A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence

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Abstract

Preliminary small studies have shown that transcranial direct current stimulation (tDCS) reduces craving in alcoholic subjects. It is unclear whether tDCS also leads to changes in clinically meaningful outcomes for alcohol dependence in a properly powered phase II randomized clinical trial. We aimed to investigate whether repetitive tDCS changes the risk of alcohol use relapse in severe alcoholics from outpatient services. Thirty-five subjects were randomized to receive active bilateral [left cathodal/right anodal over the dorsolateral prefrontal cortex (dlPFC)] repetitive (five consecutive days) tDCS (2 mA, 35 cm², two times daily stimulation for 13 min with a 20-min interval) or sham-tDCS. There were two dropouts before treatment. From 33 alcoholic subjects, 17 (mean age 45.5±8.9 S.D., 16 males) were randomized to sham and 16 (44±7.8 S.D., 16 males) to real tDCS treatment. By the end of the six months of follow-up, two subjects treated with sham (11.8%) and eight treated with real tDCS (50%) were still alcohol-abstinent [p=0.02, Long-rank (Mantel-Cox) Test, HR=0.35 (95% CI, 0.14–0.85)]. No differences with regard to changes on scores of craving, frontal function, global mental status, depressive or anxiety symptoms were observed between groups. However, subjects from the tDCS group improved with regard to their overall perception of quality of life (p=0.02), and increased their scores in the environment domain (p=0.04) after treatment. Bilateral tDCS over dlPFC reduces relapse probability in severe alcoholic subjects and results in improved perception of quality of life.

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Key words: alcoholics, dorsolateral prefrontal cortex, quality of life, relapses, tDCS.

Introduction

Alcohol dependence has become one of the most important risk factors for disease and disability (Navarro et al., 2011; Proescholdt et al., 2012). Although well-established pharmacologic treatments and bio-psychosocial therapies have been used, they have only modest or mixed success in clinical trials (Assanangkornchai and Srisurapanont, 2007; Miller et al., 2011). Besides, these approaches are often focused on managing acute or protracted withdrawal symptoms, rather than craving and/or relapse control. Efforts are thus needed to develop novel approaches to improve therapeutic success.

We hypothesized that novel therapeutic approaches to treat alcohol dependence should be targeted to specific brain areas. One potential target is the dorsolateral prefrontal cortex (dlPFC) as frontal dysfunction is a hallmark of alcoholism (Moselhy et al., 2001; Duka et al., 2011), even in alcoholic subjects with no major clinical and global cognitive deficits (Moselhy et al., 2001; Nakamura-Palacios et al., 2013). The dlPFC is a key substrate for processing of working memory (Arnsten et al., 2012), providing high-level executive control processes involved in ‘top-down’ regulation of attention and cognitive control (Cummings, 1993; Arnsten and Rubia, 2012), and thus is ultimately involved in the ability to control drinking behaviour (Duka et al., 2011). In fact, abnormal functional
connectivity between the dlPFC and the striatum predicts impairment in learning and the magnitude of alcohol craving (Park et al., 2010).

In this context, the use of a simple but effective, relatively focal and non-invasive modulator of neuroplasticity – transcranial direct current stimulation (tDCS) – can be tested as an agent to change the addictive behaviour via modulation of dlPFC excitability. Modulation of dlPFC functions with tDCS has been shown to reduce cravings for tobacco (Fregni et al., 2008a), marijuana (Boggio et al., 2010) and food in healthy subjects (Fregni et al., 2008b). For alcohol craving, positive preliminary tDCS data are available. Boggio et al. (2008b) reported that bilateral tDCS, either left cathodal/right anodal or left anodal/right cathodal, over the dlPFC reduces alcohol craving in alcoholic subjects. We subsequently showed that single (Nakamura-Palacios et al., 2012) and repetitive (da Silva et al., 2013) anodal tDCS over the left dlPFC reduced craving and depressive symptoms and improved frontal executive functions in severe alcoholics. However, a trend towards increased instances of relapse was observed in alcoholics submitted to repetitive unilateral anodal tDCS over the left dlPFC (da Silva et al., 2013). Given these results, we hypothesized that cathodal tDCS over the left dlPFC would induce an opposite effect, that is, a reduction of alcohol use relapses. Furthermore, we have recently shown that the left rostral middle frontal cortex (including the left dlPFC) together with the left cerebellar cortex are predictive for frontal executive functions in alcoholics (Nakamura-Palacios et al., 2013).

