using the Rey Complex Figure Test delay recall (RCFT-DR) (Bennett-Leyt, 1984). Raw cognitive scores were corrected and based on normative data from Italian normative samples. To minimize the “practice effect”, alternate (i.e. different) versions of the tests were used in pre- and post-treatment evaluations.

2.4. Psychophysiological evaluation

Psychophysiological evaluation consisted of an ERP evaluation with a P300 Novelty Task. The electrophysiological signals were recorded by Ag/AgCl electrodes fixed on the scalp at the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 sites, according to the International 10–20 System, referred to linked mastoids and grounded at the forehead. The bipolar electro-oculogram (EOG) was recorded from above and below the left eye. All inter-electrode impedances were kept below 3KOhm. EEG signals and EOG were filtered online using a 0.01–30 Hz. A notch filter (50 Hz) was also applied. The data were digitized with an analog/digital converter at a sampling rate of 1024 Hz and stored on a hard disk. A Mizar Sirius EEG-EP multifunctional system was used.

The P300 Novelty task consisted of a series of auditory stimuli (Standard, Target, Novel). The standard stimulus was a 500 Hz tone (duration: 200 ms; rise-fall times: 10 ms; intensity: 80 dB SPL; probability of occurrence: 0.8) while the infrequent target stimulus was a 1000 Hz tone (duration: 200 ms; rise-fall times: 10 ms; intensity: 80 dB SPL; probability of occurrence: 0.1). The novel sounds (probability of occurrence: 0.1) were unique, non-repeating sound effects (“novel”) either sampled from a sound effects compact disk or generated in the lab using a microphone to record typical environmental sounds (e.g. a key in a lock, a cup being placed on a table) (Kimble et al., 2000). These novel sounds, which were clipped to a length of 200 ms, were unidentifiable and ambiguous. The intensities of all the stimuli including novel sounds were checked using a calibrated sound-level meter (Radio Shack 33–2055) and adjusted in such a way that the intensity perceived by the subject was 80 dB. The subjects were instructed that they would hear a series of stimuli in which target tones were randomly interspersed. They were asked to ignore all other sounds and silently count the target tones. The inter-stimulus interval varied randomly between 2 and 3 s. The task lasted about 15 min.

To minimize the “practice effect” on the count of the target tones, total number of trials varied between 400 and 450, respectively for pre- and post-treatment evaluations.

2.5. ERPs analysis

Trials containing eye movements (including blinks) that exceeded ±100 µV in the eye channels were automatically rejected online, according to clinical guidelines (Duncan et al., 2009). Trials containing drift with deflections exceeding ±100 µV in any channel were also excluded. A further selection was performed in the offline analysis to reject other kinds of artifacts not detected by the automatic rejection procedure (eye movements, erratic general movements of the patient, etc).

For each subject, all the artifact-free trials were averaged per stimulus (Standard, Target, Novel) and filtered offline with a low-pass digital filter of 20 Hz. Scalp electrode activity was measured at all electrode sites, among these only Fz, Cz and Pz were analyzed. Fz, Cz and Pz were chosen for analyses because ERPs responses are largest on the midline locations. The N1 amplitude was measured as the mean voltage between 80 and 180 ms after each stimulus, while the N1 latency was defined and calculated as the midpoint latency, i.e. the time point that divided the area under the curve into two equal halves (Luck, n.d.).

The P3b amplitude was measured as the mean voltage between 250 and 500 ms in the target response. The P3a amplitude was measured as the mean voltage between 250 and 500 ms in the novel response (Luck, n.d.). The P3b and P3a latencies were also calculated respectively in the target and in the novel responses, as the midpoint latency of the same temporal window.

2.6. Statistical analysis

All analyses were conducted in SPSS, version 20.0 (SPSS, Inc., Chicago). Comparisons of demographic and clinical characteristics were performed with analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. The threshold for statistical significance was set at 0.05 (two-tailed, p < 0.05). Normality was assessed by the Shapiro–Wilk test.

The RCFT, RCFT-DR, WCST, TMTA and TMTB assessments were analyzed by means of repeated measures ANOVA, with the “group” (active vs sham) as the between-subject factor and the “time” (pre vs post) as the within-subject factor.

Amplitudes and latencies were analyzed separately for each psychophysiological components (N1 and P3) by means of repeated measures ANOVA, with the “group” (active vs sham) as the between-subject factor and the “time” (pre-tDCS and post-tDCS), the “electrode” (Fz, Cz, and Pz), and the “stimulus” (standard, target and novel for N1, and target and novel for P3) as the within-subject factors. When necessary, a post-hoc correction according to Bonferroni was then applied. Degrees of freedom were adjusted, when necessary, using the Greenhouse-Geisser epsilon coefficient for possible violations of the sphericity assumption and corrected p values are reported; the original degrees of freedom are reported together with their correction factor epsilon.

