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ARTICLE

Differential improvement in depressive symptoms for tDCS alone and combined with pharmacotherapy: an exploratory analysis from The Sertraline *Vs.* Electrical Current Therapy For Treating Depression Clinical Study

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Abstract

Transcranial direct current stimulation (tDCS) is a promising therapy for major depression treatment, although little is known of its effects in ameliorating distinct symptoms of depression. Thus, it is important, not only to increase knowledge of its antidepressant mechanisms, but also to guide its potential use in clinical practice. Using data from a recent factorial, double-blinded, placebo-controlled trial applying tDCS-alone and combined with sertraline to treat 120 depressed outpatients over 6 wk (Brunoni et al., 2013), we investigated the pattern of improvement in symptoms of depression from the Montgomery–Asberg depression scale (MADRS). First, we performed one multivariate analysis of variance with the score improvement of the 10 MADRS items as dependent variables. Significant ($p<0.05$) results were further explored with follow-up analyses of variance. TDCS (alone and combined with sertraline) improved concentration difficulties and pessimistic and suicidal thoughts. The combined treatment also improved apparent and reported sadness, lassitude and inability to feel. Indeed, tDCS/sertraline significantly ameliorated all but the 'vegetative' depression symptoms (inner tension, sleep and appetite items). We further discuss whether bifrontal tDCS over the dorsolateral prefrontal cortex could be associated with improvement in cognitive (concentration) and affective (pessimistic/suicidal thoughts) processing, while the combined treatment might have a more widespread antidepressant effect by simultaneously acting on different depression pathways. We also identified patterns of antidepressant improvement for tDCS that might aid in tailoring specific interventions for different subtypes of depressed patients, e.g. particularly those with suicidal ideation.

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Introduction

Major depressive disorder (MDD) is a highly prevalent, chronic, disabling condition (Eaton et al., 1997). As depressed patients often present with multiple different symptoms, it is important to investigate the efficacy of potential novel therapies, such as transcranial direct current stimulation (tDCS), in the improvement of these symptoms individually. Recent trials (Loo et al., 2012; Brunoni et al., 2013e) and meta-analyses (Kalu et al., 2012; Berlim et al., 2013) have shown mixed, albeit positive, results for tDCS as a treatment for MDD. However, most trials to date have used small sample sizes (for a review see Brunoni et al. (2012a)), hindering further examination of symptoms. In fact, only one study explored this matter by analysing the factor

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structure of depression (Alonzo et al., 2013), observing improvement in clusters of symptoms described as 'dysphoria' and 'retardation' (although not 'vegetative symptoms'). Nevertheless, the authors pointed out some study limitations, such as using a predetermined factor structure scale that can change from baseline, and the need to replicate their findings in other studies.

Recently, we described the results of a study in which patients were randomized to receive placebo, tDCS-only, sertraline-only and tDCS and sertraline combined (Brunoni et al., 2013e). The main findings were that tDCS alone and combined with sertraline had superior antidepressant effects (*vs*. placebo), the combined treatment displaying greater improvement. Hence, we sought to analyse the differential improvement of symptoms of these interventions. This is important to: (1) further explore the potential for clinical applicability of tDCS as a tailored intervention in the therapeutic arsenal of MDD; (2) investigate the antidepressant mechanisms of action of tDCS alone and combined with sertraline; (3) contributing to the growing literature base on tDCS, as well as expanding and comparing with prior findings of another tDCS trial (Loo et al., 2012; Alonzo et al., 2013) and (4) bridge findings from neuropsychological, phase I tDCS studies to tDCS clinical trials, an important challenge to the development of the field (Brunoni et al., 2013a).