Therefore, in this trial we first aimed to investigate whether repetitive bilateral tDCS (left cathodal/right anodal) over the dlPFC would reduce relapse probability over a prolonged time course. Secondly, we tested the impact of this type of stimulation on frontal cognitive functions. We hypothesized that active bilateral tDCS would be associated with less relapses over time.

**Method and materials**

We report this clinical trial according to CONSORT guidelines. This trial was registered under ClinicalTrials.gov number NCT01330394.

**Trial design**

This clinical trial was a parallel randomized sham controlled and single centre trial. Subjects were randomly assigned to receive real brain stimulation (tDCS group) or a simulation of this procedure (sham-tDCS group) in a 1:1 ratio (Fig. 1) using a computer-generated randomization sequence that was kept with the un-blinded study coordinator (not involved in the recruitment) and only revealed to the co-investigator conducting treatments immediately before first session.

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**Fig. 1.** Diagram of the general procedure: eligible alcoholics recruited from outpatient services were forwarded to the research centre, signed the terms of consent and were randomized to receive repetitive bilateral (cathode left/anode right over the dorsolateral prefrontal cortex) transcranial direct current stimulation (tDCS) \((n=17)\), 2 mA, 35 cm², two times daily stimulation for 13 min with 20 min interval in-between; one subject was excluded after randomization because of severe withdrawal syndrome observed in the first physical examination before the beginning of the treatment) or placebo [sham-tDCS \((n=18)\), one subject was excluded after randomization because of suspicion of cerebral ischemic process detected during the first physical examination before intervention] treatment (daily sessions for 5 consecutive days). Relapse to the use of alcohol were followed up weekly in the first four weeks and monthly in the following five months. A=anterior, P=posterior, R=right, L=left, a=anode, c=cathode, BS=brain stimulation, FAB=frontal assessment battery, MMSE=mini mental status examination, OCDS=obsessive compulsive drinking scale, HAM-D=Hamilton scale for depression, HAM-A=Hamilton scale for anxiety, WHOQOL=quality of life.
Participants

Between October and November of 2012, 35 alcohol-dependent patients meeting our inclusion criteria (see below) agreed to participate in this study. Patients were detoxified, under long-term treatment and referred from three public outpatient services specializing in mental health from the rural region of Espírito Santo state, Brazil, which follows a standard protocol for the treatment of drug addiction. This consists of psychosocial approaches – conducted by a professional team of psychologists, nurses, social workers and physicians – and pharmacotherapy including, benzodiazepines, vitamin B, disulfiram and when necessary, antidepressants, anxiolytics, antihypertensive, gastric medications and folic acid. There were two only dropouts and thus 33 of 35 (94.3%) successfully completed the study. The two dropouts were excluded after randomization but before brain stimulation. One dropout from the tDCS group showed severe withdrawal symptoms and another (from the sham-tDCS group) developed a new cerebral ischaemic lesion (see consort diagram flow in the Fig. 2).

The inclusion criteria for this study were: (1) patients between the age of 18 and 75 years; (2) meeting the criteria for alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as determined by clinical evaluation; (3) in a stable clinical condition with no need for inpatient care; (4) able to read, write and speak Portuguese; and (5) no severe withdrawal signs or symptoms at baseline. Conversely, exclusion criteria included: (1) a condition of intoxication or withdrawal due to a substance other than alcohol; (2) unstable mental or medical disorder or substance abuse or addiction other than alcohol dependence, except nicotine and/or caffeine; (3) a diagnosis of epilepsy, convulsions, or delirium tremens during abstinence from alcohol; (4) a previous history of drug hypersensitivity or adverse reactions to diazepam or other benzodiazepines and haloperidol; (5) any contraindication for electrical brain stimulation procedures such as electronic implants or metal implants; and (6) suspected pregnancy for female participants.

Ethical approval for both trials was provided by the Brazilian Institutional Review Board of the Federal University of Espírito Santo (registration 017/09), Brazil. The study was conducted in strict adherence to the Declaration of Helsinki and is in accordance with the ethical standards of the Committee on Human Experimentation of the Federal University of Espírito Santo, ES, Brazil. Subjects were fully informed about the experimental protocol and voluntarily signed an informed consent form before the start of the experiment.