3. Results

3.1. Characteristics of the sample

Demographic and clinical characteristics of the subjects are presented in Table 1. There were no significant differences between groups by age, years of education, BD subtype (i.e. BD type 1 or BD type 2), age of psychopathological onset, mood clinical measures (HDRS and YMRIS), use of psychotrophic medications and neuropsychological functioning. Compared to the sham group, a longer duration of illness (p=0.03) and a higher rates of females (p=0.03) were found in the active group. All patients tolerated tDCS without complications with
the exception of transient migraine and transient burning sensation surrounding the electrode site.

3.2. Neuropsychological evaluation

A significant time x group interaction was observed for TMTB (F(1,40)=5.82, p=0.02) and RCFT-DR (F(1,40)=4.86, p=0.03) but not for RCFT (F(1,40)=0.05, p=0.83), WCST (F(1,40)=2.46, p=0.12) and TMTA (F(1,40)=1.012, p=0.32).

Bonferroni correction (T0 vs T1) showed that TMTB at T1 was significantly lower than at T0 in the active group (p < 0.01) but not in the sham group (p=0.25) (Fig. 1) and that RCFT-DR at T1 was significantly higher than at T0 in both the groups (active: p < 0.01; sham: p=0.01) with a greater increase in the active compared to the sham group (Fig. 1). When analyses were adjusted for possible confounds (i.e. age, years of education, sex, disease duration, and IQ), the significance of the results did not change.

3.3. Event related potentials

As regards N1 amplitude and N1 latency, neither the main effects nor the interaction between factors were significant. Similarly, regarding P3 amplitude, no significant main effects and no significant interactions emerged.

As regards P3 latency, ANOVA revealed a significant group t x time interaction (F(1,29)=5.2, p=0.03); after Bonferroni correction, a significant difference emerged for the active-tDCS group alone, with a lower post-tDCS than pre-tDCS latency being detected (pre: 367.7 ms; post: 363.7 ms; p < 0.01), while no difference emerged for novel stimuli (P3a) in the active-tDCS group, or for the sham group in any stimulus (Table 2; Figs. 2 and 3).

No other significant main effects and no significant interactions emerged.

4. Discussion

To the best of our knowledge, this study represents the first attempt to utilize a 3-weeks placebo-controlled prefronto-cerebellar tDCS protocol to enhance neurocognitive functioning in patients with euthymic BD using both clinical and neurophysiological outcome measures. The rationale for the novel prefronto-cerebellar montage was that placing the anode over the left DLPFC, which is known to be hyperactive during sustained attention task (Dolan, 1996; Drevets, 2001), and the cathode over the cerebellum, which is known to be hyperactive during sustained attention task performance in bipolar disorder (Benson et al., 2008; Minichino et al., 2014a), would modulate the functioning of these areas and thereby facilitate neurocognitive performance improvements.

Our results showed that (i) TMT-B, a measure of executive functioning, decreased significantly in the active but not in the sham group, (ii) RCFT-DR, a measure of visuospatial memory, increased significantly in both groups with a greater increase in the active compared to the sham group, and (iii) that P3b latency, a measure of brain information processing stream, decreased significantly in the active but not in the sham group. No significant changes were observed in the other explored neuropsychological and psychophysiological measures.

Overall, the results of the present research suggest that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS might have a positive effect on executive functioning in euthymic BD patients. Among the three neuropsychological clinical measures we used to test
changes in executive functioning (i.e. TMTB, WCST and RCFT), only TMTB significantly improved. This finding is consistent with previous evidence showing that prefrontal tDCS significantly enhances working memory performance (Fregni et al., 2005; Boggio et al., 2006; Ohn et al., 2008; Andrews et al., 2011), which are specifically assessed by TMTB and not by WCST or RCFT (Salthouse, 2011; Sanchez-Cubillo et al., 2009).

Our second finding was an improvement in visuospatial memory (measured by RCFT-DR) in patients of both active and sham groups. This finding suggests that tDCS did not have a specific effect on this cognitive domain per se, but rather that other unspecific factors such as the placebo effect and the concomitant use of medications might have played a role.

As revealed by the significant changes in P3b, the results of the study also suggest that prefronto-cerebellar tDCS improve the context-updating function, which is central to task switching and thus relevant to working memory. Conversely, the initial perception and the automatic involuntary detection of the stimulus as well as the orienting phase of the stimulus processing were not significantly influenced by the treatment (as revealed by the non-significant changes in N1 and P3a parameters).