Methods

Study design

The Sertraline *vs.* Electric Therapy for Treating Depression Clinical Study (SELECT-TDCS) was a randomized, factorial, placebo-controlled trial in which 120 patients with depression were randomized to four groups: (1) sham-tDCS/placebo-pill (hereafter referred to as *placebo*); (2) sham-tDCS/sertraline-pill (*sertraline-only*); (3) active-tDCS/placebo-pill (*tDCS-only*); (4) active-tDCS/sertraline-pill (*combined treatment*). The study was registered at clinicaltrials.gov (NCT01033084) and approved by the local and national ethics committee, with all participants providing written, informed consent. Its methodology and main results are described elsewhere (Brunoni et al., 2011c, 2013e).

Subjects

We enrolled 120 patients' aged 18–65 yr with acute depressive episode diagnosed by two certified psychiatrists using the Portuguese-validated version of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998; Amorim, 2000). We excluded patients with other psychiatric, personality, clinical and neurologic disorders, except for anxiety symptoms when as a comorbidity.

Patients were either drug-naïve or antidepressant-free. Whether they were on pharmacotherapy or not, they were washed-out for at least five half-lives of the drug (since we only enrolled patients on Mondays, they were in fact at least 3 wk drug-free). The exception was the 23 subjects (19.3%) on benzodiazepines who were neither excluded, given that the eligibility criteria could interfere with the recruitment of a large sample size, nor washed-out, considering that this could increase attrition and also because of the similarity between some symptoms of benzodiazepine withdrawal and depression (e.g. insomnia, irritability). We capped benzodiazepine use at a maximum dose of 20 mg/day of diazepam-equivalents, did not change the dose throughout the trial, and controlled this variable during statistical analysis. Finally, participants who were currently prescribed sertraline or reported a prior lack of response to sertraline were not eligible for inclusion in our study.

Interventions

Standard tDCS devices (Chattanooga Ionto™ Dual Channel Devices, Chattanooga Group, USA) were used in our study. The anode and the cathode were placed over the scalp areas corresponding to the left and the right dorsolateral prefrontal cortex (DLPFC), respectively, procedures first used by Ferrucci et al. (2009). Theoretically, this montage can be more advantageous (as compared to other studies that place the cathode over the right supraorbital area) in modulating the left/right prefrontal imbalance observed in MDD (Walter et al., 2007; Grimm et al., 2008; Kemp et al., 2010b). In addition, repetitive transcranial magnetic stimulation (rTMS) studies that used low-frequency stimulation (which, similarly to cathodal stimulation, induces local cortical inhibition) over the right DLPFC also found significant clinical effects for depression treatment (Schutter, 2010).

The brain areas were localized using standard procedures (Nitsche et al., 2008; DaSilva et al., 2011; Brunoni et al., 2012c). We used a current density of 0.8 A/m^2 (2 mA/25 cm^2) per 30 min/d. Ten-daily tDCS sessions from Monday to Friday and two additional fortnight sessions were applied. The sham method was based on Gandiga et al. (2006) and consisted in a brief (<30–60 s) period of active stimulation to mimic skin side effects such as tingling, itching, discomfort, etc. (Brunoni et al., 2011b) before the simulated procedure. Two trained nurses were responsible for delivering the tDCS sessions and turning off the device. They neither interviewed participants nor were involved in any other aspect of the trial.

Sertraline was used in a fixed dose of 50 mg/d and started and ended simultaneously with tDCS (sertraline treatment duration was 6 wk).

Statistical analysis

All analyses were performed in SPSS 20. Relevant clinical and demographic characteristics were presented and compared at baseline. We used one-way ANOVAs and the χ^2 test for continuous and categorical