Fig. 2. Flow diagram according to CONSORT 2010.
Intervention

The intervention in this clinical trial was the non-invasive brain stimulation technique: transcranial direct current stimulation (tDCS). Direct currents were transferred via a pair of carbonated silicone electrodes (35 cm²) with a thick layer of high-conductive EEG gel beneath them [according to our previous study (Nakamura-Palacios et al., 2012)]. The electric current was delivered by an electric stimulator (Striat, Ibramed Indústria Brasileira de Equipamentos Médicos Ltd, Brazil). For tDCS, the cathode was placed over the left dlPFC (F3) while the anode was placed over the right dlPFC (F4) according to the 10–20 international system (Fig. 1). In each daily session, the currents flowed continuously twice for 13 min (2.0 mA) with a rest interval (no stimulation) of 20 min between (13:20:13 schedule) in accordance with a study showing extended after-effects with this protocol (Monte-Silva et al., 2013).

For sham tDCS, the electrodes were placed at the same positions, but the stimulator was gradually turned off after 20 s. In this way subjects remain blinded to the respective stimulation condition, as many experience the itching sensation often felt initially during stimulation (Brunoni et al., 2011). A previous study validated the sham procedure of 2 mA tDCS; showing similar blinding efficacy as with a placebo pill (Brunoni et al., 2014).

Both sham- and real-tDCS groups received one session a day for five consecutive days (Fig. 1). After the completion of repetitive DC stimulations, patients were clinically followed up weekly in the first four weeks and monthly up to six months (Fig. 1).

Outcomes

The primary outcome was alcohol use relapse as verbally assessed (information received from the patient, family or caregivers) during the entire treatment period, then weekly in a four-week follow-up period and monthly for up to six months (Fig. 1).

Secondary outcomes consisted of global physical and clinical examination including the assessment of frontal executive functions, cognitive mental status, depressive and anxiety symptoms, alcohol craving and quality of life as listed below and detailed in appendix (appendix 1 – supplementary data). They were assessed at baseline and after the five-day treatment period: (i) Frontal Assessment Battery (FAB); (ii) Mini Mental Status Examination (MMSE); (iii) Obsessive Compulsive Drinking Scale (OCDS); (iv) Hamilton Depression Rating Scale (HAM-D); (v) Hamilton Anxiety Rating Scale (HAM-A); and (vi) quality of life of the World Health Organization (WHOQOL-BREF).

All clinical measurements were conducted by one of the experimenters blinded to the brain stimulation procedures; conversely the experimenter responsible for tDCS application was blinded to all clinical outcomes for the entire period of the study.

Statistical analyses

The primary null hypothesis was that the relapse rate would not differ significantly between the group receiving real tDCS and the group receiving sham tDCS. We powered the study for a large effect size given our hypothesis that tDCS would be associated with a large reduction in relapse rate. Therefore, assuming a hazard ratio of 0.3 with a power of 80% to test the primary null hypothesis using a log-rank test and a two-sided probability of a type I error of 5%, a sample of 28 subjects would be necessary; however, to account for unexpected issues (such as dropouts) we increased the sample by 25% to 35 subjects.

The main outcome – alcohol use relapse – was defined in this study as the first episode of return to the previous uncontrolled pattern of alcohol use (drinks per day), during the treatment (first week), over the immediate follow-up (weekly for four weeks), and over a late follow-up (monthly for the following five months). This constituted ‘at risk for relapse periods’ defined in days for each person, which was analysed by the Log-rank (Mantel-Cox) test with Hazard Ratio using the Mantel–Haenszel method.

For secondary outcomes, because some data were normally distributed, and some ordinally-scaled (Shapiro–Wilk normality test, we used parametric and non-parametric tests for statistical analysis, as appropriate. Student’s t-test for two independent samples, pairwise t-tests and Chi-square tests were used to compare results between and within sham and real-tDCS groups.

When differences were found between groups in baseline scores, such as in the FAB and MMSE, scores obtained in these instruments were included in an analysis of covariance (ANCOVA), including the respective baseline values as moderator variables, and the independent group factor (sham-tDCS vs. tDCS) and repeated measure factor treatment (before and after tDCS).

