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ARTICLE

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Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology

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Abstract

Frontal lobe dysfunction is a hallmark of alcohol dependence. Recent studies have shown that a simple but powerful technique of cortical modulation – transcranial direct current stimulation (tDCS) – can induce significant cognitive changes. We therefore aimed to assess the clinical and electrophysiological (as indexed by P3) effects of tDCS of left dorsolateral prefrontal cortex (DLPFC) in different types of alcoholic patients according to Lesch's typology. We enrolled 49 alcoholic subjects, aged between 18 and 75 yr, during the subacute abstinence period to participate in this study. Subjects underwent event-related potential (ERP) registration of alcohol-related and neutral sounds before, during and after active tDCS (1 mA, 35 cm², during 10 min) or sham procedure in a counterbalanced and randomized order. Frontal assessment battery (FAB) and five items of the Obsessive Compulsive Drinking Scale were applied at the beginning and at the end of each experimental session. ERP analysis showed an increase in the mean amplitude of P3 associated with alcohol-related sounds after tDCS. This effect was not seen for neutral sounds. This change was more pronounced in Lesch IV alcoholics. Secondary exploratory analysis showed a significant improvement of FAB performance after active tDCS compared to sham tDCS in Lesch IV alcoholics only. We showed clinical and electrophysiological evidence of tDCS-induced frontal activity enhancement that was specific for Lesch IV alcoholics. Given that frontal dysfunction may contribute to the loss of control over drinking behaviour, local increase in frontal activity induced by tDCS might have a beneficial clinical impact in the future.

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Introduction

One hallmark of alcoholism is frontal lobe deficiency, as characterized by attention and working-memory deficits and executive dysfunction. This condition, especially marked by an inability to abstain from alcohol, has direct implications for its treatment (Goldstein & Volkow, 2002) and is an important predictor of outcomes following treatment (Moselhy *et al.* 2001).

Many propositions for alcoholism classification have been proposed (Babor *et al.* 1992; Cloninger *et al.* 1981; Jellinek, 1960; Schuckit, 1985). The most extensive and long-term study was conducted by Lesch *et al.* (1988) allowing the differentiation of subgroups of

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Table 1. Lesch's types of alcoholism (Bonsch *et al.* 2006; Hillemacher & Bleich, 2008; Lesch, 1988, 1990; Pombo & Lesch, 2009; Walter *et al.* 2006)

Lesch I	Lesch II	Lesch III	Lesch IV
• Development of tolerance with the appearance of early heavy withdrawal • Patients develop meta-alcoholic psychosis, like delirium tremens, and might suffer from withdrawal epileptic seizures • They tend to use alcohol to weaken withdrawal symptoms	• Anxiety and pre-morbid conflicts, suicidal intentions • They frequently become aggressive when intoxicated • Alcohol seems to be used as a strategy against anxiety	• Exhibit an aggressive and impulsive behaviour with the existence of psychiatric comorbidity • Alcohol seems to be used as a self-medication to treat an underlying affective disorder	• Disturbance or cerebral damage before the conclusion of brain development, associated with behavioural disorders and serious social problems • Alcohol may be used as self-medication for behavioural and social disorders
'Model of allergy'	'Model of anxiety or conflict'	'Alcohol as antidepressant'	'Alcohol drinking as adaptation'

patients with chronic alcoholism cross-sectionally, according to clinical, biochemical and neurophysiological factors (Lesch *et al*. 1988, 1990). In their study they identified four types of alcoholics (Table 1) that have now been very well characterized in different countries (see Zago-Gomes & Nakamura-Palacios, 2009).

In a previous study, considering different types of alcoholism according to Lesch's typology, Type IV alcoholics showed the lowest Mini-Mental Status Examination (MMSE) and Frontal Assessment Battery (FAB) overall scores compared to non-alcoholics and other Lesch types of alcoholic subjects. In a more specific analysis, even in those Type IV alcoholics with preserved mental function, executive frontal function was still significantly impaired (Zago-Gomes & Nakamura-Palacios, 2009).

Because frontal dysfunction appears to be different according to Lesch subtype of alcoholism, investigation of clinical and electrophysiological outcomes after frontal modulation with non-invasive brain stimulation in these four types (Types I–IV) may provide some insights into mechanisms of frontal dysfunction. One neuromodulation technique that has been increasingly used and tested is transcranial direct current stimulation (tDCS). In this method, a weak direct current is induced in the cerebral cortex via two electrodes usually placed over the scalp (Nitsche *et al.* 2008). Several studies have shown that this non-invasive method of brain stimulation is associated with significant changes in cortical excitability – increase or decrease according to the polarity of stimulation (Nitsche & Paulus, 2000, 2001; Zaghi *et al.* 2010).

Several studies have shown that tDCS applied to prefrontal cortex is associated with cognitive gains in healthy subjects and patients with neuropsychiatric conditions (Boggio *et al.* 2006; Fregni *et al.* 2005; Iyer *et al.* 2005; Kincses *et al.* 2004; Marshall *et al.* 2006). Fregni *et al.* (2005) showed that anodal tDCS (1 mA for 10 min) applied over the left side of the dorsolateral prefrontal cortex (DLPFC) improved working memory in healthy young subjects. Therefore, we hypothesized that modulation of DLPFC with tDCS would induce differential changes in frontal function as indexed by FAB according to Lesch's classification of alcoholism.

In addition to clinical evaluation by FAB, we also measured the P3 (or P300) component – this neurophysiological marker has been extensively used to study the consequences of alcohol effects over brain activity (Bartholow *et al.* 2007). A reduced P3 amplitude elicited by simple (Enoch *et al.* 2001) visual or auditory stimuli has been correlated to alcoholism and associated with a high risk for alcohol dependence (Bartholow *et al*. 2003, 2007; Enoch *et al.* 2001), but a larger P3 in response to a more complex alcohol-related stimuli has also been reported (Namkoong *et al.* 2004).

Therefore, in order to improve our understanding of frontal dysfunction in alcohol addiction, we examined the effects of tDCS over the left DLPFC on event-related potential (ERP) and frontal function in different types of alcoholics according to Lesch's typology, during a period of alcohol abstinence.

Methods

Subjects

Between June 2009 and November 2010, 233 alcohol-dependent outpatients were referred to a specialized

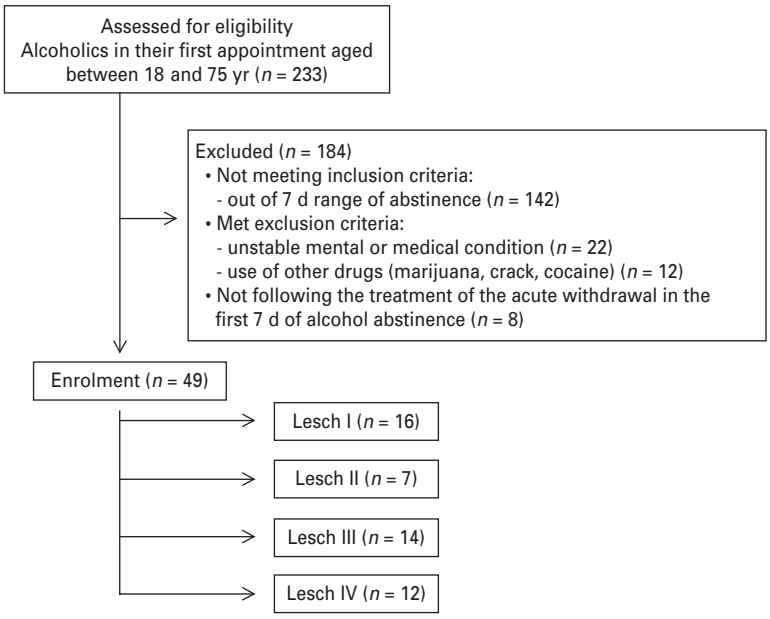

Fig. 1. Flowchart for subject enrolment. From 233 eligible subjects, 49 were selected after assessing inclusion and exclusion criteria.

public service in the Medical School Hospital of the Federal University of Espírito Santo for first-time alcohol-dependence treatment. Based on our inclusion criteria, 49 agreed to participate and were included in this study (Fig. 1).

