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Transcranial direct current stimulation combined with alcohol cue inhibitory control training reduces the risk of early alcohol relapse: A randomized placebo-controlled clinical trial

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ABSTRACT

Background: Approximately half of all people with alcohol use disorder (AUD) relapse into alcohol reuse in the next few weeks after a withdrawal treatment. Brain stimulation and cognitive training represent recent forms of complementary interventions in the context of AUD.
Objective: To evaluate the clinical efficacy of five sessions of 2 mA bilateral transcranial direct current stimulation (tDCS) for 20 min over the dorsolateral prefrontal cortex (DLPFC) (left cathodal/right anodal) combined with alcohol cue inhibitory control training (ICT) as part of rehabilitation. The secondary outcomes were executive functioning (e.g. response inhibition) and craving intensity, two mechanisms strongly related to abstinence.
Methods: A randomized clinical trial with patients (n = 125) with severe AUD at a withdrawal treatment unit. Each patient was randomly assigned to one of four conditions, in a 2 [verum vs. sham tDCS] x 2 [alcohol cue vs. neutral ICT] factorial design. The main outcome of treatment was the abstinence rate after two weeks or more (up to one year).
Results: Verum tDCS improved the abstinence rate at the 2-week follow-up compared to the sham condition, independently of the training condition (79.7% [95% CI = 69.8–89.6] vs. 60.7% [95% CI = 48.3–73.1]; p = .02). A priori contrasts analyses revealed higher abstinence rates for the verum tDCS associated with alcohol cue ICT (86.1% [31/36; 95% CI = 74.6–97.6]) than for the other three conditions (64% [57/89; 95% CI = 54–74]). These positive clinical effects on abstinence did not persist beyond two weeks after the intervention. Neither the reduction of craving nor the improvement in executive control resulted specifically from prefrontal-tDCS and ICT.
Conclusions: AUD patients who received tDCS applied to DLPFC showed a significantly higher abstinence rate during the weeks following rehabilitation. When combined with alcohol specific ICT, brain stimulation may provide better clinical outcomes.
Trial Registration: ClinicalTrials.gov number NCT03447054 https://clinicaltrials.gov/ct2/show/NCT03447054.

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1. Introduction

With around 283 million people aged 15 years and older facing serious problems related to alcohol use, alcohol use disorder (AUD) continues to represent a huge public health problem around the world [1]. In the most severe cases (which require physical follow-up), patients with severe AUD require hospital weaning assisted by medication [2]. However, a large majority of these patients, even if properly detoxified, are at risk of relapse within weeks of hospital discharge [3–5].

Considered by several neurocognitive models [6–9] and clinical theories [10,11] as a problem of self-control, persistent alcohol consumption can be understood as a profound disruption in the decision process [8,9,12,13]. Indeed, according to a dual-process model, addictive behaviors such as AUD are the consequence of the imbalance between two neurocognitive systems: an overactive *impulsive system* and an impaired *reflective system* [8,9,14–16]. An overactive impulsive system, largely amygdala-striatum dependent, reflects sensitized automatic processes operating with little intention, awareness, and effort that prompts people to engage in compulsive behaviors, whereas the reflective system, mainly prefrontal cortex dependent, is responsible for modulating (e.g., inhibition) spontaneous responses. Automatic or poorly controllable processes include cognitive biases (e.g. biased attention processing toward addiction-related cues) [15,16]. Conversely, habits and impulsive behaviors characterizing AUD cannot be brought under sufficient control by supervisory processes due to compromised executive functions [17,18]. The consequence might be a difficulty to inhibit alcohol-related prepotent responses [19], which enhances craving and the likelihood of relapse [18,20].

Coherently, the dual-process neurocognitive model of behavior and choice [21,22] applied to addiction [8,15,16,23] has led to the idea that, to be effective, a clinical intervention should modify not only deliberative processes (e.g., mental shifting, inhibitory control) but also automatic responses generated by conditioned stimuli (e.g., alcohol-related cues). The present clinical trial has endorsed this theoretical framework of addiction using brain stimulation and cognitive training to target relevant automatic and deliberate neurocognitive mechanisms in patients with AUD with the goal of improving their clinical trajectories.

Several non-invasive neuromodulatory techniques have demonstrated promising cognitive and clinical effects in the treatment of substance use disorder (e.g. Refs. [24–27]). As a painless, and well-tolerated brain stimulation technique that applies a weak direct current through surface electrodes of the scalp, transcranial direct current stimulation (tDCS) is increasingly used for the treatment of substance-use disorder [24,28]. Depending on the stimulation (i.e., anodal or cathodal), cortical excitability induces LTP-like plasticity via subthreshold neural depolarization or LTD-like plasticity via hyperpolarization, respectively [29,30]. Due to its involvement in addictive behaviors, the dorsolateral region of the prefrontal cortex (DLPFC) has been the primary target of tDCS interventions in AUD with the aim of rebalancing some of the neurocognitive processes described above [24,31–34]. Indeed, DLPFC is involved in spontaneous and cue-elicited craving, executive functioning, and the reward areas (the nucleus accumbens and ventral tegmental area) through corticostriatal loops [24,35]. Studies of addictive behaviors using tDCS with the aim to increase neural firing of the DLPFC in both of left [36–38] and right cerebral hemispheres [39] reported important clinical outcomes possibly associated with the enhancement of impulse control [40]. These outcomes were an overall better perception of quality of life [32,41], reduced craving [25,27,31,42–44], enhanced executive control [45] and a decrease in substance use [32,46–49]. Regarding alcohol relapse, tDCS (left cathodal/right anodal DLPFC) reduces the risk of relapse during the six months following two 13-min sessions per day during five consecutive days [39] at three-month follow-up, and 10 daily sessions of 20 min at six months post-discharge [31]. Regarding the causal relationship between the positive effect of tDCS on executive functioning and relapse, the results are mixed, which prevents the draw of any robust conclusions [26]. Additionally, five sessions of prefrontal tDCS administered to participants with AUD increase the functional connectivity of subnetwork involving prefrontal regions (e.g., right anterior cingulate gyrus), a phenomenon correlated with a reduction in the likelihood of relapse and impulsivity [46].

As recently suggested, one way to increase the effectiveness of brain stimulation is to combine tDCS with psychological interventions (e.g., cognitive training, psychotherapy) [50]. There are several reasons for promoting combined interventions for the treatment of addictive behaviors. First, psychological interventions (e.g., cognitive training) and neuromodulation could positively impact on distinct mechanisms in addictive behaviors [51]. Regarding cognitive training, several behavioral paradigms have been designed for clinical purposes [52,53]. For example, a training multisession consisting of moving the image of alcohol away (by pushing a joystick) was shown to reduce alcohol use and relapse in patients with a severe AUD [5,54]. However, a limitation of this paradigm is that the mechanisms of action involved in behavior change remain largely unknown [5]. Another example of behavioral intervention is an alcohol adaptation of Inhibitory Control Training (ICT), which involves training participants to respond (i.e., press a key) to neutral stimuli and withdraw their response when alcohol-related content is displayed [55]. A single session of alcohol ICT led to a reduction in alcohol consumption ad libitum among heavy social drinkers in the laboratory, but this reduction was short-lived and easily abolished by a context shift [55–57], which explains why the clinical relevance of ICT used in monotherapy seems limited [58]. Regarding the mechanisms of action of ICT, systematically matching a No-Go response with a motivational content has the potential to improve top-down inhibitory control [59], devaluate motivational cues (i.e., to reduce its positive valence) [60,61], or reinforce automatic cue/stop associations (i.e., associative inhibition) [57,61].

