Transcranial direct current stimulation: A novel approach in the treatment of vascular depression

Raffaella Zanardi [a, b, *], Sara Poletti [b], Dario Prestifilippo [b], Francesco Attanasio [b], Barbara Barbini [a, b], Cristina Colombo [a, b]

[a] IRCCS San Raffaele Scientific Institute, Department of Clinical Neurosciences, Mood Disorder Unit, Milan, Italy
[b] University Vita-Salute San Raffaele, Department of Clinical Neurosciences, Milan, Italy

ARTICLE INFO

ABSTRACT

Background: Despite the impact of depression in terms of personal suffering and socioeconomic burden, most currently available treatment options are often ineffective. A particularly difficult-to-treat depressive disorder characteristic of the elderly is vascular depression, a late-life depressive syndrome related to a variety of potential vascular mechanisms. Transcranial Direct Current Stimulation (tDCS), a non-invasive and effective somatic approach to depression, also showed positive effects on cognitive deficits.

Aim: We performed a double-blind randomized study to investigate the efficacy of tDCS as augmentation strategy to sertraline in the treatment of vascular depression, hypothesizing a positive effect in both depressive symptoms and cognitive functions.

Methods: We enrolled 93 inpatients over 60 years of age with a diagnosis of vascular depression. Depressive symptoms were weekly assessed (T0, T1, T2) with the 21-items Hamilton depression rating scale (HDRS). Cognitive functioning was evaluated with the Milan Overall Dementia Assessment (MODA) at baseline and after the treatment protocol. All patients were randomly assigned into three groups, Group I: one tDCS stimulation per day, Group II: two tDCS stimulations per day, Sham group: one sham tDCS stimulation per day. Stimulation was performed for 10 consecutive working days.

Results: A significant interaction time*treatment was observed on HDRS scores (F = 14, p < 0.001). All groups improved at T1 but whereas Group II significantly differed from the Sham group (p < 0.001) we observed no difference between Sham and Group I. At T2 all groups improved but Group II showed the greater improvement (vs. Sham p < 0.001; vs. Group I p < 0.001) and the Sham group the smallest (vs. Group I p = 0.005). A significant interaction time*treatment was also observed on MODA scores (F = 3.31, p = 0.04). Only subjects treated with tDCS improved at T2 (Group I: p < 0.001; Group II: p = 0.007). However, no difference between Group I and II was shown.

Conclusion: tDCS as augmentation treatment of an adequate pharmacotherapy is a potential strategy in the management of vascular depression, a disease known to be often unresponsive to antidepressants only. Non-invasiveness, the absence of severe side effects and the possibility of administering it to outpatients at an affordable price make tDCS an important tool in clinical practice.

1. Introduction

Depressive disorders are associated with significant worldwide morbidity and mortality [1], despite their impact in terms of personal suffering and socioeconomic burden, first-line treatment with antidepressant medications is often suboptimal in terms of efficacy, safety, and tolerability, even when combined with other clinical interventions. Only one third of patients gains remission with the first treatment and only about two thirds of patients will achieve remission of the symptomatology even with four different antidepressants over a year of treatment [2,3]. Vascular depression is known to be a particularly difficult-to-treat depressive disorder characteristic of the elderly, defined by Alexopoulos [4] as a late-life depressive syndrome due to a variety of potential vascular

* Corresponding author. Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy..
E-mail address: zanardi.raffaella@hsr.it (R. Zanardi).

mechanisms [5]. The treatment of vascular depression appears to be problematic because of drugs less efficacy, contraindications and higher adverse reactions, even somatic strategies appear to be often less effective [6]. Several neuroimaging studies have been conducted to explain the relationship between depression and vascular disease showing an increase in signal hyper-intensities in the white matter and deep grey matter of the basal ganglia [7]. These lesions have been related to a frontal system impairment cause of executive dysfunction [8], the most common clinical presentation of late-life depression. Although cognitive impairment typically related to depression usually improves during reductions of symptomatology, executive dysfunctions developed during a vascular-depression episode have been shown to persist after remission [9].