To participate in this study, patients were required to (1) be aged between 18 and 75 yr; (2) have consumed at least 30 drinks/wk in the last year on average; (3) have consumed alcohol for the last time at least 7 d before baseline; and also to (4) meet criteria for alcohol dependence according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), as determined by clinical evaluation; (5) be in a stable clinical condition with no need for inpatient care; (6) be able to read, write and speak Portuguese; and (7) have no severe withdrawal signs or symptoms at baseline. In addition, we excluded patients if they (8) met diagnostic criteria for other substance intoxication or withdrawal, or unstable mental or medical disorder other than alcohol dependence, except nicotine and/or caffeine; (9) had a diagnosis for epilepsy or convulsion or delirium tremens during abstinence from alcohol; (10) had a previous history of drug hypersensitivity or adverse reactions to diazepam or other benzodiazepines and haloperidol.

Several patients showed other systemic conditions requiring medication (e.g. hypertension, dyslipidaemia) and they entered the protocol when most of them were still under treatment for acute alcohol withdrawal (7 d after admission). Therefore, they were kept with their medications at stable dosages (56% were using diazepam, 46% vitamin B, 26% other vitamins, 24% antihypertensive, 22% antidepressants, 16% diuretics, 14% gastrointestinal medications, 6% antidiabetics, 6% antipsychotics, 6% anticonvulsants, 14% other medications) during the protocol.

Ethical approval was provided by the Brazilian Institutional Review Board at the Federal University of Espírito Santo, Brazil, which was conducted in strict adherence to the Declaration of Helsinki and is in accord with ethical standards of the Committee on Human Experimentation of the Federal University of Espírito Santo, ES, Brazil, where this study was completed.

Procedures

After having been informed of all procedures and given written informed consent, 49 outpatients diagnosed with alcohol dependence by ICD-10 were included in this study. A general procedure is shown and explained in Fig. 2. Patients were then assessed according to the following tools:

Sociodemographic and drinking behaviour characteristics

We conducted a structured interview that gathered information concerning sociodemographic data and

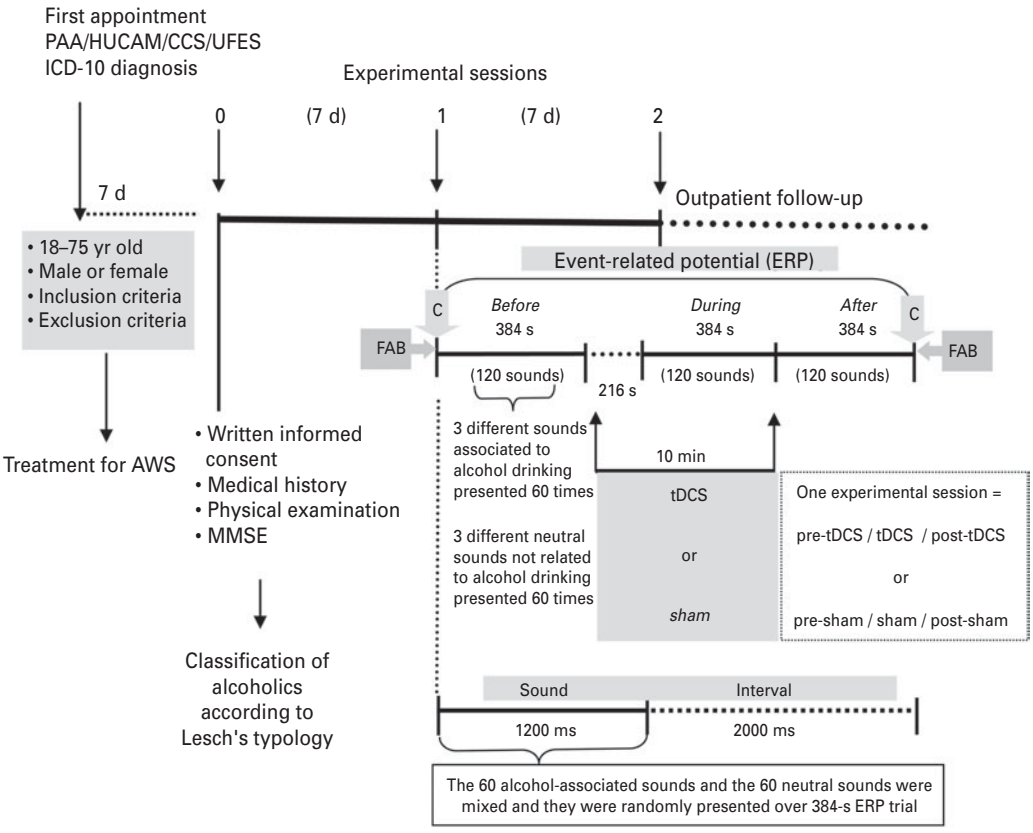

Fig. 2. General experimental protocol. Forty-nine alcoholic subjects with diagnosis according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria, aged between 18 and 75 yr, who attended for the first time at a specialized outpatient public service in the Medical School Hospital of the Federal University of Espírito Santo (PAA/HUCAM/CCS/UFES) for alcohol dependence treatment, were invited to participate in this study. Seven days after they have been started in the routine treatment offered by the outpatient service for acute alcohol withdrawal syndrome and screened for inclusion and exclusion criteria they were informed strictly about the whole protocol and asked for written informed consent. They were classified by types of alcoholism according to Lesch's typology, and followed to a structured medical history, to Mini Mental State Examination (MMSE) and a general physical examination. They were then referred to the Cognitive Sciences and Neuropsychopharmacology Laboratory from Federal University of Espírito Santo where they were submitted to event-related potential registration under random presentation of three sounds related to alcohol drinking ('opening of a beer can', 'filling a beer glass' and 'opening a beer bottle with the fall of the lid') and three neutral sounds ('opening a door', 'typewriting with a keyboard' and 'rushing of a shower') before, during and after transcranial direct current stimulation (tDCS, 1 mA, 35 cm^2, 10 min duration) or sham procedure. Seven days later they returned to the other session with tDCS or sham. Next, they had their brain activity registered under both conditions (tDCS or sham), using a cross-over design, i.e. half of incoming subjects started with tDCS and followed by sham procedure and vice versa. Frontal assessment battery (FAB) and five items of the Obsessive Compulsive Drinking Scale (C) were applied at the beginning and at the end of each experimental session. After the end of the experimental protocol, subjects were clinically followed-up in the routine assessment in the specialized outpatient service.

alcohol drinking characteristics. This interview was then followed by a global physical examination.