It is expected that more robust clinical outcomes can be obtained by combining an alcohol version of ICT with tDCS targeting specific prefrontal regions (i.e., DLPFC). Indeed, while tDCS targeting DLPFC would reduce alcohol craving and enhance cognitive control, ICT has the potential to strengthen associative/automatic inhibition and to generate a devaluation of alcohol cues. Another, but not incompatible, reason supporting the superiority of the combined intervention over monotherapy refers to the idea that the effects of tDCS may be mainly state-dependent; in other words, there is an interaction between external stimuli and the underlying state of the stimulated region or network [62]. In the same vein, we refer to the “activity-selectivity” hypothesis, which states that tDCS preferentially modulates active over inactive neural populations [63]. Consequently, tDCS and ICT in combination can be seen as an intervention promoting reduced craving or better control over it since they both engage neural prefrontal resources related to the reflective system. In sum, by modifying the suboptimal interaction between the strong alcohol-related response and the weakened control over this response, combining tDCS and an alcohol version of the ICT has the potential to protect people against alcohol relapse [8,15,16,23,64].

To improve the clinical trajectories of patients with AUD, we have combined a multisession alcohol cue ICT with stimulation of the DLPFC with tDCS. To date, only two clinical trials in patients with AUD have combined tDCS with cognitive alcohol bias modification, with little evidence of positive changes in the clinical

trajectory of patients with AUD during the year following the intervention [38,44,49]. However, both studies used different cognitive paradigms to our own study, which were not directly associated with inhibitory control (an approach bias retraining task in Ref. [49] and an attentional task in Ref. [44]). Moreover, it is important to follow and contribute to the effort to establish effective standardized parameters [40,65,66]. Indeed, past studies applied four sessions of tDCS with the anode located at F3 and the cathode at F4 with a low voltage (1 mA) [38], while recent recommendations pointed to an alternative montage (anode-F4 and cathode-F3 repeated for at least five sessions with a voltage of 2 mA during approximatively 20 min) for a better clinical efficacy [24,48,65]. It should be noted that craving reduction has been achieved in participants with AUD using both F3 anodal/F4 cathodal and the reverse montage [38,42].

By following this recommendation, we tested the hypothesis that the combination of tDCS (left cathodal/right anodal over the DLPFC) and alcohol cue ICT reduces more the risk of relapse in patients with severe AUD than other interventions using sham tDCS and neutral ICT. Although the vast majority of clinical trials in inpatients have focused on behavioral interventions and brain stimulation that reduce alcohol relapse after three months or more, a large proportion of patients relapse within a couple of weeks following discharge [3–5]. Therefore, we primary focused on early alcohol relapse, that is, two weeks after the discharge. We also investigated whether this reduction was still present several months after the end of the detoxification treatment (up to one year) and whether this clinical effect was mediated by several psychological mechanisms (i.e. cognitive control, craving, mood and cognitive bias).

2. Material and methods

2.1. Participants

The analyses were performed on 125 right-handed patients, 84 men and 41 women, with a mean age of 47 years (SD = 10). Patients were recruited while undergoing alcohol rehabilitation at the Brugmann University Hospital in Brussels, Belgium. Inclusion criteria included French-speakers between 18 and 65 years of age with severe AUD requiring alcohol rehabilitation, and the desire to stay sober for at least the first six months after detoxification. The exclusion criteria based on the International Neuropsychiatric Interview [67] included neurological history (epilepsy, head injury, and stroke), mental confusion or severe cognitive impairment, schizophrenia, chronic psychotic disorders, bipolar type 1 disorder, metal in the brain, and pregnancy. In addition, we excluded patients with a history of drug use other than alcohol. During hospitalization, abstinence was monitored using a breathalyzer during unannounced checks. Six patients who relapsed during rehabilitation were excluded from our analyses.

2.2. Design

The study was a single-blind (participants) and parallel 2 [verum vs. sham-tDCS] x 2 [alcohol cue vs. neutral ICT] full-factorial design. Patients were randomized (simple using a computer software program that generates the random sequence) to one of the four experimental conditions: (1) verum tDCS during Alcohol cue ICT (AICT); (2) verum tDCS and Neutral ICT (NICT); (3) sham tDCS and AICT; and (4) sham tDCS and NICT. Recruitment was conducted from January 2018 to March 2021. Fig. 1 depicts the screening and recruitment information.

The intervention consisted of five consecutive daily 20-min sessions of simultaneous combination of tDCS and ICT (Monday to Friday). Due to excitability, neuroplasticity, and day-dependent brain information processing parameters [68], the time of day for the intervention was evenly distributed among the groups. The ICT was started immediately after the tDCS was put in place and the instructions were correctly understood. At baseline (the Friday before the intervention) and after the intervention (the Monday after the intervention), the measurements of working memory, craving, response inhibition, verbal fluency of alcohol words and mood were recorded. The order of cognitive tasks was administered at random, followed by clinical assessment.

2.3. Transcranial direct current stimulation protocol

A bilateral direct current of 2 mA with a 30 s ramp-up and 30 s ramp-down was applied for 20 min on the DLFPC. This direct current was delivered with a 1x1 low intensity transcranial DC stimulator linked to two electrodes, with a surface sponge of 35 cm^2. The anode was placed over F4 (right DLFPC) and the cathode over F3 (left DLFPC), according to the 10–20 international system for electroencephalogram electrode placement (vertical placement). In the sham procedure, the electrodes were placed in the same positions but without stimulation, and only ramp-up and ramp-down were applied [69]. The intervention included five consecutive 20-min daily sessions that simultaneously combined tDCS and ICT.

2.4. Inhibitory control training protocol

Concurrently with tDCS, patients underwent alcohol cue or neutral ICT (AICT, NICT). In a modified version of a Go/No-Go task presented on a 15-inch laptop, participants were instructed to press a response key whenever a letter (P or R) was displayed in one of the four corners of the picture with a probability of .5, and to not respond when an alternative letter was displayed. The No-Go signal always matched the alcohol pictures, and the Go signal always matched the sports pictures. The neutral picture was associated with the Go signal, with a probability of .5. The session began with a 5-s countdown, after which a fixation cross appeared for 1500 ms–2500 ms at random, followed by an image appearing alone for 500 ms. The Go or No-Go signal was displayed in one of the four corners of the picture for 2000 ms. The task included five blocks of 64 trials: 32 Go and 32 No-Go; the same 32 images repeated twice for the AICT (eight alcohol, eight sport, and 16 neutral images), and the same 16 neutral images four times for the NICT. The participants had 2000 ms to give a response before receiving one of three possible feedbacks: “Too late,” “Correct,” or “False” (Fig. 2). The tasks, programmed with E-Prime 3.0, consisted of 360 trials and lasted between 15 and 20 min, depending on the reaction time of the patient (see Fig. 3).