Neurostimulation strategies have been proposed as treatment of depression trying to cope with functional abnormalities in cortical regions such as dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC) [10] acting on altered neuroplasticity [11,12]. Despite their effectiveness, their use is often limited by issues such as territory availability, high cost and subjective tolerability [13]. In the last years, several researches have investigated the efficacy of transcranial direct current stimulation (tDCS) in the treatment of depression [14].

tDCS is a non-invasive brain stimulation technique that uses a weak electric current (typically 1−2 mA) to induce a shift in membrane resting potentials and to cause depolarization or hyperpolarization in brain neurons [15]. These changes, that initially last from minutes to hours after the stimulation [16], lead to a long term potentiation (LTP) and long term depression (LTD) acting on neural plasticity through Nmethyl-ᴅ-aspartate (NMDA) receptors and calcium channels activity, as well as protein synthesis [15,17]. Using direct current, the electrical polarity significantly determines the effect of the stimulation: anodal stimulations increase the excitability in underlying brain regions, while cathodal reduce it [18−20].

Most shared theories about the leading mechanism of non-invasive brain stimulation techniques explain how these practices drive to the normalization of the interhemispheric imbalance observed during depressive episodes: the left hypoactivation and the right hyperactivation [21,22]. The antidepressant effect of the anodal tDCS targeted to the left DLPFC was firstly described in 2006 by Fregni et al. [23]: 1 mA applied over the left DLPFC for 20 min with the cathode placed on the right supraorbital region. More recent trials have explored the use of higher intensities (2 mA) and longer sessions (30 min) over the right DLPFC [24,25], without proved benefits on short and long-term effects. Also, a naturalistic study investigated the effect of tDCS administered two times per day showing an improvement in depressive symptoms without significant adverse effects [26]. The newest evidence-based guidelines [27] suggest a recommendation for a level of evidence B (probable efficacy) regarding the antidepressant efficacy of anodal tDCS of the left DLPFC with a right orbitofrontal cathode, on the basis of at least 10 sessions (2 mA, 20−30 min) in medicated or drug-free patients with major depressive disorder and no drug-treatment resistance [27]. No study to the best of our knowledge investigates the effect of tDCS in vascular depression.

Many studies on healthy subjects have investigated the tDCS effect in the cognitive performance modulation although conflicting results prevents any recommendation for its use as specific therapy for cognitive impairment during depression. Several studies on healthy subjects agree on the positive effect of tDCS on working memory [28,29], verbal fluency [30], language processing [31] and more complex cognitive functions [32]. In contrast, only few studies have investigated the impact of tDCS on cognitive functions in depressed patients: one of them showed a positive effect of five sessions of anodal stimulation over the left DLPFC on

working memory [33], conversely, other studies reported no significant changes of cognitive performance in depressed patients [34−37].

To investigate the efficacy of tDCS as augmentation therapy in vascular depression we arranged a double-blind randomized study hypothesizing an improvement in both depressive symptoms and cognitive performances. We expected a significative difference between one or two session per day in favour of twice-daily-protocol in reducing depressive symptoms and cognitive impairment, predicting about 40% of remission in consideration of the current specific literature.

2. Material and methods

2.1. Subjects

We enrolled 93 depressed inpatients (20 males, 73 females) over 60 years of age with a former diagnosis of Major Depressive Disorder (n = 77) or Bipolar Disorder (n = 16) according to DSM-5 criteria. All the patients presented a cerebral vascular disease (i.e. microinfartual ischemia and white matter microstructural abnormalities) documented through neuroimaging investigations, such as brain-MRI or brain-TC. Exclusion criteria were: presence of psychotic features, the presence of concomitant major psychiatric diagnosis or personality disorders, the intake of sodium channel blockers (such as carbamazepine) and calcium antagonists, lifetime alcohol and benzodiazepine abuse, the presence of contraindications to tDCS (intracranial metallic implants, present, past or family history of epilepsy, advanced cardiac or pulmonary diseases, diagnosis of terminal pathology, dependence on psychotropic substances, previous neurosurgical interventions).

All the recruited patients were non responders to one antidepressant at adequate dosage and duration, administered during the current episode (i.e. stage I of drug resistance according to Thase and Rush classification) [38]. At the beginning of the study all patients were treated with sertraline for two weeks, then a stable dosage (range dosage from 100 to 200 mg/die) was maintained throughout the study. The stimulation protocol was initiated when the therapeutic dosage was achieved. Sertraline was chosen for the absence of cardiovascular side effects [39]. All patients were taking short half-life benzodiazepines for sleeping but no benzodiazepines were administered during the day. Bipolar patients were under stable dosage of lithium for at least 1 year (blood level of lithium range 0.5−0.8 mEq/L).