Table 1. Clinical and demographic characteristics of the sample at baseline

	Placebo (n=30)	Sertraline-only (n=30)	tDCS-only (n=30)	Combined treatment (n=30)	p
Clinical characteristics					
Age, years (S.D.)	46.4 (14)	41 (12)	41 (12)	41 (13)	0.24
Women, n (%)	20 (67)	17 (56)	21 (70)	24 (80)	0.28
On benzodiazepines (%)	5 (16)	6 (20)	4 (13)	8 (26)	0.59
Benzodiazepine dose, mg/day (S.D.)	14.3 (5)	13.8 (6)	11.7 (5)	13.5 (4)	0.21
BMI, kg/m^2 (S.D.)	25.4 (5.8)	25.7 (4.2)	26.3 (5.4)	26 (5.2)	0.92
Depression characteristics, n (%)					
Refractoriness, n (%)	5 (17)	9 (30)	8 (27)	4 (13)	0.31
Severity, n (%)	17 (57)	17 (57)	20 (67)	16 (53)	0.74
Duration	12 (43)	15 (50)	19 (63)	12 (42)	0.31
Baseline MADRS scores, mean (S.D.)					
Total	31 (5.3)	30.5 (6)	31 (5.8)	30.7 (7)	0.99
Item 1	3.3 (1.2)	2.8 (1.2)	3 (1)	3.1 (1)	0.42
Item 2	3.9 (1.4)	3.6 (1.2)	3.7 (1)	3.6 (1.1)	0.57
Item 3	3.2 (0.9)	2.9 (1.3)	2.8 (1.3)	3 (1.1)	0.53
Item 4	3.1 (1.8)	3.4 (1.9)	2.9 (1.9)	3.5 (1.4)	0.49
Item 5	1.8 (1.5)	1.2 (1.3)	1.6 (1.6)	1.5 (1.5)	0.48
Item 6	3.3 (1.1)	3.7 (1.5)	3.6 (1.4)	3.9 (1.1)	0.35
Item 7	3.3 (1.3)	3.4 (1.4)	3.4 (1.4)	3.3 (1.2)	0.99
Item 8	3.4 (1.3)	3.4 (1.3)	3.7 (1.2)	3.6 (1.3)	0.58
Item 9	3.3 (1)	3.4 (1.3)	3.5 (0.9)	3.2 (1.3)	0.76
Item 10	2 (1.1)	2.7 (1.3)	2.5 (1.2)	2.1 (1.3)	0.08

Benzodiazepine dose is expressed in diazepam-equivalents. Refractoriness was characterized as the therapeutic failure of more than two adequate antidepressant treatment courses in the current depressive episode. Severity was defined as MADRS$\geqslant$30. MADRS, Montgomery–Asberg depression rating scale, BMI, body mass index. p values represent the significance of one-way ANOVAs and χ^2, respectively employed for continuous and categorical variables.

variables, respectively. Data from 120 patients were analysed; attrition was handled using the last observation carried forward for missing data imputation. As we were interested in treatments effects on symptoms of depression, we separately examined each item of the Portuguese-validated version of the Montgomery–Asberg depression rating scale (MADRS) (Gorenstein et al., 2000).

In a first step, we performed multivariate analysis of variance (MANOVA) using the difference between baseline and endpoint (week 6) scores of each MADRS item as dependent variables. We opted for this approach so as to restrict the number of analyses and so control type I error. The independent variable was treatment group (four levels) and benzodiazepine use was entered as a covariate. We also explored other clinical and demographic variables as independent variables.

A significant MANOVA model was followed-up with appropriate ANOVAs. We also described the η^2_p as the effect size measure (values of 0.01, 0.06 and 0.13, respectively, corresponding to small, medium and large effect sizes) and the power (β) of the ANOVA (Cohen, 1988). For significant (p<0.05) values, we explored the group effects using the simple contrast method.

Results

The groups were similar at baseline in all clinical and demographic variables, including age, gender, benzodiazepine use and dose and severity and refractoriness of depression. MADRS scores (total and items) were also similar at baseline (Table 1).

MANOVA and follow-up ANOVAs for changes between baseline and endpoint

The omnibus MANOVA revealed a significant group-factor ($F_{30,324}$=1.488, p=0.04, Wilks' Lambda=0.679). The variables refractoriness (p=0.1), length of the depressive episode (p=0.97), depression severity (p=0.12), age (p=0.11), gender (p=0.84) and body mass index (p=0.1) were not significant in the omnibus MANOVA, findings we discuss further below.