2.5. Primary outcomes

All patients received a follow-up phone call based on the Timeline Follow-Back method [70] at two weeks and 1, 3, 6, and 12 months after discharge from the hospital. They were asked about their alcohol use (i.e., amount of alcohol consumption at various levels, average number of drinks per day consumed, and maximum number of drinks consumed each day) with relapse defined as consumption of 60 g of alcohol on any occasion, on a single day. It should be mentioned that all patients with AUD reported aiming to remain sober for a minimum of 6 months after rehabilitation. In addition, during the phone call, patients who reported consuming at least 60 g of alcohol also showed loss of control over alcohol as evidenced by a “no” response to “Did you intend to drink as much as you did?“. To increase the accuracy of the information, we contacted a person close to the patient via telephone (e.g., general

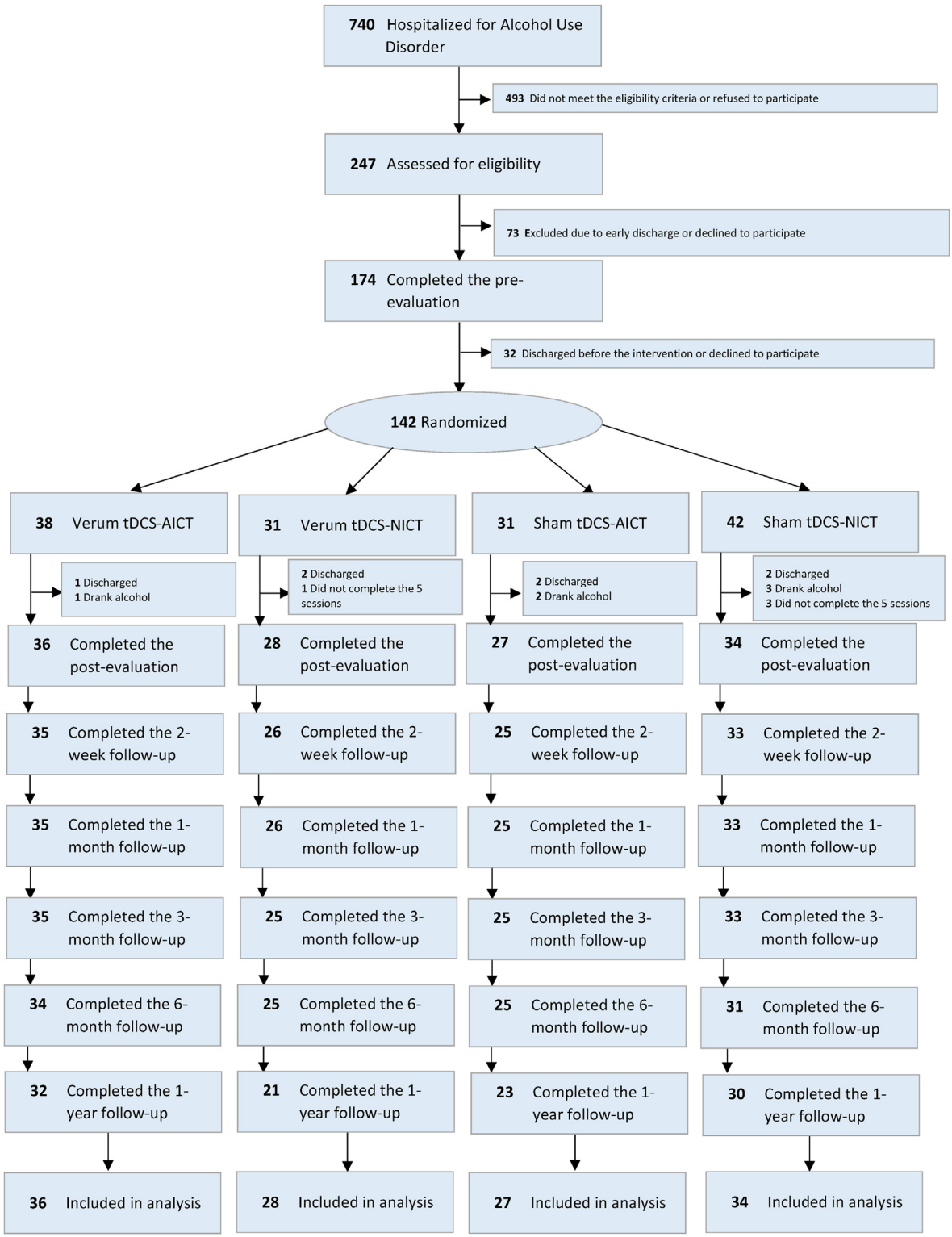

Fig. 1. Screening, recruitment, randomization, treatment completion, and follow-up completion dataAbbreviations
AICT, Alcohol cue Inhibitory Control Training; NICT, Neutral Inhibitory Control Training.

practitioner, family member) who fully confirmed that the return to alcohol use was associated with guilt, a phenomenon deemed to be due to violation of the personal goal of abstaining from alcohol. Finally, a certified clinical psychologist (Xavier Noël), blind to the type of intervention that the patients had received, oversaw contacting the patients during the follow-up period.