2.2. Clinical assessment

Depressive symptoms were assessed with the 21-items version of Hamilton depression rating scale (HDRS). HDRS was administered at baseline (T0), after one week (T1) and after two weeks (T2) of treatment. The assessment was performed by two trained psychiatrists, blind to treatment conditions, with a good interrater reliability (interclass correlation coefficient on HDRS = 0.95). Response was defined as a ≥50% reduction of HDRS score from baseline and remission was defined as a reduction to 8 points or less on the HDRS score.

Cognitive functioning was evaluated at baseline and after the treatment protocol, corrected for age and education, through the Milan Overall Dementia Assessment (MODA) [40]. MODA is an overall cognitive screening test, used to evaluate cognitive changes in people suspected of dementia or cognitive impairment. It consists of three sections: orientation scale, autonomy scale and neuropsychology tests (ie, reversal learning, attentive matrices, verbal intelligence, memory of prose, semantic verbal fluency, token test, digital gnosis, constructive apraxia, and Street completion

test). Assessments were performed by a psychologist blind to the treatment condition. To avoid the early long term potentiation effect (E-LTP, about 30−60 min) [41] cognitive assessments were performed the week following the end of treatment.

2.3. Treatment

Subjects were randomly assigned to the sham or active conditions through a computer scheduled randomization. Raters and patients were blind to study structure and treatment assignment. Patients were informed about the number of daily sessions, but they ignored whether were active or sham. Moreover, patients were unable to see which treatment was being given in other treatment groups, therefore just the single patient and the clinician who administered stimulations - different from evaluators - were aware of daily sessions number.

Patients were randomly assigned into three groups:

- Group I: 1 tDCS stimulation per day (n = 31)
- Group II: 2 tDCS stimulations per day (n = 31)
- Sham group: 1 tDCS sham stimulation per day (n = 31)

Stimulation was performed for 10 consecutive working days (two weeks from Monday to Friday) using a E.M.S. BrainSTIM© stimulator with two 5 × 5 cm sponge electrodes soaked in a saline solution (0.9% NaCl).

Subjects elected to active treatments underwent a single or double daily session of anodal tDCS, targeted to the left dorsolateral prefrontal cortex (DLPFC) with a constant current of 2 mA intensity for 30 min. Single sessions were performed in the morning whereas double sessions were performed one in the morning and one in the late afternoon. The anodal electrode was placed over F3 (according to the 10−20 international system for EEG electrode placement) and the cathode electrode over the contralateral supraorbital area. Subject elected to sham treatment underwent a 30-min daily session of tDCS where the current was delivered for only 30 s at the intensity of 2 mA then gradually decreased to zero allowing the investigators to mimic the initial somatic sensations experienced with active tDCS, without providing therapeutic effects [42,43]. Electrodes were placed in the same positions as active stimulations. Type and frequency of occurrence of tDCS side effects were collected throughout the study.

2.4. Statistical analysis

One-way analysis of variance (ANOVA) and the chi-square test were used to investigate the differences for demographic and baseline clinical variables.

To test for the effect of treatment on depressive symptomatology HDRS scores at baseline, T1, and T2 were added as within factor in a repeated measure ANOVA within the context of the General Linear Model with treatment as categorical predictor and duration of illness as nuisance covariate.

Similarly, to test for the effect of treatment on cognitive functioning, MODA scores at baseline and T2 were added as within factor in a repeated measure ANOVA with treatment as categorical predictor and duration of illness as nuisance covariate. Post-Hoc comparisons were performed with Fisher Least Significant Difference (LSD) test.

Finally, a regression within the Generalized Linear Model with a binomial distribution and a Logit link function was performed to investigate which clinical variable predicted the response to treatment and remission. Response to treatment and remission were added as dependent variables in separate analyses with variables which could affect the response to tDCS (age, duration of current episode, duration of illness and baseline HDRS score) as continuous predictors.

3. Results

The progress through the phases of the trial (enrolment of subjects, intervention allocation, follow-up, and data analysis) is showed in Fig. 1.

Clinical and demographic characteristics of the sample, baseline HDRS and MODA scores, and tDCS related side effects are shown in Table 1.