A two-tailed p-value of 0.05 or less was considered to indicate statistical significance. SPSS Statistics Base 17.0 (SPSS Inc., USA) and GraphPad Prism 5.0 (GraphPad Software Inc., USA) were employed for statistical analysis and graphic presentations.

Results

Baseline data

Baseline socio-demographic characteristics, patterns of drug use and clinical outcomes are presented in Tables 1 and 2. Alcoholic subjects were an average of 44.8 yr old in the total sample. These subjects came from the countryside, where agriculture is the main regional economic source. Thus, they were generally (84.8%) ‘low educated’ (less than 4 yr of education) with only one subject (3%) having a college degree. The majority of subjects were freelance workers or working in informal jobs (54.5%). Also, most subjects were either single
(39.4%) or, conversely, in a stable marital state (42.5%) (Table 1). They started to drink alcohol early in life with the age of onset averaging 17.5 yr old. All subjects were heavy drinkers consuming on average 17.3 drinks per day (Table 1, equivalent to an average of 240 grams of alcohol per day). Tobacco use was also common in this sample (45.5%) (Table 1).

Table 1 shows that ‘use of alcohol’ characteristics were not different between the sham- (n=17) and real-tDCS group (n=16) (Table 1).

**Primary outcome**

At the end of the 6-mth-observation period, 15 of 17 subjects from the sham-tDCS and 8 of 16 from the tDCS group had relapsed (Fig. 3). The difference in survival between groups was statistically significant at the end of the 6-mth follow-up period (p=0.021) (Fig. 3 and Table 3). By this point in time, alcoholics from the real-tDCS group had relapsed about three times less compared to alcoholics from the sham-tDCS group. The hazard ratio calculated by the Mantel–Haenszel method was 0.35 (Table 3).

**Secondary outcomes**

The total sample of alcoholic subjects showed generally no impairment of executive function. In the baseline evaluation, the total FAB score (mean of the total sample: 11.3 (2.7 s.d.)) was within the range expected in the Brazilian population, with regard to age and schooling (Rodrigues et al., 2009; Beato et al., 2012). As baseline FAB scores were different between the groups, we controlled for baseline differences in an ANCOVA model and observed significant differences of pre- vs. post-FAB performance \(F(1,30)=14.7, \ p=0.001\). However, there was no significant interaction between groups and time-points \(F(1,30)=0.75, \ p=0.39\) suggesting that the gain on FAB performance in both groups after treatment was not influenced by treatment effects. For the other cognitive assessment – MMSE – the mean score for the total sample of alcoholics was 23.2 (3.9 s.d.), which is also within the normal range, considering age and educational level, according to Crum et al. (1993). ANCOVA models also showed no significant interaction between group and time-point for this outcome \(F(1,30)=0.10, \ p=0.75\) (Table 2).
Other behavioural assessments including craving (OCDS) scores, mood (indexed by HAM-D) and anxiety (indexed by HAM-A) did not show differences between groups when comparing before treatment with after treatment ($p<0.05$ for all these comparisons, see Table 2 for details).

Table 2. Clinical measurements in alcoholics at the beginning (initial) and at the end (final) of the treatment with bilateral repetitive tDCS or placebo (sham-tDCS)