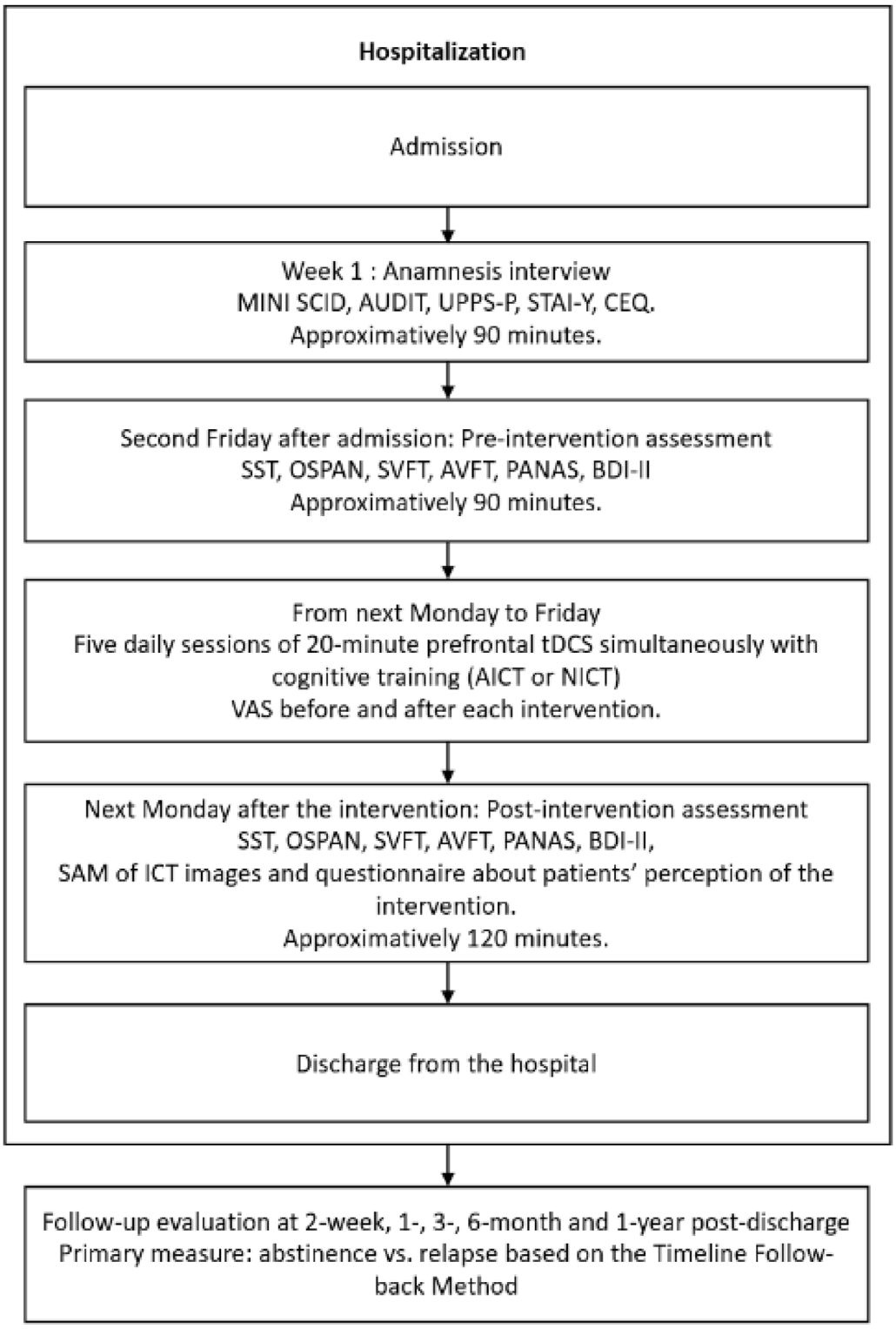

Fig. 2. Procedure details and timeline
Abbreviations: AICT, Alcohol cue Inhibitory Control Training; AVFT, Alcohol Verbal Fluency Task, BDI-II, Beck Depression Inventory II; CEQ, Craving Experience Questionnaire; NICT, Neutral Inhibitory Control Training; PANAS, Positive And Negative Affect Scale; SAM, Self-Assessment Manikin; STAI-Y, State-Trait Anxiety Inventory; SVFT, Semantic Verbal Fluency Task; UPPS-P
impulsivity scale (short version); VAS, Visual Analogic Scale.

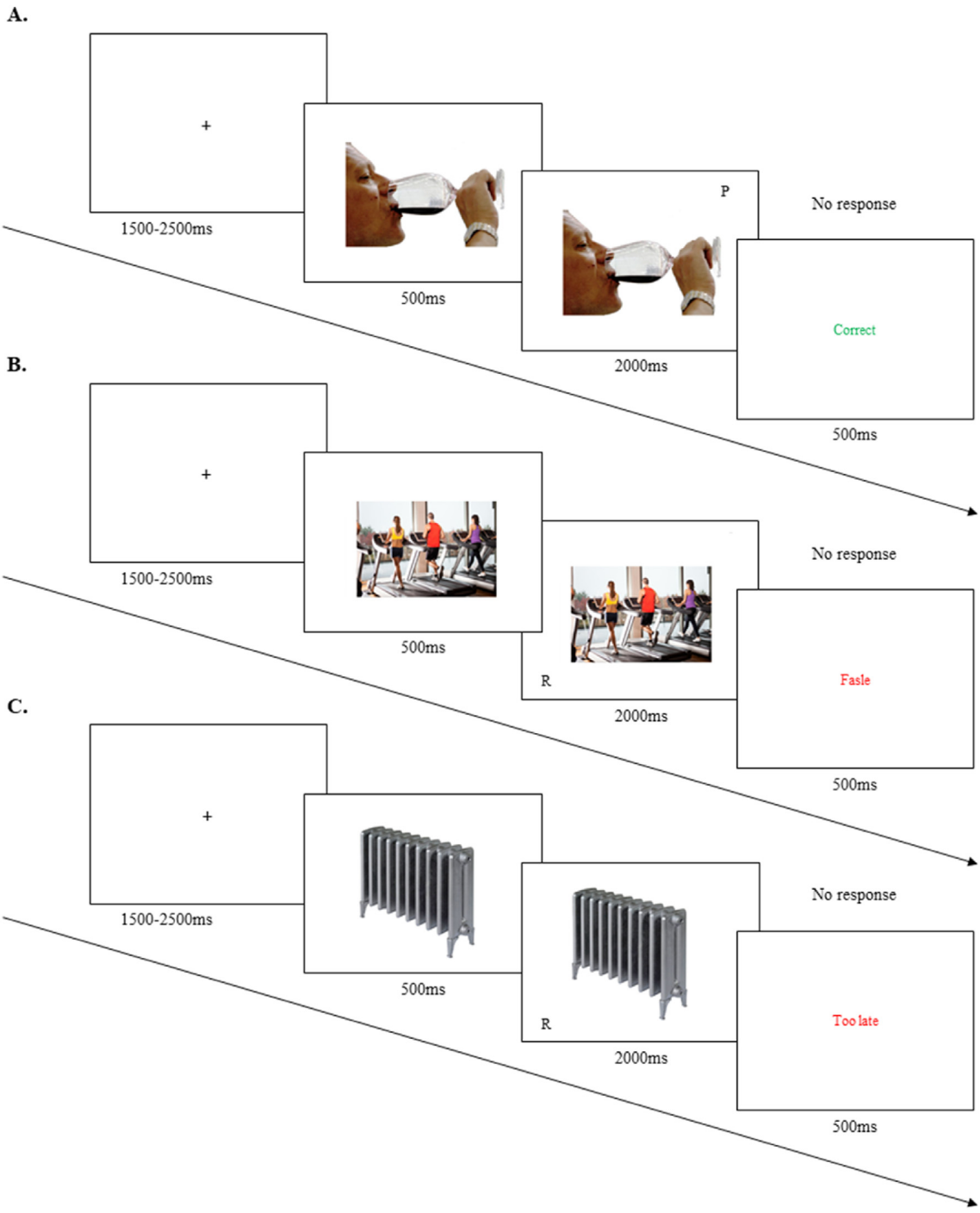

Fig. 3. Schematic representation of the trials in alcohol cue inhibitory control training
All trials had a fixation cross presented for a random duration of 1500–2500 ms, followed by A. An alcohol image followed by a No-Go signal; the patient does not press the space bar; and the feedback is "correct". B. A sport image followed by a Go signal; the patient does not press the space bar and the feedback is "False." C. A neutral image followed by a Go signal; the patient does not press the space bar and the feedback is "Too late".