Types of alcoholism according to Lesch's typology

Subjects were classified according to Lesch's typology on the basis of Lesch's decision tree (Lesch *et al.* 1990), which details the basis for the diagnostic process in this model.

MMSE

An adapted, Portuguese-language version of the MMSE was used. As in its original version, the adapted Portuguese version of the MMSE is an 11-item test with a maximum score of 30 that examines five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. A mean score between 23 and 26 would be expected according

to age and educational level for the total sample and subgroups of alcoholics (Crum *et al.* 1993).

FAB

The FAB instrument elaborated by Dubois *et al.* (2000) consists of six subsets exploring the following domains: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Each of these subsets is scored from 0 (zero) to a maximum of 3. Therefore, the potential maximum total score of the FAB is 18 (Dubois *et al.* 2000).

FAB was applied at the beginning (initial) and at the end (final) of each experimental session, more specifically, before the pre-sham or pre-tDCS, and after the end of post-sham or post-tDCS conditions.

Obsessive Compulsive Drinking Scale (OCDS)

Five items (1, 2, 4, 5, 13) from the original OCDS, which are believed to reliably assess craving in a narrow sense (see Furieri & Nakamura-Palacios, 2007), were applied at the beginning and at the end of each experimental session, i.e. before and after sham or tDCS procedure.

ERPs

Cortical potentials were acquired in the sampling rate of 1000 Hz by employing a 21-channel neurophysiological digital multifunctional system, Neuronspectrum-4/EP (Neurosoft, Russia), with electrodes placed in Fz, Cz and Pz sites on the scalp according to the international 10–20 system for EEG electrode placement (Klem *et al.* 1999) with references linked to ears. Impedance of all electrodes remained below 5 kΩ during the whole recording procedure. The amplifier's high-frequency filter was set to 35 Hz and filtered offline to 15 Hz. Registers were recorded by Neuron-Spectrum-LEP software (Neurosoft) and were analysed offline by Brain Vision Analyser 2.0 professional (Brain Products GmbH, Germany). EEG epochs were recorded for 1000 ms starting 200 ms before the onset of the auditory stimuli. This 200-ms period of time served as baseline. EEG was corrected for EOG artifacts. Artifact-free EEG segments after stimulus onset were accepted for further analyses and were averaged separately for each electrode, each category and each subject.

Subjects were seated in a comfortable chair with the head facing forwards. The ERP was conducted in a sound-attenuated and temperature-controlled room by one experimenter with two assistants placing the electrodes on the subject's scalp and handling the electrophysiological recorder coupled to a computer located behind the subject.

A method for stimulus presentation described by Heinze *et al.* (2007) was considered and adapted to establish the ERP design in the present study. Thus, the participants were exposed to two different categories of standardized auditory stimuli. One category was comprised of alcohol drinking-related sounds such as 'opening of a beer can', 'filling a beer glass' and 'opening a beer bottle with the fall of the lid'. The other category consisted of sounds unrelated to alcohol use (neutral sounds) such as 'opening a door', 'typewriting with a keyboard' and 'rushing of a shower'. These sounds had an intensity of 70 dB and were presented binaurally through headphones. Each stimulus was presented during 1200 ms with intervals of 2000 ms between them (Fig. 2). Within each category three stimuli were presented approximately 60 times in each trial. The 60 alcohol-associated sounds and the 60 neutral sounds were mixed and they were randomly presented over a 384-s ERP trial.

The stimulus-induced ERP segment was considered for a whole length of 1000 ms, including 200 ms pre-baseline and 800 ms after stimulus presentation. No explicit task was given to the subjects other than listening carefully to the stimuli during the assessment.

A complete ERP trial was run before, during and after each condition of stimulation (sham and active tDCS) (Fig. 2). Therefore, three ERP trials were conducted in each experimental session.

tDCS

Direct current was transferred by carbonated-silicone electrodes (35 cm^2) with a layer of high conductive gel for EEG underneath that was thick enough to allow the conductance of the current between the electrode surface and the scalp or the skin. The electric current was delivered by a specially developed, battery-driven, constant current stimulator (NeuroQuest Therapeutics, USA) with a maximum output of 10 mA. To stimulate the DLPFC, the anode electrode was placed over F3 according to the 10–20 international system for EEG electrode placement (Fregni *et al*. 2006*b*, 2008; Loo *et al.* 2010). The cathode was placed over the contralateral supradeltoid area. With this montage, we increased the distance between the two electrodes and therefore potentially decreased skin shunting. A constant current of 1 mA intensity was applied for 10 min (Fregni *et al.* 2005). Some subjects only reported an itching sensation at both

electrode sites at the beginning of the stimulation. We followed the safety recommendations for the use of tDCS (Brunoni *et al.* 2011; Loo *et al.* 2009).

We chose parameters of stimulation that have been shown to induce significant changes in cortical excitability that outlast the stimulation period (Nitsche & Paulus, 2000, 2001) – for instance it has been shown that 9–11 min of stimulation can induce after-effects up to 60 min; further, the parameters used in this study have been shown to be effective in inducing changes in frontal-related tasks such as working memory (Fregni *et al.* 2005; Iyer *et al.* 2005; Kincses *et al.* 2004; Marshall *et al.* 2006).

For the sham procedure, the electrodes were placed in the same position, but the stimulator was turned off after 20s in such a way that subjects felt the initial itching sensation at the beginning, but received no current for the rest of the stimulation period. This procedure allowed the blinding of subjects for the respective stimulation condition (Gandiga *et al.* 2006).

Statistical analysis

Data were presented by percentage or mean ± standard deviation (S.D.). In general, because data were not normally distributed (Shapiro–Wilk normality test) and some data are an ordinal scale we chose to use non-parametric tests. We initially compared baseline scores (such as age, number of drinks/d, baseline FAB, MMSE scores) across the four groups of alcoholism using Kruskal–Wallis test.

Paired test (Wilcoxon signed rank test) was used for OCDS scores obtained at the beginning and at the end of each experimental session for the different subgroups.

For FAB, we categorized the data in four categories: worsening (when there was a worsening of FAB scores after the intervention); no change (when scores were the same); small improvement (when there was an improvement of 0–9% in FAB scores; we chose 9% due to score distribution); and improvement (when there was an improvement of $\geqslant 9\%$). The χ^2 test was employed for comparisons among these categories.

In this study, the mean amplitude and fractional (50%) area latency was considered in a time window between 250 and 400 ms for the analysis of the cognitive component (P3) of the ERP following the recommendations made by Luck (2005). Data from averaged registers from subjects of each group (type of alcoholics) were adjusted, by subtracting every single data from the mean amplitude found for that group in the 200-ms prestimulus baseline (Handy, 2005). Therefore, all data presented in this study represent the difference of the amplitude from the mean of 200-ms baseline. A non-parametric Friedman test followed by Dunn's multiple comparison test was employed in the comparisons among conditions (pre-sham, sham, post-sham, or pre-tDCS, tDCS, post-tDCS). Kruskal–Wallis test followed by Dunn's multiple comparison test was employed in the comparisons of data among different types of alcoholics (Lesch I, II, III, IV). A two-sample *post-hoc* non-parametric paired test (Wilcoxon signed rank test) was used in all comparisons between data collected before and during or after sham or tDCS application.

A two-tailed α-level of 0.05 was used to determine statistical significance. GraphPad Prism 4.0 (GraphPad Software,Inc., USA) was used for statistical analysis and graphic presentations.