<table>
<thead>
<tr>
<th>Clinical measurements</th>
<th>Sham-tDCS (n=17)</th>
<th>tDCS (n=16)</th>
<th>Inter-group analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>10.3 (2.4)</td>
<td>12.3 (2.7)</td>
<td>$t(31)=-2.3$</td>
</tr>
<tr>
<td>Final</td>
<td>12.2 (3.1)</td>
<td>14.1 (1.4)</td>
<td>$t(31)=1.9$</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>$t(16)=-3.4$, $p=0.004$</td>
<td>$t(15)=-3.7$, $p=0.002$</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>21.9 (4.5)</td>
<td>24.6 (2.6)</td>
<td>$t(31)=-2.1$</td>
</tr>
<tr>
<td>Final</td>
<td>22.6 (3.9)</td>
<td>24.9 (3.7)</td>
<td>$t(31)=-1.6$</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>$t(16)=-0.9$, $p=0.37$</td>
<td>$t(15)=-0.07$, $p=0.94$</td>
<td></td>
</tr>
<tr>
<td>OCDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>8.4 (3.6)</td>
<td>7.3 (4.3)</td>
<td>$t(31)=0.8$</td>
</tr>
<tr>
<td>Final</td>
<td>3.3 (3.1)</td>
<td>2.8 (3.1)</td>
<td>$t(31)=0.4$</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>$t(16)=-5.4$, $p&lt;0.0001$</td>
<td>$t(15)=3.3$, $p=0.004$</td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>9.4 (7.5)</td>
<td>8.6 (8.9)</td>
<td>$t(31)=0.3$</td>
</tr>
<tr>
<td>Final</td>
<td>5.7 (4.8)</td>
<td>6.8 (1.7)</td>
<td>$t(31)=0.3$</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>$t(16)=2.9$, $p=0.01$</td>
<td>$t(15)=1.3$, $p=0.22$</td>
<td></td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>12.5 (10.4)</td>
<td>11.0 (9.0)</td>
<td>$t(31)=0.4$</td>
</tr>
<tr>
<td>Final</td>
<td>7.6 (9.2)</td>
<td>7.1 (7.3)</td>
<td>$t(31)=0.2$</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>$t(16)=2.1$, $p=0.05$</td>
<td>$t(15)=2.0$, $p=0.06$</td>
<td></td>
</tr>
</tbody>
</table>

FAB, frontal assessment battery; MMSE, mini mental status examination; OCDS, obsessive compulsive drinking scale (5-items related to craving); HAM-D, Hamilton depression rating scale; HAM-A, Hamilton anxiety rating scale.

Fig. 3. Per cent of abstinence over time (days) during (5-days) and after (following six months of follow-up) treatment with bilateral repetitive transcranial direct current stimulation (tDCS, 2 mA, 35 cm$^2$: cathode left/anode right over the dorsolateral prefrontal cortex; daily double stimulation: 13–20 min interval – 13 min; 5 consecutive days; $n=16$) or placebo (sham-tDCS; $n=17$) in severe alcoholics. $p=0.021$ between groups analysis by Log-rank (Mantel-Cox) test.

Comparisons of quality of life assessed by WHOQOF-BREF showed no significant differences between groups in all domains. However, there was a trend ($p=0.06$) (Table 4) observed towards a greater mean score in the tDCS group when compared to the sham-tDCS group after treatment in the first individual question (Q1), which relates to the individual’s overall perception of quality of life. The respective mean score of the real, but not the sham-tDCS group, was significantly greater ($p=0.02$) after treatment when compared to scores observed before treatment. Interestingly, 5 out of 17 (29.4%) subjects from the sham, but none from the real-tDCS group, shifted their perception to a worse quality of life. Additionally, 5 subjects (29.41%) from the

Table 3. Hazard analysis on the first relapse to the use of alcohol in alcoholics at the beginning (initial) and at the end (final) of the treatment with bilateral repetitive tDCS or placebo (sham-tDCS) over six months of follow-up

<table>
<thead>
<tr>
<th>Log-rank (Mantel–Cox) test</th>
<th>Chi square</th>
<th>Hazard ratio</th>
<th>95% CI of ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.33</td>
<td>0.35</td>
<td>0.14–0.85</td>
</tr>
</tbody>
</table>

Median survival

<table>
<thead>
<tr>
<th>Organic solvent</th>
<th>Sham-tDCS</th>
<th>tDCS</th>
<th>Ratio</th>
<th>95% CI of ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42.0</td>
<td>187.0</td>
<td>4.452</td>
<td>4.03 to 4.88</td>
</tr>
</tbody>
</table>
Table 4. Quality of life (WHOQOF-BREF) in alcoholics at the beginning (initial) and at the end (final) of the treatment with bilateral repetitive tDCS or placebo (sham-tDCS)