2.6. Secondary outcomes

Secondary outcomes referred to the psychological mechanisms involved in reducing relapse into alcohol. We examined several parameters measuring executive control, mood and affect and positive/negative alcohol associations on two separate occasions (i.e., three days before and three days after the intervention). The craving for alcohol was measured immediately before and after each intervention by Visual Analogic Scales (VAS). See supplementary items for a description of the tasks and the descriptive (eMethods) and psychometric details of the questionnaires (eTable 1).

2.7. Clinical evaluation

The *Alcohol Use Disorder Identification Test (AUDIT)* [71] was used to score the severity of alcohol problems (range, 0–40). The *Craving Experience Questionnaire (CEQ)* [72] scored the intensity and frequency of craving in the previous week (range, 11–77). The *Impulsivity Behavior Scale (UPPS–P)* [73] assessed five facets of impulsivity (positive urgency, negative urgency, lack of premeditation, lack of perseverance, and sensation seeking; 20 items; range, 20–80). The *State-Trait Anxiety Inventory (STAI-Y)* [74] was also administered (both 20 items; range, 20–80).

The tasks used to evaluate the perception of the intervention by the patients and the self-assessment of ICT images are presented in supplementary items.

2.8. Statistical analyses

We powered the study for a clinically relevant 30% improvement (from 50% to 80%) in abstinence rates [39] by comparing the verum tDCS-AICT with the other three groups via a logistic regression with a deviation contrast. According to G*Power 3.1.9.2, a minimum of 115 subjects would be required to observe an association between conditions and the relapse rate with an abstinence probability of 50% under H0, 80% under H1, 80% power, 5% error rate, and 25% of the sample belonging in the verum tDCS-AICT condition.

The demographic variables and questionnaires at baseline were compared between the conditions by using one-way analysis of variance (ANOVA) and Pearson chi-square test. A binomial test was performed to compare the percentage of correct assumptions of being part of the verum tDCS intervention.

The binary outcome (relapse vs abstinence) was analyzed using logistic regressions with a priori contrasts. To test the effects of verum tDCS vs sham tDCS and AICT vs NICT on abstinence rate, we first used logistic regression with a simple orthogonal contrast evaluating the main tDCS effect (C1, verum vs. sham), the main ICT effect (C2, neutral vs. alcohol cue), and the interaction of these contrasts (C3) on the abstinence rate. Second, a deviation contrast was used to test the superiority of the verum tDCS-AICT condition effect on abstinence rate, as compared to all the other conditions. The exact matrices used are reported in Table 2.

Repeated and mixed ANOVAs (Conditions x Time) were performed to assess the main effect of the intervention on craving (VAS), depressive symptoms (BDI) and affect (PANAS), verbal fluencies (alcohol, sport, neutral), inhibition response (SSRT), and working memory (OSPAN). If the distribution of the scores showed a large deviation from normality, a nonparametric test was performed. For the within-subject effects, the related sample Wilcoxon was performed, and for the between-subject effects, the Mann-Whitney test was used. Nonparametric results were only reported if they differed from the ANOVA conclusion.

All analyses were performed with IBM SPSS statistics (v. 26), except for the logistic regressions, which were performed on R Studio (v. April 1, 1103). The threshold for significant effect was $p < .05$. All p-values were corrected according to the Holm correction method.

In supplementary items, we reported the results on the relapse rate at 1, 3, 6 months and 1 year after discharge (eFigure 1 and eTable 2), VAS at each time point (eFigure 2), ICT data analyses (eFigures 3–4, eTables 3–5), self-scoring of ICT images (eTables 6–7), and the patient's perception of the intervention (see eResults).

3. Results

3.1. Demographic variables

The clinical trial was offered to 756 hospitalized patients between February 2018 and March 2020. A total of 247 patients agreed to participate in the initial clinical interview, and 174 patients started the experiment (T1). Seventy-three patients were excluded because they met the exclusion criteria (e.g., epilepsy, bipolarity) or had decided not to participate for various reasons (i.e., too much time investment, low motivation for the clinical trial, or fear of tDCS). Thirty-two patients discontinued their participation after T1 due to premature discharge. A total of 142 patients completed the five intervention sessions (see Fig. 1). Seventeen participants missed the post-intervention assessment due to alcohol consumption or early discharge. The final analysis included 125 participants.

Table 1 presents the clinical and sociodemographic characteristics of the participants. The patients received a detoxification regimen consisting mainly of decreasing doses of diazepam. There was no significant difference in the initial dose of diazepam administered between participants in the four conditions ($F(3, 121) = 1.38$, $p = .25$).

Participants guessed which group they were assigned to with an accuracy of 53%, which is not significantly greater than 50% according to a binomial test ($z = 0.54$, $p = .3$).

3.2. Primary outcome analyses

At two weeks post-discharge, 70.4% of patients (n = 88/125; CI = 62.4–78.4) were abstinent, and 29.6% relapsed (n = 37/125; CI = 21.6–37.6). Relapse rates at 1, 3, 6 months and 1 year after discharge are reported in supplementary items (eFigure 1).

Logistic regression with orthogonal simple contrasts showed a significant effect of tDCS at 2 weeks post-discharge (see Table 2, (1), C1), with a difference in abstinence rate of 19% between groups receiving verum tDCS or sham tDCS (verum tDCS 79.7% [51/64; 95% CI = 69.8–89.6] vs sham tDCS 60.7% [37/61; 95% CI = 48.3–73.1]). There was no significant effect on abstinence of ICT at 2 weeks post-discharge (AICT 66.1% [47/63; 95% CI = 54.2–78] vs. NICT 74.6% [41/62; 95% CI = 63.8–85.4]) (see Table 2, (1), C2). Logistic regression with orthogonal deviation contrasts revealed a higher abstinence in the verum tDCS condition associated with AICT than the other three conditions (see Table 2, (2), C1; verum tDCS-AICT 86.1% [31/36; CI = 74.6–97.6] vs. others 64% [57/89; CI = 54–74]).

The clinical effect of the intervention did not persist beyond two weeks after the discharge (i.e., 1, 3, 6 months, and 1 year; for more details, see supplementary eResults, eTable 2).

3.3. Secondary outcomes analyses

We found no evidence that the type of intervention significantly altered scores for craving, depression, negative or positive affect, verbal fluencies, working memory and inhibitory control (see Table 3). Based on these non-significant effects, we did not include these variables in the regression model.

Table 1
Demographic and clinical characteristics of the sample at baseline.