Results

Sociodemographic and alcohol drinking behaviour characteristics

The sociodemographic characteristics of alcohol-dependent subjects in the total sample ($n=49$) were very similar to those presented by alcohol subjects classified according to Lesch's typology (Table 1). Of 49 alcoholic subjects, 16 (32.6%) were classified as Type I, seven (14.3%) as Type II, 14 (28.6%) as Type III and 12 (24.5%) as Type IV. There were no statistically significant differences of sociodemographic characteristics across the different types of alcoholic patients (Table 2).

The mean age (±S.D.) of the alcoholic total group was 48.8±8.9 yr (Table 2). The total sample was comprised primarily of males (91.5%), in a ratio of approximately 11:1 (Table 2). These demographic characteristics are expected in the population of alcoholics in our area.

There was a statistically significant difference (Kruskal–Wallis 10.3, $p=0.02$) in the drinking behavioural characteristics among different types of alcoholics (Table 2). Type II alcoholics showed the lowest ($p<0.01$) pattern of alcohol intake (an average of 7.2 drinks/d) compared to Type IV (22.0 drinks/d), followed by Type III (12.1 drinks/d) and Type I (21.5 drinks/d).

MMSE

There was no statistically significant difference in the mean scores of MMSE among different types of alcoholics (Table 2). Except for Type IV alcoholics that showed a slightly lower mean MMSE score (22.6) than would normally be expected (Table 2), all other

Table 2. Baseline sociodemographic and drinking behavioural characteristics of different types of alcoholics classified according to Lesch's typology

	Lesch Type				Total alcoholics
	I	II	III	IV	
N (%)	16 (32.6)	7 (14.3)	4 (28.6)	12 (24.5)	49 (100)
Demographic variables					
Gender, *n* (%)					
Male	16 (100)	7 (100)	12 (85.7)	10 (83.3)	45 (91.8)
Female	–	–	2 (14.3)	2 (16.7)	4 (8.2)
Age, mean (S.D.), range	48.8 (10.7)	50.1 (8.4)	49.7 (7.1)	46.8 (9.4)	48.8 (8.9)
	29–72	37–65	36–64	27–62	27–72
Education (%)					
Elementary school	85.7	100.0	83.3	90.0	
High school	7.1	–	16.7	10.0	
Higher education	7.1	–	–	–	
Measurements of alcohol drinking behaviour					
Age at onset of alcohol use, mean (S.D.)	14.9 (4.6)	19.0 (5.4)	16.0 (3.3)	15.5 (5.4)	15.8 (4.6)
Alcohol used (drinks/d), mean (S.D.)	21.5 (20.6)	7.2 (2.6)	12.1 (8.0)	22.0 (19.3)*	17.4 (16.8)
MMSE, mean score (S.D.)	25.9 (3.5)	26.3 (1.4)	27.3 (2.7)	22.6 (6.6)	25.5 (4.4)
FAB, mean score (S.D.)	13.4 (2.4)	14.7 (2.2)	12.2 (3.3)	11.8 (3.7)*	12.8 (3.1)

MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery (comprised of scores obtained at the beginning of all experimental sessions).
* $p < 0.05$ compared to Lesch II (Dunn's multiple comparison test following Kruskal–Wallis test).

Table 3. Frontal assessment battery (FAB) scores obtained in alcoholics (total sample or classified according to Lesch's typology) before and after transcranial direct current stimulation (tDCS) or sham procedure

FAB	Lesch Type				Total
Median (25–75 IQR)	I	II	III	IV	alcoholics
N	14–16	6–7	12–13	12	44–48
Before sham	13.0 (11.8–15.0)	14.5 (13.5–16.3)	11.5 (9.0–13.8)	13.0 (7.8–14.8)	13.0 (10.3–15.0)
After sham	13.5 (12.5–15.3)	15.5 (14.0–17.3)	12.5 (10.3–14.8)	12.5 (8.8–15.0)	14.0 (11.0–15.0)
Before tDCS	14.0 (12.0–16.0)	15.0 (12.0–17.0)	13.0 (11.0–16.0)	12.5 (9.0–14.8)	14.0 (11.0–15.7)
After tDCS	15.0 (13.0–17.0)	15.0 (13.0–17.0)	15.0 (11.0–16.0)	14.0 (10.5–14.8)	14.0 (12.0–16.0)

IQR, Interquartile range.

types of alcoholics showed mean scores into or even above the range (e.g. Type III) according to age and educational level (Crum *et al.* 1993).

FAB

FAB scores obtained in the different types of alcoholics are shown in Table 3. Type IV alcoholics showed lower ($p < 0.05$) FAB scores compared to Type II.

Although we were interested in the results according to the Lesch subtypes, we conducted a global analysis (with all groups together) and found no significant differences between sham and active tDCS (Fig. 3*a*). We then compared the overall improvement by comparing the two groups of treatment (sham *vs.* active) in each of the four Lesch groups separately. χ^2 analysis showed a significant improvement of FAB scores after active tDCS compared to sham procedure ($p = 0.038$) for the Lesch IV group only (Fig. 3*b*, bottom). In the other three groups active tDCS was not associated with a beneficial improvement compared to sham tDCS (Fig. 3*b*).

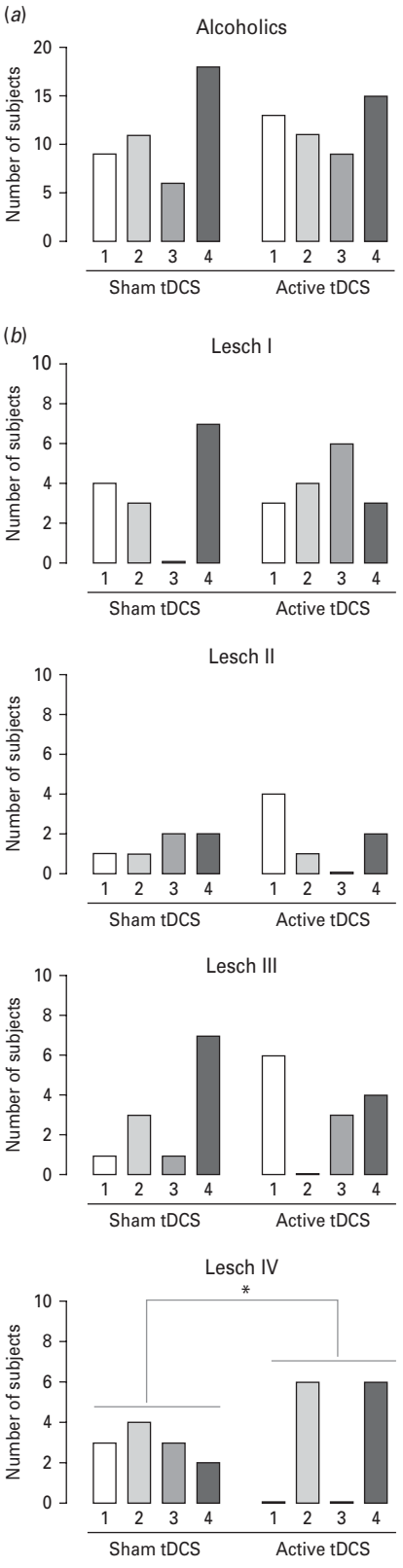

Fig. 3. (*a*) Percentage of changes (1, worsening; 2, no change; 3, small improvement; 4, improvement) of FAB performance under experimental sessions with sham tDCS or active tDCS stimulation (1 mA, 35 cm², 10 min duration) over the left dorsolateral prefrontal cortex in the total sample of alcoholics ($n=49$), and (*b*) separately in different types of alcoholics according to Lesch's typology: Type IV ($n=12$), Types I ($n=16$), II ($n=7$) and III ($n=14$). * $p<0.04$ compared to sham tDCS.