<table>
<thead>
<tr>
<th>WHOQOF-BREF</th>
<th>Sham-tDCS (n=17)</th>
<th>tDCS (n=16)</th>
<th>Inter-group analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (s.d.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual’s overall perception of quality of life</td>
<td>3.5 (0.9)</td>
<td>3.4 (1.0)</td>
<td>t(31)=−0.3, p=0.78</td>
</tr>
<tr>
<td>Initial</td>
<td>3.7 (0.6)</td>
<td>4.1 (0.8)</td>
<td>t(31)=−1.9, p=0.06</td>
</tr>
<tr>
<td>Final</td>
<td>t(16)=−0.5, p=0.65</td>
<td>t(15)=−2.6, p=0.02</td>
<td></td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual’s overall perception of their health</td>
<td>3.8 (0.8)</td>
<td>3.8 (0.9)</td>
<td>t(31)=0.05, p=0.96</td>
</tr>
<tr>
<td>Initial</td>
<td>4.2 (0.6)</td>
<td>4.0 (0.9)</td>
<td>t(31)=0.9, p=0.37</td>
</tr>
<tr>
<td>Final</td>
<td>t(16)=−1.9, p=0.07</td>
<td>t(15)=−1.1, p=0.30</td>
<td></td>
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<tr>
<td>Intra-group analysis</td>
<td></td>
<td></td>
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<tr>
<td>DOMAINS (transformed scores)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>14.5 (2.6)</td>
<td>14.0 (2.9)</td>
<td>t(31)=0.5, p=0.64</td>
</tr>
<tr>
<td>Final</td>
<td>15.5 (1.8)</td>
<td>15.1 (2.4)</td>
<td>t(31)=0.5, p=0.61</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>t(16)=−1.6, p=0.13</td>
<td>t(15)=−1.6, p=0.14</td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>14.9 (2.7)</td>
<td>14.0 (3.1)</td>
<td>t(31)=0.8, p=0.40</td>
</tr>
<tr>
<td>Final</td>
<td>15.3 (2.1)</td>
<td>14.6 (2.8)</td>
<td>t(31)=−0.9, p=0.39</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>t(16)=−0.7, p=0.52</td>
<td>t(15)=−0.8, p=0.42</td>
<td></td>
</tr>
<tr>
<td>Social relationships</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>15.0 (3.6)</td>
<td>15.8 (2.7)</td>
<td>t(31)=−0.8, p=0.45</td>
</tr>
<tr>
<td>Final</td>
<td>16.0 (3.0)</td>
<td>14.8 (3.3)</td>
<td>t(31)=1.1, p=0.27</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>t(16)=−1.4, p=0.19</td>
<td>t(15)=1.8, p=0.09</td>
<td></td>
</tr>
<tr>
<td>Environment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>14.1 (2.4)</td>
<td>13.5 (2.1)</td>
<td>t(31)=0.8, p=0.42</td>
</tr>
<tr>
<td>Final</td>
<td>14.6 (1.8)</td>
<td>14.6 (2.3)</td>
<td>t(31)=0.03, p=1.0</td>
</tr>
<tr>
<td>Intra-group analysis</td>
<td>t(16)=−1.3, p=0.23</td>
<td>t(15)=−2.2, p=0.04</td>
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WHOQOL-BREF, abbreviated instrument of quality of life of the World Health Organization (translated to Portuguese). Domains were presented in transformed scores to be comparable with the scores used in the WHOQOL-100.
sham-tDCS group and 9 out of 16 (56.25%) from the real-tDCS group had identical values, and the remaining 7 (41.18%) subjects from the sham and 7 (43.75%) from the real-tDCS group shifted their perception to a better quality of life after treatment ($X^2 = 6.12, p = 0.05$). Moreover, a greater proportion (37.5%) of subjects from the real-tDCS group perceived their quality of life as maximal (‘very good’) after treatment while only 12.5% chose this score before treatment. By contrast, a smaller proportion (5.9%) of the sham-tDCS group scored the maximum value in this question after treatment while 17.6% chose this score before the treatment. Regarding pairwise analysis, only the real-tDCS group showed a significant ($p = 0.04$) increase in the environment domain after treatment (Table 4), notably for the section related to ‘physical safety and security’ ($t(15) = -2.42, p = 0.03$).

### Adverse effects

Regarding the adverse events, besides an itching sensation and a rare mild redness of the scalp (beneath the electrodes in patients with very white skin), no other adverse events were reported by patients from both groups in this study. In fact, subjects were not able to clearly differentiate between real stimulation and the sham procedure, because 12 alcoholics out of 15 (80%) from the sham-tDCS and 13 out of 14 (92.86%) from the real-tDCS groups answered positively when they were asked whether they thought they had received real stimulation at the end of the treatment ($p = 1.0$, Fisher test for the respective between group comparison). There was missing data in two patients from the sham-tDCS and two patients from the real-tDCS group regarding blinding.