Before the introduction of sertraline patients were non responders to one antidepressant treatment at adequate dosage and duration, administered during the current episode: SSRI N = 68 (73.1%) *[Sham N = 22 (71%); Group I N = 24 (77%), Group II N = 22 (71%)]*, SNRI N = 19 (20.4%) *[Sham N = 8 (26%), Group I N = 5 (16%), Group II N = 6 (19%)]*, or TCA N = 6 (6.5%) *[Sham N = 1 (3%), Group I N = 2 (7%), Group II N = 3 (10%)]*.

In agreement with our hypothesis, a significant interaction time*treatment was observed on HDRS scores (F = 14,02 p < 0.001) (Fig. 2). Post-hoc comparison showed that all groups improved at T1 (Sham: p = 0.004; Group I: p < 0.001; Group II: p < 0.001) but whereas Group II significantly differed from the Sham Group (p < 0.001) and Group I (p = 0.003), we observed no difference between Sham and Group I. At T2 all groups improved (Sham: p = 0.02; Group I: p < 0.001; Group II: p < 0.001) but Group I showed a greater improvement compared to the Sham group (p = 0.03) and Group II showed a greater improvement compared to both the Sham group (p < 0.001) and Group I (p < 0.001).

A significant effect of treatment was also observed on response rates (χ = 31.25, p < 0.001) after the treatment protocol. Patients in the Sham group showed no response, whereas patients in active treatment Groups I and II achieved a response rate of 42% and 68% respectively. Similarly, a higher frequency of remission was observed in Group II (χ = 25.36, p < 0.001). Patients in the Sham group showed no remission, whereas 29% of patients in Group I and 58% of those in Group II achieved remission.

Finally, duration of current episode predicted response to treatment (higher duration, worse response; parameter estimate = 0,06; Wald W = 8,82; p = 0,003) and remission (higher duration, no remission; parameter estimate = 0,05; Wald E = 6,07; p = 0,013). Remission was also predicted by baseline HDRS score (higher baseline severity, no remission; parameter estimate = 0,18; Wald W = 6,15; p = 0,013).

A significant interaction time*treatment was observed also on MODA scores (F = 3.31, p = 0.04) (Fig. 3). Post-hoc comparison showed that only subjects treated with tDCS improved at T2 (Group I: p < 0.001; Group II: p = 0.007). However, no difference between Group I and II was shown. Results remained significant also when correcting for changes in depressive symptomatology (F = 4.11, p = 0.019). Considering that the three groups significantly differed for MODA baseline levels we analysed delta scores (post score minus pre score) adding baseline scores as nuisance covariate and we confirmed a significant effect of treatment (F = 3.34, p = 0.039). Changes in MODA scores were independent from clinical improvement. Adding doses of sertraline to the analyses did not significantly influence the results.