Table 4. Mean (S.D.) scores obtained in five items (1, 2, 4, 5, 13) related to craving in the Obsessive Compulsive Drinking Scale of alcoholics (total sample or classified according to Lesch's typology) before and after transcranial direct current stimulation (tDCS) or sham procedure

	Lesch Type			
OCDS	I	II	III	IV
N	10–12	5	10–11	6
Before sham	3.8 (4.7)	2.2 (1.8)	10.1 (4.9)	7.8 (5.5)
After sham	3.6 (4.3)	2.2 (3.0)	9.8 (4.3)	7.5 (5.4)
Before tDCS	6.0 (4.7)	2.6 (3.6)	9.5 (4.6)	6.0 (5.0)
After tDCS	5.8 (5.0)	2.2 (3.0)	9.4 (5.0)	6.5 (6.3)

OCDS

There was no statistically significant difference between scores obtained in the five OCDS items related to craving obtained at the beginning and the end of each experimental sham or active tDCS session (Table 4) considering those subjects that were evaluated by this instrument.

ERPs – P3

As expected, P3 waveform was not very well characterized in most of our subjects (Fig. 4), especially after the presentation of alcohol-related sounds (Fig. 4*a*). Thus, the segment where it would most likely be seen, i.e. 250–400 ms was considered in all analyses. Using this segment, we found no statistically significant differences when comparing the mean latency across different types of alcoholics and among all conditions.

The analysis of all patients (all four subgroups together) is shown in Fig. 5. After alcohol-related sounds were presented (Fig. 5*a*, left), the mean amplitude during or after either sham or active tDCS was seen to be significantly increased ($p<0.001$) compared to pre-stimulation in Fz (Fig. 5*a*, left).

The magnitude of the P3 effect under the presentation of alcohol-related sounds at the Fz site showed that the difference of the mean amplitude during *vs.* before active stimulation (Fig. 5*b*, top) was significantly

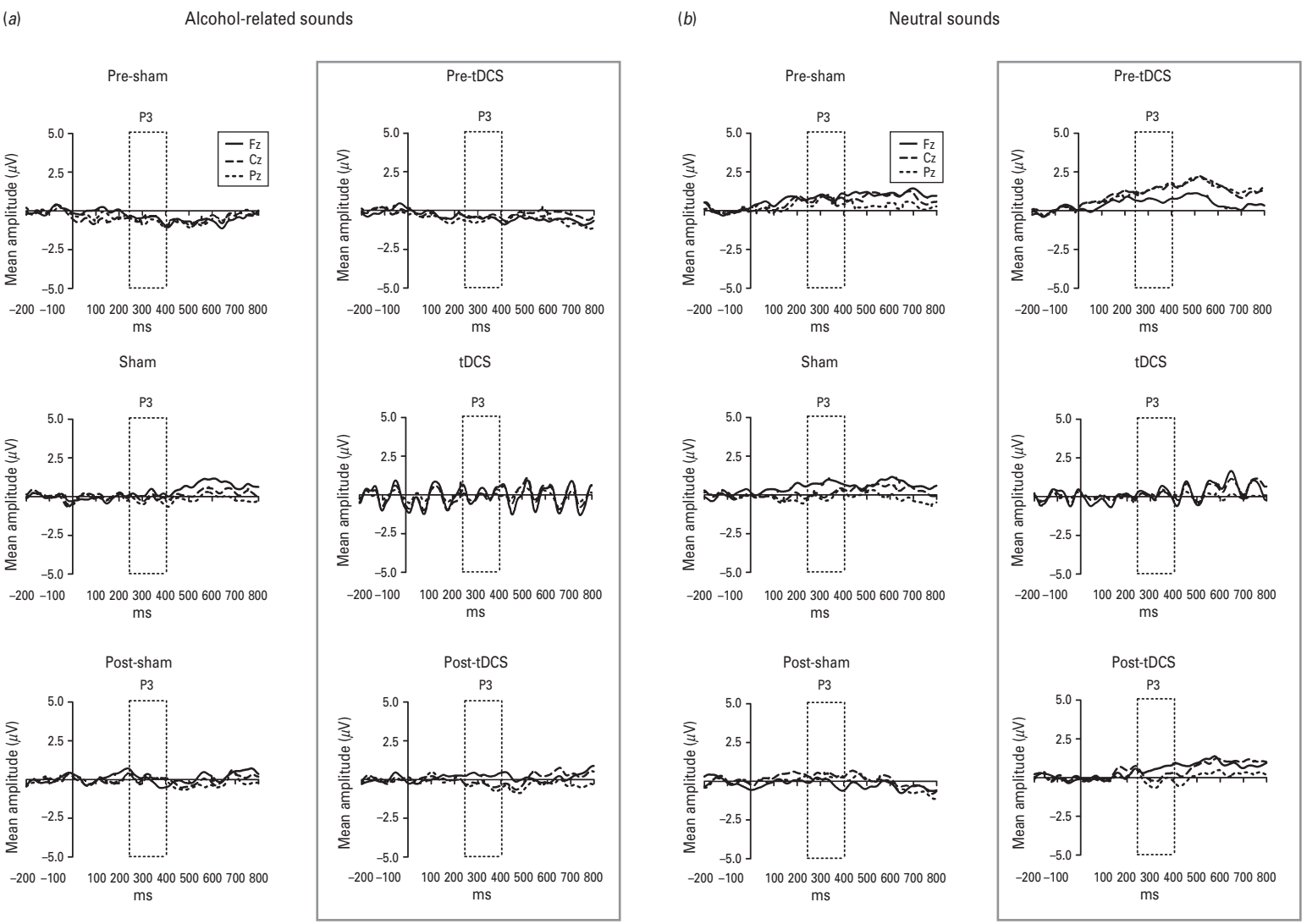

Fig. 4. Grand averages obtained in the event-related potential registered in alcoholics (total sample) in three sites [frontal (Fz), central (Cz), parietal (Pz)] under random presentation of (*a*) three sounds related to alcohol drinking ('opening of a beer can', 'filling a beer glass' and 'opening a beer bottle with the fall of the lid') and (*b*) three neutral sounds ('opening a door', 'typewriting with a keyboard' and 'rushing of a shower'), before (pre), during or after (post) transcranial direct current stimulation (tDCS, 1 mA, 35 cm², 10 min duration) (depicted boxes) or sham procedure in alcoholics. P3 = segment between 250 and 400 ms.