	Verum tDCS −AICT N = 36	Verum tDCS −NICT N = 28	Sham tDCS-AICT N = 27	Sham tDCS-NICT N = 34	F/χ^2	p value
Sex (Female/Male)	12/24	10/18	10/17	9/25	.95	.81
Age	47.94 (9.63)	46.11 (10.77)	50.07 (10.36)	44.74 (8.94)	1.65	.18
Education (in years)	13.89 (3.23)	13.04 (3.55)	13.22 (3.71)	13.03 (2.74)	0.52	.67
Smokers/Not smokers	27/9	22/6	16/11	24/10	2.88	.41
Diazepam (first dose in mg)	55.83 (30.74)	51.07 (26.71)	46.30 (28.17)	60.88 (30.98)	1.38	.25
Number of prior detoxifications	1.44 (1.83)	1.61 (2.66)	2.00 (3.11)	2.03 (2.84)	0.40	.75
Duration of AUD (in years)	9.54 (9.01)	10.07 (8.58)	13.19 (12.67)	13.37 (10.23)	1.26	.29
Maximum use of alcohol (in grams per day)	216.60 (149.15)	258.32 (181.94)	256.44 (256.97)	258.52 (123.73)	0.44	.73
Minimum use of alcohol (in grams per day)	193.80 (146.64)	198.11 (107.11)	222.70 (189.15)	225.21 (115.29)	0.42	.74
AUDIT	30.58 (5.02)	32.50 (6.28)	30.37 (6.68)	31.21 (5.16)	0.80	.50
CEQ						
Intensity of craving	24.19 (14.53)	30.14 (14.73)	27.07 (14.25)	27.85 (14.33)	0.93	.43
Frequency of craving	25.50 (15.64)	27.43 (15.48)	24.78 (13.90)	28.26 (13.21)	0.38	.76
BDI-II	19.92 (11.25)	21.82 (11.87)	20.52 (11.46)	19.26 (12.46)	0.26	.85
PANAS						
Positive affect	33.92 (8.70)	33.54 (10.55)	32.11 (10.17)	34.29 (7.23)	0.32	.81
Negative affect	21.00 (8.19)	19.75 (8.35)	17.41 (5.60)	19.62 (6.28)	1.28	.29
STAI						
State anxiety	45.50 (12.26)	50.64 (13.94)	53.22 (10.21)	49.79 (12.02)	2.22	.09
Trait anxiety	41.20 (8.68)	42.00 (10.08)	40.67 (10.87)	44.00 (10.43)	0.69	.56
UPPS-P						
Negative urgency	6.86 (2.67)	7.30 (3.34)	6.20 (2.99)	7.44 (3.18)	0.93	.43
Positive urgency	7.50 (2.27)	6.89 (2.91)	7.00 (2.52)	7.47 (2.95)	0.42	.74
Lack of premeditation	8.22 (2.58)	9.15 (3.11)	9.12 (2.86)	8.44 (2.74)	0.86	.47
Lack of perseverance	8.97 (3.08)	8.85 (3.62)	8.92 (3.33)	8.65 (3.75)	0.06	.98
Sensation seeking	6.36 (2.91)	6.78 (2.91)	4.40 (2.94)	6.09 (3.39)	3.04	.03

Values are means (SD).
Abbreviations: AICT, Alcohol Cue Inhibitory Control Training; AUDIT, Alcohol use Disorder Identification; NICT, Neutral Inhibitory Control Training; BDI-II, Beck Depression Inventory II; CEQ, Craving Experience Questionnaire; PANAS, Positive And Negative Affect Scale; STAI-A&B, State-Trait Anxiety Inventory; UPPS-P, impulsivity scale (short version).

4. Discussion

The main objective of this pre-registered randomized clinical trial was to examine whether repeated sessions of tDCS applied to the DLPFC, combined with AICT, increased the likelihood of abstinence. The brain target, as well as the behavioral paradigm, were selected on the basis of converging data showing that (1) participants with AUD exhibited impaired prefrontal functioning (e.g., hypoactivity) [6,34] associated with poor executive functions (e.g., prepotent response inhibition), which increases the likelihood of relapse [18,20]; (2) DLPFC is involved in the inhibition of behavior and craving [75]; (3) stimulating DLPFC with tDCS may reduce the risk of relapse, possibly through improved executive functioning and decreased intensity of craving [26]; (4) repeated associations of alcohol cue with No-Go responses can improve control over alcohol consumption in problem drinkers [76]. Theoretically, the methodology of the clinical trial was based on the dual-process model of addiction [14-16,64], which underlines an imbalance between a (sensitized) automatic/implicit system involved in the pursuit of alcohol-related goals and habits and a (compromised) prefrontal

Table 2
Logistic regression results on relapse rate at 2-week post discharge.

		Contrasts				2-week post discharge			
		Verum tDCS-AICT (A)	Verum tDCS -NICT (B)	Sham tDCS -AICT (C)	Sham tDCS -NICT (D)	Estimate	SE	Odds Ratio	p value
(1) Orthogonal simple contrasts	Intercept					0.90	.21	2.46	<.001
	C1: Verum vs Sham tDCS	1/2	1/2	−1/2	−1/2	0.94	.41	2.56	.02
	C2: AICT vs NICT	1/2	−1/2	1/2	−1/2	0.40	.41	1.49	.33
	C3: Interaction	1/4	−1/4	−1/4	1/4	1.01	.83	2.75	.22
(2) Orthogonal deviation contrasts	Intercept					0.9	.21	2.46	<.001
	C1: A > B = C = D	1	−1/3	−1/3	−1/3	0.34	.15	1.40	.02
	C2: B > A = C = D	−1/3	1	−1/3	−1/3	0.11	.14	1.12	.42
	C3: C > A = B = D	−1/3	−1/3	1	−1/3	−0.03	.13	.97	.84

Abbreviations: A = verum tDCS-AICT, B = verum tDCS-NICT, C = sham tDCS-AIC, D = sham tDCS-NICT; AICT, Alcohol Cue Inhibitory Control Training; NICT, Neutral Inhibitory Control Training; C1-2-3, Contrast 1-2-3; SE, Standard Error.
Logistic Regressions (1) with orthogonal simple contrasts to evaluate the effect of verum vs. sham tDCS and AICT vs. NICT on relapse rate and (2) orthogonal with deviation contrasts to compare the relapse rate of verum tDCS-AICT to that of other interventions.

deliberative system responsible for the continuous monitoring of automatic responses.