Finally, considering bipolar disorder as a potential predictor of response, we performed the same analyses excluding bipolar patients. Whereas results on HDRS score did not change compared to the whole sample, we observed a reduction in the percentage of responders (Group I: 38%, Group II: 63%) and remitted (Group I: 23%, Group II: 56%) patients in the active groups.
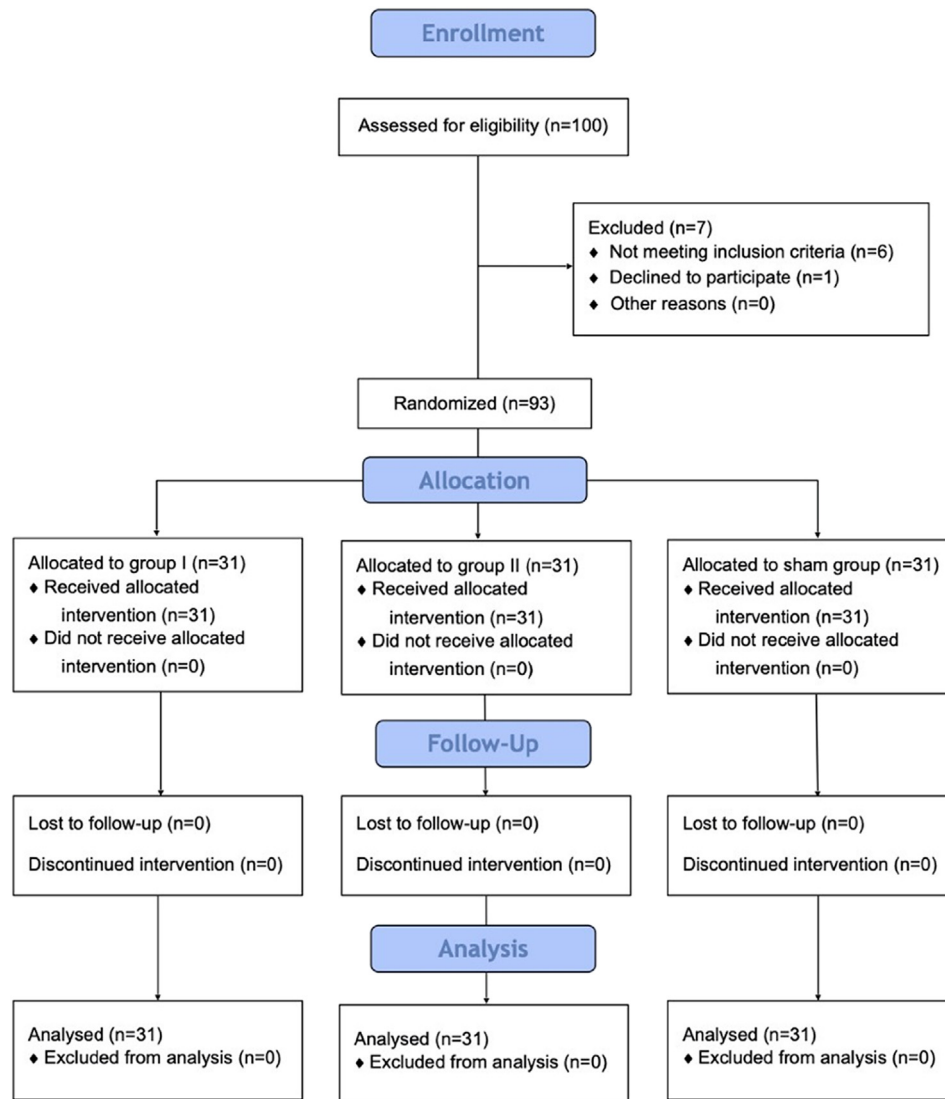
Fig. 1. Flow diagram of the progress through the phases of the trial (enrolment, intervention allocation, follow-up, and data analysis).

4. Discussion

In the present paper we investigated the efficacy of tDCS as an add-on treatment to sertraline for vascular depression. We tried to evaluate the efficacy of two versus one daily tDCS session on depressive symptoms. We also investigated the tDCS effect on cognitive functioning as measured by MODA. After two weeks of treatment all groups (I, II and Sham) showed a significant reduction of HDRS score, however, active treatment groups (I and II) achieved a significantly greater reduction compared to the sham group.

Table 1
Clinical and demographic characteristics of the sample and tDCS related side effects divided according to groups.

|	Sham (n = 31)	Group I (n = 31)	Group II (n = 31)	F/p
Age	70.54 ± 5.92	70.80 ± 5.91	73.58 ± 4.91	2.79/0.067
Age at Onset	45.71 ± 13.73	51.93 ± 13,83	43.19 ± 15.22	3.08/0.051
Duration of episode, w	22.96 ± 18.12	24.64 ± 17.82	19.32 ± 17.94	0.71/0.493
Duration of illness, y	24.84 ± 13.74	18.87 ± 14.55	30.38 ± 15.27	4.87/0.010
Sertraline dosage	143.33 ± 35.31	125.81 ± 38.99	129.03 ± 38.24	1.87/0.160
Baseline HDRS score	24.83 ± 2.65	25.48 ± 3.99	24.64 ± 5.34	0.35/0.710
Baseline MODA score	84.62 ± 5.79	82.08 ± 9.85	87.97 ± 5.94	4.90/0.009
Redness	10%	48%	55%	15.75/<0.001
Burning sensation	10%	29%	35%	6/0.049
Itching	19%	22%	22%	0.12/0.938
Tingling	16%	19%	10%	1.17/0.555
Headache	16%	12%	19%	0.48/0.787
Pain	3%	12%	10%	1.91/0.383
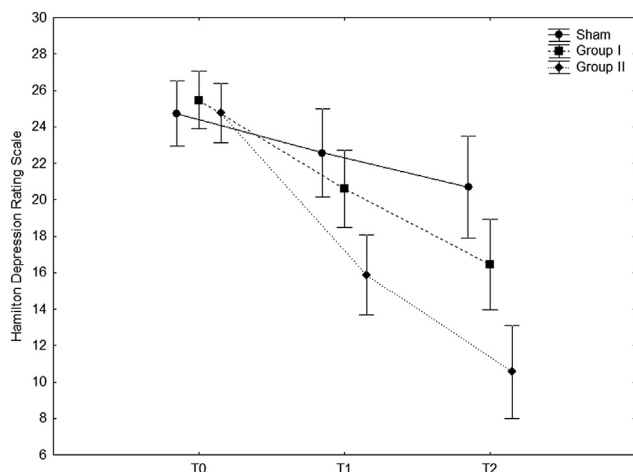
Fig. 2. Improvement in depressive symptomatology, as measured by the Hamilton Depression Rating Scale (HDRS), in the three groups. T0 = baseline, T1 = 5 days of treatment, T2 = 10 days of treatment. Whiskers are standard deviation.