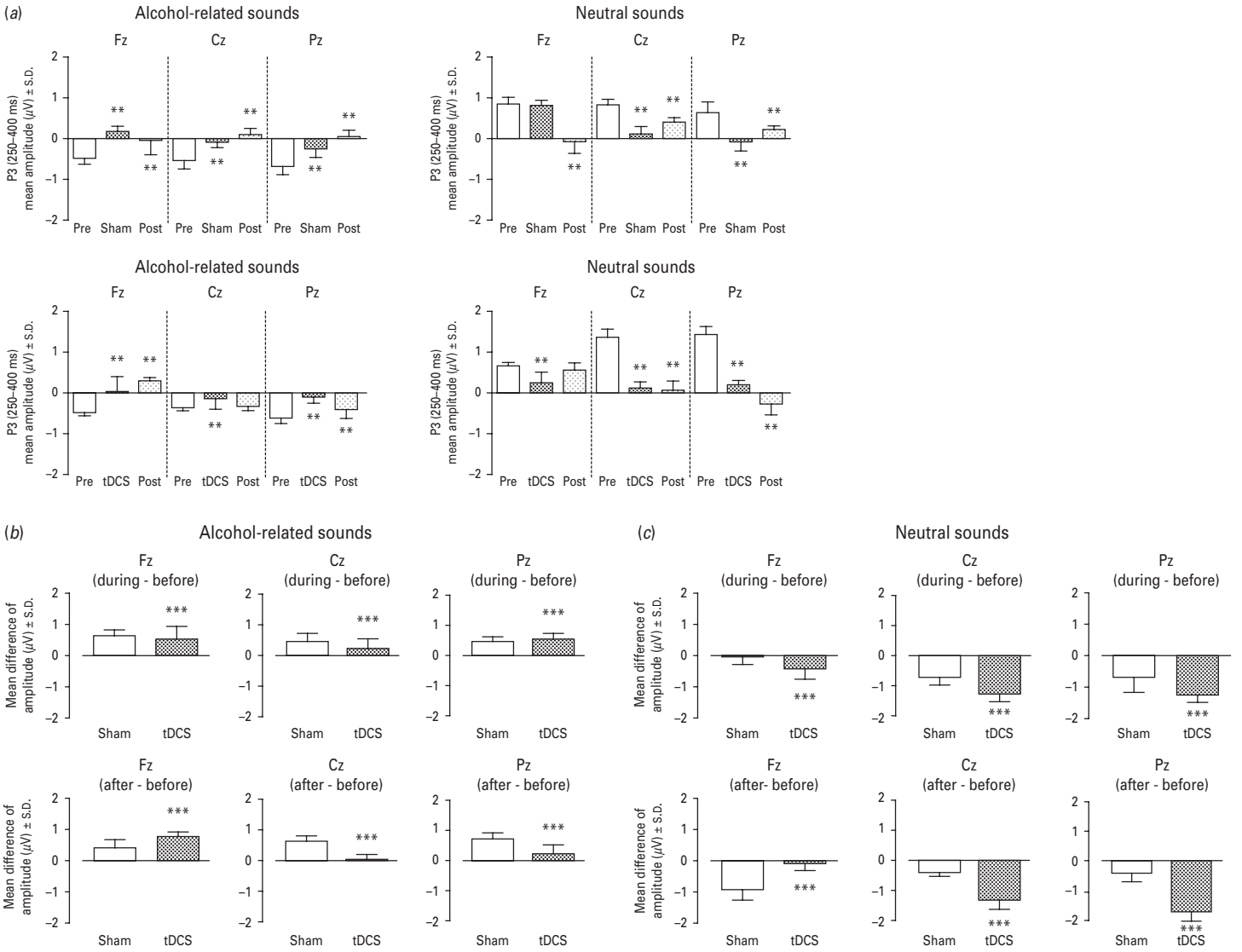

Fig. 5. (*a*) Mean amplitude (μV) $\pm$S.D. of the segment between 250 and 400 ms (P3) under presentation of sounds related to alcohol drinking or neutral sounds before (pre), during or after (post) transcranial direct current stimulation (tDCS) or sham procedure in alcoholics ($n = 48$). Panels (*b*) and (*c*) show the mean difference of amplitude obtained during (upper) or after (bottom) sham or tDCS from that obtained before these procedures during alcohol-related or neutral-sounds presentation, respectively. (*a*) ** $p < 0.001$ compared to pre (Friedman test followed by Dunn's multiple comparison test); (*b*, *c*) *** $p < 0.0001$ compared to sham (Wilcoxon signed rank test).

smaller ($p<0.0001$) compared to this difference under the sham procedure; whereas when comparing the difference of the mean amplitude after *vs*. before stimulation (Fig. 5*b*, bottom), the active tDCS induced a larger increase ($p<0.0001$) in the P3 mean amplitude compared to sham procedure. One important issue here is that during tDCS application, P3 mean amplitude was reduced but it was significantly increased after the end of active brain stimulation, suggesting a greater after-effect of tDCS on P3 mean amplitude at the Fz site.

The increase in P3 mean amplitude in Fz (after *vs*. before stimulation) when comparing active *vs*. sham tDCS was not observed in Cz and Pz as there was an opposite effect in these two sites (Fig. 5*b*, bottom: middle and right), i.e. a relative decrease in P3 mean amplitude in active tDCS compared to sham ($p<0.0001$). It was also decreased at the Cz site regarding the difference during *vs*. before stimulation compared to sham ($p<0.0001$) but increased at the Pz site ($p<0.0001$) (Fig. 5*b*, top: middle and right).

For neutral sounds (Fig. 5*a*, right) there also were statistically significant differences among mean amplitudes in the sham and active tDCS groups when comparing after *vs*. before, and during *vs*. before stimulation ($p<0.0001$) at all sites. The mean amplitude after sham was decreased ($p<0.001$) compared to pre-sham (Fig. 5*a*, top: right) and during tDCS ($p<0.001$) compared to the pre-tDCS registers in Fz (Fig. 5*a*, bottom: right). At the Cz and Pz sites the mean amplitude after sham or post-sham and tDCS or post-tDCS was also decreased ($p<0.001$) compared to pre-sham and pre-tDCS, respectively (Fig. 5*a*, right).

Considering the magnitude of these effects (Fig. 5*c*), a larger decrease in P3 amplitude after active tDCS was seen in most of the comparisons of the differences during *vs*. before ($p<0.0001$) and after *vs*. before ($p<0.0001$) compared to the differences found after sham procedure; except for the difference for after *vs*. before active tDCS that was smaller ($p<0.0001$) compared to the difference for sham procedure at the Fz site (Fig. 5*c*, left: bottom). It should be underscored that during tDCS application a downwards effect in the mean amplitude for neutral sounds was observed at the Fz site, and this effect appeared not to last immediately after the end of the stimulation, and was smaller compared to sham. Therefore, differently from alcohol-related sounds, there was no significant after-effects of tDCS on the P3 mean amplitude after neutral-sounds presentation.

In summary, results including the four Lesch groups show that there was a site-specific change (in Fz) in P3 mean amplitude after tDCS compared to sham procedure for the entire group of alcoholics. During its application, tDCS decreased the P3 mean amplitude for alcohol-related and non-related (neutral) sounds. However, after the end of tDCS application, the P3 mean amplitude was significantly increased for alcohol-related sounds and was not changed for neutral sounds.

In an analysis comparing the most discrepant alcoholic groups that differed in FAB baseline score, i.e. Lesch types II and IV, there were different patterns in ERPs under alcohol-related sounds presentation (Fig. 6*a*, *b*, respectively).