Further, studies using tDCS in patients with MDD also showed a positive effect on neuropsychological domains (Fregni et al., 2006; Blumberger et al., 2012). On the other hand, the results of the current study are inconsistent with the results of Martin et al., in which authors did not find cognitive facilitations in BD patients after prefronto-cerebellar tDCS stimulation (Martin et al., 2015); the study of Martin

![Fig. 1. Changes from T0 to T1 in Real and Sham groups in TMTB (F=5.82, p=0.02) and in RCFT-DR (F=4.86, p=0.03).](image)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Target response (P3b)</th>
<th>Novel response (P3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHAM T0</td>
<td>SHAM T1</td>
</tr>
<tr>
<td>Lat (ms) Fz</td>
<td>386.21 ± 33.72</td>
<td>391.21 ± 34.53</td>
</tr>
<tr>
<td>Cz</td>
<td>391.58 ± 32.20</td>
<td>395.42 ± 33.65</td>
</tr>
<tr>
<td>Pz</td>
<td>399.45 ± 35.70</td>
<td>398.92 ± 29.45</td>
</tr>
<tr>
<td>Amp (µV) Fz</td>
<td>5.06 ± 3.52</td>
<td>4.94 ± 1.61</td>
</tr>
<tr>
<td>Cz</td>
<td>5.88 ± 2.65</td>
<td>5.91 ± 1.41</td>
</tr>
<tr>
<td>Pz</td>
<td>9.73 ± 5.64</td>
<td>9.14 ± 5.77</td>
</tr>
<tr>
<td></td>
<td>ACTIVE T0</td>
<td>ACTIVE T1</td>
</tr>
<tr>
<td>Lat (ms) Fz</td>
<td>392.20 ± 59.80</td>
<td>357.33 ± 24.15</td>
</tr>
<tr>
<td>Cz</td>
<td>396.55 ± 59.36</td>
<td>363.37 ± 24.04</td>
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<tr>
<td>Pz</td>
<td>402.41 ± 53.15</td>
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<tr>
<td>Amp (µV) Fz</td>
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</tr>
<tr>
<td>Cz</td>
<td>6.97 ± 4.49</td>
<td>11.22 ± 5.97</td>
</tr>
<tr>
<td>Pz</td>
<td>9.24 ± 6.81</td>
<td>11.59 ± 6.00</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.
et al., however, differs from the present study as the protocol involved a smaller sample, one single stimulation session and a single blind design (Martin et al., 2015), making comparability of results difficult.

Cognitive deficits have gained considerable importance as critical features of a wide range of psychiatric disorders and represent an important therapeutic challenge (Campanella, 2013; Millan et al., 2012). While there is overwhelming evidence on the efficacy of psychotropic medications in the management of clinical symptoms of BD, cognitive gains are often poor (Deckersbach et al., 2010; Martinez-Aran et al., 2004; Robinson et al., 2006; Mann-Wrobel et al., 2011; Campanella, 2013; Millan et al., 2012). Thus, it is currently accepted that cognitive impairment may require specific integrated therapeutic approaches (Campanella, 2013; Millan et al., 2012). The results of the present study suggest that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS in euthymic BD patients may lead to better neurocognitive performance, quantified through neuropsychological and psychophysiological measures. Previous studies hypothesized that a loss of mental processes coordination could be the consequence of cerebro-cerebellar circuit disruption (Benson et al., 2008; Minichino et al., 2014a; Konarski et al., 2005; Phillips et al., 2015; Schmahmann and Sherman, 1998); it is thus speculated possible that the neurocognitive improvements observed in our patients may be at least partially attributable to a functional modulation of prefronto-cerebellar circuitry.

A limitation of the study is that all patients were required to be on a stable psychopharmacological treatment. As lithium and anticonvulsants can have an effect on sodium and calcium channels (Ketter et al., 2003; Malhi et al., 2013), it is possible that these medications may have influenced the tDCS-induced changes in neuronal excitability. However, the two groups of patients enrolled in the study did not differ in terms of pharmacological treatment. Future research into the mechanisms underlying cognitive-enhancing effects from tDCS is required to delineate the respective effects of these medications on performance outcomes. An additional limitation of the study is the repetition of neuropsychological assessments and the subsequent possible “practice effect”; however, we used alternate (i.e. different) forms of the tests in order to attenuate this possible confounder. Further, findings on executive functioning need to be tempered by the fact that there were some aspects of this domain that have not been improved by the treatment. This is probably to the fact that the concept of executive functioning is broad and includes a number of different cognitive sub-abilities such as pattern recognition, organisation, planning and problem solving. Additional studies are needed to specifically address this issue. Finally, controversial findings on the physiological effect of cathodal and anodal stimulations do exist (Medeiros et al., 2012), which need to be taken into account for interpretation of results. Among the strengths of the study, i) the research was conducted with a double-blind placebo-controlled design, ii) the sample was clinically well characterized, iii) neurocognitive changes were assessed both clinically and neurophysiologically, iv) P300 is a reliable and objective...
marker of brain information processing stream, and v) during tDCS administration, patients’ pharmacological maintenance therapies remained unchanged, allowing us to specifically account for tDCS effects.

In conclusion, the present study adds to the accumulating evidence that non-invasive stimulation of prefrontal and cerebellar cortices may improve neurocognition, and preliminarily suggests that prefronto–cerebellar tDCS could represent an inexpensive, easy to administer, non-invasive, painless and add-on therapy to treat BD euthymic patients. Improved cognitive performances during euthymia could, in turn, potentially lead to better social and functional outcomes in daily life.

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