Fig. 3. Improvement in cognitive performance, as measured by the Milan Overall Dementia Assessment (MODA), in the three groups. T0 = baseline, T2 = 10 days of treatment Whiskers are standard deviation.

Furthermore, since the first week of treatment Group II showed a significantly greater improvement compared to others. Accordingly, two daily tDCS sessions were associated with higher response (HDRS reduction $\geq$50%) and remission (HDRS $\leq$7) rates. Response to treatment and remission were predicted by the duration of the current episode and remission also by baseline severity of illness. Moreover, tDCS also led to a significant improvement in cognitive functioning although no difference was observed between Group I and II. The study participants did not report important side effects attributable to the intervention. These results are in concordance with previous studies showing the efficacy of two daily tDCS sessions on depressive symptoms: from five to ten days protocols were applied in major depressive disorder [26,44,45], bipolar disorder [44] and drug-resistant depression [46]. However, to the best of our knowledge, no study so far has compared one versus two daily tDCS sessions.

Previous studies investigating the effects of tDCS on cognitive functions reported controversial results [37]. Although different studies showed a positive effect of tDCS on cognitive functions (without cognitive training) i.e. attention and working memory [33,47,48], executive functions [49], a recent meta-analysis reported no cognitive benefits but rather a reduced practice effect for processing speed tasks [37]. The choice of a high sensitivity test for cognitive assessment and the combined tDCS-sertraline treatment could explain our results; however, further studies are needed to address this issue.

The large antidepressant effect observed in the present study could be explained by different mechanisms including treatment resistance and diagnosis. The patients in the present study had a history of only one failed antidepressant treatment (mainly first line treatment with SSRI) differently from other tDCS studies with a mean of about 3 failed treatments. Also, our sample included patients with bipolar disorder which has been associated to an increased response rate [50]. However, our results are in line with data from Brunoni [24] showing a response rate of 63% in subjects undergoing a combined treatment with tDCS and sertraline.