### Discussion

The most important result of this study is that alcoholics submitted to once-daily sessions of bilateral dIPFC tDCS (left cathodal/right anodal) for five consecutive days relapsed significantly less when compared to alcoholics who received placebo (sham-tDCS) treatment. By the end of the 6-mth follow-up period 11.8% of alcoholics from the sham-tDCS group compared with 50% of the real-tDCS group were abstaining from alcohol use. No between group differences were observed for changes in clinical measurements for frontal function, global mental status, craving, and depressive or anxiety symptoms. The overall perception of quality of life was improved in alcoholics treated with tDCS.

The sham- and real-tDCS groups were well matched by socio-demographic characteristics such as age, gender, schooling, working and marital status and also by characteristics of alcohol use, especially regarding days of abstinence before tDCS intervention. This is important, as the main clinical outcome in this study was the relapse of alcohol use after intervention.

Most treated alcoholics usually relapse to alcohol use after treatment and it may occur very rapidly (Maddux and Desmond, 1986). Many studies report that only a few treated alcoholics, around 18–21%, remain abstinent over six months after treatment (Maddux and Desmond, 1986; Moos and Moos, 2006).

The low percentage (11.8%) of subjects that remained abstinent in the sham-tDCS group by the end of 6-mth follow-up in our study was similar to the that reported by Chick et al. (2000), in a multi-centre prospective study with 581 alcoholics investigating the preventive effects of acamprosate on relapse of the use of alcohol. In this study, in both groups treated with placebo and acamprosate, only 11 and 12% of subjects, respectively, were abstinent by the end of 6 mth, showing no preventive effects of acamprosate.

By contrast, Sass et al. (1996) in their prospective study with 272 alcoholics, showed that a larger proportion of alcoholics receiving acamprosate for a year were abstinent (43%) when compared to placebo (21%) by the end of 48 wk after treatment. They concluded that acamprosate was able to treat alcohol dependence and to sustain abstinence over a two-year period. In our study, 50% of tDCS-treated alcoholics remained abstinent for over six months.

In the present study, craving was measured by a subscale of the OCDS, referring to craving over an entire day rather than acute symptoms alone, which has been recently considered as a more appropriate index in alcoholics (Kavanagh et al., 2013). Alcoholics from both groups, irrespective of placebo or real-tDCS treatments, showed significant decreases in craving after the intervention. However, there was no difference in the amount of change in craving between the two groups. It is important to underscore here that craving was assessed over a period of time rather than with cue-induced craving, which is how most tDCS studies have been previously designed when assessing the acute effects of tDCS (Boggio et al., 2008b, 2010; Fregni et al., 2008a).

This is the first study showing long-lasting beneficial modulatory effects of repetitive DC stimulation on alcohol use relapse. Interestingly, in our previous study opposite effects were observed using another tDCS montage: with anodal tDCS over the left dIPFC. In this study, there was a trend towards greater readiness for alcohol use relapse along with a larger decrease in craving (da Silva et al., 2013). This is an interesting contrast as it supports an important concept observed in tDCS studies: montage is critical to determine the effects of tDCS; we have also shown this in a pain study (Mendonca et al., 2011).

Relapse here was defined as resuming heavy alcohol intake in the previous pattern for each subject (Wesson et al., 1986; Iruzubieta et al., 2013), in a harmful manner, in opposition to what has been called lapses, slips or chipping (Maddux and Desmond, 1986), defined by sporadic drinking episodes, usually in small amounts and
self-limited (Iruzubieta et al., 2013). Craving, considered here as the uncontrolled urge to consume alcohol, is usually related to relapse, but may constitute different conditions (Miller and Gold, 1994; Sayette et al., 2000; Tiffany and Wray, 2012). Relapse may be triggered by other factors besides craving, such as mood, expectancies, intentions, self-efficacy or environment (Miller and Gold, 1994; Tiffany and Wray, 2012; Kavanagh et al., 2013). In fact, some subjects scoring high on craving scales may not relapse to alcohol use, and subjects relapsing to the use of alcohol may not show signs of craving, at least consciously (Miller and Gold, 1994; Tiffany and Wray, 2012).