The magnitude of the differences of mean amplitude during (Fig. 6*c*) or after (Fig. 6*d*) and before tDCS changed in opposite directions in Types II and IV alcoholics compared to sham at the Fz site. The during *vs*. before stimulation difference showed that in Type II alcoholics tDCS decreased ($p<0.0001$) (Fig. 6*c*, top: left) whereas in Type IV alcoholics it increased ($p<0.0001$) (Fig. 6*c*, bottom: left) the mean P3 amplitude compared to this difference under sham procedure. These opposite effects were maintained in the comparison of differences before *vs*. after stimulation ($p<0.0001$) (Fig. 6*d*, left).

Except for Cz in Lesch II (Fig. 6*c*, *d*, top: middle), all other comparisons of the differences of P3 mean amplitude during *vs*. before or after *vs*. before stimulation at the Pz site were significantly ($p<0.0001$) decreased in Lesch II (Fig. 6*c*, *d*, top: right) and increased at the Cz and Pz sites in Lesch IV (Fig. 6*c*, *d*, bottom).

Therefore, Lesch II and IV alcoholics presented different patterns of brain activity changes induced by tDCS.

Discussion

Our findings show that tDCS induces specific clinical and electrophysiological (as indexed by P3) effects in patients with alcohol dependence. Anodal active tDCS of DLPFC compared to sham procedure was associated with executive perfomance improvement as indexed by FAB scores, especially observed in Lesch IV alcoholics.

Although group analysis showed an increase in P3 amplitude in Fz after active tDCS only, in Lesch IV alcoholics, this effect was more pronounced and also observed in other sites such as Cz and Pz. For the other groups, such as Lesch II, that did not show any clinical change, electrophysiological changes presented a contrary direction: a reduction of P3 amplitude.

The first important finding was the cognitive improvement induced by tDCS in Lesch IV alcoholics. As

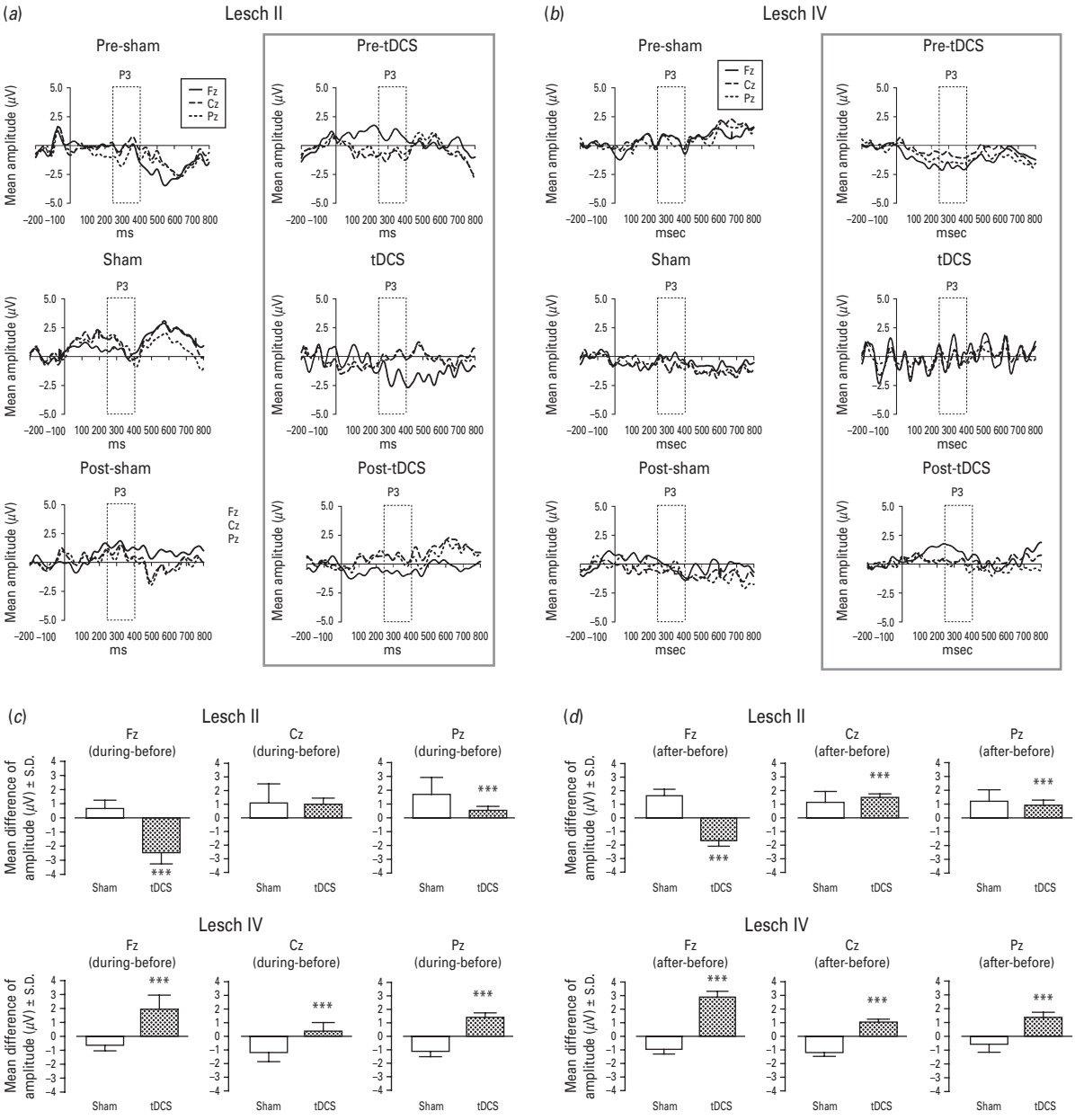

Fig. 6. Grand averages obtained in the event-related potential registered in three sites [frontal (Fz), central (Cz), parietal (Pz)] under presentation of sounds related to alcohol drinking before (pre), during or after (post) transcranial direct current stimulation (tDCS) (depicted boxes) or sham procedure in (*a*) Lesch's Type II or (*b*) Type IV alcoholics. P3 = segment between 250 and 400 ms. The mean difference of amplitude obtained (*c*) during or (*d*) after sham, or tDCS from that obtained before these procedures during presentation of alcohol-related sounds. *** $p < 0.0001$ compared to sham (Wilcoxon signed rank test).

shown in our previous study, the general analysis of frontal function by FAB shows that most alcoholic patients have lower scores compared to non-alcoholic subjects (Zago-Gomes & Nakamura-Palacios, 2009).

Electrophysiological studies confirm these findings as alcoholic subjects have reduced P3 amplitudes in the cingulate, medial, and superior frontal regions compared to controls (Chen *et al.* 2007). This pattern of decreased frontal lobe activity among alcoholics is clearly evident in Type IV alcoholics as also shown by FAB baseline scores in this group. Type IV alcoholics are those patients with disturbance or cerebral damage before the conclusion of brain development (Walter *et al.* 2006). Therefore it is conceivable that this group of patients present more profound changes in executive control-related neural networks. In this context,

the relative depolarization induced by tDCS in the DLPFC with a subsequent increase in spontaneous neuronal activity (Bindman *et al*. 1964*a*, *b*) can probably restore some of the normal activity in this functionally (and potentially anatomically) damaged area.