Several non-excluding mechanisms could explain our results. Firstly, tDCS has been shown to affect neural plasticity, promoting changes such as LTP and LTD, but also spike probability and timing [51]. These changes may influence neural information coding [52] exerting an effect on cognition [52,53]. The involvement of plasticity seems to be confirmed by studies showing that the activation of BDNF-Tr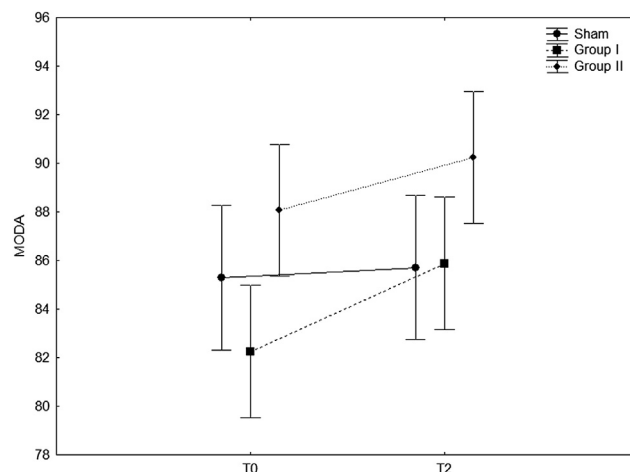kB pathways following tDCS over the motor cortex promotes motor learning 54 while the blockade of the TrkB-BDNF receptor reduced tDCS facilitating effects on memory [55]. Furthermore, tDCS has been shown to induce long-lasting changes in BDNF expression by epigenetic mechanisms [55]. These changes in neural plasticity may also explain the effects of tDCS on regional cerebral blood flow (rCBF) observed in different studies. Indeed, increases in neuron excitability as prompted by tDCS could constitute an extra "work" that needs to be supplied by increased oxygen delivery. Ten minutes of tDCS stimulation induced a significant increase in oxyhemoglobin concentration that lasted up to 8–10 min after the end of the stimulation [56]. Stimulation with tDCS has been shown to increase perfusion within brain regions closely structurally connected to the DLPFC [57]. The same authors observed a decrease in perfusion within regions associated with the default mode network (DMN) after tDCS [57]. The failure to normally down-regulate the activity of DMN during effective tasks was suggested as a biological mechanism of depression [58] and a lack of inhibition of DMN was suggested to underlie rumination in depression [59]. Therefore, tDCS might reverse these abnormalities thus facilitating mood and cognitive improvement. The impact of tDCS on rCBF could be of particular interest for the treatment of vascular depression as low left anterior frontal rCBF was observed in vascular depression compared to non-vascular depression and was associated with the duration of disease and likelihood of recurrence and relapse [60]. Accordingly, rCBF increases have been associated with decreases in depressive symptoms in depressed patients over 50 years of age [61]. Finally, improvement in symptoms characteristic of vascular depression could be prompted by changes in dopamine neurotransmission. The dopaminergic system has been suggested to be involved in the symptoms observed in vascular depression [62] and one 20 min session of tDCS at 2 mA induced, after the stimulation period, a significant decrease in extracellular dopamine in a part of the striatum involved in the reward–motivation network [63].

Strengths of the present study include single-drug resistance and pharmacologic treatment consistent in the three groups, and a relatively large sample. Furthermore, differently from previous studies, we compared the efficacy of one versus two daily sessions of tDCS showing that two daily sessions have a greater impact on depression severity but not on cognitive functioning. Prior studies have reported significant neuromodulatory effects at the lower end of stimulation intensities [64–67], however in many recent studies low current intensities have been used for the length of the whole

stimulation to mimic the sensations of a real stimulation [64,65] whereas, to avoid the biological effect due to low current stimulations, we used a protocol characterized by 0 mA and just two short 30-s current ramps up to 2 mA.

Limitations of our study are the choice of a rather unspecific cognitive measure, non-homogeneous previous psychopharmacological treatments, and the use of a sham protocol which only included one daily session. We also designed the study to evaluate the combined antidepressant augmentation effect of tDCS with sertraline. Treating all subjects with sertraline for two weeks before the beginning of the tDCS protocol we cannot exclude the following antidepressant effect of sertraline 68 and thus assess the single tDCS antidepressant effect. Finally, no follow-up analyses have been performed to investigate if the effects persist in the weeks following treatment.

5. Conclusions

tDCS is a non-invasive brain stimulation technique safe and effective in elderly depressed patients with cerebrovascular disease. Our results showed how tDCS treatment was effective in reducing both depressive symptoms and cognitive impairment when compared to sham. Two daily tDCS sessions were more effective in reducing depressive symptomatology compared to a single session per day. No differences on cognitive improvement were shown comparing one to two daily sessions. Moreover, we observed that the duration of the current episode predicts the response to treatment and remission. Further studies are needed to investigate the specific tDCS effect on cognitive functions in vascular depression and the persistence of the observed effects.

We can conclude that the combination of tDCS with an adequate pharmacological therapy is a potential therapeutic strategy in the treatment of vascular depression, a disease known to be often unresponsive to antidepressants only. Non-invasiveness, the absence of severe side effects and the possibility of administering it to outpatients at an affordable price, make tDCS an important tool in clinical practice.

CRediT author contribution statement

Raffaella Zanardi: Conceptualization, Project administration, Methodology, Writing - original draft preparation, Supervision, Data curation, Writing - review & editing, Investigation. **Sara Poletti:** Software, Data curation, Writing - original draft, Writing - review & editing. **Dario Prestifilippo:** Data curation, Writing - review & editing, Investigation. **Francesco Attanasio:** Software, Data curation, Writing - original draft, Writing - review & editing, Investigation. **Barbara Barbini:** Data curation, Writing - review & editing, Investigation. **Cristina Colombo:** Conceptualization, Supervision.

Declaration of competing interest

No known conflict of interest.

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