Follow-up ANOVAs showed significant improvement of MADRS items 1, 2, 6, 7, 8, 9, 10 (items' description and statistics displayed in Table 1). In other words, only the MADRS items 3, 4, 5, corresponding to inner tension, reduced sleep and reduced appetite, respectively, displayed no improvement in the item-by-item analysis

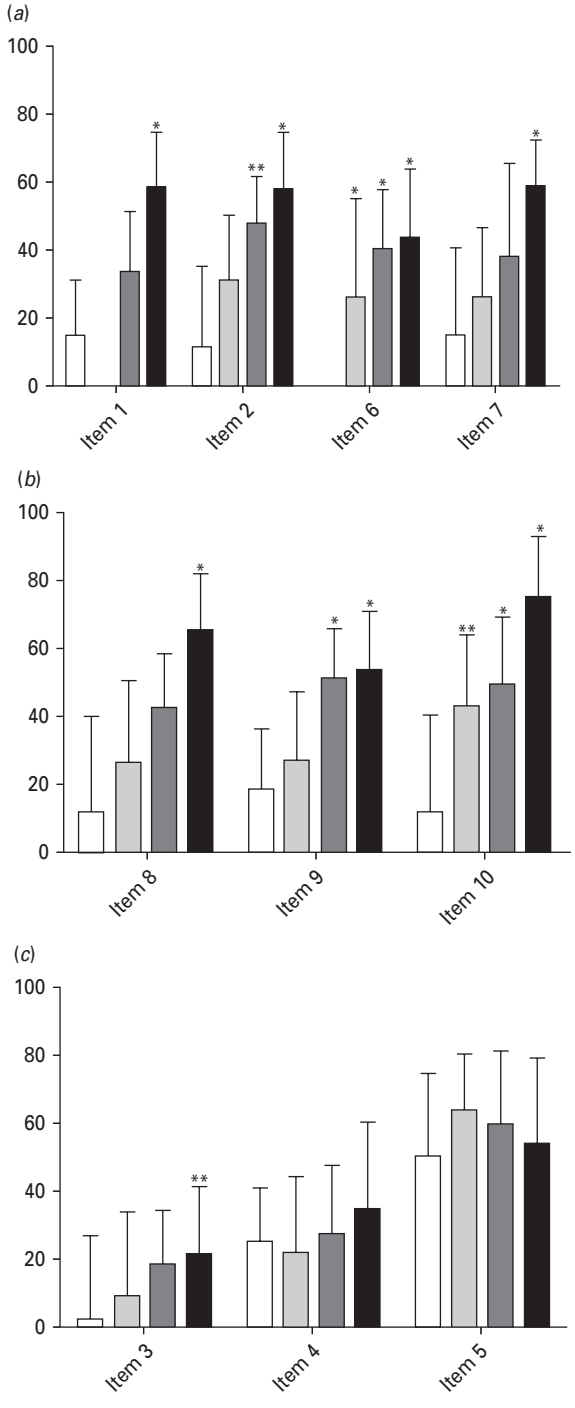

Fig. 1. Comparison of symptoms' improvement for each group. (*a, b*) Show symptoms that significantly improved for at least one active treatment. (*c*) Shows symptoms that non-specifically improved for all groups, including placebo. The vertical axis represents the percentage of improvement from baseline to endpoint. White, light gray, dark gray and black columns, respectively, represent placebo, sertraline-only, tDCS-only and combined treatment groups. (*) and (**) respectively represent a significant ($p<0.05$) and a trend ($0.05 \leqslant p \leqslant 0.056$) for the pairwise comparison against placebo. Bars represent the upper bound of the 95% confidence interval. The sertraline-only column of item 1 and the placebo column of item 6 are not displayed because there was no improvement in these cases.

among the treatment groups (Fig. 1(*c*)). For the significant results we carried out pairwise comparisons between each treatment *vs.* placebo, using the simple contrast method (Table 2).'