There are several studies showing that anodal tDCS is associated with frontal-related cognitive enhancement in healthy subjects (Fregni *et al.* 2005; Iyer *et al.* 2005; Kincses *et al.* 2004; Marshall *et al.* 2006) and in patients with neurological disorders, i.e. Parkinson's disease (PD) (Boggio *et al.* 2006). Indeed, PD is a condition also associated with a significant frontal dysfunction due to dopaminergic-related cortical activity decrease (McNamara & Durso, 2006). A previous study showed that anodal tDCS of DLPFC (same target as this study) in PD is associated with a significant improvement in working memory as indexed by task accuracy in a three-back task compared to sham tDCS (Boggio *et al.* 2006). Here, we show that the cognitive beneficial effects of tDCS are observed in another population (alcoholics) with reduced frontal activity.

Keeser *et al.* (2011) have found that a significant improvement in the accuracy of a non-verbal two-back task in healthy subjects 20–40 min after tDCS application over the left DLPFC was accompanied by increased P2 and P3 ERP component-amplitudes at the Fz electrode compared to sham tDCS and also to baseline.

Regarding brain activation under weak anodal tDCS, using the same parameters as ours (1 mA for 10 min) Merzagora *et al.* (2010) observed that tDCS over frontal area produced a local increase of the concentration of HbO_2, measured by functional near-infrared spectroscopy (fNIRS), in the underlying brain tissue that lasted for 8–10 min, with a peak effect at 6 min, after the end of the stimulation.

Our study shows not only tDCS-induced clinical improvements but also electrophysiological evidence of enhancement of neural processing in frontal areas as indexed by an increase in P3 amplitude in Fz that was more pronounced in Lesch IV alcoholics, especially in ERP registration around 6 min after the end of the stimulation.

Studies have shown a decrease of P3 amplitude in patients with alcoholism. For instance, in a study with 57 subjects with alcohol dependence, the authors showed that alcoholic subjects have decreased P3 amplitude to a visual oddball task compared to controls and that this decrease is related to frontal dysfuction as indexed by impulsiveness (Chen *et al.* 2007). Furthermore, a previous study comparing patients with frontal lesion, subcortical lesion, alcohol use and healthy controls found a reduction in P3 amplitude in the frontal lesion group and a trend for the alcohol-dependent group (George *et al.* 2004).

These findings give additional support to our results as patients with brain lesions and alcohol use – as characterized in Lesch IV – have more changes in frontal lobe activity and therefore anodal tDCS in this scenario can revert this dysfunctional frontal lobe pattern; resulting in clinical frontal lobe improvement as indexed by FAB.

tDCS effects can be explained by a change in the resting membrane threshold. Anodal tDCS leads to a local depolarization which facilitates neuronal spontaneous firing (Bindman *et al.* 1964*b*). This local increase in the likelihood of action potentials enhances stimuli processing such as those presented in this study (auditory stimuli). The enhancement of frontal processing as indexed by P3 is parallel to frontal clinical changes. In this context tDCS might be a better tool to restore activity and promote plasticity in this area as this technique induces widespread changes in cortical excitability facilitating neural processing in this area.

This facilitatory neural processing may have induced changes on the processing of alcohol-related cues, because of the difference of tDCS effects on ERPs under the presentation of alcohol-related sounds compared to neutral sounds, indexed by an increased P3 mean amplitude especially in post-stimulation ERP recording. One hypothesis to explain this finding is that, by changing cortical excitability, tDCS may have facilitated the processes that have been previously repeatedly exposed such as processing of alcohol-related cues.

The P3 or P300 component of ERPs is thought to index the operation of attention and memory processes engaged during stimulus processing (Polich, 2004, 2007). This component is classically elicited using the oddball paradigm, when two stimuli are presented in a random order. However, this component has also been elicited by different paradigms such as go/no-go tasks, delayed tasks, n-back tasks, with or without a motor response (Heinze *et al.* 2007; Keeser *et al.* 2011; Wang *et al.* 1999), suggesting that P3 may index the recognition of critical events disregarding the manner in which stimuli are presented. By facilitating the recognition of alcohol-related cues, tDCS over DLPFC may help alcoholic patients to better follow the instructions of cognitive behavioural approaches.

Besides showing in this study that an increase in frontal processing induced by tDCS as indexed by P3 amplitude leads to clinical cognitive gains, an important question is whether this tool might also

be beneficial for craving control. Although craving modulation was not the main aim of this study, we also measured craving using the OCDS. We found no significant changes in craving as indexed by this scale.

A potential reason to explain the differences compared to Boggio *et al.*'s (2008) study is the difference in design in Boggio's study, as in that study, craving was provoked with alcohol-related visual cues – this design is more powerful and sensitive to detect potential differences in craving with a given intervention such as tDCS.

However, based on current results, it is conceivable that an improvement of frontal processing could inhibit some of the processes associated with craving and alcohol abuse. In fact loss of drug-abuse behaviour control is one of the main characteristics of addiction. The loss of inhibitory control of frontal brain regions is probably critically involved with this behaviour. In a study comparing neural responses of cocaine abusers watching a cocaine-cue video with and without instructions to cognitively inhibit craving, authors showed that when subjects were inhibiting craving using cognitive instructions, there was a significant limbic inhibition (accumbens, orbitofrontal, insula, cingulate) (Volkow *et al.* 2002); suggesting that strengthening of frontal lobe function might be beneficial in this case. Future studies should administer tDCS over additional sessions in order to increase its effects as shown previously (Boggio *et al.* 2008) and perhaps combine with cognitive training.

This study has potential limitations that need to be entertained. First, the lack of significant clinical changes in the other Lesch groups might be due to lack of power. Although we included 49 subjects in this study, the four subgroups had a smaller number of subjects. Another potential reason to explain the lack of significant clinical effects for the other subgroups is that we only applied one session of stimulation and it has been shown that multiple consecutive sessions of tDCS might have a greater clinical impact (Fregni *et al.* 2006*a*).

Another potential limitation in this study is the different amount of alcohol use among the four groups. Although some random differences in alcohol use among Lesch groups is expected – as we showed in our last study (Zago-Gomes & Nakamura-Palacios, 2009), it is possible that lack of effects in Lesch II is because of a ceiling effect as their baseline was better. Although we did not see significant variability in the individuals from this group to suggest that patients with heavier use of alcohol responded better to tDCS.

A further limitation is that we did not find a significant correlation between P3 increase and FAB improvement in the Lesch IV group. One potential explanation is lack of power as this group had only 12 patients. In addition, it should be considered that the event to induce P3 was different than the stimuli used to assess FAB scores.

Finally, some of our results need to be viewed as exploratory as our main aim was to find a change in P3 and frontal-related cognitive function in the full group (all Lesch types together); and we also found a specific significant change for Lesch IV alcoholics. Although there is a biological rationale to expect large effects in Lesch IV group, these results should be interpreted with caution and confirmed in subsequent studies due to the exploratory nature of this specific analysis. Moreover, in our study, the categorization of FAB scores might not reflect optimal clinical significance. Therefore FAB results need also be interpreted with this caveat.

To our knowledge this is the first study assessing the cognitive impact of tDCS on frontal function in alcoholism as indexed by clinical and electrophysiological instruments of evaluation. In this study we showed convincing evidence that tDCS of DLPFC can change neural frontal processing; resulting in an improvement in cognitive function. This study therefore encourages future investigation using more optimized protocols of tDCS such as multiple sessions of tDCS in addition to extending this investigation, also using other methods to assess neural activity including methods with better spatial resolution, employing other cognitive stimuli, and, lastly, investigating tDCS effects on other neuropsychiatric disorders associated with frontal lobe dysfunction and other addictions.

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Statement of Interest

None.

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