Depressive and anxiety symptoms may also affect the probability for alcohol use relapse in general (Parsons et al., 1990; Willinger et al., 2002), but changes in these symptoms were not different between groups, and thus cannot account for the results of the present study. The lack of mood effects in this study may be due to electrode polarity: cathodal tDCS over the left DLPFC. Evidence has shown a lateralized effect of non-invasive brain stimulation in the prefrontal cortex for the treatment of depression (i.e. left rather than right). Anodal dlPFC stimulation is shown to have antidepressant effects (Boggio et al., 2008a; Nitsche et al., 2009; Brunoni et al., 2012; Kuo et al., 2014). Thus, the diminishing excitability effects of cathodal tDCS over left DLPFC could result in mood worsening. However HAM-D and HAM-A scores tended to decrease in both groups after repetitive sham-or real-tDCS treatment and there were no differences between groups regarding these changes.

However, changes of perceived quality of life may alter the need for alcohol use and subsequently the likelihood of relapse. It has been shown that the more severe the alcoholism the worse the quality of life perceived by alcoholic subjects (da Silva Lima et al., 2005). In this study the individual’s overall perception of quality of life was increased in alcoholics treated with tDCS at the end of the treatment. The perception of a better quality of life could be the reason for the long-lasting abstinence from alcohol in this group. By contrast the perception of a worse quality of life was observed in some subjects from the sham-tDCS group, which may have caused them to be more susceptible to relapse. Interestingly, the tDCS group showed an increase in the environment domain of the quality of life assessment, which may favour the view that the perception of a better and safer environment may help these subjects to maintain abstinence. Although intriguing, this potential relationship between tDCS modulation and quality of life in alcoholics needs to be explored in a larger sample.

In this study, the cathode was placed over the left dlPFC and the anode over the right dlPFC. A recent study in rodents describes that cathodal, but not anodal, tDCS over the frontal cortex yielded a large and long-lasting increase of extracellular dopamine levels, but not serotonin, in the striatum (Tanaka et al., 2013) in its more ventral portion, possibly including the nucleus accumbens. The prefrontal cortex, the nucleus accumbens and the ventral tegmental area are brain structures connected by mesocortical and mesolimbic dopamine pathways constituting the brain reward circuitry (Tzschentke, 2001; Nestler, 2004; Koob and Volkow, 2010; Nakamura-Palacios, 2011; Volkow et al., 2011). These pathways seem to become controlled by drugs of abuse, including alcohol (Hyman et al., 2006; Volkow et al., 2011), yielding highly addictive behaviour (Goldstein and Volkow, 2002, 2011) and impaired frontal functions (Park et al., 2010; Volkow et al., 2011), conditions that are highly related to the risk of relapse. Thus, it could be speculated that the inhibitory cortical modulation induced by cathodal tDCS over the left dlPFC would disengage the brain reward circuitry from alcohol influence favouring a reduced probability of relapse. This may possibly occur by interrupting cognitive functions attributed specifically to the left dlPFC, such as cognitive dissonance, which plays a causal role in preference changes after a difficult decision as recently demonstrated by Mengarelli et al. (2013). However, the underlying mechanisms that may be involved in the long-lasting prefrontal modulatory effects of repetitive double bilateral tDCS need to be investigated in future studies.

There are limitations of this study that need to be taken into account. The sample of alcoholics is relatively small, thus preventing us from expanding the clinical significance of our findings. Furthermore, the follow-up was based on information gathered by self-reports or reports of family members by telephone calls or through visits by a member of our research team, and not based on a regular healthcare service or on biological measurements such as laboratory or breath tests, which would have helped to gather more evidence for relapse.

In summary, repetitive bilateral tDCS over the dlPFC (left cathodal and right anodal) reduced alcohol use relapse for up to six months after treatment and increased the perception of quality of life in alcoholic subjects.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145714000984

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Statement of Interest

MAN is on the advisory board of Neuroelectrics. All the other authors (JK, LCPP, BM, GACS, FF and EMNP) reported no biomedical financial interests or potential conflicts of interest.

References