Sertraline-only vs. placebo

In this comparison we found a significant effect for MADRS item 6 ($p=0.01$) and a statistical trend for item 10 ($p=0.056$) (Table 3). In other words, participants receiving sertraline-only compared to placebo showed improvement in concentration difficulties and a trend for improvement in suicidal thoughts (Fig. 1(*a,b*)).

TDCS-only vs. placebo

Subjects receiving tDCS-only *vs.* placebo showed improvement on MADRS items 6 ($p<0.01$), 9 ($p=0.02$) and 10 ($p<0.01$) and a trend for item 2 ($p=0.052$) (Table 3). This means that these patients had significant improvement for concentration difficulties, pessimistic thoughts, suicidal thoughts and a trend for improving reported sadness (Fig. 1(*a,b*)).

Combined treatment vs. placebo

Patients receiving tDCS and sertraline compared to placebo had significant improvement on MADRS items 1, 2, 6, 7, 8, 9 and 10 ($p<0.01$ for all comparisons) – i.e. such patients improved significantly on apparent sadness, reported sadness, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. (Fig. 1(*a,b*) and Table 3). We also explored the effects of the combined treatment on the remaining items that did not reach statistical significance in the follow-up ANOVAs (Table 1), finding a trend for improvement on items 3 ($p=0.051$) and 4 ($p=0.07$) (Fig. 1(*c*) and Table 3).

Pairwise comparisons of active treatments

The combined treatment was superior to sertraline-only on items 1, 2, 7, 8 and 9 ($p \leqslant 0.01$ for all comparisons) and superior to tDCS-only on items 1 and 8 ($p=0.04$ for both). In the comparison between tDCS-only *vs.* sertraline-only, the non-pharmacological intervention was superior on items 1 ($p=0.03$) and 9 ($p=0.04$) (Table 3).

Discussion

We found the active treatments to be superior to placebo on all MADRS items, except for 'inner tension', 'reduced sleep' and 'reduced appetite'. In addition, a differential profile of improvement in symptoms was observed among treatment groups. Sertraline-only was superior to placebo for improving concentration difficulties (and a trend for suicidal thoughts) and tDCS-only was superior to placebo for improving concentration difficulties, pessimistic thoughts and suicidal thoughts (and

Table 2. Results from the follow-up analyses of variance for the items in the Montgomery-Asberg depression rating scale (MADRS). Significant ($p<0.05$) results are highlighted in bold.

MADRS item	Description	$F(3,115)$	p	η^2_P	β
Item 1	Apparent sadness	6.632	**0.000**	0.147	0.970
Item 2	Reported sadness	5.354	**0.002**	0.123	0.926
Item 3	Inner tension	1.389	0.250	0.035	0.361
Item 4	Reduced sleep	1.103	0.351	0.028	0.291
Item 5	Reduced appetite	0.515	0.673	0.013	0.152
Item 6	Concentration diff.	5.917	**0.001**	0.134	0.950
Item 7	Lassitude	3.557	**0.017**	0.085	0.775
Item 8	Inability to feel	4.636	**0.004**	0.108	0.883
Item 9	Pessimistic thoughts	4.807	**0.003**	0.111	0.895
Item 10	Suicidal thoughts	2.868	**0.040**	0.070	0.673

Each MADRS item is described, along with the statistical results of the ANOVA (F-test), the type I (p-values in bold are significant) and type II error probability ($1-\beta$), and the effect size measure (η^2_P).

a trend for reported sadness). Remarkably, patients receiving combined treatment had superior improvement in apparent and reported sadness, concentration difficulties, lassitude, inability to feel and pessimistic and suicidal thoughts, and even a trend for improvement of inner tension. The combined treatment was also superior to sertraline-only in the items related to sadness, lassitude, inability to feel and pessimistic thoughts and superior to tDCS-only for apparent sadness and inability to feel (tDCS-only was also superior to sertraline-only in these latter symptoms). These findings are discussed below.