Our first result was that regardless of the type of ICT intervention (i.e., neutral or related to alcohol), tDCS targeting the neural network including the DLPFC increased the abstinence rate by 19%, compared to sham tDCS. Crucially, this tDCS intervention was not clinically beneficial when considering time points later than two weeks post-discharge (i.e., until one-year post-discharge). To our knowledge, this is the first time that a study has demonstrated a positive impact of prefrontal tDCS administered during the rehabilitation on the risk of early relapse. This finding is coherent with numerous studies showing that prefrontal-tDCS was accompanied by a decrease in alcohol consumption [31,32,46,47,49]. Although hypothetical, a five-day course of verum prefrontal tDCS may result in increased global efficiency of brain networks and an increase in the functional connectivity of a sub-network including nodes in the right anterior cingulate gyrus in AUD [46]. This finding highlights the potential of prefrontal-tDCS to modulate network connectivity, thus potentially resulting in better integration of different regions [77] that can rebalance the *impulsive* and the *reflective* neurocognitive systems in AUD. However, the mechanisms of action of this protective effect on alcohol relapse remains to be elucidated. Indeed, contrary to our predictions and previous reports in AUD [36,37,42], neither the reduction of craving nor the improvement in executive control resulted specifically from an active prefrontal-tDCS. It should be noted that other studies found that tDCS did not help craving and executive functions in AUD [32,44,49,78]. Several explanations are eligible to account for the discrepancy between studies, namely the tDCS montage, the number of sessions, and the measurement of craving. First, although the polarity (anode on left F3 and cathode on right F4 or inversely) seems to play a role in several cognitive functions and craving [38,42], recent metanalyses recommended that right DLPFC anodal with left DLPFC cathodal tDCS could be more effective than the reverse in decreasing relapses or craving in AUD [79] (but see for reviews suggesting that polarity was not decisive in this context [26,80]). Since recent studies have demonstrated beneficial effects of tDCS montage on response inhibition [81–83], we anticipated to observe similar effects in our study. For instance, reduction in the inhibitory-control associated to the DLPFC following cathodal stimulation in turn made the participants more prone to respond with impulsive incorrect responses [81]. However, it should be noted that significant inter-individual variability in executive performance in response to prefrontal tDCS exists. A recent study by Weidler et al. [83] found evidence for this, wherein the up-regulation of right DLPFC improved response inhibition performance among alcohol and tobacco-dependent patients in the stop-signal task administered 40 min after the stimulation as opposed to healthy controls (characterized by lower impulsivity traits).

Despite the current state of evidence demonstrating the beneficial effect right anodal DLPFC stimulation casts on several executive functions including response inhibition, further investigation on the clinical expression of these effects, their persistence over time and inter-individual variability is warranted. Second, a greater number of sessions (ten) of prefrontal tDCS may induce a decrease in craving and improved executive functions in methamphetamine users [45]. However, no additional effects on craving and relapse of extended repetitive bilateral tDCS over the DLPFC in crack-cocaine users has been reported [31]. In the present study, we used the most frequently used craving measure [84], namely, the visual analogue scale including several forms of cue exposure. This instrument is simple to understand, easy to administer and score, and minimizes the risk of refusal [85]. However, unlike other instruments that investigate the retrospective frequency and duration of craving over extended periods [31,86], VAS could be sensitive to habituation during exposure to alcohol cues and is subject to the representativeness of the moment [85]. Overall, our results indicate that prefrontal-tDCS could impact on alcohol consumption in the weeks following the discharge from alcohol rehabilitation without necessary changes in craving and executive functions [47] (see also [87] for similar outcomes using rTMS).

Regarding the effects of ICTs, our results indicate a lack of alcohol-specific training effects on any of the behavioral data. This null result diverge from several studies [55,88,89] but echoes recent data showing no effects of ICT on alcohol consumed in the context of training (lab-based), or in another context (semi-naturalistic bar), nor on inhibitory control processes, or on alcohol cue-inhibition associations, or in alcohol value [58]. Our finding was also in line with broader literature on cognitive-bias-modification interventions showing weak and inconsistent effects on substance use [52,53] (but see Ref. [5] for a positive clinical effect on the abstinence rate).

Further analyses indicated that the combination of verum tDCS with AICT was more effective in reducing alcohol relapse two weeks after discharge than the other three interventions. The observed synergic effects of neurostimulation and cognitive training were consistent with prior theories and recommendations [50,62,90,91]. Indeed, the “activity-selectivity” hypothesis stresses that tDCS preferentially modulates populations of active and inactive neurons [63]. Additionally, the synergistic effect found is consistent with the view that AUD results from poor inhibitory control over alcohol-related responses [8,15,16,23,64]. When the prefrontal regions are stimulated, tDCS is assumed to modestly improve specific functions of executive control (e.g., response inhibition, enhanced response accuracy in online tasks, reduced aggression) [91–95]. Conversely, motor response training via a specific Go/No-Go task might modify behavior by changing the explicit attraction towards an object [96,97]. However, in light of the present data, the psychological mechanisms responsible for the observed relapse protection remain unknown, as it generally does for brain stimulation and behavioral training in healthy and clinical populations [5,24,31,32,49,51,52,98–101]. Indeed, we found no evidence of the intervention's effect on potential mediators, including measures of craving, response inhibition, mood, cognitive bias and working memory.

There are several limitations to the present study. First, although the protocol was randomized, it was a single-blind study, in which the participants were blinded but the experimenters were not. Therefore, the patients could have been implicitly influenced by the experimenters’ knowledge. However, this possibility is unlikely because the patients were inaccurate in guessing their assigned conditions. The second limitation is the reliance on self-reported alcohol use as a key outcome instead of in-person follow-up interviews allowing biological verification of abstinence. However, the method of interview used in the present study (based on the Timeline Follow-Back method) is considered valid for measuring recent use of alcohol and other drugs [102] and has been used in a majority of studies, including a recent one similar to the present report in many aspects [5]. Additionally, in order to increase the accuracy of the information, we also contacted a person close to the patient via telephone (e.g. general practitioner, family member) who fully confirmed that return to alcohol use. Finally, a certified clinical psychologist ignorant about the type of intervention that the patients had received contacted the patients during the follow-up period. All the patients who resumed drinking alcohol within two weeks of their discharge presented a persistent harmful alcohol use pattern, which required additional clinical counseling and re-treatment over the next 12 months. A third limitation concerns our methodology consisting of using five sessions of prefrontal tDCS for five consecutive days, while a reduction in

Table 3
Changes in scores on craving, depression, affects, verbal fluency, working memory and inhibitory control, between baseline and after intervention.