We used an item-by-item analysis instead of grouping symptoms into clusters derived from statistical analysis – as done, for instance, by Alonzo et al. (2013). However, cluster analyses have some methodological issues, including the factor structure of symptoms changing over time, and their dependence on the eligibility criteria of the sample, making replication difficult. Hence, we opted for individual analysis of each item, handling the issue of multiple comparisons by first performing an omnibus MANOVA and then analysing the items that were significant in the MANOVA. Nevertheless, our results were based on *post-hoc* analyses and, therefore, should be interpreted as a basis for hypotheses in future confirmatory studies.

We did not find specific predictors of outcome in the present analysis. Also, in our original study (Brunoni et al., 2013e), clinical and demographic variables were not predictors of outcome, except for baseline severity and refractoriness. These statistical differences are explained by the different approaches we used, namely a general linear model with only one dependent variable (MADRS scores) in the original study and a MANOVA with ten dependent variables (the items of MADRS) in the present study.

Observations regarding the original study

Some methodological considerations regarding the original study (Brunoni et al., 2013e) should be highlighted. First, a minimally-effective dose of sertraline was used, which may have been too low for some patients, therefore justifying the relative underperformance of the sertraline-only group. Indeed, we opted for a 50 mg/day sertraline dose for several reasons: (1) a higher dose would need dose escalation, which would require a longer trial duration, exposing patients in the placebo arm to a longer period without appropriate treatment; (2) a higher dose could theoretically increase the risk of treatment-emergent mania in the combined treatment group, which had been observed in the pilot phase of our study (Baccaro et al., 2010) and in other groups as well (Arul-Anandam et al., 2010) – in fact, there were more cases of (hypo)manic switches in the combined treatment group (Brunoni et al., 2011a, 2013e); (3) a higher dose could have induced more adverse effects thus impacting on treatment blinding, a relevant concern for our factorial design in which a pharmacological and non-pharmacological intervention were simultaneously tested; and (4) the primary aim of our original study was not to evaluate sertraline efficacy but rather to compare and combine tDCS with the minimally effective dose of sertraline. Nevertheless, we consider that the limited symptomatic improvement for sertraline-only points to the low dose of the medication rather than a lack of efficacy.

Another important aspect is study blinding. At endpoint, participants were asked to guess what intervention (active/sham tDCS and verum/placebo pill) they had received. Data from our original study (Brunoni et al., 2013e) revealed that patients correctly guessed both sertraline and tDCS use beyond chance. Nonetheless,

Table 3. Pairwise comparisons between interventions

	Combined treatment *vs.*			tDCS *vs.*		
	Placebo	Sertraline	tDCS	Placebo	Sertraline	Sertraline *vs.* Placebo
Difference in points (95% CI)						
Item 1	1.2 (0.4–1.9)	1.62 (0.9–2.4)	0.77 (0–1.5)	–	0.84 (0.1–1.6)	–
Item 2	1.45 (0.6–2.3)	1.36 (0.5–2.2)	–	0.81 (0–1.6)*	–	–
Item 3	0.7 (0–1.4)*	–	–	–	–	–
Item 4	0.94 (−0.1 to 2)*	–	–	–	–	–
Item 5	–	–	–	–	–	–
Item 6	1.92 (1–2.8)	–	–	1.26 (0.3–2.1)	–	1.14 (0.2–2.1)
Item 7	1.28 (0.5–2.1)	0.92 (0.1–1.7)	–	–	–	–
Item 8	1.57 (0.7–2.5)	1.28 (0.4–1.5)	0.9 (0–1.8)	–	–	–
Item 9	1.2 (0.4–2)	1 (0.3–1.8)	–	0.92 (0.2–1.7)	0.38 (0–1.54)	–
Item 10	1.04 (0.3–1.8)	–	–	0.86 (0.1–1.6)	–	0.73 (−0.02 to 1.5)*

The table displays the pairwise comparisons (contrast methods) between groups, for each MADRS item. All displayed results are statistically significant ($p<0.05$), except those marked with *, which represent a trend ($0.05 \leqslant p \leqslant 0.07$). The comparisons not displayed in the table are non-significant results. Please refer to the main text for the p values for each comparison.

considering only those who were 'almost' or 'absolutely' confident on their guessing, only sertraline (but not tDCS) was correctly guessed beyond chance. Further, tDCS responders (but not tDCS non-responders) correctly guessed their group. In addition, we extensively examined adverse effects using a structured questionnaire (Brunoni et al., 2011b) – only skin redness rates were higher in the active *vs.* sham group (25% *vs.* 8%, $p=0.03$), whereas other adverse effects such as headache, neck pain, scalp pain, tingling, itching, sleepiness, trouble concentrating and acute mood change presented similar rates in both active and sham groups. These observations suggest that patients' guesses were driven by clinical improvement rather than blinding failure, and that tDCS blinding is as reliable as sertraline blinding.

Improvement in the tDCS-only group

In this group we observed improvement in symptoms related to DLPFC activity (concentration difficulties, suicidal and pessimistic thoughts). Regarding concentration impairment, this is in line with single-session neuropsychological studies that showed that anodal tDCS over the left DLPFC acutely improves working memory (an executive function directly associated with concentration) in depressed subjects. For instance, Boggio et al. (2007) described an increase in accuracy for identifying positive imagery in a go/no-go task and Wolkenstein and Plewnia (2013) also described an enhancement of affective processing after tDCS in depressed subjects. In a sub-sample of SELECT-TDCS, we also demonstrated an enhancement of affective processing using the Stroop emotional task (Brunoni et al., 2013c) and the n-back task (Oliveira et al., 2013).

The improvement in suicidal and pessimistic thoughts is relevant because of their close clinical relationship. The MADRS item of pessimistic thoughts captures both symptoms of guilt and hopelessness. Hopelessness is significantly correlated with lower binding of 5-HT_{2A} receptors in the prefrontal cortex (van Heeringen et al., 2003) and, interestingly, 5-HT_{2A} receptor binding increases after rTMS treatment in depression (Baeken et al., 2011). Further, Wagner et al. (2011) observed that guilt was associated with activation of prefrontal areas in a neuroimaging study. The improvement of suicidal ideation after tDCS is of clinical interest given the mixed findings regarding serotonergic antidepressants increasing suicidal risk (Dudley et al., 2010). Suicidality seems to be associated with morphological alterations of the prefrontal cortex (Desmyter et al., 2011); thus, considering that anodal tDCS is applied over the DLPFC, theoretically this intervention could have improved the symptoms of suicidal thoughts. In this context, Wall et al. (2011) reported improvement of suicidal ideation using rTMS over the DLPFC in juvenile depression.

Improvement in the combined treatment group

This group was superior to placebo in the same symptoms that tDCS and sertraline alone were, and, *in addition*, in those symptoms that represent the core of depression – i.e. low mood (apparent and reported sadness), psychomotor retardation (lassitude) and anhedonia (inability to feel). In this context, another naturalistic study found that a combination of antidepressant drugs and tDCS combined had greater clinical effects in depression (Brunoni et al., 2012b). In addition, data from SELECT-TDCS (Brunoni et al., 2013f) revealed that the serotonin transporter polymorphism (5-HTTLPR) moderates tDCS effects, supporting the hypothesis of an interaction between tDCS and serotonergic drugs. Of note, critical structures in MDD pathophysiology are the circuits

between the DLPFC, the orbitofrontal cortex and the cingulate cortex (associated with voluntary and automatic regulation of emotion) and the striatum and amygdala, which are associated with emotion and reward processing (Kupfer et al., 2012). Considering that the monoaminergic nuclei are located in brainstem structures whose neurons primarily (but not only) project to the amygdala and ventral striatum and tDCS targets primarily outer cortical structures, both treatments combined could, in fact, encompass most of the limbic-cortical circuits involved in MDD pathophysiology.