		Verum-AICT N = 27		Verum-NICT N = 24		Sham-AICT N = 23		Sham-NICT N = 27		Time (1, 99)			Condition (3, 99)			Time*Condition (3, 99)		
		T1	T2	T1	T2	T1	T2	T1	T2	F	p	η^2p	F	p	η^2p	F	p	η^2p
Craving (VAS)	**Simple question**	0.79 (1.84)	0.93 (2.48)	0.37 (1.28)	0.37 (1.06)	0.26 (1.25)	0.04 (0.21)	0.74 (1.93)	0.26 (0.81)	0.79	.38	.01	1.30	.28	.04	0.79	.51	.02
	Mental imagery	1.38 (2.47)	0.97 (2.31)	0.29 (0.81)	0.08 (0.41)	1.00 (2.26)	0.09 (0.42)	1.37 (2.66)	0.56 (1.28)	9.02	<.01	.08	2.03	.12	.06	0.70	.56	.02
	Alcohol image	1.31 (2.71)	0.28 (0.70)	1.42 (2.84)	0.29 (0.81)	1.09 (2.11)	0.17 (0.83)	0.52 (1.25)	0.26 (0.81)	17.08	<.001	.15	0.58	.63	.02	0.99	.40	.03
Depression (BDI-II)	**BDI**	18.28 (10.99)	14.72 (11.59)	22.46 (12.74)	17.50 (12.57)	20.04 (10.94)	15.13 (10.34)	19.74 (12.02)	16.04 (11.24)	23.79	<.001	.19	0.48	.70	.01	0.19	.91	.01
Affect (PANAS)	**Negative affect**	20.90 (8.48)	17.90 (6.62)	19.67 (8.95)	18.00 (8.44)	17.17 (5.46)	16.91 (5.21)	19.44 (6.42)	19.70 (8.43)	2.80	.01	.03	0.76	.52	.02	1.19	.32	.04
	Positive affect	33.24 (7.50)	31.79 (9.77)	33.04 (11.00)	33.42 (8.71)	32.52 (10.46)	30.57 (9.60)	34.78 (7.19)	33.74 (7.51)	1.54	.22	.02	0.52	.67	.02	0.35	.79	.01
Alcohol verbal fluency	**Total**	15.23 (5.21)	16.92 (5.69)	16.35 (6.58)	16.54 (7.58)	15.32 (5.24)	16.10 (5.01)	15.07 (5.54)	19.00 (8.07)	10.58	<.01	.10	0.26	.86	.01	2.64	.05	.07
	Positive	2.76 (2.65)	4.26 (2.63)	3.29 (2.08)	2.99 (2.89)	3.22 (2.82)	3.14 (2.44)	3.27 (2.64)	4.05 (3.40)	2.61	.11	.03	0.32	.81	.01	2.04	.11	.06
	Negative	4.24 (4.64)	4.78 (4.53)	5.46 (4.39)	5.81 (4.71)	3.43 (3.59)	3.20 (2.67)	4.26 (3.12)	4.96 (4.08)	0.93	.34	.01	1.58	.20	.05	0.32	.81	.01
	Neutral	8.23 (5.82)	7.32 (5.39)	7.60 (4.72)	7.36 (5.03)	8.67 (5.49)	9.22 (5.46)	7.53 (4.75)	9.36 (7.32)	0.34	.56	<.01	0.44	.72	.01	1.32	.27	.04
Sport verbal fluency	**Total**	17.68 (5.96)	18.55 (6.03)	16.58 (5.11)	18.90 (5.69)	16.07 (4.53)	18.04 (4.98)	19.16 (9.10)	20.67 (7.94)	11.74	<.01	.11	1.08	.36	.03	0.43	.73	.01
	Positive	1.98 (4.45)	2.06 (3.85)	1.68 (2.16)	2.69 (2.97)	0.46 (0.82)	0.48 (0.89)	0.83 (1.47)	1.14 (1.55)	3.34	.07	.03	2.68	.05	.08	1.33	.27	.04
	Negative	0.24 (0.50)	0.44 (0.78)	0.36 (0.80)	0.28 (0.54)	0.04 (0.15)	0.14 (0.33)	0.63 (1.32)	0.48 (1.37)	0.03	.87	<.001	1.89	.14	.05	0.69	.56	.02
	Neutral	15.46 (5.19)	16.06 (5.41)	14.54 (5.66)	15.93 (5.28)	15.57 (4.54)	17.42 (4.42)	17.70 (9.18)	19.05 (7.24)	7.09	.01	.07	1.59	.20	.05	0.30	.83	.01
Semantic verbal fluency	**Total**	21.93 (5.48)	23.03 (4.48)	20.92 (5.36)	23.92 (4.51)	21.00 (4.90)	21.70 (5.15)	20.67 (6.81)	23.52 (6.71)	20.45	<.001	.17	0.25	.86	.01	1.92	.13	.06
Working memory	**PCU**	0.62 (0.12)	0.73 (0.14)	0.61 (0.17)	0.69 (0.16)	0.64 (0.41)	0.63 (0.16)	0.63 (0.15)	0.72 (0.17)	10.87	<.01	.10	0.39	.76	.01	1.34	.27	.04
Inhibitory control	**SSRT**	273.27 (124.98)	220.22 (117.19)	261.83 (185.96)	218.89 (110.86)	205.84 (117.62)	174.13 (127.92)	255.27 (96.22)	231.89 (72.73)	7.88	<.01	.07	1.70	.17	.05	0.25	.86	.01
	p(r|s)	48.72 (17.81)	45.05 (12.73)	46.46 (16.08)	43.12 (7.32)	40.09 (6.27)	41.07 (6.17)	46.44 (14.58)	45.93 (6.22)	1.42	.24	.01	2.02	.12	.06	0.65	.58	.02
	NS-hit	63.93 (38.83)	72.17 (33.70)	83.38 (19.23)	82.13 (18.18)	69.96 (23.50)	70.57 (23.72)	68.74 (39.56)	60.01 (40.04)	0.01	.92	<.01	1.98	.12	.06	1.75	.16	.05

Values are means (SD). Abbreviations: AICT, Alcohol Cue Inhibitory Control Training; NICT, Neutral Inhibitory Control Training; NS-hit, no-signal hit; BDI-II, Beck Depression Inventory II; PANAS, Positive and Negative Affect Scale; p(r|s), probability (response | signal); PCU, Partial Credit Unit; SSRT, Stop Signal Reaction Time.

craving and an improvement in cognitive control functions have been observed in individuals suffering from methamphetamine use disorder after 10 sessions of brain stimulation over a longer period (five weeks) [45]. Therefore, the lack of sessions could explain why we have failed to find enhanced executive control and reduce cravings. As the duration of the detoxification program rarely exceeds three weeks (of which a minimum of seven days must be subtracted due to the acute phase of alcohol withdrawal, which requires high doses of benzodiazepines associated with reduced cognitive efficiency), a longer protocol seems unrealistic. Subsequent protocols could include two sessions per day over five consecutive days, subject to a decrease in study feasibility due to less participant consent.

5. Conclusion

Due to its low cost, easy availability, limited side effects, and positive impact on the clinical trajectory of the patients, we recommend the use of tDCS in association with alcohol cue ICT during alcohol rehabilitation. However, it is short-lived, and further investigations are needed to ascertain whether this intervention could be more advantageous with additional follow-up sessions after a couple of weeks. Several improvements could also be considered, including the gamification of the ICT and personalization (i.e., personal goal) of the stimuli associated with the Go and No-Go responses [103]. Finally, the identification of the psychological and neural mechanisms of the acquired resilience caused by the combination between neuromodulation and ICT remains the most intriguing question [46].

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CRediT authorship contribution statement

Macha Dubuson: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Supervision, Project administration. **Charles Kornreich:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition. **Marie-Anne Vanderhasselt:** Conceptualization, Writing – review & editing. **Chris Baeken:** Conceptualization, Writing – review & editing. **Florent Wyckmans:** Formal analysis. **Clémence Dousset:** Writing – review & editing. **Catherine Hanak:** Resources. **Johannes Veeser:** Resources. **Salvatore Campanella:** Conceptualization, Methodology, Writing – review & editing. **Armand Chatard:** Writing – review & editing. **Nemat Jaafari:** Writing – review & editing. **Xavier Noël:** Conceptualization, Methodology, Resources, Formal analysis, Writing – original draft, Supervision, Project administration.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.10.386.

Data availability

The datasets generated for this study are available on request to the corresponding author.

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