Comparison between real treatments

The combined treatment was superior to tDCS-only and sertraline-only in the core symptoms of depression, further corroborating our hypothesis that the treatments combined have a synergistic and potent interaction. TDCS was superior to sertraline in improving pessimistic thoughts, possibly due to direct stimulation of the prefrontal cortex. Interestingly, tDCS was also superior in improving apparent sadness, although this is possibly explained by the underperformance of sertraline on this item, which, as previously discussed, is probably related to the relatively low dose used.

Lack of improvement in vegetative symptoms

Both the results of the cluster analysis of Alonzo et al. (2013) and ours observed no significant improvement of tDCS in 'vegetative' symptoms (reduced appetite, reduced sleep and inner tension). This is in line with data from SELECT-TDCS in which we observed decreased heart rate variability (HRV), a marker of sympathetic activity, at baseline, which did not increase after treatment with tDCS and/or sertraline (Kemp et al., 2010a; Brunoni et al., 2013d). The studies evaluating whether non-invasive brain stimulation techniques modulate HRV and the autonomous nervous system (ANS) have reported mixed results (Sampaio et al., 2012; Schestatsky et al., 2013), indicating that tDCS may have significant neuromodulation effects over the ANS only in stressful contexts, such as negative image visualization (Brunoni et al., 2013b) or intense physical exercise (Okano et al., 2013). Nonetheless, computer model studies showed that tDCS modulates subcortical structures, including the thalamus and the brainstem (Dasilva et al., 2012) – hence, further studies are necessary to investigate whether tDCS could improve vegetative symptoms.

Another possibility – specifically for 'inner tension' – might be related to the cathodal stimulation over the right DLPFC, thereby decreasing its activity. Since this area is also responsible for a later suppression response of negative emotional material, this montage could have decreased overall tDCS effects in improving inner tension (Goldin et al., 2008). Nonetheless, the study of Alonzo et al. (2013) placed the cathode over the right supraorbital area and also did not observe improvement in vegetative symptoms. Finally, the lack of improvement for 'sleep' and 'appetite' could also reflect a bias of the MADRS 'that only measures appetite and sleep *gains*. Nonetheless, other 'gold standard' depression rating scales (such as the different versions of the Hamilton and the Beck depression scales) also fail to measure clinical improvement in patients presenting increased appetite and sleep at baseline and this is, in fact, a broader issue for pharmacological and non-pharmacological MDD clinical trials (Gelenberg et al., 2008; Brunoni and Fregni, 2011).

Conclusion

TDCS-only and combined with sertraline presented distinct patterns of improvement in depressive symptoms. Interestingly, the improvement for tDCS-only can be linked to its neuromodulatory activity over the prefrontal cortex, and is in agreement with neuropsychological studies showing enhancement of non-emotional and emotional working memory processing. The combined treatment group also ameliorated the core symptoms of low mood, psychomotor retardation and anhedonia, possibly because the therapies combined have distinct mechanisms of action in MDD pathophysiology. The lack of improvement for vegetative symptoms could either reflect a limitation of these therapies in improving such symptoms or also be a characteristic of the depression scale used to assess such symptoms. To conclude, our study provides mechanistic insights of tDCS antidepressant effects and can also guide further development of tDCS as a potential, clinically relevant therapy for treating depression. We specifically highlight that the subgroup of patients with suicidal ideation could benefit from tDCS-only, given the recent findings of a possible hazardous effect of serotoninergic antidepressants in suicidality. Also, that patients with severe depression could show significant clinical gains with the combined tDCS/antidepressant therapy. Conversely, depressed patients with vegetative symptoms might not specifically benefit from non-invasive brain stimulation interventions.

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Statement of Interest

All authors report no biomedical financial interests or potential conflicts of interest.

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